This editorial refers to ‘A putative placebo analysis of the effects of LCZ696 on clinical outcomes in heart failure’, by J. McMurray et al., on page 434.

This issue of the European Heart Journal contains a major statement by the PARADIGM-HF Investigators, who present an ‘putative placebo’ analysis for LCZ696, a new medicine that yielded a remarkable reduction in total mortality and heart failure events in patients with significant heart failure with reduced ejection fraction (HF-REF). (NB: I serve as a consultant on Novartis’s cardiovascular–metabolic advisory group, and have observed the development of this molecule from its inception through the present trial. This bias should be considered when reading this commentary.)

The previously published PARADIGM-HF Trial (NCT01035255) compared LCZ696 with enalapril, one of the most commonly used angiotensin-converting enzyme inhibitors (ACE-Is), and reported an impressive reduction in death and heart failure events. However, because PARADIGM-HF used an active comparator, the authors asked a logical question: ‘What would the result have been if LCZ696 were compared with placebo?’

In order to perform this ‘putative placebo’ analysis, the authors used historical controls from previous trials comparing enalapril with placebo. Unsurprisingly, their estimate finds that LCZ696 is far superior to putative placebo for the outcomes of death and major cardiovascular events. The PARADIGM-HF trial itself and the putative placebo analysis employed cutting-edge methods and were conducted by highly credible investigators. Thus, the question is not whether the effect is real; instead, as the clinical community absorbs this welcome news, we should consider the extent to which the size of the effect can be believed and what it means for the future of clinical therapeutics for heart failure.

Previously, many cardiovascular specialists were excited about omapatrilat, an ACE-Ineutral endopeptidase (NEP) inhibitor combination developed by Bristol-Myers Squibb that showed spectacular results in trials for hypertension, especially among African American patients. Unfortunately, when once-daily dosing was advanced despite pharmacodynamic studies that suggested a need for twice-daily dosing, a heart failure trial showed only a non-significant trend toward an advantage for omapatrilat over enalapril. Further, an excess of serious angio-oedema—a condition that ironically was most severe in the African American patients who, due to a propensity for refractory hypertension, had the most to gain from this novel therapy—caused development of omapatrilat to be abandoned.

However, when Novartis’ development team announced that it was able to create an angiotensin receptor blocker (ARB)/NEP inhibitor combination, our advisory group was thrilled, and, despite many sceptics within and outside of Novartis, the end result is gratifying. Nevertheless, many questions remain following this spectacular outcomes trial.

Interpreting the findings from McMurray et al

First, how believable is the putative placebo analysis? The authors conducted a splendid trial, but any putative placebo analysis must use historical controls—a method that always entails a degree of uncertainty. One potential risk is that the patient population of the new trial differs in significant ways from those of the reference trials: a key reason to conduct randomized controlled trials is the critical importance of contemporaneous, unbiased control groups. The authors have diligently provided evidence that, other than a difference in beta-blocker use (which could perhaps be expected to disadvantage LCZ696 in this comparison), the populations appear more similar than one might expect. Of course, all historical controls are subject to the risk of unmeasured confounders and, given the >20-year interval between the reference SOLVD trial and PARADIGM-HF, scepticism is warranted.

A second issue to consider when weighing the importance of this study is constancy. Given changes in the population, the natural history of the disease, and the underlying therapeutic milieu, is the effect size of enalapril vs. placebo the same in 2014 as it was in 1994? The authors cleverly use findings from the CHARM-Alternative trial to provide a ‘mid-term’ snapshot. The data support the constancy assumption, but do not (and cannot!) definitively prove it. Substantial uncertainty thus remains, but this is true for almost all putative placebo analyses.
In addition to the usual concerns about putative placebo analyses, there are two fundamental design issues pertinent to PARADIGM-HF that call for caution when interpreting the size of the treatment effect. First, the design included a rigorous run-in phase that eliminated patients who could not tolerate either enalapril or LCZ696. This was justified by the investigators because they wanted to be certain that patients enrolled into the trial were taking the recommended dose of enalapril in order to ensure a fair test vs. LCZ696. Nevertheless, the run-in phase diminishes the generalizability of the results, especially when extrapolating to clinicians and patients who are considering whether to initiate LCZ696 in practice. At present, it is not possible to know whether the patient will tolerate this drug at the time treatment is initiated, and the key toxicities (hyperkalemia and hypotension) tend to occur early and thus would be screened out in the run-in phase.

