

Carotid Artery Stenting: indication

**Asymptomatic Carotid Artery Stenosis:
Is Really Risky? Must Be Recanalized?**

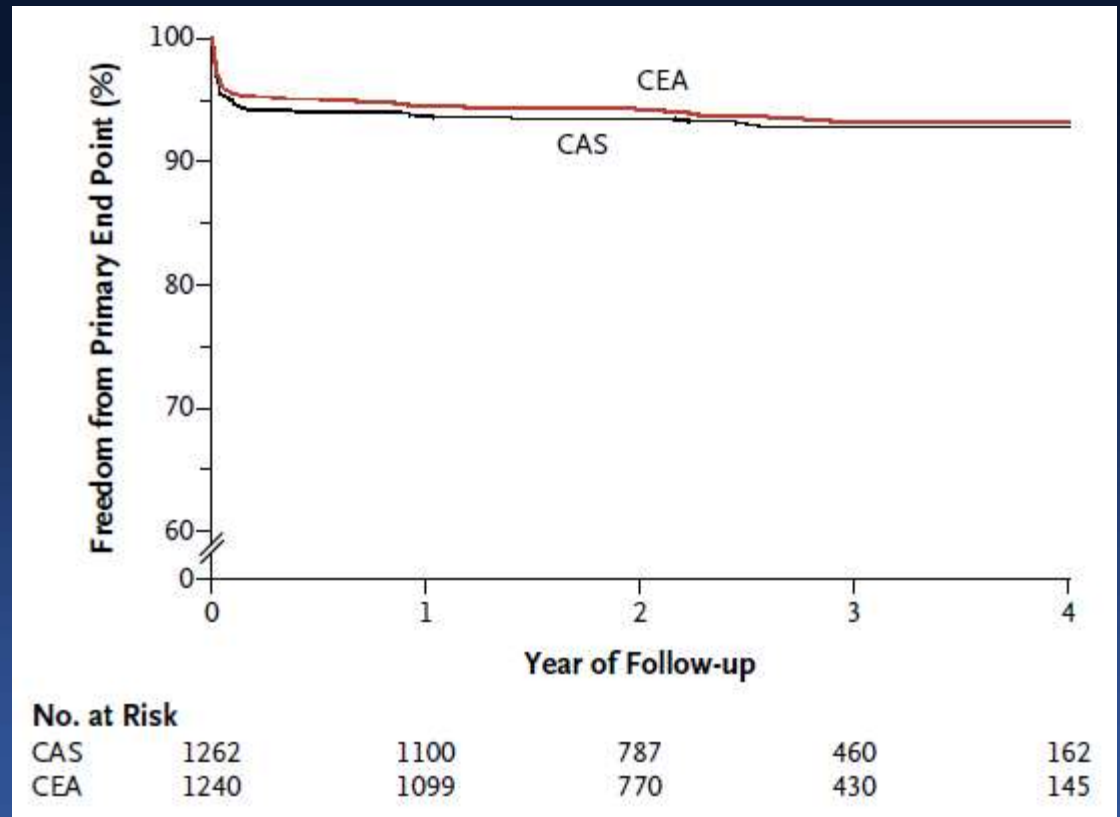
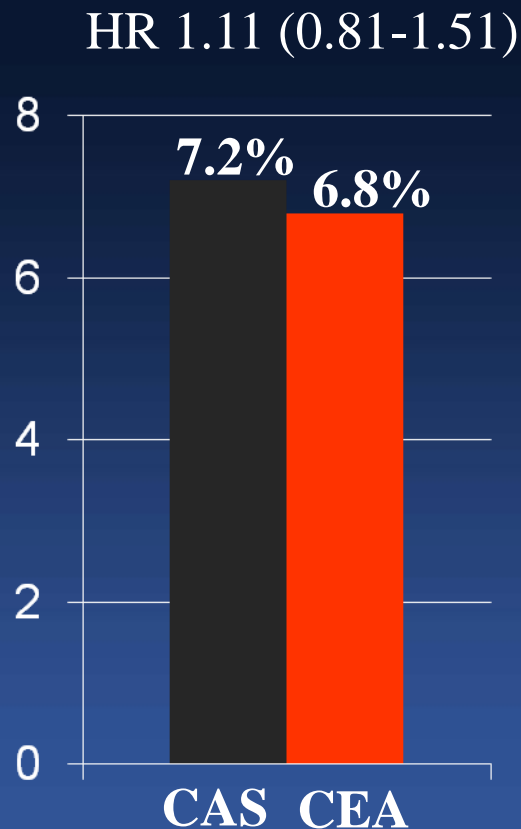
Seung-Whan Lee, MD, PhD

Professor of Medicine, University of Ulsan College of
Medicine, Asan Medical Center, Seoul, Korea

4-Year Outcomes of the CREST

Primary Endpoint :

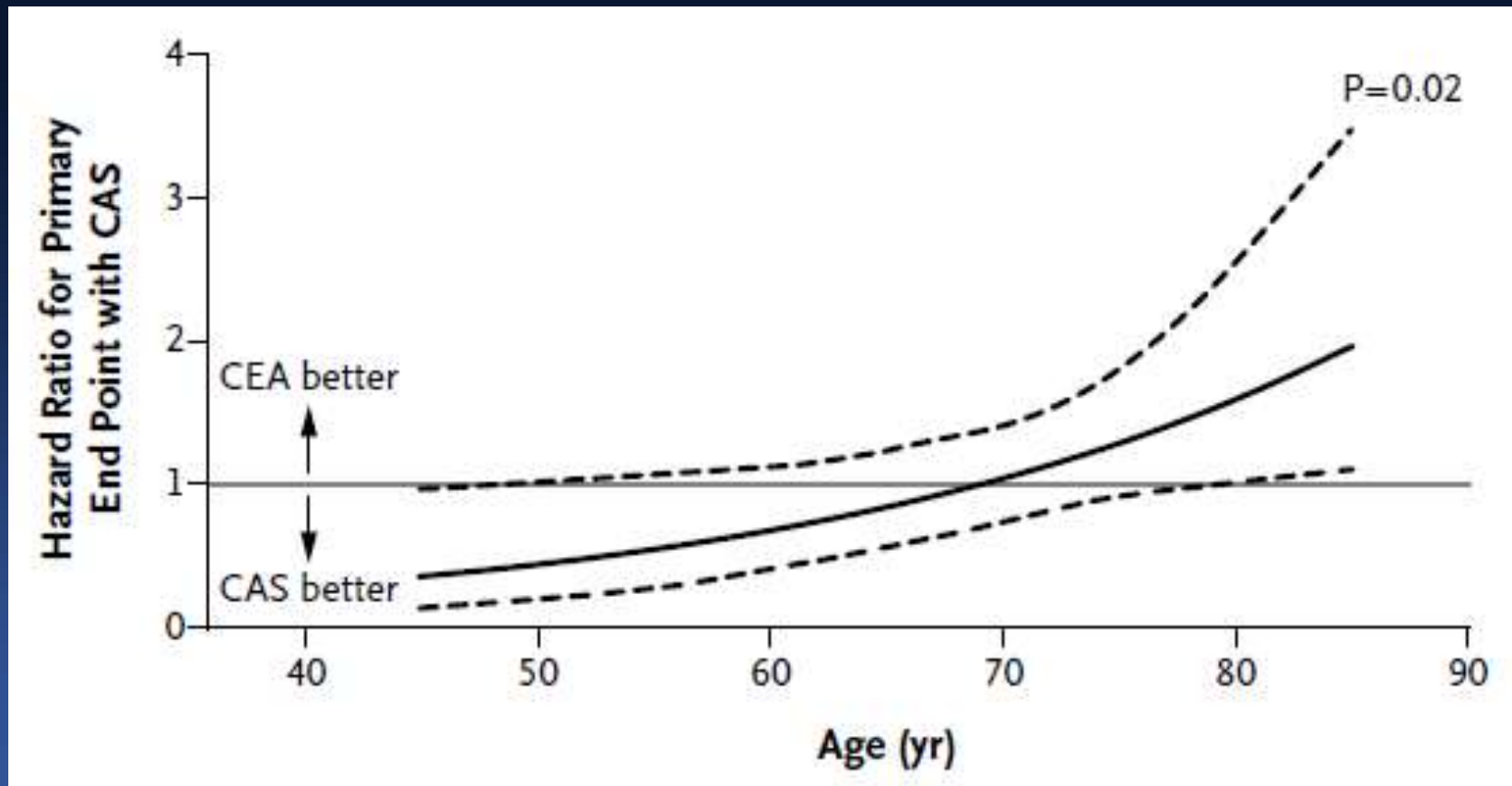
any stroke, MI, or death within 30 days + subsequent ipsilateral stroke



Brott TG, et al. N Engl J Med 2010; 363(1):11-23.

Hazard Ratio for Primary Endpoint

4-Year Outcomes of the CREST



Brott TG, et al. N Engl J Med 2010; 363(1):11-23.

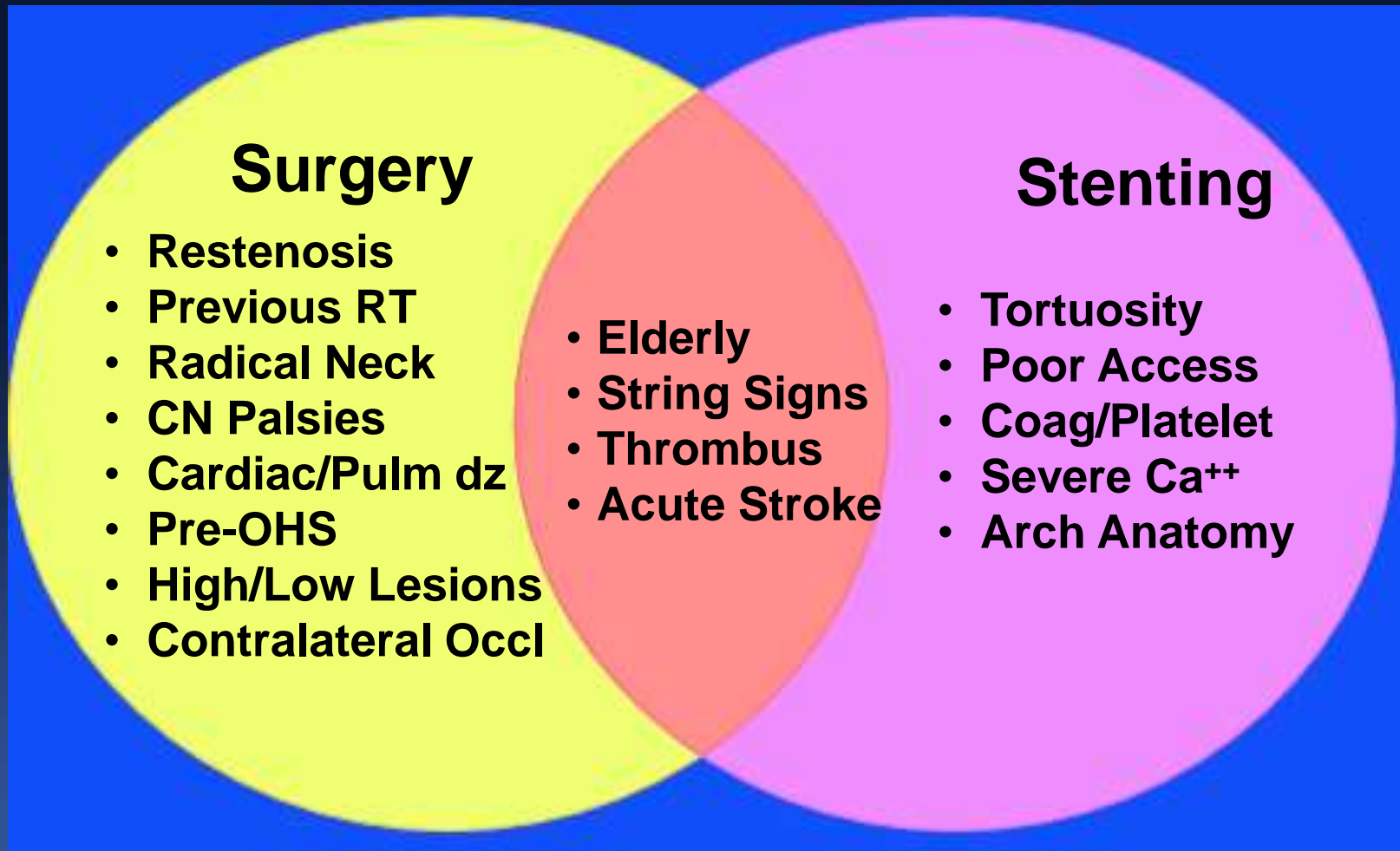
Safety of Stenting and CEA by Symptomatic Status in the CREST

