Renin-angiotensin blockade is associated with increased mortality after vascular surgery

L'inhibition du système rénine-angiotensine est lié à une augmentation de la mortalité suite à une chirurgie vasculaire

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Abstract

Purpose The outcome of patients with preoperative renin-angiotensin system (RAS) blockade, achieved either by angiotensin converting enzyme inhibitors or angiotensin receptor blocking agents, was assessed using 30-day mortality as a primary end point.

Methods An observational cohort study of 883 consecutive patients undergoing elective open abdominal aortic aneurysm repair (AAA) was undertaken and analyzed using a propensity score matched study. The data collected included medical history, anesthetic techniques, and postoperative outcomes. Logistic regression analysis identified predictors of RAS blockade: hypertension, stroke, congestive heart failure, diabetes, and heart disease. A propensity score for RAS blockade was calculated for each subject using several factors: age, sex, serum creatinine, hypertension, heart disease, congestive heart failure, stroke, diabetes, and exposure to cardiovascular medications. Subjects and controls were matched using the calculated propensity score.

Results The overall 30-day mortality rate was 3.5% (31/883 patients). The crude mortality rate in RAS blocked patients was 5.8% (21/359) vs 1.9% (10/524) in unexposed patients (odds ratio 3.2, with 95% confidence intervals [CI_{95}] 1.5-6.7; $P < 0.001$). Analysis of 261 propensity score matched pairs showed a 30-day mortality rate of 6.1% (16/261) in the RAS blocked group vs 1.5% (4/261) in unblocked patients ($P = 0.008$). The estimated odds ratio for 30-day mortality associated with RAS blockade was 5.0 (CI_{95} 1.4-27).

Conclusions Examination of 883 cases of AAA repair showed increased mortality associated with preoperative RAS blockade. A better understanding of perioperative pharmacology and physiology of RAS blockade is needed as well as future studies to identify causality.

Résumé

Objectif Le devenir des patients prenant, en préopératoire, des inhibiteurs du système rénine-angiotensine (SRA) (inhibiteurs de l'enzyme de conversion de l'angiotensine ou antagonistes du récepteur de l'angiotensine) a été évalué en utilisant le taux de mortalité à 30 jours comme critère d'évaluation principal.

Méthodes Une étude observationnelle menée auprès d'une cohorte de 883 patients consécutifs subissant une chirurgie ouverte programmée pour un anévrisme de l'aorte abdominale (AAA) a été entreprise et analysée à l'aide d'une analyse d'appariement par scores de propension. Les données recueillies incluaient les antécédents médicaux, les techniques d'anesthésie et les résultats postopératoires. L'analyse de régression logistique a permis d'identifier des variables prédisant la prise d'inhibiteurs du SRA: l'hypertension, les accidents vasculaires cérébraux, l'insuffisance cardiaque congestive, le diabète et les cardiopathies. Un score de propension pour la prise

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d'inhibiteurs du SRA a été calculé pour chaque sujet en tenant compte de plusieurs facteurs: l'âge, le sexe, la créatininémie, l'hypertension, les cardiopathies, l'insuffisance cardiaque congestive, les accidents vasculaires cérébraux, le diabète et l'exposition à des médicaments cardiovasculaires. Les sujets et et les témoins ont été appariés à l'aide du score de propension calculé.

Résultats *Le taux de mortalité global à 30 jours était de 3,5 % (31/883 patients). Le taux brut de mortalité chez les patients ayant pris un inhibiteur du SRA était de 5,8 % (21/359) contre 1,9 % (10/524) chez les patients n'y ayant pas été exposés (rapport des cotes de 3,2, avec intervalles de confiance de 95 % [IC₉₅] 1,5-6,7; P < 0,001). L'analyse de 261 paires de patients appariés par scores de propension a permis de démontrer un taux de mortalité à 30 jours de 6,1 % (16/261) pour les patients ayant pris un inhibiteur du SRA contre 1,5 % (4/261) pour les patients non exposés (P = 0,008). Le rapport de cotes estimé pour le taux de mortalité à 30 jours associé à l'inhibition du SRA était de 5,0 (IC₉₅ 1,4-27).*

Conclusions *L'examen de 883 cas de chirurgie en cas d'AAA a révélé une augmentation du taux de mortalité associé à l'inhibition préopératoire du SRA. Une meilleure connaissance de la pharmacologie peropératoire et de la physiologie de l'inhibition du SRA et d'autres études sont nécessaires pour identifier la causalité.*

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists (ARAs) are used to treat hypertension, congestive heart failure (CHF) and myocardial infarction (MI), reducing mortality and improving quality of life.[1] Inhibitors of ACE and ARAs are popular and effective with over 130,000 patients studied in randomized controlled trials (RCTs).[2] However, the conclusions of these RCTs might not be applicable to the situation of surgical patients, because none of the RCTs examined the effects of anesthesia and perioperative care.

