The Effect of ACE Inhibitors on Cardiovascular Morbidity and Mortality

Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomized trial. Lancet 1999; 353:611-6.

Clinical question **Do angiotensin-converting enzyme (ACE) inhibitors decrease the cardiovascular morbidity and mortality in hypertensive patients as compared with standard therapy of β-blockers or diuretics?**

Background On the basis of patient-oriented evidence that matters, the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommended that patients with uncomplicated hypertension be treated with a β-blocker or diuretic first line and moved ACE inhibitors to second-line treatment.[1] More recent data from the Appropriate Blood Pressure Control in Diabetes (ABCD) trial demonstrated decreased myocardial infarctions over a 5-year period with enalapril as compared with nisoldipine in patients with hypertension and type 2 diabetes.[2] This study was designed to determine whether captopril decreases cardiovascular morbidity and mortality to the same extent as diuretics or β-blockers in patients with essential hypertension.

Population studied The study enrolled 10,985 men and women with an average age of approximately 52 years. The average blood pressure at baseline was 160 over 100. The race of the patients was not stated, but probably almost all were white (the study was performed in Sweden and Finland). Patients were excluded if they had secondary hypertension, a serum creatinine concentration greater than 1.7 mg per dL, or disorders that required treatment with a β-blocker.

Study design and validity This was a multicenter (536 centers) prospective randomized open trial with blinded end points. The investigators and patients were not blinded to treatment; however, a blinded committee evaluated study end points. After enrollment, patients were randomly assigned to receive either captopril 50 mg daily given in 1 or 2 doses or conventional antihypertensive treatment with diuretics (hydrochlorothiazide 25 mg or bendrofluazide 2.5 mg once daily), β-blockers (most common were atenolol or metoprolol 50-100 mg once daily), or a combination of a diuretic and a β-blocker. Treatment was titrated to a goal diastolic blood pressure of 90 mm Hg or less. To reach this goal, captopril was increased to 100 mg once or twice daily. A calcium-channel blocker could be added to either treatment group. Baseline systolic and diastolic pressures were higher in the captopril group than in the conventional treatment group, both for previously untreated patients and those already receiving anti-hypertensive treatment. Analysis was by intention to treat, and patients were monitored for an average of approximately 6 years.

Outcomes measured The primary end point was a composite of cardiac events: fatal and nonfatal myocardial infarction, stroke, and other cardiovascular deaths. Secondary end points were new or deteriorated ischemic heart disease, congestive heart failure, atrial fibrillation, diabetes, transient ischemic attacks, and death from all causes.

Results The primary outcome of "all cardiac events" was not different between the 2 groups (3.9% vs 4.1%). The likelihood of a fatal cardiovascular event or any myocardial infarction was not different with captopril or conventional therapy. Fatal and nonfatal strokes were slightly more common in the captopril-treated group (193 vs 149, $P = .044$), though the difference probably is not clinically relevant. Mortality rates did not differ between the 2 groups.

Patients in the captopril group developed new diabetes at a significantly lower rate than with conventional therapy. The investigators separately analyzed the patients who had diabetes at the start of the trial (n = 572). Captopril was more effective than conventional therapy with regard to the primary end point, any myocardial infarction, and all fatal events.

Recommendations for clinical practice **This paper lends important evidence to what many have felt for some time: ACE inhibitors are appropriate for first-line therapy of hypertension. A higher baseline blood pressure and a longer time to achieve goal in the captopril group may explain the small increase in stroke observed in the study. This increase was offset by nonsignificant increases in other cardiovascular end points in the conventional group, rendering overall cardiovascular outcomes and total mortality not different. Additionally, significantly fewer patients developed diabetes in the captopril group. Captopril may be expected to offer hypertensive patients benefits similar to treatment with β-blockers and diuretics.**

David Hachey, PharmD
Rex W. Force, PharmD
Idaho State University
Pocatello
E-mail: force@otc.isu.edu

REFERENCES

1. Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). Arch Intern Med 1997; 157:2413-46.
2. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med 1998; 338:645-52.

