

Journal View

New Combination Improves Heart Failure Outcomes

A new product combining an angiotensin-receptor blocker (ARB) and a neprilysin inhibitor lowers mortality and hospitalization rates in patients with heart failure, compared with enalapril, concludes a trial in the *New England Journal of Medicine*.

The PARADIGM-HF trial enrolled 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40 percent or less. The patients were randomly assigned to treatment with LCZ696, consisting of the neprilysin inhibitor sacubitril and the ARB valsartan, 200 mg twice daily, or the angiotensin-converting enzyme inhibitor enalapril, 10 mg twice daily. Study medica-

tions were given in addition to recommended therapy. The main outcome of interest was a composite of cardiovascular death and heart failure hospitalization.

The study was halted early at a median follow-up time of 27 months, with evidence of “overwhelming benefit” in the LCZ696 group. The rates of the primary outcome were 21.8 percent with LCZ696 versus 26.5 percent with enalapril: hazard ratio (HR) 0.80 in the LCZ696 group.

All-cause mortality was 17.0 percent with LCZ696 and 19.8 percent with placebo, HR 0.84. The rates of death resulting from cardiovascular causes were 13.3

percent and 16.5 percent, respectively, HR 0.80. Treatment with LCZ696 was also associated with a reduced risk of heart failure hospitalization, HR 0.79. There was also significant improvement in heart failure–related symptoms and physical limitations, with about a 1-point difference in clinical summary score on the Kansas City Cardiomyopathy Questionnaire. LCZ696 was associated with higher rates of hypotension and nonserious angioedema but with lower rates of renal impairment, hyperkalemia, and cough.

Naprilysin inhibition increases levels of endogenous vasoactive peptides, counter-

acting the adverse effects of neurohormonal overactivation. The new study shows significant improvement in morbidity and mortality with LCZ696 in patients with heart failure and reduced ejection fraction, compared with enalapril. The PARADIGM-HF study “provides strong evidence that combined inhibition of the angiotensin receptor and neprilysin is superior to inhibition of the renin-angiotensin system alone in patients with chronic heart failure,” the investigators conclude [McMurray JJ, et al. *Angiotensin-neprilysin inhibition versus enalapril in heart failure*. *N Engl J Med* 2014; 371:993–1004]. ●

Good Outcomes with Blood Pressure Self-Management Program

For primary care patients with hypertension and cardiovascular risk factors, a blood pressure self-monitoring intervention—including self-titration of medications—yields greater reductions in systolic blood pressure at 1 year, concludes a randomized trial in the *Journal of the American Medical Association*.

The Targets and Self-Management for the Control of Blood Pressure in Stroke and at Risk Groups (TASMIN-SR) trial included 552 patients with hypertension, baseline blood pressure 130/80 mm Hg or higher, and a history of stroke, coronary heart disease, diabetes, or chronic kidney disease. The patients were drawn from 59 primary care practices in the United Kingdom. One group received a self-management interven-

tion, in which they self-monitored blood pressure and adjusted their medications according to an individualized self-titration algorithm. The blood pressure targets in the self-management group were office measurements of 130/80 mm Hg and home measurements of 120/75 mm Hg.

The control patients received usual care, with office-based blood pressure measurements and medication changes. Information on changes in blood pressure at 12 months' follow-up were available in 450 patients.

Blood pressure decreased from 143.1/80.5 mm Hg to 128.2/73.8 mm Hg in the self-management group versus 143.6/79.5 mm Hg to 137.8/76.3 mm Hg in the control group. After correction for

baseline values, the study intervention was associated with a reduction of 9.2/3.4 mm Hg in blood pressure. With multiple imputation for missing values, the difference was 8.8/3.1 mm Hg.

The intervention yielded comparable reductions in blood pressure across patient subgroups, and adverse events were similar between the intervention and control groups. Patients in the self-management group had greater increases in antihypertensive drug prescriptions, particularly for calcium channel blockers and thiazides.

