A Direct Comparison of Early and Late Outcomes With Three Approaches to Carotid Revascularization and Open Heart Surgery

Mehdi H. Shishehbor, DO, MPH, PrfD,* Sridhar Venkatachalam, MD,* Zhiyuan Sun, MS,† Jeevanantham Rajeswaran, MSc,† Samir R. Kapadia, MD,* Christopher Bajzer, MD,* Heather L. Gornik, MD,* Bruce H. Gray, DO,‡ John R. Bartholomew, MD,* Daniel G. Clair, MD,x Joseph F. Sabik III, MD,‖ Eugene H. Blackstone, MD‖||

Cleveland, Ohio; and Greenville, South Carolina

Objectives
The aim of this study was a comparison of risk-adjusted outcomes of 3 approaches to carotid revascularization in the open heart surgery (OHS) population.

Background
Without randomized clinical trials, the best approach to managing coexisting severe carotid and coronary disease remains uncertain. Staged carotid endarterectomy (CEA) followed by OHS or combined CEA and OHS are commonly used. A recent alternative is carotid artery stenting (CAS).

Methods
From 1997 to 2009, 350 patients underwent carotid revascularization within 90 days before OHS at a tertiary center: 45 staged CEA-OHS, 195 combined CEA-OHS, and 110 staged CAS-OHS. The primary composite endpoint was all-cause death, stroke, and myocardial infarction (MI). Staged CAS-OHS patients had higher prevalence of previous stroke (p = 0.03) and underwent more complex OHS. Therefore, the propensity score adjusted multiphase hazard function models with modulated renewal to account for staging, and competing risks were used.

Results
Using propensity analysis, staged CAS-OHS and combined CEA-OHS had similar early hazard phase composite outcomes, whereas staged CEA-OHS incurred the highest risk driven by interstage MI. Subsequently, staged CAS-OHS patients experienced significantly fewer late hazard phase events compared with both staged CEA-OHS (adjusted hazard ratio: 0.33; 95% confidence interval: 0.15 to 0.77; p = 0.01) and combined CEA-OHS (adjusted hazard ratio: 0.35; 95% confidence interval: 0.18 to 0.70; p = 0.003).

Conclusions
Staged CAS-OHS and combined CEA-OHS are associated with a similar risk of death, stroke, or MI in the short term, with both being better than staged CEA-OHS. However, the outcomes significantly favor staged CAS-OHS after the first year. (J Am Coll Cardiol 2013;62:1948–56) © 2013 by the American College of Cardiology Foundation

The prevalence of severe carotid disease (>80% stenosis of the internal carotid artery) among patients undergoing open heart surgery (OHS) for coronary artery disease is estimated to be 6% to 12% (1,2); however, the best approach to management of concomitant carotid disease in this population remains controversial in the absence of randomized clinical trials (3–5). Three approaches commonly used are staged carotid endarterectomy (CEA) followed by open heart surgery (CEA-OHS), combined CEA-OHS (i.e., concomitant CEA and OHS under a single anesthesia), and, more recently, staged carotid stenting (CAS) followed by OHS (CAS-OHS) (6). Both staged approaches expose patients to interstage events such as death, stroke, and myocardial infarction (MI), especially given the presence of severe coexisting coronary artery disease.

See page 1957
With combined CEA-OHS, despite eliminating inter-
stage risk, outcomes have been similar to those with staged
CEA-OHS (4,7) and in most cases inferior to those with
staged CAS-OHS, mainly due to higher perioperative stroke
risk (8,9). However, the validity of such comparison is
questionable because of failure to study the impact of inter-
stage events on outcomes after OHS. Furthermore, these
studies have been limited to 30-day or in-hospital endpoints.
Thus, the purpose of this study was to directly compare the 3
approaches addressing these deficiencies.

Methods

Study population. From January 1997 to August 2009, 350
patients underwent a carotid revascularization procedure
within 90 days of planned OHS at Cleveland Clinic: 45
staged CEA-OHS, 195 combined CEA-OHS, and 110
staged CAS-OHS. The study population predominantly
consisted of patients who were found to have severe carotid
artery stenosis on routine duplex ultrasonography as part of
a comprehensive evaluation before OHS. At the time of
OHS, 41 (12%) presented with unstable angina and 25 (7%)
presented with MI. From the carotid standpoint, 66 (19%)
had symptomatic carotid disease (transient ischemic attack
or stroke within 6 months) on the intervened side. Throughout
this paper, we use OHS to refer to either isolated coronary
artery bypass grafting (CABG), CABG combined with a
variety of other cardiac procedures, or non-CABG cardiac
surgery (e.g., isolated valve or aortic repair surgery). Overall,
only 27 (8%) of the OHS were non-CABG procedures. We
mandated the inclusion of only those patients who had both
carotid and OHS procedures at our institution, in part to
eliminate possible bias related to operator expertise or choice
of approach and in part to establish a known intent-to-treat
denominator for staged procedures.

