A Systematic Review of Outcomes in Patients With Staged Carotid Artery Stenting and Coronary Artery Bypass Graft Surgery

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Background and Purpose—Although current guidelines state that carotid endarterectomy is probably recommended before or concomitant to coronary artery bypass grafting (CABG) in patients with carotid stenosis, significant controversies to this recommendation still persist. Carotid artery stenting has been recently introduced as an alternative revascularization modality in high-risk patients. The aim of this study was to define, based on the published information, if carotid artery stenting is beneficial in this setting.

Methods—A search of MEDLINE and a manual search of the literature from selected articles were performed. A total of 6 studies with 277 patients reporting carotid stenting followed by staged CABG were available for this clinical outcome analysis. All were retrospective and single-center studies.

Results—The mean age was 69 years; 78% were males. Asymptomatic carotid stenosis was present in 76% of patients. The mean time to CABG was 32 days. The incidence of stroke and death associated with the stent procedure was 4.7%. Only 6 patients (2.2%) developed stroke associated with CABG. The overall combined 30-day event rate after CABG, including all events during carotid artery stenting, were as follows: minor stroke, 2.9%; major stroke, 3.2%; mortality, 7.6%; and combined death and any stroke, 12.3%.

Conclusions—In this pooled analysis, the combined incidence of death and stroke in patients undergoing carotid artery stenting and staged CABG remains elevated. These results confirm that the presence of carotid stenosis is per se a marker of risk that might persists independent of its treatment. A systematic or randomized evaluation appears warranted. (Stroke. 2008;39:361-365.)

Key Words: carotid stenosis □ carotid stent □ coronary bypass surgery

It is well established that the presence of carotid artery stenosis is a significant predictor of poor outcomes in patients undergoing coronary bypass graft surgery (CABG). The incidence of coexisting coronary and carotid artery disease varies between 2% and 14% and approximately 8% of patients undergoing CABG have a significant stenosis in an extracranial carotid artery. Current guidelines state (Class IIa; Level of Evidence C) that carotid endarterectomy (CEA) is probably recommended before CABG or concomitant to CABG in patients with symptomatic carotid stenosis or in asymptomatic patients with a unilateral or bilateral internal carotid stenosis of 80%. However, the optimal management of these patients still remains controversial in clinical practice. A recent systematic review of 97 studies, including ≈9000 patients undergoing CEA and CABG, found an incidence of 10% to 12% of death, stroke, and myocardial infarction after staged or synchronous procedures. These results have led to question the indication of a surgical approach, suggesting the need for alternative strategies and randomized information. Recently, carotid artery stenting (CAS) has been introduced as an alternative revascularization modality for patients with symptomatic or asymptomatic high-degree stenosis in the extracranial carotid arteries. Several randomized studies and registries have shown similar outcomes when compared with CEA in high-risk populations. This approach has been postulated and recently used by several groups as a less risky alternative to CEA in patients with indication for CABG. However, limited information is available in the literature to support this indication. The current study represents a review of the published information regarding outcomes in patients undergoing staged CAS followed by CABG.

Methods
A systematic review of the literature was performed. Studies were identified by an electronic search of PUBMED using advanced search options (combinations of search terms were used, including “coronary surgery,” “coronary bypass surgery,” “carotid revascularization,” “carotid stenting”), and by manual review of journals and
crossreferences of dedicated articles. Studies in which percutaneous coronary intervention was the revascularization modality were not included from the analysis. A total of 10 studies were identified.8–17 All of these identified studies, except one, included series of patients with “staged” procedures in which CAS was performed first followed by CABG. Four studies were excluded from the analysis: one because it implied a synchronous approach17 and the other 3 because they represented consecutive reports from the same institution with different time points (including the 3 CABG). The incidence of the major events at 30 days after CABG was specified as major or minor when this information was available (eg, after CAS); otherwise, it was reported as any stroke (eg, after CABG). Myocardial infarction was excluded from the analysis because this was reported in only 3 of the 6 studies; in addition, the definitions of myocardial infarction used in these studies varied, further inducing us to omit this end point in our analysis. Based on this evaluation, no significant heterogeneity among studies was found (Figure 1).

