Contralateral Occlusion and Concomitant Procedures Drive Risk of Non-ipsilateral Stroke After Carotid Endarterectomy

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WHAT THIS PAPER ADDS

This investigation uses the Vascular Quality Initiative of the Society for Vascular Surgery to better define risk and predictors of peri-operative non-ipsilateral stroke after carotid endarterectomy (CEA). Risk is rare occurring in 0.6% of CEA. Major predictors include contralateral occlusion, CEA combined with other procedures, and features portraying haemodynamic fluctuations.

Objectives: Stroke after carotid endarterectomy (CEA) has been assessed widely. However, factors enhancing non-ipsilateral stroke risk are poorly defined. The aim of this study was to identify drivers of 30 day non-ipsilateral stroke after CEA in the Vascular Quality Initiative (VQI) and assess long-term survival based on laterality of post-operative stroke.

Methods: The VQI was queried between April 1, 2003, and March 31, 2017, for all CEA. Bilateral carotid procedures within 30 days were excluded. Thirty day non-ipsilateral strokes were identified. Factors were examined to discriminate between patients with and without non-ipsilateral stroke. Univariable analysis followed by multivariable logistic regression was performed. Kaplan—Meier and log rank methods were used to estimate and compare survival.

Results: During this 14 year period, 80,230 CEA in 74,928 patients met the criteria. The average age was 70.3 ± 9.3 years. Most were male (48,506; 60%), Caucasian (73,967; 92%), smokers (60,543; 76%), and asymptomatic (43,074; 54%). Contralateral stenosis ≥70% was present in 8033 (10%) with 2239 (3%) having contralateral occlusion. In 491 (0.6%) patients, peri-operative non-ipsilateral stroke occurred. After characterising univariable associations, logistic regression identified independent drivers of non-ipsilateral stroke after CEA. Operative urgency ($p = .001$), symptomatic disease ($p < .001$) and contralateral occlusion ($p = .001$) were pre-operative drivers. Operative predictors included shunt use ($p = .008$), CEA with cardiac surgery ($p = .013$), and CEA with concomitant proximal ipsilateral endovascular intervention ($p = .01$). Use of dextran ($p = .005$) and anti-angiotensin therapy ($p = .03$) were protective. Reperfusion syndrome ($p < .001$), re-exploration ($p < .001$), myocardial infarction ($p < .001$), and intravenous treatment of hypotension ($p < .001$) or hypertension ($p < .001$) were post-operative correlates. Non-ipsilateral stroke 30 day mortality was less than ipsilateral stroke (6.1% vs. 10.3%; $p = .007$). Five year survival after non-ipsilateral stroke was 73%, and no different from ipsilateral stroke 76% ($p = .16$). Both were worse than without stroke (88%; $p < .001$).

Conclusion: Non-ipsilateral stroke after CEA is rare. Features driving risk surround global disease burden, combined procedures, and haemodynamic fluctuations. Contralateral occlusion independently increases non-ipsilateral stroke risk. Regardless of laterality or location, effects of stroke after CEA on long-term survival are similar.

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INTRODUCTION

Stroke after carotid endarterectomy (CEA) has been analysed in many formats, pursuing patient and procedural features causally linked to stroke hoping to understand and reduce operative risk. This has included institutional series, prospective randomised trials stratified by symptomatic status, and assessment of administrative databases. This literature has assessed stroke after CEA within the context of events ipsilateral to the operative side or all stroke. This is logical as most strokes after CEA are indeed ipsilateral to the operation. Yet, the real risk of stroke outside the ipsilateral territory has been appreciated. Contralateral stroke after CEA in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) was recognised in 0.3% and in the Asymptomatic Carotid Atherosclerosis Study (ACAS) in 0.4%.[1,2] Recently, in the Carotid Revascularisation Endarterectomy vs. Stenting (CREST) trial and the International Carotid Stenting Study (ICSS), non-ipsilateral stroke was identified in 0.6% and 0.2%, respectively.[3,4] In recent assessment of 10,847 CEA in the Vascular Study Group of New England (VSGNE), contralateral stroke was identified in 0.5%.[5] It has been suggested these non-ipsilateral events are more likely to be due to haemodynamic, procedural, or anatomical culprits compared with ipsilateral events. The rarity and lack of identifiable and actionable predictors has led to no discernible guideline recommendations addressing non-ipsilateral stroke risk. Therefore, the purpose of this analysis is to clarify the risk of peri-operative non-ipsilateral stroke with CEA and better define features driving and affecting its occurrence using the Vascular Quality Initiative (VQI) of the Society for Vascular Surgery. The specific effect of laterality of stroke after CEA on long-term survival was also investigated.

