



Optimal Treatment for Asymptomatic Patients with Carotid Artery Disease

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Conflicts of Interest

- **Consultant**
 - Abbott Vascular (non-compensated)
 - Becker Venture Services Group
 - Bluegrass Vascular Therapies
 - Cordis Corporation(non-compensated)
 - Covidien (non-compensated)
 - Hansen Medical
 - Medtronic (non-compensated)
 - Micell, Incorporated
 - Primacea
 - Trivascular, Inc.
 - Vortex
- **Equity**
 - Access Closure, Inc
 - Embolitech, Inc
 - Hotspur, Inc
 - Icon Interventional, Inc
 - I.C.Sciences, Inc
 - Janacare, Inc
 - Northwind Medical, Inc.
 - PQ Bypass, Inc
 - Primacea
 - Sadra Medical
 - TMI/Trireme, Inc
 - Vascular Therapies, Inc
- **Board Member**
 - VIVA Physicians (Not For Profit 501(c) 3 Organization)
 - www.vivapvd.com



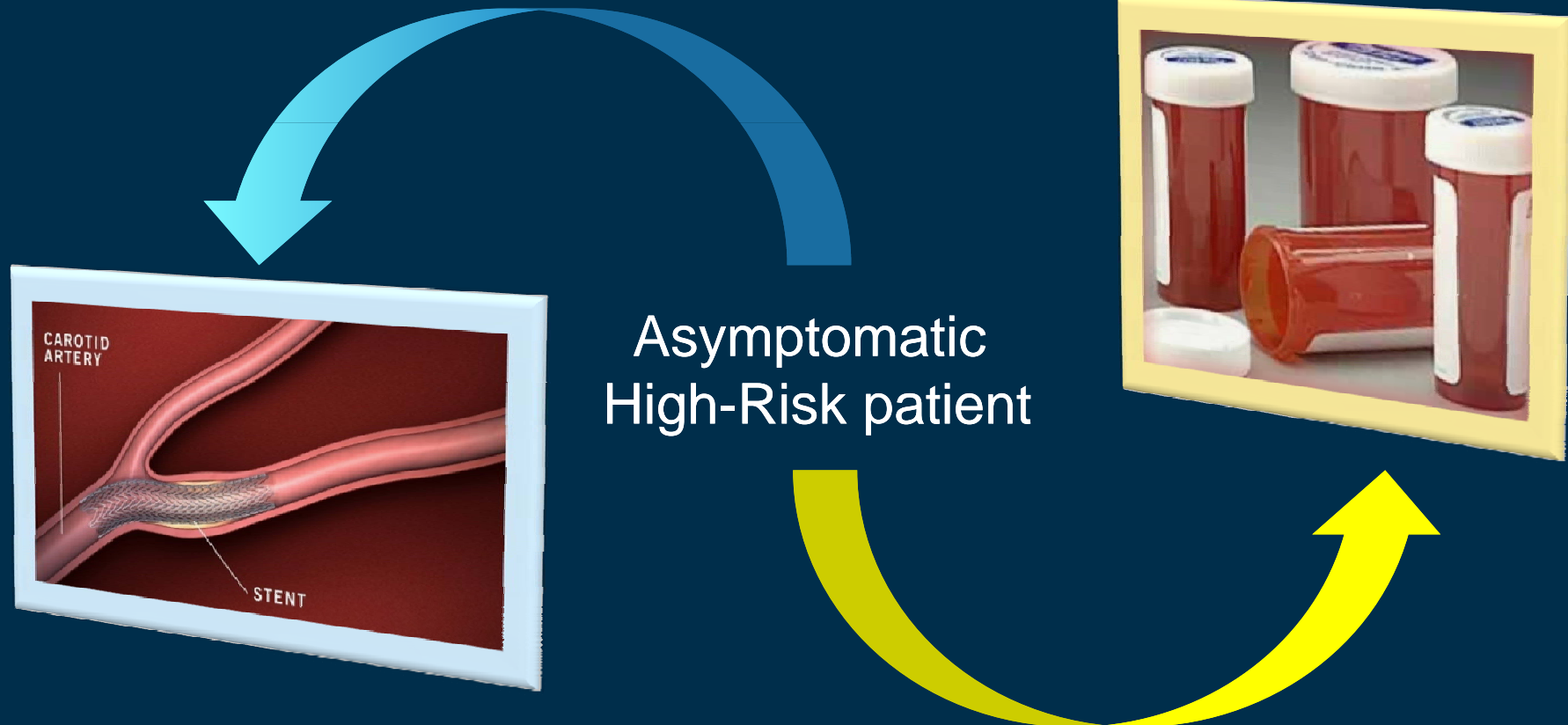
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Moving targets



Carotid stenting has evolved. Outcomes are improving and the procedure is maturing. Randomized trials (including CREST) now supported by large post-market surveillance outcomes

Medical therapy has also evolved with evidence suggesting the risk of stroke in asymptomatic patients today may be much lower than even 10 years ago

ASA



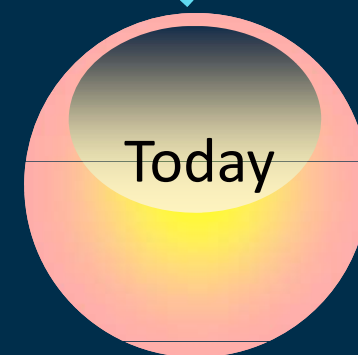
ASA
HTN RX



ASA
HTN RX (ACEI,
beta blockers)
DM Control,
Lipid Rx

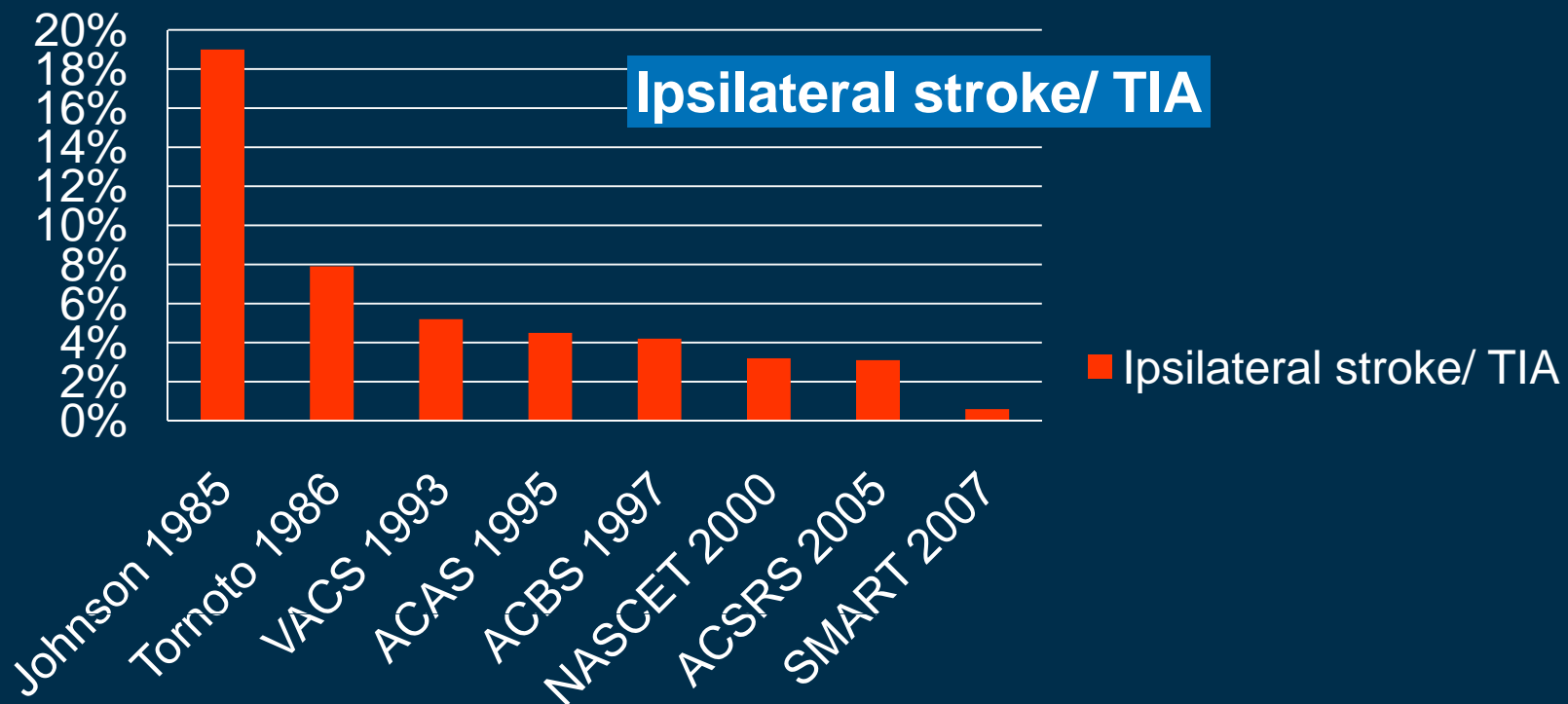


ASA
HTN RX (Tighter
control, JNC VII)
Tight DM Control
High dose statins
ACE and ARB



It may be difficult to make decisions today based on the efficacy targets defined by trials like ACAS and NASCET. Do the treatment boundaries of 3% procedural event rate still apply for asymptomatic patients today?

