

## Has the expanded use of carotid stents been justified?

### *Carotid Stents: Unleashed, Unproven*

Frank W. LoGerfo, MD

Primarily on the basis of data derived from the Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial,<sup>1</sup> the US Food and Drug Administration (FDA) has approved the use of carotid stents (CASs) in high-risk patients. The SAPPHIRE trial was published and much heralded as a randomized trial demonstrating that CASs were not inferior to carotid endarterectomy (CEA). Yet, the more recent Endarterectomy Versus Angioplasty in Patients with Symptomatic Carotid Stenosis randomized trial of CASs compared with CEA had to be stopped because the stroke rate with stents was so high that it triggered the safety guidelines of the study design.<sup>2</sup> How can we explain the striking difference in outcome between these 2 studies, and how did it happen that the FDA was so convinced of the quality and validity of the SAPPHIRE trial that it granted approval for CASs? An examination of the SAPPHIRE trial—its conduct, data collection and analysis, the circumstances of publication, the presentation to the FDA Advisory Panel, and its consequent approval—is the primary focus of this article. This is a case study of the flaws in our system for the evaluation and approval of medical devices that warrant serious reflection on our ability to properly create and act on accurate information and live up to our commitment to evidence-based decision making.

#### **Response by Samuelson et al p 1601**

As it now stands, existing studies leave us with the unfortunate but not unreasonable conclusion that no scientific basis exists for the use of CASs as approved by the FDA, and

in the absence of change, there is every reason to doubt the capability of our current system to protect the public from unnecessary risk in the future. Although this article focuses on just 1 example of how our systems are flawed at multiple levels to provide a reliable assessment of CASs and other technology, readers seeking further examples can find a wealth of related information.<sup>3–5</sup>

#### **The SAPPHIRE Trial**

The SAPPHIRE trial was originally designed as a randomized trial involving 29 centers comparing the outcome of CEA with carotid stenting. The exact details of patient selection and the rationale for the patient assignment within the trial to CEA or CAS are not completely clear from the published data. It seems that patients were seen by both a vascular surgeon and an interventionalist. If a patient was deemed by both to be suitable for either procedure, the patient was randomly assigned to CEA or CAS. If the vascular surgeon did not believe that CEA could be safely performed but the interventionalist thought CAS was appropriate, the patient was not randomized but was assigned to a stent registry. Likewise, when the opposite was true, the patient was assigned to a surgery registry. This is, in essence, an opinion-based entry criterion rather than a protocol-based criterion. A total of 2294 patients were referred for evaluation, of whom 747 met the criteria for inclusion in the study. However, only 334 of the eligible patients underwent randomization; 406 were entered into the stent registry, and 7

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.


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*Circulation* is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.106.647271



were entered into the surgical registry. This further process of exclusion represents a tremendous opportunity for bias. However, because no data are provided as to why, after meeting the protocol-defined inclusion criteria, patients were deemed acceptable to CAS but rejected for CEA, there is no way to assess the bias pattern. Ultimately, the assignment was based on opinion and was not necessarily predictable. For example, it is possible that a vascular surgeon, eager to gain experience and meet a numbers requirement for CAS credentialing, might turn down a patient for randomization to perform CAS. Such are the uncertainties of an opinion-based entry criterion.

The original intent of the study was to randomize 600 to 900 patients with a maximum sample size of 2900. The study was set up with certain statistical objectives, including the method of statistical analysis, the timing of interim analyses, the conditions for termination, and a final test to determine the primary end point. As the study unfolded, however, all of these statistical protocols were violated. The trial was terminated because of a decrease in enrollment; the interim analyses were not performed; and an alternative statistical method was used to determine the end point. After a lengthy description of the original study design, the authors state, "In early 2002, the pace of enrollment in the trial abruptly slowed, because several nonrandomized CAS registries had become available." One such registry was their own, and they chose, as permitted in the SAPHIRE design, to assign more of the study-qualified patients to their stent registry than to the randomized study. For these investigators, an incentive or requirement no longer existed to determine whether CAS was effective as soon as they had the opportunity to use CAS without such evidence. As an unfortunate consequence, their study was underpowered to answer the question it posed as to whether CAS was inferior to CEA. Despite this shortcoming, the study was published and formed the primary basis for FDA approval.

The primary end point of the trial was the cumulative incidence of death, stroke, or myocardial infarction within 30 days of the procedure or death or ipsilateral stroke between 31 days and 1 year. No significant statistical difference existed with regard to the primary end point at 30 days. At the end of 1 year, the authors, using a statistical analysis that was an alternative to the study design, reported a significant difference in the primary composite end point of 12.2% for CAS and 20.1% for CEA ( $P < 0.05$ ). This difference, in favor of CAS, is highly attributable to the differing incidence of non-Q-wave myocardial infarctions, as determined by a 2-fold elevation in creatinine kinase with a positive MB fraction. No other criteria were required for the diagnosis of myocardial infarction. For this reason, the significance of the diagnosis cannot be compared with other studies of perioperative myocardial infarction, usually using the World Health Organization criteria.<sup>6,7</sup> The inclusion of non-Q-wave infarction as an end point equivalent to death or stroke is highly controversial. The authors justified this decision by stating

that a perioperative non-Q-wave infarction confirms an increase in the risk of myocardial infarction by a factor of 27 in the subsequent 6 months. That may be true; however, for some reason, that concern was not validated by their own data in this study because no subsequent Q-wave infarctions occurred in the CEA group between 31 days and 1 year despite the higher incidence of "enzyme" infarctions. Another reason for the higher incidence of enzyme infarctions may be that the assays were done more often in the CEA group than in the CAS group because patients were studied every 24 hours while in the hospital and the CEA group on average was in the hospital 1 day longer than the CAS group. Unless the number and timing of enzyme studies were identical between the 2 groups, the data are not valid. Thus, for a number of reasons, the significance of myocardial infarction and the differences between groups represent data that cannot be relied on for any conclusion. The key issues here are stroke and death. However, the study was underpowered to determine noninferiority in outcomes under the conditions defined in the protocol, as was eventually noted by the FDA.

Missing from the SAPHIRE data is any reference to local or systemic complications of stent placement and administration of intense antiplatelet therapy. Is it possible that no such complications occurred? To put this question in perspective, at least 1 similar registry of CASs exists in which poststent cerebral hemorrhage in a patient on antiplatelet therapy is not counted as a stroke but as "other neurological."<sup>8</sup> This may or not have been the case in the SAPHIRE study, but to have no anticoagulation-related local or systemic problems in a study this large and involving major arterial stent placement via percutaneous femoral artery puncture is distinctly unusual and at least warrants some comment or verification. Also missing from SAPHIRE is any effort to identify "silent" cerebral ischemia, an outcome at least as relevant as silent myocardial ischemia. Subsequent studies have shown silent infarcts in  $\approx 40\%$  of patients even when a protective filter is used.<sup>9,10</sup> These are hard-copy, irrefutable data that warrant attention. Are these infarcts truly silent? Should we look for cognitive or emotional effects? Does embolization continue after the procedure?

The SAPHIRE study design also was unique among carotid studies in that no tracking of outcomes based on degree of stenosis took place. What was it, and was it equal in the randomized arms? If the randomization were truly applied to all eligible patients, it would be extremely unlikely that 20% of the patients in the randomized trial had recurrent stenosis as an indication. At the primary institution, the Cleveland Clinic, the reported volume of CEA between 1989 and 1995 was 371 per year.<sup>11</sup> During the overlapping interval, 1989 to 1999, the volume of redo CEA was 20 per year, or 5.4%,<sup>12</sup> a number that is consistent with other high-volume centers.<sup>13</sup> Credibility is strained to say that this fraction is now 20%, and this discrepancy adds fuel to the argument that the opinion-based entry criteria are scientifically invalid. The

reason is that recurrent stenosis is a smooth, fibrotic lesion that many believe is highly suited to CAS, with less risk of embolization during the procedure. A study that includes a large number of restenotic lesions may be favorable to CAS. Thus, we are saddled here with the appearance of bias. That bias would have been eliminated with protocol-based entry criteria.

These data were presented to the FDA at a meeting of the Circulatory System Devices Advisory Panel on April 21, 2004.<sup>14</sup> The response of the FDA staff reviewers warrants praise and is encouraging. Heng Li, PhD, the FDA statistical reviewer, summarized the randomized trial statistical analysis. The recorded minutes of Dr Li's findings stated, "Dr. Li provided a detailed explanation of the planned statistical methodology and the 'stopping' rule it incorporated. In his analysis, the evidence would not have indicated that the trial should have been stopped (and non-inferiority declared), if the original protocol had been followed."

The minutes continued: "The sponsor made unplanned comparisons between the stent registry and the CEA arm of the randomized study. Because the patient characteristics in the two groups by definition are different, a straightforward comparison is not appropriate. To address this issue, the sponsor used a propensity score method to compare the two groups, attempting to make a post-hoc claim of non-inferiority of the stent registry to the randomized CEA arm." In other words, because the data from the biased-but-randomized arm were insufficient to make the case for CAS, data from the nonrandomized arm were pulled in to an alternative statistical analysis.

Dr Li continued, "In summary, the original group sequential protocol was not followed, and the FDA was not informed of any change in protocol. Any non-inferiority claim based on the sponsor's post-hoc propensity score analysis is problematic."

Ronald Weintraub, MD, FDA consultant, reviewed the methodology of the SAPHIRE pivotal study. He stated, "The sponsor's study findings are limited because the pre-specified enrollment plan and study analysis was not carried to completion in the SAPHIRE randomized study."

