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ORIGINAL RESEARCH

Role of Renin-Angiotensin-Aldosterone System Inhibition in Patients Undergoing Carotid Revascularization

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BACKGROUND: Previous data suggest that using renin-angiotensin-aldosterone system inhibitors (RAASIs) improves survival in patients with cardiovascular diseases. We sought to investigate the association of different patterns of use of RAASIs on perioperative and 1-year outcomes following carotid revascularization.

METHODS AND RESULTS: We investigated patients undergoing carotid revascularization, either with carotid endarterectomy or transfemoral carotid artery stenting, in the VQI (Vascular Quality Initiative) VISION (Vascular Implant Surveillance and Interventional Outcomes Network) data set between 2003 and 2018. We divided our cohort into 3 groups: (1) no history of RAASI intake, (2) preoperative intake only, and (3) continuous pre- and postoperative intake. The final cohort included 73 174 patients; 44.4% had no intake, 50% had continuous intake, and 5.6% had only preoperative intake. Compared with continuous intake, preoperative and no intake were associated with higher odds of postoperative stroke (odds ratio [OR], 1.7 [95% CI, 1.5–1.9]; $P<0.001$; OR, 1.1 [95% CI, 1.03–1.2]; $P=0.010$); death (OR, 4.8 [95% CI, 3.8–6.1]; $P<0.001$; OR, 1.9 [95% CI, 1.6–2.2]; $P<0.001$); and stroke/death (OR, 2.05 [95% CI, 1.8–2.3]; $P<0.001$; OR, 1.2 [95% CI, 1.1–1.3]; $P<0.001$), respectively. At 1 year, preoperative and no intake were associated with higher odds of stroke (hazard ratio [HR], 1.4 [95% CI, 1.3–1.6]; $P<0.001$; HR, 1.15, [95% CI, 1.08–1.2]; $P<0.001$); death (HR, 1.7 [95% CI, 1.5–1.9]; $P<0.001$; HR, 1.3 [95% CI, 1.2–1.4]; $P<0.001$); and stroke/death (HR, 1.5 [95% CI, 1.4–1.7]; $P<0.001$; HR, 1.2 [95% CI, 1.17–1.3]; $P<0.001$), respectively.

CONCLUSIONS: Compared with subjects discontinuing or never starting RAASIs, use of RAASIs before and after carotid revascularization was associated with a short-term stroke and mortality benefit. Future clinical trials examining prescribing patterns of RAASIs should aim to clarify the timing and potential to maximize the protective effects of RAASIs in high-risk vascular patients.

Key Words: carotid artery stenting ■ carotid endarterectomy ■ cerebrovascular disease/stroke ■ quality and outcomes ■ renin-angiotensin-aldosterone system inhibitors

Renin-angiotensin-aldosterone system inhibitors (RAASIs) play an important role in reducing the progression of vascular atherosclerotic diseases,[1,2] and the use of RAASIs is common among patients with vascular pathologies.[3,4] Though RAASIs are commonly used for the treatment of hypertension, congestive heart failure, acute myocardial infarction, and diabetic nephropathy, there is increasing evidence that RAASIs are associated with a survival benefit among patients with symptomatic and asymptomatic vascular diseases.[1,2,5] Several large trials supported the potential benefits of angiotensin-converting enzyme inhibitors in reducing atherosclerosis progression, plaque rupture, and thrombosis after plaque rupture.[6]

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CLINICAL PERSPECTIVE

What Is New?

- In a large Medicare-linked database of patients undergoing carotid revascularization, the lack of use of renin-angiotensin-aldosterone system inhibitors (RAASIs) before and after surgery was associated with worse 1-year stroke-free survival compared with patients who used RAASIs before and after surgery (continuous).
- Discontinuation of RAASIs postoperatively was also associated with worse 1-year stroke-free survival compared with patients with continuous intake.
- These results persisted even after stratification based on the incidence of postoperative hypotension.

What Are the Clinical Implications?

- Discontinuation of RAASIs following carotid revascularization or the lack of use of RAASIs before and after carotid revascularization may contribute to worse postoperative and 1-year stroke and mortality outcomes compared with continuous RAASI intake.
- Stopping RAASIs postoperatively should be taken with extreme caution and evaluated further to clarify whether this will represent a difference in patients' outcomes.

Nonstandard Abbreviations and Acronyms

CAS	carotid artery stenting
CEA	carotid endarterectomy
RAASI	renin-angiotensin-aldosterone system inhibitor
VISION	Vascular Implant Surveillance and Interventional Outcomes Network
VQI	Vascular Quality Initiative

Because patients undergoing carotid revascularization are at increased risk of major cardiovascular events, especially embolic stroke secondary to plaque rupture before surgery or because of manipulation of the lesion during the procedure, RAASIs may have a beneficial role in preventing complications and improving survival in these patients. Nonetheless, the benefits of RAASIs either with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers have not been determined in patients undergoing carotid endarterectomy (CEA) or carotid artery stenting (CAS). There has been a debate about the safety of perioperative RAASI use in patients undergoing vascular surgery under general anesthesia because of the potential risk of perioperative hypotension.[3,7] Hypotensive complications are common with either CEA or CAS carotid revascularization procedures because of surgical manipulation of the carotid bulb during CEA as well as the effect of angioplasty and stent expansion on the carotid body during CAS.[8–10]

The effect of RAASI use in patients undergoing CEA and CAS for treatment of atherosclerotic carotid artery stenosis on postoperative major adverse cardiovascular events and 1-year survival have not been fully addressed. We also noticed that some patients who used a RAASI preoperatively stopped it on discharge. Therefore, we sought to investigate the association between different patterns of RAASI use (none, continuous, and preoperative intake) and postoperative and 1-year outcomes among patients undergoing carotid revascularization. We also assessed the factors associated with stopping RAASIs postoperatively. We also assessed the association of preoperative RAASI on postoperative hemodynamic instability requiring intravenous blood pressure medications for hypotension or hypertension.

