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).

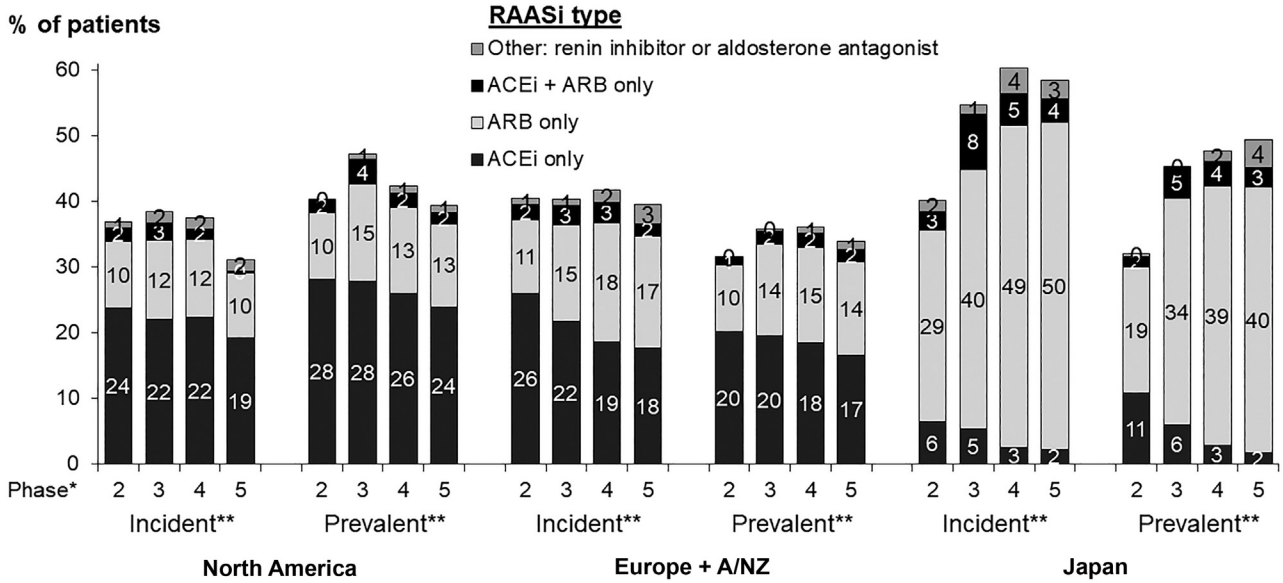

Figure 1 | Renin angiotensin-aldosterone system inhibitors (RAASi) prescription by region, Dialysis Outcomes and Practice Patterns Study (DOPPS) phase, and time on dialysis. "Other" includes any patients prescribed a RAASi other than an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor 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.

Table 1 | Patient characteristics by RAASi prescription among incident (vintage ≤120 days) patients, by region

