2018 MID-ATLANTIC
CONFERENCE

8th ANNUAL CURRENT CONCEPTS IN
VASCULAR THERAPIES

2018

Todd W GenslerMD

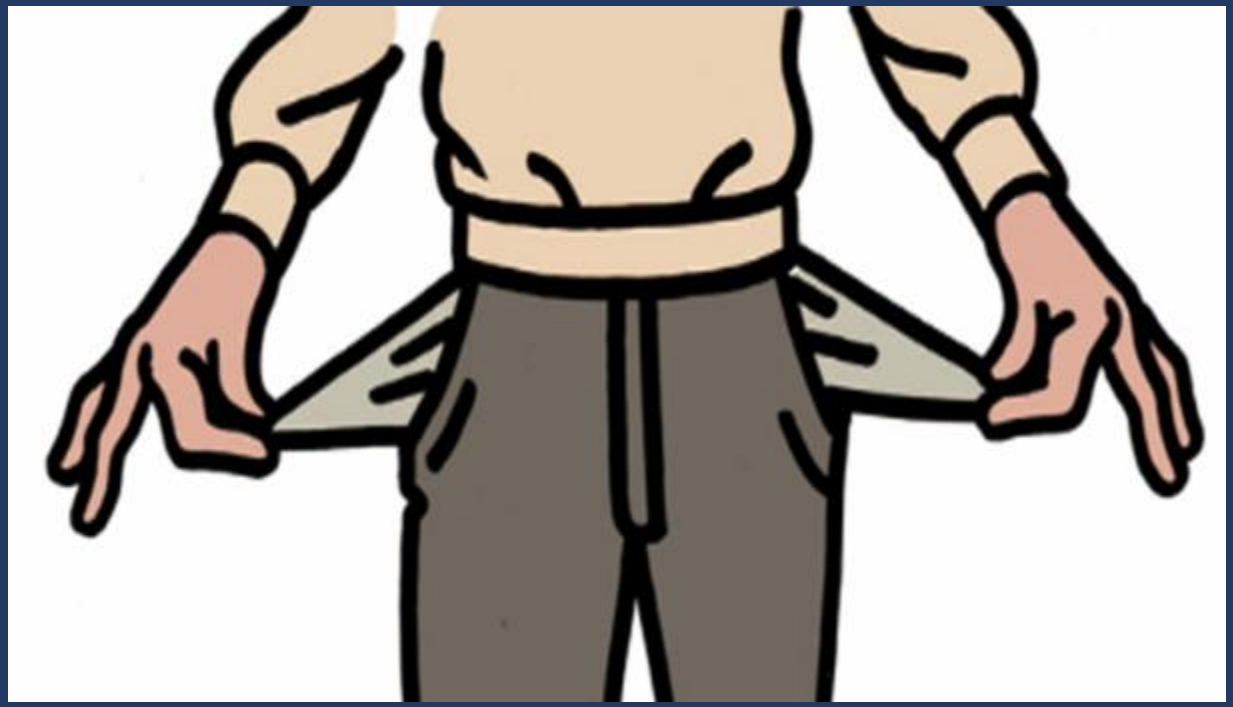
April 28, 2018

CAROTID DEBATE

High-Grade Asymptomatic Disease Should Be Repaired Selectively; Medical Management is NOT Enough

DISCLOSURES

- I have no financial disclosures



Philip A Davenport, MD, PhD

Medical Education

Ph.D. : University of Pennsylvania - 1988

M.D. : Virginia Commonwealth University - 1985

Medical Experience

Internship: Medical College of VA Hosp. (June 01, 1988 - June 01, 1989)

Residency: Mayo Graduate Sch of Medicine (July 01, 1989 - June 30, 1992)

Fellowship: Mayo Graduate Sch of Medicine (August 26, 1992 - June 30, 1993)

Stroke Statistics

- About 795,000 Americans each year suffer a new or recurrent stroke. That means, on average, a stroke occurs every 40 seconds.
- Stroke kills more than 129,000 people a year. That's about 1 of every 18 deaths. It is the 5th leading cause of death.
- On average, every 4 minutes someone dies of stroke.
- Americans paid about $95 billion in 2015 for stroke-related medical costs and disability.

EVMS
Eastern Virginia Medical School

PREVALENCE OF ASX DZ

- It is now estimated that some 6% of Americans over 65 harbor an asymptomatic carotid artery stenosis >50%

2 O'Leary, D.H., Polak, J.F., Kronmal, R.A., Kittner, S.J., Bond, M.G., Wolfson, S.K. Jr. et al. **Distribution and correlates of sonographically detected carotid artery disease in the cardiovascular health study. The CHS collaborative research group.** *Stroke*. 1992; 23: 1752–1760

3 Prati, P., Vanuzzo, D., Casaroli, M., Di Chiara, A., De Biasi, F., Feruglio, G.A. et al. **Prevalence and determinants of carotid atherosclerosis in a general population.** *Stroke*. 1992; 23: 1705–1711

Nat’l History of Asymptomatic Disease

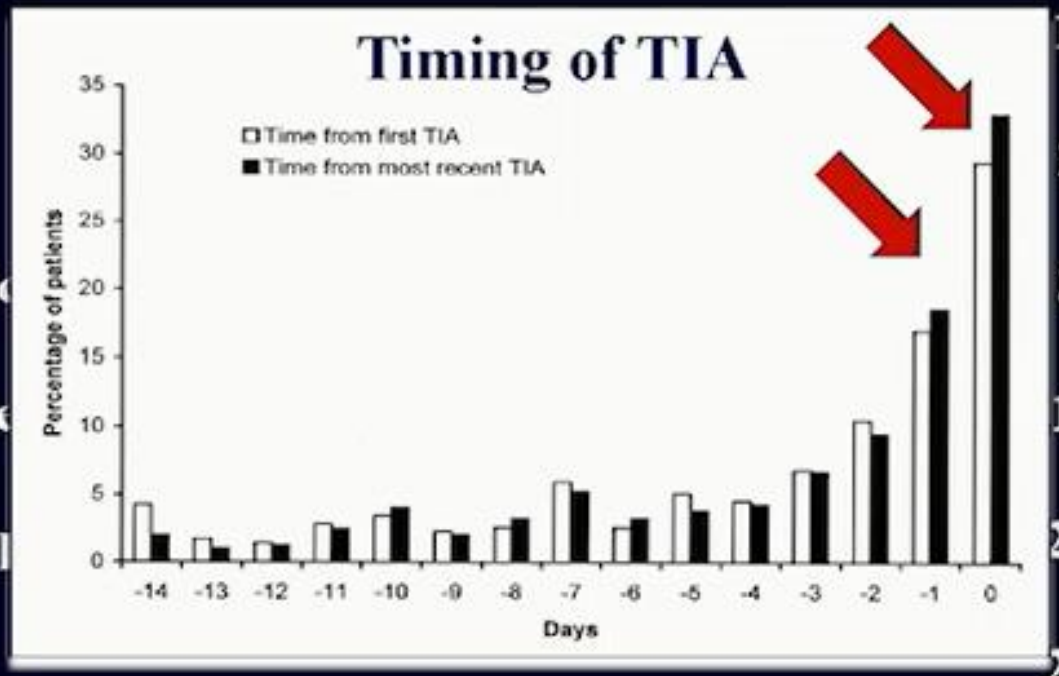
REACH REGISTRY

REduction of Atherothrombosis for Continued Health

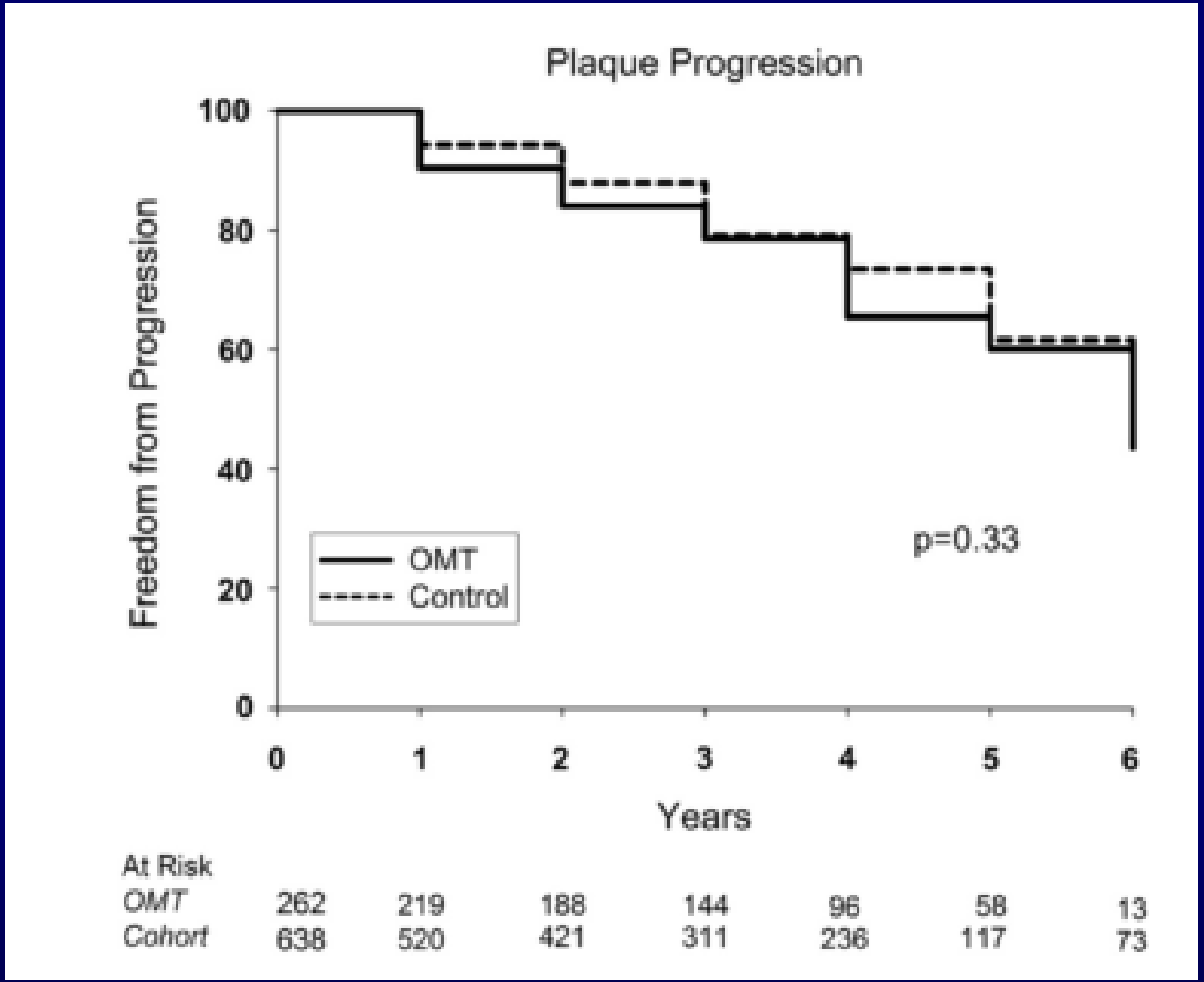
- Carotid stenosis >70% significantly increases stroke risk irrespective of the fact that 70% of this cohort were on statin medications

Stroke Without Prior TIAs

Source	Prior TIAs
Rochester, MN	10%
Ontario	12%
Australia	22%
Mayo Clinic	35%
Oxfordshire	15%
UK TIA Asp	23%
ECST	26%



Progression of Asymptomatic Carotid Stenosis Despite Optimal Medical Therapy



Conrad et al. J Vasc Surg 2013;58:128

The natural history of asymptomatic severe carotid artery stenosis

Mark F. Conrad, MD, MMSc, Michael J. Michalczyk, BS, Arina Opalacz, BS, Virendra I. Patel, MD, MPH, Glenn M. LaMuraglia, MD, and Richard P. Cambria, MD, *Boston, Mass*

Patients: 115
- *Statins:* 86%
- *ASA:* 89%
- *Statin & ASA:* 79%

Arteries: 126
- *70 – 89%:* 88 (70%)
- *90 – 99%:* 38 (30%)

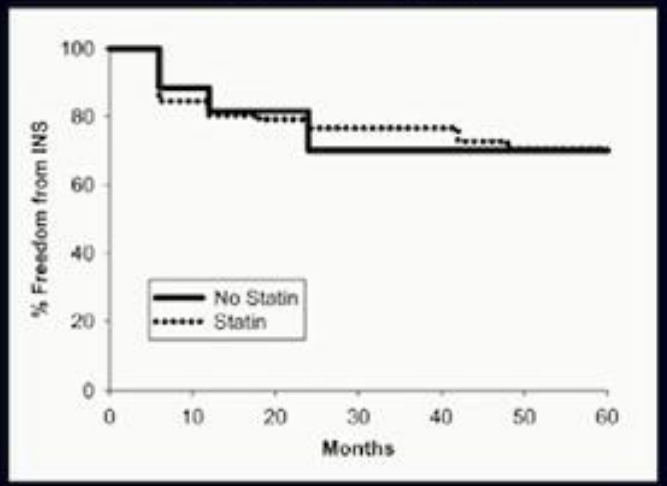
F/U: 2 – 90 (mean, 64) months

Ischemic Events: 31 Patients

- 74% Within 1 Year

CVSs: 45%

TIAs: 55%



Massachusetts General Hospital

J Vasc Surg, 2014

Predictors and clinical significance of progression or regression of asymptomatic carotid stenosis

Presented in a plenary session at the 2013 Vascular Annual Meeting of the Society for Vascular Surgery, San Francisco, Calif, May 30-June 1, 2013.

Stavros K. Kakkos, MD, PhD, RVT, Andrew N. Nicolaides, MS, PhD, FRCS, Ioanna Charalambous, Dafydd Thomas, MD, FRCP, Argyrios Giannopoulos, MD, A. Ross Naylor, MD, FRCS, George Geroulakos, MD, PhD, Anne L. Abbott, MBBS, FRACP, PhD for the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group

- A total of 1121 patients with asymptomatic carotid stenosis of 50% to 99% in relation to the bulb diameter (European Carotid Surgery Trial [ECST] method) underwent six monthly clinical assessments and carotid duplexes for up to 8 years (mean follow-up, 4 years).
- Regression occurred in 43 (3.8%), no change in 856 (76.4%), and progression in 222 (19.8%) patients.
- For the entire cohort, the 8-year cumulative ipsilateral cerebral ischemic stroke rate was zero in patients with regression, 9% if the stenosis was unchanged, and 16% if there was progression (average annual stroke rates of 0%, 1.1%, and 2.0%, respectively)
- For patients with baseline stenosis 70% to 99%, in the absence of progression (n = 349), the 8-year cumulative ipsilateral cerebral ischemic stroke rate was **12%.** In the presence of progression (n = 77), it was 21% (average annual stroke rates of 1.5% and 2.6%, respectively)

PROGRESSION IS BAD!!!!

