Higher Losartan Dose Better for Heart Failure

BY MITCHEL L. ZOLER

ORLANDO — A 150-mg/day dosage of losartan was better for preventing events in heart failure patients than was the conventional, 50-mg/day dosage in a randomized comparison involving nearly 4,000 patients followed for more than 4 years. The finding immediately created a new, standard losartan dosage for these patients, experts said.

The higher dosage also led to no significant increase in patients' stopping therapy because of adverse events, compared with the lower dosage.

"In patients with heart failure, reduced left ventricular ejection fraction, and angiotensin converting enzyme inhibitor intolerance, incremental value is derived from up-titrating angiotensin receptor blocker doses," Dr. Marvin A. Konstam said at the annual scientific sessions of the American Heart Association.

MITCHEL L. ZOLER/ELSEVIER GLOBAL MEDICAL NEWS

"If you up-titrate to 150 mg/day you're going to get better outcomes," Dr. Marvin A. Konstam said.

"If a clinician is using losartan to treat patients with heart failure, he or she must know that if you up-titrate to 150 mg/day you're going to get better outcomes," he said.

Experts agreed that the finding should be applied in practice immediately.

"All [heart failure] patients on losartan today need to be reevaluated and probably up-titrated to the high dose," said Dr. Karl Swedberg, professor of medicine at Göteborg (Sweden) University, who was not involved in the study. "Symptom improvement is not a surrogate for life prolongation. There is no way around it; if you want to give the best care for a patient you should up-titrate the dose."

This message was viewed as especially important because many heart failure patients receive inappropriately low doses of the drugs that inhibit the renin-angiotensin system: ACE inhibitors and angiotensin-receptor blockers (ARBs).

"Physicians now do not prescribe anything close to the target doses" of ACE inhibitors and ARBs, said Dr. Milton Packer, professor of medicine at the University of Texas Southwestern Medical Center in Dallas.

"In the study [reported by Dr. Konstam], the biggest difference [from the higher, 150-mg/day dosage] appeared to be in the patients with class I or II heart failure. These are the very patients in whom we don't up-titrate the doses" right now, said Dr. John G.F. Cleland, a professor of medicine at the University of Hull, England.

The Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan (HEAAL) trial enrolled patients with symptomatic, New York Heart Association class II-IV heart failure who had a left ventricular ejection fraction of 40% or less. All enrolled patients had to have known intolerance to ACE inhibitors. Patients enrolled at 255 sites in 30 countries during November 2001–March 2005. Their average age was 66 years, 70% were men, 60% were white and 22% were Asian. Patients had to be on a stable drug regimen, and most were on current standard therapy, including 72% on a beta-blocker and 38% on an aldosterone blocker; 70% had class II heart failure and 30% had class III. Randomization assigned 1,921 patients to the 150-mg/day dosage and 1,913 to the 50-mg/day regimen.

After a median follow-up of 4.7 years, the incidence of the primary end point, death or hospitalization for heart failure, occurred in 43% of patients on the higher dose and 46% on the lower dose, a 3% absolute difference that was statistically significant, reported Dr. Konstam, professor of medicine and director of the cardiovascular center at Tufts University in Boston. Concurrently with his re-

port at the meeting, the results appeared in an article published online (Lancet 2009 Nov. 17 [doi:10.1016/S0140-6736(09)61913-9]).

The incremental benefit from the 150-mg/day dosage means that treating 31 patients at the higher dose for 4 years would prevent one episode of death or hospitalization. Prespecified subgroup analyses showed that the higher dosage was usually more effective across all 38 subgroups analyzed. When the 150-mg dosage was not better it was at least as good as the lower dosage.

The most common adverse event was renal impairment, which occurred in 7% of patients on the 150-mg/day dosage and 5% of those on the lower dosage. Other relatively common adverse events were hypotension (in 3% and 2% respectively), and hyperkalemia (also in 3% and 2% respectively). But the rate of study discontinuations for these events was not significantly different between the two treatment arms. The stoppages for renal impairment were 0.65% in the high-dosage arm and 0.49% in the lower-dosage group.

"We're talking about incremental inhibition of the renin-angiotensin system. In the [drug] ranges looked at, more seems to be better. Physicians have to prescribe at the dose that's been shown to have clinical efficacy," Dr. Konstam said. The HEAAL study is the first investigation of the dose-response of an ARB using clinical outcomes in heart failure patients, and one of the few dose comparisons using clinical outcomes for any cardiovascular drug, he added.

"All these patients [with heart failure] have a very active renin-angiotensin system. That's the rationale for blocking it better," said Dr. Swedberg.

Both he and Dr. Konstam also stressed that when treating heart failure this message can probably extend to all ARBs: The highest safe dosages of all drugs in the class probably work best for heart failure patients.

The HEAAL study was sponsored by Merck, which markets losartan (Cozaar). Dr. Konstam has served as a consultant to, and received research support from, Merck. Dr. Swedberg has received research support from Merck and other drug companies, has received honoraria from AstraZeneca and Novartis, and has been a consultant to Novartis. ■