新しいクラスの薬剤は心不全においてACE阻害薬よりも優れている（Presentation #881）

PARADIGM-HF：心不全治験薬は心不全管理を変化させる可能性がある

PARADIGM-HF: Investigational heart failure drug could be poised to change the management of heart failure

レニンーアンジオテンシン系内およびそれを超えた作用を有する新たに開発された薬剤を内服した慢性心不全（HF）の患者は、HFによる入院および心血管系の原因による死亡数が少ないことが示唆されたとの第3相試験の結果が2014年European Society of Cardiology Congressホットラインセッションで発表され、同時に*New England Journal of Medicine*に掲載された。この新たな薬剤はLCZ696として知られるアンジオテンシン受容体ネプリライシン阻害薬である。PARADIGM-HFトライアルではクラスII～IVで左室駆出率40%以下の心不全患者8,399人をランダム化し、推奨治療法に加えLCZ696 200mgを1日2回（4,187人）またはエナラプリル10mgを1日2回（4,212人）内服する群のいずれかに割り付けた。トライアルが早期終了された時点（追跡期間中央値27か月）での心血管疾患による死亡または心不全による入院（一次複合アウトカム）は、LCZ696群の21.8%およびエナラプリル群の26.5%に発現した（p=0.0000002）。エナラプリルと比較し、LCZ696は心血管系の死亡リスクを20%（13.3%対16.5%；p<0.0001）低下させ、心不全による入院のリスクを21%（12.8%対15.6%；p<0.0001）低下させた。これらの結果は今後の慢性心不全治療を変えるであろう、と筆者らは述べている。

Full Text

Patients with chronic heart failure (HF) who take a newly developed drug that has effects both within and beyond the renin-angiotensin system, *instead* of the ACE inhibitor enalapril, will have fewer HF hospitalizations and die less often from cardiovascular causes, suggests a phase 3 trial presented during a Hot Line session at the 2014 European Society of Cardiology Congress.

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, MWD, 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, M.D., 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 that 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 at ESC 2014.

"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 randomized 8,399 patients with class II to IV heart failure and an ejection fraction if 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 hospitalization 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 hospitalization 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 minimize 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 corner-stone 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."

The trial was sponsored by Novartis.

Dr. Packer was a paid consultant to Novartis for time spent as Executive Committee co-chair of the PARADIGM-HF trial. Novartis also paid for his travel and accommodation in relation to PARADIGM-HF Executive Committee and Investigator meetings. Professor McMurray's employer, Glasgow University, was paid by Novartis for his time spent as Executive Committee co-chair of the PARADIGM-HF trial. Novartis paid for his travel and accommodation in relation to PARADIGM-HF Executive Committee and Investigator meetings.

Conference News

[News 01]
薬剤によりいくつかの術後合併症が減少する

[News 02]
MI後のdarapladib投与はその後のリスクを低下させない

[News 03]
新しいクラスの薬剤は心不全においてACE阻害薬よりも優れている

[News 04]
Serelaxinは心不全の院内増悪を軽減する

[News 05]
完全血行再建術はMI後の予後を改善する

[News 06]
4極リードによりCRT合併症が減少する

[News 07]
CRTにおいて代替のリード位置は安全である

[News 08]
新たな生分解性の薄いステントは有望であることが示された

[News 09]
血行再建術を回避しても安全な患者の見極め

[News 10]
治験薬はスタチンと共に作用しコレステロールを低下させる

[News 11]
糖尿病患者においてロスバスタチンはアトルバスタチンよりも選択肢として優れている可能性がある

[News 12]
ロスバスタチンは冠動脈内プラーク体積を縮小させる

[News 13]
アミオダロンはアブレーション後の短期回復を改善する

[News 14]
リバーロキサバンを用いた前治療により除細動が早められる可能性がある

[News 15]
鉄の経静脈的補給は心不全症状を改善する

[News 16]
合剤はMI後治療へのアドヒアランスを上昇させる