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HEART FAILURE

ACE inhibitors and ARBs in HFpEF

Renin-angiotensin-system (RAS) inhibitors have proven efficacy in patients who have heart failure with reduced ejection fraction (HFrEF). A registry study has now assessed the use of RAS inhibitors in patients defined as having heart failure with preserved ejection fraction (HFpEF) in a 'real-world' setting. In their study report, published in *JAMA*, the investigators write that "together with the yet greater benefit in [previous] HFrEF studies, [their study] suggests that heart failure may be on a continuous ejection fraction (EF) spectrum, with greater benefit of RAS antagonists the lower the EF".

In the setting of HFpEF, three randomized clinical trials have shown no benefit of angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) in terms of the trials' primary outcomes. However, the trials did provide some indications of benefit. Moreover, the trials have been criticized for selection bias, underpowering, and high crossover rates. A group of investigators from Sweden, therefore, set out to assess whether ACE inhibitors and ARBs are associated with beneficial effects in a 'real-world' population of patients with HFpEF.

Data were assessed for 16,216 patients enrolled in the Swedish Heart Failure Registry and with an EF ≥40% (and, therefore, considered by the investigators to have HFpEF). Of these patients, 56% were using an ACE inhibitor but not an ARB, 20% were using an ARB but not an ACE inhibitor, 2% were using both types of drug, and 23% were using neither of these medications. The investigators assessed data for the full cohort and for an age-matched and propensity-score-matched cohort ($n = 6{,}658$).

In the full cohort, survival was higher in individuals receiving an ACE inhibitor, ARB, or both, than in patients receiving neither of these RAS antagonists (86% vs 69% at 1 year and 55% vs 32% at 5 years; unadjusted HR 0.48, 95% CI 0.45–0.51, $P < 0.001$). A smaller, but statistically significant, difference in survival was noted for the matched cohort (77% for patients taking an ACE inhibitor, ARB, or both, vs 72% for patients taking neither drug at 1 year, and 36% vs 34% at 5 years; HR 0.91, 95% CI 0.85–0.98, $P = 0.008$).

Use of the RAS inhibitors interacted significantly with mean blood pressure. RAS-antagonist-associated mortality benefits were found in the patients with systolic blood pressure <90 mmHg, but not in individuals with systolic blood pressure ≥90 mmHg.

Notably, although the investigators found no statistically significant interaction with EF ($P = 0.12$), they did show that the use of these RAS inhibitors was associated with improved survival among the patients with an EF of 40–49% (HR 0.85, 95% CI 0.76–0.95, $P = 0.004$), but not among those with an EF ≥50% (HR 0.95, 95% CI 0.87–1.04, $P = 0.26$). In the discussion of their findings, the registry investigators point out that "even though EFs of 40% to 49% may not be considered normal, the benefit in this group has not previously been demonstrated".

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In an accompanying editorial in *JAMA*, Dr James Fang from Cleveland, OH, USA writes that "if all the evidence is carefully considered in its totality, it would be sound to conclude that RAS antagonists are reasonable agents to control hypertension in [patients with] HFpEF".

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Original article Lund, L. H. *et al*. Association between use of renin-angiotensin system antagonists and mortality in patients with heart failure and preserved ejection fraction. *JAMA* **308**, 2108–2117 (2012)