Medicare Evidence Development
and Coverage Advisory Committee
January 25, 2012

Management of Carotid Atherosclerosis

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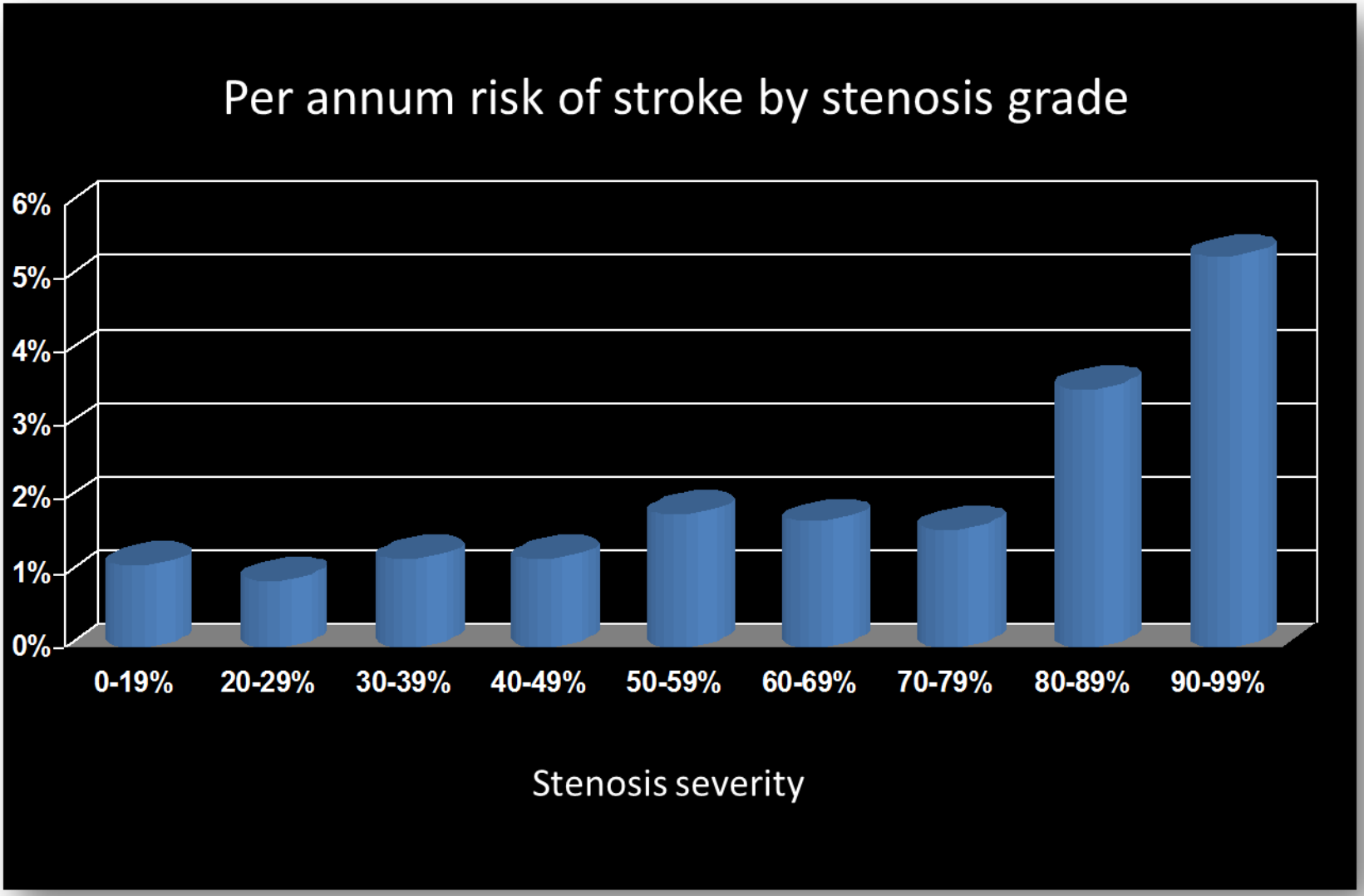
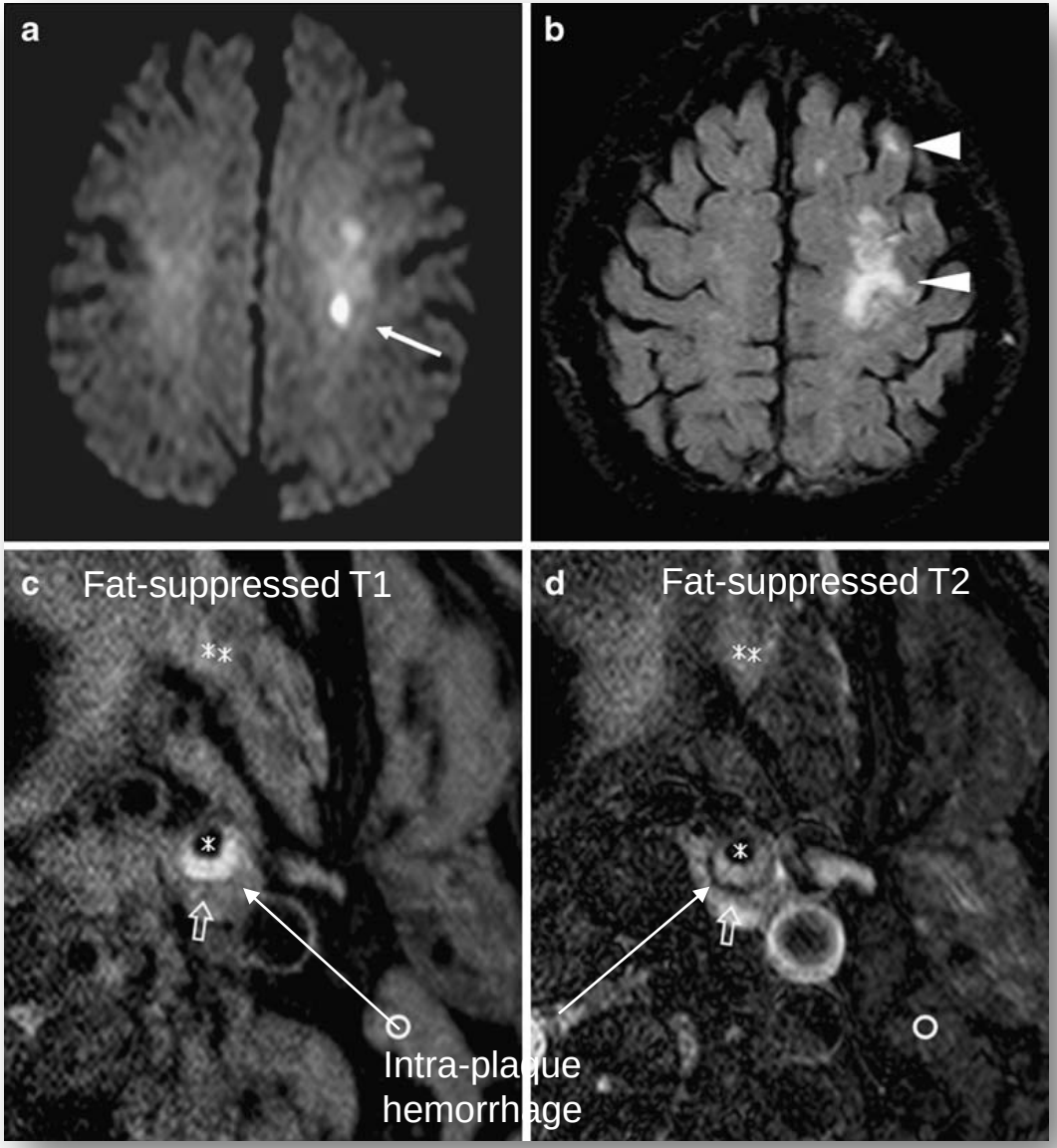
Can patients with carotid stenosis be identified as at risk for stroke?



Plaque characterization:
In search of the “loaded gun”

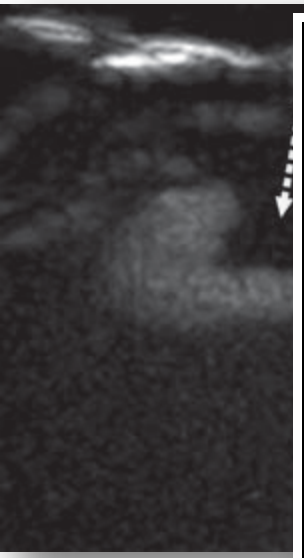


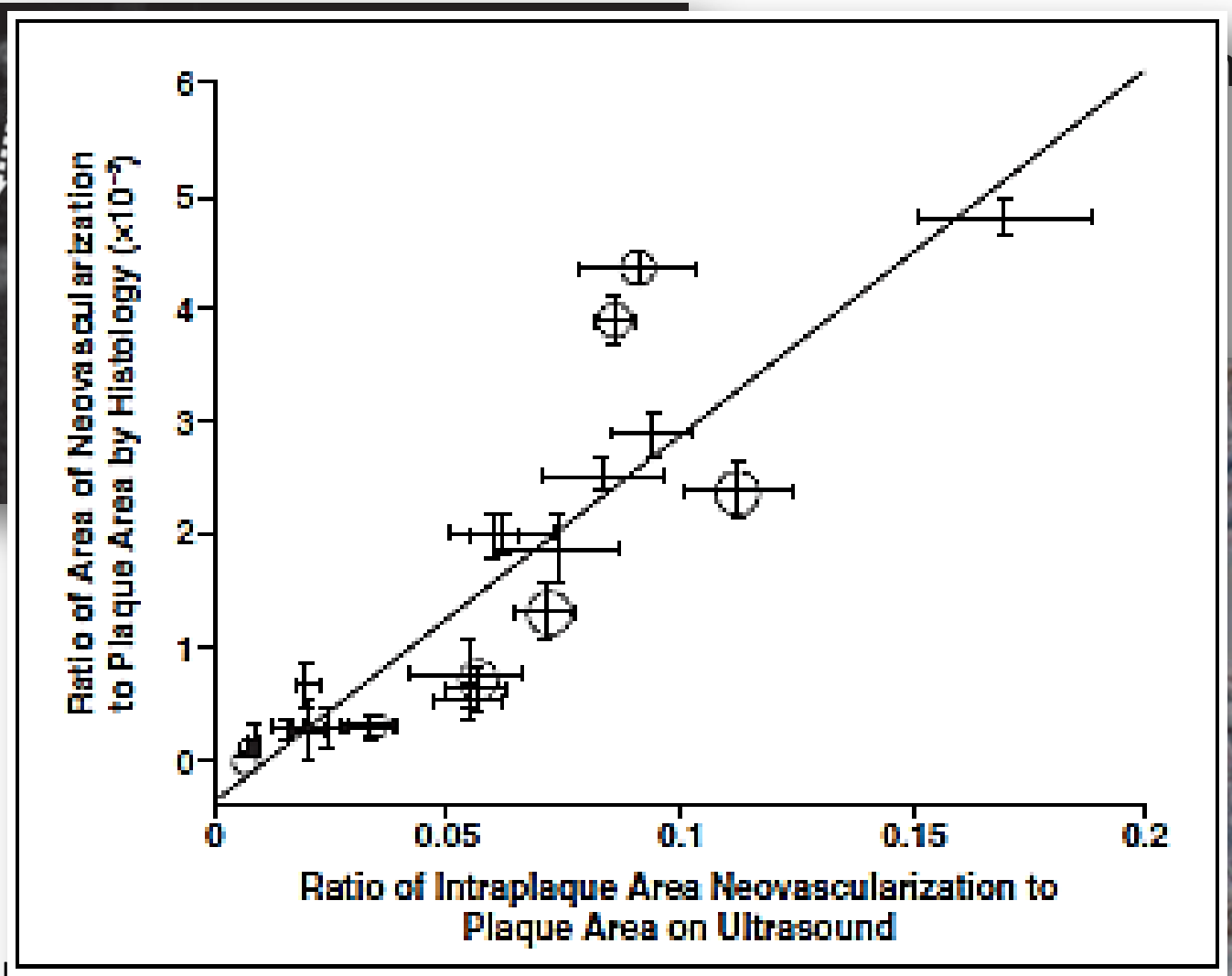
Potential importance of carotid plaque morphology

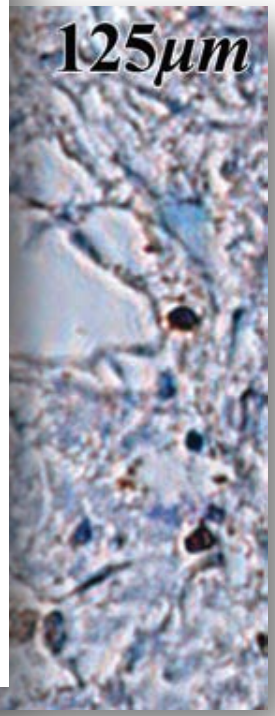
- Key factors in advanced plaque relating to activity
  - Condition of the fibrous cap/TCFA
  - Size of the necrotic core/dynamism
  - Degree of intra-plaque hemorrhage/neogenesis
  - Extent of inflammatory activity/apoptosis/proteolysis

- May have relevance in:
  - Natural history of plaque and stroke
  - Impact of medical therapy
  - Selecting the at-risk asymptomatic patient for revascularization, and *identifying the low risk patient*
  - Selecting revascularization method

Contrast-enhanced ultrasound correlates with histology

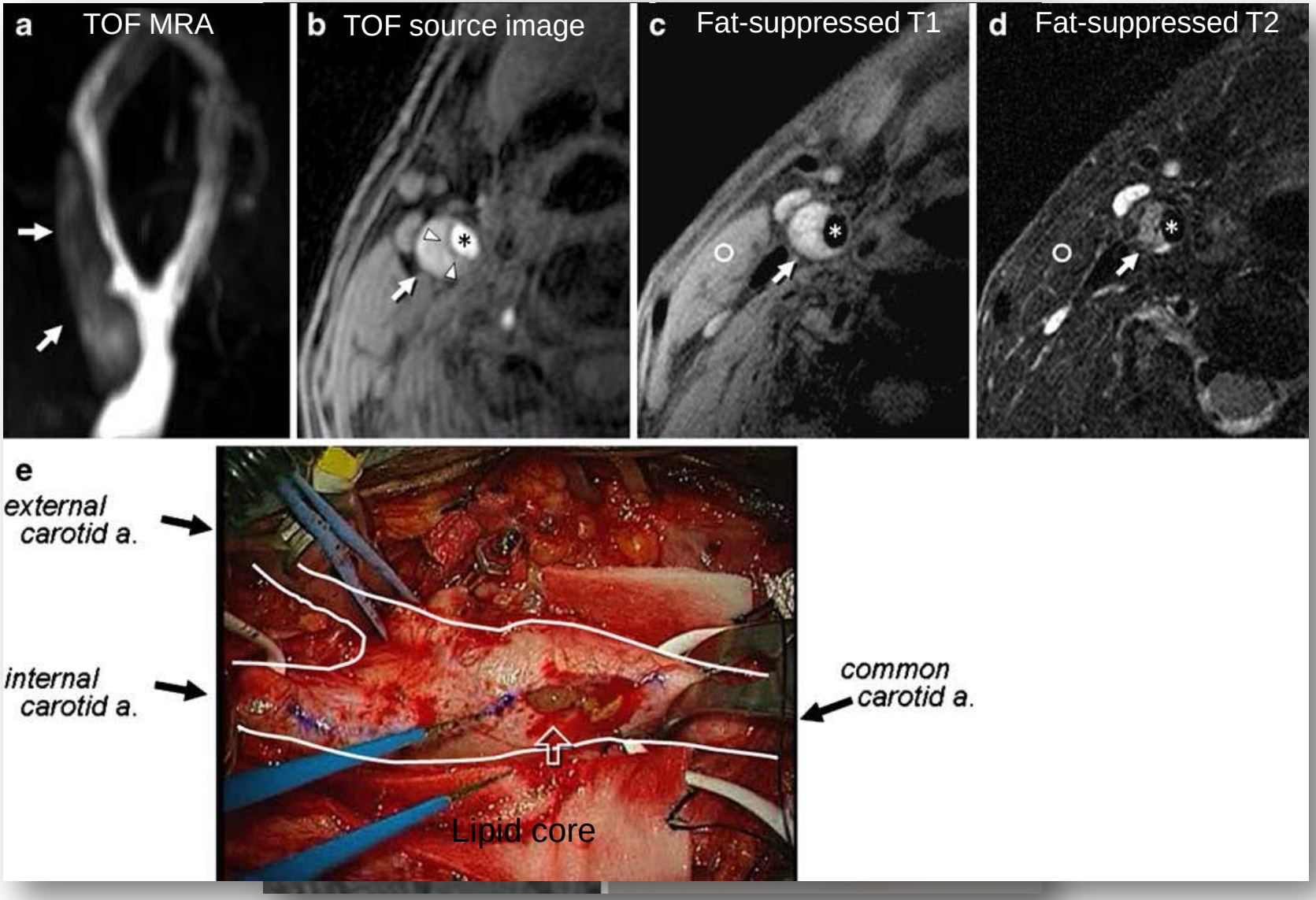






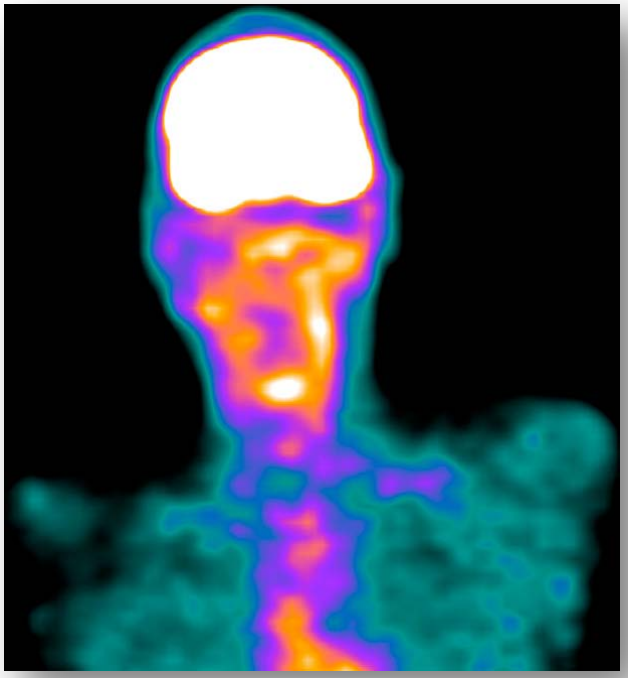
Hoogi A et al. AJ

MRI plaque characterization



Watanabe Y et al. Neuroradiology (2010) 52:253–274

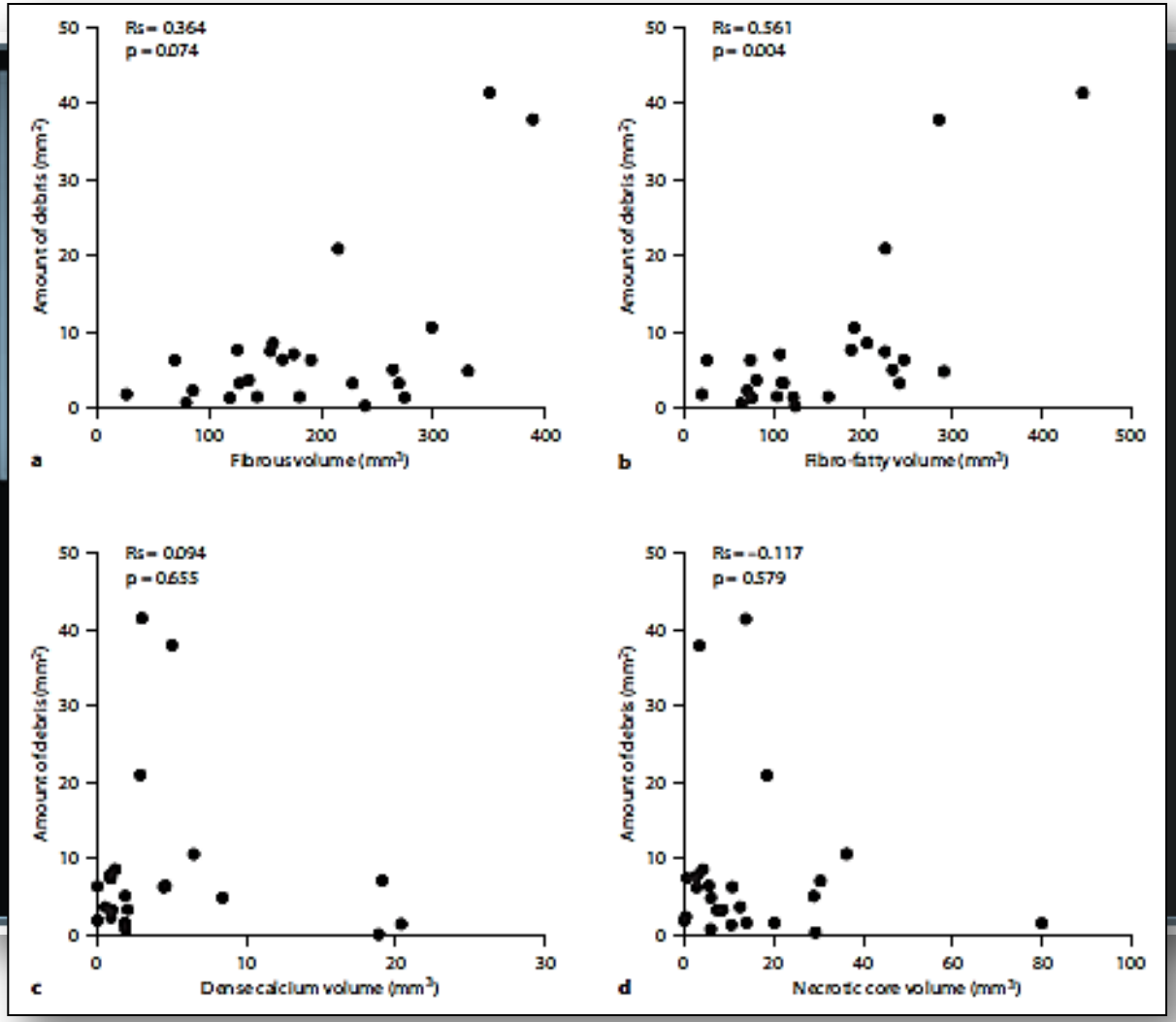
Assessment of inflammation: ^{18}F-FDG (Fluorodeoxyglucose) PET



Coronal view of a 50-70% symptomatic stenosis of the internal carotid artery on the left side in a 77-year-old male patient as shown by FDG-PET-CT imaging.

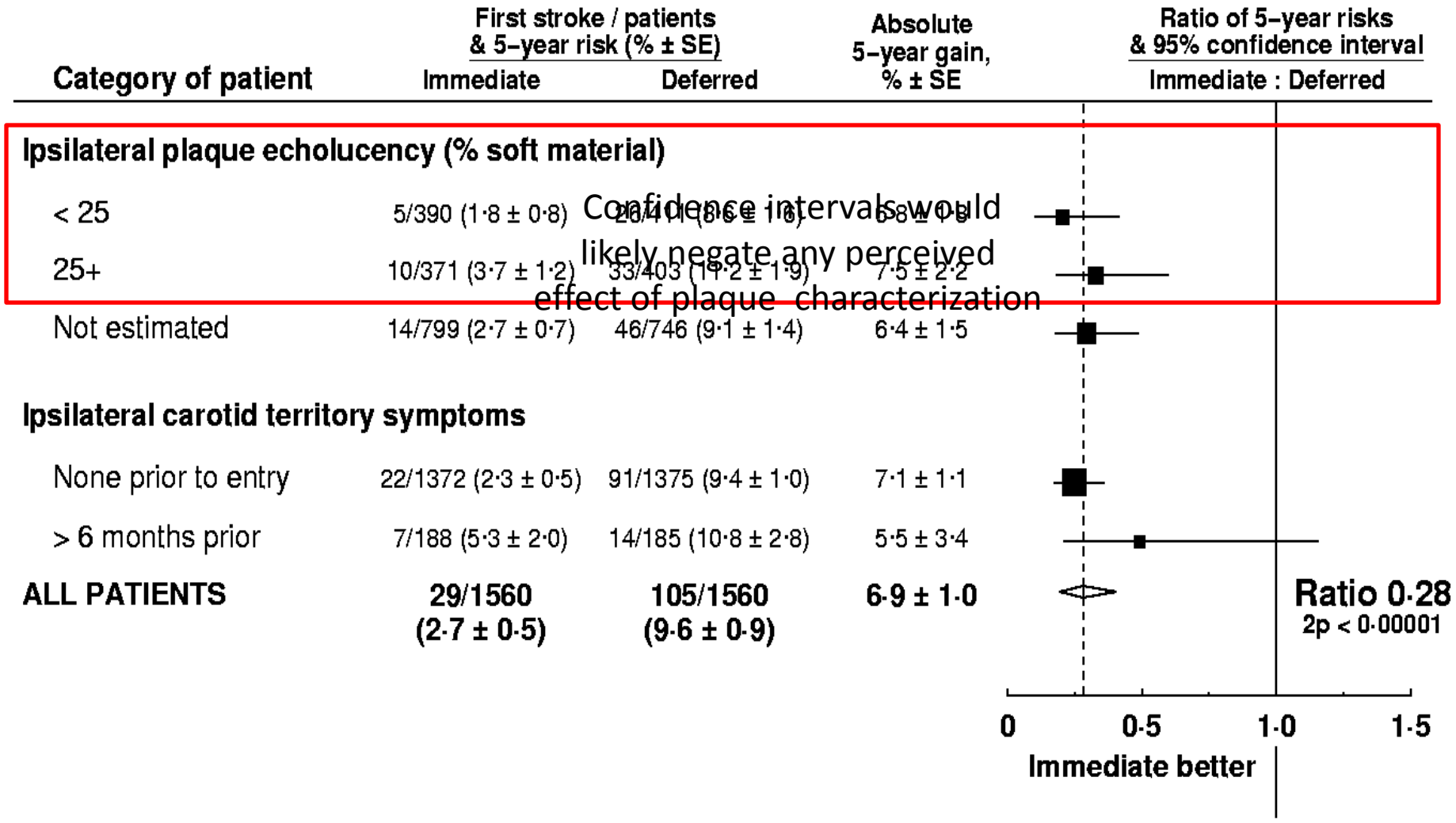
Hermus L et al. Eur J Vasc Endovasc Surg (2010) 39, 125e133

Virtual histology has a weak correlation with captured CAS debris



Inglese L et al. J Cardiovasc Surg 2009;50:735-44
Matsumoto S et al. Cerebrovasc Dis 2010;29:468–475

Plaque echogenicity not predictive outcomes in asymptomatic patients

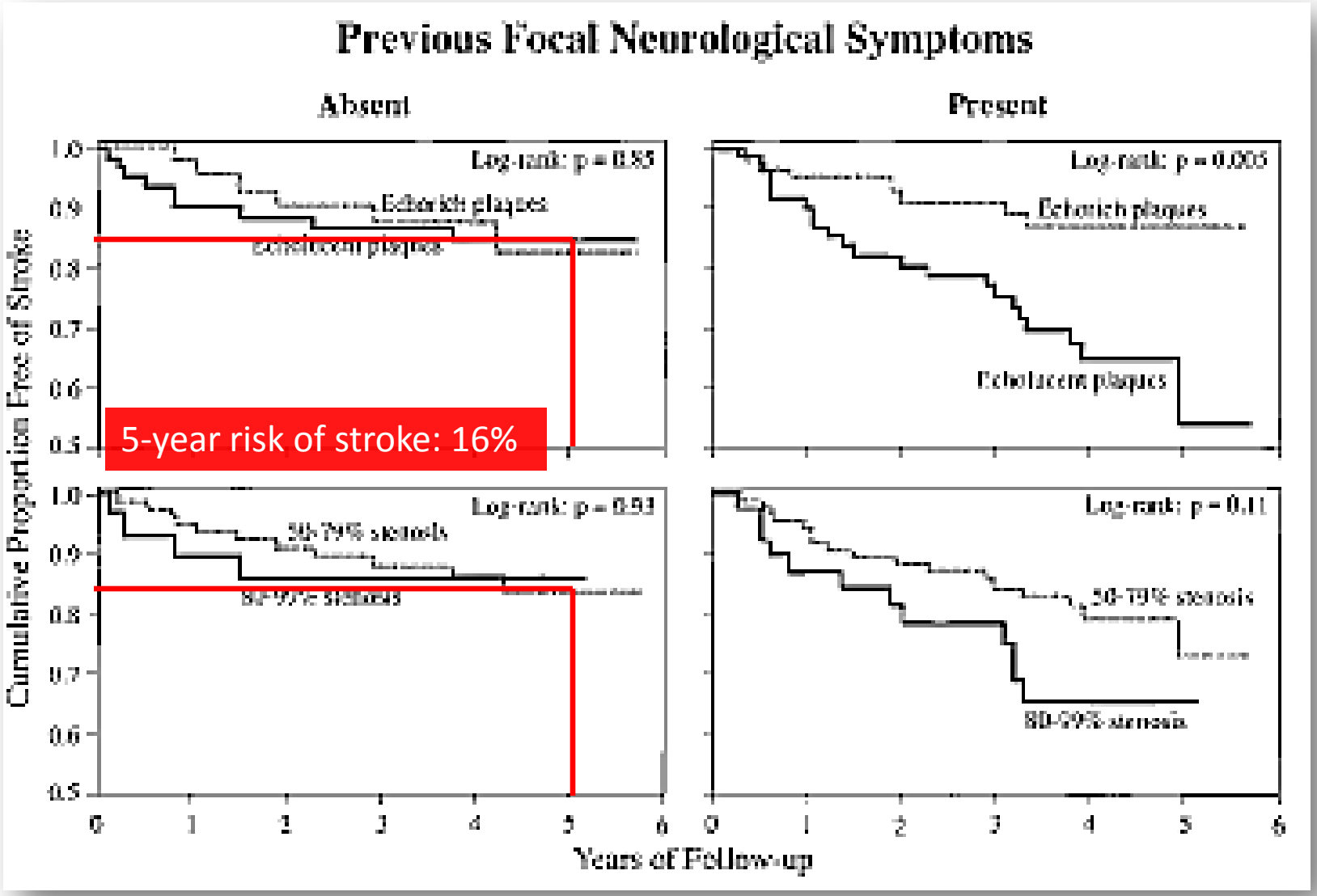


Confidence intervals would likely negate any perceived effect of plaque characterization

ACST Collaborative group, LANCET 2004;363:1491-502.

