Carotid Artery Stenting

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Carotid Stenosis and Stroke

- **~25% of stroke is due to carotid disease**, the reminder split between small-vessel disease, emboli, and Hemorrhage
- Severe carotid stenosis resulting in hemodynamic cerebral ischemia due to an incompetent circle of Willis (uncommon)
- Carotid plaque rupture resulting in:
  - Thrombus formation and carotid occlusion
  - **Atheromatous and thrombotic emboli** causing occlusion of distal intracranial vessels *(common)*

Acute Stroke therapy : ineffective for the majority of CVA

- **< 5%** of all stroke in the US arrive in time or to an adequate facility (capability) to receive either IV or IA thrombolytics, or rescue IA intervention
- Therefore prevention becomes critical

  - Hypertension control

  - Atrial fibrillation anticoagulation and appendage occlusion

  - PFO closure or medical Rx

  - **Carotid artery revascularization**

Who is at risk ?

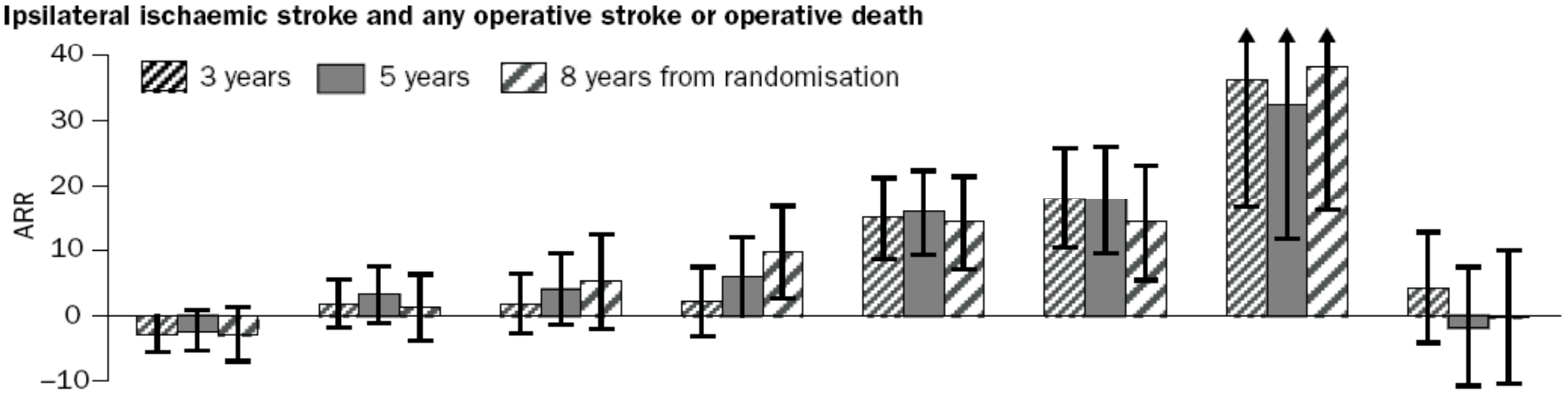
Randomized Trials of CEA Versus Medical Therapy for Carotid Artery Stenosis

Trial	N	Stenosis	Follow-Up	End Point	Medical (%)	CEA (%)	*p*	RRR (%)	ARR (%)	NNT
Symptomatic										
ECST (38)	3,018	≥80%	3 yrs	Major stroke or death	26.5	14.9	<0.001	44	11.6	8.6
NASCET (18)	659	≥70%	2 yrs	Ipsilateral stroke	26	9	<0.001	65	17	5.9
VA 309 (148)	189	>50%	1 yr	Ipsilateral stroke or TIA or surgical death	19.4	7.7	0.011	60	11.7	8.5
NASCET (19)	858	50%–69%	5 yrs	Ipsilateral stroke	22.2	15.7	0.045	29	6.5	15.4
NASCET (19)	1,368	≤50%	5 yrs	Ipsilateral stroke	18.7	14.9	0.16	20	3.8	26.3
Asymptomatic										
ACAS (22)	1,662	>60%	5 yrs	Ipsilateral stroke, surgical death	11	5.1	0.004	54	5.9	16.9
ACST (23)	3,120	≥60%	5 yrs	Any stroke	11.8	6.4	0.0001	46	5.4	18.5
VA (149)	444	≥50%	4 yrs	Ipsilateral stroke	9.4	4.7	<0.06	50	4.7	21.3

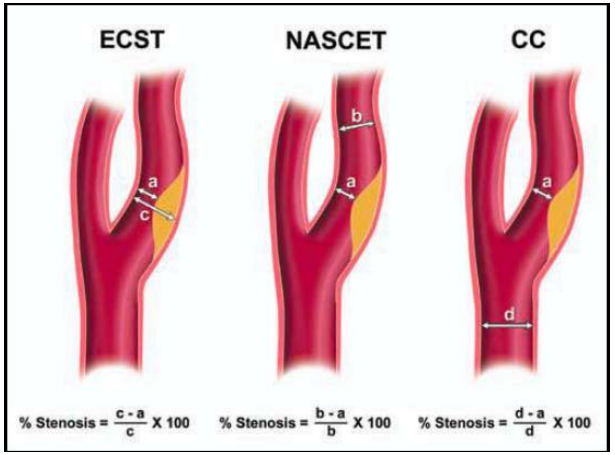
JACC 2007;49:126–70

CEA for Symptomatic Carotid Stenosis

North American Symptomatic Carotid Endarterectomy Trial (NASCET), Eupopean Carotid Surgery Trial (ECST), Veterans Affairs



ARR 3 years	–2·7	1·8	1·8	2·1	14·9	18·1	36·1	4·2
ARR 5 years	–2·2	3·2	4·0	5·9	15·8	17·7	32·4	–1·7
ARR 8 years	–2·9	1·2	5·2	9·6	14·2	14·3	38·1	–0·3
Stenosis	<30%	30–49%	50–59%	60–69%	70–79%	80–89%	90–99%	Near-occl



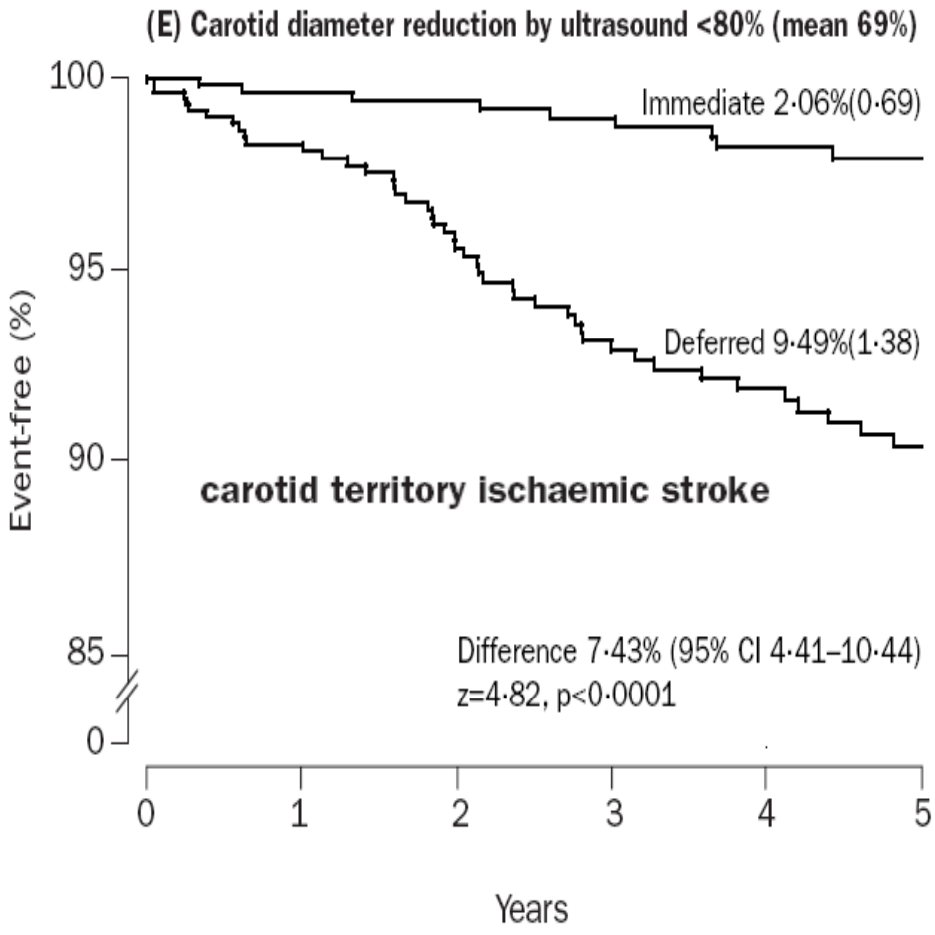
Data for 6092 patients, with 35 000 patient-years of follow-up, were therefore pooled

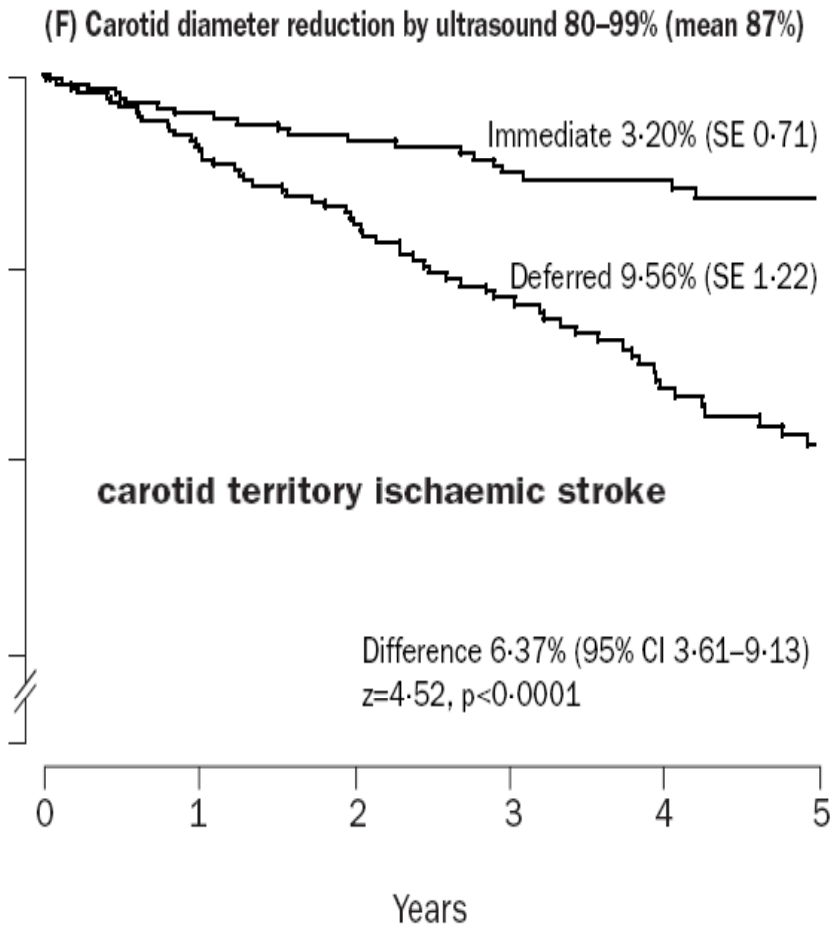
Lancet 2003;361:107–16

CEA for Asymptomatic Carotid Stenosis

Asymptomatic Carotid Surgery Trial (ACST)

During 1993–2003, 3120 asymptomatic patients with substantial carotid narrowing were randomised equally between immediate CEA (half got CEA by 1 month, 88% by 1 year) and indefinite deferral of any CEA (only 4% per year got CEA) and were followed for up to 5 years (mean 3·4 years)





Lancet 2004; 363: 1491–502

Who's at Risk ?

- **Hemispheric symptoms due to carotid disease**

  - TIA or non-disabling CVA in the proceding 6 months

  - Most predictive of future stroke

- **Severity of stenosis**

  - With symptoms, >50%

  - Without symptoms, >70%

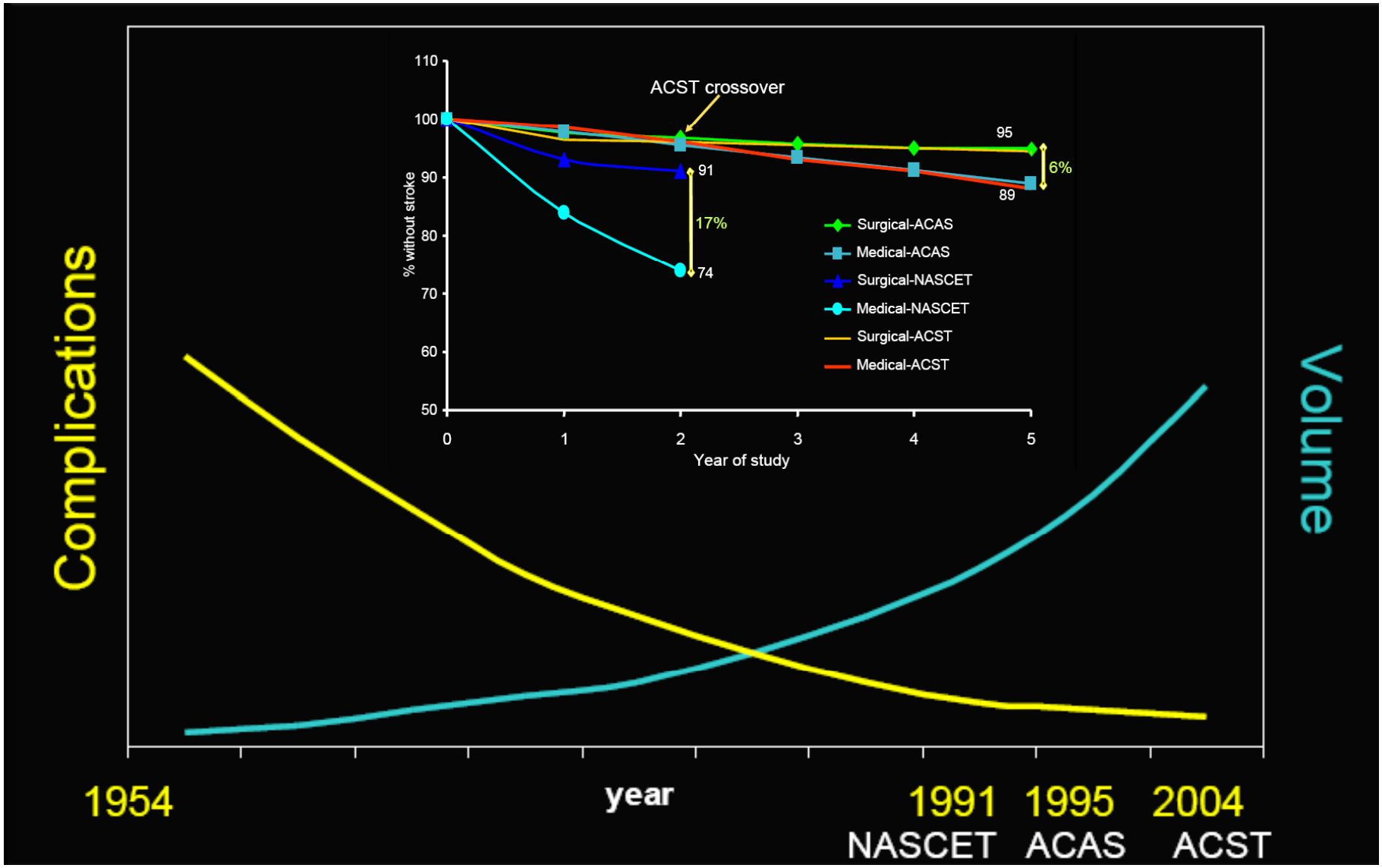
Treatment Strategy for Carotid stenosis

- Optimal Medical Treatment (OMT)
- Carotid Endartrectomy (CEA)
- Carotid Artery Stenting (CAS)