- 1,181 asymptomatic & 1,321 symptomatic patients
- Primary endpoint (periprocedural stroke, MI or death)

	CAS	CEA	HR (95% CI)	<i>P</i> <i>Value</i>
Asymptomatic	3.5%	3.6%	1.02 (0.55-1.86)	0.96
Symptomatic	6.7%	5.4%	1.26 (0.81-1.96)	0.30

Silver FL, et al. Stroke 2011; 42(3): 675-80.

High Risk Features



ESCT vs. NASCET measurement

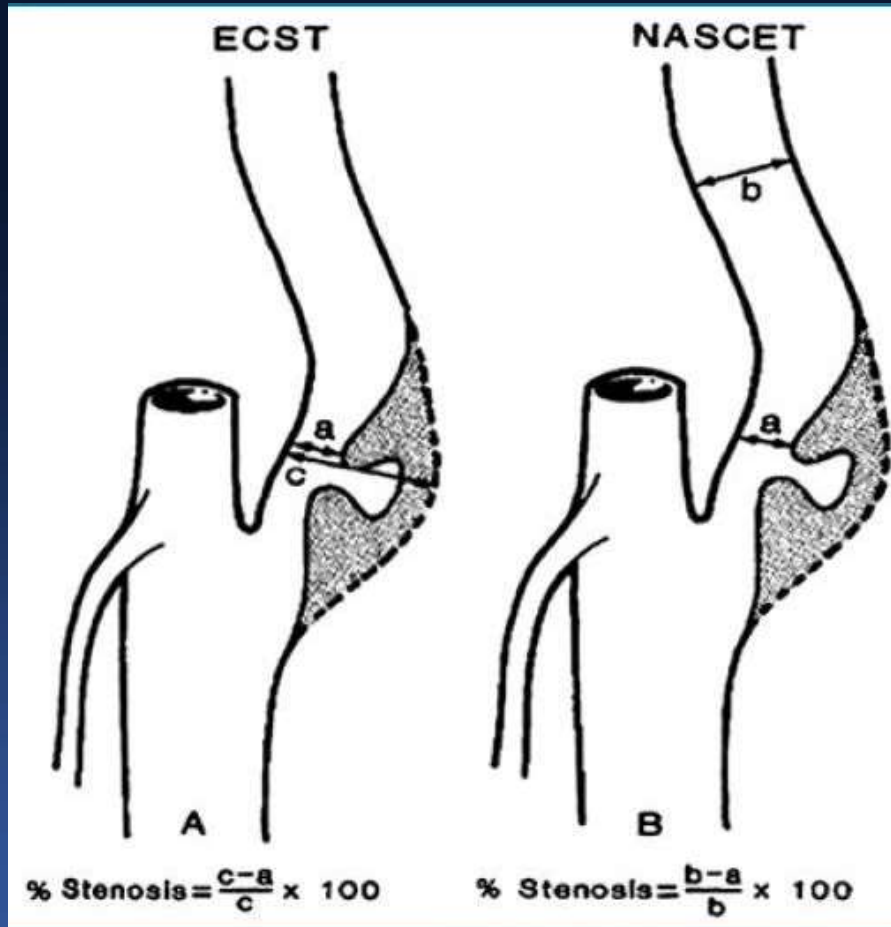


Table 1. Corresponding degrees of carotid artery stenosis (%) in NASCET and ECST.

NASCET	ECST
30	65
40	70
50	75
60	80
70	85
80	91
90	97

CEA versus Medical Therapy

Trial	N	Stenosis	Follow-Up	End Point	Medical (%)	CEA (%)	p	RRR (%)	ARR (%)	NNT
Symptomatic										

Very high stroke rate on medical group: very old story

ACAS (22)	1,002	>60%	5 yrs	Ipsilateral stroke, surgical death	11.8	6.4	0.004	46	5.4	18.5
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

CEA was significantly superior to Medical therapy, irrespective of symptom

ACCF/SCAI/SVMB/SIR/ASITN 2007 Clinical Expert Consensus
Document on Carotid Stenting J Am Coll Cardiol 2007;49:126–70

RCT's: CAS vs. OMT

Symptomatic
High-risk

None

Asymptomatic
High-risk

None

**No randomized trial comparing CAS
vs. OMT across all risk group**

None

None

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

- a) registry studies of CAS and
- b) RCT's comparing it to CEA

Indications for carotid artery revascularization

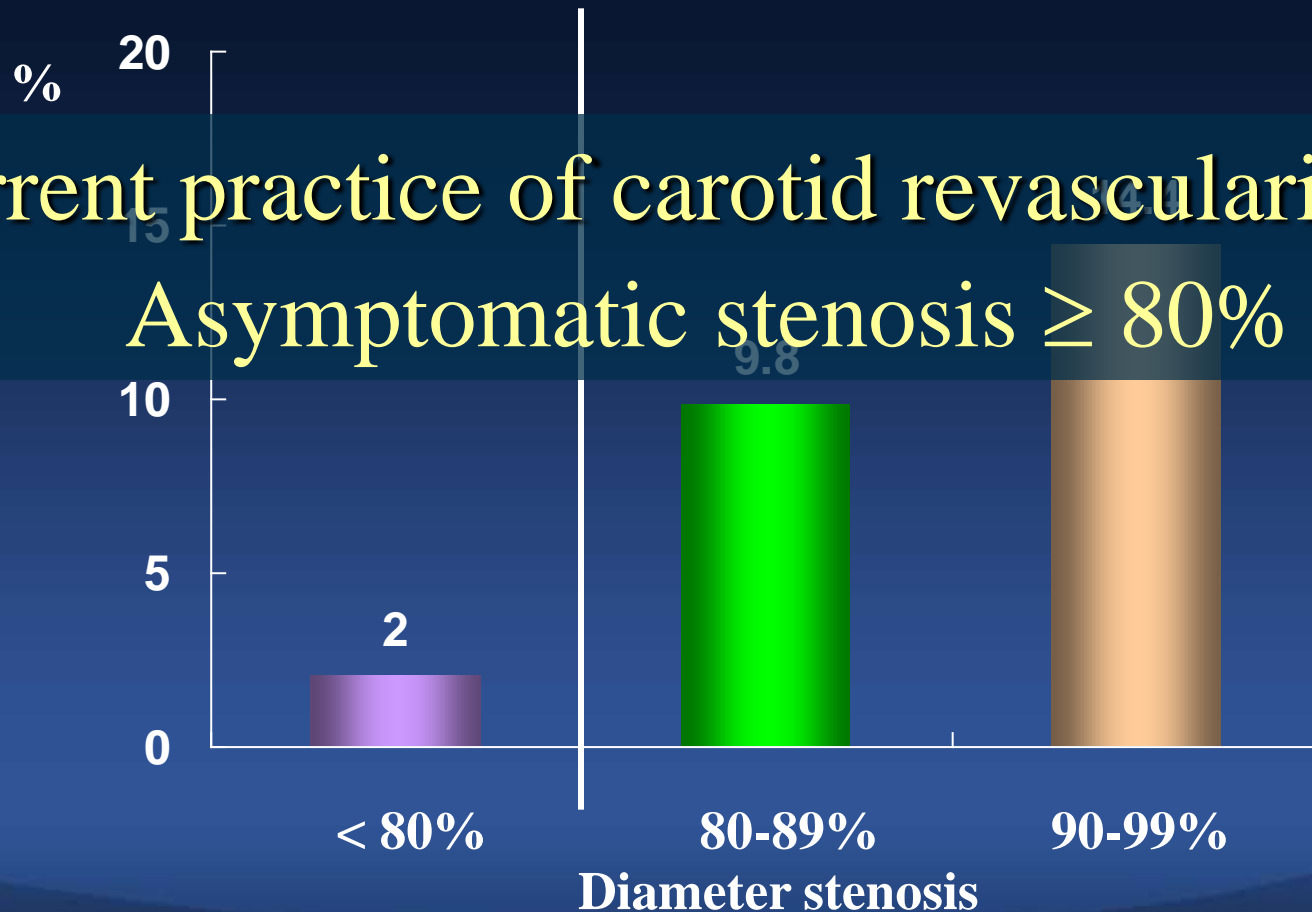
Indication level	Symptomatic stenosis	Asymptomatic stenosis
Proven	<ul style="list-style-type: none"> • 70-99% stenosis • $\geq 70\%$ • Periprocedural complication risk $< 6\%$ 	<ul style="list-style-type: none"> • $> 60\%$ stenosis • $\geq 60\%$ • Periprocedural complication risk $< 3\%$ • Life expectancy > 5 yrs
Acceptable	<ul style="list-style-type: none"> • 50-69% stenosis • $\geq 50\%$ • Periprocedural complication risk $< 6\%$ 	<ul style="list-style-type: none"> • $> 60\%$ stenosis • $\geq 60\%$ • Periprocedural complication risk $< 3\%$ • Planned CABG
Unacceptable	<ul style="list-style-type: none"> • $< 29\%$ stenosis, or • Periprocedural complication risk $> 6\%$ 	<ul style="list-style-type: none"> • $< 60\%$ stenosis or • Periprocedural complication risk $> 3\%$ • No indication for CABG

Circulation 2006;113:2021-2030

Stroke risk of asympt patients a/t stenosis at 3 years

ESCT group (2,295 pts)

Current practice of carotid revascularization
Asymptomatic stenosis $\geq 80\%$



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

TABLE 7. Summary of Recommendations Regarding the Selection of Revascularization Techniques for Patients With Carotid Artery Stenosis

	Symptomatic Patients		Asymptomatic Patients
	50% to 69% Stenosis	70% to 99% Stenosis*	70% to 99% Stenosis*
Endarterectomy	Class I LOE: B	Class I LOE: A	Class IIa LOE: B
Stenting	Class I LOE: B	Class I LOE: B	Class IIb LOE: B

