# FDA EXECUTIVE SUMMARY

## OCTOBER 11, 2007 MEETING OF THE CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

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# I. Introduction

Percutaneous delivery of a vascular stent to treat carotid artery stenosis and reduce the risk of stroke and death represents an active area of clinical research and medical device development. Alternative treatment options for this disease include carotid endarterectomy (CEA) and medical therapy. Since 2004, the U.S. Food and Drug Administration (FDA) has approved five carotid stent systems.[1 - 5] Approval of the Premarket Approval (PMA) applications for four of these devices was based on clinical data gathered from single-arm clinical studies without active controls, while approval of the other device was based on data from the SAPPHIRE randomized, controlled trial (RCT) comparing carotid artery stenting (CAS) to CEA. The indications in all 5 instances were the treatment of symptomatic and asymptomatic high-grade carotid artery stenosis in patients considered to be at high risk for adverse events from surgical revascularization, a subset of the many patients presently receiving CEA.

Patients with carotid artery stenosis who are not at high risk for adverse events from CEA represent a much larger potential patient population for CAS. These patients are free of anatomic and co-morbid risk factors believed to increase the risk of adverse events related to surgical revascularization, and thus they represent suitable surgical candidates. FDA has generally recommended that sponsors conduct an RCT with a concurrent surgical control arm to evaluate the safety and effectiveness of CAS in these patients. While several trials of this type have been initiated, none has yet been completed. In addition, it is not clear whether data from other controlled study designs could also be used to develop a reasonable assurance of safety and effectiveness for CAS in the lower-risk population and thereby lead to FDA approval.

The purpose of this meeting of the Circulatory System Device Panel is to determine what study designs are suitable for evaluating CAS in the lower-risk patient population. We also hope to identify study design modifications that might improve current subject enrollment and data collection.

# II. Clinical Significance of Carotid Artery Stenosis

Stroke is the third leading cause of death and the leading cause of disability in the United States, resulting in approximately 160,000 deaths, 500,000 new events, and 200,000 recurrent events each year.[6] In 2006, the cost of stroke was estimated at $57.9 billion.[7] Given its prevalence and impact, developing effective treatments for the prevention of primary or recurring stroke is of paramount importance.

The etiology of stroke has been estimated as follows:

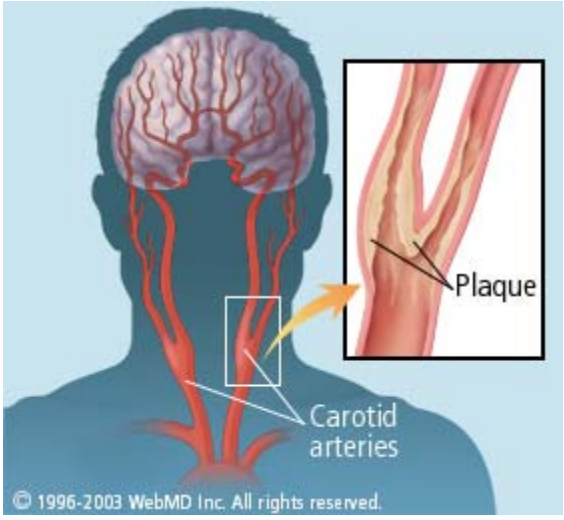
- 30% due to extra-cranial carotid artery disease

- 30% due to non-carotid artery ischemia, including cardiac embolism, lacunae infarcts, and trauma

- 20% due to hemorrhagic disease

- 20% due to vertebral-basilar disease.[8]

Carotid artery disease is typically detected using one of many potential imaging modalities, including non-invasive duplex ultrasound and invasive angiography. Carotid disease is more likely to be present in patients with coronary artery disease, patients with hypertension, and those with a history of smoking.[9] Disease detection and stroke prevention is not only appropriate for patients who have experienced previous neurological events, as at least 70% of strokes occur without previous symptoms.[10] Because up to 7% of patients over 65 years of age have been identified with carotid artery stenosis exceeding 50%,[11] understanding this atherosclerotic disease and treating it effectively is very important in this population.




**Carotid Artery Disease and Embolic Stroke**

The pathophysiology of carotid-related stroke is unique from the disease effects of other arterial systems in that ischemic injury to the end organ (in this case, the brain) is not typically the result of reduction in blood flow through the supplying vessels (carotid arteries). The presence of the Circle of Willis results in a rich collateral system that maintains adequate perfusion of the brain even when blood flow is restricted. However, embolic particles are formed at atherosclerotic carotid stenoses due to a combination of hemodynamic (e.g., turbulence and high shear stresses) and biological factors. These embolic particles traveling downstream are nearly always responsible for ischemic stroke originating from the carotid arteries.

# III. Treatment Options

Three main treatment options exist for managing clinically significant carotid artery stenosis, with varying levels of evidence supporting their use. In most cases, the indicated patient populations are defined with respect to their symptomatic or asymptomatic status. In this context, symptomatic patients are those that have experienced a neurological event affecting the hemisphere ipsilateral to the stenotic carotid artery within a specified time frame prior to treatment. The symptomatic time frame is generally defined in terms of days or months and does not necessarily include patients experiencing an acute stroke. By this definition, asymptomatic patients may have experienced prior neurological events as well, as long as the events did not occur within the specified time frame.