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 the VQI (Vascular Quality Initiative) at www.vqi.org.

Data Set

We reviewed all patients undergoing carotid revascularization (either CEA or CAS) for treatment of carotid artery stenosis in the VQI VISION (Vascular Implant Surveillance and Interventional Outcomes Network) database from 2003 to 2018. The VQI is a prospectively maintained database where patient- and procedure-related variables as well as postoperative complications for patients who underwent vascular surgery are collected from >800 centers in the United States and Canada.[11] VISION is an affiliation between the Society for Vascular Surgery VQI, and MDEpiNet (The Medical Device Epidemiology Network) that aims to improve long-term outcomes through linkage of Society for Vascular Surgery VQI index procedures to Medicare claims.[12] This is accomplished using a validated matching algorithm incorporating *Current Procedural Terminology* (*CPT*) and *International Classification of Diseases, Ninth Revision* and *Tenth Revision* (*ICD-9* and *ICD-10*) codes. The VQI-VISION database contains long-term Medicare follow-up data linked to granular VQI data using a list of *CPT*, *ICD-9*, and *ICD-10* codes.[13] Covariates collected using *ICD-9* or *ICD-10* codes include perioperative and long-term outcomes, whereas variables about demographics, comorbidities,

preoperative and discharge medications, procedural variables, and in-hospital outcomes were collected from the VQI. The VQI Research Advisory Committee approved data release for this study. Institutional review board approval and the need for patient consent were waived for this study because of the retrospective, deidentified nature of the data set.

Patient Population, Variables Definition, and Comparison Groups

All patients who underwent CEA or CAS for carotid artery stenosis from 2003 to 2018 in the VQI VISION database were identified. To answer our research question, patients were classified into 3 groups according to their pattern of pre- and postoperative RAASI intake: (1) patients with no history of RAASI intake pre- or postoperatively, (2) patients with preoperative RAASI intake and discontinuation at discharge, and (3) patients with pre- and postoperative RAASI intake. We then compared the 3 groups with patients with continuous intake as the reference group. We then stratified our outcomes based on the incidence of postoperative hypotension. Baseline patient characteristics included demographics (age, sex, race, and ethnicity), preoperative symptomatic status (amaurosis fugax, transient ischemic attack, or stroke), smoking history (none, prior, or current), degree of ipsilateral carotid artery stenosis, preoperative comorbidities (hypertension, diabetes, congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease, chronic kidney disease [CKD], and hemodialysis), preoperative medications (aspirin, statins, β-blockers, antiaggregant medications, and anticoagulants), and a history of cardiovascular procedures (major amputations, coronary artery bypass grafting or percutaneous coronary intervention, and prior CEA or CAS). Procedure factors included urgency and anesthesia type (general or local/regional). Symptomatic status included a history of ipsilateral amaurosis fugax, transient ischemic attack, or stroke within the 6 months before the procedure. Transient ischemic attacks were defined as any focal neurological symptoms lasting no more than 24 hours. CKD was defined as a preoperative estimated glomerular filtration rate of <60 mL/min, based on the preoperative creatinine level, using the Modification of Diet in Renal Disease study equation. Only patients with atherosclerotic or re-stenotic lesions were included; those with dissection, trauma, and unidentified carotid lesions were excluded from the analysis.

Outcomes

The primary outcome included a composite end point of 1-year stroke or death. Secondary outcomes included perioperative (30-day) stroke, death, the composite end point of stroke or death, as well as 1-year stroke and death. Perioperative stroke was defined as any ipsilateral or contralateral cortical, retinal, or vertebrobasilar ischemic or hemorrhagic stroke within 30 days following the index procedure or before hospital discharge. One-year stroke was defined as any ipsilateral or contralateral cortical, retinal, or vertebrobasilar ischemic or hemorrhagic stroke within 1 year after the index procedure.

Statistical Analysis

Categorical variables were conveyed as number and percentage, whereas continuous variables were conveyed as median with interquartile range or mean±SD. Baseline patients' characteristics as well as crude outcomes were compared between patients with continuous versus preoperative versus no RAASI intake by means of Pearson χ^2 and Fisher exact tests for categorical variables, and Student t test or median test for continuous variables, as appropriate. For dichotomous yes–no variables, only the yes-level values are displayed. Perioperative outcomes of patients with preoperative versus continuous versus no RAASI intake were evaluated using multivariable logistic regression analysis, adjusting for potential confounders such as age, sex, comorbidities, and preoperative medications. Variable selection was done using stepwise backward regression with a $P<0.1$. No variables were forced in the final models, because all clinically relevant variables were statistically significant on stepwise regression. Final models were clustered by center identifier to decrease bias from unmeasurable factors per hospital level and to account for intragroup correlation. Model fit and model accuracy were assessed using Hosmer-Lemeshow goodness-of-fit testing and area under the receiver operator curve, respectively. One-year outcomes were evaluated using Kaplan-Meier survival analysis, and multivariable Cox proportional hazard regression analyses were used to predict the outcomes, adjusting for potential confounders. Detailed data about the multivariable models are available in Table S1. Schoenfield residuals and log–log plots were used to assess the proportional hazards assumption. The proportional hazards assumption was not met for 1-year mortality. We therefore divided this variable into time intervals of 0 to 40 days and 40 to 365 days based on the log–log plot (Table S2).

