Intracranial Hemorrhage Is Much More Common After Carotid Stenting Than After Endarterectomy
Evidence From the National Inpatient Sample
Robert J. McDonald, MD, PhD; Harry J. Cloft, MD, PhD; David F. Kallmes, MD

Background and Purpose—Intracranial hemorrhage (ICH) is a rare and devastating complication of carotid revascularization. We sought to determine the prevalence of, type of, and risk factors associated with ICH among recipients of carotid endarterectomy (CEA) and carotid angioplasty and stenting (CAS) within the National Inpatient Sample (NIS).

Methods—Postoperative cases of ICH after CEA (International Classification of Disease 9th edition [ICD-9]: 38.12) or CAS (ICD-9: 00.63) were retrieved from the 2001 to 2008 NIS. Clinical presentation (asymptomatic versus symptomatic), discharge status, in-hospital mortality, demographics, and hospital characteristics were extracted from NIS data. Charlson indices of comorbidity were determined based on ICD-9 and clinical classification software codes. Multivariate regression was used to determine the impact of revascularization procedure type and symptom status on adverse outcomes, including ICH, in-hospital mortality, and unfavorable discharge status.

Results—Among 57,663,486 NIS hospital admissions, 215,012 CEA and 13,884 CAS procedures were performed. Symptomatic presentations represented the minority of CEA (N=10,049; 5%) and CAS cases (N=1,251; 10%). ICH occurred significantly more frequently after CAS than CEA in both symptomatic (4.4% versus 0.8%; P<0.0001) and asymptomatic presentations (0.5% versus 0.06%; P<0.0001). Multivariate regression suggested that symptomatic presentations (versus asymptomatic) and CAS procedures (versus CEA) were both independently predictive of 6-fold to 7-fold increases in the frequency of postoperative ICH. ICH was independently predictive in a 30-fold increased risk of mortality before discharge.

Conclusions—CAS procedures are associated with elevated adverse outcomes, including ICH, in-hospital death, and unfavorable discharges, especially among symptomatic presentations. (Stroke. 2011;42:2782-2787.)

Key Words: carotid endarterectomy □ carotid stenosis □ hyperperfusion syndrome □ intracranial hemorrhage □ stenting

Intracranial hemorrhage (ICH) is a rare and devastating complication after carotid revascularization, occurring in 0.2% to 0.5% of cases.1–3 However, scant data exist to determine if ICH rates differ between revascularization procedures. Preliminary results from the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) revealed positive outcomes among recipients of carotid endarterectomy (CEA) and carotid artery stenting (CAS),4 yet the relative efficacies of these 2 interventions remain under active investigation. Unfortunately, prospective studies, even as large as CREST, lack sufficient power to properly study rare complications such as ICH.5 To adequately identify rare complications, a database of a large number of hospital admissions is necessary. The National Inpatient Sample (NIS) is such a database, with information regarding hospital admissions to 20% of the yearly nonfederal hospitalizations in the United States, representing >8 million annual hospitalizations.6 We sought to determine the prevalence of, type of, and risk factors associated with ICH among recipients of CEA and CAS within the NIS.

Materials and Methods

Data Acquisition
International Classification of Diseases, 9th Revision (ICD-9) Clinical Modification7 procedure codes were used to independently identify cases of CEA (38.12, available from 2001–2008) and CAS (00.63, available from 2004–2008) from the 2001 to 2008 NIS hospital discharge database (Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality, Rockville, MD). Discharge weights were used to approximate the annual discharge census among nonfederal hospitalizations. Asymptomatic cases were separately identified from symptomatic cases using ICD-9 Clinical Modification diagnostic codes (asymptomatic codes: 433.10 and 433.30; symptomatic codes: 435.9, 362.34, 433.11). Age, gender, discharge status (including in-hospital mortality), presence of intracranial hemorrhage (ICD-9 codes: 430 [subarachnoid hem-
orrhage], 431 [intracranial hemorrhage], 432.0 [nontraumatic extradural hemorrhage], 432.9 [unspecified intracranial hemorrhage], individual comorbidities (myocardial infarction, hypertension, diabetes, hyperlipidemia, congestive heart failure, acute and chronic renal failure, and chronic obstructive pulmonary disease), length of stay, hospital teaching status, and elective admission status were extracted from the NIS data set for each procedure (CEA, CAS).

