Candesartan Therapy Hikes Hyperkalemia Risk

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ATLANTA — Candesartan therapy triples the already significant background risk of potentially serious hyperkalemia in patients with heart failure, according to a new secondary analysis of the Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity (CHARM) program.

Periodic monitoring of serum potassium is therefore "critical" in heart failure patients—and not just those on candesartan, Dr. Akshay Desai said at the annual meeting of the American College of Cardiology. "The estimate from our study would be that one would expect roughly 34 excess hyperkalemic events per 1,000 candesartan-treated patients over 3 years. However, with careful surveillance of serum potassium this risk can be substantially reduced. In the trial, seven excess serious events per 1,000 patients were noted over the 3-year duration of follow-up with careful monitoring by study investigators. We feel that this represents the unavoidable risk of candesartan therapy in this population of patients," said Dr. Desai of Brigham and Women's Hospital, Boston.

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The CHARM program involved 7,599 heart failure patients on standard therapy who were randomized in double-blind fashion to candesartan or placebo and followed for just over 3 years with regular monitoring of serum potassium. Candesartan resulted in a significant 16% reduction in the relative risk of the primary end point of cardiovascular death or heart failure hospitalization.

Hyperkalemia is well known to be a potentially life-threatening complication of treatment with renin-angiotensin-aldosterone system inhibitors. CHARM investigators categorized hyperkalemic events as "serious" if they posed a risk of death or hospitalization, and "concerning" if events were serious or would have become so if not detected early through the monitoring program, with subsequent dose adjustment or drug discontinuation.

The incidence of concerning hyperkalemia during the study was 1.8% in the placebo arm and 5.2% in the candesartan group. Serious hyperkalemic events occurred in 1.1% of the placebo group and 1.8% on candesartan. Of particular clinical relevance was the finding that hyperkalemic events were not confined to the period of candesartan dose titration; they occurred throughout follow-up, although the incidence was greater during titration, Dr. Desai continued.

Several predictors of increased background risk of concerning hyperkalemia were identified. Age greater than 75 years, being on an ACE inhibitor or spironolactone, or a history of diabetes was associated with roughly a twofold increased risk. Baseline renal insufficiency or hyperkalemia conferred a fivefold spike in risk. Candesartan therapy was associated with a threefold increase in risk of hyperkalemia, compared with placebo—but the drug's therapeutic benefit was also consistent across all patient subgroups, including those at high baseline risk for hyperkalemia. Audience member Dr. Gary S. Francis, director of the coronary intensive care unit at the Cleveland Clinic Foundation, called the new CHARM results "very important data that have practical implications." And he posed a question: "How often should we be monitoring potassium?"

Dr. Desai replied that the monitoring program used in CHARM, while quite effective in preventing serious events, is probably not readily transferrable to a less motivated real-world population.

"What I would suggest is that, particularly in patients at high baseline risk, be quite careful to measure serum potassium within a 2- to 3-week period after every dose titration, and again intermittently—even randomly—over the course of follow-up to be certain we're not doing our patients harm. Exactly what that interval should be is, I think, an open question," Dr. Desai said. ■