Patients With Severe Asymptomatic Carotid Artery Stenosis Do Not Have a Higher Risk of Stroke and Mortality After Coronary Artery Bypass Surgery

Michael Mahmoudi, MD, PhD; Peter C. Hill, MD; Zhenyi Xue, MS; Rebecca Torguson, MPH; Gholam Ali, MD; Steven W. Boyce, MD; Ammar S. Bafi, MD; Paul J. Corso, MD; Ron Waksman, MD

Background and Purpose—Stroke development is a major concern in patients undergoing coronary artery bypass grafting (CABG). Whether asymptomatic severe carotid artery stenosis (CAS) contributes to the development of stroke and mortality in such patients remains uncertain.

Methods—A retrospective analysis of 878 consecutive patients with documented carotid duplex ultrasound who underwent isolated CABG in our institution from January 2003 to December 2009 was performed. Patients with severe CAS (n=117) were compared with those without severe CAS (n=761) to assess the rates of stroke and mortality during hospitalization for CABG. The 30-day mortality rate was also assessed.

Results—Patients with severe CAS were older and had a higher prevalence of peripheral arterial disease and heart failure. Patients with severe CAS had similar rates of in-hospital stroke (3.4% versus 3.6%; \( P=1.0 \)) and mortality (3.4% versus 4.2%; \( P=1.0 \)) compared with patients without severe CAS. The 30-day rate of mortality was also similar between the 2 cohorts (3.4% versus 2.9%; \( P=0.51 \)).

Conclusions—Severe CAS alone is not a risk factor for stroke or mortality in patients undergoing CABG. The decision to perform carotid imaging and subsequent revascularization in association with CABG must be individualized and based on clinical judgment. (Stroke. 2011;42:2801-2805.)

Key Words: stroke rate ■ mortality rate ■ SEVERE carotid artery stenosis ■ coronary artery bypass grafting

Stroke is a catastrophic complication of coronary artery bypass grafting (CABG) with an incidence of \( \approx 2\% \). The vast majority of these strokes occur postoperatively within the first 24 hours and are associated with a mortality rate of \( \approx 25\% \). Although the etiology of postoperative stroke is multifactorial, hypoperfusion arising from a severely stenotic carotid artery or embolization from an ulcerated plaque, calcific debris from a diseased valve, or introduction of air during the procedure are important mechanisms. \( ^{2-5} \) Indeed, the risk of stroke in patients with carotid disease after CABG has been estimated at 1.8% in patients with stenoses <50%, 3.2% in patients with stenoses between 50% and 99%, and 10% in patients with contralateral occlusion. \( ^{1} \)

A number of randomized studies have demonstrated a clear benefit from carotid endarterectomy in reducing stroke risks. \( ^{6-8} \) These studies also identified the presence of symptoms, the degree of carotid artery stenosis (CAS), and the perioperative stroke/death rate as the 3 major determinants of the magnitude of this benefit. However, controversy remains regarding the optimal management of patients undergoing CABG who are also found to have severe CAS. Although the prevalence of “significant” CAS in patients undergoing CABG has been estimated to range from 2% to 20%, there is no clear consensus as to how best to manage these patients. \( ^{9} \) As a consequence, therapeutic strategies have ranged from CABG alone, staged carotid endarterectomy and CABG, synchronous carotid endarterectomy and CABG, as well as staged/synchronous carotid artery stenting. \( ^{10,11} \) This variety in approach to the presence of asymptomatic CAS in the CABG population has reflected the lack of clearcut data supporting the routine adoption of either carotid endarterectomy or carotid artery stenting in this population.

Given this paucity of data, we aimed to determine the impact of severe asymptomatic CAS on in-hospital rates of stroke and all-cause mortality, as well as the 30-day rate of all-cause mortality in patients undergoing isolated CABG.

Methods

Study Design and Patients
The study cohort comprised 878 consecutive patients who had undergone carotid duplex ultrasound before isolated CABG in our institution from January 2003 to December 2009. Patients who had
undergone procedures such as valve replacement or repair, aneu-
ysmectomy, atrial septal defect closure, or aortic operations were
excluded to create a homogenous group of patients. Our institutional
preoperative CABG guidelines call for preoperative carotid duplex
ultrasound in patients with a previous history of transient ischemic
attack or stroke, carotid endarterectomy or carotid artery stenting,
previously documented CAS >50%, or carotid bruits on physical
examination. Every carotid duplex ultrasound was reported by a
team of attending physicians with a special interest in intravascular
ultrasound who were not aware of any patient’s potential participa-
tion in any particular study. Severe CAS was identified in 117 of
these patients. We compared the in-hospital stroke and all-cause
mortality rates as well as the 30-day all-cause mortality rate in these
patients with those who had CAS <75%. Thirty-day follow-up was
completed in all patients. All patients provided written, informed
consent. The study complied with the Declaration of Helsinki for
investigation in human beings and was approved by the institutional
ethics committee of Washington Hospital Center.

