Atherosclerotic Carotid Bifurcation Stenosis:

Primary and Secondary Prevention Strategies

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Faculty Disclosure

- William A. Gray, MD

- For the 12 months preceding this CME activity, I disclose the following types of financial relationships:

- Honoraria received from and consulted for:
- Abbott Vascular
- Boston Scientific
- Cook
- Cordis/Johnson & Johnson
- Medtronic
- Medrad/Possis
- WL Gore

Faculty Disclosure (continued)

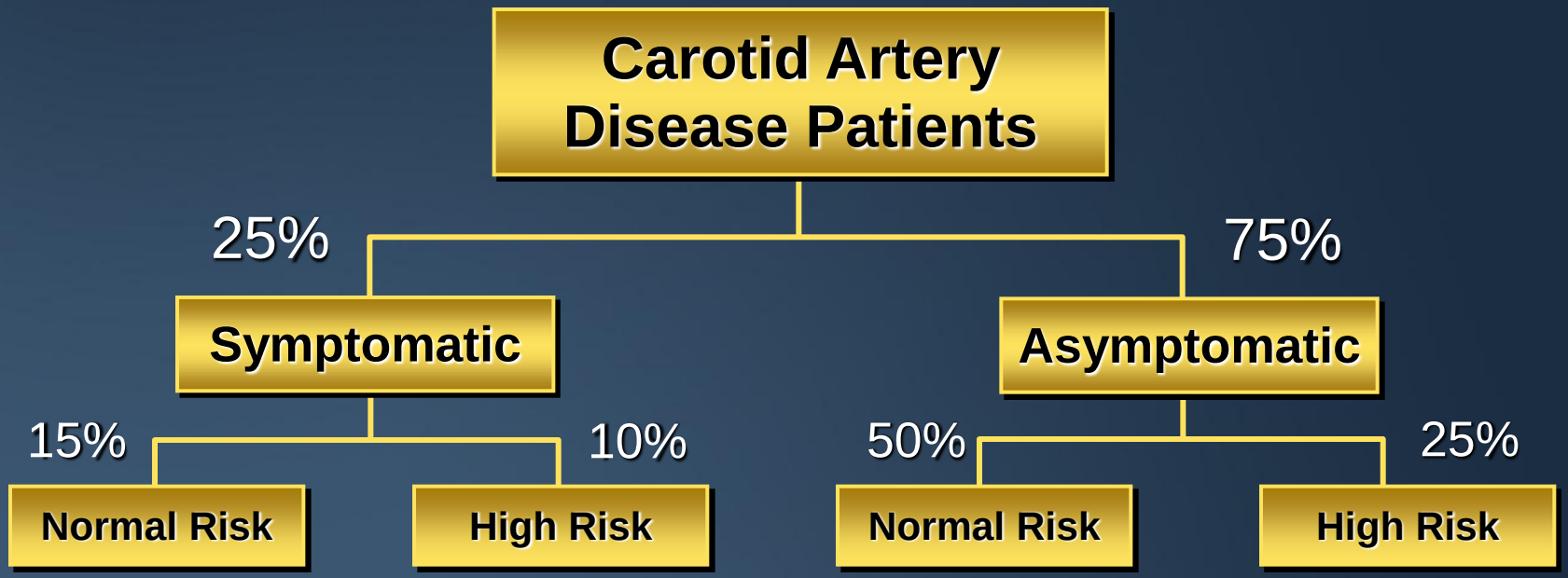
- William A. Gray, MD

- Held common stock in:
  - Biocardia
  - Contego

- Research, clinical trial, or drug study funds received from:
  - Abbott Vascular
  - Cordis/Johnson & Johnson
  - Medtronic

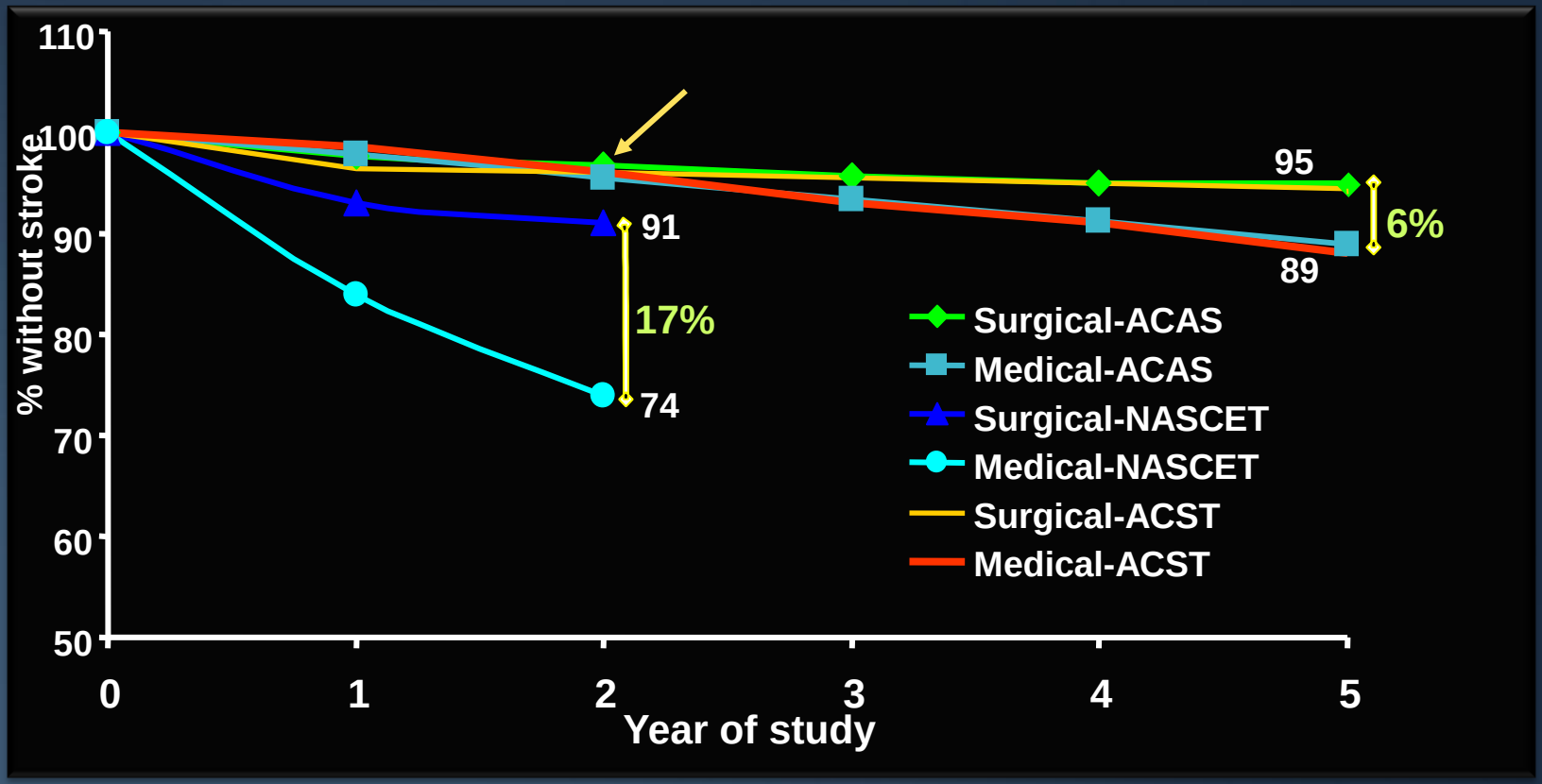
- I will be discussing products that are investigational or not labeled for use under discussion.

US population distribution of carotid disease intervention

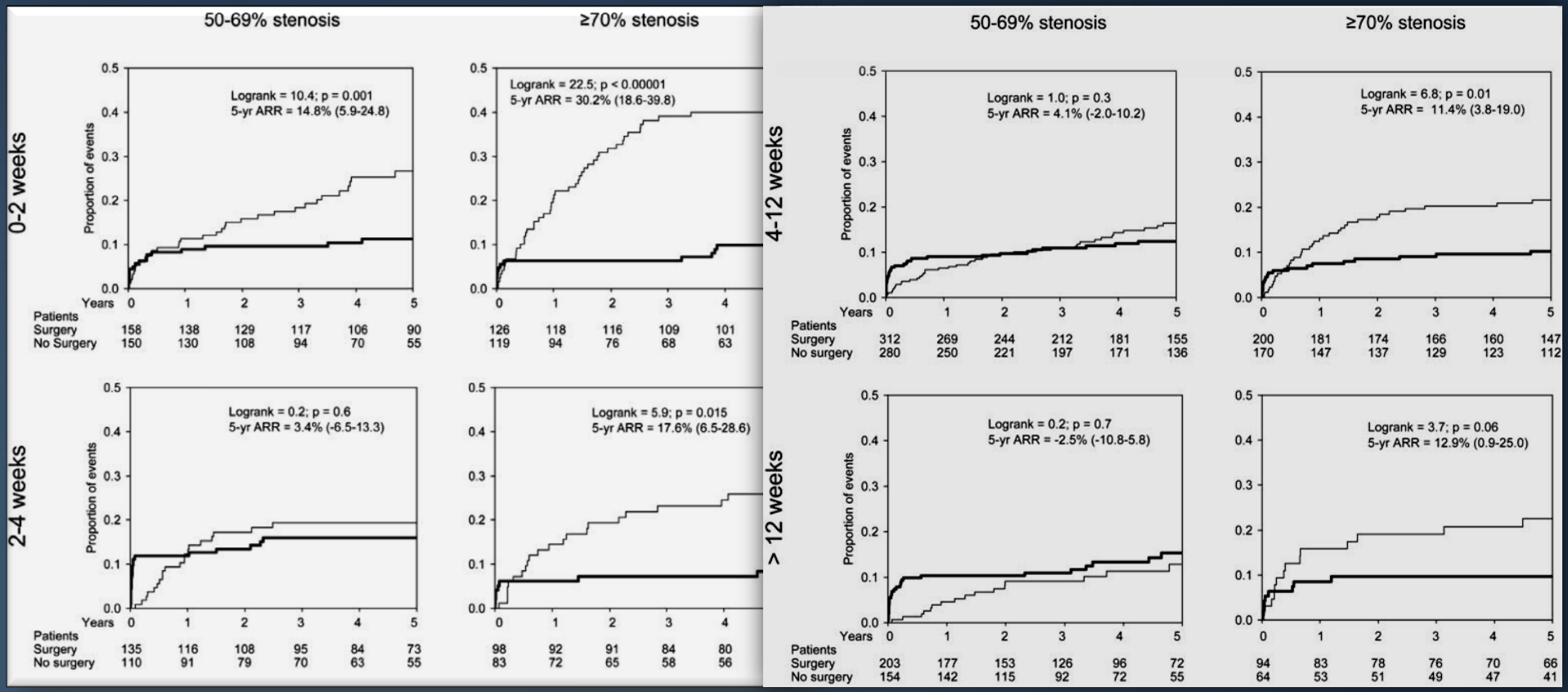


Data establishing revascularization as standard of care for secondary prevention in symptomatic patients