Patient characteristics	North America		Europe + A/NZ		Japan	
	No RAASi	RAASi	No RAASi	RAASi	No RAASi	RAASi
Patients, no. (%)	2845 (65)	1538 (35)	3288 (59)	2245 (41)	713 (47)	792 (53)
Characteristics						
Age (yr)	64.4 ± 15.0	61.0 ± 15.2	66.9 ± 14.2	62.7 ± 14.8	66.4 ± 13.1	63.8 ± 13.0
Sex (% male)	58	58	63	63	69	67
Race (% black)	20	25	2	2	0	0
Vintage (days)	49 (15, 84)	48 (11, 82)	40 (4, 80)	39 (2, 77)	37 (8, 78)	48 (17, 86)
Hemodialysis-related characteristics						
< 1 mo pre-HD nephrologist care (%)	28	25	24	18	18	18
Central venous catheter use (%)	69	66	48	42	11	7
Intradialytic weight loss (%)	2.4 ± 1.7	2.5 ± 1.6	2.0 ± 1.6	1.8 ± 1.6	2.2 ± 1.9	2.4 ± 1.8
Treatment time (min)	217 ± 33	218 ± 33	219 ± 38	224 ± 41	207 ± 39	208 ± 36
Dialysate potassium (mEq/l)	2.5 ± 0.6	2.4 ± 0.6	2.3 ± 0.7	2.4 ± 0.8	2.0 ± 0.1	2.0 ± 0.1
Laboratory and biometric measurements						
Body mass index (kg/m^2)	28.1 ± 7.0	28.0 ± 6.8	25.9 ± 5.3	26.7 ± 5.6	21.6 ± 3.7	22.0 ± 3.4
Predialysis SBP (mm Hg)	143 ± 23	149 ± 23	141 ± 22	145 ± 22	147 ± 22	153 ± 21
Hemoglobin (g/dl)	10.7 ± 1.5	10.8 ± 1.5	10.5 ± 1.6	10.6 ± 1.6	9.5 ± 1.7	9.7 ± 1.5
Serum creatinine (mg/dl)	6.1 ± 2.7	6.5 ± 2.9	6.7 ± 2.4	6.7 ± 2.6	7.8 ± 2.8	8.0 ± 2.7
Serum albumin (g/dl)	3.48 ± 0.55	3.50 ± 0.54	3.49 ± 0.62	3.52 ± 0.63	3.45 ± 0.60	3.39 ± 0.58
WBC count (10^3 cells/mm^3)	7.8 ± 2.8	7.6 ± 2.7	7.7 ± 2.8	7.6 ± 2.5	6.4 ± 2.4	6.3 ± 2.1
Serum calcium (mg/dl)	8.7 ± 0.8	8.7 ± 0.8	8.8 ± 1.0	8.8 ± 0.9	8.2 ± 0.9	8.2 ± 0.8
Serum phosphorus (mg/dl)	5.0 ± 1.6	5.2 ± 1.7	5.1 ± 1.8	5.3 ± 1.8	5.3 ± 1.6	5.3 ± 1.4
Serum potassium (mEq/l)	4.4 ± 0.7	4.5 ± 0.7	4.7 ± 0.8	4.8 ± 0.8	4.4 ± 0.7	4.5 ± 0.8
Serum potassium >5.5 mEq/l (%)	6	7	14	17	7	10
K-binding resin prescription (%)	1	1	6	10	5	7
Antihypertensive agents (%)						
Any (non-RAASi) AHA	79	90	76	87	77	92
Beta-blocker	58	66	43	50	17	25
Calcium channel blocker	45	53	41	52	51	78
Diuretic	31	41	47	64	52	61
Comorbid conditions (%)						
Coronary artery disease	45	47	38	41	27	25
Cerebrovascular disease	14	15	14	16	15	11
Heart failure	38	37	26	25	31	27
Peripheral vascular disease	25	25	25	28	13	11
Other cardiovascular disease	28	23	30	29	24	20
Cancer (nonskin)	15	10	19	14	12	8
Diabetes	57	66	35	44	44	57
Gastrointestinal bleeding	6	5	6	4	5	3
Hypertension diagnosis	85	92	82	91	80	89
Lung disease	16	15	14	12	3	3
Neurologic disease	10	7	10	10	12	6
Psychiatric disorder	21	19	16	16	5	4
Recurrent cellulitis, gangrene	8	9	5	7	4	3

AHA, antihypertensive agent; A/NZ, Australia/New Zealand; HD, hemodialysis; RAASi, renin angiotensin-aldosterone system inhibitor; SBP, systolic blood pressure; WBC, white blood cell.
Values shown are mean ± SD or %. Vintage: time since dialysis initiation.

Crude all-cause mortality rates were similar for prevalent HD patients as they were for incident HD patients. In this prevalent HD cohort, the unadjusted HR of mortality was 0.89 (95% CI 0.85–0.94) for patients prescribed versus not prescribed a RAASi. After adjustment for confounders, especially age, this association was attenuated to HR: 0.94 (95% CI 0.90–0.99) in Table 5, Model 6. Little or no evidence of effect modification was observed by diabetes, CHF, CAD, or hypertension (Table 6) in either the incident or prevalent HD cohorts.

Sensitivity analyses

Among incident HD patients, the adjusted all-cause mortality HR for BB (0.93, 95% CI 0.84–1.03) was similar to that observed for RAASi (Figure 2). In contrast, we observed a stronger association with mortality for CCB (HR: 0.79, 95% CI 0.72–0.88) and little association for diuretics (HR: 1.08, 95% CI 0.97–1.21) in adjusted models. Among prevalent HD patients, the HR ranged from 0.91 to 0.98 for these 3 antihypertensive medications. Results for CCB were unchanged when restricted to dihydropyridine CCB. When analyzing RAASi subtypes in adjusted models, a stronger inverse association with mortality was observed for ARB than for ACEi, especially in the prevalent HD cohort (Figure 2). A direct comparison among patients prescribed a RAASi showed an ~10% lower mortality rate for ARB-only versus ACEi-only (reference group): the HRs (95% CI) were 0.91 (0.76–1.10) among incident HD patients and 0.88 (0.81–0.96) among

