Effect of Angiotensin Receptor Blockers on Cardiovascular Events in Patients Undergoing Hemodialysis: An Open-Label Randomized Controlled Trial

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Background: Cardiovascular disease is the leading cause of mortality in patients with kidney failure treated with hemodialysis (HD). Although angiotensin receptor blockers (ARBs) reduce cardiovascular disease (CVD) events in patients with diabetes and chronic kidney disease, their effect in patients with kidney failure on HD therapy is not known.

Study Design: Open-labeled randomized trial.

Setting & Participants: Patients aged 30 to 80 years receiving HD 2 to 3 times weekly for 1 to 5 years at 5 university-affiliated dialysis centers.

Interventions: Treatment with ARBs (valsartan, candesartan, and losartan) versus without ARBs after stratification by sex, age, systolic blood pressure, and diabetes.

Outcomes: The primary end point is the development of fatal and nonfatal CVD events, defined as the composite of CVD death, myocardial infarction, stroke, congestive heart failure, coronary artery bypass grafting, or percutaneous coronary intervention. The secondary end point is all-cause death.

Results: 366 subjects initially were randomly assigned to an ARB or no ARB (control), but after a run-in phase, 180 were retained in each group. Mean age was 60 years, 59% were men, 51% had diabetes, and mean predialysis systolic blood pressure was 154 mm Hg. There were 93 fatal or nonfatal CVD events (52%); 34 (19%) in the ARB group and 59 (33%) in the non-ARB group. After adjustment for age, sex, diabetes, systolic blood pressure, and center, treatment with an ARB was independently associated with reduced fatal and nonfatal CVD events (hazard ratio, 0.51; 95% confidence interval, 0.33 to 0.79; $P = 0.002$). There were 63 deaths (35%); 25 (14%) in the ARB group and 38 (21%) in the non-ARB group. After adjustment, all-cause mortality differed between the 2 groups (hazard ratio, 0.64; 95% confidence interval, 0.39 to 1.06; $P = 0.1$).

Limitations: Because of the small sample size of this trial, the large effect may be a spurious finding. Use of an open-label design and 3 different agents in the ARB group might have influenced results.

Conclusion: Use of an ARB may be effective in reducing nonfatal CVD events in patients undergoing long-term HD. A larger study is required to confirm these results.

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INDEX WORDS: Cardiovascular diseases; hemodialysis patients; renin-angiotensin inhibition.

Editorial, p. 400

In Japan, patient survival on dialysis therapy is superior to that in Western countries; however, cardiovascular disease (CVD) remains the leading cause of morbidity and mortality, accounting for 30% of all deaths.[1] Because end-stage renal disease is associated with a severalfold increased risk of CVD compared with the general population,[2] measures aimed at delaying the progression of kidney disease also may delay the onset of CVD, namely congestive heart failure (CHF),[3] which is a leading cause of morbidity and mortality in patients with more advanced stages of chronic kidney disease.

Routine use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) for the treatment of patients with both diabetic kidney disease and CHF is well established.[4] In patients with diabetic and nondiabetic kidney disease, ARBs reduce proteinuria and albuminuria and delay the progression

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of kidney disease.[5] In parallel with these results, the efficacy of ARBs for the prevention of CHF has been shown in a number of large-scale clinical trials.[6,7] It therefore is reasonable to hypothesize that the use of ARBs in patients with end-stage renal disease for the prevention of CHF and CVD might be beneficial[8,9]; however, the majority of primary and secondary prevention trials for CVD have excluded patients with advanced chronic kidney disease. To date, only 1 published report has examined the potential beneficial effects of ACE inhibition on CVD in patients receiving hemodialysis (HD). The Fosinopril in Dialysis Study[10] failed to show a beneficial effect of fosinopril versus placebo on a composite primary end point entailing combined fatal and nonfatal CVD events (cardiovascular death, stroke, heart failure, myocardial infarction [MI], or revascularization). However, after adjustment for risk factors, trends were found suggesting that ACE inhibitors may be associated with a lower risk of CVD events. The present study was conducted to evaluate the efficacy of long-term use of ARBs on cardiovascular outcomes in patients undergoing HD.

