Valsartan/Sacubitril for Heart Failure
Reconciling Disparities Between Preclinical and Clinical Investigations

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Valsartan/sacubitril (Entresto, Novartis) is a combination of the neprilysin inhibitor sacubitril and the angiotensin receptor antagonist valsartan. In July 2015, the US Food and Drug Administration (FDA) approved valsartan/sacubitril through the fast-track pathway for the treatment of patients with New York Heart Association class II through IV heart failure symptoms and a reduced ejection fraction. The approval was based on the results of a single phase 3 clinical trial (PARADIGM-HF)[1] that included 8400 patients. In this trial, valsartan/sacubitril was associated with a 20% (hazard ratio, 0.80) decrease in the primary end point of death from cardiovascular cause or first hospitalization for heart failure (from 26.5% to 21.8%), when compared with the angiotensin-converting inhibitor enalapril, and a 16% (hazard ratio, 0.84) reduction in all-cause mortality (from 19.8% to 17.0%). However, recent translational science studies involving the central nervous system and the eye suggest that other effects of valsartan/sacubitril might influence its use in some patients.

Neprilysin, a plasma membrane metalloendopeptidase, is the principal enzyme for degradation of the natriuretic peptides.[1] However, this enzyme also degrades multiple peptides including angiotensin,

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endothelin 1, adrenomedullin, opioids, bradykinin, and amyloid-β peptide (Aβ). Because natriuretic peptides have salutary effects in animal models of heart failure, inhibition of natriuretic peptide degradation with neprilysin was seen as a rational approach to heart failure therapy. Pharmacologic studies demonstrated that neprilysin inhibitors increased circulating levels of the natriuretic peptides and prevented progression of left ventricular dysfunction and remodeling in animal models of heart failure.[1] Recent drug development has focused on the combination of a neprilysin inhibitor with an angiotensin receptor antagonist to achieve the beneficial effects of a neprilysin inhibitor while mitigating its vasoactive effects.

Largely absent from public discussions about the beneficial effects of valsartan/sacubitril has been the recognition that in animal models, neprilysin plays a

critical role in maintaining the homeostasis of Aβ in the brain.[2] This is relevant because accumulation of Aβ in the brain is associated with the pathogenesis of Alzheimer disease.[3] Aβ homeostasis is regulated by a balance between Aβ production through sequential cleavage of the Aβ precursor protein by secretases and either removal of Aβ from the central nervous system by transport and perfusion mechanisms or by proteolytic degradation, and neprilysin is a major degrading enzyme in the brain.[2] The "amyloid hypothesis" of Alzheimer disease is supported by studies demonstrating that (1) alteration in the homeostatic balance between Aβ production and clearance results in development of amyloid plaques and subsequent neurofibrillary tangles, synaptic loss, and neuronal cell death; (2) gene mutations that increase Aβ production cause autosomal dominant Alzheimer disease, whereas genetic variants that reduce Aβ production protect against the development of Alzheimer disease; and (3) Aβ oligomers are neurotoxic and are major precipitants of the Aβ cascade.[3] Studies in the eye suggest that a similar pathogenic mechanism may contribute to the development of age-related macular degeneration, the most common cause of legal blindness among persons older than 50 years in the United States.[4]

Neprilysin plays a pivotal role in the development of Alzheimer disease in animal models. Overexpression of neprilysin ameliorated the development of Alzheimer disease in a genetic model of Alzheimer disease.[3] Disruption of the neprilysin gene elevated oligomeric Aβ levels in the brain and accelerated the development of cognitive dysfunction in a genetic mouse model of Alzheimer disease. In addition, neprilysin levels are low in regions of the brain that are significantly affected by Alzheimer disease, but levels are normal in relatively unaffected brain areas, whereas levels of neprilysin were decreased and Aβ deposition was increased in areas of the aged brain most affected by Alzheimer disease.[3] With respect to ocular risks, neprilysin-deficient mice developed retinal pigment epithelial cell degeneration and subretinal deposits similar to those found in humans with age-related macular degeneration.[4] In addition, intravitreal administration of a recombinant form of the neprilysin catalytic domain decreased ocular Aβ levels in a mouse model of retinal degeneration.[5] These studies raise the theoretical concern that long-term administration of a neprilysin inhibitor has the potential for neurological and ocular complications in humans.

