Renin-Angiotensin-Aldosterone System Inhibitor Use and Mortality in Pulmonary Hypertension: Insights from the Veterans Affairs CART Database

Short title: RAAS inhibitors in PH

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Abbreviations list

AA - aldosterone antagonist

ACEI - angiotensin converting enzyme inhibitor

ARB - angiotensin receptor blocker

BNP - B-type natriuretic peptide

CART – Department of Veterans Affairs Clinical Assessment Reporting and Tracking Database

COPD – chronic obstructive pulmonary disease

HR – hazard ratio

mPAP - mean pulmonary artery pressure

OSA – obstructive sleep apnea

PH – pulmonary hypertension

PAH – pulmonary arterial hypertension

PAWP – pulmonary artery wedge pressure

PVR – pulmonary vascular resistance

RAAS - renin-angiotensin-aldosterone system

RHC – right heart catheterization

RV – right ventricle

VA – Veterans Affairs

Abstract

Background: The renin-angiotensin-aldosterone system (RAAS) contributes to pulmonary hypertension (PH) pathogenesis. While animal data suggest RAAS inhibition attenuates PH, it is unknown if RAAS inhibition is beneficial in PH patients.

Research question: Is RAAS inhibitor use associated with lower mortality in a large cohort of patients with hemodynamically confirmed PH?

Study design and methods: We used the Department of Veterans Affairs Clinical Assessment Reporting and Tracking Database to retrospectively study relationships between RAAS inhibitors (angiotensin converting enzyme inhibitors [ACEIs], angiotensin receptor blockers [ARBs] and aldosterone antagonists [AAs]) and mortality in 24,221 patients with hemodynamically confirmed PH. We evaluated relationships in the full and in propensity-matched cohorts. Analyses were adjusted for demographics, socioeconomic status, comorbidities, disease severity and co-medication use in staged models.

Results: ACEI/ARB use was associated with improved survival in unadjusted Kaplan-Meier survival analyses in the full cohort and the propensity-matched cohort. This relationship was insensitive to adjustment, independent of pulmonary artery wedge pressure and also observed in a cohort restricted to individuals with pre-capillary PH. AA use was associated with worse survival in unadjusted Kaplan-Meier survival analyses in the full cohort; however, AA use was less robustly associated with mortality in the propensity-matched cohort and not associated with worse survival after adjustment for disease severity, indicating that that AAs in real-world practice are preferentially used in sicker patients and that the unadjusted association with increased mortality may be an artifice of confounding by indication of severity.

Interpretation: ACEI/ARB use is associated with lower mortality in veterans with PH. AA use is a marker of disease severity in PH. ACEIs/ARBs may represent a novel treatment strategy for diverse PH phenotypes.

Introduction

Pulmonary hypertension (PH) is a common complication of cardiopulmonary and systemic disorders[1]. Irrespective of the underlying etiology, PH leads to right ventricular (RV) failure and predicts or mediates poor outcomes[1-4]. Pulmonary vasodilator therapy is available for the relatively small subgroup of patients with pulmonary arterial hypertension (PAH; Group 1 PH), but no specific therapies are available for the large group of patients with PH and increased RV afterload due to chronic heart disease, chronic lung disease or sleep-disordered breathing (Group 2 and 3 PH, respectively)[3,4]. Unfortunately, even with use of disease-specific therapies in PAH, 3-year survival is only 55%[5]. Survival in Group 2 and 3 PH is similar or even lower[6]. There is an unmet need for novel, disease-modifying treatments for PAH as well as for Group 2 and 3 PH[7,8].

Renin-angiotensin-aldosterone system (RAAS) inhibition is a widely accepted treatment for heart failure with reduced ejection fraction and systemic hypertension that exerts protective effects on the systemic vasculature and on myocardial remodeling[9,10]. Neurohormonal imbalance with increased RAAS activation is also a disease marker and potential treatment target in the RV and pulmonary vasculature in PAH[11-14]. Experimental and clinical studies suggest that RAAS inhibition may prevent PAH development and attenuate severity[15-23]. Given the benefit of RAAS inhibitors on left ventricular function and remodeling[9], their use may also benefit the RV. This is clinically relevant, since RV function determines survival in PAH and because no RV-specific therapies currently exist[24-26]. Importantly, RV failure is the final common disease pathway not just in PAH, but also in all other forms of PH. RV-targeted therapy therefore could be beneficial across the entire spectrum of PH, which is distinct from pulmonary vascular targeted therapy that is helpful in PAH but may be harmful in other forms of PH[27-32]. Evidence of RAAS activation also exists in non-PAH PH. For example, increased circulating plasma aldosterone has been reported in patients with Group 2 PH[33] and in patients with

advanced chronic obstructive lung disease and cor pulmonale[34,35], and evidence of increased RAAS signaling exists in patients with pulmonary fibrosis[36].

We used the Veterans Affairs Clinical Assessment Reporting and Tracking (CART) cohort (the single largest database on hemodynamically confirmed PH) to study relationships between RAAS inhibitors (angiotensin converting enzyme inhibitors [ACEIs], angiotensin receptor blockers [ARBs] and aldosterone antagonists [AA]) and mortality in a large cohort of patients with pre- and post-capillary forms of PH. Since the majority of patients in this cohort represent non-PAH PH[37], CART represents a unique opportunity to study the association of RAAS inhibitors with clinical outcomes in individuals with common and clinically highly relevant types of PH. We hypothesized that ACEI/ARB and AA use would be associated with improved outcomes in a population with a variety of types of PH.

Methods

See online supplement for detailed methods.

Participants

The CART cohort consists of a large, national data collection of veterans who received a heart catheterization at a VA medical center since 2005[37,38]. For this retrospective analysis, we included all veterans who received a right heart catheterization (RHC) between 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).

