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# The ELITE II study, a direct comparison of angiotensin-converting enzyme inhibition and angiotensin receptor blockade in heart failure

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**The angiotensin-converting enzyme (ACE) inhibitors are well-established therapy for patients with heart failure. In recent years, the angiotensin receptor blockers (ARBs) have emerged as alternative agents to intervene the renin-angiotensin system. In the Evaluation of Losartan in the Elderly (ELITE) study, a relatively small study designed primarily to compare the safety of the ARB losartan versus the ACE inhibitor captopril, an unexpected survival benefit (primarily due to reduction of sudden death) was observed in patients treated with losartan compared to captopril. Accordingly, the Losartan Heart Failure Survival Study - ELITE II was an international, double-blind, randomized-control trial designed to test formally the hypothesis that losartan, compared with captopril, would reduce all-cause mortality. The ELITE II study has been completed and the results were presented recently. In this issue of *Cardiology Scientific Update*, the key findings and their clinical implications of ELITE II will be discussed.**

Angiotensin-converting enzyme (ACE) inhibitors are of proven clinical benefit to reduce mortality and morbidity in patients with symptomatic chronic heart failure (CHF) and impaired systolic left ventricular function.[1,2] In clinical practice, a significant proportion of patients may discontinue using ACE inhibitors because of drug-related side effects. The availability of the angiotensin receptor blockers (ARBs) has provided an alternative approach to intervene the renin-angiotensin system. The mechanisms of action of the ARBs and their *theoretical* advantage over ACE inhibitors have been discussed in previous issues of *Cardiology Scientific Update*. These are summarized briefly in Table 1.

Losartan was the first clinically available ARB. When compared to placebo, losartan produced sustained beneficial hemodynamic effects in patients with CHF.[3] In the multinational Scandinavian trial,[4] 166 patients with New York Heart Association (NYHA) class III and IV symptoms were randomized to receive losartan 25 mg daily, losartan 50 mg daily, and enalapril 20 mg daily. Treatment was for 8 weeks and the primary endpoints were exercise tolerance as measured by 6-minute walk test, clinical and neurohormonal status. There were no significant differences between treatment groups in exercise tolerance, dyspnea-fatigue index, neurohormonal activation, left ventricular ejection fraction, or worsening of heart failure. A study with similar design and the same sample size and primary endpoints was conducted in North



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**Table 1: Biologic actions that favor ARBs over ACE inhibitors**

- Is angiotensin II escape from ACE inhibitors critical?
- Is the non-ACE dependent-angiotensin generating pathways clinically important?
- Is there an advantage for unopposed type II angiotensin receptor subtype?
- Is bradykinin-induced post-synaptic norepinephrine release harmful?
- Is bradykinin-induced cardiac and vascular remodeling advantageous?
- Is there a differential effect on aldosterone suppression?
- Are there any antiarrhythmic effects in ARB's?
- Are there differential effects on thrombotic pathways?

America by the Losartan Pilot Exercise Study Investigators.[5] Like the Scandinavian study, there were no significant differences between the treatment arms in any of the surrogate endpoints. Interestingly, there was a non-significant difference in deaths (5 in losartan 50 mg, 1 in losartan 25 mg, and none in the enalapril group).

## ELITE

The Evaluation of Losartan in the Elderly Study (ELITE) was a pilot study designed to evaluate the safety and efficacy of losartan compared with that of the ACE inhibitor captopril in elderly patients with CHF.[6] Seven hundred and twenty two patients with NYHA II to IV (mostly class II) symptoms were randomized to losartan 50 mg daily or captopril 150 mg daily. The primary endpoint was renal function (a persistent increase in serum creatinine ≥ 26.5 µmol/L). The secondary endpoint was composite of death and/or hospitalization for heart failure. After 48 weeks, there was no difference between groups in the frequency of sustained rise in serum creatinine (10.5% in both groups). However, tolerability was significantly better in the losartan group, with less patients discontinuing the medication early (12.2%) than in the captopril-treated group (20.8%). Although there was no significant different in the composite secondary endpoint, one unexpected finding was a significant difference in total mortality (4.8% in the losartan group, 8.7% in the captopril group, relative risk (RR) 0.54, 95% confidence interval (CI), 0.31-0.95, p=0.035. This difference was primarily due to a reduction in sudden cardiac death, RR 0.36, CI, 0.14-0.97. Interestingly, an electrocardiographic substudy that evaluated QT dispersion showed a significant increase in QT dispersion in the captopril group,[7] whereas a study of human atrial tissue demonstrated that captopril, but not losartan, increases myocardial norepinephrine release, suggesting that captopril might increase electrical instability.[8] Notwithstanding these interesting findings, given the small sample size and the short patient follow-up of ELITE, the beneficial effects of losartan over captopril in the ELITE study might still have been due to chance alone. A properly designed large-scale trial with mortality as primary endpoint was required to prove a survival benefit of losartan over captopril.

