Clinical Trial Design Issues for Carotid Artery Stenting

October 11, 2007 Meeting of the Circulatory System Devices Panel

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Meeting Purpose

FDA requests Panel input on the following topics:

- Clinical trial designs for carotid artery stenting in patients who are not considered high surgical risk
- Optimization of the quality of clinical data collected in these trials
Goals

- Develop clinical trials capable of demonstrating the safety and effectiveness of CAS in the non-high-risk population
  - PMA approval requires valid scientific evidence

- Mitigate potential challenges to CAS clinical trial conduct
  - Enrollment rate
  - Interpretability of data
Overview of FDA Presentation

- Introduction to CAS
- Current FDA Recommendations
  - Kenneth Cavanaugh, Ph.D.
- Clinical Evidence
  - Wolf Sapirstein, M.D., M.P.H., F.A.C.S.
- Challenges to Trial Conduct
  - Chul Ahn, Ph.D.
- Professional Society Perspectives
  - Michael Barnett, M.D.
- Conclusion
Overview of FDA Presentation

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- Challenges to Trial Conduct
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- Conclusion
Persistent neurological deficit of cerebrovascular cause
Third leading cause of death
Leading cause of disability
Annual mortality and morbidity:
- 160,000 deaths
- 500,000 new stroke victims
- 200,000 recurrent strokes
Annual cost: ≈ $57 billion

1 Stroke 37: 577 – 617 (2006)
Etiology of Stroke

- Carotid artery disease: 30%
- Non-carotid ischemia: 30%
- Hemorrhagic disease: 20%
- Vertebral-basilar disease: 20%

Carotid Artery Stenosis

- Risks due to emboli, not blood flow reduction
- Significant in 5 – 7% of patients > 65 years
- Detectable using non-invasive imaging

1 Stroke 23: 1752 – 1760 (1992)
Symptomatic Status

- **Symptomatic** – Previous ipsilateral event within a specified time frame (e.g. 6 months)

- **Asymptomatic** – Lack of events within time frame

“Asymptomatic” patients may have had prior stroke
Treatment Options

- Medical therapy
- Carotid endarterectomy
- Carotid artery stenting
Medical Therapy

Several pharmacological regimens have a role in stroke prevention

- Aspirin
- Clopidogrel / ticlopidine
- Statins
- ACE inhibitors
Carotid Endarterectomy

- Surgical excision of carotid atheroma
- Most common cardiovascular surgical procedure
- Gold standard for carotid revascularization
CEA – Symptomatic Patients

Long-term outcomes from CEA + medical therapy superior to medical therapy alone


Benefits mitigated by:
- Percent stenosis
- Operative mortality/morbidity rates

CEA – Asymptomatic Patients

- Superior long-term outcomes with CEA + medical therapy

  - CEA vs. medical therapy alone

  - Immediate CEA vs. delayed CEA

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Carotid Artery Stenting

- Endovascular delivery of implants to stabilize stenotic plaque
- Performed with embolic protection
- Different risk profile than CEA
  - Less procedure-related morbidity
  - Deployment-related embolization
CAS Approvals

- Guidant ACCULINK
- Abbott Xact
- Cordis PRECISE
- Endotex Nexstent
- ev3 Protégé
Approved Indications

- Treatment of patients at high risk for adverse events from CEA who require percutaneous revascularization and who have:
  - Either neurological symptoms and \( \geq 50\% \) stenosis
  - Or no neurological symptoms and \( \geq 80\% \) stenosis
  - An appropriately sized reference vessel diameter
April 21, 2004 Panel Meeting

- PMA for Cordis PRECISE stent
- Approvable with conditions
  - Labeling restrictions
    - High-risk indications
- Post-approval study
  - Careful follow-up
  - Data consistent with pre-market results
Challenges when using historical controls

Composite endpoints challenging for surgical vs. non-surgical comparisons

Anatomic risk factors may result in unsuitable CAS candidates

Post-approval follow-up essential
Non-High-Risk Indication

- Stents not approved for treatment of patients who are not high risk for CEA
- Represents majority of patients with carotid disease
- Need for robustly designed, prospective trials to demonstrate proof of concept and support approval of devices for non-high-risk indications
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Bases for Recommendations

