CAROTID STENTING
A 2009 UPDATE

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TREATMENT FOR CAROTID STENOSIS

- Best medical management
  - Antiplatelet therapy
  - Antihypertensive therapy
  - Control of diabetes if present
  - Antilipid therapy if needed
  - Cessation of smoking
- Carotid endarterectomy (CEA)
- Carotid artery stenting (CAS)

NATURAL HISTORY

- Asymptomatic carotid stenosis: low stroke rate (2%/year), half of which are not disabling
- Moderate surgical benefit vs medical management for asymptomatic stenosis >60%
- Selection criteria: depend on patient's age, gender, life expectancy, and perioperative complication rate

ACAS Trial. Stroke 1989;20(7):844-849
ACST Trial. Stroke 2004;35(10):2425-2427

ASYMPTOMATIC CAROTID STENOSIS

- For patients with surgical risk <3% and life expectancy >5 years:

  CEA is beneficial for asymptomatic stenosis >60%
- ACST trial: 5 year stroke rate decreased by half with CEA. No benefit for patients >75 years

SYMPTOMATIC CAROTID STENOSIS

- NASCET:
  - CEA most beneficial for symptomatic stenosis 70-99%

    (2 year stroke rate decreased from 26% to 9%)
  - Moderate benefit from CEA for symptomatic stenosis 50-69%

    (5 year stroke rate decreased from 22% to 16%)
- Perioperative stroke or death risk must be <6%

NEJM 1991;15;325(7):445-453

CEA TRIALS

- CEA trials involved patients who had an average risk of perioperative stroke or death after surgery
- Patients who had a high surgical risk owing to severe CAD were excluded

MORBIDITY AND MORTALITY FROM CEA (SUNDT CLASSIFICATION)

Grade	Risk factors	Risk (in 1,935 operations)
I	Neurologically stable; no medical or angiographic risks; with unilateral or bilateral ulcerative-stenotic carotid disease	<1% risk (5 RIND, 6 CVA)
II	Neurologically stable; no medical risks, but with angiographic risks (contralateral ICA occlusion most common)	1.8% risk (6 RIND, 7 CVA)
III	Neurologically stable; medical risks, with or without angiographic risks	4% risk (9 fatal MI, 10 RIND, 10 CVA (1 fatal))
IV	Neurologically unstable, with or without medical or angiographic risks	8.5% risk (27 CVA (8 fatal), 14 RIND, 2 fatal MI))

Sundt TM: Occlusive cerebrovascular disease. W. B. Saunders, Philadelphia, 1987

CURRENT STATUS OF CAS

- FDA approval in 2004: for high risk patients
  - with symptomatic carotid stenosis >50%
  - or asymptomatic carotid stenosis >80%

    (based on SAPPHIRE data)
- CMS approval in 2005: for high risk patients
  - with symptomatic carotid stenosis >70%
  - with symptomatic carotid stenosis >50% or asymptomatic carotid stenosis >80% if enrolled in an IDE clinical trial
  - If they participate in an FDA-mandated postapproval study

