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ORIGINAL RESEARCH

Renin-Angiotensin-Aldosterone System Inhibitors Are Associated With Favorable Outcomes Compared to Beta Blockers in Reducing Mortality Following Abdominal Aneurysm Repair

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BACKGROUND: The best medical therapy to control hypertension following abdominal aortic aneurysm repair is yet to be determined. We therefore examined whether treatment with renin-angiotensin-aldosterone system inhibitors (RAASIs) versus beta blockers influenced postoperative and 1-year clinical end points following abdominal aortic aneurysm repair in a Medicare-linked database.

METHODS AND RESULTS: All patients with hypertension undergoing endovascular aneurysm repair and open aneurysm repair in the Vascular Quality Initiative Vascular Implant Surveillance and Interventional Outcomes Network database between 2003 and 2018 were included. Patients were divided into 2 groups based on their preoperative and discharge medications, either RAASIs or beta blockers. Our cohort included 8789 patients, of whom 3523 (40.1%) were on RAASIs, and 5266 (59.9%) were on beta blockers. After propensity score matching, there were 3053 matched pairs of patients in each group. After matching, RAASI use was associated with lower risk of postoperative mortality (odds ratio [OR], 0.3 [95% CI, 0.1–0.6]), myocardial infarction (OR, 0.1 [95% CI, 0.03–0.6]), and nonhome discharge (OR, 0.6 [95% CI, 0.5–0.7]). Before propensity score matching, RAASI use was associated with lower 1-year mortality (hazard ratio [HR], 0.4 [95% CI, 0.4–0.5]) and lower risk of aneurysmal rupture (HR, 0.7 [95% CI, 0.5–0.9]). These results persisted after propensity score matching for mortality (HR, 0.4 [95% CI, 0.4–0.5]) and aneurysmal rupture (HR, 0.7 [95% CI, 0.5–0.9]).

CONCLUSIONS: In this large contemporary retrospective cohort study, RAASI use was associated with favorable postoperative outcomes compared with beta blockers. It was also associated with lower mortality and aneurysmal rupture at 1 year of follow-up.

Key Words: abdominal aortic aneurysm repair ■ aneurysm rupture ■ angiotensin-converting enzyme inhibitors ■ beta blockers

Abdominal aortic aneurysms (AAAs) are responsible for ≥10 000 deaths and ≈65 000 hospital admissions annually in the United States.[1] Given the lack of symptoms, patients with AAAs are at increased risk of rupture, and subsequently, frequent fatal outcomes.[2] Despite targeted efforts at finding pharmacological therapy for AAA growth inhibition and prevention of rupture, open surgical treatment or endovascular repair remains the gold standard treatment for AAA.[3]

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CLINICAL PERSPECTIVE

What Is New?

- This study represents the first evidence in the literature comparing renin-angiotensin-aldosterone system inhibitor versus beta blocker effect on the outcomes of patients with hypertension undergoing open abdominal aneurysm repair and endovascular abdominal aneurysm repair.
- We showed that renin-angiotensin-aldosterone system inhibitor use is associated with lower risk of mortality and aneurysmal rupture at 1 year of follow-up.
- These results persisted after propensity score matched analysis between the 2 study groups.

What Are the Clinical Implications?

- When prescribing an antihypertensive medication for patients undergoing open abdominal aneurysm or endovascular abdominal aneurysm repair, renin-angiotensin-aldosterone system inhibitors may be considered instead of beta blockers if there are no contraindications due to the favorable outcomes associated with renin-angiotensin-aldosterone system inhibitor use in this patient population.

Nonstandard Abbreviations and Acronyms

BB	beta blocker
EVAR	endovascular abdominal aneurysm repair
OAR	open abdominal aneurysm repair
RAASI	renin-angiotensin-aldosterone system inhibitor
VISION	Vascular Implant Surveillance and Interventional Outcomes Network
VQI	Vascular Quality Initiative

Optimal blood pressure control following endovascular abdominal aneurysm repair (EVAR) or open abdominal aneurysm repair (OAR) is crucial in reducing mortality and postoperative complications. Guidelines recommend that hypertension should be treated with a blood pressure goal of <140/90 mm Hg.[4,5] The use of beta blockers (BBs) was previously suggested to reduce postoperative morbidity and mortality after noncardiac surgeries. Mangano et al in 1996 demonstrated a significant reduction in mortality at 6 months, 1 and 2 years after noncardiac surgery who received perioperative atenolol compared with those who received placebo.[6] However, an analysis of 198 patients who underwent EVAR showed that BBs did not affect AAA sac regression at 1 and 2 years of follow-up.[7]

