CHEST Online Supplement

Renin-Angiotensin-Aldosterone System Inhibitor Use and Mortality in Pulmonary Hypertension

Insights From the Veterans Affairs Clinical Assessment Reporting and Tracking Database

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e-Appendix 1.

Supplemental Methods

Participants

The CART cohort is a large, national data collection of veterans who received a heart catheterization at a VA medical center since 2005. For the current analysis, we included all veterans who received a right heart catheterization (RHC) between fiscal year 2008 and 2016, had a mean pulmonary artery pressure (mPAP) of ≥25 mmHg (which defined PH during the study period), and a recorded value for pulmonary artery wedge pressure (PAWP). Since the majority of patients in this cohort exhibit non-PAH PH[1], CART represents a unique opportunity to study the effect of RAAS inhibitors on clinical outcomes in these clinically highly common and highly relevant types of PH. We have previously leveraged this database to study hemodynamic phenotypes, gender differences and pharmaco-epidemiology in the VA system[1-4]. The CART program has been described in detail[1,5,6]. The CART cohort has been validated for clinical accuracy and uses embedded software in the integrated VA health care system to collect patient data, procedural characteristics, and longitudinal outcomes to assemble the cohort. Rigorous quality control procedures are in place. Pulmonary vascular resistance (PVR) was calculated as (mPAP – PAWP)/cardiac output for each participant and then averaged. Mean arterial pressure was determined non-invasively at the time of RHC. The Colorado Multiple Institution Review Board approved this study (#14-1449).

Medication use

Medication use was ascertained using the VA medical record. Participants were considered to have "used" a medication if an *outpatient* prescription was filled within 90 days of their RHC. Participants were excluded if they died within 90 days of their RHC or had a hospital stay lasting longer than 60 days following that catheterization. This provided a minimum of 30 days to detect outpatient medication use.

RAAS inhibitor (ACEI/ARB or AA) use was the primary exposure in all analyses. Other baseline medications were considered as potential confounders and included filled prescriptions for beta-receptor antagonists, calcium-channel blockers, digoxin, diuretics, lipid lowering medications, medications for asthma or

chronic obstructive pulmonary disease, medications for diabetes mellitus, oral anticoagulants, platelet inhibitors, systemic vasodilators (including nitrates, alpha$_1$-antagonists, alpha$_2$-agonists, and direct vasodilators), H2 receptor antagonists, and proton-pump inhibitors. A full medication list is included in **e-Table 1**.

Covariates

In addition to concurrent medications, characteristics that might confound the relationship between RAAS inhibitors and mortality were collected from the VA electronic medical record. Specifically, we accounted for the following possible confounders: (1) demographic characteristics (age [modeled continuously], sex, race/ethnicity [black or African American, white, or other], and body mass index [modeled as a natural spline with fixed degrees of freedom]); (2) markers of socioeconomic status and health behaviors (current or previous history of smoking, current or previous history of alcohol abuse, quartiles of income [based on the median income of a participants home zip code according to 2006-2010 census data], and marital status); (3) comorbid medical conditions at the time the criterion for PH was met (the presence or absence of end-stage renal disease, diabetes, cirrhosis, sleep apnea, chronic obstructive pulmonary disease [COPD], asthma, interstitial lung disease, prior myocardial infarction, prior coronary intervention, congestive heart failure [CHF], valvular disease, congenital heart disease, and atrial fibrillation or flutter); and (4) co-medication use (as described in **e-Table 1**). To avoid confounding by co-medication use with another RAAS inhibitor in patients taking both AAs and ACEI/ARBs, we included the medication class not being estimated in the adjustment (e.g., if AA was the exposure of interest, we included ACEI/ARBs in the adjustment and *vice versa*).

In additional analyses for the AA user cohort, potassium levels were included as a covariate in addition to the original predictors (sex, race, age, BMI, income, tobacco, alcohol abuse and marital status). Potassium level was modeled continuously as a natural spline with 3 degrees of freedom. Levels up to 60 days prior to the procedure date were included. To explore whether disease severity is a potential modifiers of the AA-mortality relationship, we performed sensitivity analyses in adjusted models with B-type natriuretic peptide (BNP) levels and inpatient status at the time of RHC (as indicators of disease severity) included as covariates in addition to the original predictors. BNP levels up to 60 days prior to the procedure date were included.

Outcomes

The primary outcome was the rate of all-cause mortality. Risk time accrued after the 90-day window used to establish exposure status. Separation of exposure ascertainment and outcome assessment was used to avoid immortal time bias and ensure all participants had an equal chance for exposure to RAAS inhibitors. Mortality was determined using the combined VA vital status file, which has a 97.6% exact agreement with the National Death Index[7]. Because this was an observational cohort of real-world clinical care, no participant was considered "lost to follow-up" as there was no fixed study determined interval at which we expected a visit and could censor them if this visit was missing. If a participant died, then their risk time stopped accruing at the time of death. All other participants were considered to be alive and accrued risk-time until the date of data extraction.