Lisa Cannel, FDA lead reviewer, commented, "The sponsor terminated the pivotal trial early, citing too many competing studies, physicians' reluctance to randomize, and surgeons' unwillingness to refer patients. The competing studies involved CORDIS's own devices and were facilitated by CORDIS." Thus, the sponsor (CORDIS) effectively undermined its own study and placed the responsibility on its own investigators.

Despite these concerns, including the misgivings of the FDA statistician, the FDA panel of clinician experts voted 6 to 5 in favor of CASs as a legitimate alternative to CEA in both symptomatic and asymptomatic patients who fall within a broad definition of high risk. With the shortcomings of the study and the complete absence of study design or data comparing symptomatic and asymptomatic patients as

identified by the FDA staff, how did this all come about? How does a study with these shortcomings warrant publication in a major medical journal, and how, in spite of this, did the FDA panel approve the device? Such a challenge to logic and science requires that we examine the FDA approval process.

At the FDA, the data were reviewed by an advisory panel consisting of 11 voting members: 6 cardiologists, 2 interventional radiologists, 2 vascular surgeons, and 1 neurologist. All of these people submitted disclosures. Six of the voting members were acknowledged to have current or past interests in firms at issue. These interests were waived because they were in matters not related to the specific agenda. In other words, these panelists had existing interests in the corporate sponsor, but those interests were with products or devices other than CASs. Others have examined the complexities that arise under these circumstances.<sup>3,4</sup> It is notable that the FDA itself, under the Prescription Drug User Free Act, is funded by the corporate sponsor. Others have posed this question: Who then is their client, the corporation or the public?<sup>15,16</sup>

The lead author of the report was an inventor of the Angioguard embolic protection device used in the SAPHIRE Trial and was a founder of the Angioguard Corp, purchased by Johnson & Johnson in 1999, for \$40 million.<sup>17</sup> In fact, of the 15 authors of the SAPHIRE Trial, 10 acknowledged support in one form or another from the CORDIS Corp; in addition, 2 of the authors were employees of the CORDIS Corp. This level of disclosure of relationships with the corporate sponsor was unusually high but does not prove that any effective influence was exerted on the authors. The disclosure standard set by the National Institutes of Health and the Association of Medical Colleges was met.<sup>18</sup> The underlying philosophy here seems to be that once the disclosure standard is met, readers can form their own opinions. Unfortunately, however, readers cannot expunge from the literature studies such as SAPHIRE that do not follow scientific standards and, once published, can be used to create public policy. In this case, the clinical science would have to be of the highest standard to overcome the burden of competing interests; in this case, as will be shown, the science was far from that.

The specific role of the lead author is a little different. The recommendations of a recent roundtable on this very subject, including editors of the *American Heart Journal* and *The Lancet*,<sup>19</sup> concluded: "The inventor must not be involved with the clinical studies and must be excluded from enrolling patients, analyzing the data, and writing the manuscript." The publisher of SAPHIRE, however, was not responsible for approval of the inventor as the principal investigator or lead author. That, in fact, was primarily the responsibility of the author's institution and its internal review processes. Nonetheless, the publisher has the admittedly complex task of examining all aspects of a clinical study to ensure the quality of information through which (in this case) public policy was

influenced. Why dwell on these concerns about compromised science leading to public policy? Because once a product is unleashed in the medical marketplace, it is extremely difficult to reverse that decision. An entire industry, along with jobs and political influence, has developed around carotid stenting. Before FDA approval, not much was at stake, but now a monetary force has been created. Once created, the industry interest can be protected and maintained by a moving target of slightly new devices, slightly different technology, and new target populations, all of which make it extremely difficult to force the removal of a product from the marketplace.

### Other Trials

Another CAS trial that played a role in the FDA approval process is the ACCULINK for Revascularization of Carotids in High-Risk Patients (ARCHeR) trial.<sup>19a</sup> This trial is self-described as a series of 3 sequential, multicenter, nonrandomized, prospective studies. Thus, this was not even an attempt at a controlled trial. Instead, the authors used a historical control for carotid surgery when they estimated the combined adverse event rate to be an extraordinary 14.4%. Without going further, these facts alone eliminate this as a trial of sufficient scientific quality to justify a change in public policy or to bring a device to the marketplace.

Two recently published European trials favor CEA and raise serious questions about the safety of CAS. The Endarterectomy Versus Angioplasty in Patients with Symptomatic Carotid Stenosis trial was, in fact, a protocol-based randomized comparison of CAS with CEA, an essential scientific criterion not met by either of the above-mentioned trials. The trial was stopped prematurely by its safety committee for reasons of safety and futility. The rate of any stroke or death was 9.6% for CAS compared with 3.9% for CEA, with a relative risk of 2.5 (95% CI, 1.2 to 5.1;  $P < 0.01$ ). The flaws in this study included the limited carotid stenting experience requirements of the interventionalists. In addition, embolic protection devices were not used in the early phase of the trial. Nonetheless, the experimental design and conduct of this study were at a scientific standard well above the US studies. The Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE) trial<sup>20</sup> was a multinational, multicenter, randomized controlled trial of CAS versus CEA with an outcome of any stroke or death of 7.68% versus 6.51% and a relative risk of 1.19 (95% confidence interval, 0.75 to 1.92). These 30-day outcome results were interpreted to fail to confirm noninferiority of CAS; longer-term results are pending. The study was stopped prematurely for funding reasons, and many would fairly argue that, at this point, it is inconclusive. However, it is also reasonable to ask whether approval would have been granted if data from these trials had been presented to the FDA.

### Conclusions

As it stands today, the FDA has approved the use of CASs for symptomatic patients with  $>50\%$  stenosis and for asymptomatic patients with  $>80\%$  stenosis who are also “high risk.” As noted, no valid data are available on which to justify the use of stents in symptomatic patients from either the SAPHIRE or ARCHeR trial. For asymptomatic patients, it is easy to suggest that a group of patients exists who are at such high risk for surgery that CAS is justified for stroke prevention. However, the immediate question then is whether such frail patients are better off with no intervention and modern drug management with platelet inhibitors and statins. CAS is not innocuous and has its own risk factors for periprocedural hemodynamic complications, stroke, and death.<sup>21,22</sup> CAS also is associated with a significantly higher complication rate when a contralateral carotid occlusion is present, age exceeds 80 years, or ulceration of the carotid plaque is present.<sup>23</sup> These are the very same risk factors used to define high risk for surgery. Radiation-induced carotid stenosis has been considered a lesion that is better treated with CAS, but recent data demonstrate an extraordinary restenosis rate of 80%.<sup>24</sup> What then are the valid, protocol definitions of high risk that make it safer to do CAS than CEA? Currently, the Centers for Medicare and Medicaid Services is considering establishing reimbursement for CAS in high-risk asymptomatic patients and, instead of using a protocol, is proposing the following criterion: “that the determination of high-risk for CEA be performed by a surgeon credentialed to perform CEA.”<sup>25</sup> This would be an embodiment of one of the primary flaws of SAPHIRE, that is, an opinion-based criterion by a person who often can perform both CEA and CAS or may have other obligations that influence the decision. If bone fide medical criteria exist that define high risk pertaining only to surgery, it should be possible to specify them. If we do not have that information, we should perform the scientifically designed studies necessary. For the moment, no such criteria have been defined. The statement that CAS provides the opportunity for stroke prevention for patients who are too high a risk for CEA has no foundation; in fact, under these circumstances, there is reason to be concerned that CAS is harmful compared with medical therapy alone.

The bottom line here is that we need well-conducted, scientifically designed randomized trials to get answers about CASs. SAPHIRE represents a failed opportunity. The only existing randomized trial in this country is the Carotid Revascularization Endarterectomy Versus Stent Trial (CREST),<sup>26</sup> a National Institutes of Health-sponsored trial that began long before SAPHIRE but is moving comparatively slowly now that the FDA has approved CAS and CAS registries. Regrettably, we have an organ of government, the National Institutes of Health, that does not have support from another, the FDA. It is, in essence, science versus commerce and a major flaw in our system. If the FDA had refused to allow any stent registries until CREST was completed, we would now have an extensive body of valid information of

which we could be proud and on which safe public policy could be based. Instead, we have settled for unscientific studies designed to win expeditious FDA approval. As a result, CAS was approved for use in symptomatic patients, a subgroup for which we have virtually no data, and asymptomatic patients, a subgroup for which we have flawed data. This can be described as the commercialization of science. It is not what the public deserves from its faith in clinical scientists, its respect for prestigious journals and institutions, and its dependence on regulatory agencies.

In the end, no one can make a strong argument for CASs. To the contrary, the most scientifically valid data, the European studies, are unfavorable to CAS. Unfortunately, CASs, having FDA approval, are already in widespread use despite conflicting data about their safety. Going forward, physicians, editors, institutional review boards, governmental agencies, and readers must be more vigilant and critical of any commercialization of clinical research. The validity of our debate can be no better than the validity of the available data.

It should be noted that the biotechnology industry does play an essential and vital role in the advancement of medical care. As eager as industry might be to see a new proprietary device arrive successfully in the marketplace, no business entity can ultimately benefit from inaccurate information. Clinical scientists funded by industry must walk a difficult ethical line and maintain scientific rigor in the face of countervailing pressures. This balancing act protects both parties. In the case of the rush to FDA approval of CASs, the flawed data and the appearance of impropriety, whether it occurred or not, are such that a disinterested party would not agree that we have data on which public safety can depend. If we adhere to the scientific method and are committed to evidence-based medicine, we should cease debate until we complete a scientifically valid study such as CREST.


