NOVARTIS

CLCZ696BPT07 Study Results Abstract for Public Disclosure

Title

Comparative effectiveness of Sacubitril/Valsartan vs ACEi/ARB in HFrEF patients: Real Heart PT

Keywords

Sacubritril-valsartan, Heart failure, Cardiovascular outcomes

Rationale and background

Heart failure (HF) is a leading cause of hospitalization and mortality among older adults. Traditionally, the treatment algorithm included angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB). Sacubitril/valsartan (SAC/VAL) is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI), which simultaneously delivers renin–angiotensin–aldosterone system (RAAS) inhibition through valsartan and neprilysin inhibition through sacubitril. SAC/VAL has shown superiority over enalapril in reducing all-cause mortality and HF hospitalization in patients with heart failure with reduced ejection fraction (HFrEF) and New York Heart Association class II-IV who had been previously treated with an ACEi/ARB and in patients hospitalized with acute decompensated HF.

The latest guidelines on HF treatment recommend ARNI as the preferred RAAS inhibitor for HFrEF in patients who have been previously treated with an ACEi or ARB, as well as in patients naive to an ACEi or ARB. However, there is limited data on treatment effectiveness in these patients in the real-world setting and, in this sense, this secondary data study was conceived to compare the effectiveness of SAC/VAL and ACEi/ARB in delaying time to first occurrence of either death from cardiovascular (CV) causes or hospitalization due to HF in HFrEF patients in Portugal.

Research question and objectives

The research question that initiated the study was “What is the effectiveness of SAC/VAL in death from CV causes or hospitalization due to HF, compared to ACEi/ARB, in HFrEF patients?”.

The primary endpoint was to evaluate the effect of SAC/VAL compared to ACEi/ARB in delaying time to first occurrence of either death from CV causes or hospitalization due to HF in HFrEF patients.

Secondary endpoints included individual components of the primary endpoint, all-cause mortality, hospitalizations and emergency room visits, implantable cardioverter-defibrillator (ICD) implantation, changes in left ventricular ejection fraction (LVEF) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP), healthcare costs, and rates of hyperkalemia.

Study design

This was a retrospective, observational, comparative cohort study using secondary data from electronic health records (EHR) from a local health unit that provides primary, secondary and tertiary care to a resident population in northern Portugal. The study aimed to assess the comparative effectiveness of SAC/VAL versus ACEi or ARB in patients with HFrEF.

Setting

The study period ranged from January 1st, 2000 to July 31st, 2022. The index period ranged from January 1st, 2001 to July 31st, 2022. The index date corresponded to the date of initiation of the drugs of interest. Patients were assessed for clinical outcomes at 180, 810 and 1260 days post-index date.

Subjects and study size, including dropouts

The study population consisted of adult patients with HFrEF undergoing therapy with SAC/VAL or ACEi/ARB.

Variables and data sources

Study variables were retrieved from data processing of EHR. Study variables included demographic, comorbidity, medication data, healthcare resource utilization, costs and clinical outcomes.

Statistical methods

Continuous variables were described using median and interquartile range. Categorical variables were described by the number and percentage of patients in each category. A survival analysis employed Cox proportional hazard models to assess risk factors for outcome events. 95% confidence intervals (CIs) were presented for hazard ratio (HR).

Results

The study included a target cohort of patients initiating SAC/VAL (n=261) and a comparator cohort of patients initiating an ACEi or ARB (n=988). After propensity score matching on baseline covariates, the cohorts consisted of 259 patients in the SAC/VAL cohort and 983 patients in the ACEi/ARB cohort.

Regarding the composite of CV death or HF hospitalization, there was significant risk reduction for the SAC/VAL cohort at all measured time points. At 180 days, the risk was reduced by 62% (HR 0.38, 95% CI: 0.30-0.49), at 810 days by 30% (HR 0.70, 95% CI: 0.60-0.82), and at 1260 days by 21% (HR 0.79, 95% CI: 0.69-0.90). All-cause mortality was consistently lower with SAC/VAL (HRs 0.47, 0.51, 0.61). First-event analyses showed reductions with SAC/VAL in first emergency room visit for HF and first hospitalization for any cause.

ICD procedure hazards were higher in the SAC/VAL group at 810 and 1260 days (HRs 18.91 and 7.55). Improved LVEF was less likely on SAC/VAL at all timepoints. Median NT-proBNP and LVEF changes were small in both groups and correlations between NT-proBNP and LVEF change were modest in SAC/VAL and higher in ACEi/ARB. Hyperkalemia risk was higher with SAC/VAL across all timepoints (HRs 1.35, 1.30, 1.31).

Direct costs varied by category and calendar year. Medication and outpatient costs per patient were generally higher with SAC/VAL, while inpatient costs fluctuated.

Discussion

The initiation of SAC/VAL was associated with substantially lower hazards of the primary composite of CV death or HF hospitalization at 180, 810 and 1260 days which is aligned with evidence from the PARADIGM-HF trial. The consistent reduction observed for first HF-specific events, such as emergency visits, hospitalizations, and CV-specific hospitalizations, underscores the disease-modifying impact of SAC/VAL on clinical instability, which is consistent with other studies.

Biomarker and remodeling-related patterns differ from other studies, such as the PROVE-HF trial, that linked SAC/VAL to substantial NT-proBNP reductions and reverse remodeling with LVEF improvement over 6–12 months. This could be explained by residual confounding despite propensity score matching, such as higher baseline atrial fibrillation prevalence in SAC/VAL patients; missing information regarding echocardiographies or differential surveillance intensity across treatment groups.

Our analysis detected increased hazards of hyperkalemia with SAC/VAL across all timepoints, while the PIONEER-HF trial reported similar rates of hyperkalemia versus enalapril during in-hospital initiation, however, this difference may be attributed to the studied population's chronic kidney disease burden, other medication use, or laboratory monitoring frequency.

Economic trends in our data were mixed: medication and outpatient costs were generally higher with SAC/VAL, while inpatient costs fluctuated by year and were not uniformly lower, possibly due to modest sample size and site-specific practice.

Conclusion

In this retrospective cohort study of HFrEF patients, treatment with SAC/VAL was associated with clinically meaningful reductions in CV outcomes, highlighting its role as foundational therapy for HFrEF beyond controlled trial settings. Discrepant signals in LVEF improvement and hyperkalemia emphasize the need for cautious interpretation of secondary endpoints which would benefit from multi-site validation.