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The Perceptions and Reality of Carotid Stenting: An Evidence-Based Look at a Beleaguered Therapy

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
Grant/Research Support	Abraxis, Abbott, Bard, Bolton, Cook, Cordis, ev3, W.L. Gore, Lumen, Medtronic
Consulting Fees/Honoraria	Abbott, Cook, Cordis, ev3, W.L. Gore

None: Major Stock Shareholder/Equity/Royalty Income/Ownership/Founder/Intellectual Property Rights/Other Financial Benefit

- Carotid stent/embolic protection systems are not FDA approved for standard risk for CEA patients and this is an investigational use.

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Orszag & Ellis, Congressional Budget Office

- "Our country's financial health will in fact be determined primarily by the growth rate of per capita health care costs."
- Federal spending on Medicare and Medicaid is 4.6% of GDP in 2007, and without change in laws will reach 5.9% in 2017. If continued rate of growth, will reach 20% of GDP in 2050 (the same share that the entire federal budget accounts for today).
- If costs per capita tracked GDP growth, this would be 7% of GDP because of demographic changes alone.
- Total health care costs are about 16% of GDP and are projected to reach nearly 20% by 2016.
- Bulk of growth is "from the development and diffusion of new medical technologies and therapies."
- NEJM 2007 375;18

"Non-Profits"

- Profit motives by commercial and "non-profits"
- NEJM 2008
- "In the face of increasingly constrained resources, there is a realistic way of achieving better health results: conduct careful analysis to identify evidence-based opportunities for more efficient delivery of health care—whether prevention or treatment—and then restructure the system to create incentives that encourage the appropriate delivery of efficient interventions."
- Cohen JT, Neumann PJ, Weinstein MC. Does Preventive care save money? Health economics and the presidential candidates. NEJM Feb, 2008.

Themes

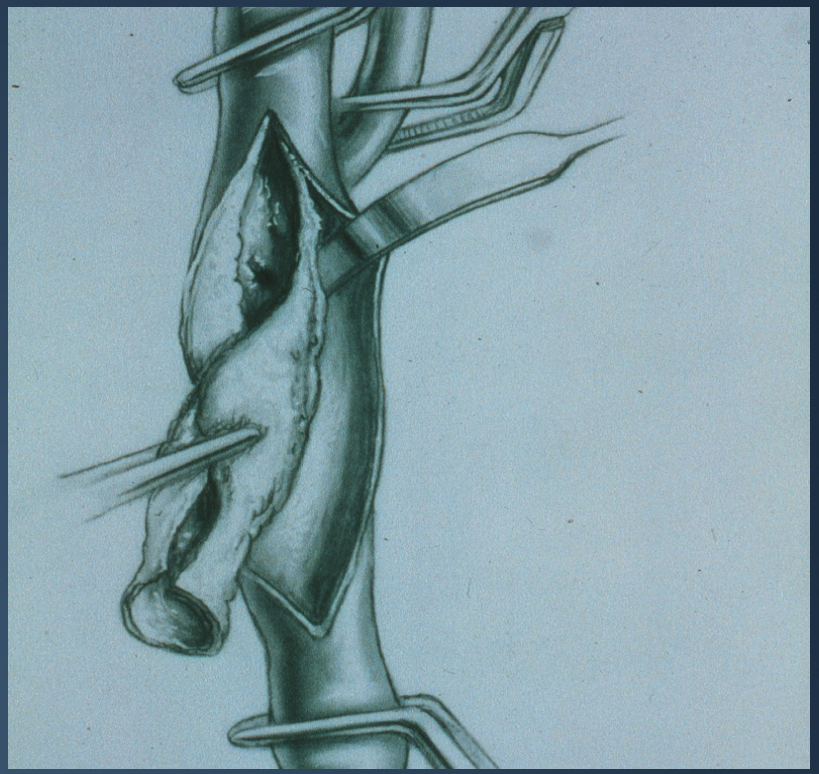
- CAS process of care is in progress and less mature than CEA
- Study data is difficult to compare between trials because of differences in
  - device development
  - operator experience (prior and ongoing)
  - procedure techniques (routine embolic protection (EPD))
  - outcome definitions (duration and severity of symptoms)
  - outcome assessment (exam window, independent neuro exam)
- Contemporary multicenter randomized trials must be supported

Learning from History

Carotid Endarterectomy (CEA)

CEA

- 1954: Eastcott, Pickering, Rob, DeBakey, Carrea
- 80's: retrospective series
- 1985 EC/IC study
- 1988 Rand report



CEA RCT's

- Symptomatic
  - NASCET
  - ECST
  - VA Trial
- Asymptomatic
  - Casanova/MACE
  - VA Trial
  - ACAS
  - ACST

TABLE 1. NET BENEFITS OF CAROTID ENDARTERECTOMY DEMONSTRATED IN RANDOMIZED, CONTROLLED TRIALS INVOLVING MORE THAN 500 PATIENTS.