Annual TIA and stroke in asymptomatic control arms of selected randomized trials



*ACAS indicates Asymptomatic Carotid Atherosclerosis Study; ECST, European Carotid Surgery Trial; ACBS, Asymptomatic Cervical Bruit Study; NASCET, North American Symptomatic Carotid Endarterectomy Trial; ACSRS, Asymptomatic Carotid Stenosis and Risk of Stroke Study; ASED, Asymptomatic Stenosis Embolus Detection Study; SMART, Second Manifestations of ARterial disease Study.

Non-Modifiable Risk Factors for Stroke

Factor	Incidence/Prevalence			
Age, y ²¹	Prevalence of first stroke (percent per 100 000)			
18–44	0.5			
45–64	2.4			
65–74	7.6			
75+	11.2			
	Incidence of first stroke (per 1000) ^{1†}			
	White men	White women	Black Men	Black women
45–54	1.4	1.0	3.5*	2.9
55–64	2.9	1.6	4.9	4.6
65–74	7.7	4.2	10.4	9.8
75–84	13.5	11.3	23.3*	13.5
85+	32.1	16.5	24.7*	21.8
Sex (age adjusted) ²¹	Prevalence (percent per 100 000)			
	Men: 2.9			
	Women: 2.3			
	Total: 2.6			



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Stroke 2011;42:517-84



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Modifiable Risk Factors

Factor	Prevalence, %		Population-Attributable Risk, %¶		Relative Risk	Risk Reduction With Treatment
Asymptomatic carotid stenosis	2–8		2–7‡		2.0	≈50% reduction with endarterectomy (see text). Aggressive management of other identifiable vascular risk factors (see text).
	ischemic stroke				(38.7 mg/dL) increase	
45–54	36.2	35.9	100	103		
55–64	53.7	55.8	100	102		
65–74	64.7	69.6	100	101		
75+	64.1	76.4	100	101		



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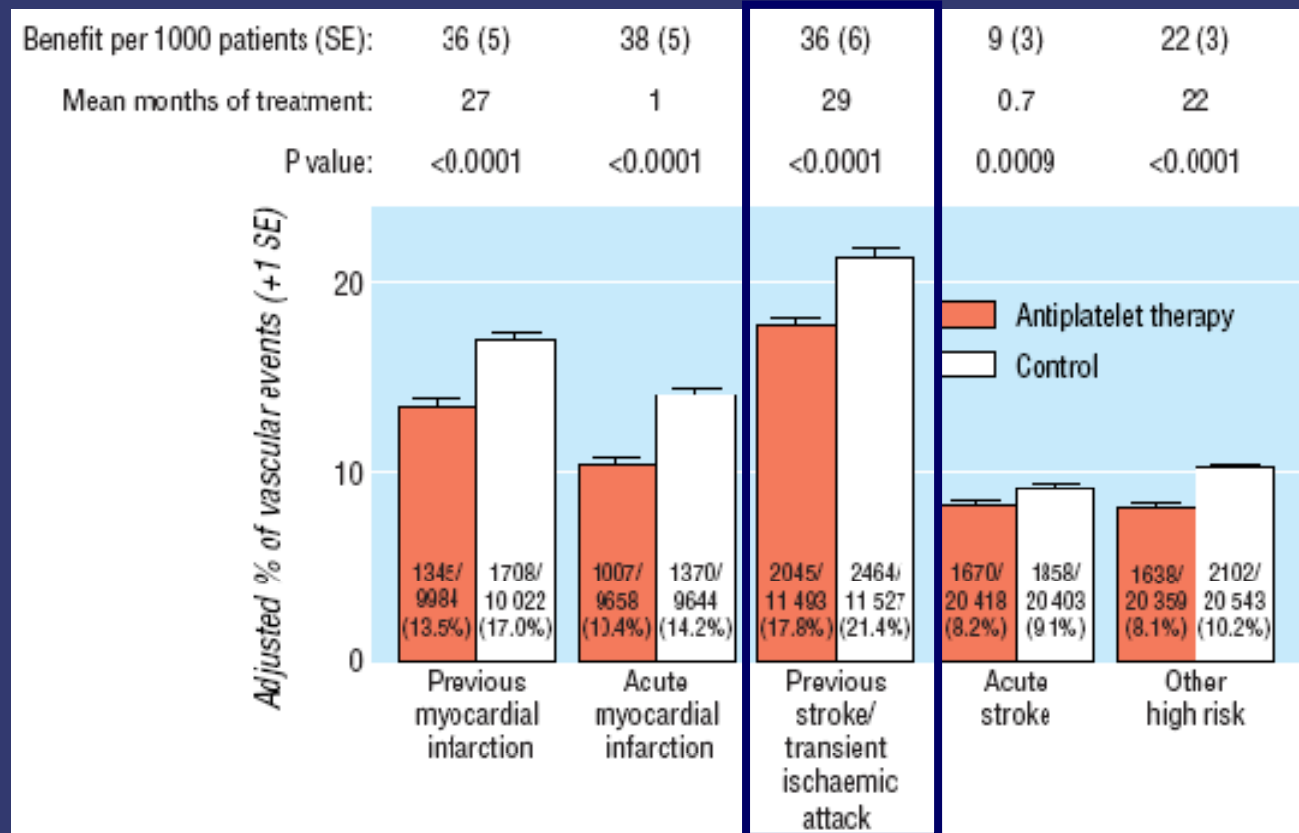
Stroke 2011;42:517-84



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Effect of Antiplatelet Therapy in Patients with TIA or Stroke

287 Studies: 135,000 Patients in Comparisons of Antiplatelet Rx vs Control



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Antiplatelet Trialists' Collaboration. BMJ 2002;324:71-86

Medical Treatments That *Did Not Exist* During Revascularization Trials

- **Modulators of Renin Angiotensin System**
 - ACE inhibitors
 - Hope
 - Angiotensin Receptor Blockers
 - Life
- **Statins**
 - HPS
 - CARDS



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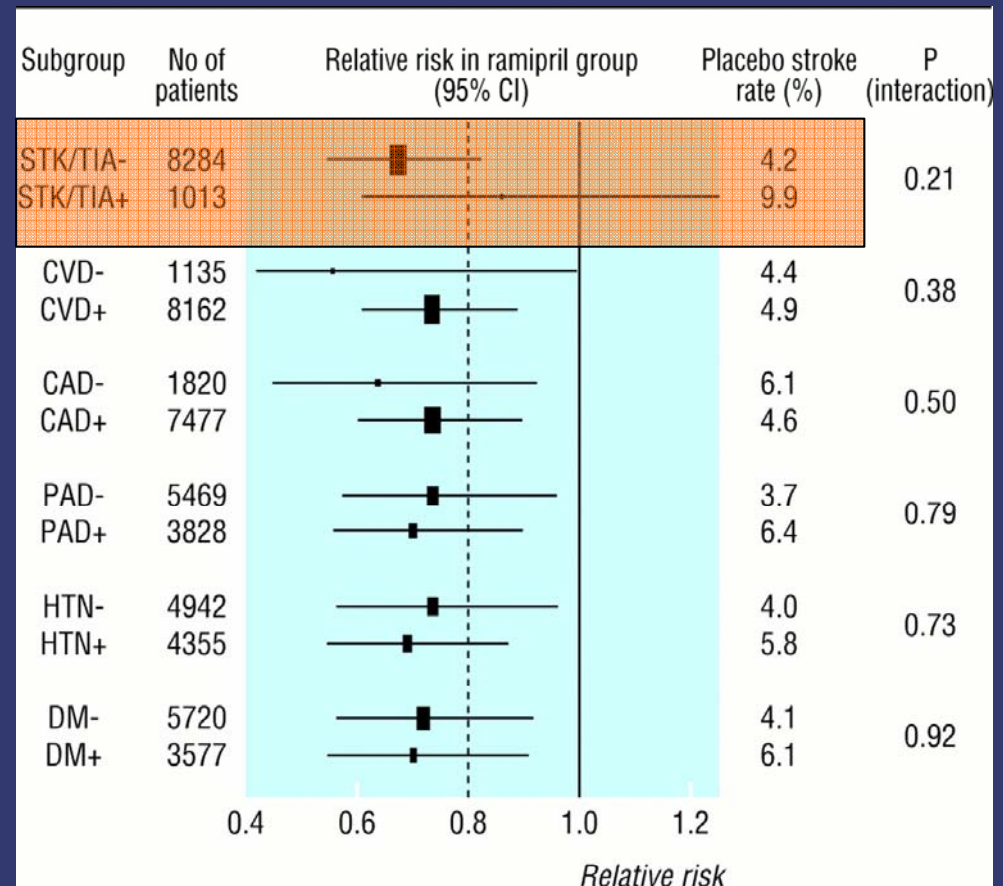


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ACE Inhibition Decreases Stroke in a High Risk Population

9297 patients with vascular disease or diabetes plus an additional risk factor randomized to ramipril or placebo f/u 4.5 yrs