Operative Techniques
After routine anesthesia and intraoperative monitoring, on-pump
CABG was performed via standard median sternotomy, extracorpo-
real circulation, and myocardial protection methods. Partial cross-
clamping of the aorta was used to perform anastomoses. Myocardial
protection was obtained with anterograde and retrograde cardiolple-
ga, as chosen by the operating surgeon. The patients were cooled to
34°C. Air was evacuated from the heart/aorta through an aortic
needle vent. Off-pump CABG was performed via either median
sternotomy or an anterior or lateral minimally invasive direct CAB
approach. Indications for these approaches and selection criteria for
off-pump CABG have been described elsewhere.12,13

Analyzed Clinical Parameters
The analyzed clinical parameters were in-hospital rates of stroke
and all-cause mortality and the 30-day rate of all-cause mortality. A
dedicated data coordinating center (Data Center, MedStar Health
Research Institute, Washington, DC) performed all data manage-
ment and analyses. The prespecified clinical and laboratory data during
hospitalization were obtained from hospital charts by a dedicated
Data Center, MedStar Health Hospitalization were obtained from hospital charts by a dedicated
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Definitions
CAS was expressed as the percentage of luminal narrowing, with the
arterial lumen distal to the stenosis as the reference diameter. Severe
CAS was defined as luminal narrowing ≥75%. Stroke was defined as
any neurologic deficit of abrupt onset caused by a disturbance in
cerebral blood supply that did not resolve within 24 hours. The
majority of strokes were confirmed by an independent neurologist
and/or by appropriate brain imaging. Dyslipidemia was defined as a
fasting cholesterol value >250 mg/dL or the use of lipid-lowering
therapy. Hypertension was defined as a blood pressure >140/
90 mm Hg or the use of antihypertensive therapy. Congestive heart
failure was defined as evidence of fluid retention due to cardiac
causes before admission. Perioperative myocardial infarction was
diagnosed in the presence of 2 or more of the following 4 parameters:
(1) typical angina lasting ≥20 minutes, (2) positive cardiac enzymes,
(3) changes on serial ECGs consistent with myocardial infarction,
and (4) at least 2 serial ECG tracings showing new ischemic changes.

Statistical Analysis
Statistical analysis was performed with SAS version 8.2 (SAS
Institute Inc, Cary, NC). Continuous and categorical variables were
expressed as mean ± SD and percentages, respectively. Student t
test was used to compare continuous variables, and the χ² test or Fisher
exact test was used to compare categorical variables. A probability
value ≤0.05 was considered statistically significant.

Table 1. Patients’ Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Severe Carotid Artery Stenosis (n=117)</th>
<th>Nonsevere Carotid Artery Stenosis (n=761)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>69.7±8.7</td>
<td>67.±8.8</td>
<td>0.004</td>
</tr>
<tr>
<td>Men</td>
<td>82 (70.1%)</td>
<td>500 (71.3%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Hypertension</td>
<td>106 (90.6%)</td>
<td>644 (84.6%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes</td>
<td>63 (53.8%)</td>
<td>342 (44.9%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>94 (80.3%)</td>
<td>591 (77.7%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Current smoker</td>
<td>47 (40.3%)</td>
<td>226 (29.7%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Family history of coronary artery disease</td>
<td>61 (52.3%)</td>
<td>421 (55.4%)</td>
<td>0.53</td>
</tr>
<tr>
<td>Body mass index, mean±SD, kg/m²</td>
<td>28.3±5.4</td>
<td>28.7±5.8</td>
<td>0.43</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>60 (51.3%)</td>
<td>205 (26.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preoperative creatinine, mean±SD, mg/dL</td>
<td>1.5±1.1</td>
<td>1.4±1.3</td>
<td>0.43</td>
</tr>
<tr>
<td>Previous history of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>28 (23.9%)</td>
<td>205 (26.9%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>50 (42.7%)</td>
<td>340 (44.7%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
<td>12 (10.7%)</td>
<td>91 (11.9%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Heart failure</td>
<td>29 (24.7%)</td>
<td>131 (17.2%)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Results
Patients’ baseline characteristics are summarized in Table 1. Patients with severe CAS were older and had a higher prevalence of peripheral arterial disease and heart failure. In the 878 patients who had preoperative carotid duplex ultrasound, 68.3% had bilateral stenosis <50%, 18.4% had 50% to 74% stenosis (12.2% unilateral and 6.2% bilateral), and 13.3% had ≥75% stenosis (10% unilateral and 3.3% bilateral).

