Carotid Artery Stenting of a Contralateral Occlusion and In-Hospital Outcomes

Results From the CARE (Carotid Artery Revascularization and Endarterectomy) Registry

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Objectives The authors sought to study the characteristics and outcomes of patients with contralateral carotid artery occlusions (CCOs) undergoing elective carotid artery stenting (CAS).

Background CCOs are associated with adverse neurological events following carotid endarterectomy.

Methods In-hospital outcomes were examined in patients with and without CCO undergoing elective CAS in the Carotid Artery Revascularization and Endarterectomy (CARE) registry. A CCO was defined as a 100% occlusion of the contralateral internal carotid artery. To minimize differences in measured comorbidities, a 3:1 propensity matching analysis was performed comparing 42 clinical and demographic variables between CCO and non-CCO patients from the CARE registry. The primary endpoint was a composite of in-hospital death, nonfatal myocardial infarction, and nonfatal stroke.

Results Between April 2005 and January 2012, 13,993 eligible patients underwent elective CAS, of whom 1,450 (10%) had CCO. There were 5,500 CAS procedures (1,375 CCO and 4,125 non-CCO) identified in the propensity analysis. The primary composite endpoint occurred in 29 (2.1%) and 107 (2.6%) patients with and without CCO, respectively (adjusted odds ratio: 0.81, 95% confidence interval: 0.53 to 1.23, p = 0.316).

Conclusions In the CARE registry, there was no evidence that the presence of a CCO was associated with an increased risk of in-hospital death, nonfatal myocardial infarction, or nonfatal stroke in patients undergoing elective CAS. These findings may have implications on the selection of carotid revascularization procedures for such patients. (J Am Coll Cardiol Intv 2013;6:59–64) © 2013 by the American College of Cardiology Foundation
Stroke is the fourth leading cause of death and was associated with approximately $74 billion in economic costs in 2010 (1). More than 80% of all strokes are ischemic in origin (2). Although carotid endarterectomy (CEA) is associated with greater long-term survival free of stroke than medical therapy (3,4), patients with high-risk contralateral carotid occlusions (CCOs), which occur in 6% to 10% of patients undergoing CEA, are at much greater risk of periprocedural death, nonfatal myocardial infarction, or stroke (5). Emerging evidence from a high-risk patient population suggests that elective carotid artery stenting (CAS) is an acceptable treatment option for patients if performed by an experienced operator in a thoughtfully selected patient population (6). However, data quantifying the prevalence and outcomes of elective CAS in patients with a CCO have not been completely described. In this study, we compared in-hospital outcomes between patients with and without CCOs undergoing elective CAS in the nationwide CARE (Carotid Artery Revascularization and Endarterectomy) registry.

Methods

The CARE registry is a nationwide program for carotid revascularization procedures operated by the NCDR (National Cardiovascular Data Registry) since 2005 to measure patient outcomes and ensure quality improvement. A description of the CARE registry has been previously published (7). Briefly, 186 centers in the United States voluntarily participate in collection and validation of demographic, medical history, and procedural data from patients undergoing either CAS or CEA. Data are collected from existing medical records using standardized definitions, collection protocols, and tools. An on-site registry manager is designated by each participating center to ensure data accuracy and timely submission to NCDR.

Study population. For the purpose of this study, we identified patients with and without a CCO undergoing elective CAS between April 2005 and January 2012. Patients were stratified by the presence or absence of neurological symptoms related to the target lesion within the past 6 months, by age <70 or ≥70 years, and by sex. There were 15,281 CAS procedures during this time. After excluding acute evolving stroke (n = 431), spontaneous dissection (n = 141), and general anesthesia (n = 716), there were 13,993 CAS procedures in the analytical cohort (Fig. 1). Pre- and post-procedure National Institutes of Health Stroke Scale assessment was performed in 9,927 (71.3%) and 9,193 (66.0%) patients, respectively, in the analytical cohort.

Definitions. CCO was defined as a 100% occluded contralateral internal carotid artery. One patient was excluded due to an indicator for CCO missing from the database. Acute evolving stroke was defined as ongoing ischemia with symptoms at the time of the procedure, as well as each of the following: sudden development of neurological deficit attributable to cerebral ischemia or infarction, onset of symptoms occurring within the prior 3 days of CAS, and progressively worsening symptomatology. Post-CAS ischemic stroke was defined as a focal neurological deficit in the absence of documented intracranial hemorrhage with residual symptoms lasting ≥24 h and combined with impaired functional outcomes. Symptoms of ischemic stroke were identified as: 1) right hemispheric or retinal; 2) left hemispheric or retinal; 3) vertebrobasilar; or 4) unknown.

