Therapeutic developments in the therapy of heart failure: lessons to be learned

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This editorial refers to ‘Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients’¹, by A.S. Desai et al., on page 1990.

The PARADIGM study examined the treatment effect of the angiotensin receptor—neprilysin inhibitor LCZ696, as compared with enalapril, in addition to other standard therapy in 8399 patients with chronic heart failure secondary to reduced systolic function. The results are impressive, as the experimental therapy was associated with highly significant reductions in both mortality and hospitalizations for congestive heart failure.¹ These findings have received widespread attention, heralded as a ‘paradigm shift’ in the therapy of heart failure. They have also generated controversy, as leaders in the field urge caution in the interpretation of both the magnitude and clinical applicability of the results.²,³ Furthermore, for the first time in the history of the pharmacotherapy of chronic heart failure secondary to reduced systolic function, the (likely) approval of LCZ696 will require physicians to make a therapeutic decision which does not involve the addition of a new drug but rather changing large numbers of patients from a proven therapeutic class of therapy to a new pharmacological approach.

In this issue of the journal, the PARADIGM investigators present an analysis of the mode of death in patients who participated in the PARADIGM study.⁴ The majority of deaths were cardiovascular (80.9%), and LCZ696, as compared with enalapril, was associated with a 20% reduction in cardiovascular deaths. The number of non-cardiovascular deaths and deaths of unknown cause were similar in the two treatment arms. Of the cardiovascular deaths, the majority were sudden (44.8%) while the second most common cause was heart failure related (26.5%). LCZ696 had similar effects on the risk of sudden and heart failure-related deaths, reducing both by 20%. The magnitude of the beneficial effect of LCZ696 on cardiovascular death was similar to the reduction observed for heart failure hospitalization. The authors suggest that the relative beneficial effect of LCZ696 on cardiovascular death was greater than that observed in previous landmark placebo-controlled studies examining the effectiveness of renin—angiotensin system antagonists in chronic heart failure secondary to reduced systolic function. In these studies, the effect of the study drug on hospitalizations for heart failure was greater than their impact on cardiac mortality. The implication is that LCZ696 has more potent effects on cardiovascular mortality than currently available inhibitors of the renin—angiotensin system. Although there are numerical differences in the relative risk reduction conferred by angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists, such differences may well result from differences in baseline characteristics of the populations studied, particularly in the background medical therapy used in earlier studies. However, the contention that LCZ696 has more potent effects is supported by a recent report from the PARADIGM investigators in which the results of the SOLVD treatment and the CHARM-Alternative studies were used to develop a putative placebo analysis of the effects of LCZ696 on clinical outcomes.⁵

The striking finding of the PARADIGM study is not the impact of LCZ696 on the mode of death. What is most impressive is that therapy with this compound had a large beneficial effect on both mortality and morbidity in a patient population already receiving the current standard of evidenced-based pharmacotherapy for chronic heart failure secondary to reduced systolic function. Concerns can be raised with respect to the run-in period design, the low numbers of patients who received devices, or the proportion of patients receiving mineralocorticoid antagonists. However, the observed result remains clear—LCZ696 improved both morbidity and mortality as compared with current, standard therapy. This positive outcome, however satisfying, serves to emphasize that our understanding of how current accepted therapies improve clinical outcome in chronic heart failure secondary to reduced systolic function remains poor. Previous important therapeutic advances have been based on careful observations concerning physiological conditions and/or counter-regulatory responses that exist in the setting of chronic heart failure, including adverse ventricular loading...
conditions, activation of the renin–angiotensin–aldosterone system, increased sympathetic nervous system activity, as well as relative tachycardia. However, despite the therapeutic rationale underlying each successful intervention, the exact mechanism(s) by which each yields benefit remains uncertain. Furthermore, current accepted therapies are used in a patient population that includes differences in heart failure aetiology, disease severity, and concomitant conditions. Within this broad range of clinical characteristics, we have no way to distinguish patients who benefit from a given therapy from those who do not.

The authors of the current report conclude that the benefits of LCZ696 are secondary to incremental effects of neprilysin inhibition.
in patients with congestive heart failure.4 Through its impact on the natriuretic peptide system, inhibition of this endopeptidase can have multiple direct and indirect cardiac, vascular, renal, and autonomic nervous system effects, many of which could be beneficial in the setting of chronic congestive heart failure. Importantly, nepriyisin plays a role in the degradation of a number of other peptide systems, including inhibition of the breakdown of angiotensin II and endothelin-1, which have potential negative therapeutic effects. This range of activity and the multiple consequent interactions with the cardiovascular system complicate our ability to understand the mechanism of the beneficial effects of nepriyisin inhibitors (Figure 1). Furthermore, since inhibition of nepriyisin can also cause an increase in vasconstrictor peptides, it has been recognized for many years that therapeutically effective endopeptidase inhibition should be combined with other agents such as angiotensin-converting enzyme inhibitors, endothelin converting-enzyme inhibitors, or, as is the case with LCZ696, in combination with an angiotensin II antagonist. Therefore, from this perspective, it should be concluded that the incremental beneficial effect of LCZ696 in the therapy of chronic heart failure secondary to reduced systolic function is actually due to the interactive combination of its two components, sacubitril and valsartan (Figure 1).

The impressive results of PARADIGM have led the Food and Drug Administration of the USA, the Health Medicines Agency of the European Union, and other regulatory authorities to grant priority review of LCZ696. Whether LCZ696 will be approved without additional studies remains uncertain; however, it is clear that further studies should be done to elucidate the best role for this compound in the therapy of chronic heart failure. The history of the development of pharmacotherapy for chronic heart failure with reduced systolic function is rich, with disappointing failures and a number of great successes. New drugs for the therapy of chronic heart failure secondary to reduced systolic function have generally been approved on the basis of positive results obtained in phase II and III clinical trials. Historically, the patient populations studied have been well defined but heterogeneous in terms of aetiology, disease severity, and concomitant conditions. Approved drugs have provided clear evidence that they reduce morbidity and/or mortality in such patient populations; however, it has always remained ambiguous exactly which patients derive benefit from such drug therapy. Once approved, it has proven difficult to carry out studies to better answer such questions as the use of a placebo-controlled approach is difficult, and funding from both industry and peer-review agencies becomes limited. There is a need to develop improved methodologies, applied in the post-approval period, which will provide a more detailed understanding of therapeutic efficacy. Such studies should attempt to identify those patients where the drugs are most effective and, more importantly, identify patient populations where they have adverse effects on outcome. These methodologies should strive to define patient characteristics that determine clinical outcome (in the case of heart failure, sudden death vs. progressive pump dysfunction), how such outcomes respond to a given therapy, and, importantly, how they interact with other therapeutic approaches (other drugs, as well as device therapies). We have made tremendous advances in the therapy of chronic heart failure secondary to reduced systolic function, and LCZ696 is certainly among them. Physicians now have an array of therapeutic options for the therapy of this common disorder. Going forward, the challenge will be to better understand the fundamental mechanisms through which beneficial effects are mediated. This should provide an avenue to further therapeutic improvement and may well provide further insights into the pathophysiology of disease progression.

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References