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Protocol

Assessing hypotension incidence and dosing strategies of sacubitril/valsartan in real-world heart failure management: protocol for a retrospective, multicentre and cohort study

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ABSTRACT

Background: The burden of heart failure (HF) and hypertension in India underscores the need for effective management strategies. Sacubitril/valsartan, an angiotensin receptor neprilysin inhibitor (ARNi), has emerged as a pivotal therapy for HF with reduced ejection fraction (HFrEF). However, concerns about hypotension often hinder optimal dosing in clinical practice. The primary objective of this study is to observe the incidence of hypotension in HFrEF patients and to evaluate the best clinical practice to achieve an optimal tolerated dose of sacubitril/valsartan without treatment discontinuation. Secondary objectives include evaluating treatment outcomes, tolerability, and factors influencing dosing adjustments.
Methods: This is the protocol of a retrospective, multicentre cohort study aimed at assessing real-world usage patterns of sacubitril/valsartan among Indian HFrEF patients. Patients aged 18-80 years diagnosed with HFrEF (left ventricular ejection fraction (LVEF) ≤40%) and initiated on sacubitril/valsartan between November 2023 and May 2024 will be included. Baseline and follow-up data, including demographics, medical history, and treatment outcomes, will be analysed using appropriate statistical tests. Data from approximately 150 healthcare facilities will be collected using a structured case report form (CRF). The study was initiated in February 2024. As of manuscript submission, 1039 individuals have been enrolled on the study. Data collection is expected to continue until the end of June 2024.
Conclusions: This study aims to contribute valuable insights into optimizing sacubitril/valsartan therapy for HFrEF patients in India, addressing concerns about hypotension and dosage optimization. The study seeks to inform clinical practice and enhance patient care by elucidating real-world usage patterns and outcomes.

Keywords: Sacubitril/valsartan, Heart failure, Reduced ejection fraction, Real-world evidence, Blood pressure, Tolerability, Effectiveness

INTRODUCTION

Heart failure (HF) imposes a significant burden in India, with prevalence estimates ranging from 1.3 million to 4.6 million and an annual incidence of 491,600–1.8 million.[1] Trivandrum heart failure registry data revealed that HF with reduced ejection fraction (HFrEF) was the most common subtype (62%), followed by HF with preserved ejection fraction (HFpEF) (20%) and HF with mid-range ejection fraction (18%), with an in-hospital mortality rate of 8.4%. Hypertension emerges as a significant contributor to HF, present in 55% of cases according to the registry, making it the second most common cause after ischemic heart disease (72%).[2] The prevalence of hypertension is projected to increase from 118 million (2000) to 214 million (2025), potentially leading to an increase in HF cases associated with hypertension.[1] As per the 2022 American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America (ACC/AHA/HFSA) Focused Update on New Pharmacological Therapy for HF, ACEI, ARB, or angiotensin receptor neprilysin inhibitor (ARNi) are now advocated for patients with chronic symptomatic HFrEF to mitigate morbidity and mortality, receiving a class I recommendation.[3]

Sacubitril/valsartan is superior to enalapril in reducing the risks of cardiovascular death and preventing hospitalization in patients with HFrEF.[4,5] The use of sacubitril/valsartan in HFrEF patients is associated with a significant reduction in blood pressure (BP) as compared to the ACEI/ARB group overall and across the eGFR spectrum, including in advanced chronic kidney disease.[4,6-8] The suggested initial dose of sacubitril/valsartan is 50 mg, to be taken orally twice daily. After 2–4 weeks, the dosage can be increased to 100 mg and further escalated to 200 mg based on the individual's tolerance.[9] However, concerns about hypotension often lead to suboptimal dosing in patients despite evidence supporting its efficacy.[10,11] The risk of hypotension poses a significant challenge to sacubitril/valsartan use, particularly in HFrEF patients, as demonstrated by retrospective studies and clinical trials.[10] The primary objectives of this retrospective study are to evaluate hypotension incidence among HFrEF patients and analyze real-world clinical practice to achieve an optimal tolerated dose of sacubitril/valsartan without treatment discontinuation. The secondary objective is to evaluate the tolerability of sacubitril/valsartan 200 mg BID after two months of treatment and dose adjustment (up-titration and down-titration) in HFrEF management.

METHODS

Study design

The ongoing study adopts a retrospective, multicenter cohort design to investigate the real-world utilization patterns of sacubitril/valsartan among adult patients diagnosed with HFrEF in India. In this retrospective real-world evidence study, patient-informed consent is not required. The study will be initiated after the Ethics Committee's approval. The study aims to comprehensively assess how sacubitril/valsartan is used in clinical practice settings across multiple centres, providing valuable insights into its application, dosing strategies, and associated outcomes.