Table 2 | Patient characteristics by RAASi prescription among prevalent (vintage >120 days) patients by region

Patient characteristics	North America		Europe + A/NZ		Japan	
	No RAASi	RAASi	No RAASi	RAASi	No RAASi	RAASi
Patients, no. (%)	7566 (58)	5451 (42)	11,118 (65)	5879 (35)	3986 (56)	3124 (44)
Characteristics						
Age (yr), mean ± SD	63.0 ± 15.2	61.1 ± 15.0	65.3 ± 14.7	62.9 ± 15.1	63.7 ± 12.7	63.1 ± 12.3
Sex (% male)	55	56	58	62	60	66
Race (% black)	28	30	2	2	0	0
Vintage (yr)	2.7 (1.2, 5.4)	2.8 (1.2, 5.2)	3.0 (1.2, 6.4)	2.7 (1.1, 5.7)	5.9 (2.3, 12.3)	4.6 (1.7, 9.1)
Hemodialysis-related characteristics						
Central venous catheter use (%)	25	24	22	21	1	1
Intradialytic weight loss (%)	3.1 ± 1.7	3.3 ± 1.7	2.8 ± 1.6	2.8 ± 1.7	3.9 ± 1.7	4.0 ± 1.7
Treatment time (min)	220 ± 35	221 ± 33	242 ± 38	245 ± 38	239 ± 31	236 ± 29
Dialysate potassium (mEq/l)	2.2 ± 0.6	2.1 ± 0.5	2.1 ± 0.7	2.1 ± 0.7	2.0 ± 0.1	2.0 ± 0.1
Laboratory and biometric measurements						
Body mass index (kg/m^2)	28.3 ± 7.0	27.5 ± 6.7	25.6 ± 5.3	25.4 ± 5.4	21.0 ± 3.2	21.1 ± 3.4
Predialysis SBP (mm Hg)	144 ± 23	153 ± 23	136 ± 23	145 ± 22	145 ± 23	155 ± 20
Hemoglobin (g/dl)	11.4 ± 1.4	11.4 ± 1.3	11.6 ± 1.5	11.5 ± 1.4	10.4 ± 1.3	10.3 ± 1.2
Serum creatinine (mg/dl)	8.3 ± 3.1	8.5 ± 3.0	8.3 ± 2.7	8.3 ± 2.7	10.8 ± 2.9	10.7 ± 2.9
Serum albumin (g/dl)	3.75 ± 0.46	3.79 ± 0.44	3.71 ± 0.52	3.76 ± 0.54	3.75 ± 0.42	3.78 ± 0.42
WBC count (10^3 cells/mm^3)	7.1 ± 2.4	7.1 ± 2.4	7.1 ± 2.3	7.2 ± 2.3	6.0 ± 2.0	5.9 ± 1.9
Serum calcium (mg/dl)	9.1 ± 0.8	9.1 ± 0.8	9.2 ± 0.8	9.1 ± 0.9	9.0 ± 0.9	9.0 ± 0.9
Serum phosphorus (mg/dl)	5.3 ± 1.6	5.5 ± 1.7	5.0 ± 1.7	5.4 ± 1.8	5.5 ± 1.5	5.5 ± 1.4
Serum potassium (mEq/l)	4.7 ± 0.7	4.8 ± 0.7	5.1 ± 0.8	5.2 ± 0.8	4.9 ± 0.8	5.0 ± 0.8
Serum potassium >5.5 mEq/l (%)	12	15	26	30	19	24
K-binding resin prescription (%)	2	3	17	20	11	13
Antihypertensive agents (%)						
Any (non-RAASi) AHA	69	88	56	80	50	85
Beta-blocker	52	68	33	50	13	25
Calcium channel blocker	35	55	24	45	32	75
Diuretic	16	22	26	40	21	31
Comorbid conditions (%)						
Coronary artery disease	46	50	41	46	32	31
Cerebrovascular disease	17	16	17	19	14	14
Heart failure	39	40	26	31	19	20
Peripheral vascular disease	27	28	30	33	16	16
Other cardiovascular disease	30	28	37	36	32	27
Cancer (nonskin)	14	10	16	13	10	10
Diabetes	54	61	30	39	29	42
Gastrointestinal bleeding	5	6	5	5	4	5
Hypertension diagnosis	86	92	78	91	64	88
Lung disease	16	16	14	13	3	3
Neurologic disease	11	11	12	12	9	7
Psychiatric disorder	21	20	17	16	5	4
Recurrent cellulitis, gangrene	10	10	9	11	4	4