Medications

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 >60 days following that catheterization. The latter 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 (see **e-Table 1** for full medication list).

Covariates

We accounted for possible non-pharmacological characteristics that might confound the relationship between RAAS inhibitor use and mortality. Specifically, we accounted for (1) demographic characteristics (age [modeled continuously], sex, race/ethnicity, and body mass index); (2) markers of socioeconomic status and health behaviors (current or previous history of smoking, current or previous history of alcohol abuse, income, marital status); (3) comorbid medical conditions; and (4) co-medication use (described in **e-Table 1**).

Outcomes

The primary outcome was the rate of all-cause mortality. Risk time accrued after the 90-day window that was 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 ACEIs/ARBs or AAs. Mortality was determined using the combined VA vital status file, which has a 97.6% exact agreement with the National Death Index[39].

Statistical analysis

Patient characteristics were compared by RAAS inhibitor use. We used the Kaplan & Meier method to estimate unadjusted associations and Cox proportional hazards regression using a complete case analysis to estimate adjusted associations of RAAS inhibitor use within 90 days of RHC and mortality. A series of planned *a priori* adjustments were performed and consistent with our previous manuscripts[40]. 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.

In separate models, we further adjusted for comorbid medical conditions or co-medication use. We did not specifically adjust for systemic hypertension since the adjustment for co-medication use addressed confounding by hypertension *via* inclusion of antihypertensives. Analyses were repeated in a cohort of propensity-matched participants where subjects were matched according to their propensity for RAAS inhibitor prescription (see online supplement for further details on propensity-matching).

In pre-specified exploratory analyses, PAWP ≤15 mmHg versus >15 mmHg was evaluated as an effect modifier in the association between RAAS inhibitor use and mortality. Given the unexpected finding suggesting worse mortality in unadjusted relationships with AA users relative to non-users and the decreased effect size with inconsistent statistical significances 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 relationships between AA use and mortality as well as ACEI/ARB use and mortality. B-type natriuretic peptide (BNP) levels 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.

Results

Patient characteristics

The final cohort included 24,221 patients (**Table 1)**. Mean age was 66.8 years. Mean follow-up was 3.6 ± 2.5 years and total follow-up was 86,632 person-years. Those who used RAAS inhibitors tended to qualitatively differ from non-medication users and tended to be slightly younger, non-white, heavier, and with a greater burden of comorbidities. In particular,

AA users appeared to have a higher prevalence of cirrhosis and alcohol use. AA users also appeared more likely to be inpatients at the time of RHC and had lower cardiac indices. **e-Table 2** details the medication inventory. We identified 14,912 subjects with a filled prescription for ACEI/ARB **(Figure 1 & Table 1)**. Of these ACEI/ARB users, 7,480 were matched with 7,480 non-users who were otherwise similar in their propensity to have used these medications **(Figure 1 & e-Table 3)**. 4,092 subjects had a prescription for AAs filled **(Figure 1 & Table 1)**. Of these, 3,936 AA users were matched to 3,936 non-users with an otherwise similar propensity to use AAs **(Figure 1 & e-Table 4)**.

ACEI/ARB use is associated with decreased mortality in veterans with PH

6,141 veterans who used ACEIs/ARBs died over 56,358 person-years (10.9 deaths per 100-person years) and 4,273 veterans who did not use ACEIs/ARBs died over 30,273 person-years (14.1 deaths per 100 person-years). ACEI/ARB use was associated with improved survival in unadjusted Kaplan-Meier survival analyses in the full and propensity-matched cohorts (**Figure 2)**. ACEI/ARB use was associated with a highly significant 18-20% reduction in the hazard of mortality in a series of consistent Cox proportional hazard models that were not dependent on demographics, health behaviors, co-morbidities and co-medication use (**Table 2**). Similar effect sizes and statistical differences were observed in the propensity-matched cohort (**Table 2**). The ACEI/ARB-mortality relationship was unaltered when accounting for plasma potassium levels or when accounting for BNP and inpatient status at the time of RHC **(Table 3)**, suggesting that potassium levels or disease severity were not confounding the relationship between ACEI/ARB use and decreased mortality. Furthermore, PAWP greater or less than 15 mmHg did not modify the relationship between ACEI/ARB use and mortality (all p-values for the interaction >0.05; **e-table 5**), suggesting the association with decreased mortality was not limited to individuals with left heart disease.

ACEI/ARB use is associated with decreased mortality in veterans with pre-capillary PH

ACEI/ARB use was also associated with improved mortality in a smaller cohort of participants with pre-capillary PH (see **e-table 6** for characteristics). In 2,875 participants with mPAP ≥25 mmHg, PAWP ≤15 mmHg, and PVR >3 Wood units, the hazard of mortality with ACEI/ARB use was 23-26% less than in non-users (HR in the model with limited adjustment=0.77, 95% confidence interval 0.69-0.85, p<0.001; HR in the model with full adjustment and accounting for comorbidity=0.74, 95% confidence interval 0.66-0.82, p<0.001).

AA use is associated with worse survival in unadjusted Kaplan-Meier survival analyses in the full cohort, but only inconsistently associated with mortality the propensity-matched cohort

1,830 veterans who used AAs died over 13,980 person-years (13.1 deaths per 100-person years) and 8,584 veterans who did not use AAs died over 72,651 person-years (11.8 deaths per 100 person-years). AA use was associated with worse survival in unadjusted Kaplan-Meier survival analyses (**Figure 3)**. Although statistically significant, the association between AA use and mortality was impacted by adjustment and varied between a 9-24% increased risk for mortality depending on the model (**Table 2**). This relationship was weakest in the model accounting for comorbidities. PAWP did not modify the relationship between AA use and increased mortality (all p-values for the interaction >0.05 when evaluated in limited and fully adjusted models; **e-table 5**).