In the end, it may be that CASs are as effective as or more effective than CEA or noninterventive medical therapy. It is our role as clinician-investigators to fully use the resources available to us to design and implement sound clinical studies. Until we have done that, we have no basis for supporting the current use of CASs.

## Disclosures

None.

## References

- Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Whitlow P, Strickman NE, Jaff MR, Popma JJ, Sneed DB, Cutlip DE, Firth BG, Ouriel K. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2004;351:1493–1501.
- Mas JL, Chatellier G, Beyssen B, Branchereau A, Moulin T, Becquemin JP, Larrue V, Lievre M, Leys D, Bonneville JF, Watelet J, Pruvo JP, Albuquer JF, Viguier A, Piquet P, Garnier P, Viader F, Touze E, Giroud M, Hosseini H, Pillet JC, Favrole P, Neau JP, Ducrocq X. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med*. 2006;355:1726–1729.
- Kassirer JP. *On the Take: How Medicine's Complicity With Big Business Can Endanger Your Health*. New York, NY: Oxford University Press; 2005.
- Angell M. *The Truth About Drug Companies: How They Deceive Us and What to Do About It*. New York, NY: Random House; 2004.
- Hawthorne F. *Inside the FDA: The Business and Politics Behind the Drugs We Take and the Food We Eat*. Hoboken, NJ: John Wiley & Sons; 2005.
- Chedrawy E, Hall R, Nedelcu V. Postoperative elevation of creatine kinase (CK-MB): does it contribute to diagnosis of myocardial infarction. *Can J Anaesth*. 1997;44:843–848.
- Landesberg G, Shatz V, Akopnik I, Wolf YG, Mayer M, Berlatzky Y, Weissman C, Mosseri M. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. *J Am Coll Cardiol*. 2003;42:1547–1554.
- Guidant Endovascular Solutions. *Clinical Update for Physicians: RX ACCULINK Carotid Stent System, PMA P040012*. Santa Clara, Calif: Guidant Endovascular Solutions; March 20, 2006.
- Maleux G, Demaerel P, Verbeken E, Daenens K, Heye S, Van Sonhoven F, Nevelsteen A, Wilms G. Cerebral ischemia after filter-protected carotid artery stenting is common and cannot be predicted by the presence of substantial amount of debris captured by the filter device. *Am J Neuroradiol*. 2006;27:1830–1833.
- Hammer FD, Lacroix V, Duprez T, Grandin C, Verhelst R, Peeters A, Cosnard G. Cerebral microembolization after protected carotid artery stenting in surgical high-risk patients: results of a 2-year prospective study. *J Vasc Surg*. 2005;42:847–853.
- Hertzer NR, O'Hara PJ, Mascha EJ, Krajewski LP, Sullivan TM, Beven EG. Early outcome assessment for 2228 consecutive carotid endarterectomy procedures: the Cleveland Clinic experience from 1989 to 1995. *J Vasc Surg*. 2001;33:663–664.
- O'Hara PF, Hertzer NR, Karafa MT, Mascha EJ, Krajewski LP, Beven EG. Reoperation for recurrent carotid stenosis: early results and late outcome in 199 patients. *J Vasc Surg*. 2001;34:5–12.
- Mozes G, Sullivan TM, Torres-Russotto DR, Bower TC, Hoskin TL, Sampaio SM, Gloviczki P, Panneton JM, Noel AA, Cherry KJ. Carotid endarterectomy in SAPHIRE-eligible high-risk patients: implications for selecting patients for carotid angioplasty and stenting. *J Vasc Surg*. 2004;39:958–965.
- Summary minutes: Meeting of the Circulatory System Devices Advisory Panel, Open Session. April 21, 2004; Gaithersburg, Md.
- How Independent Is the FDA? <http://www.pbs.org/wgbh/pages/frontline/shows/prescription/hazard/independent.html>.
- Conflict of interest ends in dismissal. *Vascular News*. September 1, 2006; 1–2.
- Ohk T. Conflicts of interest and double standards. *Endovasc Today*. 2006;5:23–24.
- Drzen JM, Curfman GD. Financial associations of authors. *N Engl J Med*. 2002;346:1901–1902.
- Holmes DR, Firth BG, James A, Winslow R, Hodgson PK, Gamble GI, Popp RL, Harrington RA. Conflict of interest. *Am Heart J*. 2004;147:228–237.
- Gray WA, Hopkins LN, Yadav S, Davis T, Wholey M, Atkinson R, Cremonesi A, Fairman R, Walker G, Verta P, Popma J, Virmani R, Cohen DJ, ARCHER Trial Collaborators. Protected carotid stenting in high-surgical-risk patients: the ARCHER results. *J Vasc Surg*. 2006;44:258–269.
- SPACE Collaborative Group. 30 Day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomized non-inferiority trial. *Lancet*. 2006;368:1239–1247.
- Gupta R, Abou-Chebl A, Bajzer CT, Schumacher HC, Yadav JS. Rate, predictors, and consequences of hemodynamic depression after carotid artery stenting. *J Am Coll Cardiol*. 2006;47:1538–1543.
- Cayne NS, Faries PL, Trocciola SM, Saltzberg SS, Dayal RD, Clair D, Rockmand CB, Jacobowitz GR, Maldonado T, Adelman MA, Lamperello P, Riles TS, Kent KC. Carotid angioplasty and stent-induced bradycardia and hypotension: impact of prophylactic atropine administration and prior carotid endarterectomy. *J Vasc Surg*. 2005;41:956–961.

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23. Hofmann R, Niessner A, Kypta A, Steinwender C, Kammler J, Kerschner K, Grund M, Leisch F, Huber K. Risk score for peri-interventional complications of carotid artery stenting. *Stroke*. 2006;37:2557–2561.
24. Protack CD, Bakken AM, Saad WA, Illig KA, Waldman DL, Davies MG. Radiation arteritis: a contraindication to carotid stenting? *J Vasc Surg*. 2007;45:110–117.
25. Centers for Medicare and Medicaid Services. Proposed decision memo for percutaneous transluminal angioplasty (PTA) of the carotid artery concurrent with stenting (CAG-00085R3). Available at: <http://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?id=194>. Accessed March 1, 2006.
26. Hobson RW, Howard VJ, Brott TG, Howard G, Roubin GS, Ferguson RD. Organizing the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST): National Institutes of Health, Health Care Financing Administration, and industry funding. *Curr Control Trials Cardiovasc Med*. 2001;2:160–164.

## Response to LoGerfo

L. Nelson Hopkins, MD

“Lies, damn lies, and statistics....” In today’s medical literature, it is possible to find “data” to support almost any position. In Endarterectomy Versus Angioplasty in Patients With Severe Symptomatic Carotid Stenosis (EVA-3S) and Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE), we have conflicting studies with significant flaws (not unlike most randomized studies). The unassailable fact is that carotid endarterectomy (CEA) is a good operation. However, many years’ experience and a body of literature demonstrate that many patients are at increased risk for CEA, as exemplified by the patients excluded from the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Atherosclerosis Study (ACAS) (identified as high-risk patients on the basis of the trial designers’ surgical experience) and the objective performance criteria (predicted risk of CEA for patients in high-risk carotid artery stenting [CAS] registries) developed by the Food and Drug Administration after rigorous literature review. As a surgeon who has performed CEA procedures over the last 30 years, who participated in NASCET, and who also has performed CAS procedures since 1994 (while participating in most Food and Drug Administration–sponsored trials), I find that nothing is more frustrating than facing a patient in whom the known risk for CEA is excessive and for whom no reimbursable alternative exists, a not uncommon scenario. In 2007, equipoise exists between CEA and CAS. The Cardiac Revascularization Endarterectomy Versus Stent Trial (CREST), like all the other CAS trials, will teach us much about CAS relative to CEA but will not eliminate one procedure or the other. Today, the important question is not “Which is better, CEA or CAS?” but rather “Which procedure is better for a given patient?” and “Are the risk factors excessive for revascularization (with either technique)?”—suggesting a role for best medical therapy.



## *The Argument to Support Broader Application of Extracranial Carotid Artery Stent Technology*

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**A**s new technology becomes available, the stent technique for the extracranial carotid artery continues to evolve into a safer, more effective therapy for stroke prevention. With the availability of embolic protection, improved stent designs, and added endovascular physician experience, outcomes for carotid artery stenting (CAS) now consistently parallel those for carotid endarterectomy (CEA). Although carotid endarterectomy was established as the gold standard for carotid revascularization, the available scientific evidence must continue to be interpreted in the context of further advancements in nearly all related areas of medicine. One multicenter randomized trial and several nonrandomized registries have successfully established the CAS indications for patients with high surgical risk and have provided evidence to support the use of CAS techniques in patients with low surgical risk. Clinicians must continue to improve their understanding of patient-specific factors and conduct research that will refine indications while optimizing current medical therapy and that will integrate CAS and carotid endarterectomy as complementary treatments.

the gold standard for extracranial carotid revascularization, the available scientific evidence must continue to be interpreted in the context of further advancements in nearly all related areas of medicine. The current research comparing CAS and CEA has not shown a clinically robust and statistically significant difference between the 2 treatments. When differences do exist, clinicians must continue to refine patient-specific indications and to conduct further research to understand these complex risk-benefit analyses in the context of advanced medical treatments and complementary revascularization techniques. The following review details the argument to support implementation of CAS technology for athero-occlusive carotid artery disease beyond the population of patients considered high risk for surgery.