Carotid revascularization and OHS. The approach to
carotid revascularization was approved by a team of cardio-
logists and vascular and cardiac surgeons according to medical
practice at that time. Individuals who underwent staged CAS-
OHS were also examined by a neurologist before CAS and
thereafter on a scheduled basis according to the carotid
stenting protocol. However, for staged and combined CEA-
OHS, neurologists were consulted on an as-needed basis.
CEA was performed with patients under general anesthesia in
both staged and combined groups. Intraoperative shunting
during CEA and carotid patching were performed at the
discretion of the vascular surgeon. An embolic protection
device was used during CAS in all patients once available
(82%). Cardiac enzymes (creatinine kinase–myocardial band
or troponin T) were routinely measured in the first 24 h after
CEA or CAS in the staged groups and within 24 h after OHS
in all patients. In the staged CEA-OHS group, OHS was
performed as early as possible; in contrast, staged CAS-OHS
patients were placed on mandatory 3 to 4 weeks of antiplatelet
treatment with aspirin and clopidogrel with consequent delay
of OHS unless worsening car-
diac symptoms necessitated early
OHS. Clopidogrel was discon-
tinued 5 days before OHS in most
patients. Cardiopulmonary bypass
(on-pump) and aortic clamping were
used in the majority of OHS procedures in all 3 groups
(Table 1).

Endpoints. The primary endpoint
was a composite of all-cause
death, stroke, and MI. Secondary
endpoints were components of
the primary endpoint. Median
follow-up for the entire cohort was
3.7 years from the time of
CEA or CAS. Twenty-five per-
cent had follow-up for over 7 years
with 10% over 10 years. Stroke
was defined as a new or worsening focal neurological event
that persisted for >24 h. MI within 72 h after OHS was based
on serum creatine kinase–myocardial band or troponin T
level >5 times the upper limit of normal in the presence of
new pathological Q-wave, new left bundle branch block, or
angiographic evidence of MI based on the universal definition
of MI (10). However, beyond this period and during the
interstage interval in staged CEA and CAS-OHS groups, MI
was diagnosed using serum creatine kinase–myocardial band
or troponin T level >3 times the upper limit of normal in the
presence of symptoms of ischemia or new electrocardio-
graphic ST–segment elevation or depression >1 mm in at least
2 contiguous leads or new left bundle branch block.

Data. To obtain the 3 study cohorts, we first used the
World Health Organization International Classification of
Diseases codes for CEA and CAS supplemented by our
carotid stent registry (11) to identify all carotid revascular-
izations performed during the study period at our institution.
We then merged these data with our Cardiovascular Infor-
mation Registry (CVIR) (12) to identify OHS within 90
days after carotid revascularization. The CVIR provides data
obtained prospectively from all cardiac surgeries performed at
Cleveland Clinic. Individuals who had CEA or CAS after
OHS were not included. Patient demographic characteris-
tics, extent of coronary disease, type of OHS performed, and
clinical outcomes were obtained from the CVIR. A manual
chart review was subsequently undertaken to obtain carotid
disease symptom status and carotid imaging data and, in
addition, to verify all interstage as well as post-OHS stroke
and MI events. The data from chart review was collected and
managed using REDCap electronic data capture tools hosted
at our institution (13). To accurately ascertain MI and stroke
events that may have occurred outside our institution, all
outpatient follow-up notes were carefully reviewed for such
documentation using our electronic medical record database
until the last follow-up date. We further supplemented
our data by telephone interviews when necessary. All-cause

Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG</td>
<td>coronary artery bypass grafting</td>
</tr>
<tr>
<td>CAS</td>
<td>carotid artery stenting</td>
</tr>
<tr>
<td>CEA</td>
<td>carotid endarterectomy</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CVIR</td>
<td>Cardiovascular Information Registry</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>NIS</td>
<td>National Inpatient Sample</td>
</tr>
<tr>
<td>OHS</td>
<td>open heart surgery</td>
</tr>
<tr>
<td>SSDI</td>
<td>Social Security Death Index</td>
</tr>
</tbody>
</table>
mortality was determined by passive follow-up using the patient’s Social Security number and the Social Security Death Index (SSDI) (14,15). Use of these data for research was approved by the Cleveland Clinic Institutional Review Board, with patient consent waived.