Statistical analysis

We used methods of Kaplan & Meier to estimate unadjusted associations and Cox proportional hazards using a complete case analysis to estimate adjusted associations of RAAS inhibitor use within 90 days of RHC and mortality. Log-rank testing (distributed as a Chi-square) was used to determine Kaplan-Meyer survival estimators. A series of planned *a priori* adjustments were performed and consistent with our previous manuscripts[4]. In the limited model, we adjusted for age, sex, race, and body mass index. In the adjusted model, we also accounted for participants' markers of socioeconomic status and health behaviors including income, tobacco use, alcohol abuse, and marital status. In separate models, we further adjusted for comorbid medical conditions or co-medication use. A random intercept (frailty term) was included to account for differences between hospitals in all primary models. Variable selection for the Cox models was justified scientifically for parameters of interest. Given the size of this cohort, there was not a statistical approach to model specification and all covariates we chosen *a priori.*

Analyses were repeated in a cohort of propensity-matched participants. Propensity scores were used to match RAAS inhibitor users with non-users that had an otherwise similar propensity to use RAAS inhibitors using the MatchIt package in R[8,9]. The propensity to use RAAS inhibitors was calculated as a logit function including

factors hypothesized to predict RAAS inhibitor use, such as comorbidity, body mass index, and co-medication use. Nearest-neighbor matching was used to create pairs of RAAS inhibitor users and non-users who had an otherwise similar likelihood of use. Only RAAS inhibitor users with a propensity score less extreme than non-users were matched (common support). Matched pairs were included only if propensity scores differed by less than 0.05 standard deviations to ensure similarity.

Because this was a large administrative cohort, careful phenotyping by World Health Organization PH group was not feasible; however, the PAWP was available for all participants. In pre-specified exploratory analyses, PAWP less than or equal to 15 mmHg versus greater than 15 mmHg was evaluated as an effect modifier in the association between RAAS inhibitor use and mortality in veterans with PH.

Given the unexpected finding suggesting worse mortality in unadjusted relationships with AA users relative to non-users and the absence of this relationship in the propensity-matched cohort, we considered additional exploratory adjustments to better understand the potential role of confounding in this relationship. In particular, we explored whether further adjustment by blood potassium level or markers of disease severity modified the relationship between AA use and mortality. B-type natriuretic peptide (BNP) level and inpatient status at the time of RHC were used as markers of disease severity.

Analyses were performed using SAS 9.4 and R 3.3.1. $p<0.05$ was considered statistically significant.

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Supplemental tables

e-Table 1: List of medications used for analyses. ACE inhibitors, angiotensin receptor blockers and aldosterone antagonists were primary exposures of interest and are shown in gray fields; all other medications were considered as potential confounders.

ACE-inhibitors	**Angiotensin receptor blockers**	**Aldosterone antagonists**	**Anticoagulants**	**Beta-blockers**
Benazepril	Azilsartan	Spironolactone	Enoxaparin	Acebutolol
Captopril	Candesartan	Eplerenone	Fondaparinux	Atenolol
Enalapril	Eprosartan		Warfarin	Betaxolol
Fosinopril	Irbesartan		Apixaban	Bisoprolol
Lisinopril	Losartan		Dabigatran	Carteolol
Moexipril	Olmesartan		Edoxaban	Carvedilol
Perindopril	Telmisartan		Rivaroxaban	Inderal
Quinapril	Valsartan		Idraparinux	Labetalol
Ramipril			Tinzaparin	Metoprolol
Trandolapril				Nadolol
Cilazapril				Nebivolol
Zofenopril				Penbutolol
Temocapril				Pindolol
Renormax				Propranolol
				Sotalol
				Timolol
Bronchodilators/ inhaled corticosteroids	**Calcium channel blockers**	**Corticosteroids**	**Digitalis**	**Diuretics**
Albuterol	Amlodipine	Celestone	Digitoxin	Amiloride
Formoterol	Clevidipine	Cortisone	Digoxin	Benzthiazide
Levalbuterol	Diltiazem	Dexamethasone		Bumetanide
Salmeterol	Felodipine	Hydrocortisone		Chlorothiazide
Terbutaline	Mibefradil	Kenacortisone		Chlorthalidone
Theophylline	Nicardipine	Methylprednisolone		Ethacrynic Acid (Ethacrynate)
Ipratropium	Nifedipine	Prednisone		Furosemide
Tiotropium	Nimodipine	Prednisone/deltazone		Hydrochlorothiazide
Beclomethasone	Nisoldipine	Benesone (betamethasone)		Indapamide
Budesonide	Verapamil	Fluticasone		Metolazone
Fluticasone	Lacidipine	Lotrisone		Torsemide
Triamcinolone				Triamterene
Montelukast				Trichlormethiazide
Zafirlukast				Cyclothiazide
Bitolterol				
Beta-sitosterol				
Pirbuterol				
Roflumilast				
Cilomilast				
Glucose-lowering agents	**H2 Blockers**	**Lipid-lowering agents**	**Platelet inhibitors**	**Proton pump inhibitors**
Acarbose	Cimetidine	Clofibrate	Clopidogrel	Esomeprazole
Exenatide	Famotidine	Fenofibrate	Prasugrel	Lansoprazole
Glipizide	Nizatidine	Gemfibrozil	Dipyridamole	Omeprazole
Glimepiride	Ranitidine	Atorvastatin	Ticlopidine	Pantoprazole
Glyburide	Roxatidine	Cerivastatin		Dexlansoprazole
Insulin Glargine		Cholestyramine		Rabeprazole
Regular Insulin		Ezetimibe		
Insulin Lispro		Fluvastatin		
NPH insulin		Lovastatin		
Metagliptin		Niacin		
Metformin		Pravastatin		
Nateglinide		Rosuvastatin		
Pioglitazone		Simvastatin		
Pramlintide		Pitavastatin		