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ASX TRIALS

- VA Cooperative Study Group
- Asx Carotid Atherosclerosis Trial (ACAS)
- Asx Carotid Surgery Trial (ACST)
- Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS)

EVMS
Eastern Virginia Medical School

VA cooperative study group

N Engl J Med 1993 Jan 28;328(4):221-7

- 444 asymptomatic men with 50-99% stenosis
- ASA vs ASA + CEA
- Endpoints:
  - TIA
  - transient monocular blindness
  - stroke
- 48 month follow up
- 8% vs 20.6% (RR=0.38)

ACAS(asymptomatic carotid atherosclerosis study)

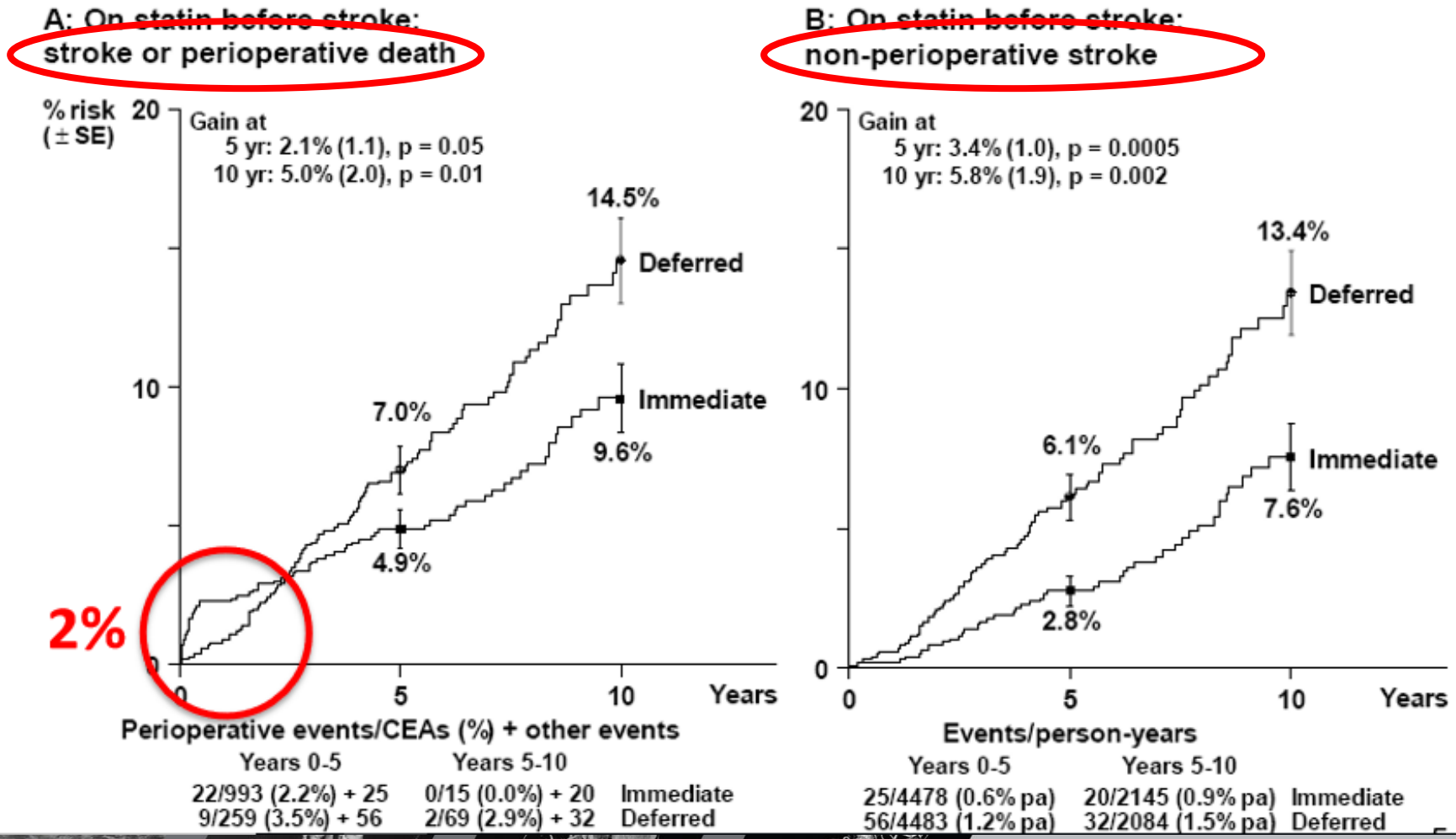
- Randomized, multicenter trial
- Total of 1662 patients with asymptomatic carotid artery stenosis of 60% or greater
- medical risk factor management for all patients; carotid endarterectomy for patients randomized to receive surgery.
- After a median follow-up of 2.7 years, the incidence of ipsilateral stroke and any perioperative stroke or death rate was significantly lower in the surgical group than with aspirin alone (5 versus 11 percent) for a relative risk reduction of 0.53 (95% CI 0.22-0.72).
- Men had an absolute risk reduction of 8 percent; the absolute risk reduction in women was only 1.4 percent.

JAMA 1995 May 10;273(18):1421-8

ACST (asymptomatic carotid surgery trial)

- 3120 asx pts w/ >60% stenosis by U/S
- Randomized b/t immed CEA and indefinite deferral of any CEA and were followed for up to 5 yrs
- Net five year risk for stroke or periop death in CEA pts was reduced by nearly half
- Absolute risk reduction over 5 yrs greater for men than for women (8.2 vs 4.08)
- 80% of patients were on statins in latter yrs of study

ACST-1: Long-term (10yr) results
Carotid surgery saves strokes, despite its 2% risk (procedural risk is much reduced by statins)

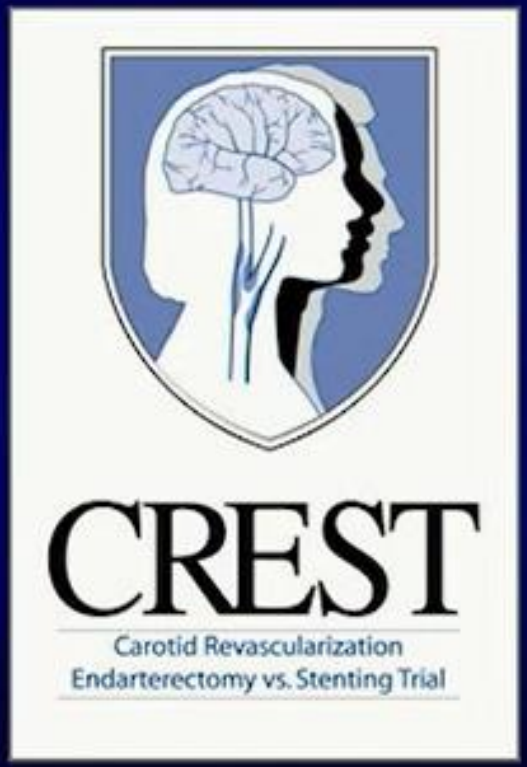


Asymptomatic Patients
Any Stroke and Death at 30-days

CAS vs. CEA	P-Value
2.5 vs. **1.4%**	0.35

CEA by: Vascular Surgeons

2.6 vs. **1.1%**	0.20



Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification

December 2010 Volume 52, Issue 6, Pages 1486–1496.e5

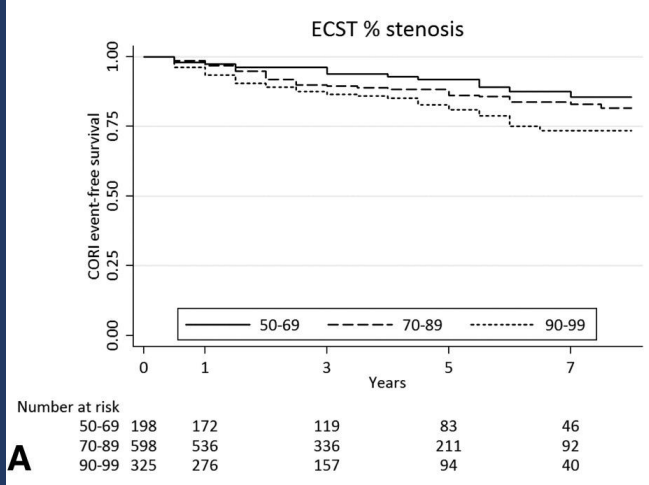
Presented at the 2010 Vascular Annual Meeting of the Society for Vascular Surgery, June 10-13, 2010, Boston, Mass.

Andrew N. Nicolaides, MS, FRCS, PhD (Hon), Stavros K. Kakkos, MD, MSc, PhD, DIC, Efthyvoulos Kyriacou, BSc, PhD, Maura Griffin, MSc, DIC, PhD, Michael Sabetai, MD, FRCS, PhD, Dafydd J. Thomas, MD, PhD, Thomas Tegos, MD, PhD, George Geroulakos, MD, PhD, Nicos Labropoulos, PhD, DIC, RVT, Caroline J. Doré, BSc, Tim P. Morris, MSc, Ross Naylor, MD, FRCS, Anne L. Abbott, MB, BS, F
Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group

JVS Journal of Vascular Surgery
Official Publication of the Society for Vascular Surgery

Ipsilateral cerebral or retinal ischemic (CORI) events (AF, TIAs, and stroke) and ipsilateral ischemic cerebral stroke for all patients and subgroups according to ECST stenosis[a] as used in this paper and NASCET stenosis[b] for comparison with previous publications that have used these methods.

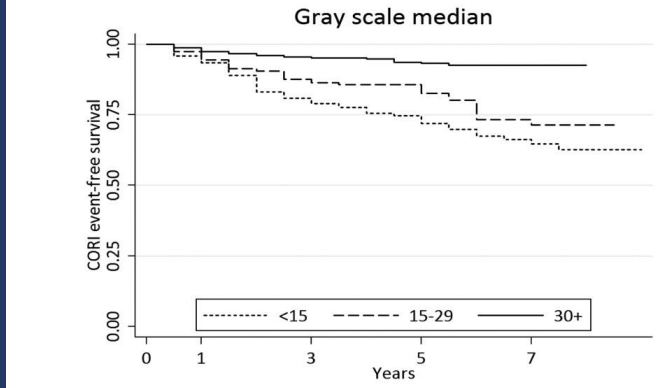
ECST stenosis (%)	NASCET stenosis (%)	No.	CORI events	Strokes
All patients		1121	130 (11.6%)	59 (5.3%)
50-69[a]	<50	198	16 (8.1%)	5 (2.5%)
70-89[a]	50-82	598	65 (10.9%)	29 (4.8%)
90-99[a]	83-99	325	49 (15.1%)	25 (7.7%)
			P = .01	*P* = .008
<80	<70[b]	514	50 (9.7%)	21 (4.1%)
80-99	70-99[b]	607	80 (13.2%)	38 (6.3%)
			P = .07	*P* = .10



Number at risk

50-69	198	172	119	83	46
70-89	598	536	336	211	92
90-99	325	276	157	94	40

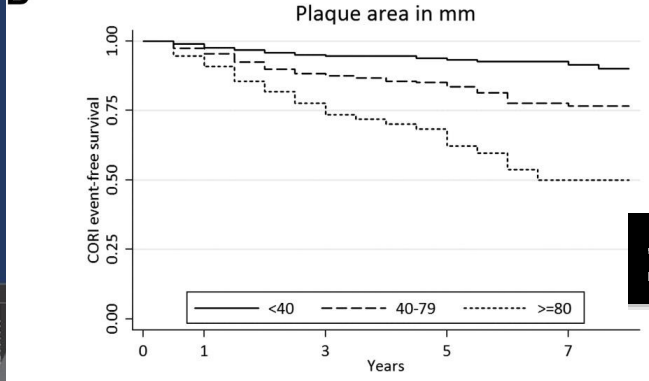
A



Number at risk

30+	609	531	343	219	96
15-29	269	244	138	86	39
<15	243	209	131	83	43

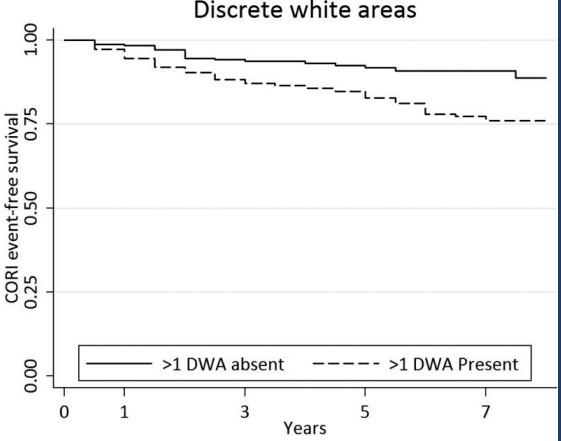
B



Number at risk

<40	518	470	302	192	86
40-79	489	416	256	162	80
80+	114	98	54	34	12

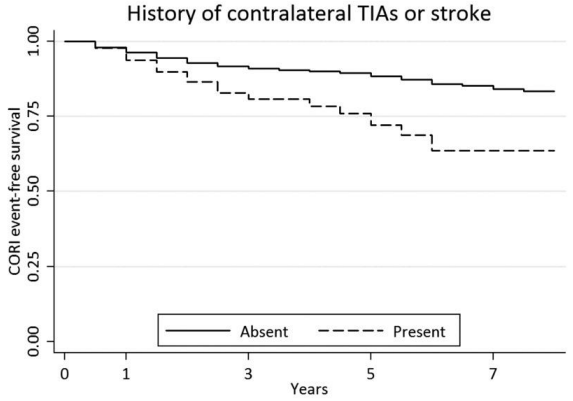
C



Number at risk

>1 DWA absent	403	346	208	127	58
>1 DWA Present	718	638	404	261	120

D



Number at risk

Absent	948	836	530	331	152
Present	173	148	82	57	26

E

Journal of Vascular Surgery 2010 52, 1486-1496.e5DOI: (10.1016/j.jvs.2010.07.021)