1.5% Absolute Reduction
34% Relative Reduction



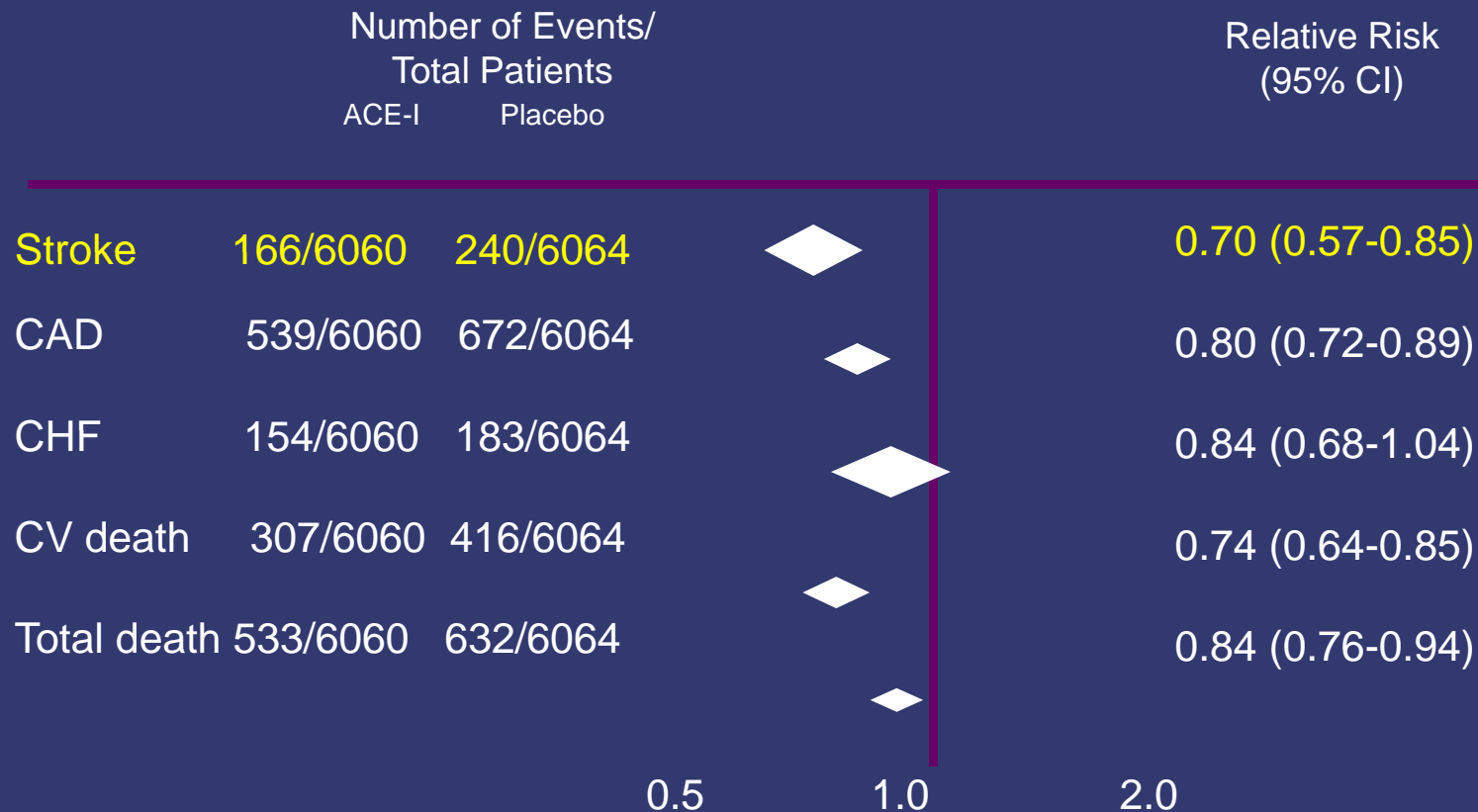
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Bosch J. BMJ 2002; 324:699



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Effect of ACE-Inhibitor Therapy vs. Placebo on Cardiovascular Endpoints



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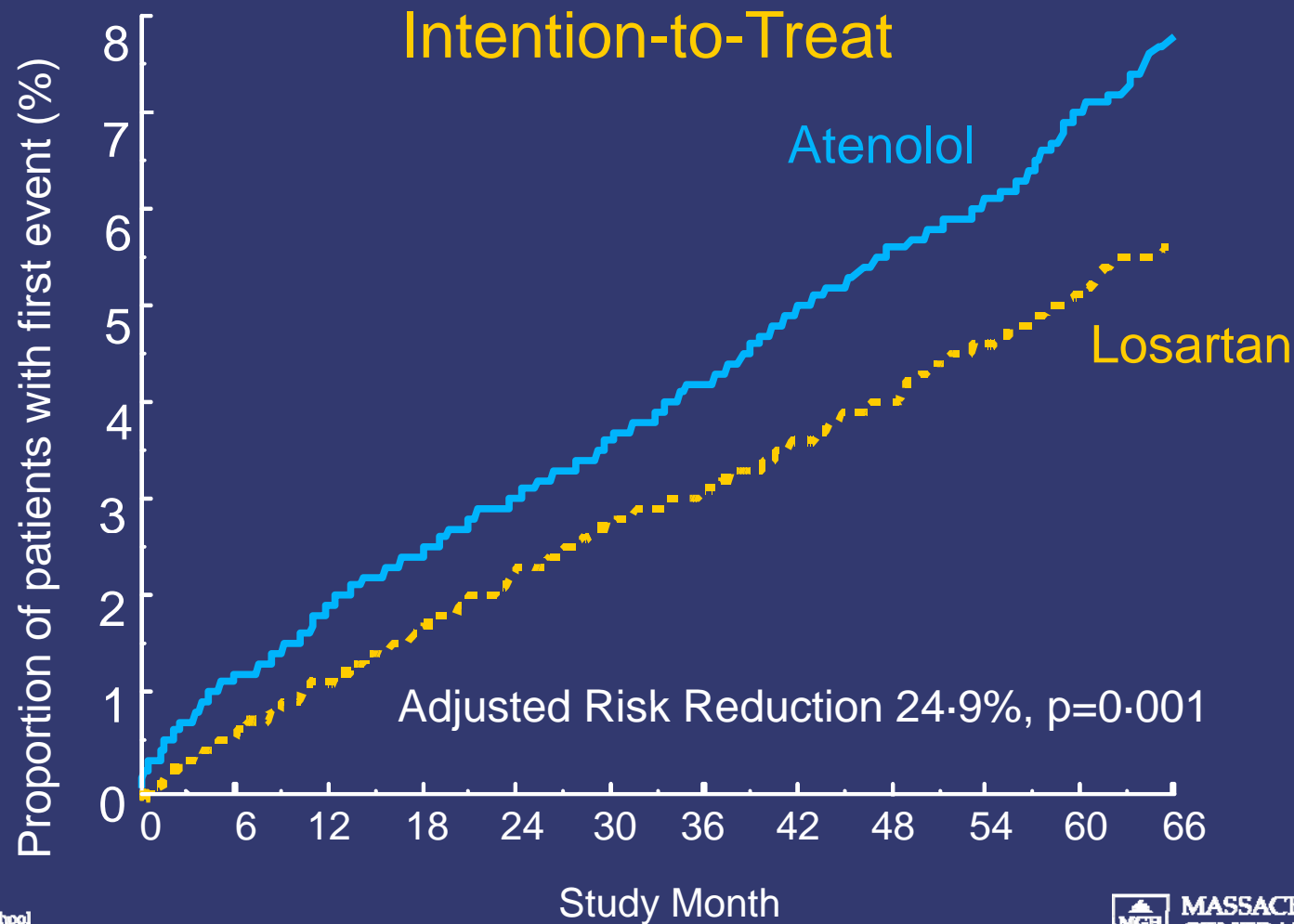
Blood Pressure Lowering Treatment Trialists' Collaboration
Lancet, 2000; 355: 1955-64; HOPE, PART2; QUIET, SCAT



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ARBs Decrease Risk of Stroke in High Risk Patients

