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

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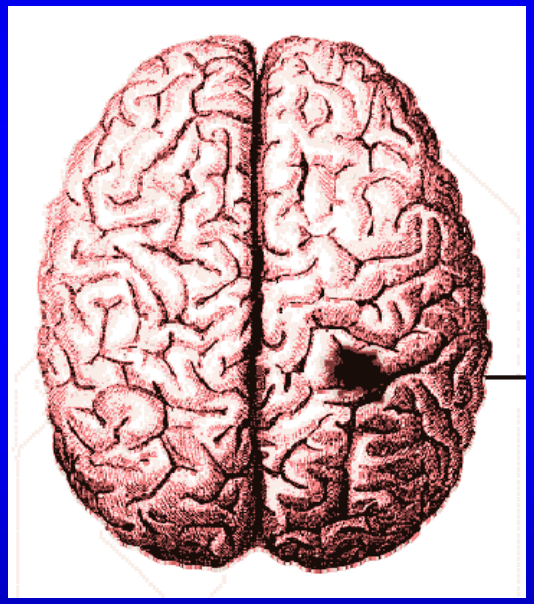
Stroke

- 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[1]
- Annual cost: ≈ $57 billion[2]



[1]*Stroke* 37: 577 – 617 (2006)
[2]*Circulation* 113: e85 – 151 (2006)

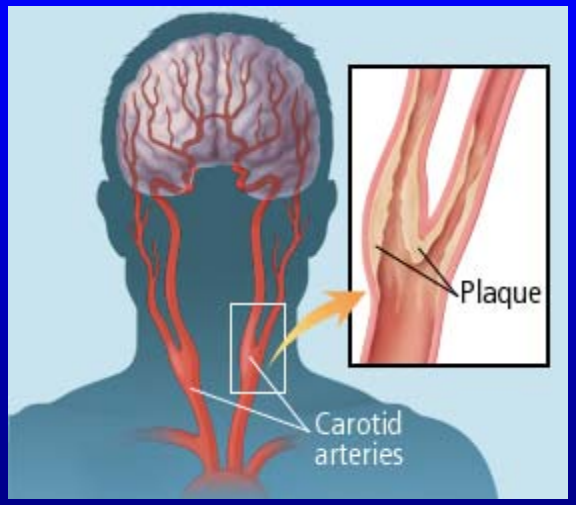
Etiology of Stroke

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

N Engl J Med 315: 860 – 865 (1986)

Carotid Artery Stenosis

- Risks due to emboli, not blood flow reduction
- Significant in 5 – 7% of patients > 65 years[1]
- Detectable using non-invasive imaging



[1]*Stroke* 23: 1752 – 1760 (1992)

Symptomatic Status

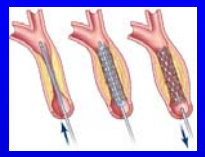
- Symptomatic – Previous ipsilateral event within a specified time frame (e.g. 6 months)
- Asymptomatic – Lack of events within time frame

"Asymptomatic" patients may have had prior stroke

Treatment Options

- Medical therapy

- Carotid endarterectomy



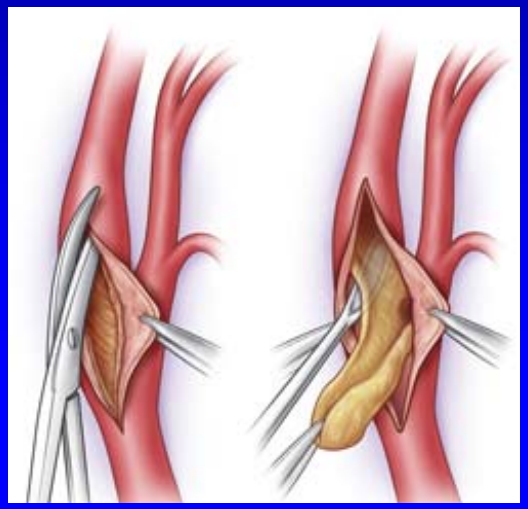
- Carotid artery stenting

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
  - NASCET - North American Symptomatic Carotid Endarterectomy Trial (1988 – 1991)[1]
  - ECST - European Carotid Surgery Trial (1981 – 1991)[2]