Perioperative blockade of the renin-angiotensin system (RAS), defined as preoperative exposure to ACE inhibitors and ARAs, remains controversial because the area has been poorly studied. The 2007 American College of Cardiology – American Heart Association guidelines[3] advise caution using ACE inhibitors perioperatively in renally impaired patients citing increased risk of renal failure.[4] Some physicians recommend holding ACE inhibitors or ARAs prior to surgery to prevent intraoperative refractory hypotension.[5,6]

Anesthetized patients depend heavily on the RAS to maintain blood pressure.[7] Hypovolemia, hyponatremia, and anemia activate the RAS to maintain blood pressure.[8] Intraoperative hypotension induced by ACE inhibitors has been reported in one large study[9] and in a meta-analysis.[10]

The ACE inhibitors have been studied in patients with CHF undergoing vascular surgery.[11] Correction for thirteen medical factors showed that ACE inhibitor exposure was protective in patients with left ventricular dysfunction (odds ratio 0.33; 95% confidence intervals [CI₉₅] 0.12-0.91; $P = 0.03$).[11] However, Miceli *et al.* have shown that perioperative ACE inhibitor therapy is associated with a doubling of the mortality rate in patients undergoing coronary artery bypass grafting surgery (CABG).[12] The purpose of this study was to test the hypothesis that preoperative RAS blockade is safe in vascular surgery patients, using 30-day postoperative mortality as the primary end point.

Methods

Following Research Ethics Board approval, consent was obtained from the attending surgeons to review the medical charts of patients undergoing abdominal aortic aneurysm (AAA) repair at two teaching hospitals from January 1, 1998 to December 31, 2005. Patients were identified for possible inclusion into the cohort based on operative bookings and the following inclusion criteria: age > 50 yr, elective AAA repair, or urgent surgery with adequate medical workup. Patients were excluded for the following reasons: trauma, emergency surgery, sepsis, combined AAA and non-vascular surgery, and surgery on bypass.

One physician reviewed all charts and abstracted information onto data sheets. Data were entered into Microsoft Excel 2003 (Microsoft Corp., Redmond, OR, USA) using Filemaker Pro 5.0 (Filemaker Inc., Santa Clara, CA, USA) computer software for conversion to a data file for statistical analysis.

The information collected included age, sex, medical history (cardiac, respiratory, renal, neurological, and endocrine), preoperative consultation and testing, vital signs, weight, renal function, preoperative medications, surgeon, and anesthetic techniques. Postoperative complications were also entered: death, arrest, arrhythmia, CHF, increased troponin, renal failure, stroke, and other complications.

Medications were grouped using the following classes: ACE inhibitors, ARAs, beta-blockers, calcium channel blockers (CaCB), diuretics, nitrates, non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase II inhibitors (COX-2 s), and HMG-CoA inhibitors (statins). An assumption was made that the patients were taking the medications as directed by the preoperative assessment clinic staff. The normal recommendation was to take all cardiac medications with the exception of diuretics, which were held on the day of surgery; NSAIDs and COX-2 inhibitors were held for five days prior to surgery.

A patient was considered to have a given medical condition under any of the following circumstances: self report, positive diagnostic testing, diagnosis in old charts, and report of the condition in preoperative consultations or in the attending anesthesiologist's note. Creatinine clearance (Cr Cl) was calculated using the Cockcroft-Gault formula.[13]

Postoperative complications were recorded based on physician diagnosis recorded in the medical chart. Infections were diagnosed based on positive laboratory culture results, even if not recorded in the medical notes. A postoperative MI – increased troponin was recorded as the result of a physician diagnosis of MI or a laboratory troponin I concentration > 0.3 ng.L^{-1} and either patient symptoms or ECG changes.