TRIAL*	DEGREE OF STENOSIS	RECENT SYMPTOMS†	ABSOLUTE REDUCTION IN RISK‡		RATE OF SURGICAL COMPLICATIONS§
			PERCENT	P VALUE	
	%				%
NASCET[4]	≥70	Yes	16.5 at 2 yr	<0.001	5.8
ECST[8]	≥60¶	Yes	11.6 at 3 yr	0.001	4.8
NASCET[6]	50–69	Yes	10.1 at 5 yr	0.005	6.7
NASCET[6]	<50	Yes	0.8 at 5 yr	0.97	6.7
ECST[9]	<40¶	Yes	Surgery group worse at 3 yr	<0.05	7.9
ACAS[5]	≥60	No	6.3 at 5 yr	0.08	2.3

MRC ACST

- Asymptomatic Carotid Surgery Trial
  - 3120 Asymptomatic patients
    - > 60% stenosis by ultrasound
    - Exclusion Criteria
      - Prior ipsilateral CEA
      - Poor surgical risk
      - Major life-threatening condition
  - All patients received appropriate medical care (antiplatelet therapy, antihypertensive treatment, and in recent years lipid-lowering therapy)
  - Risk of Stroke or Death within 30-days of CEA 3.1%
  - 5-year Stroke Risk
    - Immediate CEA – 6.4%
    - Deferred CEA – 11.8%
    - Benefit across gender?, age to 74 yo, and stroke severity
    - Stratified by stenosis, lesser degrees with more benefit

CEA RCT Summary

- Carotid endarterectomy in addition to contemporary medical therapy is beneficial in selected patients:
  - Mild stroke, TIA, amaurosis fugax in patients with stenosis of 50-99% and physician/hospital stroke/death rate < 6%
  - Asymptomatic good risk patients with stenosis of 60-99% and physician/hospital stroke/death rate < about 3%

Contemporary CEA Trends Process of Care Improvements

- Swedish vascular registry with four validation methods
  - Sweden 1994-2003: 6,182 CEA
    - 671 asymptomatic
    - In asymptomatic patients stroke/death improved from 2.1% for the entire period to 0.9% (P=.026) for the last 4 years (1999-2003)
- Kragsterman et al, J Vasc Surg 2006;44:79

Population Based Studies

- Maryland and California administrative database using several validation methods
  - California 1999-2003: 51,331CEA
    - 0.78-0.91% Annual Death rate
    - 0.45% Stroke
  - Maryland 1996-2003
    - 0.33-0.58% Annual Death rate
    - 0.29-0.65% Stroke
- Matsen et al, J Vasc Surg 2006;44:488

NSQIP Independent Assessment

- 123 VA and 14 private sector hospitals
  - 2000-2003
  - 13,622 independent nurse-review
  - 4.0% Stroke/Death/Cardiac event
  - 3.4% Stroke/Death
- Stoner et al, J Vasc Surg 2006;43:285

Contemporary CAS & CEA Use

- New York and California hospital inpatient discharge data for 2005
  - 14,785 CEA
    - 0.64% Death
    - 1.24% Post-procedure stroke
  - 2.554 CAS
    - 1.41% Death (P<.0001)
    - 2.19% Post-procedure stroke (P=.002)
- Multivariate regression showed CAS was associated with higher mortality and stroke
- Mureebe et al, SVS Annual Meeting June 2007

Carotid Artery Stenting (CAS)