Results
Baseline Characteristics
Table 1 summarizes the baseline demographics of patients from each of the 6 studies as well as the combined incidence. The majority of patients were male (78%) with a mean age of 69 years. There was an overall high prevalence of cardiovascular risk factors in most studies; diabetes was present in 36% of patients, 70% had hypertension, and 63% were smokers. There was a 26% prevalence of symptomatic patients having contralateral carotid occlusion. There were some differences in baseline demographics among studies. Age, gender, and the prevalence of diabetes were similar among the different studies. However, there was a higher prevalence of smokers and contralateral occlusion but lower prevalence of symptomatic patients in the study by Randal et al. There was a higher prevalence of symptomatic patients in the study by Ziada et al and a higher incidence of patients with high blood pressure in the study by Kovacic et al.

Figure 1. Heterogeneity evaluation among the different studies. Incidence of death and any stroke from CAS to 30 days post-CABG. Q=7.010; 5 degrees of freedom (P=0.220).

Statistical Analysis
Baseline characteristics were compared using χ² or Fisher exact test for categorical variables and Student t test for continuous variables. Probability values are 2-sided and a level <0.05 was considered statistically significant. The outcome data are presented as individual outcome (death, minor and major stroke) and as combined outcome (death/any stroke). Events are reported at 3 different time points to improve the understanding of the results, although the 30-days post-CABG event rate was considered the main clinical end point of the analysis. The actual main clinical outcome was estimated by combining observed results from each study and was expressed as proportion and 95% CI. Pooled estimation of the combined risk was calculated using the random effect analysis. A statistician performed all the analysis (P.W.). To test whether the reported risk in each study was greater than would be expected by chance, heterogeneity between the different studies was evaluated. This was performed using a Q test and further tested by Galbraith’s graph, which was concordant with the Q test.18 Based on this evaluation, no significant heterogeneity among studies was found (Figure 1).

Carotid Stent Procedure and Outcomes
Table 2 summarizes the clinical outcomes observed in each study. A total of 284 carotid lesions were treated in the 277 patients. Most lesions were treated with stent (n=280 [98%]). Most stents were self-expandable stents (n=258 [91%]). Overall, distal protection was used in 32% of the patients; however, utilization of distal protection significantly varied among studies (Table 1). The overall incidence of minor and major stroke associated with CAS was 2.9% and 1.1%,
respectively. A total of 4 patients (1.4%) died during the period of hospitalization for the stent procedure. Two patients had a cardiac-related death and 2 patients had a stroke-related death. The overall incidence of death and any stroke associated with CAS was 4.7% (95% CI: 3.06 to 8.77) and the incidence of death and major stroke was 1.8% (95% CI: 1.02 to 5.13).

Clinical Event After the Stent Procedure But Before Coronary Artery Bypass Grafting

The time interval between CAS, following hospital discharge, and CABG varied among studies (Table 1) with a mean of 32 days (range, 2 to 157 days). The study with the shortest mean waiting period was 15 days and the longest 69 days. During this period, a total of 6 (2.2%) patients died. All deaths were considered cardiac-related events. No strokes were reported.

Clinical Event After Coronary Artery Bypass Grafting and Overall Clinical Events

During the 30-day follow-up post-CABG, the combined incidence of death and stroke was 5.6% (95% CI: 3.61 to 9.64); 11 (4.2%) patients died and 6 (2.2%) developed a stroke.

The prevalence of the combined overall clinical events from the CAS procedures to 30 days after CABG is shown in Table 3 and Figure 2. The overall mortality rate was 7.6% (21 patients). Of the 21 deaths, 17 were reported as cardiac-related and 4 deaths were secondary to stroke. The overall stroke rate was 6.1% with 3.2% major stroke and 2.9% minor stroke. The combined prevalence of death and any stroke was 12.3%. Based on the random effect analysis, after taking into consideration the sample size of each individual study, the combined risk of death and any stroke for this pooled analysis was 10.6% (95% CI: 6.3 to 14.9; Figure 1).