Repaglinide
Rosiglitazone
Sitagliptan
Tolazamide
Tolbutamide
Troglitazone
Hoe901
Humulin
Novolin

Pulmonary vasodilators
Sildenafil (45+ tablets monthly)
Tadalafil (30+ tablets monthly)
Bosentan
Ambristentan
Macitentan
Treprostinil
Epoprostenol (IV only)
Iloprost
Selexipag
Riociguat

Systemic vasodilators
Alpha-blockers
Doxazosin
Phenoxybenzamine
Prazosin
Terazosin
Nitrates
Isosorbide dinitrate
Isosorbide mononitrate
Isotrate
Nitroglycerin
Alpha-Agonists
Clonidine
Apraclonidine
Guanfacine
Methyldopa
Reserpine
Direct vasodilators
Hydralazine
Minoxidil

e-Table 2: Medication use of the study cohort. Values are expressed in percent, with absolute numbers included in parentheses.

Medication class	All subjects (N = 24,221)	ACEI/ARB users (N = 14,912)	ACEI/ARB non-users (N = 9,309)	AA users (N = 4,092)	AA non-users (N = 20,129)
ACE inhibitor	49.0 (11875)	79.6 (11875)	0.0 (0)	58.2 (2382)	47.2 (9493)
Aldosterone antagonist	16.9 (4092)	20.5 (3059)	11.1 (1033)	100.0 (4092)	0.0 (0)
Alpha agonist	1.5 (360)	1.7 (254)	1.1 (106)	1.4 (56)	1.5 (304)
Angiotensin receptor blocker	13.8 (3334)	22.4 (3334)	0.0 (0)	18.8 (771)	12.7 (2563)
Anticoagulant	32.7 (7920)	34.6 (5165)	29.6 (2755)	38.9 (1591)	31.4 (6329)
Antiplatelet therapy	19.1 (4620)	21.8 (3247)	14.7 (1373)	18.3 (749)	19.2 (3871)
Beta blocker	73.4 (17788)	82.7 (12326)	58.7 (5462)	85.8 (3510)	70.9 (14278)
Bronchodilator/inhaled corticosteroid	39.3 (9516)	39.5 (5889)	39.0 (3627)	39.7 (1625)	39.2 (7891)
Calcium channel blocker	22.6 (5475)	23.4 (3483)	21.4 (1992)	14.4 (591)	24.3 (4884)
Digitalis	12.0 (2907)	14.0 (2093)	8.7 (814)	25.5 (1044)	9.3 (1863)
Diuretic	71.7 (17367)	79.3 (11830)	59.5 (5537)	90.3 (3695)	67.9 (13672)
Glucose-lowering agent	37.7 (9141)	42.9 (6395)	29.5 (2746)	41.4 (1696)	37.0 (7445)
H2 blocker	8.2 (1981)	8.7 (1294)	7.4 (687)	8.2 (336)	8.2 (1645)
Hydrochlorothiazide	7.4 (1799)	8.5 (1272)	5.7 (527)	2.7 (111)	8.4 (1688)
Lipid-lowering agent	67.7 (16407)	75.6 (11273)	55.2 (5134)	70.6 (2889)	67.2 (13518)
Nitrate	23.5 (5688)	26.1 (3896)	19.3 (1792)	27.6 (1130)	22.6 (4558)
Proton pump inhibitor	38.5 (9322)	39.9 (5950)	36.2 (3372)	41.8 (1711)	37.8 (7611)
Pulmonary vasodilator	4.0 (961)	2.7 (403)	6.0 (558)	4.3 (175)	3.9 (786)
Systemic vasodilator	10.4 (2531)	10.3 (1529)	10.8 (1002)	14.2 (583)	9.7 (1948)

e-Table 3: Matched cohort for the ACEI/ARB analyses (stratified by ACEI/ARB exposure). Values are expressed in percent, with absolute numbers included in parentheses (with the exception of age, body mass index and income, which are expressed as means with standard deviation). CABG = coronary artery bypass grafting, CHD = congenital heart disease, CHF = congestive heart failure, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, ILD = interstitial lung disease, MI = myocardial infarction, OSA = obstructive sleep apnea, PCI = percutaneous coronary intervention; RAP = right atrial pressure, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary artery wedge pressure, CI = cardiac index, PVR = pulmonary vascular resistance, MAP = mean arterial pressure.