Study participants

In the ongoing study, the patient population to be screened comprises individuals meeting specific inclusion and exclusion criteria to ensure the relevance and integrity of the research findings. The target population includes adult patients with HFrEF who have been prescribed sacubitril/valsartan and are visiting practicing clinicians in an outpatient (OP) setting within the specified timeframe.

The inclusion criteria are age 18 to 80 years, of either gender, diagnosed with HFrEF defined by an LVEF of ≤40%, and categorized as New York Heart Association (NYHA) functional class II-IV. Furthermore, individuals must have initiated sacubitril/valsartan therapy between November 2023 and May 2024, and the medication should have been prescribed either at the time of discharge from a healthcare facility or during an OP consultation.

The following patients will be excluded from the data analysis: diagnosis of HFpEF, HF predominantly resulting from right ventricular failure, pericardial disease, or congenital heart disease, and patients with missing follow-up data.

By adhering to these stringent criteria, the study aims to focus specifically on HFrEF patients who have received sacubitril/valsartan in the OP setting, thereby ensuring homogeneity within the study population, and facilitating accurate assessment of real-world usage patterns, treatment outcomes, and associated factors.

Data collection and follow-up

In this study protocol, data collection is facilitated through the extraction of patient data onto CRF. Through a retrospective approach, data from medical records of eligible patients who have been prescribed sacubitril/valsartan for the management of HFrEF are systematically extracted and documented onto the CRF. This data collection process spans 160 centres across India, offering a diverse representation of real-world clinical practices and patient populations (Figure 1).

To ensure adherence to stringent quality control standards, research coordinators will receive extensive training on the study protocol and procedures for extracting data from medical records before initiating data collection. Data security remains of utmost importance throughout the study, with access restricted solely to authorized personnel.

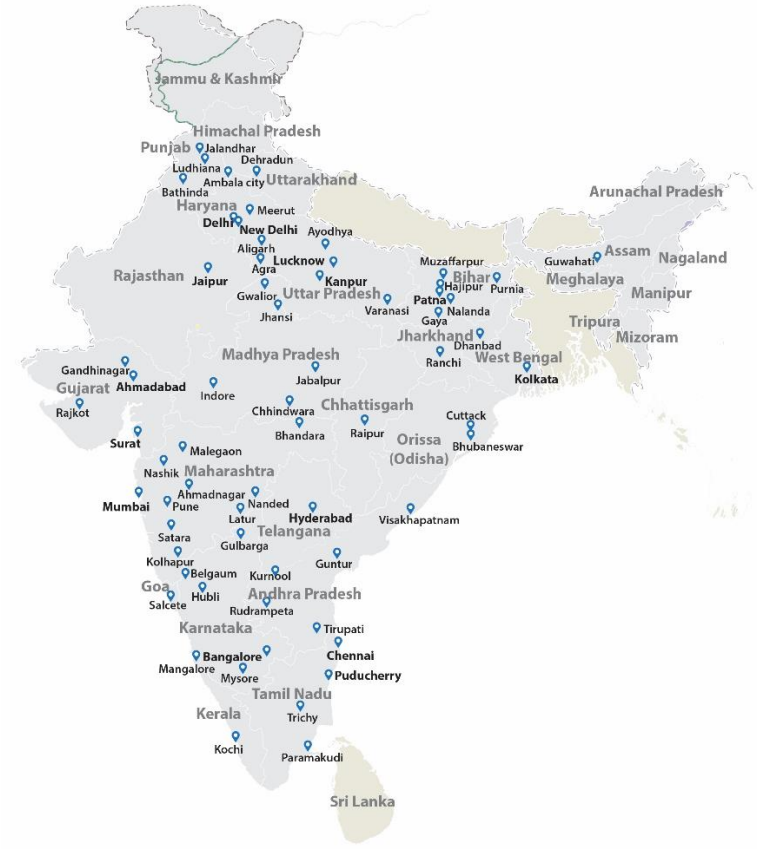

Figure 1: 160 participating centres in India.

Data items

The CRF will serve as a standardized tool for systematically capturing pertinent information regarding the selected cases, including patient demographic details, medical history, baseline characteristics, treatment regimens, dosing adjustments, adverse events, and clinical outcomes. All adverse events and reactions and their management will be recorded in the CRF.

Outcome measures

The primary outcomes are changes in both systolic and diastolic BP across different postures (sitting, lying, standing), alterations in NYHA class and percentage of patients sacubitril/valsartan 200 mg twice daily after two months of treatment initiation. Additionally, the study will retrospectively assess the tolerability of sacubitril/ valsartan.

