

Losartan versus Captopril in Congestive Heart Failure

Pitt B, Poole-Wilson P, Segal R, et al. Effects of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study Elite II. Lancet 2000;355:1582–7.

Study Overview

Objective. To determine whether losartan is more effective than captopril and is better tolerated in patients with symptomatic congestive heart failure.

Design. Randomized, double-blind controlled trial. Analysis was by intention to treat.

Setting and participants. The study was conducted at 289 medical centers in 46 countries. Subjects aged 60 years or older (85% of the cohort were required to be older than 65 years) were enrolled between June 1997 and May 1998. Patients had to have New York Heart Association (NYHA) class II–IV heart failure, a left ventricular ejection fraction of 40% or less as measured by echocardiogram or radionuclear ventriculography, and be naive to either angiotensin-converting enzyme (ACE) inhibitors or angiotensin II-receptor antagonists. (Certain patients were eligible if they had been only briefly or recently exposed to either agent.) Exclusion criteria were intolerance to ACE inhibitors or angiotensin II-receptor antagonists, systolic blood pressure less than 90 mm Hg or diastolic blood pressure greater than 95 mm Hg, stenotic valvular disease, active myocarditis or pericarditis, recent angioplasty, coronary artery bypass, myocardial infarction (MI), unstable angina, cerebrovascular events, transient ischemic attack (TIA), renal artery stenosis, or creatinine levels greater than 220 μmol .

Intervention. 3152 patients were randomized to receive losartan ($n = 1578$) or captopril ($n = 1574$). After a run-in period of 1 to 28 days, during which a single-blind placebo was administered to stabilize and assess patients and to ensure treatment adherence, patient groups began either losartan 12.5 mg once daily, titrated up to 50 mg (plus captopril-matched placebo), or captopril 12.5 mg 3 times daily, titrated up to 50 mg (plus losartan-matched placebo). Clinical evaluations were performed weekly during the titration phase and every 4 months thereafter. Laboratory assessments were done at 1 month and then every 4 months while patients remained on study drugs. Patients who discontinued treatment were followed up every 4 months, and mortality and morbidity data were collected on these patients until the study ended.

Main outcome measures. The primary endpoint was all-cause mortality; the secondary outcome was the composite of sudden cardiac death or resuscitated cardiac arrest. Other prespecified outcome variables included rate of hospitalization for all causes and for cardiovascular events, such as bypass surgery, acute MI, angina, worsening congestive heart failure, TIA, and stroke; all-cause mortality or all-cause hospital admissions; and all-cause mortality or hospital admissions for heart failure. Medication intolerance and side effects (eg, cough) were also measured. The study was designed to detect a 25% relative reduction in mortality in the group treated with losartan.

Main results. Among the study cohort, median follow-up time was 1.5 years, and only 2 patients were lost to follow-up. Baseline patient characteristics were similar in both groups: 85% of patients were aged 65 years or older, 69% were men, and 79% had a history of ischemic heart disease. Mean left ventricular ejection fraction was 31%.

During the study, there were 280 deaths (17.7%) in the losartan group compared with 250 (15.9%) in the captopril group (95.7% confidence interval [CI], 0.95 to 1.35; $P = 0.16$). The annual average mortality rate was 11.7% in patients taking losartan and 10.4% in patients taking captopril. Mortality was not statistically different among medical centers and geographic regions. The rate of sudden deaths or resuscitated cardiac arrest (9.0% in the losartan group versus 7.3% in the captopril group, $P = 0.08$) as well as total numbers of hospital admissions overall (659 versus 638) and for heart failure (270 versus 293) were similar in both groups. Moreover, no significant difference was seen in the time to first event for the combined endpoint of all-cause mortality or all-cause hospital admissions (hazard ratio, 1.07 [95% CI, 0.97 to 1.19]; $P = 0.18$). Fewer patients in the losartan group (excluding patients who died) had to discontinue treatment because of adverse side effects (9% versus 15%, $P < 0.001$); this result

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included specific drug-related events or cough. The incidence of cough severe enough to warrant discontinuation of therapy was nearly 4% in the captopril group and just over 1% in the losartan group ($P < 0.001$). The frequency of worsening heart failure was similar in both groups (25%).

Conclusion

Losartan was not superior to captopril in improving survival of elderly patients with symptomatic congestive heart failure. Losartan, however, was better tolerated than captopril.

Commentary

This study by Pitt et al is one of the first randomized controlled trials to compare an angiotensin II-receptor antagonist with an ACE inhibitor in patients with symptomatic congestive heart failure. In the original ELITE study, the same authors found that losartan was better tolerated and reduced mortality by 46%; however, mortality was a secondary endpoint and the risk reduction CI was very wide (5% to 69%) [1]. The ELITE II trial was conducted in order to confirm findings from the first trial [2]. Other ongoing studies, such as ValHeFT, CHARM [3], OPTIMAAL [4], and VALIANT [5] are investigating different angiotensin II-receptor antagonists in order to determine the superiority of these agents compared with ACE inhibitors in different types of congestive heart failure (post-MI and non-post-MI). Results from these studies are not yet available.

The strengths of the ELITE II trial were the length of follow-up (1.5 years on average), small number of patients lost to follow-up (only 2), similar baseline characteristics in both treatment groups, and intention-to-treat analysis. One weakness lay in the wide CI (0.95 to 1.35) associated with reduction in mortality. If the value of 1 is crossed, these findings suggest that losartan could be 5% worse than captopril or 35% better. For the outcome of sudden death, there was a trend toward a slightly higher risk of mortality with losartan (8.25% versus 6.4% for captopril), but again with a wide CI that included the value of 1 (1 to 1.69). In addition, a trend toward a higher rate of hospitalization was noted in

the losartan group, although this trend was not statistically significant. It would also have been useful to know more about the “adverse events” that affected study patients, since the authors did not specify types of adverse events besides cough. Further and larger studies are needed before the question of whether angiotensin II-receptor antagonists are indeed better and safer than ACE inhibitors can be determined.

Applications for Clinical Practice

This study is not strong enough to prove that losartan is equivalent to captopril. Thus, until more data are available, ACE inhibitors should remain first-line treatment for patients with congestive heart failure. It seems reasonable to use losartan if a patient develops side effects, like a cough, from an ACE inhibitor. Because other angiotensin II-receptor antagonists have not yet been adequately tested, they should not be assumed to be equivalent to losartan.

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