Study end point and sample size

Thirty-day mortality was the primary end point used to assess the safety of RAS blockade. A pilot study of the first 122 charts was undertaken. Seventy-one patients met the inclusion criteria with an observed death rate of 9.8% (7/71 patients), 29% in ACE/ARA exposed patients (5/17) *vs* 3.7% in unexposed patients (2/54) ($P = 0.002$). However, the subjects were not well matched. The observed death rate was greater than the expected rate of 4%. There was considerable uncertainty in the estimated mortality rate, especially in RAS blocked patients.

Modelling a range of death rates using PASS 2002 (NCSS LLC, Kaysville, UT, USA) showed that 780 pairs would be needed to detect a difference of 4% in death rate associated with RAS blockade (power 0.8; alpha = 0.05), assuming 15% of pairs were discordant. This number would decrease to 350 pairs if the difference in death rate was increased to 6%. It was decided to review eight years of consecutive cases (approximately 1,300 charts) expecting to find approximately 900 to 1,000 patients comprising cohort for analysis.

Statistical analysis

Data was analyzed using NCSS 2007 (NCSS LLC, Kaysville, UT, USA) and SAS 9.1 (SAS Inc, Cary, NC, USA). Continuous data variable differences were tested by Student's *t* test. Dichotomous data differences were tested by Chi square test or Fisher's modification. SAS 9.1 was used to perform the propensity score match and subsequent statistics on the matched data set, and the McNemar score was used to assess differences between exposed and unexposed subjects. Odds ratios and confidence intervals for matched pairs were estimated using a standard method.[14] Comparisons of 30-day mortality (primary end point) and major postoperative complications were planned at the start of the study. Data are reported as mean ± standard deviation unless otherwise indicated.

To avoid selection bias and confounding factors, RAS blocked subjects and unblocked patients were matched using a propensity score system.[15] A logistic regression analysis of the data set (883 patients and 49 possible factors) using SAS 9.1 (SAS Inc., Cary, NC, USA) identified predictors (all $P < 0.05$) of RAS blockade: hypertension, stroke, CHF, diabetes, and heart disease (a combined term comprised of any history of previous MI, previous CABG, arrhythmias, and/or angina). A second logistic regression analysis of the data set identified predictors (all $P < 0.05$) of mortality: age, creatinine, diabetes, ACE/ARA, and diuretic exposure. Factors affecting perioperative mortality were considered for inclusion in the model, especially those differing between the RAS blocked and unblocked groups. The model developed predicting preoperative RAS blockade included the following terms: age, sex, creatinine, CHF, heart disease, hypertension, stroke, and preoperative cardiovascular medication exposures (beta-blockers, CaCB, diuretics, and HMG-CoA reductase inhibitors [statins]). A propensity score (from 0 to 1) representing the likelihood of RAS blockade was calculated for each subject. An unexposed subject was matched to an RAS blocked subject using the MEANS procedure of the SAS 9.1 program (propensity score within 0.1). In 19 patients, the preoperative serum creatinine was estimated as 103.15 μmol·L^{-1}.

Results

Subjects

According to operating room bookings, 1,320 patients underwent AAA repair from January 1, 1998 to December 31, 2005. Manual review of charts identified 883 subjects meeting inclusion criteria. There were 437 exclusions for the following reasons: other vascular procedure performed (259), emergency surgery (157), age < 50 yr (8), missing charts (4), cancelled surgery (2), and other (7). Subject characteristics, medical history, and the results of the propensity matching process are summarized in Table 1.

Preoperative medication exposures

Examination of preoperative medication exposures revealed that 306 of 883 subjects (34%) were exposed to ACE inhibitors, and 60 of 883 subjects (7%) were exposed to ARA agents. Eight subjects were exposed to both ACE inhibitors and ARAs. The exposures of subjects to different classes of medications are reported in Table 2, including

Table 1 Patient characteristics – unmatched data and propensity score matched subjects