A P value of ≤0.05 was considered statistically significant. The above-mentioned analyses were executed using Stata version 16.1/SE software (StataCorp, College Station, TX).

RESULTS

Baseline Characteristics

Patients with preoperative intake compared with no intake and continuous intake were more likely to be

symptomatic (33.4% versus 30.5% versus 26.5%, *P*<0.001), with history of coronary artery disease (48.3% versus 40% versus 45.2%, *P*<0.001), congestive heart failure (15.9% versus 11.5% versus 13.2%, *P*<0.001), and CKD (44.3% versus 37.4% versus 40.2%, *P*<0.001), respectively. The higher comorbidity profile in patients with preoperative intake was also pertinent in a high use of preoperative medications such as β-blockers (62.4% versus 54.5% versus 60.2%, *P*<0.001) and P2Y12 inhibitors (antiplatelet drugs [clopidogrel, prasugrel, ticlopidine, ticagrelor, PAR1 inhibitor, or aggrenox]) (40% versus 36.7% versus 37.8%, *P*<0.001), as well as higher rates of prior ipsilateral CAS (3.4% versus 2.7% versus 2.7%, *P*=0.023), and major amputation (1.9% versus 1.04% versus 0.9%, *P*=0.002), respectively. They were less likely to get an elective procedure (80.9% versus 86.6% versus 89.6%, *P*<0.001) and more likely to undergo local/regional anesthesia (21.8% versus 17.9% versus 15.9%, *P*<0.001), respectively. A detailed comparison of baseline characteristics among the 3 groups is expressed in Table 1.

Factors Associated With Stopping RAASIs Postoperatively

In multivariable logistic regression, postoperative hypotension requiring intravenous blood pressure medications (odds ratio [OR], 2.2 [95% CI, 1.9–2.5]; *P*<0.001), age increase by 1 year (OR, 1.01 [95% CI, 1.004–1.01]; *P*<0.001), being symptomatic on presentation (OR, 1.16 [95% CI, 1.05–1.3]; *P*=0.003), coronary artery disease (OR, 1.27 [95% CI, 1.1–1.4]; *P*<0.001), preoperative β-blocker intake (OR, 1.1 [95% CI, 1.02–1.2]; *P*=0.015), and preoperative CKD (OR, 1.16 [95% CI, 1.03–1.2]; *P*=0.012) were all independently associated with higher odds of stopping RAASIs postoperatively. However, postoperative hypertension requiring intravenous blood pressure medications (OR, 0.8 [95% CI, 0.7–0.9]; *P*<0.001), CEA (OR, 0.6 [95% CI, 0.5–0.7]; *P*<0.001), preoperative hypertension (OR, 0.6 [95% CI, 0.5–0.7]; *P*<0.001), and procedures performed electively (OR, 0.6 [95% CI, 0.5–0.6]; *P*<0.001) were associated with lower odds of stopping RAASIs postoperatively (Figure 1).

Perioperative and 1-Year Outcomes

On univariable analysis, patients with preoperative and no RAASIs intake had higher risk of perioperative stroke (6.4% versus 3.7% versus 3.1%, *P*<0.001), death (3.2% versus 1.1% versus 0.5%, *P*<0.001), and stroke or death (8.5% versus 4.5% versus 3.6%, *P*<0.001), respectively, compared with patients with continuous intake (Table 2). After adjusting for potential confounders, preoperative and no RAASIs intake were associated with higher odds of postoperative stroke (OR, 1.7 [95% CI, 1.5–1.9]; *P*<0.001; OR, 1.1 [95% CI, 1.03–1.2]; *P*=0.010), death (OR, 4.8 [95% CI, 3.8–6.1]; *P*<0.001; OR, 1.9 [95% CI, 1.6–2.2]; *P*<0.001), and stroke/death (OR, 2.05 [95% CI, 1.8–2.3]; *P*<0.001; OR, 1.2 [95% CI, 1.1–1.3]; *P*<0.001), respectively. At 1 year, preoperative and no RAASIs intake were associated with higher odds of stroke, death, and stroke/death (Table 3). Upon dividing 1-year mortality into shorter time intervals, preoperative and no intake were associated with significantly higher rates of mortality from 0 to 40 days. From 40 to 365 days, preoperative and no intake were associated with a small, but statistically significant, increase in mortality (Table S2, Figures S1 and S2).

