Is There Any Benefit From Staged Carotid and Coronary Revascularization Using Carotid Stents? 
A Single-Center Experience Highlights the Need for a Randomized Controlled Trial

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Background and Purpose—To assess the benefits of carotid artery stenting before coronary artery bypass surgery to reduce the risk of stroke occurring during the cardiac procedure.

Methods—A prospective cohort study was performed in patients undergoing carotid artery stenting before coronary artery bypass surgery, or combined bypass and valve replacement procedures, to assess the procedures effectiveness in stroke prevention. Outcome measures including 30-day post stenting and cardiac surgery neurological complication and all-cause mortality rates were assessed.

Results—A total of 52 patients were included. Two patients underwent aortic valve replacements at the same time as coronary revascularization. No neurological complications occurred because of the stenting procedure. One cardiac death not related to coronary artery bypass surgery occurred in the 30-day follow-up period for the stent procedure. An additional 6 (11.5%) outcome events (3 strokes and 3 deaths) occurred in the 30-day follow-up period after the cardiac procedure. Three patients died of cardiac causes while awaiting their cardiac bypass procedure.

Conclusions—Our results are comparable to those in patients that undergo staged or combined carotid endarterectomy before cardiac surgery. Our small cohort study adds to the limited world literature on the subject but is not sufficiently powered to recommend alterations in practice. (Stroke. 2006;37:435-439.)

Key Words: cardiac bypass ■ carotid endarterectomy ■ stents

Perioperative stroke and ischemic encephalopathy are 2 well-recognized complications of coronary artery bypass grafting (CABG) and heart valve replacement surgery. The risk of stroke in the perioperative period has remained ≈2% for the past 3 decades. The presence of carotid disease in patients undergoing coronary artery bypass surgery has been shown to increase this risk of perioperative stroke from the cardiac procedure 3-fold. This finding provided a logical reason for the initial trials of combined or staged carotid endarterectomy in these patients in an attempt to reduce perioperative mortality. The contribution of the carotid disease in direct causation of perioperative stroke has been difficult to prove. It has been hypothesized that significant carotid disease exacerbated the effects of periods of intraoperative hypotension during cardiac bypass, resulting in relative cerebral hypoperfusion causing intraoperative stroke. However, it is also conceivable that the presence of high-grade carotid disease is purely an indicator of higher cardiovascular morbidity in these patients. Intraoperative monitoring using transcranial Doppler ultrasound has demonstrated that atheroembolism occurring as a result of aortic cross-clamping is common and also contributes to the intraoperative stroke risk. It is conceivable, although unproven, that stenotic carotids may have protected a subgroup of patients from embolic neurological complications. What is now clear is that the etiology of stroke during cardiac surgery is multifactorial, and carotid stenosis is likely to play only a minor part.

Despite this, some cardiac surgeons remain reluctant to operate on patients with carotid disease and recommend combined or staged carotid endarterectomy in all patients with carotid artery disease to reduce the risks of perioperative stroke. Other centers reserve this procedure only for patients with recent neurological symptoms. Supportive data in the form of a randomized controlled trial are lacking for either of

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these management strategies. The most recent systematic review of case series of carotid endarterectomy studies suggested that little or no benefit for stroke prevention appeared to be gained by performing staged or synchronous procedures in asymptomatic individuals undergoing pump cardiac surgery.5

Carotid angioplasty as an alternative approach to managing carotid disease in these patients was originally proposed in 1997, with 2 published case series of balloon deployed carotid stents and a further retrospective series in 2002.6–8 These small case series highlighted the fact that although technically feasible neurological complications continued to occur at time of stenting and during cardiac surgery. Our center has performed a staged carotid stenting procedure for significant carotid artery stenosis in patients listed for coronary artery bypass since April 1998. Stenting techniques have developed significantly since 1998, with reductions in morbidity and mortality. However, the effect the stenting procedure has on the overall morbidity and mortality after coronary artery bypass surgery remains unclear. We reviewed our recent experience of this 2-staged approach.