Discussion

The present studies confirm the poor prognostic implications of having carotid artery stenosis in patients undergoing CABG. These poor clinical outcomes persist despite the use of carotid revascularization. In particular, we document that carotid revascularization by means of CAS before CABG carries an elevated incidence of death and stroke. These results are similar to those reported using staged CEA and CABG.19 Of note, most of the adverse events occurred after a successful carotid stent procedure, suggesting that the concomitant presence of carotid disease in patients undergoing CABG is an important marker of risk, questioning the role of carotid revascularization.

Coexistence of carotid disease in patients undergoing CABG is a common finding. The presence of CAS has been repeatedly found as a risk factor for stroke after CABG.1,20 The calculated stroke rate for an asymptomatic patient with severe unilateral carotid stenosis is 3.0%, which increases to 5.2% and 11% if bilateral disease and contralateral occlusion are present, respectively. Symptomatic patients are associated with an 8.2% incidence of stroke.19 The presence of carotid stenosis is also associated with a significant increase in CABG mortality. In a pooled analysis, surgical mortality for

Table 2. Clinical Events in Each Individual Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Minor Stroke</th>
<th>Major Stroke</th>
<th>Death</th>
<th>Minor Stroke</th>
<th>Major Stroke</th>
<th>Death</th>
<th>Major Stroke</th>
<th>Death</th>
<th>Death/Major Stroke</th>
<th>Death/Any Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babatsi</td>
<td>1996</td>
<td>12</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gross</td>
<td>1999</td>
<td>85</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>7 (8.2)</td>
<td>10 (11.7)</td>
</tr>
<tr>
<td>Lopes</td>
<td>2002</td>
<td>49</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5 (10.2)</td>
<td>8 (16.3)</td>
</tr>
<tr>
<td>Ziada</td>
<td>2005</td>
<td>56</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>4 (7.1)</td>
<td>4 (7.1)</td>
</tr>
<tr>
<td>Randall</td>
<td>2005</td>
<td>52</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>10 (19.2)</td>
<td>10 (19.2)</td>
</tr>
<tr>
<td>Kovacic</td>
<td>2005</td>
<td>23</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
<td>1 (4.3)</td>
</tr>
<tr>
<td>Combined</td>
<td>277</td>
<td>8</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>11</td>
<td>26 (9.4)</td>
<td>34 (12.3)</td>
<td></td>
</tr>
</tbody>
</table>
patients with asymptomatic >50% carotid stenosis undergoing unprotected CABG was 4.4%. \cite{21} Although the benefits of surgical revascularization of CAS in symptomatic and asymptomatic patients have been clearly demonstrated, its role in the context of patients undergoing CABG remains controversial. In fact, the presence of CAS by itself was not found to be an independent predictor of adverse clinical events. \cite{22, 23} Overall, the results of this analysis are in agreement with the current knowledge that patients with coronary artery disease and concurrent carotid artery disease are a particular high-risk group with a significant increased risk of major cardiovascular complications.

Prevention of cerebrovascular events is the main goal of performing carotid revascularization before CABG. The present study showed that after successful carotid revascularization, the incidence of any stroke after CABG was only 2.2%. Although this incidence appears to be low and encouraging, the overall incidence of any stroke combining both carotid and coronary revascularization procedures was 6.0% with an incidence of major stroke of 3.2%. Although it is difficult to predict if the incidence of stroke would have been lower if carotid revascularization would have not been performed, the overall incidence found in this analysis appears to be similar to prior reports in patients with carotid stenosis without revascularization. \cite{21, 24} This emphasizes the concept that the presence of carotid stenosis is probably a marker of more advanced atherosclerotic disease and of high risk. This also supports that the etiology of stroke is multifactorial and not only related to the presence of carotid artery disease. \cite{4} The high surgical mortality rate found in the current analysis also highlights this concept.