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

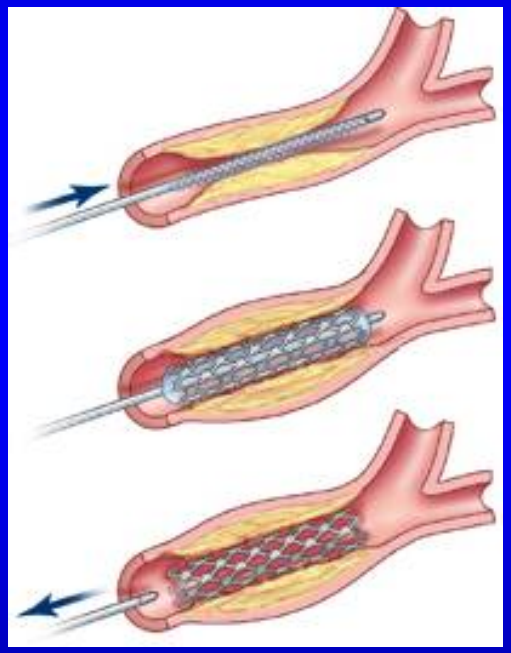
[1]*N Engl J Med* 325: 445 – 453 (1991)
[2]*Lancet* 337: 1235 – 1243 (1991)

CEA – Asymptomatic Patients

- Superior long-term outcomes with CEA + medical therapy
- ACAS - Asymptomatic Carotid Atherosclerosis Study (1987 – 1993)[1]
  - CEA vs. medical therapy alone
- ACST – Asymptomatic Carotid Surgery Trial (1993 – 2003)[2]
  - Immediate CEA vs. delayed CEA

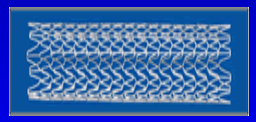
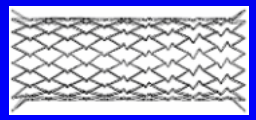
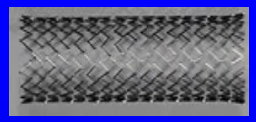
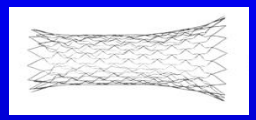
[1] *J Am Med Assoc* 273: 1421 – 1429 (1995)
[2] *Lancet 363*: 1491 – 1502 (2004)

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 ≥ 50% stenosis <u>or</u> no neurological symptoms and ≥ 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

2004 Panel Discussion

- 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

- FDA Guidance: *Carotid Stent - Suggestions for Content of Submissions to the Food and Drug Administration in Support of Investigational Device Exemption (IDE) Applications* (1996)
  - 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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Clinical Evidence Supporting Carotid Artery Stenting

Wolf Sapirstein, M.D., M.P.H., F.A.C.S.

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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)
  - ACST (2004)

Stroke Risk Due to Symptomatic Carotid Artery Disease

Percent Stenosis	Risk of Stroke Without CEA at 2 Years
50 – 69%	10%
70 – 79%	20%
80 – 89%	30%
90 – 99%	35%

Percent Stenosis	NNT To Prevent 1 Stroke
50 – 69%	13
70 – 99%	6

Based on NASCET and ECST results

Stroke Risk Due to Asymptomatic Carotid Artery Disease

Study	Percent Stenosis	Stroke Risk at 5 Years	NNT	CVA Prevented
ACAS	> 60%	11.0%	19	50/1000
ACST	> 60%	11.8%	20	53/1000

Based on ACAS and ACST results

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

Study	Stent	Subjects	Stenosis	% Symptomatic
ARCHeR (1, 2, 3)	Acculink	437	Symptomatic ≥ 50% Asymptomatic ≥ 80%[3]	24%
SECuRITY	Xact	305		21%
CABERNET	Nexstent	454		24%
CREATE	Protégé	419		17%
BEACH	Wallstent[2]	480		24%
MAVErIC (I, II)	Exponent[2]	498		42%
SAPPHIRE[1]	Precise	747		34%

[1] Randomized study
[2] Not approved by FDA
[3] CREATE also included asymptomatic subjects with 70 – 79% stenosis

