
ESC 2014: Promising New Heart Failure Drug



An investigational new heart failure drug could be poised to change the face of cardiology based on Hot Line results presented at ESC Congress 2014.

Findings from the PARADIGM-HF trial, published simultaneously in the New England Journal of Medicine, “are extraordinarily powerful and compelling; they are destined to change the management of patients with chronic heart failure for years to come,” said Milton Packer, MD, co-primary author of the study from University of Texas Southwestern Medical Center, in Dallas, Texas USA.

“This really is an astonishing result and a real breakthrough for patients with heart failure,” added John McMurray, MD, the other co-primary author, from the University of Glasgow, UK.

The new agent, an angiotensin receptor-neprilysin inhibitor (ARNI) known as LCZ696, has already been granted Fast Track status by the United States Food and Drug Administration (FDA) – a designation which can expedite the review of new medicines intended to treat serious or life-threatening conditions. Fast Track designation also allows for rolling submission in the US, which Novartis said it expects to complete by the end of 2014. The company said it aims to file in Europe in early 2015.

“To say that we are excited is an understatement. We are absolutely thrilled,” said Dr. Packer.

“Given the survival advantage of LCZ696 over currently available drugs, once this drug becomes available, it would be difficult to understand why physicians would continue to use traditional angiotensin converting-enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) for the treatment of heart failure.”

PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) first made headlines this spring when the trial was stopped early by an independent data monitoring committee based on evidence of the “overwhelming benefit” of LCZ696 compared to enalapril, an ACE inhibitor.

“We were surprised and delighted that the magnitude of the superiority was so great that the trial was stopped early by the ethical committee. That was an amazing event,” said Dr. Packer.

Full details of the findings are being released for the first time.

“The magnitude of the advantage of LCZ696 over enalapril on cardiovascular mortality was at least as large as that of enalapril over placebo during long-term treatment,” Dr. Packer reported. “This robust finding provides strong support for using this new approach instead of ACE inhibitors or ARBs in the treatment of chronic heart failure.”

PARADIGM-HF randomised 8,399 patients with class II to IV heart failure and an ejection fraction of 40% or less to either LCZ696 200 mg twice daily (n=4,187), or enalapril 10 mg twice daily (n=4,212), in addition to recommended therapy.

When the trial was stopped early, after a median follow-up of 27 months, death from cardiovascular causes or hospitalisation for heart failure (the primary composite outcome) had occurred in 21.8% of the LCZ696 group and 26.5% of the enalapril group (hazard ratio [HR] 0.80; $p=0.0000002$).

Compared to enalapril, LCZ696 reduced the risk of death from cardiovascular causes by 20% (13.3% vs 16.5%; HR 0.80; $p<0.0001$), and the risk of hospitalisation for heart failure by 21% (12.8% vs 15.6%; HR 0.79; $p<0.0001$), noted Dr. Packer. This effect was consistent across all prespecified subgroups.

Secondary outcomes were also significantly improved by LCZ696, including all-cause mortality (17.0% vs 19.8%; HR 0.84; $p<0.001$) and symptoms and physical limitations of heart failure measured on the Kansas City Cardiomyopathy Questionnaire ($p=0.001$).

"The superiority of LCZ696 over enalapril was not accompanied by important safety concerns," added Dr. Packer. The LCZ696 group had more symptomatic hypotension compared to the enalapril group (14% vs 9.2%, $p<0.001$) however this rarely required the discontinuation of treatment. In fact, fewer patients in the LCZ696 group stopped their study medication for any adverse event (10.7% vs 12.3%, $P=0.03$). Importantly, LCZ696 was not associated with an increased risk of serious angioedema, which was the main safety concern observed with a related medication – omapatrilat – in the OVERTURE trial.

Omapatrilat's association with life-threatening angioedema is related to its inhibition of ACE, neprilysin and aminopeptidase P, whereas LCZ696 avoids inhibition of ACE and aminopeptidase P. "LCZ696 was specifically designed to minimise the risk of serious angioedema by combining the neprilysin inhibitor sacubitril (AHU377) and the ARB valsartan," explained Dr. Packer.

Findings of the PARADIGM-HF trial are particularly striking when considered in the context of the current standard of care in heart failure, concluded Professor McMurray.

"The superiority of LCZ696 wasn't over placebo - it was over the gold-standard dose of the gold-standard ACE inhibitor, the absolute cornerstone of guideline-recommended, conventional therapy," he said. "On top of that, these incremental benefits were obtained in patients fully treated with the other key pharmacological therapies for this condition such as beta-blockers and mineralocorticoid receptor antagonists. All that you can ask of any new therapy in heart failure (or other chronic diseases) is to make patients live longer, stay out of hospital and feel better - and those are exactly the benefits we demonstrated with LCZ696."

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