DOPPS data suggest a possible survival benefit of renin angiotensin-aldosterone system inhibitors and other antihypertensive medications for hemodialysis patients

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Angelo Karaboyas[1], Hairong Xu[2], Hal Morgenstern[1,3], Francesco Locatelli[4], Michel Jadoul[5], Kosaku Nitta[6], Indranil Dasgupta[7], Francesca Tentori[8], Friedrich K. Port[9] and Bruce M. Robinson[1,9]

[1]Arbor Research Collaborative for Health, Ann Arbor, Michigan, USA; [2]Global Medical Affairs, AstraZeneca, Gaithersburg, Maryland, USA; [3]University of Michigan, Departments of Epidemiology and Environmental Health Sciences, School of Public Health, and Department of Urology, Medical School, Ann Arbor, Michigan, USA; [4]Alessandro Manzoni Hospital, Department of Nephrology, Lecco, Italy; [5]Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; [6]Department of Medicine, Kidney Center, Tokyo Women's Medical University, Tokyo, Japan; [7]Heartlands Hospital and University of Birmingham, Birmingham, UK; [8]DaVita Clinical Research, Minneapolis, Minnesota, USA; and [9]University of Michigan, Department of Internal Medicine, Ann Arbor, Michigan, USA

The benefits of renin angiotensin-aldosterone system inhibitors (RAASi) are well-established in the general population, particularly among those with diabetes, congestive heart failure (CHF), or coronary artery disease (CAD). However, conflicting evidence from trials and concerns about hyperkalemia limit RAASi use in hemodialysis patients, relative to other antihypertensive agents, including beta blockers and calcium channel blockers. Therefore, we investigated prescription patterns and associations with mortality for RAASi and other antihypertensive agents using data from the international Dialysis Outcomes and Practice Patterns Study (DOPPS). Cox regression was used to estimate the effect of the prescription of RAASi and other antihypertensive agents at study entry on mortality in 11,421 incident (120 days or less) hemodialysis and 37,124 prevalent (over 120 days) hemodialysis patients from DOPPS phases 2-5 (2002-2015). Over 95% of RAASi were angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. RAASi prevalence was 39% and varied minimally by CHF and CAD. The adjusted hazard ratio for RAASi (vs. no RAASi) was 0.89 (95% confidence interval 0.80-0.99) among incident and 0.94 (0.90-0.99) among prevalent hemodialysis patients, with no convincing evidence of interaction with diabetes, CAD or CHF. Inverse associations with mortality were also observed for beta blockers and calcium channel blockers, and were stronger for angiotensin receptor blockers than angiotensin-converting enzyme inhibitors, but this latter finding requires further study. Thus, our observations suggest a relatively small survival benefit of RAASi and other antihypertensive agents in hemodialysis patients, though randomized prospective studies are needed to potentially change prescribing criteria.

Correspondence: *Angelo Karaboyas, Arbor Research Collaborative for Health, 340 East Huron Street, Suite 300, Ann Arbor, Michigan 48104, USA. E-mail: Angelo.Karaboyas@ArborResearch.org*

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Renin angiotensin-aldosterone system inhibitors (RAASi), a group of antihypertensive medication classes that predominantly includes angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs), have been shown to improve outcomes for individuals without kidney failure at increased risk of cardiovascular (CV) events.[1–7] A meta-analysis of 25 randomized trials also demonstrated a decreased risk of CV events for RAASi versus placebo in patients with chronic kidney disease.[8] Blood pressure–lowering agents have been shown to be effective in reducing CV events and all-cause mortality in patients with kidney failure treated with hemodialysis (HD),[9] but the risk-benefit ratio for RAASi use specifically is unknown. A key concern is that hyperkalemia is a common side effect of RAASi; hyperkalemia is a risk factor for mortality, especially in HD patients,[10–12] because diminished renal potassium excretion causes disturbances in heart rhythm and can lead to cardiac arrest.[13] HD patients have a significant comorbidity burden[14] and CV event rates that far exceed those in the general population.[15] Although these characteristics make HD patients suitable candidates for RAASi, definitive randomized trial evidence of better CV and mortality outcomes in HD populations is still lacking because trial results have been inconsistent.[16–21] Moreover, concerns about hyperkalemia have led to more cautious prescription patterns among nephrologists.[13,22–26] A survey of nephrologist opinions[24] regarding the use of specific antihypertensive agents found

that the most common reason (88%) for not prescribing an ACEi for HD patients was "concerns about adverse reactions." Therefore, it remains unclear whether RAASi are underused in HD patients relative to other antihypertensive medications such as beta-blockers (BB), calcium channel blockers (CCB), and diuretics (i.e., whether there is a class effect).

In this study, we investigated worldwide patterns of RAASi prescription and the relationship between RAASi use and mortality in an international cohort of HD patients. We hypothesized that the benefits of RAASi use in CV risk reduction post-ischemia and preserving residual kidney function[27–29] would outweigh the risks, such as hyperkalemia, producing an overall survival advantage. Given these potential mechanisms, we also hypothesized that RAASi use would especially benefit patients new to dialysis who generally have residual kidney function and/or those with diagnosed congestive heart failure (CHF) or coronary artery disease (CAD).