## ELITE-II

The Losartan Heart Failure Survival Study – ELITE II was a multicenter, multinational, double-blind, randomized study comparing losartan with captopril in patients with CHF and systolic left ventricular dysfunction. Three thousand one hundred and fifty-two patients were recruited from 289 sites from 46 countries. Details of the methodology of ELITE II have been published recently.[9] The primary objective of ELITE II was to test the hypothesis that losartan was superior to captopril in reducing total mortality. For the primary endpoint of total mortality, the study was powered to detect a 25% treatment effect (90% power) with a target event rate of 510. The secondary outcome was sudden cardiac death and/or resuscitated cardiac arrest. Other outcomes included cardiovascular mortality and morbidity, tolerability of study medication and health-related quality of life. By design, patients had to be 60 years or older (85% were required to be over 65 years old) with NYHA class II to IV symptoms and left ventricular ejection fraction ≤40%. At least 70% of patients had to have a history of ischemic heart disease and up to 25% may have been receiving ß-blockers at the time of randomization. Patients were to be ACE inhibitor naïve or were to have received 7 days or less of treatment with an ACE inhibitor within the 3 months before randomization. After a single-blind placebo run-in period of 1 to 28 days, patients were randomized to receive losartan, titrated over 3 weeks to 50 mg daily, or captopril, titrated over 3 weeks to 50 mg three times daily.

**Table 2. Baseline patient characteristics in ELITE II**

| | Captopril n=1574 | Losartan n=1578 |
|---|---|---|
| Age (years) | 71.5 | 71.4 |
| Male (%) | 69 | 70 |
| Ejection fraction (%) | 31 | 31 |
| NYHA class II/II/IV (%) | 49/45/6 | 49/45/6 |
| Ischemic etiology (%) | 79 | 80 |
| Prior ACE inhibitor use (%) | 22 | 22 |
| ß-blocker use (%) | 23 | 24 |
| Diuretics use (%) | 78 | 77 |
| ASA use (%) | 59 | 58 |

NYHA, New York Heart Association functional class

### *Results*

The first patient was randomized on June 31, 1997. The last patient was randomized on May 29, 1998. The study was terminated on July 18, 1998. The last study visit took place on August 17, 1999. The median follow up was 555 days. A total of 3152 patients were randomized. Only two patients were lost to follow-up.

Baseline patient characteristics are shown in Table 2. The two study groups were comparable at baseline. Mean age was 71.5 years with a male predominance. Mean left ventricular ejection fraction was 31%, the majority being ischemic in etiology. By study design, <25% of the patients were on ß-blockers. Most patients were truly ACE inhibitor naïve, although about 20% had received ACE inhibitors previously for <7 days duration. The severity of CHF was evenly distributed between NYHA class II and class III and IV. This was different from the ELITE study where over two-thirds of patients had NYHA II (milder) symptoms.

Data for the primary endpoint of total mortality are shown in Table 3. There was no significant difference in all-cause mortality between the captopril and losartan groups. The event rate was 15.9% in the captopril group and 17.7% in the losartan group ($p$=0.16) and the survival curves were almost superimposable. No difference was observed in sudden death, death due to CHF, myocardial infarction, stroke, or non-cardiovascular death between the two arms. Analysis of pre-specified subgroups which included age, gender, New York Heart Association functional class, and ejection fraction more than or less than 32% did not suggest

**Table 3: Primary outcome: Total mortality**

| Captopril (n=1574) | Losartan (n=1578) | RR (95% CI) | p |
|---|---|---|---|
| 250 events, 15.9% | 280 events, 17.7% | 0.88 (0.75,1.05) | 0.16 |

RR, relative risk favoring captopril, CI, confidence intervals

that any particular subgroup benefited more or less with either drug. The only exception was the use of ß-blockers. In the small subgroup of patients who were on ß-blockers at baseline, there was a relatively greater improvement with captopril than losartan.