Patient data	Unmatched data			Propensity score matched subjects	
	Whole group (883)	RAS blockade (359)	No RAS blockade (524)	RAS blockade (261)	No RAS blockade (261)
Male	726 (82%)	298 (83%)	428 (82%)	210 (81%)	212 (81%)
Age (yr)	72 (7)	72 (7)	72 (7)	72 (7)	72 (7)
Weight (kg)	80 (16)	81 (16)	79 (15)	81 (17)	80 (15)
Heart rate (min^{-1})	70 (13)	69 (13)	70 (12)	70 (13)	70 (12)
Systolic blood pressure (mmHg)	138 (20)	139 (21)	137 (19)	139 (21)	141 (19)
Diastolic blood pressure (mmHg)	80 (21)	79 (11)	80 (25)	79 (11)	80 (12)
Mean preoperative Hgb ($g \cdot L^{-1}$)	138 (16)	136 (16)	139 (15)	136 (16)	139 (15)
Cr Cl ($mL \cdot min^{-1}$)	73 (30)	71 (31)	74 (28)	71 (30)	70 (28)
Creatinine (μmoL)	103 (56)	109 (60)	99 (52)	107 (63)	107 (68)
Medical conditions					
Hypertension	590 (67%)	319 (89%)	271 (52%)	224 (86%)	235 (90%)
Heart disease	428 (49%)	204 (57%)	224 (43%)	140 (54%)	140 (54%)
Previous MI	269 (30%)	134 (37%)	135 (26%)	93 (36%)	83 (32%)
Angina	176 (20%)	79 (22%)	97 (19%)	46 (18%)	61 (23%)
Arrhythmia	117 (13%)	69 (19%)	48 (9%)	47 (18%)	29 (11%)
Afib	79 (9%)	45 (13%)	34 (7%)	30 (12%)	19 (7%)
CHF	34 (4%)	25 (7%)	9 (2%)	14 (5.4%)	8 (3.1%)
Valvular heart disease	31 (4%)	18 (5%)	14 (3%)	9 (3.4%)	9 (3.4%)
Previous CABG	120 (13%)	66 (18%)	54 (10%)	48 (18%)	41 (16%)
Renal impairment	154 (19%)	82 (21%)	77 (15%)	53 (20%)	51 (20%)
Renal failure on HD	5 (1%)	5 (1%)	0 (0%)	3 (1.2%)	0 (0%)
Stroke	57 (7%)	38 (11%)	19 (4%)	15 (5.7%)	13 (5.0%)
TIA	51 (6%)	19 (5%)	32 (6%)	16 (6.1%)	21 (8.0%)
Seizures	11 (1%)	2 (1%)	9 (2%)	1 (0.4%)	6 (2.3%)
Any smoking history	756 (86%)	308 (86%)	448 (85%)	220 (84%)	214 (82%)
Active smokers	301 (21%)	115 (32%)	186 (36%)	82 (32%)	84 (31%)
Pack years	48 (21)	47 (21)	48 (21)	48 (21)	50 (21)
COPD	184 (21%)	78 (22%)	105 (20%)	56 (22%)	48 (18%)
Diabetes	119 (13%)	71 (20%)	48 (9%)	37 (14%)	30 (12%)
Thyroid disease	80 (9%)	32 (9%)	48 (9%)	25 (9.6%)	24 (9.2%)
Propensity score				0.49 (0.16)	0.48 (0.16)

Data are reported as mean (standard deviation) or number (%). RAS = renin-angiotensin system; RAS blockade = exposure to angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor antagonists (ARA); No RAS blockade = no exposure to ACE inhibitors or ARA; CaCB = calcium channel blocker, Cr Cl = creatinine clearance; heart disease (composed of previous MI, previous CABG, angina, and arrhythmias); MI = myocardial infarction; Afib = atrial fibrillation; CHF = congestive heart failure; CABG = coronary artery bypass grafting, HD = hemodialysis; Statin = HMG Co-A reductase inhibitor; TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease

propensity score matched subjects. The details of the propensity matching process are presented in Table 3.

Surgeons and anesthetic techniques

Prior to considering further analysis, we searched for differences in mortality related to surgeon or choice of anesthetic techniques employed. None were found. All 883 patients received a general anesthetic with inhaled agents being used in 882 (99.9%); one patient had malignant hyperthermia. Thoracic epidurals were placed in 715 (81%) patients and used during the anesthetic in 243 (28%) cases. Mean estimated blood loss was 1,267 ± 1,083 mL. Volume of fluid administered was 5,583 ± 3,282 mL, and fluid balance was positive by 3,918 ± 2,303 mL. Blood products were received and/or a cell saver was used in 521 patients (59%).