RESULTS

Descriptive analyses

Figure 1 illustrates that the vast majority of RAASi prescriptions were for either an ACEi or an ARB; relatively few were prescriptions for aldosterone receptor antagonists, direct renin inhibitors, or a combination of ACEi+ARB. ACEi prescription was twice as common as ARB prescriptions in North America and slightly more common than ARB prescriptions in Europe/Australia and New Zealand; in Japan, most RAASi prescriptions were for an ARB. RAASi prescription was less common among incident (vs. prevalent) HD patients in North America, but slightly more common in Europe/Australia and New Zealand and Japan. No clear trends in RAASi prescription were observed across Dialysis Outcomes and Practice Patterns Study (DOPPS) phases, except in Japan where the use of ARBs alone increased from 19% in DOPPS 2 (2002–2004) to 40% in DOPPS 5 (2012–2015).

Table 1 provides patient characteristics by region and RAASi prescription (yes/no) for incident HD patients. Patients prescribed a RAASi were younger and less likely to have a history of cancer, but were more likely to be diabetic. Reflecting an indication for the treatment, patients prescribed a RAASi had higher systolic blood pressure (SBP) and were more likely to be diagnosed as hypertensive and to be prescribed other antihypertensive medications. Similar relationships were observed in our prevalent HD cohort (Table 2). Table 3 shows that RAASi prescription prevalence was less frequent among nondiabetics in all 3 regions for both incident and prevalent HD patients, but similar for patients with and without CHF or CAD. In contrast to RAASi, BB prescription increased sharply over time in all 3 regions; prescription of a CCB and a diuretic was constant or increased slightly (Table 4).

RAASi and mortality

Among incident HD patients, the crude all-cause mortality rate was 0.169/year in North America, 0.144/year in Europe, and 0.054/year in Japan. Median follow-up was 1.6 years in patients both prescribed and not prescribed a RAASi. RAASi prescription was associated with a lower mortality rate (hazard ratio [HR]: 0.71, 95% confidence interval [CI] 0.64–0.78) in the unadjusted model (Table 5, Model 0). Adjustment for potential confounders attenuated this association; in Model 6, the HR (95% CI) of mortality comparing patients with versus without a RAASi prescription was 0.89 (0.80–0.99).

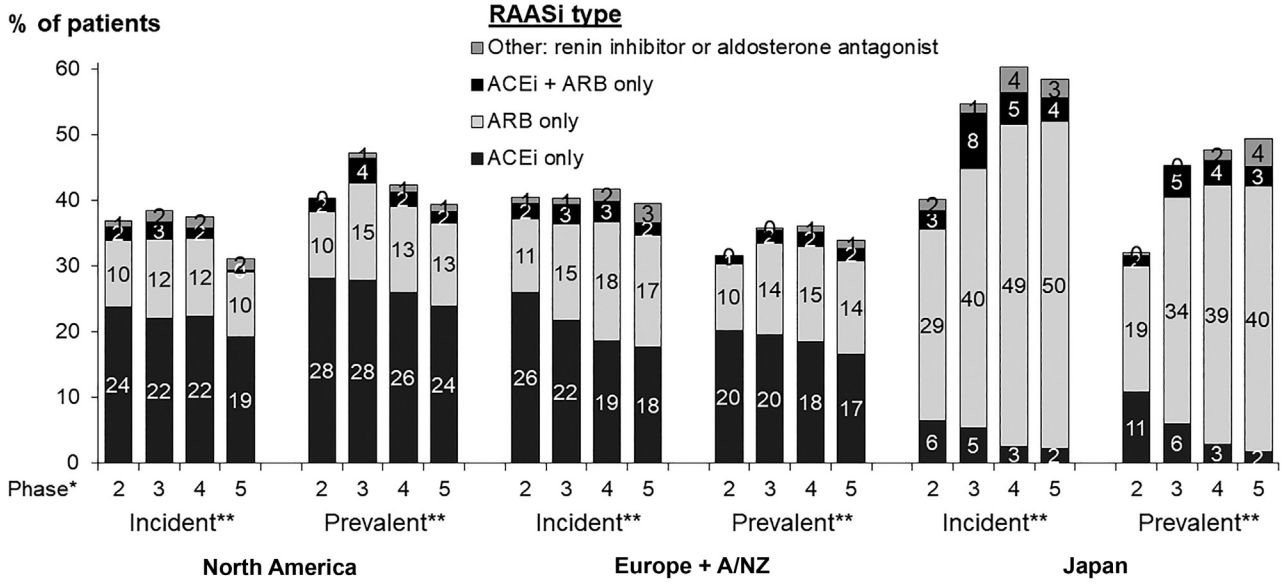

Figure 1 | Renin angiotensin-aldosterone system inhibitors (RAASi) prescription by region, Dialysis Outcomes and Practice Patterns Study (DOPPS) phase, and time on dialysis. "Other" includes any patients prescribed a RAASi other than an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). A/NZ, Australia/New Zealand. *DOPPS phase 2: 2002–2004; phase 3: 2005–2008; phase 4: 2009–2011; phase 5: 2012–2015; **Incident, on dialysis ≤120 days at study entry; prevalent, on dialysis >120 days at study entry.