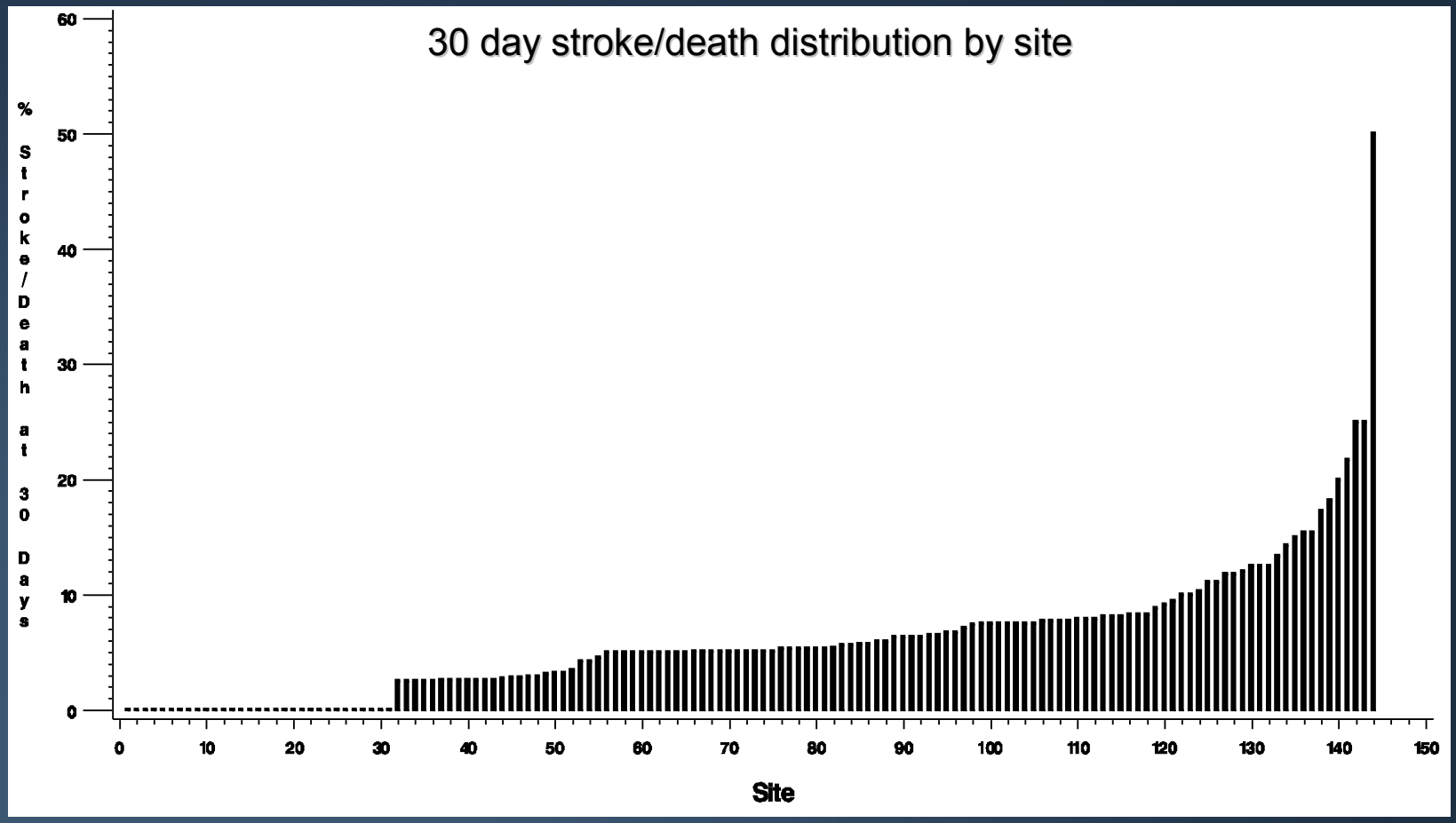
Current CAS Approvals

- FDA
  - High-risk for CEA with symptomatic >50% and asymptomatic >80% stenosis

Current CAS Coverage Under Review

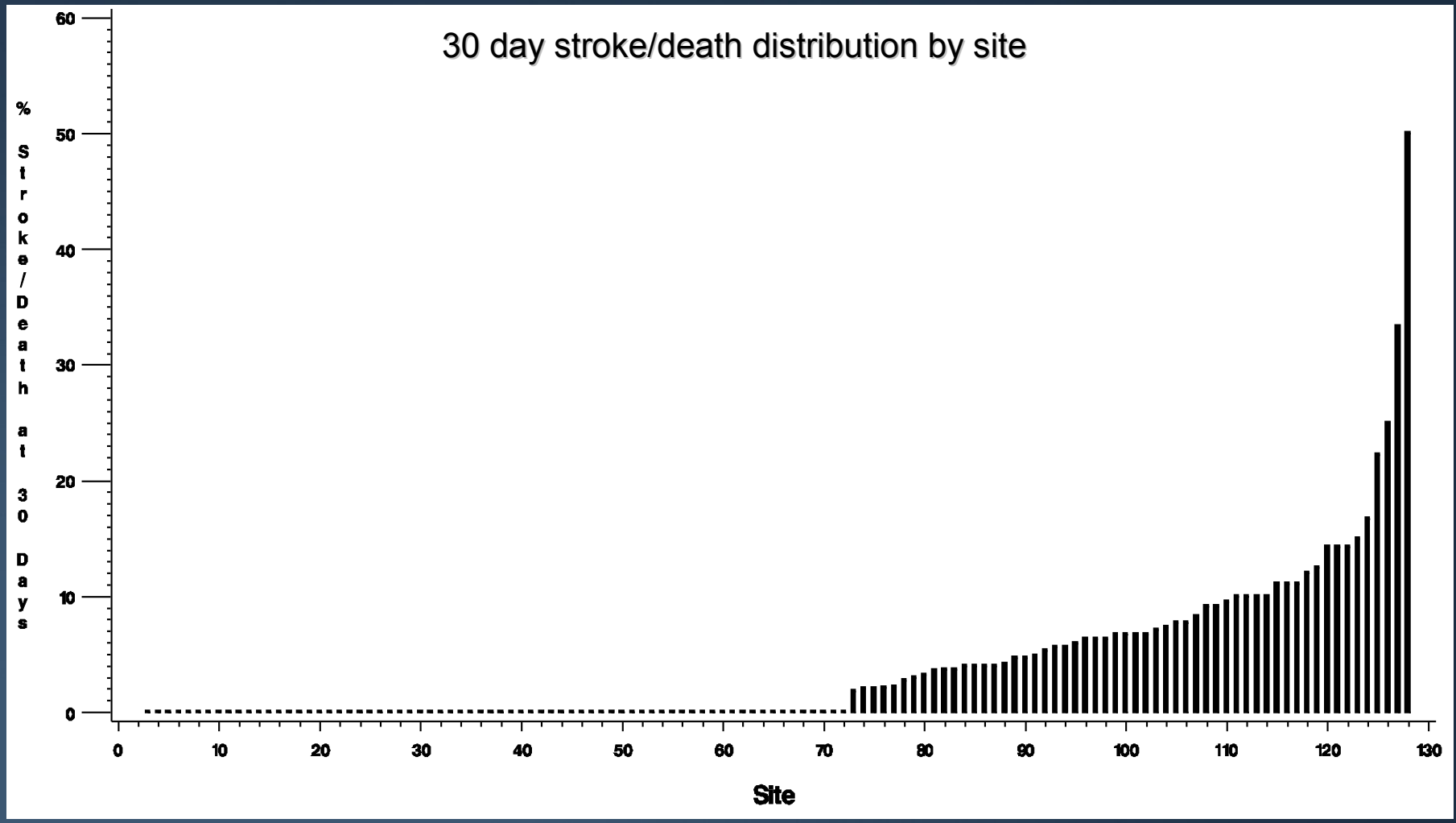
- CMS
  - High-risk for CEA, symptomatic, >70% stenosis
  - FDA approved stent and EPD—must be used
  - Facility certification required every two years
    - » Five specific standards NCD Manual 20.7B4
  - Opinion of surgeon “strongly” encouraged but not required
  - Continue coverage of Category B IDE and PAS studies

