Nephrilysin, cardiovascular, and Alzheimer’s diseases: the therapeutic split?

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Neprilysin (also known as the neutral endopeptidase, EC 3.4.24.11) is a ubiquitous transmembrane and circulating protease with a broad range of substrates. Those include natriuretic peptides (NPs), vasoactive peptides (e.g. endothelin-1, bradykinins), neuropeptides (e.g. substance P, enkephalins), and the β-amyloid (Aβ) peptide amongst others. Given the central role played by neprilysin in the metabolism of cardiovascular peptides and the Aβ peptide, neprilysin has emerged as a pharmaceutical target of interest, both in the fields of cardiovascular disease (CVD) and Alzheimer’s disease (AD). However, the strategies deployed in each field are completely opposite and one may wonder the rationale of neprilysin as a practical pharmaceutical target after all, since the populations suffering from CVD and AD are overlapping.

In cardiovascular diseases, neprilysin gained interest as responsible for the degradation of NPs and other cardiovascular peptides. The development of neprilysin inhibitors (NEPi) have aimed at prolonging and potentiating the beneficial effects of vasoactive/NPs. However, since neprilysin has a broad range of substrates with antagonist effects (vasoconstrictor and vasodilator), the use of sole NEPi (candoxatril) was ineffective for the treatment of hypertension due to an aldosterone-independent increase in Angiotensin II. To overcome this limitation, NEPi were combined either with an inhibitor of angiotensin-converting enzyme (ACEi, e.g. omapatrilat) or an angiotensin-receptor blocker (ARB, LCZ696). Both omapatrilat and LCZ696 were found, respectively, superior to enalapril (ACEi) and valsartan (ARB), for the treatment of hypertension. In the recent PARADIGM-HF trial, chronic administration of LCZ696 was found superior to enalapril for improving outcome in the treatment of chronic heart failure with reduced ejection fraction (Figure 1). Recently, this beneficial effect on mortality was shown to parallel a reduction in cardiac hospitalization and a favourable biomarker response in LCZ696-treated patients. These findings are a potential major breakthrough in the management of this severe and costly disease. Given these promising results, LCZ696 has been fast-tracked for regulatory agency approval.

One of the hallmarks of AD and cerebral amyloid angiopathy (CAA) is the deposition of Aβ peptide that accumulates in the brain long before the onset of the clinical symptoms. In healthy subjects, this accumulation is prevented by the dumping of the Aβ peptide into the blood stream where it is degraded and by the local degradation of the Aβ peptide in the brain. Several proteases such as ACE, the endothelin-converting enzyme (ECE-1), and the insulin degrading enzyme (IDE) are involved in Aβ peptide degradation, but neprilysin is the most effective of them (Figure 1). Multiple lines of evidence highlighted the crucial role of neprilysin in AD: (i) neprilysin expression is lower in the brain of AD patients, (ii) neprilysin-deficient mice develop AD-like disease, and (iii) the intracerebral infusion of the NEPi thiorphan or phosphoramidon provokes AD-like lesions. It is worth mentioning that most of the data supporting a major role of neprilysin in the degradation of the Aβ peptide were obtained in pre-clinical models, while genetic analysis in human also showed association with polymorphisms of IDE, ACE, ECE-1, and NEP genes, alone or in combination, and the development or progression of AD, although one study failed to demonstrate any association between neprilysin and AD. Nevertheless, over the past decade and based on the aforementioned pre-clinical studies, modulating neprilysin activity in the brain has been the focus of numerous preclinical researches, including the development of CNS-targeted neprilysin protein, and recombinant neprilysin engineered to degrade Aβ peptide more effectively.