Table 2 Preoperative medications

Drug class	Unmatched data				Propensity score matched subjects	
	Whole group (883)	RAS blockade (359)	No RAS blockade (524)	P value	RAS blockade (261)	No RAS blockade (261)
ACE*	306 (35%)	306 (85%)	0		225	0
ARA*	60 (7%)	60 (18%)	0		40	0
Beta-blocker	376 (43%)	174 (49%)	202 (39%)	0.006	126 (48%)	129 (49%)
CaCB	268 (30%)	117 (33%)	151 (29%)	0.227	88 (34%)	102 (39%)
Diuretics	179 (20%)	103 (29%)	76 (15%)	< 0.001	71 (27%)	62 (24%)
Statin	365 (41%)	175 (49%)	190 (36%)	< 0.001	116 (44%)	117 (45%)
NSAIDs	389 (44%)	170 (47%)	219 (42%)	0.135	118 (45%)	117 (45%)
Nitrates	106 (12%)	50 (14%)	56 (11%)	0.150	32 (12%)	32 (12%)
COX2	43 (4%)	14 (4%)	19 (4%)	0.873	12 (4.2%)	10 (4.2%)

Data are reported as number (%). * Eight patients were taking both an ACE inhibitor and an ARA. Four patients were taking ACE inhibitors and ARAs in the propensity score matched data set. RAS = renin-angiotensin system; RAS Blockade = exposure to angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor antagonists (ARA); No RAS blockade = no exposure to ACE inhibitors or ARA; CaCB = calcium channel blocker; Statin = HMG CoA reductase inhibitor; NSAIDs = non-steroidal anti-inflammatory drug; COX2 = cyclo-oxygenase 2 inhibitor

Postoperative outcomes

Postoperative outcomes for unmatched and propensity matched pairs are summarized in Table 4. Twenty-one of 359 patients with RAS blockade (5.8%) died within 30 days of surgery vs 10/524 (1.9%) of unblocked subjects (P < 0.002). Data for secondary outcomes and common postoperative complications for ACE/ARA exposed subjects and unexposed subjects are reported in Table 4.

Propensity matched pairs outcomes are also reported in Table 4 and distribution of pairs in Table 3. The matching process afforded 261 pairs of subjects, and analysis revealed 16 deaths (6.1%) in RAS blocked patients and four deaths (1.5%) in unblocked patients. One pair was concordant for death. The McNemar Score was calculated as 8.0 (P = 0.008). The estimated odds ratio for increased mortality in the matched sample was 5; CI_{95} 1.4-27. However, the matching did not control for hypertension; 94% of pairs were concordant (222 hypertensive and 24 not hypertensive) and 15 pairs discordant (two RAS blocked and 13 unexposed) (P = 0.005). Causes of death and associated conditions are reported in Table 5.

Mortality associated with medical conditions and medication exposures

Unadjusted odds ratios for 30-day mortality were calculated for medical conditions and medication exposures using the entire data set of 883 patients. Only two medical conditions were associated with 30-day mortality: diabetes (odds ratio 2.8; CI_{95} 1.2-6.1) and CHF (odds ratio 4.1; CI_{95} 1.3-12.3). Only two medication exposures were associated with increased mortality: ACE inhibitor/ARA exposure 21/359 (5.8%) vs 10/524 (1.9%) (odds ratio 3.2; CI_{95} 1.5-6.9), and diuretic exposure 15/164 (9.1%) exposed vs 16/688 (2.3%) unexposed (odds ratio 3.9; CI_{95} 1.90-8.11).

