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CLINICAL RESEARCH

The Combination of Beta Blockers and Renin-Angiotensin System Blockers Improves Survival in Incident Hemodialysis Patients: A Propensity-Matched Study

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Introduction: Although several studies suggest that the prognosis of hypertensive dialysis patients can be improved by using antihypertensive drug therapy, it is unknown whether the prescription of a particular class or combination of antihypertensive drugs is beneficial during hemodialysis.

Methods: We performed a propensity score matching study to compare the effectiveness of various classes of antihypertensive drugs on cardiovascular (CV) mortality in 2518 incident hemodialysis patients in Spain. The patients had initially received antihypertensive therapy with a renin-angiotensin system (RAS) blocker (728 patients), a ß-blocker (679 patients), antihypertensive drugs other than a RAS blocker or a ß-blocker (787 patients), or the combination of a ß-blocker and a RAS inhibitor (324 patients). These patients were followed for a maximum of 5 years (median: 2.21 yr; range: 1.04–3.34 yr).

Results: After adjustment for baseline CV risk covariates, no significant differences were observed in the risk of CV mortality between patients taking a RAS blocker and patients treated with ß-blocker–based antihypertensive therapy. The combination of a RAS blocker with a ß-blocker was associated with better CV survival than either agent alone (RAS blocker: hazard ratio [HR]: 1.68; 95% confidence interval [CI] 1.05–2.69; ß-blocker: HR: 1.59; 95% CI: 1.01–2.50; antihypertensive medication other than a RAS blocker or ß-blocker: HR: 1.67; 95% CI: 1.08–2.58).

Discussion: Our data suggested that the combination of a RAS blocker and a ß-blocker could improve survival in hemodialysis patients. Further prospective randomized controlled trials are necessary to confirm the beneficial effects of this combination of antihypertensive drugs in patients undergoing hemodialysis.

Kidney Int Rep (2017) ■, ■–■; http://dx.doi.org/10.1016/j.ekir.2017.03.001
KEYWORDS: antihypertensive drug; β-blocker; cardiovascular risk; hemodialysis; renin-angiotensin system blocker

Mortality among patients undergoing hemodialysis has improved in recent years, yet mortality rates remain unacceptably high, mostly due to cardiovascular (CV) diseases.[1] Hypertension is 1 of the main factors that contributes to the hugely increased rate of CV mortality in end-stage renal disease (ESRD).[2–4]

Hypertension is common in patients undergoing hemodialysis. Extracellular volume overload is the main pathogenic mechanism underlying hemodialysis-related hypertension,[5] although other mechanisms, such as the renin-angiotensin system (RAS) and sympathetic system hyperactivity, also contribute to maintaining hypertension in hemodialysis patients.[6,7] Isolated systolic hypertension and increased pulse pressure resulting from stiff large arteries due to arteriosclerosis are a common finding in patients undergoing hemodialysis. One large-scale epidemiological study based on USRDS data showed that pulse pressure was the most significant prognostic predictor of mortality.[8]

Antihypertensive drugs are generally prescribed to patients during hemodialysis, when hypertension persists despite the achievement of adequate dry weight.[9] Although several studies suggest that the prognosis of hypertensive dialysis patients may be improved by using antihypertensive drug therapy,[10,11]

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Received 21 January 2017; revised 24 February 2017; accepted 1 March 2017; published online 7 March 2017

it is unknown whether the prescription of a particular class or combination of antihypertensive drugs is beneficial during hemodialysis. In addition, because of the excessive CV mortality of these patients, such knowledge would be of enormous clinical usefulness.

