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Angiotensin Receptor Blockade Improves Cardiac Surgery Outcomes in Patients with Metabolic Syndrome

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Abstract

Background—Perioperative use of angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEi) in patients undergoing cardiac surgery remains controversial. The current practice of discontinuing renin-angiotensin-system inhibitors before surgery, may negate their beneficial effects in vulnerable populations including patients with metabolic syndrome who exhibit elevated renin-angiotensin system activity. We hypothesized that preoperative ARBs use is associated with reduced incidence of postoperative complications, compared to ACEi or no drug, in patients with metabolic syndrome undergoing coronary artery bypass grafting.

Methods—We used propensity matching to derive a cohort of 1,351 patients from 2,998 who underwent coronary artery bypass graftingbased on preoperative use of ARBs, ACEi, or no renin-angiotensin-system inhibitors. Our primary endpoint was a composite of adverse events occurring within 30 days after surgery: new onset atrial fibrillation/flutter, arrhythmia requiring cardioversion, perioperative myocardial infarction, acute renal failure, need for dialysis, cerebrovascular accidents, acute respiratory failure, or perioperative death.

Results—At least one adverse event occurred in 524 (38.8%) of matched cohort patients (1,184, 39.6% of all patients). Adjusting for EuroSCORE and metabolic syndrome in the matched cohort, preoperative use of ARBs was associated with lower incidence of adverse events in patients with

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metabolic syndrome compared to preoperative use of no renin-angiotensin-system inhibitors (OR 0.43;95%CI 0.19–0.99) or ACEi (OR 0.38;95%CI 0.16–0.88).

Conclusions—ARBs, but not ACEi, used preoperatively confer benefit within 30 days after cardiac surgery in patients with metabolic syndrome, suggesting potential efficacy differences of these drug classes in reducing cardiovascular morbidity and mortality in ambulatory versus surgical patients.

Perioperative management of angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs), in cardiac surgery patients remains controversial.[1] ACEi use is associated with increased incidence of hypotension and/or vasoplegic syndrome during general anesthesia which continues into the postoperative period.[2] ACEi may independently predict mortality, inotrope use, postoperative renal dysfunction and new onset postoperative atrial fibrillation after coronary bypass grafting (CABG) surgery.[3] However, more recent meta-analyses concluded that preoperative treatment with renin-angiotensin-system inhibitors (RASi) is associated with a reduced incidence of acute kidney injury (AKI),[4] perioperative myocardial injury,[5] and may provide perioperative mortality benefits in diabetic patients.[6] Yet, the practice continues of discontinuing perioperative RASi continues.[3,7]

ARBs and ACEi are often considered interchangeable. However, combining ARBs/ACEi to analyze RASi effects on incidence of postoperative adverse events after cardiac surgery, is a critical limitation because these drug classes have different mechanisms of inhibition. ACEi reduce circulating and local levels of angiotensin II (AngII) while increasing bradykinin levels, whereas ARBs can suppress inflammation and interrupt AngII-dependent and -independent receptor activation,[8] thereby blocking effects of AngII produced via non-ACE pathways[9] without increasing bradykinin levels. Thus, additional comparative analyses are essential.

Increasing evidence suggests a bidirectional pathogenic relationship between an overactive RAS and metabolic syndrome (MetS). RAS signaling, activated by several factors associated with MetS, contributes to inflammation, reactive oxygen species generation, and impaired insulin signaling.[10] Findings recently verified by a clinical trial showing that RASi reduces cardiovascular events in MetS patients.[11]

Therefore, our primary objective was to compare the effect of preoperative use of ARBs vs ACEi on incidence of adverse postoperative outcomes in the setting of CABG surgery, using no RASi therapy as comparator, stratified by presence of MetS.

Patients and Methods

We performed a retrospective analysis of patients in the Project of Ex-vivo Vein Graft Engineering via Transfection (PREVENT-IV) trial (ClinicalTrials.gov:NCT0042081) who underwent primary CABG surgery between August 2002 and October 2003 at 107 centers across the U.S. The PREVENT IV protocol was approved by institutional review boards of all participating sites, and all enrolled patients provided written informed consent.

