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# A comparison of outcomes associated with carotid artery stent placement performed within and outside clinical trials in the United States

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***Background:*** **A discrepancy between characteristics of patients treated with carotid angioplasty and stent placement (CAS) within and outside clinical trials, particularly characteristics with direct impact on clinical outcome, may limit generalization of clinical trial results. The objective of this study was to identify differences in demographic and clinical characteristics and outcomes related to CAS in patients treated within clinical trials and those treated outside clinical trials in a large national cohort.**

***Methods:*** **We determined the frequency of CAS performed within and outside clinical trials and associated in-hospital outcomes using data from the Nationwide Inpatient Survey data files from 2005 to 2009. All the in-hospital outcomes were analyzed after adjusting for potential confounders using multivariate analysis.**

***Results:*** **Of the 81,638 patients who underwent CAS, 16,078 (19.6%) underwent the procedure as part of a clinical trial. The mean age of the patients was significantly lower in patients treated with CAS as part of a clinical trial than those treated with CAS outside a clinical trial. The proportion of women and nonwhites was lower among patients treated with CAS as part of a clinical trial. The in-hospital mortality was two-fold higher among patients treated with CAS outside clinical trials (1.12% vs 0.53%; $P = .0005$). The rate of composite endpoint of stroke, cardiac events, and death was significantly higher among patients treated with CAS outside clinical trials ($P = .02$). After adjusting for age, gender, presence of renal failure, and hospital bed size, CAS performed as part of a clinical trial was associated with lower rates of in-hospital mortality (odds ratio, 0.467; 95% confidence interval, 0.290-0.751; $P = .0017$) and composite endpoint of stroke, cardiac events, and death (odds ratio, 0.752; 95% confidence interval, 0.594-0.952; $P = .0180$).**

***Conclusions:*** **Our results suggest that CAS procedures performed as part of clinical trials was associated with lower rates of in-hospital mortality and composite endpoint of stroke, cardiac events, and death in United States. These findings highlight the need for strategies that ensure appropriate adoption of CAS to ensure that the benefits observed in clinical trials can be replicated in general practice. (J Vasc Surg 2012;56:317-23.)**

Over the last few years, the U.S. Food and Drug Administration (FDA) has approved several carotid artery stents and distal protection devices. The approval of these devices was based on prospective randomized or single-arm studies conducted in United States.[1-6] The recent results of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)[7] demonstrated that the risk of the composite primary outcome of stroke, myocardial infarction, or death did not differ significantly in the group undergoing carotid artery stent (CAS) placement and the group undergoing carotid endarterectomy (CEA) for patients with symptomatic or asymptomatic carotid artery stenosis. Therefore, the question of interpretation of the results and implementation of CAS into practice, particularly with the anticipated growth in carotid stent procedures based on the results of CREST, is of paramount importance.[8]

A discrepancy between characteristics of patients treated within and outside clinical trials, particularly characteristics with direct impact on clinical outcome, may lead to reduction in anticipated benefit in practice outside clinical trials. Several professional organizations, including a consensus statement from the Brain Attack Coalition[9] and the American Heart Association/American Stroke Association Council on Stroke[10] have recommended outcomes research programs to generate knowledge about treatments, outcomes, and complications of CAS in practice to confirm that procedures and therapies are performed for appropriate indications, with rates of success and complications that are consistent with those observed in clinical trials. We performed this analysis to test the hypothesis that the rates of periprocedural events observed in patients treated with CAS in clinical trials are lower than the rates observed in CAS performed outside clinical trials (real-world experience) in both patients with symptomatic or asymptomatic carotid artery stenosis.

## METHODS

The analysis was performed using the data from the Nationwide Inpatient Sample (NIS) from 2005 to 2009.

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The NIS is the largest all-payer inpatient care database in the United States as part of the Healthcare Cost and Utilization Project (HCUP) by the Agency for Healthcare Research and Quality (AHRQ).[11-13] Briefly, NIS focuses on identification, tracking, and analyzing national trends in health care utilization, access, charges, quality, and outcomes based on data derived from approximately a 20% stratified sample of U.S. community hospitals; approximately 5 to 8 million hospital stays and all discharge data from approximately 1000 hospitals. The data comprises more than 100 clinical and nonclinical variables associated with hospital stays, including primary and secondary diagnoses, primary and secondary procedures, patients' admission and discharge status, and patient demographic information (eg, gender, age, race/ethnicity, expected payment source, total charges, and length of stay). To facilitate production of national estimates, the NIS provides both hospital and discharge weights. Detailed information on the design of the NIS is available at http://www.hcup-us.ahrq.gov.