  - Represents FDA’s current thinking and best practices
  - Non-binding

- CAS literature

- Advisory panel
Trial Design Recommendations

- Prospective, multi-center, randomized, controlled trial comparing CAS to CEA in non-high-risk subjects
- Minimize potential bias and confounding
- Non-inferiority design
  - Clinically meaningful non-inferiority margin
Clinical Trial Endpoints

Primary endpoint incorporating:
- Peri-procedural morbidity
- Longer-term rate of stroke ipsilateral to stented vessel

Example:
- Rate of death, stroke, and myocardial infarction within 30 days of the procedure, plus the rate of ipsilateral stroke from 31 – 365 days
Other Recommendations

- Long-term follow-up

- Independent and objective assessment
  - Clinical Events Committee
  - Data Safety Monitoring Board
  - Core lab analysis

- Team approach utilizing surgical, neurological, and interventional physician specialties
What Other Recommendations Should FDA Provide?

Panel input is requested to answer the following questions:
Question #1

Can acceptable non-RCT trial designs that compare carotid artery stenting to carotid endarterectomy in patients who are not at high risk for adverse events from surgical revascularization be developed?

If so, please provide recommendations regarding choice of control, subject eligibility criteria, endpoints, and selection of methodologies for minimizing bias and confounding.
Question #2(a)

Does sufficient clinical equipoise still exist so that the performance of an RCT to evaluate CAS is scientifically and ethically valid?

If so, what are the current barriers to enrollment in RCTs involving carotid revascularization?
Question #2(b)

What, if any, study parameters can be modified to facilitate enrollment in the RCTs without unduly compromising the validity of the resulting data?

Examples of study characteristics that may affect enrollment are subject eligibility criteria, follow-up type and duration, and subject recruitment methods.
Question #3

If the proof of concept of carotid stenting in non-high-risk patients is successfully demonstrated, would your study design recommendations change?

If so, in what way? For example, would you recommend a non-inferiority RCT comparing two carotid stent systems?
Question #4

What other recommendations do you have that may facilitate initiation, enrollment, completion, and interpretability of clinical trials for this indication?
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- Conclusion
Clinical Evidence Supporting Carotid Artery Stenting

Wolf Sapirstein, M.D., M.P.H., F.A.C.S.
Associate Director
Division of Cardiovascular Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Overview

- CEA studies
  - Symptomatic and asymptomatic subjects

- CAS studies
  - High-risk and non-high-risk subjects
  - Randomized and non-randomized designs
Carotid Endarterectomy for Stroke Prevention

- Extra-cranial carotid disease responsible for 30% of 700,000 annual strokes

- RCTs established role of CEA in prophylaxis
  - NASCET (1991)
  - ECST (1991)
  - ACAS (1995)
Stroke Risk Due to Symptomatic Carotid Artery Disease

<table>
<thead>
<tr>
<th>Percent Stenosis</th>
<th>Risk of Stroke Without CEA at 2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 – 69%</td>
<td>10%</td>
</tr>
<tr>
<td>70 – 79%</td>
<td>20%</td>
</tr>
<tr>
<td>80 – 89%</td>
<td>30%</td>
</tr>
<tr>
<td>90 – 99%</td>
<td>35%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percent Stenosis</th>
<th>NNT To Prevent 1 Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 – 69%</td>
<td>13</td>
</tr>
<tr>
<td>70 – 99%</td>
<td>6</td>
</tr>
</tbody>
</table>

Based on NASCET and ECST results
## Stroke Risk Due to Asymptomatic Carotid Artery Disease

Based on ACAS and ACST results

<table>
<thead>
<tr>
<th>Study</th>
<th>Percent Stenosis</th>
<th>Stroke Risk at 5 Years</th>
<th>NNT</th>
<th>CVA Prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAS</td>
<td>&gt; 60%</td>
<td>11.0%</td>
<td>19</td>
<td>50/1000</td>
</tr>
<tr>
<td>ACST</td>
<td>&gt; 60%</td>
<td>11.8%</td>
<td>20</td>
<td>53/1000</td>
</tr>
</tbody>
</table>
Level 1 Evidence for CEA in Symptomatic Patients

- > 70% stenosis with 5.8% operative risk
  - Prevents 16.5 strokes & deaths/100 patients/2 years