The association further weakened in the propensity-matched cohort. In unadjusted or adjusted analyses of the propensity-matched cohort, there was only a 6-8% increased risk for mortality with AA use, and statistical significances were markedly attenuated and not consistently achieved (**Table 2**). This raises the possibility that the association between AA use

and mortality in the full cohort may be confounded by the propensity of use AAs and, as such, may be confounded by indication and/or disease severity.

AA-mortality association is insensitive to adjustment for potassium levels, but is sensitive to adjustment for disease severity

Since an increase in hyperkalemia-associated morbidity and mortality was noted after publication of the *Randomized Aldactone Evaluation Study (RALES)*[41], we explored pre-procedural potassium levels as a potential confounder in a non-planned analysis after finding increased mortality among AA users. We found that the association between AA use and mortality was independent of potassium levels (**Table 3**). Finally, given the wide range of effect estimates and sensitivity to adjustment, we remained concerned there might be differences in disease severity between those who did and did not use AAs. Indeed, accounting for BNP and inpatient status at the time of RHC markedly attenuated the association between AA use and increased mortality in the full cohort **(Table 3)**. This supports the hypothesis that residual confounding related to disease severity was present in the full model and may have accounted for the relationship between AA use and increased mortality.

AA use does not affect mortality in veterans with pre-capillary PH

To investigate effects of AA use on mortality in veterans with pre-capillary PH, we restricted our analyses to participants who used AA and had a mPAP ≥25 mmHg, PAWP ≤15 mmHg, and PVR >3 Wood units. Both log of BNP level and inpatient status were included as predictors. The low number of deaths as well as exclusion of patients due to missing BNP values precluded confident analysis in this small cohort, and only a model with limited adjustment could be fit. In 529 participants with pre-capillary PH and a measurement for BNP (**e-table 7**), AA use was not associated with an effect on mortality (HR 0.98, 95% confidence interval 0.73-1.31, p=0.87).

Discussion

Our data are the first to evaluate the association between RAAS inhibitors and clinical outcomes in a large cohort of PH patients. We demonstrate that use of ACEIs/ARBs associates with decreased mortality. We observed a relationship between AA use and increased mortality that was no longer present when more robustly accounting for possible differences in disease severity between AA users and non-users.

Approximately 70 million patients in the US are estimated to have PH and/or RV dysfunction[42-47]. PH is a particular problem veterans, where it is common and associated with poor outcomes, yet frequently under-recognized[37,48]. In veterans, even mild increases in PA pressures are associated with increased morbidity and mortality[37]. Furthermore, PH in veterans is not only under-recognized, but also inappropriately treated[32,48]. This is important since inappropriate treatment of non-PAH forms of PH with PAH-specific drugs is associated with worse outcomes[27-32]. One factor driving the use of PAH-specific therapy in patients without PAH may be the lack of treatment options for non-PAH forms of PH. Novel therapeutic strategies for these patients are needed.

The large patient volume in the VA, high prevalence of chronic cardiopulmonary diseases and tracking of hemodynamic data through CART provide a unique opportunity to evaluate effects of pharmacologic interventions on outcomes in common PH phenotypes in a "real world" scenario. For example, we recently showed that use of H2-receptor antagonists in veterans with PH is associated with decreased mortality[40]. Survival in this cohort with relatively advanced age and multi-morbidity was relatively well preserved and maybe even better than expected for this population. This may reflect the observation that the VA system performs

similarly or better than the non-VA system on most of the nationally recognized measures of inpatient and outpatient care quality[49].

We demonstrate several findings that may contribute to understanding novel treatment strategies for PH. First, we show that ACEI/ARB use associates with decreased risk for mortality. This relationship is highly significant, relatively insensitive to adjustment and does not appear to depend on differences in demographics, comorbidity, co-medication-use, potassium levels, disease severity, or propensity to use of ACEI/ARB. Decreased mortality with ACEI/ARB use was also noted in the cohort with pre-capillary PH, suggesting that the benefit may not be simply due to appropriate treatment of left heart disease. Although confounding by indication is always possible in pharmaco-epidemiology, insensitivity to a wide range of adjustments and consistency of results in the propensity-matched cohort suggest that the association between ACEI/ARB use and mortality is less likely to be explained by confounding. While each of these approaches has limitations and opportunities for residual confounding, the strength of the complementary approach is in the mutual reinforcement or disagreement. In the case of ACEI/ARBs all approaches agreed. While not totally exculpatory, this is reassuring and adds scientific rigor. This differs from the AA analyses, where adjustments yielded different effect estimates and suggested that confounding (variably addressed by the method used) strongly influenced the observed relationship. In addition, the high level of statistical significance makes a false-positive result as a consequence of analyzing a large patient population less likely[50].

RAAS inhibitors are important treatments for left heart failure and systemic hypertension, and have shown promise in experimental PH and in exploratory clinical analyses in PAH patients[9,10,15-22]. Since the RAAS is also activated in Group 2 PH, in COPD with RV failure and other disorders associated with hypoxia and/or hypercarbia[33-36], exploring the potential benefit of RAAS inhibitors in a population predominantly characterized by group 2 and 3 PH makes conceptual sense and fills an important clinical knowledge gap. Importantly, ACEIs/ARBs are inexpensive and have a favorable side effect profile, making them an attractive treatment option.