Perioperative and 1-Year Outcomes Stratified by the Incidence of Postoperative Hypotension

On univariable analysis, patients with preoperative and no RAASIs intake had higher risk of perioperative stroke (6.2% versus 3.5% versus 3%, *P*<0.001), death (2.8% versus 0.9% versus 0.5%, *P*<0.001), and stroke or death (8% versus 4.1% versus 3.4%, *P*<0.001) compared with patients with continuous intake among patients with no postoperative hypotension. When looking at patients with postoperative hypotension, patients with preoperative and no intake had higher risk of perioperative stroke (7.1% versus 5.4% versus 4.2%, *P*=0.001), death (4.5% versus 2.8% versus 0.8%, *P*<0.001), and stroke or death (10.2% versus 4.8% versus 7.4%, *P*<0.001) compared with patients with continuous intake (Table 4). After adjusting for potential confounders, and when looking at patients with no postoperative hypotension, preoperative and no intake were associated with higher odds of postoperative stroke, death, and stroke/death, respectively. At 1 year, preoperative and no intake were associated with higher odds of stroke, death, and stroke/death (Table 5 and Figure 2).

When looking at patients with postoperative hypotension, preoperative intake was associated with higher odds of postoperative stroke (OR, 1.4 [95% CI, 1.1–1.97]; *P*=0.020), death (OR, 5.5 [95% CI, 3.1–9.8]; *P*<0.001), and stroke/death (OR, 1.9 [95% CI, 1.4–2.5]; *P*<0.001) compared with continuous intake. The group with no intake was associated with higher risk of perioperative death (OR, 3.7 [95% CI, 2.4–5.7]; *P*<0.001) and stroke or death (OR, 1.5 [95% CI, 1.2–1.9]; *P*=0.001) compared with continuous intake. At 1 year, preoperative and no intake were associated with higher odds of stroke, death, and stroke/death (Table 6).

DISCUSSION

There have been few large real-world studies investigating the medical optimization of patients undergoing carotid revascularization or other vascular surgery

Table 1. Characteristics of Patients With No, Preoperative Only, and Continuous Use of RAASIs Undergoing Carotid Revascularization

Patient characteristics	None, N=32 488	Continuous, N=36 587	Preoperative, N=4099	*P* value
Age, y, median (IQR)	74 (69–79)	73 (68–78)	74 (69–79)	<0.001
Sex				0.266
Men	16 649 (60.5)	22 166 (60.6)	2533 (61.8)	
Women	12 839 (39.5)	14 420 (39.4)	1566 (38.2)	
Race				<0.001
White	30 036 (92.5)	33 435 (91.4)	3731 (91.02)	
Black	1339 (4.1)	1723 (4.7)	210 (5.1)	
Other*	1102 (3.4)	1412 (3.9)	158 (3.8)	
Ethnicity				
Hispanic or Latino	947 (2.9)	1245 (3.4)	154 (3.8)	<0.001
Symptomatic stenosis	9899 (30.5)	9688 (26.5)	1366 (33.4)	<0.001
Comorbidities				
Diabetes	9544 (29.4)	15 715 (43)	1710 (41.8)	<0.001
Hypertension	26 349 (81.3)	35 542 (97.3)	3910 (95.9)	<0.001
Coronary artery disease	12 952 (40)	16 504 (45.2)	1974 (48.3)	<0.001
Congestive heart failure	3740 (11.5)	4830 (13.2)	651 (15.9)	<0.001
Chronic obstructive pulmonary disease	7959 (24.5)	8759 (23.9)	1005 (24.5)	0.203
Chronic kidney disease	12 142 (37.4)	14 703 (40.2)	1818 (44.3)	<0.001
Dialysis	590 (1.8)	317 (0.9)	52 (1.3)	<0.001
Contralateral occlusion	1575 (5.4)	1635 (5)	199 (5.4)	0.047
Preoperative medications				
Aspirin	26 836 (82.6)	30 974 (84.7)	3473 (84.7)	<0.001
Anticoagulant	3502 (10.8)	3786 (10.4)	467 (11.4)	0.048
B-Blocker	17 713 (54.5)	22 029 (60.2)	2557 (62.4)	<0.001
Statin	25 562 (78.7)	31 272 (85.5)	3449 (84.1)	<0.001
P2Y12 inhibitors	11 937 (36.7)	13 837 (37.8)	1640 (40)	<0.001
Smoking history				<0.001
Prior smoker	16 600 (51.1)	19 342 (52.9)	2090 (51.05)	
Current smoker	7048 (21.7)	7545 (20.6)	884 (21.6)	
Prior vascular procedures				
Prior CABG/PCI	11 168 (34.4)	14 432 (39.5)	1673 (40.8)	<0.001
Prior ipsilateral CEA	1153 (3.6)	1253 (3.4)	165 (4)	0.137
Prior ipsilateral CAS	887 (2.7)	971 (2.7)	139 (3.4)	0.023
Prior contralateral CAS/CEA	1940 (6.5)	2424 (7.3)	226 (6)	<0.001
Prior major amputation	317 (1.04)	316 (0.9)	55 (1.5)	0.002
Ipsilateral stenosis ≥80%	18 889 (59.5)	21 508 (59.9)	2467 (61.4)	0.063
Procedure factors				
Elective	28 125 (86.6)	32 778 (89.6)	3316 (80.9)	<0.001
Anesthesia				<0.001
General/converted to general	26 638 (82.1)	30 727 (84.1)	3198 (78.1)	
Local/regional	5808 (17.9)	5815 (15.9)	894 (21.8)	

CABG indicates coronary artery bypass graft; CAS, carotid artery stenting; CEA, carotid endarterectomy; IQR, interquartile range; P2Y12 inhibitors, antiplatelet drugs (clopidogrel, prasugrel, ticlopidine, ticagrelor, PAR1 inhibitor, or aggrenox); and PCI, percutaneous coronary intervention.