≥ 50%

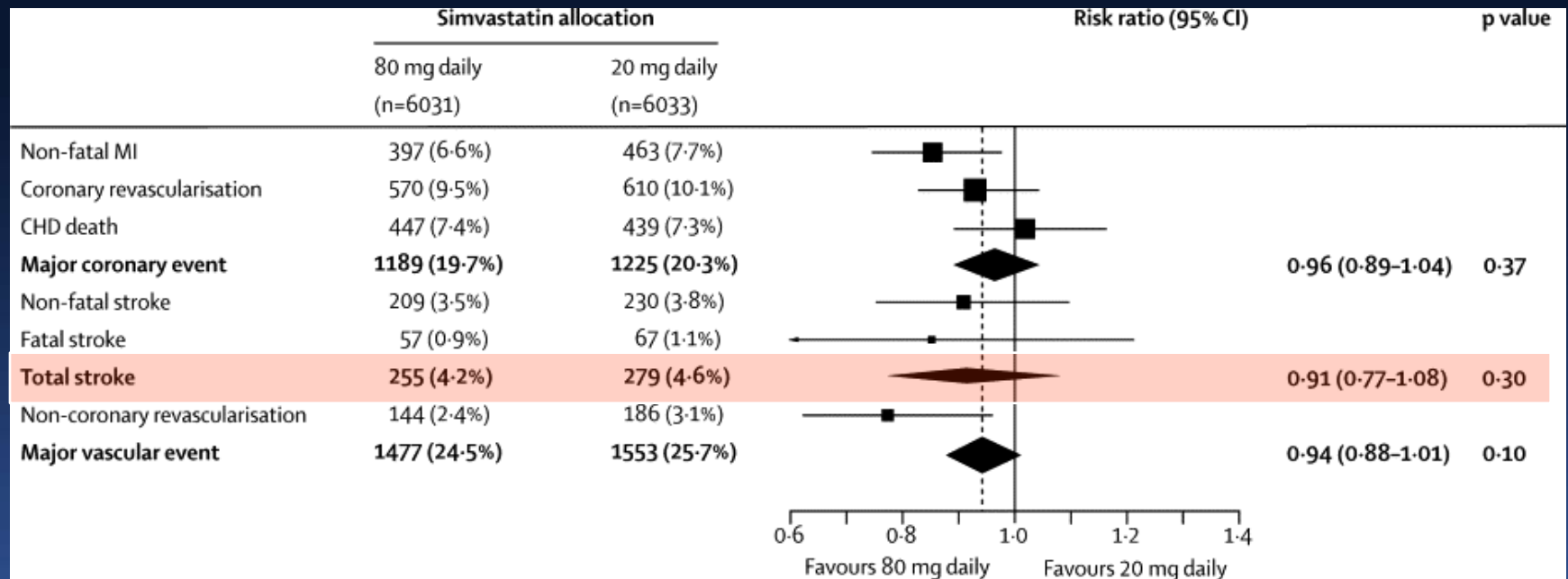
≥ 70%

The severity of stenosis is defined according to angiographic criteria by the method used in NASCET³⁷ but generally corresponds as well to assessment by sonography¹¹² and other accepted methods of measurement. See Sections 7.2 to 7.4.4 for details.
LOE indicates level of evidence.

Asymptomatic Carotid Artery Stenosis: Is Really Risky?

SEARCH: High “Residual Risk” despite intensive medical management (6.7-yr FU)

12 064 survivors of myocardial infarction



12,000 patients allocated 20 mg vs. 80 mg simvastatin
Stroke risk almost unchanged (4.2% vs. 4.6%)

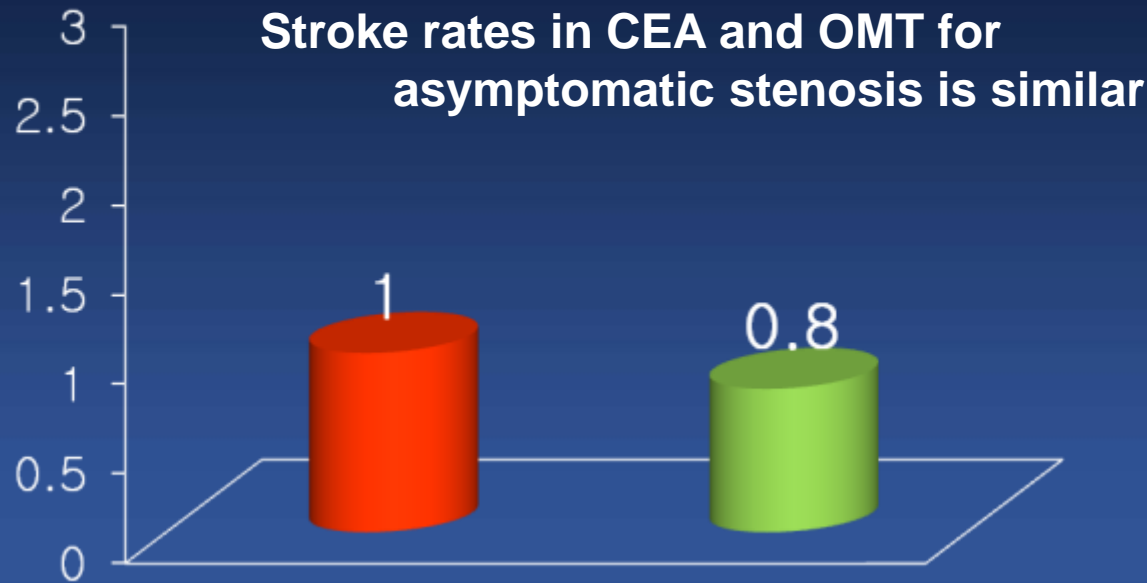
Lancet 2010;376: 1658–69

Intensive Medical Therapy

Contemporary Results of Carotid Endarterectomy for Asymptomatic Carotid Stenosis

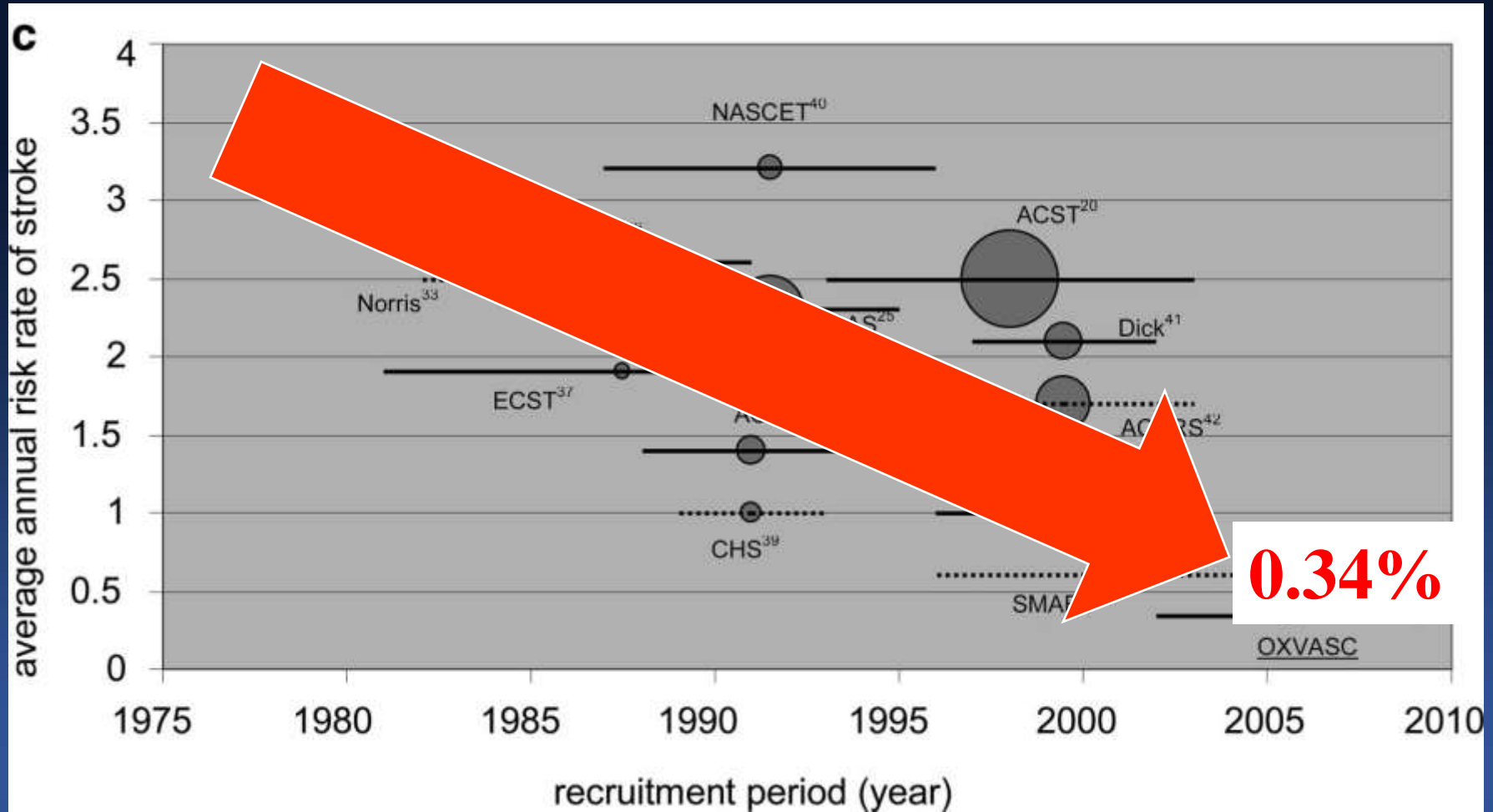
Karen Woo, MD; Joy Garg, MD; Robert J. Hye, MD; Ralph B. Dilley, MD

Average annual risk



NSQIP data (CEA) SMART (OMT) *Stroke. 2010;41:975-9*

Average annual risk rates of stroke in patients with at least 50% asymptomatic carotid stenosis



Stroke. 2010;41:e11-e17

Intensive Medical Therapy

Effects of Intensive Medical Therapy on Microemboli and Cardiovascular Risk in Asymptomatic Carotid Stenosis