Post-CAS myocardial infarction was identified by an increase and decrease in cardiac biomarkers (preferably troponin) with >1 value above the upper limit of normal, along with clinical evidence of myocardial ischemia consist-
ing of ≥1 of the following: 1) symptoms; 2) electrocardiographic changes (new ST-T changes or left bundle branch block); 3) development of pathological Q waves in the electrocardiogram; or 4) new loss of viable myocardium or new regional wall motion abnormality as evidenced by imaging (8). Cardiac biomarkers were collected at the discretion of each participating investigator following CAS.

Neurological symptom status in the target lesion was determined in all patients before CAS. Symptomatic patients were not excluded in this analysis. Symptoms included a prior history of carotid transient ischemic attack with distinct focal neurological dysfunction persisting <24 h, non-disabling stroke with a modified Rankin scale ≥3, or transient monocular blindness (amaurosis fugax) within the previous 6 months.

An acute cerebrovascular accident (CVA) following CAS was classified as sudden development of a neurological deficit attributable to cerebral ischemia or infarction, symptom onset within 3 days before and ongoing at the time of deficit attributable to cerebral ischemia or infarction, symptoms, difficulty speaking or understanding, blurred or impaired vision, dizziness, or loss of balance and coordination. The primary clinical endpoint was a composite of in-hospital death, nonfatal myocardial infarction, or nonfatal stroke. Secondary endpoints were the individual components of the composite.

**Statistical analysis.** Data are presented as means with corresponding 95% confidence intervals (CI), counts with percentages, or medians with interquartile ranges (IQR). Baseline characteristics of patients with and without CCO undergoing elective CAS were compared using standardized differences. To address potential confounders in the primary endpoint, a propensity score was calculated and each patient matched 3:1 (3 non-CCO to 1 CCO) on the basis of 42 clinical and demographic variables using the nearest-neighbor pair and a caliper width of 0.2 times the standard deviation of the logit of the propensity score (9). Absolute standardized differences were computed to evaluate matching effectiveness and are displayed in Table 1. Values <10% and closer to zero demonstrate a more balanced cohort (10).

### Table 1. Baseline Patient and Procedural Characteristics in Patients With or Without a CCO

<table>
<thead>
<tr>
<th>Demographics and risk factors</th>
<th>CCO (n = 1,450)</th>
<th>No CCO (n = 12,543)</th>
<th>Standardized Difference (%)</th>
<th>CCO (n = 1,375)</th>
<th>No CCO (n = 4,125)</th>
<th>Standardized Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>68.9 ± 9.9</td>
<td>71.1 ± 10.3</td>
<td>21.824</td>
<td>68.9 ± 9.7</td>
<td>68.9 ± 10.7</td>
<td>0.11341</td>
</tr>
<tr>
<td>Male</td>
<td>970 (66.9)</td>
<td>7,640 (60.9)</td>
<td>12.485</td>
<td>919 (66.8)</td>
<td>2,710 (65.7)</td>
<td>2.40948</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1,327 (91.5)</td>
<td>11,547 (92.1)</td>
<td>1.974</td>
<td>1,257 (91.4)</td>
<td>3,745 (90.8)</td>
<td>2.21353</td>
</tr>
<tr>
<td>History of smoking</td>
<td>1,152 (79.4)</td>
<td>9,162 (73.0)</td>
<td>15.0870</td>
<td>1,093 (79.5)</td>
<td>3,304 (80.1)</td>
<td>1.50903</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1,326 (91.4)</td>
<td>11,362 (90.7)</td>
<td>2.7732</td>
<td>1,254 (91.2)</td>
<td>3,771 (91.4)</td>
<td>0.77433</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1,268 (87.5)</td>
<td>10,953 (87.4)</td>
<td>0.3481</td>
<td>1,201 (87.3)</td>
<td>3,635 (88.1)</td>
<td>2.36431</td>
</tr>
<tr>
<td>Diabetes</td>
<td>552 (38.1)</td>
<td>4,709 (37.6)</td>
<td>1.1126</td>
<td>522 (38.0)</td>
<td>1,562 (37.9)</td>
<td>0.19982</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>682 (47.1)</td>
<td>5,355 (42.8)</td>
<td>8.8000</td>
<td>635 (46.2)</td>
<td>1,946 (47.2)</td>
<td>1.99189</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>798 (55.2)</td>
<td>7,053 (56.3)</td>
<td>2.1872</td>
<td>755 (54.9)</td>
<td>2,280 (55.3)</td>
<td>0.73090</td>
</tr>
<tr>
<td>MI within 6 weeks</td>
<td>48 (3.3)</td>
<td>311 (2.5)</td>
<td>4.9511</td>
<td>41 (3.0)</td>
<td>138 (3.3)</td>
<td>2.07719</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>246 (17.0)</td>
<td>2,258 (18.0)</td>
<td>2.6898</td>
<td>236 (17.2)</td>
<td>719 (17.4)</td>
<td>0.70489</td>
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<tr>
<td>NYHA class III/IV within 6 weeks</td>
<td>106 (7.3)</td>
<td>1,028 (8.2)</td>
<td>3.3476</td>
<td>97 (7.1)</td>
<td>287 (7.0)</td>
<td>0.37981</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurological history</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Transient ischemic attack</td>
<td>462 (31.9)</td>
<td>3,972 (31.7)</td>
<td>0.04188</td>
<td>443 (32.2)</td>
<td>1,334 (32.3)</td>
<td>0.25919</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>283 (19.5)</td>
<td>1,778 (14.2)</td>
<td>1.43063</td>
<td>266 (19.3)</td>
<td>790 (19.2)</td>
<td>0.49180</td>
</tr>
<tr>
<td>Target lesion symptoms within 6 months</td>
<td>648 (44.8)</td>
<td>5,030 (40.2)</td>
<td>1.93027</td>
<td>612 (44.5)</td>
<td>1,840 (44.4)</td>
<td>0.19505</td>
</tr>
<tr>
<td>CEA</td>
<td>346 (23.9)</td>
<td>2,841 (22.7)</td>
<td>2.8686</td>
<td>323 (23.5)</td>
<td>986 (23.9)</td>
<td>0.96969</td>
</tr>
<tr>
<td>CAS</td>
<td>145 (10.0)</td>
<td>1,296 (10.3)</td>
<td>1.0999</td>
<td>121 (8.8)</td>
<td>327 (7.9)</td>
<td>3.15205</td>
</tr>
<tr>
<td>CAS performed in a restenotic lesion</td>
<td>320 (22.07)</td>
<td>2,186 (17.43)</td>
<td>11.68</td>
<td>292 (21.24)</td>
<td>878 (21.28)</td>
<td>0.1185</td>
</tr>
<tr>
<td>CEA</td>
<td>83 (5.7)</td>
<td>358 (2.9)</td>
<td>14.2281</td>
<td>72 (5.2)</td>
<td>194 (4.7)</td>
<td>2.45373</td>
</tr>
</tbody>
</table>