We used the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) procedure codes 00.63 or 00.64 to identify the patients admitted for CAS with the corresponding diagnostic code for carotid artery stenosis with (433.11) or without (433.10) stroke. Patients who participated in the Investigational Device Exemption (IDE) category B clinical trial were identified by a secondary diagnosis of ICD-9-CM V 70.5 used in claims for Medicare qualifying clinical trial services. This national coverage policy is based on the article in §1862(a)(1)(E) of the Social Security Act for all Medicare carriers, intermediaries, Peer Review Organizations, Health Maintenance Organizations, and Competitive Medical Plans. We used the criterion that has been used previously to differentiate the symptomatic from asymptomatic patients with carotid artery stenosis.[11] If a patient's discharge diagnosis (diagnostic fields 1-15) was "carotid artery stenosis without mention of stroke" with no accompanying secondary diagnoses for transient ischemic attack (TIA; ICD-9 code 435.9), they were classified as "asymptomatic." If a patient's discharge diagnosis was either "carotid artery stenosis with stroke" or, if there was no mention of stroke, but a secondary diagnosis code included that for TIA, patients were classified as "symptomatic." Cardiovascular risk factor information was obtained from the AHRQ comorbidity data collected for each patient.

The primary outcome measures for this analysis were procedure-related complications, including postoperative neurological complications, including cerebral infarction or hemorrhage (ICD-9-CM codes 997.00–997.09) and postoperative cardiac complications (ICD-9-CM code 997.1). A patient undergoing CAS who had any of these codes under one of their secondary ICD-9-CM diagnostic codes (up to 15) was classified as having had periprocedural stroke or cardiac complications. Secondary outcome measures included discharge disposition. Discharge disposition is categorized into routine, home health care, short-term hospital, and other facility, including intermediate care and skilled nursing home, or death. We categorized routine discharge as none or minimal disability and any other discharge status as moderate-to-severe disability.

**Statistical analysis.** We compared patients' age, gender, race/ethnicity, clinical characteristics, and length of stay, periprocedural stroke or cardiac complications, discharge status, and hospitalization charges between patients who underwent CAS within clinical trials versus those who underwent CAS outside clinical trials. The statistical analyses were performed based on weighted numbers.[14] We used SAS 9.1 software (SAS Institute Inc., Cary, NC) to convert raw counts generated from the NIS database into weighted counts that we used to generate national estimates. All analyses accounted for the complex sampling design and sample discharge weights of the NIS following HCUP-NIS recommendations.[14] We used the $\chi^2$ test for categorical data and analysis of variance for continuous data to detect any significant differences in variables and endpoints between patients who underwent CAS within versus outside clinical trial settings. A logistic regression analysis was used to identify the association between participation in clinical trials and odds of (1) postprocedural stroke; (2) postprocedural cardiac complications; (3) in-hospital death; (4) composite of stroke, cardiac events, and death; and (5) none or minimal disability. We adjusted for age and gender in the initial models and adjusted for all the variables that were significantly different in the univariate analysis between patients who underwent CAS within clinical trials versus those who underwent CAS outside clinical trials. We performed two additional logistic regression analyses for all the endpoints in symptomatic and asymptomatic patients using the above-mentioned design.

## RESULTS

Of the 81,638 patients who underwent CAS, 16,078 (19.6%) underwent the procedure as part of a clinical trial. The mean age of the patients was significantly higher, with a higher proportion of patients aged ≥80 years among patients treated with CAS as part of a clinical trial than those treated with CAS outside a clinical trial (Table I). The proportion of women was lower among patients treated with CAS within clinical trials. There was also a trend in difference in race/ethnicity of patients in the two groups: the proportion of whites was higher among patients treated with CAS as part of a clinical trial. The proportion of patients with hypertension, diabetes mellitus, and congestive heart failure was similar between the two groups, but the proportion of patients with renal failure was lower among patients treated with CAS within clinical trials. There was a higher rate of admission to large hospitals (based on number of beds) in the group of patients treated with CAS as part of a clinical trial.