METHODS

Retrospective, cohort assessment of the VQI of the Society for Vascular Surgery quality database was performed. The VQI of the Society for Vascular Surgery has been well described and reviewed.[6] This national database is a quality improvement tool through the Patient Safety Organisation (PSO) of the Society for Vascular Surgery. De-identified demographic, clinical, and procedural variables are collected on each patient at each of the participating institutions and centralised. Data is collected during index hospitalisation, at 30 days and up to one year. Long-term mortality is discerned through linkage to the Social Security Death Index Masterfile of the United States government. Participation in this quality registry as a PSO and quality assurance tool for analysis was approved, and direct informed consent waived, at each participating centre's Institutional Review Board. Specific approval for this data collection and assessment was approved by the VQI PSO Research Advisory Committee. For this study's purposes, both initial operative data as well as initial surveillance visit were assessed.

Definitions and endpoints

All CEAs entered into the VQI between April 1, 2003 and March 31, 2017 were queried. Those without complete laterality or stroke data were excluded. In order to investigate non-ipsilateral stroke related to CEA, patients undergoing bilateral carotid procedures within 30 days of index CEA were excluded. Patients sustaining stroke within 30 days after CEA were identified. Stroke was further classified as ipsilateral or non-ipsilateral to the index CEA operative side. The primary endpoint was non-ipsilateral stroke defined as stroke in the cortical or ocular territory contralateral to CEA side, or in the vertebrobasilar territory within 30 days of operation. For the purposes of non-ipsilateral stroke analysis, those with both ipsilateral and non-ipsilateral territory events were considered to have non-ipsilateral stroke to determine features associated with events outside the ipsilateral territory. Forty demographic, pre-operative, operative, and post-operative factors were analysed to identify discriminators between those with ipsilateral or non-ipsilateral stroke. Operative factors included concomitant procedures. These were other open arterial surgery, or procedures on the carotid system adjacent to the endarterectomy, such as carotid-subclavian bypass or transposition, carotid-carotid or carotid-axillary bypass; proximal endovascular intervention, angioplasty or stenting of the carotid/innominate system proximal to CEA; and carotid-cardiac surgery. The degree of ipsilateral and contralateral stenosis was considered categorically as < 50%, 50–69%, or ≥70% based upon stenosis degree entered in the database. Contralateral occlusion was handled as a dichotomous covariable. Medicine use was considered dichotomously.

Statistical analysis

All statistical calculations were accomplished using STATA/SE14.2 software (StataCorp LLC, College Station, TX, USA). Continuous variables are expressed as mean ± standard deviation. Dichotomous variables are described as the percentage of cohort. Univariable analysis was performed using two tailed Student t test, or Wilcoxon rank sum testing for continuous variables where appropriate. Dichotomous variables were compared using the Pearson chi-square test. The effect of the degree of ipsilateral and contralateral stenosis on non-ipsilateral stroke was assessed using the Pearson chi-square testing for multiple variables. A p value of < .05 was considered significant. Forward stepwise logistic regression was performed to determine independent predictors of non-ipsilateral stroke. Kaplan–Meier methodology was used to calculate survival curves for patients without stroke, with ipsilateral stroke and with non-ipsilateral stroke. Curves were compared by log rank testing.