Methods
All patients since 1998 found to have a significant carotid artery stenosis on duplex ultrasound criteria during preassessment for cardiac surgery were referred to the combined vascular neuroradiology multidisciplinary team. It should be noted that routine carotid duplex ultrasound screening of all patients before cardiothoracic procedures is not performed by all surgeons at our institution, and therefore not all patients with carotid stenosis meeting our criteria for intervention would have been offered stenting and be included in this review. This sample population is therefore a nonrandomized partially selected group that will bias the outcome assessment to a degree. Patients referred to the multidisciplinary team were deemed appropriate for carotid intervention if they had a severe carotid stenosis of >80% on the side of the dominant hemisphere and a combined stenosis of the carotid arteries of >150%, a recently symptomatic carotid of >70%, or contralateral occlusion and moderate stenosis >50%. All assessments were performed using the North American Symptomatic Carotid Endarterectomy Trial criteria.9 These patients then underwent archangiography to assess the origins of the carotid vessels and to confirm the degree of stenosis; additional images to confirm circle of Willis anatomy were not routine in preassessment workup of these patients. A limited number of patients did undergo MRI scanning as part of a separate ongoing MRI cerebral perfusion study, but results from these investigations were not used to make treatment decisions.10 Where treatment was being recommended for a combined stenosis of the carotid vessels of >150%, the artery supplying the dominant hemisphere was preferentially recommended for stenting. If a vessel was found to have been symptomatic within the preceding 6 months, on further detailed questioning, it was chosen for stenting. Since 1998, stenting has been the only management strategy used in our institution to treat carotid artery stenosis meeting these criteria. If patients were unsuitable for stenting, a staged or combined carotid endarterectomy was not performed as an alternative. The timing of cardiac surgery after the stenting procedure was at the discretion of the cardiac surgeon. After the introduction of routine use of clopidogrel in carotid stenting, it was recommended that this was continued for ≥14 days. Statistical analysis was performed using SPSS 12.01 software.

Stenting Technique
All procedures were performed by an interventional radiologist (T.J.C., P.A.G.). During the study period, the endovascular technique evolved to include the routine use of dual antiplatelet therapy with aspirin and clopidogrel before stent insertion as well as the use of filter cerebral protection devices. The carotid stenting technique used in our center has been described previously.11 Procedures performed in our institution since November 2002 use 600 μg glycopyrolate in place of intra-arterial atropine to prevent perioperational bradycardia and hypotension. The 8-mm or 10-mm Monorail Carotid Wallstent (Boston Scientific Corp) was used in 90% of these procedures.

Outcome Assessment
All patients were assessed before treatment, at discharge, and 30 days after the procedure by an independent stroke neurologist (M.S.R., F.M.McK., and G.S.V.). Outcome events occurring before 30 days because of an intervening cardiac procedure were also classified by a neurologist. Outcome measures including all neurological complications occurring within the first 30 days of the procedure and those associated with the cardiac procedure were included in this study. Yearly follow-up from the date of the procedure has been maintained wherever possible with direct clinical assessment or by telephone interview and review of hospital notes and death certification. Consent for data collection and storage of information on a computerized database was obtained from each patient at the time of the procedural consent. This database is registered for audit purposes in accordance with the audit procedures of our institution.

Neurological Complications
Minor stroke was defined as a new neurological deficit lasting >24 hours but <7 days. Major stroke was defined as a new neurological deficit that persists >7 days. This classification has then been subdivided at 30 days postevent into nondisabling stroke if the Oxford modified handicap score was 0 to 2 or disabling stroke if the Oxford modified handicap score was ≥3.12

Results
A total of 65 patients were referred to the multidisciplinary team for assessment of staged carotid stenting before coronary revascularization between April 1998 and July 2005. A total of 52 patients had significant carotid artery disease according to our intervention criteria that was treated before cardiac surgery. The 13 remaining patients were referred back to their cardiothoracic surgeon with a recommendation to proceed without carotid intervention because they were shown to have combined stenosis of <150% at angiography. Additional history obtained at the time of stenting revealed that 7.7% (4 of 52) of our patients had transient neurological symptoms within the preceding 6 months and, therefore, in 3 cases were treated despite the combined stenosis being <150%. All patients were due to undergo cardiac bypass surgery, and 2 patients required aortic valve replacement as well. Patient demographics of the treated patients are summarized in Table 1.