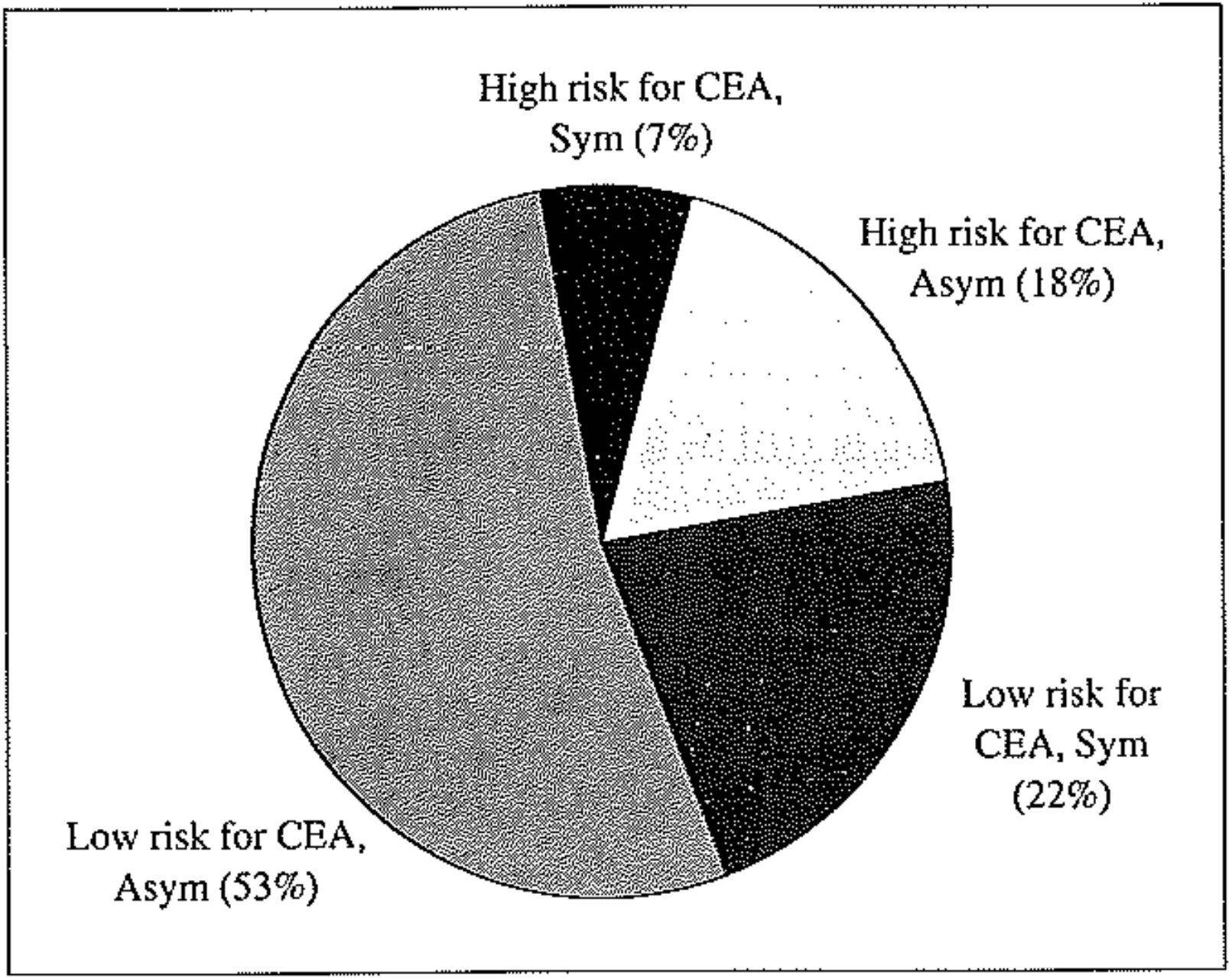


Figure 2.—Symptoms of patients in the US receiving CEA.