*Other includes Asian, American Indian or Alaskan Native, Native Hawaiian or other Pacific Islander, or more than one race.

procedures.[14–19] Those that have been reported show that use of antiplatelet medications and statin therapy preoperatively and at discharge are associated with reduced 30-day mortality and improved 5-year survival following several vascular surgery procedures. However, the effect of pre- and postoperative use of RAASIs in patients undergoing carotid revascularization is not well studied. The present study was executed

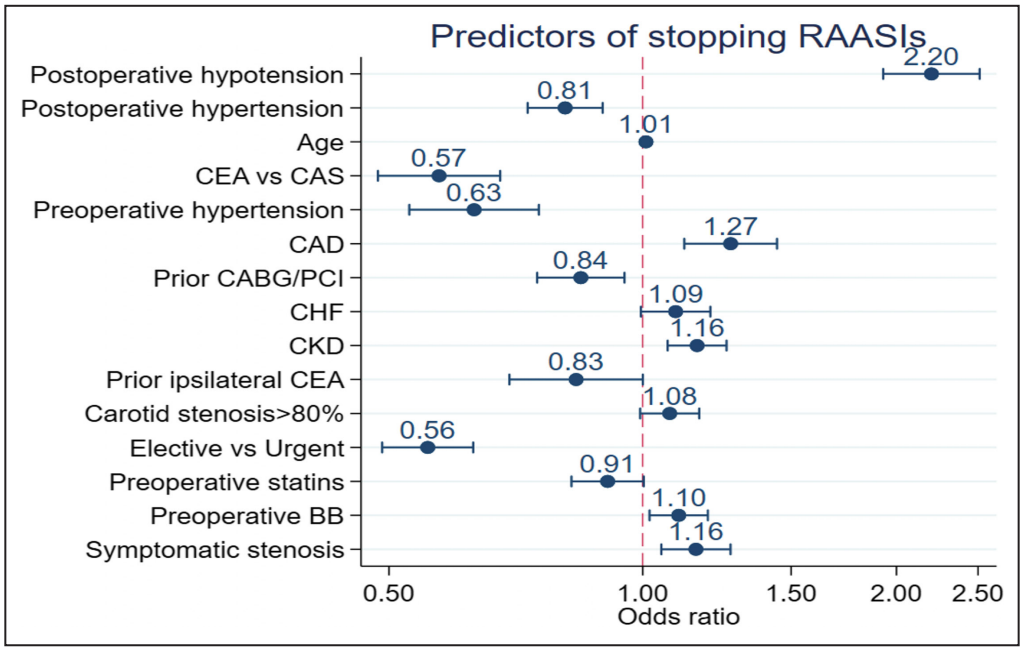

Figure 1. Factors predicting stopping renin-angiotensin-aldosterone system inhibitors (RAASIs) postoperatively.
BB indicates beta blockers; CABG, coronary artery bypass graft; CAD, coronary artery disease; CAS, carotid artery stenting; CEA, carotid endarterectomy; CHF, congestive heart failure; CKD, chronic kidney disease; and PCI, percutaneous coronary intervention.

to assess the association between different patterns of RAASIs intake and postoperative outcomes, as well as short-term survival among patients undergoing carotid revascularization. We found that compared with continuous RAASI intake, preoperative and no RAASI intake are associated with higher risk of perioperative stroke, death, and composite stroke or death, as well as worse stroke-free survival at 1 year of follow-up.

Recognizing and amending variation in RAASI use at discharge after CAS and CEA is of importance because of the survival benefits among patients with various cardiovascular diseases.[1,2,5,20] Although carotid artery revascularization procedures reduce stroke risk, based on data from large clinical trials,[21,22] simultaneous measures including effective medical therapies for stroke risk reduction are strongly recommended.[23] In addition, an analysis of optimal medical therapy after carotid artery revascularization being conducted in the ongoing CREST-2 (Carotid Revascularization Endarterectomy Versus Stent Trial 2). This trial compares long-term stroke risk among asymptomatic patients with carotid artery stenosis treated with revascularization plus optimal medical therapy versus optimal medical therapy alone.[24]

The survival benefits associated with RAASI intake among patients with symptomatic and asymptotic vascular diseases have been established in previous reports in selected patients.[5,25] In our study, we were able to establish the survival benefit at 1 year associated with RAASI use following carotid revascularization by comparing patients who never used RAASIs versus patients with continuous intake. Although continuous RAASI intake was also associated with survival benefit compared with patients with preoperative intake only, the possibility of reverse causality is high in this scenario. These patients were highly likely to develop a serious postoperative complication requiring them to stop RAASIs. Several factors, including the incidence of postoperative hypotension requiring intravenous vasoactive medication, carotid artery revascularization modality (CAS versus CEA), effective medical therapy, symptomatic presentation, the presence of prior coronary artery disease, and CKD, significantly and independently predicted discontinuation of RAASIs