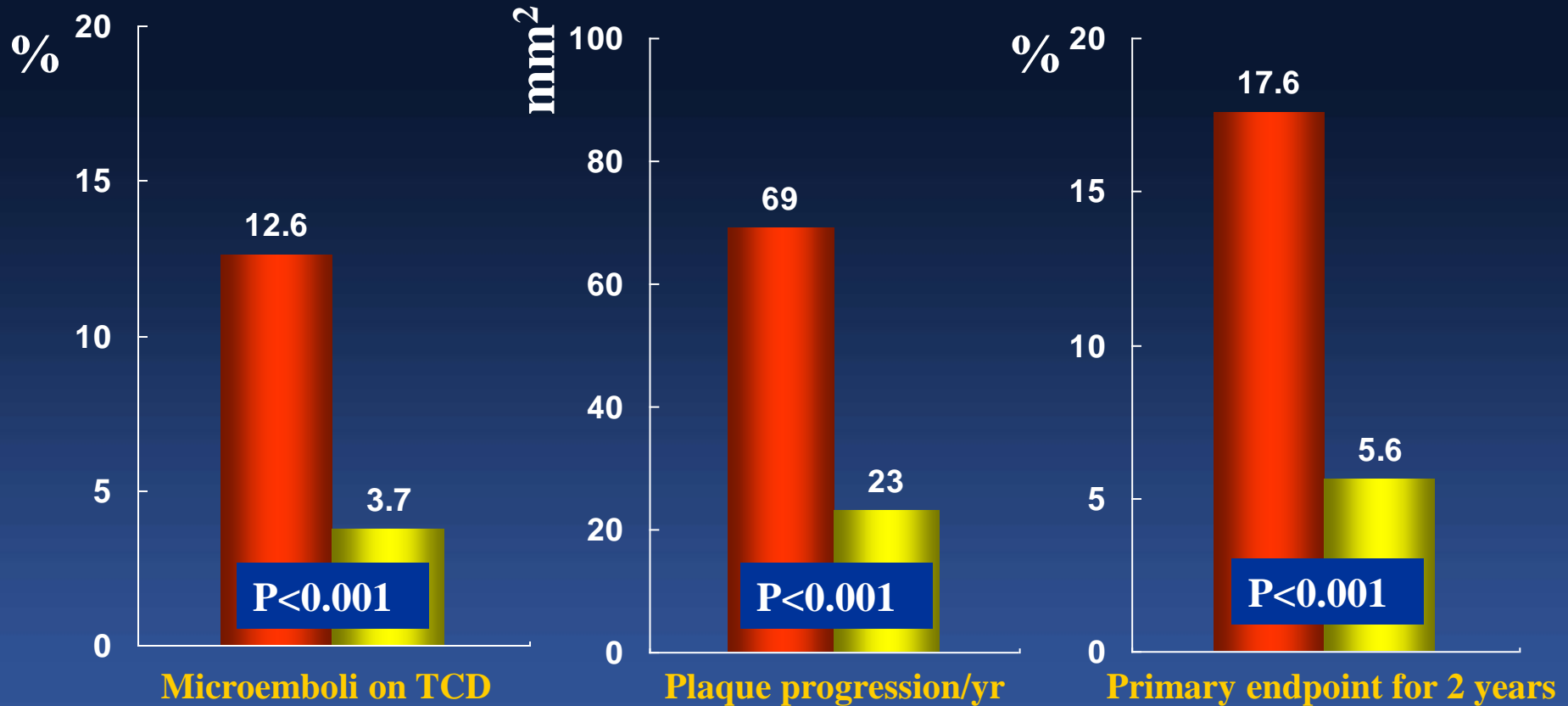
ARCHIVES EXPRESS

J. David Spence, MD; Victoria Coates, BA, HBSc; Hector Li, MD; Arturo Tamayo, MD; Claudio Muñoz, MD, PhD; Daniel G. Hackam, MD, PhD; Maria DiCicco, RVT; Janine DesRoches, RVT; Chrysi Bogiatzi, MD; Jonathan Klein, MD; Joaquim Madrenas, MD, PhD; Robert A. Hegele, MD

- Asymptomatic carotid stenosis (>60%)
- 199 pts, between Jan 2000 and Dec 2002: Usual care group
- 269 pts, between Jan 2003 and July 2007: Intensive medical therapy group
- Outcome values
 1. Micro-emboli on TCD
 2. cardiovascular events
 3. rate of plaque progression
 4. baseline medical therapy, before and since 2003

Clinical outcomes

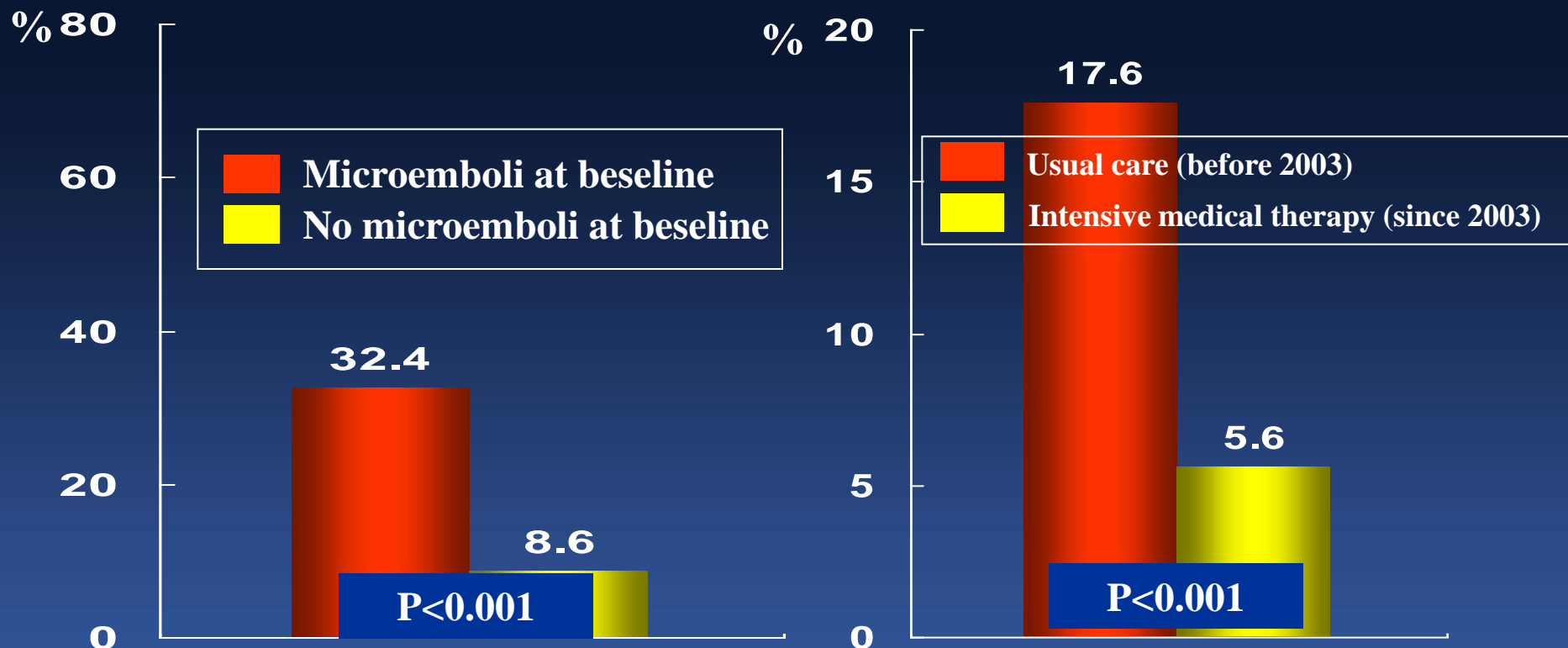
■ Usual care (before 2003) ■ Intensive medical therapy (since 2003)



Primary endpoint: stroke, death, MI, or carotid endarterectomy upon symptom development.

Clinical outcomes for 2 years

Primary endpoint: stroke, death, MI, or carotid endarterectomy upon symptom development.



- Less than 5% of Asymptomatic Carotid Stenosis patients can benefit from revascularization
- Only those with microemboli should be considered for endarterectomy or stenting

Arch Neurol. 2010;67(2):180-186

Asymptomatic Carotid Artery Stenosis: who is risky?

Identifying Which Patients With Asymptomatic Carotid Stenosis Could Benefit From Intervention

Kosmas I. Paraskevas, MD; J. David Spence, MD, FRCPC; Frank J. Veith, MD;
Andrew N. Nicolaides, MD, FRCS, PhD (Hon)

interventions. Performing CEA or carotid artery stenting on those with >80% stenosis as currently practiced in many centers ignores the fact that many strokes occur in patients with moderate stenosis, which may be identified by the presence of TCD embolic signals or unstable plaques using ultrasound. Thus, the approach of selective intervention will lead to a refinement of the current indications for CEA and would also reduce costs spent on unnecessary or even harmful procedures.

Stroke. 2014;45:3720-3724

Identifying Which Patients With Asymptomatic Carotid Stenosis Could Benefit From Intervention

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patients with ACS may go on to have a stroke. It is therefore important to identify specific subgroups of ACS patients who despite MT are still at increased risk ($>2\%/y$) and may require a carotid intervention. Identification of these high-risk ACS patients is crucial to target carotid revascularization procedures appropriately and to avoid excessive use of unnecessary

Stroke. 2014;45:3720-3724

Plaque change: incidence of regression, progression and occlusion in relation to baseline stenosis class (8 yrs FU)

Stenosis class	Regression, No. (%)	No change, No. (%)	Progression, No. (%)	Occlusion, No. (%)	Total, No. (%)
50%-59%	0	61 (66)	30 (33)	1 (1.1)	92 (100)
60%-69%	3 (3.1)	59 (61)	34 (35)	1 (1.0)	97 (100)
70%-79%	9 (2.8)	262 (81)	50 (15)	1 (0.3)	322 (100)
80%-89%	16 (4.7)	252 (78)	45 (14)	8 (2.5)	321 (100)
90%-95%	15 (5.4)	214 (76)	31 (11)	20 (7.1)	280 (100)
95%-99%	0	8 (89)	0	1 (11)	9 (100)
Total	43 (3.8)	856 (76)	190 (17)	32 (2.9)	1121 (100)
χ^2 : P =	.031	-	<.001	<.001	

3.8%

76%

17%

2.9%

incidence of ipsilateral cerebral or retinal ischemic (CORI) events in relation to changes in severity of stenosis (8 yrs FU)