Unfavorable discharges were identified from NIS data as discharges requiring skilled care (short-term hospitalization, skilled nursing facility, home health care). Unadjusted and age-adjusted Charlson comorbidity scores were computed using recorded ICD-9 Clinical Modification and Clinical Classification Software (CCS) codes found within NIS data as described elsewhere.8–10

Statistical Analysis

All statistical analyses were performed by using software (JMP version 9 and SAS version 9; SAS Institute, Cary, NC). Categorical data were displayed as relative frequencies (percentages) and compared using χ² tests of significance. Continuous data were presented as median scores with interquartile ranges because of non-normal data distributions and were compared using the Wilcoxon signed-rank tests of significance.8 Significance was estimated by using P<0.05. Predictors of ICH and in-hospital mortality were identified using multivariate logistic regression analysis. Categorical data were transformed into stratified categorical data for analysis in these models. Separate models were constructed for in-hospital mortality (mortality model), ICH (ICH model), and unfavorable discharges (discharge model) among CAS and CEA recipients. Estimated coefficients for each variable were transformed to reflect the odds ratios (OR) comparing odds of 2 probabilities within the binomial response variable.

Results

Demographic Characteristics

The distribution of carotid revascularizations documented in the 2001 to 2008 NIS, sorted by procedure type and clinical presentation, are shown in Table 1. CEA procedures significantly outnumbered CAS procedures in both symptomatic (CEA: N=10 049, 89%; CAS: N=1251, 11%) and asymptomatic presentations (CEA: N=204 963, 94%; CAS: N=12 633, 6%); however, a higher percentage of CAS procedures, relative to CEA procedures, were performed on
symptomatic presentations (10% versus 5%; \( P<0.0001 \)). In contrast to CEA recipients who had statistically insignificant differences in age between symptomatic and asymptomatic groups (\( P=0.16 \)), symptomatic presentations who received CAS were significantly younger than their asymptomatic counterparts (median age, 65 versus 72 years; \( P<0.0001 \); Table 1). Teaching facilities performed a higher proportion of CAS interventions relative to nonteaching facilities (77% versus 23%; \( P<0.0001 \)); yet, as a whole, symptomatic presentations were more commonly treated with CEA at both teaching (\( P<0.0001 \)) and nonteaching institutions (\( P<0.0001 \)). Unadjusted and age-adjusted Charlson comorbidity indices revealed that symptomatic presentations were associated with lower overall morbidities relative to asymptomatic presentations (CAS, \( P<0.0001 \); CEA, \( P<0.0001 \)). These observations were corroborated by investigation of individual comorbidities, because asymptomatic presentations were associated with higher rates of hypertension (\( P<0.0001 \)) and diabetes (\( P<0.0001 \)), and chronic obstructive pulmonary disease (\( P<0.0001 \)). However, symptomatic cases were associated with higher rates of renal failure (\( P<0.0001 \)) and history of myocardial infarction (\( P<0.0001 \)).

Outcome Characteristics

Intracranial hemorrhage rates were 10-times higher among asymptomatic cases undergoing CAS versus CEA (CAS, 0.06%; CAS, 0.5%; \( P<0.0001 \); Table 1, all ages outcomes). Among symptomatic presentations, the frequency of hemorrhage was 6-fold higher among CAS procedures, relative to CEA procedures (4.4% versus 0.8%, \( P<0.0001 \)). In-hospital mortality rates were similar between asymptomatic presentations undergoing CEA and CAS (0.5% versus 0.6%; \( P<0.0831 \)). Further, in-hospital mortality rates were substantially higher among symptomatic presentations; among this subgroup, recipients of CAS were significantly more likely to experience in-hospital death than CEA recipients (6.2% versus 4.0%; \( P<0.0001 \)). Unfavorable discharges were slightly higher in CEA cases, relative to CAS cases, among asymptomatic and symptomatic presentations, but these differences were not found to be significant.

When outcomes were sorted by age, patients younger than 70 years had lower in-hospital mortality and unfavorable discharge rates than patients 70 years or older, irrespective of clinical presentation or revascularization procedure (Table 1, age-sorted outcomes). In contrast, recipients of CAS younger than 70 years who presented symptomatically had higher rates of intracranial hemorrhage compared to similarly treated individuals 70 years or older (5.0% versus 3.3%). In all other subgroups (asymptomatic CAS recipients, symptomatic CEA recipients, asymptomatic CEA recipients), patients 70 years or older had higher rates of ICH relative to younger patients.

Analysis of Hemorrhage Etiology and Outcomes

The etiologies of postoperative hemorrhage among CEA and CAS recipients, along with vital status at the time of discharge, are shown in Table 2. In general, subarachnoid hemorrhage (ICD-9 430) accounted for 39% and 42% of all hemorrhage cases for CEA and CAS, respectively. ICH (ICD-9 431) accounted for a majority of the remaining cases of hemorrhage for CEA (60%) and CAS (57%). ICD-9 codes 432.0 (nontraumatic extradural hemorrhage) and 432.9 (unspecified intracranial hemorrhage) were minor contributors to NIS discharge records reporting ICH. Among NIS records reporting subarachnoid hemorrhage after carotid revascularization, CAS recipients, relative to CEA recipients, had a significantly higher in-hospital death rate generally (22% versus 13%; \( P<0.0001 \)) and among symptomatic (17% versus 11%; \( P<0.0001 \)) and asymptomatic (28% versus 14%; \( P<0.0001 \)) presentations. NIS records reporting ICH after carotid revascularization were more dramatic and show that CAS recipients had 2- to 3-times the death rate generally (71% versus 31%; \( P<0.0001 \)) and among symptomatic (52% versus 31%; \( P<0.0001 \)) and asymptomatic (82% versus 31%; \( P<0.0001 \)) presentations when compared to CEA recipients.