## A. Medical Therapy

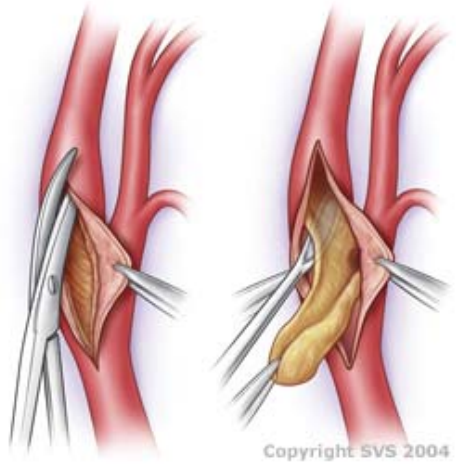
Several different medical strategies have been investigated for lowering the risk of stroke. For example, aspirin has been shown to lower the risk of stroke in patients with a prior stroke or transient ischemic attack (TIA).[12] Additionally, management of lipids via statin therapy and reduction in hypertension using angiotensin-coverting enzyme (ACE) inhibitors have also been shown to reduce the risk of stroke in patients with associated risk factors.[13 - 16]

The use of antiplatelet medicines such as clopidogrel has recently been explored, with results suggesting that clopidogrel and clopidogrel/aspirin regimens can produce results equivalent to aspirin alone in secondary stroke prevention.[17 - 18] Because patients may not always respond to a single antiplatelet drug, the use of double or triple antiplatelet therapy may also be a treatment option. However, the use of multiple antiplatelet drugs may increase the risk of hemorrhage.[19]

A significant amount of medical therapy data has also been collected as control data on surgical trials, some of which are discussed below.

## B. Carotid Endarterectomy

Carotid endarterectomy, whereby the stenotic carotid artery is opened surgically and the atheromatous plaque is excised, was introduced in 1953.[20] Thirty years later, it became the most frequently performed vascular surgical procedure in the United States. Today over 130,000 CEA procedures are performed annually in the United States, and it represents the current gold standard for carotid revascularization in certain patient populations. The key role of CEA in treating both symptomatic and asymptomatic carotid lesions was shown through the results of several large-scale, randomized clinical studies comparing CEA to medical therapy. Prior to the performance of these trials, the exact role of CEA was uncertain.




**Plaque Removal During Carotid Endarterectomy**

The North American Carotid Endarterectomy Trial (NASCET) and European Carotid Surgery Trial (ECST) both demonstrated that prophylactic CEA plus aspirin significantly reduced the risk of stroke in symptomatic patients with greater than 50% carotid artery stenosis as compared to aspirin alone.[21 – 22] One stroke was prevented during a two-year period for every six (6) patients treated with 70% or greater stenosis, provided the peri-operative mortality and stroke rate was less than 6%. Treatment of fifteen (15) patients with 50 - 69% stenosis is needed to prevent one stroke, and this benefit was eliminated if the peri-operative mortality and morbidity exceeded 2%. No benefit was observed for patients with less than 50% stenosis and for whom the operative mortality and morbidity rates exceeded 10%. The key NASCET findings are summarized below.

**NASCET: Kaplan-Meier Estimates of Event Rates at Two Years Post-Procedure**

| Event Type | Medical Arm (n = 331) | Surgical Arm (n = 328) | Absolute Difference (± Standard Error) | Risk Reduction |
|---|---|---|---|---|
| Ipsilateral stroke | 26.0% | 9.0% | 17.0 ± 3.5%* | 65% |
| Any stroke | 27.6% | 12.6% | 15.0 ± 3.8%* | 54% |
| Any stroke or death | 32.3% | 15.8% | 16.5 ± 4.2%* | 51% |

* $p < 0.001$.

Asymptomatic carotid lesions were studied in two completed, randomized trials: the Asymptomatic Carotid Atherosclerosis Study (ACAS) in North America, and the European Asymptomatic Carotid Surgery Trial (ACST).[23 - 24] ACAS explored the effects of CEA plus aspirin versus aspirin alone in subjects with asymptomatic stenosis greater than 60%, while ACST examined the affects of immediate CEA versus the delay of CEA until it was definitively indicated. Although there are some differences in the analyses performed for the two studies, it can be estimated from the results that eighteen (18) patients need to be treated to prevent 1 stroke at 5 years, a benefit obtained if the peri-operative risk is < 3%. Some additional key findings from these two studies are summarized below.

**ACAS: Kaplan-Meier Estimates of Event Rates at Five Years Post-Procedure**

| Event Type | Medical Arm (n = 834) | Surgical Arm (n = 825) | Risk Reduction* | Significance |
|---|---|---|---|---|
| Ipsilateral stroke or any peri-operative stroke or death | 11.0% | 5.1% | 53% [22% to 72%] | $p < 0.005$ |

* 95% confidence intervals also provided.

**ACST: Kaplan-Meier Estimates of Event Rates at Five Years Post-Procedure**

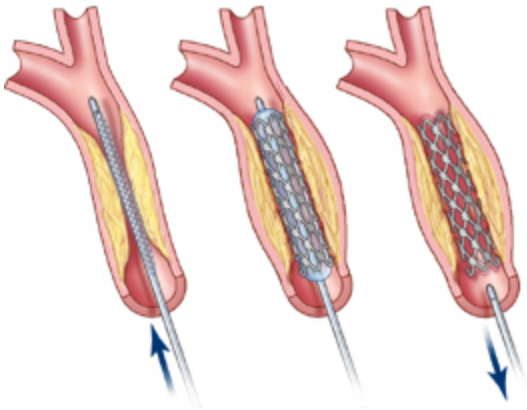
| Event Type | Deferred CEA (n = 1560) | Immediate CEA (n = 1560) | Absolute Difference* | Significance |
|---|---|---|---|---|
| Any stroke | 11.0% | 3.8% | 7.2% [5.0% to 9.4%] | $p < 0.0001$ |
| Any stroke or any peri-operative stroke or death | 11.8% | 6.4% | 5.4% [3.0% to 7.8%] | $p < 0.0001$ |

* 95% confidence intervals also provided.

Despite the successes of CEA, some potential patients who may benefit from carotid revascularization do not make ideal surgical candidates for various reasons. The benefit that CEA provides in preventing stroke will be eliminated in the event of an unacceptably high procedural morbidity and mortality risk. Such risk can exist due to systemic co-morbidities, many of which are itself risks for carotid artery disease, such as coronary artery disease and diabetes. An increased risk for complications with CEA is also encountered with a hostile operative field, such as an inaccessible lesion location, previous radiation therapy in the neck, and contralateral laryngeal nerve injury.