The mean length of stay (days ± standard deviation) was 3.1 ± 4.9 days in patients treated with CAS outside clinical trials versus 2.1 ± 3.1 days in patients treated with CAS within clinical trials ($P < .0001$; see Table I). The in-hospital mortality was two-fold higher among patients treated with CAS outside clinical trials (1.12% vs 0.53%;

**Table I.** Characteristics and outcomes of patients with carotid artery stenosis treated with carotid artery stent placement in groups defined by whether procedure is performed within or outside clinical trials (NIS 2005-2009)

| | *Patients undergoing carotid artery stent placement* | | |
|---|---|---|---|
| | *Patients treated outside clinical trials* | *Patients treated within clinical trials* | P *value* |
| Overall number (%) | 65,560 | 16,078 | |
| Gender | | | |
| Women | 26,407 (40.28) | 6086 (37.86) | .0164 |
| Age (mean) ± SD | 70.3 ± 10.5 | 72.3 ± 9.1 | <.0001 |
| Age strata (years) | | | |
| <65 | 17,833 (27.2) | 2947 (18.2) | <.0001 |
| 65-79 | 34,298 (52.3) | 9519 (59.2) | |
| ≥80 | 13,429 (20.5) | 3611 (22.5) | |
| Race/ethnicity[a] | | | |
| White | 43,436 (85.06) | 11,362 (89.22) | .0927 |
| Black | 2406 (4.71) | 466 (3.65) | |
| Hispanic | 2466 (4.82) | 451 (3.54) | |
| Other | 2756 (5.39) | 455 (3.57) | |
| Comorbid conditions | | | |
| Hypertension | 48,122 (73.40) | 12,074 (75.09) | .2066 |
| Diabetes mellitus | 20,151 (30.73) | 4690 (29.16) | .1054 |
| Congestive heart failure | 7012 (10.69) | 1568 (9.75) | .2424 |
| Renal failure | 6007 (9.16) | 1245 (7.74) | .058 |
| US region | | | |
| Northeast | 12,621 (19.25) | 3390 (21.08) | .9838 |
| Northcentral | 15,217 (23.21) | 3784 (23.53) | |
| South | 25,883 (39.47) | 6088 (37.86) | |
| West | 11,839 (18.05) | 2816 (17.51) | |
| Hospital bed size | | | |
| Small | 5190 (7.96) | 1830 (11.43) | .0022 |
| Medium | 12,960 (19.88) | 1759 (10.99) | |
| Large | 47,033 (72.15) | 12,410 (77.57) | |
| Hospital location and teaching status | | | |
| Rural | 1619 (2.48) | 487 (3.04) | .529 |
| Urban nonteaching | 24,057 (36.90) | 6762 (42.26) | |
| Urban teaching | 39,508 (60.61) | 8750 (54.69) | |
| Length of stay | 3.1 ± 4.9 | 2.1 ± 3.1 | <.0001 |
| Total hospitalization charges | $50,929 (47,560-54,288) | $40,722 (36,019-45,424) | <.0001 |
| Discharge status | | | |
| None or minimal disability | 59,109 (90.16) | 15,330 (95.34) | <.0001 |
| Moderate or severe disability | 5676 (8.65) | 662 (4.11) | <.0001 |
| In-hospital complications | | | |
| Postprocedural mortality | 736 (1.12) | 85 (0.53) | .0005 |
| Postprocedural stroke | 1305 (1.99) | 283 (1.76) | .3966 |
| Postprocedural cardiac complications | 1478 (2.25) | 295 (1.83) | .2332 |
| Postprocedural stroke and or cardiac complications | 2693 (4.11) | 564 (3.51) | .1732 |
| Composite endpoint[b] | 3220 (4.91) | 619 (3.85) | .0235 |

*NIS,* Nationwide Inpatient Sample.
[a]Race/ethnicity is not uniformly reported in NIS database.
[b]Composite endpoint of postprocedural stroke, cardiac complications, and/or death.