Indication for Intervention

- Neurological symptomatology
- Degree of carotid stenosis
- Medical co-morbidities
- Vascular and local anatomical features
- Carotid plaque morphology

Carotid Endartrectomy



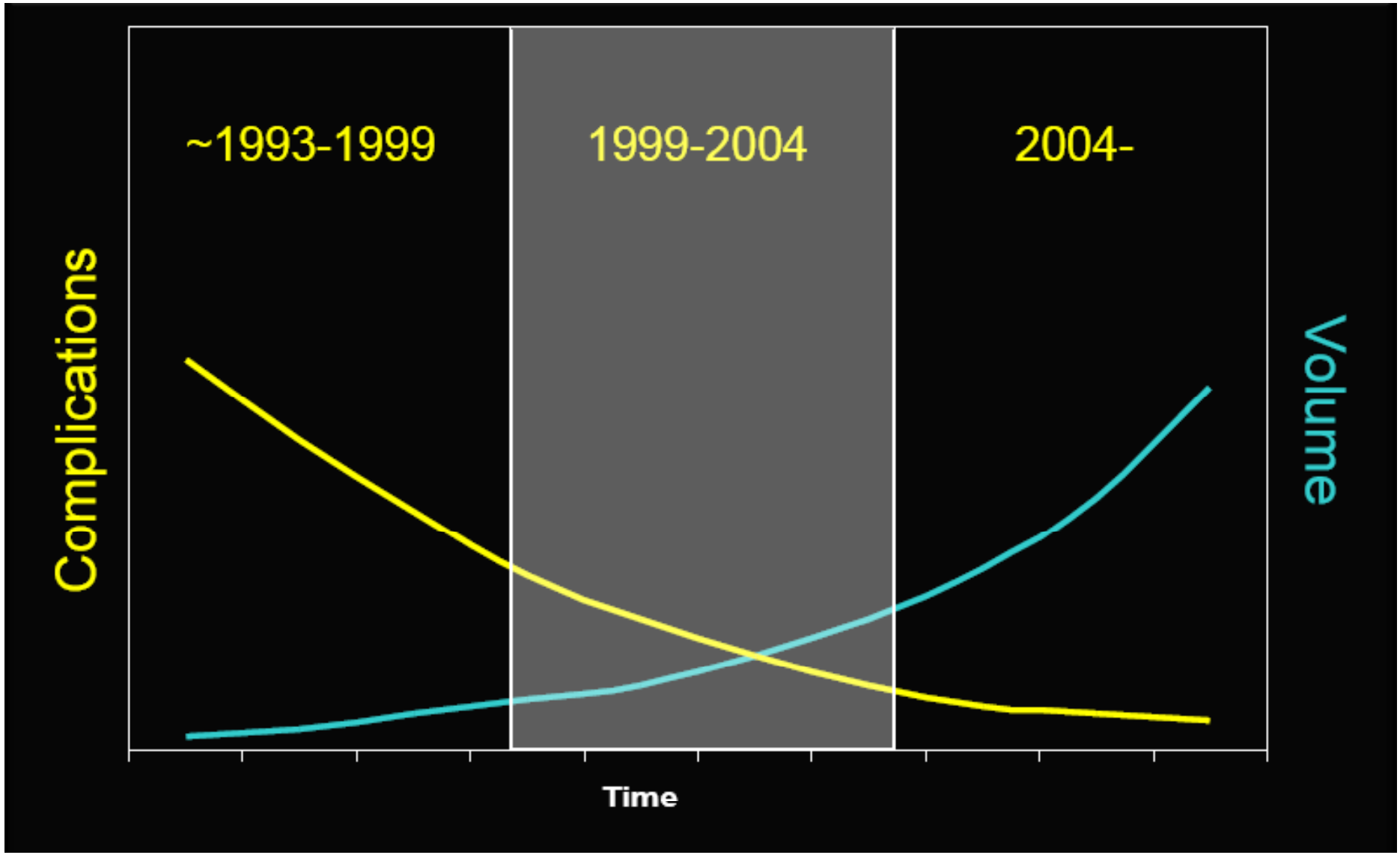
CEA : AHA Standards

- **Symptomatic carotid stenosis: <6% CEA stroke and death rate**
- **Asymptomatic carotid stenosis: <3% CEA stroke and death rate**

NASCET and ACAS Exclusions

- Age>79
- Prior ipsilateral CEA
- Unstable coronary syndrome
- Myocardial infarct in previous 6 months
- Cardiac valvular or rhythm abnormality likely to cause embolic cerebrovascular symptoms
- Contralateral occlusion
- A more severe lesion cranial to the surgical lesion
- Contralateral CEA within previous 4 months
- Uncontrolled hypertension or diabetes
- Organ failure likely to cause death within 5 years
- Total occlusion
- Major surgical procedure in previous 30 days
- Prior severe CVA
- Progressing neurologic syndrome

Carotid Artery Stent



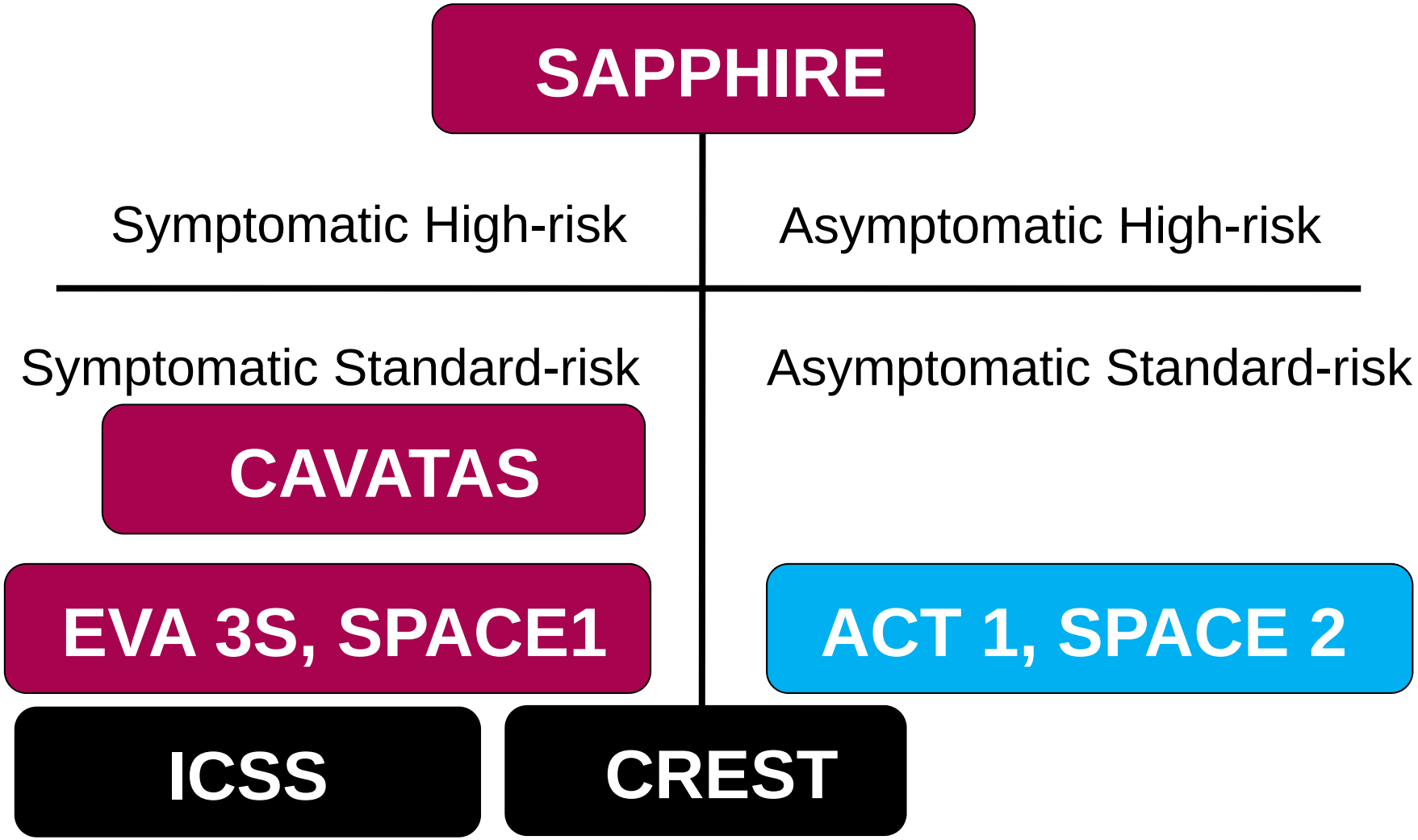
Controversies in Carotid Intervention

- Is there a role for carotid artery stent as primary intervention for carotid artery stenosis ?

  CEA vs CAS

- Is optimal medical therapy enough for patients with carotid artery stenosis ?
- Stent design
- Embolic Protection Devices

RCT for Carotid Stenosis : CAS vs CEA



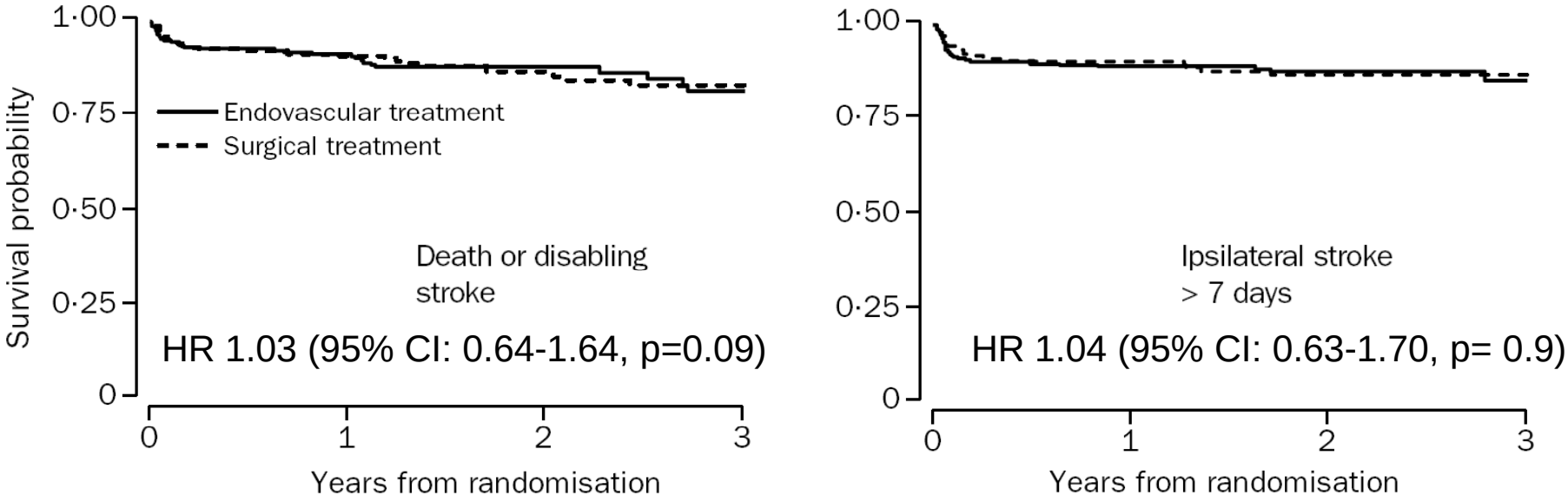
CEA vs CAS

Symptomatic Carotid Stenosis

CAVATAS

Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study

In a multicentre clinical trial, we randomly assigned 504 patients with carotid stenosis to endovascular Tx (n=251, stent 26%, no EPD) or CEA (n=253).



Lancet 2001;357:1729-37

EVA 3S

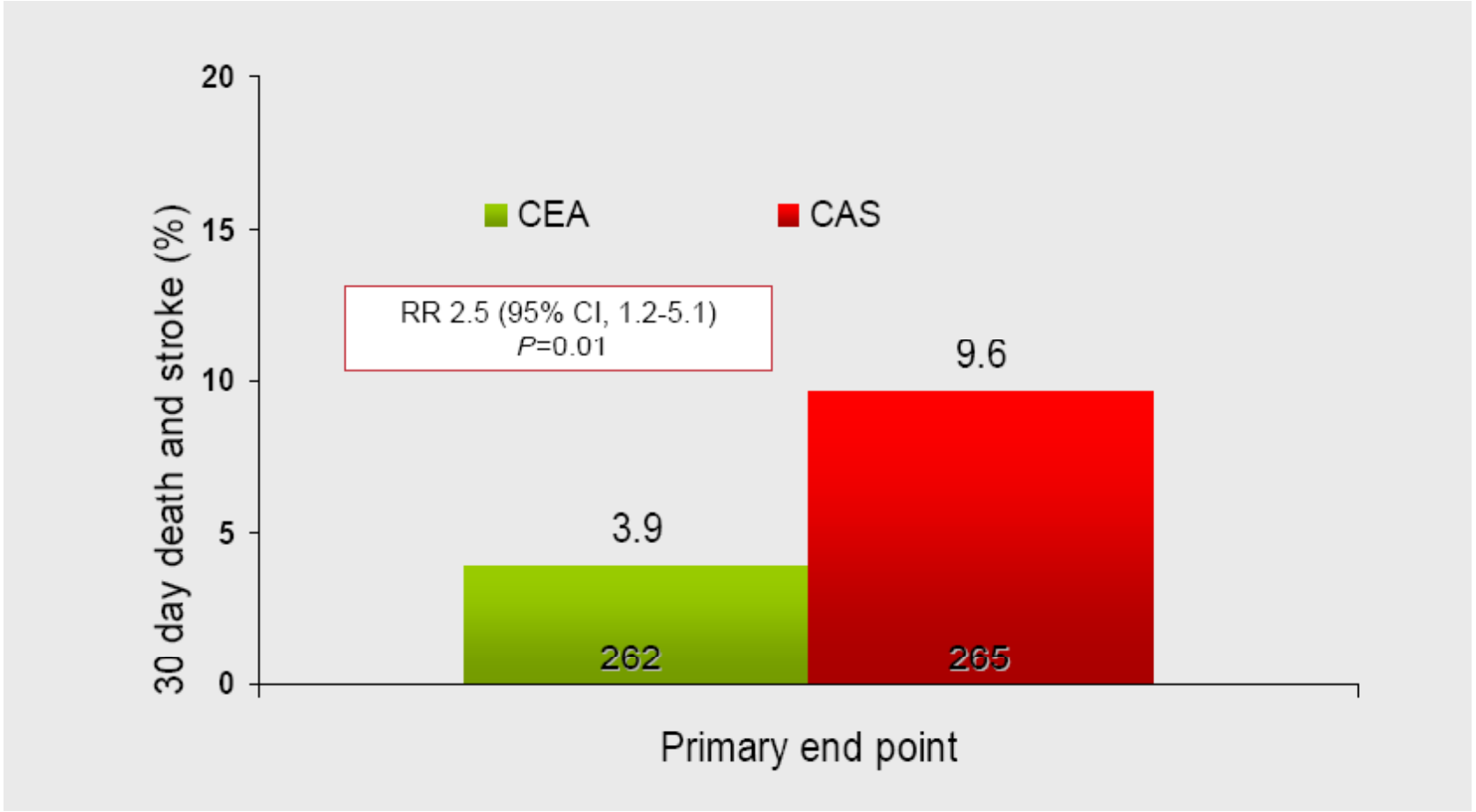
Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis

- Randomized, multicenter, non-inferiority trial of standard surgical risk patients with symptomatic carotid stenosis > 60%
  - 527 patients
  - Primary endpoint: 30-day death and stroke
  - Secondary endpoint: 30-day MAE plus ipsilateral stroke to 4 yrs
- 30 centers in France
- CAS Operator experience : 5 cases needed

N Engl J Med 2006;355:1660-71

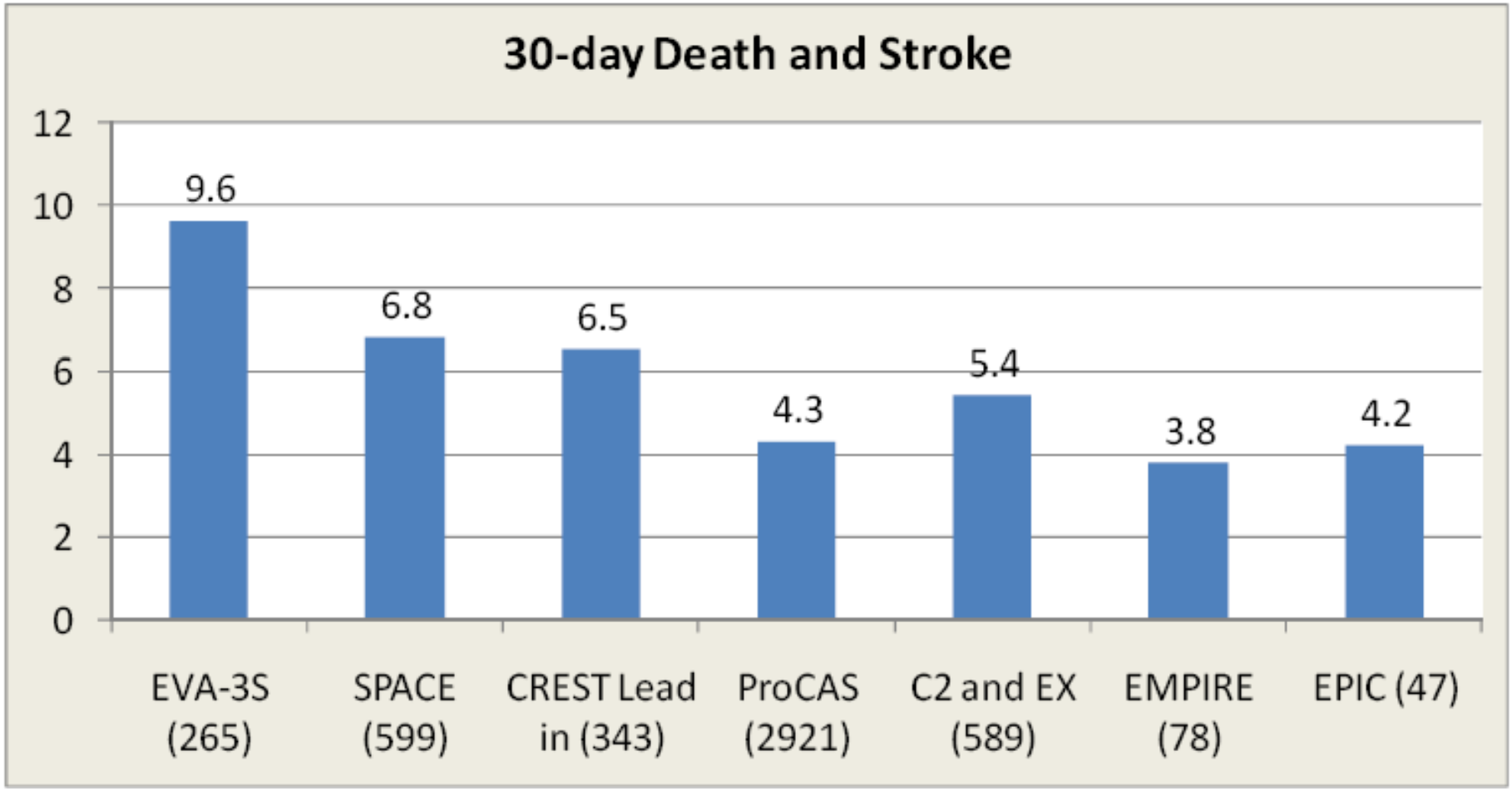
EVA 3S

Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis

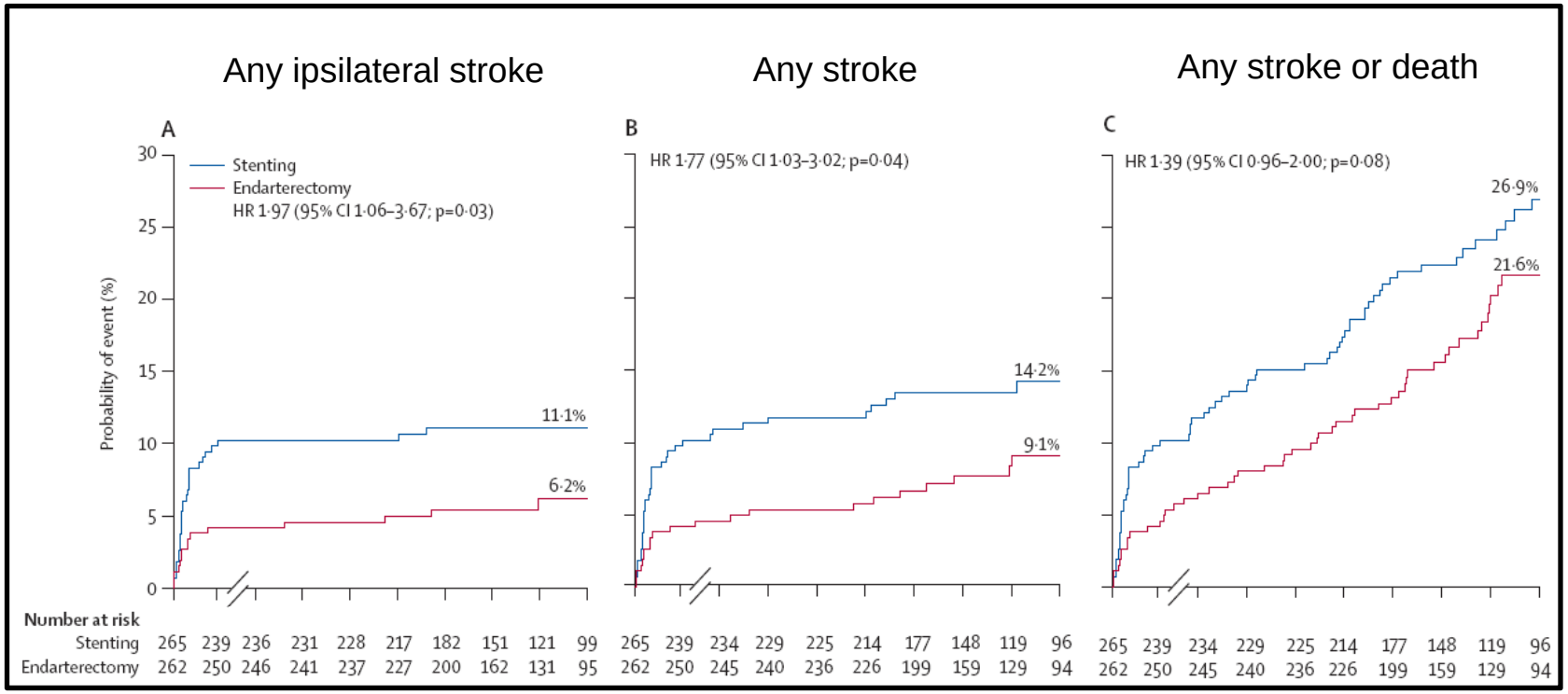


N Engl J Med 2006;355:1660-71

EVA-3S vs Other studies in Symptomatics : Influence of Experience



EVA 3S : 4-year Outcomes



4 year risk of non-procedural stroke 4.6% CEA vs 3.7% CAS

Lancet Neurol 2008;7:885-92

SPACE

30 day results from the SPACE trial of stent-protected angioplasty versus CEA in symptomatic patients: a randomised non-inferiority trial

- Randomized, multicenter non-inferiority study of CEA vs.

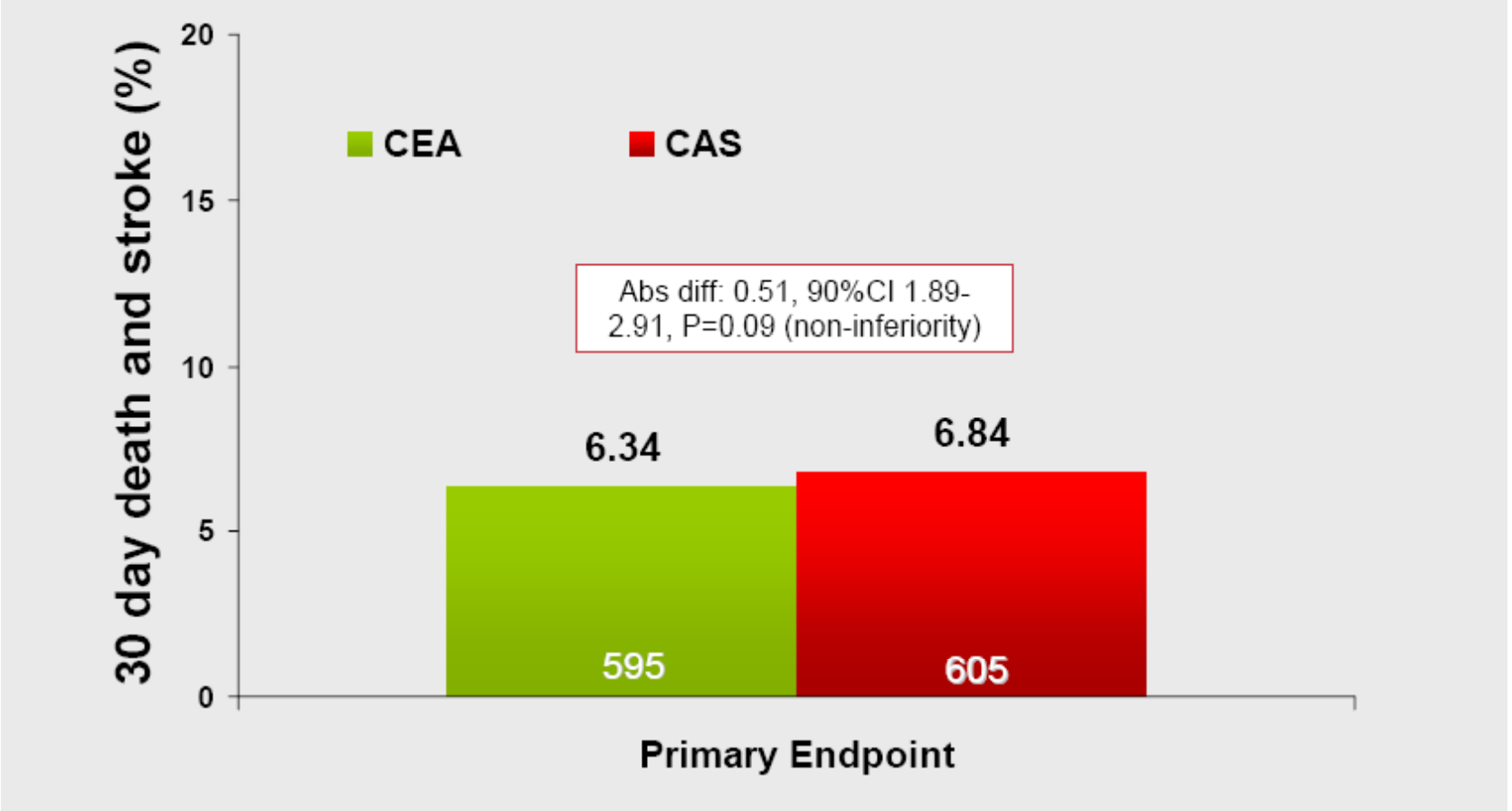
  CAS in standard surgical risk symptomatic patients with

  70% carotid stenosis
- Primary endpoint 30-day ipsilateral stroke and death
- EPD use at discretion of operator (Only 27% EPD use)

Lancet 2006;368:1239-47

SPACE

30 day results from the SPACE trial of stent-protected angioplasty versus CEA in symptomatic patients: a randomised non-inferiority trial



Lancet 2006;368:1239-47

SPACE : 2-year Outcomes

	CAS	CEA	HR (95% CI)
Any stroke between randomization and 2 years	10.9%	10.1%	1.10 (0.77-1.57)
Ipsilateral ischemic stroke between 31 days and 2 years	2.2%	1.9%	1.17 (0.51-2.70)

Lancet Neurol 2008;7:893-902

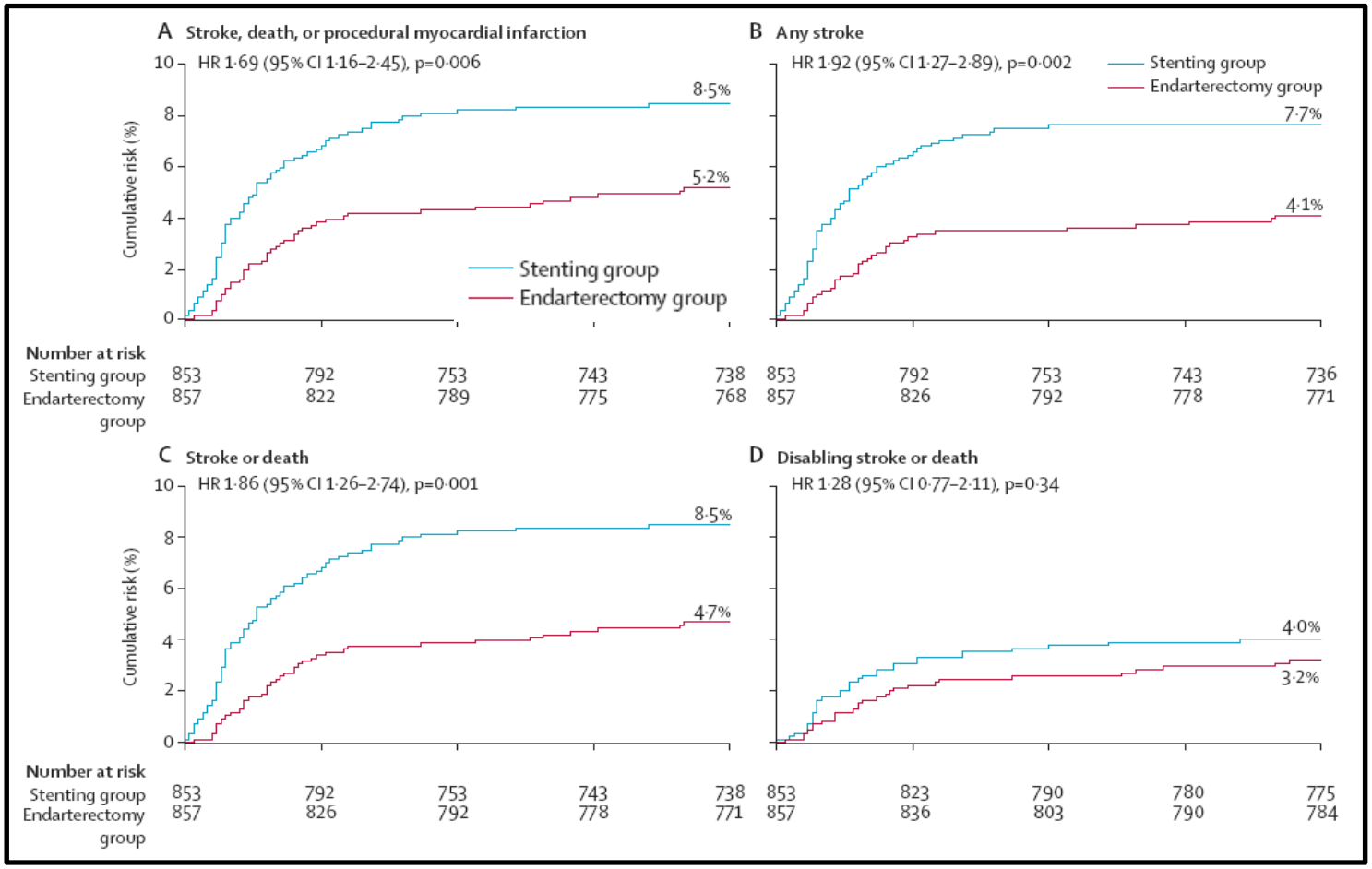
SPACE : Conclusions

- Stopped due to lack of continued funding
- Did not achieve statistical endpoint of non inferiority due to this early termination
- EPD was used in only 27% of patients
- Nevertheless, results appear to be comparable between stent and surgery
- If a patient has been treated successfully without any complications, the risk of stroke is very small and very comparable between CEA and CAS