Furthermore, secondary endpoints will be evaluated to provide additional insights into the current utilization of sacubitril/valsartan. These secondary outcomes include assessing changes in clinical signs and symptoms of HF, changes in NT-proBNP levels (if data is available), determining the percentage of patients requiring down-titration of sacubitril/valsartan (from 200 mg to 100 mg; 100 mg to 50 mg; and 50 mg to 0 mg (i.e., treatment discontinuation), and identifying reasons for down-titration or treatment discontinuation. Additionally, the study will analyze the time taken for patients to reach each up-titration level of sacubitril/valsartan (100 mg and 200 mg) and the median time required to achieve the maximum dosage of sacubitril/valsartan, i.e., 200 mg twice daily. These comprehensive endpoints collectively aim to provide a thorough evaluation of sacubitril/valsartan therapy in managing HF while also assessing its tolerability and potential dose adjustments in clinical practice.

Statistical analysis

Demographic and other qualitative parameters, such as age, gender distribution, comorbidities, and treatment adherence, will be summarized using frequency and percentage tables. This approach will offer a comprehensive overview of the patient population under investigation, allowing for the identification of any notable trends or associations.

Quantitative parameters, including BP and pulse rate, will undergo analysis using the paired t-test, contingent upon the satisfaction of normality assumptions. This statistical test will enable the comparison of pre- and post-treatment measurements within each patient, thereby assessing the impact of sacubitril/valsartan therapy on physiological parameters.

For qualitative parameters measured on an ordinal scale, such as NYHA class or severity of symptoms, the Wilcoxon signed rank test will be employed. This non-parametric test is suitable for analysing paired data with an ordinal or graded structure, allowing for the assessment of treatment-induced changes in subjective endpoints.

Observations from the study cohort will be summarized using descriptive statistics, including measures such as mean, standard deviation, median, and interquartile range. These statistics will provide a concise summary of continuous variables' central tendency and variability, offering insights into the overall effectiveness and tolerability of sacubitril/valsartan therapy in real-world clinical settings.

The study was initiated in February 2024. As of the submission of this manuscript, 1039 individuals have been enrolled on the study. Data collection is expected to continue until the end of June 2024, with the analysis and interpretation of results anticipated to be completed by the end of July.

DISCUSSION

If the annual incidence of HF in patients with systolic blood pressure (SBP) of 144–154 mmHg is 0.1% to 0.6%, as demonstrated in the hypertension optimal treatment and United Kingdom Prospective Diabetes Study trials, respectively, then the number of new HF cases due to hypertension may increase from 118 000–708 000 per year in 2000 to 214 000–1.3 million per year in 2025, conservatively assuming that the bulk of patients with hypertension in India have a SBP in the 144–154 mmHg range. After 5 years of HF incidence based upon the year 2000 estimates for hypertension, the total number of HF patients accrued could range from 590,000 to 3.5 million; with an estimated 50% mortality at 5 years, the prevalence of HF due to hypertension alone could be estimated to range from 295 000 to 1.8 million. However, this possibly represents an underestimate due to conservative estimates of the prevalence of hypertension, as well as the linear relationship between the risk of HF and BP that occurs for values even <140 mmHg.[1]

The introduction of sacubitril/valsartan represents a significant advancement in HF management, as highlighted by leading cardiovascular guidelines for its efficacy in reducing morbidity and mortality among patients with chronic symptomatic HFrEF. As the first agent in the ARNi class, sacubitril/valsartan is FDA-approved for HFrEF patients with NYHA class II, III, or IV symptoms, offering a valuable alternative to ACE inhibitors or ARBs. Its integration alongside standard HF therapies has demonstrated significant BP reduction compared to ACEIs/ARBs, even in patients with advanced chronic kidney disease. Sacubitril/valsartan has shown superiority over enalapril in reducing cardiovascular death risks and preventing hospitalizations in HfrEF patients.[3,12]

Achieving optimal dosing of sacubitril/valsartan can be challenging due to concerns regarding hypotension, which often leads to potential treatment discontinuation. Despite these challenges, sacubitril/valsartan remains a cornerstone of HF therapy and an essential component of guideline-directed medical treatment.[10,13]

Recognizing the importance of optimizing sacubitril/valsartan dosing in real-world settings, this study aims to evaluate the incidence of hypotension among HFrEF patients and assess the feasibility of dose titration to achieve optimal tolerated doses. This study holds several strengths, including its status as one of the pioneering real-world investigations into sacubitril/valsartan's efficacy and safety. It aims to identify barriers hindering the attainment of target doses and reasons for treatment discontinuation, thereby contributing to a better understanding of treatment adherence, persistence, epidemiology, and prescribing patterns. Through this study, clinicians can enhance their knowledge of sacubitril/valsartan utilization and its impact on HF patient outcomes, ultimately improving treatment strategies and patient care.

CONCLUSION

In summary, this study delves into real-world applications of sacubitril/valsartan therapy in HFrEF patients, aiming to optimize treatment outcomes by assessing dosing strategies and hypotension incidence. With HF and hypertension burdens rising in India, the study's insights hold promise for informing clinical guidelines and enhancing patient care. Overall, tailored dosing strategies and vigilant monitoring are emphasized to improve sacubitril/valsartan therapy efficacy and patient quality of life in HFrEF management.

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