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Review Article

Sacubitril/valsartan: A novel angiotensin receptor-neprilysin inhibitor

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ABSTRACT

Objective: To describe the efficacy, superiority and safety profile of the first-in-class angiotensin receptor-neprilysin inhibitor "Sacubitril/Valsartan" as compared to ACE inhibitor and ARB in heart failure patients, reviewing data available from both clinical and pre-clinical studies. Evidences on health care utilization outcomes such as hospitalizations and emergency department visits were also evaluated.
Material (data source): **Sources**: Medical literature on 'Sacubitril/Valsartan' and 'Angiotensin Receptor-Neprilysin Inhibitor' was identified by searching databases (including, but not limited to, PubMed, Embase and HighWire) for articles published since 1991, bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the companies developing the drug.
Search Strategy: We conducted separate searches for each of the interventions of interest. The timeframe for both searches spanned the period from January 1991 to the most recently published data available and focused on PubMed, Embase and HighWire indexed articles. The search strategies included a combination of indexing terms as well as free-text terms included separately in 'Keywords' section. To supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent relevant reviews and meta-analysis. Searches were last updated on 12th July 2017.
Selection: Studies in patients with hypertension who received sacubitril/valsartan combination drug were included. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well-controlled trials with appropriate statistical methodology was preferred. Relevant pharmacodynamics and pharmacokinetics data was also included.
Data evaluation: Many clinical trials have been conducted comparing the efficacy of sacubitril/valsartan with other anti-hypertensives. The trials have shown sacubitril/valsartan to be more effective in improving symptoms and physical limitations, reducing the risk of Cardiovascular (CV) death, Heart Failure (HF) hospitalization, and the overall mortality and morbidity compared to its counterparts.
Conclusion: Effective reduction of blood pressure to accepted goals is the key to reduce the risk of CV events and stroke. Dual inhibition of neprilysin and the angiotensin receptor with sacubitril/valsartan may represent an attractive and serendipitous therapeutic approach for a range of CV diseases, including hypertension and HF, in which vasoconstriction, volume overload and neuro-hormonal activation play a part in pathophysiology. Sacubitril/Valsartan appears to be more efficacious in reducing blood pressure than currently available ACEi and ARBs with a similar safety and tolerability profile. Besides, pleiotropic benefits like HbA_{1c} reduction, better eGFR progression and a greater decrease in BP and serum creatinine levels make this drug a novel addition to the current hypertension armamentarium.

Contents

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1. Introduction

Heart Failure (HF) is a major and growing health challenge in India and the developing countries. It is one of the most important causes of morbidity and mortality in the industrialized world. The incidence and prevalence estimates of HF are unreliable in India because of the lack of surveillance systems to adequately capture these data. Regardless of this, the prevalence of HF in India is possibly on the rise as India remains doubly burdened by the rise in the risk factors of traditional cardiovascular disease and by the persistence of pre-transitional diseases such as rheumatic heart diseases, endomyocardial fibrosis, tuberculous pericardial disease and anaemia. Burden of HF in India due to hypertension is extrapolated to be 3.5–7 million (estimate of about 4–5 million) and HF due to myocardial infarction is 2.1 million to 8.4 million (estimate of about 4–5 million) while an annual mortality due to HF around 0.1–0.16 million.[1–3]

With resources like cardiac resynchronization therapy and the heart transplant program available on a limited basis, pharmacotherapy still remains the primary treatment option. The latest results from SPRINT trial indicate that intensive blood pressure lowering to a target <120 mmHg is superior to routine management with a target of <140 mmHg in high-risk non-diabetic hypertensives, including elderly patients. An intensive strategy resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group.[4,5]

Sacubitril/Valsartan (brand name Entresto™, previously known as LCZ696) is a combination drug developed by Novartis®. It is a first-in-class angiotensin receptor-neprilysin inhibitor approved for the treatment of hypertension. It consists of the angiotensin receptor blocker (ARB) 'valsartan' and the neprilysin inhibitor 'sacubitril', in a 1:1 mixture by molecule count. The combination is thereby marketed as an "Angiotensin Receptor-Neprilysin Inhibitor" (ARNi).[6]

Currently, sacubitril/valsartan combination has been approved in more than 57 countries including India. The U.S. Food and Drug Administration approved sacubitril/valsartan combination in July 2015 for the treatment of patients with New York Heart Association (NYHA) class II through IV HF symptoms and a reduced ejection fraction (HFrEF) based on the results of the PARADIGM-HF trial.[6,7] It has now been included as a Class I B recommendation by the 2016 ESC and ACC/AHA/HFSA guidelines.[8–10]

2. Mechanism of action

Neprilysin, also known as membrane metallo-endopeptidase (MME), neutral endopeptidase (NEP), cluster of differentiation 10 (CD10), and common acute lymphoblastic leukemia antigen (CALLA), is an enzyme that in humans is encoded by the *MME* gene. It is found in many tissues, particularly in kidney on the brush border of proximal tubules and on glomerular epithelium. It is the principal enzyme for degradation of multiple vasoactive peptides (VAP) including natriuretic peptides, angiotensin, endothelin 1, adrenomedullin, opiods and amyloid-β peptide (Aβ). It cleaves peptides at the amino side of hydrophobic residues and inactivates

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