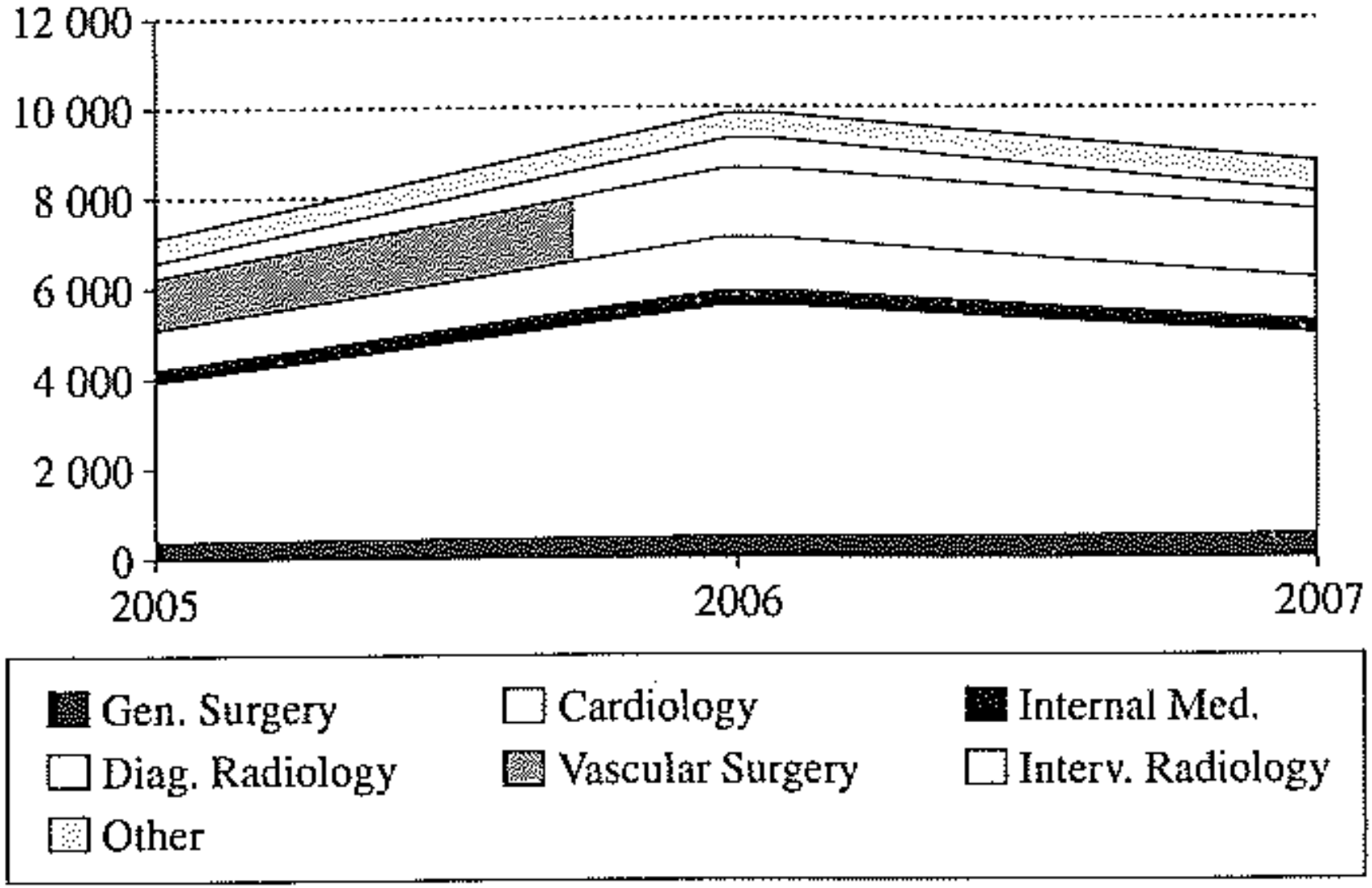


Figure 3.—Review of carotid stent procedures in the US medicare system from 2005-2007.

HISTORY OF CAS

- The acceptable morbidity and mortality for CAS has not been clearly defined
  - Most patients are non-NASCET/non-ACAS eligible
  - CAS technology is continually improving

HISTORY OF CAS

- Early CAS studies without EPD had high rates of adverse events at 30 days
  - EVA-3S trial (1998): Naylor AR et al.
  - Wallstent trial (2001): Alberts MJ et al.

WALLSTENT TRIAL

- Prospective, randomized, multicenter study of 219 patients with symptomatic carotid stenosis >60%
- Stroke and death rate at one year was 12.1% in the CAS group and 3.6% in the CEA group

  (p = 0.022)

Stroke 2001;32:325-d

WALLSTENT TRIAL

- CAS was performed without EPD by inexperienced surgeons
- Stroke rate was 3.9 times higher among patients treated without EPD than among patients treated with EPD