As hypothesized, we demonstrate benefit of ACEIs/ARBs in post-capillary PH. However, these drugs were also associated with improved survival in participants with pre-capillary PH. This finding is unusual for PH therapies, as treatment may improve outcomes in selected groups with pre-capillary PH but worsen outcomes in those with post-capillary PH[3]. While we could not differentiate between Group 1 or Group 3 PH in our cohort, the burden of comorbidities in the VA suggests that most patients with pre-capillary disease exhibit a Group 3 phenotype (39% of our patients had a diagnosis of COPD; 15% had a diagnosis of OSA). Prior studies suggest increased RAAS activation may contribute to RV dysfunction in lung disease[34,35] and may mediate PAH development[15]. As such, the survival benefit observed in our smaller pre-capillary PH cohort is biologically plausible, especially since RV dysfunction is common in the CART population[51]. Future studies will need to corroborate our findings in additional well-phenotyped PH populations and identify mechanisms of how ACEIs/ARBs exert their potential protective effects. Such studies should also answer the important question if protective ACEI/ARB effects target the RV, the pulmonary vasculature, both, or perhaps other organ systems. Such studies will need to address whether benefits of ACEIs/ARBs extend to both Group 1 and Group 3 PH or are limited to one of these groups. Studies manipulating angiotensin signaling in PAH patients are currently ongoing (NCT01181284, NCT01884051). Our data suggest that additional studies evaluating ACEI/ARB use in Group 3 PH may be warranted.

We found an unexpected association between AA use and increased mortality in the full cohort. However, in counter-point to the findings with ACEI/ARB use, this association exhibited a less robust level of statistical significance[50], was variable, and only inconsistently observed in the propensity-matched cohort. Furthermore, this association was sensitive to adjustment for disease severity. This suggests that residual confounding related to disease severity was likely present in full and unadjusted models using the full cohort. In CART, AA use in veterans with PH appears to be a marker of disease severity rather than a mediator of worse survival. Our results suggest that sicker patients may have received AA rather than patients with milder

disease, which may reflect the typical clinical practice of adding therapies in patients with advanced or refractory symptoms. Two previous studies suggest that AA therapy is indeed prescribed preferentially in patients with greater pulmonary vascular disease burden. In the ARIES trial of ambrisentan for PAH, enrolled patients were treated with spironolactone based on the discretion of their personal physician[19]. Analysis of these patients demonstrated that 61% of patients were prescribed spironolactone to treat "RV failure", "refractory edema", or "electrolyte imbalances". Each of these scenarios suggests spironolactone use to offset or mitigate end-organ damage caused by PAH. Second, in a recent single-center cohort study, patients prescribed AA therapy had more severe RV contractile dysfunction, and a trend toward higher PAWP and more frequent loop diuretic use[52]. As a result, care must be taken when interpreting associations between AA use and mortality, and future observational studies should be particularly mindful of the potential for confounding by indication[52].

Our study has limitations. Unmeasured or residual confounding can complicate the inference in observational studies. While a number of the adjustments were intended to isolate RAAS inhibition from a suite of potentially causative health-focused behaviors (e.g., a "healthy-user" paradigm), residual confounding may well persist and adjustment for health behaviors like exercise and diet was not possible. Confounding by indication is also common in pharmaco-epidemiology and appears to have been a particular problem in the association with AA use. This reinforces the need for cautious inference[53]. In addition, all-cause mortality is not "cause-specific"[54]. Cause-specific mortality was not available for the CART cohort and non-cardiovascular explanations for our findings are possible. As such, we cannot determine if beneficial effects of ACEIs/ARBs were due to effects on the pulmonary vasculature, the RV or other mechanisms. While follow-up RHC data are available for a subgroup of CART subjects and could help answer this question, analysis of these patients outside of a controlled clinical trial would introduce selection bias since repeat RHCs tend to be performed in sicker patients with an unsatisfying treatment response. We used RAAS inhibitor exposure near the time of

RHC as a marker of individuals who likely had significant exposure. Documentation of one outpatient prescription fill may not be a robust surrogate marker for consistent RAAS use *vs.* non-use and represents a limitation of the data source. This misclassification of measured exposure relative to the exposure of interest is likely; however, because this non-differential misclassification is not conditioned on the outcome, it Is likely conservative and may bias observed results toward the null hypothesis. Information on cumulative doses and/or duration of use would have strengthened the study; however, this was not measured and relationships using these important biologic gradients are not available to support casual inference on our data. Lastly, the strong male predominance in our cohort limits generalizability. Gender differences in the response to spironolactone therapy have been reported[55], and it is possible that specific effects of AAs on subgroups of patients were not captured despite rigorous adjusting.

Nonetheless, this is the largest single cohort of individuals with invasively confirmed PH and we believe our data support ongoing study of RAAS signaling in diseases with increased RV afterload. In particular, the association with benefit among those using ACEIs/ARBs was robust in several models and cohorts and, alongside strong pre-clinical data, may justify randomized controlled study of ACEIs/ARBs in patients with PAH and other forms of PH. ACEIs/ARBs are relatively inexpensive and have a favorable side effect profile. If our results can be confirmed in additional cohorts and in prospective, randomized studies, ACEIs/ARBs may represent an attractive treatment strategy for the large proportion of patients with non-PAH PH phenotypes.

Conclusions

We demonstrate in a large cohort of veterans with invasively confirmed PH that ACEI/ARB use associates with a decreased risk for mortality. This relationship is insensitive to adjustment and is also observed in patients with pre-capillary PH, suggesting the observed

benefit is not simply explained by appropriate treatment of left heart disease. AA use appears to be a marker of disease severity in PH. If these hypothesis-generating results can be confirmed in prospective, randomized clinical studies, ACEIs/ARBs may represent an attractive and novel treatment strategy for diverse PH phenotypes.

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Figure legends

Fig. 1: Study sample. Cohorts studied included the full study cohort as well as limited cohorts used for propensity matched analyses.