Variable	All subjects (N = 14,960)	ACEI/ARB users (N = 7,480)	ACEI/ARB non-users (N = 7,480)	p-value
Age	67.4 (9.9)	67.2 (9.9)	67.5 (10.0)	0.13
Sex (male)	96.3 (14401)	96.2 (7196)	96.3 (7205)	0.7
Race				0.61
• White	78.0 (11666)	77.7 (5809)	78.3 (5857)	
• Black	20.0 (2993)	20.3 (1516)	19.7 (1477)	
• Other	2.0 (301)	2.1 (155)	2.0 (146)	
Body mass index	31.4 (6.9)	31.5 (6.9)	31.3 (6.9)	0.12
Socioeconomic status				
• Tobacco use	62.2 (9311)	62.5 (4677)	62.0 (4634)	0.47
• Alcohol abuse	10.7 (1602)	10.5 (788)	10.9 (814)	0.49
• Income	50015 (17349)	49858 (17043)	50172 (17650)	0.27
Marital status				0.84
• Married	50.2 (7507)	49.8 (3727)	50.5 (3780)	
• Divorced	29.1 (4349)	29.2 (2186)	28.9 (2163)	
• Single	12.7 (1904)	12.9 (964)	12.6 (940)	
• Widowed	8.0 (1200)	8.1 (603)	8.0 (597)	
Comorbidities				
• Asthma	5.6 (834)	5.7 (423)	5.5 (411)	0.67
• Atrial fibrillation/flutter	35.2 (5272)	35.2 (2635)	35.3 (2637)	0.97
• CHD	0.6 (88)	0.5 (40)	0.6 (48)	0.39
• CHF	65.6 (9807)	65.8 (4920)	65.3 (4887)	0.57
• Cirrhosis	7.9 (1176)	7.7 (577)	8.0 (599)	0.5
• CKD/Dialysis	37.9 (5666)	37.9 (2837)	37.8 (2829)	0.89
• COPD	39.8 (5955)	39.5 (2952)	40.1 (3003)	0.39
• Diabetes	50.6 (7573)	51.1 (3824)	50.1 (3749)	0.22
• Hypertension	90.8 (13585)	93.6 (7001)	88.0 (6584)	<.001
• ILD	0.8 (117)	0.7 (55)	0.8 (62)	0.52
• OSA	15.7 (2342)	15.7 (1174)	15.6 (1168)	0.89
• Prior MI, PCI or CABG	41.4 (6189)	41.4 (3093)	41.4 (3096)	0.96
• Valvular heart disease	42.1 (6299)	41.8 (3128)	42.4 (3171)	0.48
Medications				
• ACE inhibitor	39.9 (5968)	79.8 (5968)	0.0 (0)	<.001
• Aldosterone antagonist	13.2 (1975)	13.5 (1008)	12.9 (967)	0.32
• Alpha agonist	1.4 (208)	1.5 (113)	1.3 (95)	0.21
• Angiotensin receptor blocker	10.9 (1638)	21.9 (1638)	0.0 (0)	<.001
• Anticoagulant	33.1 (4950)	33.1 (2478)	33.0 (2472)	0.92
• Antiplatelet therapy	17.4 (2597)	17.6 (1313)	17.2 (1284)	0.53
• Beta blocker	70.4 (10536)	70.9 (5301)	70.0 (5235)	0.24
• Bronchodilator/inhaled corticosteroid	39.9 (5962)	39.7 (2966)	40.1 (2996)	0.62
• Calcium channel blocker	23.6 (3533)	23.8 (1780)	23.4 (1753)	0.6
• Digitalis	10.2 (1532)	10.4 (775)	10.1 (757)	0.63
• Diuretic	68.7 (10276)	69.1 (5170)	68.3 (5106)	0.26
• Glucose-lowering agent	34.8 (5209)	35.4 (2650)	34.2 (2559)	0.12
• H2 blocker	8.1 (1217)	8.3 (618)	8.0 (599)	0.57
• Hydrochlorothiazide	6.8 (1024)	7.0 (523)	6.7 (501)	0.48
• Lipid-lowering agent	64.7 (9683)	64.9 (4854)	64.6 (4829)	0.67
• Nitrate	23.0 (3434)	23.4 (1750)	22.5 (1684)	0.2
• Proton pump inhibitor	39.0 (5827)	38.7 (2895)	39.2 (2932)	0.54
• Pulmonary vasodilator	4.2 (631)	4.2 (316)	4.2 (315)	0.97
• Systemic vasodilator	12.0 (1789)	12.0 (894)	12.0 (895)	0.98

Hemodynamics				
• RAP (mmHg)	12.0 (5.7)	12.0 (5.6)	12.1 (5.8)	0.12
• mPAP (mmHg)	35.1 (8.5)	35.0 (8.5)	35.1 (8.6)	0.44
• PAWP (mmHg)	21.2 (7.4)	21.4 (7.3)	21.0 (7.4)	<.001
• CI (L/min/m^2)	2.5 (0.7)	2.4 (0.7)	2.5 (0.7)	<.001
• PVR (Wood units)	2.9 (2.1)	2.9 (2.0)	3.0 (2.1)	0.04
• MAP (mmHg)	93.0 (10.1)	93.7 (10.3)	92.3 (9.8)	<.001

e-Table 4: Matched cohort for the AA analyses (stratified by AA exposure). Values are expressed in percent, with absolute numbers included in parentheses (with the exception of age, body mass index and income, which are expressed as means with standard deviation). CABG = coronary artery bypass grafting, CHD = congenital heart disease, CHF = congestive heart failure, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, ILD = interstitial lung disease, MI = myocardial infarction, OSA = obstructive sleep apnea, PCI = percutaneous coronary intervention; RAP = right atrial pressure, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary artery wedge pressure, CI = cardiac index, PVR = pulmonary vascular resistance, MAP = mean arterial pressure.