We began with 3,014 PREVENT-IV participants, however, patients who received both ARB and ACEi preoperatively (n=26) were excluded to allow for independent assessment of class effects. In the final study population (n=2,988) 3 groups were identified according to their preoperative RASi use: ARBs (n = 193); ACEi (n = 1,055), and no RASi therapy (n = 1,740). Baseline characteristics of these groups are presented in Table 1. RASi were started/restarted postoperatively at the discretion of the treating physician. We identified a subpopulation of patients with diagnostic criteria of MetS as set forth by the National Cholesterol Education Program - Adult Treatment Panel III (NCEP-ATP III) (Table 2) [12].

Propensity Matching and Modeling Methods

To study treatment effect in this observational dataset, we used propensity matching to balance patient factors across the treatment groups. Multinomial logistic regression was used to calculate a propensity for membership in each of the 3 treatment groups based on the following factors: metabolic syndrome, age > 75 years, sex, obesity, diabetes, hypertension, hypercholesterolemia, congestive heart failure, left ventricular (LV) dysfunction, history of atrial fibrillation, recent MI, renal failure and cerebrovascular disease. Using the Pharmacological Toolbox[13] we then matched 3 patients who received no RASi therapy and 3 patients who received ACEi to each ARB patient in three rounds of nearest-neighbor triplet matching with a caliper of 0.25. We compared the covariate balance before and after propensity matching using standardized mean differences (SMD) and the tableone package in R (v.3.1.1.,www.r-project.org). Factors with SMD<0.1 after propensity matching were deemed balanced.

Outcome Definition

The primary outcome was a composite of major perioperative adverse events (MPAE) occurring within 30 days of index surgery (Table 3). The criteria for all outcomes were in accordance with the STS National Adult Cardiac Database, except perioperative myocardial infarction, which was described based on an elevation in the plasma level of CK-MB >10 times the upper limit of normal within 24 hours after surgery and adjudicated by the PREVENT IV Clinical Events Committee. The secondary endpoint was incidence of postoperative inotropic requirements.

Statistical Analysis

Modeling Methods—To account for the data structure in the matched cohort, the univariate association of MPAE and postoperative inotrope use with the treatment groups was assessed in 3 separate generalized estimating equation (GEE) models (comparing ARBs vs no RASI, ARBs vs ACEi, and ACEi vs. no RASI, respectively) to account for the data structure in the matched cohort. For the primary MPAE outcome, we also performed multivariate GEE modeling adjusting the treatment group effect for EuroSCORE, MetS, and their interactions. If an interaction effect was non-significant it was dropped from the final MPAE outcome model. Modeling was performed in SAS v. 9.4 (SAS Institute Inc., Cary, NC), and $p<0.05$ was considered statistically significant.

Sensitivity Analyses—To verify that the association between preoperative ARB use and MPAE is not measuring the effects of RASi therapy started postoperatively and thereby

introducing confounding class-specific association results, we identified patients who received *de novo* ACEi between surgery and hospital discharge. We performed a sensitivity analysis of the association of MPAE with preoperative ARBs vs no RASi, restricting the cohort to only those not receiving ACEi postoperatively (n=1100).

Results

Compared to ACEi therapy in the full cohort, preoperative ARBs use was higher in women and hypertensive patients, and lower in patients with LV dysfunction and those with a history of MI. Although RASi overall were used more often in patients with MetS (21.2% of the study cohort), CHF, and cerebrovascular disease, the incidence of these comorbidities was not different between patients receiving ARBs versus ACEi preoperatively (Table 1). Interestingly, 40.6% of the patients with a history of MI (20.2% with MI within 30 days of enrollment) and 65.5% of hypertensive patients received no RASi therapy preoperatively.

Preoperative RASi and Patient Outcomes

In the overall cohort, 1,184 (39.6%) of patients experienced an MPAE and 33 (1.1%) died within 30 days after surgery. In the matched cohort, 524 (38.8%) patients experienced a MPAE and 14 (1%) died within 30 days of surgery. Univariate GEE analyses of treatment groups showed no significant difference in incidence of MPAE in the ARBs (n=70,36.3) vs no RASi (n=219, 37.8%, p=0.69) or the ACEi (n=235,40.6%,p=276) groups (Table 4). No perioperative deaths occurred in the ARBs treated group compared to 10 (1.7%) in the ACEi group. No patients in the ARBs group required postoperative cardioversion compared to 2.6% in the ACEi group (p=0.03). New onset POAF between drug classes, was higher in the ACEi group compared to the group that received no RASi (28.2% vs 24.9%); however, no significant difference was found between drug classes.