Fig. 2: Angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) use is associated with decreased mortality in veterans with pulmonary hypertension. (A) Kaplan-Meier curves for the outcome of mortality for ACEI/ARB users and non-users for the full cohort (14,912 users; 9,309 non-users). Five-year mortality in ACEI/ARB users was 35.0% (5,212 events) compared to 41.2% in non-users (3,837 events). **(B)** Kaplan-Meier curves for the outcome of mortality for the propensity matched cohort (7,480/group). ACEI/ARB use was defined as use of either medication class within 90 days of right heart catheterization. Group comparisons were performed by log-rank test. Chi Sq = 154.8 for (A); Chi sq = 65.8 for (B).

Fig. 3: Aldosterone antagonist (AA) use is associated with increased mortality in veterans with pulmonary hypertension, with a less robust association in the propensity matched cohort. (A) Kaplan-Meier curves for the outcome of mortality for AA users and non-users for the full cohort (4,092 users; 20,129 non-users). Five-year mortality in AA users was 39.2% (1,606 events) compared to 37.0% in non-users (7,443 events). **(B)** Kaplan-Meier curves

for the outcome of mortality for the propensity matched cohort (3,936/group). AA use was defined as use within 90 days of right heart catheterization. Group comparisons were performed by log-rank test. Chi sq = 14.1 for (A); Chi sq = 4.5 for (B). Note lower Chi square value and less robust statistical significance in the propensity matched cohort.

Tables

Table 1: Characteristics of the study cohort. 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 = 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)
Age					
• <45 years	1.9 (452)	2.0 (295)	1.7 (157)	3.7 (152)	1.5 (300)
• 45-54 years	8.1 (1968)	8.2 (1220)	8.0 (748)	11.3 (461)	7.5 (1507)
• 55-64 years	34.2 (8287)	35.7 (5322)	31.9 (2965)	41.1 (1683)	32.8 (6604)
• 65-74 years	35.3 (8538)	35.1 (5239)	35.4 (3299)	31.6 (1295)	36.0 (7243)
• 75-84 years	17.0 (4116)	16.1 (2406)	18.4 (1710)	10.9 (444)	18.2 (3672)
• ≥85 years	3.6 (860)	2.9 (430)	4.6 (430)	1.4 (57)	4.0 (803)
Sex (male)	96.6 (23395)	97.2 (14492)	95.6 (8903)	97.1 (3972)	96.5 (19423)
Race					
• White	76.6 (18545)	75.2 (11218)	78.7 (7327)	70.9 (2903)	77.7 (15642)
• Black	21.3 (5165)	22.7 (3379)	19.2 (1786)	27.0 (1106)	20.2 (4059)
• Other	2.1 (511)	2.1 (315)	2.1 (196)	2.0 (83)	2.1 (428)
Body mass index					
• Underweight (<18.5)	0.8 (186)	0.6 (84)	1.1 (102)	0.6 (25)	0.8 (161)
• Normal (≥18.5 - 25)	16.9 (4090)	15.8 (2353)	18.7 (1737)	16.8 (688)	16.9 (3402)
• Overweight (≥25 - 30)	29.2 (7068)	28.5 (4253)	30.2 (2815)	29.1 (1189)	29.2 (5879)
• Obese (≥30 - 35)	25.0 (6051)	25.3 (3766)	24.5 (2285)	24.3 (993)	25.1 (5058)
• Severely obese (≥35)	28.2 (6826)	29.9 (4456)	25.5 (2370)	29.3 (1197)	28.0 (5629)
Socioeconomic status					
• Tobacco use	62.1 (15048)	62.3 (9288)	61.9 (5760)	62.9 (2572)	62.0 (12476)
• Alcohol abuse	11.1 (2687)	11.1 (1657)	11.1 (1030)	14.2 (582)	10.5 (2105)
• Income ($/year)	49886 (17439)	49628 (17215)	50299 (17785)	49378 (16872)	49989 (17551)
Marital status					
• Married	48.7 (11805)	48.0 (7162)	49.9 (4643)	46.4 (1900)	49.2 (9905)
• Divorced	29.9 (7240)	30.4 (4529)	29.1 (2711)	31.7 (1298)	29.5 (5942)
• Single	13.7 (3324)	14.3 (2132)	12.8 (1192)	15.7 (641)	13.3 (2683)
• Widowed	7.6 (1852)	7.3 (1089)	8.2 (763)	6.2 (253)	7.9 (1599)
Comorbidities					
• Asthma	5.4 (1315)	5.4 (807)	5.5 (508)	5.6 (230)	5.4 (1085)
• Atrial fibrillation/flutter	34.0 (8239)	34.1 (5082)	33.9 (3157)	38.3 (1568)	33.1 (6671)
• CHD	0.6 (146)	0.5 (81)	0.7 (65)	0.4 (17)	0.6 (129)
• CHF	68.7 (16636)	73.4 (10947)	61.1 (5689)	90.5 (3705)	64.2 (12931)
• Cirrhosis	7.3 (1780)	6.3 (933)	9.1 (847)	11.8 (483)	6.4 (1297)
• CKD	35.0 (8468)	32.6 (4867)	38.7 (3601)	36.3 (1486)	34.7 (6982)
• COPD	38.6 (9358)	36.8 (5492)	41.5 (3866)	37.8 (1546)	38.8 (7812)
• Diabetes	52.7 (12771)	55.8 (8326)	47.7 (4445)	55.2 (2257)	52.2 (10514)