Renin-angiotensin-aldosterone-system inhibitors (RAASIs) play an important role in reducing the progression of vascular atherosclerotic diseases[8–10] and the use of RAASIs is common among patients with vascular pathologies.[11,12] It has been suggested that activation of the renin-angiotensin system plays a central role in the pathogenesis of AAA. However, limited studies have indicated that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) can inhibit the growth and rupture of AAAs.[13–15] An observational study by Kristensen et al showed that treatment with ACEIs or ARBs was associated with a comparable reduction in mortality, but not in surgery, for patients with AAAs.[16]

Optimal management of AAA requires an interdisciplinary approach combining the best medical management and operative repair. The current evidence surrounding the best antihypertensive medication is insufficient and warrants further investigation. In this study, we seek to use the new Vascular Quality Initiative (VQI) Vascular Implant Surveillance and Interventional Outcomes Network (VISION) database to examine the association between RAASIs versus BBs and the short- and long-term outcomes of AAA repair in a large nationally representative sample of patients.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to VQI at www.vqi.org.

Data Set

Patients with hypertension undergoing OAR and EVAR in the Society for Vascular Surgery VQI-VISION database from January 1, 2003, to December 31, 2018, were queried. The Society for Vascular Surgery VQI is a prospectively maintained data set that includes multiple variables related to patients' demographic, procedural factors, and postoperative outcomes from more than 900 hospitals in the United States and Canada.[17] Information on baseline characteristics, operative notes, and in-hospital outcomes are extracted from patient charts. VISION is an affiliation between the Society for Vascular Surgery VQI and Medical Device Epidemiology Network, which purposes to improve long-term outcomes through the linkage of Society for Vascular Surgery VQI index procedures to Medicare claims.[18] This is achieved through the use of a validated matching algorithm using Current Procedural Terminology, *International Classification of Diseases,*

Table 1. Baseline Characteristics

Demographics	Before matching			After matching		
	Beta blocker N=5266 (59.9%)	RAASI N=3523 (40.1%)	Standardized difference	Beta blocker N=3053	RAASI N=3053	Standardized difference
Age, y, median (IQR)	75.6±7.6	74.8±7.2	0.1	75.4±7.6	75.5±7	−0.01
Procedure type			0.1			0.002
EVAR	4613 (87.6)	3235 (91.8)		2763 (90.5)	2765 (90.6)	
OAR	653 (12.4)	288 (8.2)		290 (9.5)	288 (9.4)	
Female sex	1188 (22.6)	713 (20.2)	0.06	744 (24.4)	646 (21.2)	0.08
Race						0.07
White	4779 (90.8)	3232 (91.7)	0.03	2762 (90.5)	2824 (92.5)	
Black	275 (5.2)	163 (4.6)		166 (5.4)	125 (4.1)	
Other*	209 (4)	128 (3.6)		123 (4)	104 (3.4)	
Hispanic or Latino ethnicity	112 (2.1)	122 (3.5)	0.08	69 (2.3)	98 (3.2)	0.06
Body mass index, kg/m^2	27.2 (24.2–30.9)	27.7 (24.6–30.8)	−0.04	27.6±5.5	27.8±5.3	−0.03
Symptomatic	444 (8.4)	217 (6.2)	0.09	242 (7.9)	180 (5.9)	0.08
Smoking			0.07			0.03
Never	721 (13.7)	466 (13.2)		443 (14.5)	415 (13.6)	
Prior	3140 (59.7)	2009 (57)		1764 (57.8)	1765 (57.8)	
Current	1403 (26.6)	1047 (29.7)		844 (27.7)	872 (28.6)	
Comorbidities						
Coronary artery disease	2710 (51.5)	893 (25.3)	0.56	896 (29.3)	893 (29.2)	0.002
Congestive heart failure	911 (17.3)	219 (6.2)	0.35	204 (6.7)	219 (7.2)	0.02
Chronic obstructive pulmonary disease	1971 (37.4)	1125 (32)	0.11	1010 (33.1)	1026 (33.6)	0.01
Chronic kidney disease	2270 (43.1)	1250 (35.5)	0.16	1187 (38.9)	1211 (39.7)	0.02
Dialysis	106 (2)	15 (0.4)	0.14	9 (0.3)	15 (0.5)	0.03
Diabetes	1024 (19.4)	846 (24)	0.11	574 (18.8)	463 (15.2)	0.09
Family history of abdominal aortic aneurysm	398 (7.6)	286 (8.1)	0.02	253 (8.3)	254 (8.3)	0.0005
Maximum aortic diameter, mm, median (IQR)	58±10.4	57±10	0.09	57.7±10.1	57.2±10.1	0.04
Prior vascular procedures						
Prior carotid endarterectomy /carotid arterystenting	335 (6.4)	192 (5.5)	0.04	176 (5.8)	179 (5.9)	0.004