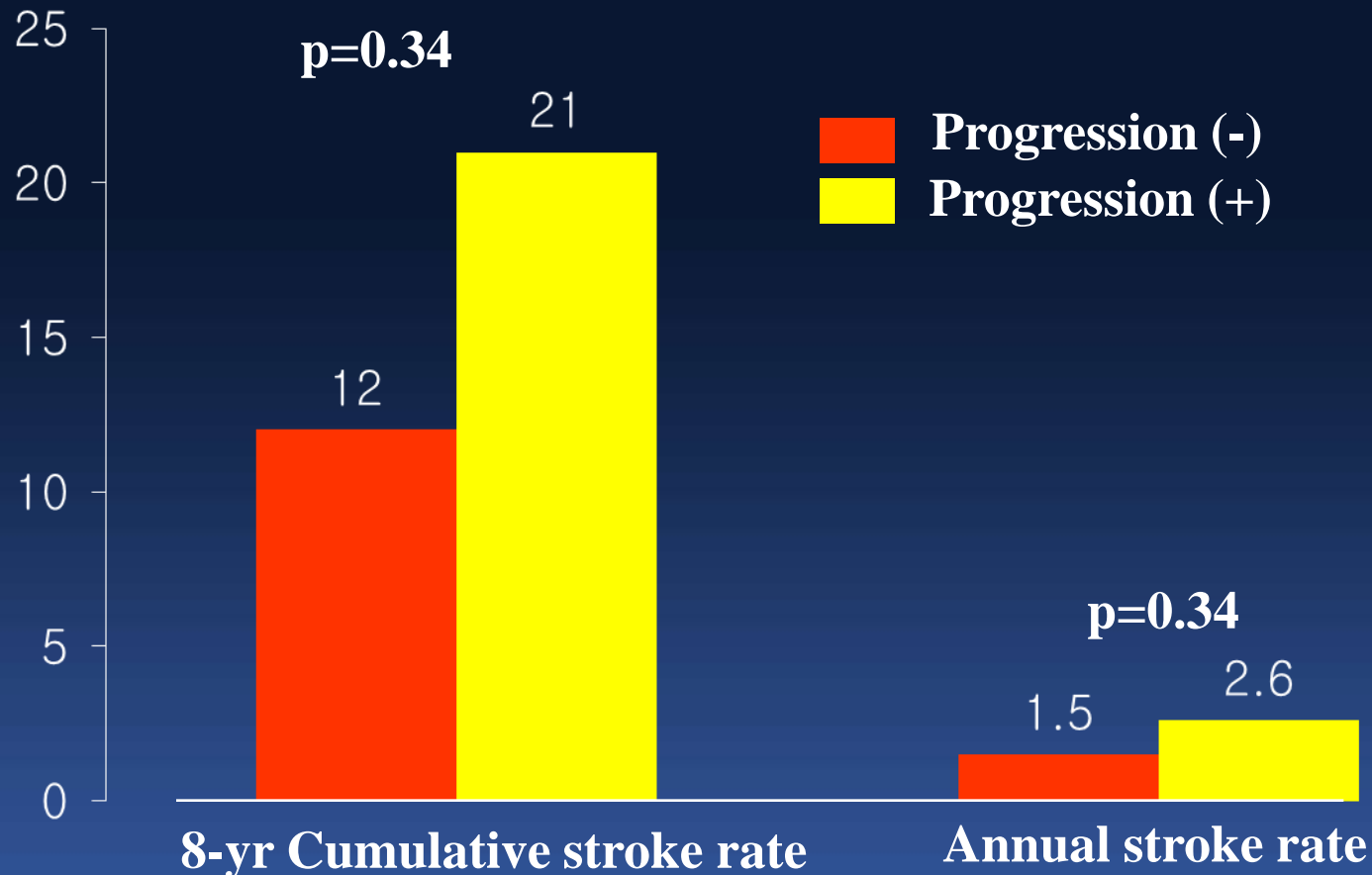
<i>Stenosis change</i>	<i>No events, No. (%)</i>	<i>Amaurosis fugax, No. (%)</i>	<i>TIA, No. (%)</i>	<i>Stroke, No. (%)</i>	<i>Total, No. (%)</i>	<i>All events, No. (%)</i>
Regression	43 (100)	0	0	0	43 (100)	0
No change	768 (90)	16 (1.9)	32 (3.7)	40 (4.7)	856 (100)	88 (10)
Progression	180 (81)	6 (2.7)	17 (7.7)	19 (8.6)	222 (100)	42 (19)
Total	991 (88)	22 (2.0)	49 (4.4)	59 (5.3)	1121 (100)	130 (12)
RR	-	1.52	2.15	1.92	-	1.93
95% CI	-	0.60-3.84	1.22-3.80	1.14-3.25	-	1.38-2.71

Younger age, high grades of stenosis, absence of discrete white areas in the plaque, and taking lipid lowering therapy were independent baseline predictors of increased incidence of regression.

High serum creatinine, male gender, not taking lipid lowering therapy, low grades of stenosis, and increased plaque area were independent baseline predictors of progression.

Kakkos SK et al. J Vasc Surg 2014;59:956-67

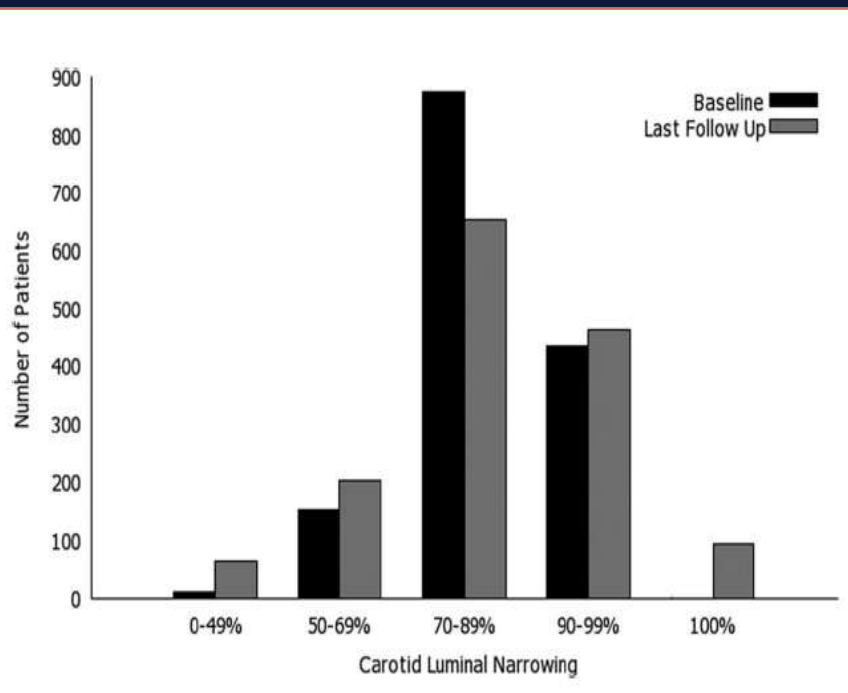
70-99% stenosis, stroke rate for 8 yrs



Only 9 (30%) of 30 strokes occurred in progression group

Annual Progression Rate and Ipsilateral Neurological Events in Asymptomatic Carotid Stenosis

Carotid stenosis category distribution at baseline and last follow-up

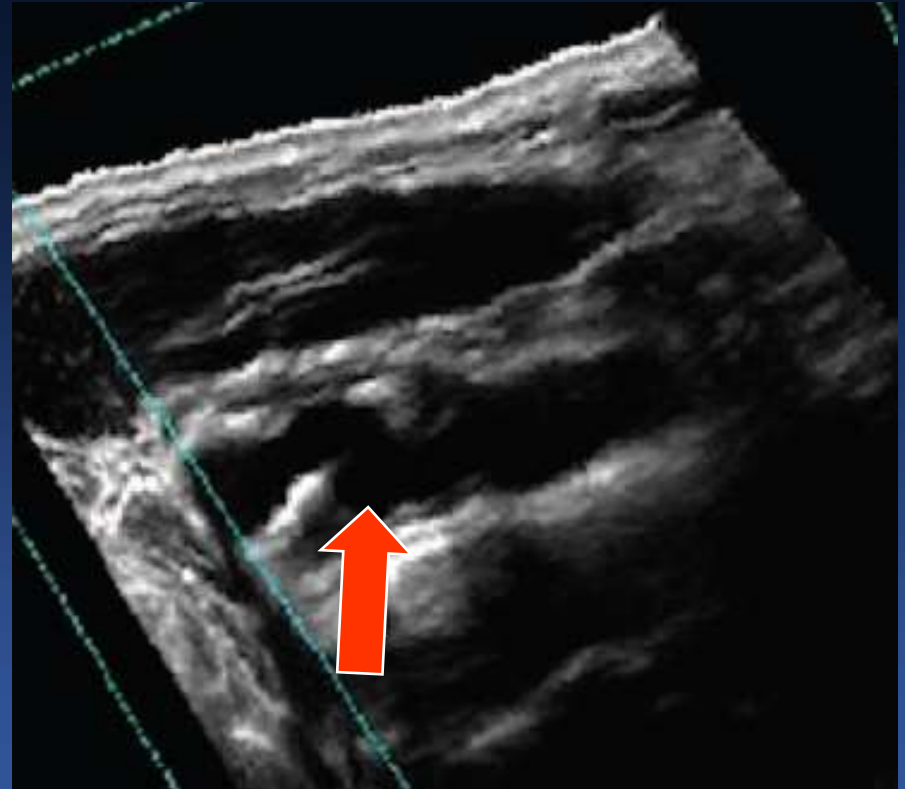
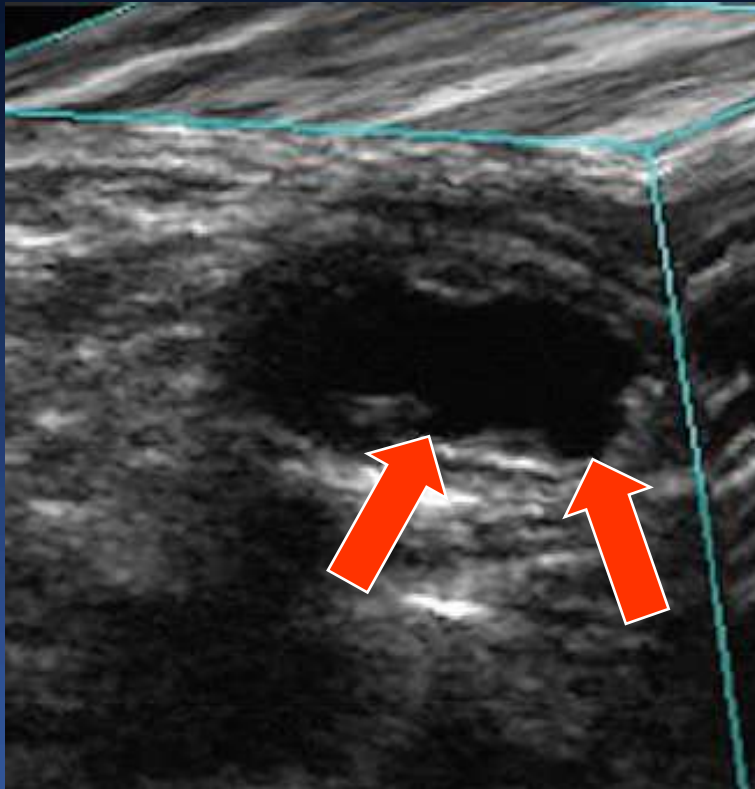


Independent predictor for events

Independent Variables	IRR	P Value	95%	CI
Diabetes	1.150*	0.020	1.090	2.130
Prior contralateral symptoms	1.500	0.010	1.110	2.020
Systolic blood pressure	1.000	0.320	1.000	1.010
Diastolic blood pressure	1.010	0.070	1.000	1.030
Carotid luminal narrowing	0.990	0.900	0.800	1.210
Yearly rate of change	1.660	0.000	1.270	2.170
-2 or -3 categories	4.63E-006	0.990	4.80E-002	4.50E+209
-1 category	0.780	0.440	0.420	1.470
+1 categories	1.410	0.150	0.890	2.220
+2 categories	4.030	0.000	1.820	8.930
+3 categories	7.560	0.010	1.810	31.560

Hirt LS et al Stroke. 2014;45:702-706

Carotid plaque images obtained with 3D ultrasound and analyzed on 3D Quantify software