Variable	All subjects (N = 7,872)	AA users (N = 3,936)	AA non-users (N = 3,936)	p-value
Age	64.3 (9.4)	64.3 (9.5)	64.3 (9.4)	0.93
Sex (male)	97.0 (7636)	97.1 (3821)	96.9 (3815)	0.69
Race				0.84
• White	71.4 (5622)	71.6 (2819)	71.2 (2803)	
• Black	26.7 (2098)	26.4 (1039)	26.9 (1059)	
• Other	1.9 (152)	2.0 (78)	1.9 (74)	
Body mass index	31.7 (7.1)	31.7 (7.1)	31.7 (7.1)	0.83
Socioeconomic status				
• Tobacco use	63.0 (4956)	63.3 (2491)	62.6 (2465)	0.54
• Alcohol Abuse	14.5 (1142)	14.2 (558)	14.8 (584)	0.41
• Income	49398 (17290)	49284 (16820)	49513 (17748)	0.56
Marital status				0.62
• Married	47.3 (3723)	46.9 (1845)	47.7 (1878)	
• Divorced	30.9 (2436)	31.6 (1243)	30.3 (1193)	
• Single	15.5 (1224)	15.3 (601)	15.8 (623)	
• Widowed	6.2 (489)	6.3 (247)	6.1 (242)	
Comorbidities				
• Asthma	5.6 (439)	5.5 (217)	5.6 (222)	0.81
• Atrial fibrillation/flutter	38.5 (3032)	38.4 (1510)	38.7 (1522)	0.78
• CHD	0.4 (34)	0.4 (17)	0.4 (17)	1.00
• CHF	90.3 (7110)	90.2 (3549)	90.5 (3561)	0.65
• Cirrhosis	11.9 (934)	11.4 (448)	12.3 (486)	0.19
• CKD/Dialysis	37.5 (2955)	36.8 (1447)	38.3 (1508)	0.16
• COPD	38.4 (3019)	38.4 (1510)	38.3 (1509)	0.98
• Diabetes	55.9 (4401)	55.5 (2183)	56.4 (2218)	0.43
• Hypertension	91.1 (7174)	91.1 (3586)	91.2 (3588)	0.94
• ILD	0.4 (33)	0.4 (15)	0.5 (18)	0.6
• OSA	17.1 (1344)	17.0 (671)	17.1 (673)	0.95
• Prior MI, PCI or CABG	46.3 (3645)	46.6 (1835)	46.0 (1810)	0.57
• Valvular heart disease	33.5 (2639)	33.4 (1315)	33.6 (1324)	0.83
Medications				
• ACE inhibitor	58.6 (4613)	57.5 (2265)	59.7 (2348)	0.06
• Aldosterone antagonist	50.0 (3936)	100.0 (3936)	0.0 (0)	<.001
• Alpha agonist	1.4 (111)	1.4 (56)	1.4 (55)	0.92
• Angiotensin receptor antagonist	16.6 (1310)	18.7 (736)	14.6 (574)	<.001
• Anticoagulant	38.7 (3044)	38.4 (1512)	38.9 (1532)	0.64
• Antiplatelet therapy	18.4 (1451)	18.5 (730)	18.3 (721)	0.79
• Beta blocker	85.5 (6728)	85.4 (3360)	85.6 (3368)	0.8
• Bronchodilator/inhaled corticosteroid	40.0 (3147)	39.9 (1572)	40.0 (1575)	0.95
• Calcium channel blocker	15.5 (1223)	14.9 (586)	16.2 (637)	0.11
• Digitalis	23.0 (1809)	23.1 (911)	22.8 (898)	0.73
• Diuretic	89.9 (7078)	89.9 (3539)	89.9 (3539)	1.00
• Glucose-lowering agent	42.3 (3331)	41.7 (1643)	42.9 (1688)	0.31
• H2 blocker	8.3 (657)	8.4 (330)	8.3 (327)	0.9
• Hydrochlorothiazide	2.7 (211)	2.8 (111)	2.5 (100)	0.44
• Lipid-lowering agent	70.7 (5564)	71.0 (2793)	70.4 (2771)	0.59
• Nitrate	28.0 (2204)	27.7 (1091)	28.3 (1113)	0.58
• Proton pump inhibitor	41.5 (3264)	41.5 (1633)	41.4 (1631)	0.96
• Pulmonary vasodilator	4.1 (324)	4.2 (167)	4.0 (157)	0.57
• Systemic vasodilator	14.2 (1119)	14.1 (555)	14.3 (564)	0.77
Hemodynamics				