Thirty-day follow-up was performed in all patients, with 94.2% (49 of 52) undergoing the cardiac surgical procedure that had been proposed after stenting. Our long-term follow-up data range from 30 days to 5 years, with a mean follow-up of 2.1 years. All 52 patients remained event-free during and immediately after the carotid stenting procedure. Table 2 summarizes outcome events from both the stenting and cardiac bypass procedures. At the time of 30-day follow-up, excluding events related to any cardiac procedure performed within 30 days of stenting, 1 patient had died. This event occurred at 24 days during sleep at home, no postmortem was performed, and heart failure before the patient’s CABG and valve replacement procedure was the presumed...
TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n=52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>68</td>
</tr>
<tr>
<td>Male:female</td>
<td>45:7</td>
</tr>
<tr>
<td>Carotid treated left:right</td>
<td>36:16</td>
</tr>
<tr>
<td>Delay between carotid and cardiac operation (range)</td>
<td>2–60 days</td>
</tr>
<tr>
<td>Combined stenosis (mean/median/range)</td>
<td>%</td>
</tr>
<tr>
<td>Treated vessel stenosis (mean/median/range)</td>
<td>%</td>
</tr>
<tr>
<td>Contralateral preocclusive 99% or occluded 100%</td>
<td>%</td>
</tr>
<tr>
<td>Symptoms within 6 months</td>
<td>4 (7.6%)</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>40 (76.9%)</td>
</tr>
<tr>
<td>Hypercholesterolemia*</td>
<td>47 (90.4%)</td>
</tr>
<tr>
<td>Smoker (current or previous)</td>
<td>46 (88.4%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16 (30.7%)</td>
</tr>
<tr>
<td>Male:female</td>
<td>45:7</td>
</tr>
</tbody>
</table>

*Total cholesterol >5 mmol/L.

TABLE 2. Outcomes

<table>
<thead>
<tr>
<th>Events Within 30 Days of CABG</th>
<th>Events &gt;30 Days After Stent Before CABG</th>
<th>Perioperative Events Within 30 Days of CABG</th>
<th>Combined Total Outcome All Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor stroke</td>
<td>% (n) 95% CI</td>
<td>% (n) 95% CI</td>
<td>% (n) 95% CI</td>
</tr>
<tr>
<td>Major stroke</td>
<td>0 (0) 0–5.7</td>
<td>0 (0) 0–5.7</td>
<td>1.9 (1) 0.3–10.1</td>
</tr>
<tr>
<td>Stroke death</td>
<td>0 (0) 0–5.7</td>
<td>0 (0) 0–5.7</td>
<td>3.8 (2) 1.0–12.9</td>
</tr>
<tr>
<td>Other death</td>
<td>1.9 (1) 0.3–10.1</td>
<td>3.8 (2) 1.0–12.9</td>
<td>3.8 (2) 1.0–12.9</td>
</tr>
<tr>
<td>Stroke and death</td>
<td>1.9 (1) 0.3–10.1</td>
<td>3.8 (2) 1.0–12.9</td>
<td>13.5 (7) 6.6–25.2</td>
</tr>
</tbody>
</table>

cause of death. This was the only event occurring not related to a cardiac procedure occurring within 30 days of stenting. Two additional cardiac deaths occurred before the cardiac surgery being performed at 56 days and 59 days, respectively. One patient experienced delay to cardiac surgery because of worsening cardiac function, and the other experienced a fatal myocardial infarction, at another institution, 3 days before his cardiac surgery, 59 days after the stenting procedure.

Combined 30-day outcomes for the carotid stenting procedure and cardiac procedure include 3 strokes (1 minor and 2 major nondisabling), all ipsilateral to the stented vessel, 2 cardiac deaths, and 2 stroke-related deaths (1 ischemic and 1 hemorrhagic) occurring in the 30-day postoperative period for the cardiac procedure. Only 1 of these procedural strokes occurred at the time of the cardiac operation; this patient was unrousable after anesthetic and eventually died 28 days later. The 1 minor and 2 major strokes occurred between 24 hours and 48 hours after the bypass procedure. On an intention-to-treat basis and including all stroke, cardiac death, and deaths in those patients awaiting treatment, the overall event rate for stroke and all death is 19.2% (10 of 52) with an ipsilateral stroke and stroke death rate of 7.7% (4 of 52). The stroke and all-cause mortality for patients who underwent both procedures is 14.3% (7 of 49), with ipsilateral stroke and stroke death rate being 8.2% (4 of 49).

**Discussion**

The benefits of carotid intervention in symptomatic carotid disease are well documented and accepted. The recently published asymptomatic carotid surgery trial has now highlighted the benefits that endarterectomy may offer in a selected group of patients diagnosed with asymptomatic carotid stenosis. The place for carotid intervention in asymptomatic patients routinely before CABG and cardiac valve replacement remains controversial, particularly because it is still unclear what additional workload carotid intervention before coronary artery bypass surgery would place on overstretched vascular services. The most recent statistics compiled by the Society of Cardiothoracic Surgeons of Great Britain and Ireland show that 25 277 CABG procedures were performed in the United Kingdom in 2003. Limited angiographic data are available on the frequency of concurrent carotid disease in those patients undergoing CABG so direct estimates of the number of these patients requiring intervention cannot be made. However, it is known that the prevalence of significant carotid disease (>50%) in patients with triple vessel coronary disease is ≈25%, which suggests that up to 6000 procedures may be required per year in the United Kingdom for benefit to be shown from carotid intervention.