Discussion

Perioperative use of ACE inhibitors or ARAs remains controversial. Randomized controlled trials demonstrating the clinical effectiveness of ACE inhibitors and ARAs in the medical setting may not be applicable perioperatively, because none of the RCTs examined the effects of anesthesia and perioperative care on RAS blockade. It is not known if a drug interaction exists between RAS blocking medications and inhaled anesthetic agents. A possible explanation for intraoperative hypotension in RAS blocked patients is impaired Ca^{2+} binding in vascular smooth muscle cells. Vascular myocyte contraction can be initiated by angiotensin 2 binding to the angiotensin 1 (AT1) receptor.[16] Protein kinase C (PKC) is involved in multiple intracellular pathways, including sensitizing the AT1 and angiotensin 2 (AT2) receptors.[17] Inhaled anesthetics inhibit PKC causing decreased activity of the AT1 receptor and increased activity of the AT2 receptor causing decreased vascular tone.[16-19] Bradykinin has also been implicated as a possible intermediary.[20]

In the present study, RAS blockade was associated with an increased mortality within 30 days of surgery in vascular surgery patients (uncorrected odds ratio 3.2; CI_{95} 1.5-6.9). Differences in underlying medical conditions and medication exposures between RAS blocked patients and unexposed patients were identified. Separation of the effects of a medication from the medical condition for

Table 3 Matched pairs analysis – distribution of concordant and discordant matched pairs for preoperative factors in propensity score matching and postoperative outcomes. The number of pairs was 261

	Concordant pairs		Discordant pairs		McNemar P value
	Factor present both subjects	Factor absent both subjects	Factor present in RAS blocked blockade but absent in no RAS unblocked blockade	Factor absent in RAS blocked blockade but present in no RAS unblocked blockade	
Preoperative medical conditions					
Sex (Male)	182	21	30	28	0.90
Hypertension	222	24	2	13	0.007
Heart disease	96	77	44	44	1.0
CHF	3	242	11	5	0.21
Stroke	3	236	12	10	0.83
Diabetes	12	206	25	18	0.36
Preoperative medication exposures					
Beta-blockers	85	91	41	44	0.83
CaCB	40	111	48	62	0.21
Diuretics	70	98	46	47	1.0
Statins	24	152	47	38	0.38
Post operative outcomes					
Death < 30 days	1	242	15	3	0.008
MI/increased troponin	6	180	40	35	0.645
Postoperative heart failure	5	220	20	16	0.618
Postoperative stroke	0	255	5	1	0.219
Postoperative renal failure	1	202	30	28	0.896
Postoperative hemodialysis	0	247	12	2	0.013

Data are reported as numbers. RAS = renin-angiotensin system; RAS blockade = exposure to angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor antagonists (ARA); No RAS blockade = no exposure to ACE inhibitors or ARA; CaCB = calcium channel blocker; CHF = congestive heart failure; Heart disease (composed of previous myocardial infarction, previous coronary artery bypass grafting, angina, and arrhythmias); MI/increased troponin = postoperative myocardial infarction (troponin I > 0.3 $ng \cdot L^{-1}$); Statins = HMG Co-A reductase inhibitors

which it is prescribed is problematic. The possibility exists that ACE/ARAs are prescribed to patients who are medically less fit, which would account for the observed differences. Differences in underlying medical conditions were addressed by propensity score matching predicting the preoperative likelihood that a patient would be exposed to an ACE inhibitor or ARA prior to surgery.

Matching based only on age and sex, as was done in other studies,[21] predisposes towards poor matching of subjects. To reduce selection bias and confounding, a propensity matching system was developed to match exposed and unexposed subjects. Logistic regression analysis of the 883 cases identified five predictors of ACE inhibitor/ARA exposure: hypertension, stroke, CHF, diabetes, and heart disease. Hypertension was the strongest predictor of preoperative ACE/ARA exposure. Additional analysis of the data set identified preoperative diuretic exposure as a factor associated with mortality. Cardiovascular medication exposures were different between RAS blocked and unblocked patient populations. A propensity

score model was developed that incorporated the above information and known preoperative predictors thought to be associated with mortality in this patient population.[22-30] The model incorporated the following terms: age, sex, creatinine, hypertension, heart disease, CHF, diabetes, stroke, and cardiovascular medication exposures (beta-blocker, CaCB, diuretic, and statins). The patients were then matched on the calculated propensity score predicting the likelihood that patients would be preoperatively prescribed an ACE inhibitor or ARA to block the RAS.

This matching method afforded 261 pairs of subjects. The 30-day mortality of the RAS blocked patients was 16/261 deaths (6.1%) compared with 4/261 (1.5%) for the unblocked patients (odds ratio 5.0; CI_{95} 1.4-27; $P = 0.008$). The patients were well matched for all medical conditions except hypertension, despite having 94% of the pairs matched concordantly. There were 15 discordant pairs for a preoperative diagnosis of hypertension, two pairs RAS blocked *vs* 13 pairs unblocked (McNemar score 8; $P = 0.008$).

