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No benefit from addition of aliskiren to 'gold standard' ACE inhibitor

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In one of the largest trials ever conducted in patients who have heart failure with reduced ejection fraction—a measure of the heart's ability to pump blood—the investigational drug aliskiren failed to show superiority over full-dose treatment with the existing "gold standard" therapy, the angiotensin-converting enzyme (ACE) inhibitor enalapril, researchers reported at the American College of Cardiology's 65th Annual Scientific Session.

Aliskiren works by blocking a hormonal system in the body called the renin-angiotensin system (RAS), which has detrimental effects on the heart, blood vessels and kidneys. Previously, the first drugs that blocked RAS, ACE inhibitors, were shown to improve survival and reduce hospital admissions in people with heart failure and reduced ejection fraction. Later studies suggested that adding a second type of drug called an angiotensin receptor blocker (ARB), which interrupts RAS in a different way than an ACE inhibitor, led to even better outcomes for these patients. The present study failed to confirm the benefit of adding a third type of RAS blocker, a direct renin inhibitor, to ACE inhibitor treatment, said John J.V. McMurray, M.D., professor of medical cardiology at the University of Glasgow in the United Kingdom and lead author of the study.

"Aliskiren was not better either when used in combination with enalapril or when used alone in a head-to-head comparison with enalapril," McMurray said. "The primary endpoint was not reduced significantly in either of those comparisons."

The multicenter, randomized, double-blinded ATMOSPHERE trial enrolled 7,016 patients-¬-78 percent male, average age 63—with heart failure whose hearts were unable to pump blood at the normal rate and who had already been treated with enalapril or another ACE inhibitor plus a beta blocker. Patients were not eligible for the study if they had extremely high blood pressure, symptoms of low blood pressure, markedly reduced kidney function, or if they had previously experienced adverse effects when treated with an ACE inhibitor. Study participants were randomly assigned to take enalapril alone, the renin inhibitor aliskiren alone, or both drugs. Neither the patients nor their doctors knew which treatment group patients were assigned to until the end of the trial. The primary endpoint was a composite of death from cardiovascular causes or hospitalization for heart failure.

After a median follow-up time of three and a half years, the rate of death from cardiovascular causes or hospitalization for heart failure was 34.6 percent in the group treated with enalapril alone, 33.8 percent in the group treated with aliskiren alone, and 32.9 percent in the group treated with both drugs. These differences were not statistically significant. Patients in the group that received both drugs were at higher risk for symptoms of low blood pressure compared with those who received enalapril alone, 13.8 percent versus 11 percent, which was a significant difference. Patients in the combination-therapy group were also more likely to experience elevated serum creatinine concentration—4.1 versus 2.7 percent—and elevated potassium concentration—17.1 versus 12.5 percent.

"These are problems you want to avoid," McMurray said. Adverse event rates with aliskiren alone were generally similar to those seen with enalapril alone.

The failure to confirm the beneficial effect of adding aliskiren to an ACE inhibitor may be explained by the fact that, in contrast to the

previous studies with ARBs, in the ATMOSPHERE trial patients assigned to combination therapy received aliskiren on top of a full therapeutic dose of an ACE inhibitor, McMurray said.

"There seems to be a ceiling to the benefit that can be obtained with renin-angiotensin system blockers," he said. "Above a certain level of blockade, there are more adverse effects and no additional benefit. These findings also tell us that it is very hard to improve on the results obtained with ACE inhibitors."

The latter finding, McMurray said, emphasizes the importance of another recent heart failure trial, known as PARADIGM-HF, in which a new combination agent, sacubitril/valsartan, showed superior results to full-dose enalapril. McMurray was the co-principal investigator for PARADIGM-HF.

Taken together, he said, the results of ATMOSPHERE and PARADIGM-HF "suggest that once you have maximized the benefits obtainable with an ACE inhibitor, the only way to further improve outcomes is to switch the patient to sacubitril/valsartan."

A limitation of the ATMOSPHERE trial is that while the trial was underway, European drug regulators ordered that aliskiren be discontinued in all patients with diabetes and that no additional patients with diabetes be enrolled. This action was taken after results from two other trials suggested that patients with diabetes might have worse outcomes when treated with aliskiren plus an ACE inhibitor or ARB. However, in ATMOSPHERE, neither aliskiren alone nor the combination of aliskiren with enalapril was associated with worse outcomes in patients with diabetes, McMurray said.

More information: John J.V. McMurray et al. Aliskiren, Enalapril, or Aliskiren and Enalapril in Heart Failure, *New England Journal of*

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