The incidence of other postoperative adverse events (notably acute renal failure) as well as postoperative inotrope requirement were similar between treatment groups. Univariate analysis of the associate of treatment group with postoperative inotrope use found no significant difference in the rate of inotrope us in ARB treated (n=125,64.8%) compared to no RASi (n=340,58.7%,p=0.12) or ACEi (n=341,58.9%,p=0.16)

Adjusted Regression Models Including Interaction with Metabolic Syndrome

We used multivariate GEE to evaluate the interaction effect of RASi with presence of MetS on incidence of MPAE in the matched cohort. Multivariable logistic regression models of MPAE adjusted for EuroSCORE and MetS, showed statistically significant interactions of ARBs with MetS when compared either to no RASi or ACEi use. In patients with MetS, preoperative ARBs treatment was associated with lower incident MPAE when compared to no RASi (OR 0.44; 95%CI 0.19–0.99,p=0.049) or ACEi (OR 0.38; 95%CI 0.16–0.889,p=0.025), suggesting a potential differential effect of preoperative ARB use in these patients (Table 5). Conversely, no treatment association was seen in the cohort of patients without MetS. Interaction terms between either RASi drug class and EuroSCORE were not significant. Thus, any potential beneficial effects of ARBs may not extend to other at-risk subpopulations based on their comorbidity profiles.

Sensitivity Analysis

The ORs for MPAE were consistent even after excluding patients who received *de novo* ACEi postoperatively (n=251 in matched sample). In this restricted cohort, preoperative ARBs were not significantly associated with incidence of MPAE when compared to no RASi therapy in a main effects model (OR 0.79; 95%CI 0.53–1.17). However, in a model that included the interaction between ARBs and MetS, the effect remained significant (p=0.04), and the relative odds reduction in patients with MetS was larger compared to the unrestricted cohort (adjusted OR 0.32; 95%CI 0.12–0.84). Taken together, these findings indicate that the association of preoperative ARBs with reduced MPAE in patients with MetS is unlikely to be a measure of the effect of introducing ACEi therapy postoperatively, but rather is specific to ARB use.

Comment

Although our study was not powered to define the mechanisms responsible for reduced MPAE in patients taking preoperative ARBs, we provide evidence of their physiologic plausibility. We hypothesize that patients with MetS are more dependent on medical control of risk factors, and also mount a greater inflammatory response to preioperative stress,[14] which can be attenuated by ARBs, resulting in reduced MPAE.

MetS significantly increases the risk for adverse perioperative outcomes, including acute renal failure, stroke, postoperative cognitive dysfunction,[15] postoperative atrial fibrillation and mortality.[16] In these patients, an overactive RAS strongly links to increased obesity and hyperlipidemia[12] with all RAS signaling components found in visceral adipocytes[17], contributing to the pathogenesis of obesity and hypertension. Further, there is increasing evidence for non-ACE-dependent AngII production in human tissues.[18] Plasma AngII levels increase significantly during cardiopulmonary bypass[19] and do so despite treatment with ACEi.[20] The increase in available AngII may play a causative role in the pathogenesis of adverse perioperative outcomes across several organ systems.[21]

Angiotensin receptor Type 1 (AT_1) expression is upregulated in hyperlipidemia,[22] and is associated with constitutively active signaling independent of AngII.[23] AT_1 receptors control inflammation by directly regulating IL-6 expression and monocyte-macrophage homing via enhanced expression of chemokines and chemotaxis, as well as blood pressure and fluid retention actions of AngII.[24] AT1 receptors are inhibited by ARBs, whereas the AT_2 receptors are cardio-protective, anti-inflammatory and regulate apoptosis and are not inhibited by ARBs.[25]

The RAS system is manipulated by ACEi and ARBs, yet these 2 drugs act at distinctly different sites along the pathway. ACEi inhibit ACE at the point of conversion to the vasoactive peptide whereas ARBs selectively block the AT_1 receptor. This highly selective blockade allows unopposed AT_2 receptor signaling thereby attenuating any inflammatory response.[25] Therefore, the associated reduction in MPAE among patients who took ARBS preoperatively in this study, may be related to their anti-inflammatory action. Indeed, ARB usage has been shown to reduce inflammation.[26]

In several studies, ACEi and ARB patients have not been evaluated separately, nor has preoperative dual therapy been noted. Rather, these distinctly different drugs have been combined in their analyses.[3,27] We believe this represents a significant residual confounder as key pharmacological differences between the 2 classes of drugs associate with different clinical effects in the perioperative setting. [25]

Our findings suggest that the efficacy paradox between ACEi and ARBs that has emerged from large clinical trials of treatments for hypertension in the ambulatory population,[28] may not extend to the acute perioperative care of patients undergoing CABG, where ARBs appear to reduce the incidence of composite MPAE, particularly in patients with MetS.