## C. Carotid Artery Stenting

The most recently introduced treatment option for carotid artery stenosis is the endovascular delivery and expansion of devices intended to compress and stabilize the stenotic plaque against the vessel wall, first with balloon angioplasty and later with implantable stents. When CAS was first introduced in the late 1980s, the procedure was initially associated with unacceptable rates of deployment-related embolism. This risk is believed to have been mitigated somewhat by the use of catheter-based embolic protection devices designed to capture and remove debris liberated during the procedure, although the specific contribution of these devices to CAS outcomes has not been completely assessed.[25]



**Carotid Artery Stenting**

While this less invasive procedure offers some putative advantages to CEA, the specific role and relative value of CAS as compared to CEA for carotid revascularization has yet to be fully established. In the United States, approval to market carotid stent systems has focused on patients who are believed to be at high risk for adverse events from CEA, with only one RCT conducted in this population. This study, SAPPHIRE, demonstrated equivalence between CAS and CEA.[26]

Several non-randomized feasibility studies, such as CaRESS,[27] have been conducted. While results from these feasibility studies have suggested that CAS results are non-inferior to CEA in a lower-risk population, definitive evidence for safety and effectiveness of specific stent systems in this critical patient population is currently lacking. There is presently a need for carefully designed, prospective trials to address the role of CAS in the lower risk patient population with carotid disease.

# IV. Regulatory History of CAS

## A. Approved Devices and Indications

To date, FDA has approved PMAs for five (5) carotid stent systems. The presently approved carotid stents, when used in conjunction with the embolic protection devices with which they were studied clinically, are indicated for the treatment of patients at high risk for adverse events from CEA who require percutaneous revascularization and meet the following criteria:

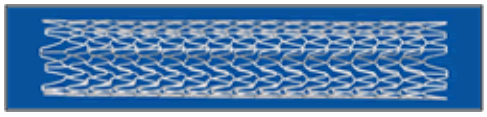
- Patients must have either (a) neurological symptoms and ≥ 50% stenosis of the common or internal carotid artery or (b) no neurological symptoms and ≥ 80% stenosis of the common or internal carotid artery.

- The reference vessel diameter at the target lesion must be amenable to stenting, based on the available stent sizes.

It is important to note that FDA has not approved any carotid stent system for treatment of patients who are not considered high surgical risk, that is, the patient population that is the subject of this advisory panel meeting.

The approved devices are listed below, along with their PMA number and approval date.

- Abbott Vascular (formerly Guidant) ACCULINK™ and RX ACCULINK™ Carotid Stent Systems (P040012) – August 30, 2004[1]

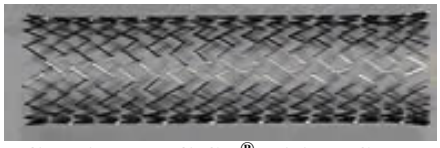


**Abbott Vascular ACCULINK™ Carotid Stent**

- Abbott Vascular Xact® Carotid Stent System (P040038) – September 6, 2005[2]

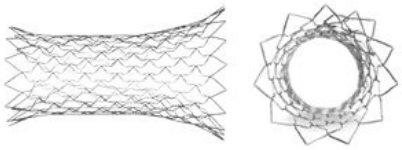
**Abbott Vascular Xact® Carotid Stent**

- Cordis PRECISE® Nitinol Stent System (P030047) – September 22, 2006[3]



**Cordis PRECISE® Nitinol Stent**

- Boston Scientific (formerly Endotex) Nexstent® Carotid Stent and Delivery System, and Nexstent® Carotid Stent and Monorail® Delivery System (P050025) – October 27, 2006[4]



**Boston Scientific Nexstent® Carotid Stent**

- ev3 Protégé® GPS™ and Protégé® RX Carotid Stent Systems (P060001) – January 24, 2007[5]

**ev3 Protégé® Carotid Stent**

## B. Previous Advisory Panel Recommendations

The Circulatory System Devices Panel previously discussed carotid stenting issues during an April 21, 2004 meeting, when the SAPPHIRE trial was reviewed as part of the PMA review for the Cordis PRECISE Nitinol Stent System. The panel voted 6 – 5 that the PMA be found "approvable with conditions" for a high surgical risk population.[28] These conditions included modifications to the post-approval evaluation plan and the device labeling. The device labeling recommendations were aimed at clearly restricting use of this device to a patient population with specific factors that would make them higher risk for the standard surgical approach.

In addition to voting on PMA approval, the panel also made the following comments on carotid stenting studies as a whole:

- Comparison of carotid stenting data to historical surgical controls raises concerns about the comparability of the enrolled patient populations and study endpoints.

- The use of composite major adverse event rates as a primary endpoint may be problematic when comparing surgical and non-surgical outcomes because these procedures present different risk profiles.

- The rate of myocardial infarction should be included as a component of the primary endpoint of any CAS trial.

- Patients with anatomic risk factors such as excessive vessel tortuosity and heavy lesion calcification may not be good candidates for CAS.

- Continued follow-up of carotid stenting results in the post-approval environment was critical.

It should be noted that all manufacturers of approved stent systems have complied with this last comment. Data from FDA post-approval studies has been concordant with pre-market clinical trial results.

# V. FDA Recommendations for CAS Clinical Trials in Lower-Risk Patients

In 1996, FDA published guidance on carotid stenting clinical studies. This document, titled, *Carotid Stent - Suggestions for Content of Submissions to the Food and Drug Administration in Support of Investigational Device Exemption (IDE) Applications*, stated that, "A long-term, randomized concurrent control trial (RCT) versus carotid endarterectomy will likely be necessary to demonstrate the safety and effectiveness of carotid stenting due to the low rate of stroke in patients after carotid endarterectomy."[29] While single-arm CAS studies have been used successfully to support PMA approval for carotid stents in high surgical risk patient populations, FDA continues to recommend that sponsors investigating the use of CAS in the non-high-risk population conduct a prospective, multi-center RCT to demonstrate the non-inferiority of CAS to CEA. FDA believes that a well-executed randomized trial will minimize potential sources of bias, avoid confounding, and thereby produce clear and unambiguous results.

