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EDITORIAL COMMENT

How Should We Address Carotid Artery Stenosis Around the Time of Open-Heart Surgery?*

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The prevalence of carotid artery stenosis is 3.4% to 22% in patients undergoing open-heart surgery (OHS) (1,2). Evidence from a prior era suggested stroke rates as high as 9.2% after bypass surgery in patients with carotid artery stenosis (3). Current clinical consensus guidelines favor revascularization of patients with symptomatic carotid stenosis before cardiac surgery but state that the efficacy of this practice is not established in those patients with asymptomatic severe stenosis (4). Nevertheless, this latter group represents the majority of patients that undergo carotid revascularization before OHS.

Although it is true that patients who have carotid artery stenosis have an increased risk of perioperative stroke during OHS, this may not be a causal relationship. Pre-operative carotid revascularization is performed with the rationale of decreasing watershed infarcts related to hemodynamic perturbations encountered during OHS. However, patients with carotid artery stenosis and coronary artery disease necessitating coronary artery bypass grafting (CABG) surgery may be at preferentially higher risk for concomitant atheroma in the ascending aortic arch, the manipulation of which during surgery can cause embolic stroke (5). This risk is not attenuated by pre-operative carotid revascularization. Also, the performance of cardiac surgery and concomitant anesthesia has markedly changed since initial reports raising concerns for stroke in this population emerged. Operative time, a well-known risk factor for stroke with OHS, is modifiable through judicious operative planning or with use of hybrid coronary revascularization. Modern anesthesia techniques in high-risk patients that may decrease risk of stroke include careful hemodynamic monitoring and cerebral monitoring (6). Finally, carotid revascularization before OHS carries its own significant risk of periprocedural stroke. In asymptomatic patients, the average risk is 2% to 5% in the modern era, with many patients in this population carrying risk factors known to be associated with adverse periprocedural events (7,8). Hence, the performance of carotid revascularization must reduce the risk of peri-OHS stroke by such a large degree that it overcomes this upfront significant periprocedural risk in order to justify its routine performance. In the midst of this uncertainty regarding risk-benefit ratios, it is unknown how frequently pre-OHS carotid revascularization is performed in the United States in the modern era. Also unknown is what the prevailing practices are regarding modality (carotid endarterectomy [CEA] versus carotid artery stenting [CAS]) and timing (staged vs. combined with OHS) of the pre-OHS carotid revascularizations.

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To investigate this further, in this issue of *JACC: Cardiovascular Interventions*, Feldman et al. (9) performed the largest and most contemporary examination of three different revascularization strategies of carotid artery stenosis around the time of OHS. From the National Inpatient Sample (NIS), data from more than 7 million hospital stays each year were queried

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to identify more than 22,000 concurrent carotid revascularizations and CABG surgeries during the same hospitalization. An analysis of practice patterns between 2004 and 2012 demonstrated a significant decline in the overall strategy of CEA and CABG during the same hospitalization, with increased proportions of staged CEA and decreased proportions of combined CEA. The rates of CAS in this patient population did not change, and CAS was much less frequently utilized than CEA overall.

These trends are concerning given observational evidence comparing CEA and CAS among patients needing OHS (10). Within 30 days of OHS, a strategy of staged CEA was associated with the highest rate of a combined endpoint consisting of death, stroke, and myocardial infarction, driven primarily by a higher risk of myocardial infarction. Combined CEA with OHS was similar to staged CAS with OHS in the first 30 days; however, the strategy involving CAS was associated with far fewer late-phase composite events. Further, results from the SAPPHIRE (Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy) trial suggest that CAS may provide particular benefit in high cardiac risk patients when compared with CEA, again due to a substantial decrease in perioperative myocardial infarction with CAS (11).

Despite evidence supporting the use of CAS, it remains an underused strategy in this population. This may be partially driven by significant restrictions on reimbursement for the procedure by the Center for Medicare & Medicaid Services. Interestingly, even within the choice to pursue surgical revascularization, despite evidence suggesting that staged CEA may put patients at higher risk than combined CEA with OHS, the use of staged CEA is rising. The trends noted in the current study are a valuable contribution to the literature, and reflect a potential venue to improve outcomes among patients requiring OHS and carotid revascularization.

