

NATIONAL PBM COMMUNICATION • October 31, 2011

Target Dose of Angiotensin II Receptor Antagonists in Patients with Heart Failure

- When using losartan or valsartan for the treatment of heart failure (HF), it is recommended that patients be titrated to target doses (i.e., losartan 150 mg daily; valsartan 160 mg twice daily), whenever possible.
- In an analysis of HF registry data of 5139 patients in Sweden, those treated with candesartan, had improved survival compared to patients who received losartan: 1 year survival 90% vs. 83%, 5 year survival 61% vs. 44%, respectively; hazard ratio [HR] 1.43 95% CI 1.23 to 1.65; P<0.001). (1)
 - However, at the time of establishing the registry, the target dose of losartan was 50 mg daily whereas the current target dose in HF is 150 mg daily. The target dose for candesartan was 32 mg daily, similar to the current recommendation.
 - Very few patients (18%) were at more than 50% of the currently recommended target dose for losartan (i.e., 150 mg daily) whereas about a third reached a similar level for candesartan. (1)
- The losartan target dose of 150 mg daily in patients with HF is based on results of the Heart Failure endpoint Evaluation with the Angiotensin II Antagonist Losartan (HEAAL) study. This study compared losartan 50 mg with losartan 150 mg daily, with the primary endpoint of all-cause mortality and HF hospitalizations in 3846 patients with HF and a left ventricular ejection fraction (LVEF) < 40% who were intolerant to an angiotensin-converting enzyme inhibitor (ACEI) (86% reported intolerance due to cough). Seventy-two percent of patients received concomitant treatment with a beta-adrenergic blocker. After a median of 4.7 years of follow-up, treatment with losartan 150 mg (mean 129±39 mg) resulted in a 10% decrease in the risk for death or HF hospitalization compared to patients on losartan 50 mg (mean 46±11 mg) (losartan 150 mg 43.0% vs. losartan 50 mg 46.3%; HR 0.90 95% CI 0.82-0.99; P=0.027). Hyperkalemia, hypotension, kidney impairment, and angioedema all occurred more frequently in the losartan 150 mg treatment group compared to the 50 mg dose, with no difference in discontinuations due to these adverse events. (2)
- Review of the above data prompted an evaluation of data in VA patients with HF to identify if there was a potential gap in the recommended target dose and the prescribed dose of angiotensin II receptor antagonists used in the management of HF.
- According to VA data from 1/1/2011 to 3/31/2011, approximately 14,500 patients with a diagnosis of systolic HF were being treated with losartan, with 44% prescribed ≥ 50% of the target dose of 150 mg, and an average daily dose of 66 mg. During this same timeframe, approximately 10,600 patients with HF were treated with valsartan, with 51% prescribed ≥ 50% of the target dose of 320 mg (recommended 160 mg twice daily), and an average daily dose of 156 mg. Data with candesartan are not provided due to low utilization in VA.
- Losartan is not currently FDA approved for use in HF, and the target dose of 150 mg that was studied in the HEAAL trial is higher than the maximum recommended dose used for other indications (e.g., hypertension). Losartan is available in 25 mg, 50 mg and 100 mg tablets. Of the other available angiotensin II receptor antagonists, valsartan and candesartan are FDA approved for the treatment of HF.
- Losartan is available on the VA National Formulary (VANF). Valsartan is also available on the VANF, restricted to treatment of patients with systolic HF. VA National Clinical Recommendations for the use of the angiotensin II receptor antagonists are available on the PBM Web sites (www.pbm.va.gov and <http://vawww.pbm.va.gov>). Patients with systolic HF should receive an ACEI, beta-adrenergic blocker, diuretic, and aldosterone antagonist, as indicated. In some patients (e.g., African-Americans) hydralazine/nitrates may be appropriate as well. An angiotensin II receptor antagonist may be considered in patients with systolic HF who are intolerant to an ACEI.
- **Recommendation:** When using losartan or valsartan for the treatment of HF, it is recommended that patients be titrated to target doses (i.e., losartan 150 mg daily; valsartan 160 mg twice daily), whenever possible.

REFERENCES

1. Eklind-Cervenka M, Benson L, Dahlström U, et al. Association of candesartan vs losartan with all-cause mortality in patients with heart failure. JAMA 2011;305:175-82.
2. Konstam MA, Neaton JD, Dickstein K, et al., for the HEAAL Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomized, double-blind trial. Lancet 2009;374:1840-8.

ACTIONS

- **Facility Director (or physician designee):** Forward this document to the Facility Chief of Staff (COS).
- **Facility COS and Chief Nurse Executives:** Forward this document to all appropriate providers who prescribe these medications (e.g., cardiologists, primary care providers and clinic staff, including contract providers, etc.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.
- **ACOS for R&D:** Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).