NASCET: Profound benefit of CEA in symptomatic patients



Benefit of CEA decreases with time from event



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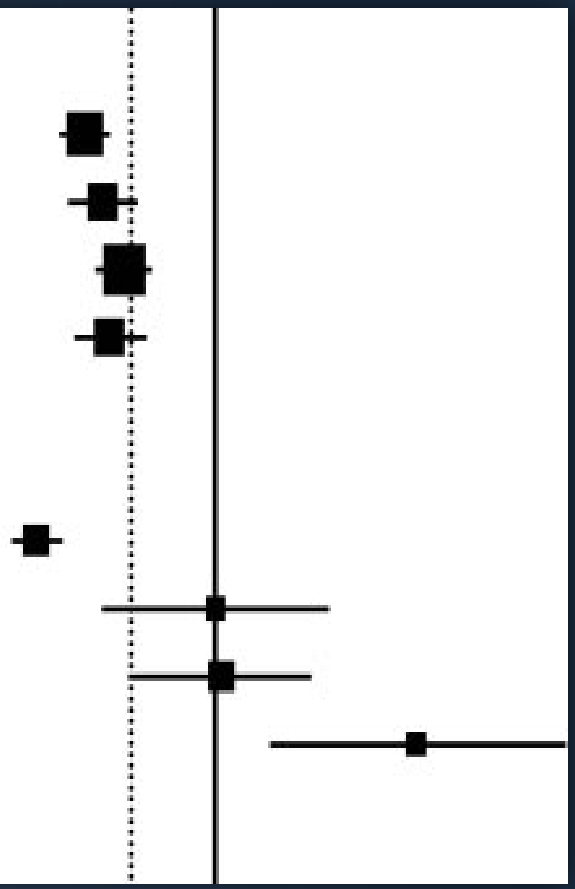
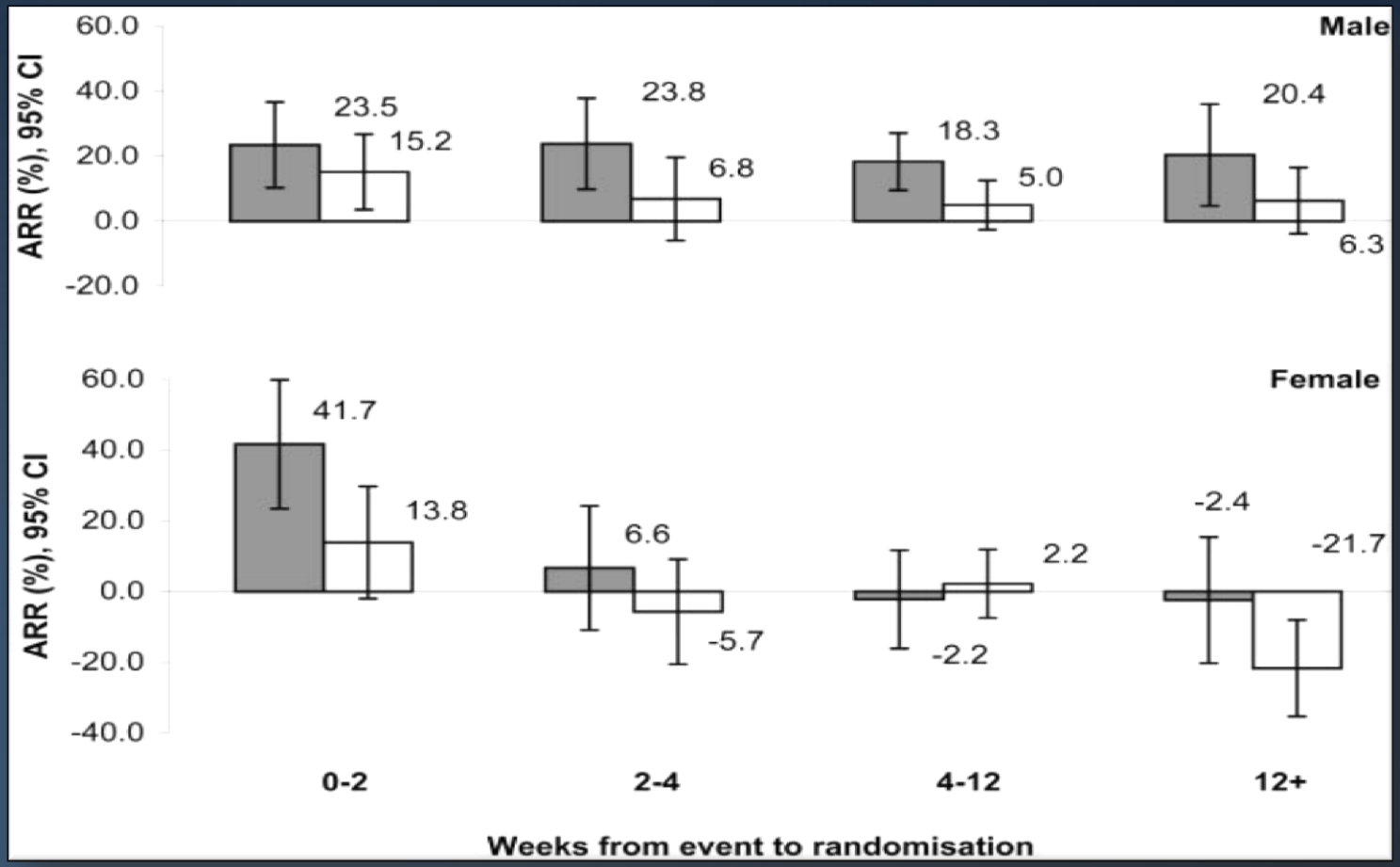
Effect of CEA timing especially pronounced in females