- 50 - 69% stenosis with 6.7% operative risk
  - Prevents 10.1 strokes & deaths/100 patients/5 years

- < 50% stenosis with < 1% operative risk
  - Prevents 1 stroke & death/100 patients/5 years

Based on NASCET and ECST results
Level 1 Evidence for CEA in Asymptomatic Patients

- $> 60\%$ stenosis with operative risk $< 3\%$
  - Prevents 5 strokes & deaths/100 patients/5 years
  - Need to treat 20 patients to prevent 1 stroke

- $< 60\%$ stenosis
  - No benefit to CEA

Severity of stenosis did not affect CVA risk

Based on ACAS and ACST results
Trials Evaluating CAS

Study Designs:
- Randomized, controlled trials (CEA control)
- Non-randomized studies
  - Concurrent controls
  - Single-arm studies

Subject population considerations:
- Surgical risk status
- Symptomatic status
- Severity of stenosis
- Other demographics (e.g. gender, age)
# High Surgical Risk Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Stent</th>
<th>Subjects</th>
<th>Stenosis</th>
<th>% Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARCHeR (1, 2, 3)</td>
<td>Acculink</td>
<td>437</td>
<td>Symptomatic ≥ 50%</td>
<td>24%</td>
</tr>
<tr>
<td>SECuRITY</td>
<td>Xact</td>
<td>305</td>
<td></td>
<td>21%</td>
</tr>
<tr>
<td>CABERNET</td>
<td>Nexstent</td>
<td>454</td>
<td>Asymptomatic ≥ 80%³</td>
<td>24%</td>
</tr>
<tr>
<td>CREATE</td>
<td>Protégé</td>
<td>419</td>
<td></td>
<td>17%</td>
</tr>
<tr>
<td>BEACH</td>
<td>Wallstent²</td>
<td>480</td>
<td></td>
<td>24%</td>
</tr>
<tr>
<td>MAVErIC (I, II)</td>
<td>Exponent²</td>
<td>498</td>
<td></td>
<td>42%</td>
</tr>
<tr>
<td>SAPPHIRE¹</td>
<td>Precise</td>
<td>747</td>
<td></td>
<td>34%</td>
</tr>
</tbody>
</table>

1 Randomized study  
2 Not approved by FDA  
3 CREATE also included asymptomatic subjects with 70 – 79% stenosis
## Surgical Risk Factors

<table>
<thead>
<tr>
<th>Anatomic Factors</th>
<th>Co-Morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous CEA with restenosis</td>
<td>Age $\geq 75$ years</td>
</tr>
<tr>
<td>Prior radiation treatment of neck</td>
<td>Unstable angina</td>
</tr>
<tr>
<td>High cervical lesion</td>
<td>NYHA class III/IV for CHF</td>
</tr>
<tr>
<td>Contralateral carotid occlusion</td>
<td>LVEF $&lt; 30%$</td>
</tr>
<tr>
<td>Significant bilateral carotid stenosis</td>
<td>MI within past 6 weeks</td>
</tr>
<tr>
<td>Inability to flex neck</td>
<td>Multi-vessel coronary artery disease with $\geq 70%$ stenosis</td>
</tr>
<tr>
<td>Presence of tracheostomy/stoma</td>
<td>Need for post-procedure CABG or valve replacement</td>
</tr>
<tr>
<td>Contralateral laryngeal nerve palsy</td>
<td>Dialysis-dependent renal failure</td>
</tr>
<tr>
<td>Radical neck dissection</td>
<td>Severe pulmonary disease</td>
</tr>
</tbody>
</table>
## Pivotal Single-Arm CAS Studies in High Surgical Risk Subjects