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In PARADIGM-HF, adverse effects related to memory, cognition, and dementia were not increased and valsartan/sacubitril did not alter Aβ homeostasis in the brains of young nonhuman primates or in the cerebrospinal fluid of normal volunteers.[1] These studies do not fully dispel concern, however, because patient follow-up in PARADIGM-HF was relatively short; Alzheimer disease–specific, dementia-related adverse events were not prespecified; and executive dysfunction, a pathognomonic finding in Alzheimer disease, was not measured. Furthermore, young monkeys and normal human volunteers do not have presenile plaque or blood-brain barrier dysfunction, both of which have the potential to increase the leakage of drugs into the central nervous system. By contrast, patients with heart failure have multiple risk factors for both Alzheimer disease and blood-brain barrier disruption including older age, hypertension, elevated cholesterol levels, cerebrovascular disease, and diabetes.[6] In addition, the duration of time necessary for patients to manifest cognitive or behavioral symptoms is not immediate and is likely dependent on whether they had preclinical amyloid plaque already present in the brain or in the eye.

The theoretical risks associated with valsartan/sacubitril moved the FDA to require the sponsor to conduct a "multicenter, randomized, double-blind, active-controlled trial to evaluate the effects of Entresto compared to valsartan on cognitive function as assessed by a comprehensive neurocognitive battery and [positron emission tomography] imaging in patients with chronic heart failure with preserved ejection fraction."[7] The timetable for the final report is March 2022. In light of the preclinical data, substantive steps should be taken to acquire data in a more timely manner among patients with heart failure and reduced ejection fraction rather than waiting until 2022 to learn the effects of valsartan/sacubitril in patients with heart failure and preserved ejection fraction who have a different prognosis and clinical phenotype.

There is equipoise regarding the utility of valsartan/sacubitril in patients with heart failure that will likely result in a cohort of patients receiving valsartan/sacubitril and a second cohort treated with traditional therapy of an angiotensin-converting inhibitor or an angiotensin receptor antagonist. Useful information could therefore be obtained by comparing changes in neurocognitive measures and retinal morphology in the 2 cohorts using a postmarket surveillance system created through a public-private partnership model, such as recently proposed by the Medical Device Registries Task Force.[8] Planning for the study should leverage the expertise of heart failure, Alzheimer disease, and age-related macular degeneration specialists; statisticians; industry representatives; and ethicists. Existing resources that include data repositories such as the Patient-Centered Outcomes Research Institute network might provide an effective infrastructure to facilitate data acquisition and analytics. Studies in appropriate animal models that develop amyloid pathology and subsequent cognitive dysfunction could provide important and timely signals regarding whether valsartan/sacubitril crosses the blood-brain barrier and whether it influences markers of Alzheimer disease, age-related macular degeneration, or both.

In an era when information accrual from genetic animal models can outpace the collection of data from patients enrolled in traditional clinical trials, it will be important to develop effective mechanisms for reconciling differences that emerge from these 2 sources. Although the risks of neprilysin inhibition in the brain and in the eye remain speculative, the emergence or worsening of cognitive or visual impairments would be devastating for patients with heart failure regardless of their age or prognosis. Therefore, a prudent approach would be to follow high-risk patients closely with cognitive assessments, amyloid positron emission tomography, and retinal imaging until definitive answers emerge. How physicians, investigators, the pharmaceutical industry, and federal regulators respond to this challenge can set a comforting precedent for how to reconcile similar differences between preclinical and clinical data that will likely arise in the future.

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