$P = .0005$). The rate of composite endpoint of stroke, cardiac events, and death was significantly higher among patients treated with CAS outside clinical trials ($P = .02$). The rate of moderate-to-severe disability at discharge was significantly higher in patients treated with CAS outside clinical trials compared with those treated within clinical trials (8.65% vs 4.11%; $P < .0001$). The mean hospital charges were $50,929 in patients treated with CAS outside clinical trials compared with $40,722 in those treated within clinical trials ($P < .001$).

After adjusting for age and gender, presence of renal failure, and hospital bed size, CAS performed within clinical trials was associated with lower rates of none or minimal disability (odds ratio [OR], 0.367; 95% confidence interval [CI], 0.230-0.588; $P < .0001$; Table II). After adjusting for age, gender, renal failure, and hospital bed size, CAS performed within clinical trials was associated with lower rates of in-hospital mortality (OR, 0.467; 95% CI, 0.290-0.751; $P = .0017$) and composite endpoint of stroke, cardiac events, and death (OR, 0.752; 95% CI, 0.594-0.952; $P = .0180$). In the subgroup analysis, the rate of none to minimal disability was higher among patients treated within clinical trials for both asymptomatic (OR, 2.0; 95% CI, 1.6-2.5; $P < .0001$) and symptomatic (OR,

**Table II.** Multivariate analyses evaluating the effect of carotid artery stent placement performed within clinical trials on various discharge outcomes in patients treated with carotid artery stent placement (NIS 2005-2009)

| | *Unadjusted OR* | | *OR adjusted for age and gender* | | *OR adjusted for age, gender, and potential confounders*[a] | |
|---|---|---|---|---|---|---|
| *Outcomes* | *OR (95% CI)* | P *value* | *OR (95% CI)* | P *value* | *OR (95% CI)* | P *value* |
| None to minimal disability | 2.237 (1.809-2.767) | <.0001 | 2.337 (1.885-2.896) | <.0001 | 2.377 (1.914-2.951) | <.0001 |
| Postprocedural stroke | 0.877 (0.651-1.181) | .3867 | 0.850 (0.629-1.149) | .2896 | 0.848 (0.627-1.146) | .2822 |
| Postprocedural cardiac complications | 0.812 (0.560-1.177) | .2708 | 0.791 (0.544-1.151) | .2204 | 0.785 (0.540-1.142) | .2056 |
| Postprocedural mortality | 0.469 (0.291-0.756) | .0019 | 0.463 (0.288-0.745) | .0015 | 0.467 (0.290-0.751) | .0017 |
| Composite endpoint[b] | 0.775 (0.614-0.978) | .0316 | 0.756 (0.598-0.957) | .0198 | 0.752 (0.594-0.952) | .0180 |

*CI,* Confidence interval; *NIS,* Nationwide Inpatient Sample; *OR,* odds ratio.
[a]Model adjusted for age, gender, renal failure, and hospital bed size.
[b]Composite endpoint of postprocedural stroke, cardiac complications, and/or death.

1.9; 95% CI, 1.3-2.9; $P = .0028$) patients. There was a trend toward lower rates of composite endpoint among asymptomatic patients (OR, 0.816; 95% CI, 0.6-1.0; $P = .109$) but not in symptomatic patients (OR, 1.08; 95% CI, 0.6-1.9; $P = .5$) treated within clinical trials.

## DISCUSSION

We found in our analysis that CAS performed within clinical trials was associated with lower rates of in-hospital mortality and composite endpoint of stroke, cardiac events, and death in the United States. The mean hospital charges were higher in patients treated with CAS outside clinical trials compared with those treated within clinical trials. These findings have important implications for generalization of results derived from clinical trials evaluating CAS. Another observational, retrospective cohort study[15] identified similar challenges with adoption of CAS outside clinical trials by stratifying localities based on incremental rates of CAS performed after Medicare coverage was introduced. Localities with higher adoption of CAS observed higher 90-day mortality, 270-day mortality, and 270-day combined outcomes. Our study identifies the differences between outcomes in CAS patients recruited in clinical trials but does not explain the reasons. There are several possibilities that may account for our findings and implications that need to be considered. If the patient population outside clinical trials has a higher prevalence of adverse characteristics, then the benefit of CAS observed in clinical trials is unlikely to be reproduced in general practice. If the differential results are more likely to be related to operator-related factors, the benefit of CAS observed in clinical trials is again unlikely to be reproduced in general practice. Similarly, the cost-effectiveness of the procedure that is currently derived from data derived from clinical trials is less likely to be acceptable.