(*Continued*)

Table 1. Continued

Demographics	Before matching			After matching		
	Beta blocker N=5266 (59.9%)	RAASI N=3523 (40.1%)	Standardized difference	Beta blocker N=3053	RAASI N=3053	Standardized difference
Prior coronary artery bypass graft/percutaneous coronary intervention	2345 (44.5)	698 (19.8)	0.55	713 (23.4)	698 (22.9)	0.01
Prior lower extremity revascularization, bypass/peripheral vascular intervention	470 (8.9)	222 (6.3)	0.099	241 (7.9)	206 (6.7)	0.04
Preoperative medications						
Aspirin	3609 (68.5)	2256 (64)	0.09	1983 (65)	1954 (64)	0.02
P2Y12 antagonist	792 (15)	336 (9.5)	0.17	331 (10.8)	316 (10.4)	0.01
Statin	4014 (76.2)	2520 (71.5)	0.11	2222 (72.8)	2165 (70.9)	0.04

EVAR indicates endovascular abdominal aneurysm repair; IQR, interquartile range; OAR, open abdominal aneurysm repair; and RAASI, renin-angiotensin-aldosterone system inhibitor.
*Asian, American Indian or Alaskan Native, Native Hawaiian or Pacific Islander, or mixed race.

Ninth Revision, and *International Classification of Diseases, Tenth Revision* (*ICD-9* and *ICD-10*) codes.[19] The need for institutional review board approval and individual informed consent is waived for this study given the deidentified information from participating institutions in VQI-VISION.

Variable Definitions

Patients with information on pre- and postoperative use of BBs and RAASIs were included. Patients were divided into 2 groups based on their use of BBs versus RAASIs. Patients who were on BBs and RAASIs at the same time were excluded to study the independent effect of each drug separately (Figure S1). Premedication use is collected from the office visit before the procedure. Postoperative use is collected based on the list of discharge medications prescribed to the patient upon discharge. Patients with ruptured AAAs or concomitant procedures were also excluded.

Baseline characteristics included patients demographics (age, sex, race, ethnicity), body mass index, smoking (never, prior, and current), comorbidities (diabetes, hypertension, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, dialysis), family history of AAA repair, prior vascular surgery (prior coronary artery bypass grafting/percutaneous coronary intervention, prior carotid endarterectomy/carotid artery stenting, prior lower limb revascularization), maximum aortic diameter, symptomatic presentation, and preoperative medication usage. Coronary artery disease was defined as any history of angina or myocardial infarction (MI).

Outcomes

Outcomes were compared between RAASIs and BBs. The primary outcomes included 1-year all-cause mortality and rupture. Secondary outcomes included 1-year all-cause aneurysm-related reintervention, perioperative (30-day) mortality, and in-hospital leg ischemia, intestinal ischemia, MI, respiratory complications, renal complications, and nonhome discharge. MI was diagnosed either with a clinical picture related to ischemia, ECG changes, or an increase in myocardial enzymes. Leg ischemia was defined as loss of previously palpable pulses or previously present Doppler signals, decrease of >0.15 in the ankle-brachial index, development of ischemic rest pain, or tissue loss. Intestinal ischemia was defined as colonoscopic evidence of ischemia, bloody stools with death before colonoscopy/laparotomy, or other documented clinical diagnosis. Respiratory complications were defined as pneumonia or requiring a ventilator following extubation. Renal complications were defined as a creatinine increase of >0.5 mg/dL or requiring dialysis. Reintervention was