There are asymptomatic patients at high risk of stroke?
COMBINATION SCORES: ACSRS

a)Stenosis alone: 0.59

b)Stenosis + clinical features (smoking, contralateral stroke/TIA): 0.66

c)Stenosis + plaque characteristics + previous contralateral TIA/stroke: 0.82

Nicolaides AN et al. ACS and cerebrovascular risk stratification. J Vasc Surg. 2010;52:1486-96

CRITICAL STENOSIS, VULNERABLE PLAQUE, PRIOR C/L TIA/CVA IS BAD

ADDITIVE EFFECT IS WORSE

TCD microembolus detection

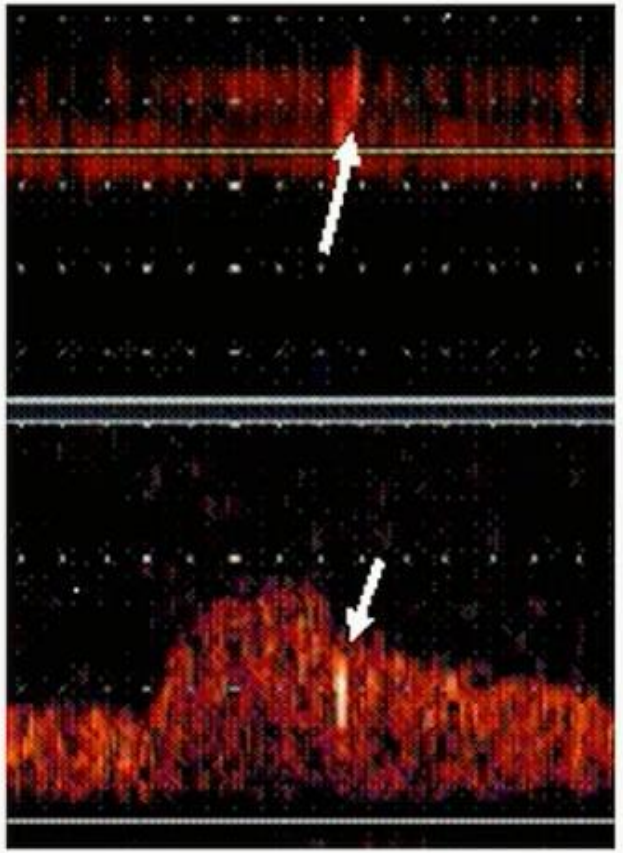
319 ACS patients
between 2000 and 2004

10% had microemboli

1-year Stroke Risk	
No Emboli	Emboli
1%	15.6

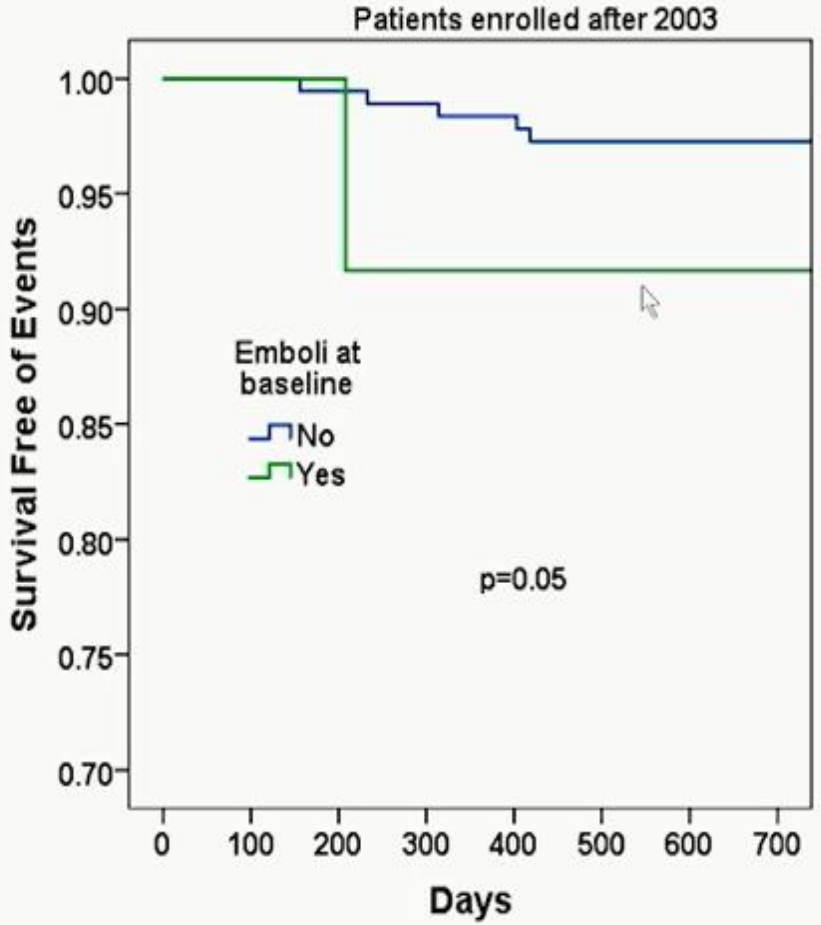
95% CI (1.01 -1.36) (4.1-79)

p<0.0001



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

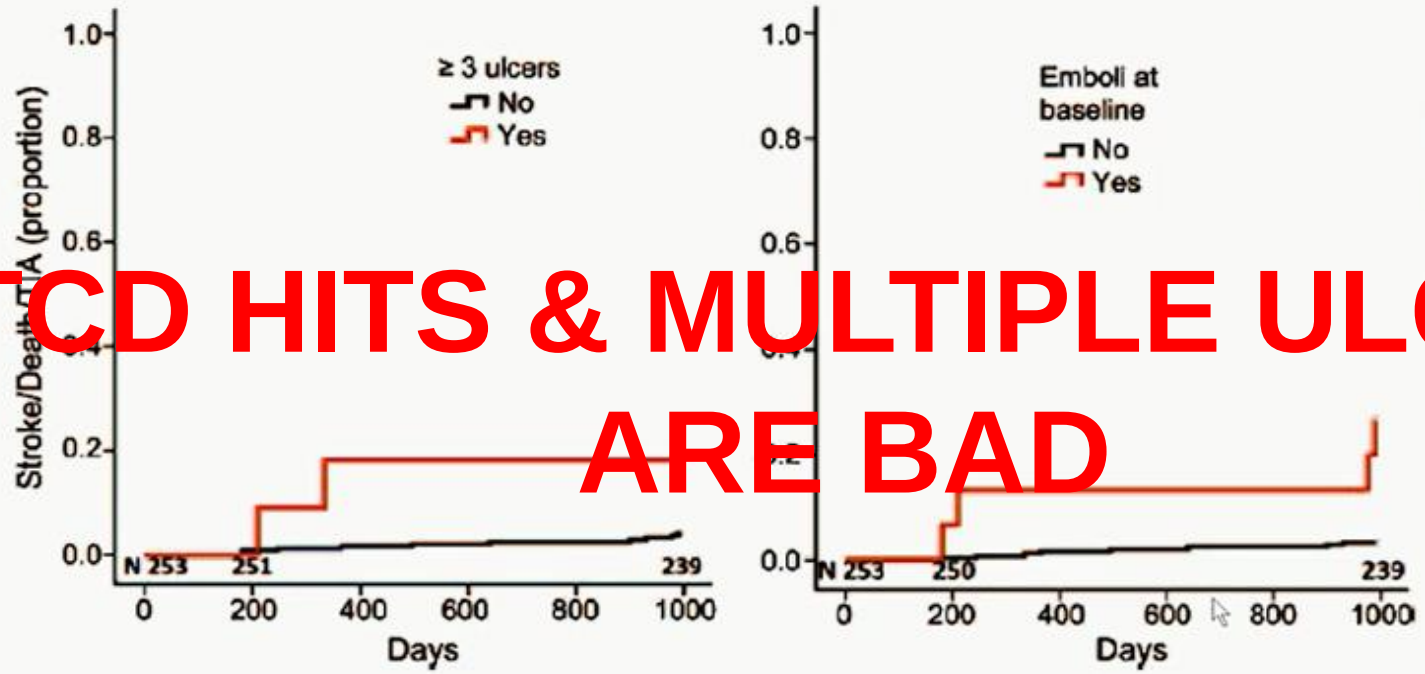
Microemboli predict risk despite intensive medical therapy



Spence JD J Vas Ultrasound 2015; 39:183–187.

3 or more ulcers adds 5% risk to microemboli (greater than equal 2/hr)

Ulceration vs microemboli in ACS



So another 5% based on ulcers

TCD HITS & MULTIPLE ULCERS ARE BAD

Madani A, ...Spence JD. Neurology 2011;77:744–750

WE HAVE TO FIND THIS PLAQUE BEFORE IT FINDS OUR PATIENT'S BRAIN

Primary Aims

In patients with ≥70% asymptomatic stenosis, to assess:

- The treatment differences between medical management and **CEA**
- The treatment differences between medical management and **CAS**

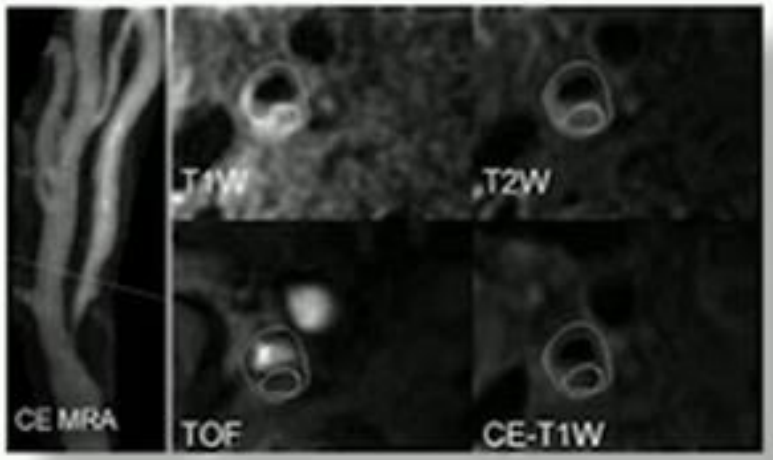
Primary endpoint: any stroke or death within 44 days of randomization or ipsilateral ischemic stroke thereafter up to 4 years

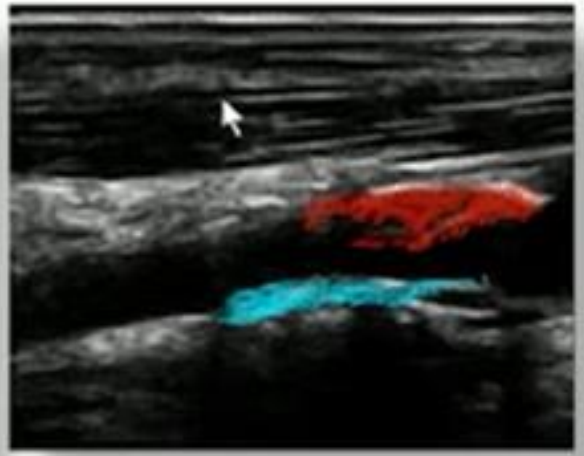
CREST-M (Imaging)

- **Goal**: To determine whether carotid plaque disruption may be influenced by **biomechanical forces** acting in combination with **morphological changes** occurring within the plaque

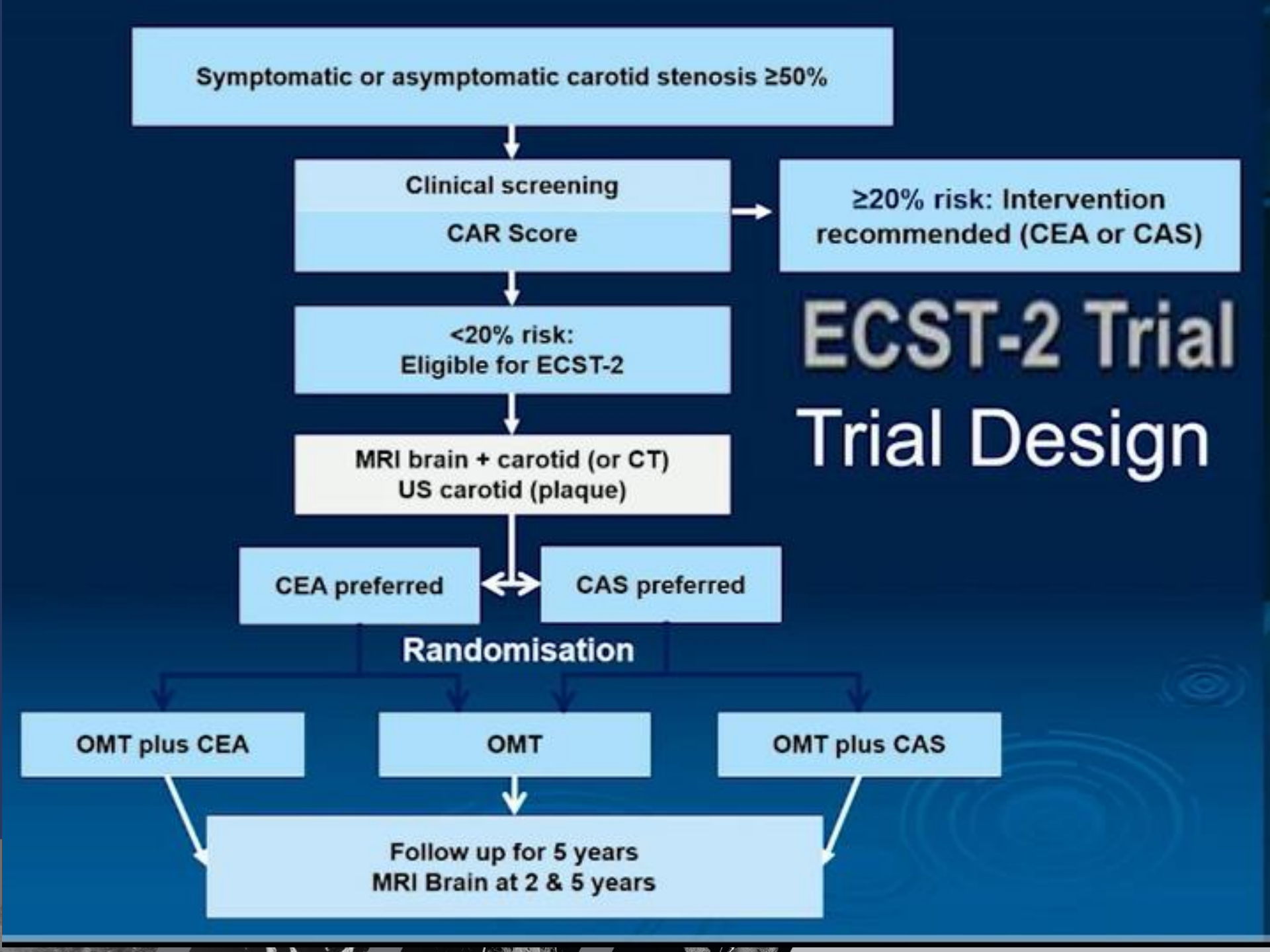
- **Enrollment goal**: 500 patients across all CREST-2 sites