Data for the secondary and combined endpoints are shown in Table 4. There was no significant difference in the incidence of sudden death/resuscitated cardiac arrests between the captopril and losartan groups, although there appeared to be a trend favoring captopril. There was no significant difference in all-cause hospitalization, or hospitalization due to CHF, myocardial infarction, or stroke/transient ischemic attack. Furthermore, there was no significant difference in the combined endpoint of all-cause mortality and all-cause hospitalization. Finally, heart failure-related events, including hospitalization, death, or discontinuation of drugs, were similar in both groups.

Tolerability was once again significantly better with losartan. A significantly higher number of patients on captopril discontinued the study drug due to an adverse event. The incidence of cough was also significantly lower in the losartan group.

## Discussion

In summary, the results of ELITE II, involving over 3000 patients, demonstrate that patients with CHF treated with captopril versus losartan have comparable mortality rate, incidence of sudden death, and resuscitated arrests, all-cause hospitalizations, as well as CHF-related events. Patients treated with losartan, however, experience less adverse effects compared to those treated with captopril. One can therefore conclude from the results of ELITE II that the ARB losartan is *not* superior to the ACE inhibitor captopril in reducing total mortality in patients with CHF. It should be noted, however, the study was not powered formally to detect equivalence. Results of ELITE II also refute the unexpected

**Table 4. Secondary and other outcomes**

| | Captopril (n=1574) | Losartan (n=1578) | RR (95% CI) | p |
|---|---|---|---|---|
| Sudden death/resuscitated arrests | 115, 7.3% | 142, 8.9% | 0.80 (0.63,1.03) | 0.08 |
| All cause mortality/hospitalization | 707, 44.9% | 752, 47.7% | 0.94 (0.85,1.04) | 0.21 |

observations of ELITE of a beneficial effect of losartan on mortality, underscoring the severe limitations in interpreting the results of trials with small sample size and short duration of follow-up. The positive interaction with the use of ß-blockers favoring captopril is open to interpretation.[7,8] However, extreme caution should be exercised in interpreting these data since the number of patients taking ß-blockers at the time of randomization was very small, ie, <24%. At this time, only the baseline and key outcome data of ELITE II have been presented and additional data, such as dosing information pre- and post- randomization, further subgroup data, as well as data from the neurohormone and Holter monitoring substudies, are forthcoming. In this regard, some of the theoretical and yet clinically unproven differences between ARBs and ACE inhibitors are listed in Table 1. Hopefully, forthcoming data from the substudies will address some of these issues, while providing mechanistic insights to the results of ELITE II.

The superior tolerability of losartan over captopril demonstrated in ELITE II is consistent with previous observations from patients with hypertension and CHF.[5,10] Indeed, the favorable side effect profile of losartan documented from a large number of patients in ELITE II will provide reassurance to clinicians when faced with the decision to prescribe an alternative agent to intervene the renin-angiotensin system in patients with CHF who are intolerant to ACE inhibitors.

Although the ELITE II study suggests that monotherapy with an ARB is no better than monotherapy with an ACE inhibitor, preliminary data suggest that combination therapy with an ARB and an ACE inhibitor may be beneficial in patients in CHF.[11] This pharmacologic approach is currently under active investigation in two multicenter trials, the Valsartan Heart Failure Trial (Val-HeFT) and the Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity (CHARM) study.

What are the clinical implications of the ELITE II study? Considering the well-documented benefits of ACE inhibitors in patients with CHF,[1,2] ACE inhibitors should remain the treatment of choice in patients with CHF. None of the ARBs are at present approved for the treatment of heart failure. However, in patients who are intolerant to ACE inhibitors, the results of ELITE II indicate that they would likely benefit from an ARB with cardioprotective effects comparable to the ACE inhibitors and with an acceptably low incidence of side effects.

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