RESULTS

Patients and stroke

From April 1, 2003, through March 1, 2017, 80,230 CEA in 74,928 patients were identified. Age was 70.3 ± 9.3 years. Gender was male in 48,506 (60%); 43,074 (54%) were asymptomatic. There were 1469 patients experiencing

stroke within 30 days of CEA for an overall peri-operative stroke rate of 1.8%. Ipsilateral stroke alone occurred in 978 (1%) CEA. Non-ipsilateral stroke occurred in 491 (0.6%). This was non-ipsilateral alone in 418 (0.5%), and both ipsilateral and non-ipsilateral in 73 (0.09%). Most non-ipsilateral strokes were identified prior to discharge ($n = 474$; 97%). Non-ipsilateral stroke occurred in similar temporal profile to ipsilateral stroke. Stroke was recognised within 6 h in 61% of non-ipsilateral events and in 60% of ipsilateral stroke ($p = .82$). Non-ipsilateral stroke was ocular in 44 patients (9%), vertebrobasilar or unspecified in 113 (23%) and hemispheric in 334 (68%).

Demographics, anatomy, and pre-operative variables

The majority (92%) of patients undergoing CEA in VQI were Caucasian (Table 1).

There were no differences in diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, and renal insufficiency or dialysis dependence between those with and without peri-operative non-ipsilateral stroke. There were no significant differences in rates of overall prior carotid intervention, prior contralateral CEA or carotid angioplasty and stenting (CAS), or anatomical high risk features between the two groups. However, redo carotid procedure (4% vs. 2%; $p = .03$) and history of neck irradiation (2.5% vs. 1.4%; $p = .04$) were more common in those with non-ipsilateral stroke. Those sustaining non-ipsilateral stroke were less likely to have duplex ultrasound as their only imaging modality prior to operation (30% vs. 33%; $p = .12$). More patients with non-ipsilateral stroke underwent CTA pre-operatively (55% vs. 50%; $p = .04$). Pre-operative use of antiplatelet agents, dual antiplatelet therapy, and beta blockers was not significantly different while use of statin (76% vs. 80%; $p = .02$) and anti-angiotensin agents (45% vs. 52%; $p = .006$) was less frequent in non-ipsilateral stroke. Those experiencing stroke in the non-ipsilateral territories were more often symptomatic (64% vs. 46%; $p < .001$). The degree of contralateral stenosis ($<50\%$, $50-69\%$, or $\geq70\%$; $p = .001$) was significantly associated with non-ipsilateral stroke while the degree of ipsilateral stenosis also tended to be more severe ($<50\%$, $50-69\%$, or $\geq70\%$; $p = .084$). Contralateral occlusion was present more often in those with non-ipsilateral stroke (6% vs. 3%; $p = .001$). Significant pre-operative features in non-ipsilateral strokes included facility living status (2.3% vs. 1.2%; $p = .05$), and urgent operation (within 24 h of admission or discharge pending CEA) (21% vs. 13%; $p < .001$).

Operative and post-operative variables

Operative associations with non-ipsilateral stroke were related to CEA performed concomitantly with other surgery (Table 2). Length of operation (142.48 min vs. 118.84 min; $p < .001$), CEA combined with cardiac surgery (5% vs. 2%; $p < .001$), CEA with other open arterial surgery (2% vs. 1%; $p = .005$), and CEA with proximal endovascular intervention (3% vs. 1%; $p = .005$) were all significant

Table 1. Baseline (pre-operative) information on demographics, comorbidities, anatomy, diagnostic factors and medical therapy in patients with and without non-ipsilateral (N-I) stroke after CEA