INTERSTAGE DEATH. Because this was an intention-to-treat analysis, it was important that we identify individuals in the staged groups who underwent CEA or CAS but died within 90 days before their planned OHS. For this, we used the SSDI to first identify all deaths within 90 days after every CEA or CAS performed at our institution during the study period. This was followed by a chart review to determine whether these individuals were scheduled for OHS at the time of carotid revascularization. Individuals so identified were included in their respective cohorts. The Carotid Stent Registry was additionally used to verify deaths among CAS patients within 90 days.

Statistical analysis. BASELINE CHARACTERISTICS. Baseline characteristics of the 3 groups were compared using chi-square test for categorical variables and Kruskal-Wallis nonparametric test for continuous variables. Most baseline characteristics did not differ significantly among the 3 groups (Table 1). Specifically, the prevalence of symptomatic carotid disease,

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Staged CEA-OHS (n = 45)</th>
<th>Combined CEA-OHS (n = 195)</th>
<th>Staged CAS-OHS (n = 110)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic and comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>72 ± 9 (45)</td>
<td>70 ± 8 (195)</td>
<td>71 ± 9 (110)</td>
<td>0.11</td>
</tr>
<tr>
<td>Female</td>
<td>11/45 (24)</td>
<td>57/195 (29)</td>
<td>31/110 (28)</td>
<td>0.81</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37/45 (82)</td>
<td>171/195 (88)</td>
<td>98/110 (89)</td>
<td>0.50</td>
</tr>
<tr>
<td>Pharmacologically treated diabetes</td>
<td>12/43 (28)</td>
<td>79/194 (41)</td>
<td>30/104 (29)</td>
<td>0.07</td>
</tr>
<tr>
<td>Diabetes requiring insulin</td>
<td>3/43 (7)</td>
<td>25/193 (13)</td>
<td>10/104 (10)</td>
<td>0.44</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>9/45 (20)</td>
<td>37/195 (19)</td>
<td>25/110 (23)</td>
<td>0.74</td>
</tr>
<tr>
<td>Smoking</td>
<td>40/44 (91)</td>
<td>144/194 (74)</td>
<td>84/109 (77)</td>
<td>0.06</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>5/45 (11)</td>
<td>16/195 (8)</td>
<td>5/110 (5)</td>
<td>0.30</td>
</tr>
<tr>
<td>History of peripheral arterial disease</td>
<td>17/42 (40)</td>
<td>68/195 (35)</td>
<td>38/104 (37)</td>
<td>0.78</td>
</tr>
<tr>
<td>History of MI</td>
<td>27/42 (64)</td>
<td>96/195 (49)</td>
<td>53/104 (51)</td>
<td>0.21</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>13/45 (29)</td>
<td>56/195 (29)</td>
<td>35/110 (32)</td>
<td>0.84</td>
</tr>
<tr>
<td>History of atrial fibrillation/flutter</td>
<td>7/37 (19)</td>
<td>6/155 (4)</td>
<td>10/89 (11)</td>
<td>0.01</td>
</tr>
<tr>
<td>History of ventricular arrhythmia</td>
<td>8/37 (22)</td>
<td>15/155 (10)</td>
<td>8/89 (9)</td>
<td>0.08</td>
</tr>
<tr>
<td>History of OHS</td>
<td>14/45 (31)</td>
<td>15/195 (8)</td>
<td>30/110 (27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>47 ± 11 (44)</td>