Table 2. Univariable Perioperative Outcomes

Outcome	Preoperative, N (%), N=4099	Continuous, N (%), N=36 587	None, N (%), N=32 488	*P* value
Stroke	263 (6.4)	1152 (3.1)	1210 (3.7)	<0.001
Death	131 (3.2)	199 (0.5)	351 (1.1)	<0.001
Stroke or death	349 (8.5)	1304 (3.6)	1459 (4.5)	<0.001

Table 3. Perioperative and 1-Year Outcomes After Adjusting for Potential Confounders

	Stroke		Death		Stroke/death	
Perioperative and 1 y	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Perioperative						
Continuous	Reference					
None	1.1 (1.03–1.2)	0.010	1.9 (1.6–2.2)	<0.001	1.2 (1.1–1.3)	<0.001
Preoperative	1.7 (1.5–1.9)	<0.001	4.8 (3.8–6.1)	<0.001	2.05 (1.8–2.3)	<0.001
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
1-y						
Continuous	Reference					
None	1.15 (1.08–1.2)	<0.001	1.3 (1.2–1.4)	<0.001	1.2 (1.17–1.3)	<0.001
Preoperative	1.4 (1.3–1.6)	<0.001	1.7 (1.5–1.9)	<0.001	1.5 (1.4–1.7)	<0.001

HR indicates hazard ratio; and OR, odds ratio.

postoperatively in patients who used RAASIs in the preoperative period. The likelihood of stopping RAASIs was higher after CAS compared with CEA. This practice can be justified by the high risk of postoperative hypotension associated with expandable stents following CAS.[10,26–28] It was also shown in prior observational studies that the blood pressure of older adults decreases in the years preceding death. Therefore, people who are taken off their blood pressure medications may be closer to death than those who stay on them.[29]

In an attempt to overcome the possibility of reverse causality for patients with hypotension, we stratified patients with respect to the incidence of postoperative hypotension. Discontinuation of RAASIs postoperatively continued to have worse postoperative as well as 1-year stroke or death among patients with and without postoperative hypotension. These findings are clinically significant, given the ongoing debate on the safety of angiotensin-converting enzyme inhibitors in the preoperative period in patients undergoing vascular procedures, especially under general anesthesia.[7,30,31] However, evaluation of the effect of RAASIs preoperatively was not associated with increased risk of hypotension (OR, 0.97 [95% CI, 0.9–1.03]; *P*=0.282). Although preoperative RAASIs were associated with higher odds of postoperative hypertension (OR, 1.1 [95% CI, 1.02–1.1]; *P*=0.003), we do not believe that this finding is clinically relevant.

The possible pathophysiology behind the results in this study, indicating decreased morbidity and mortality in patients using RAASIs, can be explained by several prior reports indicating that administration of angiotensin-converting enzyme inhibitors improves cerebral blood flow despite the decrease in systemic arterial blood pressure.[32,33] These hemodynamics are mainly driven by the reduction of peripheral vascular resistance, increase in cardiac output, and dilation of cerebral vessels. A prior study by Werner et al demonstrated that intravenous injection of captopril enhanced neurological outcomes of cerebral ischemia in normotensive rats.[34] The underlying mechanism suggested was that either the reduction of angiotensin I level or the increase in kinin concentrations mitigated the ischemic brain injury. Studying the effect of captopril on hyperlipidemic rabbits showed that captopril reduced the total aortic intimal surface covered with atherosclerotic lesions, decreased the cellularity and cholesterol content of atherosclerotic plaques, and increased their extracellular matrix. Therefore, not only did captopril reduce the anatomic extent of atherosclerotic lesions, but it also had stabilizing effects, making it less liable to rupture.[35]

Because RAASIs may have a beneficial role in improving survival of patients undergoing carotid revascularization, stopping RAASIs postoperatively may increase the risk of cerebral ischemia, and hence perioperative stroke. Over the long term, RAASIs play an important role in stopping the progression of vascular atherosclerotic diseases through mediating several

Table 4. Univariable Perioperative Outcomes Stratified by the Incidence of Postoperative Hypotension

	No hypotension				Hypotension			
Outcome	Preoperative, N=3311 N (%)	Continuous, N=33 224 N (%)	None, N=28 897 N (%)	*P* value	Preoperative, N=774 N (%)	Continuous, N=3291 N (%)	None, N=3516 N (%)	*P* value
Stroke	205 (6.2)	1005 (3)	1008 (3.5)	<0.001	55 (7.1)	137 (4.2)	191 (5.4)	0.001
Death	93 (2.8)	172 (0.5)	249 (0.9)	<0.001	35 (4.5)	25 (0.8)	97 (2.8)	<0.001
Stroke or death	265 (8)	1135 (3.4)	1186 (4.1)	<0.001	79 (10.2)	158 (4.8)	262 (7.4)	<0.001

Table 5. Perioperative and 1-Year Outcomes After Adjusting for Potential Confounders Among Patients With No Hypotension

	Stroke		Death		Stroke/death	
Perioperative and 1 y	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Perioperative						
Continuous	Reference					
None	1.1 (1.0005–1.2)	0.049	1.6 (1.3–1.9)	<0.001	1.1 (1.05–1.3)	0.002
Preoperative	1.7 (1.5–2.03)	<0.001	4.4 (3.4–5.7)	<0.001	2.02 (1.7–2.3)	<0.001
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
1-y						
Continuous	Reference					
None	1.14 (1.06–1.2)	<0.001	1.3 (1.2–1.4)	<0.001	1.2 (1.1–1.3)	<0.001
Preoperative	1.4 (1.2–1.6)	<0.001	1.7 (1.5–1.9)	<0.001	1.5 (1.4–1.7)	<0.001

HR indicates hazard ratio; and OR, odds ratio.

processes implied in vascular diseases pathophysiology.[1,2,36–38] Consequently, continuous RAASI use should improve survival among these patients.