• Hypertension	90.6 (21944)	93.3 (13919)	86.2 (8025)	90.8 (3716)	90.6 (18228)
• ILD	0.7 (164)	0.6 (85)	0.8 (79)	0.4 (15)	0.7 (149)
• MI, PCI or CABG	41.7 (10103)	43.3 (6460)	39.1 (3643)	46.5 (1901)	40.7 (8202)
• OSA	15.2 (3685)	15.3 (2280)	15.1 (1405)	17.1 (700)	14.8 (2985)
• Valvular heart disease	39.4 (9551)	37.6 (5608)	42.4 (3943)	32.9 (1345)	40.8 (8206)
Hemodynamics					
• RAP (mmHg)	12.1 (5.7)	12.2 (5.6)	11.9 (5.9)	13.3 (6.2)	11.8 (5.5)
• mPAP (mmHg)	35.3 (8.5)	35.3 (8.4)	35.2 (8.7)	37.0 (8.7)	35.0 (8.5)
• PAWP (mmHg)	21.5 (7.5)	22.1 (7.4)	20.6 (7.6)	23.6 (7.7)	21.0 (7.4)
• CI (L/min/m^2)	2.4 (0.7)	2.4 (0.7)	2.5 (0.7)	2.2 (0.7)	2.5 (0.7)
• PVR (Wood units)	3.0 (2.1)	2.9 (1.9)	3.1 (2.3)	3.1 (2.1)	2.9 (2.1)
• MAP (mmHg)	93.1 (10.2)	93.6 (10.5)	92.2 (9.7)	91.4 (11.3)	93.4 (10.0)
Disease severity					
• Inpatient status	48.2 (11685)	51.5 (7680)	43.0 (4005)	67.8 (2036)	45.5 (9649)
• BNP (pg/ml)	1,081 (2197)	1,060 (2111)	1,119 (2346)	1,334 (2665)	995 (2006)

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.

Table 2: Cox proportional hazard models for ACEI/ARB exposure and for AA exposure. Summarized are the hazard ratios of death (HR with 95% confidence intervals) associated with exposure to an ACEI or ARB (upper panel) or for exposure to an AA (lower panel). 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**	**HR: ACEI/ARB**	**p-value**
Unadjusted	0.78 (0.75,0.81)	<.001	0.82 (0.78,0.86)	<.001
Limited adjustment[*]	0.81 (0.78,0.84)	<.001	0.82 (0.78,0.86)	<.001
Full adjustment[†]	0.81 (0.78,0.84)	<.001	0.82 (0.78,0.86)	<.001
Full adjustment[†] + Comorbidity[§]	0.78 (0.75,0.81)	<.001	0.80 (0.76,0.84)	<.001
Full adjustment[†] + Co-medication use[‡]	0.80 (0.76,0.83)	<.001	0.81 (0.77,0.85)	<.001
AA	**HR: AA**	**p-value**	**HR: AA**	**p-value**
Unadjusted	1.11 (1.05,1.16)	<.001	1.07 (1.01,1.15)	0.03
Limited adjustment[*]	1.24 (1.18,1.31)	<.001	1.07 (1.00,1.15)	0.04
Full adjustment[†]	1.24 (1.18,1.30)	<.001	1.07 (1.00,1.14)	0.05
Full adjustment[†] + Comorbidity[§]	1.09 (1.03,1.14)	<.01	1.08 (1.01,1.15)	0.03
Full adjustment[†] + Co-medication use[‡]	1.16 (1.10,1.22)	<.001	1.06 (0.99,1.13)	0.08

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

‡ Co-medication use included all non-H2RA medications included in Table E1

// Participants in the restricted cohorts were considered in models with full adjustment

[#]n=24,221; [##]n=14,960 for ACEI/ARB analyses, n=7,872 for AA analyses

Table 3: Exploratory Cox proportional hazard models for ACEI/ARB or AA exposure in veterans including adjustment for potassium level or disease severity. Fully adjusted models for entire cohort and propensity-matched cohort (from table 2) are included for reference.

	Full Cohort		Propensity-matched Cohort	
ACEI/ARB	**HR: ACEI/ARB**	**p-value**	**HR: ACEI/ARB**	**p-value**
Full adjustment[†]	0.81 (0.78,0.84)	<.001	0.82 (0.78,0.86)	<.001
Full adjustment[†] with further adjustment for potassium	0.80 (0.77,0.83)*	<.001	0.81 (0.77,0.85)**	<.001
Full adjustment[†] with further adjustment for disease severity[§]	0.72 (0.67,0.78)[#]	<.001	0.77 (0.70,0.85)[##]	<.001
AA	**HR: AA**	**p-value**	**HR: AA**	**p-value**
Full adjustment[†]	1.24 (1.18,1.30)	<.001	1.07 (1.00,1.14)	0.05
Full adjustment[†] with further adjustment for potassium	1.23 (1.17,1.30)*	<.001	1.08 (1.01,1.15)***	0.03
Full adjustment[†] with further adjustment for disease severity[§]	1.05 (0.96,1.14)[#]	0.28	1.04 (0.93,1.16)[###]	0.48

Definition of abbreviations: ACEI = Angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; AA = aldosterone antagonists; BNP = B-type natriuretic peptide; HR = hazard ratio

† Full adjustment accounts for age, sex, race/ethnicity, body mass index income, tobacco use, alcohol abuse, and marital status

§ Adjustment for disease severity also accounts for B-type natriuretic peptide level and inpatient admission