• RAP (mmHg)	13.1 (6.0)	13.3 (6.2)	12.8 (5.9)	<.001
• mPAP (mmHg)	36.7 (8.7)	37.0 (8.7)	36.5 (8.7)	0.01
• PAWP (mmHg)	23.1 (7.7)	23.6 (7.7)	22.6 (7.5)	<.001
• CI (L/min/m^2)	2.3 (0.7)	2.2 (0.7)	2.4 (0.7)	<.001
• PVR (Wood units)	3.0 (2.1)	3.1 (2.1)	3.0 (2.1)	0.21
• MAP (mmHg)	92.4 (11.0)	91.5 (11.2)	93.3 (10.7)	<.001

e-Table 5: Interactions between PAWP and ACEI/ARB exposure or AA exposure. Summarized in the table are the hazard ratios (95% CI) for the interaction term of ACEI/ARB exposure (upper panel) or AA exposure (lower panel) by PAWP category for the assessed models. The PAWP category has a cut-point of 15 mmHg as indicated in the table. For this aim, model 1 (limited adjustment) and model 3 (full adjustment with com-morbidities as co-variates) were included. The same analyses were run using the ACEI/ARB or AA propensity matched cohort. P-values >0.05 indicate that PAWP is not an effect modifier of the relationships between RAAS inhibitor use and mortality. Results are presented with and without adjustment in the full cohort and the smaller cohort of participants who used RAAS inhibitors compared to participants with an otherwise similar propensity to use RAAS inhibitors who did not use these medications.

	Full Cohort		Propensity-matched Cohort	
ACEI/ARB	**HR: ACEI/ARB**	**p-value for interaction**	**HR: ACEI/ARB**	**p-value for interaction**
Limited adjustment*: PAWP 15	1.04 (0.94,1.14)	0.46	0.99 (0.89,1.12)	0.92
Full adjustment† + Comorbidity§: PAWP 15	1.08 (0.98,1.18)	0.11	1.01 (0.90,1.13)	0.92
AA	**HR: AA**	**p-value for interaction**	**HR: AA**	**p-value for interaction**
Limited adjustment*: PAWP 15	1.05 (0.92,1.21)	0.44	0.92 (0.77,1.10)	0.34
Full adjustment† + Comorbidity§: PAWP 15	1.10 (0.96,1.27)	0.16	0.91 (0.76,1.09)	0.30

Definition of abbreviations: ACEI = Angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; AA= aldosterone antagonists; RAAS = renin angiotensin aldosterone system; HR = hazard ratio

** Limited adjustment accounts for age, sex, race/ethnicity, and body mass index*

† Full adjustment accounts for the limited model and income, tobacco use, alcohol abuse, and marital status

§ Comorbidity included the presence or absence of end-stage renal disease / dialysis, diabetes mellitus, cirrhosis, sleep disordered breathing, chronic obstructive pulmonary disease or asthma, interstitial lung disease, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass graft, congestive heart failure, valvular heart disease, congenital heart disease, atrial fibrillation, and/or atrial flutter

e-Table 6: Characteristics of patients with precapillary PH stratified by ACEI/ARB use. Precapillary PH was defined as mPAP ≥25 mmHg, PAWP ≤15 mmHg, and PVR >3 Wood units. Values are expressed in percent, with absolute numbers included in parentheses (with the exception of income, hemodynamics and BNP levels, which are expressed as means with standard deviation).

Variable	All subjects (N = 2,875)	ACEI/ARB users (N = 1,422)	ACEI/ARB non-users (N = 1,453)
Age			
• <45 years	1.4 (39)	0.9 (13)	1.8 (26)
• 45-54 years	7.8 (223)	6.5 (93)	8.9 (130)
• 55-64 years	33.7 (970)	33.3 (473)	34.2 (497)
• 65-74 years	34.8 (1001)	35.7 (507)	34.0 (494)
• 75-84 years	18.9 (542)	20.3 (288)	17.5 (254)
• ≥85 years	3.5 (100)	3.4 (48)	3.6 (52)
Sex (male)	94.6 (2719)	95.4 (1357)	93.7 (1362)
Race			
• White	72.3 (2080)	70.0 (996)	74.6 (1084)
• Black	25.3 (728)	27.6 (393)	23.1 (335)
• Other	2.3 (67)	2.3 (33)	2.3 (34)
Body mass index			
• Underweight (<18.5)	1.7 (50)	1.3 (18)	2.2 (32)
• Normal (≥18.5 - 25)	26.9 (773)	23.6 (336)	30.1 (437)
• Overweight (≥25 - 30)	33.5 (964)	34.5 (490)	32.6 (474)
• Obese (≥30 - 35)	21.5 (619)	22.5 (320)	20.6 (299)
• Severely obese (≥35)	16.3 (469)	18.1 (258)	14.5 (211)
Socioeconomic status			
• Tobacco use	66.9 (1922)	66.0 (939)	67.7 (983)
• Alcohol abuse	12.2 (351)	11.6 (165)	12.8 (186)
• Income ($/year)	49759.5 (17760)	49474.7 (17663)	50038.2 (17856)
Marital status			
• Married	46.0 (1322)	44.4 (631)	47.6 (691)
• Divorced	31.9 (917)	32.1 (456)	31.7 (461)
• Single	14.1 (406)	15.0 (214)	13.2 (192)
• Widowed	8.0 (230)	8.5 (121)	7.5 (109)
Comorbidities			
• Asthma	4.7 (136)	4.1 (59)	5.3 (77)
• Atrial fibrillation/flutter	25.7 (738)	28.2 (401)	23.2 (337)
• CHD	0.9 (26)	1.1 (16)	0.7 (10)
• CHF	58.2 (1673)	66.5 (945)	50.1 (728)
• Cirrhosis	9.1 (262)	7.1 (101)	11.1 (161)
• CKD	28.3 (814)	28.3 (402)	28.4 (412)
• COPD	54.5 (1566)	52.0 (739)	56.9 (827)
• Diabetes	43.7 (1257)	50.6 (719)	37.0 (538)
• Hypertension	86.2 (2477)	94.0 (1336)	78.5 (1141)
• ILD	1.2 (35)	1.1 (16)	1.3 (19)
• MI, PCI or CABG	37.6 (1082)	42.1 (598)	33.3 (484)
• OSA	12.9 (370)	12.8 (182)	12.9 (188)
• Valvular heart disease	26.7 (767)	28.3 (402)	25.1 (365)
Medications			
• ACE inhibitor	39.2 (1127)	79.3 (1127)	0.0 (0)
• Aldosterone antagonist	12.4 (356)	15.9 (226)	8.9 (130)
• Alpha agonist	1.4 (39)	1.7 (24)	1.0 (15)
• Angiotensin receptor antagonist	10.9 (313)	22.0 (313)	0.0 (0)
• Anticoagulant	26.9 (773)	29.5 (420)	24.3 (353)
• Antiplatelet therapy	16.1 (463)	19.8 (281)	12.5 (182)
• Beta blocker	59.5 (1710)	74.6 (1061)	44.7 (649)
• Bronchodilator/inhaled corticosteroid	52.1 (1497)	52.3 (744)	51.8 (753)
• Calcium channel blocker	22.8 (655)	24.8 (352)	20.9 (303)
• Digitalis	11.5 (330)	13.6 (194)	9.4 (136)
• Diuretic	58.9 (1694)	70.4 (1001)	47.7 (693)
• Glucose-lowering agent	29.8 (857)	38.0 (540)	21.8 (317)

