

Angiotensin 2 Type 1 Receptor Blockade with Neprilysin Inhibition for Chronic Heart Failure: A New Paradigm?

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A new treatment for heart failure (HF) combining angiotensin 2 type 1 receptor blockade with inhibition of the widespread membrane-bound enzyme, neprilysin (NEP), seems likely to take treatment of chronic heart failure (CHF) a major step forward. Neurohormonal pathways are central to the evolution and progression of HF irrespective of the exact initial triggering cardiac injury or overload, and our current evidence-based treatments for this condition depend upon antagonism of the renin-angiotensin-aldosterone (RAAS) and sympathetic nervous (SNS) systems through prescription of angiotensin converting enzyme inhibitors (ACEIs), angiotensin 2 type 1 receptor blockers (ARBs), mineralocorticoid antagonists (MRAs) and blockers of beta-adrenoceptors (beta blockers). Properly deployed, these therapies reduce 1-year mortality to less than half than that suffered by patients with HF in the pre-1980s era.^{1,2} However, despite this clear impact upon the outcome of this deadly syndrome, 5-year mortality in CHF remains greater than 50%. This poor outlook plus the continuing high prevalence of HF mandates an ongoing search for more effective treatments.³

The therapeutic advances outlined above were established by the turn of the 21st century and until now, trials of new neurohormonal interventions over the last 15 years have been largely disappointing. Examples include therapeutic trials, all based on impeccable rationales and supported by encouraging preclinical data and positive phase 1 and 2 clinical data of endothelin 1 antagonists, arginine vasopressin blockers and direct renin inhibitors.⁴⁻⁶ When subjected to the test of full phase 3 randomised controlled clinical trials, none of these approaches has proven to reduce cardiovascular or all-cause mortality in HF, although some secondary end-points such as readmission with recurrent, acute decompensated HF may show a beneficial trend and useful niche applications have developed such as the use of endothelin antagonists in pulmonary hypertension and of AVP blockers in accelerating correction of hyponatraemia complicating HF. In the 1990s, an effort was made to add enhancement of beneficial endogenous adaptive responses

to HF (exemplified by activation of the natriuretic peptide system) together with the established efficacy of blockade of the “culprit” RAAS by combining ACEI with neutral endopeptidase (NEP, EC 3.4.24.11) inhibition. This enzyme plays a role in the degradation of the natriuretic peptides (NPs) which have an array of biological actions beneficial in HF including natriuresis, diuresis, vasodilation, suppression of the RAAS and SNS and antihypertrophic and antifibrotic effects. Despite some promising findings such as reduction in rates of readmission for HF, mortality was not lowered by the “ACEI-NEPI” approach and the combination caused an unacceptable rate of angioedema leading to cessation of clinical trials of these agents.⁷

However, the combination of NEP inhibition with angiotensin receptor blockade appears to offer a true beneficial advance without an increased burden of side effects. LCZ 696 consists of the NEP inhibitor sacubitril and the ARB valsartan. After initial success in surrogate endpoint trials in hypertension and HF with preserved ejection fraction, this approach has now passed its sternest test to date in a phase 3 trial (“PARADIGM-HF”) in CHF with reduced ejection fraction.⁸ In centres in the United States, United Kingdom, Canada and Sweden, 8442 patients were randomised to receive either LCZ 200 mg twice daily or enalapril 10 mg twice a day in addition to other guideline-based therapy. Patients were selected for relatively high risk of recurrent acute HF and mortality by inclusion criteria comprising New York Heart Association (NYHA) class II to IV HF, a left ventricular ejection fraction less than 40% (later shifted to 35%) and plasma B type cardiac peptide levels above set thresholds (BNP or NT-proBNP at least 150 or 600 pg/mL respectively or 100 and 400 pg/mL respectively if admission to hospital for HF had been required within 12 months prior to randomisation). Exclusion criteria included symptomatic hypotension, systolic blood pressure below 100 mmHg at screening or 95 mmHg at randomisation, eGFR below 30 mL/min per 1.73m², elevated serum potassium and a history of angioedema or unacceptable side effects on either ACEI or ARBs.

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The trial was halted early, after median follow-up of 27 months, because of emerging overwhelming benefit from LCZ696 therapy. The primary end-point, death or rehospitalisation with HF occurred in 914 (21.8%) of patients receiving LCZ696 versus 1117 (26.5%) in those given enalapril (hazard ratio 0.80 with 95% CI, 0.73 to 0.87; $P < 0.001$). All-cause mortality considered as a stand-alone end-point was also reduced (hazard ratio 0.86 [0.76 to 0.93] $P < 0.001$) as was death from cardiovascular causes (HR 0.80 [0.71 to 0.89], $P < 0.001$). LCZ also reduced rate of readmission for HF by 21% and improved HF symptoms ($P < 0.001$). With respect to safety, treatment with LCZ696 was associated with more symptomatic hypotension with systolic pressures below 90 mmHG (2.7 versus 1.4%, $P < 0.001$) but, importantly, less renal impairment (serum creatinine elevated to 2.5 mg/dL or more, 3.3 versus 4.5%; $P = 0.007$) and less hyperkalemia (serum potassium over 6.0 mmol/L, 4.3 versus 5.6%; $P = 0.007$).

When compared with historical placebo rates of clinical events recorded in a previous landmark placebo-controlled trial of enalapril, in PARADIGM-HF the relative risk reduction for the composite end-point of death or readmission with HF for LCZ696 compared with placebo was 43% (95% CI, 34% to 50%; $P < 0.0001$), for cardiovascular death 34% (21% to 44%; $P < 0.0001$), HF hospitalisation 49% (39% to 58%; $P < 0.0001$) and for all-cause mortality 28% (95% CI, 15% to 39%; $P < 0.0001$). Analyses based on previous placebo-controlled trials of candesartan gave putative risk reductions relative to placebo of 39% (95% CI, 27% to 48%; $P < 0.0001$) for the composite outcome of cardiovascular death or HF hospitalisation, 32% (95% CI, 16% to 45%; $P < 0.0001$) for cardiovascular death, 46% (33% to 56%; $P < 0.0001$) for HF hospitalisation, and 26% (95% CI, 11% to 39%; $P < 0.0001$) for all-cause mortality.⁹

This is the first time a new pharmaceutical approach has demonstrated such clear cut, across-the-board benefit to HF in the last 15 years. The power of this trial supports Food and Drug Administration (FDA) approval for its use in CHF. Some caveats apply. Duration of experience and exposure to this drug class (now dubbed “ARNIs”) to date is relatively brief. Whether or not adverse effects emerge over time remains to be seen. NEP catalyses metabolism of a wide range of substrates in addition to the natriuretic peptides including, but not limited to, enkephalins, tachykinins, endothelin 1, angiotensin 2, bradykinin, and amyloid beta.^{10,11} The central role of the latter in cerebral amyloid accumulation and dementing processes has been highlighted recently and the effects of ARNIs upon cognitive function will be subject to close ongoing scrutiny.¹² However, given

the clear net benefit for multiple key outcomes over a 2-year period in PARADIGM HF, it seems highly likely that in the near future this new treatment will become recommended as the first-line therapy in CHF.

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