# Intracranial Hemorrhage Complicating Carotid Artery Stenting and Carotid Endarterectomy

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**See related article, pages 2782–2787.**

There are now 2 options for revascularization of patients with significant carotid artery stenosis, carotid artery stenting (CAS), approved by the Food and Drug Administration in May for conventional risk patients, and carotid endarterectomy (CEA). In this issue of *Stroke*, McDonald et al[1] utilize International Classification of Diseases 9th revision codes from the National Inpatient Sample (NIS) hospital discharge database to study intracranial hemorrhage (ICH), mortality, and discharge disposition after CAS or CEA during 2001 to 2008. This database study illustrates both the power and the weaknesses of such a large retrospective review. With 229 000 patients in a study, infrequent events can be detected in numbers adequate to yield statistically significant group differences. Such is the case with the ICH rates for asymptomatic patients after the procedure. Fortunately, in such patients ICH appears to be a rare event after either CAS or CEA, with rates <1%. For symptomatic patients, the NIS database rate of ICH was of concern and higher after CAS at 4.4% ICH vs 0.8% ICH after CEA.

Weaknesses of a retrospective database review include diagnostic imprecision and limited capability to describe important baseline differences between groups. For example, in the NIS database 136 (41%) of the ICH are attributed to International Classification of Diseases 9th revision code 430, subarachnoid hemorrhage (SAH). However, documented cases of SAH after CAS and CEA are rare and proportionately much less frequent than ICH. In an active CAS site, Xu et al[2] report only 2 cases of SAH over a 10-year period. Recently published CAS stenting trials report only the total stroke rate and do not segregate it into ischemic vs ICH and SAH. The only randomized trial to do so was BEACH, which in 2006 reported a 0.1% rate of SAH with CAS (1 of 747 cases).[3] In the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST),[4] 2 cases of SAH occurred during the periprocedural period among the 2502 patients; both were SAH occurring in those randomized to CEA (1 of those did not undergo a procedure). Important differences between patients undergoing CAS compared to those undergoing CEA are likely for the years reported by McDonald et al and would not have been captured by the NIS database. CAS case procedure reimbursement by the Centers for Medicare and Medicaid Services required enrollment in a registry trial (2001–2008) or required that the patient be considered at "high risk" for CEA (2005–2008). Examples of features that would qualify for this high-risk designation include class III/IV congestive heart failure, unstable angina, contralateral carotid occlusion, neck radiation, previous ipsilateral CEA, and tandem carotid lesions. Although Table 1 in the McDonald study shows the groups to be balanced on several traditional stroke risk factors, the factors for high risk of CEA are not included. Therefore, their study is likely comparing a predominantly high-risk surgical population (CAS) to a predominantly standard-risk population (CEA). These high-risk features, required for Centers for Medicare and Medicaid Services reimbursement, may explain the higher in-house mortality and unfavorable discharges. Whether these same preexisting features also influence the rate of ICH is unknown.

For the symptomatic group in which the ICH rates and differences are of concern, the characteristics at baseline could be fundamental confounders. Grouping of the symptomatic International Classification of Diseases 9th revision codes does not allow breakdown of the proportions of symptomatic patients who had preceding stroke vs transient ischemic attack or vs amaurosis. In symptomatic patients who sustained stroke as the indication for revascularization, the International Classification of Diseases 9th revision codes cannot provide information on stroke severity or timing of the revascularization. Having a higher percentage of more severe stroke revascularized soon after the stroke could explain the CAS and CEA differences, both for ICH and for mortality. Such a scenario is plausible given that CAS was performed in greater proportions in academic centers (77%; tertiary referral for large strokes), whereas CEA was performed in greater proportion at nonteaching centers (23%), where CEA after stroke has often been delayed. To control for these potential patient selection differences would require a large randomized trial comparing the 2 procedures in standard-risk patients.

CREST was such a trial.[4] The patients were well-balanced with regard to risks for intervention, and the average time to procedure was <7 days for both symptomatic groups. In contrast to the results of McDonald et al, the rate of ICH in CREST was very low for CAS (0.3%; 4 of 1262) and was as low as it was for CEA (0.2%; 3 of 1240); the difference is not statistically significant. We have not found evidence to suggest the rates in CREST are artifactually low. Ascertainment of ICH (and SAH) was likely more sensitive for CREST

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patients than for the NIS database patients because of the protocol-specified neurological assessments performed at 18 to 54 hours and 30 days after the procedure. The dual antiplatelet therapy standard for CAS therapy was monitored; in CREST, 88% of the CAS patients were using dual antiplatelet therapy immediately before, during, and up to 4 weeks after the procedure. Therefore, the rates in CREST suggest that for standard-risk patients ICH (ICH and SAH) is rare, and ICH is unlikely in symptomatic patients after CAS at experienced treatment centers.

The potential mechanisms of ICH after revascularization are well-discussed by the authors. Unfortunately, International Classification of Diseases 9th revision codes do not distinguish whether the ICH were symptomatic or asymptomatic, whether they were primary or hemorrhage transformation of an existing ischemic stroke, or whether any were contrast staining of an ischemic area after an angiogram. Early reperfusion of a preexisting ischemic area likely explains the higher rate of ICH observed in the NIS database for symptomatic patients compared to asymptomatic patients. The role of hyperperfusion syndrome is discussed in detail including interesting possible anatomic stent placement issues. However, data on the strongest predictor of hyperperfusion syndrome, namely preprocedure high-grade stenosis, are not available in this article. An intriguing factor in ICH associated with CAS is the role of the dual antiplatelet therapy (concurrent use of clopidogrel and aspirin) compared to standard monotherapy with CEA (aspirin alone). In CREST, the use of dual antiplatelet therapy was not rigorously captured for the CEA patients. Because the rates of ICH were so low for both CAS and CEA, a clinically important risk for dual antiplatelet therapy would seem unlikely in patients at standard risk. The NIS database does not inform this question.

In summary, the study of McDonald et al raises appropriate concerns regarding the occurrence of ICH after carotid revascularization. For the present, data from 2 Food and Drug Administration-monitored trials performed at multiple centers across North America would suggest ICH is an infrequent complication for both CAS and CEA. For the future, studies utilizing International Classification of Diseases codes should be more informative. The databases will improve with regard to diagnostic precision. Comparisons of CAS and CEA with regard to ICH and other complications will become more reliable now that CAS has been approved for patients at standard risk.

## Disclosures

None.

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