Optimization of ACE inhibitor therapy in heart failure

See doi:10.1053/euhj.2001.3112 for the article to which this Editorial refers.

The clinical syndrome of heart failure results in impaired quality of life, exercise intolerance, frequent hospital admissions and high mortality. Each of these can be of importance for a patient with heart failure. Ideal drug treatment for heart failure should result in improvement in all of these end-points. However, it is now well established that there can be dissociation between short- and long-term effects of pharmacological agents. For example, both enoximone and milrinone can improve symptoms in the short term but result in increased mortality, mainly due to an increase in sudden presumed arrhythmic death[1-3]. As a result of this and the dominance of survival data for drug regulatory requirements, the effects of many drugs on end-points other than survival are relatively unstudied. However, improvement in symptoms, quality of life and ability to exercise rather than survival, may be a higher priority for heart failure patients, particularly the elderly.

ACE inhibitor therapy provides a good example of this data disparity, with clear evidence of survival benefit but conflicting information on the effects on exercise. The study in this edition by Cooke et al. again raises the issue of the optimal dose of ACE inhibitor therapy in heart failure[3]. The study relates the pathophysiology of exercise intolerance in heart failure to vasodilator therapy with ACE inhibitors. The study was performed with a small sample of 12 heart failure patients in a crossover design, testing the effects of 5 mg and 20 mg of lisinopril on exercise capacity. The low-dose of lisinopril had more favourable effects on aerobic exercise capacity than the 20 mg dose. Although this is an elegant study, several issues relevant to the application of these findings to heart failure patients remain uncertain. For example, although the study demonstrated beneficial effects on aerobic exercise capacity, there were no data to support extension of these benefits to overall improvements in quality of life. Many heart failure patients are severely limited by concomitant conditions and thus data on exercise capacity alone are not convincing enough to mandate this dose. In addition, how the effects observed in this study will translate to the patient receiving standard beta-blocker therapy is uncertain.

Other studies have compared different doses of ACE inhibitors in heart failure patients. A recent comparison of low (5 mg . day\(^{-1}\)) and high dose enalapril (40 mg . day\(^{-1}\)) in heart failure patients demonstrated no greater suppression of angiotensin II, aldosterone or catecholamines with the high dose compared with the low dose[4]. There were no differences in exercise duration or VO\(_2\) between the two groups. However, there was a trend for a reduction in a pre-specified clinical composite end-point (hospital admission, emergency room visit, death, sustained increase in diuretic) in the high-dose group. The ATLAS trial compared (very) low-dose lisinopril (2·5 to 5 mg . day\(^{-1}\)) with (very) high-dose lisinopril (35 mg . day\(^{-1}\)) in 3614 patients with heart failure[5]. There was no statistically significant difference in survival (primary end-point) between the two groups although there was a significant reduction in hospital admissions for heart failure and the combined end-point of death or hospital admission with the high dose. These data support a beneficial effect on clinical outcome with higher dose ACE inhibitor therapy but do not preclude a similar advantage with an intermediate dose which may be more practical and efficient.

Thus, while it is clear that ACE inhibitor therapy should be used to treat patients with heart failure, uncertainty remains regarding the optimal dose. How do we incorporate this information into the clinical decision making for individual patients? A fundamental concept of evidence-based medicine is that we should take the overall clinical trial results obtained from various heterogeneous patient groups and apply these to individual patients. There are many circumstances where we must make assumptions beyond the available evidence until such time as (hopefully) further evidence gaps are filled. One argument is to assume that the apparent beneficial effects of high dose ACE inhibitor therapy on expensive hospital readmissions should outweigh any lesser effect on aerobic exercise capacity and be justified on the basis of cost effectiveness. Worsening heart failure occurs commonly in heart failure patients and will contribute to the impaired quality of life for these individuals. Thus, this argument for higher-dose therapy is reasonable. No clear evidence-based recommendations can be made regarding the effects of ACE inhibitors at different doses on survival alone. The practical reality though is that many patients with heart failure may not tolerate the high doses of ACE inhibitor required to achieve these benefits. Thus, we may end up with many patients receiving intermediate doses, such as the equivalent of lisinopril 20 mg daily, where the effects on hospital
readmissions and worsening heart failure may be less pronounced. This moderate approach is more in keeping with the average dose actually achieved in the large-scale ACE inhibitor survival trials[6,7] and in our view is a reasonable target.

A more attractive future option would be to tailor therapy to the individual patient. This would allow optimization of drugs and dosage to achieve the optimal outcomes for that individual patient. Tailoring therapy to achieve a desired neurohormonal response and improve outcomes has been demonstrated[8] and further large-scale clinical trials are ongoing in this area. In the meanwhile we should ensure that evidence-based therapies are more widely applied in general to all patients with heart failure, continue to debate dosage while supporting additional more definitive studies.

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References