- **Additional testing**: Carotid MRA, Carotid ultrasound, carotid ultrasound cine-loop, Brain MRI





Huston J et al, AJNR 2016
Lal BK et al, J Vasc Surg 2017


Symptomatic or asymptomatic carotid stenosis ≥50%
Clinical screening
CAR Score
≥20% risk: Intervention recommended (CEA or CAS)
<20% risk:
Eligible for ECST-2
MRI brain + carotid (or CT)
US carotid (plaque)
CEA preferred
CAS preferred
Randomisation
OMT plus CEA
OMT
OMT plus CAS
Follow up for 5 years
MRI Brain at 2 & 5 years
ECST-2 Trial
Trial Design

Primary Outcome

ECST-2 Progress

- 32 centres enrolled
- 285 patients randomised to 15 Nov 2017
  - Number needed for MRI-based study=320 with 2 years follow-up
- 110 included with MR plaque imaging
  - Number needed for MR plaque imaging analysis=244 with 2 years follow-up

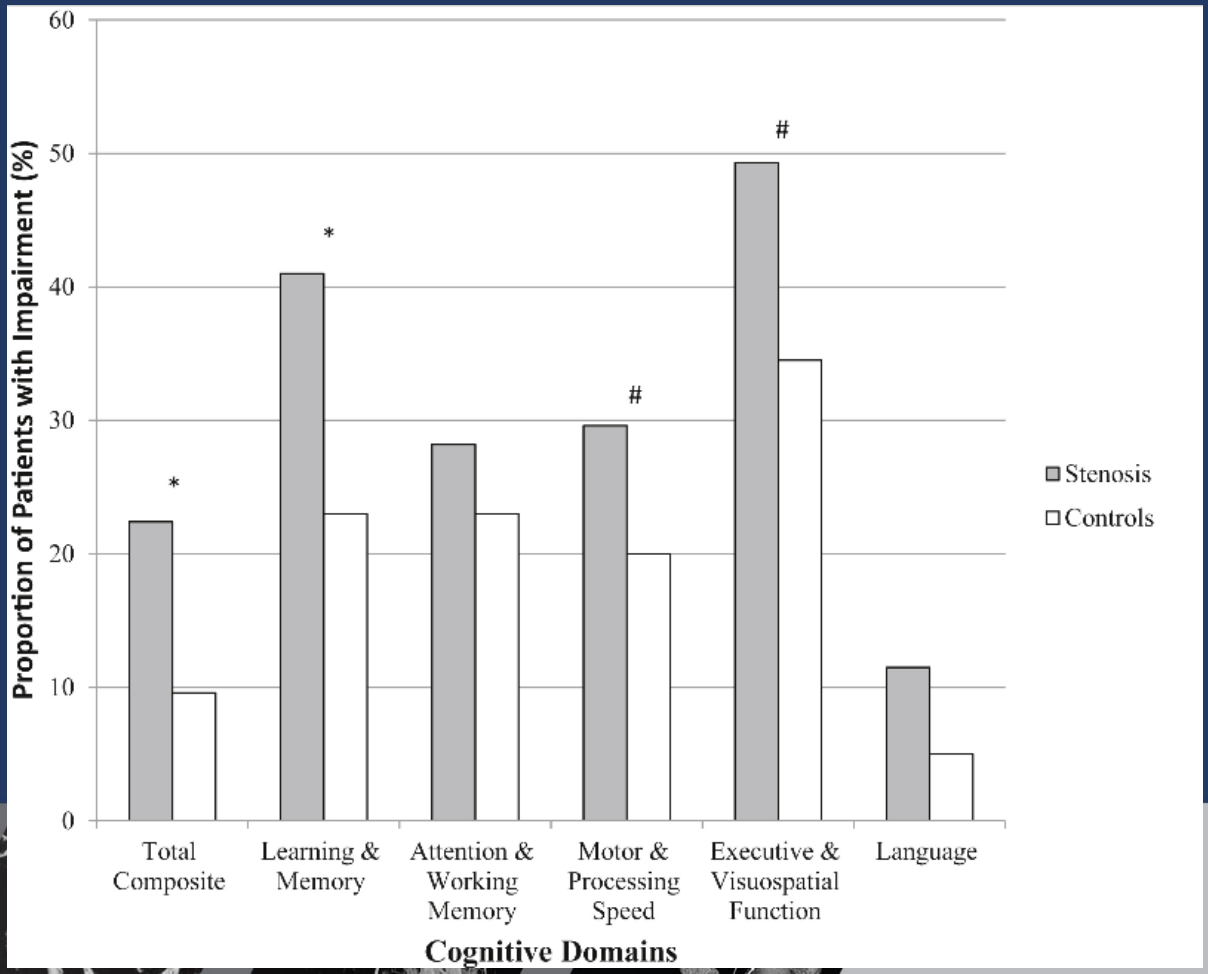
Asymptomatic carotid stenosis is associated with cognitive impairment

Presented at the late-breaking clinical trials session of the
Surgery, National Harbor, Md, June 8-11, 2016.

JVS Journal of Vascular Surgery
Official Publication of the Society for Vascular Surgery

Brajesh K. Lal, MD, Moira C. Dux, PhD, Siddhartha Sikdar, PhD, Carly Goldstein, BA, Amir A. Khan, PhD, John Yokemick, BA, RVT, Limin Zhao, MBBS, RVT
From the Society for Vascular Surgery

October 2017 Volume 66, Issue 4, Pages 1083–1092



Floor C. Bakker
Catharina J. M. Klijn
Aagje Jennekens-Schinkel
L. Jaap Kappelle

Cognitive disorders in patients with occlusive disease of the carotid artery: a systematic review of the literature

Studies: 18

Male: 75%

Mean Age: 50-65 Years

COGNITIVE DEFICITS:

Sx & Asx Studies: 14/ 18 (78%)

* **Asx Studies:** 3 (100%)

J Neurol, 2000

ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline

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

	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: A
Stenting	Class I LOE: B	Class I LOE: B	Class IIb LOE: B

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: 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. *Circulation.* 2011;124:e54–e130.

This article is copublished in the *Journal of the American College of Cardiology* and *Stroke*.

(*Circulation*. 2011;124:e54-e130.)

Stroke

Systematic Review of Guidelines for the Management of Asymptomatic and Symptomatic Carotid Stenosis

Anne L. Abbott, Kosmas I. Paraskevas, Stavros K. Kakkos, Jonathan Golledge, Hans-Henning Eckstein, Larry J. Diaz-Sandoval, Longxing Cao, Qiang Fu, Tissa Wijeratne, Thomas W. Leung, Miguel Montero-Baker, Byung-Chul Lee, Sabine Pircher, Marije Bosch, Martine Dennekamp and Peter Ringleb

DOI http://dx.doi.org/10.1161/STROKEAHA.115.003390
Stroke. 2015;46:3288-3301
Originally published October 8, 2015

Conclusions—This systematic review has identified many opportunities to modernize and otherwise improve carotid stenosis management guidelines.

Editor's Choice — Management of Atherosclerotic Carotid and Vertebral Artery Disease: 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS)

Eur J Vasc Endovasc Surg (2018) 55, 3–81

Writing Group [a], A.R. Naylor, J.-B. Ricco, G.J. de Borst, S. Debus, J. de Haro, A. Halliday, G. Hamilton, J. Kakisis, S. Kakkos, S. Lepidi, H.S. Markus, D.J. McCabe, J. Roy, H. Sillesen, J.C. van den Berg, F. Vermassen,
ESVS Guidelines Committee [b], P. Kolh, N. Chakfe, R.J. Hinchliffe, I. Koncar, J.S. Lindholt, M. Vega de Ceniga, F. Verzini,
ESVS Guideline Reviewers [c], J. Archie, S. Bellmunt, A. Chaudhuri, M. Koelemay, A.-K. Lindahl, F. Padberg, M. Venermo

- While awaiting data from CREST-2, ECST-2, ACST-2, and ACTRIS and the development of validated algorithms for patient selection, the presence of one or more clinical and/or imaging features such as silent infarction on CT/MRI, stenosis progression, large plaque area, large juxta-luminal black area (JBA) on computerized plaque analysis, plaque echolucency,

Recommendation 17	Class	Level	References
In "average surgical risk" patients with an asymptomatic 60–99% stenosis, carotid endarterectomy should be considered in the presence of one or more imaging characteristics that may be associated with an increased risk of late ipsilateral stroke,[a] provided documented perioperative stroke/death rates are <3% and the patient's life expectancy exceeds 5 years	IIa	B	13,35,54,84–94, 96,97

RECOMMENDATIONS FOR ASX CAROTID STENOSIS

- HIGH GRADE LESIONS (80-99%)
- PROGRESSION OF DISEASE
- VULNERABLE PLAQUE
  - GSM <15
  - PLAQUE AREA >80
  - JUXTA-LUMINAL BLACK AREA > 8 cm^2
- CONTRALATERAL CVA or OCCLUSION (↓ CV RESERVE)
- MULTIPLE TCD “HITS”
- MULTIPLE ULCERATIONS

Results of the ROADSTER multicenter trial of transcarotid stenting with dynamic flow reversal

Presented at the Late Breaking Clinical Trials Session at Vascular Interventional Advances (VIVA) 2014, November 4-7, 2014.

Christopher J. Kwolek, MD, Michael R. Jaff, DO, J. Ignacio Leal, MD, L. Nelson Hopkins, MD, Rasesh M. Shah, MD, Todd M. Hanover, MD, Sumaira Macdonald, MD, Richard P. Cambria, MD
The ROADSTER Investigators and Executive Committee members

Instructions for Use
ENROUTE® Transcarotid Neuroprotection System (NPS)

Indications for Use

The ENROUTE Transcarotid Neuroprotection System (ENROUTE Transcarotid NPS) is intended to provide transcarotid vascular access, introduction of diagnostic agents and therapeutic devices, and embolic protection during carotid artery angioplasty and stenting procedures for patients diagnosed with carotid artery stenosis and who have appropriate anatomy described below:

- Adequate femoral venous access
- Common carotid artery reference diameter of at least 6 mm
- Carotid bifurcation is a minimum of 5 cm above the clavicle as measured by duplex Doppler ultrasound (DUS) or computerized axial tomography (CT) angiography or magnetic resonance (MR) angiography.

Contraindications

The ENROUTE Transcarotid NPS is contraindicated for use in patients exhibiting the following conditions:

- Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated
- Patients with unresolved bleeding disorders
- Patients with severe disease of the ipsilateral common carotid artery
- Uncontrollable intolerance to flow reversal (i.e. pre-conditioning does not result in in tolerance to vessel occlusion/flow reversal)

Roadster 2 Exclusion Criteria

- EXCLUSION CRITERIA:
- Each potential patient must be screened to ensure that they do not meet any of the following exclusion criteria. This screening is to be based on known medical history and data available at the time of eligibility determination and enrollment.
- Patient has an alternative source of cerebral embolus, including but not limited to:
  - Patient has chronic atrial fibrillation.
  - Patient has had any episode of paroxysmal atrial fibrillation within the past 6 months, or history of paroxysmal atrial fibrillation requiring chronic anticoagulation.
  - Knowledge of cardiac sources of emboli. e.g. left ventricular aneurysm, intracardiac filling defect, cardiomyopathy, aortic or mitral prosthetic heart valve, calcific aortic stenosis, endocarditis, mitral stenosis, atrial septal defect, atrial septal aneurysm, or left atrial myxoma).
  - Recently (<60 days) implanted heart valve (either surgically or endovascularly), which is a known source of emboli as confirmed on echocardiogram.
  - Abnormal angiographic findings: ipsilateral intracranial or extracranial arterial stenosis (as determined by angiography or CTA/MRA ≤ 6 months prior to index procedure) greater in severity than the lesion to be treated, cerebral aneurysm > 5 mm, AVM (arteriovenous malformation) of the cerebral vasculature, or other abnormal angiographic findings.
- Patient has a history of spontaneous intracranial hemorrhage within the past 12 months, or has had a recent (<7 days) stroke of sufficient size (on CT or MRI) to place him or her at risk of hemorrhagic conversion during the procedure.
- Patient had hemorrhagic transformation of an ischemic stroke within the past 60 days.
- Patient with a history of major stroke attributable to either carotid artery (CVA or retinal embolus) with major neurological deficit (NIHSS ≥ 5 OR mRS ≥ 3) likely to confound study endpoints within 1 month of index procedure.
- Patient has an intracranial tumor.

Exclusion Criteria Roadster 2

- Patient has an evolving stroke.
- Patient has neurologic illnesses within the past two years characterized by fleeting or fixed neurologic deficit which cannot be distinguished from TIA or stroke, including but not limited to: moderate to severe dementia, partial or secondarily generalized seizures, complicated or classic migraine, tumor or other space-occupying brain lesions, subdural hematoma, cerebral contusion or other post-traumatic lesions, intracranial infection, demyelinating disease, or intracranial hemorrhage).
- Patient has had a TIA or amaurosis fugax within 48 hrs prior to the procedure.
- Patient has an isolated hemisphere.
- Patient had or will have CABG, endovascular stent procedure, valve intervention or vascular surgery within 30 days before or after the intervention.
- Myocardial Infarction within 72 hours prior to the intervention.
- Presence of a previous placed intravascular stent in target vessel or ipsilateral CCA or significant CCA inflow lesion.
- Occlusion or [Thrombolysis In Myocardial Infarction Trial (TIMI 0)] "string sign" >1cm of the ipsilateral common or internal carotid artery.
- An intraluminal filling defect (defined as an endoluminal lucency surrounded by contrast, seen in multiple angiographic projections, in the absence of angiographic evidence of calcification) whether or not it is associated with an ulcerated target lesion.
- Ostium of Common Carotid Artery (CCA) requires revascularization.
- Patient has an open stoma in the neck.
- Female patients who are pregnant or may become pregnant.
- Patient has history of intolerance or allergic reaction to any of the study medications or stent materials (refer to stent IFU), including aspirin (ASA), ticlopidine, clopidogrel, statin or contrast media (that can't be pre medicated). Patients must be able to tolerate statins and a combination of ASA and ticlopidine or ASA and clopidogrel.
- Patient must have a life expectancy <3 years without contingencies related to other medical, surgical, or interventional procedures as per the Wallaert Score and patients with primary, recurrent or metastatic malignancy who do not have independent assessment of life expectancy performed by the treating oncologist or an appropriate specialist other than the physician performing TCAR.

