Is more better? About dose levels of ACE inhibitors in chronic heart failure

Chronic heart failure remains a common and dangerous syndrome. Within the last decade there has been considerable progress in the understanding and treatment of this condition. ACE inhibitors have become established[1] and more recently beta-blockers have been demonstrated to provide improved survival and reduced morbidity[2,3]. The understanding of chronic heart failure has increased with the acceptance of the neuroendocrine concept[4]. The addition of spironolactone has therefore received wide acceptance based on the RALES study[5]. Non-pharmacological management has also improved with the acceptance of heart failure clinics, left ventricular assist devices, implantable cardioverter-defibrillators and heart transplantation.

In evaluating these treatment options one has to consider many aspects of heart failure. When we apply these experiences, how should we individualize our treatment? What dose of an agent should be used and which patients respond more favourably than others? How will our treatment respond in patients at higher risk (usually the sicker patients)? What about the elderly and the diabetics? The answers to these questions should emerge from clinical trials. However, a new randomized trial for each question is not realistic and it is important to gain additional answers from the large trials.

The value of ACE-inhibitor therapy in chronic heart failure has been established by a number of randomized trials[1,6]. In addition we have learned from the HOPE study the importance of treating diabetics without heart failure with the ACE inhibitor ramipril[7]. The dose levels of ACE inhibitors were enalapril 20 mg twice daily in CONSENSUS I and 10 mg twice daily in SOLVD, with daily mean dose levels of 18.4 mg and 16.6 mg, respectively. With this approach to management we only know that initiation of therapy by forced titration will work: starting low and increasing to a target dose over some weeks. However, dose levels in clinical practise remain low and practising physicians are hesitant to titrate an ACE inhibitor in sicker patients.

The rationale for titrating an ACE inhibitor to higher dose levels is to optimize neuroendocrine suppression. This approach has been studied by Pacher and co-workers[8]. In a non-randomized trial, they found that captopril >75 mg . day\(^{-1}\) induced greater neuroendocrine suppression and improved prognosis more than captopril <75 mg . day\(^{-1}\). MacFayden[9] found that many patients on clinically relevant doses of ACE inhibitors still had clearly elevated plasma levels of angiotensin II and aldosterone, suggesting inadequate neuroendocrine suppression in many patients.

The ATLAS trial was designed to address the important question whether a high dose of the ACE-inhibitor lisinopril is better than a low dose to improve prognosis[10]. It should be kept in mind that most patients had been on chronic therapy with an ACE-inhibitor and all patients tolerated a run-in period on open lisinopril treatment. The main finding was an 8% non-significant lower risk of all-cause mortality in the high dose group and a 12% significant lower risk of the combined risk of death or hospitalization for chronic heart failure. The overall tolerability was similar in the two dose groups. The power of the trial was reduced by a high withdrawal rate in both treatment groups and a marked crossover to open therapy.

Additional subgroup analysis of the ATLAS trial has been performed by Rydén and co-workers and presented in this issue[11]. They have studied patients at higher risk for cardiovascular death among the patients in ATLAS and in particular diabetics. They found that the effect of high dose lisinopril was consistent across a wide range of high risk groups, including patients with low serum sodium, increased serum creatinine, higher age and diabetics. Importantly, they found the higher dose levels well tolerated among these patients. Many subgroups have been evaluated and provide interesting insights into this database.

The extended analysis of the ATLAS study, as presented, gives further support and emphasizes...
the importance of treating patients with chronic heart failure with ACE inhibitors. All patients with left ventricular dysfunction and chronic heart failure should be evaluated for ACE-inhibitor therapy. Practising physicians should be reassured about the good tolerability of ACE inhibitors, and of lisinopril in particular. Treatment should be initiated by slow forced titration to a target dose. Based on ATLAS and other trials it is not clear what the optimal dose level is but my interpretations are:

- Higher dose levels of documented ACE inhibitors are better than low dose levels.
- Forced titration to a dose level of at least 20 mg daily of lisinopril or enalapril, captopril 50 mg three daily times, ramipril 10 mg daily or trandolapril 4 mg four times daily should be performed in all patients.
- There is still uncertainty over whether 35 mg of lisinopril is better than 20 mg, but better neuroendocrine protection is obtained by the higher dose levels.
- Patients at higher risk (e.g. diabetics) and tolerating the initiation of an ACE inhibitor, will also benefit more from the high dose strategy. As their relative risk reduction is similar to the reduction seen in patients at lower risk, even more patients will be saved by this improved management in these patients at higher risk.

By disseminating the experience now well documented to all physicians managing patients with chronic heart failure, cardiologists will help these patients to obtain the benefits from modern pharmacological therapy, in particular with ACE inhibitors.

K. SWEDBERG
Department of Medicine, Sahlgrenska University Hospital Östra, Göteborg, Sweden

References


Cardiogenic shock: a call for aggressiveness

See page 1928 for the article to which this Editorial refers

Since it has become possible to detect and treat life-threatening arrhythmias effectively, cardiogenic shock has become the main cause of in-hospital death after acute myocardial infarction.

The incidence of cardiogenic shock has remained stable over the last years with reported in-hospital frequencies ranging from 5% to 15% depending on the definition used[1].

In this issue, Menon and colleagues[2] evaluated the outcome of patients with cardiogenic shock in two large trials of thrombolytic therapy. In the Global