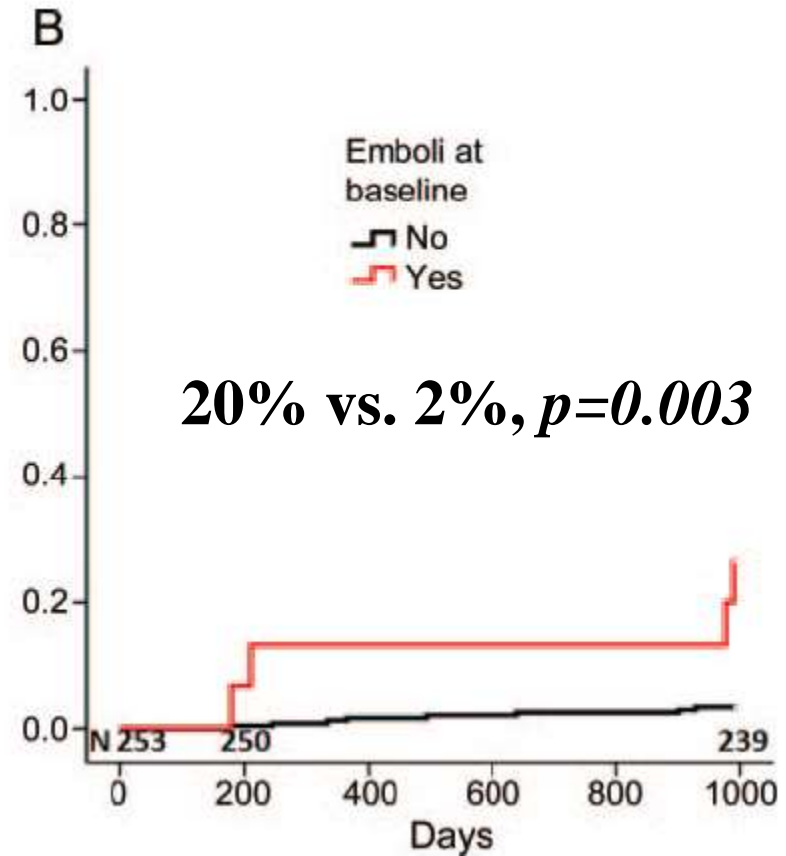
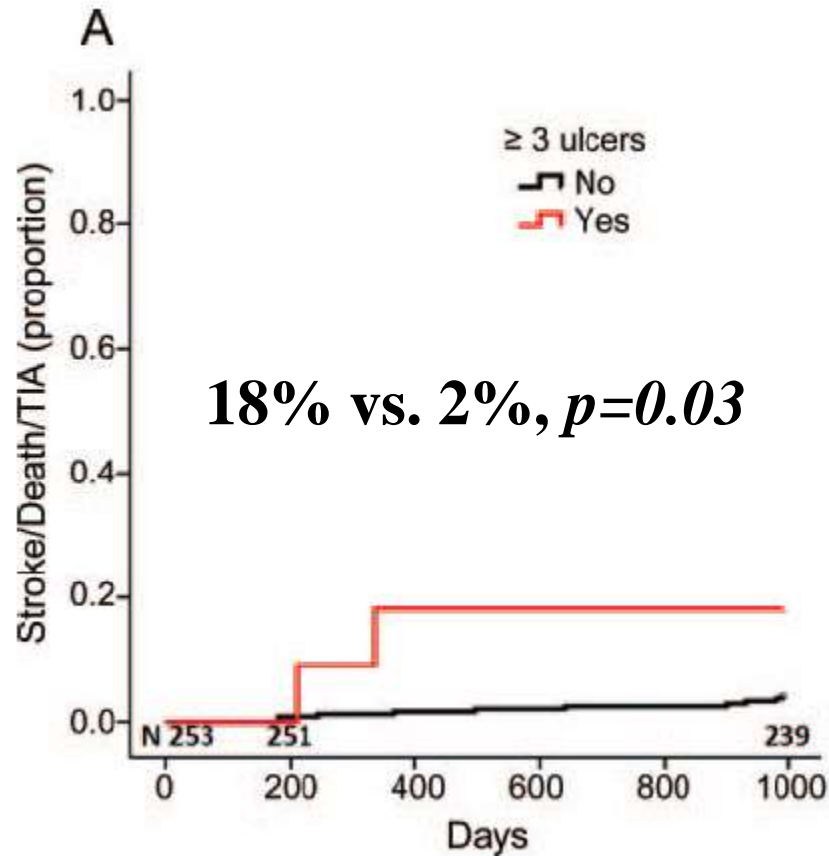
Mandani A, et al. Neurology. 2011 ;77:744-50

Stroke/Death/TIA a/t 3 ulcers/microemboli

Carotid stenosis >60% by Doppler ultrasound

≥ 3 ulcers

Emboli at baseline

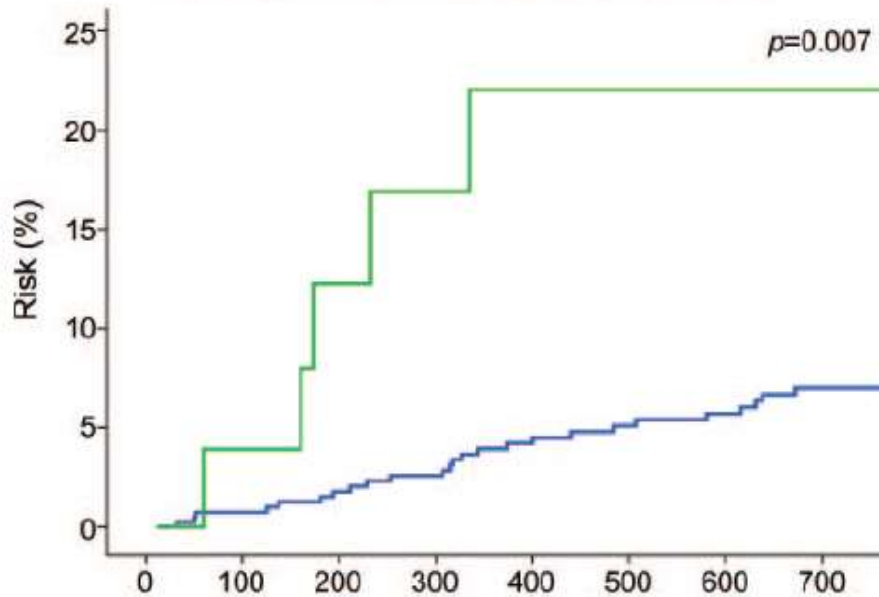


Mandani A, et al. *Neurology*. 2011 ;77:744-50

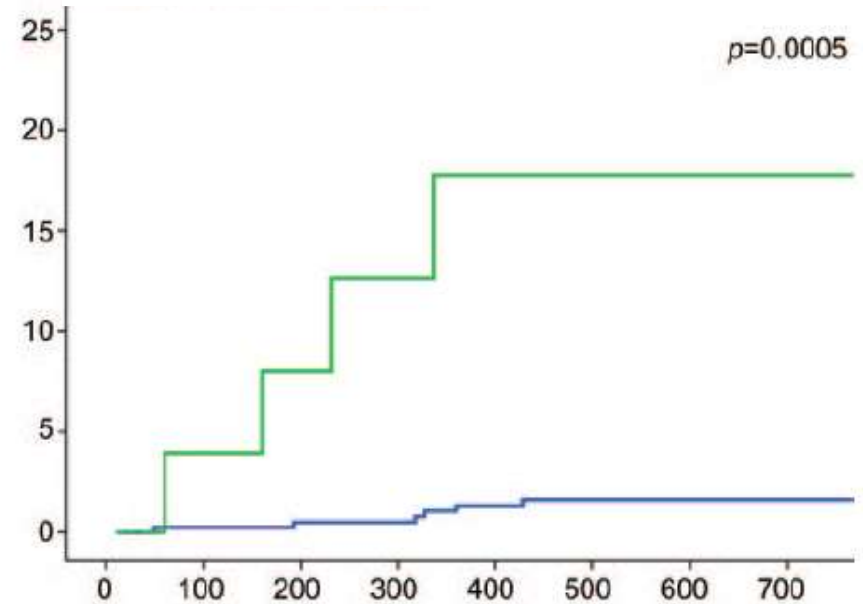
Ultrasonic Plaque Echolucency & Emboli Signals

Carotid stenosis >60% by Doppler ultrasound

Ipsilateral stroke/TIA



B Ipsilateral stroke

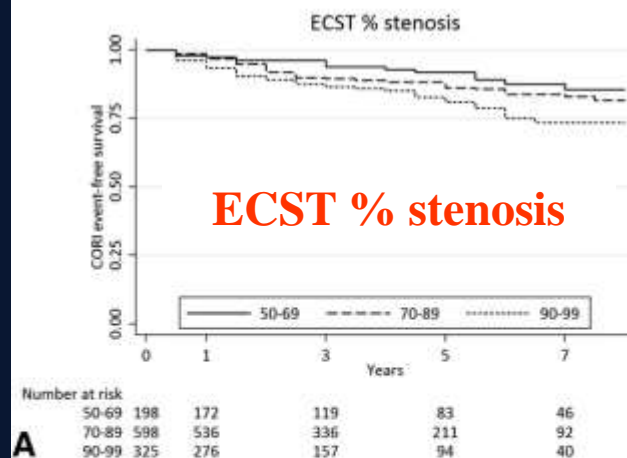


Topakian R, *et al.* Neurology. 2011;77:751-8

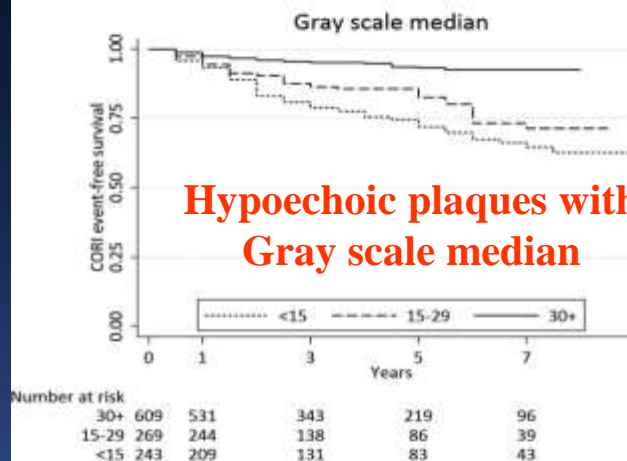
Asymptomatic carotid stenosis and risk of stroke

	HR	95% CI	p value
lipid-rich necrotic core	7.21	1.12-46.28	0.037
Sonographic progression of stenosis	7.00	1.13-41.34	0.036
History of stroke	11.03	1.23-99.36	0.032
Volume of clinically asymptomatic ischemic brain lesions	1.14	1.03-1.25	0.008

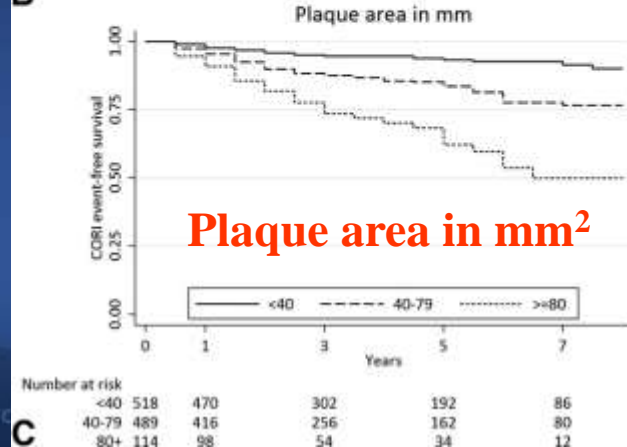
Mono ML et al. Cerebrovasc Dis. 2012;34:343-50