Variable	No N-I stroke ($n = 79739$)	N-I stroke ($n = 491$)	p-value
Demographic			
Mean age ± SD, years	70.3 ± 9	70.5 ± 10	.461
Male	48208 (6)	298 (61)	.916
Caucasian	73520 (92)	447 (91)	.302
Ever smoker	60175 (76)	368 (75)	.791
Hypertension	70708 (89)	448 (91)	.064
Diabetes mellitus	27951 (35)	175 (36)	.779
CAD	21585 (27)	131 (27)	.992
CHF	8194 (10)	39 (8)	.093
COPD	17717 (22)	114 (23)	.595
CRF	1025 (1)	5 (1)	.602
Stress test performance	6458 (24)	36 (22)	.514
Preoperative facility placement[a]	986 (1.24)	11 (2.25)	.045
Creatinin ≥ 1.5 mg/dL	11689 (15)	66 (13)	.447
Anatomical and diagnostic features			
Symptomatic stenosis	36844 (46)	312 (64)	<.001
Prior ipsilateral CEA/CAS[b]	1757 (2)	18 (4)	.028
Prior contralateral CEA	10672 (13)	65 (13)	.925
Prior contralateral CAS	567 (0.7)	5 (1)	.420
Any prior CEA/CAS	12996 (16)	88 (18)	.387
Radiation	1080 (1.36)	12 (2.45)	.038
Anatomical high risk features	3030 (5)	21 (6)	.478
Ipsilateral carotid stenosis grade			.084
$<50\%$	1720 (3)	12 (4)	
$50-69\%$	7047 (14)	53 (18)	
$\geq70\%$	42130 (83)	229 (78)	
Contralateral carotid stenosis grade			.001
$<50\%$	26381 (57)	125 (50)	
$50-69\%$	12032 (26)	58 (23)	
$\geq70\%$	7967 (17)	66 (27)	
Contralateral carotid occlusion	2210 (3)	29 (6)	.001
Pre-operative duplex ultrasound	66236 (84)	402 (82)	.387
Duplex ultrasound only	26536 (33)	147 (30)	.117
Pre-operative CTA	39588 (50)	267 (55)	.043
Pre-operative MRA	12581 (16)	91 (19)	.104
Pre-operative arteriogram	5657 (7)	32 (7)	.621
Medical therapy			
Beta blocker	47540 (60)	293 (60)	.978
Aspirin	66050 (83)	406 (83)	.955
P2Y inhibitors	23206 (29)	141 (28)	.855
Dual antiplatelet therapy	18996 (24)	115 (23)	.835
Pre-operative anti-angiotensin	33514 (52)	172 (45)	.006
Statin	63812 (80)	372 (76)	.020

Data are presented as n (%) unless stated otherwise. CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; CEA = carotid endarterectomy; CAS = carotid angioplasty and stenting; CTA = computed tomography angiography; MRA = magnetic resonance angiography; SD = standard deviation.
[a] Pre-operative facility placement includes living in a nursing home or being homeless *versus* living at home.
[b] Index procedure being a redo CEA.

Table 2. Operative and post-operative factors in patients with and without non-ipsilateral (N-I) stroke after CEA

Variable	No N-I stroke ($n = 79739$)	N-I stroke ($n = 491$)	p-value
Operative factors			
Mean length of operation $\pm$ SD, min	118.8 $\pm$ 51	142.5 $\pm$ 77	<.001
Urgent operation	10090 (13)	121 (21)	<.001
CEA with cardiac surgery	1408 (2)	25 (5)	<.001
CEA with other arterial surgery	885 (1)	12 (2)	.005
Ipsilateral proximal hybrid endovascular procedure	510 (1)	14 (3)	<.005
Shunt	42988 (54)	296 (61)	.005
Dextran	8318 (10)	31 (6)	.003
Protamine	52126 (66)	302 (62)	.078
Eversion technique (versus longitudinal)	10010 (13)	69 (14)	.293
Type of anaesthesia			.511
local	1254 (2)	6 (1)	
regional	5620 (7)	29 (6)	
general	72711 (91)	453 (93)	
EEG monitoring	22752 (29)	146 (20)	.533
Stump pressure use	7504 (9)	39 (8)	.272
Post-operative factors			
Dysrhythmia	1453 (2)	33 (7)	<.001
Hypotension requiring IV treatment	8182 (10)	110 (22)	<.001
Hypertension requiring IV treatment	13745 (17)	136 (28)	<.001
Myocardial infarction	638 (1)	17 (3)	<.001
Reperfusion syndrome	127 (0.2)	7 (1)	<.001
Re-exploration of neck	1326 (2)	40 (8)	<.001