The authors also used the NIS data to perform a comparative effectiveness analysis of the various strategies for carotid revascularization around OHS. This portion of the study highlights important hazards of performing outcome analyses on administrative data. The authors attempted a rigorous statistical analysis of the data available in the NIS. However, due to the nature of data, the analyses have several important limitations.

First, the NIS provides administrative data on a wide range of clinical conditions and relies on accurate coding of inpatient stays. However, administrative data often contain gaps in clinical information and clinical context, which can be limiting in analyses of processes of care (12). To circumvent this problem, validation of the coding information is paramount before reliable conclusions can be drawn from studies using these data. For example, "symptomatic carotid status" was used in this study using an administrative coding algorithm that the authors specified. Symptomatic carotid stenosis is defined as a transient ischemic attack or stroke within 6 months that can be attributed to the ipsilateral carotid stenosis. This cannot be ascertained within the NIS, as many of the administrative codes used to define symptomatic stenosis cannot be guaranteed to be "historical" codes, and could easily be used to refer to stroke or transient ischemic attack symptoms that occur during the hospitalization after the procedure.

Second, observational studies are subject to treatment selection bias, whereby comparisons may be biased due to marked differences in baseline differences in patients, including physicians' knowledge of unmeasured prognostic variables that alter treatment decisions and outcomes (13). To this end, propensity matching is a strategy that is commonly used. The propensity score is a measure of the likelihood that a patient received a certain treatment based on background characteristics. The score can be used in the analysis as another weight in the weighted logistic regression, as was done in this study. However, appropriate use of propensity analysis requires sufficient commonality between the treatment groups. Longmore et al. (14) performed an important analysis of the comparability of patients undergoing CEA and CAS using the National Cardiovascular Data Registry for Carotid Artery Revascularization and Endarterectomy (CARE). They described limited overlap between patients undergoing CEA and CAS, and even after stratification by propensity score quintile, found significant residual differences between the 2 groups in ischemic heart disease, rates of myocardial infarction within 6 weeks of revascularization, and history of carotid restenosis. This would suggest that the referral patterns for patients undergoing CEA and CAS are too vastly different to allow appropriate comparisons. Thus, the outcomes presented by Feldman et al. (9) are likely to be subject to significant treatment selection bias, despite the use of propensity score analysis.

An important study by Jalbert et al. (15) demonstrates the significance of complete clinical, procedural, and provider information in comparative effectiveness studies of carotid revascularization. The authors linked Medicare data to 2 large disease-specific registries and compared outcomes associated with CEA and CAS. Unadjusted, CAS was associated with an increased mortality risk. This association persisted after adjustment for patient-level factors alone. However, after further adjustment for provider factors, any differences between CAS and CEA were attenuated or completely abrogated, including mortality. Using a stepwise manner, these authors demonstrated the hazard of using incomplete information in comparative effective analyses. The medical literature is littered with administrative analyses of carotid revascularization that cannot account for these issues, and hence, contradict information from several well-performed randomized trials.

Finally, the study by Feldman et al. (9) is limited by significant measurement bias. Patients undergoing CAS are often enrolled in post-marketing and investigational device exemption trials that require routine neurological assessments post-procedure, whereas patients undergoing CEA undergo neurological assessments on an as-needed basis. The rates of strokes detected are directly related to the rigor of the post-procedure neurological assessment (16), and as a result, the reported rates of stroke in patients undergoing CEA will be lower than the actual rate of stroke, biasing results in favor of CEA.

Taken together, these limitations, common to observational studies, diminish the strength of the comparative effective analysis provided by Feldman et al. (9). Although the total number of patients studied is very large, the size of a study has no influence on these methodological biases. However, the analysis of trends described in their paper allows us as a field to self-reflect on current practice patterns for this common clinical scenario. The limitations of comparative effectiveness analyses given differences in referral patterns and baseline characteristics among these patients highlight the need for a rigorous randomized clinical trial to address the optimal strategy for addressing asymptomatic carotid stenosis in patients who require OHS.

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