AHA, antihypertensive agent; A/NZ, Australia/New Zealand; HD, hemodialysis; RAASi, renin angiotensin-aldosterone system inhibitor; SBP, systolic blood pressure; WBC, white blood cell. Values shown are mean ± SD or % shown. Vintage: time since dialysis initiation.

prevalent HD patients. Next, additional adjustment for serum K had no impact on the RAASi-mortality association in either the incident or prevalent HD cohort. Analyses of medication-region interaction terms revealed no evidence of an effect modification by region for any of the antihypertensive medications tested (Supplementary Table S1). Finally, using propensity-score matching rather than covariate adjustment to account for potential confounders resulted in very similar findings: the mortality HR (95% CI) for RAASi (vs. non-RAASi) was 0.87 (0.76–1.00) among incident HD patients and 0.94 (0.88–1.00) among prevalent HD patients.

DISCUSSION

In this analysis of a large international HD cohort study, prescription of RAASi was 39% overall and varied widely by region, length of time on HD, and diabetes status, but varied minimally by history of CHF or CAD. RAASi prescription was associated with an 11% lower all-cause mortality rate among incident HD patients and a 6% lower mortality rate among prevalent HD patients, with no evidence of interaction—contrary to our hypothesis—with diabetes, CAD, or CHF. Inverse associations with mortality were also observed for BB and CCB, and appeared stronger for ARB than ACEi.

Randomized trials of RAASi in HD patients have yielded mixed results. Results from two studies[17,18] of Japanese HD patients showed that the CV event rate was lower in the group randomized to ARB than in the control group, while another trial[19] did not show any differences in outcomes for ARB versus the control group. Zannad *et al.*[20] similarly found a minimal difference in CV event rate for patients randomized

Table 3 | Number and percentage of HD patients prescribed RAASi, by region, time on dialysis, and subgroup of selected patient variables

	North America				Europe + A/NZ				Japan			
	Incident		Prevalent		Incident		Prevalent		Incident		Prevalent	
Subgroup	*N*	% RAASi	*N*	% RAASi	*N*	% RAASi	*N*	% RAASi	*N*	% RAASi	*N*	% RAASi
Diabetic												
No	1675	30	5496	38	3333	37	11,308	31	734	46	4624	39
Yes	2548	39	7173	45	2121	46	5580	41	757	59	2455	53
Congestive heart failure												
No	2299	36	6642	41	4061	41	12,246	33	1064	54	5693	44
Yes	1395	34	4295	42	1413	40	4681	39	430	49	1395	46
Coronary artery disease												
No	2034	34	5694	40	3365	39	9665	33	1114	53	4866	44
Yes	1691	36	5237	43	2145	42	7250	37	381	51	2225	43
Hypertension diagnosis												
No	479	22	1239	29	776	25	2997	18	228	38	1799	21
Yes	3225	37	9682	43	4701	43	13,856	38	1259	55	5259	52

A/NZ, Australia/New Zealand; RAASi, renin angiotensin-aldosterone system inhibitor.
Incident, on dialysis ≤120 days at study entry; prevalent, on dialysis >120 days at study entry.

to an ACEi in a study of HD patients in France. Cice *et al.*[16] found adding an ARB to a standard antihypertensive regime, including an ACEi, was associated with lower all-cause mortality, CV deaths, and hospitalization in HD patients with impaired left ventricular function (left ventricular ejection fraction <40%). Results from 2 meta-analyses[30,31] of randomized trials showed that RAASi use led to reduced left ventricular mass in dialysis patients. The first meta-analysis[30] also examined the association of RAASi with endpoints of fatal and nonfatal CV events. The authors concluded treatment was not associated with a "statistically significant" risk reduction. That conclusion, however, is misleading; the pooled risk ratio (0.66) was imprecisely estimated (95% CI 0.35–1.25), based on only 3 trials[17,18,20] with inconsistent results.

A large observational study[32] of postmyocardial infarction (MI) ACEi use in two cohorts (~1000 dialysis patients and 145,000 individuals not on dialysis) identified lower 30-day mortality for ACEi users in both cohorts, though ACEi prevalence was much lower (39% vs. 60%) in the dialysis cohort, reflecting potential fear of hyperkalemia and/or underuse post-MI. Our finding that RAASi prescription did not vary by patient history of CHF or CAD is surprising because their use is strongly recommended for patients with these conditions in the general population. Although high-level evidence is lacking in dialysis patients, guidelines preferentially recommend their use for patients with these conditions.[33] Our analysis, however, did not identify modification of the HR for the RAASi-mortality association by CAD or CHF.