Based on both published guidance and on evolving understanding of the CAS literature, FDA currently provides the following recommendations for the design of a randomized study:

- The primary study endpoint should incorporate both peri-procedural morbidity and the longer-term rate of stroke ipsilateral to the stented vessel. An example of such an endpoint is the composite rate of all death, stroke, and myocardial infarction within 30 days of the procedure, plus the rate of ipsilateral stroke from 31 – 365 days post-procedure.

- A non-inferiority trial design may be utilized.

- The non-inferiority margin ("delta") used to demonstrate non-inferiority between CAS and CEA must be prospectively defined either absolutely or as a proportion of the control primary endpoint rate. The non-inferiority margin must also rule out a clinically significant difference in event rates, regardless of its definition.

- Long-term follow-up can provide additional evaluation of the durability of the stenting procedure.

- Studies should incorporate the use of a Clinical Events Committee for adjudication of adverse events and a Data Safety Monitoring Board for evaluation of study progress and outcomes. In addition, the use of core lab analysis should help to minimize variability in data interpretation.

- A team approach utilizing a vascular surgeon, neurologist, and interventionalist at each site is recommended in order to minimize selection and treatment bias.

# VI. Available Clinical Evidence of Safety and Effectiveness

Several randomized and non-randomized multi-center clinical studies evaluating CAS performance in various populations have been reported. The following section summarizes some of the key studies in this field.

## A. SPACE: RCT in Symptomatic, Non-High-Risk Patients

The Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial was a randomized study intended to test the hypothesis that CAS is non-inferior to CEA in symptomatic patients with high-grade carotid artery stenosis.[30] A total of 1,200 patients were enrolled in Germany, Austria, and Switzerland. The original sample size was calculated as 1,900 subjects, but only 1,200 subjects were enrolled. Patients were required to have carotid artery stenosis of at least 70% as determined by duplex ultrasound, and have experienced TIA or completed stroke within the previous 180 days with a modified Rankin score of less than 4. Surgical risk status was not a factor in enrollment. The primary response variable was a composite of ipsilateral stroke or death within 30 days of the procedure.

Subjects were enrolled between March 2001 and February 2006, and were randomly allocated to treatment with CEA (n = 595) or CAS (n = 605). The use of shunting during the CEA procedures and the use of embolic protection devices during the CAS procedures were optional. The operators in the CEA arm were required to have performed at least 25 consecutive carotid endarterectomies and provide mortality and morbidity rates for those procedures. The operators in the CAS arm were required to have performed at least 25 successful angioplasty or stenting procedures.

The patient demographics and lesion characteristics were similar in the two treatment groups. The 30-day results for 1,183 treated patients are provided below. The CEA results were generally more favorable than the CAS results.

**SPACE Results at 30 Days Post-Procedure**

| **Study Arm** | | **CEA (n = 584)** | **CAS (n = 599)** | **Absolute Difference (CAS – CEA)*** |
|---|---|---|---|---|
| **Primary Response Events:** | | 37 (6.3%) | 41 (6.8%) | 0.51% [-1.89% – 2.91%] |
| **Death** | | 5 (0.9%) | 4 (0.7%) | |
| **All Stroke** | | 36 (6.2%) | 45 (7.5%) | |
| **Ipsilateral Stroke** | Ischemic Stroke | 30 (5.1%) | 39 (6.5%) | |
| | Hemorrhagic Stroke | 5 (0.9%) | 1 (0.2%) | |
| | Disabling Stroke** | 17 (2.9%) | 24 (4.0%) | |

* 90% confidence intervals provided.
** Stroke resulting in a modified Rankin score of ≥ 3.

An interim analysis conducted on these data resulted in an upper confidence interval of the absolute difference between the CAS and CEA results that exceeded the non-

inferiority margin for the study, which was prospectively defined as 2.5%. Thus, the results failed to demonstrate that CAS was non-inferior to CEA. Because the interim analysis indicated that an unacceptably high number of additional subjects would need to be enrolled to provide the non-inferiority of CAS, further subject recruitment was halted.

While this trial did not demonstrate that CEA was superior to CAS, the authors concluded that the results suggest that the widespread use of CAS is not justified at the present time because the trial did not reveal any evidence that CAS is non-inferior to CEA. While only 30-day results have been presented so far, collection and analysis of 6 – 24 month data is ongoing and may indicate different trends at longer time points. Possible limitations of the SPACE trial results are unequal training requirements for the CEA surgeons and interventionalists, the fact that the use of embolic protection devices was not required, and the limited length of follow-up at publication.[31 - 32] Others have commented that the requirements regarding training and embolic protection device usage do not represent bias or affect the validity of the results.[33 – 34]

## B. EVA-3S: RCT in Symptomatic, Non-High-Risk Patients

The Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial was a randomized clinical study involving patients in France with carotid artery stenosis of at least 60% as determined by duplex ultrasound and angiography, and with a TIA or completed stroke within the previous 120 days.[35] Patients were excluded for a disabling stroke resulting in a modified Rankin score of 3 or more. Surgical risk status was not a factor in enrollment. The primary response variable was a composite of stroke or death within 30 days of the procedure. The required sample size was calculated as 872 patients to achieve 80% statistical power and a maximum type I error of 5%, assuming a CEA event rate of 5.6%, a CAS event rate of 4%, and using a non-inferiority margin of 2%.

The operators in the CEA arm were required to have performed at least 25 carotid endarterectomies in the year prior to enrollment. The operators in the CAS arm were required to have performed at least 12 carotid stenting procedures or 35 stenting procedures in the supra-aortic trunks, of which 5 needed to be in the carotid arteries. Trainees could perform CAS procedures under the supervision of an operator who qualified for the study. The use of embolic protection devices in the CAS arm began in February 2003.

Enrollment commenced in November 2000, and 520 subjects had been randomly allocated to treatment with CEA (n = 259) or CAS (n = 261) when enrollment was halted in September 2005 due to safety concerns. The 30-day results for these 520 subjects are provided below.