Abu Rahma AF et al., J Vasc Surg 2002;36:437-42.

Plaque echogenicity not predictive outcomes in asymptomatic patients



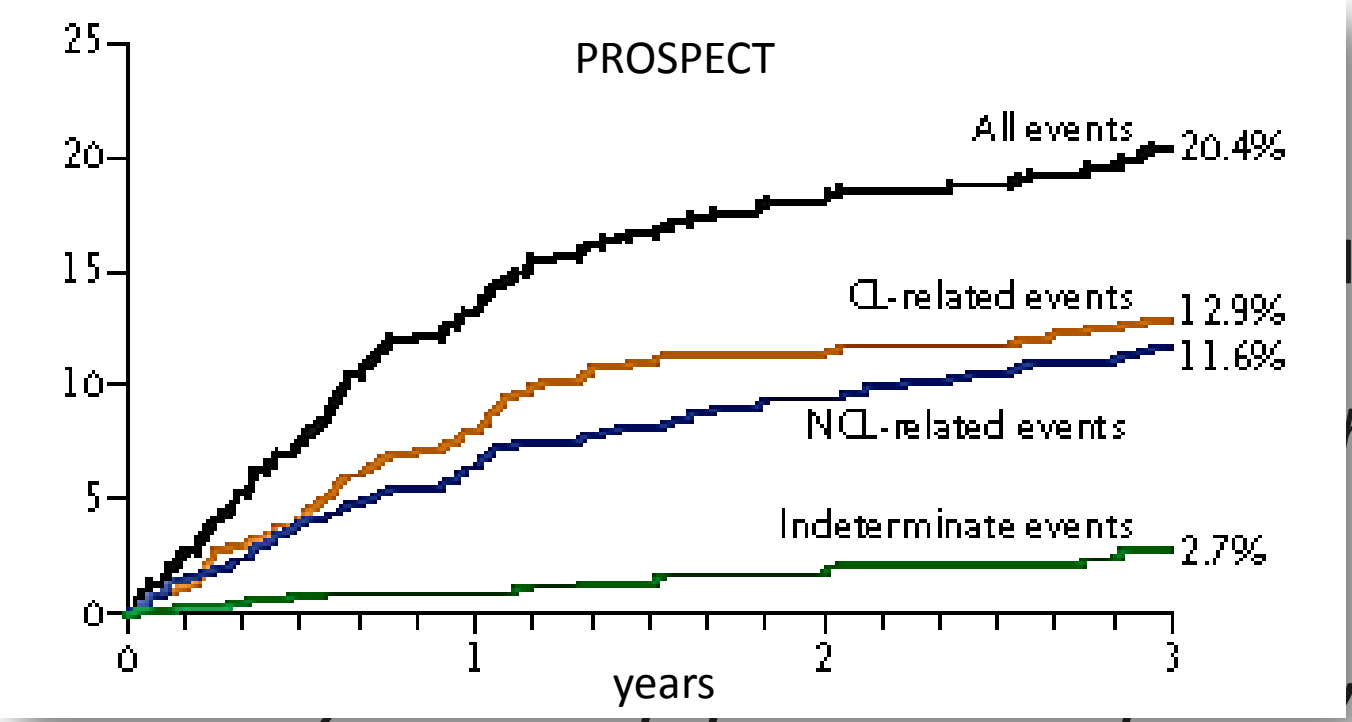
Gronholdt M-LM et al. Circulation 2001; 104: 68-73.

Carotid stenosis progression predicts stroke

Study	Follow-up Duration (Yrs.)	Rate of Ipsilateral TIA/Stroke	
		Disease Progression (to >80%)	No Disease Progression
Roederer et al.	3.0	46%	1.5%
Mansour et al.	3.7	37.5%	4.2%
Mackey et al.	3.6	19.2%	2.9%
Muluk et al.	2.3	21.0%	11.9%

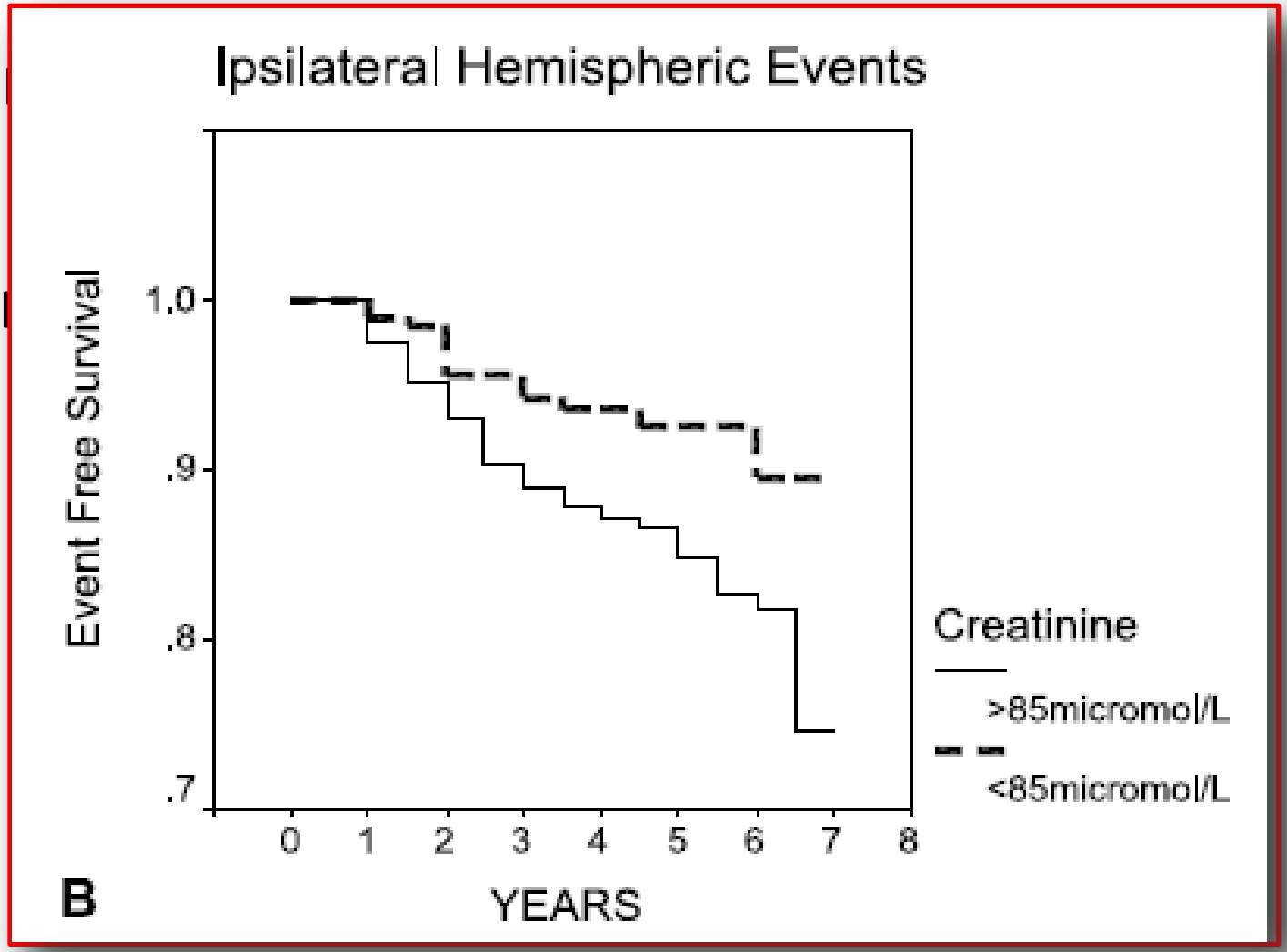
Perspectives on plaque characterization and stroke event prediction

- In asymptomatic carotid stenosis, per annum rates of stroke events either with natural history (~2%-4%) or post-CEA or CAS (1.0%-1.5%) low
  - PR
- Any ac linical utility
  - *Hig hin a cli*
- ***There e data to drive decision-making based on advanced plaque characterization in asymptomatic patients***



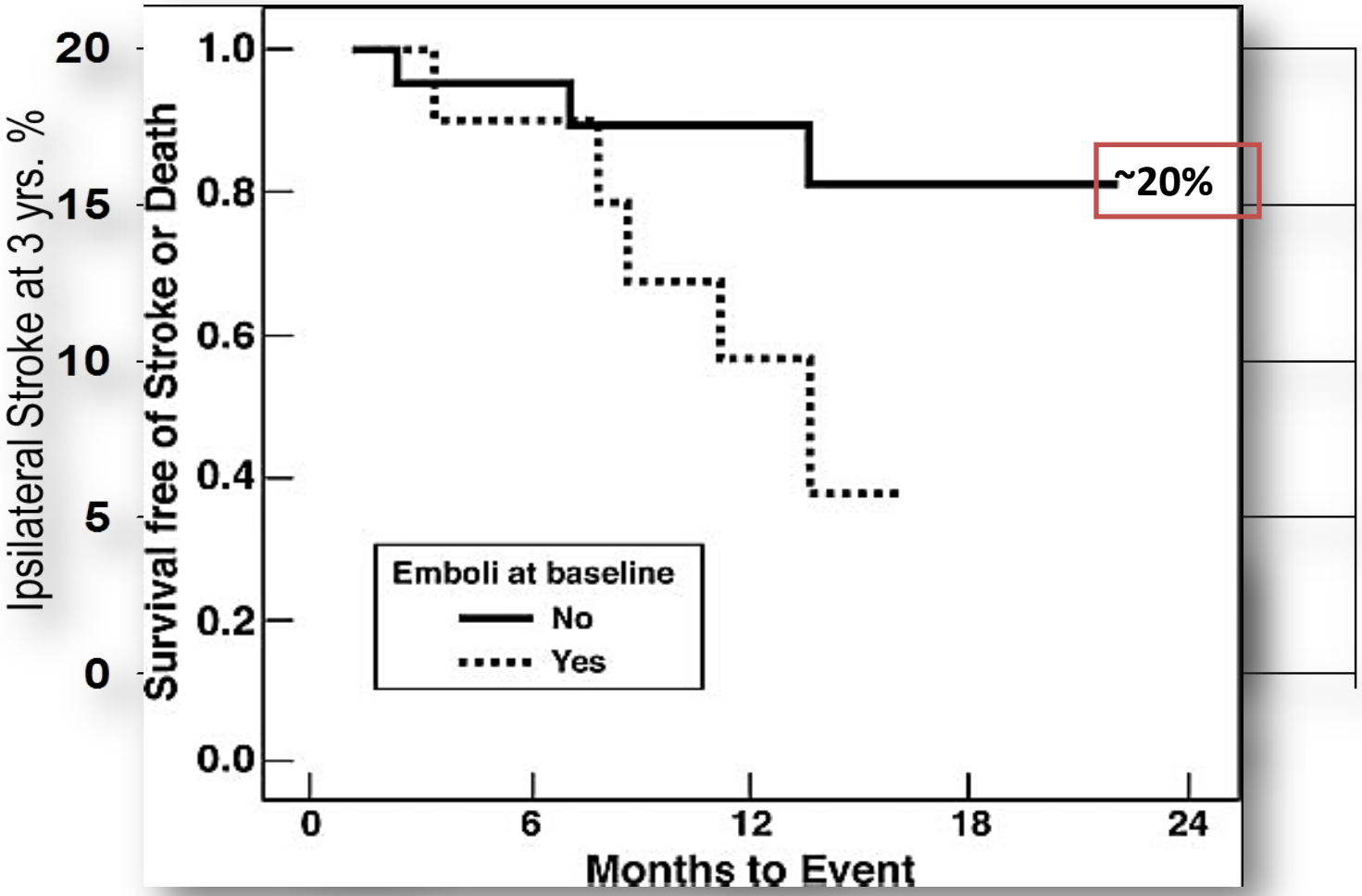
Clinical predictors of high(er) stroke risk in carotid stenosis

- Co
- Re



Eur J Vasc Endovasc Surg 2005;30:275-84

Intracranial signaling:
Asymptomatic infarction on CT scans identifies a high(er) risk group



Tegos T J et al. Int Angiol. 2001 Jun;20(2):110-7

Spence JD et al. *Stroke*. 2005;36:2373-2378

Intracranial signaling: Cerebrovascular reserve predicts stroke incidence in small pilot studies

Study	ICA stenosis	Method	Sample Size	***Annual Stroke Risk (%)***
Yamauchi 1992	>70%	PET	40	57
Gur 1996	>70%	TCD	44	10.5
Vernieri 1999	Occlusion	TCD	42	11.9
Silvestrini 2000	>70%	TCD	94	13.9
Marcus 2001	>70%	TCD	59	3.8
Marshall 2003	>80% or Occlusion	TCD	35	20

Carotid stenosis remains the most relevant and reliable predictor of stroke outcomes

TABLE 2. Unadjusted Cumulative 5-Year Risks of Vascular Events by Carotid Plaque Characteristic

	N	5-Year IS Risk	N	5-Year MI Risk	N	5-Year VD Risk	N	5-Year Combined Risk
No plaque	17	1.3%	23	2.0%	34	2.2%	62	5.0%
Any plaq								10.4%
Number								
1 plaq								5.7%
>1 pl								13.5%
Surface								
Regula								9.7%
Irregul								16.8%
Stenosis								
<40%								9.3%
40–60								23.0%
>60%								35.8%
Location								
Internal carotid artery/BIF only	48	3.4%	67	4.1%	84	4.5%	158	9.6%
Common carotid artery	4	2.6%	12	11.3%	16	14.0%	26	22.5%

Surface			
Regular	42	3.0%	68
Irregular	10	8.5%	11
Stenosis			
<40%	45	3.2%	64
40–60%	2	3.0%	7
>60%	5	13.4%	9

BIF indicates bifurcation.

Stroke. 2006 Nov;37(11):2696-701.

Conclusions regarding risk stratification of patients with asymptomatic carotid stenosis

- Additional stroke risk may predicted by:
  - Stenosis severity
  - Stenosis progression
  - Cerebrovascular reserve
  - Plaque characteristics

  Asymptomatic emboli

  Co-morbidities:

  -Renal insufficiency

  -Contralateral symptoms

- However randomized control studies to date have selected patients based on stenosis severity and symptom status, and have excluded co-morbidities.
  - Other potential predictors of increased risk have not been systematically studied

- ***Most importantly, the concept of the "low risk" patient has not clearly been defined, nor identified***

Can the carotid patient be identified as high risk for surgery?

High surgical risk patients are defined as having higher than expected death/stroke

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

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

NASCET and ACAS Exclusions

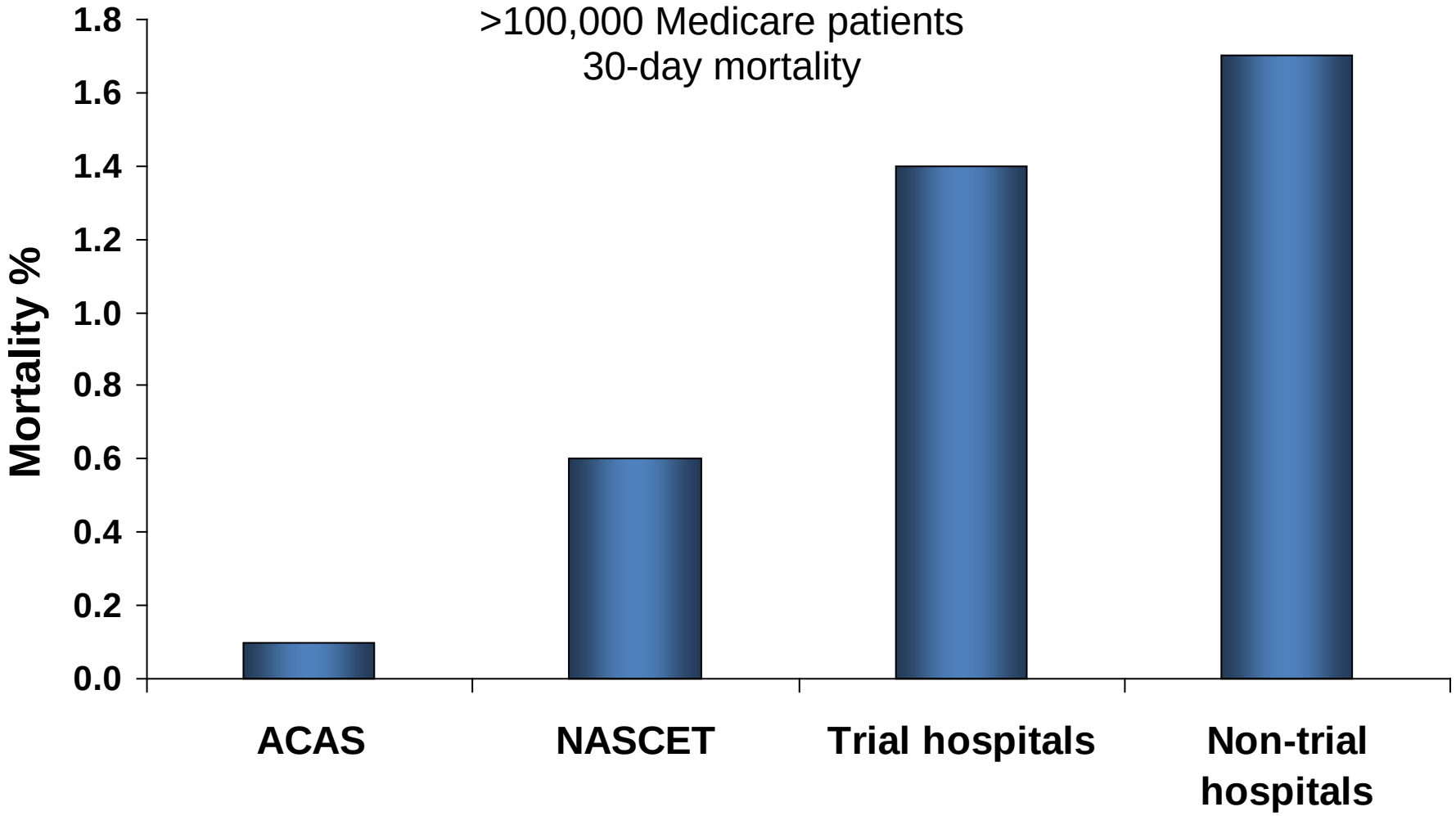
- Age>79
- Prior ipsilateral CEA
- Unstable coronary syndrome
- Myocardial infarct in previous 6 months
- Cardiac valvular or rhythm abnormality likely to cause embolic cerebrovascular symptoms
- Contralateral occlusion
- A more severe lesion cranial to the surgical lesion
- Contralateral CEA within 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

Assessing CEA outcomes in high surgical risk patients

There are no randomized trials
in high surgical risk patients
to guide recommendations for therapy

Any realistic assessments of CEA outcomes would be required to be neurologically controlled/audited (increases stroke rates 2-3 fold)

Post-trial CEA outcomes suggest results not generalizable to non-trial patients



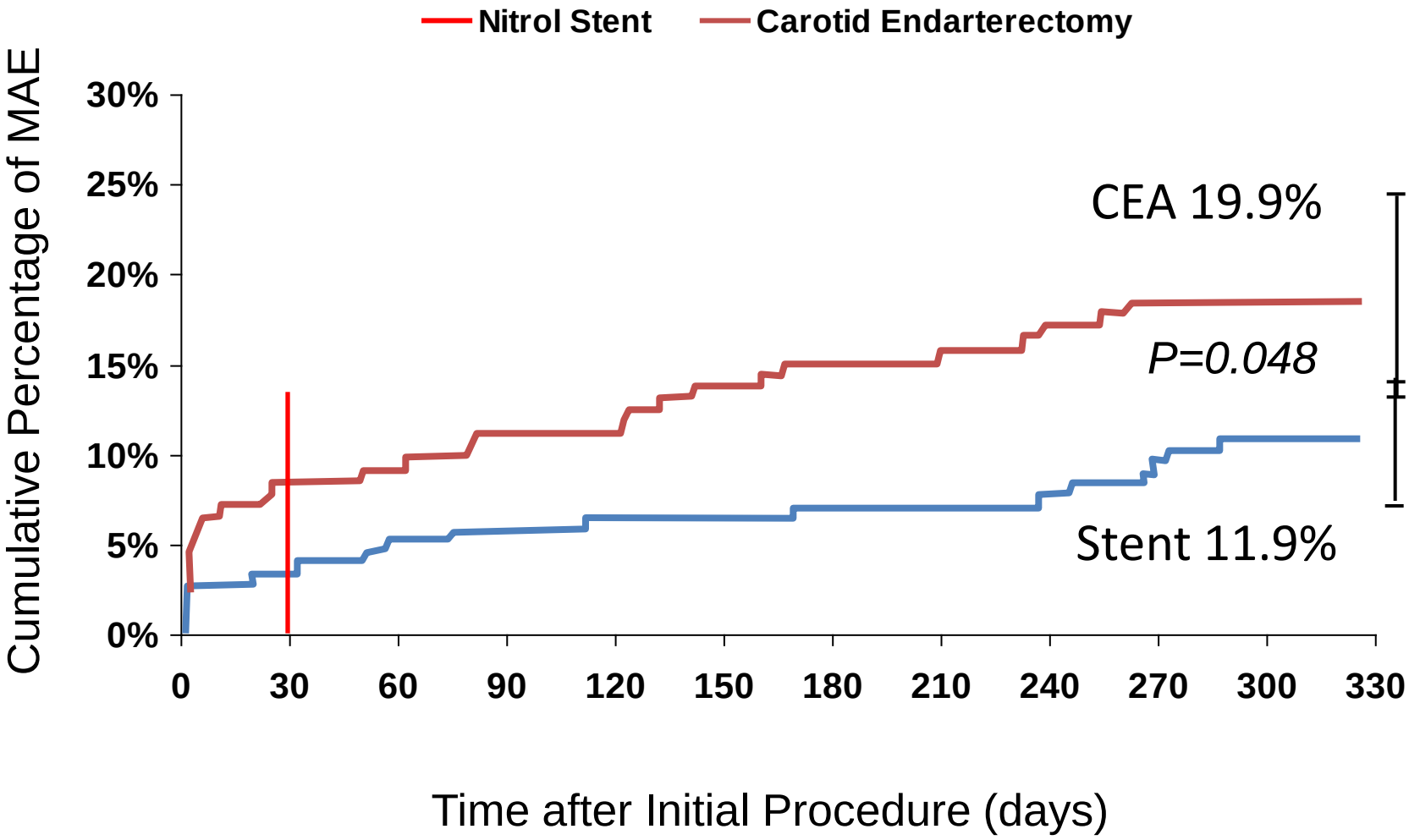
Wennberg, et al., *JAMA*, 279: 1278-1281, 1998

High surgical risk CEA: Increased risk of stroke/death

- Age >75 years: 7%-10%
- Congestive heart failure: 8%-9%
- Co-existent CAD requiring bypass surgery: 8%-10%
- Contralateral carotid occlusion:
  - ACAS – 2% increase over medical therapy
  - NASCET – 14.3%
- Prior CEA and recurrent stenosis: 8%-10%
  - Mayo Clinic
  - Cleveland Clinic
- Renal insufficiency:
  - Cr >1.5 mg%: 8.2%
  - Cr >2.9 mg%: 43%

Daily PO et al. *J Thor Cardiovasc Surg*; June 1996:111(6), 1185-93
Goldstein LB et al. *Stroke* April 1998:29(4), 750-53
Wong JH et al. *Stroke* May 1997; 28(5), 891-98

High surgical risk outcomes demonstrated in RCT SAPPHIRE

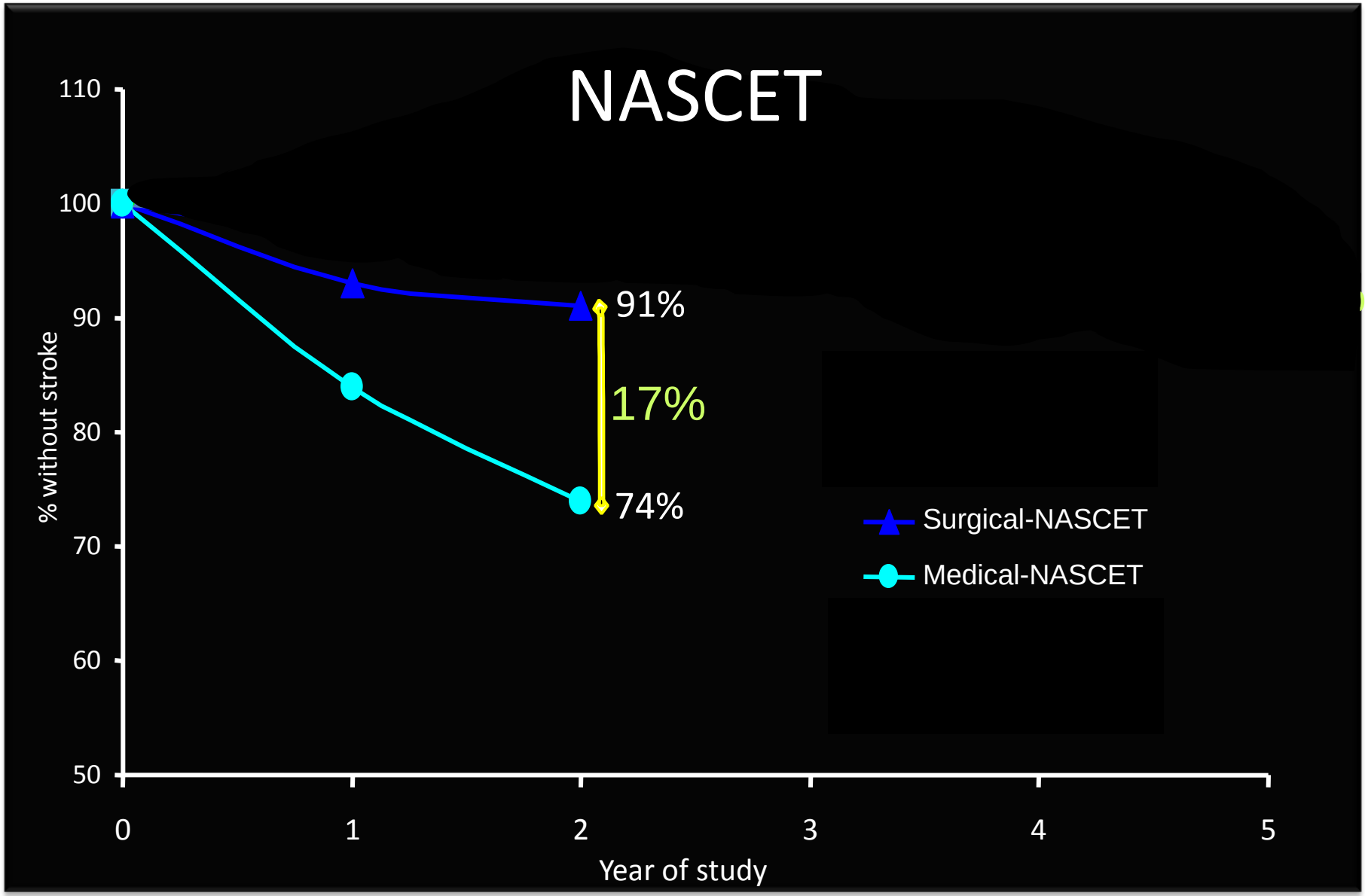


Patients at high risk for CEA

Both observational and randomized data strongly suggest that not only that there are patients who are at increased risk for CEA, but also that such patients can be reasonably identified by medical and surgical comorbidities

Do the data support CEA as preferred alternative to BMT in symptomatic patients?