• H2 blocker	6.6 (191)	6.8 (97)	6.5 (94)
• Hydrochlorothiazide	9.0 (260)	11.3 (161)	6.8 (99)
• Lipid-lowering agent	60.1 (1728)	73.6 (1046)	46.9 (682)
• Nitrate	16.3 (469)	21.7 (309)	11.0 (160)
• Proton pump inhibitor	39.0 (1122)	40.0 (569)	38.1 (553)
• Pulmonary vasodilator	16.0 (461)	11.0 (157)	20.9 (304)
• Systemic vasodilator	5.7 (164)	6.6 (94)	4.8 (70)
Hemodynamics			
• RAP (mmHg)	8.1 (4.2)	8.0 (4.0)	8.2 (4.5)
• mPAP (mmHg)	34.9 (8.8)	33.8 (8.1)	36.0 (9.4)
• PAWP (mmHg)	11.1 (3.1)	11.6 (2.9)	10.7 (3.3)
• CI (L/min/m^2)	2.3 (0.5)	2.3 (0.5)	2.3 (0.6)
• PVR (Wood units)	5.4 (2.8)	5.1 (2.4)	5.8 (3.1)
• MAP (mmHg)	93.4 (9.8)	94.3 (10.3)	92.4 (9.3)
Disease severity			
• Inpatient status	38.7 (1114)	43.7 (621)	33.9 (493)
• BNP (pg/ml)	926 (2082)	793 (1325)	1,081 (2701)

Definition of abbreviations: BNP = B-type natriuretic peptide, CABG = coronary artery bypass grafting, CHD = congenital heart disease, CHF = congestive heart failure, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, ILD = interstitial lung disease, MI = myocardial infarction, OSA = obstructive sleep apnea, PCI = percutaneous coronary intervention; RAP = right atrial pressure, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary artery wedge pressure, CI = cardiac index, PVR = pulmonary vascular resistance, MAP = mean arterial pressure.

e-Table 7: Characteristics of patients with precapillary PH stratified by AA use. Precapillary PH was defined as mPAP ≥25 mmHg, PAWP ≤15 mmHg, and PVR >3 Wood units. Values are expressed in percent, with absolute numbers included in parentheses (with the exception of income, hemodynamics and BNP levels, which are expressed as means with standard deviation).