It is very likely that patients treated with CAS within clinical trials have more favorable characteristics than those treated as part of routine practice (cherry-picking phenomenon).[16] Therefore, the differences in outcomes observed in our study could be predominantly due to differences in baseline clinical and angiographic characteristics. There is adequate evidence from such comparisons between within trial and outside trial patients for both CEA and aneurysm embolization. Such issues have been previously highlighted in interpretation and application of the North American Symptomatic Carotid Endarterectomy Trial (NASCET), Asymptomatic Carotid Atherosclerosis Study (ACAS), and the International Subarachnoid Aneurysm Trial (ISAT). An analysis of 113,300 Medicare patients undergoing CEA during 1992 and 1993 in "trial hospitals" (those participating in NASCET and ACAS, n = 86) and "nontrial hospitals" (all other nonfederal institutions performing CEAs, n = 2613) reported[17] that Medicare patients' perioperative mortality following CEA outside clinical trials was substantially higher than that reported in the trials, even in those institutions that participated in the randomized studies. Similarly, the overall in-hospital mortality was 6% in ISAT[18] (randomized trial comparing endovascular and surgical aneurysm treatment) compared with the 26% in-hospital mortality observed for subarachnoid hemorrhage admissions in the United States[19,20] % in-hospital mortality in the Japanese Standard Stroke Registry Study.[21] These observations suggest that patients treated in the NASCET, ACAS, and ISAT had more favorable baseline clinical and procedural characteristics compared with those observed in the general population questioning generalization of results.[16] A prominent difference between patients treated within and outside clinical trials was that those treated with CAS outside clinical trials were younger and more likely to be <65 years of age. In our previous analysis of patients undergoing CAS in the United States[22] age ≥70 years was an important predictor of postoperative stroke and cardiac complications post-procedure after adjustment for gender and other comorbid conditions. Therefore, the higher rate of adverse events in patients treated with CAS outside clinical trials would have been augmented with comparable proportion of older patients.

For trials involving the performance of CAS, the trial steering and/or credentialing committee develops criteria to ensure that practitioners have adequate experience and expertise in performing the procedure before the beginning

of the trial. The operators performing CAS outside clinical trials are unlikely to be qualified to the same extent. The variations in operator experience and impact on CAS outcomes were highlighted by the difference in the results of the Endarterectomy vs Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial[7,22] and CREST trial. The 1-month stroke and death rate associated with CAS was prominently higher in the EVA-3S trial compared with CREST (9.6% and 5%, respectively). In CREST, each interventionalist was required to submit data on 10 to 30 cases previously performed and depending on these data had to perform up to 20 lead-in cases[23] Due to such rigorous criteria, 116 of the 427 practicing CAS operators were not approved for participation in the CREST trial. In contrast, EVA-3S required much lower prerequisites that required interventionalists perform at least 12 CAS or five CAS if the operator had performed 35 stent procedures in the supra-aortic trunks.

In a previous report,[24] the cost-effectiveness of CAS versus CEA in patients with severe carotid stenosis was considered to be at high surgical risk for CEA. The analysis assumed that the rates of ipsilateral stroke, myocardial infarction, and death were the same as those observed in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial. Incremental cost-effectiveness ratios (ICERs) for a 1-year postprocedure period for CAS vs CEA treatment was $67,891 (range, -$129,372 to $379,661). Another report[25] determined the cost-effectiveness of CAS with an embolic protection device versus CEA in average surgical risk patients with moderate-to-severe carotid stenosis. The analysis assumed that the rates of ipsilateral stroke, myocardial infarction, and death were the same as those observed in the CREST trial. The estimated ICER for CAS versus CEA treatment for a 4-year postprocedure period was $229,429. Both analyses demonstrated an unfavorable ICER for CAS (compared with CEA). If the rates of adverse events were higher than those observed in clinical trials, the estimated cost per additional death ($5,000), major stroke ($26,410), minor stroke ($17,716), and myocardial infarction ($29,652) is expected to contribute negatively to the already unfavorable ICER associated with CAS.