Revascularization of severe symptomatic carotid stenosis results in significant reduction in stroke



What role does CAS play in the standard surgical risk *symptomatic* patient?

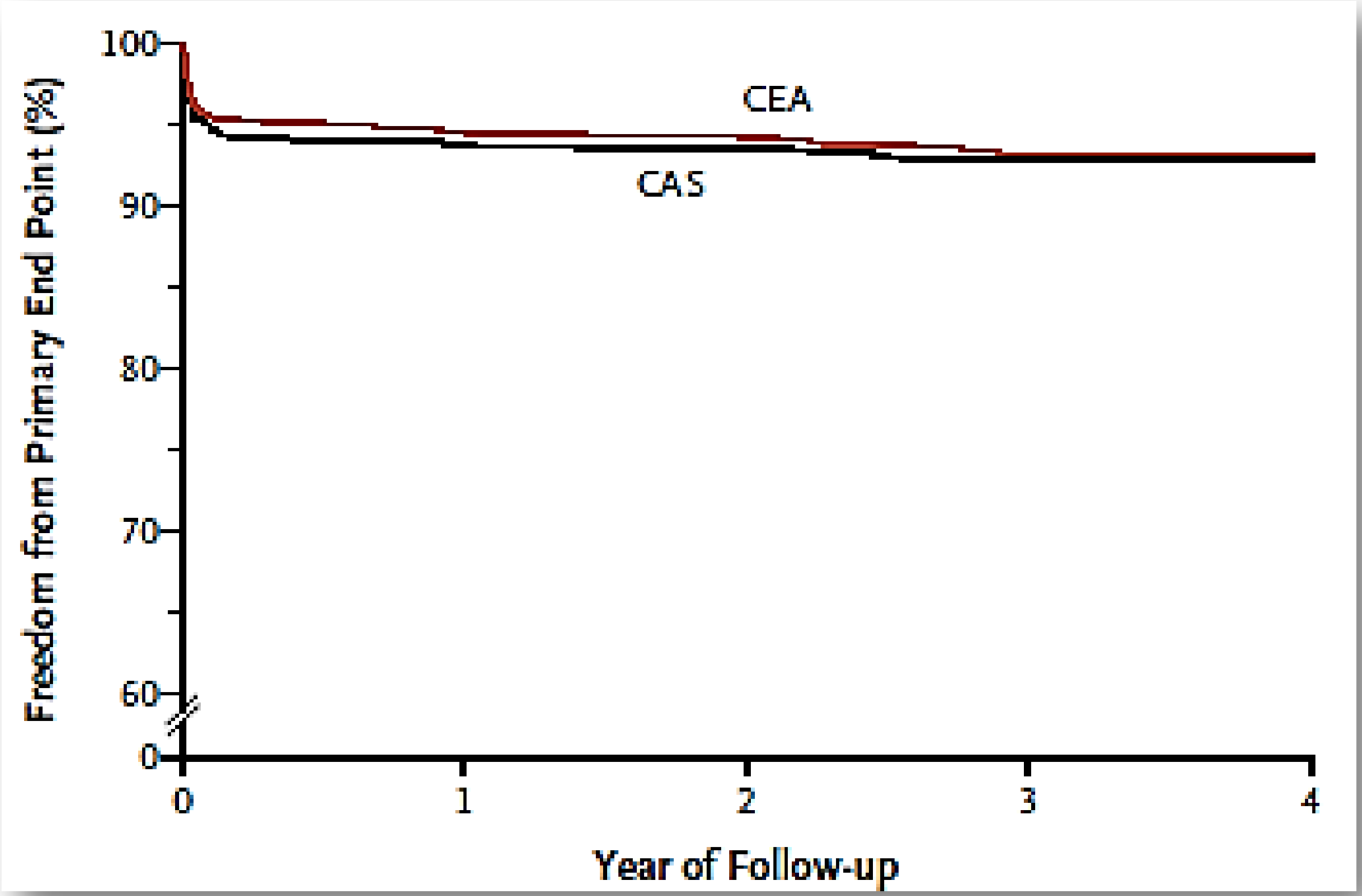
Multicenter randomized trials of CAS vs. CEA

Trial	30-Day Outcome (Death/Stroke)		
EVA-3S (30 days)	CEA: 3.9%	CAS: 9.6%	p=0.01
SPACE (30 days)	CEA: 6.3%	CAS: 6.8%	p=0.09
ICSS (120 days)	CEA: 4.7%	CAS: 8.5%	p=0.001
CREST (Symptomatic Only)	CEA: 5.4%	CAS: 6.7%	p=0.30

Critical trial construct and conduct issues limit the value of EU CEA and CAS outcomes

Trial	EPD Use	MI Ascertainment	Operator Experience
EVA-3S	+	0	0
SPACE	½+	0	++
ICSS	+	0	0
CREST	++	++	++

CREST outcomes:
CEA and CAS are no different for the primary endpoint



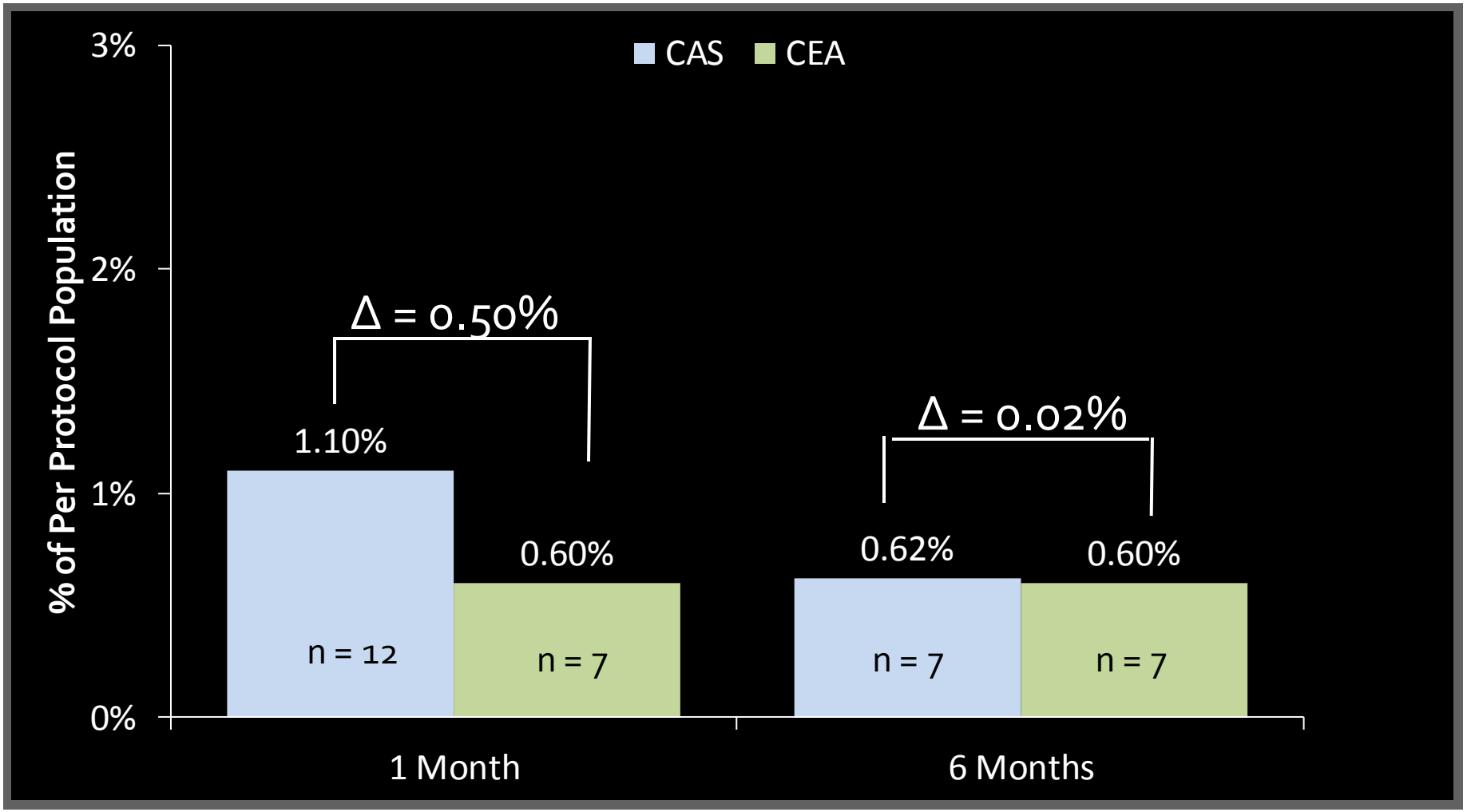
The material differences between CEA and CAS in CREST composite endpoints are in minor stroke and MI

Per protocol	CAS N = 1,131	CEA N = 1,176	Difference	Unadjusted p-value*
All Death, Stroke, or MI	5.8% (65)	5.1% (60)	0.7%	0.5200
Death	0.53% (6)	0.26% (3)	0.27%	0.3335
Any Stroke	4.1% (46)	1.9% (22)	2.2%	0.0019
Major Stroke	0.9% (10)	0.4% (5)	0.5%	0.2005
Minor Stroke	3.2% (36)	1.5% (18)	1.7%	0.0088
MI	2.0% (22)	3.4% (40)	-1.5%	0.0387

* Fisher's exact p-values were not adjusted for multiple comparisons; p-values for descriptive purposes only

Gray et al. Circulation. In press

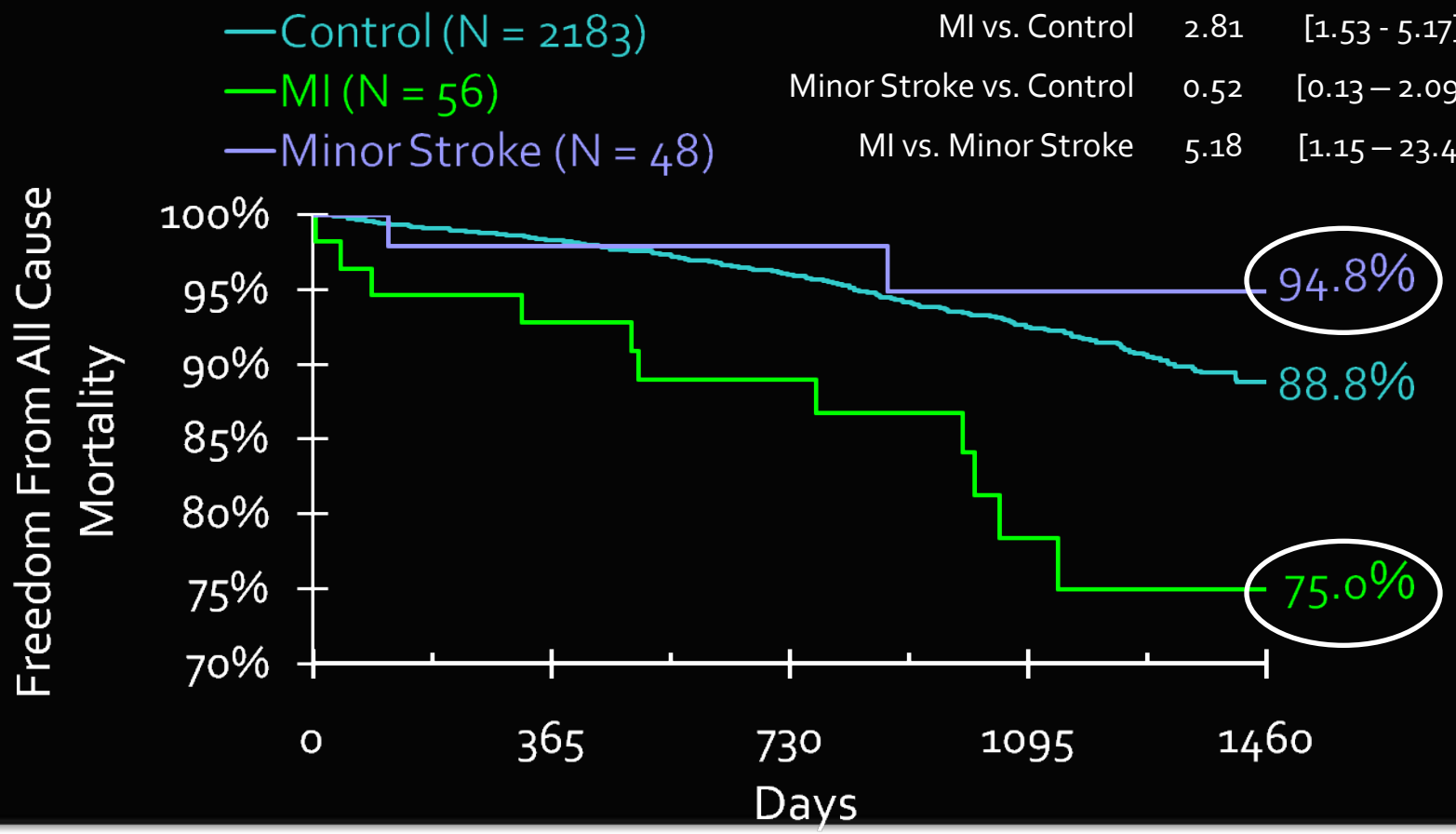
NIHSS neurological residual deficits from CEA and CAS minor strokes occur with very low frequency and are equal at 6 months



Gray et al. Circulation. In press

Long-term mortality: No association with minor stroke but strong association with MI

Comparison	HR	HR Confidence Interval	Log Rank P-value
MI vs. Control	2.81	[1.53 - 5.17]	0.0005
Minor Stroke vs. Control	0.52	[0.13 – 2.09]	0.34
MI vs. Minor Stroke	5.18	[1.15 – 23.4]	0.02



Gray et al. Circulation. In press

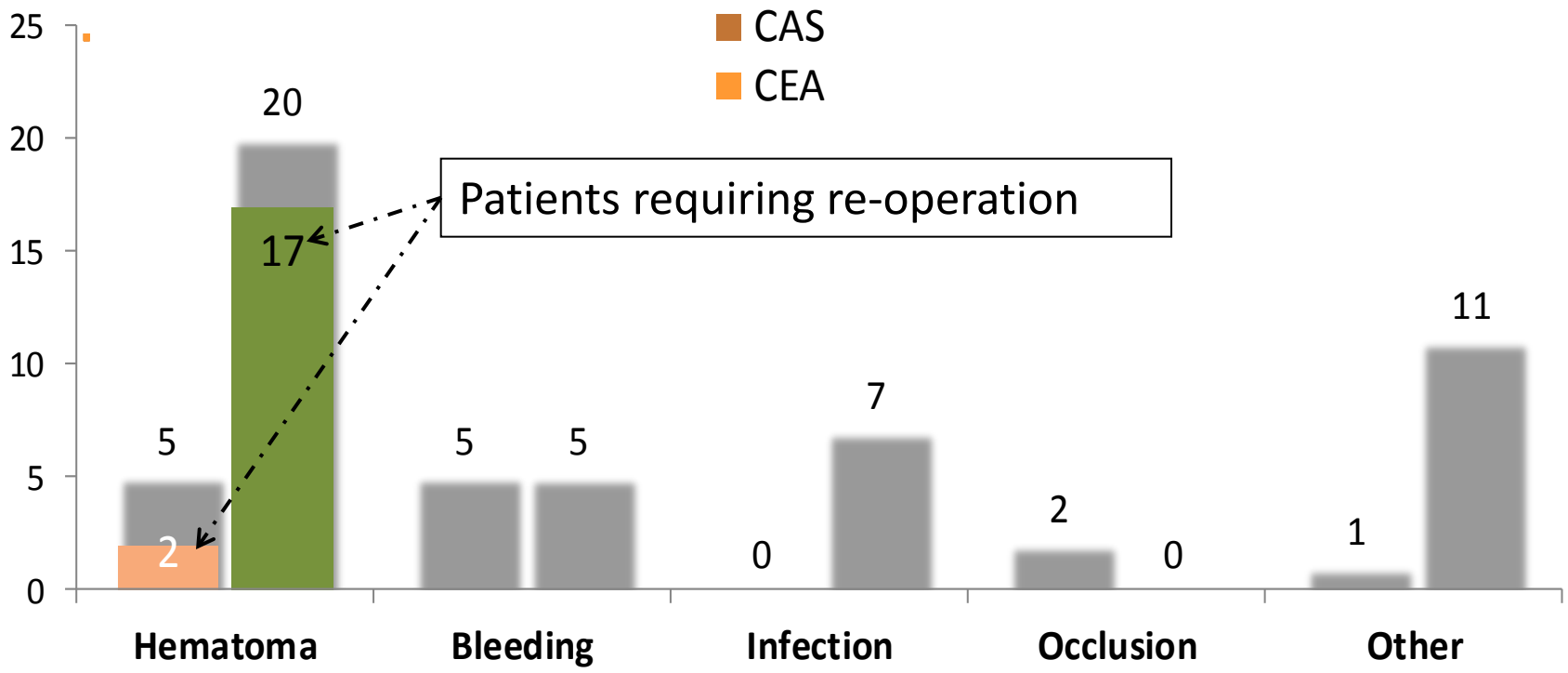
CREST:
Fate of CEA cranial nerve injury

	CAS N = 1,131	CEA N = 1,176	p-value
Procedure related cranial nerve injury	0.0%	5.3% (62/1176)	<0.0001
Unresolved at one month	0.0%	3.6% (42/1176)	<0.0001
Unresolved at six months	0.0%	2.1% (25/1176)	<0.0001

Gray et al. Circulation. In press

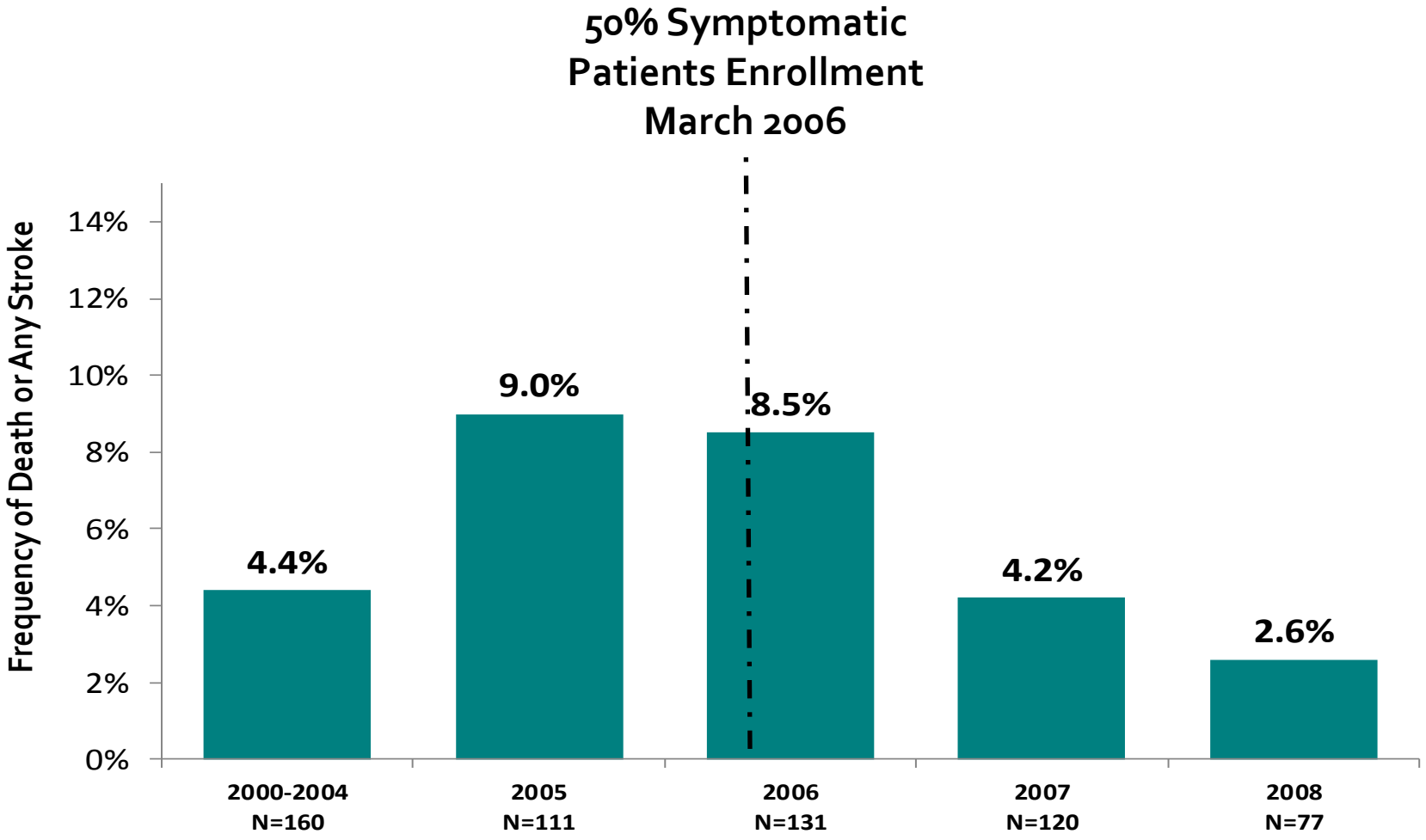
CREST:
Access complications greater with CEA

Per Protocol	CAS N = 1,131	CEA N = 1,176	p-value
Access Site Complication Requiring Treatment	1.1%	3.7%	0.0001



Gray et al. Circulation. In press

Evolutionary outcome improvement for CAS within CREST (not seen with CEA): Death or any stroke in symptomatic patients



Gray et al. Circulation. In press

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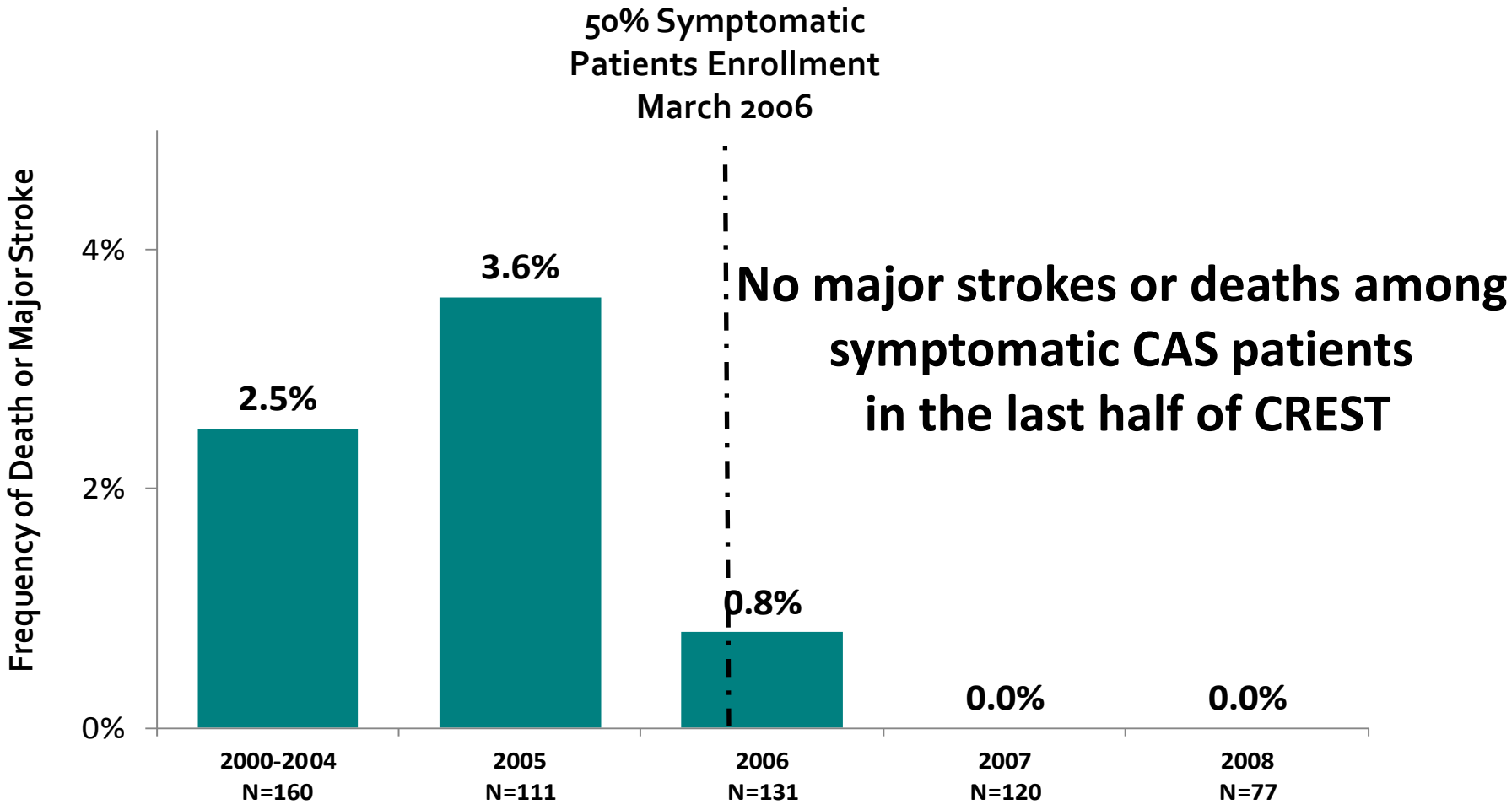
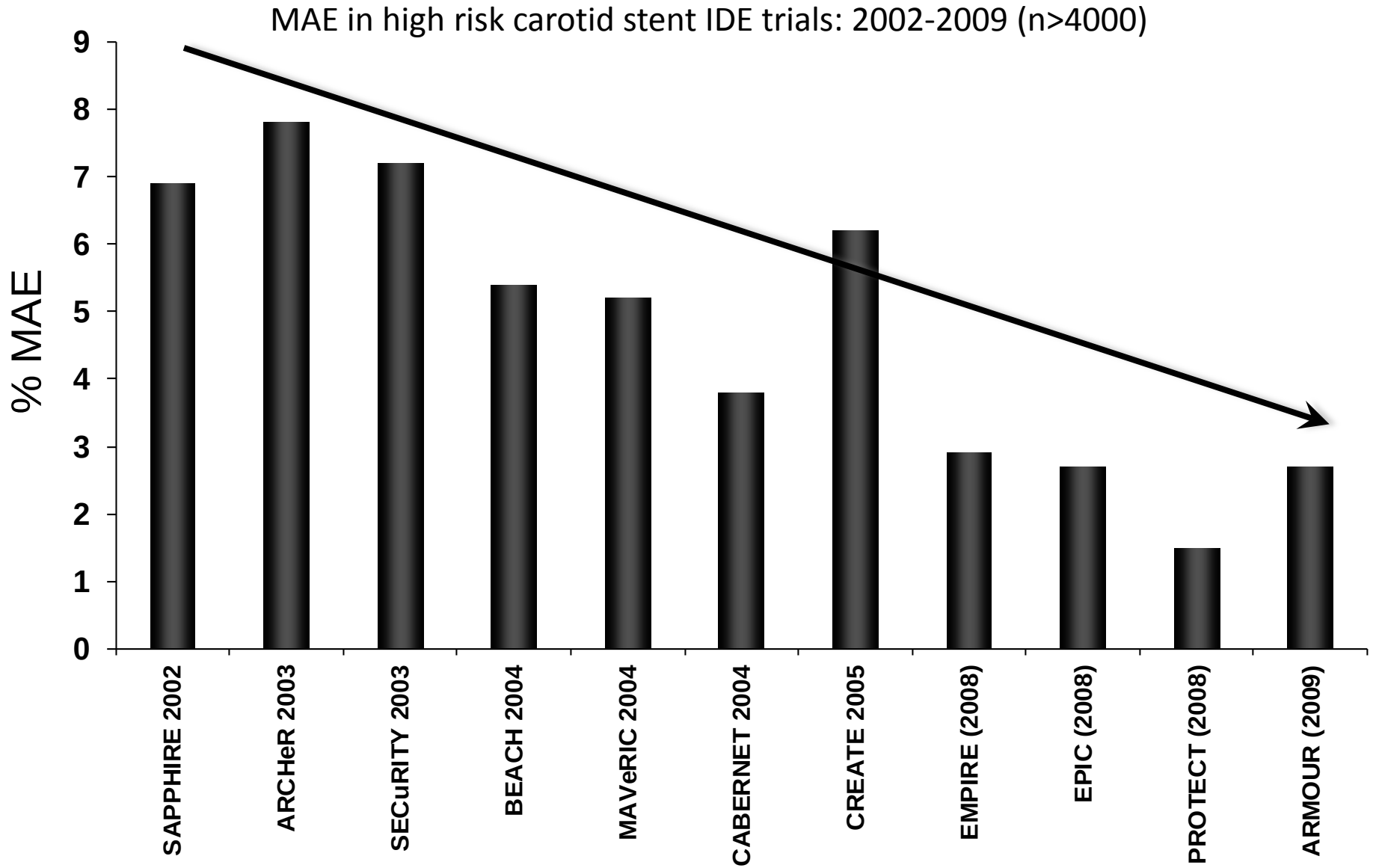


