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CME

Spironolactone Reduces Cardiovascular and Cerebrovascular Morbidity and Mortality in Hemodialysis Patients

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JACC JOURNAL CME

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CME Objective for This Article: At the conclusion of this activity, the learner should be able assess whether spironolactone treatment reduces the high incidence of cardiovascular and cerebrovascular morbidity and mortality in hemodialysis patients.

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Spironolactone Reduces Cardiovascular and Cerebrovascular Morbidity and Mortality in Hemodialysis Patients

Objectives This study sought to assess whether spironolactone treatment reduces the high incidence of cardiovascular and cerebrovascular (CCV) morbidity and mortality in hemodialysis (HD) patients.

Background Aldosterone receptor blockers reduce cardiac-related events, but the efficacy of the agents in HD patients is unclear.

Methods A 3-year randomized trial involving 5 clinics was performed. Of the 309 oligoanuric HD patients enrolled in the study, 157 patients were randomly assigned to receive 25 mg/day of spironolactone without any restriction on dietary potassium intake (treatment group), and 152 patients were assigned to a control group. The primary outcome was a composite of death from CCV events or hospitalization for CCV events, and the secondary outcome was death from all causes.

Results During the 3-year follow-up, the primary outcome occurred in 5.7% of patients in the treatment group and in 12.5% of patients in the control group. Hazard ratios (HRs) for the primary outcome for treatment were 0.404 (95% confidence interval [CI]: 0.202 to 0.809; $p = 0.017$) and 0.379 (95% CI: 0.173 to 0.832; $p = 0.016$) before and after adjustment, respectively. The secondary outcome was significantly reduced in the treatment group compared with the control group (6.4% vs. 19.7%; HRs: 0.355 [95% CI: 0.191 to 0.662; $p = 0.002$] and 0.335 [95% CI: 0.162 to 0.693; $p = 0.003$] before and after adjustment, respectively). Gynecomastia or breast pain was reported in 16 patients (10.2%) in the treatment group. Serious hyperkalemia led to treatment discontinuation in 3 patients (1.9%).

Conclusions Aldosterone receptor blockade using spironolactone may substantially reduce the risk of both CCV morbidity and death among HD patients; however, larger-scale studies are recommended to further confirm its efficacy. (Effects of Spironolactone on Cardio- and Cerebrovascular Morbidity and Mortality in Hemodialysis Patients; NCT01687699) (J Am Coll Cardiol 2014;63:528–36) © 2014 by the American College of Cardiology Foundation

Patients with end-stage renal disease (ESRD) undergoing dialysis are at a particularly high risk of cardiovascular and cerebrovascular (CCV) disease, accounting for 40% to 50% of deaths (1,2). Medical therapy involving the use of agents for the renin-angiotensin-aldosterone system (RAAS) is expected to have a significant impact, because the results of large-scale trials have shown that angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are beneficial for CCV events in the general population (3–5). However, data supporting the positive effects of these agents in ESRD patients on dialysis are limited (6). For this, it is necessary to evaluate the RAAS components that need to be blocked, so that favorable outcomes can be obtained in patients with different disease severity levels or complications.

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Recent studies suggest that the protection mechanism of these blockers could be attributed to a change in either the qualitative or quantitative pathological functions of aldosterone rather than that of angiotensin II (7). In fact, a series beginning with RALES (Randomized Aldactone Evaluation Study) has shown a strong association of aldosterone with a risk of cardiovascular events, including sudden cardiac death (SCD) (8–10). The interactions between cardiovascular disease and cerebrovascular disease have been widely developed over the past 2 decades, and aldosterone blockade has shown protective effects on ischemic cerebral infarct size and cerebrovascular remodeling in stroke-prone rats (11,12). Therefore, clinicians have attempted to improve the outcomes of dialysis patients by managing CCV disease using aldosterone blockade, including spironolactone. However, lack of detailed information on the adverse-effects profile of spironolactone for dialysis patients limits its use.The major concern with administrating spironolactone to patients with renal failure is life-threatening hyperkalemia. Nevertheless, oligoanuric patients requiring dialysis may not be at a risk of spironolactone-induced hyperkalemia when extrarenal potassium disposable (e.g., colonic transport) is marginal. Our pilot study (13) and several previous small studies (14,15) have suggested that spironolactone can be safely administered to patients under hemodialysis (HD) without the development of serious hyperkalemia.

On the basis of these data, we designed DOHAS (Dialysis Outcomes Heart Failure Aldactone Study) to test the hypothesis that daily treatment with low-dose spironolactone would significantly reduce the risk of death from all causes and CCV morbidity in patients with ESRD undergoing HD.

Methods

Patients. Eligibility criteria were determined by reviewing the medical records and laboratory data of patients. HD patients who were at least 30 years of age, had undergone