Limitations

Our results are based on a post-hoc analysis of data collected during a prospective multi-center randomized controlled trial. We analyzed effects of preoperative ARBs or ACEi on major postoperative adverse events, but not the effects of perioperative or postoperative therapy. However our sensitivity analysis, which excluded patients with *de novo* ACEi therapy initiated postoperatively, showed similar results. Finally, we acknowledge that the preoperative ARBs cohort was relatively small.

Conclusions

In EuroSCORE-adjusted analyses, we found no significant association of preoperative ARBs use with major perioperative adverse events. However, in patients with MetS, preoperative ARB use was associated with a reduction (approximately 60%) in the odds of developing 30-day MPAE. We believe this is the first evidence of a class-specific beneficial effect of preoperative ARBs in patients with MetS, a frequent comorbidity in patients undergoing CABG. Further investigations are needed to clarify the specific mechanism that drives ARBs protection in patients with MetS, and to evaluate long-term effects of ARBs in these patients.

Abbreviations and Acronyms

AKI	Acute kidney injury
AngII	Angiotensin II
ARB	Angiotensin Receptor Blocker
ACEi	Angiotensin-Converting Enzyme inhibitor
CVA	Cerebrovascular Accident
CABG	Coronary Artery Bypass Graft
EuroSCORE	European System for Cardiac Operative Risk Evaluation Score
MPAE	Major Perioperative Adverse Events
MetS	Metabolic Syndrome

MI	Myocardial Infarction
NCEP-ATPIII	National Cholesterol Education Program-Adult Treatment Panel III
PREVENT IV	Project of Ex-vivo Vein Graft Engineering via Transfection
POAF	Postoperative atrial fibrillation/flutter
TIA	Transient Ischemic Attack
RASi	Renin-Angiotensin System inhibitor

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TABLE 1

Characteristics of the study population by preoperative RAS Inhibitor Use

	Full Cohort				Matched Analysis Cohort			
	Preoperative RAS Inhibitor Use				Preoperative RAS Inhibitor Use			
	No RASi (N = 1740)	ARBs (N = 193)	ACEi (N = 1055)	SMD	No RASi (N = 579)	ARBs (N = 193)	ACEi (N = 579)	SMD
Demographics								
Age ≥75 years	204 (11.7)	27 (14.0)	126 (11.9)	0.045	73 (12.6)	27 (14.0)	63 (10.9)	0.063
Female Gender	346 (19.9)	56 (29.0)	220 (20.9)	0.142	156 (26.9)	56 (29.0)	151 (26.1)	0.044
Race				0.162				0.170
Caucasian	1590 (91.4)	174 (90.2)	955 (90.5)		524 (90.5)	174 (90.2)	523 (90.3)	
Black	76 (4.4)	8 (4.1)	53 (5.0)		26(4.5)	8 (4.1)	28 (4.8)	
Asian	17 (1.0)	6 (3.1)	9 (0.9)		7 (1.2)	6 (3.1)	6 (1.0)	
Hispanic	42 (2.4)	3 (1.6)	26 (2.5)		17 (2.9)	3 (1.6)	17 (2.9)	
Native American	5 (0.3)	2 (1.0)	5 (0.5)		1 (0.2)	2 (1.0)	3 (0.5)	
Other	10 (0.6)	0 (0.0)	7 (0.7)		4 (0.7)	0 (0.0)	2 (0.3)	
Clinical Risk Factors								
* Obesity: BMI >30	661 (38.0)	88 (45.6)	491 (46.5)	0.116	253 (43.7)	88 (45.6)	257 (44.4)	0.025
* Hypertension	1140 (65.5)	179 (92.7)	920 (87.2)	0.475	542 (93.6)	179 (92.7)	538 (92.9)	0.023
*Hypercholesterolem ia	1301 (74.8)	153 (79.3)	825 (78.2)	0.071	474 (81.9)	153 (79.3)	477 (82.4)	0.053
* Diabetes	521 (29.9)	94 (48.7)	510 (48.3)	0.261	273 (47.2)	94 (48.7)	272 (47.0)	0.023
Metabolic Syndrome	187 (10.7)	41 (21.2)	219 (20.8)	0.193	121 (20.9)	41 (21.2)	120 (20.7)	0.008
Congestive heart failure	128 (7.4)	22 (11.4)	138 (13.1)	0.127	50 (8.6)	22 (11.4)	57 (9.8)	0.061
LV Dysfunction				0.160				0.034
Normal	1136 (65.3)	126 (65.3)	584 (55.4)		388 (67.0)	126 (65.3)	380 (65.6)	
Moderate (LVEF 30%–50%)	537 (30.9)	58 (30.1)	393 (37.3)		169 (29.2)	58 (30.1)	174 (30.1)	
Severe (LVEF< 30%)	67 (3.9)	9 (4.7)	78 (7.4)		22 (3.8)	9 (4.7)	25 (4.3)	
Atrial flutter/fibrillation	117 (6.7)	16 (8.3)	78 (7.4)	0.040	43 (7.4)	16 (8.3)	42 (7.3)	0.026
Cigarette smoker				0.094				0.059
never	527 (30.3)	64 (33.2)	345 (32.7)		181 (31.3)	64 (33.2)	203 (35.1)	
former	802 (46.1)	93 (48.2)	469 (44.5)		292 (50.4)	93 (48.2)	269 (46.5)	