ROADSTER 2: Clinical Outcomes

Patients Treated Per Protocol

	ROADSTER 1 n=203		ROADSTER 2 n=362		ROADSTER 2 n=385	
	Patients with 30-day F/U		*Patients with 30-day F/U*		*All Patients*	
Stroke/Death/MI	6	3.0%	4	1.1%	4	1.0%
Stroke	1	0.5%	3	0.8%	3	0.8%
Death	2	1.0%	1*	0.3%	1*	0.3%
MI	3	1.5%	0	0.0%	0	0.0%
Stroke/Death	3	1.5%	4	1.1%	4	1.0%
Neurological Death	0	0.0%	0	0.0%	0	0.0%
CN (permanent)	0	0.0%	0	0.0%	0	0.0%

*One patient expired ~2 weeks post-procedure due to ruptured AAA.

Long-Term Outcomes of Carotid Endarterectomy Versus Stenting

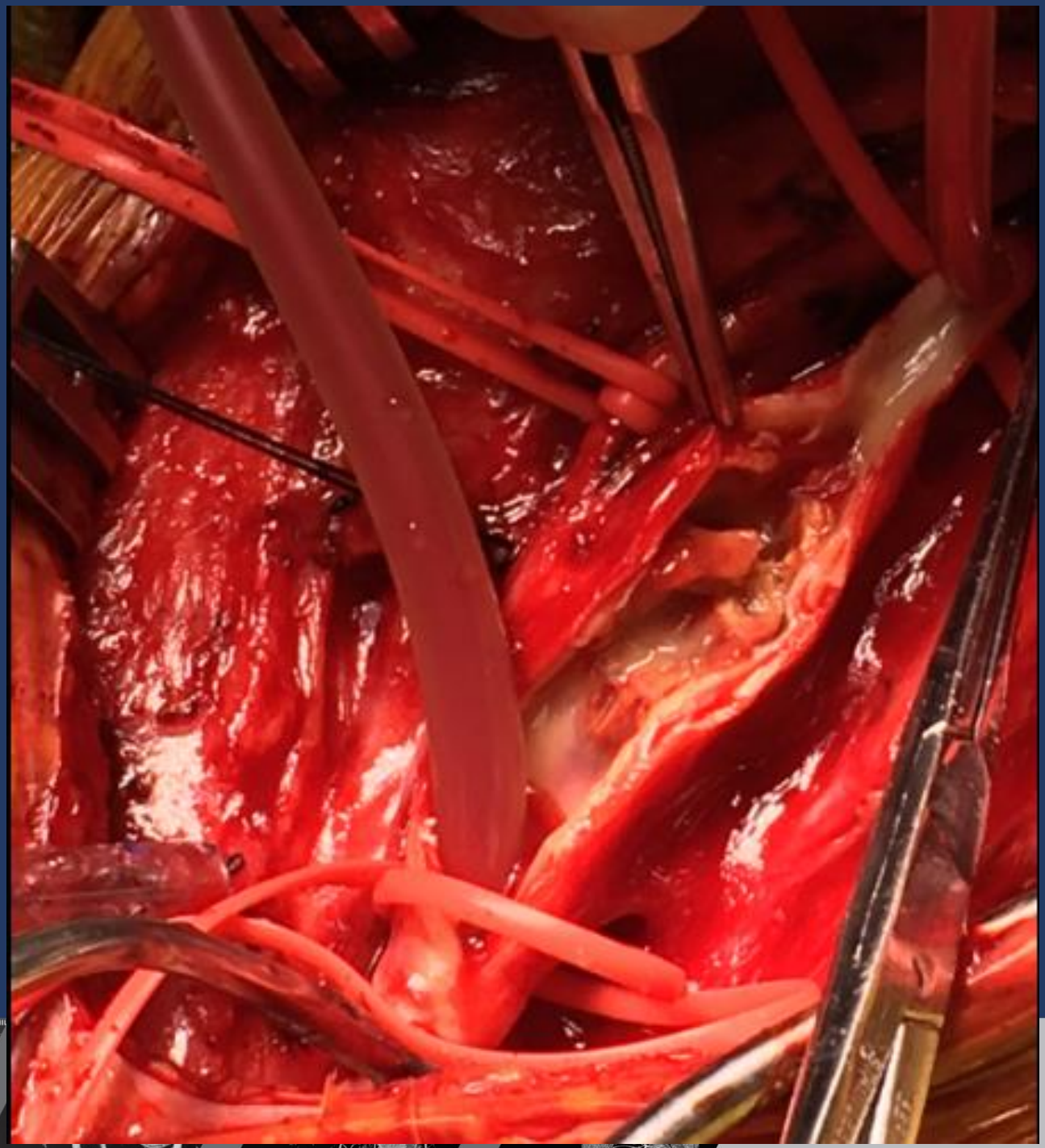
Patients with significant carotid-artery stenosis (n=15,525)

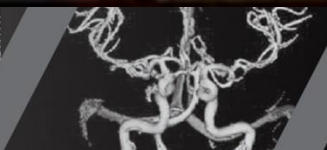
Observational Cohort

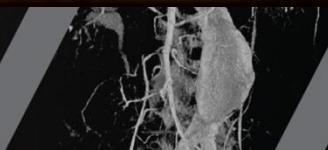
Carotid Endarterectomy (n = 13,410)	Long-Term Stroke + 30-Day MI + Death	Carotid-Artery Stenting (n = 2,115)
9.7%	Risk-Adjusted Cohort (% of patients, HR 1.57, 95% CI 1.43-1.73)	16.3%
11.1%	2:1 Propensity Matched (% of patients, HR 1.55, 95% CI 1.31-1.83)	16.3%

Hussain et al. *Ann Surg.* May 2017.

ANNALS OF SURGERY
A Monthly Review of Surgical Science Since 1885







Todd W Gensler MD, FACS
twgensle@sentara.com

ROADSTER 2: Baseline Characteristics

Parameter	n=429
Age ≥75	41.4%
Female	33.7%
Symptomatic	24.9%
Physiologic Risk Factors only	31.7%
Anatomic Risk Factors only	41.5%
Both Physiologic & Anatomic Risk Factors	26.8%
Top 3 Physiologic Risk Factors	
Age ≥ 75 Years (17.9% as sole criterion)	42.0%
Hx of CAD (≥2 vessel disease)	14.7%
COPD	5.6%
Top 3 Anatomic Risk Factors	
High Cervical Stenosis	25.4%
Restenosis after CEA	20.0%
Hostile Neck	17.0%

ROADSTER 2: FDA Endpoints to Date

Patients Treated Per Protocol

Acute	n=385	
Acute Device Success	385	100.0%
Technical Success	385	100.0%
30 Days	**n=362**	
Procedural Success	357	98.6%

Primary Endpoint Analysis

- **Acute device success** is defined as the ability to insert the device, establish flow reversal, and remove the device
- **Technical success** is defined as acute device success plus the ability to deliver interventional tools
- **Procedural success** is defined as technical success in the absence of hierarchical stroke, death or myocardial infarction

ACT1 – 5-year outcome

CEA vs CAS

NEJM, 2016

Asymptomatic Patients <80 yrs

- Major CVA/ death	0.6% vs 0.6%
- Minor stroke	1.1% vs **2.4%**
- **5 yr** stroke risk	5.3% vs 6.9%

CAS is 'non-inferior'

Xact closed-cell stent with Emboshield CPD only

Study Design

- Retrospective, population-based cohort study (2002-2015)
- Linked Ontario health administrative databases
  - Population, 13.5 million
  - Single-payer health system
  - Validated for CEA/CAS and stroke/MI coding
- Propensity Score Matched Analysis
  - 1 CAS : 2 CEA based on > 50 covariates

Hussain et al. Clin Invest Med. 2016;39(2):E73-8

Results

Overall Cohort

15,525 Patients

13,410 CEA
2,115 CAS

Matched Cohort

6,282 Patients

4,172 CEA
2,110 CAS

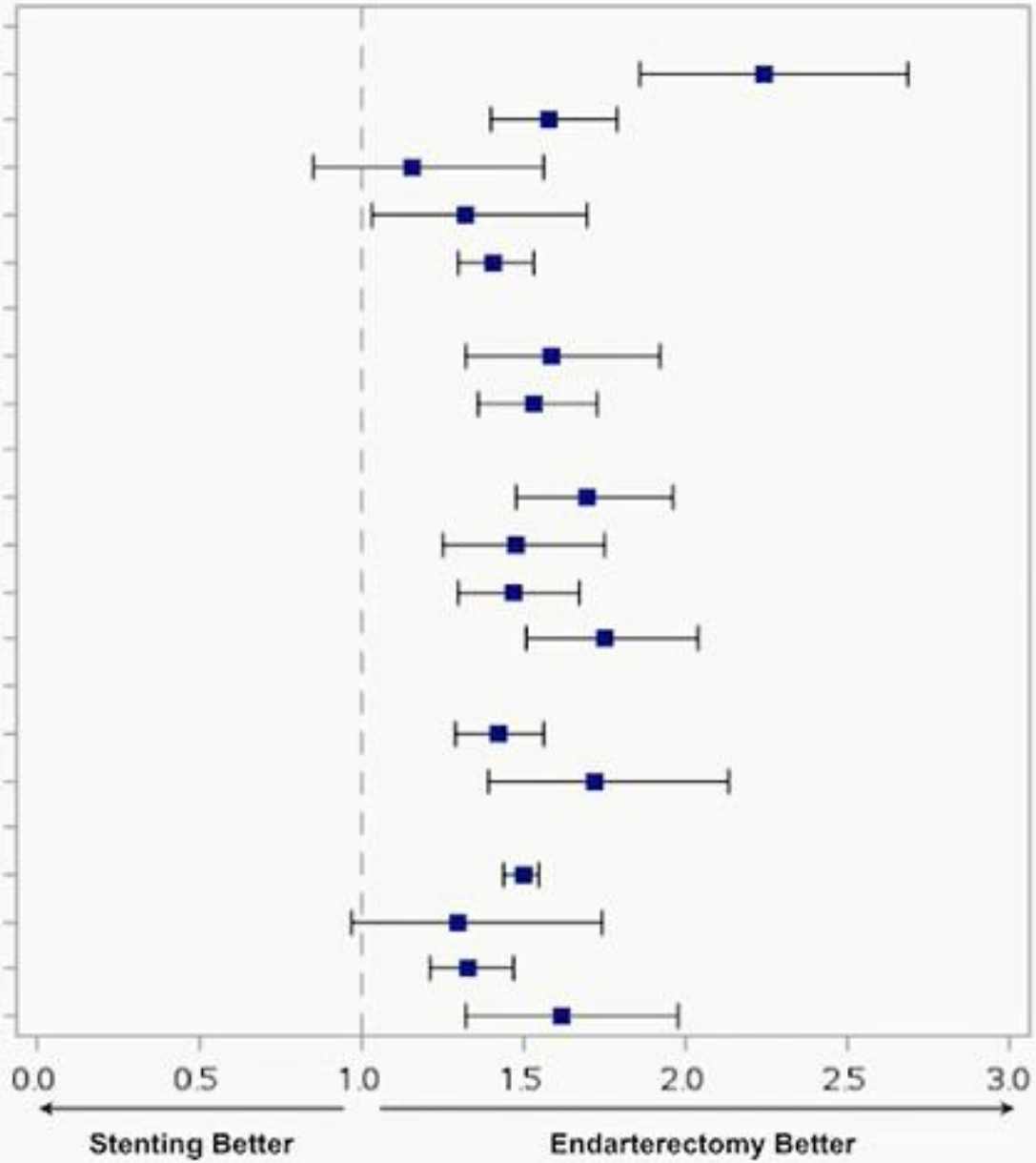
Matched Cohort Characteristics

Characteristic	CEA (N = 4,172)	CAS (N = 2,110)
Age	70±10	70±11
Female	33%	34%
Symptomatic Carotid	54%	53%
Comorbidity Score ≥ 2	38%	39%
CAD	27%	27%
CHF	7%	7%
COPD	30%	30%
Prior CEA	4%	3%
Urgent Admission	45%	46%

Stroke and Death Outcomes

Outcome	CEA (N = 4,172)	CAS (N = 2,110)	Matched HR (95% CI)
13-Yr Stroke	9.4%	13.1%	1.50 (1.21-1.86)
Stroke ≤ 30 Days	3.8%	5.8%	1.54 (1.17-2.04)
Stroke > Day 30	5.9%	7.8%	1.44 (1.18-1.74)
13-Yr Death	29%	36%	1.38 (1.28-1.50)
Death ≤ 30 Days	1.1%	3.3%	3.07 (2.29-4.11)
Death > Day 30	28%	34%	1.31 (1.21-1.42)

Subgroup	Endarterectomy n (%)	Stenting n (%)
Age		
≤64 (n = 4,314)	257 (6.9)	105 (17.3)
65-69 (n = 2,763)	212 (8.7)	43 (13.2)
70-74 (n = 3,042)	276 (10.4)	47 (12.4)
75-79 (n = 2,987)	298 (11.4)	65 (17.0)
≥80 (n = 2,419)	260 (13.0)	84 (20.0)
Sex		
Male (n = 10,289)	823 (9.3)	222 (15.8)
Female (n = 5,236)	480 (10.6)	122 (17.2)
Date of procedure		
2002 – 2004 (n = 3,622)	397 (12.1)	72 (22.0)
2005 – 2007 (n = 4,151)	382 (10.8)	107 (17.8)
2008 – 2010 (n = 3,796)	291 (9.0)	78 (14.0)
2011 – 2014 (n = 3,956)	233 (7.0)	87 (13.8)
Symptomatic stenosis*		
Yes (n = 6,605)	661 (12.1)	197 (17.6)
No (n = 8,920)	642 (8.1)	147 (14.8)
Diabetes		
Yes (n = 5,306)	490 (10.8)	142 (18.1)
IDDM (n = 665)†	66 (12.3)	19 (14.7)
NIDDM (n = 3,135)†	305 (11.4)	80 (17.9)
No (n = 10,219)	813 (9.2)	202 (15.2)