CAPTURE: N=4225



No stroke/death in 22% 31/144 sites

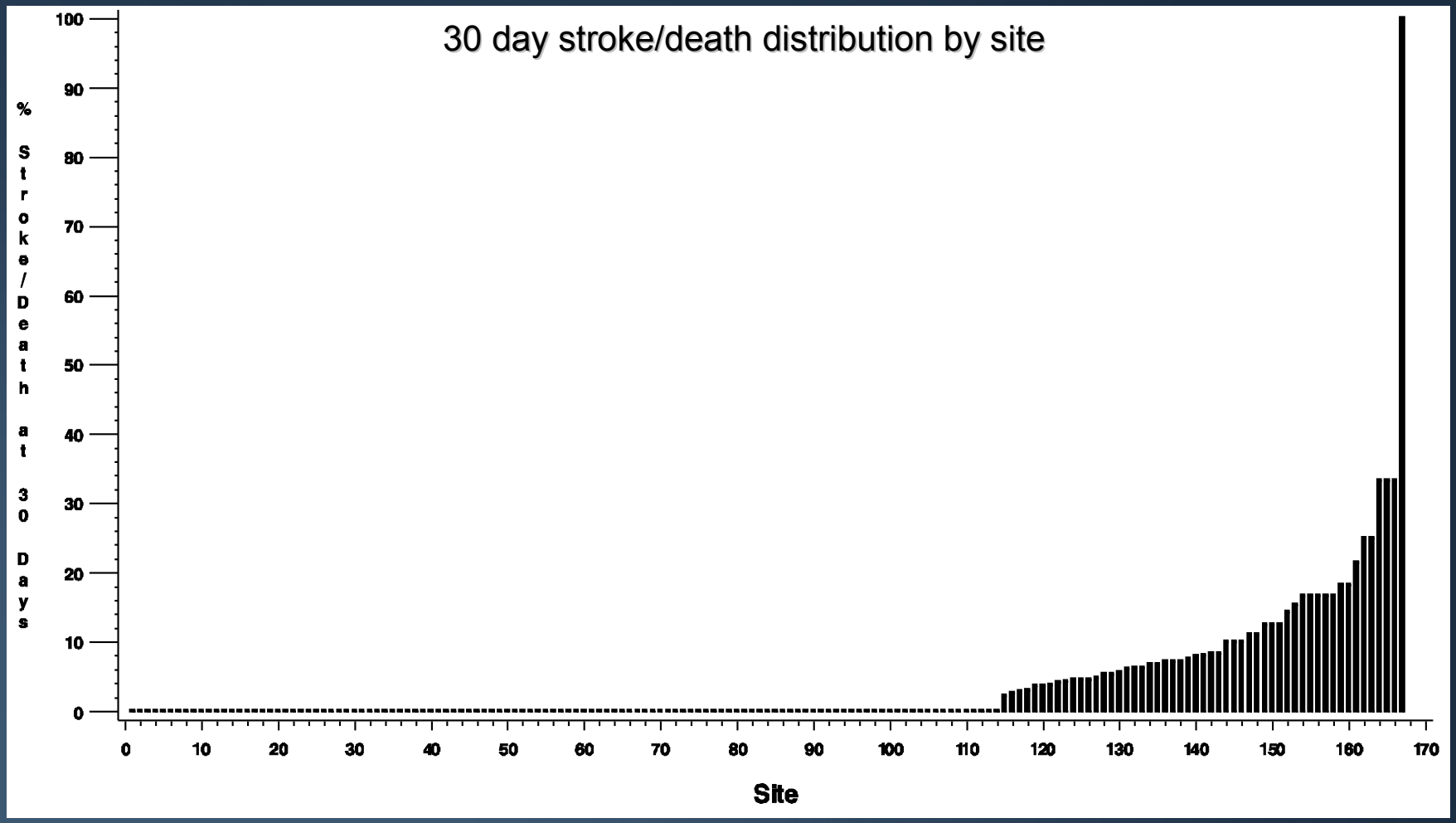
EXACT: n=2124



No stroke/death in 56% (72/128)of sites

n=128 sites

CAPTURE 2: n=1987



No stroke/death at 69% (115/167) of sites

Process of Care: Risk Factors for CAS

- Advanced age
- Recent symptoms < 2 weeks
- Poor access--arch and iliofemoral
- Tortuosity—unable to use EPD
- Severe calcification
- Free-floating thrombus
- String sign
- Experience level of interventionalist

Early or Stopped Randomized Multicenter Trials

Early CAS in a US RCT

Alberts, *Stroke* 2001

- Stopped trial of 219 patients with symptomatic 60%-90% stenosis were randomized to CEA or CAS
- 7Fr system, no embolic protection
- Results at 1yr:
  - CAS 12.2% Ipsilateral Stroke
  - CEA 3.6% Ipsilateral Stroke
  - P=0.022

CAVATAS Interventionalist Criteria

- Radiologist with training in neuroradiology and angioplasty
- 88% of patients symptomatic
- 74% PTA/26% stent
- 0% EPD

- Cavatas 2 ongoing

CAVATAS

Carotid and Vertebral Artery Transluminal Angioplasty Study

Lancet 2001

	Endovascular group (n=251)	Surgical group (n=253)	p
Major outcome events			
Death	7 (3%)	4 (2%)	NS
Disabling stroke	9 (4%)	11 (4%)	NS
Non-disabling stroke	9 (4%)	10 (4%)	NS
Death or disabling stroke	16 (6%)	15 (6%)	NS
Death or any stroke	25 (10%)	25 (10%)	NS
Other outcome events			
Cranial nerve palsy	0	22 (9%)	<0·0001
Peripheral nerve palsy	0	2 (1%)	NS
Haematoma (requiring surgery or extending hospital stay)	3 (1%)	17 (7%)	<0·0015
Myocardial infarction (non-fatal)	0	3 (1%)	NS
Pulmonary embolus	0	2* (1%)	NS

Patients were analysed by intention to treat. Values are numbers (%). NS=non-significant. *Fatal in one patient and analysed as a death.

EVA-3S

- Stopped non-inferiority trial randomizing symptomatic patients to CEA or CAS
- Sponsored by French Department of Health
- Experience level for interventionalist
  - At least 12 CAS
  - 35 stents in supraortic trunk, including 5 CAS
  - Supervision by experienced interventionalist
  - No difference in outcomes by interventionalist prior experience level

EVA-3S: 30-day Results

NEJM 2006

CEA arm (n=262):

- Any stroke/death 3.9%
- 2 had stenting within 48 hours of surgery

CAS arm (n=265):

- Any stroke/death 9.6% (P=.01)
- 13 crossed over to CEA
- + EPD 7.9% vs –EPD 25%

First elective EPD use stopped then trial stopped prematurely

EVA-3S: Later follow-up

- Periprocedural stroke or death or non-periprocedural ipsilateral stroke rates after 4 years
  - CEA 6.2%
  - CAS 11.1%
  - HR 1.97, 95% CI 1.06-3.67; P=.03
- Non-periprocedural ipsilateral stroke rates after 4 years were low and similar
- "Carotid stenting is as effective as carotid endarterectomy for middle-term prevention of ipsilateral stroke, but the safety of carotid stenting needs to be improved before it can be used as an alternative to carotid endarterectomy in patients with symptomatic carotid stenosis,"
  - Mas et al, Lancet Neurology, published online September 6, 2008. European Stroke Conference 2008, May 14.