ICSS

The trial enrolled 1713 patients (stent, n=855; CEA group, n=858)

The primary outcome is the 3-year rate of fatal or disabling stroke. The main outcome for the interim safety analysis was the 120-day rate of stroke, death, or MI



Lancet 2010;375:985-97

ICSS-MRI

New ischaemic brain lesions on MRI after stenting or CEA

	Carotid stenting (n=124)	Carotid endarterectomy (n=107)	OR (95% CI)	p*
At least one new lesion	62 (50%)	18 (17%)	4·94 (2·67–9·16)† 5·21 (2·78–9·79)‡	<0·0001 <0·0001
Single lesion	18 (15%)	9 (8%)	..	..
Multiple lesions	44 (35%)	9 (8%)	..	..
Location of lesions				
Ipsilateral carotid circulation only	34 (27%)	14 (13%)	..	..
Ipsilateral carotid and non-ipsilateral (contralateral carotid or vertebrobasilar) circulations	22 (18%)	3 (3%)	..	..
Non-ipsilateral (contralateral carotid or vertebrobasilar) circulations only	6 (5%)	1 (1%)	..	..
Ischaemic events in patients with new DWI lesions§	9 (7%)	3 (3%)	..	..
Hemispheric stroke	8 (6%)	3 (3%)	..	..
Retinal infarct	1 (1%)	0	..	..
TIA	0	0	..	..
None	53 (43%)	15 (14%)	..	..

Lancet Neurol 2010;9:353–62

CREST

The Carotid Revascularization Endarterectomy vs. stenting Trial

- It is the largest randomized prospective study of CAS vs. CEA
- Total 2,502 patients with either symptomatic (n = 1,321) or asymptomatic (n = 1.181) carotid stenosis who were randomized to CEA or carotid stenting at 117 centers in the United States and Canada over a 9-year period.
- The primary endpoint (composite of any stroke, MI, or death within 30 days plus subsequent ipsilateral stroke)
- Periprocedural Complications:any periprocedural stroke, MI, or death
- Data is available for follow-up median 2.5 years

ASA 2010 Feb 26

CREST

The Carotid Revascularization Endarterectomy vs. stenting Trial

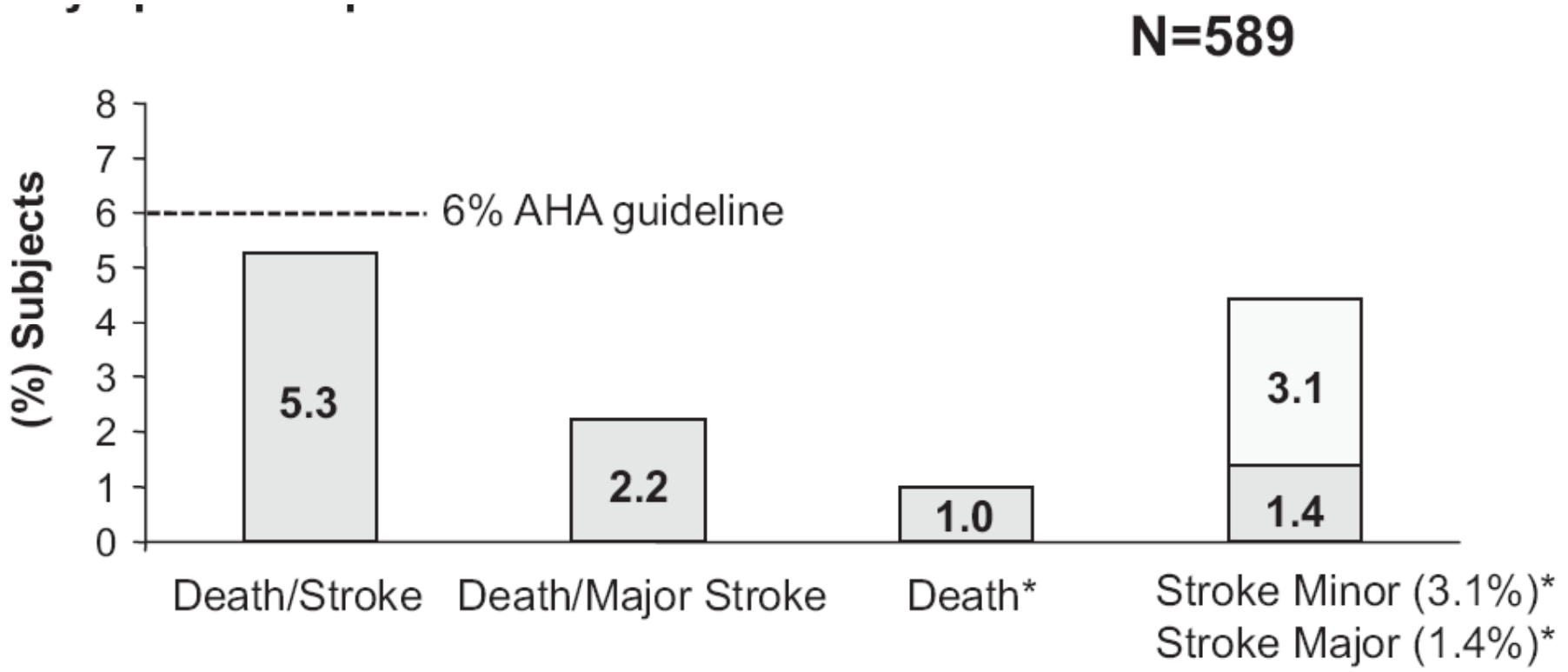
	Stent	CEA	HR(95% CI)	P value
Primary Endpoint (%)	7.2	6.8	1.11 (0.81-1.51)	NS
Periprocedural Cx (%)	5.2	4.5	1.18 (0.82-1.68)	NS
Stroke (%)	4.1	2.3	1.79 (1.14-2.82)	0.01
MI (%)	1.1	2.3	0.50 (0.26-0.94)	0.03

- The rate for stroke and death in carotid stenting was the lowest yet reported in any randomized trial.
- Significant advances in technology, technique and patient selection.
- Stenting offers a reasonable alternative to CEA.

ASA 2010 Feb 26

EXACT/CAPTURE 2

30-day major adverse events in symptomatic patients < 80 years



Circ Cardiovasc Intervent 2009;2:159

Invasive treatment recommendation
Carotid Stenosis in symptomatic patients

- The available level I evidence suggests that for symptomatic patients, CEA is currently the best option [A].
- Mid-term stroke prevention after successful CAS is similar to CEA [A].
- CAS should be offered to symptomatic patients, if they are at high risk for CEA, in high-volume centers with documented low peri-procedural stroke and death rates or inside an RCT [C].
- Critical issue
  - More evidence is required to establish the role of CAS in symptomatic CAD, both in the peri-procedural period as well as in the long term.

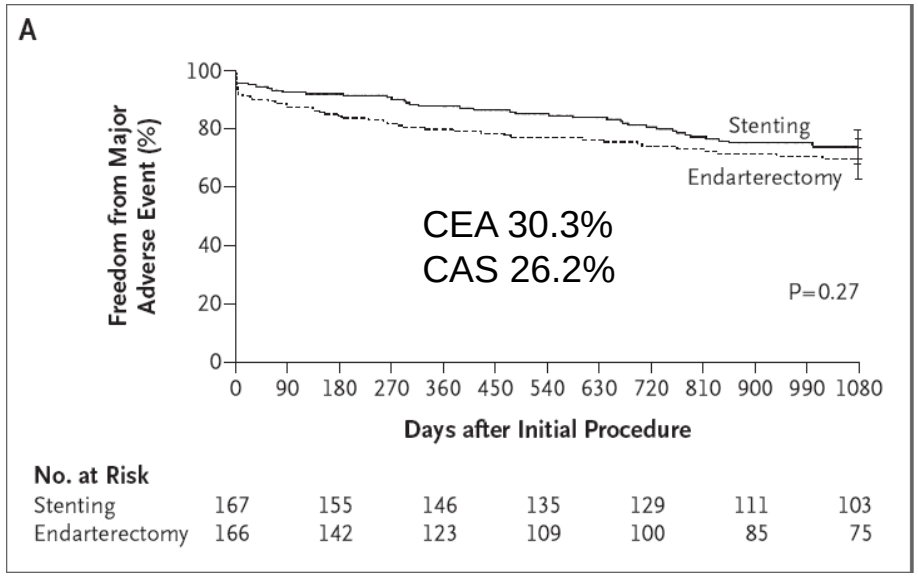
CEA vs CAS

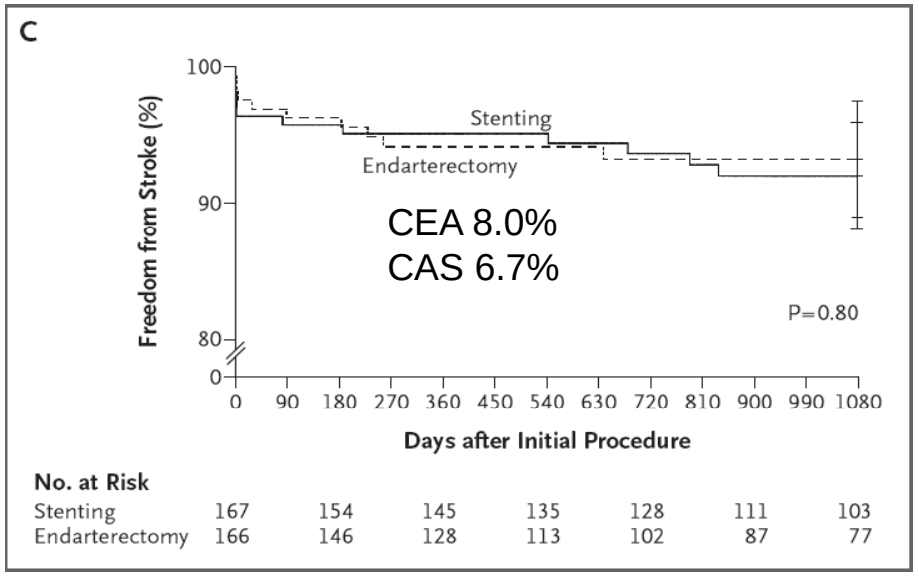
Asymptomatic Carotid Stenosis

SAPPHIRE

Long-Term Results of CAS versus CEA in High-Risk Patients (non-inferiority)

Randomized trial comparing CAS with the use of an EPD to CEA in high-surgical risk 334 patients.a symptomatic at least 50% an asymptomatic at least 80% stenosis

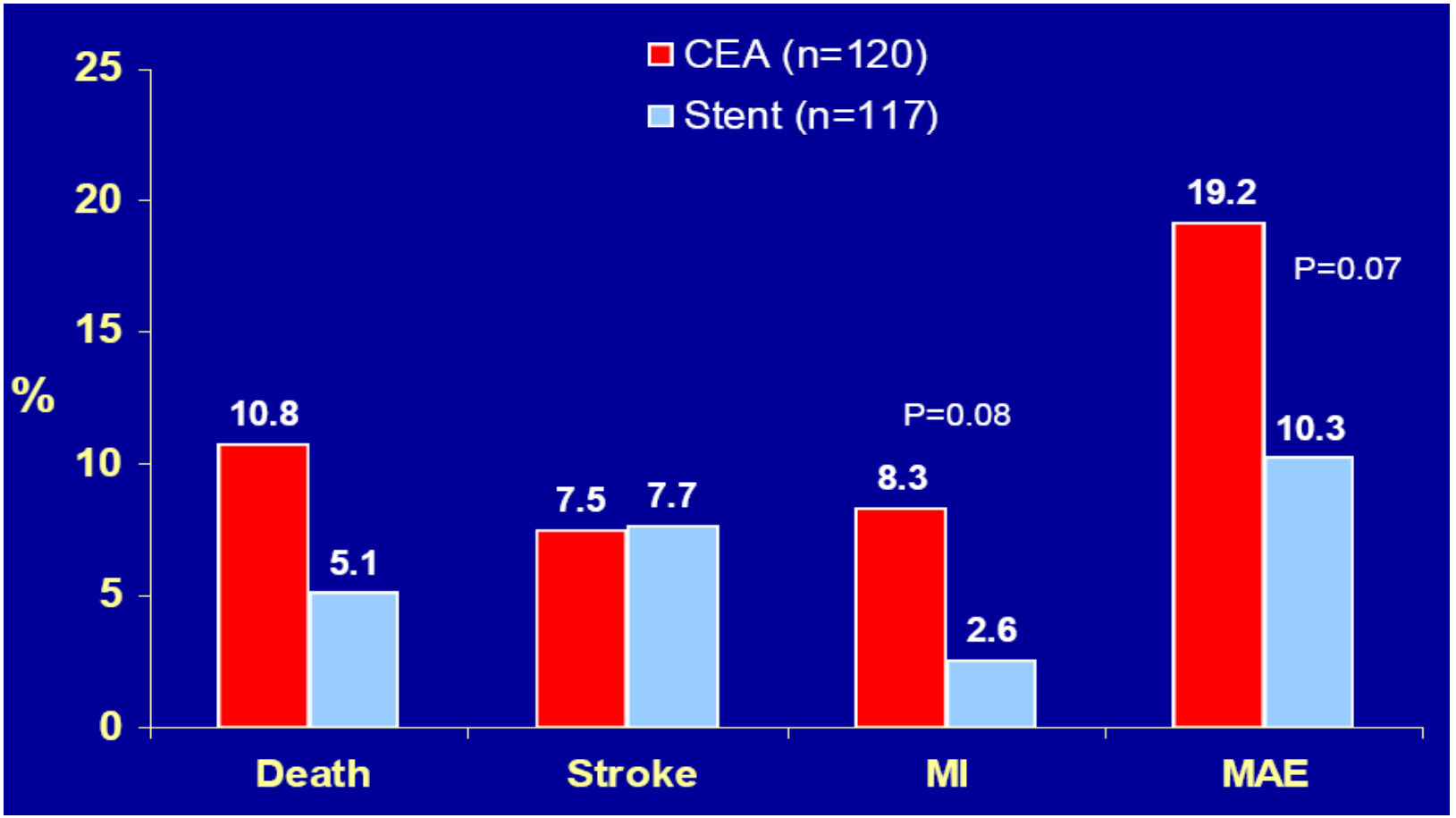




MAE : death, MI, or stroke within 30 days or death or ipsilateral stroke between 31 & 1080 days
Stroke : stroke within 30 days or ipsilateral stroke between 31 days and 1080 days

N Engl J Med 2008;358:1572-9

SAPPHIRE Asymptomatic (N=237) : 360-day MAE



SAPPHIRE is not powered for subgroup analysis

N Engl J Med 2004;351:1493-501

Long-term results of carotid artery stenting

Objective: Data regarding the long-term efficacy of carotid artery stenting (CAS) are still scarce. As demonstrated by several major randomized controlled trials (RCT) comparing the efficacy of carotid endarterectomy (CEA) vs medical therapy, even after successful carotid revascularization late ipsilateral stroke occurs in 5-13% at 5 years. Therefore, major concerns also remain about the durability of the CAS procedure in terms of stroke prevention. The purpose of this study was to review long-term results after carotid stent implantation in a large cohort of patients.