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

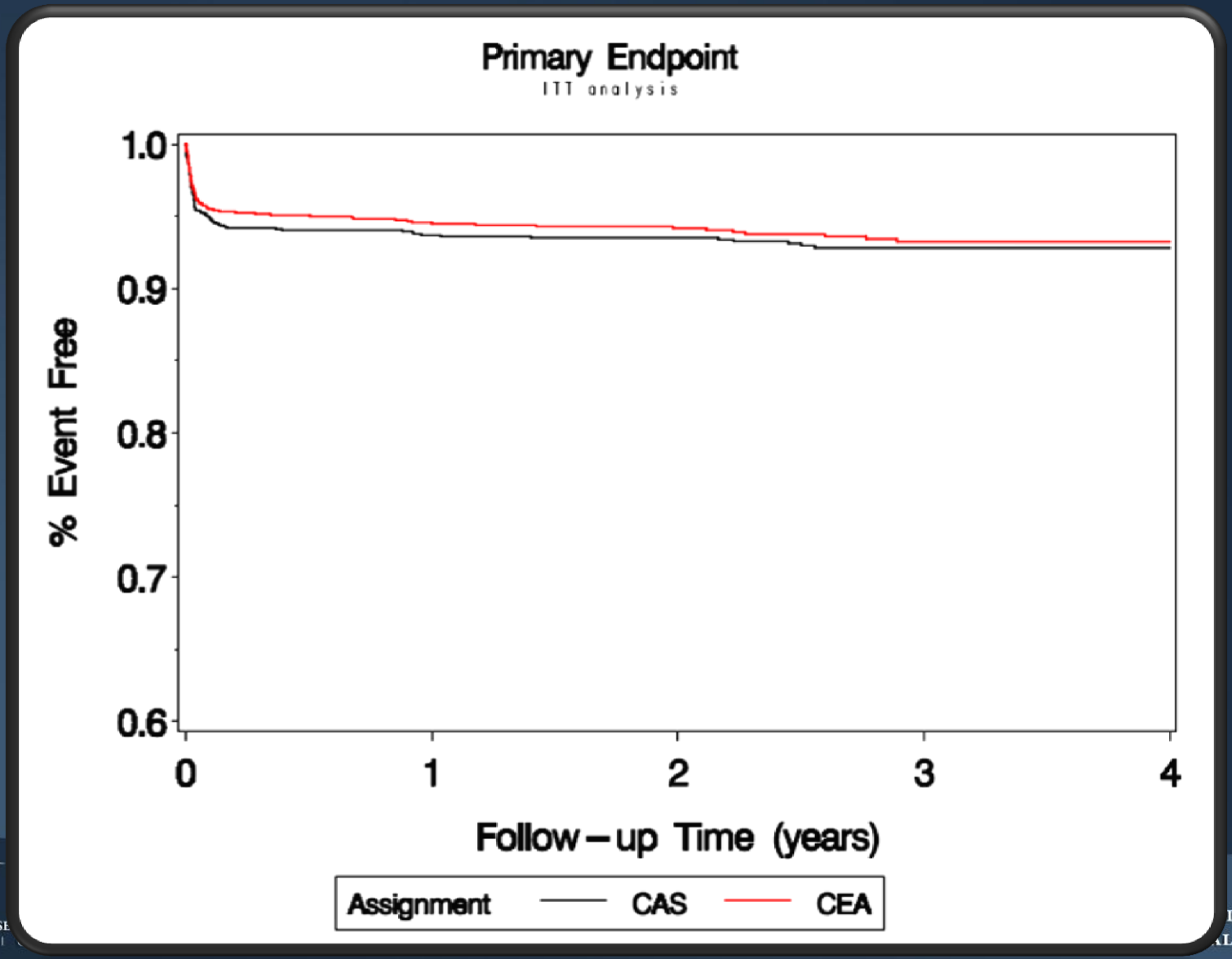


Sex, stenosis and time to CEA all influence benefit of CEA



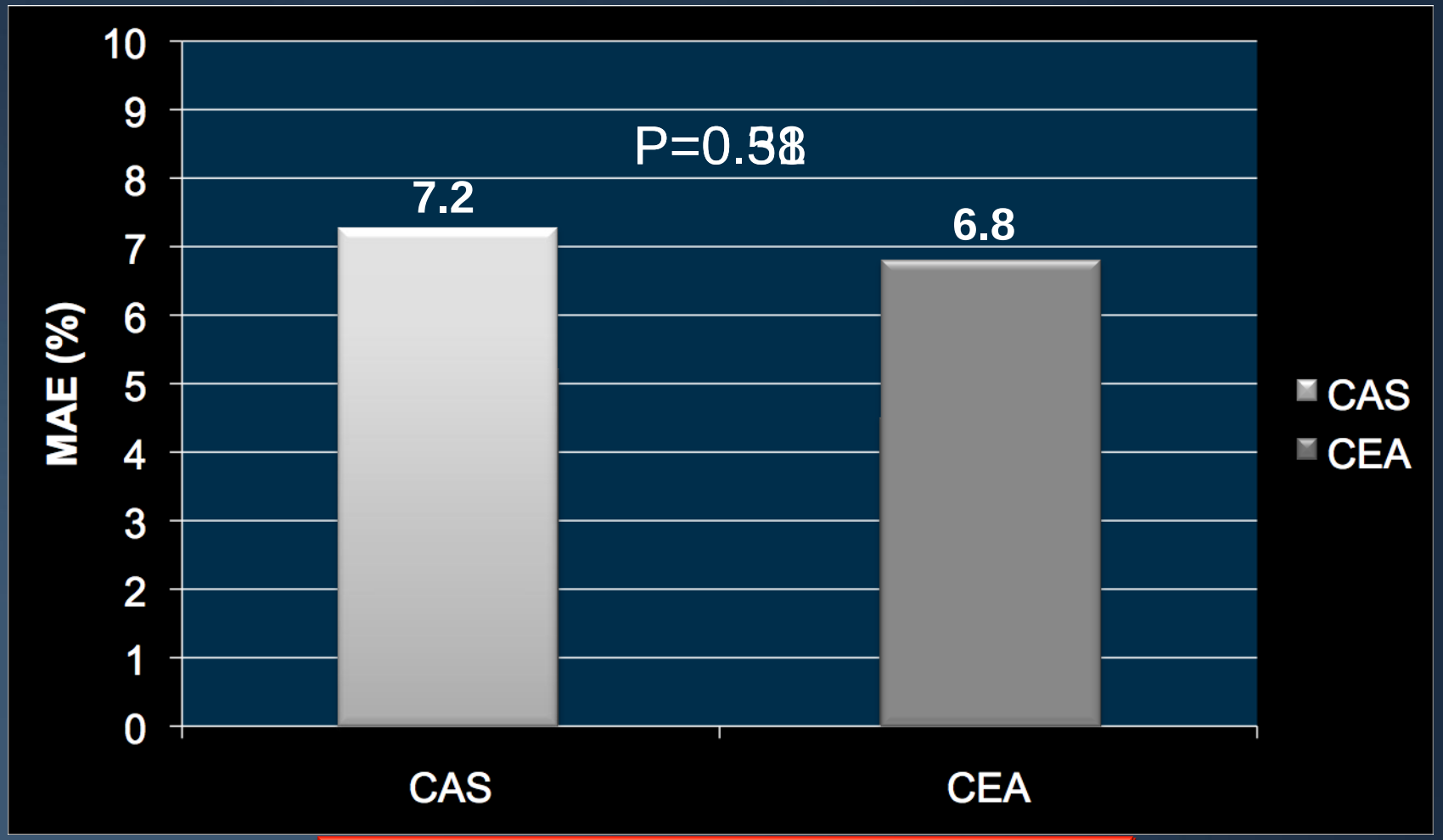
Choice of
CEA and CAS

Stroke prevention efficacy equal between CAS and CEA in CREST



Primary endpoint 1-4 years (mean 2.5)

Peri-procedural outcomes (D/S/MI)



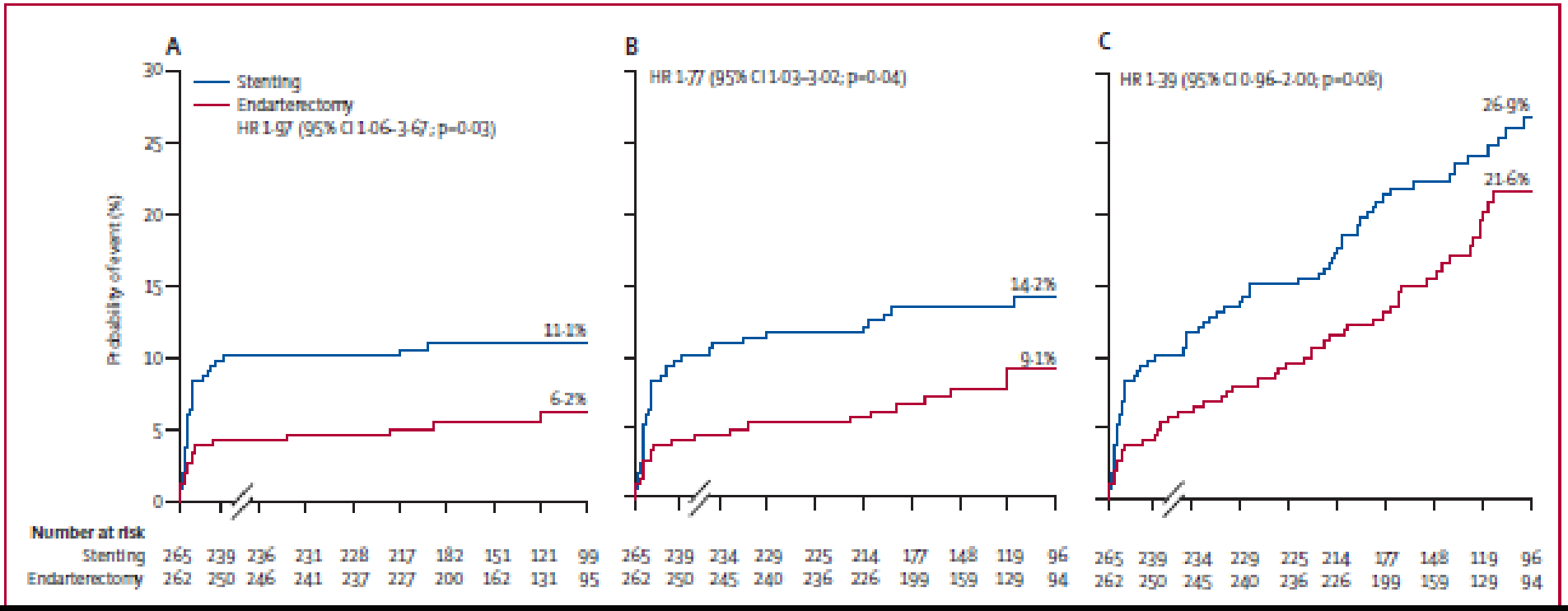
HR 1.11 95% CI: 0.81-1.51

End Point	Periprocedural Period				
	CAS	CEA	Absolute Treatment Effect of CAS vs. CEA (95% CI)	Hazard Ratio for CAS vs. CEA (95% CI)	P Value
	no. of patients (% ±SE)		*percentage points*		
Myocardial infarction					
Asymptomatic patients	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 patients	7 (1.0±0.4)	15 (2.3±0.6)	−1.2 (−2.6 to 0.1)	0.45 (0.18 to 1.11)	0.08
Any periprocedural stroke or postprocedural ipsilateral stroke					
Asymptomatic patients	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 patients	37 (5.5±0.9)	21 (3.2±0.7)	2.3 (0.1 to 4.5)	1.74 (1.02 to 2.98)	0.04
Any periprocedural stroke or death or postprocedural ipsilateral stroke					
Asymptomatic patients	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 patients	40 (6.0±0.9)	21 (3.2±0.7)	2.8 (0.5 to 5.0)	1.89 (1.11 to 3.21)	0.02
Primary end point (any periprocedural stroke, myocardial infarction, or death or postprocedural ipsilateral stroke)					
Asymptomatic patients	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 patients	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

