Studies examine whether therapies for heart failure are associated with improved survival

November 27 2012

An analysis of two heart failure therapies finds differing outcomes regarding improvement in survival, according to two studies appearing in the November 28 issue of *JAMA*.

In one study, Adrian F. Hernandez, M.D., M.H.S., of the Duke Clinical Research Institute, Durham, N.C., and colleagues examined the clinical effectiveness of aldosterone antagonist therapy and associations with long-term outcomes of older patients discharged from a hospitalization for heart failure.

"Aldosterone antagonist therapy [a diuretic drug] for heart failure and reduced ejection fraction [a measure of how well the left ventricle of the heart pumps with each contraction] has been highly efficacious in randomized trials. However, questions remain regarding the effectiveness and safety of the therapy in clinical practice," according to background information in the article.

The researchers examined outcomes of eligible patients hospitalized with heart failure and reduced ejection fraction using clinical registry data linked to Medicare claims from 2005 through 2010. The primary outcomes measured for the study were all-cause mortality, cardiovascular readmission, and heart failure readmission at 3 years, and readmission associated with hyperkalemia (higher than normal levels of potassium in the circulating blood) at 30 days and 1 year.

Of the 5,887 patients (average age, 78 years) who met the inclusion

criteria from 246 hospitals, 1,070 (18.2 percent) received a prescription for an aldosterone antagonist at hospital discharge. The researchers found that rates of all-cause mortality (49.9 percent vs. 51.2 percent) and cardiovascular readmission (63.8 percent vs. 63.9 percent) were similar between the treatment groups at 3 years. The cumulative incidence rates of arrhythmia (5.4 percent vs. 3.9 percent) and elective readmission for an arrhythmia control device (6.5 percent vs. 4.2 percent) were higher for the treated group. Analysis of the data indicated that there were no significant differences in mortality and cardiovascular readmission.

The authors also found that the cumulative incidence of the first heart failure readmission was significantly lower in the treated group (38.7 percent vs. 44.9 percent). The hyperkalemia readmission rates at 30 days (2.9 percent vs. 1.2 percent) and 1 year (8.9 percent vs. 6.3 percent) were higher in the treated group; however, hyperkalemia was seldom the primary diagnosis for these readmissions, and the absolute increase in hyperkalemia as a primary diagnosis was small.

The authors add that a potential explanation for their findings is that aldosterone antagonists have limited effectiveness regarding mortality in real-world settings among older patients. "One potential reason for limited effectiveness may be a lack of adherence to or persistence with therapy. … Our findings highlight the importance of conducting clinical trials that can be easily generalized to real-world practice and in which the most vulnerable patient groups are well represented."

Use of ACE Inhibitors, ARB's, Associated With Improved Survival Among Certain Patients With Heart Failure

In another study, Lars H. Lund, M.D., Ph.D., of the Karolinska Institutet, Stockholm, Sweden, and colleagues conducted a study to

examine whether renin-angiotensin system (RAS) antagonists (i.e., angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs] are associated with reduced mortality in heart failure patients with preserved ejection fraction.

"Up to half of patients with heart failure have normal or near-normal ejection fraction, termed heart failure with preserved ejection fraction (HFPEF) or diastolic heart failure. The mortality in HFPEF may be as high as in heart failure with reduced ejection fraction (HFREF) or systolic heart failure, but there is no proven therapy," according to background information in the article.

The study included 41,791 patients in the Swedish Heart Failure Registry, from 64 hospitals and 84 outpatient clinics between 2000 and 2011. Of these, 16,216 patients with HFPEF (ejection fraction of 40 percent or greater; average age, 75 years; 46 percent women) were either treated (n = 12,543) or not treated (n = 3,673) with RAS antagonists. Analyses was conducted of the data to determine the association between use of RAS antagonists and all-cause mortality, with use of a matched cohort. The researchers included 20,111 patients with ejection fraction of less than 40 percent for the HFREF consistency analysis.

In the overall HFPEF group, crude 1-year survival was 86 percent for patients receiving RAS antagonists vs. 69 percent for patients not receiving RAS antagonists; and 5-year survival was 55 percent vs. 32 percent, respectively. In the matched HFPEF cohort, 1-year survival was 77 percent for treated patients vs. 72 percent for untreated patients. Five-year survival was 36 percent vs. 34 percent, respectively.

"There is currently no consensus on the use of RAS antagonists in patients with HFPEF. In our study, use of RAS antagonists was associated with reduced all-cause mortality in a broad unselected population of patients with HFPEF. Our results together with the signal

toward benefit in randomized controlled trials suggest that RAS antagonists may be beneficial in patients with HFPEF, but this should be confirmed in an appropriately powered randomized trial," the authors conclude.

Editorial: Heart Failure Therapy - What Should Clinicians Believe?

In an accompanying editorial, James C. Fang, M.D., of University Hospitals Case Medical Center, Cleveland, examines the question of what physicians should conclude from these 2 observational studies that would appear to contradict the clinical trial evidence.

"If all of the evidence is carefully considered in its totality, it would be sound to conclude that (1) renin-angiotensin system antagonists are reasonable agents to control hypertension in heart failure with preserved ejection fraction, and (2) aldosterone antagonists are effective drugs in heart failure with reduced ejection fraction but should be used carefully and selectively. Although clinical trials should remain the gold standard for testing hypotheses, observational studies bridge the gap from the scientific rigor of clinical trials to real-world experience. Clinical trials are a reminder of the rigor of medicine as a science; observational studies are a reminder that medicine is still an art."

More information: JAMA. 2012;308(20):2097-2107
JAMA. 2012;308(20):2108-2117
Editorial: *JAMA*. 2012;308(20):2144-2146