Results of studies examining potential renoprotective properties of RAASi have been mixed. Some studies have demonstrated a strong association between RAASi use and slower chronic kidney disease progression.[27–29] On the other hand, others observed that discontinuation of RAASi led to improved kidney function in smaller studies of advanced

Table 4 | Prescription of antihypertensive medications, by region, DOPPS phase, and time on dialysis

	North America				Europe + A/NZ				Japan			
DOPPS phase[a]	D2	D3	D4	D5	D2	D3	D4	D5	D2	D3	D4	D5
Incident HD patients[b]												
No. of patients	1313	294	1191	1585	1997	613	1589	1334	463	225	312	505
Prescription (%)												
Beta-blocker	47	63	67	67	38	41	50	55	13	22	20	30
CCB	45	47	48	51	44	40	45	50	63	67	61	70
Diuretic	35	33	32	37	51	49	55	60	52	58	56	61
Prevalent HD patients[b]												
No. of patients	2361	2310	4272	4074	3976	4994	4953	3074	1605	2012	1675	1818
Prescription (%)												
Beta-blocker	44	56	62	64	30	38	43	47	11	17	21	24
CCB	44	43	43	43	29	29	33	33	51	53	49	51
Diuretic	15	17	19	21	23	30	33	37	20	26	26	28

A/NZ, Australia/New Zealand; CCB, calcium channel blocker; DOPPS, Dialysis Outcomes and Practice Patterns Study; HD, hemodialysis.
[a]D2, DOPPS phase 2: 2002–2004; D3, phase 3: 2005–2008; D4, phase 4: 2009–2011; D5, phase 5: 2012–2015.
[b]Incident, on dialysis ≤120 days at study entry; prevalent, on dialysis >120 days at study entry.

Table 5 | Association between RAASi and all-cause mortality by level of adjustment

Model	Covariate adjustment	Incident HD patients[a] (*N* = 11,421; 1906 events)	Prevalent HD patients[a] (*N* = 37,124; 8217 events)
0	Stratified by DOPPS phase, country	0.71 (0.64–0.78)	0.89 (0.85–0.94)
1	M0 + age	0.82 (0.74–0.90)	0.95 (0.91–1.00)
2	M1 + sex, black race, vintage	0.82 (0.74–0.90)	0.95 (0.91–1.00)
3	M2 + 13 comorbidities[b]	0.86 (0.78–0.95)	0.95 (0.90–0.99)
4	M3 + HD treatments[c]	0.89 (0.80–0.98)	0.94 (0.89–0.99)
5	M4 + BMI, albumin, calcium, phosphorus, hemoglobin	0.88 (0.80–0.98)	0.93 (0.88–0.97)
6	M5 + beta-blocker, CCB, diuretic	0.89 (0.80–0.99)	0.94 (0.90–0.99)

BMI, body mass index; CCB, calcium channel blocker; DOPPS, Dialysis Outcomes and Practice Patterns Study; HD, hemodialysis; RAASi, renin angiotensin-aldosterone system inhibitor.
Hazard ratio (95% CI) of all-cause mortality for RAASi versus no RAASi shown.
[a]Incident, on dialysis ≤120 days at study entry; prevalent, on dialysis >120 days at study entry.
[b]Comorbidities listed in Table 1.
[c]Less than 1 month of pre-HD nephrologist care (incident HD cohort only), catheter use, treatment time, intradialytic weight loss, dialysate K, K-binding resin.

chronic kidney disease patients.[34,35] A randomized trial is currently underway[36] to address this research question. In our study of HD patients, many subjects have already lost residual kidney function, especially those in our prevalent HD cohort, and so results from our incident HD cohort would better capture any potential effects of RAASi on mortality through slowing or accelerating decline in kidney function.