**EVA-3S Results at 30 Days Post-Procedure**

| Study Arm | CEA (n = 259) | CAS (n = 261) |
|---|---|---|
| **Primary Response Events** | 10 (3.9%) | 25 (9.6%) |
| **Death** | 3 (1.2%) | 2 (0.8%) |
| **All Stroke** | 9 (3.5%) | 24 (9.2%) |
| Fatal Stroke | 2 (0.8%) | 1 (0.4%) |
| Non-Fatal Stroke | 7 (2.7%) | 23 (8.8%) |
| Disabling Stroke* | 1 (0.4%) | 7 (2.7%) |

* Stroke resulting in a modified Rankin score of 3 or more with an increase of 2 or more over the score before the stroke.

The patient demographics and lesion characteristics were generally similar in the two treatment groups. A higher proportion of the patients in the CEA arm had a history of stroke than in the CAS arm (20.1% vs. 12.6%). A higher proportion of the patients in the CAS arm had an occlusion of the contralateral carotid artery than in the CEA arm (5.0% vs. 1.2%).

Enrollment was stopped on the advice of the Data Safety Committee because of the high rate of stroke in the CAS arm of the study. The rate of the primary response variable in the CEA arm of the study was lower than expected (3.9% vs. 5.6%), and the rate of the primary response variable in the CAS arm of the study was higher than expected (9.6% vs. 4.0%). Given these results, the committee believed that the trial would not likely meet its objective of demonstrating equivalence, even if additional subjects were enrolled.

As with SPACE, some physicians believe that the training requirements for the CAS operators were inadequate, and that requiring the use of embolic protection devices during the entire study might have resulted in improved CAS results. The appropriateness of the medical regimen used in some subjects, specifically single antiplatelet therapy, has also been called into question.[36] Longer-term follow-up data are being collected and analyzed to assess the durability of both procedures.

## C. CaRESS: Non-Randomized, Concurrently Controlled Trial

The Carotid Revascularization using Endarterectomy or Stenting Systems (CaRESS) feasibility trial was conducted to compare CAS and CEA in a broad population of patients with symptomatic carotid stenosis (≥ 50%) or asymptomatic carotid stenosis (≥ 75%).[27, 37] To better mimic the spectrum of patient characteristics encountered during standard clinical practice, subject enrollment was not limited to high-risk surgical candidates. The primary endpoint of this feasibility study was the rate of death and stroke at 30 days post-procedure.

A total of 397 subjects were enrolled from April 2001 to December 2002. The study was not randomized; subjects were allocated into either the CAS or CEA arm based on the mutual preference of the subject and treating physician. The ratio of CEA to CAS subjects was maintained at 2:1. Stenting was performed using the Boston Scientific

Wallstent, with embolic protection provided by the Medtronic GuardWire Plus system. The subject demographics and medical characteristics were fairly well-balanced between the two arms despite the lack of randomization, as indicated if the following table.

**Baseline Demographics and Medical Characteristics for CaRESS Trial**

| Study Arm | CEA | CAS |
|---|---|---|
| **Subjects Enrolled** | 254 | 143 |
| **Mean Age (Years)** | 71.4 | 71.2 |
| **Males** | 63.4% | 60.1% |
| **Mean Height (cm)** | 169.6 | 170.6 |
| **Mean Weight (kg)** | 78.5 | 81.9 |
| **Symptomatic Subjects** | 32.7% | 30.8% |
| **Subjects with > 75% Stenosis** | 89.4% | 94.4% |
| **History of TIA** | 27.2% | 22.4% |
| **History of CVA** | 16.1% | 19.6% |
| **History of Either TIA or CVA** | 37.0% | 37.1% |
| **Coronary Artery Disease** | 63.0% | 67.8% |
| **Congestive Heart Failure** | 16.5% | 13.3% |
| **Hypertension** | 81.1% | 81.1% |
| **Hypercholesterolemia** | 69.7% | 63.6% |
| **Diabetes Mellitus** | 24.0% | 29.4% |
| **Peripheral Vascular Disease** | 40.6% | 45.5% |
| **History of Smoking** | 78.0% | 79.0% |
| **History of Prior CEA** | 11.4% | 30.1%* |
| **History of Prior CAS** | 0.0% | 5.6%** |

* Significantly higher than the CEA arm ($p < 0.0001$).
** Significantly higher than the CEA arm ($p < 0.001$).

Eighty-seven percent (87%) of the CEA patients were considered high-risk for surgery. Similarly, 84% of the CAS patients were considered high surgical risk. High-risk status was defined as the presence of at least one of the following criteria:

- Age ≥ 80 years
- New York Heart Association (NYHA) class III/IV for congestive heart failure
- Chronic obstructive pulmonary disease
- Contralateral stenosis ≥ 50%
- Prior CEA or CAS
- Prior coronary artery bypass grafting.

Kaplan-Meier estimates of the event rates at 30 and 365 days post-procedure are provided below, along with the observed rates of restenosis and carotid revascularization. There were no significant differences between the two groups for any outcome.

**Kaplan-Meier Estimates of CaRESS Event Rates**
(Freedom from event ± standard error)

| Timing of Events | ≤ 30 Days | | ≤ 365 Days | |
|---|---|---|---|---|
| **Study Arm** | **CEA** | **CAS** | **CEA** | **CAS** |
| **Death** | 99.6 ± 0.4% | 100.0 ± 0.0% | 93.4 ± 1.7% | 93.7 ± 2.2% |
| **Stroke** | 96.4 ± 1.2% | 97.9 ± 1.2% | 90.2 ± 2.0% | 94.5 ± 2.0% |
| **MI** | 99.2 ± 0.6% | 100.0 ± 0.0% | 97.6 ± 1.1% | 98.3 ± 1.2% |
| **Death/Stroke** | 96.4 ± 1.2% | 97.9 ± 1.2% | 86.4 ± 2.3% | 90.0 ± 2.7% |
| **Death/Stroke/MI** | 95.6 ± 1.3% | 97.9 ± 1.2% | 85.7 ± 2.4% | 89.1 ± 2.8% |
| **Restenosis*** | | | 3.6% (7/192) | 6.3% (7/111) |
| **Carotid Revascularization*** | | | 1.0% (2/192) | 1.8% (2/112) |

* Actual observed events listed.