**Values are mean ± SD or n (%), and are before and after propensity matching.**

**CAS = carotid artery stenting; CCO = contralateral carotid artery occlusion; CEA = carotid endarterectomy; EPD = embolic protection device; MI = myocardial infarction; NYHA = New York Heart Association.**
Odds ratios with 95% CI are reported for the primary and secondary endpoints. The primary endpoint was also stratified by asymptomatic and symptomatic patients, age <70 or ≥70 years, sex, and whether CAS was performed for de novo or restenotic lesions. Sensitivity analyses were performed using traditional univariate and multivariable modeling on the entire cohort. A multivariable model was constructed in the full analytical cohort, sequentially adjusting for demographic and clinical characteristics, cardiovascular risk factors, and lastly, prior neurological history. All statistical analyses were performed using the SAS version 9.2 software (SAS Institute, Cary, North Carolina). A 2-sided p value ≤0.05 was considered statistically significant.

Results

Between April 2005 and January 2012, 15,281 patients underwent elective CAS at 180 participating CARE centers. After exclusions, there were 13,993 patients forming the analytical cohort. The median (IQR) number of CAS procedures by center was 45 (19 to 98). Of these patients, 1,450 (10%) had a CCO before the index procedure (IQR: 6.2% to 15.9% across centers).

Baseline, neurological, and procedural characteristics for patients with and without a CCO are presented in Table 1, both before and after matching. Before matching, patients with CCO were younger, more frequently male, and more likely to have a history of past or current smoking, recent myocardial infarction, and neurological events before CAS. Non-CCO patients were more likely to have undergone previous CAS, whereas CCO patients were more likely to have had a previous ischemic stroke, restenosis, or symptoms of a target lesion (Table 1). After propensity matching, the standard differences or baseline covariables depicted in Table 1 ranged from 0.11 to 6.9.

In-hospital events for the matched cohort as well as for subgroups by age, symptom, and sex are shown in Table 2. The primary composite endpoint occurred in 2.1% of CCO patients and in 2.6% of non-CCO patients, p = 0.316. The in-hospital mortality rate is depicted in Table 2. Overall, there were 28 deaths in the matched cohort: 16 were due to neurological causes, 6 cardiac, 2 pulmonary, 1 vascular, 1 due to infection, and 2 were from other causes. One post-CAS stroke was hemorrhagic, which occurred in a CCO patient.