Table 6 | Effect modification for association between RAASi and mortality

Subgroup	Incident HD patients: HR (95% CI) for RAASi versus non-RAASi	Incident HD patients: Intx *P* value	Prevalent HD patients: HR (95% CI) for RAASi versus non-RAASi	Prevalent HD patients: Intx *P* value
Overall	0.89 (0.80–0.99)		0.94 (0.90–0.99)	
Diabetes		0.20		0.62
No	0.83 (0.71–0.97)		0.93 (0.87–1.00)	
Yes	0.95 (0.82–1.08)		0.95 (0.89–1.02)	
Congestive heart failure		0.95		0.99
No	0.90 (0.78–1.03)		0.94 (0.88–1.01)	
Yes	0.89 (0.77–1.03)		0.94 (0.87–1.02)	
Coronary artery disease		0.42		0.89
No	0.85 (0.73–0.99)		0.95 (0.88–1.02)	
Yes	0.92 (0.81–1.06)		0.94 (0.88–1.00)	
Hypertension diagnosis		0.56		0.86
No	0.82 (0.59–1.13)		0.93 (0.81–1.07)	
Yes	0.90 (0.81–1.01)		0.94 (0.90–1.00)	

CI, confidence incidence; HR, hazard ratio; Incident, on dialysis ≤120 days at study entry; Intx, interaction; prevalent, on dialysis >120 days at study entry; RAASi, renin angiotensin-aldosterone system inhibitor.
HR for RAASi versus non-RAASi, adjusted as in Table 5, Model 6.
Intx *P* value reflects a test of the null hypothesis that the RAASi effect (HR) is the same for patients with and without each comorbidity listed in the table (i.e., no effect modification of the HR).

Hyperkalemia is a key concern for HD patients,[10–12] and it was slightly more prevalent among patients who had been on RAASi. This is not unexpected in a cross-sectional study due to the negative feedback loop between RAASi use and K level (i.e., if RAASi use increases serum K, but patients with high serum K were less likely prescribed a RAASi, thereby reducing the positive cross-sectional association) and confirms results from a smaller prior study by Knoll *et al.*[37] Hyperkalemia can be treated or minimized by K-binding medications, diuretics, correcting the metabolic acidosis, and/or dietary K restriction, with the latter used as first-line therapy. We do not have information on dietary interventions but observed greater prescription of diuretics and K binders in RAASi-treated patients (Tables 1 and 2). K-binding resins were infrequently used in our data, especially in North America (1%), but may provide an opportunity for RAASi use in a greater proportion of HD patients, although patient adherence is a limitation of K-binding resins.

Although our primary objective was to estimate the effect of RAASi prescription on all-cause mortality, our study also provides a detailed summary of international variation in RAASi prescription patterns in HD patients over the past 15 years by time on dialysis and patient subgroups. We noted that ARB prescription vastly exceeded ACEi prescription in Japanese HD patients, which was not observed by Lopes *et al.*[38] in an analysis of DOPPS phase 1–2 data (1996–2004). This recent increased preference of ARB over ACEi in Japan (Figure 1) is consistent with the later commercial availability of ARB, and may also have been influenced by favorable trial results among Japanese HD patients.[17,18] The prescription prevalence of RAASi types other than ACEi or ARBs was <5% in all regions. We thus hesitate to draw conclusions about other RAASi types (aldosterone antagonists, direct renin inhibitors) for which we lacked the statistical power to analyze individually; thus, we suggest additional study to investigate potential benefits of these medications in dialysis patients.

We performed several analyses to provide context for our finding that RAASi prescription was associated with lower mortality. First, we analyzed ACEi and ARBs separately. The results of this sensitivity analysis, which was not the main focus or hypothesis of the current work, were consistent with previous results of a DOPPS analysis,[38] showing that the strongest inverse associations with clinical outcomes were observed for ARB and BB prescription, with minimal association between ACEi and mortality. While the current study focuses on RAASi, the relationship between other antihypertensive medications and mortality are shown in Figure 2. BB prescription, which has increased sharply over time in all regions (Table 4), was also associated with lower mortality, consistent with previous research.[38,39] Results for CCB were compelling, as the inverse association between treatment and mortality was much stronger in the incident HD patient cohort, which may be less prone to bias. Minimal association between diuretic prescription and mortality was observed in both the incident and prevalent HD patient cohorts. By narrowing the focus to RAASi, however, we were able to

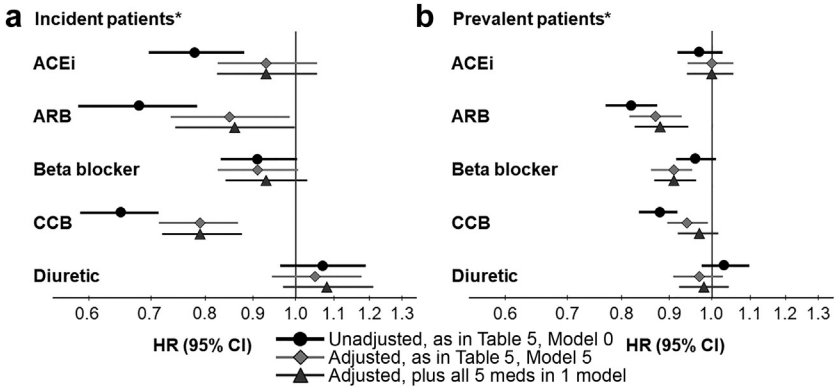

Figure 2 | Associations between antihypertensive medications and mortality in (**a**) incident dialysis patients and (**b**) prevalent dialysis patients. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blocker; CI, confidence interval; HR, hazard ratio. *Incident, on dialysis ≤120 days at study entry; prevalent, on dialysis >120 days at study entry.