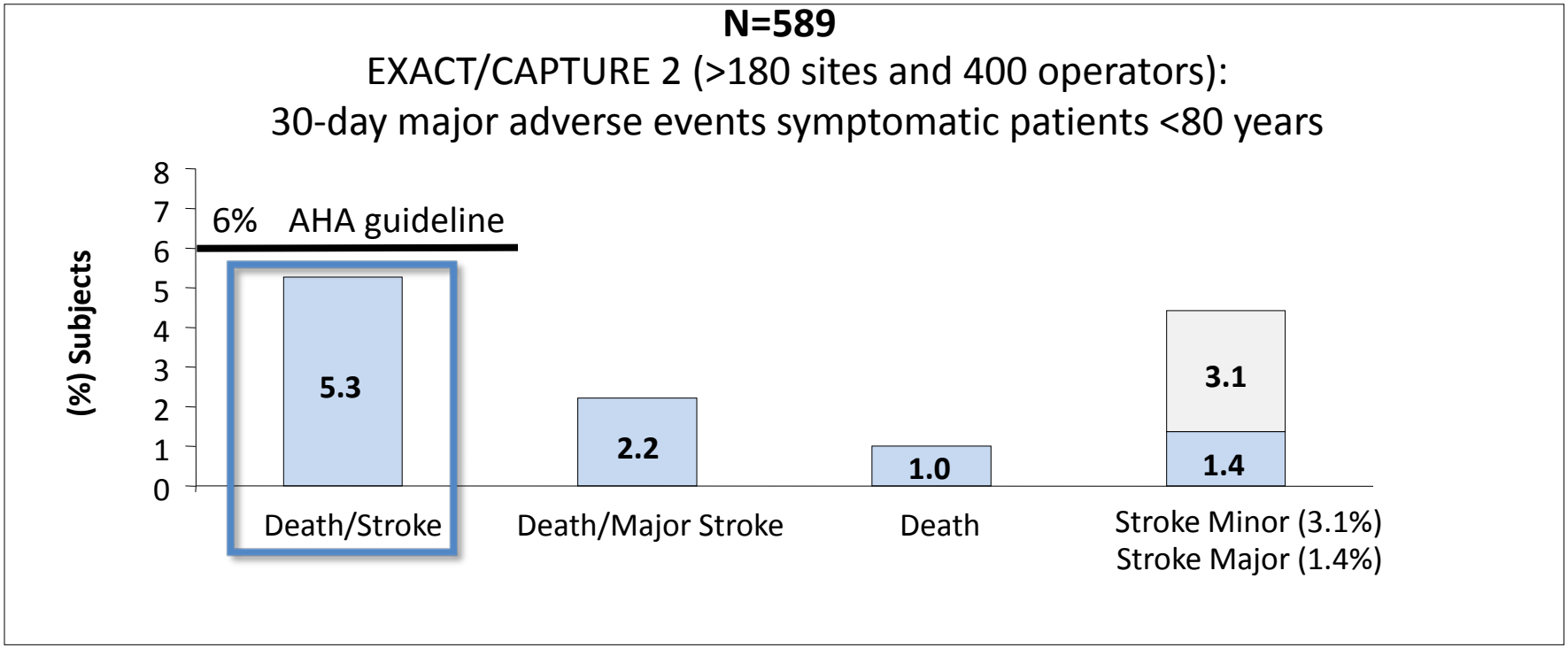
Gray et al. Circulation. In press

Macro-evolution in CAS outcomes demonstrating remarkable progression in past decade



CAS achieves AHA guidelines in symptomatic patients

Large, prospective, multicenter neurologically-audited/independent adjudication single arm studies in high-surgical risk patients



Hierarchical- Includes only the most serious event for each patient and includes only each patient first occurrence of each event.

Gray et al. Circ Cardiovasc Interv. 2009 Jun;2(3):159-66

2011 Multi-Society Guideline Document

2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/ SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease: Executive Summary

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery

Developed in Collaboration With the American Academy of Neurology and Society of Cardiovascular Computed Tomography

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Symptomatic patients

9. Recommendations for Selection of Patients for Carotid Revascularization*

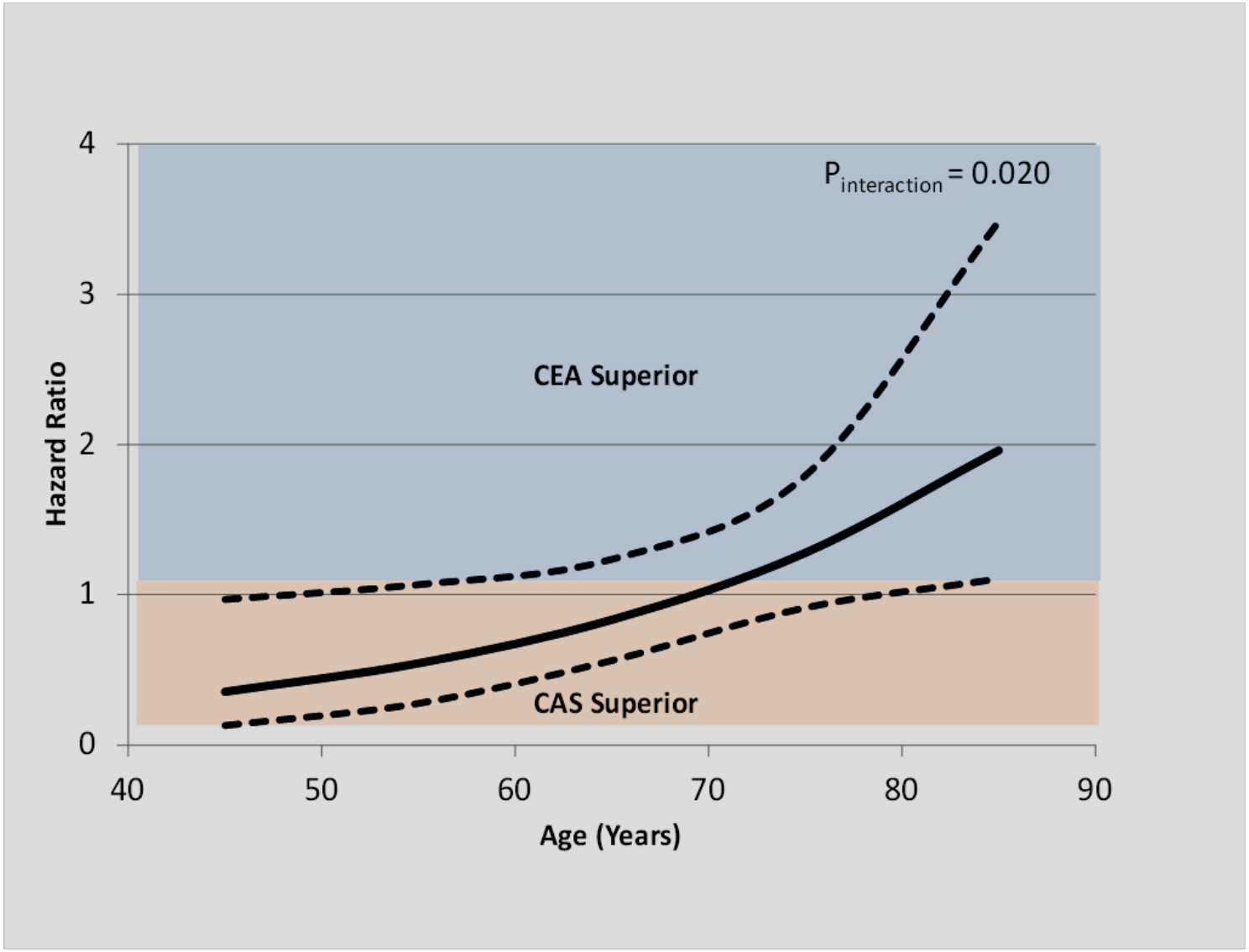
2. CAS is indicated as an alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the internal carotid artery is reduced by more than 70% as documented by noninvasive imaging or more than 50% as documented by catheter angiography and the anticipated rate of periprocedural stroke or mortality is less than 6%.[39] *(Level of Evidence: B)*

50% as documented by catheter angiography[35–38] *(Level of Evidence: B)* and the anticipated rate of perioperative stroke or mortality is less than 6%.

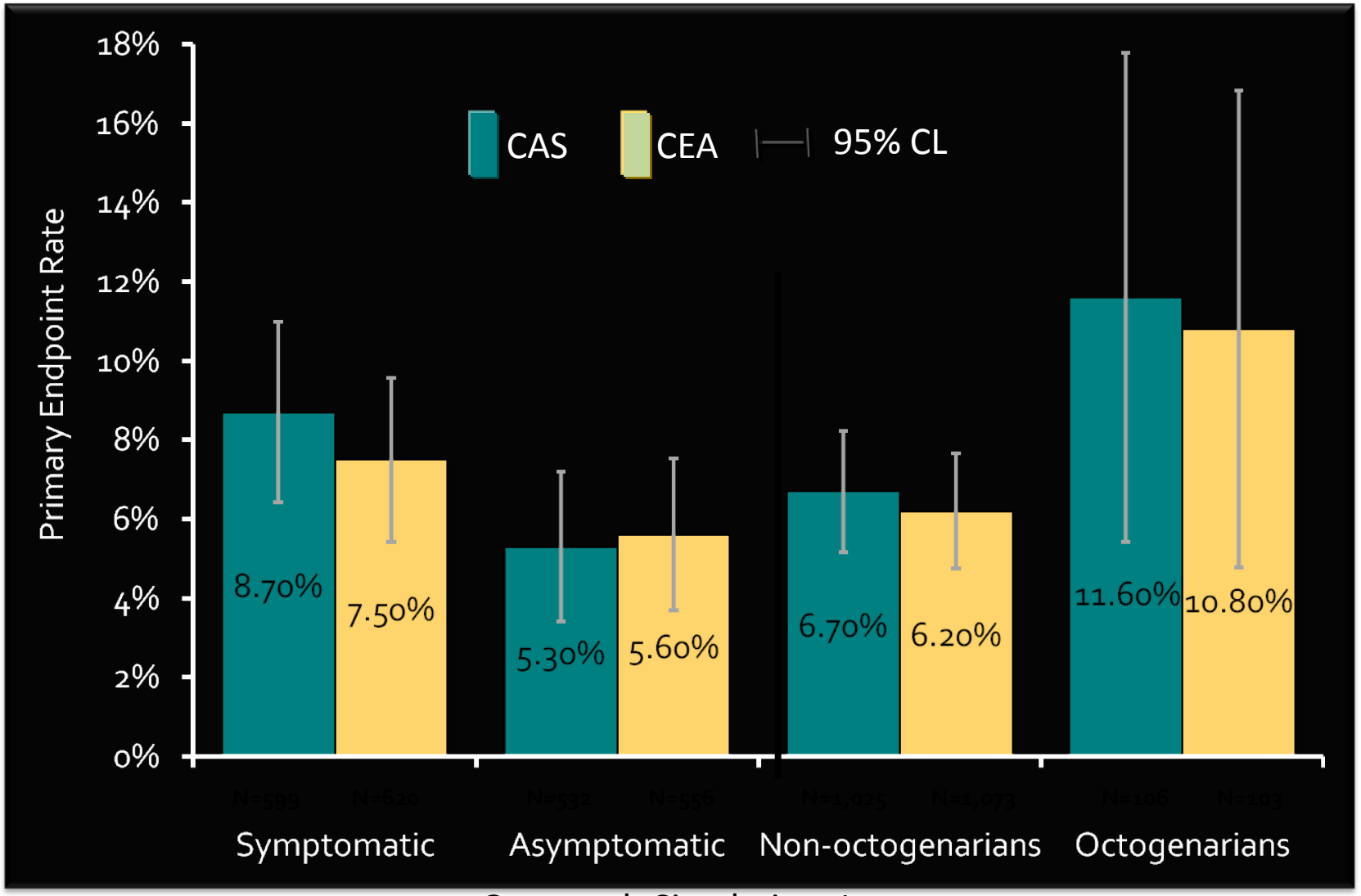
cularization should be guided by an assessment of comorbid conditions, life expectancy, and other individual factors and should include a thorough discussion of the risks and benefits of the procedure with an understanding of patient preferences. *(Level of Evidence: C)*

What about CEA and CAS and age, gender, and time from symptom event?

CREST 4 year primary outcome by age: does the "best fit" line tell the real story?



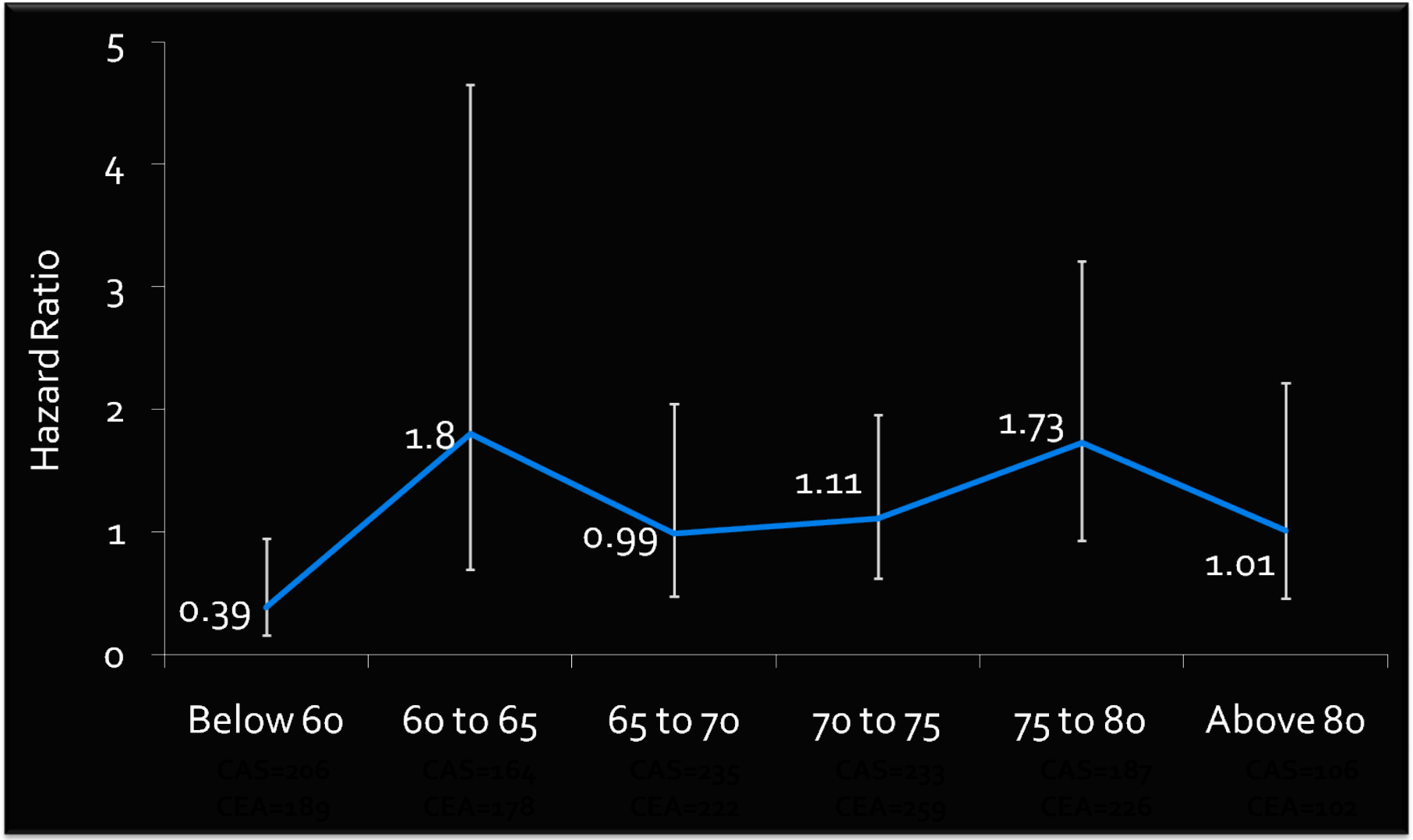
No difference between CEA and CAS for the primary composite endpoint by symptomatic or octogenarian status in CREST



Gray et al. Circulation. In press

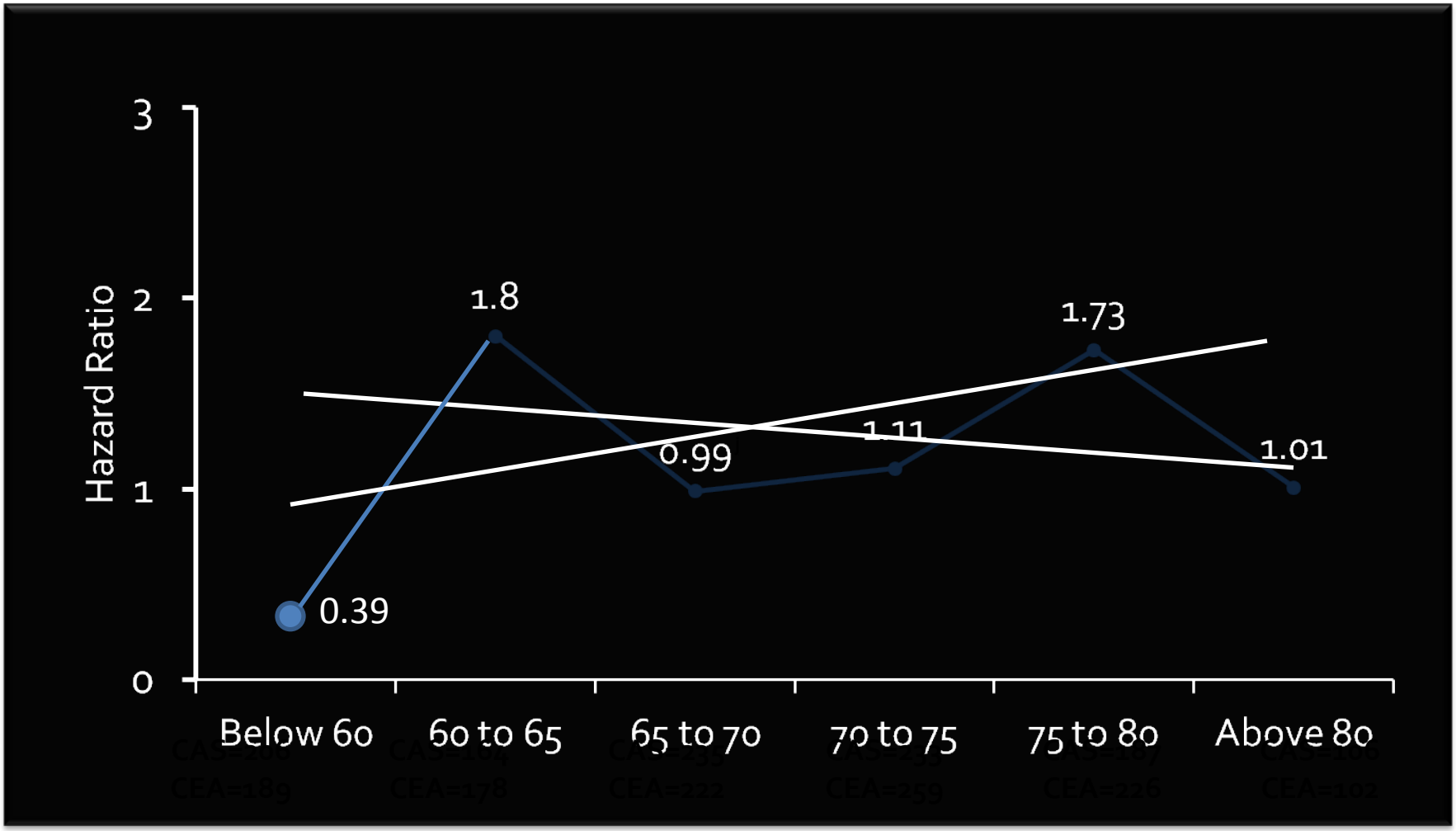
No age trend in CREST: Hazard Ratio by age group

Per protocol analysis



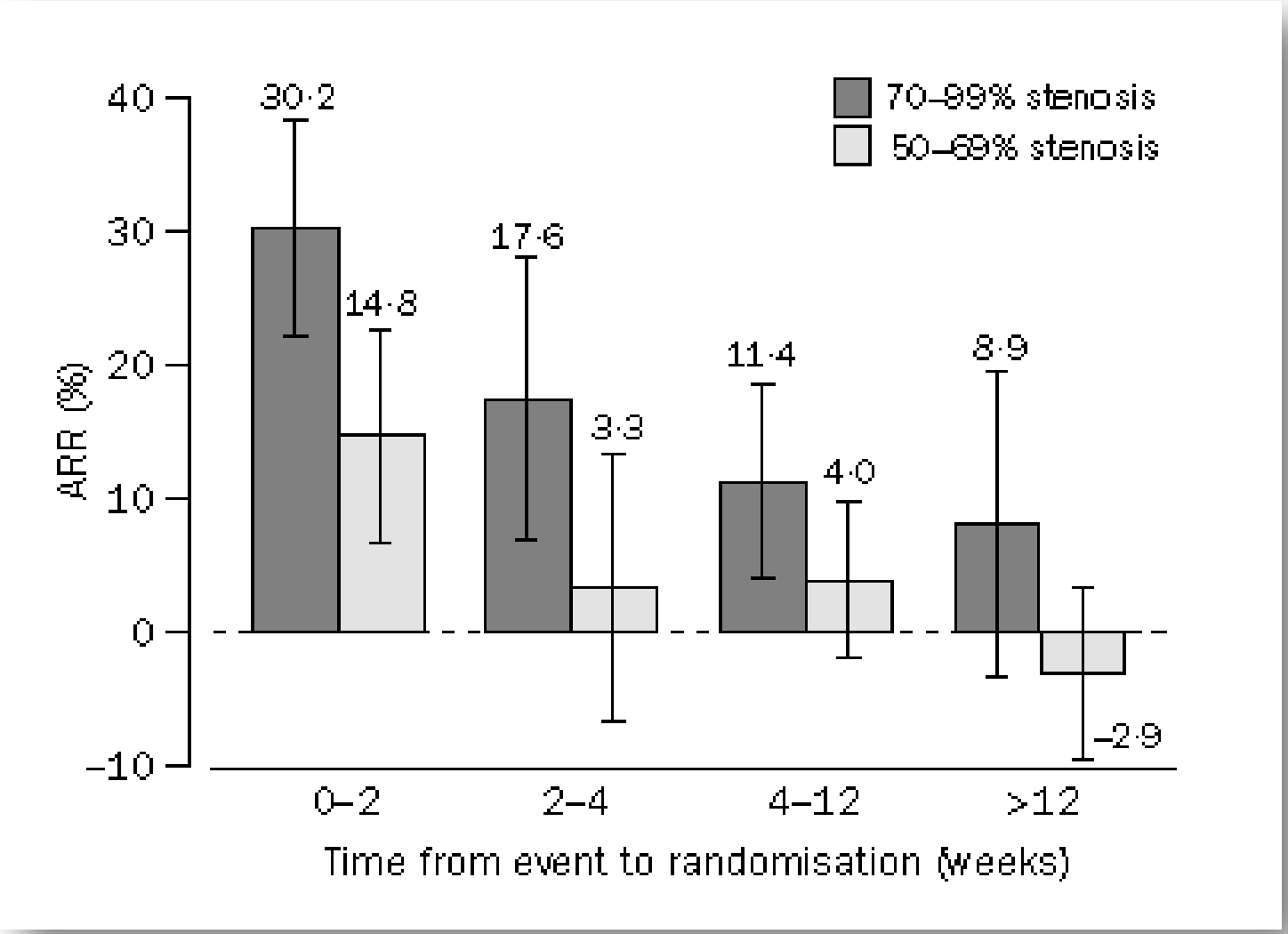
Gray et al. Circulation. In press

Comparative “best fit” line skewed by good CAS outcomes in young patients, and not by poor outcomes in aged



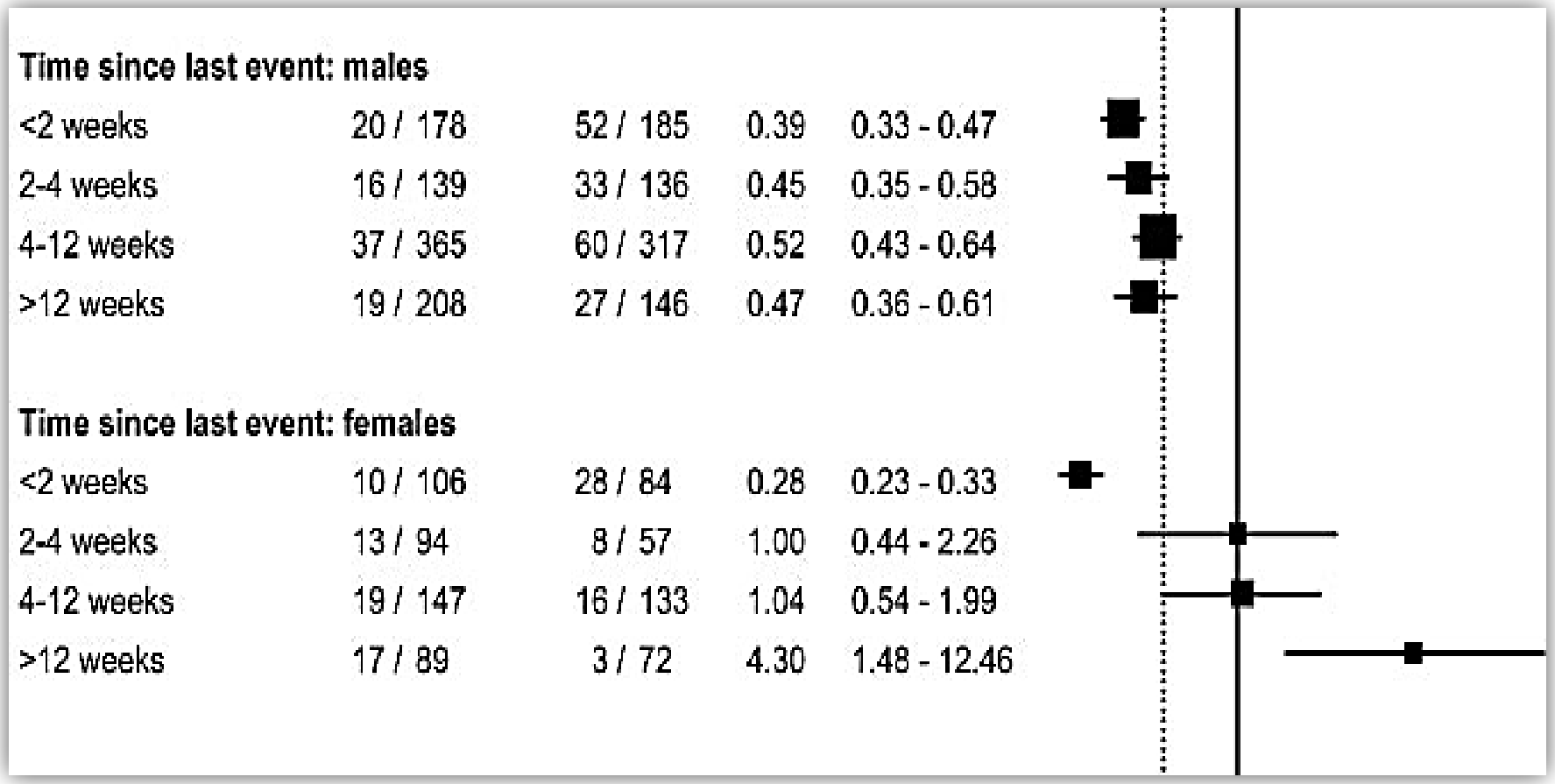
Gray et al. Circulation. In press

Benefit of CEA decreases as time from neurologic symptom increases



Rothwell PM et al. Lancet 2004. 363(9413): 915-924.

