**The ELITE Study**

**What are its Implications for the Drug Treatment of Heart Failure?**

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**Summary**

Angiotensin II type 1 (AT₁) receptor antagonists inhibit the renin-angiotensin system more completely than ACE inhibitors, and do not increase bradykinin levels as ACE inhibitors do. ACE inhibitors have been proven to increase survival and improve quality of life in patients with congestive heart failure (CHF). At the 48-week follow-up of the Evaluation of Losartan in the Elderly (ELITE) Study, the AT₁ receptor antagonist losartan (at a dosage of 50 mg/day) was found to be superior to captopril 50mg 3 times daily in terms of its effects on total mortality, total mortality and/or hospitalisation for CHF, and hospitalisation for any reason. Hospitalisation for CHF was the same for both drugs. Adverse effects occurred in 12 and 21% of those receiving losartan and captopril, respectively. Cough, rash, angioedema or taste disturbances/reduced appetite prompted the cessation of drug treatment in 0 and 7% of those receiving losartan and captopril, respectively. Until additional data are available, this author recommends that elderly patients with CHF and an abnormal or normal left ventricular ejection fraction, and who are unable to tolerate ACE inhibitors, should receive losartan 50 mg/day.

Renin acts on angiotensinogen to form angiotensin I.[1] Angiotensin converting enzyme (ACE) is a peptidyl carboxypeptidase that catalyses the conversion of angiotensin I to the active octapeptide angiotensin II in the blood and in other tissues, including the heart, kidneys, lungs, brain and adrenal glands.[2] All of the known actions of the renin-angiotensin system are mediated by angiotensin II.[2]

Angiotensin II interacts with at least 2 membrane-bound receptors: type 1 (AT₁) and type 2 (AT₂).[2] The AT₁ receptor mediates most of the actions of angiotensin II, such as vasoconstriction, sympathetic nervous system stimulation and aldosterone release.[2] Because the AT₁ receptor is responsible for the cardiovascular effects of angiotensin II, blockade of this receptor should more completely inhibit the renin-angiotensin system compared with ACE inhibition.[2]

The benefits of ACE inhibitors have been associated with the blockade of angiotensin II production and to a reduction in bradykinin breakdown.[3,4] Bradykinin contributes to the haemodynamic effects of ACE inhibitors but may also cause some of their adverse effects, such as cough, hypotension, renal dysfunction and angioedema.[3-7]

Orally active, nonpeptide AT₁ receptor antagonists such as losartan, valsartan and candesartan cilexetil can block the AT₁ receptor without increasing bradykinin levels.[8-10] Since angiotensin II may be produced by alternative pathways,[11-14] AT₁ receptor antagonists may block the effects of angiotensin II more completely than ACE inhibitors.
1. Haemodynamic Effects of ACE Inhibitors in Congestive Heart Failure (CHF)

ACE inhibitors are balanced vasodilators, in that they act by decreasing both preload and afterload. ACE inhibitors decrease systemic vascular resistance, arterial pressure, left ventricular and right ventricular end-diastolic pressures, cardiac work and myocardial oxygen consumption, and increase cardiac output. They decrease circulating levels of angiotensin II, decrease sympathetic nervous system activity, stimulate prostaglandin synthesis and decrease sodium and water retention by inhibiting angiotensin II–mediated stimulation of aldosterone release. ACE inhibitors have also been shown to reduce complex ventricular arrhythmias in patients with congestive heart failure (CHF) in many studies,[15-19] but not in all.[20]

2. Effects of ACE Inhibitors on Survival in Patients with CHF

ACE inhibitors improve symptoms, quality of life and exercise tolerance in patients with CHF. Table I shows that ACE inhibitors also increase survival in patients with CHF associated with an abnormal left ventricular ejection fraction (LVEF).[21-25] Furthermore, it shows that ACE inhibitors should be standard therapy for all elderly patients with CHF associated with an abnormal LVEF unless there are specific contraindications to their use.

3. Effects of ACE Inhibitors on Survival in Patients Post–Myocardial Infarction

The Survival and Ventricular Enlargement (SAVE) Trial[26] investigated the effects of captopril in patients with myocardial infarction and an LVEF ≤40%. At the 42-month follow-up, captopril reduced mortality by 16% (8% in patients aged ≤55 years, 13% in patients aged 56 to 64 years and 25% in patients aged ≥65 years) compared with placebo. At the 1-year follow-up of patients with anterior myocardial infarction in the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Trial,[27] zofenopril decreased mortality or severe CHF by 32% in patients aged <65 years and by 39% in those ≥65 years, compared with placebo. In the Trandolapril Cardiac Evaluation Study,[28] patients with myocardial infarction and an LVEF ≤35% were studied over a 24- to 50-month follow-up period. Compared with placebo, trandolapril decreased mortality by 22% and progression to severe CHF by 29%.

On the basis of these data, ACE inhibitors should be administered to all elderly patients after a myocardial infarction who have CHF, an anterior myocardial infarction or an LVEF ≤40%, unless there are specific contraindications to their use.

Table I. Effects of ACE inhibitors on survival in patients with congestive heart failure (CHF)

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
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<tr>
<td>Co-Operative North Scandinavian Enalapril Survival Study (CONSENSUS)[21]</td>
<td>Compared with placebo, enalapril reduced mortality by 40% at 6 months, 31% at 1 year and 27% at the end of the study</td>
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<td>Veterans Administration Co-Operative Vasodilator-Heart Failure Trial II (V-HeFT II)[22]</td>
<td>At a 2-year follow-up, enalapril decreased mortality by 28% compared with hydralazine plus isosorbide dinitrate</td>
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<td>Studies of Left Ventricular Dysfunction (SOLVD) Treatment Trial[23]</td>
<td>At a 41-month follow-up, compared with placebo, enalapril decreased mortality by 16%, deaths attributable to progressive CHF by 22%, and mortality or hospitalisation for worsening CHF by 26%</td>
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<tr>
<td>Acute Infarction Ramipril Efficacy (AIRE) Study[24]</td>
<td>At a 25-month follow-up of patients with myocardial infarction and CHF, compared with placebo, ramipril reduced mortality by 27% (2% in patients aged &lt;65 years and 36% in those aged ≥65 years)</td>
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<tr>
<td>Overview of 32 randomised trials of the effects of ACE inhibitors on mortality and morbidity in patients with heart failure[25]</td>
<td>Compared with placebo, ACE inhibitors decreased total mortality by 23% and mortality or hospitalisation for CHF by 35%</td>
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