Stroke 2004;35:E18-E20

- DWI abnormalities with EPD have decreased from 29% to 7%

AJNR 2001:1251-1259

CAVATAS

CAROTID AND VERTEBRAL ARTERY TRANSLUMINAL ANGIOPLASTY STUDY

- 504 patients randomized to CEA vs carotid angioplasty alone (25% also received stents)
- No difference in 30 day death or disabling stroke rates (6.3% for CEA, 6.4% for CAS)
- 30 day all stroke and death rate 10% in each group
- No substantial difference in the rate of ipsilateral stroke was noted with survival analysis up to 3 years after randomization

  (adjusted hazard ratio=1.04, 95% CI 0.63-1.70, p=0.9)

Lancet 2001;357(9270):1729-37

ELOCAS

EUROPEAN LONG TERM CAROTID ARTERY STENTING

- Largest restropective registry in 4 high volume European centers:
  - 2172 patients treated with CAS (>85% with EPD)
  - Combined stroke and death rate:
    - 4.1% at 1 year
    - 10.1% at 3 years
    - 15.5% at 5 years

J Cardiovasc Surg 2005:241-247

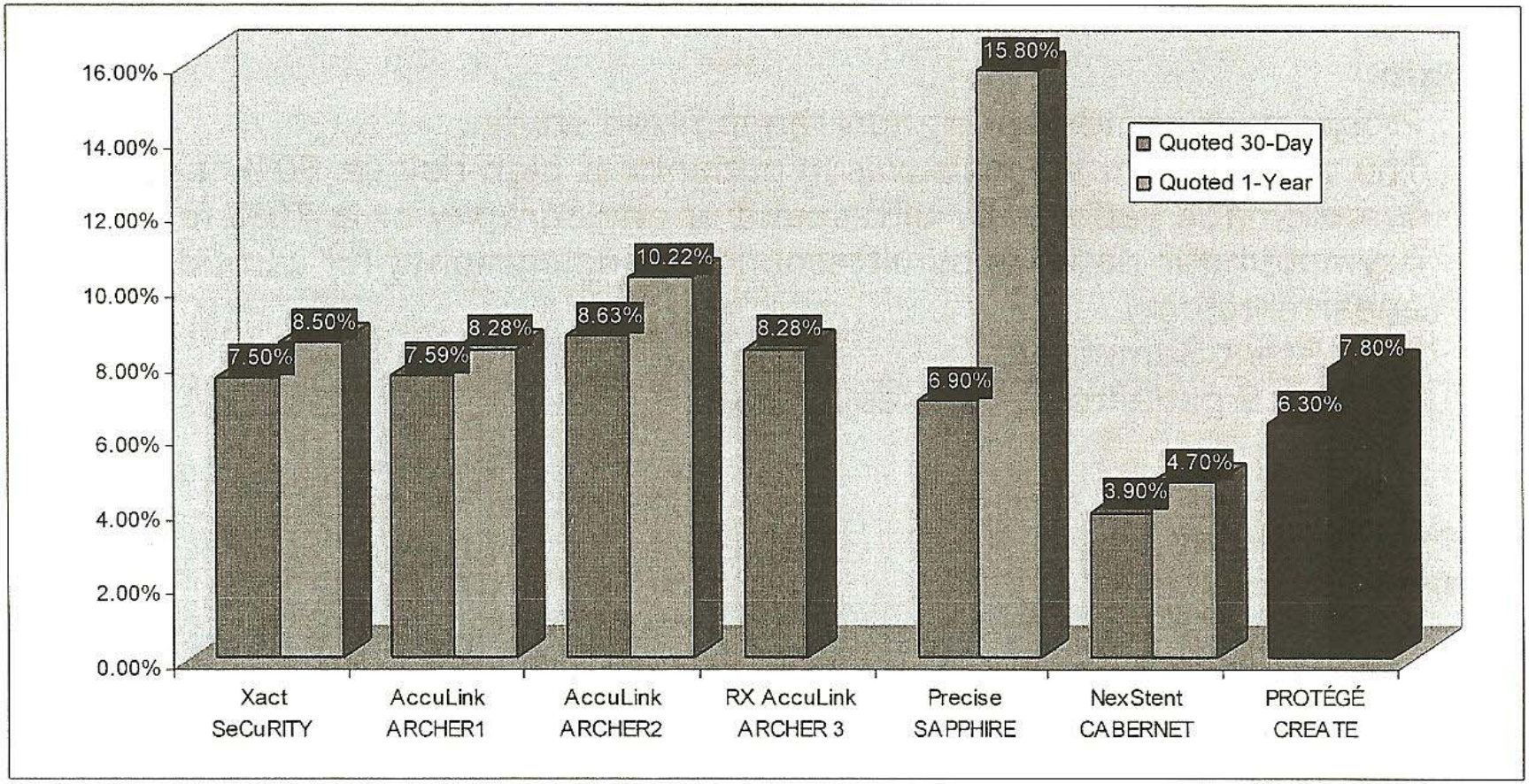
HISTORY OF CAS

- Later studies using EPD (SAPPHIRE, CaRESS)
  - Similar morbidity and mortality rates after CAS compared with CEA in high risk patients

CAS TRIALS

- High risk registries
- Randomized clinical trials: CAS vs CEA
  - High risk: SAPPHIRE
  - Normal risk: CREST, ACT I, EVA-3S, SPACE
- Post market surveillance studies

High-Risk Carotid Registry Summary of Primary Endpoint Results



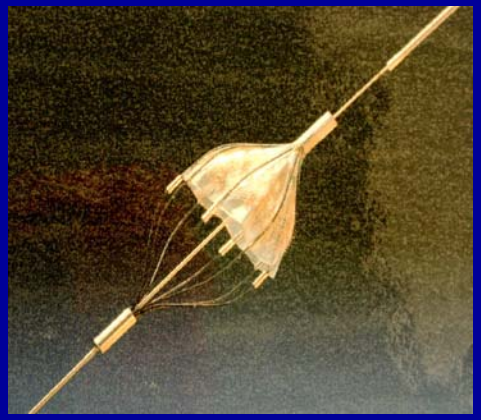
Source: SSEDs; PROTÉGÉ® RX Carotid Stent System IFU.

CAROTID STENTING (CAS)
VS
CAROTID ENDARTERECTOMY (CEA)?

SAPPHIRE TRIAL