Effect of CEA timing especially pronounced in females



Time since last event: males				
<2 weeks	20 / 178	52 / 185	0.39	0.33 - 0.47
2-4 weeks	16 / 139	33 / 136	0.45	0.35 - 0.58
4-12 weeks	37 / 365	60 / 317	0.52	0.43 - 0.64
>12 weeks	19 / 208	27 / 146	0.47	0.36 - 0.61
Time since last event: females				
<2 weeks	10 / 106	28 / 84	0.28	0.23 - 0.33
2-4 weeks	13 / 94	8 / 57	1.00	0.44 - 2.26
4-12 weeks	19 / 147	16 / 133	1.04	0.54 - 1.99
>12 weeks	17 / 89	3 / 72	4.30	1.48 - 12.46

Rothwell PM et al. Stroke 2004 Dec:35 (12):2855-61

Timing of CAS after index event

ICSS	Stenting group (n=828)	Endarterectomy group (n=821)	p value*
Time from randomisation to treatment (days)	9 (5–17)	11 (5–24)	<0·0001
≤14	578 (70%)	469 (57%)	..
>14	250 (30%)	352 (43%)	..
Time from most recent event to treatment (days)	35 (15–82)	40 (18–87)	0·013
≤14	205 (25%)	151 (18%)	..
>14	623 (75%)	668 (81%)	..

Data are number (%) or median (IQR) in the per-protocol analysis. Three patients in the endarterectomy group were randomised more than 12 months after onset of symptoms. The date of the most recent event was unknown in two patients (endarterectomy group). *Mann-Whitney U test.

Table 2: **Time from randomisation and from most recent ipsilateral event to allocated treatment**

Brown MM et al. Lancet 2010 (9719): 985-997

	Peri-procedural period						4-year period					
	CAS group: number of events (%[SE])*	CEA group: number of events (%[SE])*	Treatment effect (95%CI)	HR (95%CI)†	p value	Interaction p value	CAS group: number of events (%[SE])‡	CEA group: number of events (%[SE])‡	Treatment effect (95%CI)	HR (95%CI)†	p value	Interaction p value
Symptomatic patients												
Primary endpoint§												
Men	23 (5·4%[1·1])	26 (6·1%[1·2])	−0·7 (−3·8 to 2·4)	0·88 (0·50 to 1·55)	0·66	0·04	29 (6·9%[1·2])	33 (8·5%[1·5])	−1·7 (−5·4 to 2·1)	0·87 (0·53 to 1·44)	0·59	0·19
Women	22 (9·2%[1·9])	9 (4·0%[1·3])	5·2 (0·7 to 9·6)	2·33 (1·07 to 5·07)	0·033	-	26 (11·7%[2·2])	17 (8·2%[1·9])	3·5 (−2·2 to 9·2)	1·49 (0·81 to 2·74)	0·20	..
Myocardial infarction												
Men	3 (0·7%[0·4])	12 (2·8%[0·8])	−2·1 (−3·9 to −0·4)	0·25 (0·07 to 0·88)	0·030	0·11					..	..
Women	4 (1·7%[0·8])	3 (1·3%[0·8])	0·3 (−1·9 to 2·5)	1·26 (0·28 to 5·63)	0·76	-					..	..
Stroke¶												
Men	19 (4·4%[1·0])	15 (3·5%[0·9])	0·9 (−1·7 to 3·5)	1·28 (0·65 to 2·52)	0·47	0·17	25 (6·0%[1·2])	23 (6·2%[1·3])	−0·2 (−3·7 to 3·2)	1·10 (0·62 to 1·94)	0·74	0·41
Women	18 (7·5%[1·7])	6 (2·7%[1·1])	4·8 (0·9 to 8·8)	2·80 (1·11 to 7·07)	0·030	-	23 (10·4%[2·1])	14 (6·9%[1·8])	3·6 (−1·8 to 9·0)	1·58 (0·81 to 3·08)	0·18	..
Stroke or death‖												
Men	22 (5·1%[1·1])	15 (3·5%[0·9])	1·6 (−1·1 to 4·4)	1·49 (0·77 to 2·87)	0·23	0·25	28 (6·7%[1·2])	23 (6·2%[1·3])	0·5 (−3·0 to 3·9)	1·23 (0·71 to 2·14)	0·46	0·56
Women	18 (7·5%[1·7])	6 (2·7%[1·1])	4·8 (0·9 to 8·8)	2·80 (1·11 to 7·07)	0·030	-	23 (10·4%[2·1])	14 (6·9%[1·8])	3·6 (−1·8 to 9·0)	1·58 (0·81 to 3·08)	0·18	..
Asymptomatic patients												
Primary endpoint§												
Men	12 (3·2%[0·9])	14 (3·5%[0·9])	−0·4 (−2·9 to 2·2)	0·93 (0·43 to 2·01)	0·85	0·72	19 (5·5%[1·3])	17 (5·0%[1·2])	0·5 (−2·9 to 4·0)	1·24 (0·65 to 2·39)	0·52	0·83
Women	9 (4·2%[1·4])	7 (3·7%[1·4])	0·5 (−3·3 to 4·3)	1·18 (0·44 to 3·16)	0·75	..	11 (5·7%[1·7])	9 (4·8%[1·6])	0·9 (−3·7 to 5·4)	1·08 (0·45 to 2·62)	0·86	..
Myocardial infarction												
Men	4 (1·1%[0·5])	9 (2·3%[0·7])	−1·2 (−3·0 to 0·6)	0·48 (0·15 to 1·56)	0·22	0·74	..	..	..	..	..	..
Women	3 (1·4%[0·8])	4 (2·1%[1·0])	−0·7 (−3·3 to 1·9)	0·67 (0·15 to 3·01)	0·60	-	..	..	..	..	..	..
Stroke¶												
Men	8 (2·1%[0·7])	5 (1·3%[0·6])	0·8 (−1·0 to 2·7)	1·75 (0·57 to 5·37)	0·33	0·82	15 (4·4%[1·1])	8 (2·7%[1·0])	1·7 (−1·2 to 4·7)	2·16 (0·91 to 5·10)	0·08	0·71
Women	7 (3·3%[1·2])	3 (1·6%[0·9])	1·7 (−1·3 to 4·6)	2·11 (0·55 to 8·15)	0·28	-	9 (4·8%[1·6])	5 (2·7%[1·2])	2·1 (−1·8 to 6·0)	1·59 (0·53 to 4·75)	0·40	..
Stroke or death‖												
Men	8 (2·1%[0·7])	5 (1·3%[0·6])	0·8 (−1·0 to 2·7)	1·75 (0·57 to 5·37)	0·33	0·82	15 (4·4%[1·1])	8 (2·7%[1·0])	1·7 (−1·2 to 4·7)	2·16 (0·91 to 5·10)	0·08	0·71
Women	7 (3·3%[1·2])	3 (1·6%[0·9])	1·7 (−1·3 to 4·6)	2·11 (0·55 to 8·15)	0·28	-	9 (4·8%[1·6])	5 (2·7%[1·2])	2·1 (−1·8 to 6·0)	1·59 (0·53 to 4·75)	0·40	..

~230-240 symptomatic women treated with CAS

However, CAS appears to be more effective than CEA in the symptomatic female in EVA-3S and ICSS

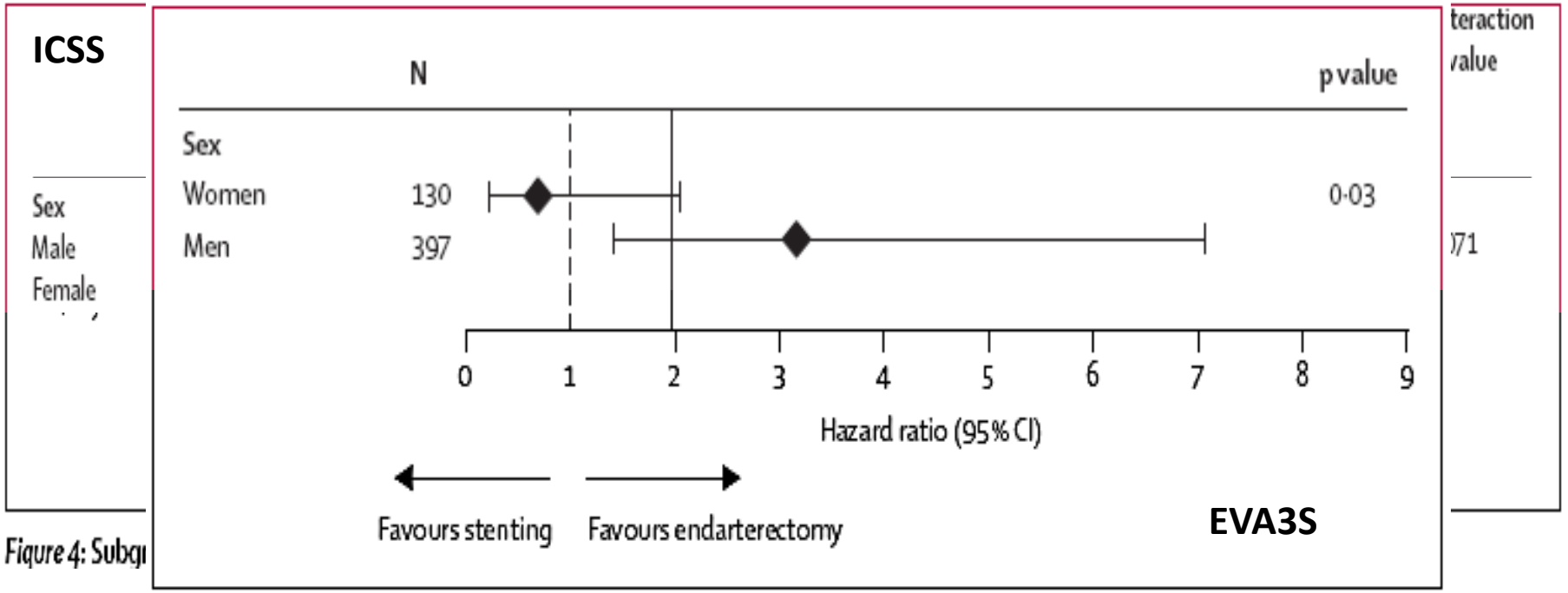
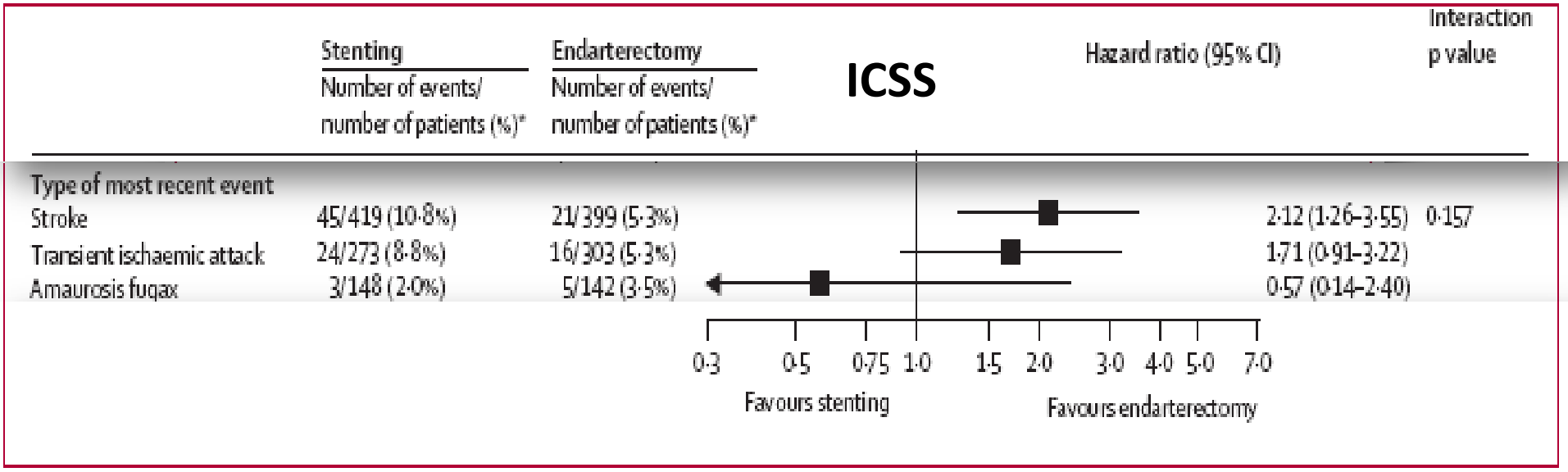


***Figure 4*: Hazard ratios (stenting *vs* endarterectomy) and 95% CIs for ipsilateral stroke (including periprocedural stroke or death) in various subcategories**

p values are associated with treatment-covariate interaction tests. The thick vertical line is the hazard ratio (stenting *vs* endarterectomy) in the overall population.

CEA and CAS: outcomes by index symptom

Predefined exploratory subgroup analyses



Summary of CEA and CAS in symptomatic patients

- CEA proven far superior to medical care
- CAS and CEA appear equivalent in outcomes and stroke prevention in CREST and in large, controlled single arm studies of high surgical risk patients
  - European trials flawed and therefore interpretation of primary results limited
  - Significant rapid and continued improvement in outcomes in CAS over past decade; CEA outcomes excellent, plateau'd
  - More wound complication/re-op and cranial nerve injury with CEA
- Earlier intervention with greater benefit, especially in women
- Women probably do somewhat better with CAS than CEA (EVA-3S and ICSS), no difference in men
- Patients with amaurosis and TIA may do better with CAS

What is the preferred therapy for stroke prevention for asymptomatic patients?

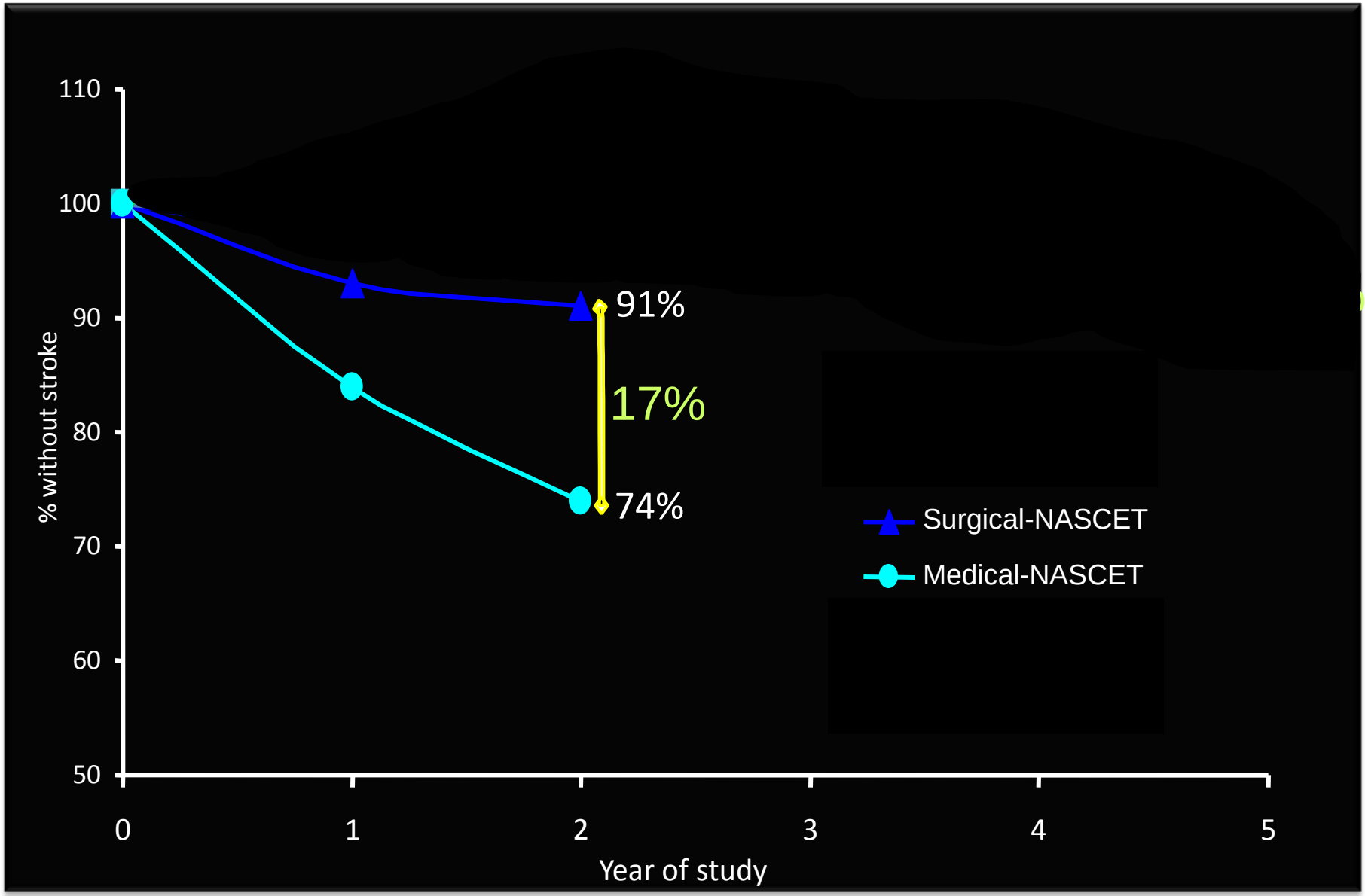
The best available evidence supports revascularization as a principal treatment option in asymptomatic patients

- Two RCTs show superiority of revascularization over medical therapy for asymptomatic patients

- Systematic review and population based studies purporting to show improvements in best medical therapy over time has significant flaws

- Claims that medical therapy has greatly reduced stroke rates can therefore only be viewed as hypothesis-generating at best, and do not supplant Tier 1 evidence showing clear patient benefits from revascularization

Revascularization of severe carotid stenosis results in significant reduction in stroke



The support for medical therapy without revascularization for severe asymptomatic carotid stenosis rests on retrospective analyses

Medical (Nonsurgical) Intervention Alone Is Now Best for Prevention of Stroke Associated With Asymptomatic Severe Carotid Stenosis. Results of a Systematic Review and Analysis

Anne L. Abbott

Stroke published online Aug 20, 2009;
DOI: 10.1161/STROKEAHA.109.556068

Significant methodological flaws with Abbott review

- Mainly based on observational data (8 of 11 studies)
- Most of the asymptomatic patients in the included studies would not be candidates for revascularization
  - Sixty percent (60%) of patients in the systematic review did not meet current AHA guidelines for revascularization
- The heterogeneity of the populations across studies makes it inappropriate to include in a single analysis
  - Earlier studies had a higher minimum stenoses than later studies
  - Studies used different imaging modalities
  - Some studies excluded patients with any prior CV events
  - Some studies included patients with prior revascularizations
- Medical management was variable across studies
  - Not clearly adjudicated across studies
  - Other causes of stroke were not controlled for, such as atrial fibrillation

Studies included in Abbott analysis are inclomplete

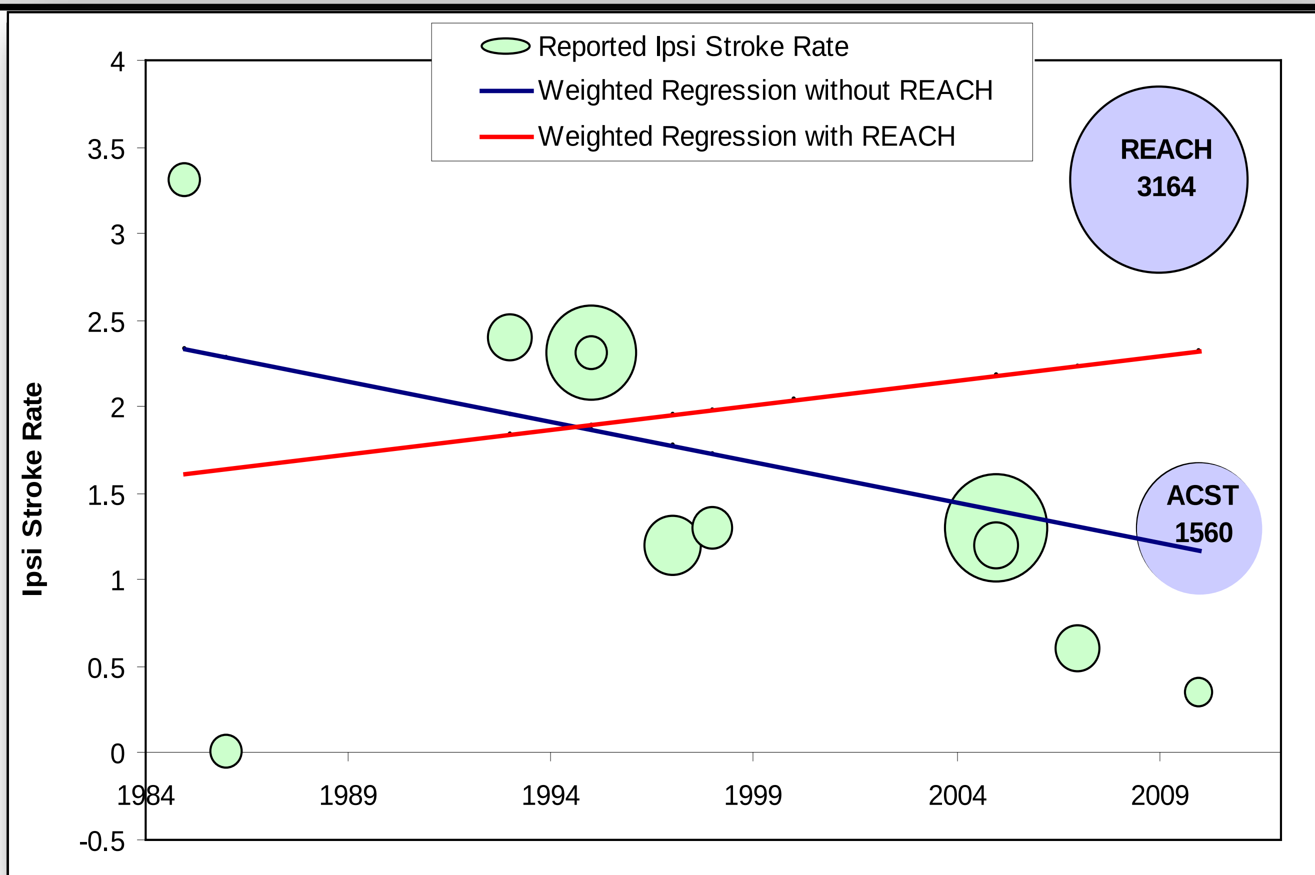
		Ipsilateral Stroke		Ipsilateral Stroke/TIA		Any Territory Stroke		Any Territory Stroke/TIA	
Study	Sample Size	Raw Data	KM Estimates	Raw Data	KM Estimates	Raw Data	KM Estimates	Raw Data	KM Estimates
Johnson, 1985[76]	121	3.3	. . .	19.0	. . .	. . .	. . .	. . .	. . .
Toronto, 1986[2]	113	0	. . .	7.9 (all TIA)	. . .	1.9	. . .	10.7	11.0
VACS, 1993[10]	233	2.4	. . .	5.2	. . .	3.0	. . .	6.1	. . .
ACAS, 1995[11]	834	2.3	2.2	4.5	3.8	3.8	3.5	. . .	. . .
ECST, 1995[77]	127	2.3	1.9	. . .	. . .	. . .	. . .	. . .	. . .
ACBS, 1997[78]	357	1.2	1.4	3.4	4.2	2.1	2.5	5.8	. . .
CHS, 1998[82]	185	1.3	1.0	. . .	. . .	2.6	2.3	. . .	. . .
NASCET, 2000[3]	216	. . .	3.2	. . .	. . .	. . .	. . .	. . .	. . .
ACSRS, 2005[79]	1115	1.3	1.7	3.1	3.4	. . .	2.1	. . .	4.1
ASED, 2005[80]	202	1.2	1.0	3.2	3.1	2.4	2.2	5.6	5.1
SMART, 2007[81]	221	0.6	. . .	. . .	. . .	0.7	. . .	. . .	. . .

Largest randomized trial in asymptomatic carotid disease is omitted (ACST, 1500 medically treated patients)

Poor documentation of medical therapies, heterogeneity in populations

	Johnson[76]	Toronto[2]	VACS[10]	ACAS[11]	ECST[77]	ACBS[78]	CHS[82]	NASCET[3]	ACSRS[79]	ASED[80]	SMART[81]
Male	. . .	60	100	66	71	40‡	46	68	61	68	73
Mean age, y	. . .	67	65	67‡	64	65‡	73.3	66	70	74	65
Current Smoker	. . .	. . .	49	24	50	35‡	18	33	18	14	42
Ever smoker	. . .	77	91	. . .	. . .	. . .	61	. . .	71	73	90
Hypertension	. . .	66	64	64	50‡	47‡	71	60	63	72	. . .
Ischemic heart disease	. . .	77	57	69	33	39‡	38	36	34	52	59
High cholesterol	. . .	32	. . .	. . .	. . .	50‡	. . .	32‡	60	67	. . .
Diabetes	. . .	14	27	21	14	20‡	26	22	21	17	21
Atrial arrhythmia	. . .	. . .	14	. . .	. . .	0	4	0	3	0	. . .
PVD	. . .	70	59	. . .	24	23‡	8	15‡	40	33	45
Nonipsilateral stroke/TIA	0	0	33	27	100	0	0	100	20	42	0
Antiplatelet therapy†	0	≤51	100*	100*	56‡	50	about 0	95%‡	84	88	63
Antilipid therapy	. . .	. . .	. . .	. . .	. . .	. . .	10	. . .	25	75D	45
Antihypertension therapy	. . .	. . .	. . .	. . .	. . .	. . .	62	. . .	60	77D	63
Other known embolic sources excluded	no	no	no	no	yes	yes	no	yes	no	yes	no

Critical appraisal of Abbott analysis



If the systematic review's analysis had adjusted for minimum stenosis and included more recent studies (REACH and ACST) the trend in stroke rates would have been in the opposite direction (p = 0.55)

Largest and most recent REACH study (N = 3164) published after the systematic review contradicts the review findings

Aichner FT, et al. *Eur J Neurol* 2009; 16:902-908.