Methods: This retrospective investigation involved 3179 CAS procedures performed at four European carotid high-

The annual rate of neurological complications after CAS was comparable to that of conventional surgery as demonstrated by large RCTs involving both symptomatic patients (NASCET, ECST) and asymptomatic patients (ACAS, ACST)

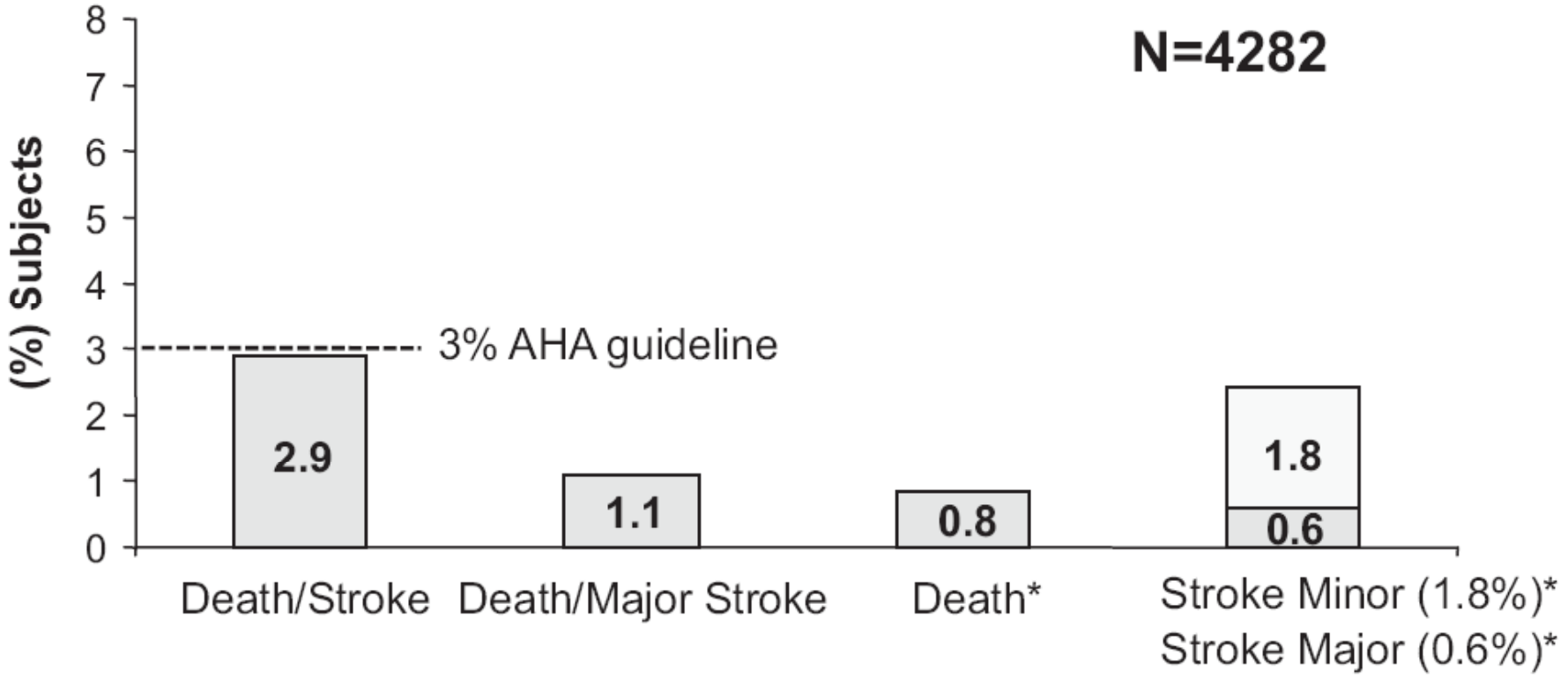
respectively, 98.4%, 96.1%, and 94%. Uni- and multi-variate analyses showed that stent characteristics (material/design/free-cell area) were not significantly associated with time to in-stent restenosis or time to reintervention.

Conclusion: Our long-term results in a large cohort of patients validated CAS as a durable procedure for stroke prevention. The annual rate of neurological complications after CAS was comparable to that of conventional surgery as demonstrated by large RCTs involving both symptomatic patients (North American Symptomatic Carotid Endarterectomy Trial [NASCET] and European Carotid Surgery Trial [ECST]) and asymptomatic patients (Asymptomatic Carotid Atherosclerosis Study [ACAS] and Asymptomatic Carotid Surgery Trial [ACST]). (J Vasc Surg 2008;48:1431-41.)

J Vasc Surg 2008;48:1431-41

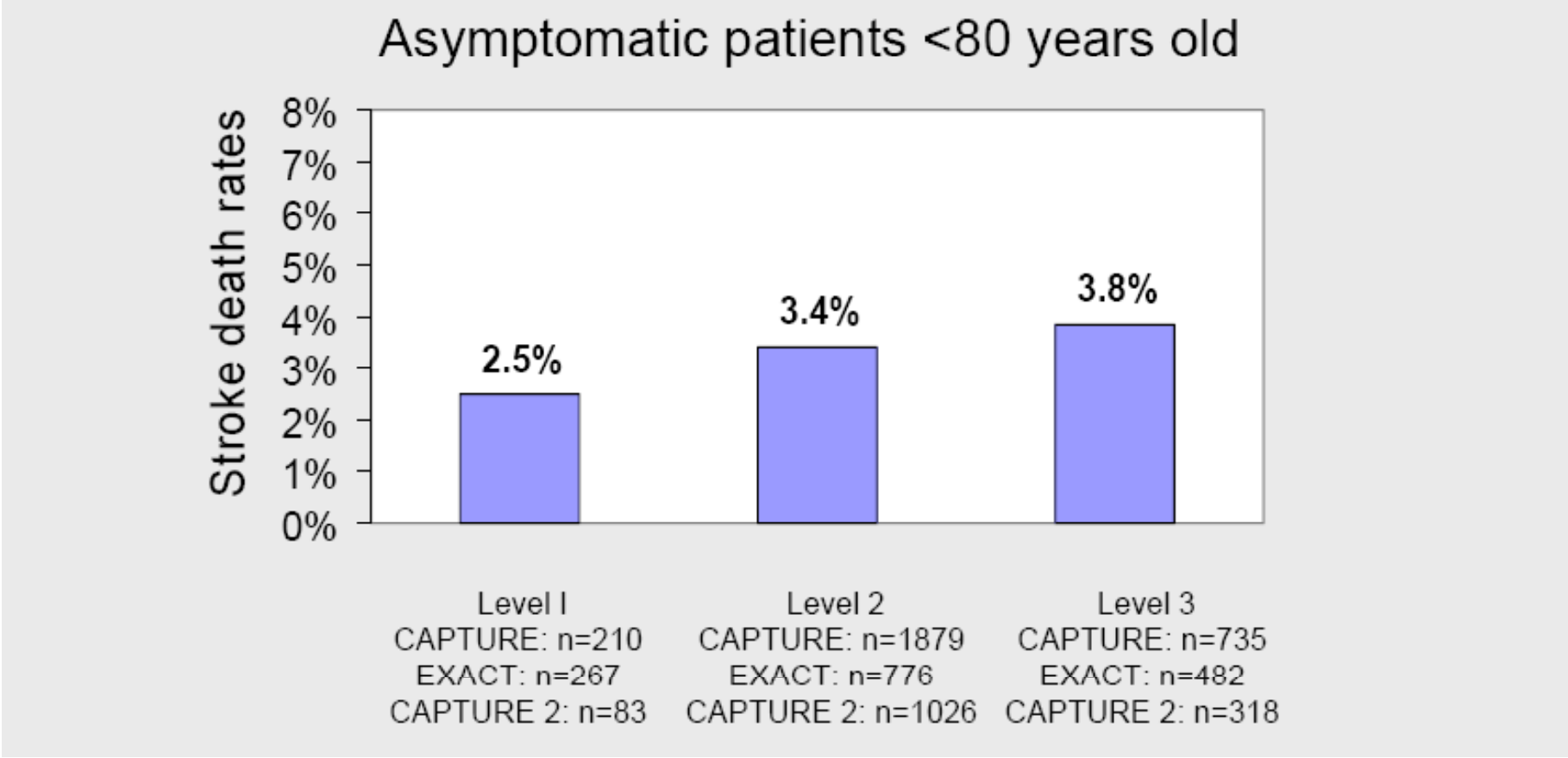
EXACT/CAPTURE 2

30-day major adverse events in asymptomatic patients < 80 years



Circ Cardiovasc Intervent 2009;2:159-166

Influence of Experience : PMS Outcomes



Circ Cardiovasc Intervent 2009;2:159-166

Invasive treatment recommendation
Carotid Stenosis in asymptomatic patients

- Meanwhile, it is advisable to offer CAS in asymptomatic patients only in high-volume centres with documented low peri-procedural stroke and death rates or within well-conducted clinical trials [C].

- Critical issue

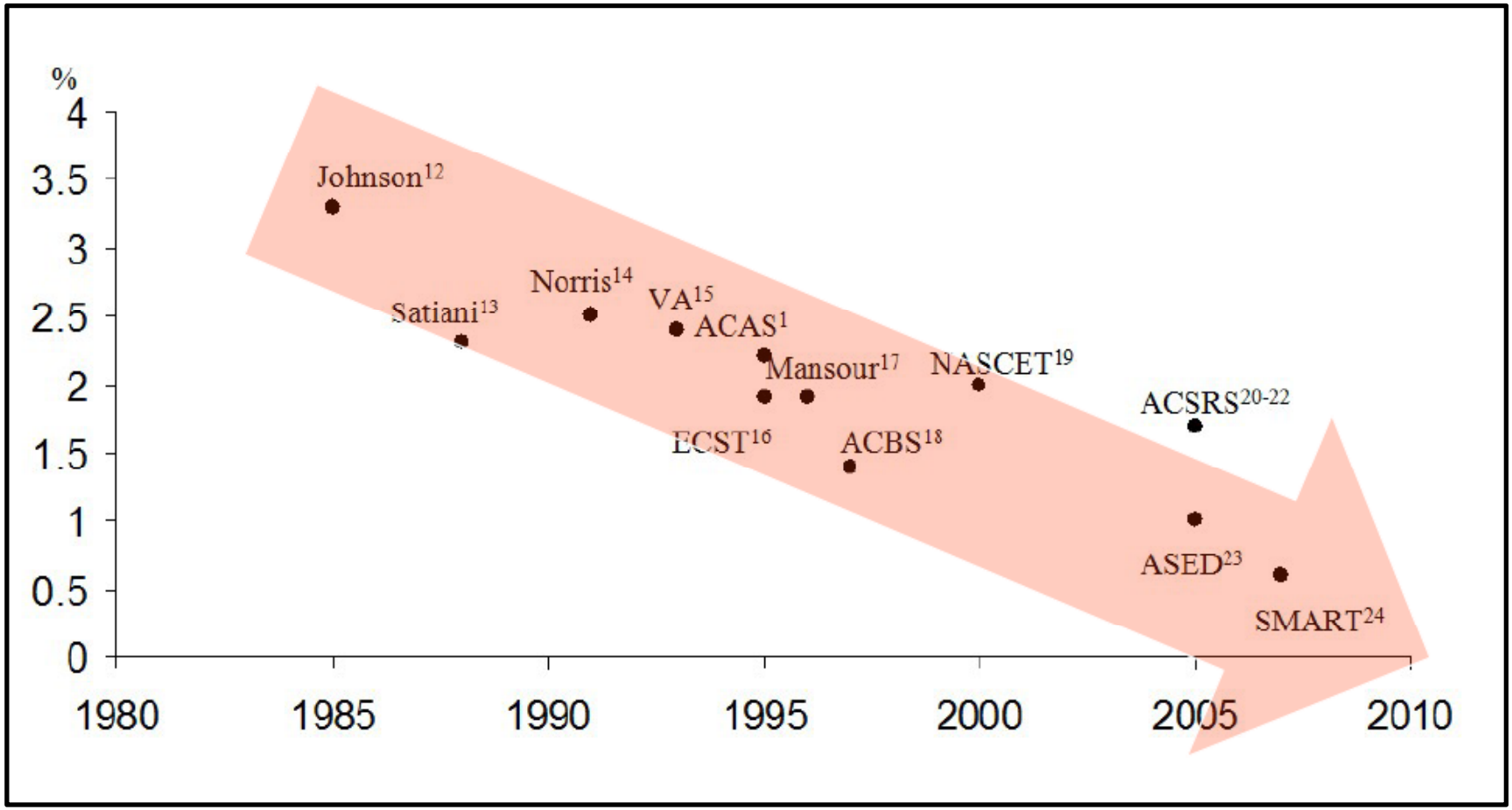
  — The benefit from CAS in asymptomatic patients with carotid artery stenosis is still to be demonstrated.