<td>48 ± 12 (185)</td>
<td>48 ± 11 (98)</td>
<td>0.48</td>
</tr>
<tr>
<td>CEA and CAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of TIA</td>
<td>9/44 (20)</td>
<td>43/194 (22)</td>
<td>27/110 (25)</td>
<td>0.83</td>
</tr>
<tr>
<td>History of stroke</td>
<td>6/44 (14)</td>
<td>21/194 (11)</td>
<td>24/110 (22)</td>
<td>0.03</td>
</tr>
<tr>
<td>Previous carotid revascularization</td>
<td>5/45 (11)</td>
<td>13/195 (7)</td>
<td>20/110 (18)</td>
<td>0.01</td>
</tr>
<tr>
<td>Contralateral carotid 80%–99% stenosis</td>
<td>2/45 (4)</td>
<td>22/195 (11)</td>
<td>6/109 (6)</td>
<td>0.13</td>
</tr>
<tr>
<td>Contralateral carotid occlusion</td>
<td>7/45 (16)</td>
<td>24/195 (12)</td>
<td>13/109 (12)</td>
<td>0.81</td>
</tr>
<tr>
<td>Symptomatic carotid stenosis on the intervened side</td>
<td>10/45 (22)</td>
<td>32/195 (16)</td>
<td>24/110 (22)</td>
<td>0.42</td>
</tr>
<tr>
<td>OHS*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-vessel coronary artery disease</td>
<td>28/45 (62)</td>
<td>115/187 (61)</td>
<td>52/90 (58)</td>
<td>0.81</td>
</tr>
<tr>
<td>Left main disease</td>
<td>14/41 (34)</td>
<td>64/166 (39)</td>
<td>28/83 (34)</td>
<td>0.71</td>
</tr>
<tr>
<td>Unstable angina at admission for OHS</td>
<td>6/42 (14)</td>
<td>32/195 (16)</td>
<td>3/104 (3)</td>
<td>0.003</td>
</tr>
<tr>
<td>MI at admission for OHS</td>
<td>9/42 (21)</td>
<td>15/195 (8)</td>
<td>1/104 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery bypass graft surgery</td>
<td>35/42 (83)</td>
<td>187/195 (96)</td>
<td>92/104 (88)</td>
<td>0.006</td>
</tr>
<tr>
<td>Aortic valve surgery</td>
<td>6/42 (14)</td>
<td>43/195 (22)</td>
<td>35/104 (34)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mitral valve surgery</td>
<td>13/42 (31)</td>
<td>19/195 (10)</td>
<td>19/104 (18)</td>
<td>0.001</td>
</tr>
<tr>
<td>Any aortic root or ascending aorta or arch surgery</td>
<td>0/42 (0)</td>
<td>11/195 (6)</td>
<td>15/104 (14)</td>
<td>0.003</td>
</tr>
<tr>
<td>Any atrial fibrillation procedure</td>
<td>3/42 (7)</td>
<td>1/195 (0.5)</td>
<td>9/104 (9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Congenital ASD/PFO suture closure</td>
<td>3/42 (7)</td>
<td>1/195 (0.5)</td>
<td>2/104 (2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Aortic cross clamp</td>
<td>40/42 (95)</td>
<td>170/195 (87)</td>
<td>89/104 (86)</td>
<td>0.26</td>
</tr>
<tr>
<td>Cardiopulmonary bypass</td>
<td>41/42 (98)</td>
<td>174/195 (89)</td>
<td>90/104 (87)</td>
<td>0.14</td>
</tr>
<tr>
<td>Circulatory arrest</td>
<td>0/42 (0)</td>
<td>7/195 (4)</td>
<td>10/104 (10)</td>
<td>0.02</td>
</tr>
<tr>
<td>Intra- or post-operative intra-aortic balloon pump</td>
<td>0/42 (0)</td>
<td>3/195 (2)</td>
<td>2/110 (2)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Values are mean ± SD (n representing available patient numbers) or n/N (%) (representing available patient number). *Staged CEA-OHS (n = 42) and staged CAS-OHS (n = 104) had 3 and 6 interstage deaths, respectively.