### **Scientific Evidence for CEA**

The surgical outcomes and indications for CEA have been studied more closely than any other surgical procedure. In the 1970s and 1980s, scientific evidence for the efficacy of CEA was lacking. Two randomized trials failed to find a reduction in stroke or death rates among surgically treated patients because of high perioperative morbidity.<sup>1,2</sup> Reported rates for combined stroke and death were as high as 20%.<sup>3–5</sup> In 1982 to 1983, an audit conducted by the Cerebrovascular Section of the American Association of Neurological Surgeons found no consensus for surgical indications, type of operation, or use of intraoperative monitoring.<sup>4</sup> Furthermore, the authors of a large study of CEA among Medicare recipients alleged that

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### **Response by LoGerfo p 1610**

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#### **Introduction**

The outcomes for CAS have been improving over the past 10 years and now appear nearly equivalent to those for CEA. In fact, many historical similarities are seen in the development of these 2 techniques. Although CEA was established as

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(*Circulation*. 2007;116:1602-1610.)

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*Circulation* is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.106.670034

32% of cases were performed for questionable or inappropriate indications.<sup>6</sup>

From this controversial setting grew 4 multicenter, randomized clinical trials: the North American Symptomatic Carotid Endarterectomy Trial (NASCET),<sup>7,8</sup> European Carotid Surgery Trial (ECST),<sup>9,10</sup> Asymptomatic Carotid Atherosclerosis Study (ACAS),<sup>11</sup> and Asymptomatic Carotid Surgery Trial (ACST).<sup>12</sup> At a time when the validity and indications for CEA were in question, these 4 studies established the role for CEA and helped define a new standard for medical research. With publication of the results of NASCET<sup>8</sup> and ECST,<sup>10</sup> performing CEA for symptomatic patients with 70% to 99% (NASCET) carotid stenosis or selected patients with 50% to 69% stenosis became a class IA indication within the American Heart Association guidelines.<sup>13</sup> This means that CEA had demonstrated efficacy on the basis of data derived from multiple randomized clinical trials.

The general population of patients with carotid stenosis is different from those who met the strict NASCET eligibility criteria.<sup>14</sup> NASCET collaborators excluded patients if they were  $\geq 80$  years of age or had severe intracranial stenosis; liver, kidney, or lung failure; cardiac valve or rhythm disorder; previous ipsilateral CEA; uncontrolled hypertension or diabetes mellitus; or recent myocardial infarction (MI) or major surgery.<sup>8</sup> For the purposes of the trial, these patients were considered to have confounding risks for perioperative morbidity (high surgical risk). Since NASCET, patients undergoing carotid revascularization often have been divided into low-surgical-risk and high-surgical-risk groups. More recently, classification of patients by their surgical risk has been the foundation of the CAS trials.

The practice of CEA also is quite different now, nearly 20 years after NASCET began. Continued advances have molded surgical technique. These include the timing of surgery after neurological symptom onset, synthetic patch grafts, new shunt designs, new antiplatelet medications, and differing methods of perioperative management.<sup>15–18</sup> As these new methods of CEA were introduced into clinical use, very few were reestablished with class IA evidence.

For asymptomatic lesions, the degree of benefit is not as large, and the indications for surgical revascularization are still debated. Although the first 3 randomized trials in asymptomatic patients failed to identify a reduction in stroke or death for CEA,<sup>19–21</sup> in ACAS and ACST, a 5.4% to 5.9% absolute risk reduction was identified over 5 years.<sup>11,12</sup> The risks of surgery and angiography detract from the potential benefit, and a perioperative morbidity of  $>3\%$  minimizes any benefit. However, since ACAS was published, nearly 75% of CEAs in the United States are performed on asymptomatic patients (versus 34% in 1981).<sup>22</sup>

In the major clinical trials, carefully selected patients with low surgical risk were operated on by highly experienced surgeons at high-volume medical centers. Other studies have shown that the low complication rates seen in NASCET and

ACAS are not always obtained within the general population. Reported perioperative stroke and death rates range from 0%<sup>23</sup> to 11.1%<sup>24</sup> for symptomatic patients and 0%<sup>25</sup> to 5.5%<sup>24</sup> for asymptomatic patients.

Use of 1992 to 1993 mortality data from 113 000 Medicare recipients showed that patients treated in hospitals participating in NASCET or ACAS had a 1.4% perioperative mortality.<sup>14</sup> This rate compares with 0.6% reported in NASCET and 0.1% reported in ACAS.<sup>8,11</sup> In this Medicare population-based study, CEA-related mortality rates were higher (2.5%) for low-volume hospitals<sup>14</sup> (although other reports have found only small differences in mortality based on hospital volume [0.2%]).<sup>26</sup>

Numerous factors have been shown to influence the combined stroke and death rates for patients undergoing CEA. Common medical comorbidities and their associated rates for perioperative stroke and death include the following: congestive heart failure, 8.6%<sup>27,28</sup>; age  $>75$  years, 7.5%<sup>27,28</sup>; postendarterectomy restenosis, 10.8%<sup>29</sup>; ipsilateral carotid siphon stenosis, 13.9%<sup>27</sup>; intraluminal thrombus, 10.7% to 17.9%<sup>27,30</sup>; contralateral carotid occlusion, 14.3%<sup>31</sup>; and CEA combined with coronary artery bypass grafting, 16.4% to 26.2%.<sup>32,33</sup> However, in these cases, the natural history of the carotid disease also is less favorable. Therefore, the decision for surgical treatment is heavily dependent on patient-specific factors, including medical/surgical history, anatomic characteristics, and institutional experience.

In the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) “natural history” study, the mean duration of follow-up for 1115 patients with asymptomatic internal carotid artery stenosis treated with medical therapy alone was 37.1 months.<sup>34</sup> This trial has identified subgroups of patients having asymptomatic carotid stenosis with increased risk for stroke and death. The group with the highest risk (82% to 99% stenosis by NASCET criteria,<sup>8</sup> history of contralateral transient ischemic attack, and serum creatinine level  $>0.085$  mmol/L) had a 4.3% annual ipsilateral stroke rate compared with 0.7% in the group with the lowest risk.<sup>34,35</sup> However, at this time, the data are insufficient to tell us the true natural history of patients with severe asymptomatic carotid stenosis and significant medical comorbidities. This population of patients is likely at substantially higher risk for stroke than the low-surgical-risk patients studied in all of the major CEA trials.<sup>36</sup>

Several medical societies have set standards for complication rates in their CEA guidelines. Among them, the guidelines for the AHA<sup>13</sup> and the Canadian Neurosurgical Society<sup>37</sup> establish a 6% limit for surgical risk in symptomatic patients<sup>13</sup> and 3% limit for surgical risk in asymptomatic patients, assuming  $>5$ -year life expectancy.<sup>33</sup> Other medical societies such as the Canadian Stroke Consortium do not endorse CEA for asymptomatic patients at all.<sup>38</sup>

## Medical Treatment for Cerebrovascular and Extracranial Carotid Artery Atherosclerotic Disease

The indications for extracranial carotid revascularization and the acceptable rates for periprocedural complications were based on the risk of treating the disease without surgery. However, since the major randomized trials of CEA were initiated, the treatments that constitute best medical therapy also have continued to improve.

In NASCET, the primary medical intervention was 1300 mg/d aspirin.<sup>8</sup> This dose of aspirin is no longer used because lower doses have proved equally efficacious with fewer gastrointestinal side effects.<sup>39–41</sup> Aspirin alternatives such as clopidogrel and ticlopidine are available,<sup>15,18</sup> and the aspirin-dipyridamole combination was shown to be more effective than aspirin alone.<sup>42</sup>

Methods for blood pressure control were not specified in NASCET, and at the time, blood pressure goals were more loosely defined. Today, it is understood that blood pressures <120 to 130/70 mm Hg are optimum for cardiovascular risk reduction in patients with medical comorbidities.<sup>13,43,44</sup> For primary stroke prevention, a large meta-analysis found that regardless of the agent used, a 10-mm Hg reduction in systolic blood pressure produced a 31% relative risk reduction for stroke.<sup>45</sup> Often, a carefully balanced combination of medications is required for optimum blood pressure control.<sup>45</sup> For secondary stroke prevention, proven agents include angiotensin-converting enzyme inhibitors<sup>43,46</sup> and the combination of a thiazide diuretic with angiotensin-converting enzyme inhibitor.<sup>46</sup> Diabetes mellitus and tobacco use also are known risk factors, but achieving proof of benefit with specific treatments has been more elusive.<sup>13,47–51</sup>

Over the past 10 years, statins have assumed a prominent role in cerebrovascular and cardiovascular risk modification.<sup>52–56</sup> In a recent review of 180 patients undergoing CAS, a significantly higher 30-day rate of stroke, MI, or death was identified among patients who were not receiving preprocedural statin therapy.<sup>57</sup> A similar result was obtained for symptomatic patients undergoing CEA.<sup>58</sup> In a third study of patients receiving medical treatment for severe carotid artery disease, statin use was associated with significantly lower rates of stroke, MI, or death.<sup>59</sup>

Although the medical treatments for carotid atherosclerotic disease and related comorbidities have advanced considerably over the past 20 years, comprehensive evaluations that prove the additive benefit of combination therapy are lacking, and use of these adjunctive treatments is low. For example, a study published in 2004 analyzed private insurance data of prescriptions filled after CEA from 1999 to 2001.<sup>60</sup> Prescriptions were supplied to 1049 patients at the following rates throughout the first postoperative year: statins, 38%;  $\beta$ -blockers, 24%; calcium channel blockers, 19%; angiotensin-converting enzyme inhibitors, 19%; diuretics, 13%; angiotensin receptor blockers, 6%; and nonaspirin antiplatelets, 5%. Therefore, medical treatment outcomes and guidelines

for surgical intervention may depend on periodic reevaluation and adjustment of the risk-to-benefit analysis.