Limitations

Our study has several important limitations. The analysis was done using the VQI data set, which is an observational registry; thus, causal conclusions cannot be made, given the fact that this is a retrospective review of prospectively collected data. More importantly, the indication of RAASI discontinuation postoperatively is unknown, leaving abundant room for reverse causality. It also precludes attempts to have a clear answer as to whether there are certain settings in which discontinuing RAASIs is warranted. We tried to overcome this possibility through the stratified analysis as well as careful adjusting in the multivariable models. However, there could have been residual confounding from other variables not captured in this registry. In addition, stopping RAASIs might have occurred secondary to developing acute kidney injury. Unfortunately, we were not able to stratify based on the incidence of acute kidney injury, because this information is not available in this data set. Thankfully, this percentage of patients developing acute kidney injury following carotid revascularization is rare and should not impact our results. Also, sometimes discontinuation of any medication postoperatively may be temporary because of other events occurring in this

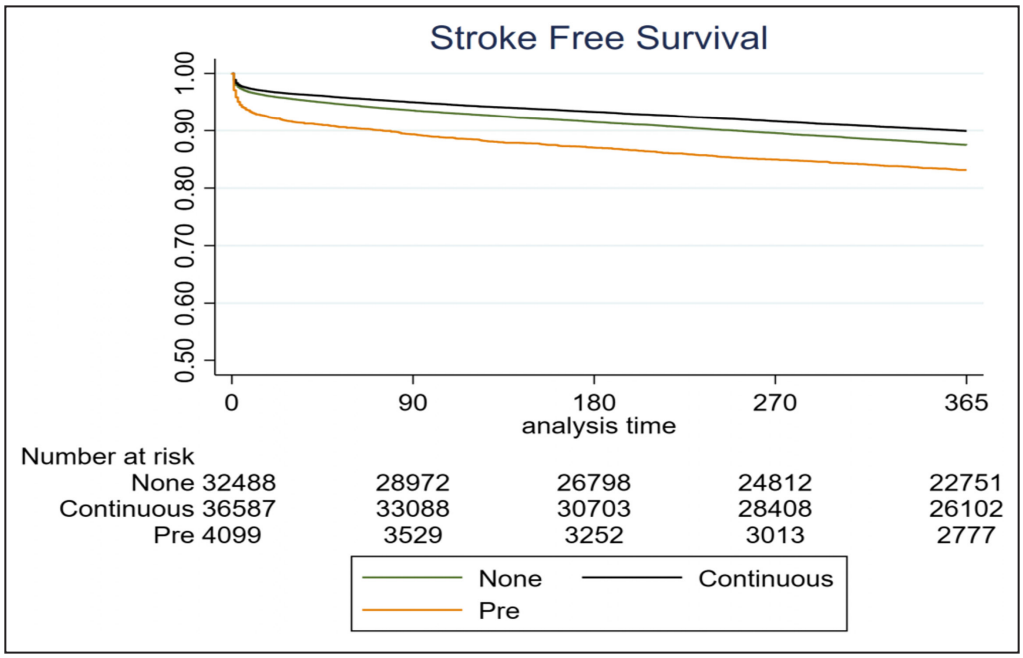

Figure 2. Freedom from stroke or death at 1year between patients with preoperative (Pre) vs none vs continuous use of renin-angiotensin-aldosterone system inhibitors.

Table 6. Perioperative and 1-Year Outcomes After Adjusting for Potential Confounders Among Patients With Hypotension

	Stroke		Death		Stroke/death	
Perioperative and 1 y	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Perioperative						
Continuous	Reference					
None	1.2 (0.96–1.6)	0.108	3.7 (2.4–5.7)	<0.001	1.5 (1.2–1.9)	0.001
Preoperative	1.4 (1.1–1.97)	0.020	5.5 (3.1–9.8)	<0.001	1.9 (1.4–2.5)	<0.001
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
1-y						
Continuous	Reference					
None	1.2 (1.01–1.5)	0.037	1.6 (1.3–1.9)	<0.001	1.4 (1.2–1.6)	<0.001
Preoperative	1.3 (1.1–1.6)	0.006	1.7 (1.3–2.3)	<0.001	1.4 (1.2–1.7)	0.001

HR indicates hazard ratio; and OR, odds ratio.

period. Because medication use was not measured after hospital discharge, it is not possible to establish whether these medications were resumed in subsequent follow-up visits. Although it is possible that patients discharged without RAASIs eventually were instructed to begin or resume taking these medications in the outpatient setting or after the event rendering discontinuation subsides, this possibility has not been addressed in this registry. However, it has been shown that patients are more likely to use evidence-based medical therapies if they are prescribed them on discharge than if they are initiated in an outpatient setting.[39] Another limitation of this study is the lack of data on RAASI use in transcarotid artery revascularization. We aimed to look at 1-year outcomes and used VISION to link VQI to Medicare data. This limited our cohort up to 2018 (VISION data), which included a limited number of patients with transcarotid artery revascularization. Future study on the effect of RAASI use pattern in transcarotid artery revascularization is warranted once adequate 1-year data are available. Despite these limitations, we believe this study conveyed an important understanding of the association between RAASI use and outcomes of carotid revascularization procedures. These data provide a foundation for a future randomized clinical trial clarifying the timing of drug use to maximize the protective effects while minimizing complications of RAASI in high-risk vascular patients.