The operative characteristics and in-hospital complications of the 2 cohorts are summarized in Tables 2 and 3. The 2 cohorts differed in the number of diseased coronary arteries and the urgency of CABG (Table 2). With regards to in-hospital complications, there were no significant differences in the rates of stroke (3.4% versus 3.6%; P=1.0), all-cause mortality (3.4% versus 4.2%; P=1.0), or any of the other examined clinical parameters (Table 3). The 30-day rate of all-cause mortality was also similar between the 2 cohorts (3.4% versus 2.9%; P=0.51; the Figure).

Discussion
The main findings of this single-center, retrospective registry is that in patients undergoing isolated CABG, the presence of asymptomatic, severe CAS is not associated with either an increased risk of in-hospital stroke or all-cause mortality or an increased risk of 30-day all-cause mortality.

Stroke remains a devastating complication of CABG, with an incidence of ≥2%.1 Risk factors predisposing to postoperative stroke after conventional on-pump CABG include advanced age, carotid artery disease, peripheral arterial dis-
ease, hypertension, depressed ejection fraction, manipulation of the aorta, and atrial fibrillation.14–17 Furthermore, the pathogenic mechanisms responsible for the development of postoperative stroke are thought to differ between off-pump and on-pump CABG, with systemic inflammation, disturbance of the coagulation cascade, prolonged myocardial ischemia, atrial cannulation, aortic manipulation, atrial fibrillation, and the adverse effects of cardioplegia believed to be key mediators for the development of post-on-pump CABG stroke.14–19 By contrast, myocardial stunning after off-pump CABG is thought to be a critical factor in the development of postoperative stroke in this cohort.20

The optimal therapeutic strategy for patients undergoing CABG who are found to have asymptomatic, severe CAS remains a matter of considerable debate. Current practice ranges from performing isolated CABG to synchronous/staged carotid intervention and CABG. Indeed, the American College of Cardiology/American Heart Association guidelines recommend prophylactic carotid endarterectomy (CEA) as a measure to reduce the risk of perioperative stroke in patients with severe CAS undergoing CABG. This recommendation has been based largely on the results of several randomized studies that examined the benefits of CEA over medical therapy in preventing stroke in patients with CAS.6,7 However, in patients with asymptomatic, severe CAS undergoing CABG, evidence for a protective effect of prophylactic carotid intervention is lacking, and some investigators have doubted its effectiveness as a stroke-reducing measure.

In a study of 139 consecutive patients with severe, unilateral, asymptomatic CAS undergoing CABG (73 patients having no carotid artery surgery and 66 patients having CEA), Gaudino et al21 reported no differences in the inhospital rates of stroke (0% versus 0%; P=1.0) or mortality (1.4% versus 1.5%; P>0.05). However, during follow-up (>5 years), more patients in the no carotid surgery group developed cerebral events ipsilateral to the CAS (24.3% versus 1.6%; P<0.0001), whereas 18% required carotid surgery. The authors therefore concluded that although CEA does not confer any neurologic protection in the perioperative period, carotid intervention would be favorable on the basis of logistic and economic considerations. In a smaller series of 50 patients with asymptomatic CAS ≥70% undergoing CABG without prophylactic CEA, Ghosh et al22 demonstrated no adverse cerebrovascular events within 30 days of surgery. During a median period of 68 months, the overall risk of death, cerebrovascular events, and myocardial infarction was 4% during the first 30 days postoperatively and 8% thereafter.

The low risk of perioperative stroke in patients with severe, asymptomatic, unilateral CAS undergoing CABG has been further confirmed by a number of other studies.23–25 In their retrospective study of 461 patients who underwent elective off-pump CABG after screening for CAS, Manabe et al23 identified no significant differences in the incidence of stroke or mortality in those with and without significant CAS. Similarly, in their analysis of 61 consecutive patients undergoing cardiac surgery who were found to have unilateral, asymptomatic 70% to 99% CAS, Baiou et al24 found that no patient had experienced a stroke in the perioperative period whereas 4.9% had died within 30 days of surgery, all as a consequence of myocardial infarction. Further compelling evidence against a direct causal relation between postcardiac surgery stroke and significant CAS has been provided by Li et al.25 In their cohort of 4335 patients undergoing CABG, aortic valve replacement, or both, the total stroke rate was 1.8%. Among this population, 5.3% of the strokes were of the large-vessel type, and 76.3% of strokes occurred in patients without significant CAS.