" Everything has been said before, but since nobody listens we have to keep going back and beginning all over again.. "

Andre Gide, Le Traite du Narcisse 1891

Original Contributions

Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women

Conclusions.—During an average follow-up of 4.1 years, treatment with oral conjugated equine estrogen plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary disease. The treatment did increase the rate of thromboembolic events and gall-bladder disease. Based on the finding of no overall cardiovascular benefit and a pattern of early increase in risk of CHD events, we do not recommend starting this

angiographic studies, the relative risk was 0.50 (95% confidence interval 0.43-0.56).

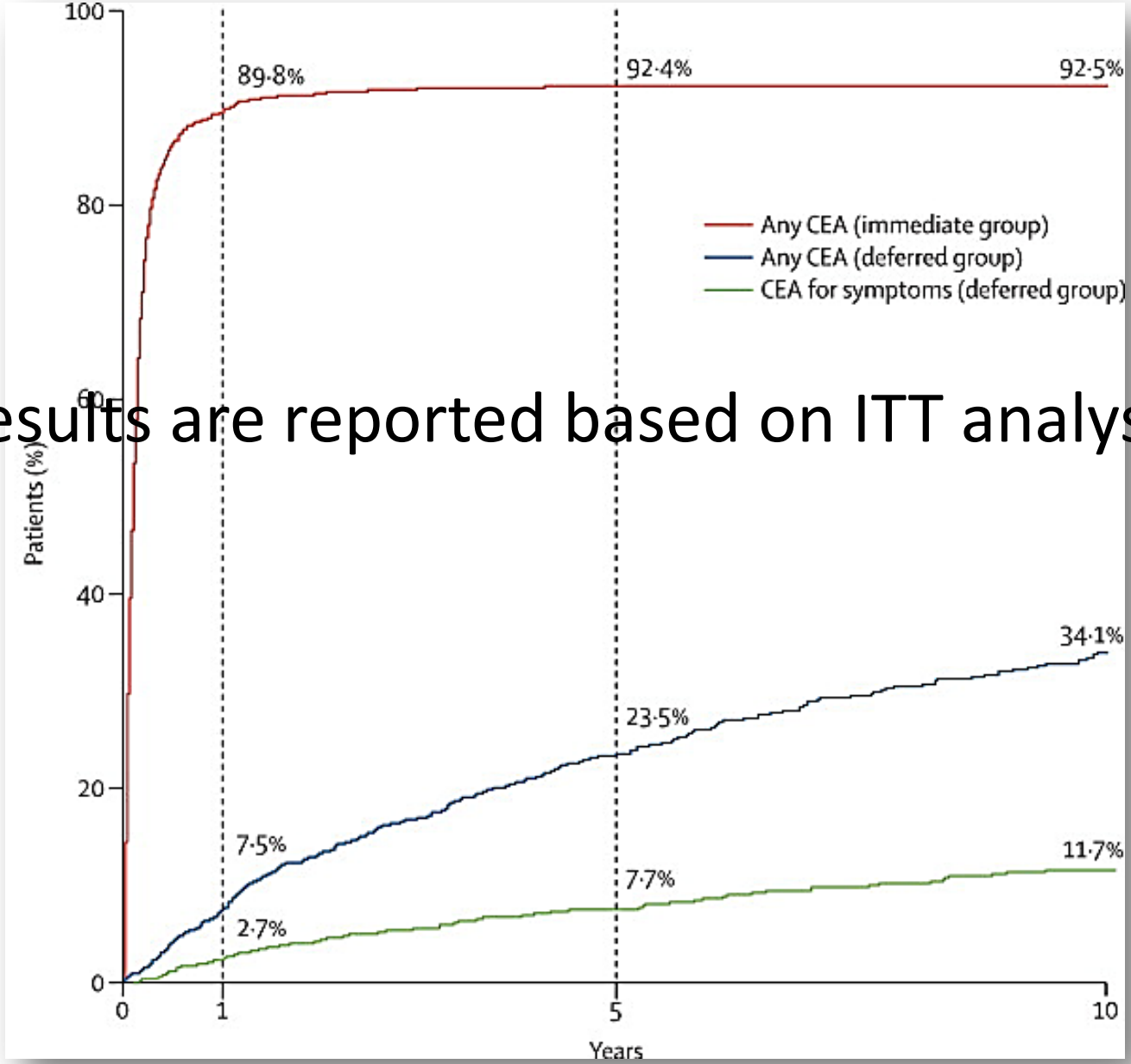
Stampfer MJ et al JAMA 1998; 280(7): 605-613.

Hulley S et al JAMA 1998; 280(7): 613-647-63.

Randomized trial data in asymptomatic patients
ACST trial

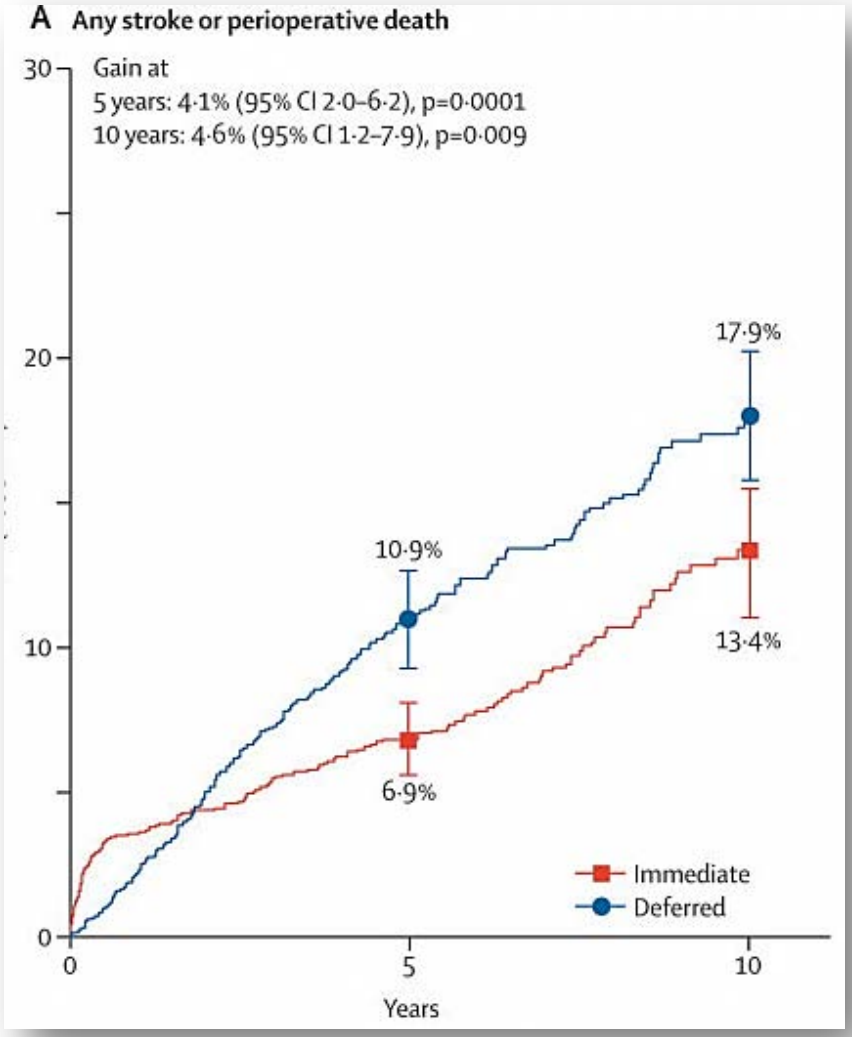
- Asymptomatic patients with standard surgical risk
- Randomized trial
  - CEA vs. non-directed medical care
- 5 year follow-up published 2004, 10 year in 2010
- Primary endpoint:
  - Any stroke or peri-operative death

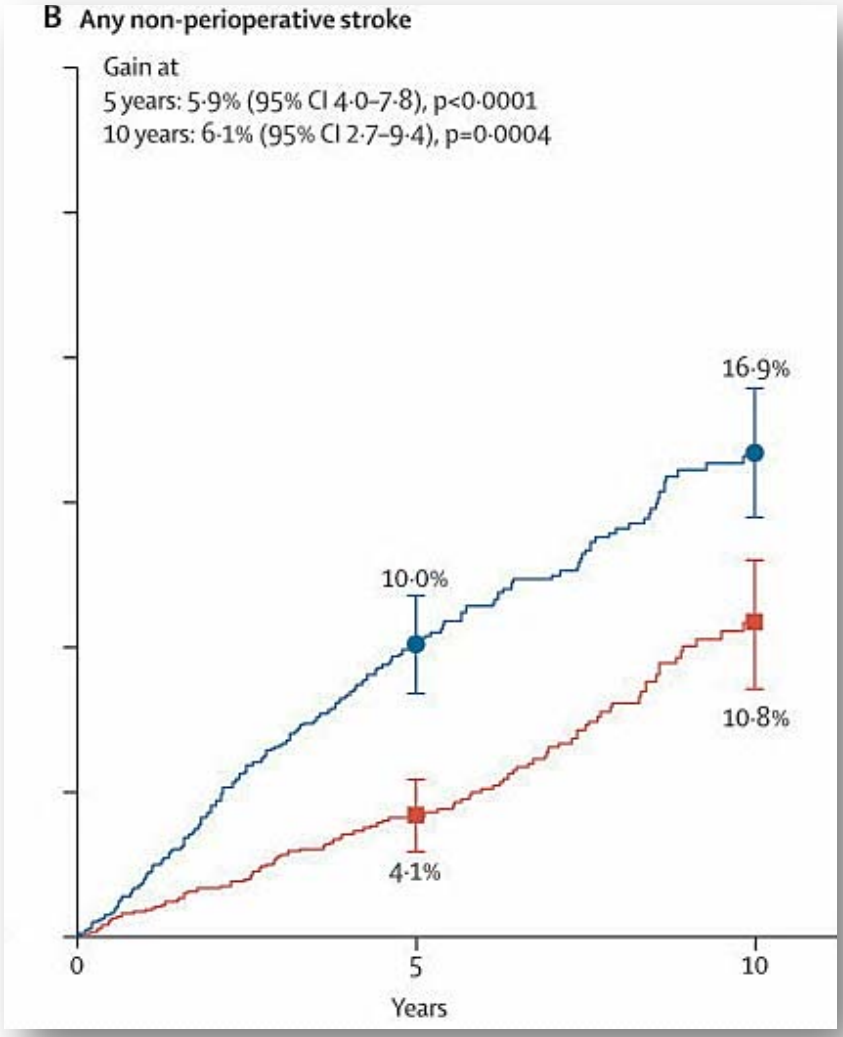
Rate and implication of cross-over in ACST



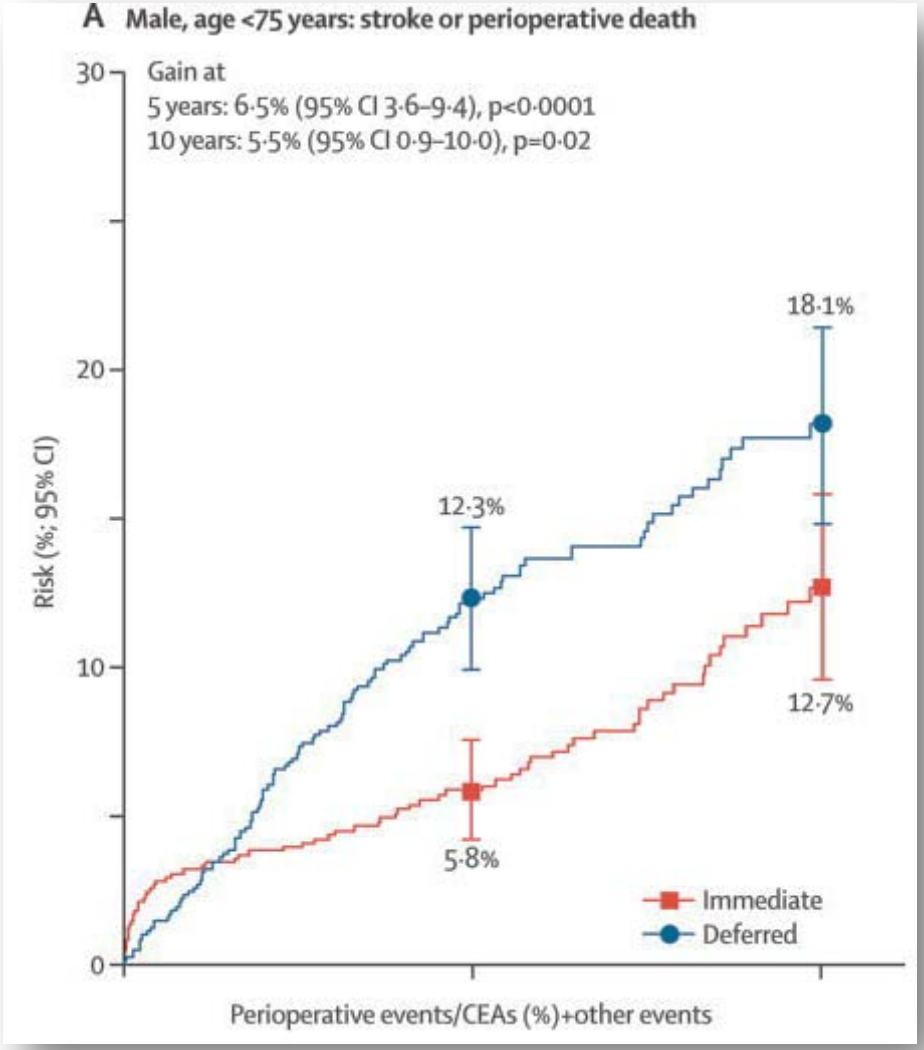
Results are reported based on ITT analysis

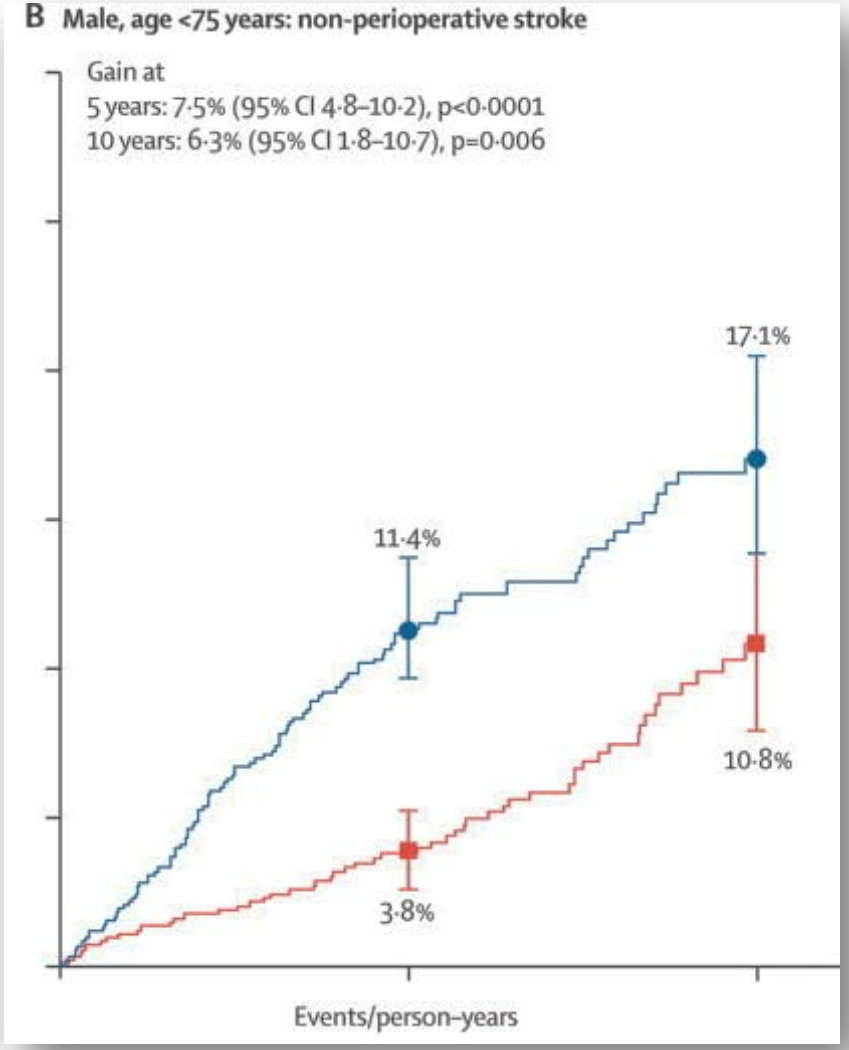
ACST 10 year outcomes:
Significant and sustained benefit from revascularization



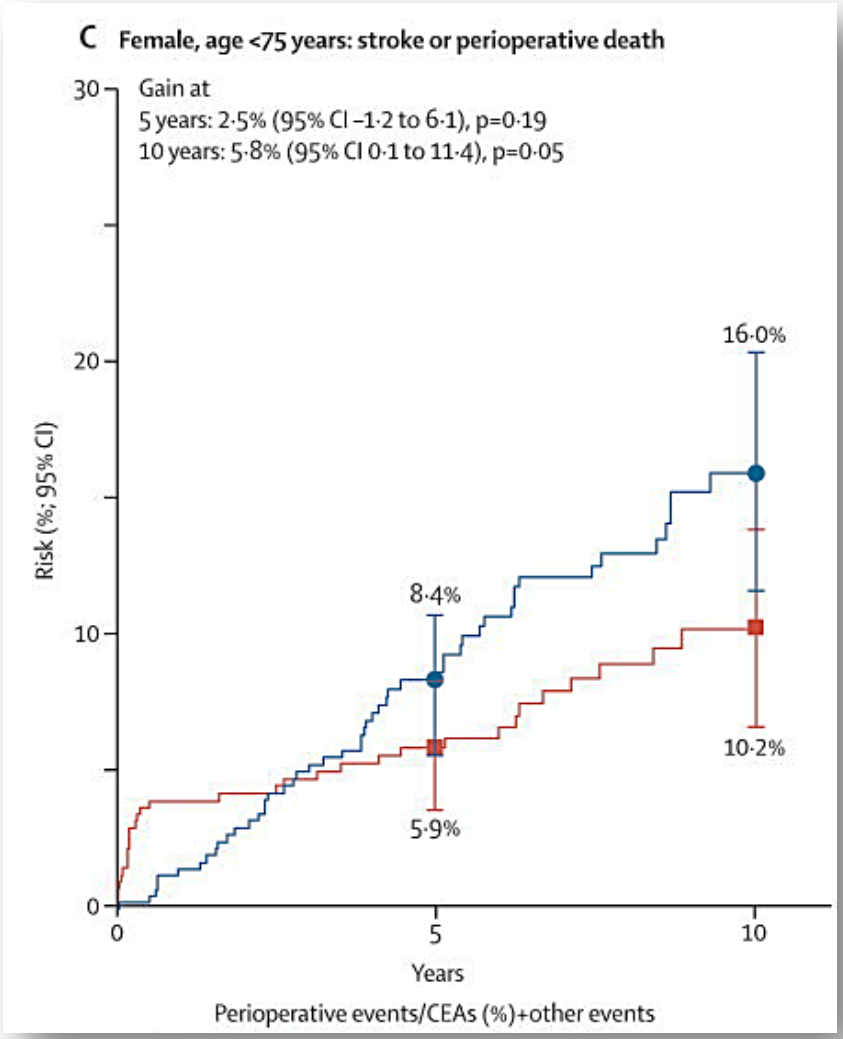


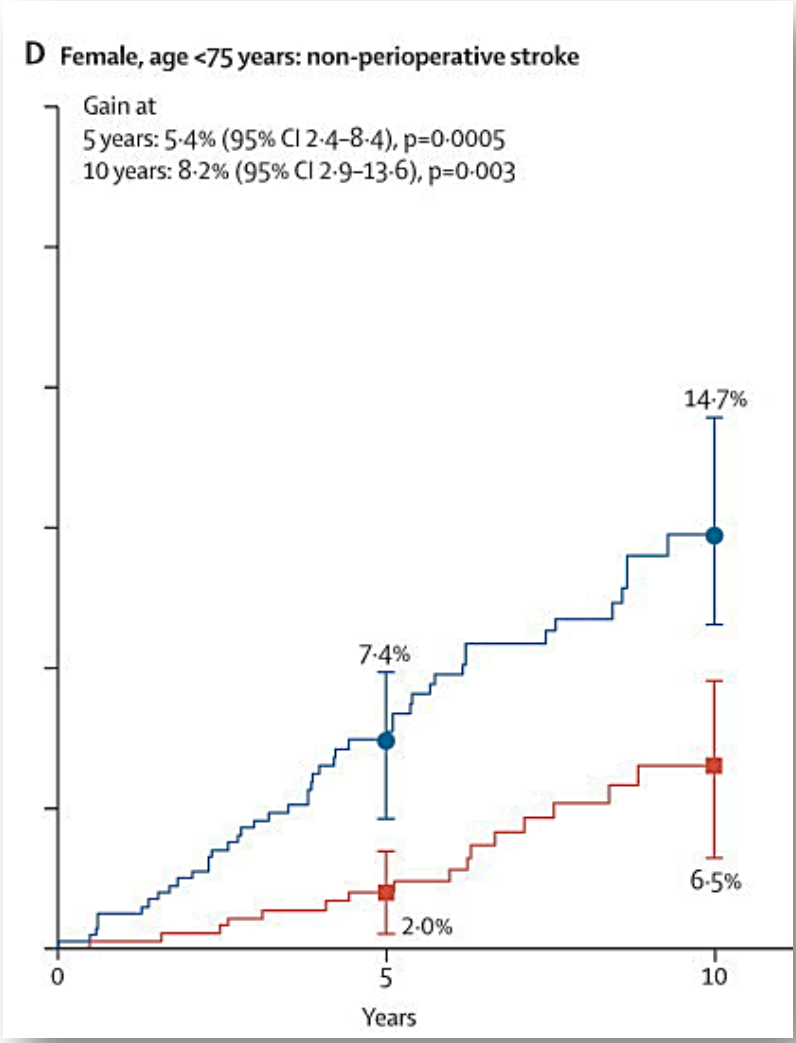
ACST outcomes:
Men benefit from revascularization





ACST outcomes:
Women benefit from revascularization





ACST outcomes:
CEA results in contralateral stroke reduction

	Allocated immediate CEA (n=1560)	Allocated deferral of any CEA (n=1560)
Mean follow-up (years) during first 5 years	3·4	3·4
Carotid strokes*	0.7%	2.2%
Ipsilateral	13 (3+4+6)	62 (24+11+27)
Contralateral	11 (3+3+5)	35 (9+8+18)
Unknown laterality	6 (5+0+1)	8 (6+0+2)
Subtotal†	30 (11+7+12)	105 (39+19+47)
Other strokes		
Ischaemic vertebrobasilar	8 (1+1+6)	8 (1+0+7)
Haemorrhagic	4 (0+2+2)	7 (4+0+3)
Subtotal	12 (1+3+8)	15 (5+0+10)
Total‡	42 (12+10+20)	120 (44+19+57)
5-year risk of stroke	3·8%	11·0%

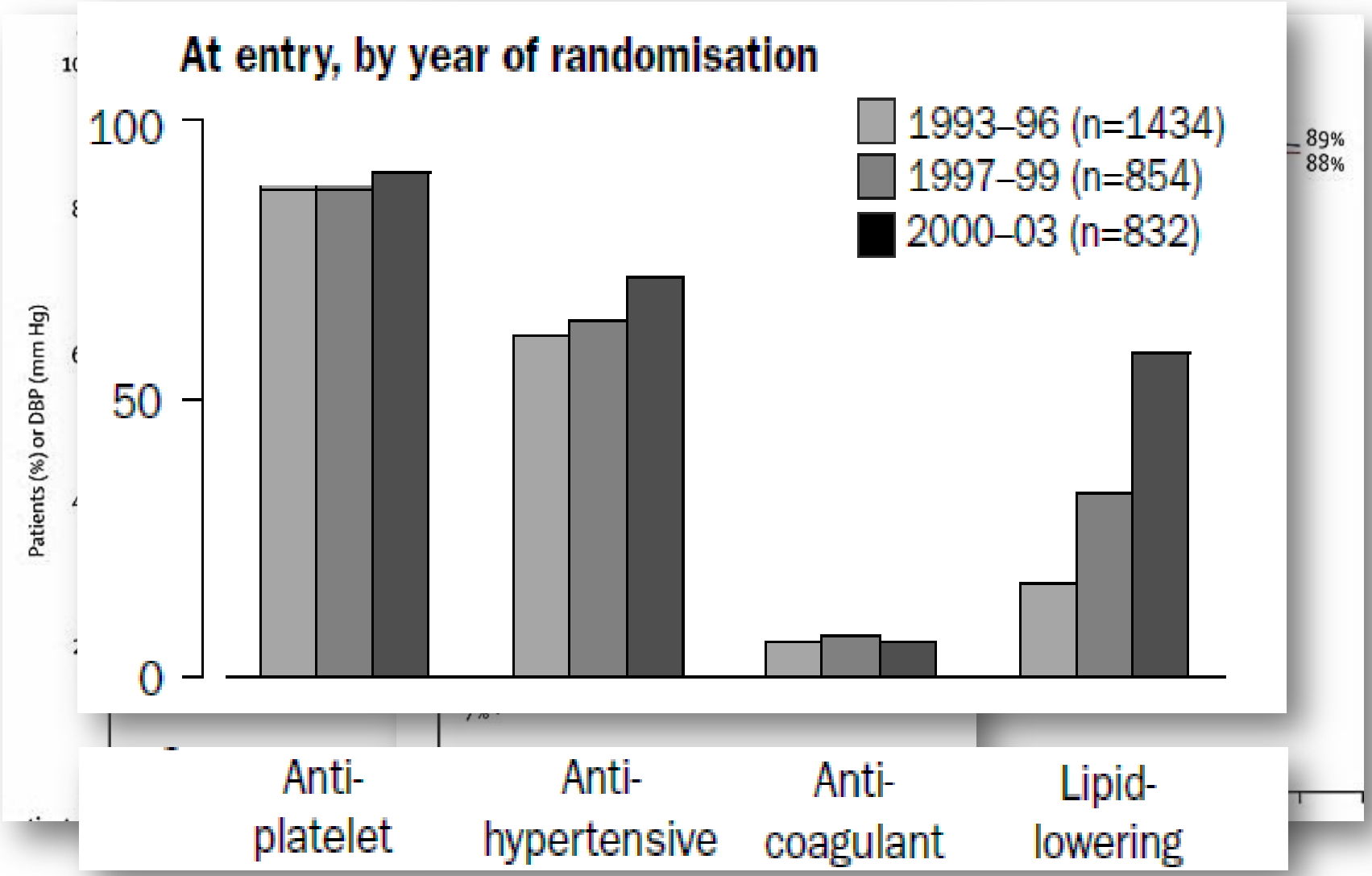
ACST outcomes:
More than ½ of deferred strokes are disabling

Category of stroke (□) or patient (■)	Number with stroke/patients and 5-year risk (%[SE]) Immediate CEA	Deferral	Absolute 5-year gain (95% CI)	Ratio of 5-year risks (95% CI) Immediate CEA:deferral
Severity of worst stroke after randomisation				
Non-disabling	12/1560 (1·1% [0·3])	47/1560 (4·3% [0·6])	3·1% (1·8:4·4)	
Disabling or fatal	18/1560 (1·6% [0·4])	58/1560 (5·3% [0·7])	3·7% (2·1:5·2)	