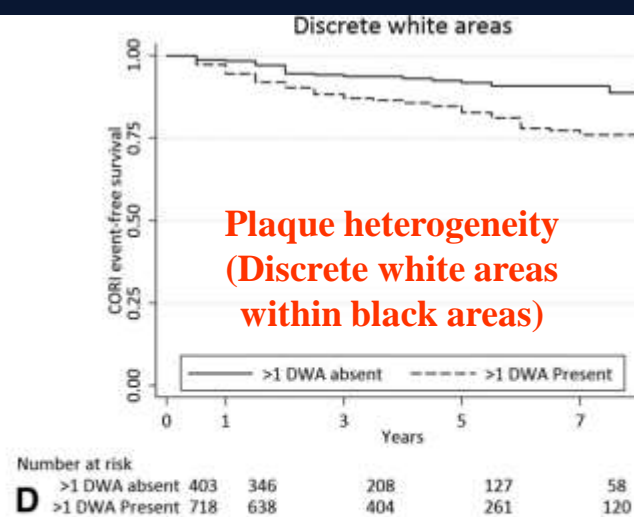
A



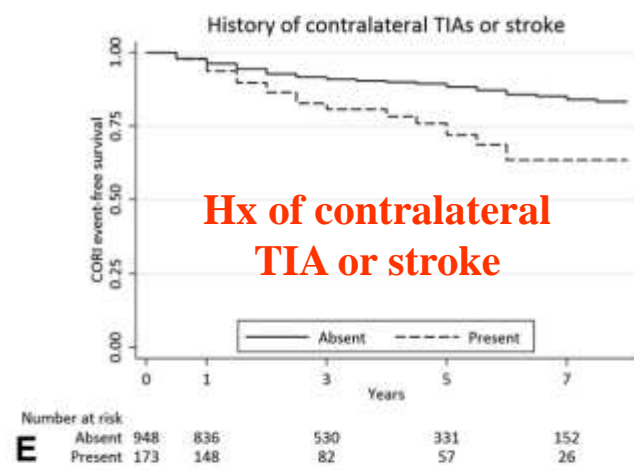
B



C



D

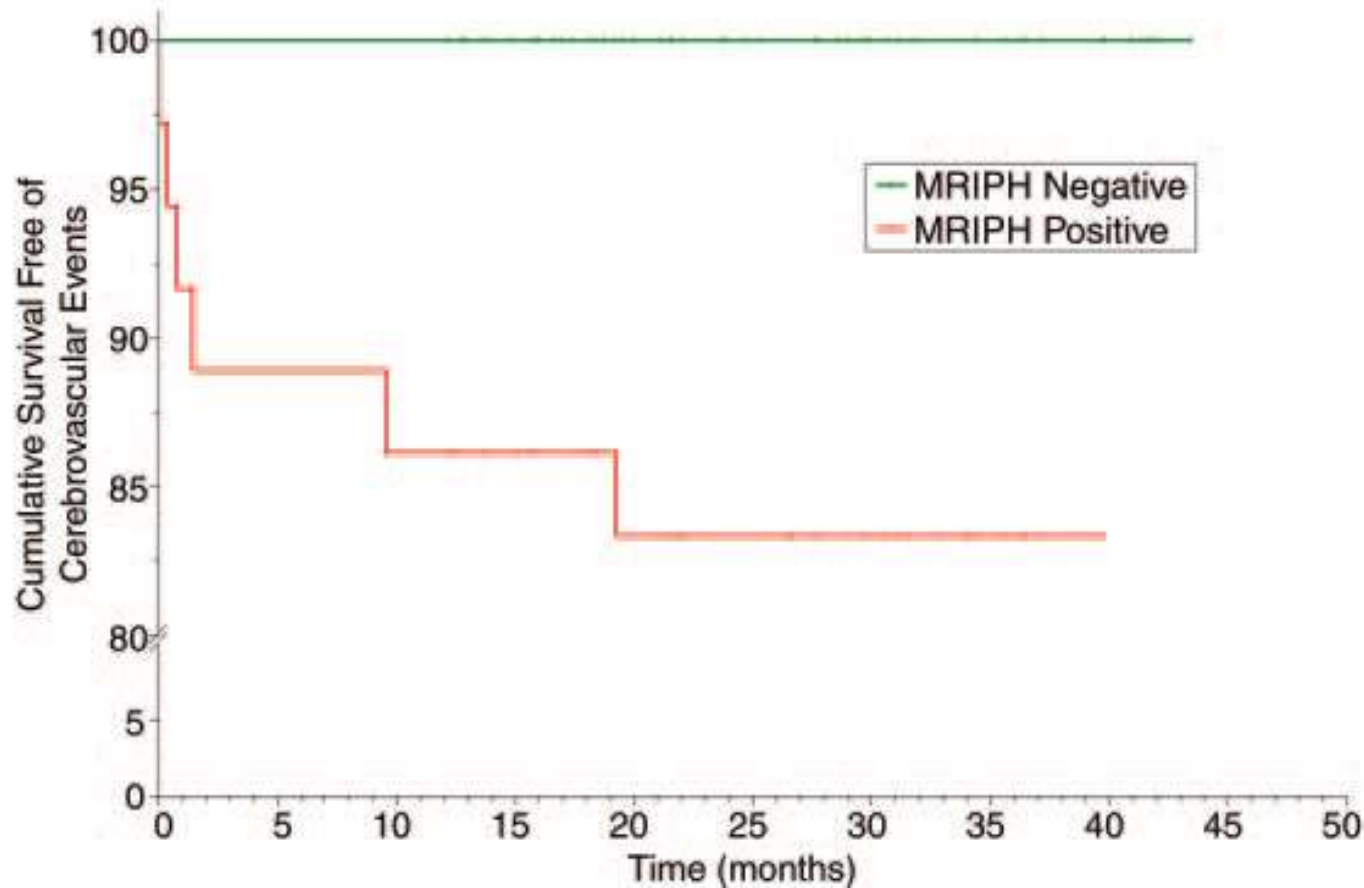


E

Ultrasonic Plaque Features

J Vasc Surg 2010;52:1486-96

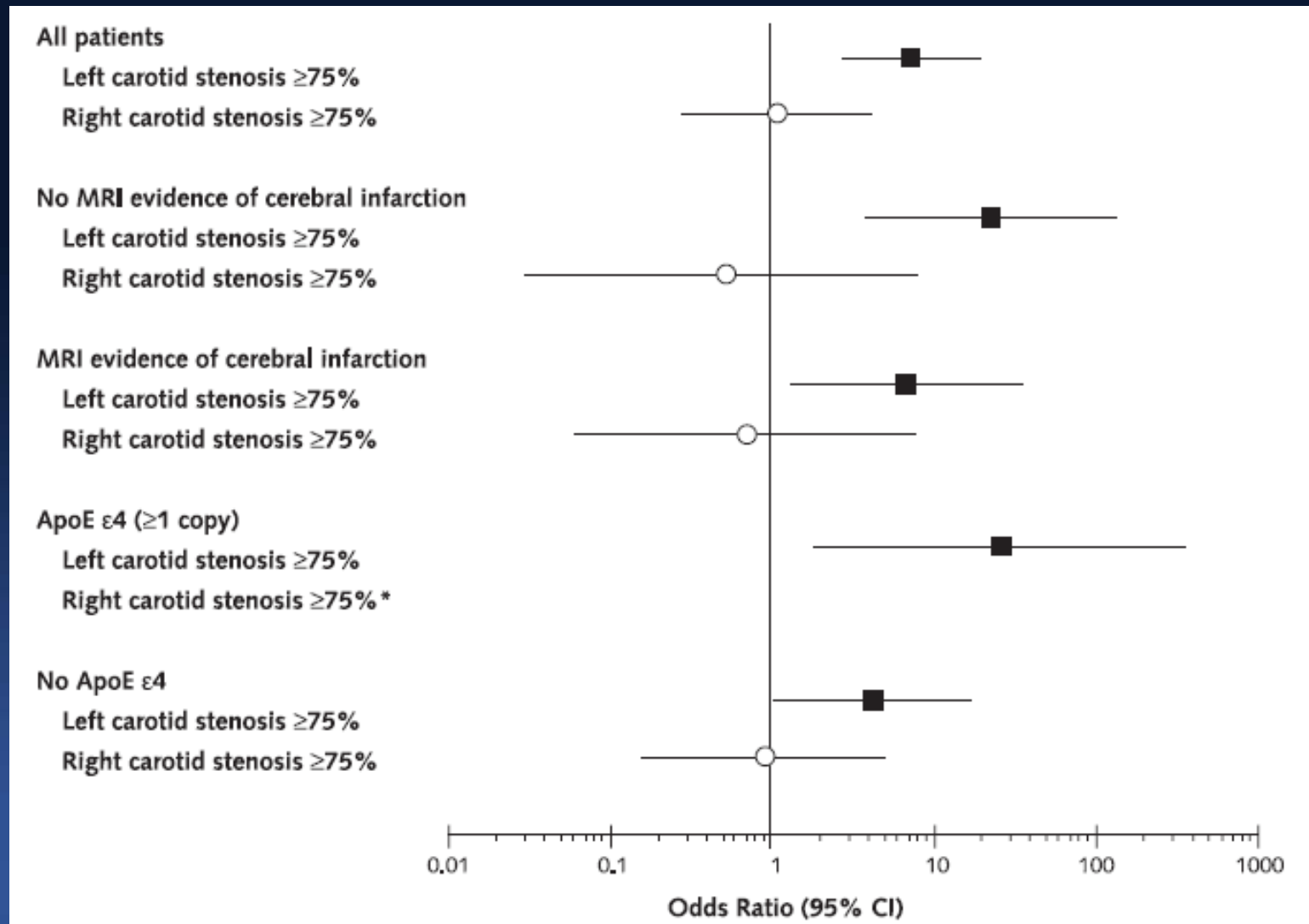
MR Imaging –Intraplaque Hemorrhage



b.

Radiology . 2012;252:502-508

Cognitive impair/decline a/w severe (>75%) stenosis



Ann Intern Med 2004;140:237-47

Neurocognitive and Neurologic Function at Baseline and 3 Months After stenting

Chronic internal carotid occlusion (n=20)

	Successful Group (n=12)			Unsuccessful Group (n=7)		
	Baseline	3 mo After Procedure	P Value	Baseline	3 mo After Procedure	P Value
ADAS score	7.7±8.9	5.7±7.1	0.024	8.7±9.7	9.7±11.1	0.268
MMSE score	25.8±3.8	27.7±2.7	0.015	24.7±5.6	25.7±4.9	0.422
Color Trail Making A, seconds	123.2±68.6	99.3±51.5	0.017	141.3±101.0	138.3±103.7	0.799
Color Trial Making B, seconds	196.2±99.3	175.1±85.5	0.169	176.8±82.1	182.0±92.3	0.397
Verbal fluency	26.3±14.0	27.3±10.2	0.937	27.5±9.4	25.3±6.5	1.0
NIHSS score	0.6±0.9	0.4±0.7	0.157	0.6±0.8	0.6±0.8	
Barthel Index	97.5±8.7	98.8±4.3	0.317	95.7±7.3	97.1±3.9	0.317

Stroke. 2011;42:2850-4

Executive & memory function after carotid stenting

Unilateral asymptomatic ICA > 60 % stenosis (N=20)

- **Set shifting**

- TMTest Part B: -0.75 ± 1.43 vs. -1.2 ± 1.48 , $p = 0.003$

**Executive & memory function improved
after stenting even in patients with ACS
and normal executive and memory function**