Surgical Risk Factors

Anatomic Factors	Co-Morbidities
Previous CEA with restenosis	Age $\geq$ 75 years
Prior radiation treatment of neck	Unstable angina
High cervical lesion	NYHA class III/IV for CHF
Contralateral carotid occlusion	LVEF < 30%
Significant bilateral carotid stenosis	MI within past 6 weeks
Inability to flex neck	Multi-vessel coronary artery disease with $\geq$ 70% stenosis
Presence of tracheostomy/stoma	Need for post-procedure CABG or valve replacement
Contralateral laryngeal nerve palsy	Dialysis-dependent renal failure
Radical neck dissection	Severe pulmonary disease

Pivotal Single-Arm CAS Studies in High Surgical Risk Subjects

	ARCHeR 2	SECuRITY	CABERNET	CREATE
Stent	ACCULINK	Xact	Nexstent	Protégé
Manufacturer	Guidant	Abbott	Endotex	ev3
Subjects	278	305	454	419
Primary Endpoint Rate	9.7%	8.5%	4.7%	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%)

* 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

	Randomized CAS Arm	Randomized CEA Arm	CAS Registry
Number of Subjects	167	167	406
Death, Stroke, MI at 30 Days	6.8%	11.4%	8.8%
Death, Stroke, MI at 360 Days	18.2%	27.0%	21.9%

- 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

N Engl J Med 351: 1493 – 1501 (2004)

Non-High-Risk CAS Studies

- SPACE
- EVA-3S
- CaRESS
- Ongoing trials

SPACE

- 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

SPACE Results

	CAS (N = 599)	CEA (N = 584)
Primary Endpoint Rate	**6.8%**	**6.3%**
Death at 30 Days	**0.7%**	**0.9%**
Stroke at 30 Days	**7.5%**	**6.2%**

- Interim analysis: Differences between CAS and CEA rates exceeded non-inferiority margin
  - Unacceptably high number of additional subjects needed to demonstrate non-inferiority

Lancet 368: 1239 – 1247 (2006)

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

	CAS (N = 261)	CEA (N = 259)
Primary Endpoint Rate	**9.6%**	**3.9%**
Death at 30 Days	**0.8%**	**1.2%**
Stroke at 30 Days	**9.2%**	**3.5%**

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

N Engl J Med 355: 1660 – 1671 (2006)

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

[1] *Lancet Neurol* 6: 101 - 102 (2007)
[2] *Eur J Vasc Endovasc Surg* 33: 48 – 49 (2007)
[3] *Lancet Neurol* 6: 295 – 196 (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

	CEA (N = 254)	CAS (N = 143)
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%**

* $p < 0.0001$
** $p < 0.001$

J Endovasc Ther 10: 1021 – 1030 (2003)

CaRESS Results

	≤ 30 Days		≤ 365 Days	
	CEA	CAS	CEA	CAS
Death	0.4%	0%	6.6%	6.3%
Stroke	3.6%	2.1%	9.8%	5.5%
MI	0.8%	0%	2.4%	1.7%
Death + Stroke	3.6%	2.1%	13.6%	10.0%
Death + Stroke + MI	4.4%	2.1%	14.3%	10.9%

- Surgical risk status not an outcome predictor
- Phase II study proposed

J Vasc Surg 42: 213 – 219 (2005)

Non-High-Risk Study Summary

- 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

	CREST	ICSS	ACT I	TACIT
Location	N. America	Europe	N. America	N. America, Europe
Control	CEA	CEA	CEA	Medical Therapy
Target Enrollment	2,500	1,500	1,658	2,500
Symptomatic Status	Symptomatic, Asymptomatic	Symptomatic	Asymptomatic	Asymptomatic

J Vasc Surg 45: A158 – A163 (2007)

Cerebrovasc Dis 18: 69 – 74 (2004)

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Challenges to Clinical Trial Conduct and Development

Chul Ahn, Ph.D.

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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

Concluding Remarks for RCT

- 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

Concluding Remarks for Non-RCT

- 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

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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

2006 AHA/ASA Guidelines on CEA in Symptomatic Patients

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}

Stroke 37: 577 – 617 (2006)

AHA/ASA Guidelines on CAS in Symptomatic Patients 2006

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

2006 AHA/ ASA Guidelines on CEA and CAS in Asymptomatic Patients

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

Stroke 37: 1583 – 1633 (2006)

2007 ACC/SCAI/SVMB/SIR and ASITN Consensus Document on CAS

"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"

J Am Coll Cardiol 49: 126 – 170 (2007)

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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