ASD = atrial septal defect; CAS = carotid artery stenting; CEA = carotid endarterectomy; MI = myocardial infarction; OHS = open heart surgery; PFO = patent foramen ovale; TIA = transient ischemic attack.
contralateral 80% to 99% carotid stenosis, and contralateral carotid occlusion were similar. However, individuals in the staged CAS-OHS group had more previous strokes \((p = 0.03)\) and carotid revascularization procedures \((p = 0.01)\). Additionally, they more frequently underwent complex OHS consisting of CABG combined with aortic valve \((p = 0.02)\) or aortic repair surgery \((p = 0.003)\). To adjust for these differences in baseline characteristics, we used propensity score methodology based on 31 variables (Online Appendix). Because there are 3 groups, we used polytomous logistic regression analysis to generate the propensity model. Doing so guarantees that the calculated set of probabilities representing the 3 propensity scores for each patient total 100%.

**TIME-TO-EVENT ANALYSIS.** Time zero for all time-to-event analyses was the time of CEA or CAS. Freedom from events was assessed nonparametrically by the Kaplan-Meier method (Fig. 1) and parametrically using a multiphase hazard model that assumed nonproportional hazards over time (16) (Online Appendix). Two types of time to event analysis were performed. The first was an intention-to-treat assessment of the 3 strategies from time zero without regard to when OHS was performed. The second analysis treated OHS as a time-varying covariable for the staged approaches. However, a time-varying covariable generally enters such analysis as a single step change in risk (hazard), and events after OHS do not behave in this simple fashion. Therefore, we borrowed from the industrial arena the so-called modulated renewal method for incorporating a time-varying covariable. In such an analysis, time zero is reset at the time of OHS, allowing the early high-risk phase of hazard to peak and then decline in a manner that fit the data well. Such an analysis creates virtually 5 mutually exclusive patient subgroups because the staged CEA-OHS and staged

![Figure 1 Unadjusted Comparison of Primary Composite Endpoint and Death in the Study Population According to Approach](image-url)

**Figure 1** Unadjusted Comparison of Primary Composite Endpoint and Death in the Study Population According to Approach

(A) Kaplan-Meier curves for the primary composite endpoint are shown for the 3 approaches with CEA or CAS as time zero. The staged CAS-OHS approach was associated with significantly lower composite outcomes overall (log-rank \(p < 0.001\)). (B) The 3 groups had similar rates of death (log-rank \(p = 0.49\)). (C) Composite outcomes stratified by OHS among staged CEA-OHS and staged CAS-OHS patients (time zero reset at OHS). The composite events during the period before OHS (interstage) in the staged CEA-OHS group explain the significant differences seen in A. The interstage events are better illustrated in the expanded view (D). CAS = carotid artery stenting; CEA = carotid endarterectomy; OHS = open heart surgery.
CAS-OHS approaches each have 2 periods of risk (interstage or before OHS and after OHS): 1) staged CAS, before OHS; 2) staged CAS, after OHS; 3) staged CEA, before OHS; 4) staged CEA, after OHS; and 5) combined CEA-OHS. In presenting analyses of modulated renewal datasets, we specify the specific contrasts of interest, obtained by selecting 1 of these 5 subgroups as the reference group and incorporating the remaining 4 subgroups in the analysis. We clearly identify the reference subgroup for specific contrasts. The results are presented as adjusted hazard ratio (HR) with 95% confidence interval (CI).

COMPETING RISKS ANALYSIS. For staged patients, competing risks analyses were conducted to understand how a composite event before OHS competed with OHS within 90 days after CEA or CAS (all patients were expected to have OHS within 90 days by inclusion criteria) (Fig. 2). In this analysis, freedom from each event was estimated by a non-parametric product limit method (17) and the hazard for each competing event was estimated by the parametric multiphase hazard method.

RISK-ADJUSTED COMPARISON OF ENDPOINTS. Using propensity score obtained from a parsimonious propensity model with 31 baseline variables (Online Tables 1 and 2), a baseline risk-adjusted comparison of 3 groups was performed for composite endpoint and death. A 5-fold multiple imputation was used to handle missing data (18). The C-statistic was indicative of good discrimination (0.84). The propensity adjusted models were verified by performing a subgroup analysis of staged CEA and CAS-OHS cohorts using propensity matching (Online Fig. 3). In this comparison, there were 32 matched pairs that represented 71% of the staged CEA-OHS cohort. The hazard plots for each of the 3 groups using propensity-adjusted multiphase hazard function modeling demonstrated overlapping early and late hazard phases (Fig. 3). Hence, group comparisons were performed simultaneously for both phases. Nevertheless, the analyses of early and late events were presented separately, given their clinical usefulness. Furthermore, to accurately interpret the results during the early hazard phase in the 2 staged cohorts, separate comparisons were conducted for interstage composite outcomes and death. All analyses were performed using SAS statistical software version 9.2 (SAS Institute, Cary, North Carolina). A detailed description of the statistical methods used is provided in the Online Appendix.

Results

Interstage events with the 2 staged approaches. The median staging intervals for CEA-OHS and CAS-OHS were 14 (interquartile range, 6 to 43) days and 47 (interquartile range, 39 to 61) days, respectively. Of the 9 interstage deaths, 3 occurred in staged CEA-OHS and 6 in staged CAS-OHS (p = 0.77) (Table 2). The staged CEA-OHS group experienced significantly higher interstage MI compared with staged CAS-OHS (24% vs. 3%; p < 0.001), but interstage strokes were similar (Table 2). Hence, interstage composite events differed significantly between staged CEA-OHS and CAS-OHS cohorts (p < 0.001) (Table 2, Fig. 1D). In a propensity-adjusted analysis, staged CAS-OHS had significantly lower risk of interstage composite events (Table 3). Similar results were obtained using propensity-matched analysis (adjusted HR: 0.33, 95% CI: 0.11 to 0.96;
Interstage deaths were similar between the 2 groups (Online Table 4).