Table 4 Postoperative outcomes and RAS blockade

Outcome	Unmatched Data			Propensity Score Matched Subjects		
	Whole Group (883)	RAS Blockade (358)	No RAS Blockade (525)	RAS Blockade (261)	No RAS Blockade (261)	McNemar P Value
Death < 30 days	31 (4%)	21 (6%)	10 (2%)	16[*] (6.3%)	4[*] (1.8%)	0.008
All in hospital deaths	38 (4%)	25 (7%)	13 (3%)			
Cardiac arrest	23 (3%)	14 (4%)	9 (2%)			
Arrhythmia	118 (13%)	45 (13%)	73 (14%)			
MI/increased troponin	149 (17%)	74 (21%)	75 (14%)	46 (18%)	41 (16%)	0.645
CHF	87 (10%)	47 (13%)	40 (8%)	25 (9.6%)	21 (8.0%)	0.618
Stroke	10 (1%)	5 (1%)	5 (1%)	5 (1.9%)	1 (0.4%)	0.219
Renal failure	96 (10%)	49 (14%)	47 (9%)	31 (12%)	29 (11%)	0.896
New dialysis	24 (3%)	17 (5%)	7 (1%)	12 (4.6%)	2 (0.8%)	0.013
Any infection	144 (16%)	58 (16%)	86 (16%)			
Pneumonia	82 (9%)	32 (9%)	50 (10%)			
UTI	12 (1%)	6 (2%)	6 (1%)			
Re-operation	57 (6%)	25 (7%)	32 (6%)			
Delirium	115 (13%)	46 (13%)	69 (13%)			
Prolonged ileus	64 (7%)	21 (6%)	43 (8%)			
DVT	8 (2%)	2 (1%)	6 (1%)			
PE	4 (1%)	0 (0%)	4 (1%)			
Any complication	714 (81%)	299 (83%)	415 (80%)			

Data are reported as number (%); * Both patients died in one pair of the matched data

RAS = renin-angiotensin system; RAS blockade = exposure to angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor antagonists (ARA); No RAS blockade = no exposure to ACE inhibitors or ARA; Death < 30 days = death within 30 days of surgery; MI/increased troponin = diagnosed MI or troponin I over 0.3 ng·L^{-1}[†], and either patient symptoms or electrocardiogram (ECG) confirmed changes in ECG trace; CHF = congestive heart failure; DVT = deep vein thrombosis; PE = pulmonary embolus; ICU = intensive care unit (same as critical care unit); UTI = urinary tract infection. All in hospital deaths represents all patients that died without discharge from hospital from the day admitted for AAA surgery: data range 1 to 148 days

† In the majority of cases, the increase in troponin I was small (< 3 ng·L^{-1})

Analysis of known medical risk factors[22-30] was performed on the entire cohort to assess perioperative mortality. In this data set only, CHF, diabetes, and poor renal function (Cr Cl < 45 mL·min^{-1}) were predictors of 30-day mortality. Hypertension was not a predictor of mortality in this data set nor is hypertension a known predictor of mortality in this patient population. Given the background information from the medical literature and the high percentage of concordant pairs matched with hypertension, it seems unlikely that hypertension played a major role in the observed increased mortality, but nonetheless, hypertension remains a possible confounding variable.

Nine diabetics died in this cohort of patients. Preoperative diagnosis of diabetes was used as a matching variable, and the matching methodology appears to have controlled for diabetes. However, none of the RAS unblocked diabetics in the data set died. The possibility exists that diabetes may be playing some role in the observed increased rate of death due to RAS blockade despite good matching for diabetes.

Patients exposed to ACE inhibitors/ARA agents are likely to be exposed to other cardiovascular medications: beta-blockers, diuretics, and statins (all $P < 0.01$). Although controversial, possible protective effects of some cardiovascular medications were considered. In the present study, exposure to beta-blockers,[31-34] statins,[35] or CaCB[36] showed no effect on mortality. Only ACE inhibitors/ARA exposure and diuretic exposure were predictive of increased 30-day mortality.