The results of the CaRESS study indicate that CEA and CAS outcomes are comparable up to one year post-procedure. The study also demonstrates that a non-randomized, concurrently-controlled study can be conducted without resulting in unbalanced baseline covariates between the two arms. However, the majority of enrolled patients were considered high surgical risk, and so the applicability of the results obtained to the non-high-risk population is not clear.

## D. SAPPHIRE: RCT in High Surgical Risk Patients

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial was conducted to determine the non-inferiority of CAS (using the Cordis PRECISE Nitinol Stent System) to CEA in high surgical risk patients with symptomatic stenosis (≥ 50%) or asymptomatic stenosis (≥ 80%) of the common or internal carotid artery.[26] The primary response variable was the rate of death, stroke, or MI up to 30 days post-procedure, plus the rate of death and ipsilateral stroke from 31 – 360 days post-procedure.

A total of 747 high surgical risk patients were enrolled between August 1, 2000 and June 11, 2002. High surgical risk was defined either in terms of conditions affecting the operative site in the neck of the subjects or co-morbid medical conditions. After enrollment, the patients were re-evaluated by a team of surgeons, interventionalists, and neurologists to determine if they were suitable to be randomized. Of these 747 patients, 406 patients (54%) were considered to be at too high a risk for adverse events from surgery to be randomized, and were treated with CAS. An additional 7 patients (1%) were considered unsuitable for CAS and were treated with CEA. The remaining 334 patients (45%) were considered to be suitable for treatment by either method and were randomized in equal proportions to CAS or CEA.

The major adverse events observed in the study are provided below, both as absolute numbers and percentages. The patients in the two randomized groups were similar in terms of demographics and medical conditions. The patients in the stent registry group were not comparable to the randomized patients, and the data for this group are included for comparison only.

**Summary of the SAPPHIRE Study Results**

| Study Phase | | Randomized Trial | | CAS Registry |
|---|---|---|---|---|
| | | CEA Arm | CAS Arm | |
| **Subjects Enrolled** | | 167 | 167 | 406 |
| **Primary Endpoint Events*** | | 32 (19.2%) | 20 (12.0%) | 64 (15.8%) |
| **Events 0 - 30 Days** | **Death** | 4 (2.4%) | 2 (1.2%) | 9 (2.2%) |
| | **Stroke** | 5 (3.0%) | 6 (3.6%) | 20 (4.9%) |
| | **MI** | 10 (6.0%) | 4 (2.0%) | 7 (1.7%) |
| | **Major Bleeding** | 17 (10.2%) | 15 (9.0%) | 52 (12.8%) |
| | **Bradycardia/Asystole** | 5 (3.0%) | 14 (8.4%) | 13 (3.2%) |
| **Events 0 - 360 Days** | **Death** | 21 (12.6%) | 12 (7.2%) | 41 (10.1%) |
| | **Stroke** | 12 (7.2%) | 10 (6.0%) | 37 (9.1%) |
| | **MI** | 12 (7.2%) | 5 (3.0%) | 11 (2.7%) |
| | **Severe Hypotension** | 5 (3.0%) | 29 (17.4%)** | 63 (15.5%) |
| | **Cranial Nerve Injury** | 8 (4.8%)† | 0 (0.0%) | 0 (0.0%) |
| | **Target Lesion Revascularization††** | 4.3%† | 0.6% | 0.8% |

* Rate of death, stroke, or MI up to 30 days post-procedure, plus the rate of death and ipsilateral stroke from 31 – 360 days post-procedure.
** Significantly greater than the rate for the CEA arm ($p < 0.01$).
† Significantly greater than the rate for the CAS arm ($p < 0.05$).
†† Calculated using Kaplan-Meier estimates.

The primary analysis resulted in an absolute difference of -7.2% between the CAS and CAE arms (95% confidence interval: -16.4% to 0.7%). These results demonstrated that CAS is non-inferior to CEA. The adverse events rates for the two randomized arms were found to be equivalent, except as noted above. The adverse event rates for the CAS registry were generally comparable to those of the randomized CAS arm, although the stroke rate was notably higher in the registry.

The SAPPHIRE trial demonstrated that outcomes for CAS and CEA are equivalent in patients who were originally considered to be high surgical risk. The fact that 45% of the entire SAPPHIRE cohort was subsequently deemed suitable for randomization may suggest that RCTs for the non-high-risk population should enroll at a sufficient rate. However, it is important to note that clinical equipoise may have shifted since the initiation of SAPPHIRE enrollment in 2000, as evidenced by the fact that enrollment in the randomized phase diminished sharply 12 months after study initiation.

## E. Single-Arm Studies in High Surgical Risk Patients

Four single-arm pivotal clinical studies of CAS with embolic protection have been conducted in order to support marketing approval for various carotid stent systems. These studies were all conducted in high surgical risk subjects with symptomatic and asymptomatic carotid artery stenosis. The criteria for high surgical risk were similar but not identical in all studies, and as with SAPPHIRE the risk factors involved anatomical

conditions in the neck of the patient and co-morbid medical conditions. Some common eligibility criteria are presented below:

- Symptomatic (≥ 50% stenosis) or asymptomatic (≥ 70% or 80% stenosis) of the internal and/or common carotid artery. Symptoms are defined as ipsilateral stroke, TIA, or amaurosis fugax within 180 days of the procedure.

- Vessel anatomy suitable for use of stent system with embolic protection

- Presence of at least one high-risk criterion, as defined in the following table:

**Surgical Risk Factors Included in Single-Arm CAS Studies for High-Risk Subjects***

| Anatomic Factors | Co-Morbidities |
|---|---|
| Previous CEA with restenosis | Age ≥ 75 years |
| Previous radiation treatment to the neck | Unstable angina |
| High cervical lesion | NYHA class III/IV for congestive heart failure |
| Occlusion of contralateral carotid artery | Left ventricular ejection fraction < 30% |
| Significant bilateral carotid artery stenosis | Myocardial infarction within past 6 weeks |
| Inability to flex neck due to cervical disorders | Multi-vessel coronary artery disease with ≥ 70% stenosis |
| Presence of tracheostomy/stoma | Need for coronary artery bypass graft or valve replacement after the procedure |
| Contralateral laryngeal nerve palsy | Dialysis-dependent renal failure |
| Radical neck dissection | Severe pulmonary disease, including home oxygen therapy or forced expiration volume in one second < 50% of predicated value |

* Not all risk criteria were included in every study. Some risk factors varied slightly between studies.