LIFE: Fatal/Nonfatal Stroke



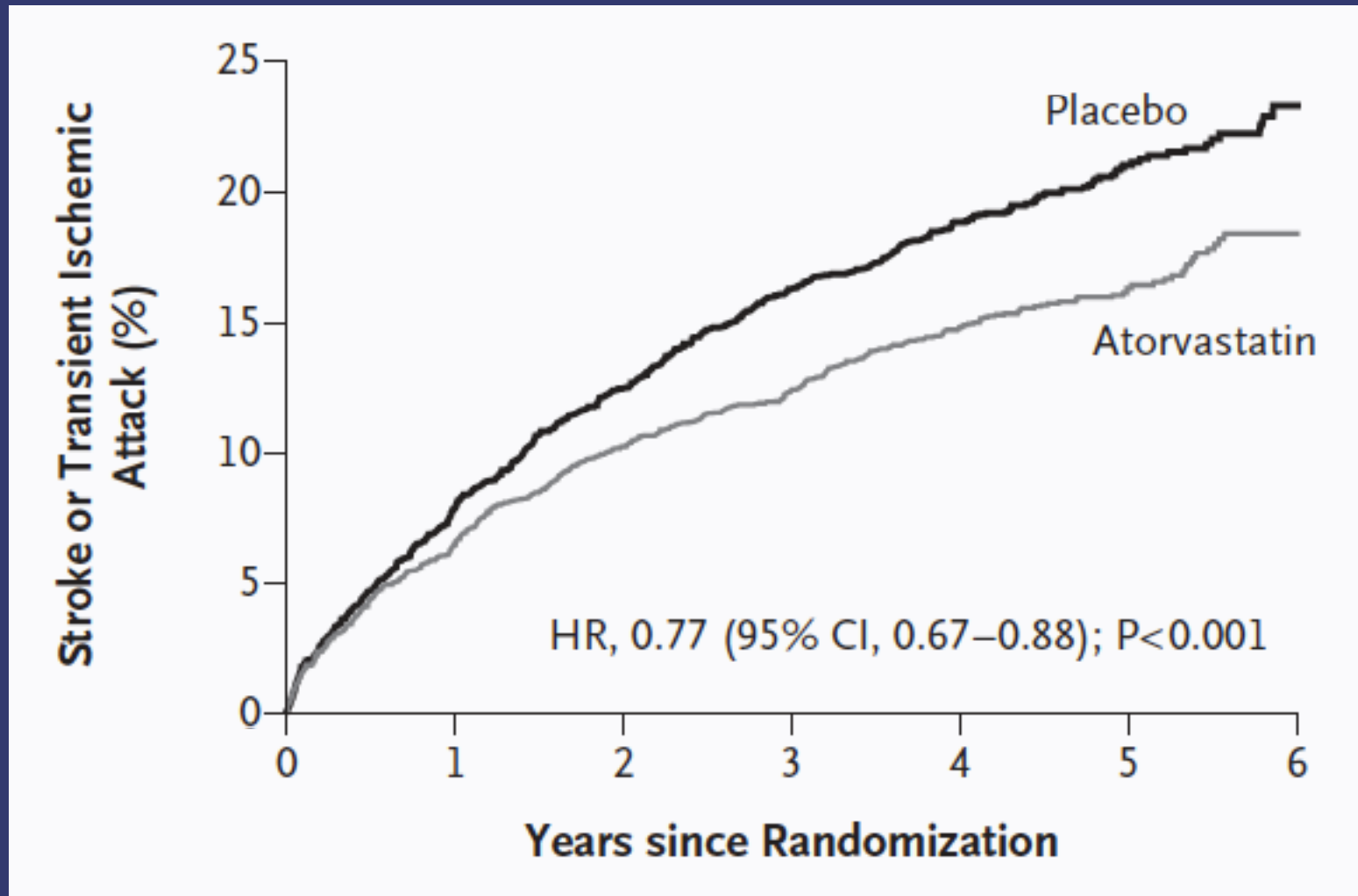
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B Dahlof et al. Lancet 2002;359:995-1003



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SPARCL: High Dose Atorvastatin vs Placebo In Patients with Prior CVA/TIA



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N Engl J Med 2006;355:549-559



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Atorvastatin Reduces the Risk of Cardiovascular Events in Patients With Carotid Atherosclerosis

A Secondary Analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial

- 1007 patients with carotid stenosis (not requiring revascularization) at baseline
 - 3271 patients had no carotid stenosis at baseline
- All patients had stroke/TIA within 6 months of randomization
 - Randomized to Atorvastatin 80 mg/d vs Placebo
 - No known CHD
 - LDL Cholesterol between 100-190 mg/dL



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Stroke 2009;40



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Atorvastatin Reduces the Risk of Cardiovascular Events in Patients With Carotid Atherosclerosis

A Secondary Analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial

- Of those patients with carotid artery stenosis at baseline...
 - Atorvastatin lowered any stroke risk by 33%
 - Atorvastatin lowered any CHD event by 43%
 - Later carotid revascularization was reduced by 56%!



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Stroke 2009;40



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Atorvastatin Reduces the Risk of Cardiovascular Events in Patients With Carotid Atherosclerosis

A Secondary Analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Trial

- However, read the **fine print....**

Subgroup With Carotid Stenosis

Assessment of carotid stenosis was not required by the SPARCL protocol and was done at investigator discretion. However, in 4278 (90.4%) of the SPARCL subjects, carotid stenosis was identified by the investigators at patient randomization into the study and noted in the Case Report Form (CRF) as present, absent, or unknown. If present, the percent degree of stenosis was to be indicated. The

diagnosis was not otherwise reviewed or adjudicated. Side of the stenosis, method of diagnosis, and validation of the degree of narrowing were not requested and are not available for analysis.



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The Best Available Evidence Supports Intervention as an Option for Asymptomatic Patients

- Two RCTs show superiority of revascularization over medical therapy for asymptomatic patients
- Systematic review purporting to show improvements in best medical therapy over time has significant flaws
- Claims that medical therapy has greatly reduced stroke rates should be viewed as hypothesis-generating at best, and should not supplant Tier 1 evidence showing small but clear patient benefits from revascularization
- CREST demonstrates equivalence of CAS vs. CEA revascularization therapies for asymptomatic patients



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Two RCTs Completed a Decade Apart Show Significant Benefits of Revascularization Over Best Medical Therapy

Revascularization Lowers Stroke and Death Rates in Two Randomized Trials

Study	Treatment Arm	Perioperative Stroke and Death	5 yr Ipsilateral Stroke and Death	5 Yr All Stroke and Death
ACAS (1987-1993)	CEA + BMT	2.3%	5.1%	-
	BMT	NA	11.0%	-
ACST (1999-2003)	CEA + BMT	3%	-	6.9%
	BMT	NA	-	10.9%

- CEA = Carotid endarterectomy
- BMT = Best Medical Therapy

* Chatuverdi et al. Carotid Endarterectomy – An evidence-based review, *Neurology* 2005; 65: 794-801.

** Haliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, Thomas D. Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: an RCT. *Lancet* 2004; 363: 1491–1502.



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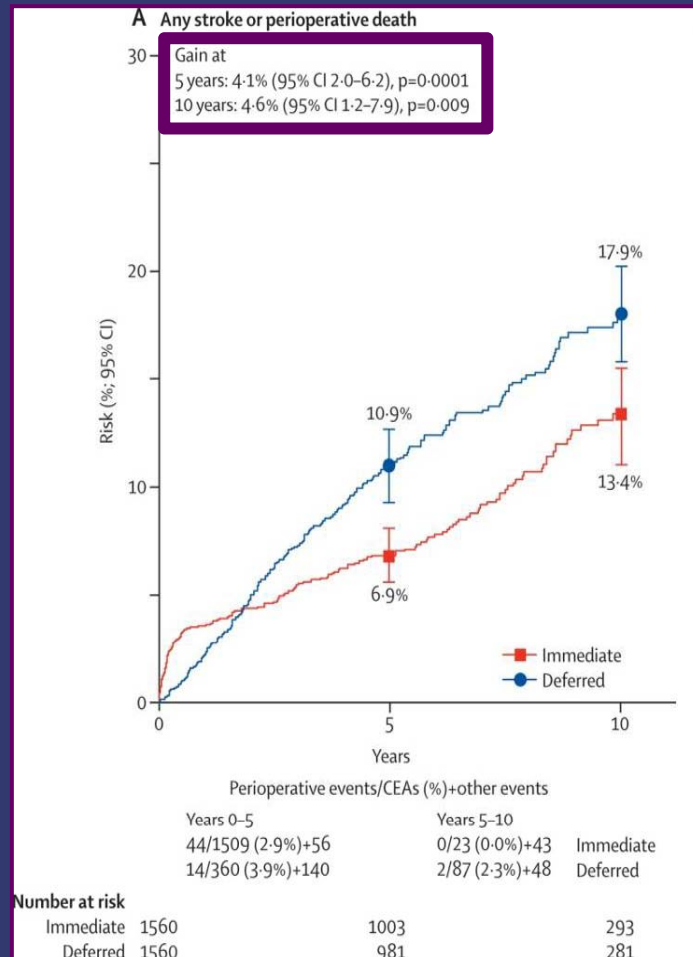


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Temporal Changes in the Risk of “Any” and “Ipsilateral” Stroke following CEA for Asymptomatic Carotid Stenosis

Trial	Years	Publication Year	Any	Ipsilateral
ACAS	1-5	1995	17.5%	11.0%
ACST	1-5	2004	11.8%	5.3%
ACST	6-10	2009	7.2%	3.6%

ACST 10-year Follow-up Results Provide Most Rigorous Comparison Of Revascularization And BMT (Lancet 2010)



- 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 younger than age 75 years