Long-term outcomes for both CEA and CAS

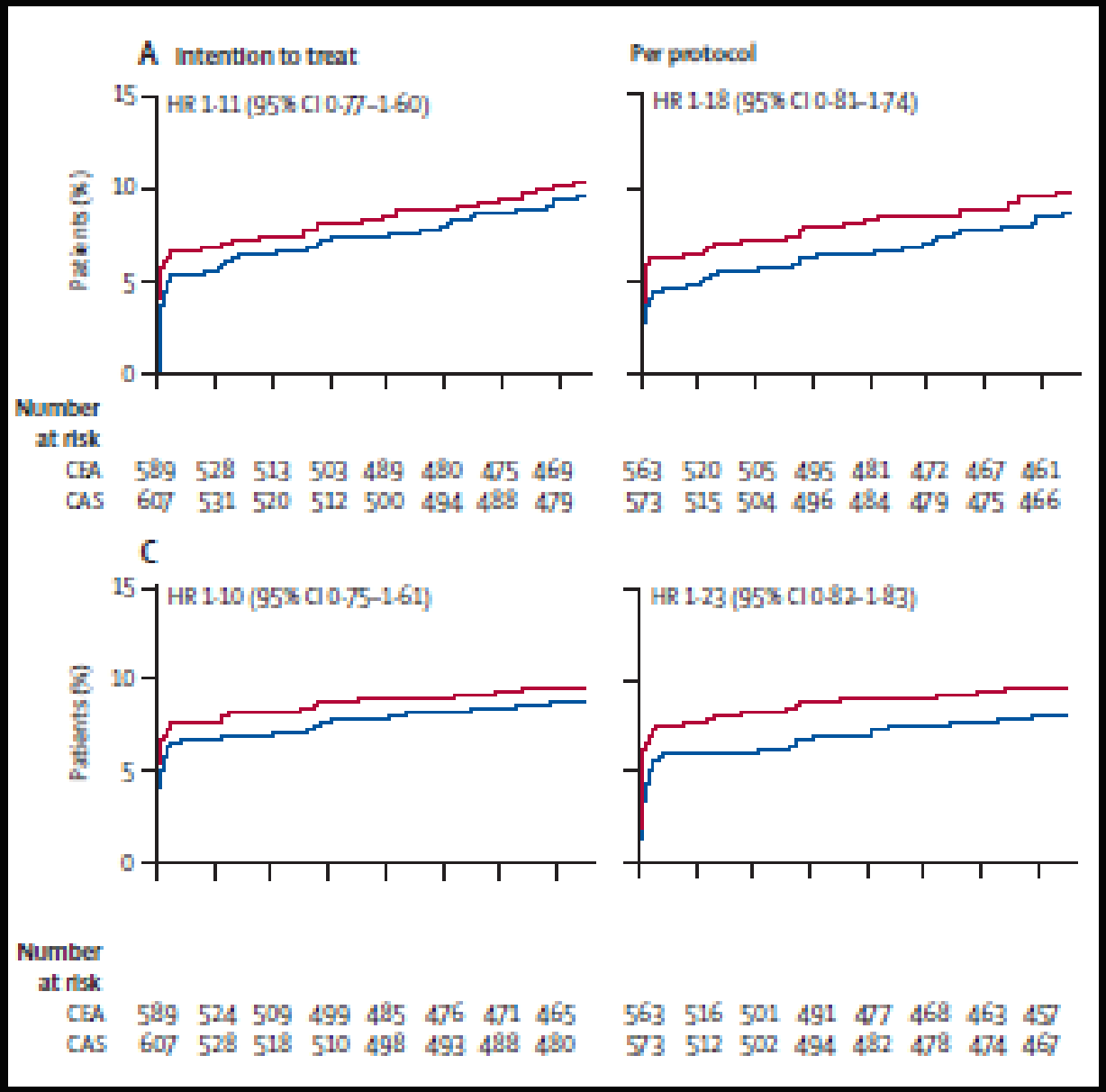
Stroke prevention efficacy equal between CEA and CAS
EVA-3S: 4-year outcomes

Any ipsilateral stroke | Any stroke | Any stroke or death



Stroke prevention efficacy equal between CEA and CAS

SPACE: K-M plots of 2-year outcomes

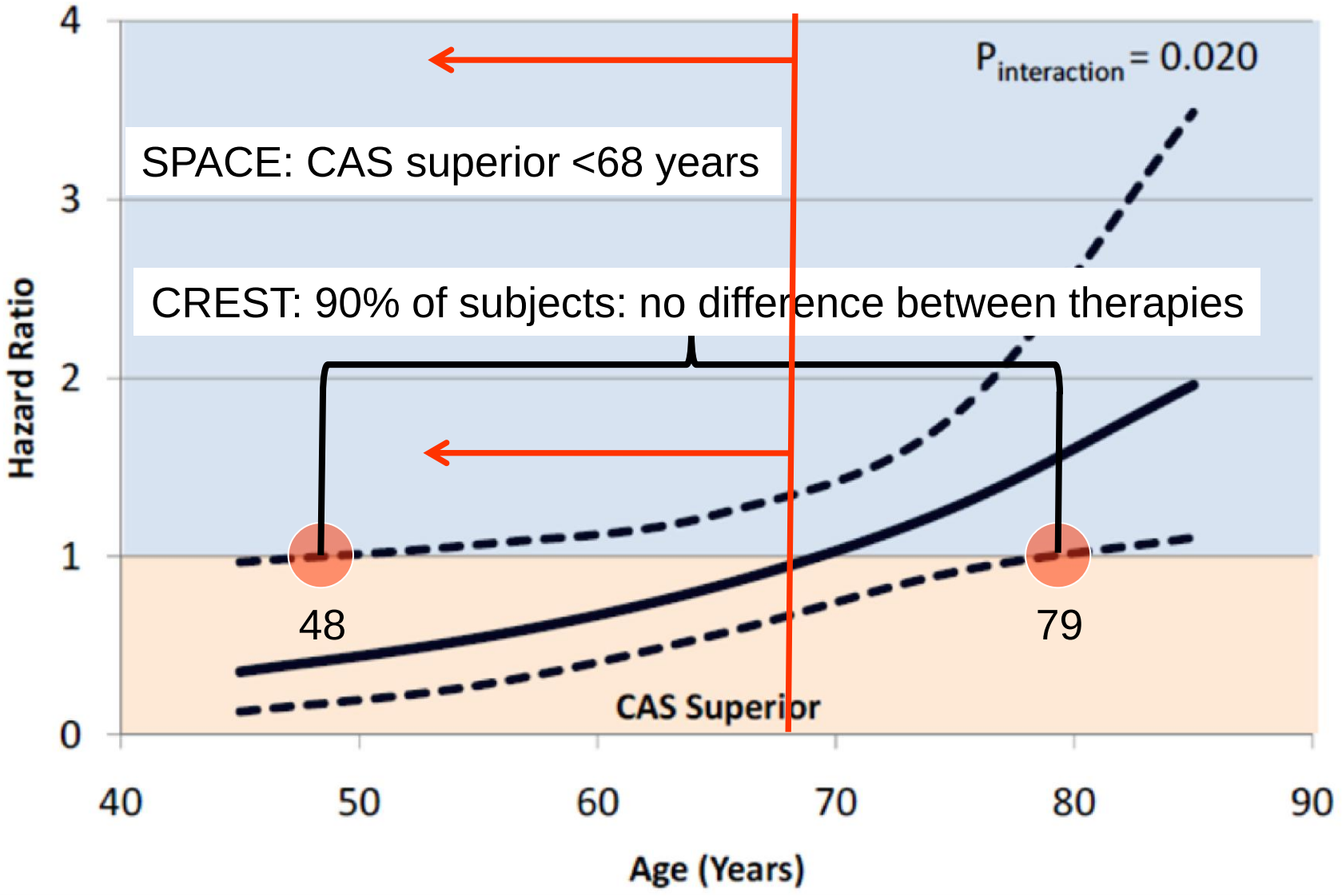


Ipsilateral stroke and vascular death

30-day stroke/death plus ipsilateral stroke to 2 years

Examine randomized data on patient cohorts favoring specific revascularization

Age differential: Similarity among trials



What does CREST, and other trials, tell us about CAS in standard risk patients?

- CREST
  - B[illegible]
  - V[illegible]
- SP[illegible]
  - CAS better in younger (<68 years)