	Full Cohort				Matched Analysis Cohort			
	Preoperative RAS Inhibitor Use				Preoperative RAS Inhibitor Use			
	No RASi (N = 1740)	ARBs (N = 193)	ACEi (N = 1055)	SMD	No RASi (N = 579)	ARBs (N = 193)	ACEi (N = 579)	SMD
current	411 (23.6)	36 (18.7)	241 (22.8)		106 (18.3)	36 (18.7)	107 (18.5)	
Prior MI	352 (20.2)	17 (8.8)	235 (22.3)	0.252	61 (10.5)	17 (8.8)	56 (9.7)	0.039
Prior PCI	425 (24.4)	47 (24.4)	296 (28.1)	0.056	156 (26.9)	47 (24.4)	172 (29.7)	0.080
Renal failure	39 (2.2)	7 (3.6)	19 (1.8)	0.075	14 (2.4)	7 (3.6)	16 (2.8)	0.047
History of dialysis	11 (0.6)	3 (1.6)	7 (0.7)	0.059	5 (0.9)	3 (1.6)	6 (1.0)	0.042
Cerebrovascular disease	197 (11.3)	30 (15.5)	152 (14.4)	0.083	81 (14.0)	30 (15.5)	92 (15.9)	0.036
Prior carotid surgery	51 (2.9)	11 (5.7)	36 (3.4)	0.091	24 (4.1)	11 (5.7)	25 (4.3)	0.048
Prior stroke	84 (4.8)	12 (6.2)	67 (6.4)	0.044	37 (6.4)	12 (6.2)	37 (6.4)	0.005
Prior TIA	67 (3.9)	15 (7.8)	55 (5.2)	0.113	25(4.3)	15 (7.8)	35 (6.0)	0.097
COPD	266 (15.3)	31 (16.1)	176 (16.7)	0.025	82 (14.2)	31 (16.1)	83 (14.3)	0.035
Other procedures	188 (10.8)	20 (10.4)	107 (10.1)	0.014	71 (12.3)	20 (10.4)	61 (10.5)	0.040
CPB use	1364 (78.4)	157 (81.3)	834 (79.1)	0.049	446 (77.0)	157 (81.3)	457 (78.9)	0.071
CPB duration (min)	103.41 (36.80)	104.97 (32.13)	104.92 (36.64)	0.029	105.35 (38.68)	104.97 (32.13)	103.11 (36.37)	0.041
EuroSCORE	4.77 (2.75)	4.87 (2.80)	4.91 (2.86)	0.033	4.95 (2.89)	4.87 (2.80)	4.73 (2.69)	0.051

Values represent n (%); or mean ± SD. ACEi = angiotensin converting enzyme inhibitor;

ARB = angiotensin receptor blocker; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass;

EuroSCORE = European System for Cardiac Operative Risk Evaluation; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous intervention;