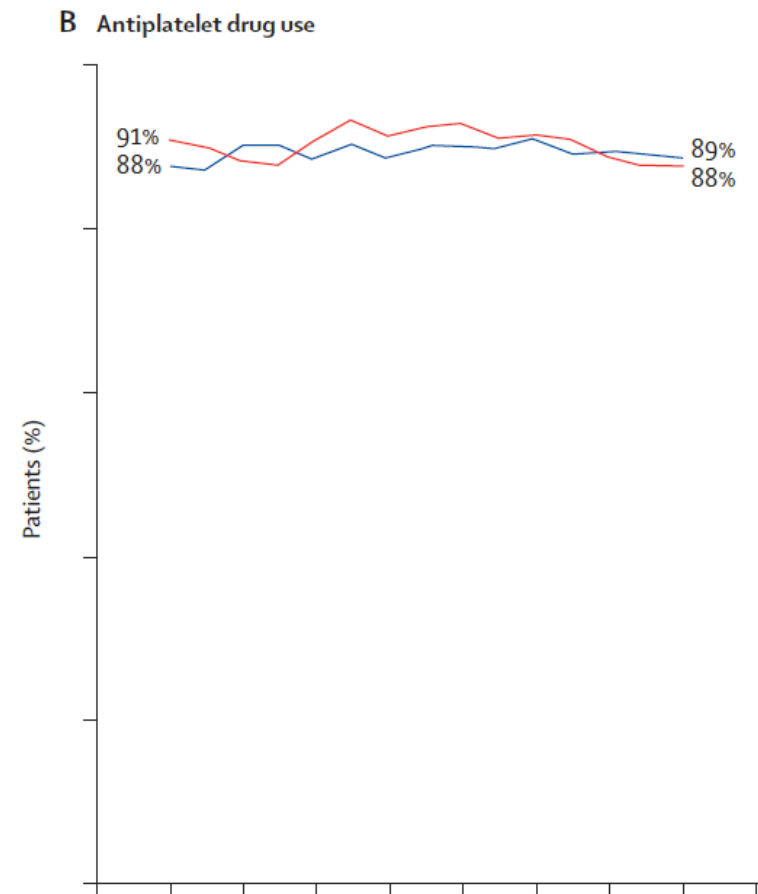
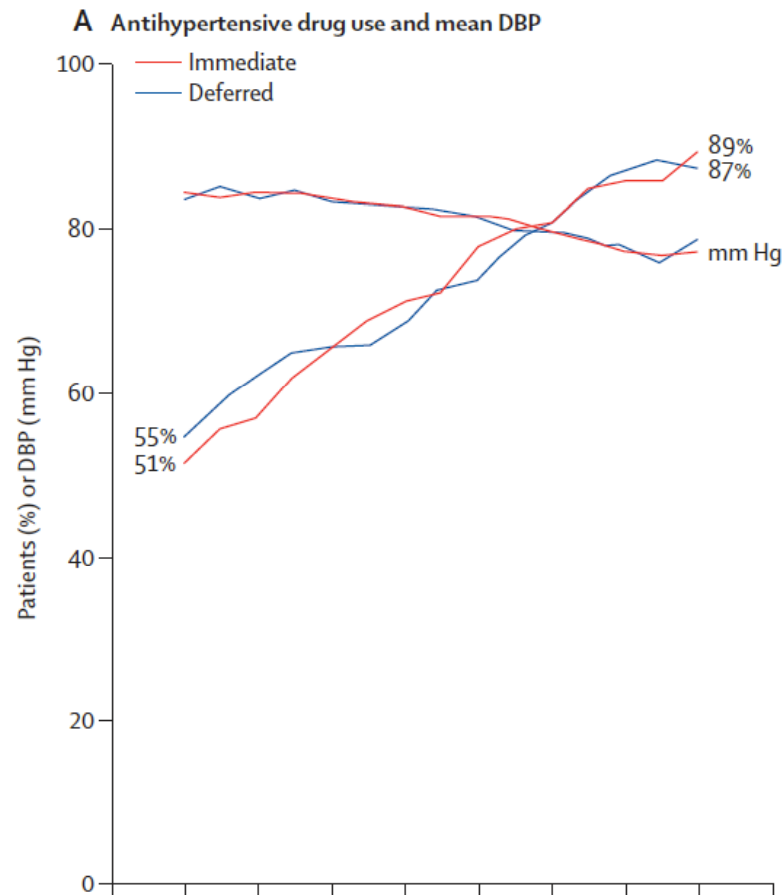
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Halliday A, et al. 10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomized trial. *Lancet* 2010;376:1074-84.



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10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial 3120 Patients



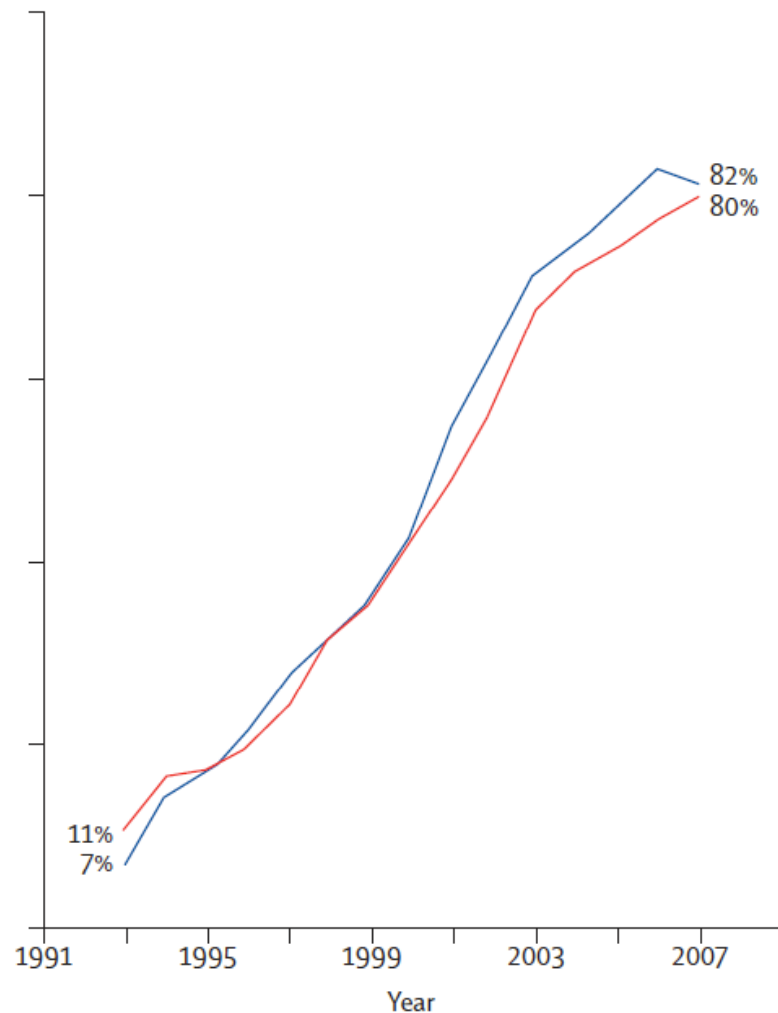
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10-year stroke prevention after successful carotid endarterectomy for asymptomatic stenosis (ACST-1): a multicentre randomised trial 3120 Patients

D Lipid-lowering drug use

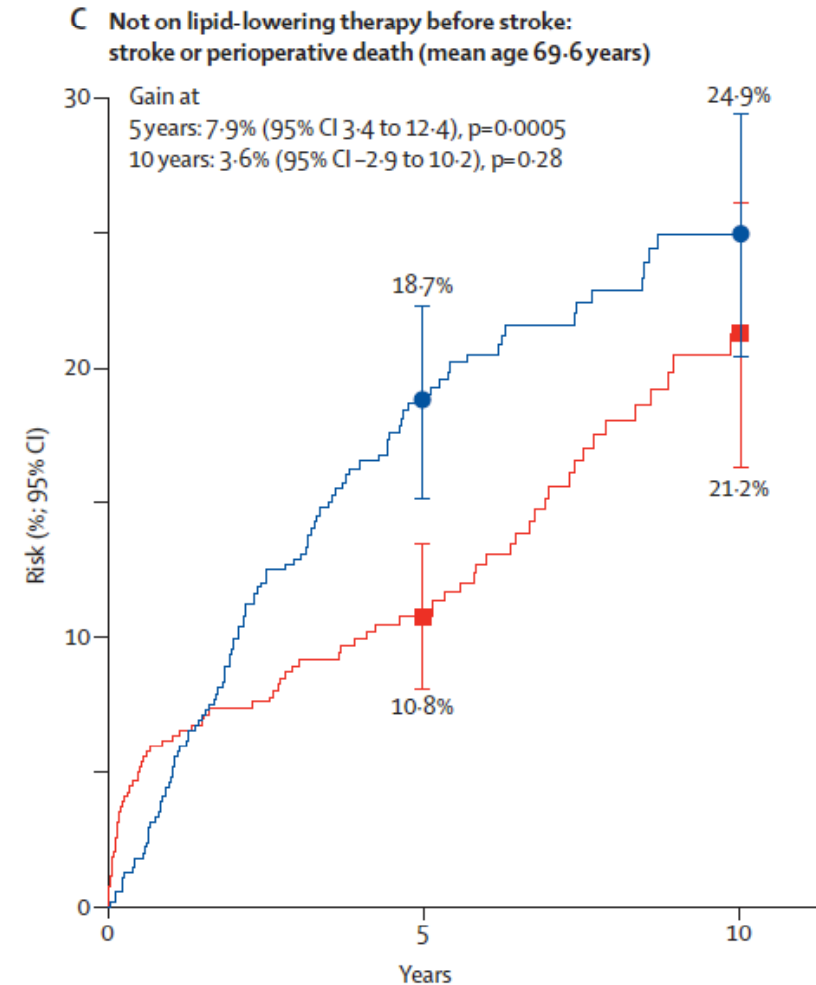
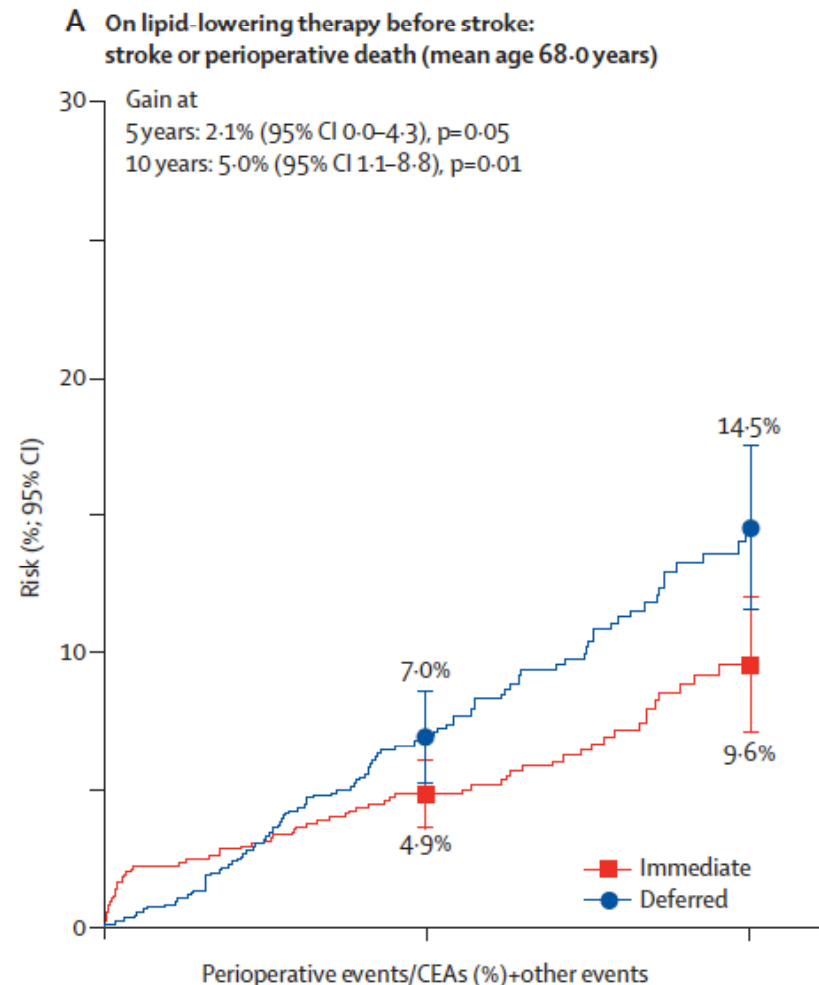