Data are presented as n (%) unless stated otherwise. CEA = carotid endarterectomy; EEG = electroencephalography; SD = standard deviation; IV = Intravenous.

factors. Of the 73 patients suffering bilateral stroke, three (4%) underwent CEA with proximal or distal endovascular intervention, four (5%) were combined with cardiac surgery, and three (4%) were with another arterial procedure. Collectively, these 10 patients accounted for 14% of bilateral strokes and 20% of contralateral strokes associated with CEA and concomitant procedures. Shunt use (61% vs. 54%; $p = .005$) showed significant association with non-ipsilateral stroke. Of 29 patients with non-ipsilateral stroke and contralateral occlusion, 27 (93%) were shunted. Shunt use was more common in those with contralateral occlusion sustaining non-ipsilateral stroke (93% vs. 74%; $p = .02$). Use of local, regional, or general anaesthesia had no effect on the occurrence of contralateral stroke. Cerebral monitoring techniques to include electroencephalography (EEG) and stump pressure did not affect contralateral stroke risk.

Hypotension requiring IV treatment (22% vs. 10%; $p < .001$), dysrhythmia (7% vs. 2%; $p < .001$), neck re-exploration (8% vs. 2%; $p < .001$), reperfusion syndrome (1% vs. 0.16%; $p < .001$) and hypertension requiring IV treatment (28% vs. 17%; $p < .001$) were post-operative factors significantly more common in non-ipsilateral strokes. Those undergoing urgent carotid revascularisation were more likely to experience reperfusion syndrome compared with elective CEA (0.39% vs. 0.13%; $p < .001$).

Logistic regression model of non-ipsilateral stroke

After multivariable logistic regression, significant, independent drivers of non-ipsilateral stroke after CEA were identified. Symptomatic disease (OR 1.7; 95% CI 1.3–2.1; $p < .001$) contralateral occlusion (OR 1.9; 95% CI 1.3–2.8; $p < .001$), and urgent operation (OR 1.5; 95% CI 1.2–2.0; $p = .001$) were pre-operative drivers. Anti-angiotensin treatment (OR 0.8; 95% CI 0.6–0.97; $p = .03$) was protective. Predictors during operation included shunt use (OR 1.3; 95% CI 1.1–1.7; $p = 0.008$), CEA combined with cardiac surgery (OR 1.9; 95% CI 1.1–3.1; $p = .013$), and CEA with concomitant, proximal endovascular intervention (OR 2.6; 95% CI 1.3–5.4; $p = .01$). Use of dextran (OR 0.6; 95% CI 0.4–0.9; $p = .01$) appeared protective. Reperfusion syndrome (OR 6.3; 95% CI 2.8–14.1; $p < .001$), neck re-exploration (OR 5.6; 95% CI 3.9–8.1; $p < .001$), myocardial infarction (OR 2.0; 95% CI 1.4–2.8; $p < .001$), and intravenous treatment of hypotension (OR 2.5; 95% CI 2.0–3.3; $p < .001$) or hypertension (OR 1.9; 95% CI 1.5–2.3; $p < .001$) were significant post-operative correlates with non-ipsilateral stroke (Table 3).

Effect of non-ipsilateral stroke on survival

Thirty day mortality after ipsilateral stroke was significantly higher than non-ipsilateral stroke (10.3% [101/978] vs. 6.1% [30/491]; $p = .007$). Five year survival estimates stratified by stroke laterality showed no differences in negative impact of stroke. Non-ipsilateral (73%) and ipsilateral (76%) stroke five year survival were not different (log rank $p = .16$). Both were significantly worse than survival without peri-operative stroke (88%) (log rank $p < .001$ and

Table 3. Multivariable regression model of pre-, peri-, and postoperative factors predicting non-ipsilateral stroke after CEA