Medical Treatment

Medication as an effective alternative to revascularization

- Antihypertensive medication
- Lipid lowering agent
- Antiplatelet therapy

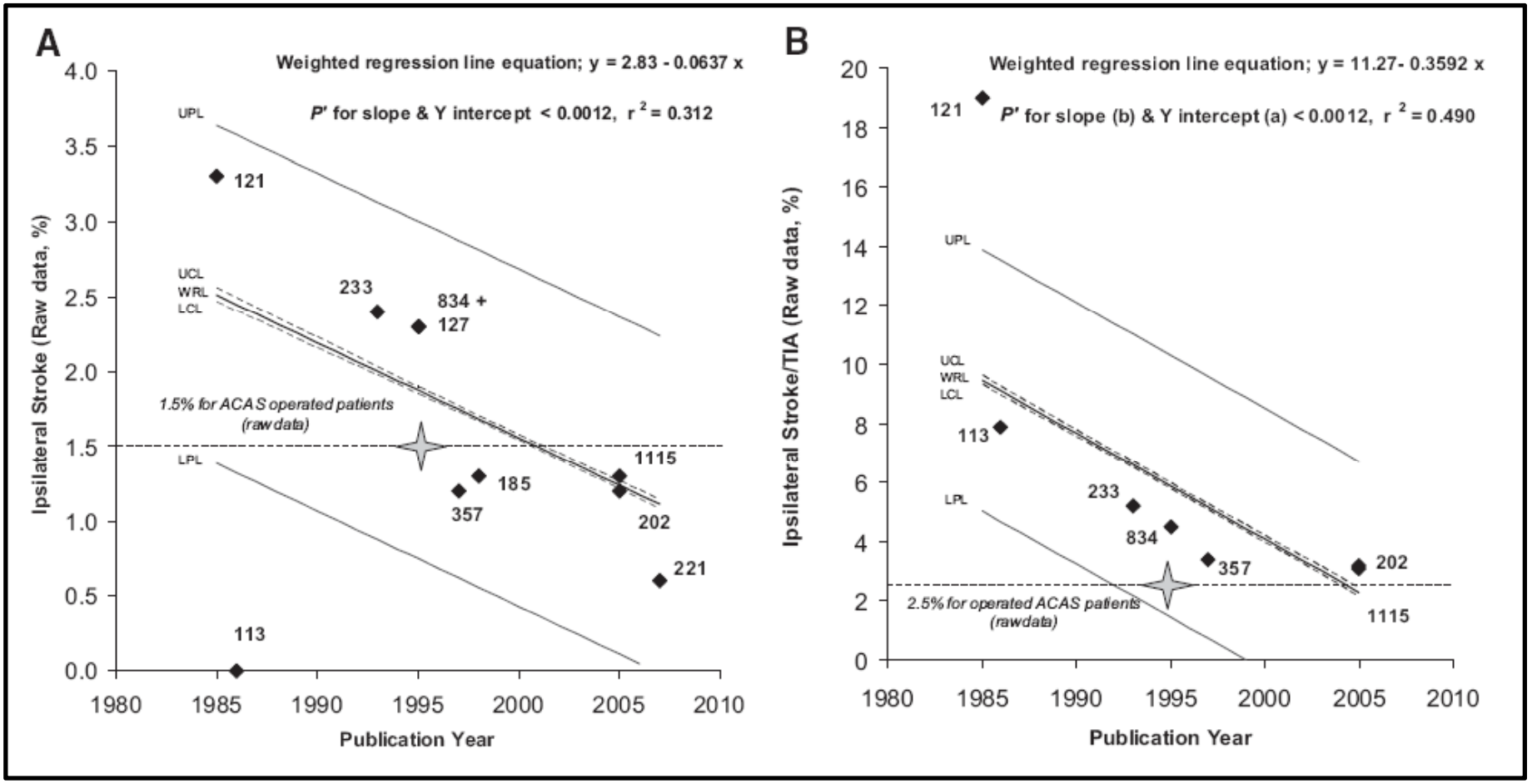
Temporal changes (1985-2008) in the annual average rate of ipsilateral stroke in patients with >50% asymptomatic carotid stenosis who were treated medically



Eur J Vasc Cardiovasc Surg 2009

Medical (Nonsurgical) Intervention Alone Is Now Best for Prevention of Stroke Associated With Asymptomatic Severe Carotid Stenosis

Results of a Systematic Review and Analysis



Stroke 2009;40:e573-83

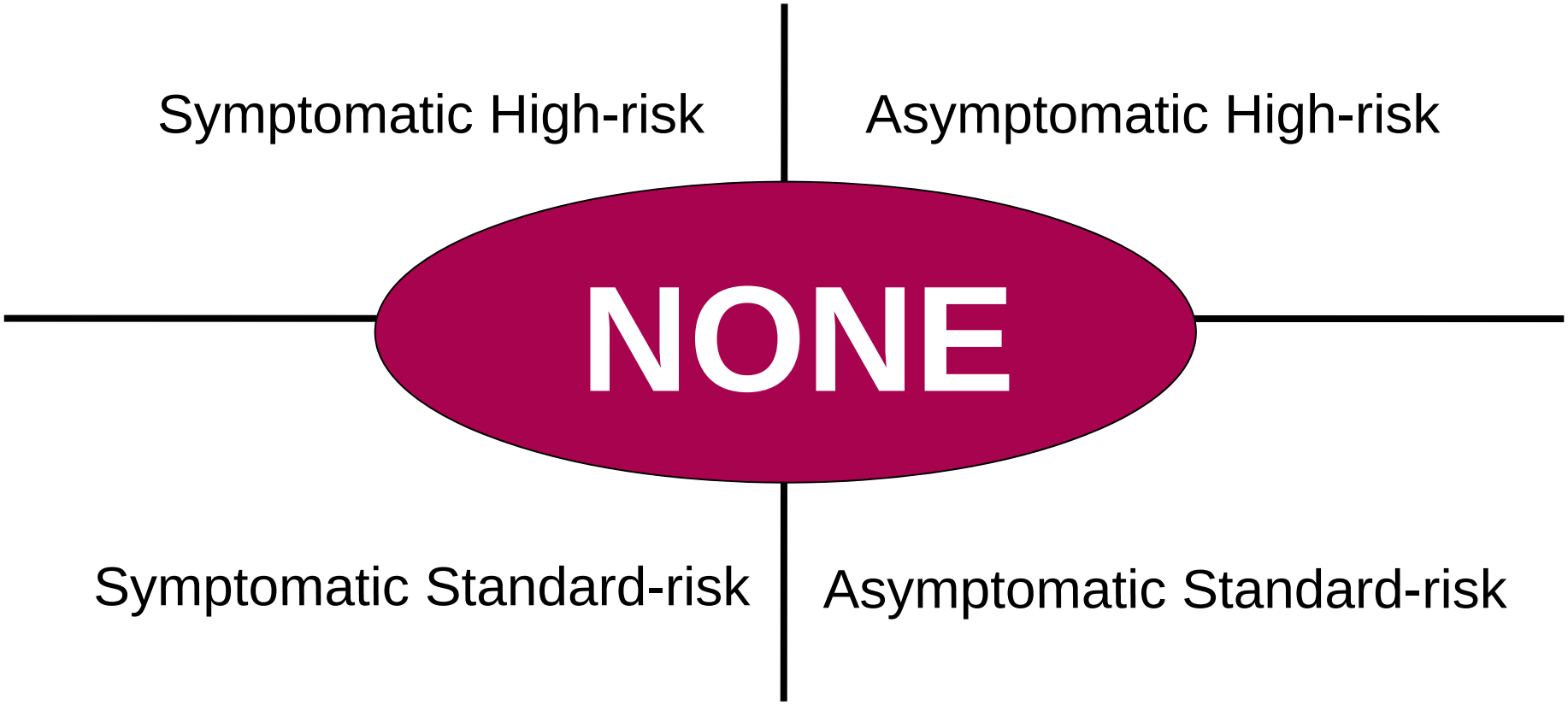
SPARCL

High-Dose Atorvastatin after Stroke or Transient Ischemic Attack

Outcome	Atorvastatin Events (%)	Placebo Events (%)	Placebo Group *P* value*	Adjusted Hazard Ratio (95% CI)	Treatment *P* Value
Cerebrovascular end points					
Stroke					
With CS	55 (11.2)	83 (16.1)	0.113	0.67 (0.47, 0.94)	0.0197
Without CS	210 (11.2)	228 (12.3)		0.90 (0.74, 1.08)	0.2413
Carotid revascularization					
With CS	16 (3.2)	37 (7.2)	<0.001	0.44 (0.24, 0.79)	0.0057
Without CS	13 (0.7)	7 (0.4)		1.83 (0.73, 4.59)	0.1980

N Engl J Med 2006;355:549-59

RCT : CAS vs. OMT for stroke prevention



In absence of “head to head” trials vs. OMT only infer ability of CAS to prevent stroke based on:

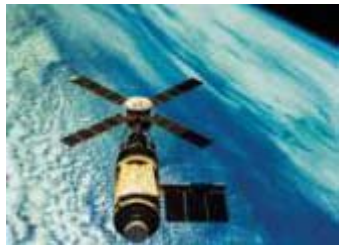
1.Registry studies of CAS

2.RCT’s comparing it to CEA

Medical Treatment

- There is a compelling evidence that modern medical therapy can mitigate risk of stroke
- It is imperative to identify which patients are best suited to OMT versus intervention, which can only be evaluated in RCT’s

SPACE 2



A randomized, controlled, open label, multi-center trial

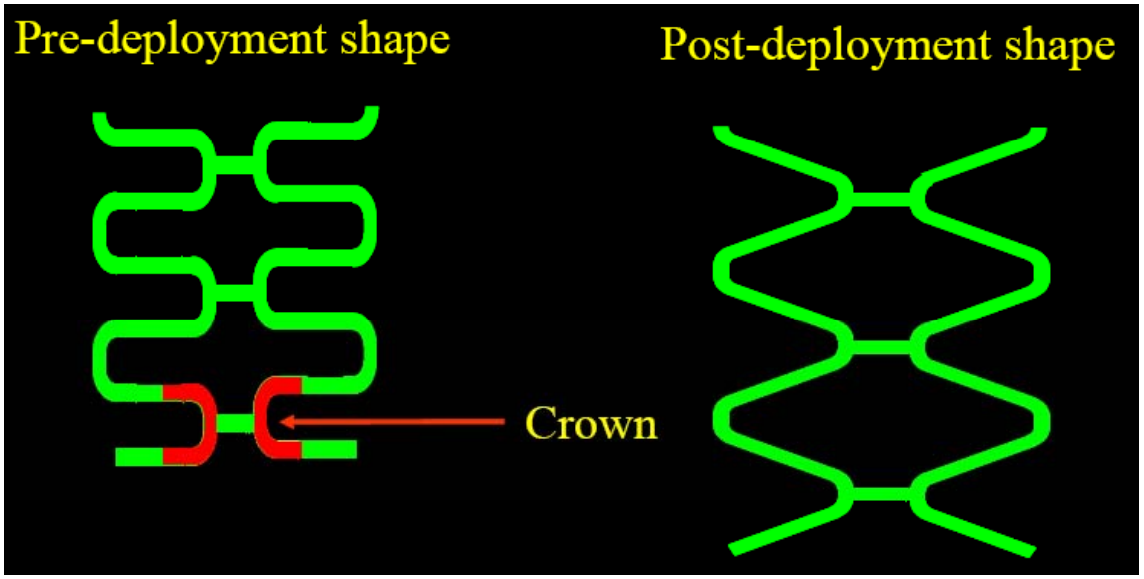
1º Endpoint: 30-Day stroke/death (all cause) plus ipsilateral ischemic stroke from 31 days to 5 years