The next step is identification of strategies to reduce the discrepancy between outcomes of CAS within clinical trials and those performed outside clinical trials. One option is a dedicated investment in outcomes research and using results to guide practices. The Report of the National Heart, Lung, and Blood Institute (NHLBI) Working Group on Outcomes Research[26] in Cardiovascular Disease concluded that a dedicated investment in cardiovascular outcomes research could directly improve the care delivered in the United States. The Karolinska Stroke Update Consensus Statement 2004[27] recommended a more restrictive policy stating that "carotid revascularization should be restricted to centers at which the practice and complication rates are regularly monitored by surgeons and neurologists/stroke physicians and at which complication rates of CEA are comparable to those found in the clinical trials demonstrating efficacy. Monitoring should be prospective and independent of the surgeon involved and should be done with consideration of the applied indications for CEA and the resulting case mix at each center." Another option is to involve interventionalists actively in quality improvement initiatives. The prospective registry, Modification of Outcomes by Lowering Ischemic Events after Reconstruction of Extracranial Vessels (MOLIERE)[28] demonstrated that surgeon involvement in a prospective manner is a prerequisite for them to evaluate, compare, and improve their practice. Participation in the registry ensured that indications and stroke or death rates for participating surgeons were ascertained and within acceptable rates.

We used the data from the NIS, which provides minimal details on the severity of neurological deficits, diagnostic study results, and procedural details, and thereby certain analyses using severity or propensity adjustment could not be performed.[29,30] The NIS data also depend on the accuracy of diagnoses and procedures listed on discharge summaries and on the data collection system. We identified patients who participated in the IDE category B clinical trial using a secondary diagnosis of ICD-9-CM V 70.5. While the accuracy of this code is not known, the code is essential for reimbursement from Medicare for procedures that are not currently reimbursed as part of routine care. Therefore, it is reasonable to assume that hospital coding systems would pay diligence to ensuring the accuracy of the code in billing claims. However, the methods of neurological ascertainment for adverse events may be more rigorous with independent neurologist ascertainment in clinical trials as opposed to self-ascertainment in routine practice[31] Furthermore, some carotid stent trials require measurement of cardiac enzymes within 24 hours, regardless of symptoms that may increase the detection rate of minor myocardial ischemia[32] Therefore, the rates of adverse events may be artificially lower in patients treated in routine practice due to independent surveillance and acquisition of tests per protocol. We used primary ICD-9-CM codes for identifying symptomatic status, which has a true positive rate of up to 84% in previous population-based studies.[33] However, the accuracy of codes used for identification of carotid artery stenosis with (433.11) or without (433.10) stroke was substantially enhanced by concurrent use of procedures codes for CAS and CEA. Use of both primary and secondary diagnostic codes for identifying symptomatic stenosis is likely to overestimate the actual rate of symptomatic status, and thus certain asymptomatic patients were possibly classified as symptomatic in our analysis[33] The discharge functional outcome cannot be measured with the available data, and the closest index was using the destination of discharge as done in previous studies using NIS data.[34]

Our results suggest that CAS performed within clinical trials was associated with lower rates of in-hospital mortality and composite endpoint of stroke, cardiac events, and death in the United States. These findings highlight the need for strategies that ensure appropriate adoption of CAS

so that the benefits observed in clinical trials can be replicated in general practice.

## AUTHOR CONTRIBUTIONS

Conception and design: AQ, SC
Analysis and interpretation: SC, MK
Data collection: SC
Writing the article: AQ, SC, HM, SM, RK, GR
Critical revision of the article: AQ, MK
Final approval of the article: AQ
Statistical analysis: SC
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Overall responsibility: AQ, SC

