EDITORIAL

ACE inhibitors: back to prime time?

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In the early 1990s, randomised clinical trials testing ACE inhibition in patients with left ventricular systolic dysfunction and heart failure ushered in a new era in cardiovascular (CV) medicine. Trials such as SAVE, SOLVD, AIRE and TRACE demonstrated that ACE inhibitors prolonged life in such patients, and this class of drugs soon became the cornerstone of treatment in patients with left ventricular dysfunction.[1–4] An ancillary, yet unexpected, benefit of ACE inhibition in several of these trials was the observation of fewer myocardial infarctions (MIs) in the active treatment arms.[5 6] A natural extension of the ACE inhibitor hypothesis was to test these agents in patients with vascular disease, but without heart failure or left ventricular dysfunction. The QUIET trial, a small study testing quinapril in subjects with coronary disease, showed a neutral effect on clinical event reduction.[7]

Subsequently in 2000, the HOPE study expanded the benefits of ACE inhibition, in this case with ramipril, to patients aged 55 years or older who had established atherosclerosis (in any arterial bed) or diabetes.[8] By design, these patients could not have heart failure or known left ventricular dysfunction. As well as demonstrating a reduction in CV mortality, ramipril was also associated with statistically significant reductions in MI and stroke. The EUROPA study, in 2003, further extended the benefits of ACE inhibition, using perindopril, to essentially all patients with coronary heart disease, independent of age or left ventricular function.[9] Thus, for nearly a decade and a half, ACE inhibitors enjoyed the limelight for their important effect on CV outcomes in a broad range of patients. In a sense, they were prime-time players.

However, staying on top is not easy. A spate of trials with ACE inhibitors during this decade—namely, PEACE,[10] IMAGINE[11] and DREAM,[12] failed to replicate the clinical benefits noted in earlier studies, albeit in different patient populations. Although concerns surrounding trial design, patient selection, and chosen end points may partly explain the neutral effect on CV outcomes noted in these studies, the ACE inhibitor shine seemed to have worn off. Although there did not appear to be any harm from ACE inhibitors, the apparent lack of benefit, particularly in a resource-constrained healthcare system, suggested a need for reappraisal. Many clinicians concluded that stable coronary patients, when optimally treated with other evidence-based treatments, including antiplatelet agents, β blockers, statins and revascularisation, no longer required ACE inhibition. Trials such as HOPE were considered out-dated, in that evidence-based treatments were not broadly applied in that trial, which began in 1994, even before the first large statin trial, 4S, was published.[13] The cost effectiveness of adding an ACE inhibitor to other treatments in ''low-risk'' patients with CV disease came into question.

A closer evaluation of the data, however, would suggest that ACE inhibitors exert benefit in patients across a broad range of CV risk. The HOPE investigators subsequently showed consistent benefit of ramipril in their study population, independent of tertile of risk.[14] The EUROPA trial, evaluating perindopril in over 12 000 subjects with coronary heart disease, selected lower-risk patients than HOPE, and demonstrated a significant 20% reduction in hard CV events, a remarkably similar effect to that seen in HOPE. These CV benefits in EUROPA were also consistent across tertiles of risk. The lowest risk tertile in EUROPA had an annual CV event rate that was lower than that in the overall PEACE population.[15] Although the effect of trandolapril on CV outcomes in PEACE was neutral, there was a consistent effect of perindopril even in EUROPA's lowest risk tertile. Additionally, a PEACE subanalysis demonstrated a mortality benefit in subjects with impaired renal function.[16] These observations were further strengthened by a recent meta-analysis of the HOPE, EUROPA and PEACE trials, which confirmed a clinically and statistically significant reduction in mortality, MI, and stroke, with ACE inhibition, across a broad spectrum of CV risk.[17] Thus, until better risk stratification tools become available, it would seem reasonable to use ACE inhibition for the vast majority of patients with vascular disease.

After publication of the EUROPA trial, perindopril was approved for CV protection by both the Federal Drug Agency (FDA) in the US, and by the European Medicines Evaluation Agency (EMEA) in Europe. In this issue of the journal, the EUROPA investigators present a cost-effectiveness analysis of perindopril in reducing CV events in patients with stable coronary heart disease (***see article on page 1081***).[18] Several features of this analysis deserve special mention. The median incremental cost per quality-adjusted life year gained was £9700, with an interquartile range of £6400–£14 200. This incremental cost certainly compares favourably with many other accepted treatments in CV medicine and beyond. It also comes in

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Abbreviations: CV, cardiovascular; EMEA, European Medicines Evaluation Agency; FDA, Federal Drug Agency; MI, myocardial infarction

considerably below the threshold for good value of £20 000–£30 000, as recommended by the National Institute for Health and Clinical Excellence in the UK.[19]

The field of cost-effectiveness analysis has been controversial for years. Whereas some argue about the validity of the science behind such analyses, others are more concerned about biases based upon how such analyses are funded. In fact, it has been shown that cost-effectiveness analyses funded by pharmaceutical companies are less likely to demonstrate negative findings, and more likely to reveal favourable findings, than those studies funded through non-profit sources.[20 21] Although the EUROPA analysis was funded through a grant from Servier Laboratories, the manufacturer of perindopril, the authors had full access to the EUROPA database, and the freedom to conduct their own analyses, as well as to publish their findings independently of the funding source. Additionally, all authors have provided full disclosure and any potential conflicts of interest.

Any cost-effectiveness analysis is only as good as the study or studies upon which it is based. The ''gold standard'' therefore for cost-effectiveness analyses is to base them upon large, randomised clinical trials. Importantly, the EUROPA trial itself was a well-conducted, randomised clinical trial involving more than 12 000 patients with stable coronary heart disease, demonstrating that perindopril reduced the risk of major CV events by approximately 20%. Based upon the inclusion criteria and clinical characteristics of the patients in EUROPA, the study findings were deemed to be applicable to a real world general practice. Subsequently, both the FDA and EMEA approved the use of perindopril for patients similar to those studied in EUROPA.

The authors of this EUROPA cost-effectiveness analysis have taken care to provide a complete technical report on the web and to perform additional sensitivity analyses for five illustrative patients reflecting varying levels of risk. In addition, they have assumed that treatment would last for 5 years, similar to the duration of the EUROPA study, but also evaluated the cost effectiveness of lifetime treatment. Overall, the cost effectiveness of 5 years of treatment compared with a lifetime of treatment was similar. Because health-related quality of life data were not collected in the EUROPA study, they estimated these scores from a Welsh health survey, a potential limitation in the interpretation of their findings. Given that the incremental benefit of ACE inhibition across a spectrum of trials ranges between 15% and 25%, it remains important to tailor cost-effectiveness analyses to specific healthcare environments.

This thoughtful cost-effectiveness analysis of the EUROPA study reminds us of the powerful clinical benefits of ACE inhibition in patients with coronary heart disease. Beyond this, it demonstrates that the use of an ACE inhibitor in such patients, in this case perindopril, is money well spent within the UK healthcare system. Perhaps the most important outcome of this analysis is to re-focus the limelight on ACE inhibitors, and to move them back into the starting line-up, ready for prime time.

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