<table>
<thead>
<tr>
<th></th>
<th>ARCHeR 2</th>
<th>SECURITY</th>
<th>CABERNET</th>
<th>CREATE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stent</strong></td>
<td>ACCULINK</td>
<td>Xact</td>
<td>Nexstent</td>
<td>Protégé</td>
</tr>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Guidant</td>
<td>Abbott</td>
<td>Endotex</td>
<td>ev3</td>
</tr>
<tr>
<td><strong>Subjects</strong></td>
<td>278</td>
<td>305</td>
<td>454</td>
<td>419</td>
</tr>
<tr>
<td><strong>Primary Endpoint Rate</strong></td>
<td>9.7%</td>
<td>8.5%</td>
<td>4.7%</td>
<td>7.8%*</td>
</tr>
<tr>
<td><strong>Death ≤ 30 Days</strong></td>
<td>6 (2.2%)</td>
<td>3 (1.0%)</td>
<td>2 (0.5%)</td>
<td>8 (1.9%)</td>
</tr>
<tr>
<td><strong>Stroke ≤ 30 Days</strong></td>
<td>15 (5.4%)</td>
<td>19 (6.2%)</td>
<td>15 (3.4%)</td>
<td>20 (4.8%)</td>
</tr>
<tr>
<td><strong>MI ≤ 30 Days</strong></td>
<td>8 (2.9%)</td>
<td>1 (0.3%)</td>
<td>1 (0.2%)</td>
<td>4 (1.0%)</td>
</tr>
<tr>
<td><strong>Ipsilateral Stroke 31 – 365 Days</strong></td>
<td>3 (1.1%)</td>
<td>3 (1.0%)</td>
<td>3 (0.7%)</td>
<td>3 (0.8%)</td>
</tr>
</tbody>
</table>

* Does not include contralateral strokes that were not considered procedure-related
SAPPHIRE

CAS (Precise + Angioguard) vs. CEA
- Non-inferiority RCT
- Registries for subjects unsuitable for randomization

747 subjects enrolled
- 334 randomized to CAS or CEA
- 406 in CAS registry
- 7 in CEA registry
**SAPPHIRE Results**

<table>
<thead>
<tr>
<th></th>
<th>Randomized CAS Arm</th>
<th>Randomized CEA Arm</th>
<th>CAS Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>167</td>
<td>167</td>
<td>406</td>
</tr>
<tr>
<td>Death, Stroke, MI at 30 Days</td>
<td>6.8%</td>
<td>11.4%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Death, Stroke, MI at 360 Days</td>
<td>18.2%</td>
<td>27.0%</td>
<td>21.9%</td>
</tr>
</tbody>
</table>

- CAS is non-inferior to CEA
- Slow enrollment in randomized arms
  - Prevalence of single-arm CAS studies
  - Insufficient power to analyze superiority of CAS to CEA

Non-High-Risk CAS Studies

- SPACE
- EVA-3S
- CaRESS
- Ongoing trials
Randomized trial of CAS vs. CEA (2001 – 2006)
- 35 centers in Germany, Austria, and Switzerland

Non-inferiority hypothesis
- Delta = 2.5%

Endpoint: Death + ipsilateral stroke at 30 days

1,900 subjects planned
- Symptomatic carotid stenosis > 70%
- Exclusion criteria included surgical risk factors
Interim analysis: Differences between CAS and CEA rates exceeded non-inferiority margin

- Unacceptably high number of additional subjects needed to demonstrate non-inferiority
EVA-3S

- Randomized trial of CAS vs. CEA (2000 – 2005)
  - 30 centers in France

- Non-inferiority hypothesis
  - Delta = 2%

- Endpoint: Death + stroke at 30 days

- 527 subjects
  - Symptomatic carotid stenosis > 60% (> 70% for first half)
  - Exclusion criteria include surgical risk factors
EVA-3S Results

<table>
<thead>
<tr>
<th></th>
<th>CAS (N = 261)</th>
<th>CEA (N = 259)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint Rate</td>
<td>9.6%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Death at 30 Days</td>
<td>0.8%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Stroke at 30 Days</td>
<td>9.2%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Enrollment halted due to DSC concerns
- Unacceptably high stroke rate in CAS arm
- CAS not likely to be shown non-inferior to CEA

SPACE and EVA-3S Concerns

- EPD use not required throughout study duration\(^1\)

- Different training requirements for operators in CAS and CEA arms\(^2\)

- Subset analyses of EVA-3S\(^3\):
  - No learning curve effect
  - Statistically significant EPD use effect

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\(^2\) Eur J Vasc Endovasc Surg 33: 48 – 49 (2007)
CaRESS

- Non-randomized, concurrently controlled comparison of CAS to CEA
  - 14 centers in the U.S.
  - Intended as “real-world” study
  - Symptomatic (≥ 50%) and asymptomatic (≥ 75%) subjects
  - Not restricted by surgical risk status