Table 2. In-Hospital Complications After Matching

	Beta blocker N=3053	RAASI N=3053		RAASI vs beta blocker	
	No. (%)	No. (%)	*P* value	OR (95% CI)	*P* Value
Death	29 (0.9)	8 (0.3)	0.001	0.3 (0.1–0.6)	0.001
Leg ischemia	25 (0.8)	14 (0.5)	0.077	0.6 (0.3–1.07)	0.081
Intestinal ischemia	10 (0.3)	17 (0.6)	0.178	1.7 (0.8–3.7)	0.183
Myocardial infarction	14 (0.5)	2 (0.1)	0.003	0.1 (0.03–0.6)	0.010
Respiratory complications	49 (1.6)	34 (1.1)	0.097	0.7 (0.4–1.07)	0.099
Pneumonia	17 (0.6)	12 (0.4)	0.352	0.7 (0.3–1.5)	0.354
Renal complications	61 (9.2)	44 (8.4)	0.637	0.9 (0.6–1.4)	0.637
Nonhome discharge	284 (9.3)	166 (5.4)	<0.001	0.6 (0.5–0.7)	<0.001

OR indicates odds ratio; and RAASI, renin-angiotensin-aldosterone system inhibitor.

defined as any repeat procedure related to the initial AAA repair or complications after discharge.

Statistical Analysis

Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as median with interquartile range or mean±SD. After comparing baseline characteristics between patients using BBs versus RAASIs, propensity scores were produced for each variable using log-odds. A multivariable model was estimated with all statistically significant variables including age, procedure type, diabetes, history of coronary artery disease, history of chronic obstructive pulmonary disease, chronic kidney disease, congestive heart failure, prior coronary artery bypass graft or percutaneous coronary intervention, and dialysis. The logistic model was clustered by center identifier. Treatment cohorts were matched on these propensity scores using a calibration of 0.05. Intergroup differences were tested with the McNemar test for categorical variables and paired *t* test or Wilcoxon matched-pairs signed-rank test for continuous variables as appropriate. Logistic regression analysis was used to compare perioperative outcomes. Kaplan–Meier analysis, log-rank tests, and Cox proportional hazards regression were used to compare 1-year outcomes. All analysis was accomplished using Stata SE version 16.1 (StataCorp LP, College Station, TX). A *P* value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 8789 patients were included in the analysis. Of these, 3523 (40.1%) patients were on RAASIs and 5266 (59.9%) were on BBs. Patients on BBs were older (75.6±7.6 versus 74.8±7.2), had higher rates of congestive heart failure (17.3% versus 6.2%), chronic kidney disease (43.1% versus 35.5%), dialysis (2% versus

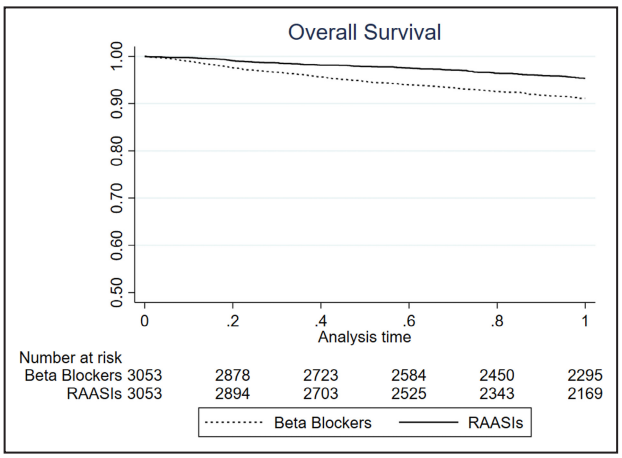

Figure 1. One-year freedom from mortality after matching. RAASIs indicates renin-angiotensin-aldosterone system inhibitors.

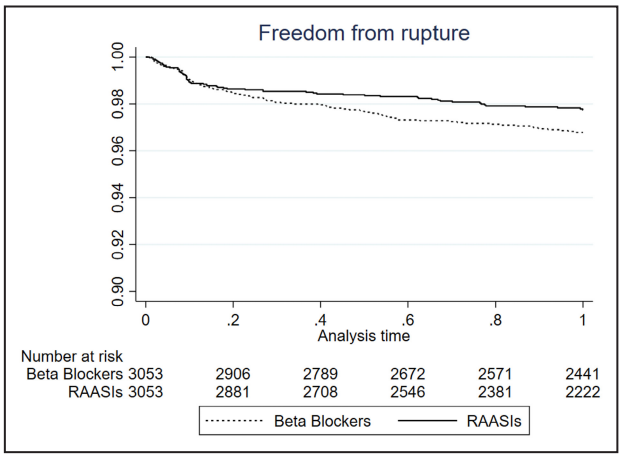

Figure 2. One-year freedom from rupture after matching. RAASIs indicates renin-angiotensin-aldosterone system inhibitors.