A previous trial showed good reductions in systolic blood pressure with self-monitoring and self-titration, but that study included few patients with cardiovascu-

lar disease or other high-risk conditions. The TASMIN-SR trial shows a significant 1-year reduction in systolic blood pressure with the self-management approach in hypertensive patients at high risk of cardiovascular events. Blood pressure self-monitoring with self-titration “is feasible and achievable in a high-risk population without special equipment and by following a modest amount of training and additional family physician input,” the researchers write [McManus RJ, et al. *Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized clinical trial*. *JAMA* 2014; 312:799–808]. ●

What's Behind Rising Rates of Obstetric Renal Failure?

Recent increases in obstetric acute renal failure are limited to women with hypertensive disorders of pregnancy, suggests a report in the *British Medical Journal*.

The retrospective analysis included nearly 2.2 million hospital deliveries in Canada, excluding Quebec, between 2003 and 2010. Based on ICD-10 codes, the rate of obstetric acute renal failure increased by 61 percent during this period: from 1.66 per 10,000 deliveries in 2003 to 2004 to 2.68 per 10,000 in 2009 to 2010. There was also a 21 percent in-

crease in the rate of postpartum hemorrhage, along with a slight increase in risk of hypertensive disorders of pregnancy. However, the temporal trend in renal failure remained significant after adjustment for these and other risk factors.

On further analysis, the increase in obstetric renal failure occurred exclusively in women with hypertensive disorders of pregnancy. This group showed an adjusted increase of 91 percent: from 15.6 to 28.8 per 10,000 deliveries. The trend was even more pronounced among wom-

en who had gestational hypertension with significant proteinuria: adjusted increase 171 percent. Of 58 excess cases of acute renal failure in 2009 to 2010, 47 were in women with hypertensive disorders of pregnancy and 42 in women with gestational hypertension and significant proteinuria.

In both the United States and Canada, the rates of obstetric acute renal failure have increased over the past decade. This large analysis of Canadian data suggests that this trend is limited to women

with hypertensive disorders of pregnancy, with an even sharper increase in the smaller group of women with gestational hypertension and significant proteinuria. These trends raise the possibility that some aspect of preeclampsia management may be leading to an increased risk of obstetric acute renal failure [Mehrabadi A, et al. *Hypertensive disorders of pregnancy and the recent increase in obstetric acute renal failure in Canada: population based retrospective cohort study*. *BMJ* 2014; 349:g4731]. ●

Atypical Antipsychotics Linked to AKI Risk

Older adults taking atypical antipsychotic drugs may be at increased risk of acute kidney injury (AKI), reports a study in the *Annals of Internal Medicine*.

Ontario health data were used to identify 97,777 adults aged 65 or older who received a new outpatient prescription for an oral atypical antipsychotic drug between 2003 and 2012. The drugs of interest were quetiapine, risperidone, and olanzapine. These patients were matched to the same number of control individuals with no

such prescription. The rates of hospitalization for AKI, based on hospital diagnosis codes, within 90 days of the atypical antipsychotic prescription were compared between groups.

The patients prescribed atypical antipsychotics were at significantly increased risk of hospitalization with AKI: relative risk (RR) 1.73. The association remained significant in a subpopulation of patients with available data on serum creatinine levels: AKI risk was 5.46 versus 3.34 percent, for

an absolute risk increase of 2.12 percent. Atypical antipsychotic drugs were also associated with an increased risk of hypotension, RR 1.91; acute urinary retention, RR 1.98; and all-cause mortality, RR 2.39.

Some adverse outcomes associated with atypical antipsychotic drugs, including hypotension, acute urinary retention, and the neuroleptic malignant syndrome or rhabdomyolysis, are known causes of AKI. These population-based data suggest an increased risk of AKI in older adults pre-

scribed atypical antipsychotic drugs.

Atypical antipsychotic drugs are also linked to other adverse outcomes that might explain the increase in AKI. “The findings support current safety concerns about the use of these drugs in older adults,” the investigators conclude [Hwang YJ, et al. *Atypical antipsychotic drugs and the risk for acute kidney injury and other adverse outcomes in older adults: a population-based cohort study*. *Ann Intern Med* 2014; 161:242–248]. ●