The most robust data set available in this regard is the recently published systematic review of case series and trials of endarterectomy and coronary surgery performed by Naylor et al. This work confirmed the historical data in Brener’s article from 1987. They demonstrated that stroke risk is <1.8% in patients with no significant stenosis (<50%), increasing to 5.2% in patients with bilateral carotid disease and 11.2% in patients with a unilateral carotid occlusion. These historical outcome data can be compared with studies assessing patients who have undergone combined and staged carotid endarterectomy or stenting. Published case series and systematic reviews report complication rates of stroke and death with combined and staged procedures ranging from 2.4% to 17.7%. Naylor’s systematic review suggests that the 30-day stroke risk, including both operative procedures, is 5.4% (CI, 3.4 to 7.2) for a combined and 3.7% (CI, 1.8 to 5.5) for a staged procedure. If we are to include stroke and death from any cause, the respective rates become 9.5% (CI, 7.2 to 11.8) for synchronous and 6.6% (CI, 4.4 to 8.8) for a staged procedure. These figures were derived from the selected and
limited data set available in the literature, and are therefore inherently affected by publication bias, but provided little justification for preoperative carotid intervention with endarterectomy in patients with moderate bilateral carotid disease because the complication rates for procedures are not statistically different from the natural history data available.

The use of carotid angioplasty or stenting as an alternative to carotid endarterectomy before cardiac surgery has been proposed as a less risky carotid revascularization strategy. The literature on carotid stenting contains numerous case series in which stenting is being performed as an alternative to carotid endarterectomy in “high-risk” patients outside of randomized trials. The recently published SAPPHIRE trial of stenting in high-risk patients included >80% of its patients from those with ischemic heart disease.23 The more specific literature highlighting those patients in whom the “high-risk” indication for stenting was imminent cardiac surgery is limited to 3 published case series, with a combined patient population of 109 patients.6–8 Outcome events occurred in 8.25% (9 of 109) of these patients, of which 4 were strokes, 1 resulting in death. The strokes in these reports all occurred in relation to the stenting procedure, with 6 additional deaths after the cardiac procedure.

Our combined minor stroke, major stroke, and death rate for our study group of 19.2% (10 of 52) on an intention-to-treat basis is higher than documented previously in the literature. What is not clear from previous literature is whether the 3 deaths that occurred before the cardiac procedure in our series would have been included in the analysis of whether the 3 deaths that occurred before the cardiac procedure. The strokes in these reports all occurred in relation to the stenting procedure, with 6 additional deaths after the cardiac procedure.

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Our case series of 52 patients undergoing carotid stenting concurs with previous findings from endarterectomy studies before cardiac surgery but fails to show any significant benefit in prevention of stroke or death when compared with the historical untreated data set. This is despite the fact that no complications occurred around the time of stent insertion. However, a small data set reporting 0 event rates means very little, and we must remind ourselves that complication rates from stenting could be as high as 5.7%.24,25 It is possible that the carotid procedure by adding delay to the bypass procedure in ≥3 of our patients may have contributed to their deaths of cardiac cause. The limitations of our nonrandomized observational study are recognized, but these data add to the limited world literature on stenting before cardiac surgery.

With the lack of evidence, the continued use of carotid intervention in these patients with carotid stenting is difficult to support. Ongoing studies in our center using MRI scanning and dexam reactivity testing to assess the cerebrovascular reserve, and collateral circulation via the circle of Willis, in patients undergoing carotid intervention may highlight a group of patients at higher risk for perioperative hypoperfusion during the cardiac procedure, allowing better-targeted carotid intervention in the future.10 However, there is a need for a randomized controlled trial of patients with significant carotid disease undergoing cardiac surgery with no previous carotid intervention compared with those undergoing either stenting or endarterectomy as a staged procedure. The current practice based on nonrandomized data appears to have very little impact on eventual outcomes and may result in unnecessary procedures in up to 25% of the cardiac surgery population. However, because some cardiac surgeons refuse to perform cardiac bypass procedures unless the carotid arteries have been treated, a randomized trial seems the only way to answer this question. At present, because of the reluctance of the cardiac surgeons, the decision-making process at the multidisciplinary team meeting is usually biased toward intervention without evidence to support it. We accept that a randomized study will require a considerable shift in attitudes away from the present management strategy used in many centers worldwide and may prove problematic in its first stages. Our centers management policy with regard to stenting outside of such a trial is currently under review.

References

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