Variable	All subjects (N = 529)	AA users (N = 110)	AA non-users (N = 419)
Age			
• <45 years	1.1 (6)	1.8 (2)	1.0 (4)
• 45-54 years	7.0 (37)	8.2 (9)	6.7 (28)
• 55-64 years	32.1 (170)	43.6 (48)	29.1 (122)
• 65-74 years	35.3 (187)	30.9 (34)	36.5 (153)
• 75-84 years	18.9 (100)	11.8 (13)	20.8 (87)
• ≥85 years	5.5 (29)	3.6 (4)	6.0 (25)
Sex (male)	95.8 (507)	96.4 (106)	95.7 (401)
Race			
• White	69.4 (367)	62.7 (69)	71.1 (298)
• Black	27.2 (144)	34.5 (38)	25.3 (106)
• Other	3.4 (18)	2.7 (3)	3.6 (15)
Body mass index			
• Underweight (<18.5)	1.9 (10)	0.0 (0)	2.4 (10)
• Normal (≥18.5 - 25)	30.4 (161)	27.3 (30)	31.3 (131)
• Overweight (≥25 - 30)	33.3 (176)	35.5 (39)	32.7 (137)
• Obese (≥30 - 35)	16.8 (89)	14.5 (16)	17.4 (73)
• Severely obese (≥35)	17.6 (93)	22.7 (25)	16.2 (68)
Socioeconomic status			
• Tobacco use	62.9 (333)	66.4 (73)	62.1 (260)
• Alcohol abuse	14.2 (75)	14.5 (16)	14.1 (59)
• Income ($/year)	49019.7 (17145)	49251.5 (18914)	48958.9 (16673)
Marital status			
• Married	42.5 (225)	42.7 (47)	42.5 (178)
• Divorced	32.3 (171)	30.9 (34)	32.7 (137)
• Single	15.5 (82)	17.3 (19)	15.0 (63)
• Widowed	9.6 (51)	9.1 (10)	9.8 (41)
Comorbidities			
• Asthma	3.8 (20)	3.6 (4)	3.8 (16)
• Atrial fibrillation/flutter	31.8 (168)	43.6 (48)	28.6 (120)
• CHD	0.6 (3)	0.0 (0)	0.7 (3)
• CHF	74.7 (395)	92.7 (102)	69.9 (293)
• Cirrhosis	8.9 (47)	12.7 (14)	7.9 (33)
• CKD	34.8 (184)	36.4 (40)	34.4 (144)
• COPD	56.9 (301)	45.5 (50)	59.9 (251)
• Diabetes	47.6 (252)	51.8 (57)	46.5 (195)
• Hypertension	91.3 (483)	93.6 (103)	90.7 (380)
• ILD	0.9 (5)	0.0 (0)	1.2 (5)
• MI, PCI or CABG	42.5 (225)	47.3 (52)	41.3 (173)
• OSA	16.6 (88)	17.3 (19)	16.5 (69)
• Valvular heart disease	32.3 (171)	30.9 (34)	32.7 (137)
Medications			
• ACE inhibitor	43.5 (230)	58.2 (64)	39.6 (166)
• Aldosterone antagonist	20.8 (110)	100.0 (110)	0.0 (0)
• Alpha agonist	0.8 (4)	0.0 (0)	1.0 (4)
• Angiotensin receptor antagonist	11.2 (59)	11.8 (13)	11.0 (46)
• Anticoagulant	31.4 (166)	39.1 (43)	29.4 (123)
• Antiplatelet therapy	19.3 (102)	16.4 (18)	20.0 (84)
• Beta blocker	69.0 (365)	79.1 (87)	66.3 (278)
• Bronchodilator/inhaled corticosteroid	55.6 (294)	47.3 (52)	57.8 (242)
• Calcium channel blocker	18.0 (95)	11.8 (13)	19.6 (82)
• Digitalis	21.6 (114)	41.8 (46)	16.2 (68)
• Diuretic	76.2 (403)	92.7 (102)	71.8 (301)
• Glucose-lowering agent	32.1 (170)	42.7 (47)	29.4 (123)

• H2 blocker	6.8 (36)	9.1 (10)	6.2 (26)
• Hydrochlorothiazide	5.1 (27)	2.7 (3)	5.7 (24)
• Lipid-lowering agent	63.5 (336)	71.8 (79)	61.3 (257)
• Nitrate	20.8 (110)	29.1 (32)	18.6 (78)
• Proton pump inhibitor	47.6 (252)	49.1 (54)	47.3 (198)
• Pulmonary vasodilator	20.4 (108)	18.2 (20)	21.0 (88)
• Systemic vasodilator	8.9 (47)	10.9 (12)	8.4 (35)
Hemodynamics			
• RAP (mmHg)	8.5 (4.4)	8.8 (4.8)	8.5 (4.3)
• mPAP (mmHg)	34.6 (8.7)	32.3 (6.9)	35.3 (9.1)
• PAWP (mmHg)	11.6 (2.9)	12.2 (2.7)	11.4 (2.9)
• CI (L/min/m^2)	2.2 (0.5)	2.1 (0.5)	2.2 (0.5)
• PVR (Wood units)	5.5 (2.8)	5.0 (2.0)	5.6 (3.0)
• MAP (mmHg)	91.8 (10.1)	91.6 (11.6)	91.9 (9.7)
Disease severity			
• Inpatient status	59.5 (315)	70.0 (77)	56.8 (238)
• BNP (pg/ml)	926 (2082)	1,102 (2493)	880 (1960)

Definition of abbreviations: BNP = B-type natriuretic peptide, CABG = coronary artery bypass grafting, CHD = congenital heart disease, CHF = congestive heart failure, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, ILD = interstitial lung disease, MI = myocardial infarction, OSA = obstructive sleep apnea, PCI = percutaneous coronary intervention; RAP = right atrial pressure, mPAP = mean pulmonary arterial pressure, PAWP = pulmonary artery wedge pressure, CI = cardiac index, PVR = pulmonary vascular resistance, MAP = mean arterial pressure.