Summary

- CAS is associated with **early and sustained 30-50%** higher risks of long-term stroke & death
- Differences driven by increased risks of stroke and death within 30 days and after 30 days with CAS
- Observed regardless of age, sex, carotid artery symptoms, year of procedure or diabetic history

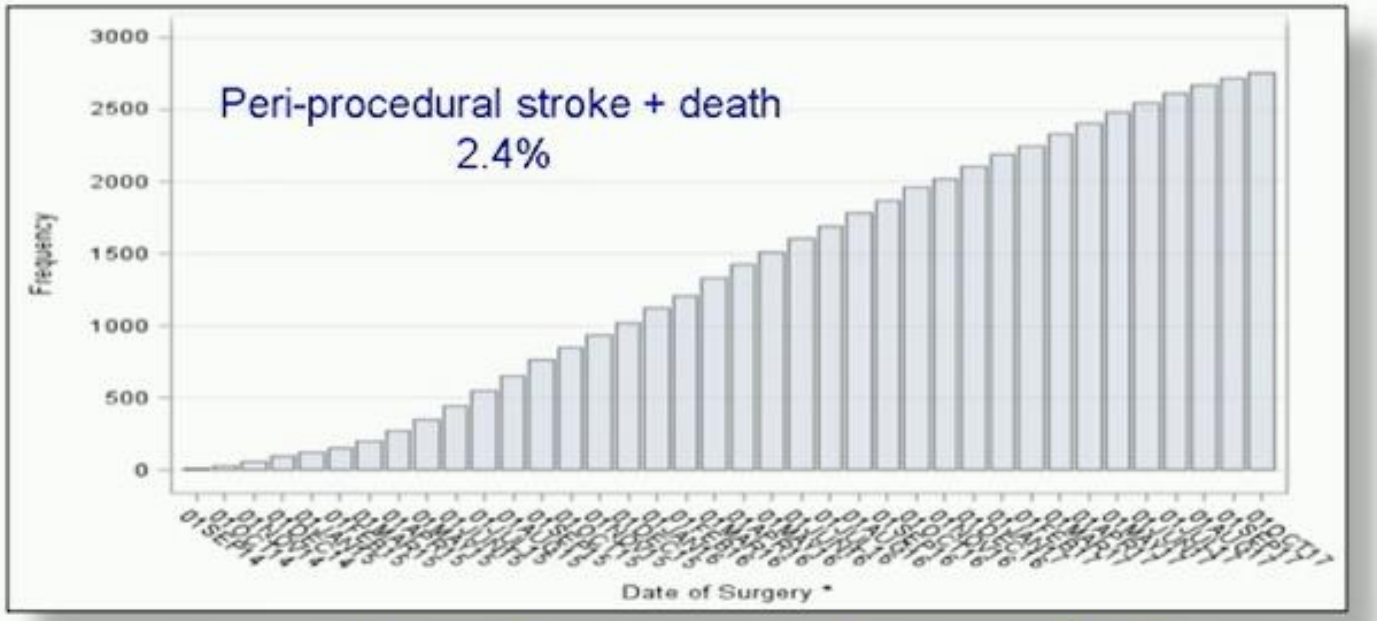
Best method TCD microemboli

How can we identify the ~10-15% who might benefit from intervention?

- TCD microemboli √
- Reduced cerebrovascular reserve √
- Ulceration on 3D ultrasound ? √
- Juxtaluminal black plaque ? √
- ? Echolucency
- ? Plaque composition/texture on ultrasound
- ? Neovascularization on ultrasound
- ?Intraplaque hemorrhage on MRI
- ?Plaque inflammation on PET/CT
- ? Plaque roughness on ultrasound

Bogiatzi C, Cocker MS, Beanlands R, Spence JD. Identifying high-risk asymptomatic carotid stenosis. Expert Opin Med Diagnostics 2012;6(2):139-51.

C2R



Approved sites	Approved interventionists	Total enrollment	Prospective enrollment	Symptomatic	Asymptomatic	Post CEA restenosis
94	192	2919	2165	43.6%	38.6%	17.8%

Medical Management Core

Percentage of CREST2 enrolled patients in-target for each risk factor

Risk Factor	Baseline	1 Month	4 Month	Last Follow Up
SBP	61.6%	70.4%	77.8%	83.3%
LDL	41.5%	55.8%	65.9%	63.5%
Non HDL	44.4%	59.0%	65.3%	65.3%
HgA1C1	47.3%	48.0%	47.8%	49.8%
Smoking	79.1%	79.8%	79.9%	80.2%
Physical Activity	50.4%	55.4%	61.4%	62.4%
Weight	23.5%	25.7%	27.3%	28.6%

The Stroke Risk In ACS Patients on Good Medical Management Is So Low That All Should Be Treated Medically: Stratification Of Risk Is Of Little Value

A/Prof Anne L. Abbott
Neurologist
School of Public Health & Preventive Medicine
Monash University & The Alfred Hospital, Melbourne, Australia

FACTCATS.org

We Have Passed A Procedural Era for >50% ACS

Continued Fall in Stroke Risk

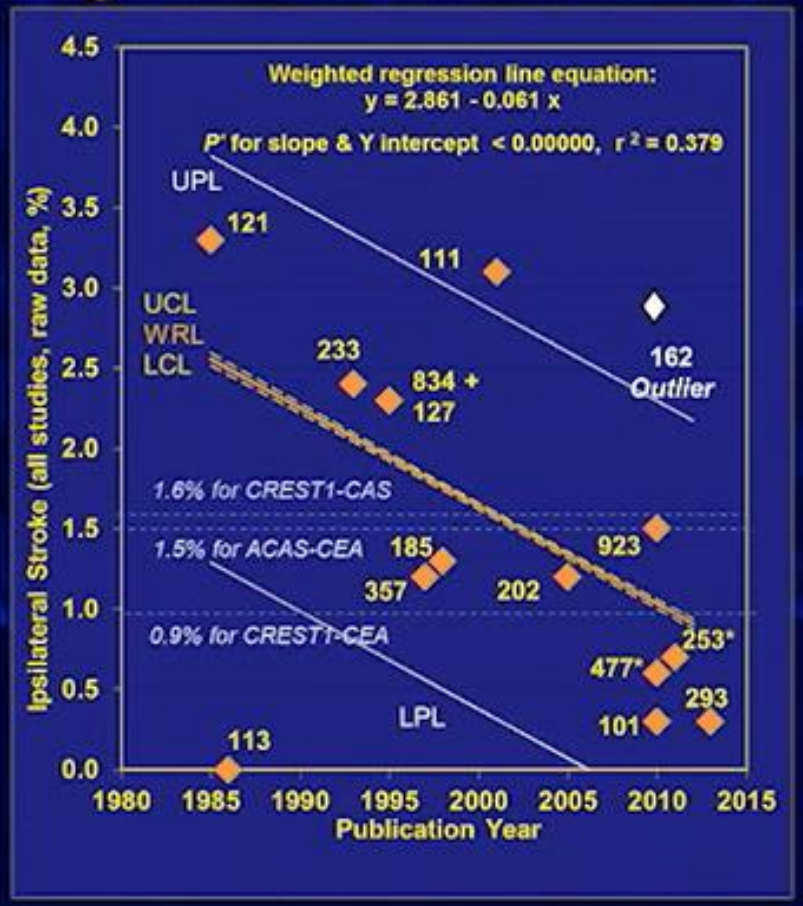
'Medical Management/Revascularization' Alone

Annual Ipsilateral Stroke Rate
(Raw data,%)

1.7% fall in Absolute Rate

67 % fall in Relative Rate to 0.8%

1985-2013



Updated meta-analysis to the end of 2013.
Abbott et al, Frontiers in Neurology, October 2017 |

Today 4.0% or Fewer Patients with 50-99% ACS Could Benefit from CEA or CAS after Diagnosis!

- Average annual ipsilateral stroke rate is **<0.8%.**
- About **half** the strokes not are due to the stenosis.
- Average age of diagnosis: **70 yrs**
- Average survival is **10 years** (0.8 x 10 = 4.0%)
- 4% assumes the 30-day stroke/death rate always= **0%**

Abbott Stroke, 2009; Abbott et al, Frontiers of Neurology, 2017; Inzitari, NEJM, 2000.

Disproven/Improbable Markers of 'High-Risk' Patients likely to Benefit from CEA or CAS

1-9 from European Soc. for Vascular Surgery Guideline, 2017

CEA (Class IIa) or CAS (Class IIb) endorsed for 50-99% ACS if ≥1 of these or others unspecified markers:^

1. Silent Infarct on CT *
2. Asymptomatic stenosis progression *
3. Plaque echolucency on U/S *
4. Intra-plaque haemorrhage on MRI
5. Plaque area *
6. Juxtaluminal black areas on U/S *
7. Contralateral TIA/stroke *
8. Impaired C.V. reactivity
9. Transcranial embolic signals +/- echolucency
10. [80-99% stenosis] *

^ And if peri-procedural stroke/death rate <3%, patient life expectancy >5 years. Naylor et al, EJVES, 2017

** From the ACSRS Study by Nicolaides et al; HR/ORs up to 10.6 but statistical & clinical significance are not the same.*

Asymptomatic Stenosis Progression: Improbable

ACSRS: Kakkos et al JVS 2014 ; Hirt et al, Stroke 2014; NASCET

	n	Recruited	Risk Factor Prevalence	Annual Ipsilateral Stroke
Kakkos et al ACSRS (4Y)				
11-99%*	1121	1998-2002	20%	2%
70-99% *	449	"	13%	2.6%
80-99%*	325	"	11%	3.1%
[Hirt at al ACST (1Y)^				
>50%**	1469	1993-2003	32%	<6.3% (stroke/TIA)
>50% ***	"	"	3%	<18% (stroke/TIA)
>50% ****	"	"	0.6%	<20% (stroke/TIA)]

*^Asymptomatic for >6 months; *Change in ≥1 category* or 1 category** or 2 categories*** or 3 categories****

Abbott says this is best risk stratifier

The ACSRS Model: The Best Bet So Far

Kakkos et al, JVS 2013

History contralateral stroke/TIA present, Degree stenosis (83-99% NASCET), Discrete white areas & Juxtaluminal black areas

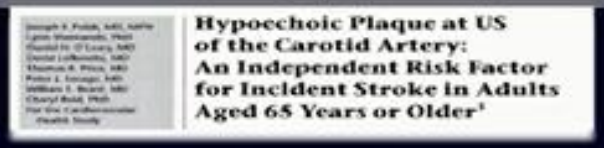
n	Recruited	Prevalence of Lowest-Highest Risk Factor Combinations	Average Annual Ipsilateral Stroke Rate
1211	1998-2002	734/1121 = 65%	<1%
≥50%		94/1121 = 8%	1-1.9%
ECST=		134/1121 = 12%	2-3.9%
≥11%		125/1121 = 11%	4-5.9%
NASCET		34/1121 = 3%	6-10%
(4 Yrs)			10% maximum

** 25% of statins at recruitment according to an associated publication*

1.0% in vascular surgeons

Results of CEA: Asx Stenosis

	Year	# Patients	% CVA/Death
ACAS	1995	724	2.3%
ACST	2004	1,348	3.1%
CREST (Asx)	2011	1,196	1.4%

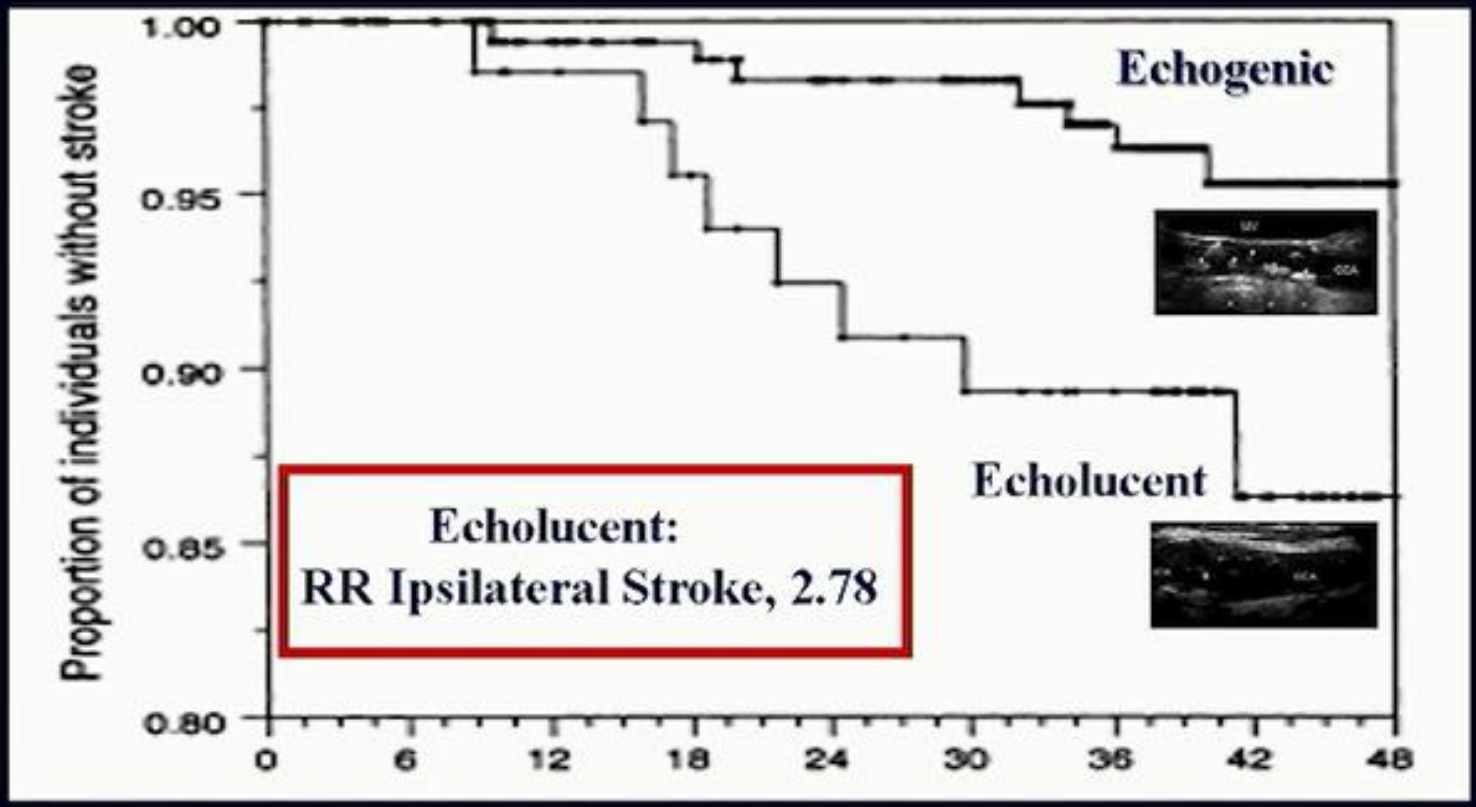


Hypoechoic Plaque at US of the Carotid Artery: An Independent Risk Factor for Incident Stroke in Adults Aged 65 Years or Older[1]