EVA-3S: My take

- Many recently symptomatic patients enrolled
  - High risk for CAS with current EPD
- 267 subjects treated with CAS at 30 centers from 2000-2005
  - Wide variety of stents and EPD
- Experience level for CEA operator
  - Minimum 25 CEA previous year
  - *de facto* quality threshold

SPACE

- Stopped non-inferiority trial randomized 1214 symptomatic patients to CEA or CAS at 37 centers in Germany, Switzerland, and Austria
- Sponsored by Germany's Federal Ministry of Education and Research, German Research Foundation, German Neurological Society, German Neuroradiological Society, Deutsche Rontgengesellschaft, Guidant, Boston Scientific, and Sanofi-Aventis
- Experience level of interventionalists
  - 2001: 25 successful consecutive PTA or stent procedures
  - After 2002, 10 interventions under experienced guidance
  - CAS Specialty: INR > IR > IC
  - Lancet 2006

Stent-protected Percutaneous Angioplasty of the Carotid artery vs. Endarterectomy (SPACE)

Study Population

randomized	1,200	
	CAS	CEA
Consent withdrawn	6	11
ITT-pop	599	584
Not treated	1	1
Switched tx	13	6
PP-pop	585	577
Protect-device	yes 172	no 413

SPACE-Brussels-May 2006

Stent-protected Percutaneous Angioplasty of the Carotid artery vs. Endarterectomy (SPACE)

Results – Primary Endpoint (ITT)

Ipsilateral stroke (any) and death between randomization and day 30

	CAS (N=599)	CEA (N=584)
Primary endpoint	41 (6.84%)	37 (6.34%)

Absolute difference (95% CI): 0.51% (-2.37% to 3.39%); p=0.09

Odds ratio (95% CI): 1.09 (0.69 to 1.72))

SPACE-Brussels-May 2006

SPACE

Primary Event Rates by Age (Predefined subgroup analysis)

	CAS	CEA
≤75	5.92% (29/490)	5.94% (26/438)
>75	11.01% (12/109)	7.53% (11/146)

SPACE: Later follow-up

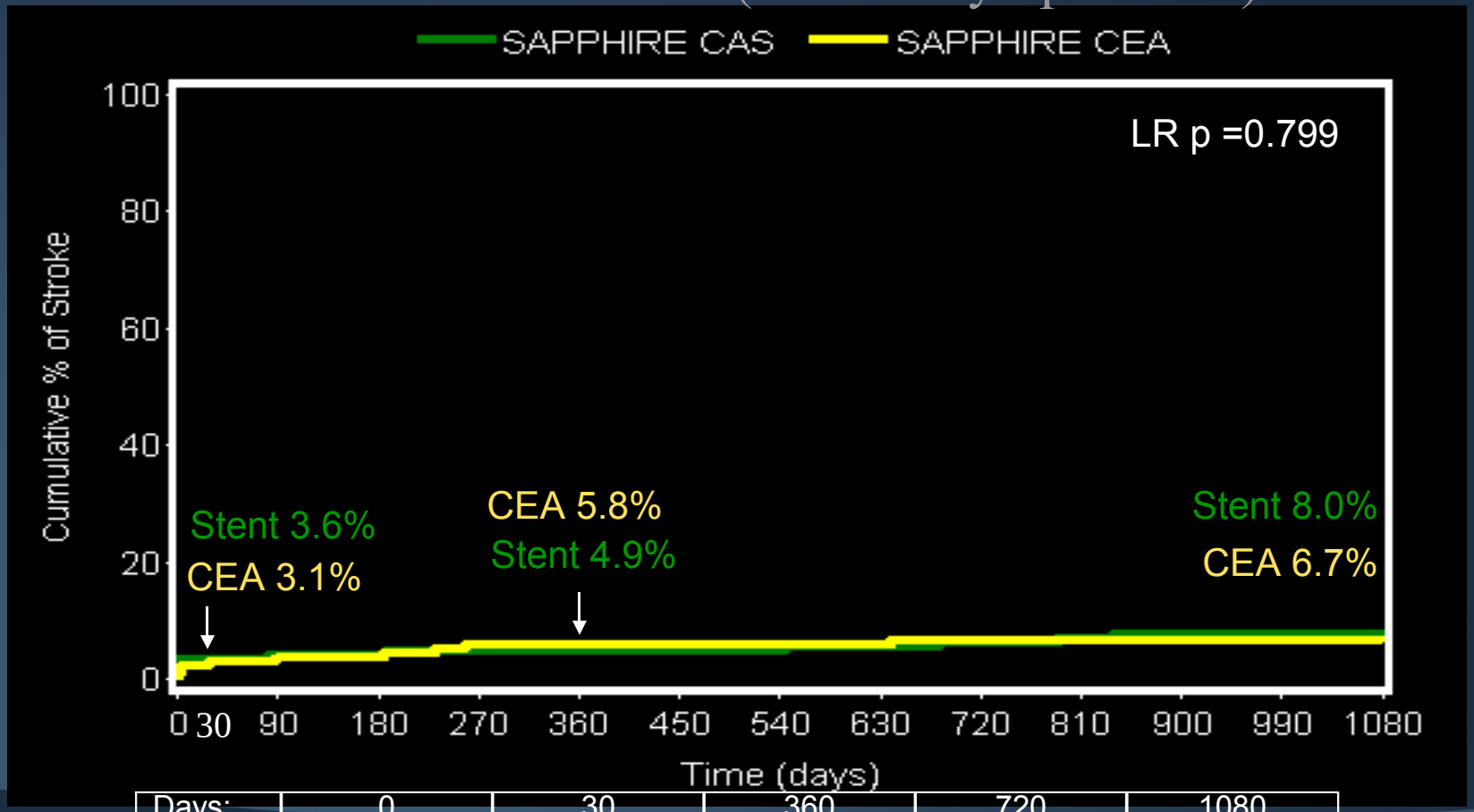
- Periprocedural stroke or death, plus ipsilateral ischemic stroke within 2 years
  - CEA 8.8%
  - CAS 9.5%
  - HR 1.10, 95%CI 0.75-1.61, P=.62
- Recurrent ischemic events after the periprocedural period at 2 years
  - CEA 1.9% (n=10)
  - CAS 2.2% (n=12)
  - HR 1.17, 95%CI 0.51-2.70, P=n.s.
- After 2 years, the rate of recurrent ipsilateral ischemic strokes is similar for both treatment groups
  - Eckstein et al, Lancet Neurology, published online Sept 6, 2008.