In the general population, RAS blockers (i.e., angiotensin-converting enzyme inhibitors [ACEI] and angiotensin receptor blockers [ARB]) and ß-blockers have been shown to exert beneficial effects on CV events, particularly left ventricular hypertrophy, coronary heart disease (CHD), and heart failure.[12–16] Studies comparing the efficacy of various antihypertensive treatments in reducing CV risk in ESRD patients have yielded controversial results.[8,17–21] Some have suggested that RAS blockers are superior to other antihypertensive drugs in reducing left ventricular hypertrophy and preventing CV risk.[20] The CV benefits of ß-blockers have also been reported. A large epidemiological study performed in the United States concluded that ß-blockers improved survival and may even have induced CV protection in dialysis patients.[8] A randomized controlled trial that involved patients with left ventricular hypertrophy who underwent hemodialysis reported that the ß-blocker atenolol was superior to the RAS blocker lisinopril in preventing CV morbidity and all-cause hospitalizations.[22]

To compare the effects of different classes of antihypertensive drugs on CV mortality in patients undergoing maintenance hemodialysis, we performed an observational study (propensity-matched analysis) of a large cohort of patients who initially received antihypertensive therapy with a RAS blocker (ACEI or ARB), a ß-blocker, other antihypertensive drugs, or the combination of a RAS blocker and a ß-blocker.

MATERIALS AND METHODS

Dialysis Facilities Operated by Fresenius Medical Care in Spain

The Spanish National Health System covers the treatment of ESRD (dialysis and kidney transplantation) for the entire population and is financed through the budget of the 17 Autonomous Communities into which the Spanish state is divided. Patients with ESRD are referred to public hospitals or to dialysis facilities owned by the main dialysis companies, with which the National Health System has agreements. Patients treated at the 63 Fresenius Medical Care dialysis facilities in Spain represent approximately one-quarter of the whole hemodialysis population in Spain. These patients are similar in age, sex, etiology of kidney disease, and baseline comorbidities to the entire hemodialysis population in Spain, as reflected in a previous publication.[23]

Patients

Patients admitted to the 63 Fresenius Medical Care dialysis facilities in Spain who initiated hemodialysis between January 1, 2009 and December 31, 2012 were screened for inclusion in the study. The inclusion criteria were as follows: age older than 18 years; incident hemodialysis (<90 days on renal replacement therapy before starting hemodialysis in Fresenius Medical Care facilities and no previous kidney transplantation or peritoneal dialysis); registration in the EuCliD database and the Fresenius Medical Care clinical data system[23]; prescription of hemodialysis based on a regimen of 3 sessions per week (4 h each); and receiving a stable dose of antihypertensive medication (the same type and dose of antihypertensive drugs for at least 2 months before inclusion in the study). Exposure to antihypertensive medications was obtained from electronic prescription data, which is included in the EuCliD database. All patients gave their written informed consent for data evaluation on admission to the Fresenius Medical Care center.

Study Design

Baseline was set at 3 months after the date of renal replacement therapy. At baseline, we collected the following variables and comorbidities that, according to the existing literature, seem to be associated with antihypertensive medication and outcome: age, blood pressure (systolic and diastolic), pulse pressure, heart rate, ultrafiltration per session (all calculated as the average of the measurements taken during the baseline period, i.e., before the hemodialysis session), sex, vascular access, and potassium levels. The comorbidities recorded at baseline were diabetes mellitus, heart failure, CHD, arrhythmia, and stroke. We recorded antihypertensive medication classified according to the corresponding codes of the Anatomical Therapeutic Chemical (ATC) classification system. Patients were classified into 4 groups according to their antihypertensive medication, as follows: (i) RAS blockers (ATC group C09); (ii) ß-blockers (ATC group C07); (iii) any other antihypertensive medication not including RAS blockers or ß-blockers, peripheral vasodilators (ATC group C04), calcium-channel blockers (ATC group C08), and other drugs (ATC group C02); and (iv) combined RAS blockers and ß-blockers (ATC group C07 + ATC group C09). See Supplementary Table S1 for further details on prescriptions.

Patients were followed for a maximum of 5 years until December 31, 2014 (median: 2.21 yr; range; 1.04–3.34 yr). Patients who discontinued hemodialysis because of recovery of renal function, those who were transferred to hemodialysis facilities other than

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