CONCLUSIONS

This study shows that both discontinuation of RAASIs postoperatively and the lack of RAASI use pre- and postoperatively are associated with higher risk of perioperative stroke or death as well as worse stroke-free survival at 1 year following carotid revascularization. Future clinical trials examining prescribing patterns of RAASIs should aim at clarifying the timing of drug use to maximize the protective effects while minimizing complications of RAASIs in high-risk vascular patients.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S2
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Variables adjusted for in the multivariable logistic and cox regression analysis

Outcome	Variables
Perioperative stroke	Age, symptomatic status, CKD, procedure type, sex, ethnicity, hypertension, diabetes, CAD, prior CABG/PCI, CHF, COPD, dialysis, urgency, anesthesia, preoperative aspirin, preoperative statin, and preoperative beta blockers.
Perioperative death	Age, symptomatic status, CKD, dialysis, procedure type, diabetes, CAD, CHF, COPD, dialysis, urgency, anesthesia, and preoperative statin.
Perioperative stroke/death	Age, symptomatic status, CKD, procedure type, sex, ethnicity, hypertension, diabetes, CAD, prior CABG/PCI, CHF, COPD, dialysis, urgency, anesthesia, preoperative aspirin, preoperative statin, and preoperative beta blockers.
One-year stroke	Age, symptomatic status, CKD, dialysis, procedure type, sex, ethnicity, hypertension, diabetes, CAD, CHF, COPD, urgency, preoperative statin, and preoperative aspirin.
One-year death	Age, symptomatic status, CKD, dialysis, procedure type, sex, preoperative smoking, diabetes, CAD, CHF, COPD, ipsilateral stenosis>80%, urgency, anesthesia, preoperative aspirin, preoperative P2Y12 antagonist, preoperative statin, and preoperative beta blockers.
One-year stroke/death	Age, symptomatic status, CKD, dialysis, procedure type, sex, preoperative smoking, hypertension, diabetes, CAD, CHF, COPD, urgency, anesthesia, preoperative aspirin, preoperative P2Y12 antagonist, preoperative statin, and preoperative beta blockers.

Table S2. The association between one-year mortality and RAASI intake divided by time intervals

One-year	HR (95% CI)	P value
Continuous	Reference	
None	1.3 (1.2-1.4)	<0.001
Pre	1.7 (1.5-1.9)	<0.001
0-40		
None	1.8 (1.6-2.2)	<0.001
Pre	4.01 (3.2-5.01)	<0.001
40-365		
None	1.2 (1.1-1.3)	<0.001
Pre	1.3 (1.1-1.5)	<0.001

Figure S1. Perioperative outcomes

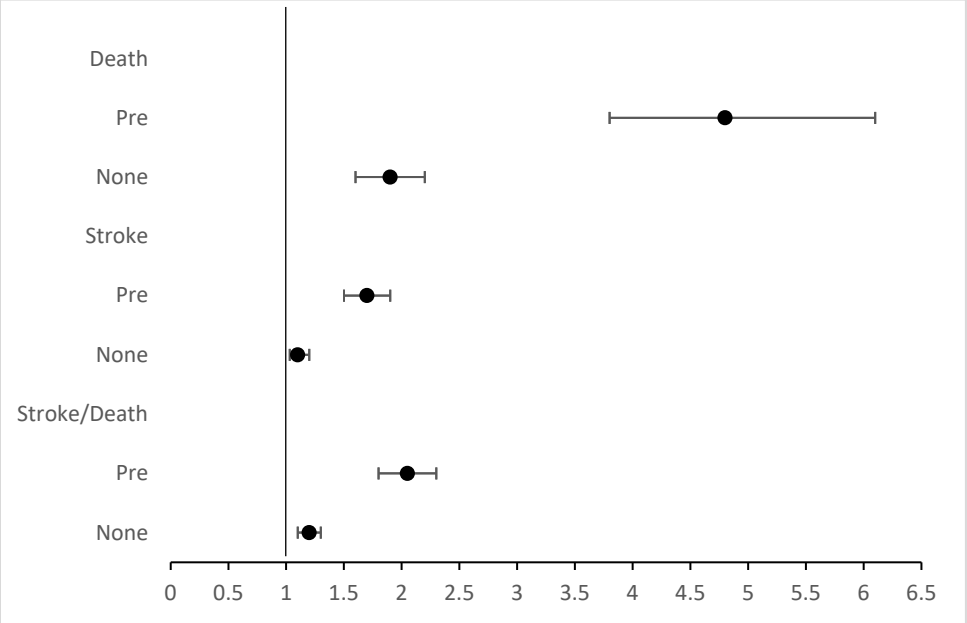

Figure S2. One-year outcomes