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Lancet 2010;376:1074



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Recent Systematic Review Questions Revascularization Benefits after Reporting Improved Stroke Trend on BMT*

- 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



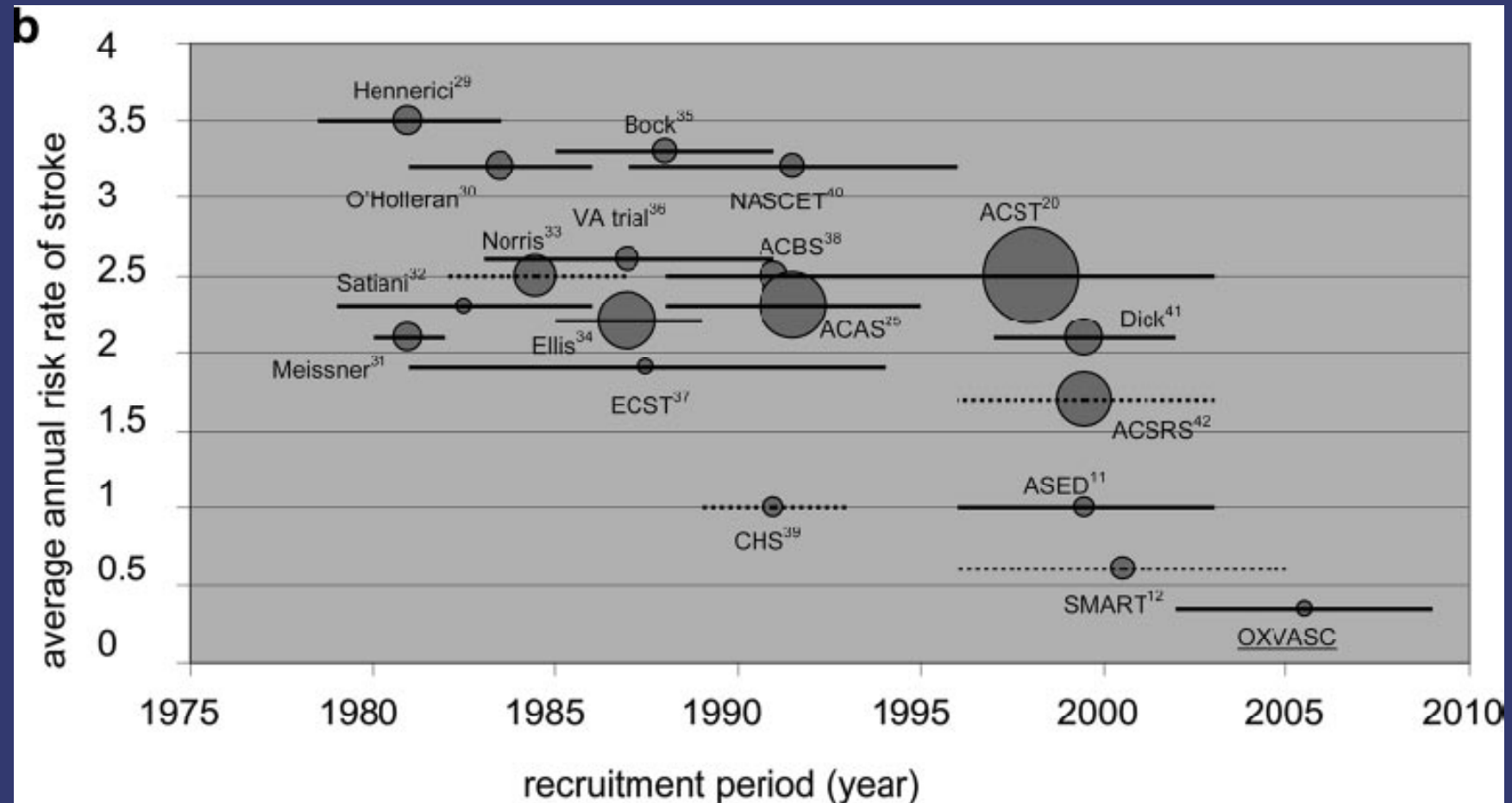
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* Abbott AL. Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. *Stroke*. 2009.

Medical Treatment for Asymptomatic Carotid Stenosis



Asymptomatic Carotid Stenosis Clinical Trials



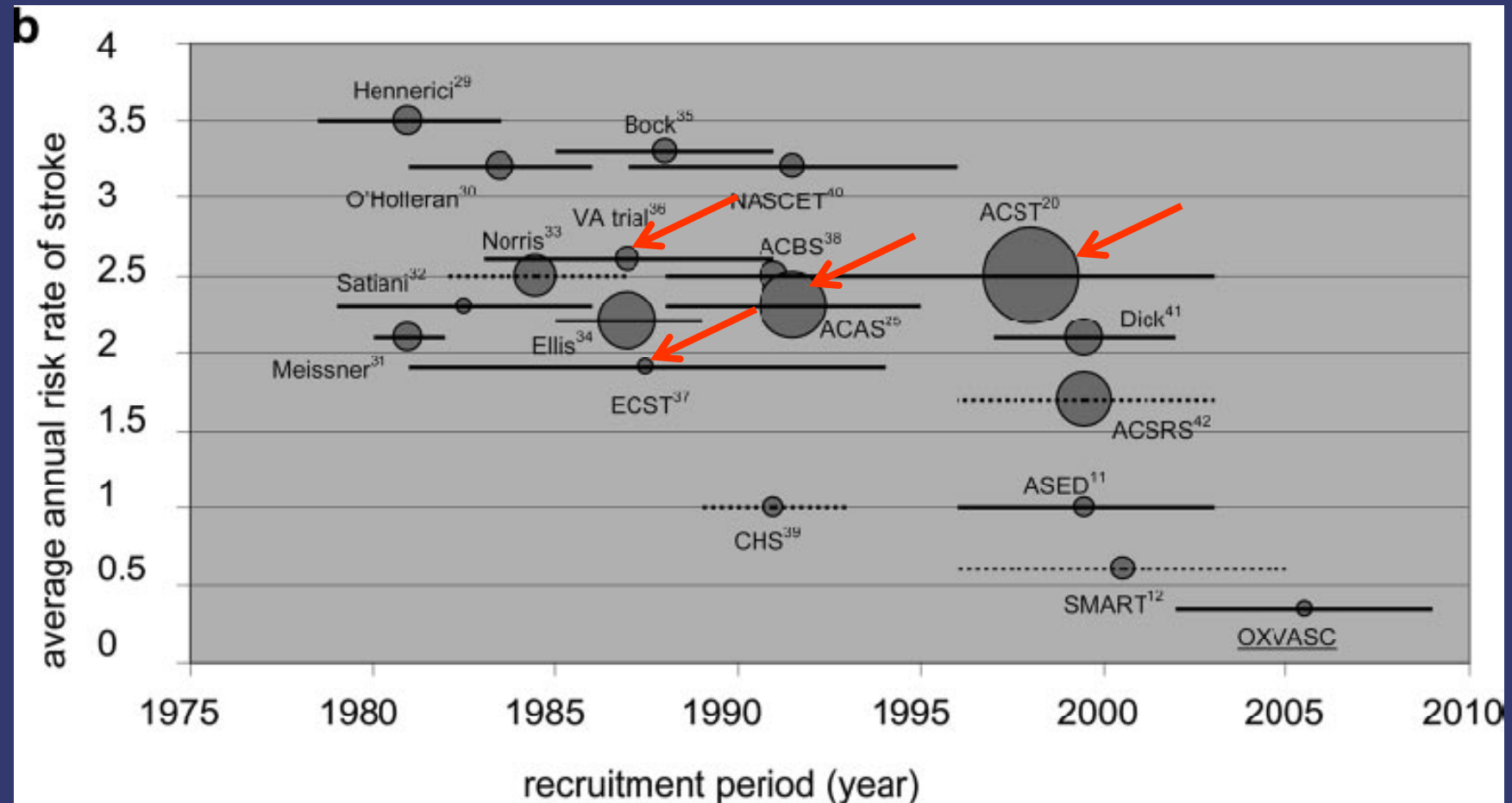
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Abbott AL. *Stroke*. 2009 Oct;40(10):e573-83.