Timing for coronary revascularization after stenting is an important feature, even more so in the context of patients presenting with acute coronary events. The mean waiting period between interventions in this analysis was 32 days. Six patients (2.2%) died during this waiting period, all due to coronary events. This raises concerns regarding the appropriate medical management while waiting for CABG. Systemic hypotension produced by stimulation of the carotid baroreceptor may occur in patients undergoing CAS. \cite{25} The duration of hypotension can be as long as several days to weeks and may have played a role in impairing myocardial perfusion in this high-risk group of patients with advanced coronary artery disease. Thus, this may have contributed, at least in part, to the occurrence of cardiac events during the waiting period in this analysis. This suggests that close clinical and hemodynamic monitoring may be critical after successful CAS to reduce the risk of cardiac complications while waiting for CABG. Antiplatelet treatment is also of relevance during the waiting period. The current standard of care is to use dual antiplatelet therapy with aspirin and clopidogrel for 4 weeks after CAS. To avoid an increase in bleeding complications associated with dual antiplatelet treatment during CABG, and the thrombotic complications after CAS if dual antiplatelet treatment is prematurely discontinued, patients need to wait approximately 30 days between interventions. \cite{26} The balance between the bleeding/thrombotic risk associated with CAS and the risk for a coronary event while waiting for surgery is difficult to determine and, to date, there is no clear consensus on the optimal management of these patients. Some groups have proposed performing CABG the same day after successful CAS using only aspirin and heparin and to start clopidogrel immediately after CABG. Others have proposed the use of short-acting glycoprotein IIb/IIIa inhibitors during CAS and performing CABG 4 to 6 hours after stenting. \cite{27} Ultimately, some groups have proposed performing CABG as soon as needed based on the clinical presentation of the patient, irrespective of the use of dual antiplatelet treatment. The bleeding versus thrombotic concerns, as well as the potential cardiac complications of post-CAS hypotension, raise the question of whether concomitant or immediate versus staged interventions is the best approach when CAS is elected as the revascularization modality. These are important unresolved issues that need to be taken into consideration when defining the most appropriate treatment as well as planning a randomized evaluation that will provide the definitive answers to the role of CAS in this growing patient population.

**Limitations**

These data are derived from a selected and limited data set available in the literature and therefore affected by publication bias. Although the number of patients in each individual study is rather small and there were some differences in baseline characteristics, the results were comparable based on the heterogeneity analysis suggesting valid conclusions. Most

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**Table 3. Combined Incidence (%) of Major Clinical Events After Revascularization**

<table>
<thead>
<tr>
<th></th>
<th>Minor Stroke</th>
<th>Major Stroke</th>
<th>Death</th>
<th>Death/Major Stroke</th>
<th>Death/Any Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post CAS (at discharge)</td>
<td>2.9</td>
<td>1.1</td>
<td>1.4</td>
<td>1.8</td>
<td>4.7</td>
</tr>
<tr>
<td>After CAS, before CABG</td>
<td>0</td>
<td>0</td>
<td>2.2</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>30 days post-CABG</td>
<td>NA</td>
<td>2.2</td>
<td>4.1</td>
<td>5.6</td>
<td>5.6</td>
</tr>
<tr>
<td>Overall</td>
<td>2.9</td>
<td>3.2</td>
<td>7.6</td>
<td>9.4</td>
<td>12.3</td>
</tr>
</tbody>
</table>

Figure 2. Major clinic events from CAS to 30 days after CABG.
of the stent procedures were performed in the initial phase of the development of this new revascularization alternative with a significant proportion of interventions performed without distal protection. Although it appears clear that operator experience and the use of distal protection devices are important factors of procedural success, the incidence of stroke associated with the stent intervention in the current analysis was 4.0% and the incidence of death and any stroke was 4.7%, results that are similar or even lower than the currently reported complications.6,7

Conclusions

The presence of carotid artery stenosis is associated with a significant increase in death and stroke in patients undergoing CABG. The current systematic review of the published data shows that the incidence of stroke and death remains elevated despite pretreatment with CAS with results similar to those observed when CEA is used. Therefore, the overall need for carotid revascularization in patients also requiring CABG still remains uncertain. Prospective, randomized studies are warranted to fully elucidate the best therapeutic approach in this growing patient population.

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Disclosures

None.

References

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