While the chronic use of NEPi appears beneficial for the treatment of chronic CVD (hypertension and heart failure), it may compromise Aβ peptide degradation in the brain, and may thus accelerate AD and CAA progression, in patients at risk of developing AD (e.g. genetic factors, vascular factors). Indeed, the crossing of the blood-brain barrier (BBB) by NEPi is anticipated to be deleterious in those at-risk patients since intracerebral infusion of the NEPi provokes AD lesions in animal models (Figure 1). However, it is practically impossible to anticipate the passage of a drug through the BBB. For instance, the NEPi candoxatril and thiorphan do...
not cross the BBB, while S-acetylthiorphan$^{31}$ and its benzyl ester$^{32}$ do. AHU-377 and its active metabolite LBQ657 are both under the 400 kDa molecular weight that seems to make solutes eligible for crossing the BBB.$^{33}$ However, AHU-377 and LBQ657 contain both polar groups as well as two hydrophobic benzyl rings, which make any prediction very difficult. Importantly, patients with AD exhibit dysfunction of the BBB, which alters its permeability and may void any permeability prediction.$^{34}$ Since neuropathological $\alpha$-$\beta$ accumulation in AD occurs decades ahead of clinical symptoms, early dysfunction of the BBB is anticipated in those patients. The dysfunction of the BBB is not restricted to AD and CAA as other pathologies are also accompanied by alterations of the BBB.$^{35}$ Hence, experiments should be undertaken to determine whether the NEPi moieties of LCZ696 (AHU-377 or LBQ657) can be detected across the BBB in this context of pre-AD or mild cognitive impairment, AD and CCA. However, such experiments are extremely difficult to conduct and preclinical results are difficult to extrapolate to humans. It is therefore important to first evaluate the crossing of AHU-377 or LBQ657 across the BBB using conventional lipid partition assays to evaluate lipid solubility of these drugs. It could be interesting to analyse the response of AD biomarkers in the cerebrospinal fluid of the patients treated with either ACEi or ARB,$^{36}$ or LCZ696 in future trials: an increase may indicate a perturbation of the cerebral catabolism of the $\alpha$-$\beta$ peptide, while a decrease may indicate the progression of AD.$^{37}$ In a recent correspondence McMurray et al.$^{38}$ disclosed that LCZ696 treatment in cynomolgus monkeys led to an increase in CSF $\alpha$-$\beta_{1-40}$ and $\alpha$-$\beta_{1-42}$ but not in the brain. In addition, a 2-week LCZ696 administration in human healthy volunteers did not modify $\alpha$-$\beta_{1-40}$ and $\alpha$-$\beta_{1-42}$ levels in CSF.

These findings would argue in favour of the cerebral safety of LCZ696 administration over a short period of time. However, since these data are not yet published, it is impossible to further discuss these findings. It is noteworthy that the altered metabolism of $\alpha$-$\beta$ peptides in monkey may impair the use of CSF $\alpha$-$\beta$ peptide measurement as a biomarker for the diagnostic of AD. As a complement to the measurement of AD biomarkers in the CSF, amyloid PET scan could also be used to evaluate $\alpha$-$\beta$ accumulation in both groups of patients. Finding no difference in AD biomarker in the CSF and amyloid PET scan between patients who received LCZ696 or usual RAAS antagonists would argue in favour of the drug’s safety while differences would hint for a potential interaction between LCZ696 and AD. Alternatively, since the PARADIGM-HF trial, which as other trials excluded patients with AD, is now completed, a cognitive evaluation could be part of the safety measurements conducted in the ongoing PARAGON-HF trial that will assess the effect of LCZ compared with valsartan in CHF patients with preserved left ventricular ejection fraction.$^{39}$ In a recent correspondence, by McMurray et al.$^{38}$ indicated that dementia-related adverse effect were not increased in the arm treated with LCZ696 and confirmed that serial cognitive tests will be performed in the PARAGON-HF trial$^{38}$; this letter point is critical since the evaluation of the cognitive function was not defined in the original PARADIGM-HF article.$^{5}$ However, whether the duration of follow-up of this trial will be sufficient to exclude any deleterious effect of LCZ696 on cognitive function remains unknown, given that these effects may appears years after beginning of the disease. A follow-up of the patients treated may be advisable long after the end of the trials to confirm the safety of LCZ696.

**Figure 1** Schematic representation of the role of neprilysin in cardiovascular and Alzheimer’s diseases (black lines); effects of neprilysin inhibition are indicated as red lines. The question marks indicate a possible crossing of neprilysin inhibitor across the blood-brain barrier (blue arrow) that needs to be evaluated.
It is worth mentioning that the argumentation developed hereinafter should be balanced by two main aspects. First, it has been shown that vascular diseases, such as hypertension, were risk factors for the progression of AD. Furthermore, the administration of either ACEi or ARB was shown to be beneficial in AD, by limiting the impact of vascular diseases on the progression of AD. Hence, one may anticipate a potential protective effect of the LCZ696 through its ARB activity (valsartan). Another critical aspect is time; indeed, patients suffering from CHF are mostly elderly, hence with a limited lifespan. Therefore, the potential deleterious effects of a yet-to-be-determined deleterious central neprilysin inhibition may not be expressed prior to the death of the patients. However, results from clinical registries or prognostic score suggest that the 5-year survival for CHF patients optimally treated with recommended guidelines therapy has improved over time and now approaches 40–50%. Furthermore, the patients who benefited the most from the LCZ696 treatment were not the most severe patients (NYHA II), and are expected to have a better survival. Finally, since LCZ696 improved survival of those patients, their exposure to LCZ696 will also increase.

In conclusion, we would like first to congratulate the investigators of the PARADIDM-HF trial for the compelling beneficial results of LCZ696 in the treatment of chronic heart failure. However, we believe that the safety associated with the chronic use of inhibitors neprilysin, especially in patients at-risk of AD (e.g. genetic factors, vascular factors, pre-AD, mild cognitive impairment), should clearly be addressed as it has been addressed for other NEPi (thiorphan or candesartan) or ACEi (enalapril) [14]. We hope this opinion will open a thoughtful discussion on that matter, in order to determine which patients would benefit the most from this very promising drug.

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References


