EDITORIAL COMMENT

Sparing a Little May Save a Lot
Lessons From the Studies Of Left Ventricular Dysfunction (SOLVD)*

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Over the past 20 years, attention to the renin-angiotensin-aldosterone system has brought marked success in the treatment of heart failure (HF). With the publication of the Randomized Aldactone Evaluation Study (RALES) trial, spironolactone became another cornerstone of therapy for the treatment of patients with New York Heart Association (NYHA) functional class III to IV HF (1). Based on the studied benefits of spironolactone, some practices have extended the use of spironolactone to other patients with less severe HF. However, a recent study cautioned against liberalizing the use of spironolactone to patients outside the RALES study (2), and current professional guidelines recommend spironolactone for patients with NYHA functional class III/IV HF only when added to angiotensin-converting enzyme (ACE) inhibitor and beta-blocker therapy (3,4). The study by Domanski et al. (5) in this issue of the Journal provides more information about the impact of diuretic choice and, more importantly, a glimpse of the possible effects of potassium-sparing diuretics when used in patients with less severe HF. Unfortunately, we do not know which potassium-sparing diuretics were used, although it is most likely that spironolactone was used in most patients, rather than amiloride or triamterene. With this in mind, and given the recognized importance of aldosterone, the discussion will be focused on spironolactone.

In the Studies Of Left Ventricular Dysfunction (SOLVD), Domanski et al. (5) compared the outcomes of patients on a potassium-sparing diuretic with patients taking only a non–potassium-sparing diuretic. Several differences between these two study populations should be noted to clarify how the current analysis fits into existing practices. The SOLVD program started in 1986 and comprised two studies totaling 6,797 patients with a left ventricular (LV) ejection fraction ≤ 35%. Patients were enrolled in the prevention trial (n = 4,228) if they were asymptomatic (6) or into a treatment trial (n = 2,569) if they were symptomatic.

Of the 6,797 patients, 3,915 were on no diuretic, 68 were on a potassium-sparing diuretic alone, and 338 were on both a potassium-sparing and non–potassium-sparing diuretic. Because of the difficulty in analyzing such a small population of patients with potassium-sparing diuretic alone, the authors’ main analysis combines the group of patients using potassium-sparing diuretics alone with the group using both types. Although combining these two groups may be fraught with error, the main purpose of the study was to analyze the effects of potassium-sparing diuretic (presumably spironolactone) regardless of other therapies. In the end, when a multivariable analysis adjusting for other clinical factors and medication use is performed, potassium-sparing diuretics appear to win. Their use was associated with a significant benefit, with a risk of approximately 0.75 for cardiovascular events (hospitalization for HF, death from cardiovascular disease, all-cause death, combined) compared with patients using non–potassium-sparing diuretics alone. Not surprisingly, if no diuretic was required the event rates were significantly lower. In an earlier analysis of SOLVD, no diuretic use was associated with a lower risk for arrhythmic death, compared with any diuretic use, while adjusting for other factors (8). Although the use of any diuretic compared with no diuretic was not evaluated in a multivariable model, it appears those patients not requiring any diuretic have the best health. This appears to be the case in other studies as well (9).

Possible mechanisms. Two main mechanisms may be contributing to the effects of potassium-sparing diuretics. First, the effects may be due to preserving potassium levels either extracellularly or intracellularly. Previous analysis from the SOLVD database demonstrated a decreased risk for arrhythmic death in patients taking a potassium-sparing diuretic. Although potassium levels were statistically different between those taking potassium-sparing diuretics and those taking non–potassium-sparing diuretics (4.40 vs. 4.32, p < 0.0001), the difference does not appear to be clinically significant, and potassium supplements did not have any clear effect (8). However, mild plasma potassium deficiencies may not be the only consideration, as intracellular levels of potassium as well as magnesium may play an important role by affecting cardiac function and contributing to arrhythmias (10,11). In addition, these effects on prevention of sudden death may be even more important in patients

See page 705

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with less severe HF, where this is an important mode of death rather than pump failure.