The single-arm studies all included composite primary response variables based on 30-day and 365-day events and hypotheses based on achieving a target value for this endpoint. The target value was derived from literature controls and depended on the proportions of enrolled subjects with anatomical and co-morbid risk factors. The results of these four studies are summarized in the following table.

**Summary of Single-Arm CAS Studies in High Surgical Risk Subjects**

| **Study** | ARCHeR 2[1] | SECuRITY[2] | CABERNET[4] | CREATE[5] |
|---|---|---|---|---|
| **Investigational Stent** | ACCULINK | Xact | Nexstent | Protégé |
| **Manufacturer** | Guidant | Abbott Vascular | Endotex | ev3 |
| **Subjects Enrolled** | 278 | 305 | 454 | 419 |
| **Primary Endpoint Events (Rate)** | 9.7% | 26 (8.5%) | 19 (4.7%) | 29 (7.8%)* |
| Death ≤ 30 days | 6 (2.2%) | 3 (1.0%) | 2 (0.5%) | 8 (1.9%) |
| Stroke ≤ 30 days | 15 (5.4%) | 19 (6.2%) | 15 (3.4%) | 20 (4.8%) |
| MI ≤ 30 days | 8 (2.9%) | 1 (0.3%) | 1 (0.2%) | 4 (1.0%) |
| Ipsilateral stroke 31 – 365 days | 3 (1.1%) | 3 (1.0%) | 3 (0.7%) | 3 (0.8%) |

* Contralateral strokes that were not considered procedure-related were not included in the primary endpoint for this study.

For each of these studies, the results supported PMA approval of the investigational stent for use in high surgical risk patients.

### F. Ongoing Trials

Three large-scale, multi-center RCTs comparing CAS to CEA in non-high-risk patients are currently enrolling subjects. One, the Carotid Revascularization Endarterectomy vs. Stent Trial (CREST), includes both symptomatic and asymptomatic subjects[38]. The others, the Carotid Angioplasty and Stenting vs. Endarterectomy in Asymptomatic Subjects Who are at Standard Risk for CEA with Significant Extracranial Carotid Stenotic Disease Trial (ACT I) and the International Carotid Stenting Study (ICSS), include only asymptomatic and symptomatic subjects, respectively.[39 - 40] No results from the pivotal phases of these studies are yet available. Another RCT comparing CAS to medical therapy in asymptomatic patients, the Transatlantic Asymptomatic Carotid Intervention Trial (TACIT), is in the planning stages.[41] The results of these trials are expected to provide additional clarification of the role of CAS in treating symptomatic and asymptomatic carotid artery stenosis in patients who are also suitable CEA candidates.

## VII. Challenges to Clinical Trial Conduct and Development

### A. Randomized, Controlled Trials

While FDA recommends that RCTs be conducted to evaluate CAS in the non-high-risk population, conducting these studies is not without its own set of challenges. Perhaps the central concern is that these studies may enroll patients more slowly than anticipated. Slow enrollment increases the likelihood that clinical practice or the device design will change significantly over the course of the investigation. Such changes may call into question the generalizability and clinical relevance of the resulting data if such time trends are important.

Slow enrollment may be due partly to the preferences of enrolling investigators who may frequently believe that potential subjects would be better served by one treatment versus the other, and should therefore not be enrolled in the study. In addition, the potential subjects themselves may decline to enroll in the studies because they are uncomfortable with the concept of randomization, especially if the subject is faced with treatment via either a surgical procedure or a minimally invasive alternative that may be perceived as more desirable. Thus, while RCTs may provide the highest level of clinical trial evidence, reliance on RCTs may paradoxically not allow investigators to acquire the required evidence in a reasonable time frame leading to premature study termination of well-designed trials.

## B. Non-Randomized, Concurrently Controlled Trials

Another study design option for comparing CAS and CEA is a non-randomized study design in which subjects are allocated to either the CAS or CEA arm based on physician judgment and subject agreement, not through a formal randomization process. Such a study may experience more rapid enrollment because patients can be enrolled based on physician and patient preferences. However, the interpretability of the resulting data may be questioned due to the possible inability to adequately contain bias and confounding factors and produce comparable treatment and control groups, as described below.

**Bias**

Bias is a process introduced during the design, implementation, or analysis of the study in which investigators and subjects can effect a spurious increase or decrease in the magnitude of the study findings. Because there are, in general, no statistical methods to evaluate and correct for the effects of bias, its impact can be difficult to assess quantitatively.

In a non-randomized study, allowing the investigator to exercise their judgment in recruiting subjects and selecting treatment options for them can introduce considerable bias (selection bias).[42] For example, the investigator may prefer one particular treatment for their healthier subjects, which is likely to result in this particular treatment appearing to have more favorable outcomes relative to the other treatment, regardless of its actual merit. One way to help assess the possibility of selection bias is through the maintenance of screening logs that indicate which patients were recruited into each arm and which were ultimately not enrolled. Another scheme that may potentially reduce selection bias is the use of an interdisciplinary team approach when recruiting patients.

Bias may also occur through the care that a subject receives during the procedural and follow-up periods (treatment bias) and the evaluation of study endpoints (assessment bias). However, it is important to note that an RCT comparing CAS to CEA may also be subject to these forms of bias both because the investigator will not be blinded to the study arm in which the subject is enrolled and because investigators may represent multiple physician specialties. A carefully designed clinical protocol can mitigate these sources of bias.

