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HEART FAILURE

LCZ696—a PARADIGM shift in treatment for heart failure

Dual inhibition of neprilysin and angiotensin receptors with LCZ696 reduces mortality and hospitalization for heart failure (HF) compared with currently recommended treatment using an angiotensin-converting enzyme (ACE) inhibitor. This finding comes from the PARADIGM-HF trial, which was presented at the ESC Congress 2014 in Barcelona, Spain and simultaneously published in *The New England Journal of Medicine*.

ACE inhibitors have been the foundation of treatment for patients with HF with reduced ejection fraction (HFrEF) ever since enalapril was shown to reduce mortality in the late 1980s and early 1990s. β-Blockers, angiotensin-receptor blockers, and mineralocorticoid-receptor antagonists have subsequently shown some incremental benefits when used in combination with an ACE inhibitor. Indeed, in an editorial that accompanied the trial publication, Mariell Jessup (University of Pennsylvania, PA, USA) points out that the FDA last approved a new oral drug for patients with HFrEF in 2005.

LCZ696 combines a neprilysin inhibitor (sacubitril) and an angiotensin-receptor blocker (valsartan). Neprilysin is a neutral endopeptidase that degrades vasoactive peptides such as natriuretic peptides, bradykinin, and adrenomedullin. Neprilysin inhibition is thought to counteract the neurohormonal activation that leads to vasoconstriction, sodium retention, and maladaptive remodelling and, therefore, to complement and augment the effects of inhibiting the renin–angiotensin–aldosterone system. Previously, neprilysin inhibition has been combined with an ACE inhibitor, but some patients experienced serious angio-oedema in clinical trials. Therefore, LCZ696 includes an angiotensin-receptor blocker instead of an ACE inhibitor to minimize the risk of this adverse effect.

bahri altay/Alamy

In the double-blind PARADIGM-HF trial, investigators randomly allocated 8,442 patients with NYHA class II–IV HF and an ejection fraction ≤40% to receive either LCZ696 (200 mg twice daily) or enalapril (10 mg twice daily), in addition to recommended therapy. The trial was stopped early (median follow-up 27 months) because of an overwhelming benefit with LCZ696 therapy.

The composite primary end point (cardiovascular mortality and hospitalization for HF) occurred in 21.8% of patients receiving LCZ696 compared with 26.5% of those receiving enalapril (HR 0.80, 95% CI 0.73–0.87, $P<0.001$). LCZ696 was also associated with significant reductions in all-cause mortality (HR 0.84, 95% CI 0.76–0.93, $P<0.001$), cardiovascular mortality (HR 0.80, 95% CI 0.71–0.89, $P<0.001$), and hospitalization for worsening HF (HR 0.79, 95% CI 0.71–0.89, $P<0.001$).

Commenting on these findings, Professor Henry Krum from Monash University, VIC, Australia, who was not involved in the PARADIGM-HF trial, highlights that the study "met its predetermined primary end point, but also that there was a stand-alone all-cause mortality benefit. Furthermore, patients felt better, so living longer and ... staying out of hospital is a slam-dunk efficacy result."

However, treatment with LCZ696 was associated with a higher incidence of hypotension compared with enalapril therapy, and Professor Krum believes that "hypotension (systolic blood pressure decrease of 2.7 mmHg compared with the ACE inhibitor) is something that needs to be watched". Nevertheless, this adverse effect rarely led to LCZ696 discontinuation. Indeed, discontinuation of the study drug owing to an adverse effect occurred more often with enalapril than with LCZ696 (12.3% versus 10.7%; $P=0.03$). Enalapril was associated with the occurrence of renal impairment, hyperkalaemia, and cough.

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The trial investigators conclude that "the magnitude of the beneficial effect of LCZ696, as compared with enalapril, on cardiovascular mortality was at least as large as that of long-term treatment with enalapril, as compared with placebo". In her editorial, Professor Jessup agrees that "the beneficial results seen in PARADIGM-HF may apply to a wide spectrum of patients, even those who are currently receiving the best possible therapy".

Similarly, Professor Krum predicts that dual angiotensin-receptor and neprilysin inhibition will replace ACE inhibitors as the cornerstone therapy for patients with HFrEF, but "price and cost-effectiveness will be major issues going forward". However, "given the large reductions in mortality and hospitalization (both relative and absolute)," Krum believes that "this will be a very cost-effective therapy".

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