**n=21,586; **n=13,211; [#]n=5,823; [##]n=3,302; ***n=7,349; [###]n=2,676*

Figure 1

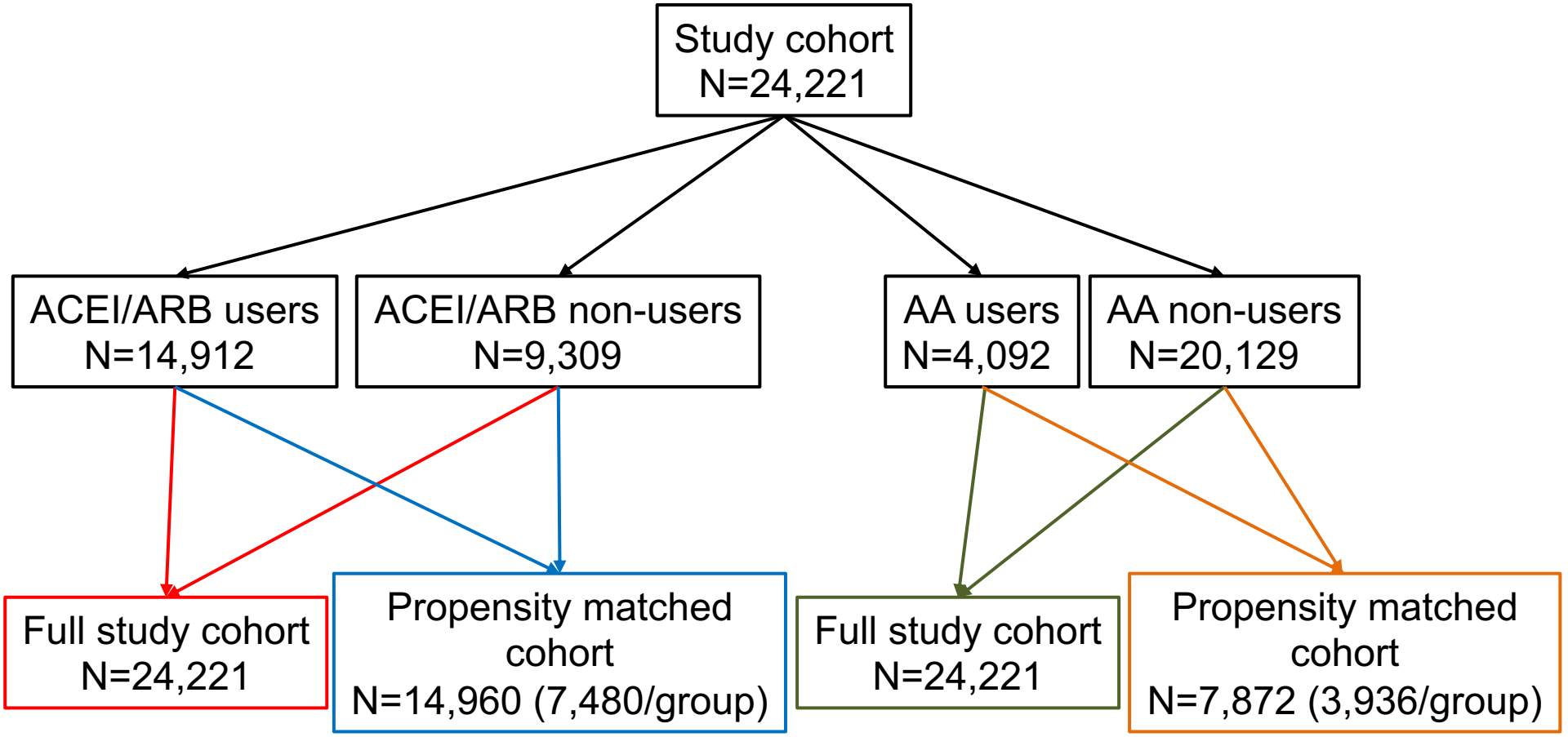

Study cohort
N=24,221
ACEI/ARB users
N=14,912
ACEI/ARB non-users
N=9,309
AA users
N=4,092
AA non-users
N=20,129
Full study cohort
N=24,221
Propensity matched
cohort
N=14,960 (7,480/group)
Full study cohort
N=24,221
Propensity matched
cohort
N=7,872 (3,936/group)