METHODS

Study Design and Procedures

This was a prospective, controlled, randomized, open-label trial with add-on of ARBs. The study was conducted at 5 dialysis centers in the Saitama region, Japan, and was approved by the Ethics Committee of the Saitama Medical University Hospital. All patients provided written informed consent. All study procedures were performed in accordance with the principles of the Declaration of Helsinki. All patients received 2 to 3 HD treatments weekly. Eligibility criteria included age of 30 to 80 years; dialysis duration of at least 12 months, but less than 5 years; 2 to 3 HD sessions weekly; and predialysis systolic blood pressure (SBP) greater than 160 mm Hg or greater than 150 mm Hg if receiving antihypertensive agents. The major exclusions to participation were the use of ARBs or ACE inhibitors.

Randomization was performed by using the dynamic allocation method after stratification by sex, age, SBP, and diabetes.[11] Using this method, every time a participant was registered, the number of participants was balanced according to the stratification and simultaneously the balance of 2 groups. All patients were randomly assigned to open-label treatment with an ARB or no ARB (control) for 36 months. In the ARB group, patients underwent a 3-month single-blind run-in period. The choice of ARBs was at the discretion of the physician. Patients received a test dose of losartan of 50 mg/d, candesartan of 8 mg/d, or valsartan of 80 mg/d. Patients with symptomatic hypotension or SBP less than 100 mm Hg were excluded from the study. The study medication dose for each ARB was titrated monthly until the target SBP of less than 150 mm Hg was achieved. Escalation of the ARB dosage was as follows: losartan up to 100 mg/d, candesartan up to 12 mg/d, and valsartan up to 160 mg/d. In the control group, ARBs were not permitted. Concomitant antihypertensive therapy was allowed in both groups until the target SBP of less than 150 mm Hg was reached, with the exception of ACE inhibitors or other nonstudy ARBs.

Study End Points

The primary end point was the occurrence of fatal and nonfatal cardiovascular events, defined as the composite of cardiovascular death, nonfatal MI and stroke, coronary artery bypass grafting or percutaneous coronary intervention, and CHF. The secondary end point was all-cause mortality.

MI was defined by clinical symptoms combined with the new appearance of Q waves and ST-segment elevation on at least 2 electrocardiograms obtained on separate occasions and/or increase in levels of creatinine kinase-MB greater than 250 U/L and troponin greater than 0.25 ng/mL. Stroke was defined by clinical symptoms combined with evidence from computed tomographic study and/or perfusion magnetic resonance image data. CHF was defined according to the guidelines of the American College of Cardiology and American Heart Association.[12]

Target hemoglobin level was greater than 10 g/dL (hemoglobin in g/dL may be converted to g/L by multiplying by 10). Hemoglobin levels were determined monthly. Calcium and phosphate measurements were determined at the discretion of the physician and are not compared between groups.

Statistical Methods

Results are expressed as mean ± SEM or percentage. Comparisons between treatment groups were made by using Student *t*-test or Mann-Whitney test when applicable for continuous variables and using χ^2 test for categorical variables. Differences among treatment groups in postrandomization measures were evaluated by using analysis of variance for blood pressure and hemoglobin and χ^2 test for events. Cumulative event-free curves were created by means of Kaplan-Meier analysis, and differences between the 2 treatment groups were analyzed by using log-rank test.

Cox proportional hazards regression analyses were performed for comparison of the 2 treatment groups after adjustment for the dynamic stratification variables (age, sex, SBP, and diabetes) and center effect. These data are presented as hazard ratios and 95% confidence intervals. Statistical significance was set at P less than 0.05. All statistical analyses were performed using StatView, version 5.0 (SAS Institute Inc, Cary, NC).

RESULTS

A total of 1,567 patients were screened (Fig 1). Of these, 366 patients were randomly assigned; 183 to an ARB and 183 to no ARB (control). Six patients discontinued the study during the 3-month single-blind run-in period; 3 in the ARB group because of excessive blood pressure de-