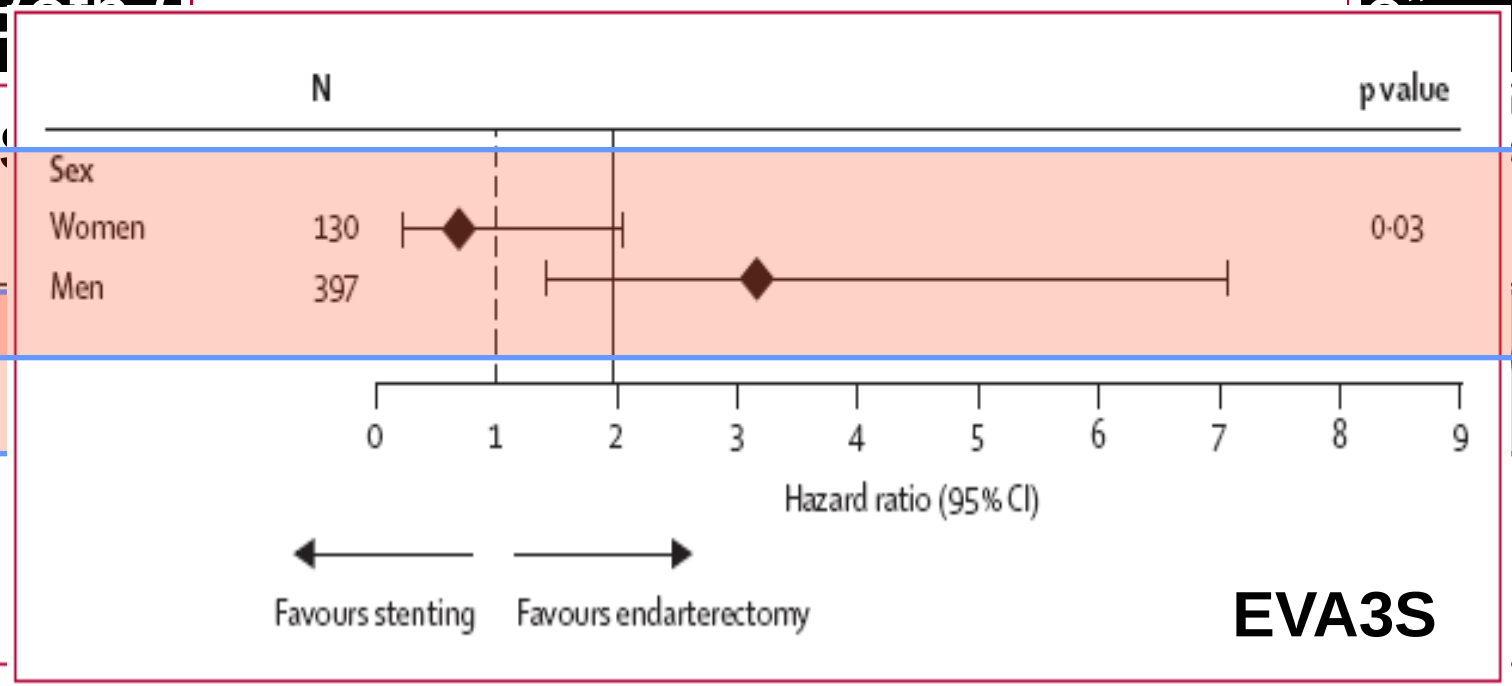
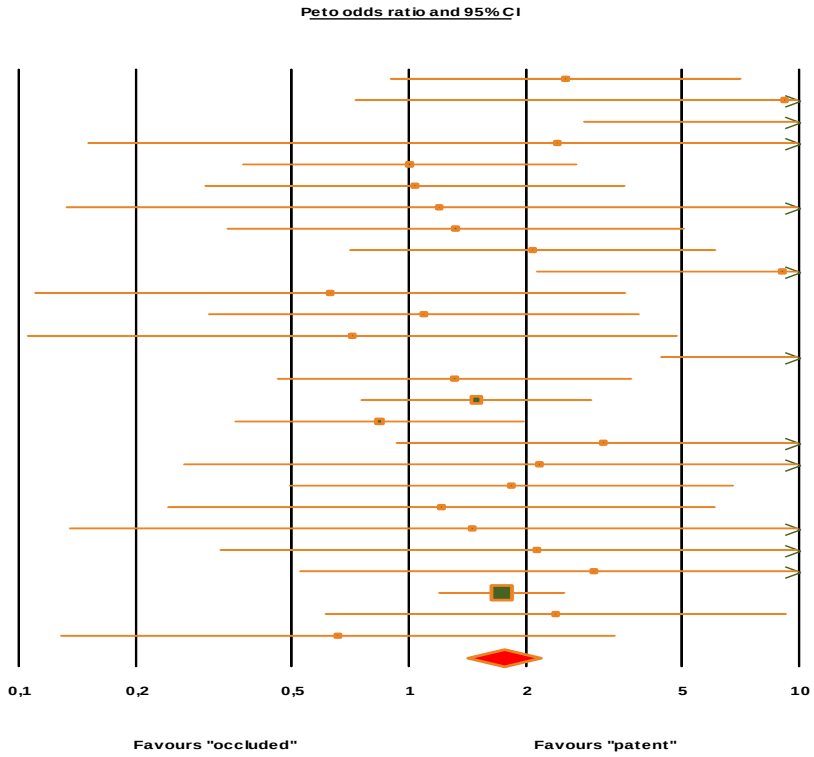


Figure 4: Hazard ratios (stenting *vs* endarterectomy) and 95% CIs for ipsilateral stroke (including periprocedural stroke or death) in various subcategories
p values are associated with treatment-covariate interaction tests. The thick vertical line is the hazard ratio (stenting *vs* endarterectomy) in the overall population.

Poor outcomes with contralateral carotid occlusion and CEA

30-day any stroke or death after CEA with/without contralat. occlusion

Study name	Peto odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Lees 1981	2,523	0,890	7,155	1,740	0,082
Hertzer 1982	9,183	0,723	116,664	1,710	0,087
Peitzman 1982	32,139	2,787	370,675	2,781	0,005
Takolander 1983	2,404	0,149	38,720	0,619	0,536
Sachs 1984	1,005	0,372	2,715	0,010	0,992
Moore 1984	1,037	0,298	3,611	0,057	0,954
Nunn 1988	1,197	0,131	10,899	0,159	0,873
Mackey 1990	1,318	0,340	5,118	0,399	0,690
ECST 1991	2,077	0,700	6,162	1,317	0,188
NASCET 1991	9,061	2,106	38,978	2,961	0,003
Perler 1992	0,629	0,109	3,626	-0,519	0,604
Mattos 1992	1,093	0,305	3,923	0,137	0,891
Jansen 1993	0,716	0,104	4,909	-0,340	0,734
Sandmann 1993	17,782	4,385	72,108	4,029	0,000
Goldstein 1994	1,310	0,457	3,753	0,503	0,615
Riles 1994	1,489	0,748	2,966	1,133	0,257
Lacroix 1994	0,842	0,356	1,994	-0,391	0,696
da Silva 1996	3,152	0,921	10,784	1,829	0,067
Aungst 1998	2,162	0,263	17,793	0,717	0,473
Locati 2000	1,832	0,491	6,839	0,901	0,367
AbuRahma 2000	1,212	0,239	6,142	0,232	0,816
Jordan 2002	1,454	0,134	15,764	0,308	0,758
Pulli 2002	2,130	0,326	13,935	0,789	0,430
Balotta 2002	2,981	0,522	17,034	1,228	0,219
Tu 2003	1,730	1,184	2,529	2,830	0,005
Domenig 2003	2,380	0,605	9,358	1,241	0,215
Grego 2005	0,658	0,127	3,407	-0,499	0,618
	1,741	1,404	2,158	5,055	0,000



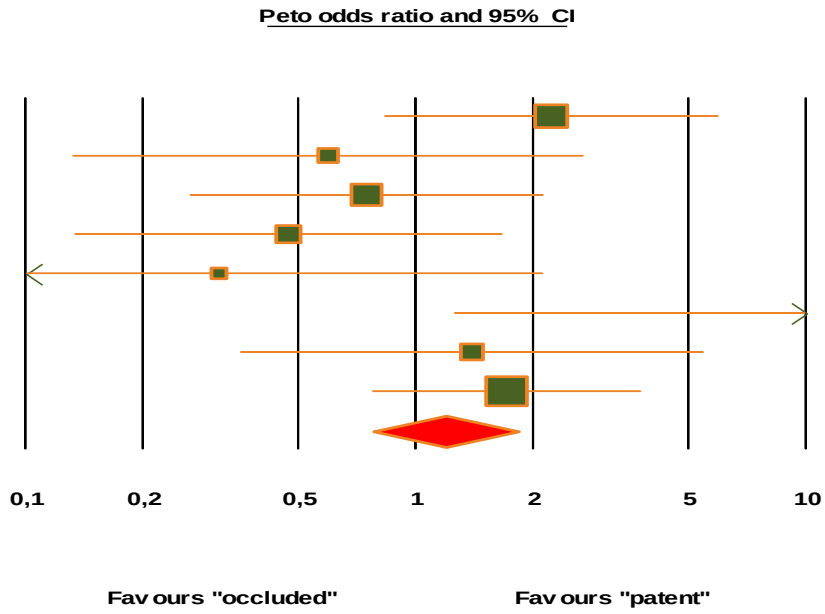
Fixed effects model, no sig. heterogeneity; p = 0.128

Meta-analysis of Randomized Trials Comparing Carotid Endarterectomy and Endovascular Treatment T. Luebke, M. Aleksic, J. Brunkwall EJVES 2007

No differential in outcomes with contralateral carotid occlusion and CAS

30-day any stroke or death after CAS with/without contralat. occlusion

Study name	Statistics for each study				
	Peto odds ratio	Lower limit	Upper limit	Z-Value	p-Value
McKevitt 2004	2,228	0,826	6,011	1,581	0,114
Reimers 2004	0,597	0,131	2,713	-0,668	0,504
Sabeti 2004	0,749	0,262	2,141	-0,539	0,590
Hofmann 2006	0,473	0,133	1,681	-1,158	0,247
Mas 2006	0,314	0,046	2,136	-1,185	0,236
Safian 2006	20,697	1,247	343,502	2,114	0,035
Verzini 2006	1,395	0,353	5,505	0,475	0,635
White 2006	1,712	0,769	3,808	1,317	0,188
	1,189	0,775	1,823	0,793	0,428



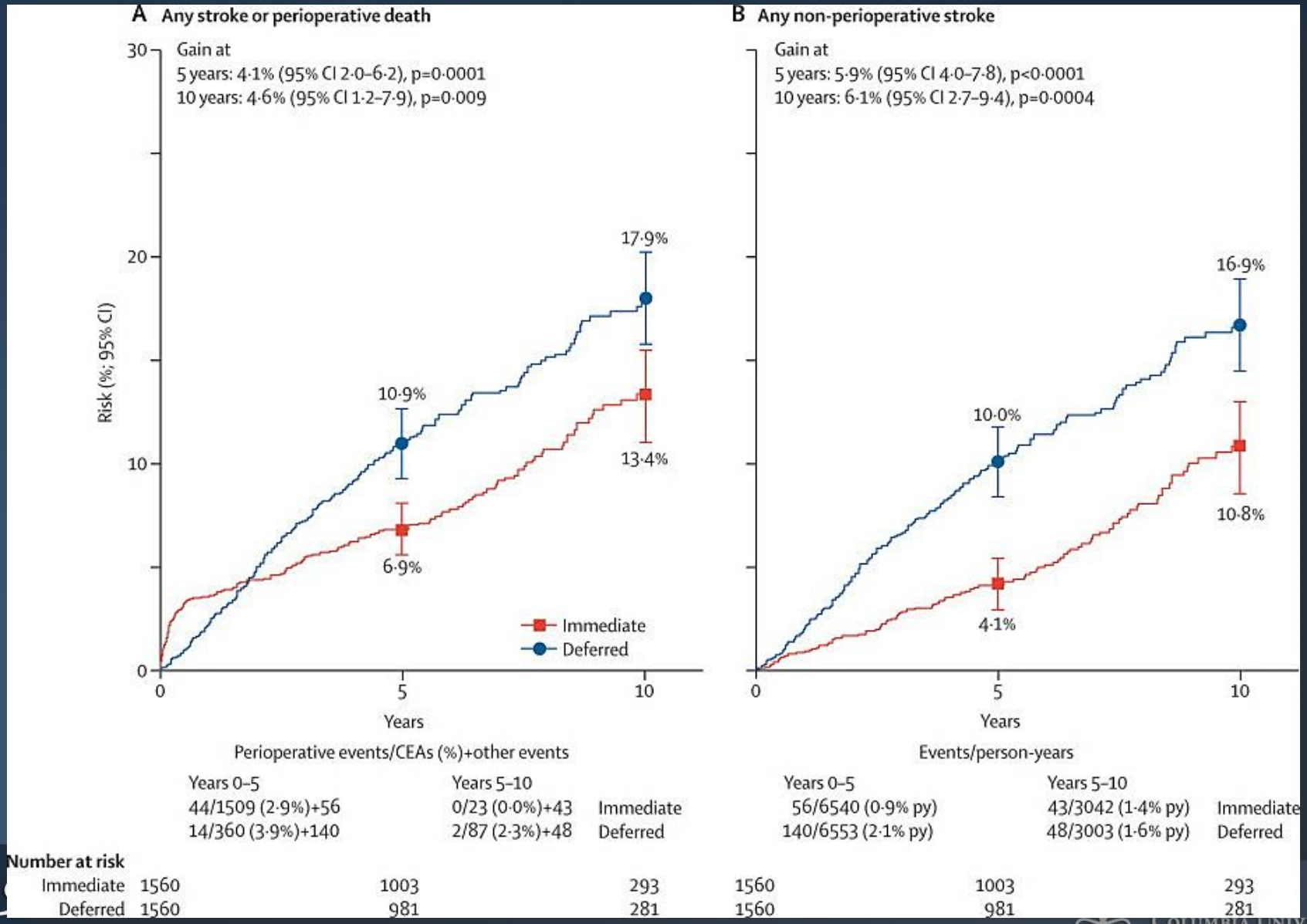
Fixed effects model, no sig. heterogeneity; p = 0.108