Predictor	Non-ipsilateral stroke	
	OR (95% CI)	p-value
Pre-operative factors		
Contralateral occlusion	1.9 (1.3–2.8)	.001
Symptomatic	1.7 (1.3–2.1)	<.001
Urgency	1.5 (1.2–1.9)	.001
Pre-operative anti-angiotensin	0.8 (0.6–0.97)	.027
Peri-operative factors		
CEA/proximal intervention	2.6 (1.3–5.4)	.010
CEA with cardiac surgery	1.9 (1.1–3.1)	.013
Shunt	1.3 (1.0–1.7)	.008
Dextran	0.6 (0.4–0.9)	.011
Post-operative factors		
Reperfusion	6.3 (2.8–14.1)	<.001
Re-exploration of neck	5.6 (3.9–8.1)	<.001
IV treatment for hypotension	2.5 (2.0–3.3)	<.001
Myocardial infarction	2.0 (1.4–2.7)	<.001
IV treatment for hypertension	1.8 (1.5–2.3)	<.001

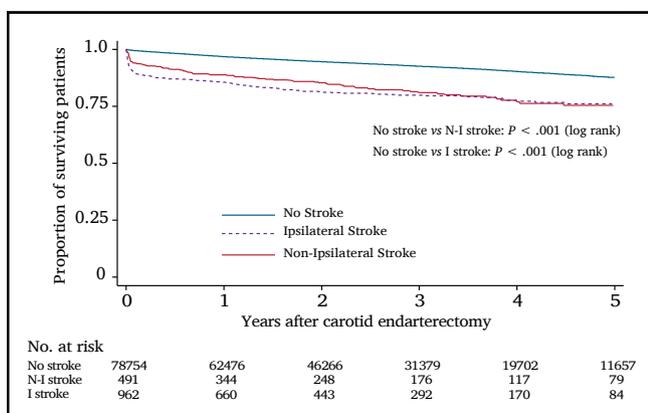CEA = carotid endarterectomy; IV = intravenous; OR = odds ratio; CI = confidence interval.

Figure 1. Kaplan–Meier estimates of five year survival after carotid endarterectomy in those without stroke, and in those sustaining ipsilateral peri-operative 30 day stroke, and non-ipsilateral 30 day stroke. Survival after both non-ipsilateral and ipsilateral stroke was significantly worse than in those without stroke (presented statistical comparison gross survivals unadjusted for confounders). There is no statistically significant difference in five year survival between ipsilateral and non-ipsilateral stroke. N-I = non-ipsilateral; I = ipsilateral.

$p < .001$, respectively) (Fig. 1). Over the first three years after CEA, however, ipsilateral stroke had slight but significantly worse survival estimates ($p < .001$) largely due to increased 30 day mortality.

DISCUSSION

The literature describing operative stroke risk after CEA focuses on ipsilateral or all stroke or combined stroke and death after CEA. Many contributing risk factors have been implicated.[7–13] The relationship between these and non-ipsilateral stroke risk with CEA is unclear, and little commentary on stroke risk beyond ipsilateral or all stroke exists. After developing an interest in this element of CEA risk, risk and features surrounding contralateral stroke were recently characterised using nearly 11,000 CEA in the Vascular Study Group of New England (VSGNE).[5] Operative urgency, length and CEA combined with ipsilateral, endovascular intervention were identified as drivers of contralateral stroke. Yet, only 59 events were identified, so this compelled the authors to pursue larger investigation to better clarify peri-operative stroke outside the territory of the operated CEA. This current communication used the national VQI aiming to provide more granular detail on non-ipsilateral events. The rare nature of non-ipsilateral events was again reinforced.

Symptomatic status previously appeared irrelevant to non-ipsilateral stroke considering the prospective carotid trial data. In the surgical arms of ACAS and NASCET this occurred similarly in 0.3% and 0.4%, respectively.[1,2] The previous VSGNE analysis also indicated no correlation between symptoms and contralateral stroke risk.[5] Yet, herein symptomatic status revealed its importance. It is well established that all stroke and ipsilateral stroke risk are connected with symptomatic status.[8,10,14] The natural implication being that friable, symptomatic plaque increases

ipsilateral risk. It would seem logical symptomatic status may mark those with added disease burden, or more diffuse vulnerable disease.