- Phase I study enrolled 397 subjects (2001 – 2002)
  - Enrollment 2:1 in favor of CEA
  - 32% symptomatic
  - 86% considered high risk for surgery
## CaRESS Demographics

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

* p < 0.0001
** p < 0.001
### CaRESS Results

**Surgical risk status not an outcome predictor**

**Phase II study proposed**

<table>
<thead>
<tr>
<th></th>
<th>≤ 30 Days</th>
<th>≤ 365 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CEA</td>
<td>CAS</td>
</tr>
<tr>
<td>Death</td>
<td>0.4%</td>
<td>0%</td>
</tr>
<tr>
<td>Stroke</td>
<td>3.6%</td>
<td>2.1%</td>
</tr>
<tr>
<td>MI</td>
<td>0.8%</td>
<td>0%</td>
</tr>
<tr>
<td>Death + Stroke</td>
<td>3.6%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Death + Stroke + MI</td>
<td>4.4%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

RCT results failed to prove non-inferiority of CAS to CEA
- Interpretability and acceptance of results challenged by study design aspects

Non-randomized study results suggest non-inferiority of CAS
- Feasibility study
- Known covariates were well-balanced
- Indeterminate effect of unknown covariates
# Ongoing Non-High-Risk RCTs

<table>
<thead>
<tr>
<th>Location</th>
<th>CREST</th>
<th>ICSS</th>
<th>ACT I</th>
<th>TACIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>N. America</td>
<td>Europe</td>
<td>N. America</td>
<td>N. America, Europe</td>
</tr>
<tr>
<td>Target Enrollment</td>
<td>2,500</td>
<td>1,500</td>
<td>1,658</td>
<td>Medical Therapy</td>
</tr>
<tr>
<td>Symptomatic Status</td>
<td>Symptomatic, Asymptomatic</td>
<td>Symptomatic</td>
<td>Asymptomatic</td>
<td>Asymptomatic</td>
</tr>
</tbody>
</table>

Overview of FDA Presentation

- Introduction to CAS
- Current FDA Recommendations
- Clinical Evidence
- Challenges to Trial Conduct
- Professional Society Perspectives
- Conclusion
Challenges to Clinical Trial Conduct and Development

Chul Ahn, Ph.D.
Cardiovascular and Ophthalmic Devices Branch
Division of Biostatistics
Office of Surveillance and Biometrics
Center for Devices and Radiological Health
Overview

Challenges to randomized, controlled trials
- Slow enrollment

Challenges to non-randomized, concurrently controlled trials
- Comparability between treatment groups
- Selection bias
Randomized, Controlled Trials

- In a well-designed and well-conducted RCT, we expect that all patient covariates, measured or unmeasured, are **balanced** between the two treatment groups.

- The two treatment groups are **comparable** and the observed treatment difference is an unbiased estimate of the true treatment difference.

- Concern: **slow enrollment**
Slow Enrollment

- Increases likelihood that clinical practice or the device design will change over the course of the investigation
- Such changes may call into question the generalizability and clinical relevance of the resulting data
What Causes Slow Enrollment?

- Preferences of enrolling investigators who may frequently believe that potential subjects would be better served by one treatment versus the other, and therefore should not be enrolled in the study.

- Potential subjects themselves may decline to enroll in the studies because they are uncomfortable with the concept of randomization.
A well-designed and well-conducted RCT provides the highest level of clinical trial evidence.

However, reliance on RCTs may paradoxically not allow investigators to acquire the required evidence in a reasonable time frame.
Non-Randomized, Concurrently Controlled Trials

- Subjects are allocated to either the CAS or CEA arm based on factors such as physician judgment and subject agreement.

- No guarantee that patient covariates, measured or unmeasured, are balanced between the two treatment groups.

- Two treatment groups may not be comparable.
Selection Bias

Allowing the investigator to exercise their judgment in recruiting subjects and selecting treatment options for them can introduce considerable bias.

Other types of bias also exist:
- Treatment bias
- Assessment bias

RCT may also be subject to these two biases because the investigator will not be blinded.
Example of Selection Bias

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.
Confounded Results Due to Selection Bias

- If the patient characteristics are not comparable between the two study arms due to selection bias, the study results may be confounded.