Salmeterol for Nocturnal Asthma

Lockey RF, DuBuske LM, Friedman B, Petrocella V, Cox F, Rickard K. Nocturnal asthma: effect of salmeterol on quality of life and clinical outcomes. Chest 1999; 115:666-73.

Clinical question **Does salmeterol (Serevent) improve quality of life and clinical outcomes in patients who have moderate asthma with nocturnal symptoms?**

Background Patients who have asthma with nocturnal symptoms have poor sleep quality and decreased daytime cognitive function compared with healthy patients. Many recent clinical trials evaluating specific treatment interventions have included tools assessing quality-of-life parameters in addition to measuring objective outcomes. This trial was designed to study the effect of the long-acting β-agonist salmeterol on quality-of-life and clinical outcomes of patients with asthma.

Population studied A total of 474 patients with asthma were recruited from US specialty clinics. All subjects had a forced expiratory volume in 1 second (FEV_1) of 40% to 80% of predicted norms, documented semireversible airway obstruction, nocturnal symptoms, and a decrease in waking peak expiratory flow (PEF). All of the subjects used inhaled albuterol as needed. In addition, 112 regularly took theophylline, and 301 regularly used inhaled corticosteroids. Patients were excluded if they were pregnant or lactating, were ill, used another long-acting β-agonist, were on controller medications other than theophylline or inhaled corticosteroids, or had recent controller medication dosage changes. The mean age was 39 years (range = 12 to 76 years).

Study design and validity This was a randomized double-blinded placebo-controlled multicenter clinical trial. Subjects were randomly assigned to receive either inhaled salmeterol 42 µg twice daily or inhaled placebo twice daily while continuing their prestudy medications. They were instructed to keep diaries documenting albuterol use and frequency of nighttime asthma-related awakenings. They were also asked to rate their asthma symptoms. Baseline asthma quality-of-life questionnaire, FEV_1, and PEF data were collected. Subjects were evaluated at 4, 8, and 12 weeks using questionnaire scores, pulmonary function tests, and diary review. Those experiencing an exacerbation during the study were treated at the discretion of the investigators. Data were analyzed on an intention-to-treat basis.

Outcomes measured Outcomes measured included questionnaire scores, FEV_1, PEF, nighttime awakenings, asthma symptoms, and supplemental albuterol use.

Results The treatment groups were similar at baseline. Both treatment groups showed significant improvement in their asthma quality-of-life scores compared with baseline ($P \leq .001$). However, improvement in the salmeterol group was significantly greater than in the placebo group ($P \leq .005$). The PEF measurements of the salmeterol group were significantly improved compared with placebo at all intervals ($P \leq .002$). At 8 and 12 weeks, FEV_1 measurements in the salmeterol group were significantly improved compared with placebo ($P \leq .004$). By week 12, the salmeterol group had 49% less asthma-related awakenings from baseline compared with a 21% decrease in these events in the placebo group ($P < .001$; number needed to treat [NNT] = 3.6). Also by week 12, salmeterol had significantly reduced mean daytime symptom scores by 50% from baseline; the placebo group had a 26% reduction in these scores ($P < .001$). The number of subjects experiencing an asthma exacerbation was significantly higher in the placebo group than with the salmeterol group (30% vs 20%, respectively; $P = .02$; NNT = 10). Rates of study withdrawal due to adverse events were similar: 6% in the placebo group and 4% in the salmeterol group. Insomnia (2%) and headache (2%) were reported separately by patients in the salmeterol group compared with 0% for each in the placebo group. This difference did not reach statistical significance.

Recommendations for clinical practice **Adding salmeterol to the treatment regimen of clinically stable adolescents and adults with moderate asthma experiencing nocturnal symptoms significantly improves self-reported asthma-related quality-of-life scores and clinical outcomes. These results support the National Institutes of Health's current asthma guidelines. The guidelines encourage physicians to add long-acting bronchodilators to the treatment regimen of patients with moderate asthma who are already taking anti-inflammatory medication and continue to have daytime or nighttime symptoms.[1] Clinicians should anticipate future studies comparing long-acting inhaled β-agonists in**