What doesn't CREST tell us?

- Does not address the growing opinion that "modern" medical therapy obviates the need for revascularization for primary prevention
- There are no prospective comparative data in patients with established severe asymptomatic carotid stenosis that would support this contention:
  - the data that do exist support revascularization

Approach to primary prevention

ACST: 10 year outcomes

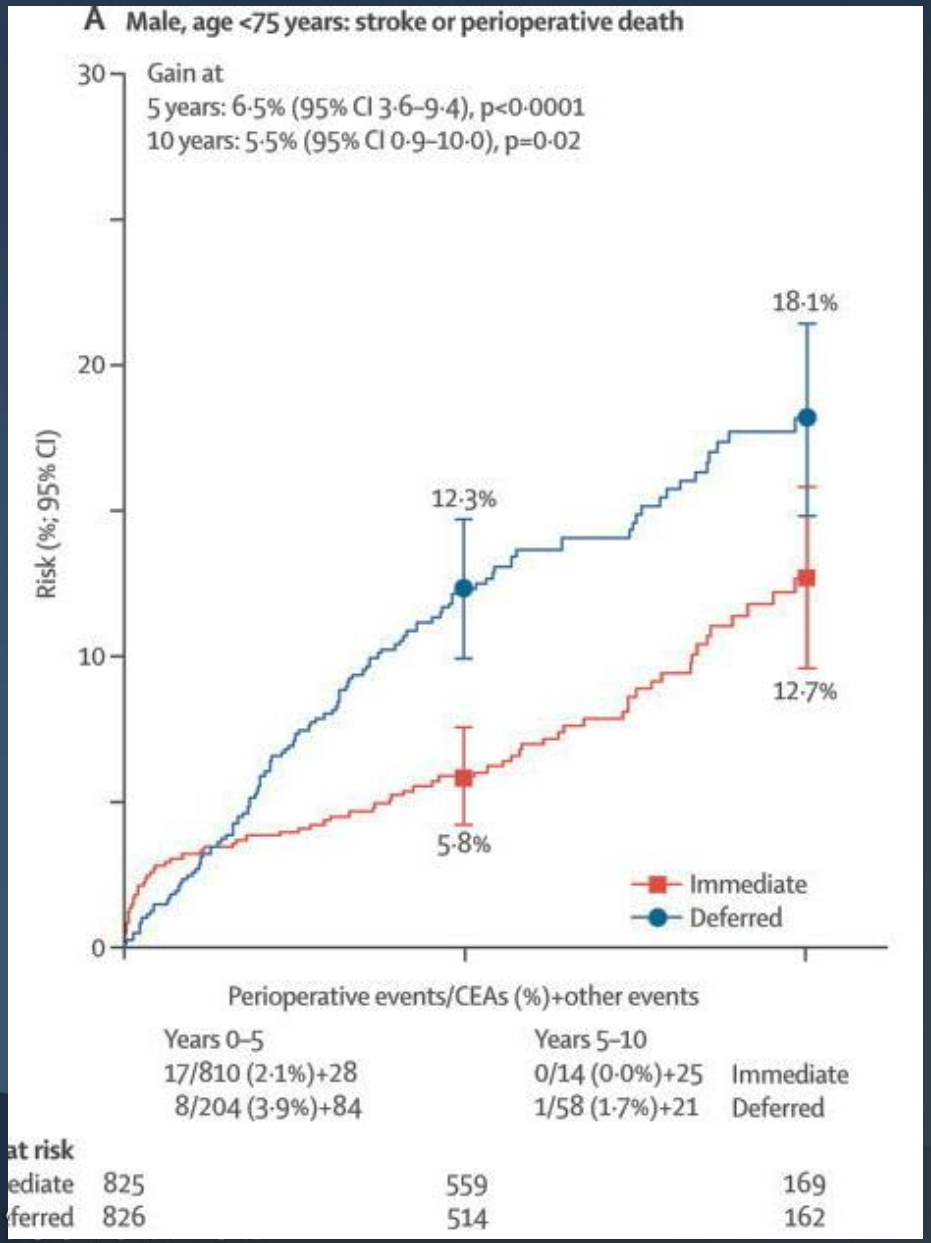


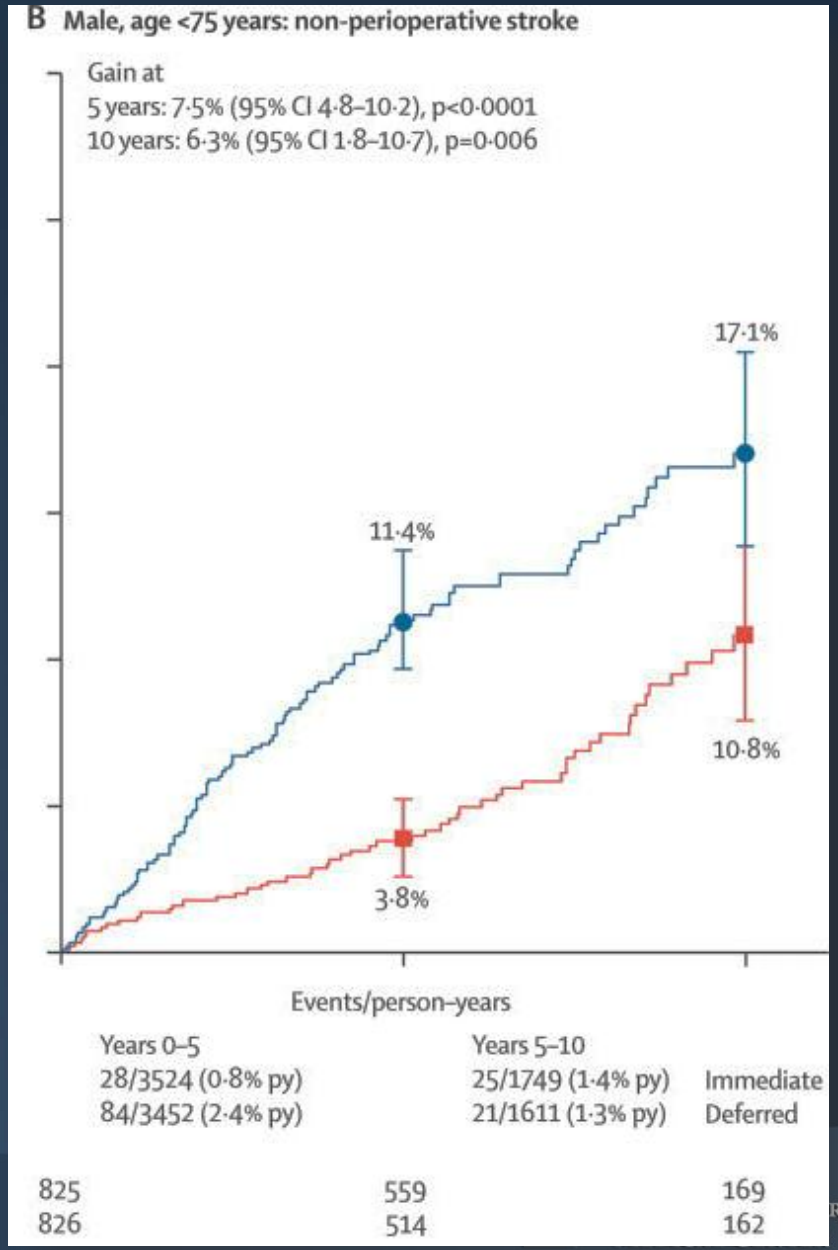
Perioperative events/CEAs (%)+other events			
Years 0–5	Years 5–10		
44/1509 (2·9%)+56	0/23 (0·0%)+43	Immediate	
14/360 (3·9%)+140	2/87 (2·3%)+48	Deferred	

Events/person-years			
Years 0–5	Years 5–10		
56/6540 (0·9% py)	43/3042 (1·4% py)	Immediate	
140/6553 (2·1% py)	48/3003 (1·6% py)	Deferred	