- Any perceived treatment effect may be due to an imbalance of clinically relevant prognostic factors between the CAS and CEA groups.
Confounded Results

If there exists a significant difference in two arms, we cannot determine whether this difference is due to treatment or due to confounders.
Example of Confounded Results

- If control group has older and sicker patients than treatment group, the lower success rate with the control group may be due to these patient characteristics, NOT because the new device is more effective.

- Other potential confounders include investigational site and physician training and experience.
Dilemma with Non-RCT (1)

- Known and measured confounders may be controlled by statistical methods such as covariate adjusted analysis or propensity score analysis, but there are still unknown or unmeasured confounders.

- Therefore, we never know whether we were entirely successful.
Dilemma with Non-RCT (2)

- If the two treatment groups were not comparable, no statistical methods can correct this to make them comparable.

- Furthermore, we cannot know whether they are comparable until the end of the study.

- Non-RCT may not be least burdensome, and may pose a higher risk for the sponsor.
Bias and confounding cannot be expected to be completely eradicated in a non-RCT.

A key panel question, however, will be whether potential problems related to bias and confounding in a non-randomized CAS trial can be sufficiently minimized through careful study design and execution such that it is reasonable for a study sponsor to choose this pathway.
Overview of FDA Presentation

- Introduction to CAS
- Current FDA Recommendations
- Clinical Evidence
- Challenges to Trial Conduct
- Professional Society Perspectives
- Conclusion
Professional Society Perspectives on Carotid Revascularization

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Overview

Medical society recommendations for treatment of carotid stenosis
- CEA
- CAS

AHA/ACC recommendations classified by:
- Class: Strength of recommendation
- Level: Strength of supporting evidence
Recommendation Classes

Class I: Agreement or evidence that the procedure or treatment is useful and effective

Class II: Conflicting evidence or divergence of opinion on utility of procedure or treatment
  - Class IIa: Weight of evidence in favor
  - Class IIb: Evidence is less well established

Class III: Agreement or evidence that the procedure or treatment is harmful or not useful or effective
Levels of Evidence

Level A: Data derived from multiple RCTs

Level B: Data derived from a single RCT or from non-randomized studies

Level C: Expert opinion or case studies
Ipsilateral severe stenosis (70 - 99%)
CEA is recommended by a surgeon with a perioperative morbidity and mortality < 6% {Class I, Level A}

Ipsilateral moderate stenosis (50 - 69%)
CEA is recommended, depending on patient-specific factors such as age, gender, comorbidities, and severity of initial symptoms {Class I, Level A}

Ipsilateral Stenosis < 50%
No indication for CEA {Class III, Level A}
Among patients with severe stenosis (> 70%)
CAS is not inferior to CEA and may be considered:
- In patients who are difficult to access surgically
- In patients who have medical conditions that greatly increase the risk of surgery
- When other specific circumstances exist
- Class IIb, Level B

CAS is reasonable when performed by operators with established periprocedural morbidity and mortality rates of 4% to 6%, similar to that observed in trials of CEA and CAS.
- Class IIa, Level B
Prophylactic CEA is recommended for:
Highly selected patients with high-grade stenosis, when performed by surgeons with < 3% morbidity/mortality rates
- Class I, Level A

Prophylactic CAS:
Might be a reasonable alternative to endarterectomy in asymptomatic patients at high risk for CEA
- Class IIb, Level B
- Uncertainty whether these patients should have either CAS or CEA due to peri-procedural and one-year event rates

“At the present time there is insufficient evidence to support CAS in high-risk patients with asymptomatic stenosis less than 80% or in any patient without high-risk features”
Overview of FDA Presentation

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Summary

- CAS currently approved for treatment of carotid stenosis in high surgical risk patients

- Safety and effectiveness relative to CEA not yet demonstrated in non-high-risk subjects

- FDA currently recommends RCT for this indication
Panel Input

Panel input is needed to determine whether RCTs are necessary to gather evidence that:

- Outcomes from CAS and CEA procedures in general are equivalent

- Specific carotid stents are safe and effective in the non-high-risk population

Panel also encouraged to recommend steps to increase enrollment and optimize data collection