In competing-risks analyses, the composite events peaked in the perioperative period after CEA (Fig. 2A) before the planned OHS, driven mainly by interstage MI (Online Fig. 1); however, this did not occur in the staged CAS-OHS group (Fig. 2B). Furthermore, in propensity-adjusted analysis, the interstage interval compared with the rest of the early hazard phase marked a period of significant risk of composite events with staged CEA-OHS (adjusted HR: 5.47, 95% CI: 1.98 to 15.17; p = 0.001), although this was not noted with staged CAS-OHS (adjusted HR: 0.95, 95% CI: 0.37 to 2.48; p = 0.92).

**Comparison of all 3 approaches.** **EARLY HAZARD PHASE.** Using the conventional time interval of 30-days post-OHS (inclusive of interval deaths), both staged CAS-OHS and combined CEA-OHS patients had similar unadjusted composite event rates that were significantly lower compared with staged CEA-OHS patients (p = 0.003). This was for the most part related to more interstage MIs with staged CEA-OHS (p < 0.001) (Table 2). Despite the similarity in composite outcomes between staged CAS-OHS and combined CEA-OHS patients at 30 days post-OHS, the former had more MIs (mostly interstage), whereas the latter experienced more strokes perioperatively (Table 2, Online Fig. 2). Based on hazard plots using the multiphase model (Fig. 2A), the period of early risk was substantially longer and predominated up to approximately 1 year for all groups. During this time period, the unadjusted composite event rates among the 3 groups demonstrated similar trends, with the staged CEA-OHS having the highest risk (Table 2).

In propensity-adjusted analysis with the intention-to-treat approach, the early-phase risk of the composite endpoint was similar with both staged CAS-OHS and combined CEA-OHS (adjusted HR: 0.99, 95% CI: 0.61 to 1.62; p = 0.97) (Table 3). Among the 3 groups, staged CEA-OHS patients experienced the highest risk. With modulated renewal at OHS, a significantly higher interstage risk was seen with staged CEA-OHS (adjusted HR: 3.74, 95% CI: 1.78 to 7.89; p < 0.001) but not with staged CAS-OHS (adjusted HR: 0.76, 95% CI: 0.33 to 1.76; p = 0.52) when both were compared with combined CEA-OHS (Table 3). Of note, the period after OHS did not differ significantly among all 3 groups during the early phase (Table 3). Similar propensity-adjusted analysis for mortality revealed no differences (Online Table 4).

**LATE HAZARD PHASE.** Beyond the early hazard phase (>1 year), staged CAS-OHS patients experienced significantly lower risk of composite outcomes compared with combined CEA-OHS patients (adjusted HR: 0.35, 95% CI: 0.18 to 0.70; p = 0.003) and staged CEA-OHS patients (adjusted HR: 0.33, 95% CI: 0.15 to 0.77; p = 0.01 (Table 3). However, staged CEA-OHS and combined CEA-OHS had a similar risk of composite outcomes (adjusted HR: 1.05, 95% CI: 0.57 to 1.96; p = 0.87) (Table 3). There were no differences in mortality among the 3 groups (Online Table 4).

**Discussion**

Among the 3 common approaches in the management of concomitant severe carotid and coronary artery disease, our
results demonstrate no significant difference in composite outcomes between staged CAS-OHS and combined CEA-OHS in the short term. However, beyond 12 months, the staged CAS-OHS option appears to be a better choice. Staged CEA-OHS has the highest risk during both early and late phases. These findings were consistent regardless of multiple adjustments using propensity score and propensity matching and adjusting for interstage events among the staged groups. Competing risks and multiphase analyses with modulated renewal clearly highlighted the importance of interstage interval for the staged approaches. During this interval, staged CEA-OHS, unlike staged CAS-OHS, was associated with a significantly higher risk of interstage MI given the presence of concomitant severe coronary artery disease.