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Medical Treatment for Asymptomatic Carotid Stenosis



Randomized Trials



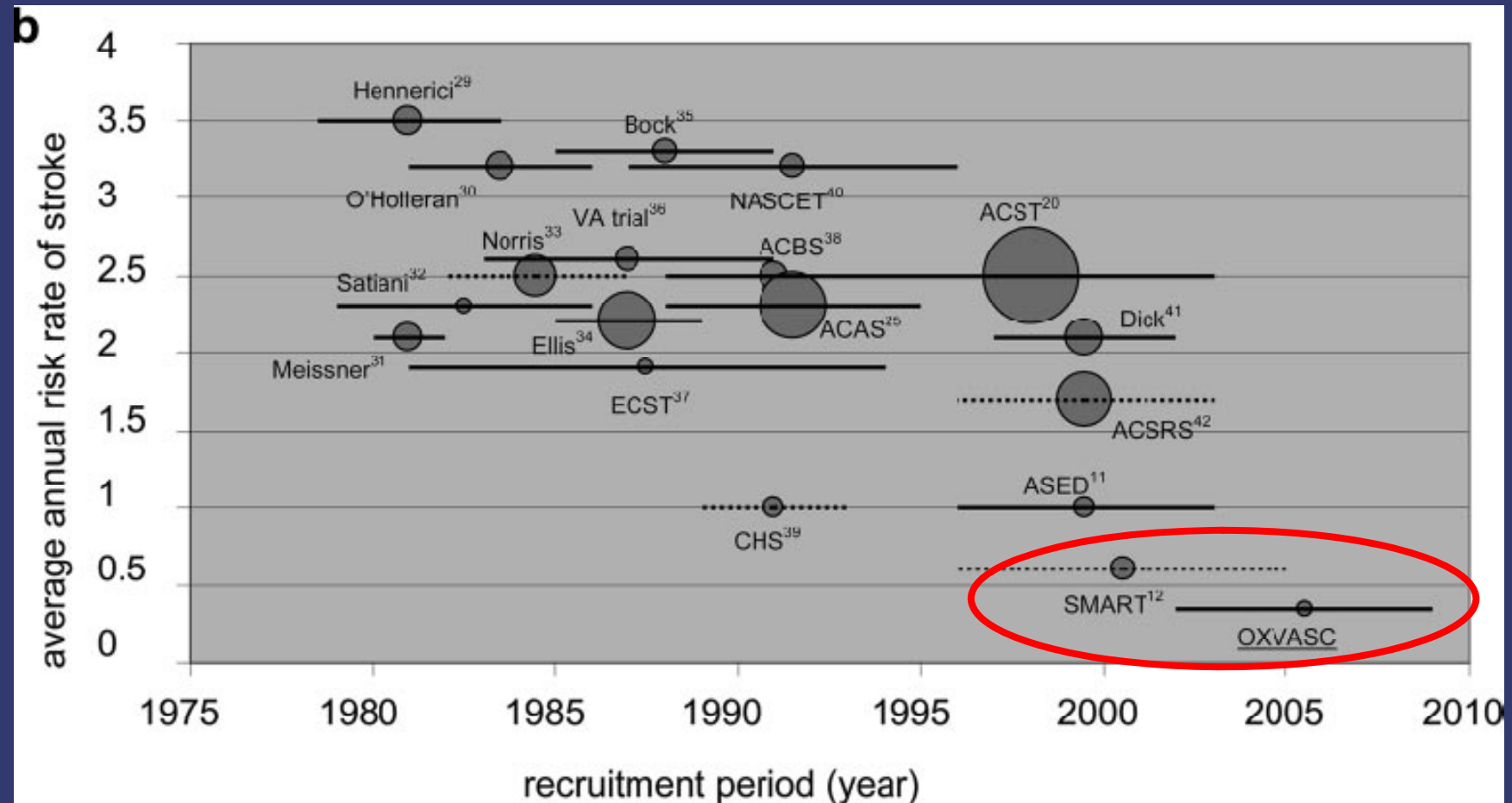
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Medical Treatment for Asymptomatic Carotid Stenosis



Is the annual risk of stroke less than 1%?



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Abbott AL. *Stroke*. 2009 Oct;40(10):e573-83.



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Medical Treatment for Asymptomatic Carotid Stenosis

SMART Study (Goessens et al. Stroke, 2007)

- 221 patients with >50% carotid stenosis
- PSV >150 cm/sec, only 96 pts had PSV >210
- Stroke 2.7% over 3.6yrs, deaths not assessed
- 7% had carotid repair

Oxford Vascular Study (Marquardt Stroke, 2010)

- 101 patients with >50% carotid stenosis, 3 years
- Only 32 patients had 70-99%
- <0.5% stroke risk per year
- 1.8% TIA, vascular death 7.7%

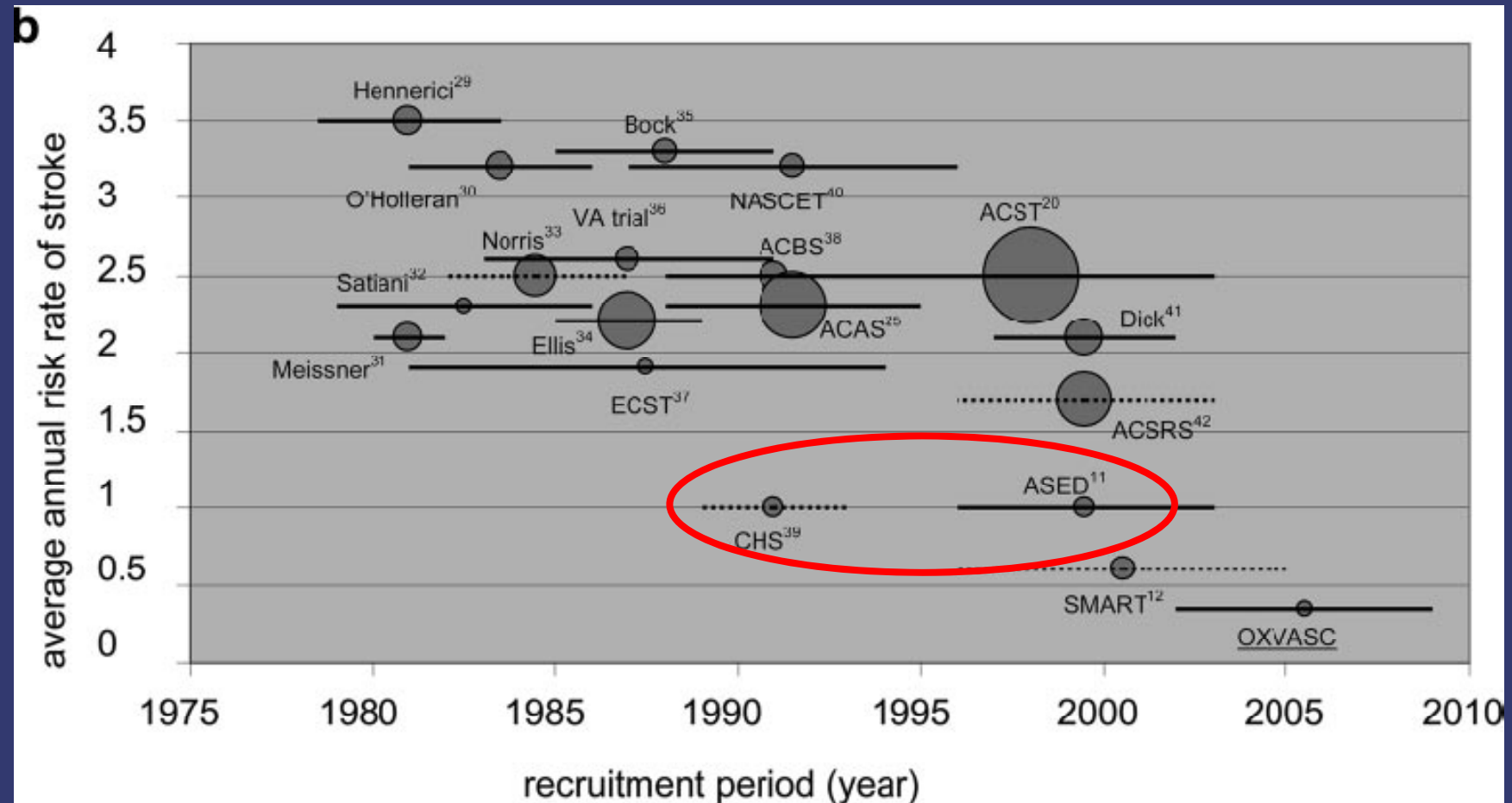


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Medical Treatment for Asymptomatic Carotid Stenosis



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Is the annual risk of stroke about 1%?

Abbott AL. *Stroke*. 2009 Oct;40(10):e573-83.