expand on the work of Lopes *et al.*[38] by stratifying all analyses by time on dialysis, comparing patient characteristics by RAASi prescription, showing how different levels of adjustment impact the RAASi-mortality association, and investigating effect modification by patient comorbidities. Our finding of stronger associations with ARB prescription compared with ACEi prescription is generally consistent with previous findings,[17,18,38] and it is supported by previous research showing greater serum K increases for those starting ACEi versus ARB therapy among patients with renal insufficiency.[40]

Our study had some limitations. Results may have been subject to confounding by indication because patients were prescribed a RAASi for reasons that may reflect health status and mortality risk. We adjusted for several risk factors in the analysis, but residual confounding may exist. We attempted to use an instrumental variable analysis with HD facility as the instrument[41] to further address this issue, but an F-statistic of 1.6 in the first-stage model was prohibitively low—an indication of a weak instrument—and thus this approach was not pursued further. Another issue is that because some patients were exposed to RAASi treatment previous to DOPPS enrollment, a negative response to this treatment, perhaps related to hyperkalemia or other side effects, may have to led to discontinuation of the treatment before study entry. If these patients had a greater mortality risk, our results might be biased toward a RAASi benefit. Our cohort of incident HD patients is less prone to this bias than the prevalent HD cohort due to the minimal time between HD initiation and study entry. Further, using longitudinal DOPPS data, 91% and 86% of patients prescribed a RAASi remained on a RAASi 4 and 8 months later, respectively; 95% and 91% of patients not prescribed a RAASi were also not prescribed a RAASi 4 and 8 months later, respectively. These data provide some evidence that our exposure variable, RAASi prescription at DOPPS enrollment, provides a reasonable snapshot of an individual patient's exposure to RAASi therapy during HD, although misclassification due to predialysis RAASi treatment is possible. Although we considered treating RAASi use as a time-dependent variable, this approach would have likely resulted in an exaggerated survival benefit due to the inability to adjust for all confounders in a time-dependent manner, including predictors of short-term risk of death that might influence discontinuation of RAASi and other medications. Finally, we analyzed RAASi prescription as a dichotomous variable (yes/no) because dosage data were not widely available.

Our study also had a number of strengths. We did not exclude any patients based on clinical characteristics, in contrast to many randomized trials[16–20] that used narrow inclusion criteria to estimate the effects of RAASi in HD patients. Results of our large nationally representative study, although an observational design, are thus more likely generalizable to the target population of in-center HD patients in each country. Additionally, this design allowed the study of regional trends over many years. Standardized collection of medication data resulted in a consistent definition of the exposure across DOPPS phases and countries. Many potential confounders were captured to minimize bias, although we were careful not to adjust for expected mediators (e.g., serum K, SBP) in the causal pathway. Although the large sample provided us sufficient statistical power to detect weak-to-moderate associations, it is especially important in this context to interpret both the magnitude and precision of each estimated HR and 95% CI rather than relying on statistical tests of whether associations were "statistically significant."[42]

In summary, HD patients prescribed a RAASi had lower mortality rates than those not prescribed a RAASi. We did not observe a higher likelihood of RAASi prescription among patients with class-specific indications such as CHF or CAD or among patients new to dialysis for whom RAASi use may potentially help to preserve residual kidney function. In contrast to our hypothesis that RAASi use may be especially beneficial in such patients, the RAASi-mortality association was similar among patients with or without CHF and CAD, and among incident and prevalent HD patients; however, we did find that this association was stronger for ARBs than ACEi, which warrants further study. RAASi prescription was lower than other antihypertensive classes, including BB and

CCB, which were also associated with favorable outcomes. This study suggests a relatively small survival benefit of RAASi and other antihypertensive agents and provides further evidence supporting prescription of these medications in HD patients, although a randomized study is warranted to address prescribing criteria.

