CLCZ696AJP04 Study Results Abstract for Public Disclosure

Title

Effectiveness of Entresto (Sacubitril/Valsartan) to blood pressure control in Japanese patients with hypertension: the database analysis of electronic medical records

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NIS Type

Non-Interventional Study (NIS) with Secondary Use of Data

Keywords

Hypertension, Sacubitril/Valsartan, Real-world evidence, Japan

Rationale and background

In hypertension therapy, there are many issues disrupting therapeutic adherence such as polypharmacy and clinical inertia. Hypertension has no symptom so that patients may not feel a strong need for treatment or may be distracted by side effects or burden of the therapy. On the other hand, it is reported that higher blood pressure (BP) contributes with higher cardiovascular (CV) events.

Sacubitril/Valsartan is a first-in-class angiotensin receptor-neprilysin inhibitor (ARNI) was granted an expanded indication for use of the therapy in patients with hypertension in addition to chronic heart failure (HF). Simultaneous inhibition of neprilysin and renin-angiotensin-aldosterone system (RAAS) with Sacubitril/Valsartan showed the stronger antihypertensive effects and higher responder rates than valsartan or olmesartan, angiotensin receptor blockers (ARB), in patients with essential hypertension in several randomized control trials. However, there are no reports of the responder rates and adverse event (AE) rates in actual clinical practices of the drug.

In this study we investigated the effectiveness of Sacubitril/Valsartan in BP control among Japanese patients with hypertension in a real-world setting by database analysis of electronic medical records.

Research question and objectives

To investigate the effectiveness of Sacubitril/Valsartan in lowering BP to the goals in hypertensive patient treated with Sacubitril/Valsartan.

Study design

This study was a non-interventional, secondary use of data, retrospective, cohort study, and the data to be extracted in this study were used as secondary use of collected patient information in the database (JAMDAS) owned by m3 Inc.

Setting

The target population for this study was patients with essential hypertension. Of patients who met the eligibility criteria, they were divided into two groups: the Sacubitril/Valsartan group were patients treated with Sacubitril/Valsartan, and the Conventional drug (Angiotensin-converting enzyme inhibitor [ACEi]/ARB, ACEi/ARB plus hydrochlorothiazide [HCTZ], calcium channel blocker [CCB]) -control groups were patients treated with conventional antihypertensive drugs. Eligibility criteria were shown in Section 9.3.1.

Subjects and study size, including dropouts

From a feasibility check of the database from May 2021 to May 2022, there were 4,279 patients with hypertension with a prescription of Sacubitril/Valsartan, and 2,721 patients had BP data. Thus, approximately 60% of all patients had BP data. From data from April 2021 to April 2022, 3,602 patients had a prescription of Sacubitril/Valsartan with hypertension and with or without HF, and 2,431 patients had a prescription of Sacubitril/Valsartan with a

diagnosis of both HF and hypertension; thus, approximately two-thirds of all patients were comorbid with HF. We estimated at least 703 (60% of 1,171 [3,602 - 2,431]) patients would have been eligible, who were with hypertension without HF, which must have been prescribed Sacubitril/Valsartan QD, and had BP data.

Variables

The following information was extracted from JAMDAS in this study. Human genome and genetic information were not collected.

- Treatment status of antihypertensive drugs
- Patient characteristics
- BP
- Laboratory test
- Physical examination
- Events

Data sources

The data for this study was retrieved from JAMDAS, which is provided by m3 Inc., Tokyo. The designated contract research organization (CRO), Mebix, Inc., Tokyo, performed the analysis according to the contract agreement.

Statistical methods

All analyses were performed by Mebix, Inc. using SAS software (SAS Institute Inc., Cary, NC). The details of the statistical analysis were defined in the statistical analysis plan (SAP). Only aggregated data were extracted and reported to Novartis in an anonymized manner. Statistical testing included paired t-tests, two-sample t-tests, and χ^2 tests, as appropriate, with a two-sided significance level of 0.05 and 95% confidence intervals. Multivariate logistic regression analysis was used to assess associations between patient characteristics and BP goal attainment. Adverse events (AEs) were identified using ICD-10 codes and text-mining of free-text comments in medical records.

Results

In this real-world retrospective cohort study, 29.8% of Japanese patients with hypertension treated with Sacubitril/Valsartan achieved the blood pressure (BP) targets recommended by the JSH2019 guidelines within 8 weeks. Mean reductions in systolic and diastolic BP were −15.6 mmHg and −6.0mmHg, respectively. Patients with Grade I hypertension, aged ≥75 years, or with cerebrovascular disease were more likely to reach BP goals. AEs such as hypotension and diuresis-related symptoms were more frequent during summer, but discontinuation rates remained low (≤1.0%).

Discussion

This study confirms the effectiveness and safety of Sacubitril/Valsartan in routine clinical practice in Japan. Elderly patients and those with cerebrovascular disease showed higher BP goal attainment, likely due to more lenient targets and intensified management. Sacubitril/Valsartan was frequently used in combination with calcium channel blockers (CCBs), often replacing ARBs. Seasonal trends in adverse events suggest the need for dose adjustments and careful monitoring during summer. Limitations in propensity score matching highlight the complexity of real-world prescribing patterns and suggest the need for advanced analytical methods in future studies.

Conclusion

Sacubitril/Valsartan is effective and well-tolerated for BP management in Japanese hypertensive patients in real-world settings. Patients with Grade I hypertension, aged ≥75 years, and those with cerebrovascular disease may derive particular benefit. The combination of Sacubitril/Valsartan with CCBs was common among responders. Seasonal monitoring and dose adjustments, especially for concomitant diuretics, may help mitigate adverse events and optimize treatment outcomes.

List of abbreviations

AE	Adverse event
ACEi	Angiotensin-converting enzyme inhibitor
ARB	Angiotensin receptor blocker
BNP	Brain natriuretic peptide
BP	Blood pressure
CCB	Calcium channel blocker
CI	Confidence interval
CRO	Contract Research Organization
CV	Cardiovascular
HCTZ	Hydrochlorothiazide
HF	Heart failure
JSH	Japanese Society of Hypertension
JSH2019	Japanese Society of Hypertension Guidelines for Management of Hypertension 2019
NI	Non-Interventional
NIS	Non-Interventional Study
RAAS	Renin-angiotensin-aldosterone system