Table 3. Freedom From 1-Year Events Before and After Matching

	Before matching			After matching		
	Beta blocker N=5266 (%)	RAASI N=3523 (%)	*P* value	Beta blocker N=3053 (%)	RAASI N=3053 (%)	*P* value
Survival	90.1	95.5	<0.001	91.1	95.3	<0.001
Freedom from rupture	96.8	97.8	0.007	96.8	97.7	0.03
Freedom from reintervention	95.3	95.3	0.884	95.7	95.3	0.364

RAASI indicates renin-angiotensin-aldosterone system inhibitor.

0.4%), coronary artery disease (51.5% versus 25.3%), and chronic obstructive pulmonary disease (37.4% versus 32%). They also had higher rates of prior coronary artery bypass grafting/percutaneous coronary intervention (44.5% versus 19.8%), and preoperative use of P2Y12 antagonist (15% versus 9.5%) and statins (76.2% versus 71.5%); standardized differences were all >0.10 (Table 1). Propensity score matching (PSM) revealed 2 groups of 3053 matched pairs of patients. After PSM, there were no significant differences in baseline demographics and comorbidities between study groups (standardized differences were all <0.10; Table 1).

Perioperative and In-Hospital Outcomes

After PSM, RAASI use was still associated with lower risk of postoperative mortality (odds ratio [OR], 0.3 [95 % CI, 0.1–0.6]), myocardial infarction (OR, 0.1 [95% CI, 0.03–0.6]), and nonhome discharge (OR, 0.6 [95% CI, 0.5–0.7]). There was no longer a statistically significant difference between the 2 groups in the risk of leg ischemia, respiratory complications, pneumonia, and renal complications (Table 2).

One-Year Outcomes

Before PSM, RAASI use was associated with lower mortality (hazard ratio [HR], 0.4 [95% CI, 0.4–0.5], *P*<0.001) and lower risk of aneurysmal rupture (HR, 0.7 [95% CI, 0.5–0.9]). These results persisted after PSM for mortality (HR, 0.4 [95% CI, 0.4–0.5]) and aneurysmal rupture (HR, 0.7 [95% CI, 0.5–0.9]; Figures 1 and 2). There was no difference between the 2 groups in the risk of aneurysmal-related reintervention before and after PSM (Tables 3 and 4).

DISCUSSION

In this large retrospective cohort study, we examined the effects of RAASIs and BBs on postoperative and 1-year outcomes in patients with hypertension undergoing AAA repair. We found that RAASIs were associated with a significant reduction in in-hospital MI, 30-day mortality, and nonhome discharge following EVAR and OAR compared with BBs. RAASIs were also associated with a lower risk of mortality and aneurysmal rupture at 1 year of follow-up. RAASIs were associated with lower odds of in-hospital renal complications, respiratory complications, leg ischemia, intestinal ischemia, and pneumonia before PSM. However, these differences were not statistically significant after PSM. These results suggest that RAASIs may provide favorable protection against fatal outcomes in patients undergoing EVAR and OAR.

It is thought that AAA pathogenesis involves the activation of proinflammatory signaling pathways, mediating a shift in the extracellular matrix homeostasis of the abdominal aortic wall, which subsequently leads to the degradation of matrix proteins by matrix metalloproteases.[20,21] Subsequently, inflammatory cytokines mediate the infiltration of macrophages and lymphocytes, which causes weakening of the arterial wall. Eventually, this will promote AAA growth and rupture as well as thrombus formation.[20–22] The possible pathophysiology behind the lower risk of mortality and aneurysmal rupture associated with RAASI use in this study can be tracked back to the role of angiotensin II in the pathogenesis of AAA.[23,24] This includes leucocyte infiltration followed by inflammatory responses, extracellular matrix protein degradation through activation

Table 4. One-Year Outcomes Before and After Matching

	Before matching		After matching	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Death	0.4 (0.4–0.5)	<0.001	0.5 (0.4–0.6)	<0.001
Aneurysmal rupture	0.7 (0.5–0.9)	0.008	0.7 (0.5–0.9)	0.031
Reintervention	1.01 (0.8–1.2)	0.884	1.1 (0.9–1.4)	0.364