## Carotid Artery Angioplasty and Stent Placement

Into this sophisticated and evolving medical landscape, CAS was introduced as a means to revascularize diseased vessels while minimizing the risks from open surgery or general anesthesia. NASCET-like evidence of benefit and safety of CAS has been required before its widespread use. This is due, in part, to the proven efficacy of CEA and to the earlier shortcomings of surgical revascularization.

The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) was the first randomized trial that compared endovascular and surgical treatments for patients with carotid stenosis.<sup>61</sup> A total of 504 patients were enrolled in the trial between 1992 and 1997; the results were published in 2001. The trial was designed to compare balloon angioplasty with CEA. When stents became available, they were incorporated into the trial (26% of cases).

The trial involved 24 centers in Europe, Australia, and Canada. Like previous trials of CEA, high-risk surgical patients were excluded from enrollment. This included patients with recent MI, poorly controlled hypertension or diabetes mellitus, renal disease, respiratory failure, inaccessible carotid stenosis, or severe cervical spondylosis.

The results showed no statistically significant difference between endovascular and surgical treatment in the rate of disabling stroke or death within 30 days (6.4% CAS versus 5.9% CEA). No significant difference in ipsilateral stroke existed during 3 years of follow-up. Significant restenosis (70% to 99%) occurred in 14% of the endovascular group and 4% of the surgical group, but surgical patients had a higher incidence of neck hematoma and cranial nerve injury. Because these early results showed very similar outcomes (0.5% difference), they generated significant interest in the technique and helped support further investigation.

## CAS Before Embolic Protection

The early trials with CAS did not include embolic protection. Many of the major neurological complications of CAS are due to embolization of atheromatous material from the aortic arch or the carotid plaque.<sup>62–65</sup> Devices that capture the embolic debris released during CAS have significantly improved procedural safety.<sup>62,65–69</sup> Before implementation of embolic protection, the randomized CAS trials had unfavorable results caused by a high rate of perioperative morbidity. In this way, early CAS trials reflected the early results with CEA trials because both treatments had initially high rates of perioperative morbidity.

The Wallstent trial was the first multicenter randomized trial designed to evaluate the equivalence of CEA and CAS.<sup>70,71</sup> A total of 219 symptomatic patients with 60% to 99% stenosis were enrolled. The 30-day rates for any stroke or death were 12.1% with CAS and 4.5% with CEA

( $P=0.049$ ). The primary end point of ipsilateral stroke, procedure-related death, or vascular death at 1 year was reached by 12.1% of those randomized to CAS and 3.6% of those randomized to CEA ( $P=0.022$ ). The trial was terminated by the Data Safety and Monitoring Committee after an interim analysis as a result of worse outcomes for the CAS group.

### CAS After Introduction of Embolic Protection

The Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) trial was one of the first trials to use embolic protection.<sup>72,73</sup> It was a multicenter, nonrandomized, prospective study comparing CAS with embolic protection ( $n=143$ ) and CEA ( $n=254$ ). Patients were both symptomatic (32%) and asymptomatic (68%) with low and high surgical risk. A key feature of this trial was the nonrandomized treatment assignment. The type of procedure was chosen by the treating physician and the patient. A prespecified algorithm for treatment selection was not used. Although this may have allowed selection bias, the CaRESS trial represented a more generalized perspective on carotid revascularization and more closely represents a “real-world” approach in which each patient gets the operation best suited to his or her clinical and anatomic substrate in the opinion of the operator.

The baseline characteristics of the groups were similar, except those with prior carotid intervention were more often assigned to CAS. The results showed no statistically significant difference between CAS and CEA for death or stroke at 30 days (2.1% CAS versus 3.6% CEA) or 1 year (10.0% CAS versus 13.6% CEA). There also was no significant difference for rates of restenosis, residual stenosis, repeat angiography, and need for carotid revascularization. The overall morbidity and mortality rate approached the standards set by NASCET<sup>7,8</sup> and ACAS<sup>11</sup> and represents the lowest rates among the major CAS trials to date. Some attribute the low stroke and death rates to the treating physicians’ ability to consider patient-specific factors and to successfully assign patients to the safer therapy on that basis.

### CAS for Patients With High Surgical Risk

The Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial successfully established the CAS indication for patients with high surgical risk.<sup>36</sup> SAPPHIRE ( $n=344$ ) was a randomized, multicenter trial designed to demonstrate the statistical noninferiority of CAS. Enrolled patients had symptomatic stenosis of at least 50% or asymptomatic stenosis of at least 80%.

Combined rates of MI, stroke, and death within 30 days were 4.8% for CAS and 9.8% for CEA ( $P=0.09$ ). This difference in perioperative outcomes is due partly to a greater number of MIs in the CEA group ( $P=NS$ ). Although not reported together in SAPPHIRE, the 30-day rate of stroke plus death was  $\approx 4.8\%$  in the CAS group and  $\approx 5.6\%$  in the CEA group.

At 1 year, 12.2% of patients undergoing CAS had reached the primary end point compared with 20.1% with CEA (noninferiority analysis:  $P=0.004$ ; superiority analysis: intention to treat,  $P=0.053$ ; as treated,  $P=0.048$ ). CAS was superior to CEA with respect to MI (2.5% versus 8.1%;  $P=0.03$ ) and major ipsilateral stroke (0% versus 3.5%;  $P=0.02$ ).

At 3 years, the major event rate was 25.5% for CAS and 30.3% for CEA ( $P=0.20$ ) (J.S. Yadav, MD; unpublished data; 2005). The incidences of death, ipsilateral stroke, and target lesion revascularization all favored CAS over CEA but were not statistically significant.

The carotid registries are nonrandomized outcome records for symptomatic and asymptomatic CAS patients with high surgical risk. Although they do not provide direct comparison with CEA, they do help to establish the adverse event rates among a population of high-surgical-risk patients. The Carotid Artery Revascularization Using the Boston Scientific FilterWire EX/EZ and the EndoTex NexStent (CABERNET) collaborators found a 3.9% 30-day rate of stroke or death.<sup>74</sup> The investigators of ACCULINK for Revascularization of Carotids in High-Risk Patients (ARCHeR;  $n=581$  patients) found a 30-day stroke or death rate of 6.9%.<sup>75</sup> The 1-year composite outcome was 9.6% (30-day rate of MI, stroke, or death plus the 1-year rate of ipsilateral stroke). Carotid Revascularization With ev3 Arterial Technology Evolution (CREATE;  $n=419$  patients) showed a 6.2% rate of MI, stroke, and death within 30 days.<sup>76</sup> Independent predictors of death or stroke included the duration of filter deployment, preoperative neurological symptoms, and renal insufficiency. The investigators of Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients (BEACH;  $n=747$  patients) found a 30-day MI, stroke, or death rate of 5.8%.<sup>77</sup> The German Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK) registry ( $n=1888$  patients) included patients with standard surgical risk.<sup>78</sup> The in-hospital rate of death and stroke was 3.8% and improved from 6.3% in 1996 to 1.9% in 2004 ( $P=0.021$ ).

### CAS for Patients With Standard Surgical Risk

The Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE) trial<sup>79</sup> evaluated outcomes between CAS and CEA for patients with low surgical risk. Conducted at multiple centers in Europe, SPACE compared the safety and efficacy of CAS against CEA in patients with symptomatic carotid artery stenosis ( $\geq 70\%$  by duplex ultrasonography,  $\geq 50\%$  by NASCET criteria,<sup>8</sup> or  $\geq 70\%$  by ECST criteria<sup>9</sup>).

Among 1183 randomized patients, the 30-day rate of ipsilateral stroke or death was 6.84% for CAS and 6.34% for CEA.<sup>79</sup> This 0.51% difference was not statistically significant. Embolic protection was not required; it was used in only 27% of cases. Subgroup analysis showed the 30-day rate of

ipsilateral stroke or death was 7.3% with and 6.7% without embolic protection.

Because of a prespecified analysis for noninferiority, the trial authors concluded, "SPACE failed to prove the non-inferiority of carotid-artery stenting. . . ." In this analysis for noninferiority, the authors reasoned that an arbitrary cutoff of 2.5% difference in primary outcome could separate inferiority from noninferiority. That is, CAS is noninferior to CEA only if the 90% confidence interval (CI) of the absolute difference does not exceed 2.5%. SPACE had a 90% CI of  $-1.89\%$  to  $2.91\%$ . However, the clinical relevance of 2.5%, rather than 2.91%, at the outer limit of the CI has not been established.

Furthermore, the CI varies with the size of the study population and the frequency of outcome events. When the SPACE planning committee placed the limit of noninferiority at 2.5%, they also intended to enroll 1900 patients and estimated that the rate of primary outcome events would be  $\approx 5\%$ . No provision was made to modify the 2.5% cutoff if the trial ended early or if the outcome events occurred at a higher rate. The authors also noted in their discussion that they underestimated their enrollment needs. Given the results at the interim analysis,  $>2500$  patients would have been needed to achieve an 80% power. Because of this need to significantly increase the size of the trial and a "lack of funds,"<sup>79</sup> the steering committee elected to close the trial early, leaving the prespecified analysis for noninferiority in limbo. Therefore, the SPACE authors based their conclusions on an underpowered analysis for noninferiority. The 0.51% difference in perioperative stroke or death was not statistically significant and is well within the published differences between individuals, institutions, and variations of CEA. In addition, the lack of standardized use of embolic protection devices confounds the interpretation of the study.