METHODS

Data source

The DOPPS is a large international prospective cohort study of patients age 18 years of age and older treated with in-center HD. Detailed information regarding study design is on the DOPPS website http://www.dopps.org; maintenance HD patients were randomly selected from national samples of dialysis facilities in each country.[43,44] Study approval and patient consent were obtained as required by national and local ethics committee regulations. In this analysis, DOPPS phase 2–5 (2002–2015) data from 12 countries in 3 regions were used: North America (Canada, United States), Europe/ANZ (Belgium, France, Germany, Italy, Spain, Sweden, United Kingdom, Australia, New Zealand), and Japan. Data on demographics, comorbid conditions, laboratory values, and prescriptions were abstracted from medical records at study entry (baseline) using uniform and standardized data collection tools.

The exposure of interest was prescription of a RAASi at baseline. Medications classified as RAASi were ACEi, ARBs, aldosterone receptor antagonists, and direct renin inhibitors. For the outcome of all-cause mortality, follow-up started at baseline and continued until death, study phase end, or 7 days after leaving the facility, loss to follow-up, transplantation, or switch to home dialysis (whichever occurred first).

Among an eligible cohort of 57,107 patients, 5795 were excluded due to lack of any prescription data, 521 were excluded due to missing information on time since dialysis initiation ("vintage"), and 2246 were excluded due to insufficient follow-up by the HD facility. All of the remaining 48,545 patients were included in the analyses: 11,421 "incident" HD patients (vintage $\leq$120 days at baseline) and 37,124 "prevalent" HD patients (vintage $>$120 days at baseline).

Statistical analysis

Because RAASi prescription at, or soon after, dialysis initiation in part reflects the care patients received in the advanced chronic kidney disease stages (before transition to dialysis), all analyses were conducted separately among incident and prevalent HD patients. We described the prevalence of RAASi, BB, and CCB prescription by region and DOPPS phase. Within each region, we summarized patient characteristics by RAASi prescription (yes/no) and prevalence of RAASi prescription by patient subgroups: history of diabetes, CHF, CAD, and hypertension.

We estimated the association (hazard ratio [HR] and 95% confidence interval [CI]) between baseline RAASi and all-cause mortality, adjusting for potential confounders. This fixed baseline-exposure approach, especially with incident HD patients, is less susceptible to confounding by indication than a time-dependent approach because change in RAASi prescription over time depends on changes in serum K and health status, which are difficult to control by adjustment for time-dependent covariates. Furthermore, to the extent that serum K is also a mediator in the RAASi-mortality causal pathway, we would not want to adjust for it. Cox regression models were stratified by DOPPS phase and country, accounting for facility clustering using robust sandwich covariance estimators. The key assumption of proportional hazards was confirmed via log-log survival plots and testing the interaction between log-time and RAASi. We used a series of progressively adjusted models to observe how accounting for potential confounders, all measured at baseline, impacted the association between RAASi and mortality. Levels of adjustment are described in detail in Table 5. We did not adjust for SBP because SBP levels were likely affected by RAASi treatment before study entry, and it would not be appropriate to adjust for a mediator of the exposure effect (i.e., previous RAASi $\rightarrow$ baseline SBP $\rightarrow$ mortality). Effect modification of the RAASi-mortality association was assessed for 4 risk factors: history of diabetes, CHF, CAD, and hypertension.

We performed sensitivity analyses to test the robustness of our findings. First, to better frame the RAASi-mortality association, we similarly estimated the mortality HR for 3 other types of antihypertensive medications: BB, CCB, and diuretics. For CCB, we further divided medications into dihydropyridine and non-dihydropyridine. Second, we analyzed ACEi and ARBs separately because these are the 2 most common types of RAASi. Third, we assessed the impact of adjustment for baseline serum K, which may be a confounder and/or mediator of the RAASi-mortality relationship. Fourth, we investigated potential effect modification by region. Finally, in a *post hoc* analysis in response to an anonymous reviewer, we used propensity-score matching rather than covariate adjustment in our primary analyses. A greedy matching algorithm was used to match untreated patients with RAASi-treated patients (1:1 match, without replacement).

To deal with missing covariate data, we used multiple imputation, assuming that data were missing at random. Missing covariate values were multiply imputed using the Sequential Regression Multiple Imputation Method by IVEware.[45] Results from 20 such imputed data sets were combined for the final analysis using Rubin's formula.[46] The proportion of missing data was $<$10% for all variables used for covariate adjustment, with the exception of pre-HD nephrologist care (32% in the incident cohort). All analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC).

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Table S1. Association between antihypertensive medications and all-cause mortality: interaction by region.

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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