This theory seems plausible as the presence of more severe bilateral disease correlated with stroke outside the ipsilateral territory. Further, use of on table antiplatelet therapy with Dextran, reserved in many centres for patients deemed to have coarse residual disease or endarterectomy surface, was noted to be protective while pre-operative use of antiplatelet or statin drugs were not. This brings into question whether more advanced disease is present in those sustaining non-ipsilateral stroke.[15] The protective effect of anti-angiotensin therapies agrees with studies showing these have unique beneficial effects on the carotid artery wall and may be preventive of more global disease.[16]

Although some may shunt obligatorily, many are selective and the need for shunt use was shown to be an independent feature of non-ipsilateral stroke, probably reflecting poor cerebral anatomic collateralisation or disseminated disease burden limiting collateral flow. Again, the fact that standard pre-operative medical therapy had little influence on non-ipsilateral stroke after CEA may also point toward the pathophysiology of non-ipsilateral stroke being more haemodynamic in nature than ipsilateral stroke.

Contralateral stenosis and occlusion may be logical, predisposing markers for the haemodynamic nature of non-ipsilateral stroke. Yet, this was not the case in the initial VSGNE study.[5] Contralateral occlusion specifically was not found to be predictive of contralateral stroke although there was a trend of association. The rarity of contralateral, peri-operative stroke was surmised, and sample size likely led to lack of power and type II error. This appears to be the case as larger VQI assessment indicates contralateral occlusion is indeed a strong, independent predictor of non-ipsilateral stroke. Contralateral occlusion is a controversial factor in overall stroke risk after CEA.[8,10,11,14,17] At Massachusetts General Hospital, assessment commented on the importance of contralateral occlusion in all stroke after CEA (OR 2.92; 95% CI 1.34–6.38) in over 3000 CEA operations.[8] Contralateral occlusion, however, played no role in ipsilateral stroke. The effect of severe ($\geq$70%) contralateral stenosis or occlusion (SCSO) on stroke outcomes was investigated further.[14] Presence of SCSO carried higher risk of any stroke (2.8% vs. 1.5%; $p = .024$), death (2.2% vs. 1.1%; $p = .027$), and any stroke or death (4.3% vs. 2.4%; $p = .008$). However, there was no difference in the occurrence of ipsilateral stroke between those with and without SCSO (1.5% vs. 1.2%; $p = .38$). SCSO was an independent predictor of any stroke (OR 1.8; 95% CI 1.0–3.3; $p < .001$) and any stroke or death (OR 1.7; 95% CI 1.1–2.7; $p = .02$) but had no influence on ipsilateral stroke. Adding the current investigation, the authors conclude contralateral occlusion is an important, but subtle, risk factor for poorer operative outcomes with CEA. However, it does not inherently increase ipsilateral stroke and most of its intrinsic risk is related to its effect on non-ipsilateral events and global cardiovascular disease burden. This feature may explain why contralateral occlusion's role in CEA risk has remained difficult to define.

Another aspect of non-ipsilateral stroke after CEA is its relationship with concomitant arterial operations. CEA combined with cardiac surgery increasing non-ipsilateral stroke risk is seemingly rational. Overall stroke risk of isolated cardiac surgery has improved over time. Risk ranges from 1—3% with today's coronary bypass up to 6—8% with multivalve procedures.[18,19] Cerebral embolism from manipulation of the proximal aorta, as well as the cardiopulmonary bypass circuit are potential culprits. Hypoperfusion and pan-vascular inflammation have also been implicated, and rhythm disturbances during or after operation are also problematic.[20] These mechanisms place both sides of the brain at risk. Adding CEA may augment the potential for non-ipsilateral stroke.[21] After univariable significance in the prior VSGNE dataset, however, CEA with cardiac surgery failed to remain predictive in multivariable modelling for contralateral stroke.[5] Not until this larger VQI analysis of non-ipsilateral stroke was the impact of adding cardiac surgery to CEA obvious. Yet, other mechanisms are clearly important as this only represented 5% of non-ipsilateral stroke after CEA. Further, the risk of non-ipsilateral stroke with combined CEA/CABG at experienced centres can be 2% or lower.[22] In this assessment, it was also 2% reflecting generally appropriate selection for these procedures and quality of operative care across the country.

