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HEART FAILURE

PHASE II PARAMOUNT TRIAL OF LCZ696

As the PARAMOUNT investigators explain in their report published in the *Lancet*, "atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) ... act to defend the heart from volume and pressure overload, a protective mechanism recently shown to be deficient early in the development of heart failure with preserved ejection fraction (HFpEF)." Solomon *et al*. therefore set out to test whether inhibition of neprilysin, which degrades ANP and BNP (but not NT-pro-BNP), would augment this protective mechanism and be beneficial in patients with HFpEF.

Neprilysin is known to break down angiotensin II in addition to the natriuretic peptides. Because inhibition of neprilysin might, therefore, result in high levels of angiotensin II, the PARAMOUNT investigators decided to test a neprilysin inhibitor in combination with an angiotensin-receptor blocker in their multinational, randomized, phase II trial. LCZ696, which contains molecular moieties of both the neprilysin inhibitor AHU377 and valsartan, was thus compared with valsartan alone in 301 patients with HFpEF. The primary end point of PARAMOUNT was change in NT-pro-BNP levels (thought to reflect left ventricular wall stress) from baseline to 12 weeks.

At the 12-week follow-up, a greater reduction in NT-pro-BNP levels was noted in the LCZ696 group compared with the patients assigned to receive valsartan (ratio of change for LCZ696/valsartan 0.77, 95% CI 0.64–0.92, $P=0.005$). LCZ696 was also associated with a greater reduction in blood pressure at this time point. However, the greater reduction in NT-pro-BNP levels in the LCZ696 group was still apparent after adjustment for changes in blood pressure, and was, therefore, considered to be independent of the blood-pressure-lowering effect. A similar, but not statistically significant, trend was found at 36 weeks. Rates of adverse events did not differ between the two groups over 36 weeks.

Although PARAMOUNT was not powered to test clinical status or cardiovascular end points, LCZ696 was associated with a reduction in left atrial volume and with more cases of improved NYHA class than valsartan. The investigators nevertheless remind report readers that "any clinical benefit ... needs to be prospectively confirmed in an adequately sized trial".

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Original article Solomon, S. D. *et al.* The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* doi:10.1016/S0140-6736(12)61227-6