Figure 2

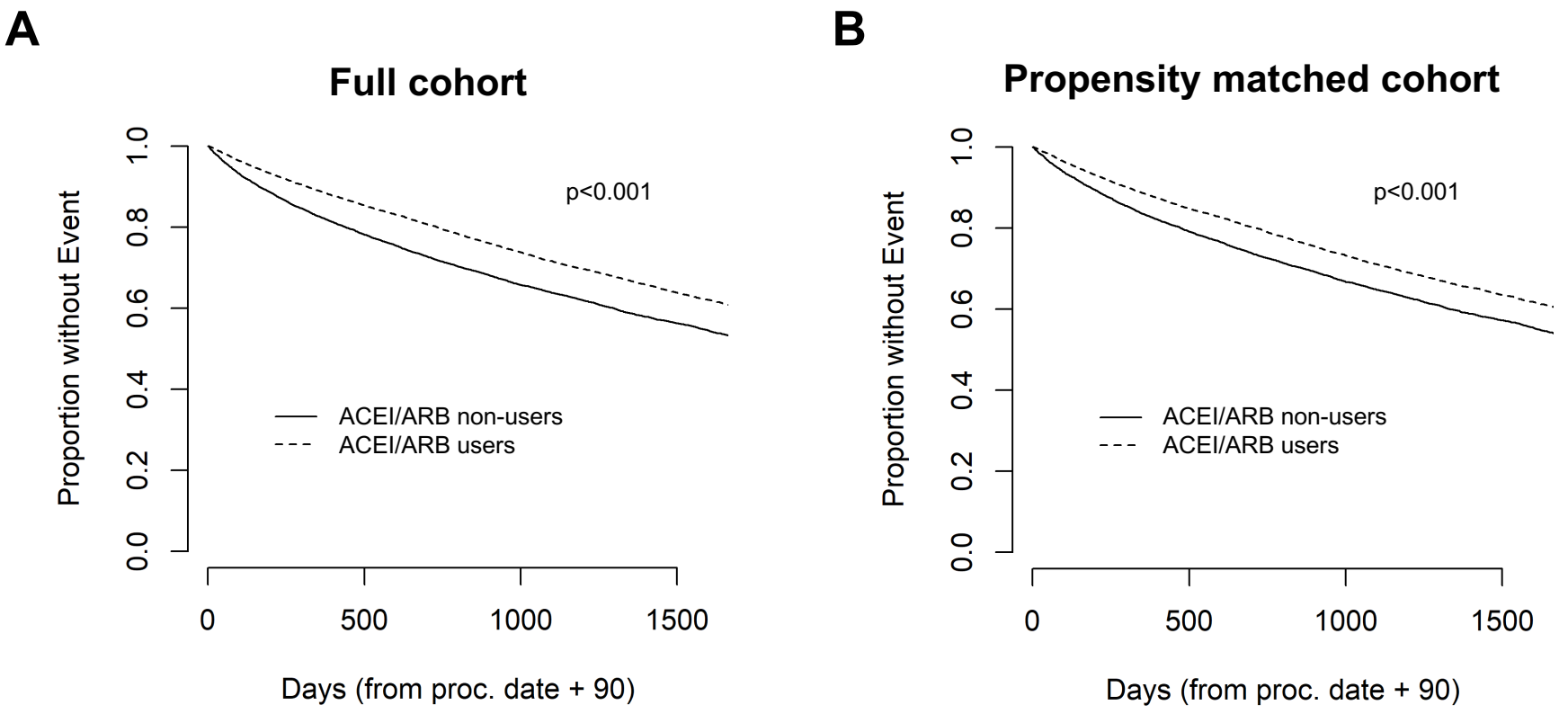
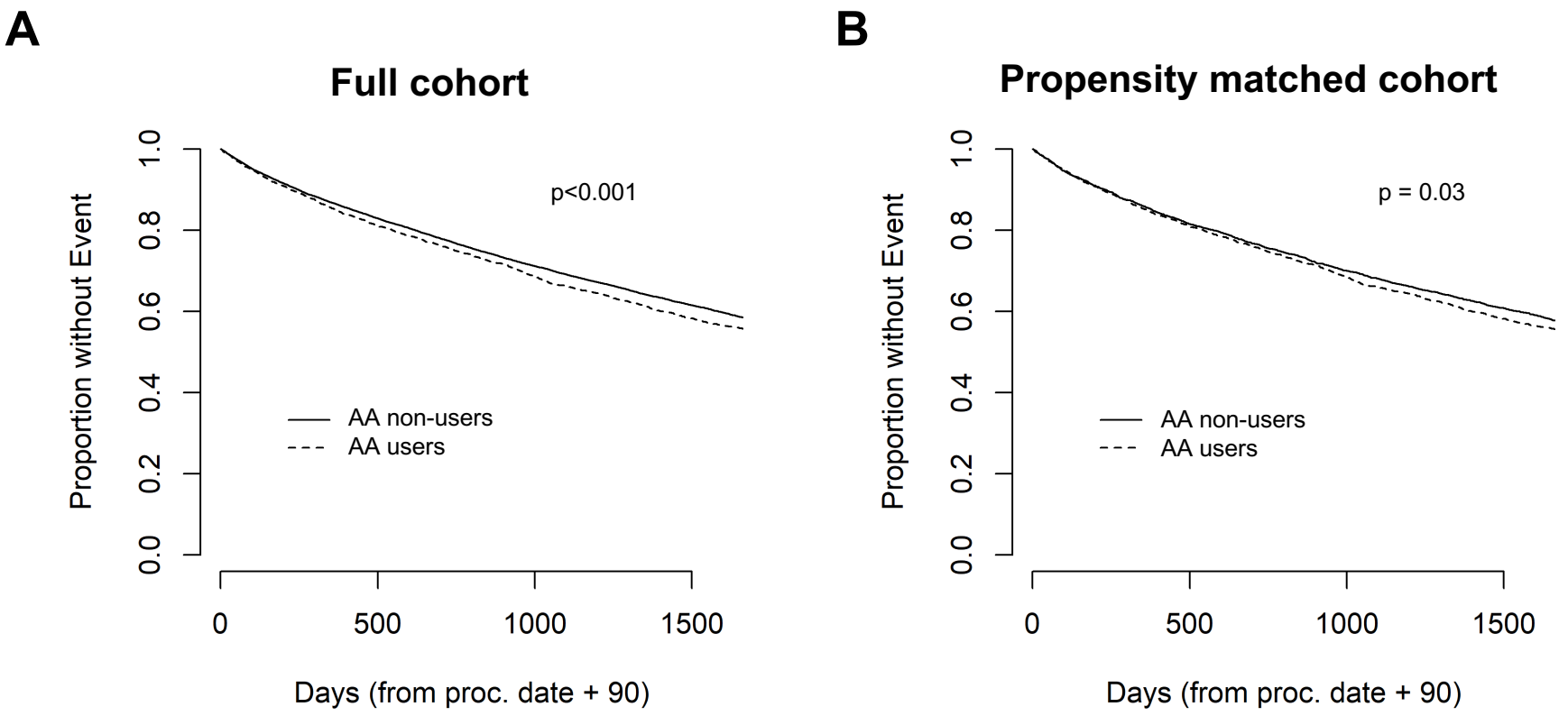

A
Full cohort
Proportion without Event
0.0
0.2
0.4
0.6
0.8
1.0
p<0.001
ACEI/ARB non-users
ACEI/ARB users
0
500
1000
1500
Days (from proc. date + 90)
B
Propensity matched cohort
Proportion without Event
0.0
0.2
0.4
0.6
0.8
1.0
p<0.001
ACEI/ARB non-users
ACEI/ARB users
0
500
1000
1500
Days (from proc. date + 90)

Figure 3


A
Full cohort
Proportion without Event
0.0
0.2
0.4
0.6
0.8
1.0
p<0.001
AA non-users
AA users
0
500
1000
1500
Days (from proc. date + 90)
B
Propensity matched cohort
Proportion without Event
0.0
0.2
0.4
0.6
0.8
1.0
p = 0.03
AA non-users
AA users
0
500
1000
1500
Days (from proc. date + 90)