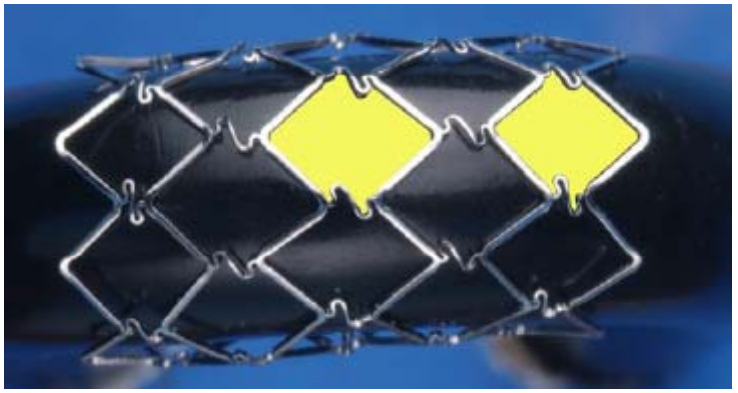
Asymptomatic Stenosis ≥50%

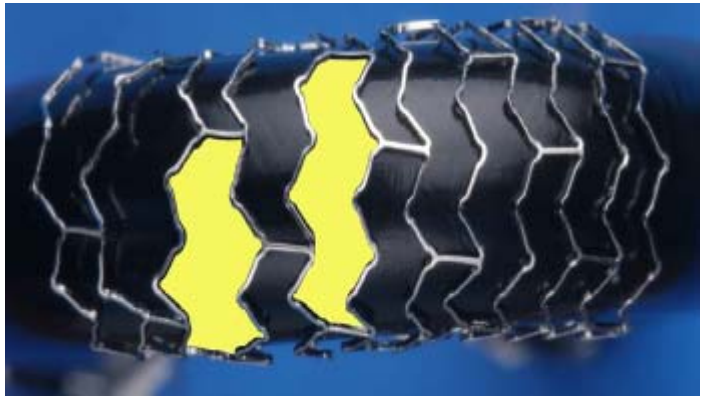
BMT	CEA	CAS
20%	40%	40%

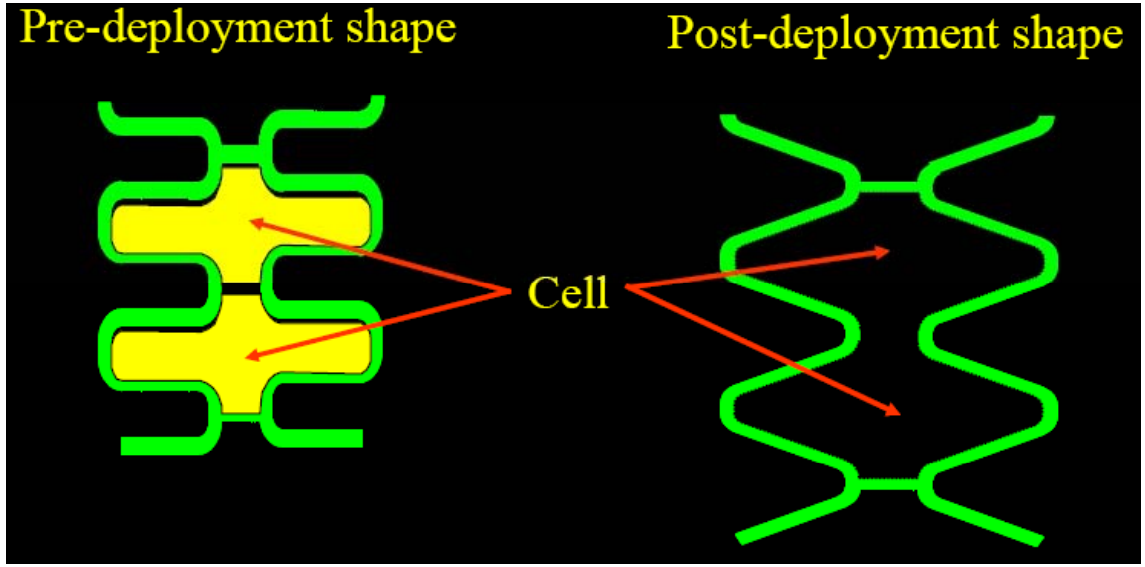
3640 patients ages 50-85 years

Stent Design Features

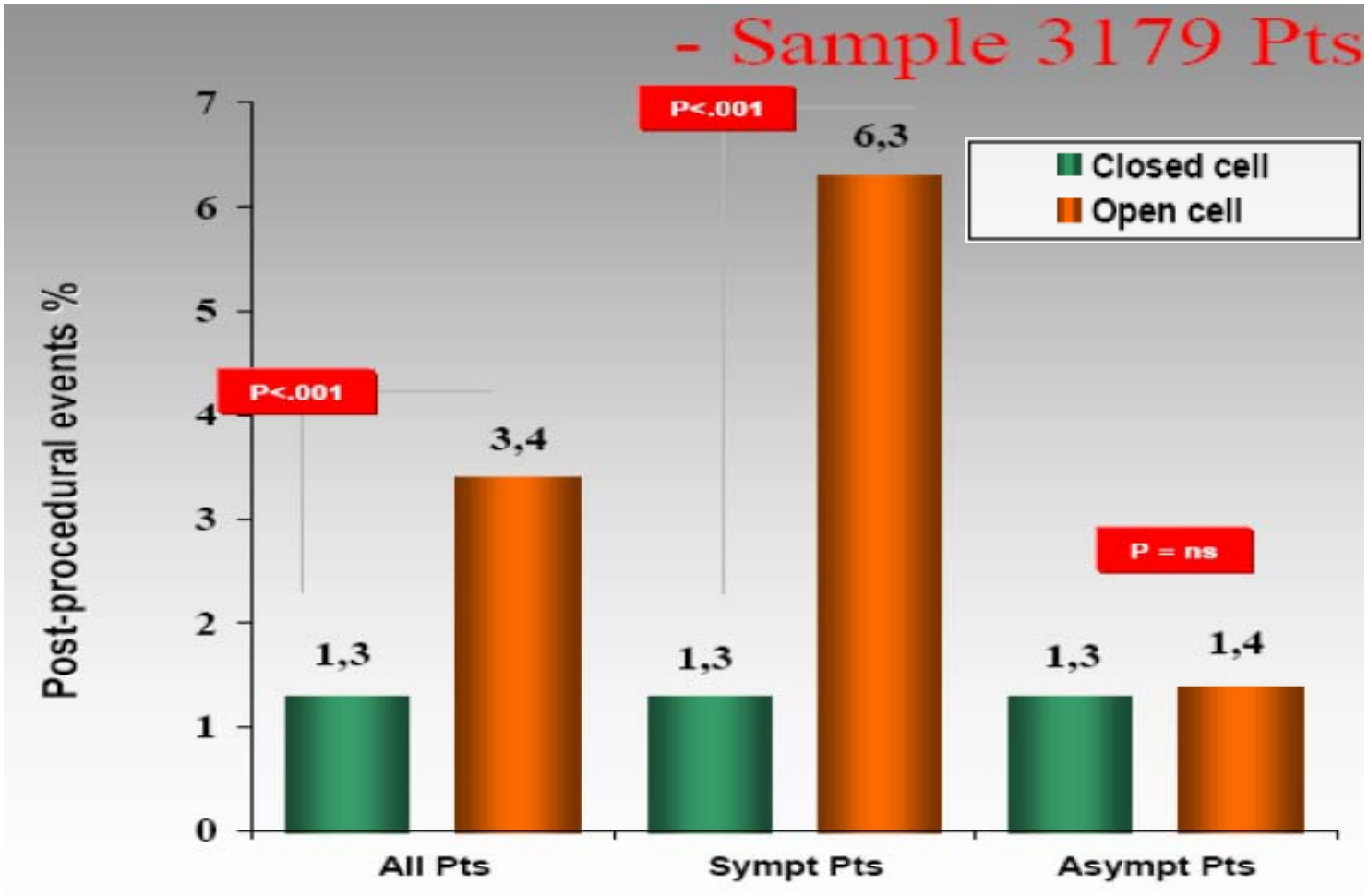








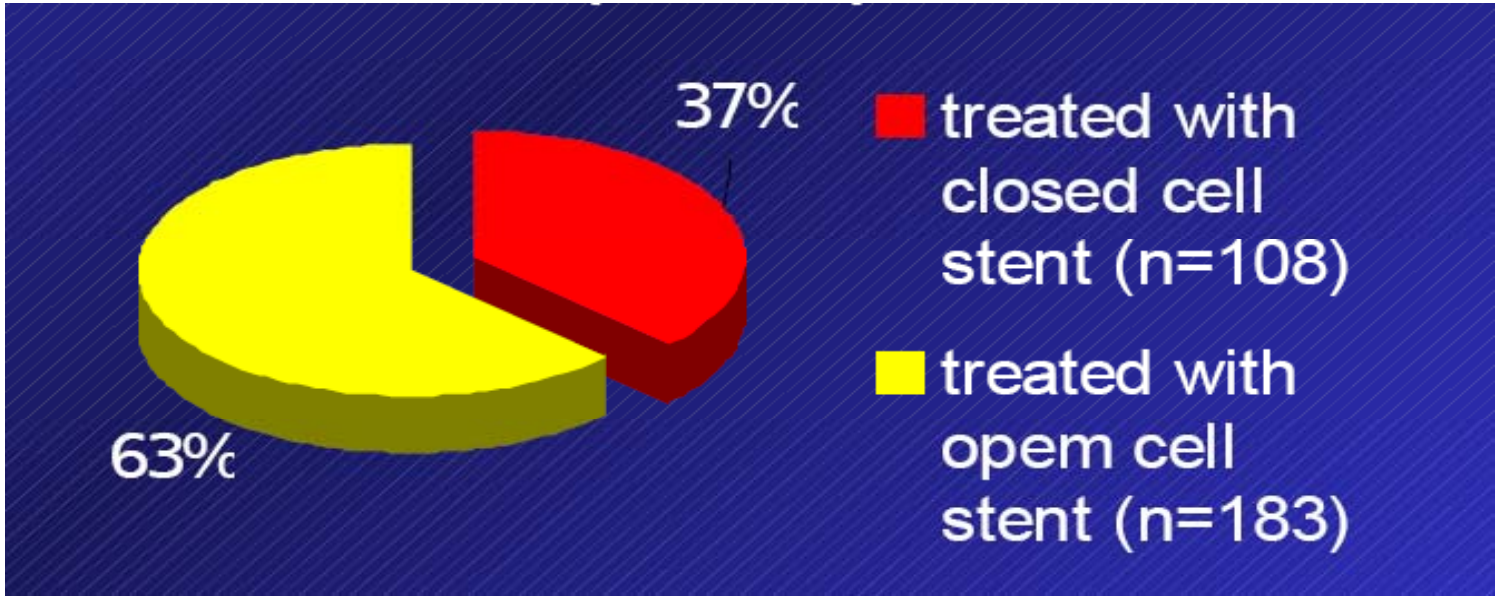
Open vs. Closed Cell Stents : Late events days 0 to 30



Bosiers et al. EJVES

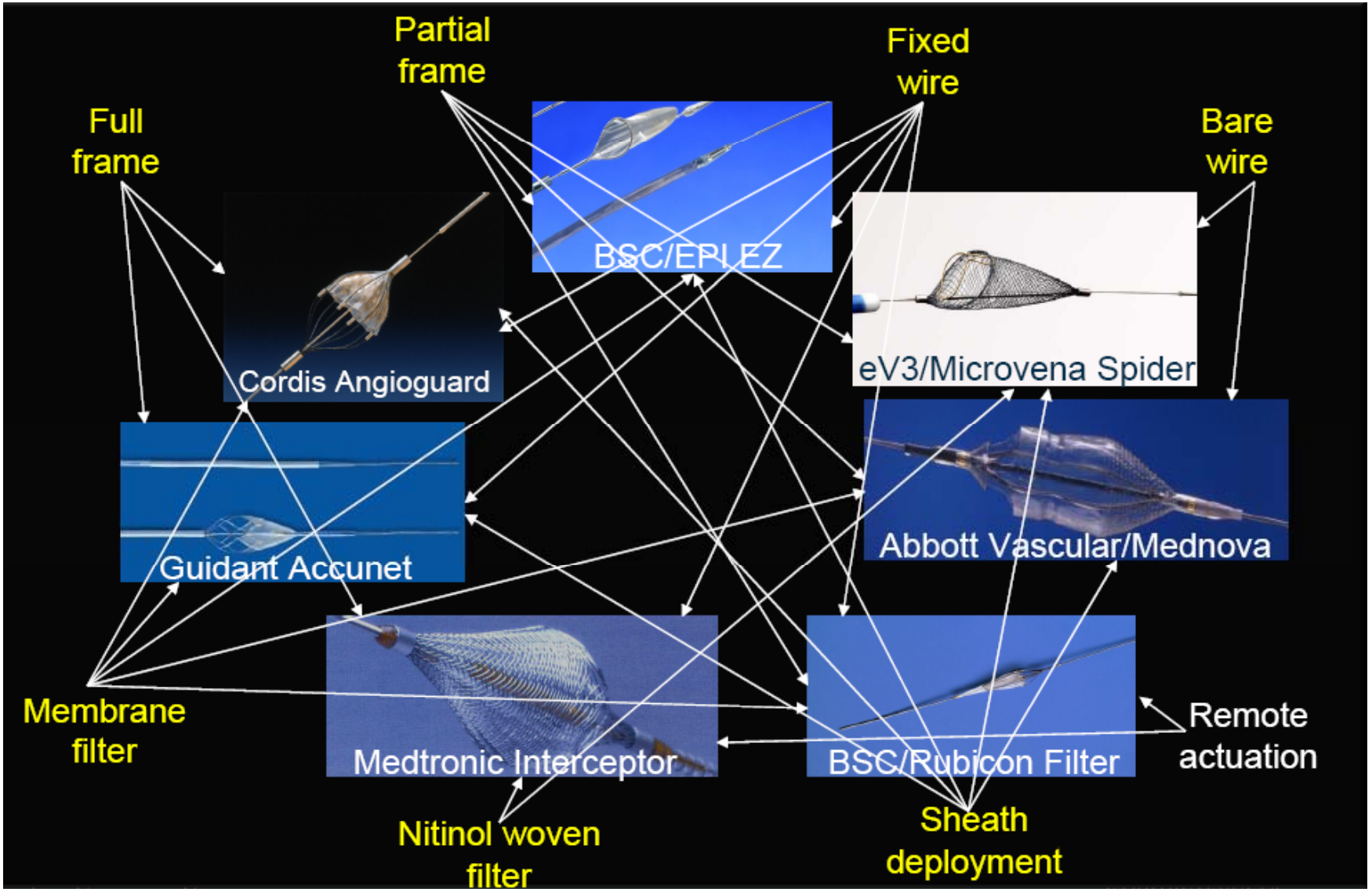
Stents for symptomatic lesions (N=291)

183 open-cell and 108 closed-cell stents



- The acute and subacute results of carotid stenting were not significantly different between open and closed cell stents.
- There is a trend towards better acute results with open cell stents in symptomatic patients.

Embolic Protection Devices



Emboli Prevention Devices

- All major centers have found >50% lower stroke rates with EPD
  - Wholey Registry: 6753 No EPD vs. 4221 w EPD
    Stroke/Death 5.3% vs.. 2.23%
  - Kastrup Meta-analysis: 2537 No EPD vs. 896 w EPD
    Stroke/Death 5.5% vs.. 1.8%
  - ICAROS: N=418 (52.4% with EPD)
    Stroke 5% vs. 2.3%
  - EVA-3S: Study protocol amended after 80 patients
    4/15 vs. 5/58 3.9 fold higher risk
- Latest generation of devices are smaller and more deliverable

A randomized trial of carotid artery stenting with and without cerebral protection

a prospective, randomized, single-center study of carotid artery stenting with or without a distal cerebral protection filter. A 1:1 scheme was used to randomize 36 carotid artery stenting procedures in 35 patients.

	Cerebral protection		
Defect	*Yes (n = 18)*	*No (n = 18)*	*P*
Any MRI diffusion defect	13 (72%)	8 (44%)	.09
Any ipsilateral diffusion defect	12 (67%)	7 (39%)	.09
Average No. of defects	6.1	6.2	NS
DW MRI defect size, mean mm^3	16.63	15.61	NS

J Vasc Surg 2008;47:760-5

A randomized trial of carotid artery stenting with and without cerebral protection

	Cerebral protection	
	Yes (n = 18)	*No (n = 18)*
Non-Q-wave MI	1	0
Hypotension	2	3
Orthostatic hypotension	1	0
Minor stroke	2	1
Major stroke	0	1
Gastrointestinal bleeding	0	1
Bradycardia (asymptomatic)	0	1
Hyperperfusion syndrome	0	1
ICA vasospasm	1	0
Femoral bleed	0	1
Retroperitoneal hematoma	0	1

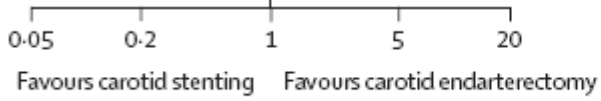
J Vasc Surg 2008;47:760-5

ICSS-MRI

New ischaemic brain lesions on MRI after stenting or CEA

Cerebral Protection Devices

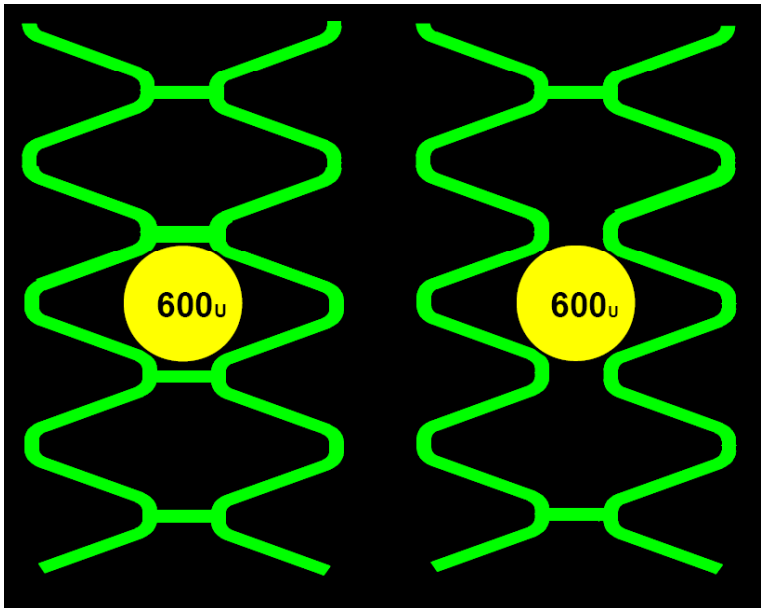
	Carotid stenting		Carotid endarterectomy		OR (95% CI)	p
	DWI positive, n (%)	Total, n	DWI positive, n (%)	Total, n		
Centre policy of using cerebral protection devices						
No	25 (34)	73	10 (16)	61	2·70 (1·16–6·24)	0·019
Yes	37 (73)	51	8 (17)	46	12·20 (4·53–32·84)	
Total	**62 (50)**	**124**	**18 (17)**	**107**	**5·21 (2·78–9·79)**	

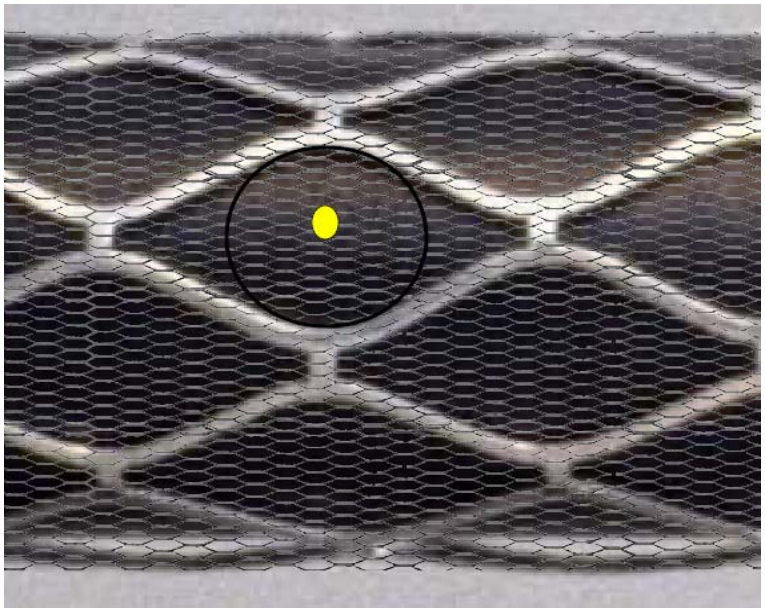


Lancet Neurol 2010; 9: 353–62

Most embolic particles are less than 100µm

Neither Stents nor Filters Control these Emboli





Conclusions

- With the advent of CAS, the management of the patient with carotid disease is in evolution.
- For symptomatic patients, CEA is currently the best option.
- CAS should be offered to symptomatic patients, if they are at high risk for CEA, in high-volume centers with documented low peri-procedural stroke and death rates.
- It is advisable to offer CAS in asymptomatic patients only in high-volume centres with documented low peri-procedural stroke and death rates.
- Need additional data comparing CAS to contemporary medical therapy in both high and standard-risk patients (SPACE2 etc)
- The effect of stent design and EPD role should be defined.

Thank you for attention !