The second possibility may be a direct role of spironolactone on the myocardium and endothelium. The role of aldosterone in HF has been known for decades, but only recently has it received widespread attention after the publication of the RALES trial (12,13). The reason for the deserved attention to aldosterone is in part due to its role in hypertrophy and fibrosis (14), as well as its persistence despite ACE inhibition (15). Several lines of evidence, beyond its effects on sodium retention and possible effects on edema, support mechanisms of aldosterone blockade. Aldosterone has been implicated in organ fibrosis (12), and a recent substudy of RALES showed a decrease in serum markers of collagen synthesis in patients taking spironolactone (16). There may be effects on remodeling as demonstrated by Tsutamoto et al. (17) in a small study of nonischemic patients with mild-to-moderate HF, where spironolactone use over four months improved LV volume and mass compared with placebo. In addition, there appears to be a favorable decrease in neurohormones such as B-type natriuretic peptide (15). Further support of improved remodeling comes from a study showing improved ventricular volumes and function as well as exercise tolerance in patients with chronic HF in a dose-dependent fashion (18). Endothelial function also appears improved with spironolactone, as demonstrated in a small study of NYHA functional class II/III HF patients (19). Finally, there may be other unexplored mechanisms exerting local effects on the myocardium (20).

Limitations. As the authors state, retrospective studies do not provide definitive proof that non-potassium-sparing diuretics cause more rapid HF progression. In general, clinical trials are needed to test hypotheses generated from an analysis like this one, but in the context of RALES (1) and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) (21) there appears to be ample proof for wider use of aldosterone blockade. It is difficult to understand all the myriad reasons a particular type of diuretic is chosen. The reason one class is selected over another one may not be the true underlying mechanism for its benefit. Other limitations include knowing the frequency of spironolactone use, dosing of diuretics, and the long-term maintenance of potassium-sparing diuretics when they are not directly evaluated in a clinical trial. However, in general, decreased long-term treatment would favor equality for both groups and lessen the effect size. Also, the ability to tolerate potassium-sparing diuretics may only be a survival marker, as in those who do not need any diuretic. Although an adjustment was made for this by incorporating the serum creatinine level into the model, and potassium levels do not appear to be clinically different, there may be other mechanisms of tolerability associated with survival (8).

Future directions. It is interesting that diuretics may affect HF progression or even development of HF as demonstrated by the recent Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) (22). The choice of a diuretic has largely focused on a decision for control of hypertension, volume status, or maintaining potassium levels. As the results of the recently published EPHESUS (21) and the Domanski et al. (5) study are reviewed, it appears there is more to potassium-sparing diuretics than meets the eye.

The Domanski et al. (5) study provides important information to fill in the gap regarding aldosterone blockade in patients with LV dysfunction and less severe HF. The EPHESUS trial showed that the addition of eplerenone, a selective aldosterone blocker, to standard therapy of an ACE inhibitor and beta-blocker in post-myocardial infarction patients with LV dysfunction and HF provided a significant mortality benefit (21). The totality of evidence suggests routine use of aldosterone blockade in a much larger group of patients with HF. In general, clinical trials that demonstrate such a profound benefit in high-risk patients with HF, as in RALES, and lower risk patients, such as EPHESUS, indicate widespread benefit. Furthermore, there has not been a situation where a therapy worked in high-risk as well as lower risk groups without a benefit in an intermediate group. Thus, the evidence from the Domanski et al. (5) study complements these landmark clinical trials, so we should consider broadening the indication for aldosterone blockade to all patients with LV dysfunction and HF. However, to implement this, we would need to extend care through disease management programs to carefully monitor and prevent adverse effects previously described by Bozkurt et al. (2) and Whellan et al. (23). Although some may argue eplerenone should be used because of potentially lower rates of side effects, spironolactone use has to be considered given the cost difference. Physicians will need to monitor for side effects and hyperkalemia, just as adverse effects are currently monitored for routine medications such as coumadin, beta-blockers, and ACE inhibitors.

Importantly, as ALLHAT demonstrated, testing inexpensive medications in a head-to-head fashion provides important and sometimes unexpected information that can help identify the best combination of therapies. Although one could hope for a clinical trial involving asymptomatic or NYHA functional class II HF patients testing spironolactone versus a non-potassium-sparing diuretic, there may be more interesting trials in the future. Given the impressive evidence for aldosterone blockade, one example would be to test other diuretics with a background of an aldosterone blocker, especially when ALLHAT is considered. This is not a new idea. Others have called for clinical trials evaluating diuretic therapy because diuretics have been used for decades, yet have not been subjected to large-scale clinical trials (24). Furthermore, high doses of diuretic therapy are associated with mortality, but it is unclear if this is a selection bias or a true causal relationship (9). Another group to study the benefits of spironolactone include pa-
patients with diastolic heart failure given the role of aldosterone in hypertrophy and fibrosis. Therefore, it is now time to turn to providing the evidence for non-potassium-sparing diuretics and study spironolactone in diastolic failure, as well as testing strategies of care that determine the ideal combination of therapies.

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