Addition of proximal endovascular intervention to CEA is also a factor driving non-ipsilateral stroke risk involving combined procedures. While rarely performed, some have suggested the addition of retrograde endovascular intervention to CEA adds minimal, if any, risk.[23] Stroke and death risk with this tandem lesion strategy has recently been reported to be more substantial, however.[24] This led to recommending caution and for select use of this hybrid procedure with consideration of alternative operative conducts. Although these past analyses of this technique did not reveal specific non-ipsilateral stroke outside of reperfusion pathophysiology, the VSGNE assessment of contralateral stroke also reported this strategy as a predictive factor.[5] This is probably the result of arch and branch manipulation from a cervical approach in addition to reperfusion.

While causality and chronology are difficult to establish, the independent association between the post-operative features of reperfusion, re exploration, myocardial infarction, and need for intravenous treatment of blood pressure fluctuations and contralateral stroke is sensible. This also speaks to the expanded aetiologies of non-ipsilateral stroke judged against the largely operative thromboembolism of ipsilateral stroke. In these identified risk factors of non-ipsilateral stroke after CEA, both thrombo-embolism and haemodynamic variability are indicted.

Both recent European Society for Vascular Surgery and Society for Vascular Surgery guidelines for carotid artery disease management have recognised the features detailed herein relating to stroke complicating CEA.[25,26] These include the clear importance of symptomatic status and the salient yet unclear role of contralateral occlusion. The importance of haemodynamic management and avoidance of reperfusion syndrome is detailed. Combined CEA with cardiac surgery is a recommended option in appropriately selected patients. In the European Society for Vascular Surgery recommendations, use of open, retrograde proximal intervention with CEA is considered the preferred approach in most patients with tandem lesions. However, neither of these documents provides insight into how any of these or other risk factors interplay into the risk of non-ipsilateral stroke specifically.

The relative impact of non-ipsilateral stroke on long-term survival after CEA was estimated to provide context within the debate regarding later risk implications of carotid intervention complications.[27,28] Non-ipsilateral stroke seems to carry less operative mortality yet reduces late survival in a way similar to ipsilateral stroke. Thus, there is no evidence indicating laterality or location of stroke after CEA affects long-term survival differently. This has consequences for comparative investigation of various carotid angioplasty and stenting platforms with CEA.

There are several limitations to this analysis. Over the time period studied, this cohort represents a minority of carotid endarterectomies performed in the United States. The analysis was retrospective leading to identification and selection biases. VQI is a surgeon and institution reported quality assurance tool and as such, may suffer from underreporting and misclassification of events. Only items within the quality registry could be evaluated. There may be other factors, or uncaptured characteristics of these items, contributing to non-ipsilateral stroke which are not appreciated. For instance, the anatomical status of the vertebrobasilar system prior to CEA is not collected. Neither is the degree and severity of post-operative hypertension or hypotension documented. Linking survival to the Social Security Death Index may introduce lag time and reporting bias. Finally, rarity of non-ipsilateral stroke after CEA may lead to type II error throughout this analysis restricting ability to identify important factors in occurrence and limiting statistical analysis. However, this is a specific discussion of stroke outside the ipsilateral territory after CEA and furthers prior investigations providing more explicit detail on risk and predictors.

CONCLUSIONS

Stroke outside of the ipsilateral territory after CEA is rare. Features driving risk surround global disease burden and symptoms, complex and combined procedures, and haemodynamic fluctuations during or after operation. Contralateral occlusion independently increases non-ipsilateral stroke risk. In this assessment, both embolic and haemodynamic aetiologies are implicated. Regardless of laterality or location, negative effects of stroke after CEA on long-term survival are similar. The potential risks and benefits in recommending medical therapies, such as dextran or anti-angiotensin agents, specifically to prevent non-ipsilateral stroke in higher risk patients requires study.

CONFLICT OF INTEREST

None.

FUNDING

None.

APPENDIX A. SUPPLEMENTARY DATA

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