Treatment options influenced by medical co-morbidities

- CEA can be performed in high-risk patients with cardiac, stroke and death rates well within accepted standards [B].
- For asymptomatic patients at ‘extremely’ high risk (several medical comorbidities at the same time), best medical treatment might be the best option instead of invasive intervention [C].
- CAS is associated to higher risk of embolisation in octogenarians [B]. CEA is performed in octogenarians without increased risk of embolisation and with an acceptable rate of neurological and cardiac complications [C].
- CAS should not be offered to asymptomatic ‘high-risk’ patients if the peri-interventional complication rate is >3% [C].

Treatment options according to vascular and local anatomical features

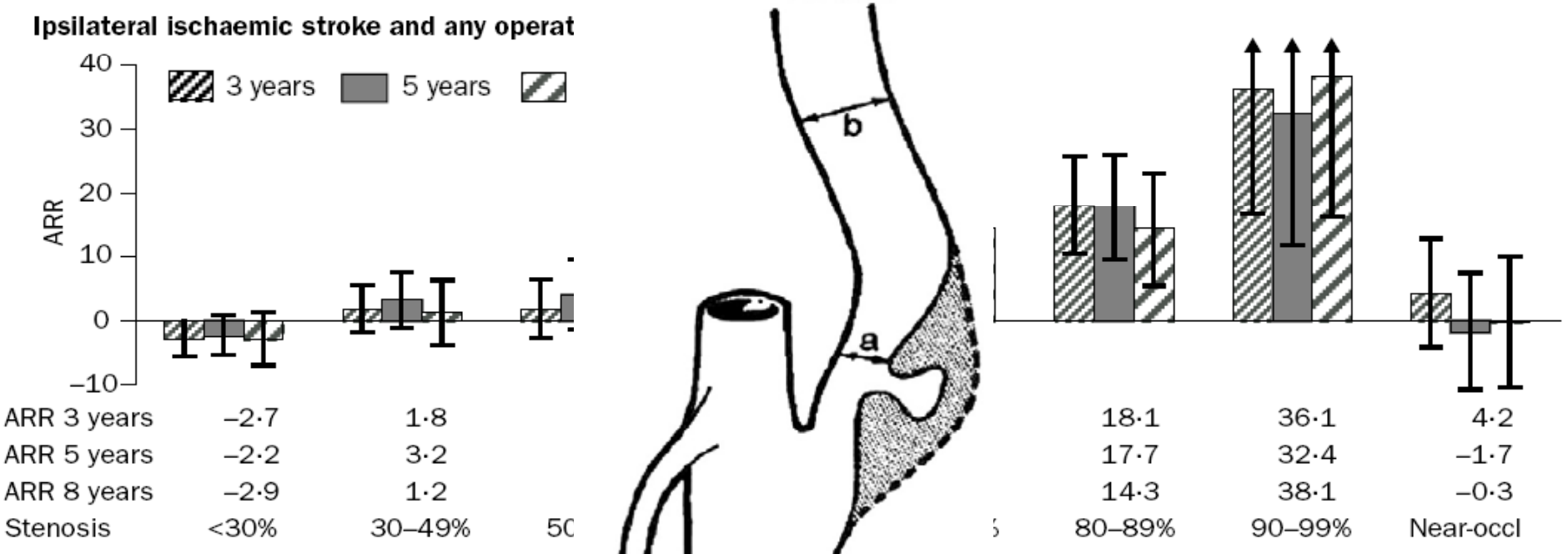
- CAS is indicated in case of contralateral laryngeal nerve palsy, previous radical neck dissection, cervical irradiation, with prior CEA (restenosis), with high bifurcation or intracranial extension of a carotid lesion, provided that the peri-interventional stroke or death rate is higher than that accepted for CEA [C].
- CAS is not advisable in patients with extensive aortic and supra-aortic vessel plaques, calcification and tortuosity, unless performed in high-volume centres with documented low peri-procedural stroke and death rate [C].

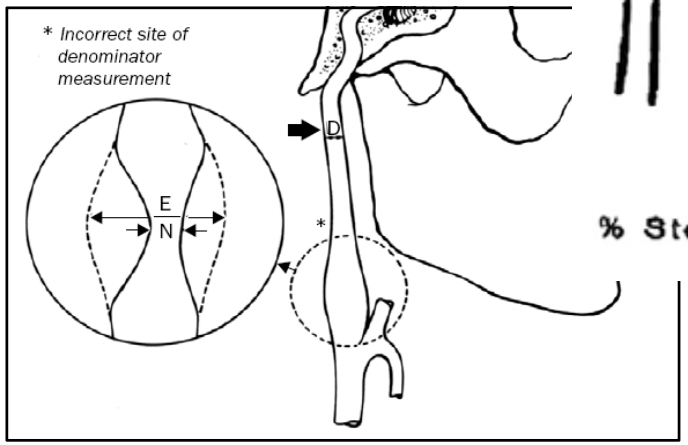
Treatment options
according to carotid plaque morphology

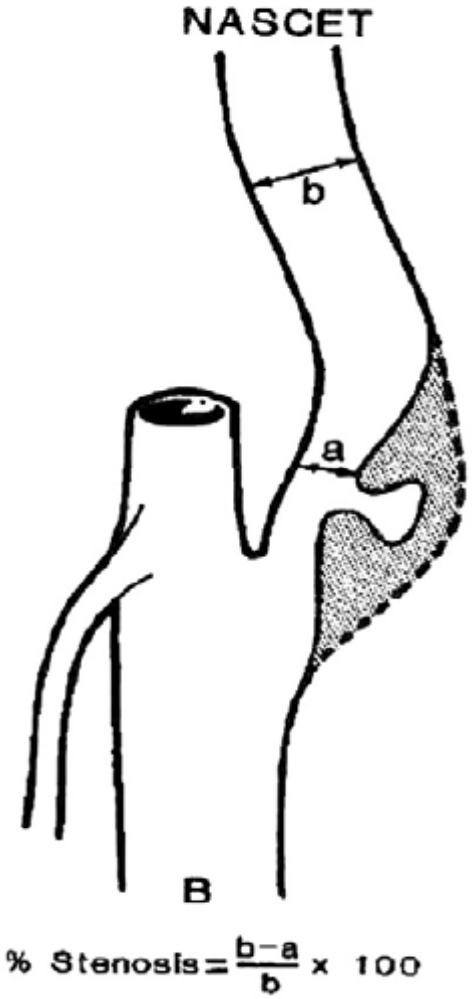
- Plaque morphology should be assessed in all cases before invasive treatment [B].
- The plaque at risk of peri-procedural embolisation should be identified by validated imaging (GSM, etc.) or other diagnostic techniques such as biological markers [C].
- Critical issues
- The brain protection device (BPD) used during the endovascular procedure cannot protect from late embolisation. The selection of carotid plaques at lower embolic potential is essential to reduce late complications.
- There is no randomised trial demonstrating the superiority of one stent compared to others (tapered vs. straight, open- vs. closed cell) in the reduction of neurological complications.

CEA for Symptomatic Carotid Stenosis

North American Sym ndarterectomy Trial (NASCET), Eupo ery Trial (ECST)







ET and VA309
osis

Lancet 2003;361:107–16

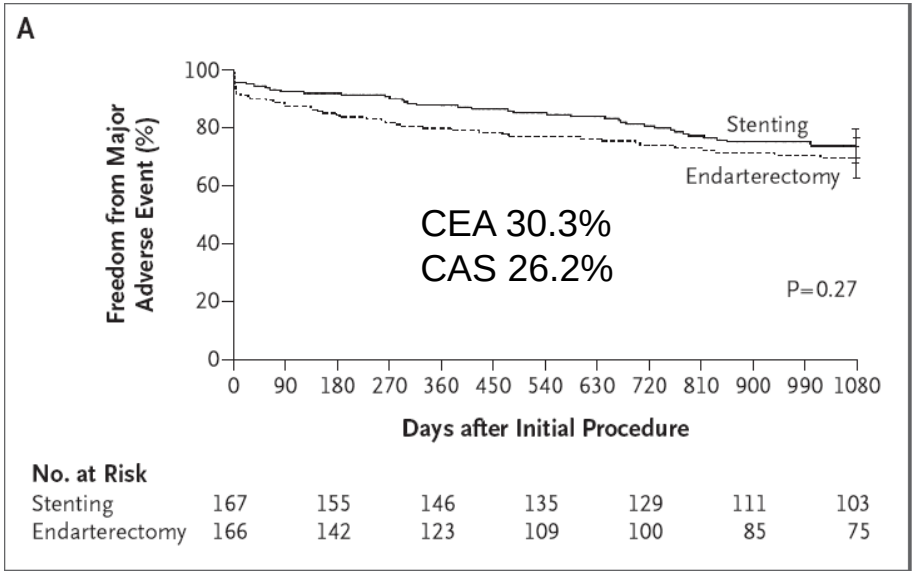
High Risk in SAPPHIRE

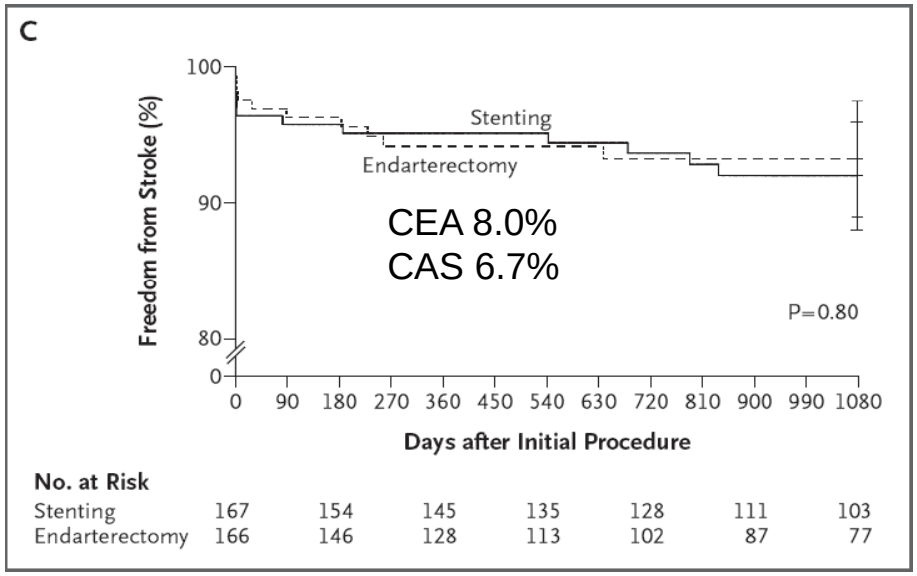
- Congestive heart failure (New York Heart Association class III/IV) and/or a known severe left ventricular dysfunction
- Open heart surgery needed within 6 weeks
- Recent MI
- Unstable angina (Canadian Cardiovascular Society Class III/IV)
- Severe pulmonary disease.

SAPPHIRE

Long-Term Results of CAS versus CEA in High-Risk Patients (non-inferiority)

Randomized trial comparing CAS with the use of an EPD to CEA in high-surgical risk 334 patients.a symptomatic at least 50% an asymptomatic at least 80% stenosis





MAE : death, MI, or stroke within 30 days or death or ipsilateral stroke between 31 & 1080 days
Stroke : stroke within 30 days or ipsilateral stroke between 31 days and 1080 days

Among symptomatic patients, the rates of the composite end-point were 32% and 21.7% in the CAS and CEA groups, respectively

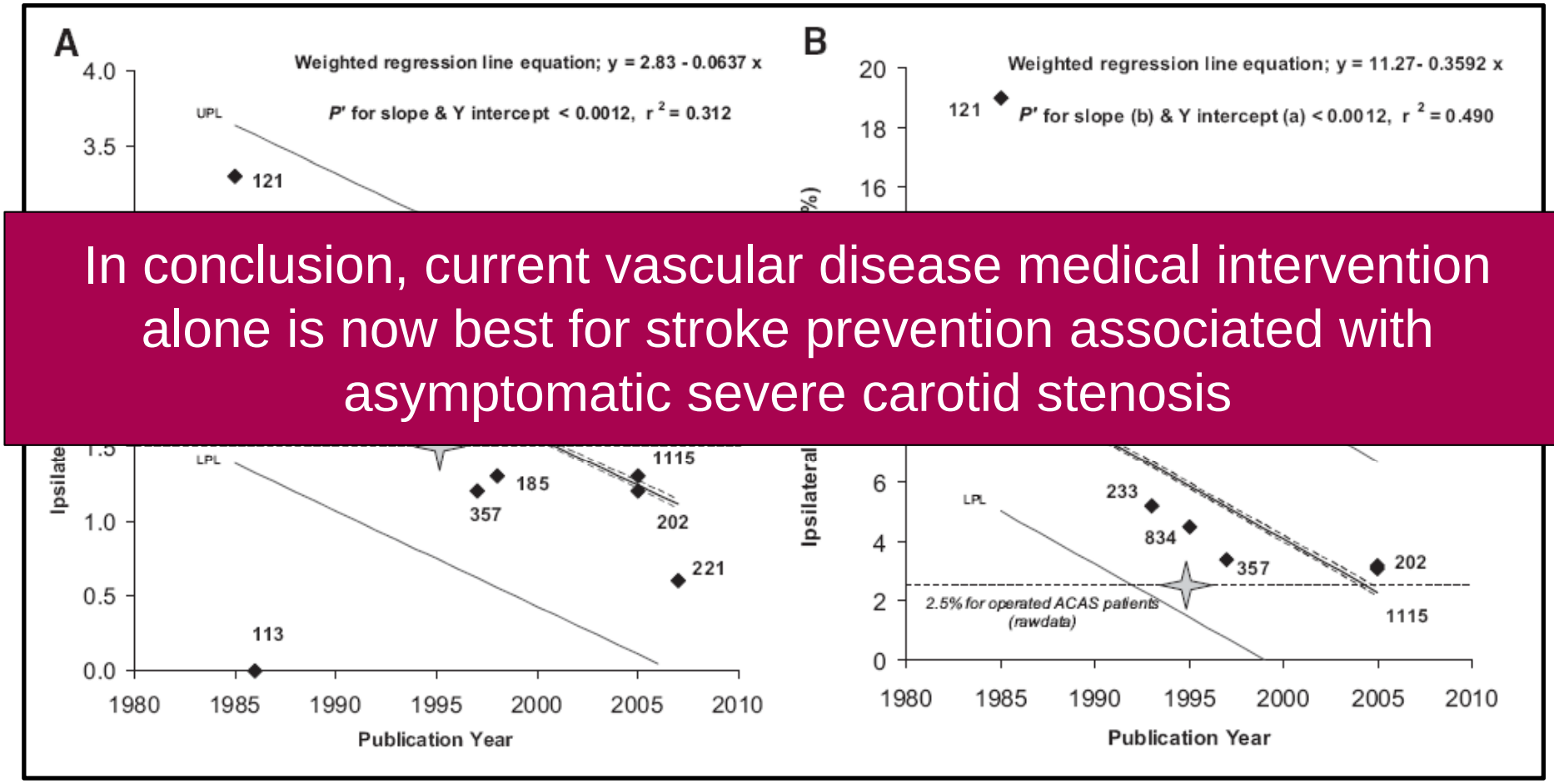
N Engl J Med 2008;358:1572-9

EVA 3S : Conclusions

- Prototypical low operator experience multi-center trial
- Outcomes for CAS in EVA-3S for symptomatic standard risk patients are higher than the contemporary cohorts
- Nevertheless long term outcomes for stroke prevention demonstrate equivalence with CEA

Medical (Nonsurgical) Intervention Alone Is Now Best for Prevention of Stroke Associated With Asymptomatic Severe Carotid Stenosis

Results of a Systematic Review and Analysis



In conclusion, current vascular disease medical intervention alone is now best for stroke prevention associated with asymptomatic severe carotid stenosis

Stroke 2009;40:e573-83