The staged CAS-OHS and combined CEA-OHS groups had similar early phase composite outcomes. However, the staged CAS-OHS group had more interstage MIs, whereas the combined CEA-OHS group experienced more periprocedural strokes (Table 2). Furthermore, staged CAS-OHS was associated with fewer late-phase composite events, mainly driven by lower mortality (Tables 2 and 3). Although the exact mechanism for the long-term mortality advantage of staged CAS-OHS over combined CEA-OHS is not known, it is possible that the greater number of periprocedural (7% vs. 2%) and up to 1 year (8.7% vs. 1.8%) strokes seen with combined CEA-OHS could partially explain this finding. The differential risk of stroke and MI seen with the 2 approaches is an important finding that should be discussed with the patient and considered when selecting the best approach to treat severe combined carotid and coronary artery disease.

This study is unique for several reasons. Given the non-proportional nature of risk over time, a multiphase hazard model was used rather than the more conventional Cox model. This enabled stratification of risk into 2 distinct, but overlapping early and late hazard phases. Importantly, the duration of the early hazard phase (1 year) indicated that 30-day or in-hospital outcome comparisons may be inadequate. Furthermore, with staged approaches, published data to date have failed to account for the impact of interstage events on future outcomes. This was addressed in our study using OHS as a time-varying covariable supplemented by a modulated renewal process that enables the inclusion of interstage events as a risk factor for outcomes after OHS. Our analysis indicates that the interstage events are extremely important and explain the significant outcome differences among the 3 approaches. Given the greater number of interstage MIs with the staged CEA-OHS strategy, a less invasive approach using CAS or a combined CEA-OHS would significantly decrease this risk. Despite the availability of 3 different approaches in this setting, studies thus far have not reported on simultaneous risk-adjusted 3-group comparison using a comprehensive time-to-event methodology. However, 2-group comparisons reported by Gopaldas et al. (7), Ziada et al. (8), and Timaran et al. (9) provide useful insights despite important limitations.

Ziada et al. (8) compared 30-day outcomes among staged CAS-OHS (n = 56) and combined CEA-OHS (n = 112) groups. A trend toward fewer strokes or MIs was noted with CAS-OHS after propensity adjustment (p = 0.06), whereas no difference was seen for combined death, MI, or stroke (p = 0.12) (8). Our study extends these findings by the addition of a staged CEA-OHS group, a larger sample size, greater use of embolic protection devices (82% vs. 14%), and time-to-event analysis accounting for interstage events.

Timaran et al. (9) similarly compared in-hospital outcomes with staged CAS-OHS (n = 887) and combined CEA-OHS (n = 26,197) using the National Inpatient Sample (NIS) database. Despite the large sample, the data were limited by noninclusion of interstage death and MI. In adjusted multivariable analysis, the stroke risk increased by 66% with the combined CEA-OHS strategy. Likewise, the combined CEA-OHS group experienced more strokes than the staged CAS-OHS group in our study, with a trend toward significance (p = 0.06) despite a higher baseline prevalence of stroke among the latter.

For the 2 CEA-based approaches, Gopaldas et al. (7) found no significant difference for in-hospital death and stroke in a multivariable analysis using the NIS database. However, interstage death and MI were not included. The inclusion of interstage events in our analysis demonstrate increased risk with staged CEA-OHS compared with combined CEA-OHS, albeit in the short term.
The majority of combined CEA-OHS procedures are performed electively: 76% in our study and 77% nationwide (NIS data) (9). Hence, CAS-OHS would be a feasible option for most patients. Based on the findings of this study, we believe that staged CAS-OHS should be considered a first-line strategy if the 3- to 4-week delay to OHS is clinically acceptable. Whether multivessel percutaneous coronary intervention in conjunction with CAS is better or similar to CABG in this specific patient population is a subject that needs to be addressed in the future.

**Study limitations.** Despite addressing several limitations with the available literature, this is a single-center study, and the decision regarding the choice of procedure must always take into account institutional expertise. Although our results are based on prospectively collected data, this is a retrospective study and therefore lacks the advantages of a double-blind, randomized trial that may account for unknown confounders. To answer the question of confounding related to better operator experience and increased adoption of CAS over time, we included the interval from 1997 to date of CEA or CAS procedure in the propensity score analysis. The decision to limit the staging interval to 90 days among the staged cohorts is rather arbitrary. We believe that most patients with significant coronary disease would have undergone OHS within this time window. Also, the cause of death could not be reported because such data were not available through the SSDI. Finally, the lack of a control group with no carotid intervention is another limitation that may be difficult to overcome in contemporary practice.

**Conclusions**

The study found staged CAS-OHS to be comparable to the combined CEA-OHS approach in the short-term risk of death, stroke, or MI. However, beyond the first year, staged CAS-OHS is associated with a significantly lower composite risk. Staged CEA-OHS poses a substantial risk of interstage MI in the OHS population and hence should be avoided if possible. In choosing between staged CAS-OHS and combined CEA-OHS, the increased risk of interstage MI with the former and perioperative stroke with the latter is an important consideration despite similar risks for the early composite endpoint.