**Confounding Factors**

Whereas bias occurs through a process intrinsic to the design or implementation of the study, a confounded result is due to an extrinsic source. Confounding occurs when a significant finding is believed to be due to the treatment delivered, but which is instead due to the presence of extrinsic, confounding factors. For example, if the patient characteristics are not comparable between the two study arms due to selection bias or other factors, the study results may be confounded because any perceived treatment effect may in fact be due to an imbalance of clinically relevant prognostic factors between the

CEA and CAS groups. Other potential confounding factors include investigational site characteristics and physician training and experience.

A well-designed RCT is expected to remove the effects of known and unknown confounders. For a non-randomized trial, statistical techniques such as multivariate analysis and propensity score-based methods[43] or exclusion of patients possessing confounding covariates can only remove the effects of known and measured confounders; any effects of unknown or unmeasured confounders will still be present. However, extensive prior clinical trials research regarding carotid revascularization over the last 25 years may have identified all major clinically relevant confounding factors, minimizing the impact of unknown confounders on the measured results.

**Some Potential Sources of Bias and Confounding for Non-Randomized Trials**

| Bias | Confounding |
|---|---|
| Patient selection | Patient-level covariates |
| Patient treatment | Investigational site |
| Endpoint assessment | Physician experience |

In summary, bias and confounding cannot be expected to be completely eradicated in a non-RCT trial. There will always be concerns regarding these potential problems. A key panel question, however, will be whether potential problems related to bias and confounding in a non-RCT carotid trial can be sufficiently minimized through careful study design and execution such that it is reasonable for a manufacturer to choose this pathway.

# VIII. Professional Society Perspectives

The American Heart Association (AHA)/American Stroke Association (ASA) Stroke Council has published guidelines for primary prevention of ischemic stroke and prevention of stroke in patients with prior ischemic stroke or TIA.[6, 9] These guidelines were affirmed by the American Academy of Neurology (AAN). For patients with recent stroke or TIA and ipsilateral carotid artery stenosis of 50 – 99%, these societies recommend CEA performed by a surgeon with a perioperative morbidity and mortality of less than 6%. However, patients with carotid artery stenosis of 50 – 69% should be carefully selected. In patients with greater than 70% stenosis with anatomic factors or co-morbidities that increase their risk for surgical adverse events, CAS can be considered, and is a reasonable alternative when performed by operators with perioperative morbidity and mortality rates of 4 - 6%

For patients with asymptomatic extracranial carotid artery stenosis, these societies recommend carotid endarterectomy in high surgical risk patients with 60 – 99% asymptomatic carotid stenoses performed by surgeons with less than 3% morbidity and mortality rates. Selection of these patients should be based on the individual risks and benefits posed by the procedure. In addition, the authors state carotid angioplasty and stenting might be a reasonable alternative to CEA in high surgical risk asymptomatic

patients. However, the authors raise the possibility that these patients may not benefit by either procedure, based on the reported perioperative and overall event rates at one year post-procedure.

The American College of Cardiology (ACC), in collaboration with the Society for Cardiovascular Angiography and Interventions (SCAI), the Society for Vascular Medicine and Biology (SVMB), the Society for Interventional Radiology (SIR), and the American Society of Interventional and Therapeutic Neuroradiology (ASITN), has recently issued a consensus document on carotid stenting.[44] These societies state that there is currently insufficient evidence to support CAS in patients who are not high surgical risk. The authors also state that the results of ongoing randomized trials will determine whether lower-risk patients should be treated with CAS.

Each of these positions is consistent with FDA's determination that the safety and effectiveness of CAS in the non-high-risk population has not been shown for any device. Additional data from well-designed clinical trials will be necessary to expand the treatment recommendations for CAS.

# IX. Conclusions

Carotid artery stenting may represent a valuable treatment option for symptomatic and asymptomatic carotid artery stenosis in patients who are not a high risk for adverse events from CEA. FDA currently recommends that study sponsors conduct randomized, controlled trials comparing CAS to CEA, both to determine whether CAS in general produces clinical outcomes equivalent to CEA in these patients, and to generate data that would provide a reasonable assurance of safety and effectiveness to support a PMA for specific carotid stent systems for the non-high-risk indication. However, no trials of this type have yet been completed. For a variety of reasons, manufacturers and investigators have raised concerns that RCTs are not feasible to study this treatment area

Due to these concerns, FDA requests expert input from the Circulatory System Devices Panel on whether an RCT is necessary to appropriately evaluate CAS in lower-risk patients. FDA also requests recommendations for optimizing CAS study design and enrollment for the non-high-risk indication.

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# Appendix A: List of Abbreviations Used

**AAN:** American Academy of Neurology
**ACAS:** Asymptomatic Carotid Atherosclerosis Study
**ACC:** American College of Cardiology
**ACE:** angiotensin-converting enzyme
**ACST:** Asymptomatic Carotid Surgery Trial
**ACT I:** Carotid Angioplasty and Stenting vs. Endarterectomy (CEA) in Asymptomatic Subjects Who are at Standard Risk for CEA with Significant Extracranial Carotid Stenotic Disease Trial
**AHA:** American Heart Association
**ASA:** American Stroke Association
**ASITN:** American Society of Interventional and Therapeutic Neuroradiology
**CAE:** carotid endarterectomy
**CaRESS:** Carotid Revascularization using Endarterectomy or Stenting Systems
**CAS:** carotid artery stenting
**CREST:** Carotid Revascularization Endarterectomy vs. Stent Trial
**CVA:** cerebrovascular accident
**ECST:** European Carotid Surgery Trial
**EVA-3S:** Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis
**FDA:** U.S. Food and Drug Administration
**ICSS:** International Carotid Stenting Study
**IDE:** Investigational Device Exemption
**NASCET:** North American Carotid Endarterectomy Trial
**NYHA:** New York Heart Association
**PMA:** Premarket Approval
**RCT:** randomized, controlled trial
**SAPPHIRE:** Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy
**SCAI:** Society for Cardiovascular Angiography and Interventions
**SIR:** Society for Interventional Radiology
**SPACE:** Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy
**SVMB:** Society for Vascular Medicine and Biology
**TACIT:** Transatlantic Asymptomatic Carotid Intervention Trial
**TIA:** transient ischemic attack