## REFERENCES

1. Wholey MH, Al-Mubarek N, Wholey MH. Updated review of the global carotid artery stent registry. Catheter Cardiovasc Interv 2003;60:259-66.
2. Massop D, Dave R, Metzger C, Bachinsky W, Solis M, Shah R, et al. Stenting and angioplasty with protection in patients at high-risk for endarterectomy: SAPPHIRE worldwide registry first 2,001 patients. Catheter Cardiovasc Interv 2009;73:129-36.
3. Gray WA, Hopkins LN, Yadav S, Davis T, Wholey M, Atkinson R, et al. Protected carotid stenting in high-surgical-risk patients: the Archer results. J Vasc Surg 2006;44:258-68.
4. Iyer SS, White CJ, Hopkins LN, Katzen BT, Safian R, Wholey MH, et al. Carotid artery revascularization in high-surgical-risk patients using the carotid WALLSTENT and FilterWire EX/EZ: 1-year outcomes in the BEACH Pivotal Group. J Am Coll Cardiol 2008;51:427-34.
5. Higashida RT, Popma JJ, Apruzzese P, Zimetbaum P, MAVErIC I and II Investigators. Evaluation of the Medtronic exponent self-expanding carotid stent system with the Medtronic guardwire temporary occlusion and aspiration system in the treatment of carotid stenosis: combined from the MAVErIC (Medtronic AVE self-expanding CaRotid stent system with distal protection in the treatment of carotid stenosis) I and MAVErIC II trials. Stroke 2010;41:e102-9.
6. Gray WA. A cardiologist in the carotids. J Am Coll Cardiol 2004;43:1602-5.
7. Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010;363:11-23.
8. Millennium Research. Group. Crest clinical trial results find that carotid artery stenting is as safe and effective as conventional surgery. Available at: http://mrg.net/News-and-Events/Press-Releases/CREST-CLINICAL-TRIAL-RESULTS-FIND-THAT-CAROTID-ART.aspx. Accessed February 2012.
9. Alberts MJ, Latchaw RE, Selman WR, Shephard T, Hadley MN, Brass LM, et al. Recommendations for comprehensive stroke centers: a consensus statement from the Brain Attack Coalition. Stroke 2005;36:1597-616.
10. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, et al; American Heart Association/American Stroke Association Council on Stroke; Council on Cardiovascular Radiology and Intervention; American Academy of Neurology. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. Circulation 2006;113:e409-49.
11. McPhee JT, Schanzer A, Messina LM, Eslami MH. Carotid artery stenting has increased rates of postprocedure stroke, death, and resource utilization than does carotid endarterectomy in the United States. J Vasc Surg 2005;2008:1442-50, 50 e1.
12. Qureshi AI, Ezzeddine MA, Nasar A, Suri MF, Kirmani JF, Janjua N, et al. Is IV tissue plasminogen activator beneficial in patients with hyperdense artery sign? Neurology 2006;66:1171-4.
13. Khatri R, Tariq N, Vazquez G, Suri MF, Ezzeddine MA, Qureshi AI. Outcomes after nontraumatic subarachnoid hemorrhage at hospitals offering angioplasty for cerebral vasospasm: a national level analysis in the United States. Neurocrit Care 2011;15:34-41.
14. Nationwide Inpatient Sample. (NIS). Overview available at: http://www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed February 2012.
15. Groeneveld PW, Yang L, Greenhut A, Yang F. Comparative effectiveness of carotid arterial stenting versus endarterectomy. J Vasc Surg 2009;50:1040-8.
16. Qureshi AI, Hutson AD, Harbaugh RE, Stieg PE, Hopkins LN. Methods and design considerations for randomized clinical trials evaluating surgical or endovascular treatments for cerebrovascular diseases. Neurosurgery 2004;54:248-64; discussion: 264-7.
17. Wennberg DE, Lucas FL, Birkmeyer JD, Bredenberg CE, Fisher ES. Variation in carotid endarterectomy mortality in the Medicare population: trial hospitals, volume, and patient characteristics. JAMA 1998;279:1278-81.
18. Molyneux A, Kerr R, Stratton I, Sandercock P, Clarke M, Shrimpton J, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. Lancet 2002;360:1267-74.
19. Qureshi AI, Suri MF, Nasar A, Kirmani JF, Divani AA, He W, Hopkins LN. Trends in hospitalization and mortality for subarachnoid hemorrhage and unruptured aneurysms in the United States. Neurosurgery 2005;57:1-8; discussion: 1-8.
20. Ikawa F, Ohbayashi N, Imada Y, Matsushige T, Kajihara Y, Inagawa T, Kobayashi S. Analysis of subarachnoid hemorrhage according to the Japanese Standard Stroke Registry Study–incidence, outcome, and comparison with the International Subarachnoid Aneurysm Trial. Neurol Med Chir (Tokyo) 2004;44:275-6.
21. Cambria RP. Commentary on: Mas JL, Chatellier G, Beyssen B, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. N Engl J Med 2006;355:1660-1671. Perspect Vasc Surg Endovasc Ther 2007;19:201-3.
22. Khatri R, Chaudhry SA, Vazquez G, Rodriguez GJ, Hassan AE, Suri MF, et al. Age differential between outcomes of carotid angioplasty and stent placement and carotid endarterectomy in general practice. J Vasc Surg 2012;55:72-8.
23. Hopkins LN, Roubin GS, Chakhtoura EY, Gray WA, Ferguson RD, Katzen BT, et al. The Carotid Revascularization Endarterectomy versus Stenting Trial: credentialing of interventionalists and final results of lead-in phase. J Stroke Cerebrovasc Dis 2010;19:153-62.
24. Maud A, Vázquez G, Nyman JA, Lakshminarayan K, Anderson DC, Qureshi AI. Cost-effectiveness analysis of protected carotid artery stent placement versus endarterectomy in high-risk patients. J Endovasc Ther 2010;17:224-9.
25. Khan AA, Chaudhry SA, Sivagnanam K, Hassan AE, Suri MFK, Qureshi AI. Cost-effectiveness of carotid-artery stent placement versus endarterectomy in patients with carotid stenosis. J Neurosurg May 2012; [Epub ahead of print].
26. Krumholz HM, Peterson ED, Ayanian JZ, Chin MH, DeBusk RF, Goldman L, et al; National Heart, Lung, and Blood Institute working group. Report of the National Heart, Lung, and Blood Institute working group on outcomes research in cardiovascular disease. Circulation 2005;111:3158-66.
27. The Karolinska Stroke Update Consensus Statement 2004. Available at: http://www.strokeupdate.org/ALLCURRENT/Consensus/Consensus_2004/Cons_carotis_2004.htm. Accessed February 2012.
28. Nault P, Elkouri S, Daniel V, Blanchard ME, Okrainec K; Québec Vascular Outcome Research Team with Electronic eXpertise (Vortex). Modification of outcomes by lowering ischemic events after reconstruction of extracranial vessels (MOLIERE): an internet-based prospective study to evaluate and improve the effectiveness of carotid endarterectomy. J Vasc Surg 2008;47:530-6.
29. Qureshi AI, Vazquez G, Tariq N, Suri MF, Lakshminarayan K, Lanzino G. Impact of International Subarachnoid Aneurysm Trial results on treatment of ruptured intracranial aneurysms in the United States. J Neurosurg 2011;114:834-41.