Sapphire Design Interventionalist Criteria

- 334 patients at high risk for CEA randomized to CAS versus CEA
- Interventionalists selected by
  - "an incidence of periprocedural stroke or death of less than 6%"
  - total CAS experience
    - median: 64
    - range: 20-700
  - ITT CAS 30 day S/D/MI = 4.8%
  - NEJM 2004, 2008

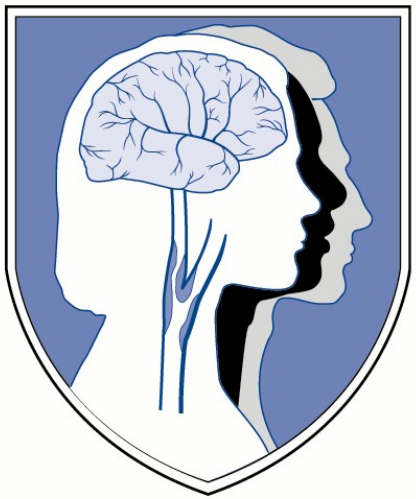
Cumulative Percentage of Stroke to 30 Days & Ipsilateral Stroke from 31-1080 Days

All Randomized Patients (>70% Asymptomatic)



Days:	0	30	360	720	1080
Stent:	167	159	147	130	107
CEA:	167	154	131	104	82

Carotid Revascularization Endarterectomy vs Stenting Trial



CREST

Carotid Revascularization Endarterectomy vs. Stenting Trial

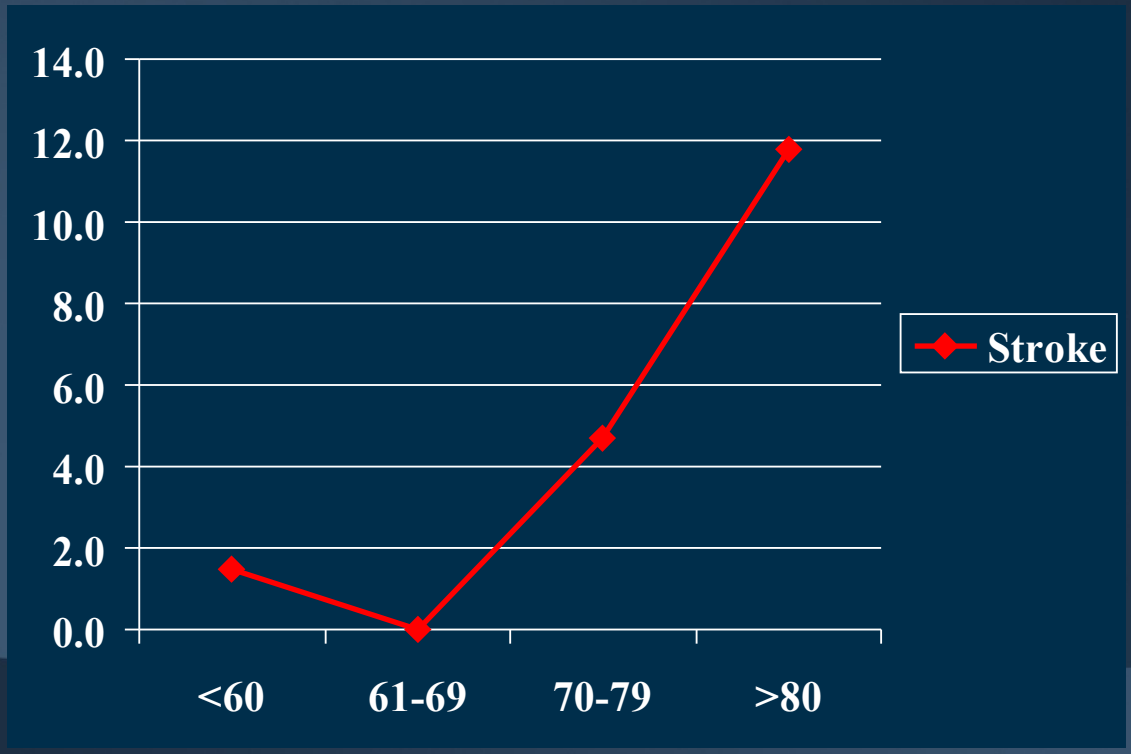
- Randomized, prospective, multicenter trial
- NINDS/Abbott sponsored
- > 2500 subjects enrolled
- Symptomatic (>50%) and asymptomatic (>60%) patients