STENTING AND ANGIOPLASTY WITH PROTECTION IN PATIENTS AND HIGH RISK FOR ENDARTERECTOMY

- Randomized (CEA and CAS) multicenter trial of high risk patients, 167 patients in each arm
- Symptomatic carotid stenosis >50% (1/3 patients)
- Asymptomatic carotid stenosis >80% (2/3 patients)



NEJM 2004;351:1565-1567

SAPPHIRE Trial Results:

Event Categories	Randomized Stent (N = 167)		Randomized CEA (N = 167)		P-Value	Non-Randomized Stent (N = 406)	
Primary Endpoints	n/N	%	n/N	%		n/N	%
MAE – Death, MI or stroke to 30-Days and death or ipsilateral stroke from 31-360 days	20/167	12.0	32/167	19.2	0.10	64/406	15.8
Death (All Cause)	12/167	7.2	21/167	12.6	0.14	41/406	10.1
Stroke	10/167	6.0	12/167	7.2	0.83	37/406	9.1
Major Ipsilateral Stroke	1/167	0.6	5/167	3.0	0.21	13/406	3.2
Minor Ipsilateral Stroke	6/167	3.6	3/167	1.8	0.50	16/406	3.9
Myocardial Infarction (Q or NQ)	5/167	3.0	12/167	7.2	0.13	11/406	2.7
TIA	11/167	6.6	5/167	3.0	0.20	28/406	6.9
Major Bleeding	15/167	9.0	17/167	10.2	0.85	54/406	13.3
Cranial Nerve Injury	0/167	0.0	8/167	4.8	0.01	0/406	0.0
Severe Hypertension	29/167	17.4	5/167	3.0	<0.01	63/406	15.5
Bradycardia	14/167	8.4	5/167	3.0	0.06	14/406	3.4
Vascular Complications	9/167	5.4	N/A	N/A	-	10/406	2.5
Device/Procedure Related Events	0	0.0	0	0.0	-	0	0.0
Efficacy Measures							
Lesion Success	145/158	91.8	N/A	N/A	N/A	368/407	90.4
Procedure Success	140/159	88.1	N/A	N/A	N/A	355/404	87.9
Device Success	145/159	91.2	N/A	N/A	N/A	363/405	89.6
ANGIOGUARD Success	152/159	95.6	N/A	N/A	N/A	372/406	91.6
Cumulative % of TLR at 360 Days		0.06		4.3	0.04		0.8
Cumulative % of MAE at 360 Days		12.2		20.1	0.05		16.0

