HHS Public Access

Author manuscript

Circulation. Author manuscript; available in PMC 2017 July 19.

Published in final edited form as:

Circulation. 2016 July 19; 134(3): e11–e12. doi:10.1161/CIRCULATIONAHA.116.023311.

Response to Letter Regarding Article, "Combined Angiotensin Receptor Antagonism and Neprilysin Inhibition"

Scott A. Hubers, MD and **Nancy J. Brown, MD**

Department of Medicine, Vanderbilt University Medical Center

We would like to thank Rajapakse et al for expanding on our point about neprilysin's role in amyloid beta degradation from our review article on combined angiotensin receptor antagonism and neprilysin inhibition.[1] Rajapakse et al raised the concern that neprilysin inhibition may predispose patients to Alzheimer disease due to decreased degradation of amyloid beta, a key component of the neural plaques and deposits diagnostic of the disease. Therefore, it was suggested that individuals receiving neprilysin inhibition therapy should receive careful attention and may necessitate monitoring of amyloid beta levels.

We agree with Rajapakse et al about the need for further research on neprilysin's role in amyloid beta degradation and clinical outcomes such as Alzheimer disease. In addition to what was discussed in the review article, LBQ657, the metabolite of sacubitril and the inhibitor of neprilysin, crosses the blood-brain barrier and achieves a mean C_{max} of 19.2 ng/mL in the cerebrospinal (CSF) of healthy volunteers treated with 14 days of valsartan/sacubitril 400 mg daily.[2] Whether the finding of increased soluble amyloid beta (1–38) after treatment with valsartan/sacubitril compared to placebo was the result of neprilysin inhibition by LBQ657 or from changes in one of the other amyloid beta degradation pathways is not known.

We would like to point out that the Food and Drug Administration (FDA), as part of the approval process for valsartan/sacubitril, has required the sponsor to conduct a multicenter, randomized, active-controlled trial comparing valsartan/sacubitril to valsartan alone on cognitive function, as measured by neurocognitive tests and positron emission tomography (PET) imaging.[3] Results from this study will likely take several years, as the final report is due to the FDA in 2022. Given the prolonged time for Alzheimer disease to be clinically recognized, these long term trials will likely be more informative than shorter trials.

References

1. Hubers SA, Brown NJ. Combined angiotensin receptor antagonism and neprilysin inhibition. Circulation. 2016; 133:1115–24. [PubMed: 26976916]
2. Langenickel TH, Tsubouchi C, Ayalasomayajula S, Pal P, Valentin MA, Hinder M, Jhee S, Gevorkyan H, Rajman I. The effect of LCZ696 (sacubitril/valsartan) on amyloid-beta concentrations

Address for Correspondence: Scott A. Hubers, MD, Vanderbilt University Medical Center, Medicine, 1161 21st Avenue South, D-3100 MCN, Nashville, Tennessee 37232, UNITED STATES, 615-343-8701, 615-343-2551 (fax), scott.hubers@vanderbilt.edu.

Disclosures

Dr Brown served on an adjudication committee for angioedema for valsartan/sacubitril trials and serves as a consultant to Novartis. Dr Hubers reports no conflicts.

in cerebrospinal fluid in healthy subjects. Br J Clin Pharmacol. 2016; 81:878–90. [PubMed: 26663387]

3. New Drug Application Approval Letter. Food and Drug Administration; http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/207620Orig1s000ltr.pdf. Accessed May 20, 2016