

Comparative Effects of ACE Inhibitors and Angiotensin II Receptor Blocking Agents on Left Ventricular Volumes in Elderly Patients with Heart Failure

Based on a presentation by Marvin A. Konstam, MD

Presentation Summary

A radionuclide ventricular function substudy of the Evaluation of Losartan in the Elderly (ELITE) trial was undertaken to compare the effects of captopril, an angiotensin converting enzyme (ACE) inhibitor, and losartan, one of the new angiotensin II receptor blocking agents, on the process of ventricular dilatation in elderly patients with heart failure and reduced left ventricular ejection fractions.

The substudy results suggested that both agents prevent left ventricular dilation associated with adverse remodeling, which is seen in patients with heart failure and reduced left ventricular ejection fraction.

As a result, the decreased mortality among heart failure patients observed with losartan in ELITE, the primary study, are likely to be mediated through drug effects that are different from the relative effects on left ventricular remodeling seen in this substudy.

Analysis of the investigation shows that the angiotensin II receptor blocker losartan and angiotensin converting enzyme (ACE) inhibitor captopril both prevent left ventricular dilatation, according to Marvin A. Konstam, MD.

"ACE inhibitors are well-accepted standard therapy for patients with heart failure and a low left ventricular ejection fraction," Dr. Konstam said, "One mechanism for the reduction in mortality and disease progression by ACE inhibitors is likely to be prevention of adverse ventricular remodeling and dilatation," he added.

The rationale for conducting this radionuclide ventricular function

substudy was partly based on previous reports from the Studies of Left Ventricular Dysfunction (SOLVD) investigation, noting that placebo treatment was associated with progressive left ventricular dilatation in patients with left ventricular dysfunction and congestive heart failure. In contrast, treatment with an ACE inhibitor resulted in an early and sustained reduction in left ventricular end diastolic volume.^{1,2}

In this substudy of the ELITE trial, Dr. Konstam and fellow researchers compared the effects of captopril with those of losartan in the process of ventricular dilatation in elderly patients with heart failure and reduced left ventricular ejection fraction.

Study Design

The ELITE trial was a prospective, randomized, double-blind, 48-week investigation that evaluated the safety and efficacy of losartan versus captopril in elderly patients with heart failure and reduced left ventricular ejection fractions. The primary endpoint was the frequency of worsened renal function, as defined by an increase in serum creat-

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inine of at least 0.3 mg/d; other endpoints included treatment discontinuation and death and/or hospital admissions because of heart failure.

The 722 patients included in the primary trial all met the criteria for New York Heart Association functional class II to IV heart failure, had an ejection fraction of 40% or less, and were aged 65 years or older. Patients who had any previous history of ACE inhibitor use were excluded.

After randomization, patients were given 48 weeks of treatment with either captopril, which was titrated up to a target dose of 50 mg three times a day, or losartan, which was titrated up to 50 mg once a day. "Although the primary endpoint of worsened renal function was no different between the two drug groups," Dr. Konstam noted, "losartan was associated with a significant reduction in mortality compared to captopril," Dr. Konstam said.

Thirty-three of the ELITE patients were enrolled in the radionuclide substudy by the principal investigators. Of these, 29 were evaluable; 16 of whom

were randomized to captopril and 13 of whom were randomized to losartan.

Among the substudy patients, the mean age was 72 years, the average baseline ejection fraction was 30%, the majority were men who had an ischemic etiology, and all had either New York Heart Association functional class II or III heart failure. Baseline left ventricular end-diastolic volumes averaged 143 mL/m² for those randomized to receive captopril and 135 mL/m² for those in the losartan group. Dr. Konstam noted that none of the baseline characteristics, including left ventricular end-diastolic volumes, were significantly different between the two treatment groups.

Left and right ventricular volumes were assessed through radionuclide scans that were taken at baseline; during the last, or 48th week, of drug treatment; and again 5 days after treatment was discontinued. The significance of measurements across treatment groups was examined by analysis of covariance with correction for baseline characteristic differences.

Substudy Results

According to Dr. Konstam, "differences between drugs were not statistically significant." Changes in blood pressure and heart rate were minimal in both drug groups, and after 48 weeks of treatment with either agent, the heart rate was reduced by 10 to 12 beats per minute. However, when it was evaluated 5 days after treatment withdrawal, this reduction was slightly diminished.

Left ventricular end-diastolic volume decreased by 12 mL/m² among captopril patients and 7 mL/m² among losartan patients by the last week of treatment. "After discontinuing the study drug for 5 days, there was a detriment in this beneficial change from baseline," Dr. Konstam said, adding that "the increase in end-diastolic volume between study week 48 and the 5-day follow up was significant in those taking losartan." "After drug withdrawal," he continued, "the decrease in end-diastolic volume continued to be significant in the capto-

pril group, but the differences between drugs were not statistically significant," (Table).

"There was a nonsignificant trend toward increased left ventricular ejection fraction with both drugs at 48 weeks, which disappeared after drug withdrawal," Dr. Konstam observed. "Increases in right ventricular ejection fraction reached statistical significance among losartan patients, but this effect diminished after drug discontinuation."

Conclusion

"In elderly patients with heart failure who were treated for 48 weeks, both losartan and captopril reduced heart rate from baseline, and both drugs reduced left ventricular volumes," Dr. Konstam said. "The reduced left ventricular volumes indicate that both agents prevent the progressive left ventricular dilatation seen with placebo in previous studies."

The effect of captopril on left ventricular end-diastolic volume was sustained after drug withdrawal, whereas that of losartan was not, but this improvement did not constitute a statistically significant difference between the two drugs. Losartan also significantly increased right ventricular rejection fraction, but this change was not sustained after drug withdrawal. Reverse remodeling was observed with captopril treat-

Table. Change in Volume from Baseline (mL/m²)

Drug	EDV		ESV	
	48 Weeks	WD	48 Weeks	WD
Losartan (n = 13)	-7.2 ± 2.9*	-2.7 ± 2.7	-6.9 ± 4.7	-2.3 ± 3.9
Captopril (n = 16)	-11.6 ± 2.1†	-7.9 ± 2.2†	-9.4 ± 2.2†	-5.6 ± 2.9‡

*P < 0.05
 †P < 0.005 for change versus B.
 ‡P = 0.07
 Between-drug differences P = NS

ment. Both drugs prevented adverse remodeling.

"These findings indicate that both treatments are effective in preventing left ventricular remodeling," Dr. Konstam noted.

... REFERENCES ...

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