Although the quoted studies are small in sample size and nonrandomized, when they are combined with the facts that the risk of stroke in patients with severe, asymptomatic CAS undergoing CABG is relatively low, that up to 85% of patients who develop a stroke have no evidence of ipsilateral significant CAS, and that ≈80% of post-CABG stroke

### Table 2. Patients’ Operative Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Severe Carotid Artery Stenosis (n=117)</th>
<th>Nonsevere Carotid Artery Stenosis (n=761)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of diseased vessels</td>
<td>1 6 (5.1%)</td>
<td>12 (1.6%)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>2 11 (9.4%)</td>
<td>126 (16.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 100 (85.5%)</td>
<td>623 (81.8%)</td>
<td></td>
</tr>
<tr>
<td>Left main disease ≥50%</td>
<td>33 (28.2%)</td>
<td>180 (23.7%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>50 (42.7%)</td>
<td>389 (51.1%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Emergency</td>
<td>67 (78.4%)</td>
<td>372 (48.9%)</td>
<td>0.82</td>
</tr>
<tr>
<td>No. of grafts</td>
<td>1 1 (0.9%)</td>
<td>7 (0.92%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 7 (5.9%)</td>
<td>36 (4.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 28 (23.9%)</td>
<td>188 (24.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 45 (38.5%)</td>
<td>280 (36.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 26 (22.2%)</td>
<td>178 (23.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 9 (7.7%)</td>
<td>48 (6.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;6 1 (0.9%)</td>
<td>24 (3.2%)</td>
<td></td>
</tr>
<tr>
<td>On-pump surgery</td>
<td>57 (48.7%)</td>
<td>429 (56.4%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Intra-aortic balloon pump use</td>
<td>8 (6.8%)</td>
<td>40 (5.3%)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Data are presented as no. (%). SD indicates standard deviation.

### Table 3. In-Hospital Complications

<table>
<thead>
<tr>
<th>Variable</th>
<th>Severe Carotid Artery Stenosis (n=117)</th>
<th>Nonsevere Carotid Artery Stenosis (n=761)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>4 (3.4%)</td>
<td>27 (3.6%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Mortality</td>
<td>4 (3.4%)</td>
<td>32 (4.2%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Perioperative myocardal infarction</td>
<td>5 (4.3%)</td>
<td>30 (3.9%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>60 (51.3%)</td>
<td>341 (44.9%)</td>
<td>0.23</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>13 (1.7%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4 (3.4%)</td>
<td>31 (4.1%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Septicaemia</td>
<td>1 (0.9%)</td>
<td>34 (4.5%)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Data are presented as no. (%).
patients have magnetic resonance imaging evidence of multiple areas of infarction involving the posterior areas of the brain, they can make a convincing argument against a global recommendation for synchronous carotid intervention in patients with asymptomatic, severe CAS requiring CABG.

Although relatively small in sample size, our results add to the growing body of evidence arguing against routine synchronous carotid intervention in patients undergoing CABG who are also found to have asymptomatic, severe CAS. However, there is no doubt that such an approach is indicated in a selected cohort of patients, such as those with the most severe disease in association with unstable cardiac symptoms and/or significant comorbidities. A number of studies have confirmed the safety and efficacy of such a combined approach, whereas others have attributed a higher incidence of adverse events, including stroke and death, after combined procedures. However, in a landmark case-controlled study of 35,539 patients from the New York State Cardiac Database undergoing isolated CABG or combined CABG and CEA, Ricotta et al found that the major morbidity attributed to the combined approach was in fact related to patient comorbidities rather than the result of adding CEA to the CABG procedure. In addition to our main finding that in-hospital stroke and mortality rates do not differ between those with and without severe CAS undergoing isolated CABG, the stroke and mortality rates in our entire cohort are also consistent with rates reported in other series.

Clinical registries serve as excellent complements to randomized clinical studies, as the former provide critical information in a wider patient population. However, registries do suffer from well-established limitations, and ours is no exception. Our study lacks long-term follow-up, and as a consequence, the results cannot be extrapolated beyond the 30-day period. The diagnosis of postoperative stroke was often based on an independent neurologist and appropriate brain imaging, but a detailed preoperative neurololgic assessment was not performed in all patients. There was no postoperative neuropsychological testing for the assessment of subtle changes in mentation and behavior that may have resulted from multiple cerebral microinfarctions. Additionally, it is a relatively small, retrospective study, which does not allow for definitive conclusions and presents the common potential skews associated with this type of study.

Conclusions

The etiology of post-CABG stroke is complex and multifactorial. Although severe CAS may contribute to the development of this most catastrophic complication, our data add to the growing body of evidence that this role is unlikely to be a critical one in patients undergoing isolated CABG. As a consequence, until such time as level I evidence becomes available, the management of such patients must be individualized and based on sound clinical judgment.

Disclosures

None.

References


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