Source: Summary of Safety and Effectiveness Data. PMA: PO30047. 22-Sep-06.

SAPPHIRE TRIAL

At 3 years, the incidence of stroke was virtually identical for CAS and CEA (7.1% for CAS and 6.7% for CEA, p = 0.945), indicating that CAS is non-inferior to CEA.

NEJM 2008;358:1572-1579

SAPPHIRE TRIAL
CONCLUSION

In high risk patients with severe carotid stenosis, no significant difference could be shown in long term outcomes between CAS and CEA

NEJM 2008;358:1572-1579

SAPPHIRE TRIAL
CRITICISM

- >400 patients were excluded after initial inclusion
- 2/3 patients are asymptomatic and high risk
- In symptomatic patients, the primary endpoint did not differ
- 20% patients were treated for carotid restenosis

CaRESS TRIAL

CAROTID REVASCULARIZATION USING ENDARTERECTOMY OR STENTING SYSTEMS

- Multicenter non-randomized non-inferiority trial comparing CAS with CEA, 397 patients not all high risk
- Symptomatic patients with carotid stenosis >50% (1/3 patients)
- Asymptomatic patients with carotid stenosis >75% (2/3 patients)

J Vasc Surg 2005:213-219

CaRESS TRIAL

- Risk of stroke, death or MI:
  - 30 day results:

    2.1% for CAS and 4.4% for CEA, p=NS
  - 1 year results:

    10% for CAS and 13.6% for CEA, p=NS

EVA-3S TRIAL

ENDARTERECTOMY VS ANGIOPLASTY IN PATIENTS WITH SYMPTOMATIC SEVERE CAROTID STENOSIS

- Multicenter randomized non-inferiority trial comparing CAS with CEA in 527 patients with symptomatic stenosis >60%, not high risk
- 30 day results: risk of stroke and death significantly higher in CAS group compared with CEA group (9.6% vs 3.9%; p=.01)
- No significant difference between the two groups in the 30 day incidence of MI

NEJM 2006;355:1660-1671

EVA-3S TRIAL

- 30 day incidence of disabling stroke or death was higher with CAS than CEA (3.4% vs 1.5%)
- No difference was seen between centers when the experience of the performing physician or the hospital workload was taken into account

EVA-3S TRIAL

- At 6 months, the incidence of stroke or death continues to be lower with CEA:

  6.1% after CEA vs 11.7% after CAS (p=.02)
- Study terminated in September 2005 for reasons of safety and futility

EVA-3S TRIAL
CRITICISM

- Lack of experience of investigators and number of trained site/operators in CAS
  - No centralized training qualification process
  - 2/3 of trial sites were under tutelage at the beginning of their randomized participation
- Lack of standardized techniques resulted in unnecessary morbidity
  - Use of EPDs was not widespread
  - No predilatation in >80% of procedures
- Significant anesthesia in 30% of procedures

EVA-3S TRIAL

- At 4 years: Cumulative probability of periprocedural stroke or death and nonprocedural ipsilateral stroke was higher with CAS than with CEA (11.1% vs 6.2%, p=0.03)
- Periprocedural risk (within 30 days) is higher with CAS
- After the periprocedural period, the risk of ipsilateral stroke was low and similar in both treatment groups
- Probability of restenosis >50% at 3 years was more evident with CAS than with CEA