Cardiovascular Health Study

Patients: 4,886 ≥ 65 Yrs

Mean F/U 3.3 Yrs

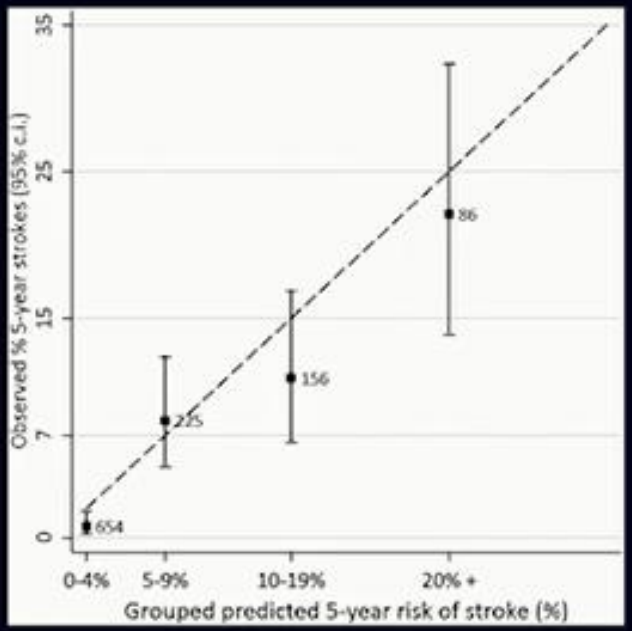


Radiology, 1998

Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification

Andrew N. Nicolaides, MS, FRCS, PhD (Hon),[a] Stavros K. Kakkos, MD, MSc, PhD, DIC,[a] Efthyvoulos Kyriacou, BSc, PhD,[b] Maura Griffin, MSc, DIC, PhD,[a] Michael Sabetai, MD, FRCS, PhD,[a] Dafydd J. Thomas, MD, PhD,[c] Thomas Tegos, MD, PhD,[a] George Geroulakos, MD, PhD,[a,d] Nicos Labropoulos, PhD, DIC, [illegible], Ross Naylor, MD, FRCS,[e] and Anne L. Abbott, MB, BS, FRACP, PhD,[b] for the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group, *London and Hatfield, United Kingdom; Limassol, Cyprus; Stony Brook, NY; and Melbourne, Australia*

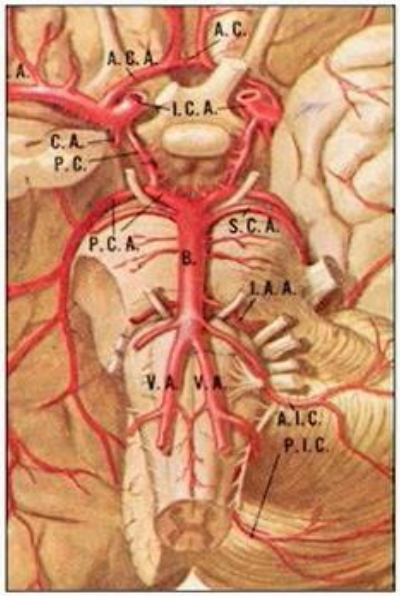
5-Year Stroke Risk Asx Patients



ultrasonic plaque features can be used to stratify risk and may lead to refinement of the indications for carotid endarterectomy.

J Vasc Surg, 2010

-Only 1/316 patients with a new occlusion had a stroke at the time of occlusion
-That's 0.3% - well below the risk of stenting or CEA
-The Circle of Willis protects the brain from a carotid occlusion. It is not like a left main coronary lesion; it is not a widowmaker; it is not a ticking time bomb
-Preventing occlusion is not a valid indication for intervention



Yang C, Bogiatzi C, Spence JD. JAMA Neurol. 2015 Sep 21:1-7

What Is Good Medical Treatment For Asymptomatic Patients With Carotid Stenosis?

What Can It Do To The Plaque?
How Low Should LDL Cholesterol (LDL-C) Be Pushed?
How To Get There?
SAMMPRIS Proves It Can Be Done!

Richard Bulbulia
Consultant Vascular Surgeon and Co-PI ACST-2
MRC Population Health Research Unit
CTSU, Nuffield Department of Population Health
University of Oxford

3 choices for asymptomatic carotid stenosis

ACST-2

Carotid Guidelines 2017

esvs

EUROPEAN SOCIETY OF CARDIOLOGY®

All asx carotid pts should be on intensive lipid lowering Rx

LDL-C Lowering

Intensive statin therapy

40-80 mg atorvastatin or 20-40 mg rosuvastatin

(Irrespective of baseline lipid profile)

New developments to fight residual risk…

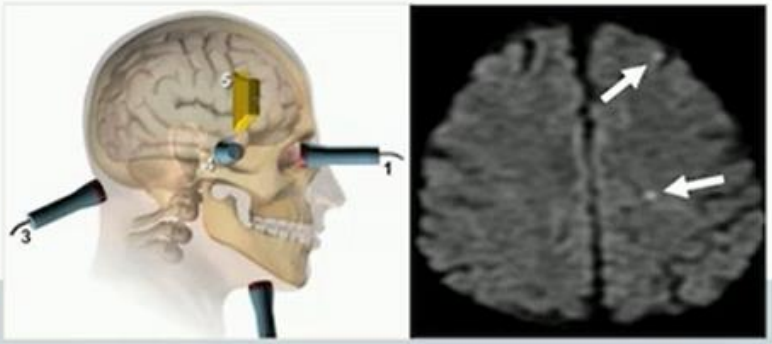
- **Anti-thrombotic therapy**
  - COMPASS (2.5 mg rivaroxaban bd + aspirin v aspirin alone)
  - Risk of stroke halved
- **Blood pressure lowering therapy**
  - SPRINT (low v very low BP targets)
  - 121 mmHg v 136 mmHg SBP (15mmHg) for 3 years
  - 25% reduction in MVE
  - *Doubling of SAE due to study intervention:*
  - *220 [4.7%] v 118 [2.5%], largely driven by acute renal failure*
- **Lipid-lowering therapy: PCSK-9 Inhibition**
  - FOURIER (Evolocumab)
  - 23% reduction in risk of stroke

Triple medical therapy effective, but residual risk remains

- Aspirin reduces CV risk by around 20%, but effect on 'carotid' stroke unclear
- ? Aim for SBP ~120 mmHg to prevent CV events (but at a cost)
- Intensive LDL lowering safe and effective
- **Carotid intervention halves any residual risk**

Microembolization

- **Carotid Intervention is effective in stroke prevention in appropriately selected patients**
  - Brott et al, NEJM 2010, 2016
  - Halliday et al, Lancet 2010
- **Procedure-related embolization detected on TCD or MRI is common in 20-70% of patients**

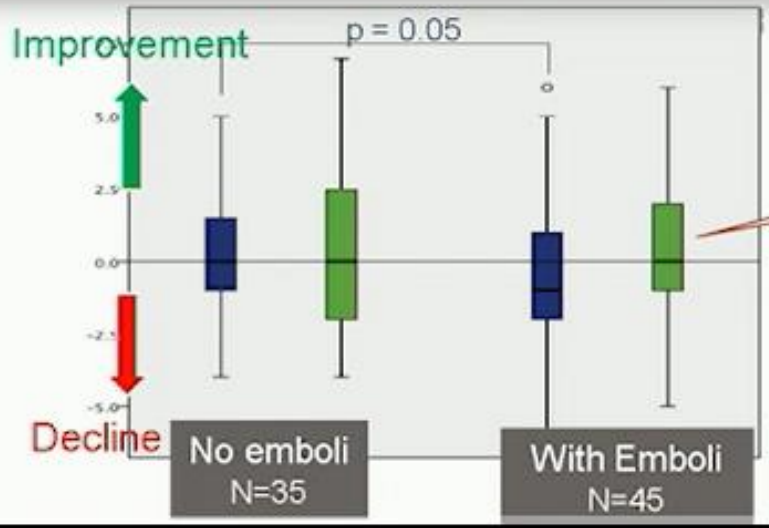


Prospective neurocognitive evaluation of patients undergoing carotid interventions

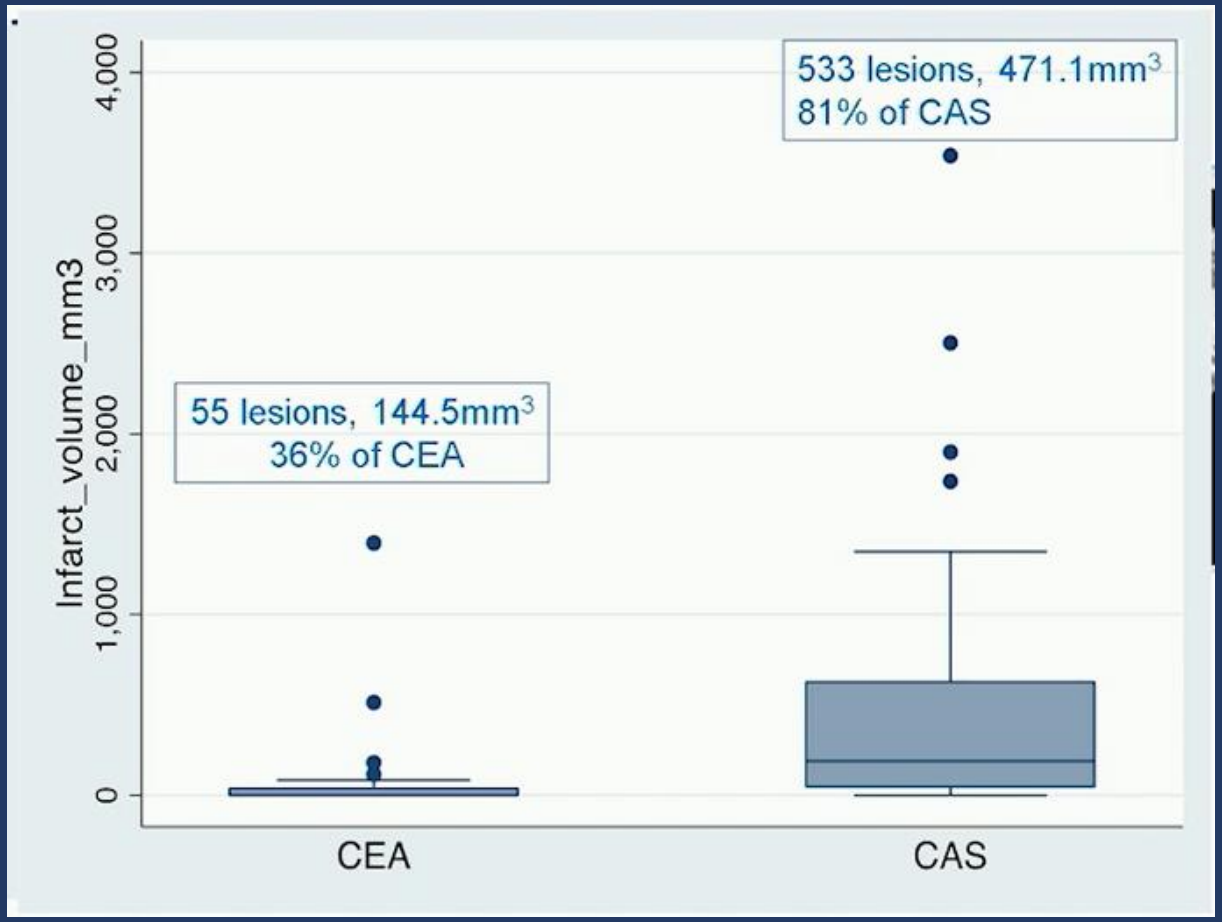
Wei Zhou, MD,[a,b] Elizabeth Hitchner, MA,[a] Kathleen Gillis, RNP,[a] Lixian Sun, MS,[c] Rebecca Floyd, BS,[d] Barton Lane, MD,[f] and Allyson Rosen, PhD,[d,e] *Palo Alto and Stanford, Calif*

Microembolization is associated with transient cognitive decline in patients undergoing carotid interventions

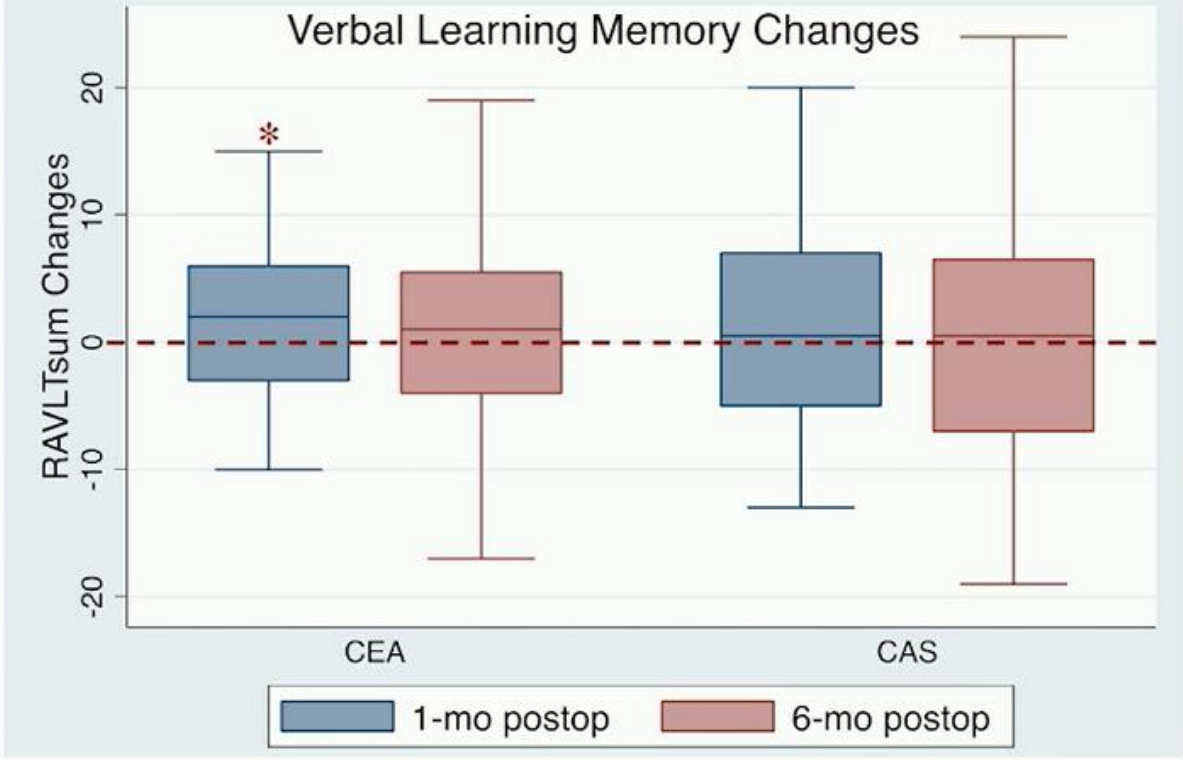
Elizabeth Hitchner, MA,[a] Brittanie D. Baughman, MS, MBA,[a] Salil Soman, MD,[b] Becky Long, BS,[a] Allyson Rosen, PhD,[a] *and* Wei Zhou, MD,[a,c] *Palo Alto and Stanford, Calif; and Cambridge, Mass*