30. Qureshi AI, Suri MF, Nasar A, Kirmani JF, Ezzeddine MA, Divani AA, et al. Changes in cost and outcome among US patients with stroke hospitalized in 1990 to 1991 and those hospitalized in 2000 to 2001. Stroke 2007;38:2180-4.
31. Chaturvedi S, Aggarwal R, Murugappan A. Results of carotid endarterectomy with prospective neurologist follow-up. Neurology 2000;55: 769-72.
32. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. N Engl J Med 2004;351:1493-501.
33. Broderick J, Brott T, Kothari R, Miller R, Khoury J, Pancioli A, et al. The greater Cincinnati/Northern Kentucky Stroke Study: preliminary first-ever and total incidence rates of stroke among blacks. Stroke 1998;29:415-21.
34. Qureshi AI, Chaudhry SA, Hassan AE, Zacharatos H, Rodriguez GJ, Suri MF, et al. Thrombolytic treatment of patients with acute ischemic stroke related to underlying arterial dissection in the United States. Arch Neurol 2011;68:1536-42.

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**REQUEST FOR SUBMISSION OF SURGICAL ETHICS CHALLENGES ARTICLES**

The Editors invite submission of original articles for the Surgical Ethics Challenges section, following the general format established by Dr. James Jones in 2001. Readers have benefitted greatly from Dr. Jones' monthly ethics contributions for more than 6 years. In order to encourage contributions, Dr. Jones will assist in editing them and will submit his own articles every other month, to provide opportunity for others. Please submit articles under the heading of "Ethics" using Editorial Manager, and follow the format established in previous issues.