Keterpal et al.[9] showed that exposure to ACE inhibitors and diuretics increased intraoperative hypotension but did not increase the rate of postoperative complications. In the present study, patients exposed to ACE/ARA agents were more likely to be exposed to diuretics: 103/359 (29%) in the ACE/ARA exposed patients vs 76/524 (15%) in the non ACE/ARA exposed ($P < 0.001$). Perioperative hypotension may be a possible contributor to increased mortality, but it was not tracked well in our data set.

In this study, preoperative diuretic exposure (all types grouped together) was a significant predictor of death

Table 5 Causes of death and associated factors

Cause of death	Unmatched data			Propensity score matched subjects	
	Whole Group (31)	RAS blockade (21)	No RAS blockade (10)	RAS blockade (16)	No RAS blockade (4)
Cardiac cause	17 (55%)	9 (42%)	8 (80%)	11 (53%)	4 (100%)
• MI	9 (29%)	10 (47%)	7 (70%)	7 (44%)	3 (75%)
• Cardiac arrest	8 (26%)	7 (33%)	4 (40%)	4 (25%)	1 (25%)
Respiratory cause	2 (6%)	1 (13%)	1 (10%)	0 (0%)	0 (0%)
• Pulmonary embolus	1 (3%)	0 (0%)	1 (10%)	0 (0%)	0 (0%)
MSOF Present	12 (38%)	10 (48%)	2 (20%)	8 (50%)	0 (0%)
Renal failure present	16 (52%)	12 (62%)	4 (40%)	9 (56%)	0 (0%)
New dialysis present	8 (26%)	7 (33%)	1 (10%)	5 (31%)	0 (0%)
Sepsis present	6 (16%)	5 (24%)	1 (10%)	4 (25%)	1 (25%)
Well enough for transfer to floor bed prior to death	11 (35%)	5 (24%)	6 (60%)	1 (6.3%)	3 (75%)

Data will not sum to 100%, percentages are calculated within columns with denominator determined by number of patients within column. Some patients had multiple counts

RAS = renin-angiotensin system; RAS blockade = exposure to angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor antagonists (ARA); No RAS blockade = no exposure to ACE Inhibitors or ARA; MI/cardiogenic shock = cause of death directly related to myocardial infarction and including cardiogenic shock; MSOF = multi-system organ failure

within 30 days of surgery (odds ratio 3.9; CI_{95} 1.9-8.1). The propensity matching system achieved good matching for all preoperative cardiovascular medication exposures, including diuretics. Based on this data set, it appears that diuretics are not playing a role in perioperative RAS blockade associated mortality. However, the data set may not be large enough to rule out an interaction with diuretics and medications that block the RAS.

In regards to postoperative outcomes, approximately 80% of patients suffered a postoperative complication, albeit the majority of complications were minor. In addition to increased mortality, RAS blocked patients were more likely to need postoperative hemodialysis (McNemar score 7.14; $P < 0.013$) despite not having a higher rate of postoperative renal failure. The matched group of patients did not have increased rates of other common major postoperative complications: MI, CHF, renal failure, and stroke. A higher percentage of RAS blocked patients died with multi-system organ failure (Table 5).

There are several limitations related to this study. The use of retrospective data from chart review to study clinical questions has marked limitations, for example, only association but not causality can be demonstrated. Another weakness of chart review studies is the inability to adequately control for exposures other than the exposure of interest. The best way to test the perioperative safety of RAS blockade would be to conduct a prospective randomized trial in patients undergoing major surgeries with sufficient washout of active metabolites (*circa* ten days).

In conclusion, we assessed patients with preoperative exposure to ACE inhibitors and ARA agents in terms of their outcomes with perioperative blockade of the RAS. Our data suggest that blockade of the RAS is associated with increased 30-day in-hospital mortality. Hypertension could not be excluded as a possible confounding variable. An association between chronic blockade of the RAS and increased 30-day mortality was found. It is not known if stopping these medications prior to surgery would alter this finding. A careful evaluation of the risks and benefits of ACE inhibitors or ARA agents should be factored into the decision for their continuance up to the time of major surgery. More studies are needed to evaluate the mechanism of the drug interaction of agents that block the renin-angiotensin system and anesthetic agents. The potential roles played by diabetes and medication exposures (especially diuretics) should also be considered in the design of future related studies.

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