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Age-Related Divergence of Risk-Benefit Relationship of Spironolactone Treatment for Heart Failure With Preserved Ejection Fraction*

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Heart failure with preserved ejection fraction (HFpEF) is the most common form of HF and is nearly unique to the older population, especially in older women, in whom >80% of incident HF is HFpEF (1). Objectively measured exercise intolerance, quality of life, and hospitalization and death rates are similar to HF with reduced EF (HFrEF). Despite its importance, optimal therapy of HFpEF is unknown, and essentially all HFpEF trials have missed their primary endpoints (1).

Against this background, multiple secondary or post hoc analyses have sought to determine not only why these trials were neutral, but also whether there were certain groups that had greater apparent benefit. The TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial has perhaps undergone the most such analyses, including 1 that intriguingly suggested that there may have been significant benefit if sites outside the Americas had been excluded (2). This, along with absence of other effective therapy, led the American College of Cardiology/American Heart Association/Heart Failure Society of America to include spironolactone in the updated HF management guideline. However, it was given the weakest possible endorsement (Class IIb, Level of Evidence: B-R). The guideline also stated only for “appropriately selected patients.” However, criteria for selection do not include cautions regarding older age.

In this issue of *JACC: Heart Failure*, Vardeny et al. (3) sought to provide additional information regarding what is arguably the most important subset of patients in the TOPCAT trial—those in the older age ranges. The investigators separated participants by 3 age categories (<65, 65 to 74, and ≥75 years of age). Forty-one percent of participants were ≥75 years of age, providing good power to examine this key group, which was more commonly

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women and had lower body mass index and estimated glomerular filtration rate than did younger participants.

The authors' findings indicate that although there was no effect of age on efficacy, older age significantly and substantially increased the rates of the primary adverse safety endpoint by >2.5-fold. The safety endpoint was quite clinically meaningful: discontinuation due to an adverse event of interest, including hyperkalemia, rise in creatinine to ≥3.0 mg/dl, gynecomastia, or intolerance. The secondary safety endpoint, which included noncardiovascular death, was also much more frequent in both older age groups. It is important to note that this much higher rate of adverse events occurred despite: 1) typical trial participant selection criteria that exclude the sickest, most frail and vulnerable patients who are also overwhelmingly older; 2) careful, protocol-mandated monitoring during the trial; and 3) significantly lower final doses in the older age groups. Thus, it is likely that these findings may significantly underestimate the true rate of adverse effects that would be expected in a typical older population in typical clinical settings.

This stark age divergence in the risk-benefit of spironolactone in HFpEF should give pause regarding its clinical application in older patients who constitute the vast majority of patients with the HFpEF syndrome. Even in younger patients, spironolactone and other aldosterone inhibitors cause hyperkalemia and worsening of renal function, particularly in patients with reduced baseline renal function. Even before the present report, concerns had been raised regarding the widespread use of spironolactone in older patients following other clinical trials. Indeed, the risks of clinically applying data from spironolactone trials, in which patient selection and monitoring are ideal, to a general, older population are not theoretical. Following the publication of the RALES (Randomized Aldactone Evaluation Study) showing efficacy in patients with acute HFrEF, a Canadian population-based study found that the use of spironolactone in patients >65 years of age (mean age 78 ± 74 years) had increased from 3.4% before publication of the RALES study to 14.9% afterward. Patients who began spironolactone after RALES study were, on average, 13 years older than the patients who were enrolled in the RALES study. As a result, the study further found that hospitalization rates for hyperkalemia had increased >4-fold and associated mortality had increased by >6-fold. The mechanism of these dramatic findings had been unclear but might be explained by the Vardeny et al. (3) current report. Another trial showed that the prescription of spironolactone in older patients hospitalized with HF increased substantially in the United States after publication of the RALES study. More than one-third of spironolactone prescriptions were provided to patients who did not meet enrollment criteria of the trial, and many had characteristics that placed them at high risk for hyperkalemia. In that study, multivariable analyses showed that the factors associated with prescriptions not meeting enrollment criteria included advanced age, noncardiovascular comorbidities, discharge to skilled nursing facilities, and care provided by physicians without board certification (4). Several subsequent case series have described patients with hyperkalemia requiring hos- pitalization, some of whom died, and many patients in these series were elderly, in whom the serum creatinine value often overestimates true renal function. Important lessons from these studies are: 1) a much higher rate of adverse events is usually observed in the "real world," in which clinicians may do less monitoring than in trials; 2) the actual patients who are treated within trials are far different than general

clinical patients, and this divergence is more stark in the older age ranges; and 3) compared with those selected for trials, older patients with HF in practice are far less compliant, have far less social support, and have far more cognitive dysfunction, comorbidities, and polypharmacy that further increase risk for adverse medication-related outcomes. Thus, adverse events in real-world settings are usually substantially higher in patients with multiple comorbidities, who were likely generally excluded from the TOPCAT trial. In sum, several lines of evidence suggest that the results reported by Vardeny et al. (3) for higher age-related rates of adverse safety outcomes are likely to be considerably magnified in the "real world."

As new therapies are introduced, it is always important to examine the specific patterns of age effects on risk-benefit, as these can vary widely. For instance, interventions for ischemic heart disease, particularly surgical and percutaneous interventions, often show higher absolute benefit in older patients despite higher relative risk of complications compared with younger persons, such that the net age-related risk-benefit can be more favorable with older age. Others, such as in the current case with spironolactone, can show similar efficacy but higher risks of adverse outcomes. The final pattern commonly seen is the most adverse: lower efficacy and higher risk of adverse effect. Vardeny et al. (3) are congratulated for providing critical age-specific risk-benefit pattern data for spironolactone, specifically for the older HFpEF subgroup.

The risks of spironolactone therapy should of course be balanced with potential for efficacy. However, despite multiple prior clinical trials, spironolactone has not shown a clear, consistent, and strong signal for benefit in HFpEF, in stark contrast to its strong, conclusive benefit in HFrEF. For example, in a large meta-analysis of 16,321 patients with HFpEF from 15 randomized, controlled trials, spironolactone had a neutral effect on cardiovascular death, all-cause mortality, and cardiac hospitalizations (5). Similarly, the primary outcome of the overall TOPCAT trial, by formal, protocol-specified primary outcome analysis, was neutral (2). In the present study, which limited analyses to the non–protocol-specified (post hoc) "Americas" subset, the 18% reduction in primary outcome from spironolactone in older patients with HFpEF was counterbalanced by a 154% increase in the primary safety event.

A final, perhaps most important, note about therapeutic selection in older patients is that in-depth studies consistently show that preferences for goals of therapy among older patients often differ substantially from younger patients, with greater emphasis on quality of life (and on physical and cognitive function which drive it) than on quantity of life. In this regard, a randomized, blinded, placebo-controlled trial of spironolactone that assessed physical function and quality-of-life outcomes specifically in unselected older patients with HFpEF was neutral (6). Therapeutic decisions, particularly in older patients and those with multiple comorbidities, should always be individualized and based on patient-specific risk profiles and shared decision making with patients and their families.

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