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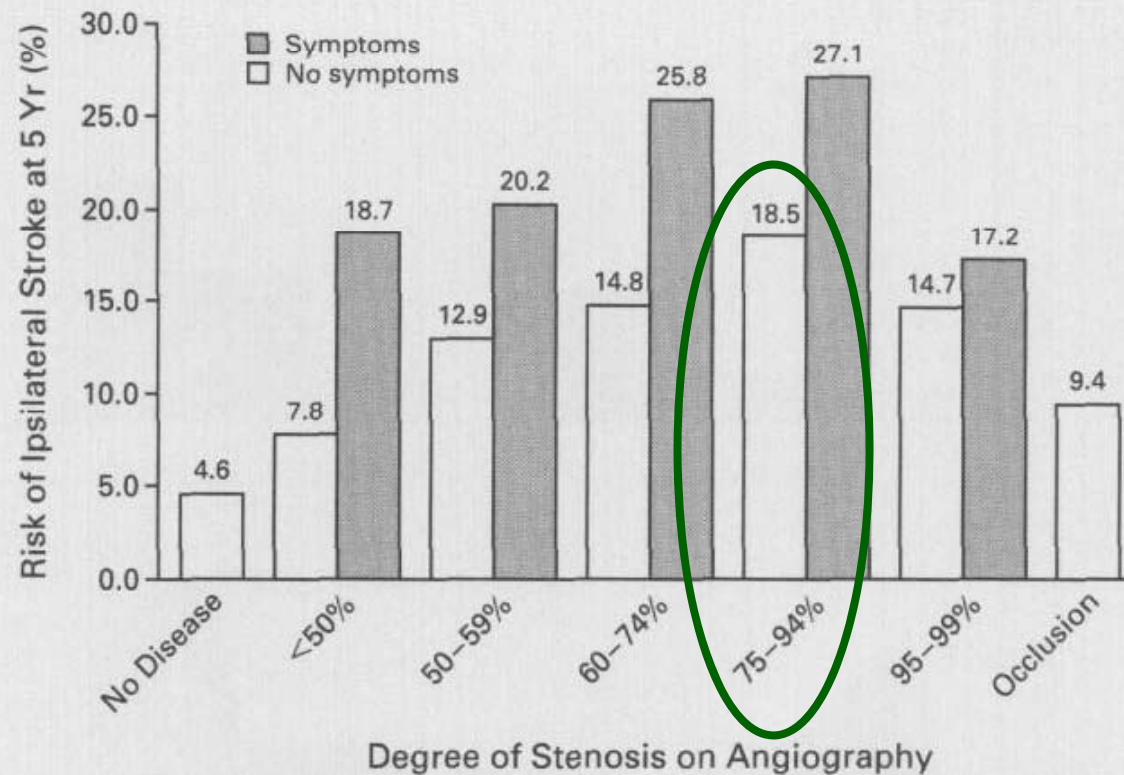


Figure 1. The Risk of a First Ipsilateral Stroke at Five Years after Study Entry in the Territories of Carotid Arteries with and without Symptoms, According to the Degree of Stenosis.

Stenosis of 95 to 99 percent represents near-occlusion. The numbers of patients with symptomatic carotid-artery stenosis were as follows: <50 percent stenosis, 690; 50 to 59 percent stenosis, 238; 60 to 74 percent stenosis, 267; 75 to 94 percent stenosis, 196; and 95 to 99 percent stenosis, 58. For asymptomatic carotid-artery stenosis, the numbers of patients were as follows: no disease, 471; <50 percent stenosis, 1496; 50 to 59 percent stenosis, 108; 60 to 74 percent stenosis, 113; 75 to 94 percent stenosis, 74; 95 to 99 percent stenosis, 29; and occlusion, 86.



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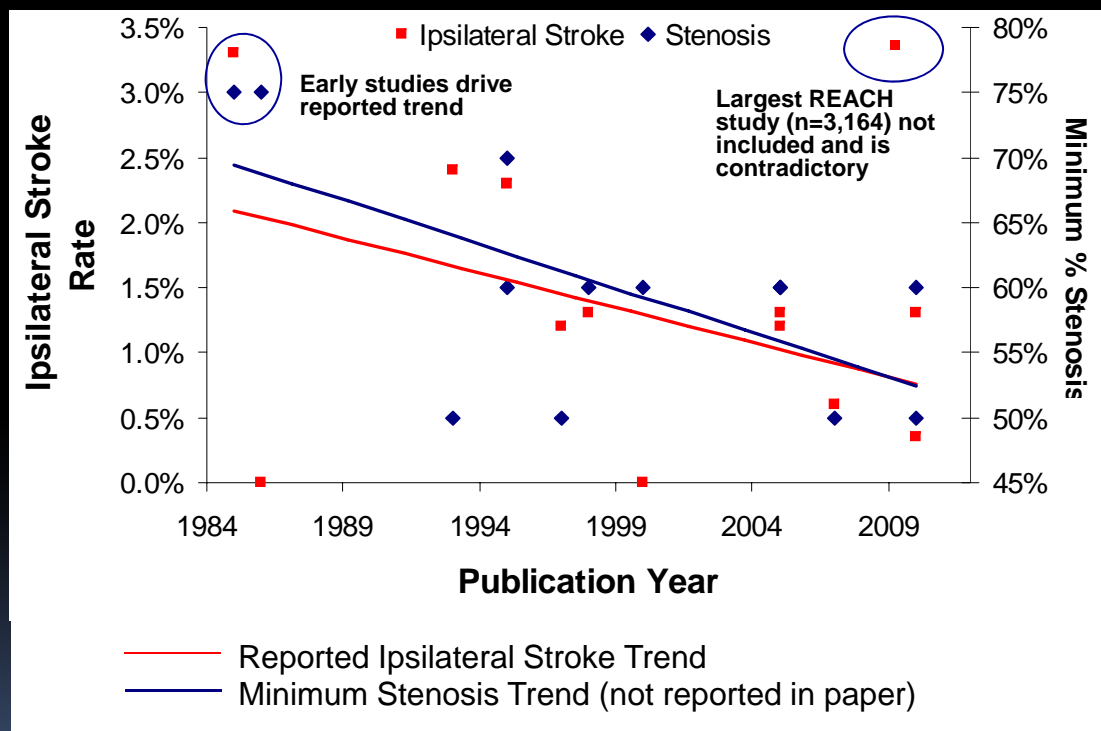
NASCET: Inzitari et al. NEJM 2000;342:1693



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

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

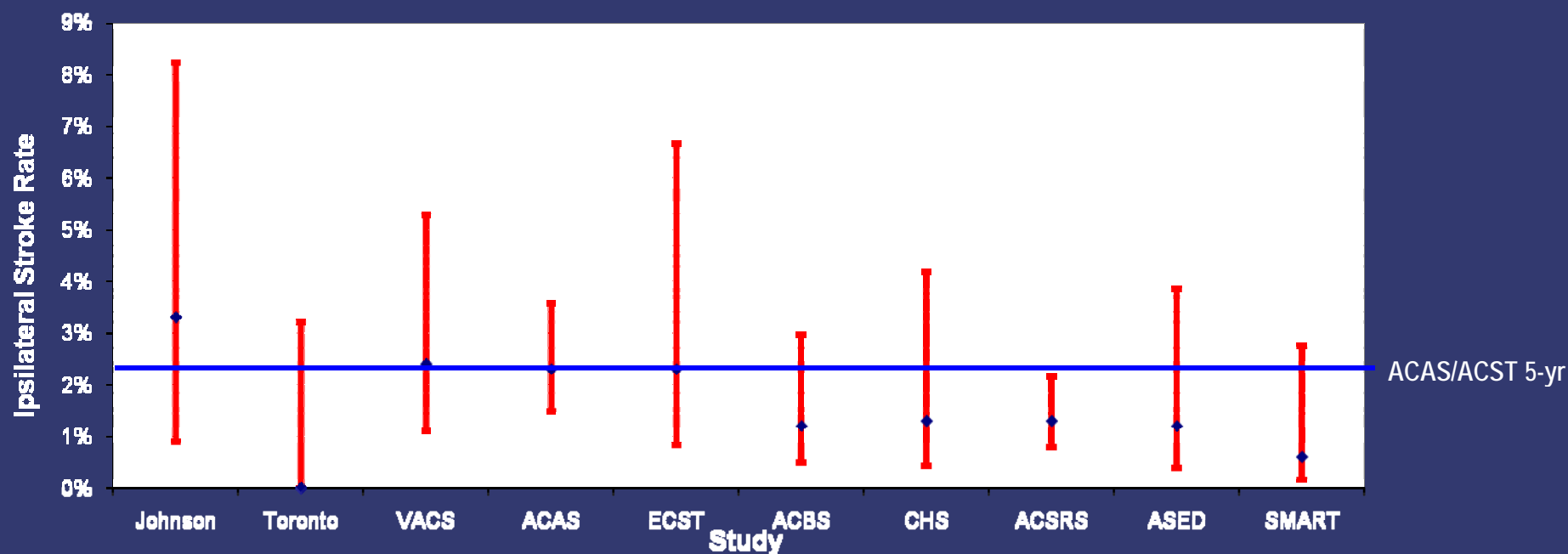


- Systematic review did not adjust for carotid stenosis thresholds
- Early studies with more complex patients drove observed stroke trend
- Largest and most recent REACH study ** (N = 3164, published after the systematic review) contradicts the review findings
- If the systematic reviews' analysis had included minimum % stenosis as a covariate, there would not have been a significant trend in stroke rates ($p = 0.33$)

* 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.

Confidence Intervals Overlap From Study To Study And Are Not Significantly Different From RCTs



- Comparison of the confidence intervals from studies included in the systematic review overlap with ACAS/ACST annualized stroke rate of 2.3%

*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.



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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%)



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