ACST outcomes:
Deferred surgery has twice the complication rates

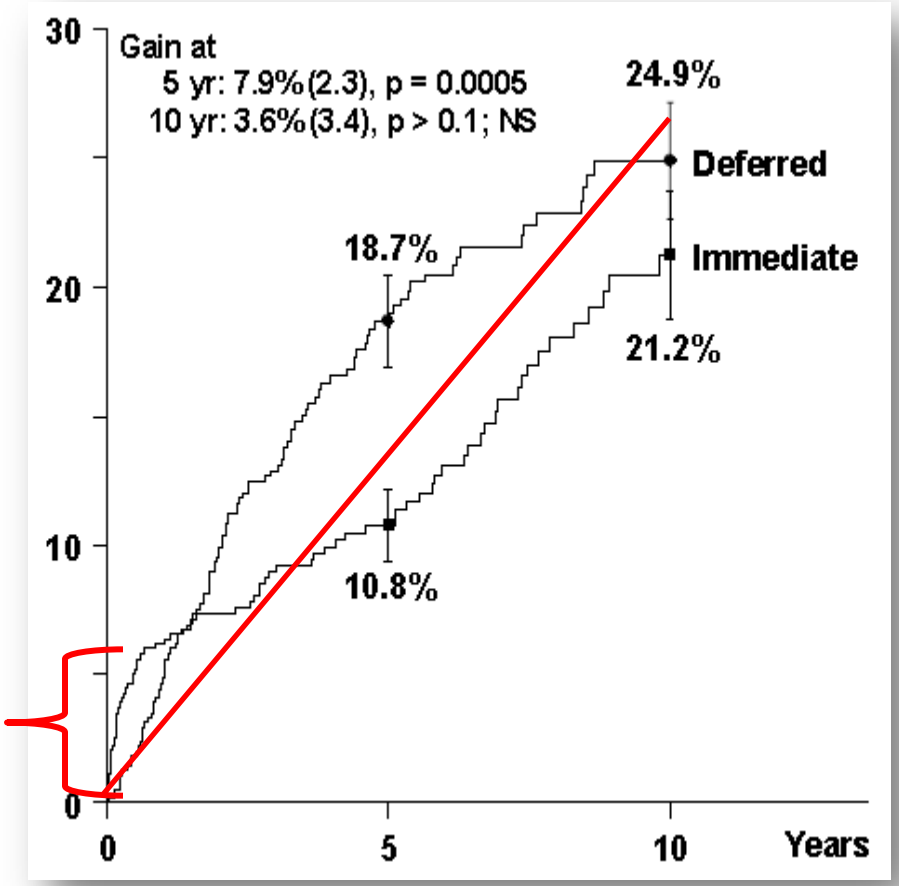
Perioperative mortality and morbidity (ie, within 30 days of CEA)	**Immediate CEA**	**Deferred CEA**
Stroke deaths†	10	2
Disabling strokes	9	3
Non-disabling strokes	16	6
Cardiac deaths	5	0
Non-fatal myocardial infarctions	10	0
Other deaths	0	0
Any perioperative stroke or death	40	11‡
% of number of CEAs	2·8%	4·5%
(95% CI)	(2·0–3·9)	(2·2–8·0)

Significant medication penetration in ACST

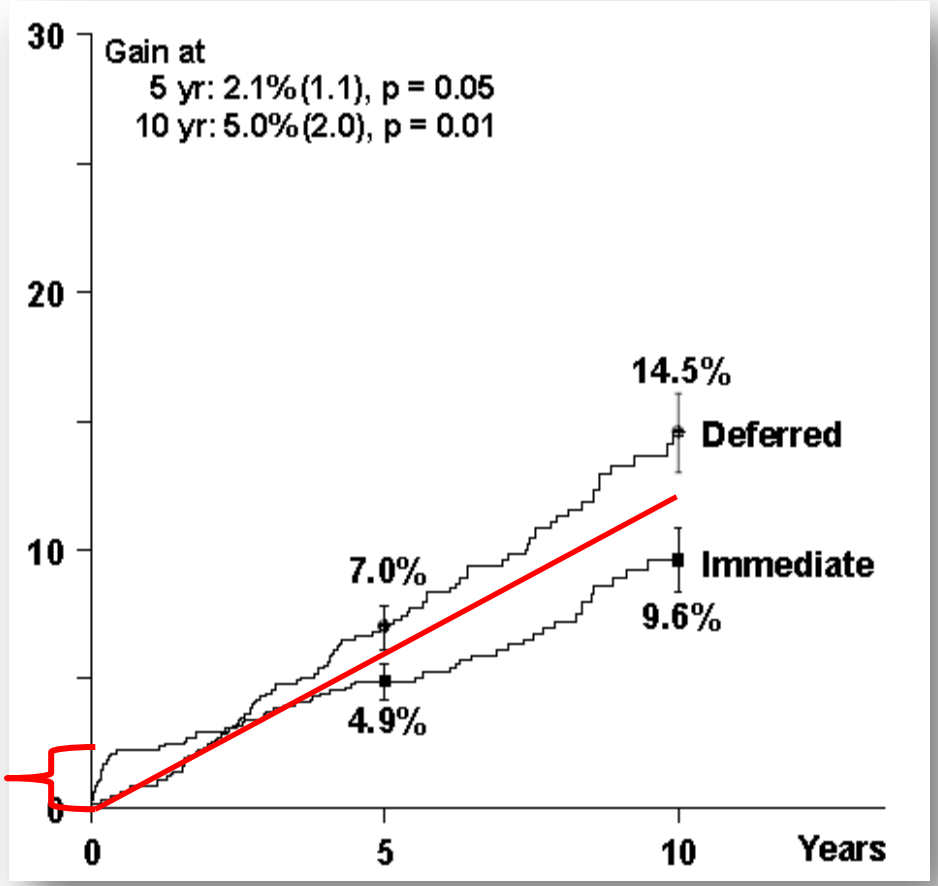


ACST:
Population with lipid-lowering Rx demonstrate continued benefit with CEA

Not on lipid-lowering therapy at entry



On lipid-lowering therapy at entry



Best Medical Therapy in carotid artery disease: what's missing

- Knowledge as to the correct "cocktail" of medication class, specific to carotid-related targets
  - What is "Best Medical Therapy"?
    - What BP med? What target BP?
    - Which lipid med? What target lipid levels? For LDL? For HDL?
    - How do we improve smoking cessation rates?

- Measures and assurances of compliance and side effect issues
  - NHANES reports <25% patients achieve BP goal

- Randomized data showing equivalence or superiority to revascularization in *asymptomatic severe carotid stenosis*

What role does CAS play in the standard surgical risk *asymptomatic* patient?

Periprocedural outcomes in CREST: No difference between CAS and CEA for Asx

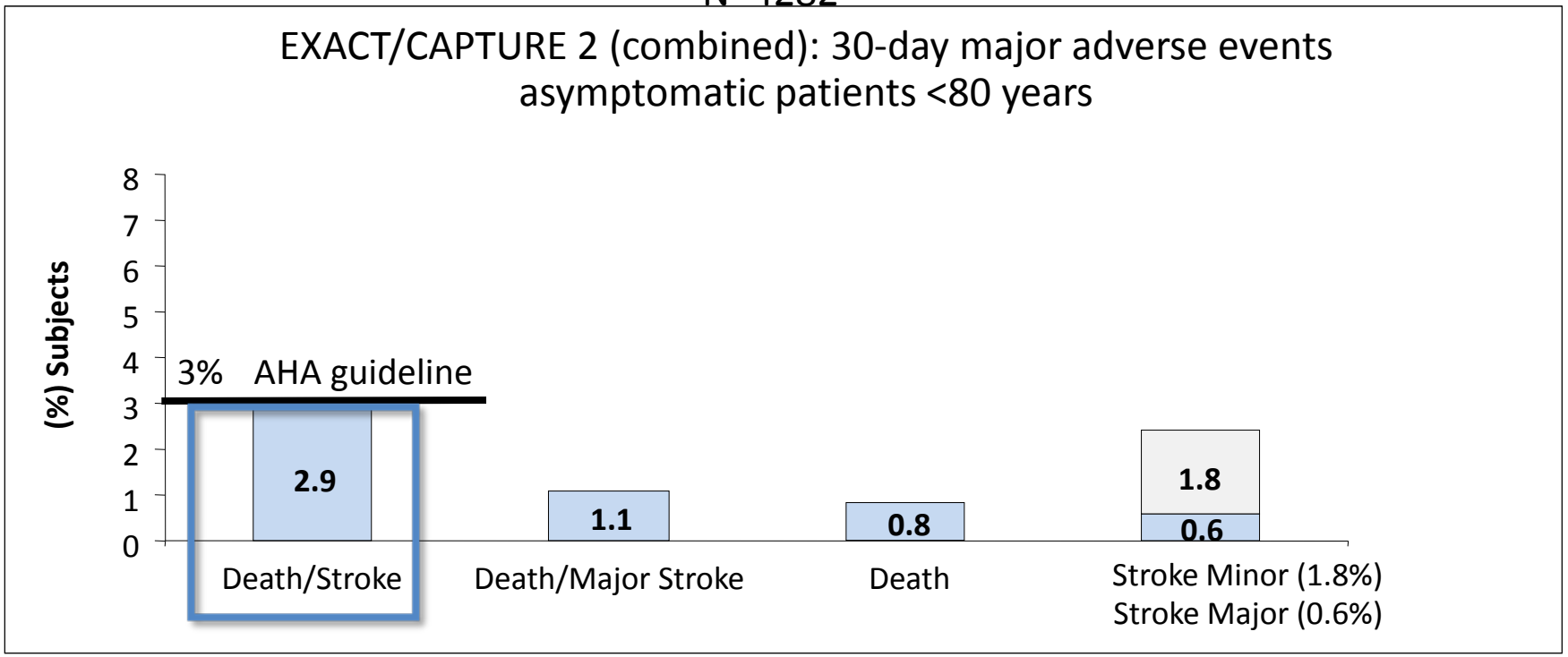
	CAS No. of Events (Proportion ± SE‡)	CEA No. of Events (Proportion ± SE‡)	Percent Absolute Treatment Effect (95% CI)‡	HR (95% CI)§	P‖
MI end point					
Asymptomatic	7 (1.2 ± 0.4)	13 (2.2 ± 0.6)	−1.0 (−2.5 to 0.4)	0.55 (0.22 to 1.38)	0.20
Symptomatic	7 (1.0 ± 0.4)	15 (2.3 ± 0.6)	−1.2 (−2.6 to 0.1)	0.45 (0.18 to 1.11)	0.083
Stroke end point (any stroke within periprocedural† period)					
All stroke end points					
Asymptomatic	15 (2.5 ± 0.6)	8 (1.4 ± 0.5)	1.2 (−0.4 to 2.7)	1.88 (0.79 to 4.42)	0.15
Symptomatic	37 (5.5 ± 0.9)	21 (3.2 ± 0.7)	2.3 (0.1 to 4.5)	1.74 (1.02 to 2.98)	0.043
Major stroke					
Asymptomatic	3 (0.5 ± 0.3)	2 (0.3 ± 0.2)	0.2 (−0.6 to 0.9)	1.50 (0.25 to 9.95)	0.66¶
Symptomatic	8 (1.2 ± + 0.4)	6 (0.9 ± 0.4)	0.3 (−0.8 to 1.4)	1.32 (0.46 to 3.80)	0.61¶
Minor stroke					
Asymptomatic	12 (2.0 ± 0.6)	6 (1.0 ± 0.4)	1.0 (−0.4 to 2.4)	2.06 (0.77 to 5.51)	0.15
Symptomatic	29 (4.3 ± 0.8)	15 (2.3 ± 0.6)	2.0 (0.1 to 4.0)	1.91 (1.03 to 3.57)	0.042
Primary end point (any stroke, MI, or death within periprocedural† period)					
Asymptomatic	21 (3.5 ± 0.8)	21 (3.6 ± 0.8)	0.0 (−2.2 to 2.1)	1.02 (0.55 to 1.86)	0.96
Symptomatic	45 (6.7 ± 1.0)	35 (5.4 ± 0.9)	1.4 (−1.2 to 3.9)	1.26 (0.81 to 1.96)	0.30

Symptomatic 45 (6.7 ± 1.0) 35 (5.4 ± 0.9) 1.4 (−1.2 to 3.9) 1.26 (0.81 to 1.96) 0.30

CAS achieves AHA guidelines in asymptomatic patients

Large, prospective, multicenter neurologically-audited/independent adjudication single arm studies in high-surgical risk patients

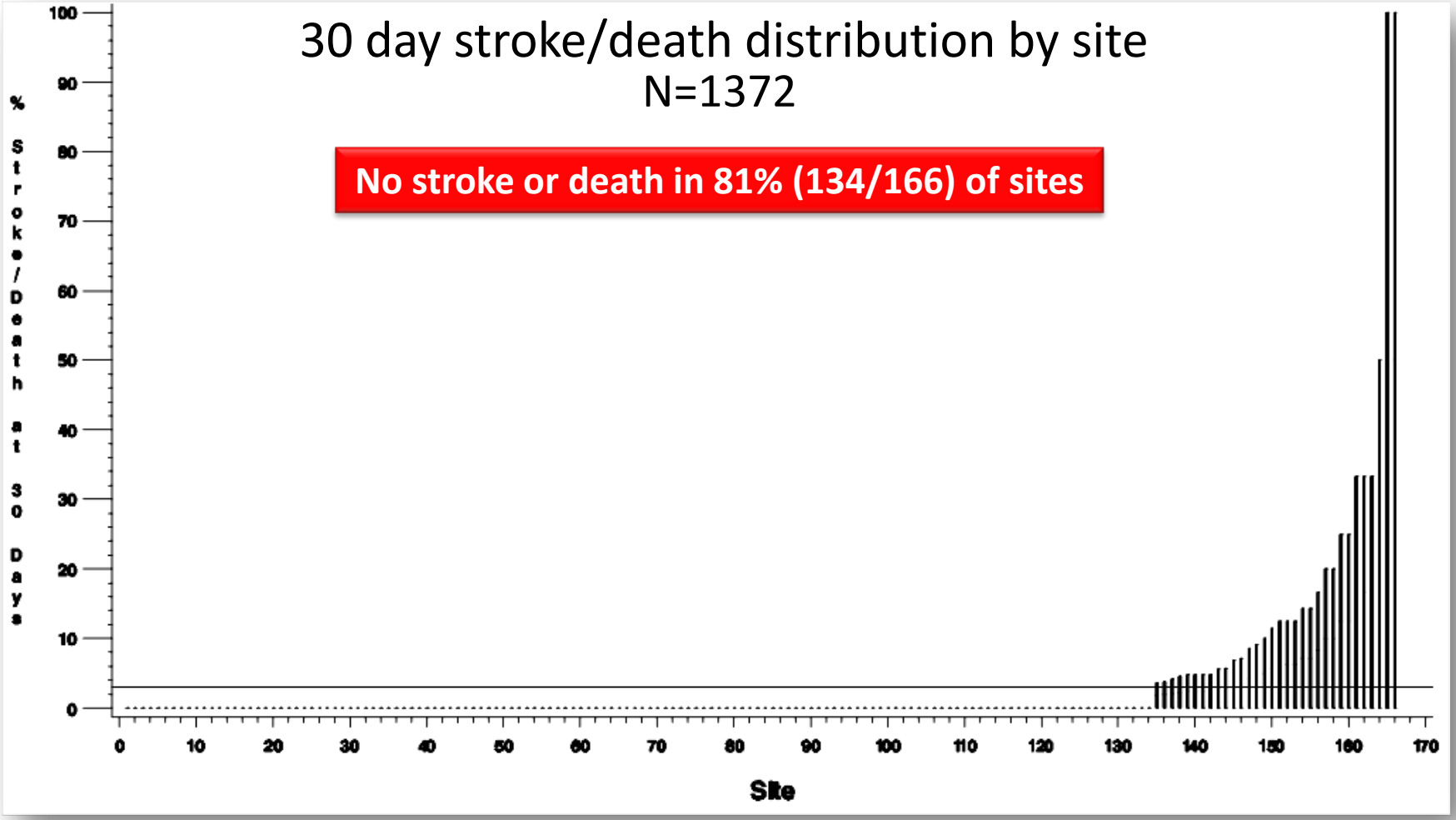
N=4282



Hierarchical- Includes only the most serious event for each patient and includes only each patient first occurrence of each event.

Gray et al. Circ Cardiovasc Interv. 2009 Jun;2(3):159-66

CAPTURE 2: Asymptomatic <80 y.o. patients



Gray et al. JACC Cardiovasc Interv. 2011 Feb;4(2):235-46

Contemporary outcomes demonstrate continued improvement for CAS in asymptomatic patients: ACT 1 Lead-in patients

Event	30 days, N=118
Death, Stroke and MI*	1.7%
All Stroke and Death*	1.7%
Major Stroke and Death*	0.0%
Death	0.0%
All Stroke	1.7%
Major Stroke	0.0%
Minor Stroke	1.7%
MI	0.0%
	31-365 days, N=77
Ipsilateral Stroke	0.0%

***Hierarchical – Includes only the most serious event for each patient**

2011 Multi-Society Guideline Document: Asymptomatic patients

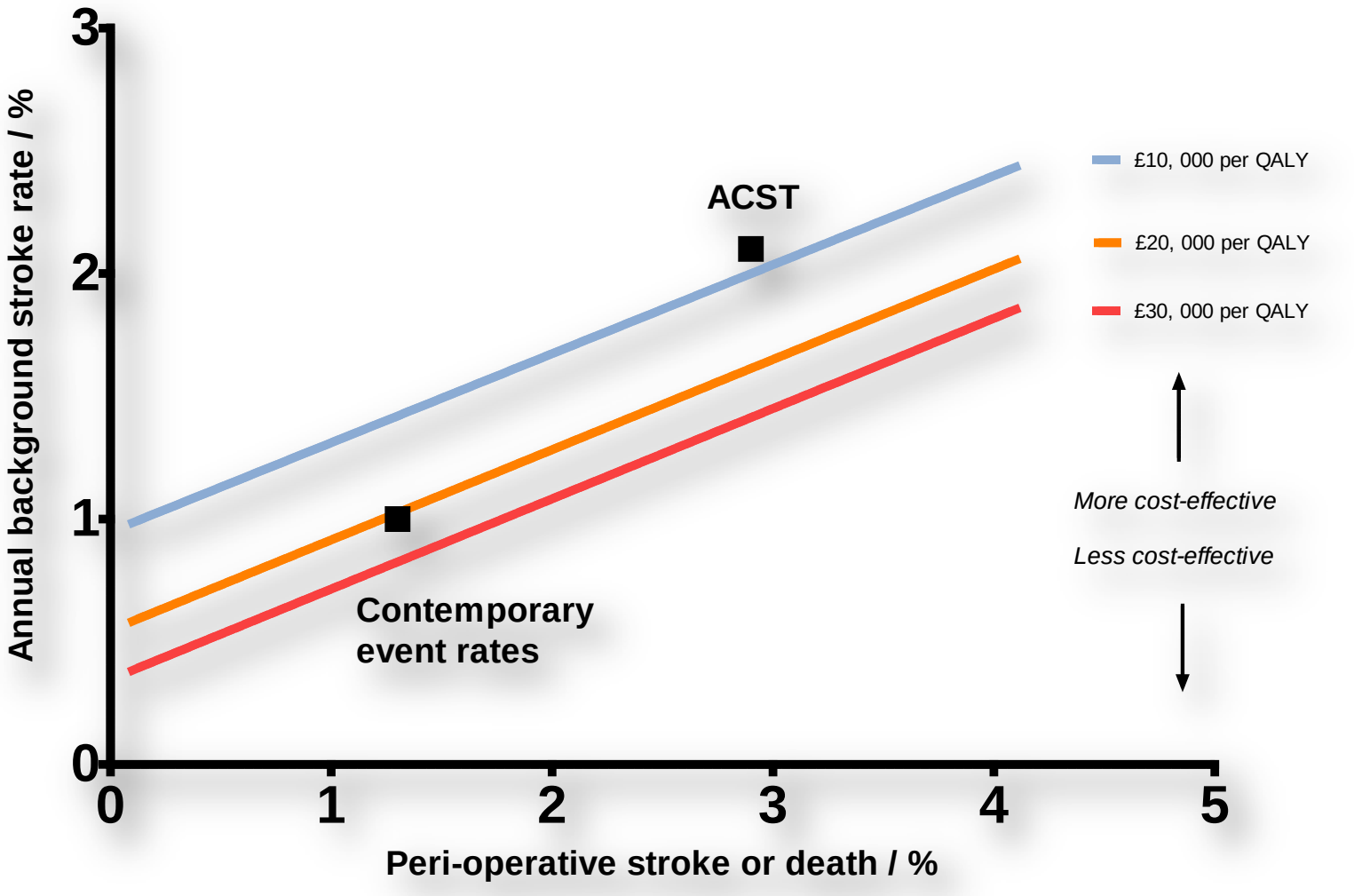
Class IIa

1. It is reasonable to perform CEA in asymptomatic patients who have more than 70% stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low.[38,40–44] *(Level of Evidence: A)*
2. It is reasonable to choose CEA over CAS when revascularization is indicated in older patients, particularly when arterial pathoanatomy is unfavorable for endovascular intervention.[39,45–49] *(Level of Evidence: B)*
3. It is reasonable to choose CAS over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery.[50–54]§ *(Level of Evidence: B)*

Managing patients with asymptomatic carotid stenosis: Summary

- Asymptomatic carotid stenosis is a risk factor for stroke
- Surgical revascularization therapy is proven beneficial vs. unmonitored (but probably real world) medical therapy
- CAS outcomes have demonstrated similar outcomes to CEA (CREST), achieved AHA guidelines, and now is Class 2b recommendation in asymptomatic patients (CEA Class 2a)
- The role of medical therapy remains a tantalizing but unproven alternative to revascularization in patients with established severe carotid stenosis.
  - Until such time as this benefit is demonstrated to be superior, the available randomized controlled data support revascularization in suitable patients

Patient level (ACST) cost-effectiveness analysis for carotid revascularization



Ankur Thapar: Imperial College, London

Final perspectives on CEA, CAS and Best Medical Therapy

- The judicious and selective use of these therapies can result in overall improved patient outcomes:
  - Fewer strokes, fewer MI's
  - Less disability and less CV mortality

- CEA and CAS have complementary, not competitive roles in the patient requiring revascularization

Thank you

Back-up slides

Carotid stenosis: Public Health Implications

- Stroke is the 3rd leading cause of death and *the leading cause of disability* in the US
- Carotid disease is estimated to be responsible for between 12% and 21% of all anterior circulation strokes
- This translates into roughly 90,000-150,000 strokes/year in the US
  - The average age of carotid patient in studies over the past 20 years is ~68-72
- The result is that carotid territory stroke is a significant public health issue, and especially affects the Medicare population

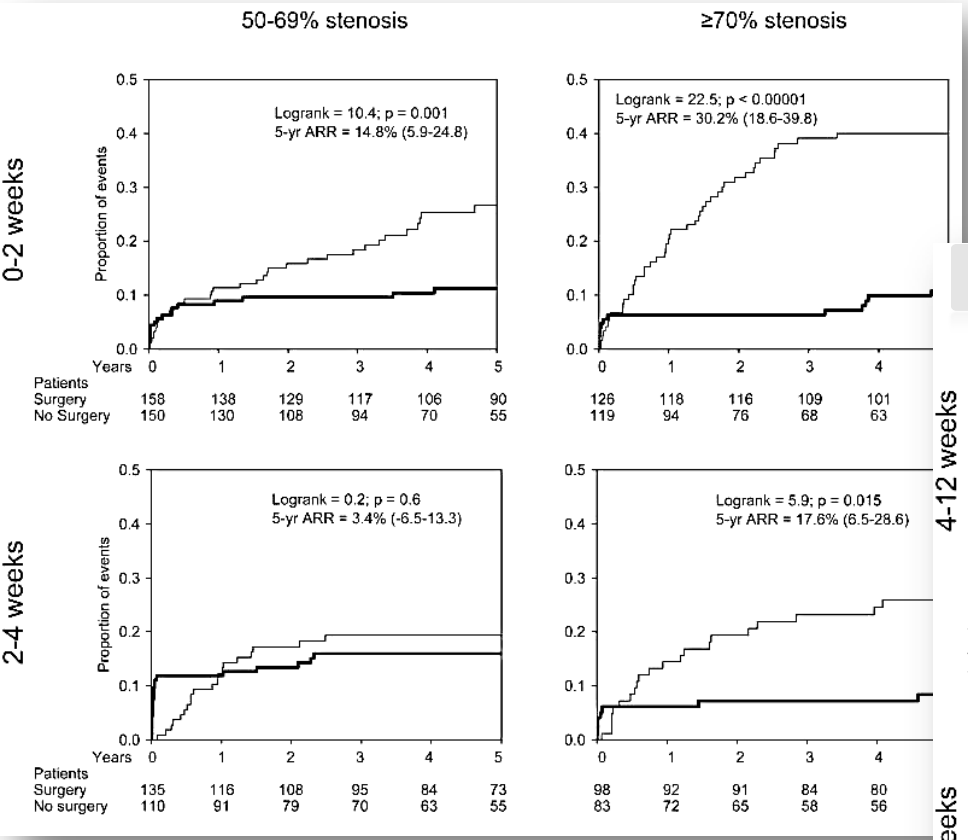
MRI acquisition and enhancements

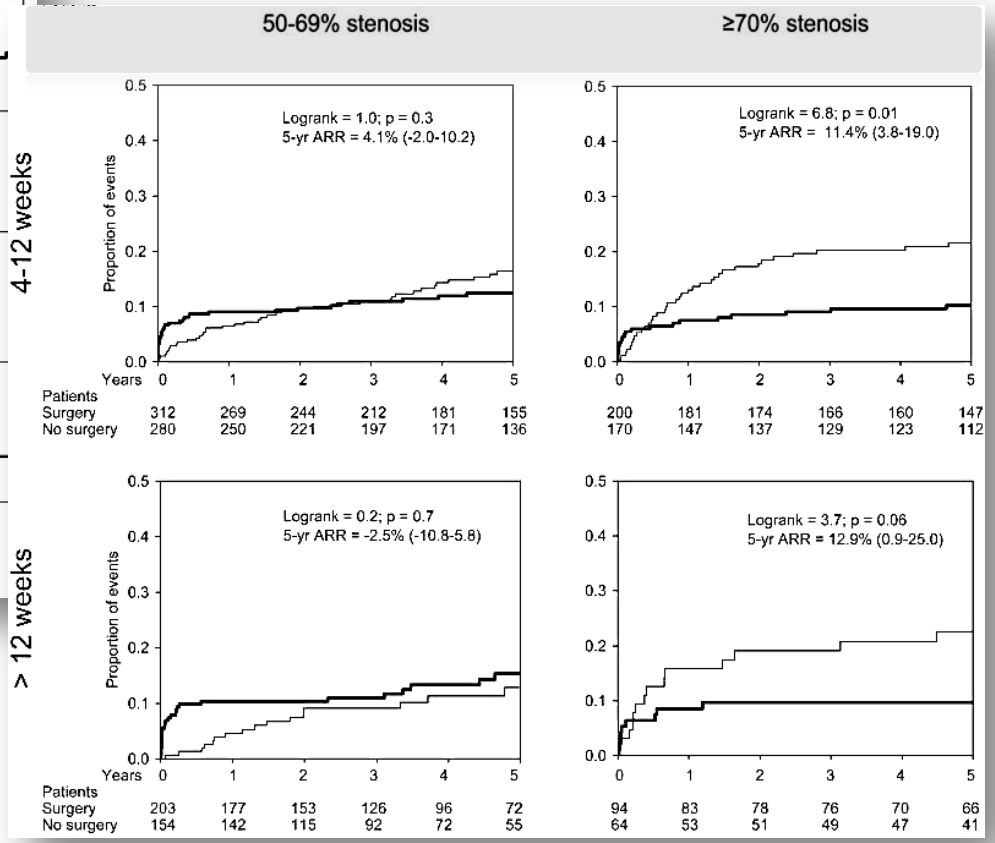
- Fat-suppression
  - Reduces adjacent fat signals allowing better plaque characterization
- Contrast imaging
  - Gadolinium
    - Differentiates fibrous cap from lipid core
    - USPIO (ultra-small paramagnetic iron oxide) allows detection of macrophage infiltration
- Advances in receiver coil and pulse sequence design have resulted in high spatial resolution imaging of plaques