HR indicates hazard ratio.

of proteases, and vascular oxidative stress.[25,26] In small rodent models of AAA induced by angiotensin II infusion or intra-aortic elastase infusion, it was found that administration of ACEIs and ARBs significantly mitigates the development of AAAs.[14,27–29] Several studies in animals and humans have shown the presence of a local renin-angiotensin system in the heart, kidney, and blood vessels.[30,31] Subsequently, the renin-angiotensin system may have essential regulatory functions and pathophysiological impact on these organs.[32] In this study, we also showed that RAASI use was also associated with a 90% reduction in the odds of in-hospital MI following AAA repair. This finding is clinically important because MI is deemed to be the principal cause of operative mortality following AAA repair.[33,34]

Although no prior studies compared RAASIs versus BBs in patients undergoing AAA repair, the role of BBs and ACEIs in patients with AAAs has previously been discussed. In accordance with the results of this study, a previous retrospective study of the Canadian administrative database of 15 326 patients with AAAs admitted to the hospital showed that patients who received ACEI before admission were significantly less likely to present with ruptured aneurysm (OR, 0.82 [95% CI, 0.74–0.90]). On the other hand, such protective associations were not observed for BBs (OR, 1.02 [95% CI, 0.89–1.17]), calcium channel blockers (OR, 1.01 [95% CI, 0.89–1.14]), alpha-blockers (OR, 1.15 [95% CI, 0.86–1.54]), ARBs (OR, 1.24 [95% CI, 0.71–2.18]), or thiazide diuretics (OR, 0.91 [95% CI, 0.78–1.07]).[22] Another retrospective analysis of the Danish nationwide registries showed that treatment with ACEIs or ARBs was associated with a comparable reduction in mortality but not in surgery for AAA, among patients with AAA.[16] Furthermore, an analysis of 198 patients undergoing EVAR showed that BB therapy did not affect AAA sac regression at 1 and 2 years of follow-up.[7] Conversely, a combined case–control and follow-up study of patients with first-time hospital admission for rupture AAA and controls with AAA without rupture in Denmark from 1996 to 2012 showed that the use of renin-angiotensin system blockade was not associated with a lower risk of rupture AAA or lower case mortality following rupture.[35] Furthermore, a prospective cohort study of 1701 patients with AAA showed that patients treated with ACEIs had a significant increase in an AAA diameter growth rate of 0.67 mm/year compared with no ACEI treatment.[36] However, these findings were limited by the absence of information on smoking status, a small number of ACEI-treated subjects (n=169), and the inclusion of older-generation ACEIs (eg, captopril, enalapril, and lisinopril), whereas today newer ACEIs such as ramipril or perindopril would be more likely to be prescribed. It was also previously demonstrated that BB use was associated with a significant reduction in postoperative mortality after OAR. However, this was compared with patients who did not use BBs.[37]

Limitations

This study should be interpreted considering several limitations. Our analysis was based on a data set, and the results are therefore subject to selection and confounding bias. The possibility of reverse causality is unavoidable in this study. It is possible that patients on BBs had higher comorbidity profiles compared with patients on RAASIs, which contributed to their worse outcomes. Although performing PSM was an attempt to account for differences in covariates, confounders not captured in the data set were not adjusted for. However, we believe the confounding effect is minimal and will not change our conclusion. Also, medication use was not measured beyond hospital discharge. Therefore, any change in medication beyond this period was not captured. Although it is possible that patients may have started or discontinued the medication, we were not able to address this possibility in this registry. However, it was previously proven that patients are more likely to use evidence-based medical therapies when they are prescribed on discharge compared with if they are initiated in an outpatient setting.[38] Finally, blood pressure levels as well as dosage and duration of drug administration can affect aneurysm therapy. However, this information was not recorded in this data set. Despite these limitations, by proving that RAASI use was associated with lower morbidity and mortality compared with BBs in a large real-world cohort of patients undergoing AAA repair, our results contribute significantly to the existing evidence. Although prior small randomized trials have investigated the effect of ACEIs and BBs on AAA growth rates,[39,40] large randomized controlled trials powered to compare different antihypertensive drugs effects on different outcomes of AAA repair are less likely to be performed. Consequently, achieving higher levels of clinical evidence may not be feasible.

