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=1251; 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;42:00-00.)

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 Modification) 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-
Table 1. Characteristics of Carotid Artery Stenting and Carotid Endarterectomy Recipients

<table>
<thead>
<tr>
<th></th>
<th>CAS (N=13 884)</th>
<th>CEA (N=215 012)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Symptomatic</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td></td>
<td>N=1251 (10%)</td>
<td>N=12 633 (90%)</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>65 (54–75)</td>
<td>72 (65–79)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>45.8</td>
<td>39.3</td>
</tr>
<tr>
<td>Elective admission (%)</td>
<td>32</td>
<td>73</td>
</tr>
<tr>
<td>Teaching facility (%)</td>
<td>77</td>
<td>60</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson score, median (IQR)</td>
<td>1 (1–2)</td>
<td>2 (1–2)</td>
</tr>
<tr>
<td>Charlson score (age-adjusted)</td>
<td>4 (2–5)</td>
<td>4 (4–5)</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>37.3</td>
<td>53.4</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>54.4</td>
<td>65.1</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>19.1</td>
<td>26.6</td>
</tr>
<tr>
<td>Congestive heart failure (%)</td>
<td>11.0</td>
<td>11.5</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>3.9</td>
<td>1.4</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>14.5</td>
<td>17.4</td>
</tr>
<tr>
<td>Acute renal failure (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic renal failure (%)</td>
<td>11.2</td>
<td>8.2</td>
</tr>
<tr>
<td>Outcomes (all ages)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH (all, %)</td>
<td>4.4</td>
<td>0.5</td>
</tr>
<tr>
<td>In-hospital death (%)</td>
<td>6.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Unfavorable discharge (%)</td>
<td>36.9</td>
<td>9.9</td>
</tr>
<tr>
<td>Outcomes (age younger than 70 y), N (%)</td>
<td>788 (63)</td>
<td>5158 (41)</td>
</tr>
<tr>
<td>ICH (all, %)</td>
<td>5.0</td>
<td>0.4</td>
</tr>
<tr>
<td>In-hospital death (%)</td>
<td>5.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Unfavorable discharge (%)</td>
<td>27.9</td>
<td>6.4</td>
</tr>
<tr>
<td>Outcomes (age 70 y or older), N (%)</td>
<td>463 (37)</td>
<td>7475 (59)</td>
</tr>
<tr>
<td>ICH (all, %)</td>
<td>3.3</td>
<td>0.5</td>
</tr>
<tr>
<td>In-hospital death (%)</td>
<td>6.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Unfavorable discharge (%)</td>
<td>52.3</td>
<td>12.2</td>
</tr>
</tbody>
</table>

CAS indicates carotid artery stenting; CEA, carotid endarterectomy; COPD, chronic obstructive pulmonary disorder; ICH, intracerebral hemorrhage; IQR, interquartile range.

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. 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
Intracranial hemorrhage rates were 10-times higher among CAS procedures, relative to CEA cases (4.4% versus 0.8%; \( P<0.0001 \)). In-hospital mortality rates were similar between asymptomatic presentations undergoing CAS and CEA (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, CAS 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, 5.09; \( P<0.0001 \)), and encounter unfavorable discharges (OR, 7.22; \( P<0.0001 \)) relative to asymptomatic presentations; Finally, patients with ICH diagnosed after revascularization were 30-times more likely to die than those with uncomplicated carotid revascularizations (ICH model: OR, 29.83; \( P<0.0001 \)).

Female patients were more likely to encounter ICH after carotid revascularization (OR, 1.49; \( P=0.0011 \)) but were no more likely to die during hospitalization (OR, 0.96; \( P=0.5198 \)). Females were 29% more likely to have unfavorable discharges relative to male counterparts after adjustment for age and clinical characteristics (OR, 1.29; \( P=0.00376 \)). Increasing age was negatively predictive of reductions in hemorrhage risk but positively predictive of in-hospital mortality and unfavorable discharges (Table 2). Unadjusted Charlson comorbidity scores were predictive of increased risk of ICH and (ICH model: OR, 1.94 per unit change; \( P<0.0001 \)), in-hospital death (mortality model: OR, 1.40 per unit change; \( P<0.0001 \)), and unfavorable discharges (discharge model: OR, 1.87; \( P<0.0001 \)). 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 asymptomatic 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 peri-procedural 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 peri-procedural 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 sub-arachnoid 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 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. 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

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

Stroke. published online August 11, 2011;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2011/08/11/STROKEAHA.111.618769

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2012/08/08/STROKEAHA.111.618769.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
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

(Stroke. 2011;42:2782-2787.)

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