Endarterectomy Versus Angioplasty in Patients With Severe Symptomatic Carotid Stenosis (EVA-3S) was designed as a multicenter, noninferiority randomized trial to compare the efficacy of CAS versus CEA for the secondary prevention of ischemic stroke.<sup>80</sup> A total of 527 patients with  $>60\%$  stenosis were enrolled. The trial was ended after an interim analysis showed that the 30-day rate of any stroke or death was significantly higher in the CAS group (9.6%) than the CEA group (3.9%;  $P=0.01$ ).

Early in the trial, use of embolic protection was not required. However, patients treated without embolic protection experienced a 25% rate of stroke or death within 30 days (5 of 20 patients). These results prompted a protocol change by the EVA-3S safety committee, and this complication rate clearly does not represent the practice of CAS in other regions.

EVA-3S compared groups of physicians with unequal experience. The surgeons who performed CEA were fully trained and had performed at least 25 endarterectomies in the year before trial entry. However, the endovascular physicians were certified after completing as few as 5 to 12 carotid stent placements (5 carotid stents among at least 35 stent proce-

dures to supra-aortic vessels or 12 carotid stents). Other endovascular physicians were allowed to enroll study patients while simultaneously undergoing training and certification. The resulting 9.6% rate of stroke and death overall is higher than in other randomized trials.

A subgroup analysis based on the experience of the CAS physicians showed a 12.3% stroke and death rate among established endovascular physicians who were tutored in CAS during the trial.<sup>80</sup> This compares with 7.1% among those tutored in CAS during their endovascular training and 10.5% among experienced CAS physicians. Although the authors note that the differences between groups of endovascular physicians were not statistically significant, EVA-3S was not powered for this analysis. Therefore, this trial may have identified a group of "high-risk" endovascular physicians, and further research is needed.

EVA-3S does serve an important function by highlighting the importance of embolic protection and rigorous training and credentialing for CAS physicians. However, EVA-3S should not be used to judge the overall safety and effectiveness of CAS for treating carotid artery disease.

### Ongoing Trials

The Carotid Revascularization Endarterectomy Versus Stent Trial (CREST) is ongoing. Enrollment criteria include  $>50\%$  symptomatic carotid stenosis or  $>70\%$  asymptomatic stenosis. Primary end points include death, stroke, or MI at 30 days and ipsilateral stroke within 60 days. Multiple centers in North America are enrolling patients, with a final goal of 2500.

CREST included a rigorous credentialing phase for CAS providers.<sup>81</sup> Endovascular physicians are required to perform up to 20 monitored procedures. CREST has shown a 4.6% 30-day stroke and death rate during the lead-in phase. Rates of MI, stroke, and death were 5.7% for symptomatic patients and 3.5% for asymptomatic patients. These rates are similar to the published guidelines for CEA.<sup>13</sup> Similar stroke and death rates were observed for both men and women<sup>82</sup> and for those treated with or without embolic protection.<sup>83</sup> For patients  $\geq 80$  years of age,<sup>84,85</sup> the 30-day stroke and death rate was 12.1%. This is significantly higher than for patients 60 to 69 years of age (1.3%) and 70 to 79 years of age (5.3%;  $P=0.0006$ ).<sup>84</sup>

Other ongoing trials include the International Carotid Stenting Study (ICSS), the Asymptomatic Carotid Stenosis, Stenting Versus Endarterectomy Trial (ACT I), ACST-2, and the Transatlantic Asymptomatic Carotid Intervention Trial (TACIT). The favorable results of CAVATAS and the finding of higher restenosis rates in the carotid angioplasty arm resulted in the initiation of ICSS, also known as CAVATAS-2.<sup>86</sup> This multinational trial randomizes symptomatic patients who are equally suited for CAS or CEA. Embolic protection is recommended.

ACT I is randomizing low-surgical-risk patients with asymptomatic carotid stenosis (80% to 99%) at multiple

centers in North America.<sup>87,88</sup> The primary analysis will include rates of MI, stroke, and death within 30 days of treatment and 5-year stroke-free survival.

TACIT is in the development stage. Both standard-risk and high-surgical-risk patients with asymptomatic carotid stenosis will be randomized into 1 of 3 treatment arms.<sup>89,90</sup> The first arm will be optimal medical therapy only (antiplatelet, antilipidemic, antihypertensive, strict diabetes control, and smoking cessation). The second and third arms will be optimal medical therapy plus CEA or CAS with embolic protection. Planned enrollment is 2400 patients. The primary end point is the 3-year rate of all stroke and death. Secondary end points include rates of transient ischemic attack and MI, economic cost, quality-of-life analysis, neurocognitive function, and carotid restenosis.

### Conclusions

The CAS technique continues to evolve into a safer and more effective treatment as new technology becomes available. However, CAS is now at a point in its development in which the focus of future clinical research should change. With the availability of embolic protection, improved stent designs, and added endovascular physician experience, outcomes for CAS now consistently parallel those for CEA.

Just as surgeons have learned over the years which patients should not be offered CEA, endovascular physicians are learning clinical and anatomic features that predict elevated risk for CAS. Therefore, endovascular physicians must rigorously apply the lessons learned in the CAS trials to avoid treating patients who are clearly at higher risk for complications with endovascular stenting. Patient-specific factors and individual clinician variability are critically important for outcome, but this is underemphasized among large randomized trials. A greater need exists to reduce morbidity and mortality by integrating CAS and CEA as complementary therapies while optimizing current medical treatments.

Future trials should refine indications within a multimodality, comprehensive treatment protocol for groups of unelected patients. Evaluating treatment within these protocols will aim to improve patient outcomes overall, regardless of the specific treatments used. This paradigm more closely models the real clinical environment and is in line with the current NIH Roadmap for Interdisciplinary Research.<sup>91</sup> The TACIT trial may be a step in this direction by clarifying outcomes between revascularization and modern best medical therapy.

Further analysis of the ACSRS study also may clarify the stroke risk for patients receiving optimal medical therapy. This may identify “high-risk” groups with asymptomatic lesions who will benefit most from carotid revascularization.

Additional trials such as CaRESS,<sup>72,73</sup> in which the physician teams tailor the therapy rather than randomly assigning patients to treatment arms, may demonstrate reductions in perioperative complications and may allow further refinements in stroke risk analysis. However, thorough descriptions

of the treatment selection algorithms are necessary to allow broader application of the results within clinical practice.

By integrating CEA and CAS as complementary therapies, we can improve patient outcomes. To accomplish this integration, appropriately credentialed endovascular physicians should be given full access to the CAS technique. They should be allowed to offer CAS to their patients according to their professional discretion. As with any surgical or interventional procedure, endovascular physicians know that their outcomes must meet society expectations. The medical regulatory agencies, health insurance carriers, patients, and physicians everywhere are watching.

### Acknowledgments

Thanks go to Mary Ann Kedron, PhD, MBA (University at Buffalo Neurosurgery), and Chester Fox, MD, for their critical review of this manuscript.

### Disclosures


Dr Hopkins reports receiving industry grant support from Boston Scientific, Cordis, and Micrus; honoraria from Bard, Boston Scientific, Cordis, and Medsn; and consultant fees from Abbott, Bard, Boston Scientific, Cordis, EndoTex, and Micrus. Dr Hopkins is a stockholder or shareholder of Boston Scientific, EndoTex, APW Holding Inc, and Micrus and serves on the board, as a trustee, or in an officer position for Access Closure, marketRx, and Micrus. Dr Levy reports receiving industry grant support and honoraria from Boston Scientific and Cordis; serving as an expert witness for multiple legal depositions and as a consultant for a malpractice case; receiving patent royalties from Zimmer Spine; and receiving support from Abbott Vascular and ev3 for carotid stent training. Dr Siddiqui reports receiving a local University at Buffalo grant and honoraria from the American Association of Neurological Surgeons' Course and Emergency Medicine Conference. Drs Samuelson and Yamamoto report no conflicts.

### References

1. Fields WS, Maslenikov V, Meyer JS, Hass WK, Remington RD, MacDonald M. Joint study of extracranial arterial occlusion, V: progress report of prognosis following surgery or nonsurgical treatment for transient cerebral ischemic attacks and cervical carotid artery lesions. *JAMA*. 1970;211:1993–2003.
2. Shaw DA, Venables GS, Cartlidge NE, Bates D, Dickinson PH. Carotid endarterectomy in patients with transient cerebral ischaemia. *J Neurol Sci*. 1984;64:45–53.
3. Easton JD, Sherman DG. Stroke and mortality rate in carotid endarterectomy: 228 consecutive operations. *Stroke*. 1977;8:565–568.
4. Fode NC, Sundt TM Jr, Robertson JT, Peerless SJ, Shields CB. Multi-center retrospective review of results and complications of carotid endarterectomy in 1981. *Stroke*. 1986;17:370–376.
5. Mattos MA, Modi JR, Mansour AM, Mortenson D, Karich T, Hodgson KJ, Barkmeier LD, Ramsey DE, Sumner DS. Evolution of carotid endarterectomy in two community hospitals: Springfield revisited: seventeen years and 2243 operations later. *J Vasc Surg*. 1995;21:719–728.
6. Winslow CM, Solomon DH, Chassin MR, Koscoff J, Merrick NJ, Brook RH. The appropriateness of carotid endarterectomy. *N Engl J Med*. 1988;318:721–727.
7. Barnett HJ, Taylor DW, Eliasziw M, Fox AJ, Ferguson GG, Haynes RB, Rankin RN, Clagett GP, Hachinski VC, Sackett DL, Thorpe KE, Meldrum HE. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis: North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*. 1998;339:1415–1425.
8. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic

- patients with high-grade carotid stenosis. *N Engl J Med*. 1991;325:445–453.
9. European Carotid Surgery Trialists' Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. *Lancet*. 1991; 337:1235–1243.
  10. MRC European Carotid Surgery Trialists. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet*. 1998;351: 1379–1387.
  11. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA*. 1995;273:1421–1428.
  12. Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, Thomas D. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial. *Lancet*. 2004;363:1491–1502.
  13. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Schwamm LH, Tomsick T. 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. *Stroke*. 2006;37:577–617.
  14. 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: 1278–1281.
  15. CAPRIE Steering Committee. A randomised, blinded, trial of Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE). *Lancet*. 1996;348:1329–1339.
  16. Bond R, Rerkasem K, Rothwell PM. Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. *Stroke*. 2003;34:2290–2301.
  17. Gasecki AP, Ferguson GG, Eliasziw M, Clagett GP, Fox AJ, Hachinski V, Barnett HJ. Early endarterectomy for severe carotid artery stenosis after a nondisabling stroke: results from the North American Symptomatic Carotid Endarterectomy Trial. *J Vasc Surg*. 1994;20:288–295.
  18. Gent M, Blakely JA, Easton JD, Ellis DJ, Hachinski VC, Harbison JW, Panak E, Roberts RS, Sicurella J, Turpie AG. The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. *Lancet*. 1989;1: 1215–1220.
  19. Mayo Asymptomatic Carotid Endarterectomy Study Group. Results of a randomized controlled trial of carotid endarterectomy for asymptomatic carotid stenosis. *Mayo Clin Proc*. 1992;67:513–518.
  20. Hobson RW, 2nd, Weiss DG, Fields WS, Goldstone J, Moore WS, Towne JB, Wright CB, for the Veterans Affairs Cooperative Study Group. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. *N Engl J Med*. 1993;328:221–227.
  21. Solis MM, Ranval TJ, Barone GW, Eidt JF, Barnes RW. The CASANOVA study: immediate surgery versus delayed surgery for moderate carotid artery stenosis? *Stroke*. 1992;23:917–919.
  22. Halm EA, Chassin MR, Tuhrim S, Hollier LH, Popp AJ, Ascher E, Dardik H, Faust G, Riles TS. Revisiting the appropriateness of carotid endarterectomy. *Stroke*. 2003;34:1464–1471.
  23. Jordan WD Jr, Voellinger DC, Fisher WS, Redden D, McDowell HA. A comparison of carotid angioplasty with stenting versus endarterectomy with regional anesthesia. *J Vasc Surg*. 1998;28:397–403.
  24. Hartmann A, Hupp T, Koch HC, Dollinger P, Stapf C, Schmidt R, Hofmeister C, Thompson JL, Marx P, Mast H. Prospective study on the complication rate of carotid surgery. *Cerebrovasc Dis*. 1999;9:152–156.
  25. Naylor AR, Hayes PD, Allroggen H, Lennard N, Gaunt ME, Thompson MM, London NJ, Bell PR. Reducing the risk of carotid surgery: a 7-year audit of the role of monitoring and quality control assessment. *J Vasc Surg*. 2000;32:750–759.
  26. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, Welch HG, Wennberg DE. Hospital volume and surgical mortality in the United States. *N Engl J Med*. 2002;346:1128–1137.
  27. Goldstein LB, McCrory DC, Landsman PB, Samsa GP, Ancukiewicz M, Oddone EZ, Matchar DB. Multicenter review of preoperative risk factors for carotid endarterectomy in patients with ipsilateral symptoms. *Stroke*. 1994;25:1116–1121.
  28. Goldstein LB, Samsa GP, Matchar DB, Oddone EZ. Multicenter review of preoperative risk factors for endarterectomy for asymptomatic carotid artery stenosis. *Stroke*. 1998;29:750–753.
  29. Meyer FB, Piegras DG, Fode NC. Surgical treatment of recurrent carotid artery stenosis. *J Neurosurg*. 1994;80:781–787.
  30. Villarreal J, Silva J, Eliasziw M, Sharpe B, Fox A, Hachinski V, Barnett HJ. North American Symptomatic Carotid Endarterectomy Trial: prognosis of patients with intraluminal thrombus in the internal carotid artery. *Stroke*. 1998;29:276. Abstract.
  31. Gasecki AP, Eliasziw M, Ferguson GG, Hachinski V, Barnett HJ. Long-term prognosis and effect of endarterectomy in patients with symptomatic severe carotid stenosis and contralateral carotid stenosis or occlusion: results from NASCET: North American Symptomatic Carotid Endarterectomy Trial (NASCET) Group. *J Neurosurg*. 1995;83:778–782.
  32. Kresowik TF, Bratzler D, Karp HR, Hemann RA, Hendel ME, Grund SL, Brenton M, Ellerbeck EF, Nilasena DS. Multistate utilization, processes, and outcomes of carotid endarterectomy. *J Vasc Surg*. 2001;33:227–235.
  33. Moore WS, Barnett HJ, Beebe HG, Bernstein EF, Brenner BJ, Brott T, Caplan LR, Day A, Goldstone J, Hobson RW II, Kempczinski RF, Matchar DB, Mayberg MR, Nicolaides AN, Norris JW, Ricotta JJ, Robertson JT, Rutherford RB, Thomas D, Toole JF, Trout HH III, Wiebers DO. Guidelines for carotid endarterectomy: a multidisciplinary consensus statement from the ad hoc committee, American Heart Association. *Stroke*. 1995;26:188–201.
  34. Nicolaides AN, Kakkos SK, Griffin M, Sabetai M, Dhanjil S, Tegos T, Thomas DJ, Giannoukas A, Geroulakos G, Georgiou N, Francis S, Ioannidou E, Dore CJ. Severity of asymptomatic carotid stenosis and risk of ipsilateral hemispheric ischaemic events: results from the ACSRS study. *Eur J Vasc Endovasc Surg*. 2005;30:275–284.
  35. Nicolaides AN, Kakkos S, Griffin M, Geroulakos G, Ioannidou E. Severity of asymptomatic carotid stenosis and risk of ipsilateral hemispheric ischaemic events: results from the ACSRS study. *Eur J Vasc Endovasc Surg*. 2005;30:275–284.
  36. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Whitlow P, Strickman NE, Jaff MR, Popma JJ, Snead DB, Cutlip DE, Firth BG, Ouriel K. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2004;351: 1493–1501.
  37. Findlay JM, Tucker WS, Ferguson GG, Holness RO, Wallace MC, Wong JH. Guidelines for the use of carotid endarterectomy: current recommendations from the Canadian Neurosurgical Society. *Can Med Assoc J*. 1997;157:653–659.
  38. Perry JR, Szalai JP, Norris JW. Consensus against both endarterectomy and routine screening for asymptomatic carotid artery stenosis: Canadian Stroke Consortium. *Arch Neurol*. 1997;54:25–28.
  39. Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. *N Engl J Med*. 1991;325:1261–1266.
  40. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324:71–86.
  41. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom Transient Ischaemic Attack (UK-TIA) aspirin trial: final results. *J Neurol Neurosurg Psychiatry*. 1991;54:1044–1054.
  42. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study, 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci*. 1996;143:1–13.
  43. Progressive Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001;358:1033–1041.
  44. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560–2572.
  45. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. *Stroke*. 2004;35:1024–1033.

46. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients: Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000;342:145–153.
47. Abbott RD, Yin Y, Reed DM, Yano K. Risk of stroke in male cigarette smokers. *N Engl J Med*. 1986;315:717–720.
48. Colditz GA, Bonita R, Stampfer MJ, Willett WC, Rosner B, Speizer FE, Hennekens CH. Cigarette smoking and risk of stroke in middle-aged women. *N Engl J Med*. 1988;318:937–941.
49. Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Rosner B, Speizer FE, Hennekens CH. Smoking cessation and decreased risk of stroke in women. *JAMA*. 1993;269:232–236.
50. Mast H, Thompson JL, Lin IF, Hofmeister C, Hartmann A, Marx P, Mohr JP, Sacco RL. Cigarette smoking as a determinant of high-grade carotid artery stenosis in Hispanic, black, and white patients with stroke or transient ischemic attack. *Stroke*. 1998;29:908–912.
51. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837–853.
52. Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, Silleisen H, Simunovic L, Szarek M, Welch KM, Zivin JA, for the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549–559.
53. Amarenco P, Labreuche J, Lavalley P, Touboul PJ. Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. *Stroke*. 2004;35:2902–2909.
54. Collins R, Armitage J, Parish S, Sleight P, Peto R, for the Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. *Lancet*. 2004;363:757–767.
55. Adult Treatment Panel III. Executive Summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486–2497.
56. Plehn JF, Davis BR, Sacks FM, Rouleau JL, Pfeffer MA, Bernstein V, Cuddy TE, Moye LA, Piller LB, Rutherford J, Simpson LM, Braunwald E, for the CARE Investigators. Reduction of stroke incidence after myocardial infarction with pravastatin: the Cholesterol and Recurrent Events (CARE) study. *Circulation*. 1999;99:216–223.
57. Groschel K, Ernemann U, Schulz JB, Nagele T, Terborg C, Kastrup A. Statin therapy at carotid angioplasty and stent placement: effect on procedure-related stroke, myocardial infarction, and death. *Radiology*. 2006;240:145–151.
58. Kennedy J, Quan H, Buchan AM, Ghali WA, Feasby TE. Statins are associated with better outcomes after carotid endarterectomy in symptomatic patients. *Stroke*. 2005;36:2072–2076.
59. Ravipati G, Aronow WS, Ahn C, Channamsetty V, Sekhri V. Incidence of new stroke or new myocardial infarction or death in patients with severe carotid arterial disease treated with and without statins. *Am J Cardiol*. 2006;98:1170–1171.
60. Betancourt M, Van Stavern RB, Share D, Gardella P, Martus M, Chaturvedi S. Are patients receiving maximal medical therapy following carotid endarterectomy? *Neurology*. 2004;63:2011–2015.
61. CAVATAS Investigators. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet*. 2001;357:1729–1737.
62. Angelini A, Reimers B, Della Barbera M, Sacca S, Pasquetto G, Cernetti C, Valente M, Pascotto P, Thiene G. Cerebral protection during carotid artery stenting: collection and histopathologic analysis of embolized debris. *Stroke*. 2002;33:456–461.
63. Castellani L, Causin F, Danieli D, Perini S. Carotid stenting with filter protection: correlation of ACT values with angiographic and histopathologic findings. *J Neuroradiol*. 2003;30:103–108.
64. Jaeger HJ, Mathias KD, Hauth E, Drescher R, Gissler HM, Hennigs S, Christmann A. Cerebral ischemia detected with diffusion-weighted MR imaging after stent implantation in the carotid artery. *Am J Neuroradiol*. 2002;23:200–207.
65. Kastrup A, Groschel K, Krapf H, Brehm BR, Dichgans J, Schulz JB. Early outcome of carotid angioplasty and stenting with and without cerebral protection devices: a systematic review of the literature. *Stroke*. 2003;34:813–819.
66. Al-Mubarak N, Roubin GS, Vitek JJ, Iyer SS. Microembolization during carotid stenting with the distal-balloon antiemboli system. *Int Angiol*. 2002;21:344–348.
67. Kastrup A, Nagele T, Groschel K, Schmidt F, Vogler E, Schulz J, Ernemann U. Incidence of new brain lesions after carotid stenting with and without cerebral protection. *Stroke*. 2006;37:2312–2316.
68. Theron JG, Payelle GG, Coskun O, Huet HF, Guimaraens L. Carotid artery stenosis: treatment with protected balloon angioplasty and stent placement. *Radiology*. 1996;201:627–636.
69. Villalobos HJ, Harrigan MR, Lau T, Wehman JC, Hanel RA, Levy EI, Guterman LR, Hopkins LN. Advancements in carotid stenting leading to reductions in perioperative morbidity among patients 80 years and older. *Neurosurgery*. 2006;58:233–240.
70. Alberts MJ, for the Publications Committee of WALLSTENT. Results of a multicenter prospective randomized trial of carotid artery stenting vs. carotid endarterectomy. *Stroke*. 2001;32:325. Abstract.
71. Alberts MJ, McCann R, Smith TP, Stack R, Roubin G, Schneck M, Haumschild D, Iyer S, for the Schneider Wallstent Endoprostheses Clinical Investigators. A randomized trial of carotid stenting vs. endarterectomy in patients with symptomatic carotid stenosis: study design. *J Neurovasc Dis*. 1997;2:228–234.
72. CaRESS Steering Committee. Carotid Revascularization using Endarterectomy or Stenting Systems (CaRESS): phase I clinical trial. *J Endovasc Ther*. 2003;10:1021–1030.
73. CaRESS Steering Committee. Carotid Revascularization Using Endarterectomy or Stenting Systems (CaRESS) phase I clinical trial: 1-year results. *J Vasc Surg*. 2005;42:213–219.
74. Hopkins LN, for the CABERNET investigators. Results of Carotid Artery Revascularization Using the Boston Scientific FilterWire EX/EX and the EndoTex NexStent: results from the CABERNET clinical trial. Presented at: the EuroPCR Conference; May 26, 2005; Paris, France.
75. Gray WA, Hopkins LN, Yadav S, Davis T, Wholey M, Atkinson R, Cremonesi A, Fairman R, Walker G, Verta P, Popma J, Virmani R, Cohen DJ. Protected carotid stenting in high-surgical-risk patients: the ARCHeR results. *J Vasc Surg*. 2006;44:258–268.
76. Safian RD, Bresnahan JF, Jaff MR, Foster M, Bacharach JM, Maini B, Turco M, Myla S, Eles G, Ansel GM. Protected carotid stenting in high-risk patients with severe carotid artery stenosis. *J Am Coll Cardiol*. 2006;47:2384–2389.
77. White CJ, Iyer SS, Hopkins LN, Katzen BT, Russell ME. Carotid stenting with distal protection in high surgical risk patients: the BEACH trial 30 day results. *Catheter Cardiovasc Interv*. 2006;67:503–512.
78. Zahn R, Roth E, Ischinger T, Mark B, Hochadel M, Zeymer U, Haerten K, Hauptmann KE, von Leitner ER, Schramm A, Kasper W, Senges J. Carotid artery stenting in clinical practice: results from the Carotid Artery Stenting (CAS)-registry of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK). *Z Kardiol*. 2005;94:163–172.
79. Ringleb PA, Allenberg J, Bruckmann H, Eckstein HH, Fraedrich G, Hartmann M, Hennerici M, Jansen O, Klein G, Kunze A, Marx P, Niederkorn K, Schmiedt W, Solymosi L, Stinge R, Zeumer H, Hacke W. 30 Day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet*. 2006;368:1239–1247.
80. Mas JL, Chatellier G, Beyssens B, Branchereau A, Moulin T, Becquemin JP, Larue V, Lieve M, Leys D, Bonneville JF, Watelet J, Pruvo JP, Albucher JF, Viguier A, Piquet P, Garnier P, Viader F, Touze E, Giroud M, Hosseini H, Pillet JC, Favrole P, Neau JP, Ducrocq X. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med*. 2006;355:1660–1671.
81. Hobson RW 2nd, Howard VJ, Roubin GS, Ferguson RD, Brott TG, Howard G, Sheffert AJ, Roberts J, Hopkins LN, Moore WS. Credentialing of surgeons as interventionalists for carotid artery stenting: experience from the lead-in phase of CREST. *J Vasc Surg*. 2004;40:952–957.
82. Howard VJ, Brott TG, Qureshi AI, Lutsep HL, Howard G, Hobson RW II, for the CREST Investigators. Gender and periprocedural stroke and death following carotid artery stenting: results from the CREST lead-in phase. *Stroke*. 2004;35:253. Abstract.

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83. Roubin GS, Brott TG, Hopkins LN, for the CREST Investigators. Developing embolic protection for carotid stenting in the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST). *Circulation*. 2003;108 (suppl 4):IV-687. Abstract.
  84. Hobson RW II, Howard VJ, Roubin GS, Brott TG, Ferguson RD, Popma JJ, Graham DL, Howard G. Carotid artery stenting is associated with increased complications in octogenarians: 30-day stroke and death rates in the CREST lead-in phase. *J Vasc Surg*. 2004;40:1106–1111.
  85. Howard G, Hobson RW II, Brott TG, for the CREST Investigators. Does the stroke risk of stenting increase at older ages? Thirty-day stroke death rates in the CREST lead-in phase. *Circulation*. 2003;8 (suppl 4):V-461. Abstract.
  86. Featherstone RL, Brown MM, Coward LJ, for the ICSS Investigators. International carotid stenting study: protocol for a randomised clinical trial comparing carotid stenting with endarterectomy in symptomatic carotid artery stenosis. *Cerebrovasc Dis*. 2004;18:69–74.
  87. Press release (January 18, 2005): Abbott announces groundbreaking new trial in stroke prevention. Available at: [http://www.abbott.com/global/url/pressRelease/en\\_US/60.5:5/Press\\_Release\\_0227.htm](http://www.abbott.com/global/url/pressRelease/en_US/60.5:5/Press_Release_0227.htm). Accessed January 14, 2007.
  88. Carotid stenting vs surgery of severe carotid artery disease and stroke prevention in asymptomatic patients (ACT I). Available at: <http://www.clinicaltrials.gov/ct/show/NCT00106938?order=1>. Accessed January 14, 2007.
  89. ACST-2 and TACIT to answer the asymptomatic carotid question. *Interventional News*. 2006;20. Available at: <http://www.cxvascular.com/InterventionalNews/InterventionalNews.cfm?ccs=296&cs=1874>. Accessed December 23, 2006.
  90. Rundback J. Update on the TACIT trial. *Endovascular Today*. 2006; August:93–94.
  91. Division of Strategic Coordination, Office of Portfolio Analysis and Strategic Initiatives, National Institutes of Health. NIH roadmap for medical research. Available at: <http://www.nihroadmap.nih.gov/>. Accessed December 23, 2006.

## Response to Samuelson et al

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The heart of this controversy is embodied in these 2 perspectives. Dr Hopkins views the Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial and the US Food and Drug Administration approval of carotid stenting as entirely legitimate and goes further to argue in favor of expanded indications for stenting. My view is that the SAPPHIRE trial is scientifically unsound, with flaws in design, conduct, and data analysis, a view corroborated by the Food and Drug Administration statistician and staff reviewers. My explanation for Food and Drug Administration approval is the pervasive influence of industry on every aspect of clinical science. How can readers sort this out? My suggestion is to focus on the SAPPHIRE trial and decide whether or not it meets the level of scientific conduct appropriate to making a major policy decision, especially one in which the risk to the public is stroke. As for the various other trials, it is the usual conduct of these debates to pick apart each of them so that the argument becomes diluted by a “he said, she said” atmosphere. Rather than engage in this conduct, it was my decision to concentrate on the data and circumstances surrounding Food and Drug Administration approval to best illustrate the magnitude of the flaws in our system. Readers should assume a highly critical and demanding posture whenever a clinical study favors approval of a new high-revenue device. In the end, the only protector of the patients’ welfare is our commitment as physicians to caring for our patients. This is true whether we act on behalf of individual patients or on behalf of public health.