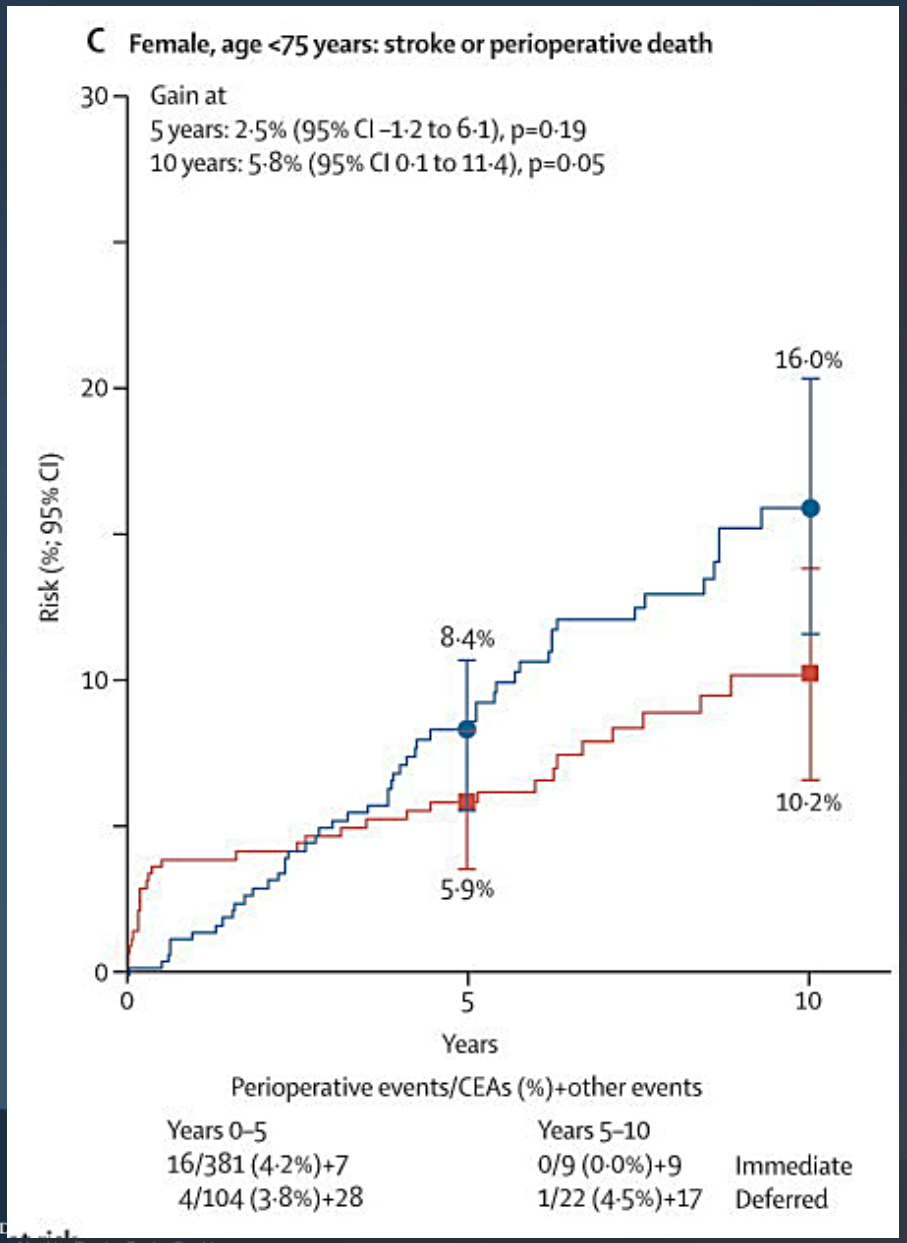
Number at risk						
Immediate	1560	1003	293	1560	1003	293
Deferred	1560	981	281	1560	981	281

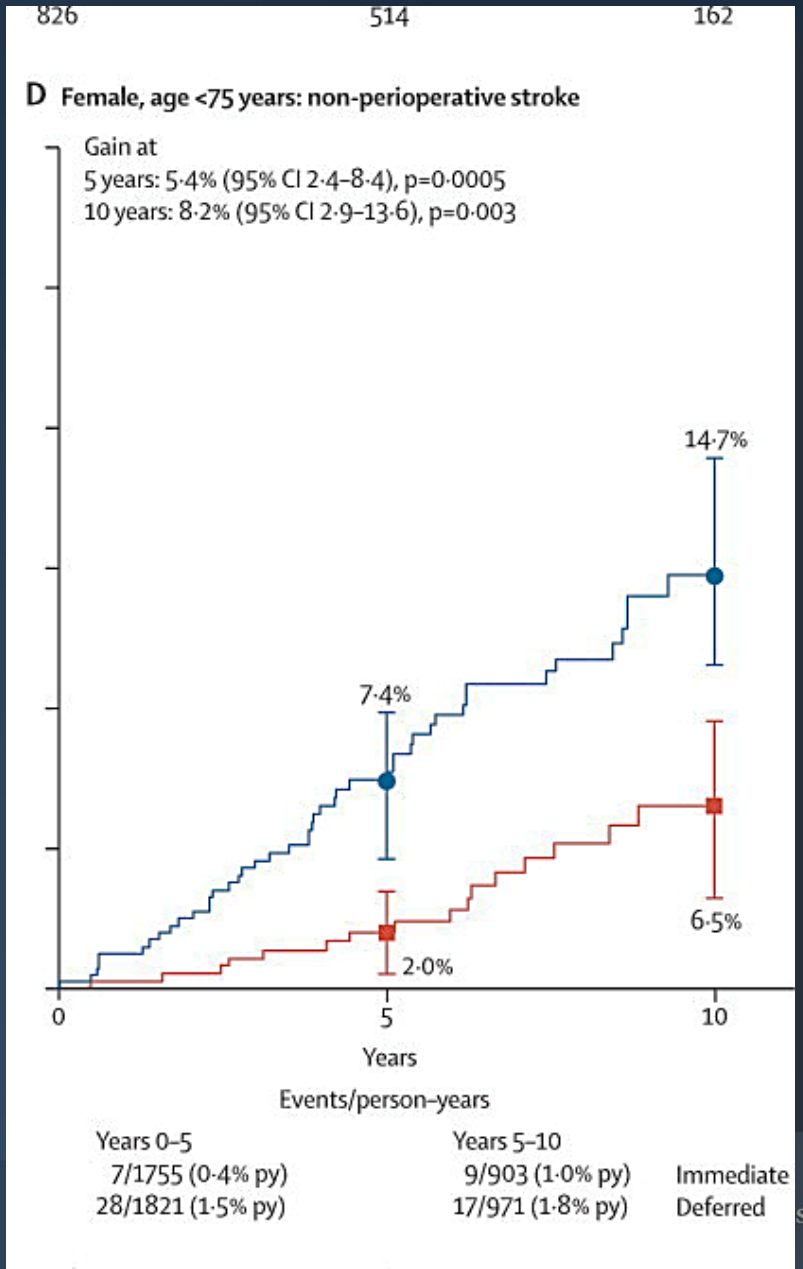
ACST outcomes: men



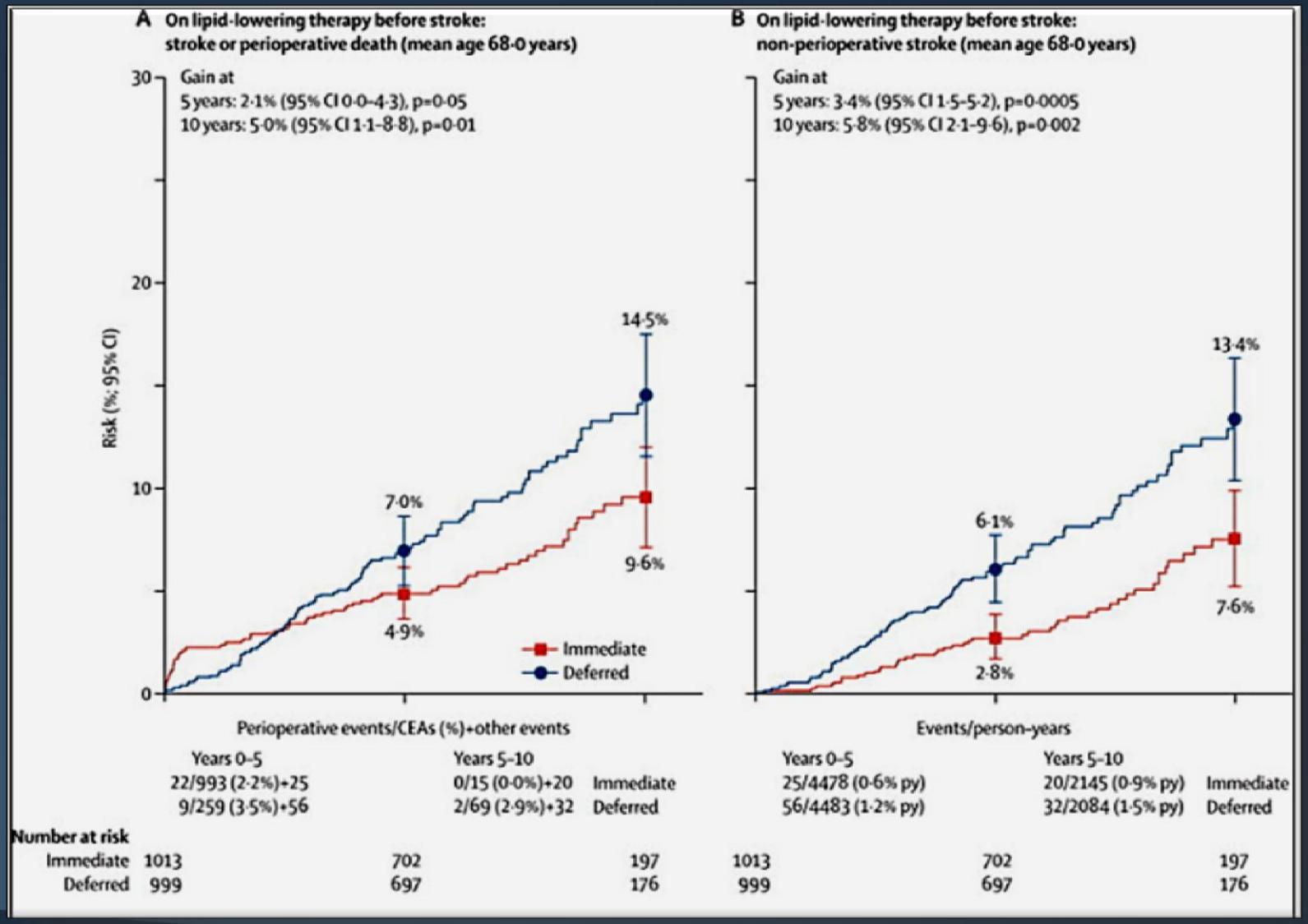


ACST outcomes: women





ACST 10 year data: statins



Halliday A et al. Lancet. 2010 September 25; 376(9746): 1074–1084

Support for medical therapy

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

Studies included in analysis: ACST missing

		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	. . .	. . .	. . .