Multivariate Regression Model Results

Multivariate logistic regression analysis, after adjusting for other model variables, showed that CAS recipients were
6-times more likely to have postoperative ICH (ICH model: OR, 6.07; \( P<0.0001 \)) and significantly more likely to experience in-hospital mortality (mortality model: OR, 1.63; \( P=0.0001 \)), relative to CEA recipients. Further, CEA recipients were significantly more likely to encounter unfavorable discharges relative to CEA discharges (OR, 1.21; \( P<0.0001 \)). Symptomatic patients were significantly more likely to experience ICH (ICH model: OR, 6.81; \( P<0.0001 \), die during hospitalization (mortality model: OR, 1.49 per unit change; \( P=0.0001 \)), in-hospital death (mortality model: OR, 1.49 per unit change; \( P<0.0001 \)), and unfavorable discharges (discharge model: OR, 1.49 per unit change; \( P=0.0001 \)). Among comorbidities included in the ICH model, all but acute renal failure and hypertension were individually predictive of reduced risk of ICH (Table 3). In contrast, the presence of acute renal failure, myocardial infarction, and congestive heart failure were individually predictive of increased risk of in-hospital mortality and unfavorable discharges, whereas hyperlipidemia, chronic renal failure, diabetes, and hypertension were individually predictive of reduced risk of in-hospital mortality and unfavorable discharges (Table 2).

### Discussion

The results of this review of outcomes after carotid revascularization procedures within the 2001 to 2008 NIS revealed that recipients of CAS are significantly more likely to experience intracranial hemorrhage, in-hospital death, and unfavorable discharges relative to recipients of CEA. The data that symptomatic presentations, particularly among younger individuals, treated with CAS were significantly and substantially more likely to experience ICH relative to symptomatic presentations treated with CEA and to asymptomatic presentations in general were unexpected findings. Whereas the absolute differences in hemorrhage rates are striking, the relative hemorrhage rates after CAS versus CEA as well as the markedly elevated death rate associated with CAS after hemorrhage corroborate with previous reports. Because previous studies have not directly compared hemorrhage rates between revascularization procedures in the context of clinical presentation, our findings permit juxtaposition of the relative and absolute incidence rates of these rare adverse events on a much larger study population. These results...
strongly argue for judicious use of CAS among symptomatic presentations because adverse outcomes are more common, particularly in this subgroup, regardless of patient demographics or clinical characteristics.

Our findings are corroborated by the recent report by the CREST group, which showed that aggregate risks for periprocedural stroke and death were higher for CAS versus CEA recipients who presented with symptomatic disease as compared to asymptomatic patients. In contrast to our findings, the CREST study did not specifically address hemorrhage as an outcome, nor did they attempt to extricate the combined event rates of periprocedural death and stroke. In addition to the recent CREST safety study, the results of the CAPTURE2 (Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events) study also suggest a higher rate of postoperative stroke among symptomatic, relative to asymptomatic, CAS recipients. Further, the results of the earlier CAPTURE study by Fairman et al found that the incidence of major stroke was higher among symptomatic compared to asymptomatic presentations and that 23% of these strokes were hemorrhagic in nature. Our findings complement these earlier studies by comparing the rates of adverse events between CEA and CAS, examining the specific types of hemorrhagic stroke observed among subgroups, and providing a much larger population-based sample. However, we acknowledge that our findings suggest higher overall rates of hemorrhagic stroke among individuals with ICH and subarachnoid hemorrhage compared to these reports. Assuming that a minority of strokes are hemorrhagic in nature, our findings still suggest a hemorrhage rate twice that of the recent CREST report. This discrepancy could be a result of nonuniform operator experience or demographic differences between study participants in the CREST trial and the general population sampled in the NIS dataset.

The reasons for disparities in adverse outcomes between symptomatic CAS and CEA cases are unclear because our data suggest symptomatic CAS recipients are, relative to symptomatic CEA recipients, younger with fewer comorbidities, suggesting that the excess risk of hemorrhage within this group is not a simple function of advanced age or disease. In fact, our findings suggest that symptomatic recipients of CAS younger than age 70 years are at greatest risk for development of hemorrhage. Because ICH is thought to be a result of cerebral hyperperfusion syndrome, a condition arising from baroreceptor dysregulation of cerebral blood flow and free radical–mediated endothelial damage in the preoperative chronically hypoperfused state, it is possible that CAS procedures are more likely to result in postoperative hyperperfusion.