<table>
<thead>
<tr>
<th><strong>Table 3</strong> Propensity-Adjusted 2-Staged Group and 3-Group Comparisons for the Primary Composite Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comparison of 2-staged approaches: intention to treat with modulated renewal at OHS</strong> (n = 155)</td>
</tr>
<tr>
<td><strong>Early hazard phase</strong></td>
</tr>
<tr>
<td>Staged CEA before OHS vs. staged CEA-OHS</td>
</tr>
<tr>
<td>Late hazard phase</td>
</tr>
<tr>
<td>Staged CAS-OHS vs. staged CEA-OHS</td>
</tr>
<tr>
<td><strong>Comparison of all 3 approaches: intention to treat (N = 350)</strong></td>
</tr>
<tr>
<td><strong>Early hazard phase</strong></td>
</tr>
<tr>
<td>Staged CEA-OHS vs. combined CEA-OHS</td>
</tr>
<tr>
<td>Staged CEA-OHS vs. combined CEA-OHS</td>
</tr>
<tr>
<td>Staged CEA-OHS vs. combined CEA-OHS</td>
</tr>
<tr>
<td><strong>Late hazard phase</strong></td>
</tr>
<tr>
<td>Staged CAS-OHS vs. combined CEA-OHS</td>
</tr>
<tr>
<td>Staged CEA-OHS vs. combined CEA-OHS</td>
</tr>
<tr>
<td>Staged CAS-OHS vs. staged CEA-OHS</td>
</tr>
</tbody>
</table>

*OHS is a time-varying covariable in the model. The modulated renewal process resets time zero at OHS for the staged CEA-OHS and staged CAS-OHS groups. Comparison restricted to the interstage interval.

In summary, the available literature and the findings of our study demonstrate a consistent pattern in favor of the staged CAS-OHS strategy in this population (8,9). Despite these data, in the United States, only 3% of patients with concomitant severe carotid and coronary artery disease undergo staged CAS-OHS (9), suggesting the need to consider revising our current strategies while we await a randomized trial.

In the management of concomitant severe carotid and coronary disease, an important argument in favor of the combined CEA-OHS approach is urgency to revascularize the coronary arteries, given that the CAS-OHS strategy incurs a delay of at least 3 to 4 weeks for dual antiplatelet therapy before OHS. However, it is important to note that the majority of combined CEA-OHS procedures are performed electively: 76% in our study and 77% nationwide (NIS data) (9). Hence, CAS-OHS would be a feasible option for most patients. Based on the findings of this study, we believe that staged CAS-OHS should be considered a first-line strategy if the 3- to 4-week delay to OHS is clinically acceptable. Whether multivessel percutaneous coronary intervention in conjunction with CAS is better or similar to CABG in this specific patient population is a subject that needs to be addressed in the future.

**Study limitations.** Despite addressing several limitations with the available literature, this is a single-center study, and the decision regarding the choice of procedure must always take into account institutional expertise. Although our results are based on prospectively collected data, this is a retrospective study and therefore lacks the advantages of a double-blind, randomized trial that may account for unknown confounders. To answer the question of confounding related to better operator experience and increased adoption of CAS over time, we included the interval from 1997 to date of CEA or CAS procedure in the propensity score analysis. The decision to limit the staging interval to 90 days among the staged cohorts is rather arbitrary. We believe that most patients with significant coronary disease would have undergone OHS within this time window. Also, the cause of death could not be reported because such data were not available through the SSDI. Finally, the lack of a control group with no carotid intervention is another limitation that may be difficult to overcome in contemporary practice.

**Conclusions**

The study found staged CAS-OHS to be comparable to the combined CEA-OHS approach in the short-term risk of death, stroke, or MI. However, beyond the first year, staged CAS-OHS is associated with a significantly lower composite risk. Staged CEA-OHS poses a substantial risk of interstage MI in the OHS population and hence should be avoided if possible. In choosing between staged CAS-OHS and combined CEA-OHS, the increased risk of interstage MI with the former and perioperative stroke with the latter is an important consideration despite similar risks for the early composite endpoint.

**References**


Key Words: carotid artery stenting ■ carotid endarterectomy ■ open heart surgery.

APPENDIX

For an expanded methods section and supplemental tables and figures, please see the online version of this article.