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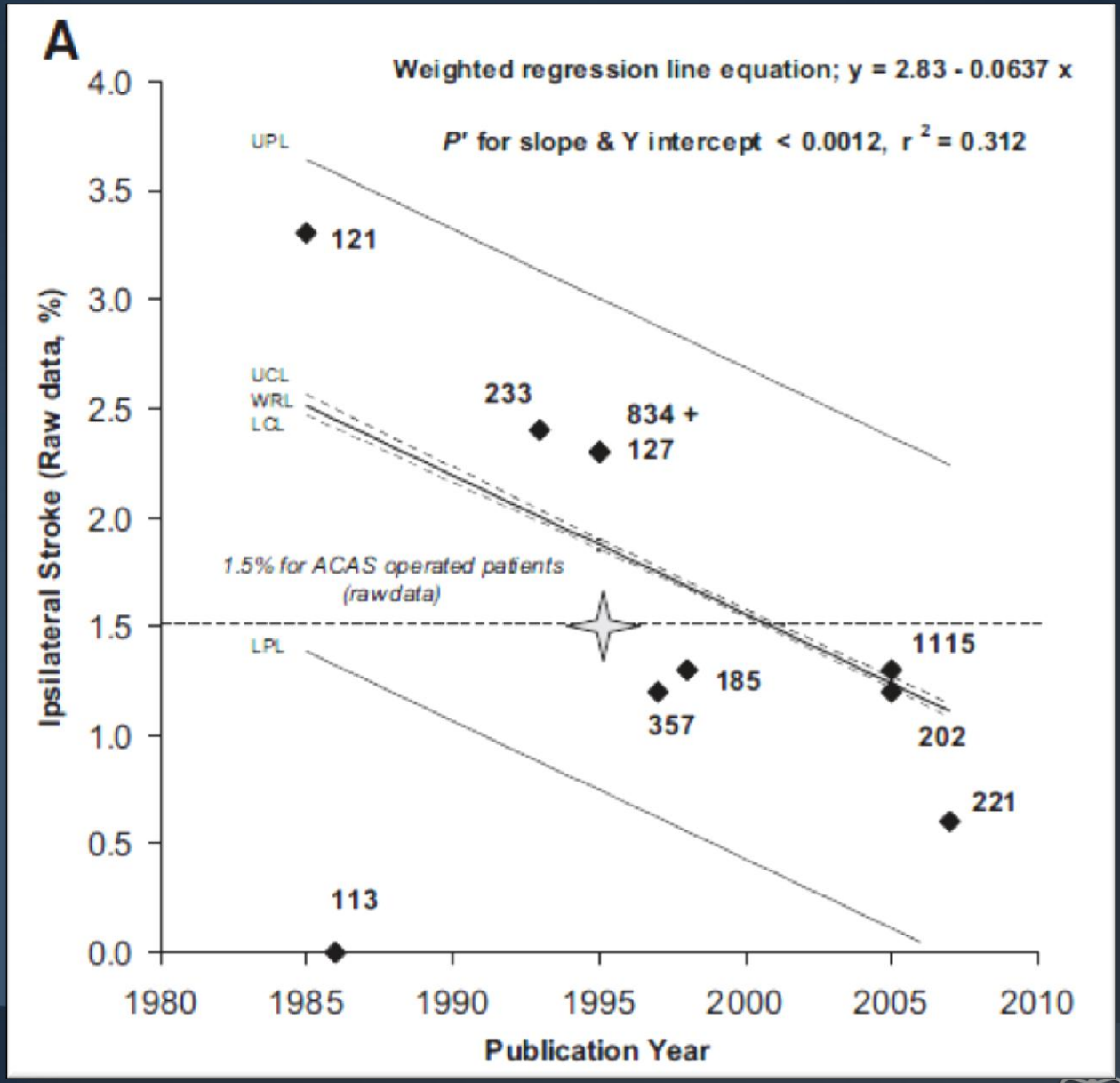
Proposed trends in medical outcomes

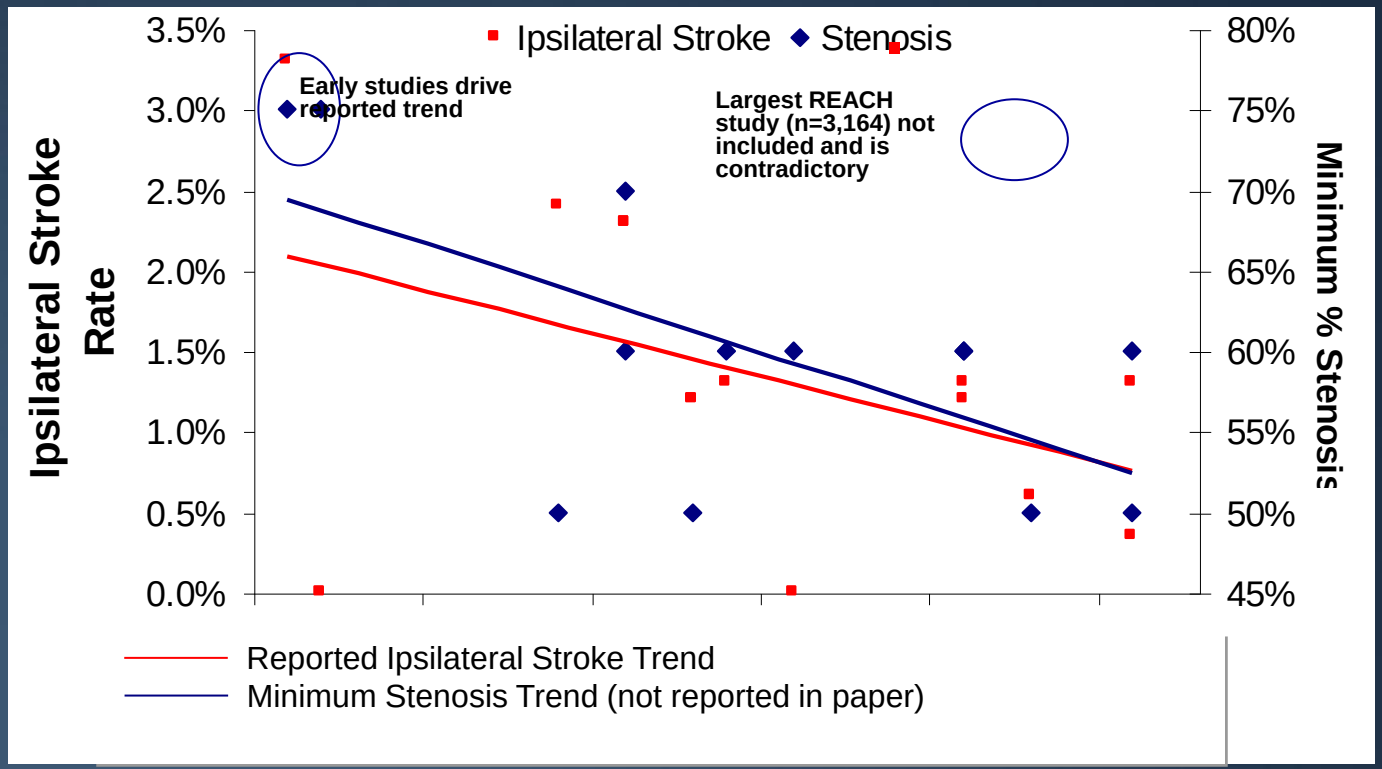


Documentation medical therapy

	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

Differences In Study Populations from the Systematic Review* Drive Its Conclusions

The Change in Minimum Stenosis Thresholds in Studies Over Time Mirrors the Reported Decline In Stroke Rates



* Abbott AL. 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 Oct;40(10):e573-83.*

** Aichner FT, et al. High cardiovascular event rates in patients with asymptomatic carotid stenosis: the REACH registry. *Eur J Neurol.* 2009; 16:902-908.

Trends in medical outcomes: what's missing

- Knowledge as to the correct "cocktail" of medication class, specific to carotid-related targets
- Measures of compliance and side effect issues
- Randomized data showing equivalence or superiority to revascularization in *asymptomatic severe carotid stenosis*

The Carotid "Prescription"

- ASA 81 mg/d
  - No role for dual antiplatelet therapy for stroke "prevention"
- Antihypertensive Therapy
  - Angiotensin Converting Enzyme Inhibitor
  - Angiotensin Receptor Antagonist
- Lipid Lowering Therapy
  - LDL-Cholesterol <100 mg/dL
- Tobacco Cessation
- Glycemic Control (HbA1C <7.0%)

Conclusion

- Secondary prevention:
  - Patients with symptomatic disease should undergo revascularization ASAP following a TIA or non-disabling stroke.
- CREST definitively established both CEA and CAS as safe and effective revascularization options for patients requiring primary or secondary prevention
- Medical therapy for asymptomatic patients may have improved to a point where equipoise exists and a trial vs. revascularization is appropriate