ACE inhibitor or a β-blocker, the two mainstays of heart failure treatment, can be started in either order and be safe and effective, according to results from more than 1,000 patients.

Until now, treatment of patients with heart failure usually began with an ACE inhibitor or an angiotensin-receptor blocker, primarily for historic reasons: ACE inhibitors were proven effective for treating heart failure first. But results from a head-to-head trial now show that both options are equivalent. An ACE inhibitor or a β-blocker can be started first, followed by the other drug, and patients have similar outcomes, Ronnie Willenheimer, M.D., reported at the annual congress of the European Society of Cardiology.

The study was designed to change practice. The data support using a β-blocker first in selected patients, commented Kenneth Dickstein, M.D., a cardiologist at the University of Bergen (Norway). "It remains a clinical question [as to] who should get a β-blocker first and who should first get an ACE inhibitor or angiotensin-receptor blocker."

"The results suggest free choice. A physician can start treatment based on individual judgment of each patient," said Dr. Willenheimer, a cardiologist at Universitet Hospital Malmo (Sweden). "For patients with tachycardia or ischemic cardiomyopathy, I'd start with a β-blocker," he told this newspaper.

Dr. Willenheimer has received honoraria from the German division of Merck, which sponsored the study and markets a formulation of the β-blocker bisoprolol (Concor) that is approved in the United States for treating heart failure. In the United States, generic bisoprolol and its trade formulation (Zebeta) are approved only for treating hypertension. β-Blockers approved for treating heart failure are carvedilol (Coreg) and metoprolol succinate (Toprol XL).

The study enrolled 1,010 patients aged 67 years or older (the mean age was 72 years) with New York Heart Association class II to IV heart failure in 20 countries. Their average left ventricular ejection fraction was 29%. Patients were randomized to start treatment with either 1.25 mg of bisoprolol once daily or 2.5 mg of the ACE inhibitor enalapril (Vasotec) once daily. The bisoprolol dosage was increased every 2 weeks until the bisoprolol dosage was 10 mg once daily or the enalapril dosage was 10 mg b.i.d. Monotherapy was continued to a total duration of 6 months, after which the second drug was begun with a similar up-titration scheme. Patients were followed for an average of 1.2 years.

By all efficacy measures used, the bisoprolol-first strategy was not inferior to the enalapril-first regimen. The study's primary end point was the time to first all-cause death or all cause hospitalization. Follow-up on an intention-to-treat basis, these events occurred in 33.2% of the bisoprolol-first patients and 38.8% of those in the enalapril-first arm. On a per-protocol basis, the event rates were 32.4% in the bisoprolol-first patients and 33.1% in the enalapril-first group (Circulation 2005;112:2426-35).

The incidence of treatment-related adverse events was also similar in both groups. However, in patients treated with bisoprolol first, the results showed a trend toward an improved survival benefit and a trend toward a higher frequency of worsening heart failure requiring hospitalization, especially early in the study.

These findings are probably class effects, Dr. Willenheimer said. In both treatment groups, the drug that was started first was lowest in patients with mild renal dysfunction at baseline, de- creased of 0.12 mg/dL and 0.07 mg/dL, respectively. Mean baseline brain natriuretic peptide level was 640 pg/mL for the nesiritide group and 538 pg/mL for the control group.

A patient can start treatment based on individual judgment of each patient.

**A** **physician can start treatment based on individual judgment of each patient.**

**DR. WILLENHEIMER**

By all efficacy measures used, the bisoprolol-first strategy was not inferior to the enalapril-first regimen. The study’s primary end point was the time to first all-cause death or all cause hospitalization. Follow-up on an intention-to-treat basis, these events occurred in 33.2% of the bisoprolol-first patients and 38.8% of those in the enalapril-first arm. On a per-protocol basis, the event rates were 32.4% in the bisoprolol-first patients and 33.1% in the enalapril-first group (Circulation 2005;112:2426-35).

The incidence of treatment-related adverse events was also similar in both groups. However, in patients treated with bisoprolol first, the results showed a trend toward an improved survival benefit and a trend toward a higher frequency of worsening heart failure requiring hospitalization, especially early in the study.

These findings are probably class effects, Dr. Willenheimer said. In both treatment groups, the drug that was started first was lowest in patients with mild renal dysfunction at baseline, decreased of 0.12 mg/dL and 0.07 mg/dL, respectively. Mean baseline brain natriuretic peptide level was 640 pg/mL for the nesiritide group and 538 pg/mL for the control group.

By all efficacy measures used, the bisoprolol-first strategy was not inferior to the enalapril-first regimen. The study’s primary end point was the time to first all-cause death or all cause hospitalization. Follow-up on an intention-to-treat basis, these events occurred in 33.2% of the bisoprolol-first patients and 38.8% of those in the enalapril-first arm. On a per-protocol basis, the event rates were 32.4% in the bisoprolol-first patients and 33.1% in the enalapril-first group (Circulation 2005;112:2426-35).

The incidence of treatment-related adverse events was also similar in both groups. However, in patients treated with bisoprolol first, the results showed a trend toward an improved survival benefit and a trend toward a higher frequency of worsening heart failure requiring hospitalization, especially early in the study.

These findings are probably class effects, Dr. Willenheimer said. In both treatment groups, the drug that was started first was lowest in patients with mild renal dysfunction at baseline, decreased of 0.12 mg/dL and 0.07 mg/dL, respectively. Mean baseline brain natriuretic peptide level was 640 pg/mL for the nesiritide group and 538 pg/mL for the control group.