30-Day death/stroke rate for the 2nd half of CREST symptomatic and asymptomatic patients

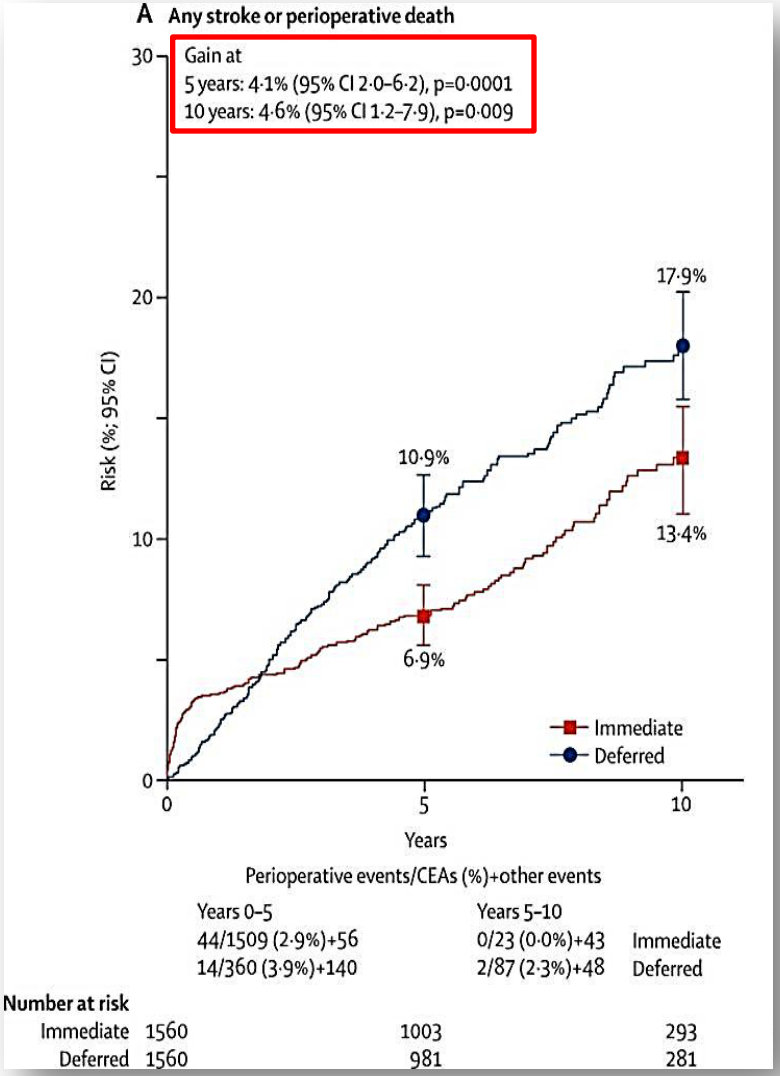
	Event Rate±SE (N)		Difference
	CAS	CEA	95% CL
2nd Half of Patients	3.73% (21/563)	2.38% (14/588)	1.35% [-0.64%, 3.34%]

Benefit of CEA decreases with time from event





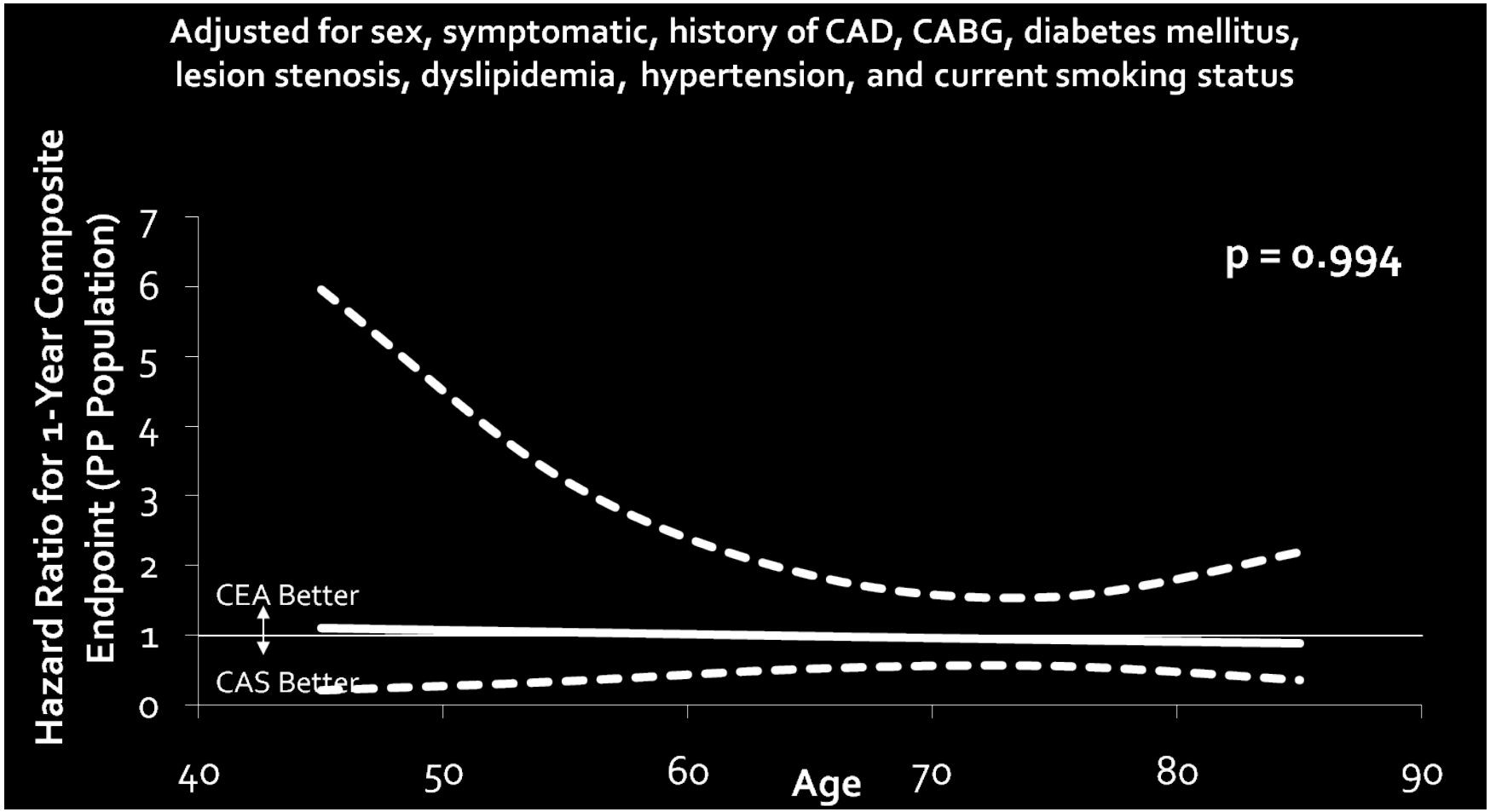
ACST 10-year results are the most rigorous comparison of revascularization and BMT to date



- Revascularization continues to show statistically significant benefit at 5- and 10-year follow up
- Patients followed up to 2009
- Patients received intensive medical therapy
  - 80% of subjects on lipid lowering drugs
  - 88% of subjects on anti-hypertensives
  - 88-89% of subjects on anti-platelets
- Post-hoc analysis found CEA benefit was clearest for patients on lipid-lowering medication or less than age 75 years

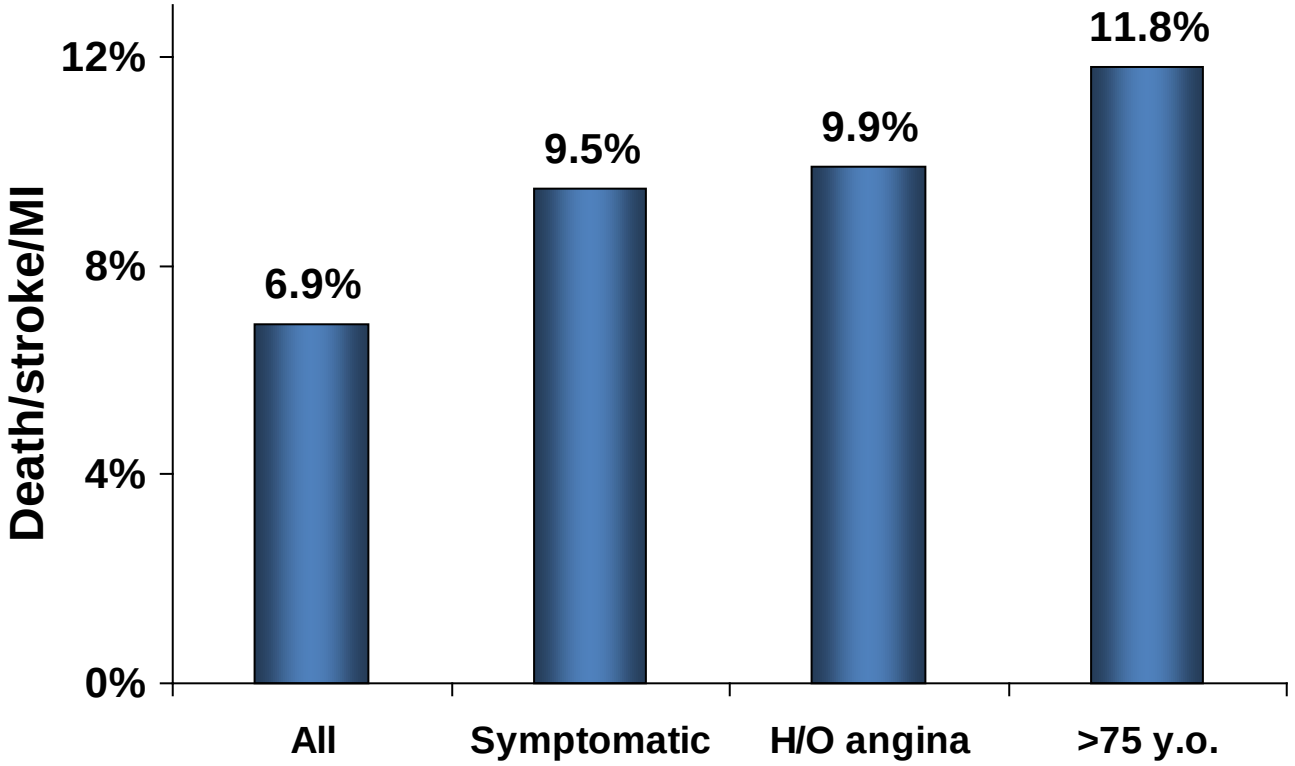
* Halliday A, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomized trial. *Lancet* 2010;376:1074-84.

Analysis of Interaction between Age and Treatment on 1-Year Composite Endpoint (2nd Half of CREST)



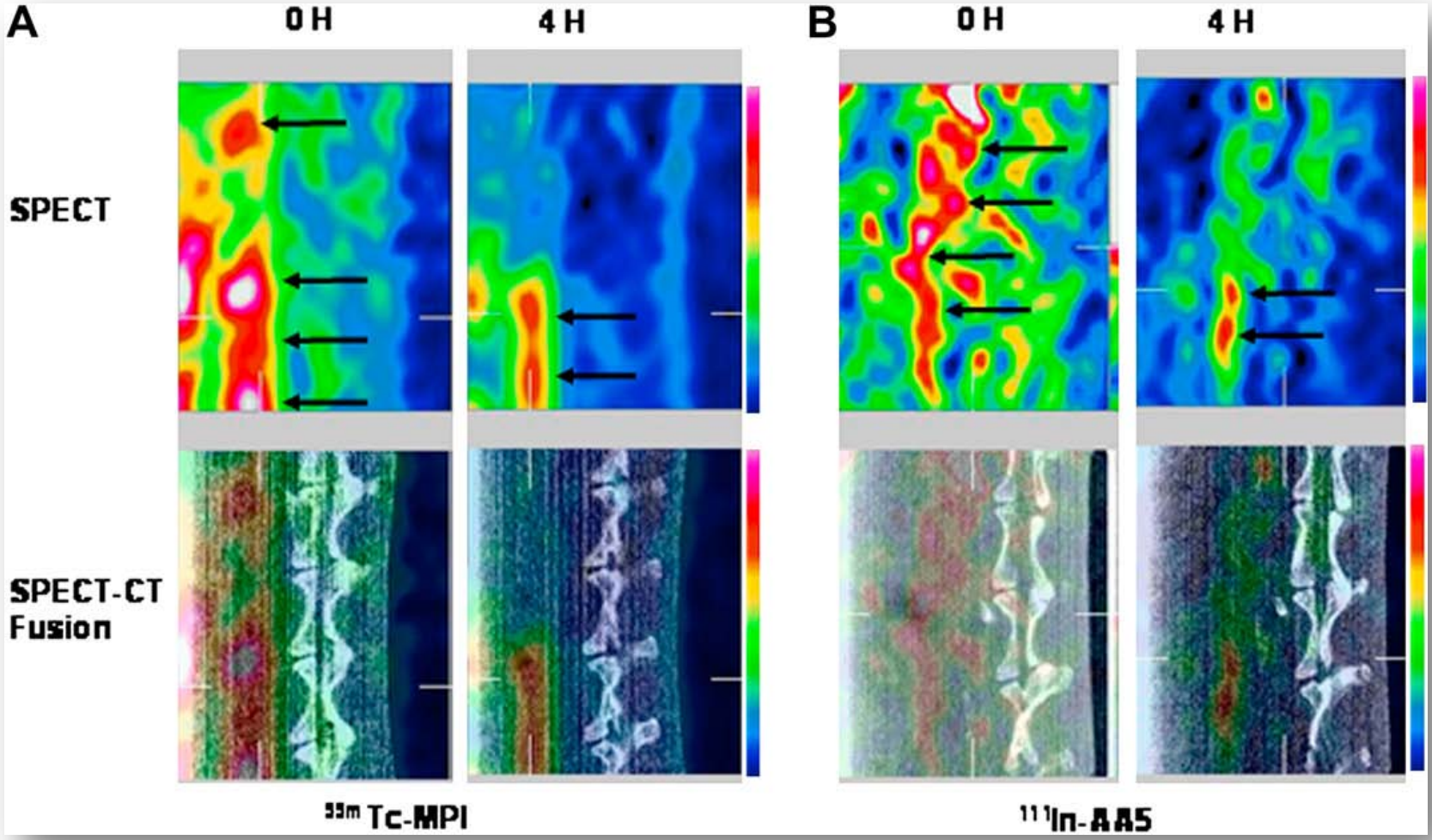
CEA in US academic centers confirms non-trial, higher risk patients do less well

12 sites in-hospital retrospective outcomes>1100 patients



McCrory DC et al. *Stroke* 1993;24:1285-1291

Assessment of proteolysis: Labeled MMPI
Assessment of apoptosis: Annexin A5



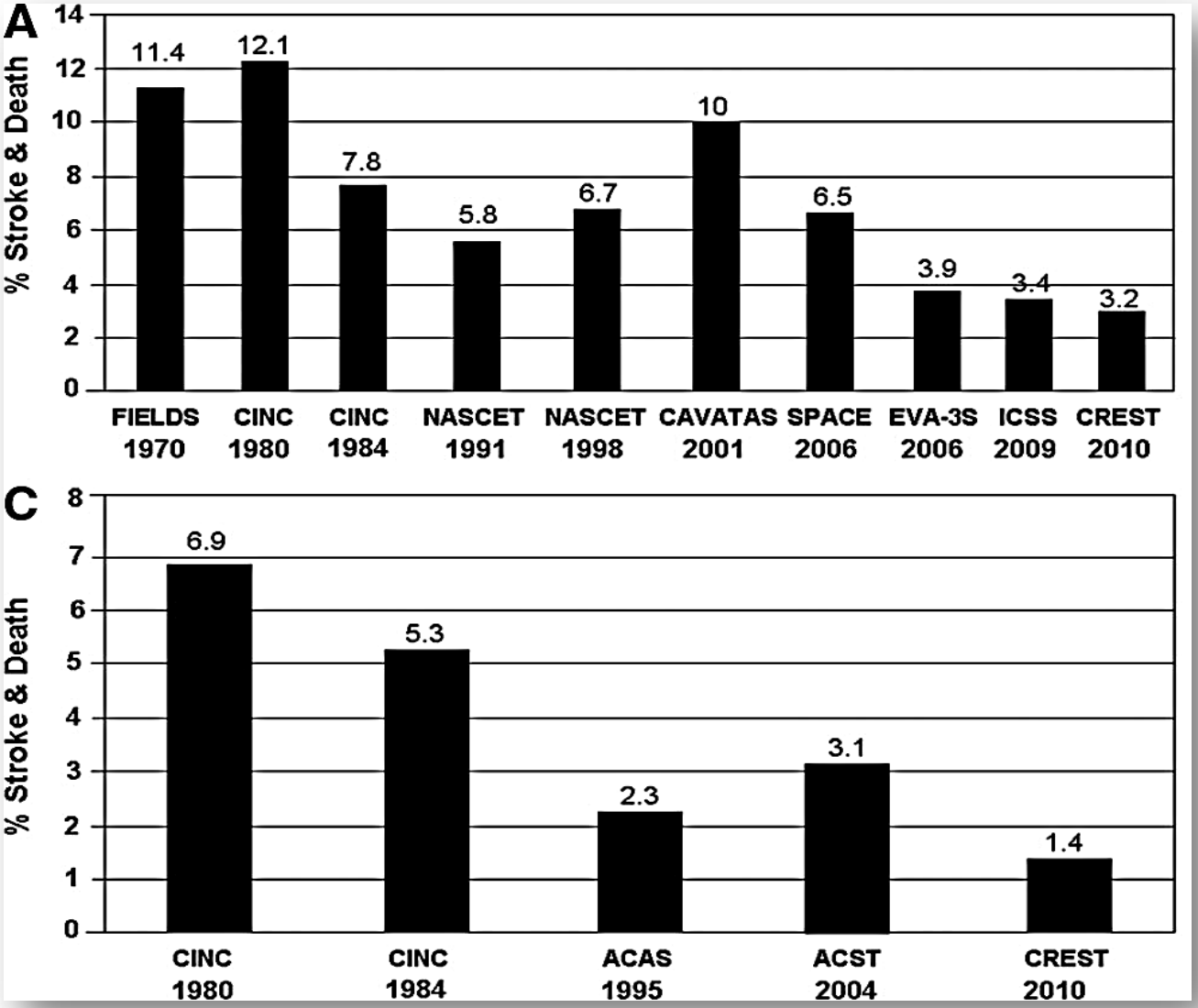
Hypercholestrolemic rabbit aorta

Hermus L et al. Eur J Vasc Endovasc Surg (2010) 39, 125e133

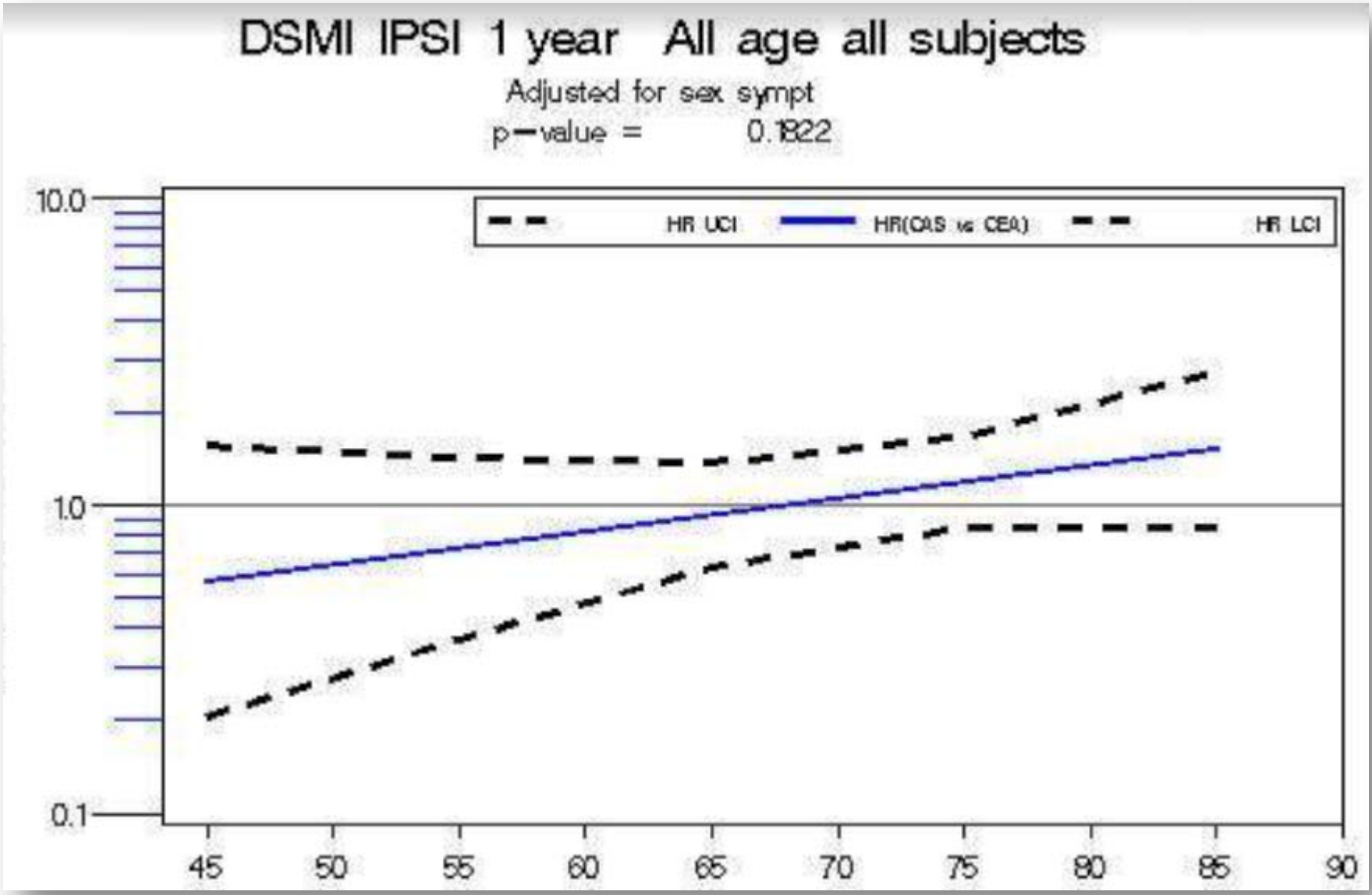
Macro-evolution in CEA outcomes over the past 4 decades

Symptomatic

Asymptomatic



No difference by age between CAS and CEA: PP analysis and appropriate log scale

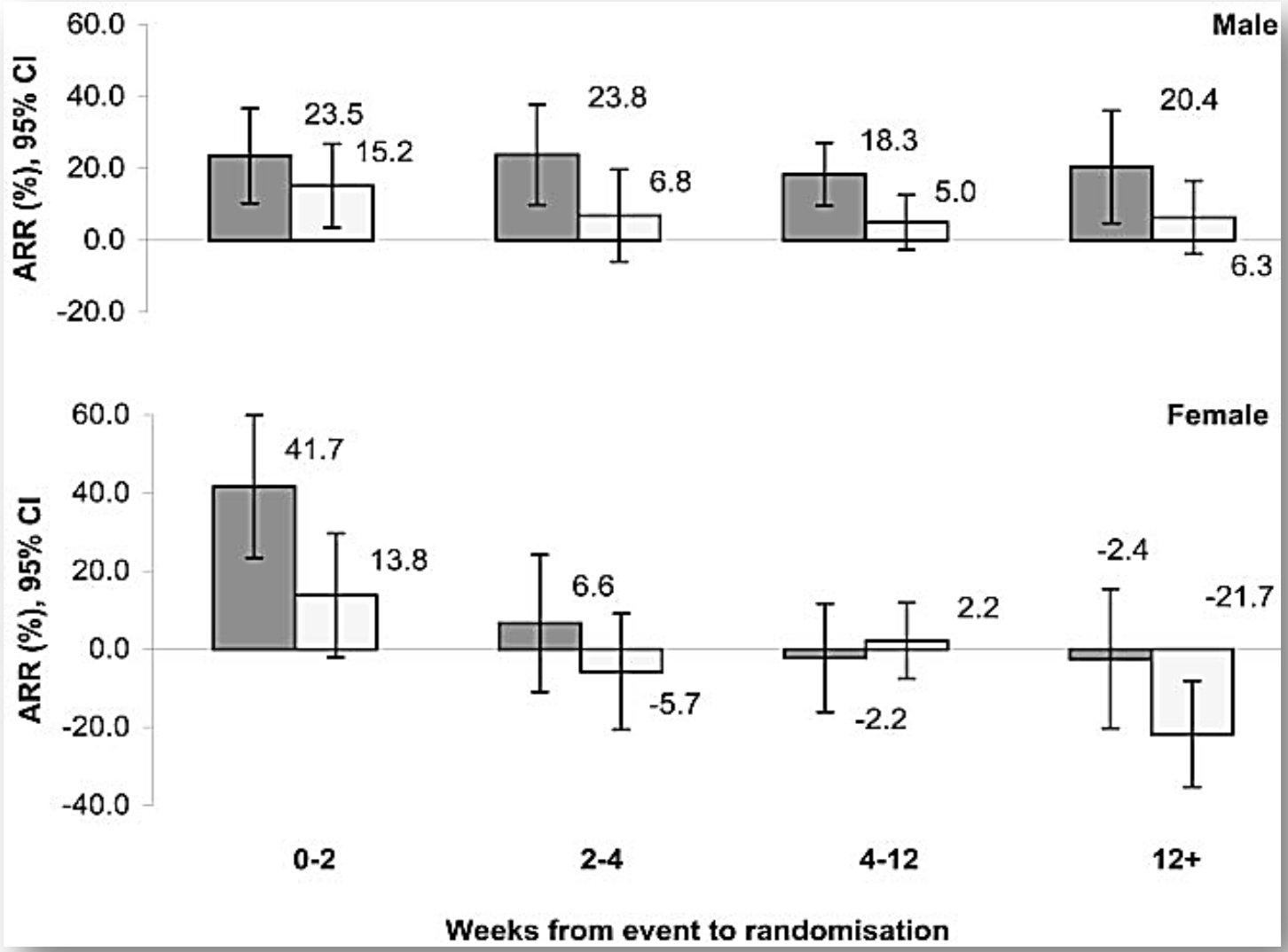


CAS in high surgical risk asymptomatic patients

Class IIb

1. Prophylactic CAS might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography, 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established.[39] *(Level of Evidence: B)*
2. In symptomatic or asymptomatic patients at high risk of complications for carotid revascularization by either CEA or CAS because of comorbidities,‖ the effectiveness of revascularization versus medical therapy alone is not well established.[42,43,47,50–53,56–58] *(Level of Evidence: B)*

Sex, stenosis and time to CEA all influence benefit of CEA



Rothwell PM et al. Stroke 2004 Dec:35 (12):2855-61

High surgical risk CEA: Increased risk of stroke/death

- Cleveland Clinic experience
  - 10 years of CEA
- 3061 operations retrospectively designated high risk if they had:
  - CAD
  - COPD
  - CRI
- Outcomes for in-hospital stroke/death
  - High risk: 7.4%
  - Low risk: 2.9%
  - $p<0.0005$

Ouriel et al. *J Vasc Surg* 2001 Apr 3; 33(4): 728-32

These analyses purport observational trends in medical outcomes in patients with carotid stenosis