- working memory**

- Digit span backward: -0.41 ± 0.61 vs. -0.58 ± 0.76 , $p = 0.052$

- **Both verbal and visual memory**

- Rey Auditory Verbal Learning Test: 0.35 ± 1.04 vs. -0.22 ± 0.82 , $p = 0.011$

- Delayed ROC Figure: 0.27 ± 1.26 vs. -0.22 ± 1.01 , $p = 0.024$

J Neurosurg 2012;116:179-84

Identifying high-risk ACS

Imaging factor

- Ultrasonographic progression
- TCD: embolus detection
- Ultrasound : echolucency and neovascularity
- 3D-ultrasound: ulceration
- MRI: intraplaque hemorrhage
- PET: plaque inflammation/cerebral blood flow reserve

Clinical factor

- History of stroke
- Neurocognitive/executive/memory dysfunction

History of stroke

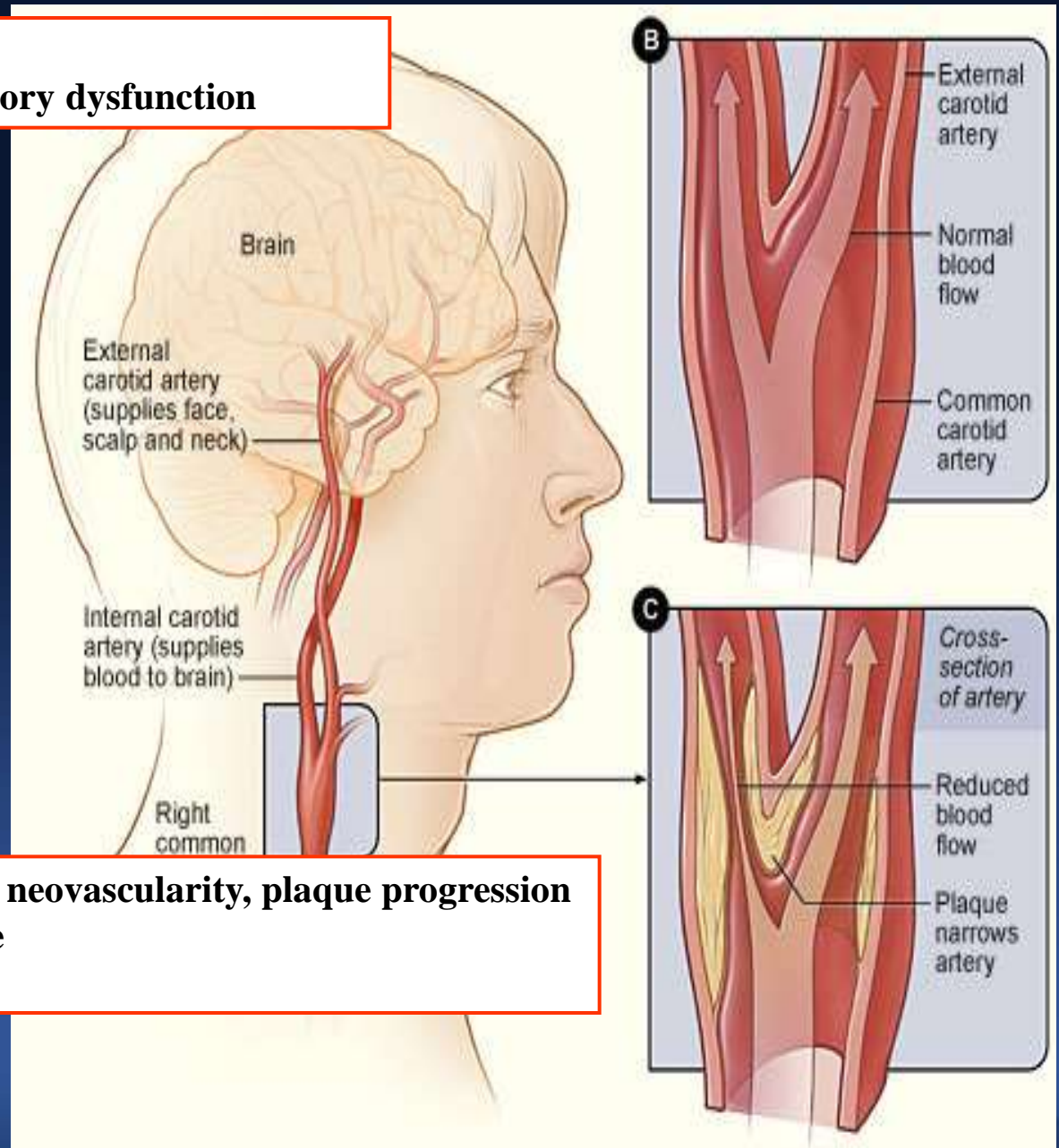
Neurocognitive/executive/memory dysfunction

TCD: embolus detection

USG: Ulceration, echolucency, neovascularity, plaque progression

MRI: Intraplaque hemorrhage

PET: Plaque inflammation



Management of ACS



Manage Overall Cardiovascular Risk	
Diet and Lifestyle <ul style="list-style-type: none"> • Nutrition counseling • Maintenance of optimal body weight • Smoking assessment and cessation counseling 	Pharmacotherapy <ul style="list-style-type: none"> • Aspirin 75 – 325 mg daily • Statin/lipid-lowering therapy (all patients) • Antihypertensive therapy <ul style="list-style-type: none"> • Goal BP < 140/90 mmHg

Manage Risk of Associated Stroke	
Stenosis < 60%	Stenosis 60 - 99%
<ul style="list-style-type: none"> • Educate • Manage medically • Follow clinically for • Imaging at interval • Revascularization not indicated 	<ul style="list-style-type: none"> • Assess patient overall risk, comorbidities, and life expectancy • Assess procedural risk of stroke or death (based on imaging characteristics on imaging) • Discuss risks and benefits of revascularization with the patient

Patients/plaque risk evaluation

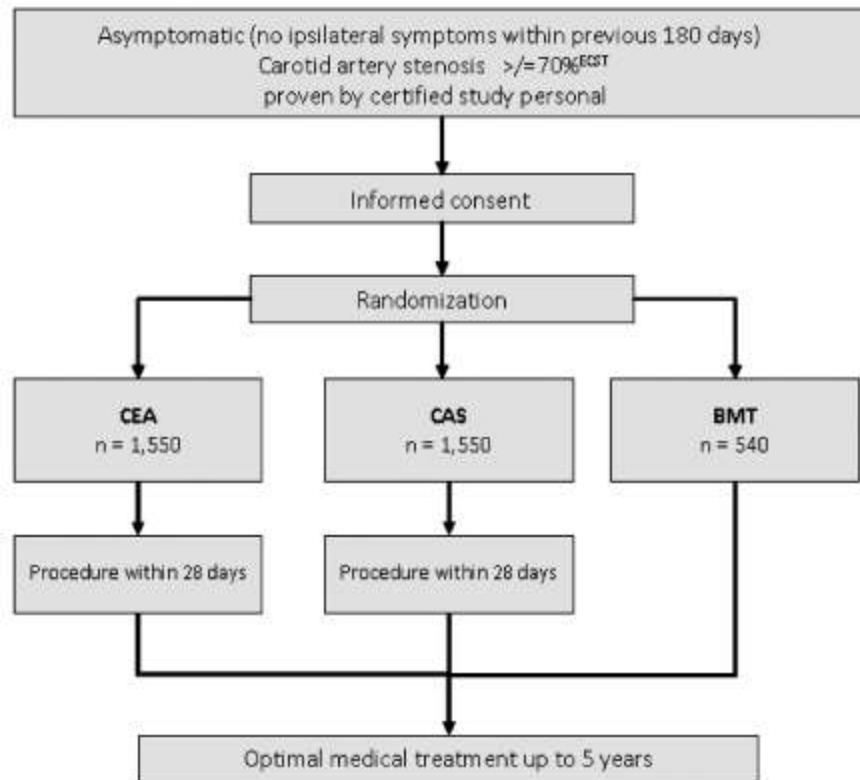
Asymptomatic carotid stenosis: Think differently

- Overall annual risk of stroke was about 1% in more recent studies of medically managed asymptomatic carotid stenosis .
- Most patients with ACS ($\sim 95\%$) would be better off with intensive medical therapy than with intervention.
- Management should be primarily aimed at reducing the *overall risk of adverse cardiovascular events* in patient with ACS rather than on management of the stenosis itself.
- This management strategy should include lifestyle interventions, optimized multi-agent pharmacotherapy, and intervention in carefully selected individuals.

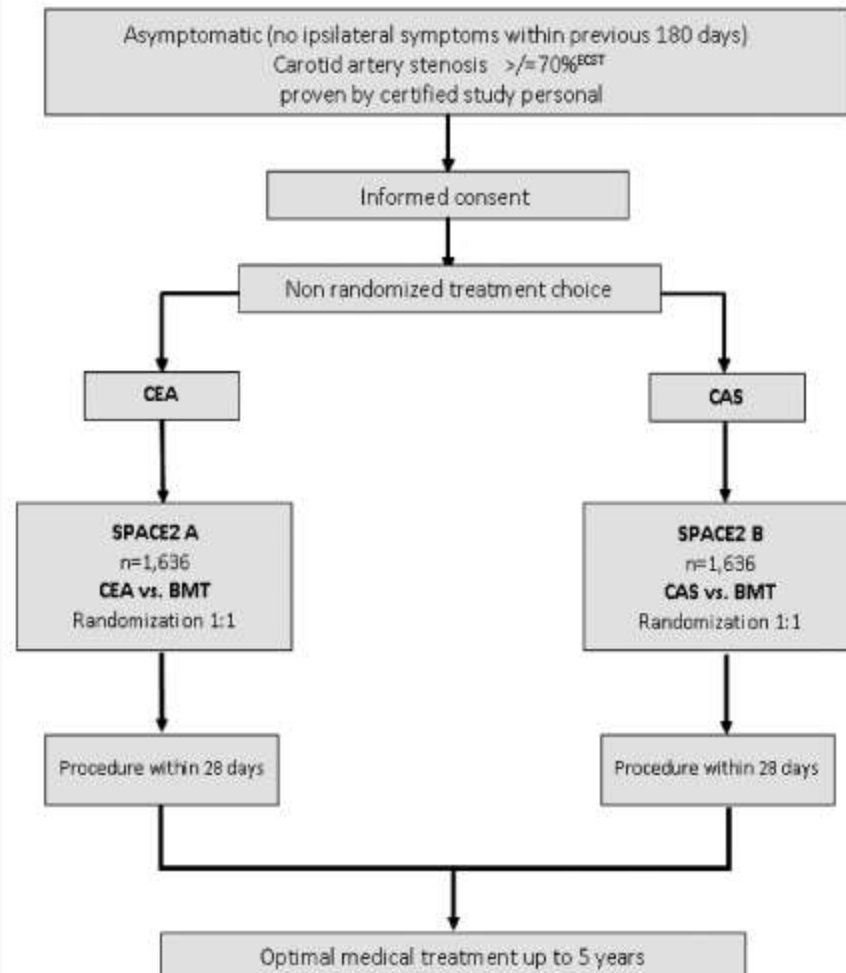
SPACE-2 Design



old design



new design



Carotid artery revascularization: indication

Symptomatic $\geq 50\%$

Asymptomatic $\geq 80\%$

(by ESCT, $\geq 70\%$ by NASCET)

**Asymptomatic: 60-80% needing
future stroke risk stratification**

Thank you for your attention