

Reviewer 1:

This review, submitted by Nirav Patel et al., discusses safety paradigms associated with chronic use of the heart drug, valsartan/sacubitril (formerly known as LCZ696 and currently marketed by Novartis as Entresto) in patients at risk of Alzheimer's disease (AD). Valsartan/sacubitril has been approved by the US Food and Drug Administration for the treatment of heart failure, and functions by inhibiting an enzyme known as neprilysin. Neprilysin plays a critical role in breaking down various peptides in cells, including natriuretic peptides (NPs), vasoactive peptides (e.g. endothelin-1, bradykinins), neuropeptides (e.g. substance P, enkephalins), and the beta-amyloid (A β) peptide. Although some cardiovascular benefits are achieved using a neprilysin inhibitor (NPI), recent laboratory studies involving the central nervous system implicate NPI in the development of AD in animal models. Therefore, a prudent approach involves following high-risk patients closely with cognitive assessments. Tests for detecting cerebrospinal fluid (CSF) β A peptide levels and amyloid plaques in clinical trials are also necessary.

Comments: 1) It should be noted that patients with heart failure AND preserved ejection fraction (HFpEF) currently represent almost half of all HF cases, and is projected to become the predominant form of HF in the future. The authors should - summarize the most recent and ongoing HFpEF clinical trials in this manuscript.

-- Done, please see line --- "In clinical practice, approximately 50% of the HF patients have a preserved left ventricular ejection fraction (HFpEF)---"

2) The mechanism proposed for underlying neprilysin inhibitor in the metabolism of cardiovascular peptides and the A β peptide is not well elucidated. A schematic description is necessary.

-- Done - I am including a schematic illustration please see Figure

3) The authors split the review paper into different sections with subtitles. However, some sections are overlapping.

-- I have created different sections so it is easy to follow. I know there is some overlapping since this syndrome has lot of overlapping information. We reduced/eliminated redundancy where possible.

4) Some of the most recent publications related to this topic are not included, such as Feldman AM et al JAMA 2016 and Hubers SA et al circulation 2016.

-- I have not included review articles in this manuscript.

5) Occasional grammatical and spelling errors are found throughout the manuscript.

-- Reviewed and edited out

Reviewer 2:

This is a nice review of the novel agent Enresto with some focus on potential neurological side effects. Overall the article is well written, please correct some

grammatical and typo issues In the first para of "Goals of Therapy" section please add Sympathetic nervous system to RAAS since beta blockers are also listed Please use Entresto consistently since LCZ696 is no more applicable as a name Please also mention ongoing cognitive function studies with Entresto

Done. The drug is referred to as its generic sacubitril-valsartan throughout the manuscript with association to its trade name Entresto.