CREST Interventionalist Criteria

- At least one interventionalist with 10-30 CAS procedures with complication rate acceptable to the IMC (symptomatic S/D < 6%)

Periprocedural Stroke in Octogenarians

- **Increasing proportion of Lead-In patients suffered stroke or death with increasing age (P=.00017)**



CREST Lead-in Results

- N=1246:
  - Death, Stroke, MI at 30 days = 5.0%
    - 7 (<1%) Death
    - 46 (3.7%) Strokes
    - 10 (<1%) MI
  - Death and Stroke alone = 3.9%
  - DS by symptomatic status:
    - Symptomatic 5.6%, Asymptomatic 3.4%
  - Rates include octogenarians

ACT 1
Study Design

- Prospective, randomized, non-inferiority, multi-center trial
- 3:1 randomization ratio of CAS to CEA
- IMC/SMC and lead-in enrollment (151 enrolled)
- Maximum of 1658 randomized subjects (>600 enrolled)
- Prescribed contemporary medical therapy guidelines for all patients
- Subjects followed at 1, 6, 12 months post-procedure and annually for 5 years

Key Inclusion Criteria

- Subject ≥ 18 and < 80 years of age.
- Subject asymptomatic
  - no stroke or TIA (hemispheric or ocular) within the 180 days prior to the procedure
  - neurologist must confirm status
- Carotid stenosis ≥70% and ≤99% by carotid duplex (accredited lab) or angiography (visual estimate)

Primary Endpoint *Composite*

- Any stroke*, myocardial infarction and death during 30-day post procedural period
- Ipsilateral stroke* between 31 and 365 days post procedure

*Independent neurologic assessment

Secondary Endpoints

- Acute device success
- Procedural success
- Prespecified composite morbidity index:
  - cranial nerve injury
  - bleeding, vascular and/or wound complications requiring treatment
  - access artery, renal, airway and general anesthesia complications
- Freedom from ipsilateral stroke and mortality at 2, 3, 4 and 5 years
- Freedom from clinically indicated target lesion revascularization (TLR)

ACT 1: Outcomes

Lead In Patients

Event	30 days, N=145
Death, Stroke and MI*	1.4%
All Stroke and Death*	1.4%
Major Stroke and Death*	0.0%
Death	0.0%
All Stroke	1.4%
Major Stroke	0.0%
Minor Stroke	1.4%
MI	0.0%
	31-365 days, N=106
Ipsilateral Stroke	0.0%

ACST-2

- ACST-2 is a randomized trial comparing CEA and CAS that was designed to be easily integrated routine health care.
- Sites are screened for track records (signed by neurologist) of interventionalists and surgeons, with a blended stroke/death rate of </=4% for asymptomatic patients and </=8% for symptomatic patients.
- CEA and CAS techniques and equipment must be appropriate for routine clinical practice, and EP is optional.

ACST-2

- Subjects in whom CEA and CAS are anatomically praticable are randomized 1:1 to CEA or CAS.
- The main outcomes are 1-month stroke/MI/death and long term stroke (5 or more years).
- Randomization and 1-month evaluations are performed by the study doctor, and long term follow up is primarily though direct contact from the ACST office.

Process of Care: Risk Factors for CAS

- Advanced age
- Recent symptoms < 2 weeks
- Poor access--arch and iliofemoral
- Tortuosity—unable to use EPD
- Severe calcification
- Free-floating thrombus
- String sign
- Experience level of interventionalist

Perceptions and Reality of CAS Summary

- Multicenter randomized trials define the ideal therapy for patients
- They are required in world of “comparative effectiveness”
- Most previous CAS randomized trials were stopped
- Many trials addressing role of CAS in standard risk for CEA cohort:
  - CREST completed enrollment
  - ACST-2, ICSS, SPACE-2?, TACIT?
  - ACT 1 actively enrolling in US
    - Surgeon and interventionalist criteria are relatively strict
    - Routinely use embolic protection
    - ACT 1 excludes high risk for CEA and more high risk for CAS subjects than other trials