CONCLUSIONS

In conclusion, RAASI use was associated with favorable postoperative outcomes compared with BB use. It was also associated with lower mortality and aneurysmal rupture at 1 year of follow-up. These findings suggest that RAASIs may be involved in multiple aspects of vascular inflammation of several blood vessels besides blood pressure control.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Figure S1

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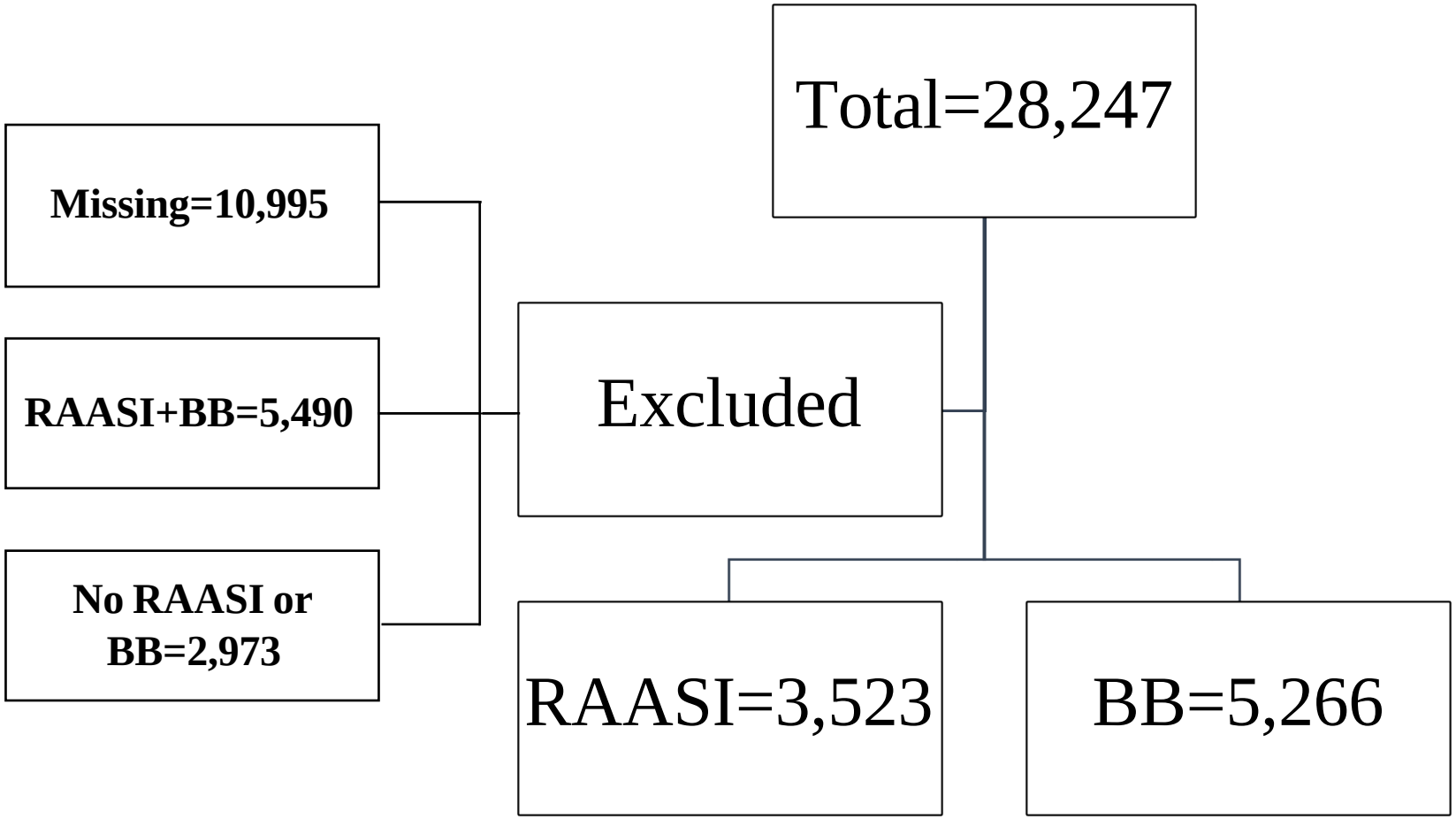
SUPPLEMENTAL MATERIAL

Figure S1. Inclusion and exclusion criteria.



RAASI: Renin-angiotensin-aldosterone system inhibitor; BB: Beta blocker.