Ace inhibitors in heart failure. What dose?

The role of ACE (angiotensin converting enzyme) inhibitors in the treatment of heart failure is now well establised. A large body of published work has demonstrated relief of symptoms, increased exercise performance, a reduction in hospital admissions and superiority to conventional vasodilators. Three large survival studies (CONSENSUS-1,1 V-HEFT II,2 and SOLVD3 have also shown that enalapril can alter the natural history of heart failure with a significant improvement in long-term prognosis. Similarly, the SAVE,4 AIRE,5 ISIS 4,6 and GISSI 3' studies demonstrated an improvement in prognosis following myocardial infarction with captopril, ramipril, and lisinopril. Many more ACE inhibitors have recently become available. The British National Formulary now lists five for the treatment of cardiac failure. The clinical benefit of these drugs to patients is beyond doubt and they now represent a cornerstone in the treatment of heart failure.8 However, there are a number of important unresolved issues with regard to their clinical use. The most important of these is the optimal dose required to achieve the full benefit of ACE inhibitor action.

The target doses of the ACE inhibitor used in each study are summarised in the box. For the most part, these target doses were achieved. For example, in CONSENSUS-1 the mean dose of enalapril was 18.4 mg daily. Despite these high-dose protocols market research has shown that, in general practice, much lower doses of ACE inhibitors are being used for the treatment of chronic heart failure. When enalapril is used, 42%, of the doses are 5 mg or less, 75% of the doses of captopril are 75 mg or less and 65% of lisinopril prescriptions are for 10 mg or less. The information from the large outcome studies is mostly based on higher doses but it is possible that significant clinical benefit in terms of symptoms is being achieved at these lower doses. Alternatively, general practitioners may be cautious in increasing the dose of an ACE inhibitor because they are concerned with the possibility of precipitating hypotension, reducing renal function, or causing cough. Certainly many doctors remain wary of ACE inhibitors in heart failure and refer patients to a local physician to initiate therapy in hospital. Some patients may be started on an ACE inhibitor in hospital at the lowest dose, but never have this dose increased when they return to the community. The actual reasons are, at present, unknown. However, since low-dose ACE inhibitor therapy has become common practice in the treatment of heart failure, there is a need to ascertain whether the benefits observed in terms of the nature history at high doses, will similarly be achieved with the lower dose regimens.

The pharmacological data on this group of drugs are relevant to the question of dose. Many of the deleterious effects of chronic heart failure are due to the effects of high levels of angiotensin II which causes vasoconstriction and fluid retention. In pharmacodynamic terms, ACE inhibitor action is mediated by reversible binding to plasma ACE, resulting in competitive inhibition of the conversion of angiotensin I to angiotensin II. Different ACE inhibitors are often classified according to their time course of action into long acting (eg, enalapril, lisinopril) and short acting (eg, captopril). However, the duration of action of all ACE inhibitors will increase with dose so that a large dose of captopril may have a longer effect that a small dose of enalapril. There are very few comparative data on the doses of different ACE inhibitors and so extrapolation from the original survival studies to other ACE inhibitors is almost impossible. Whether prolonged ACE inhibition is a desirable goal in heart failure is unknown. Theoretically, a constant reduction of afterload on the failing left ventricle with a long-acting drug seems desirable (if that is the mode of action) but there is no conclusive evidence to support this. Long-acting ACE inhibitors in chronic heart failure might predispose to the development of renal insufficiency and a greater problem with syncope, because of the sustained hypotensive effects. However, this theoretical risk has not been borne out in large clinical studies. The relation between clinical outcome of therapy and plasma drug concentration, plasma ACE activity, tissue ACE activity and plasma angiotensin II concentration is unknown. While the pharmacological data on ACE inhibitor action highlight the need for more comparative data on the different drugs, the question of whether low-dose ACE inhibition would provide the same long-term benefits as high-dose therapy is unanswered. This can only be achieved by large clinical trials.

There are few clinical reports of ACE inhibitor dosage at the current time; such data that do exist are from studies with small patient numbers and inadequate power compared to ongoing trials. In one study of 40 patients with severe heart failure, a 5 mg daily dose of enalapril produced significant improvement in symptoms and a mortality rate of 10% compared to 45% in the group treated with conventional vasodilators.9 In a comparative study between high and low doses of ACE inhibitor in a group of 85 patients with moderate to severe heart failure, patients on the low dose of captopril (less than 75 mg daily) demonstrated no change in clinical parameters, but those in the high dose group (75 mg daily or greater) improved significantly.10 A further study11 of 27 patients with severe heart failure compared a low dose of enalapril (2.5 mg twice daily) with a high dose (15 mg twice daily). Patients on the high dose had significantly fewer clinical events such as death, hospitalisation, or an increase in heart failure therapy. A study using quinapril showed that the improvement in exercise time for 225 patients with mild to moderate heart failure was dose related.12

There are two large investigations now taking place. The NETWORK study compares high and low dose enalapril in 1500 patients with symptomatic heart failure. The trial has a combined endpoint of clinical symptoms, hospitalisation rates, and mortality. The NETWORK study relies on
the recruitment of patients with a diagnosis of heart failure from general practice. Patients are referred to hospital for confirmation of the diagnosis and enrolled into one of three treatment groups. The doses of enalapril in the different groups are 2.5 mg twice daily, 5 mg twice daily or 10 mg twice daily. The follow up period will last six months. The authors are members of the NETWORK Steering Committee.

The Assessment of Treatment with Lisinopril And Survival (ATLAS) study is comparing low and high dose lisinopril in 3000 patients. Two groups of patients will be compared. The first group will be on low-dose lisinopril (2.5 or 5 mg once daily) and the other group will be on high-dose lisinopril (up to 35 mg once daily). The follow-up period is three years and the primary endpoint is mortality.

ACE inhibitors have an important role in the treatment of patients with heart failure. They not only improve symptoms and reduce hospital admissions but also extend life. When these two important trials are published we should know what dose of ACE inhibitors to use in order to achieve the maximum benefit for our patients, both in terms of symptom improvement and prognosis, at least for the two drugs in this category. For the present, doctors should prescribe the doses shown to be beneficial in the large trials.


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Elizabeth Blackwell (1821–1910) was born in Bristol, UK, the third daughter and third of nine children of a sugar refiner who migrated with his family to the USA in 1832. She became a medical student at the University of Geneva in the State of New York, where she received a degree (1849) and then returned to England. Her medical training was greatly helped by James Paget at St Bartholomew’s Hospital. While a resident at La Maternite hospital, Paris, France, she contracted purulent ophthalmia from a patient and lost one eye. In 1851 she returned to New York and joined her sister in practice. When still in England, her name was included in the British Medical Register, the first woman doctor to be registered. She was present on 11 July 1898 at the new Royal Free Hospital Medical School. She died on May 31, 1910 in Hastings, UK.
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