Recently, Park et al reported hyperperfusion after carotid stenting of individuals at high risk was directly related to the location of the atheromatous lesion; stent deployment within the carotid bulb body was associated with a 6-fold higher rate of hyperperfusion relative to stent deployment within apical lesions. Similar reports are absent in the endarterectomy literature. Because cerebrovascular dysregulation is a proposed mechanism of hyperperfusion syndrome, it is possible that stent deployment to the carotid body uniquely stuns the baroreceptor reflex because of stretching forces. In addition to procedural differences, differences in perioperative and postoperative management might play a causative role in hemorrhage rates. Kawamata et al have shown that significant attenuation in cerebral hyperperfusion can be achieved through strict management of perioperative blood pressure. Differences in anticoagulation and antiplatelet therapy utilization also might explain this dramatic difference in hemorrhage and death rates because antiplatelet therapy is more common after stent deployment. Further, the implementation and safety of dual antiplatelet therapy regimens within this symptomatic subset remain unknown and untested. Debate continues regarding the safety of dual antiplatelet therapy as the favorable findings of NASCET (North American Symptomatic Carotid Endarterectomy Trial) and CARESS (Clopidogrel and Aspirin for the Reduction of Emboli in Symptomatic Carotid Stenosis) are contested by the MATCH (Management of Atherothrombosis with Clopidogrel in High-risk patients) study in which combination therapy was associated with higher rates of cerebral hemorrhage than monotherapeutic regimens. Because symptomatic cases are the most likely to have distal cerebral ischemia and concomitant microvascular disruption in the blood–brain barrier, aggressive antiplatelet/anticoagulation regimens might be expected to predispose this subgroup to hemorrhage.

Although the literature on hyperperfusion and ICH after endarterectomy is extensive, few reports specifically focus on hyperperfusion and ICH after carotid stent deployment. These previous studies, however, were limited by small sample sizes and the absence of comparative CEA cohorts. In a recently published single-center study, Iwata et al reported that hyperperfusion, as determined using Single-Photon Emission Computed Tomography (SPECT), occurred in 14% of patients who underwent CAS. In this same study, ICH occurred in 33% of the cases of hyperperfusion or ≈5% of all CAS cases. Unfortunately, that previous study also lacked a comparative CEA cohort, and thus no conclusions could be drawn regarding the relative prevalence of ICH and hyperperfusion between CEA and CAS. In 2008, Timaran et al utilized 1 year of NIS data to report on ICH after carotid revascularization. Their efforts also suggested that CAS, relative to CEA, is associated with significantly higher rates of death and ICH. Our current study expands on their initial work by providing nearly 10-times the patient sample size and by separately examining symptomatic and asymptomatic presentations.

The primary limitations of this current study are intrinsic shortcomings in the NIS database. First, despite the utility of the NIS, the predefined data structure of this database prevents evaluation of clinical metrics not included in the study design. In the case of this study, the NIS lacks data that would permit independently diagnosis of hyperperfusion among cases of ICH. As such, we were unable to directly associate the presence of hyperperfusion with outcomes to determine, on a population scale, if hyperperfusion occurs more frequently among recipients of CAS and if hyperperfusion is necessarily the most predictive of ICH or adverse outcomes. Second, it remains unclear if some of the disparity in ICH frequency observed between recipients of CAS versus CEA is a consequence of diagnostic bias resulting from
increased CT head scan use among recipients of CAS. Because the NIS relies on ICD-9 coding in lieu of Current Procedural Terminology (CPT) coding commonly used in diagnostic radiology, differences in scan utilization rates between CAS and CEA recipients cannot be completely characterized. However, the NIS contained a limited amount of ICD-9 coding data on noncontrast CT head utilization, and these results revealed similar scan rates between revascularization procedures. Third, it is well-established that the NIS contains coding errors in the form of incorrect data or omissions in data. Fortunately, such errors follow a random distribution and do not manifest in a systemic fashion to alter the statistical outcomes because they are diluted within the enormous size of the NIS data set.

Conclusions
Our findings suggest that the risks of postoperative ICH, in-hospital mortality, and unfavorable discharges are much higher among recipients of CAS relative to CEA. In particular, the risk of ICH is particularly high among patients who present symptomatically who undergo CAS deployment, despite being younger and healthier than symptomatic counterparts who undergo CEA. Although symptomatic presentations represent the minority of revascularization procedures, our results underscore the need for further study to identify the causes leading to the observed disparities in clinical outcomes between CAS and CEA.

Disclosures
None.

References
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