There were 1,170 CAS procedures performed on restenotic lesions. Of these, 292 were among the CCO cohort and 878 were among the non-CCO cohort. The primary outcome occurred in 1.7% versus 2.1% of CCO versus non-CCO patients, respectively, p = 0.79. In 4,330 CAS procedures performed in de novo lesions, 1,083 were among CCO patients and 3,247 were among non-CCO patients. The primary outcome occurred in 2.2% versus 2.7%, respectively, p = 0.348. When stratified by symptom status, age, or sex, the presence or absence of a CCO was not associated with a difference in the primary endpoint between asymptomatic (p = 0.120) or symptomatic (p = 0.956) patients, in patients younger (p = 0.426) or older (p = 0.093) than 70 years, or in men (p = 0.942) or women (p = 0.093) (Table 2).

Results of sensitivity analyses using univariate and multivariable modeling for the entire cohort are shown in Figure 2. The unadjusted odds ratio (OR) of a CCO predicting the primary outcome was 0.80 (95% CI: 0.55 to 1.16, p = 0.239). After adjustment for demographic and cardiovascular risk factors, the OR was 0.91 (95% CI: 0.62 to 1.34, p = 0.641). The addition of prior neurological history did not substantially alter the relationship (OR: 0.88, 95% CI: 0.60 to 1.29, p = 0.50). These results are concordant with outcomes relative to the propensity matched cohort.

Discussion

In this nationwide registry of patients undergoing carotid artery revascularization, the prevalence of CCOs in patients undergoing elective carotid artery stenting was 10%. The rate of composite in-hospital events, including death, nonfatal myocardial infarction, and nonfatal stroke, did not differ between patients with and without a CCO after elective CAS. Lastly, CCO was not associated with higher complications following CAS in older patients or individuals with prior neurological symptoms.
The prognosis of medically treated patients with carotid artery stenosis and a CCO is poor, with 2-year stroke rates ranging from 40% to 70% (11,12). This excess risk is believed to be related to inadequate collateral circulation at the level of the circle of Willis (13), from compromised ipsilateral blood supply in the setting of a complete CCO. CCO is a well-recognized high-risk anatomic criterion for patients undergoing CEA (5). Patients with CCO have higher rates of perioperative stroke and death, as observed in both the NASCET (North American Symptomatic Carotid Endarterectomy Trial) (14) and ACAS (Asymptomatic Carotid Atherosclerosis Study) (15) trials. In NASCET, the 30-day stroke and death rate was 14.3% among patients with a CCO, although more recent work suggests the rate is decreasing over time (5). Although the mechanism for increased risk is not fully understood, it is commonly believed to be related to a reduction in blood flow during cross-clamping of the ipsilateral common carotid artery during endarterectomy (16).

To our knowledge, the clinical efficacy and safety of CAS in patients with carotid stenosis and a CCO has been evaluated in only 7 previously published, retrospective studies (17–23), with a combined sample size of <500 patients who underwent CAS in the setting of a CCO. As expected, these studies varied widely in terms of design and sample size, ranging from 18 (21) to 191 (23) patients. Other limitations of these studies included most being a single-center design (18,19,21,22), inconsistent use of distal protection devices on a routine basis between studies (21,23), and few using a control group of patients without a CCO (20,23). Nevertheless, event rates in these studies ranged from 0% to 7.7% for death and 0% to 2.1% for major CVA, both in agreement with results from the present analysis; and in the largest study, in-hospital mortality and major CVA event rates were 1.6% versus 1.4% for patients with and without a CCO undergoing CAS, respectively (23). Our work also represents the largest sample size to date assessing outcomes of CCO patients undergoing CAS with the widespread application of distal embolic protection devices, therefore reflecting contemporary CAS practice in the United States.

Although we did not directly compare the outcomes of CEA with CAS in patients with a CCO in the CARE registry, CEA is known to be associated with increased risk in the presence of CCO, whereas CAS appears to be safe in this group of patients, potentially due to the widespread implementation of embolic protection devices during balloon inflation and stent deployment. CAS appears to be a reasonable revascularization option for patients with a contralateral carotid occlusion if anatomically suitable for CAS.

**Study limitations.** Several important limitations associated with our study should be noted. First, intermediate and long-term follow-up for CARE patients is not available. Second, as a retrospective observational analysis, comparing...
CCO with non-CCO, the presence of unmeasured confounders is inherent. Finally, we did not compare outcomes of CAS in the setting of a CCO with either medical therapy or CEA. According to recent results from CARE (17), the characteristics of patients referred for CAS differ markedly from those referred for CEA, with more comorbidities in patients referred for CAS, thus making comparisons of the 2 treatment strategies from observational databases problematic. Nonetheless, we believe that an indirect inference regarding the potential advantages of CAS relative to other strategies in this group of patients is warranted.

Conclusions

In this study, approximately 10% of CAS procedures were performed in a setting of a CCO. There was no evidence that the presence of a CCO was associated with an increased risk of in-hospital death, nonfatal myocardial infarction, or nonfatal stroke in patients undergoing elective CAS. These findings may have implications on the selection of carotid revascularization procedures for such patients.

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REFERENCES


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