Second, the trial was stopped early by the Data Monitoring Committee (DMC). The concern here is not with the action of the DMC, as the data clearly showed a profound reduction in serious clinical outcomes including death, which merited early discontinuation for benefit. Rather, the issue is whether the magnitude of the result is generalizable. Historically, when trials are stopped early, they tend to represent a selection of extreme results and the true effect is typically smaller than that estimated by the trial.9,10 The PARADIGM-HF investigators, one of whom ‘wrote the book’ on effect size,11 counter that PARADIGM-HF actually reached its projected number of events and that after the conclusion of the trial’s active phase, the legacy effect showed continued separation of the event curves rather than the convergence that might be expected.

Other issues have been raised regarding the interpretation of PARADIGM-HF. Despite a population comprising participants with HF-REF, few patients were availed of implantable cardioverter/defibrillators (ICDs) or biventricular pacing. These technologies have been shown to reduce death and disability in patients with HF-REF, and thus it is uncertain whether access to them would have mitigated some of the treatment benefit. Although there was no significant heterogeneity by region, the trial was not powered to evaluate any differences in treatment effect as a product of care patterns.

**Implications for clinical care**

What does this mean for clinical care? Although the US Food and Drug Administration and other regulatory agencies must examine the primary data, the European Medicines Agency has granted a rare accelerated review to LCZ696.12 and clinicians, patients, and payers will face decisions about how to incorporate the compound into practice. In the event that further development occurs, regulators, health system gatekeepers, and clinicians will be presented with thorny questions: Should LCZ696 replace generic ACE-Is in patients who meet the criteria used in PARADIGM-HF? Should the results be extrapolated beyond the exact population enrolled in the trial? For health systems, the cost-effectiveness calculations are likely to estimate that LCZ606 will be a bargain, but pricing and reimbursement may prove contentious. It is to be hoped that the sponsor will work with health systems and national coverage approaches to emphasize value-based pricing and access for patients with limited financial means.

**What about additional uses of LCZ696?** A major trial is underway in patients with heart failure with preserved ejection fraction, and another trial is being planned for patients with acute decompensated heart failure. However, the big topic for discussion will be hypertension. Despite the large number of generic blood pressure medicines, refractory hypertension remains a huge problem, with some estimates identifying hypertension as the leading remedial cause of death and disability.13 This is especially true for economically disadvantaged minority groups in countries with developed economies, and these populations may preferentially benefit from the ARB/NEP inhibitor combination. Given the important potential clinical benefit, there is an urgent need for trials to examine LCZ696 in other areas of medicine.

The statistics on drug development are well known. Despite some contention about the exact numbers,14–16 the expense of bringing a new medicine to market is driven more by the costs of capital and of failures than by the direct costs of developing the new molecule. Rarely are major successes in this arena the result of totally rational planning, but in this case the previous work done on omapatrilat gave a boost to developers at Novartis, in concert with excellent trialists who had learned from previous heart failure trials. In a field with so many failures, this programme stands as an exemplar. Although I believe the effect in practice will be smaller than estimated in this trial with its run-in phase, deficits in use of ICDs and biventricular pacing, and early stopping by a diligent DMC, I also believe that the result is sufficiently large to merit early and widespread adoption in practice. Effective pricing, uptake by health systems, and new evidence-generating trials can continuously guide clinicians in the use of LCZ696 to achieve optimal outcomes for individuals and populations.

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**References**