SMD = Standardized Mean Differences; TIA = transient ischemic attack;

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Table 2

Diagnostic Elements of Metabolic Syndrome

Criteria	Lab Value		Drug		Diagnosis
Elevated Triglycerides	≥ 150 mg/dL (1.7 mmol/L)	Or	Fibrate	Or	High Triglycerides
Low HDL	< 40 mg/dL (1.0 mmol/L) Men < 50 mg/dL (1.3 mmol/L) Women	Or	STATIN	Or	Hypercholeterolemia
Hypertension	Systolic ≥ 130 mmHg and/or Diastolic ≥ 85 mmHg	Or	Antihypertensive	Or	Hypertension
Hyperglycemia	> 100 mg/dL (5.5 mmol/L)	Or	Glycemic Medication	Or	Diabetes
Obesity	BMI ≥ 30				

(Patients diagnosed with metabolic syndrome met the following accepted criteria as defined by lab value, drug use, or diagnosis by the NCEP-ATPIII)

Table 3

Outcome Distribution by RAS Groups in Matched Cohort

	No RASi (N = 579)	ARBs (N = 193)	ACEi (N = 579)	Total (N = 1351)
Major Periop Adverse Outcome	219 (37.82%)	70 (36.27%)	235 (40.59%)	524 (38.79%)
Pt died on or before 30 days	4 (0.69%)	0 (0.00%)	10 (1.73%)	14 (1.04%)
Peri-index CABG MI	60 (10.36%)	18 (9.33%)	58 (10.02%)	136 (10.07%)
Re-intubation	17 (2.94%)	6 (3.11%)	18 (3.11%)	41 (3.03%)
Any AFIB/Flutter AE	144 (24.87%)	48 (24.87%)	163 (28.15%)	355 (26.28%)
Any Renal Failure AE	40 (6.91%)	12 (6.22%)	47 (8.12%)	99 (7.33%)
Any CVA/TIA AE	10 (1.73%)	4 (2.07%)	11 (1.90%)	25 (1.85%)
Cardioversion	9 (1.55%)	0 (0.00%)	15 (2.59%)	24 (1.78%)
Dialysis	4 (0.69%)	0 (0.00%)	6 (1.04%)	10 (0.74%)

TABLE 4

GEE Regression models of postoperative outcomes in Matched Cohort

Univariable analysis	All (n=1,351)	Preoperative RAS inhibitor use			Group comparison p-Values			
		No RASi (n=579)	ARBs (n=193)	ACEi (n=579)	ARBs vs ACEi vs No RASi	ARBs Vs No RASi	ACEi Vs No RASi	ARBs Vs ACEi
Major Perioperative Adverse Events (composite)	524 (38.8%)	219 (37.8%)	70 (36.3%)	235 (40.6%)	0.452	0.685	0.319	0.276
Postoperative inotrope use	806 (59.7%)	340 (58.7%)	125 (64.8%)	341 (58.9%)	0.271	0.124	0.952	0.155

Values represent n (%)

ARB = angiotensin receptor blockers;

ACEi = angiotensin receptor blockers;

RASi = renin angiotensin system inhibitors

TABLE 5

Multivariable GEE analysis of postoperative outcomes in Matched Cohort

Multivariable analysis	Preoperative RAS inhibitor treatment group comparisons					
	ARBs vs no RASi		ACEi vs no RASi		ARBs vs ACEi	
	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)
Major Perioperative Adverse Events (composite outcome)						
EuroSCORE	<.0001	1.131 (1.076, 1.190)	<0.0001	1.127 (1.079, 1.178)	<0.0001	1.120 (1.062, 1.181)
Metabolic syndrome with reference treatment	0.494	1.158 (0.761, 1.763)	0.498	1.156 (0.760, 1.761)	0.464	1.167 (0.771, 1.766)
Treatment effect by metabolic syndrome						
With metabolic syndrome	0.049	0.439 (0.194, 0.996)	0.573	1.166 (0.685, 1.985)	0.025	0.381 (0.163, 0.888)
Without metabolic syndrome	0.493	1.139 (0.785, 1.654)	0.296	1.154 (0.882, 1.509)	0.940	0.986 (0.682, 1.425)

ARB = angiotensin receptor blockers; ACEi = angiotensin receptor blockers;

CI = confidence interval; OR = odds ratio; RASi = renin angiotensin system inhibitors