SPACE TRIAL

STENT-SUPPORTED PERCUTANEOUS ANGIOPLASTY OF THE CAROTID ARTERY VS ENDARTERECTOMY

- Multicenter randomized non-inferiority trial comparing CAS with CEA in patients with symptomatic stenosis >50%, not high risk
- 37 centers in Germany, Austria and Switzerland
- Use of EPDs was at the discretion of the participating center
- 1214 patients were randomized (613 in CAS group; 601 in CEA group)
- Non inferiority threshold was set at 2.5%

Lancet 2006;368:1239-1247

SPACE TRIAL

- 30 day results: stroke and death rate 6.8% in CAS group, 6.3% in CEA group
- Absolute difference 0.51% (-1.9% vs 2.9%, 95% CI; p=.09))
- This exceeded the threshold of 2.5%
- Patient recruitment was stopped after 1214 patients
- 73% patients received a stent without an EPD

SPACE TRIAL

- At 2 years: no difference in clinical outcome between CAS and CEA (5% vs 6.3% mortality, hazard ratio 1.11)
- Restenosis >70% more common after CAS (10.7% vs 4.6%, $p<0.01$)
- Patients >68 years had a significantly lower risk of primary endpoint after CEA compared with CAS
- CEA remains the preferred treatment for symptomatic carotid stenosis

SPACE TRIAL

- Outcome event (ipsilateral stroke or death) was not related to the use of EPD
- 25% procedures were performed with EPD
- Only half of complications occurred during the actual stent and angioplasty procedure

ICSS TRIAL
INTERNATIONAL CAROTID STENTING STUDY

- Symptomatic carotid stenosis >50% within 6 months of randomization
- 1710 patients were included from 49 centers in the ITT analysis: 853 CAS and 857 CEA
- 30 day rate of stroke, MI or death: 5.1% for CEA vs 8.5% for CAS (p=0.004)

XVIII European Stroke Conference 2009

CREST TRIAL

CAROTID REVASCULARIZATION ENDARTECTOMY VS STENT

- NIH/NINDS sponsored multicenter randomized trial comparing CAS with CEA in patients with asymptomatic stenosis >60% and symptomatic stenosis >50%
- 30 day-4 yr rate of stroke, MI or death
- Recruitment of 2522 patients in 118 sites in North America was completed in July 2008
- 53% patients symptomatic and 47% patients asymptomatic

CREST TRIAL

- Analyses based on the pool of these patients will provide 90% power to detect treatment differences in the two groups
- One year follow-up was scheduled in July 2009
- Publication of one year data in March 2010
- Follow-up will last for 4 years

CREST TRIAL

New Data on Risk of CAS in Octogenarians

- 749 lead-in patients undergoing CAS (31% symptomatic, 69% asymptomatic)
- Patients were separated into 4 age categories (<60, 60-69, 70-79, >80 years)
- An increasing proportion of patients suffered stroke and death with increasing age (p=.0006)
  - 1.7% under age 60
  - 1.3% aged 60-69
  - 5.3% aged 70-79
  - 12.1% age >80

ONGOING CAS TRIALS

- High risk registries:
  - CHOICE (Guidant/Abbott)
  - VIVA (BARD VIVEXX stent and Abbott Emboshield)
  - EMPIRE (Gore NPS and any approved stent)
  - Fibernet (Lumen BioMedical and any approved stent)
  - ARMOUR (mo.Ma and any approved stent)
  - SAPPHIRE PMS (Cordis Angioguard and Precise stent)

ONGOING CAS TRIALS

- Standard risk registries:
  - CREST (Guidant/Abbott system)
  - ACT I
  - TACIT

CONCLUSION

- CAS has outcomes that are inferior to CEA for treatment of symptomatic carotid stenosis
- CAS technology and expertise of operators are improving

LESSONS LEARNED

- Experience counts!
- Patient selection for CAS is crucial
- Participation in clinical trials
- Until CREST data are published, limit CAS to high risk patients who meet criteria for revascularization