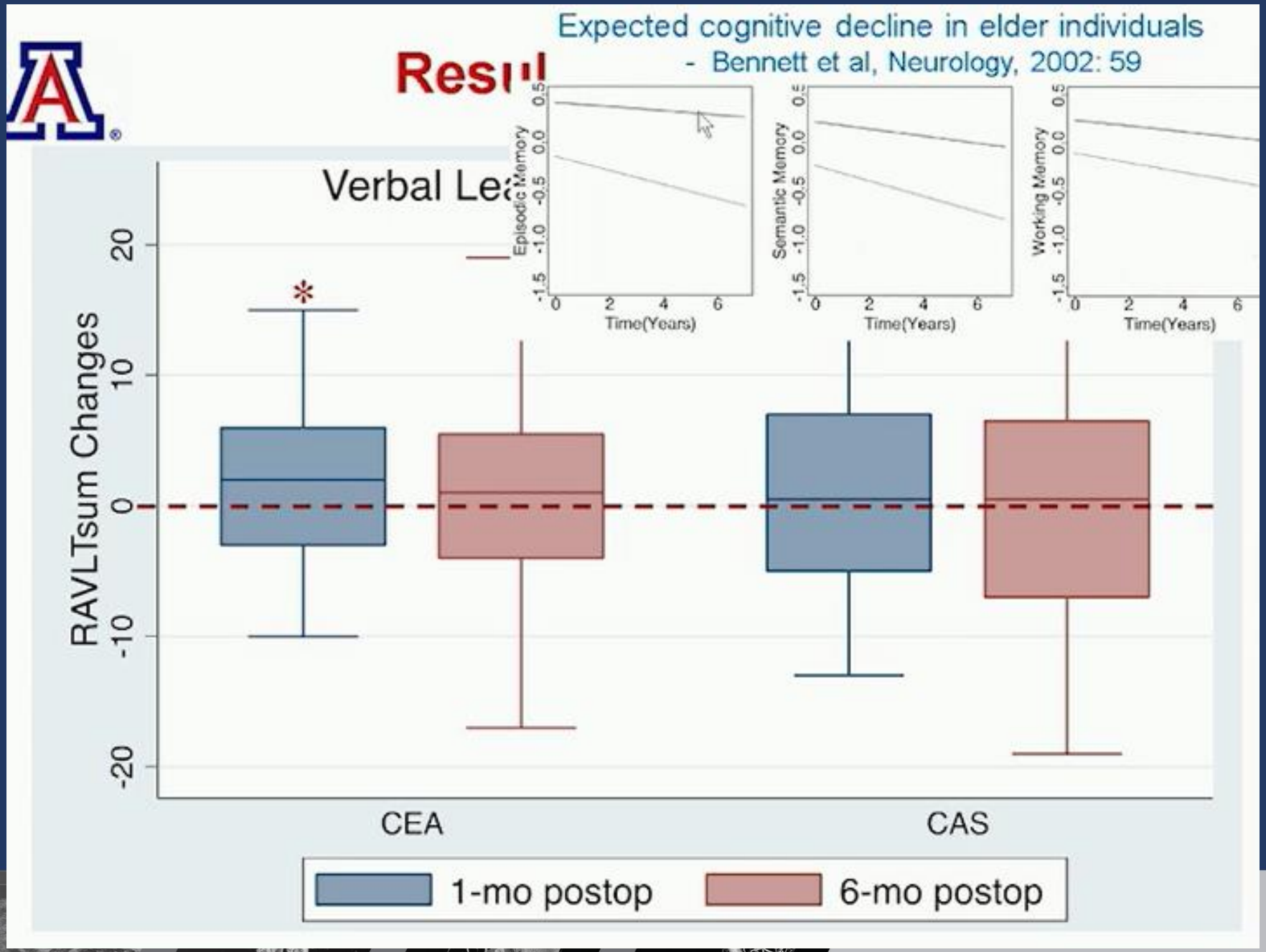


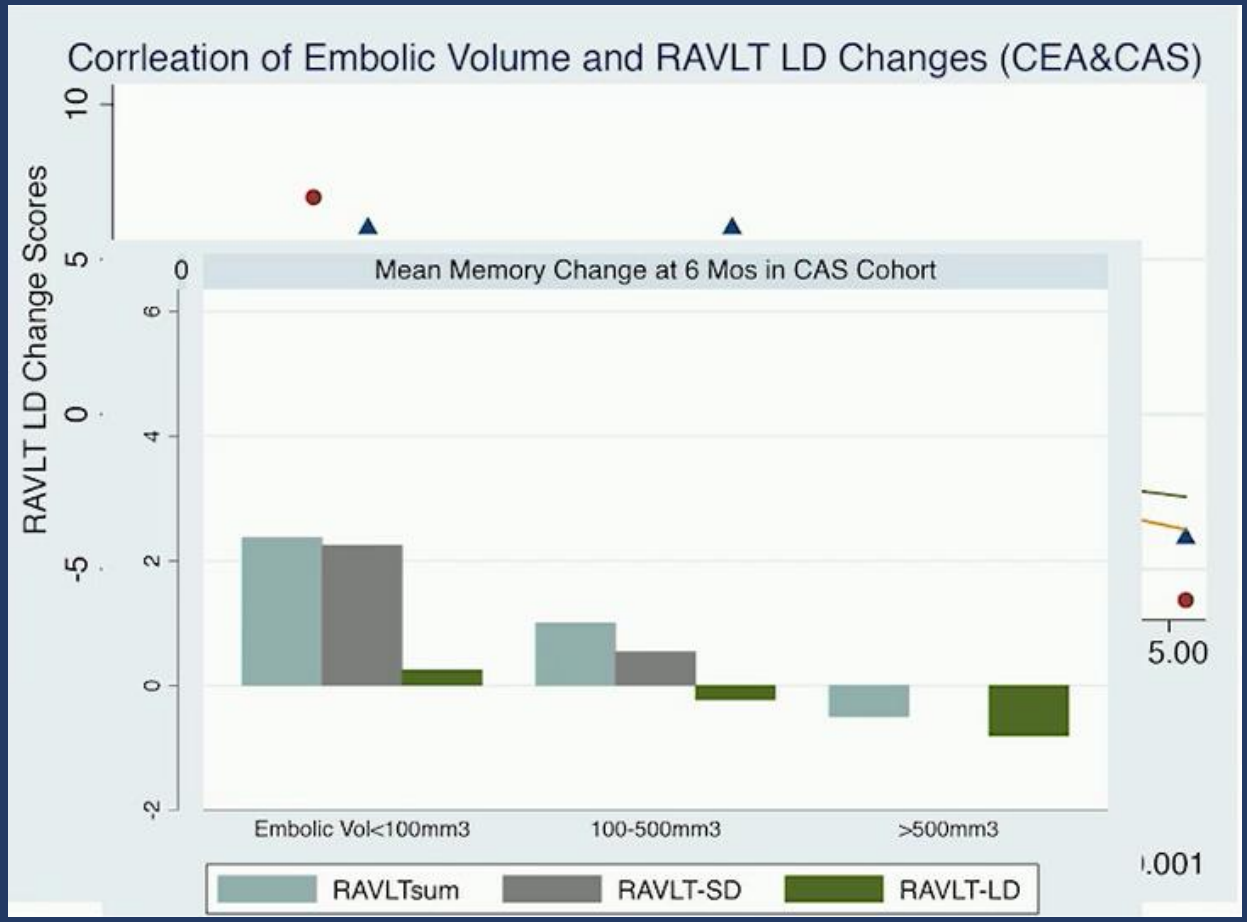
Decline @ 1 mo, recovered @ 6 mo


533 lesions, 471.1mm3
81% of CAS
55 lesions, 144.5mm3
36% of CEA
Infarct_volume_mm3
0
1,000
2,000
3,000
4,000
CEA
CAS

Results – CEA vs. CAS




Expected cognitive decline in elder individuals
- Bennett et al, Neurology, 2002: 59
Episodic Memory
Semantic Memory
Working Memory
Time(Years)
RAVLTsum Changes
20
10
0
-10
-20
CEA
CAS
1-mo postop
6-mo postop


Corrleation of Embolic Volume and RAVLT LD Changes (CEA&CAS)
RAVLT LD Change Scores
10
5
0
-5
Mean Memory Change at 6 Mos in CAS Cohort
6
4
2
0
-2
Embolic Vol<100mm3
100-500mm3
>500mm3
RAVLTsum
RAVLT-SD
RAVLT-LD
5.00
.001

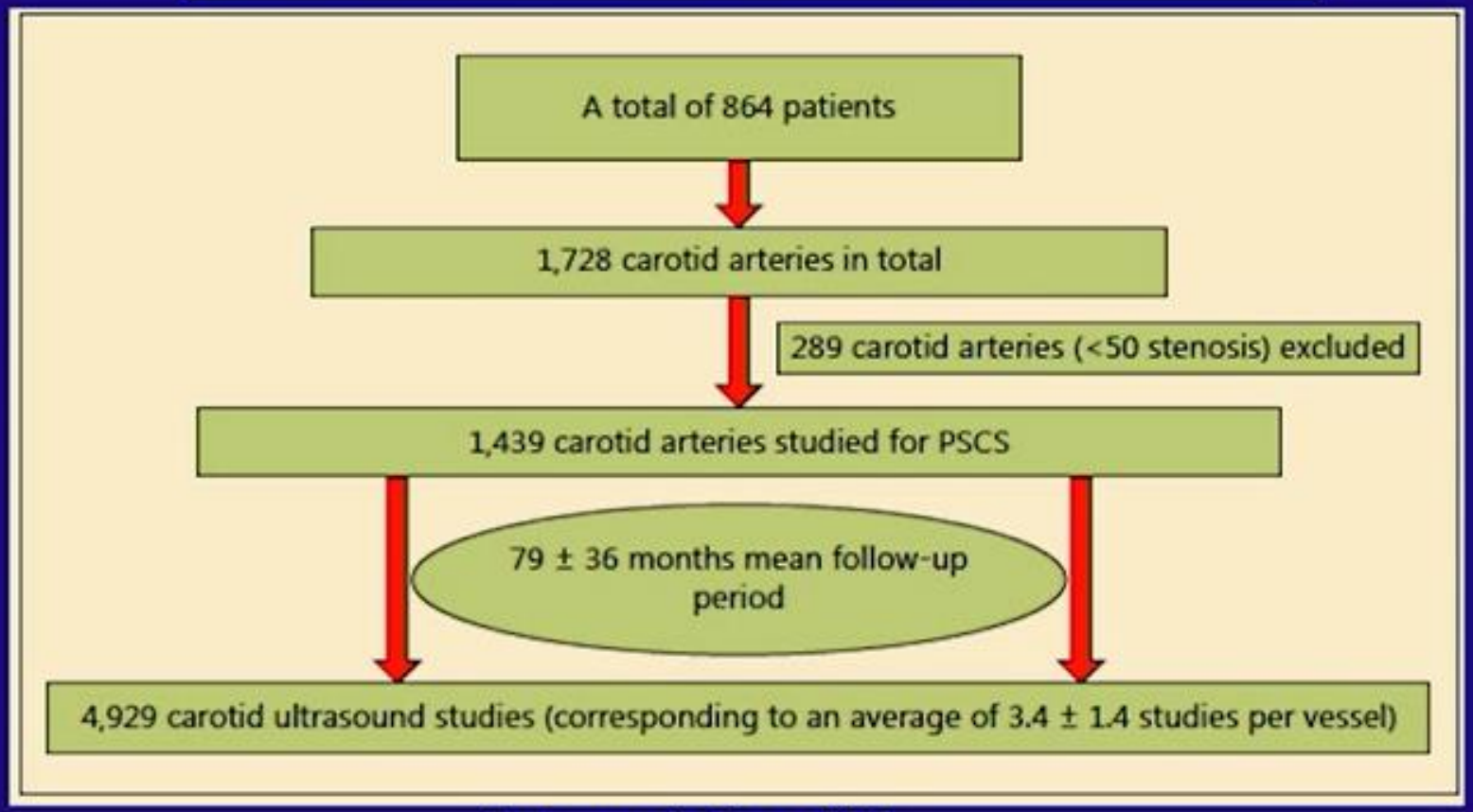
Summary

- Carotid intervention tends to have a positive effect on memory function
- Procedure-related DWI lesions hinder the cognitive benefits of carotid interventions
- Sizes of lesions correlate to long-term memory changes

Optimal Medical Management Reduces Risk of Disease Progression and Ischemic Events in Asymptomatic Carotid Stenosis Patients: A Long-Term Follow-Up Study

Zubair Shah[a] Reza Masoomi[a] Rashmi Thapa[a] Mashhood Wani[a] John Chen[c] Buddhadeb Dawn[a] Marilyn Rymer[b] Kamal Gupta[a]

[a]Division of Cardiovascular Diseases, and [b]Department of Neurology, University of Kansas Medical Center, and [c]Division of Health Services Research, University of Kansas, Kansas City, KS, USA



Cerebrovascular Disease 2017

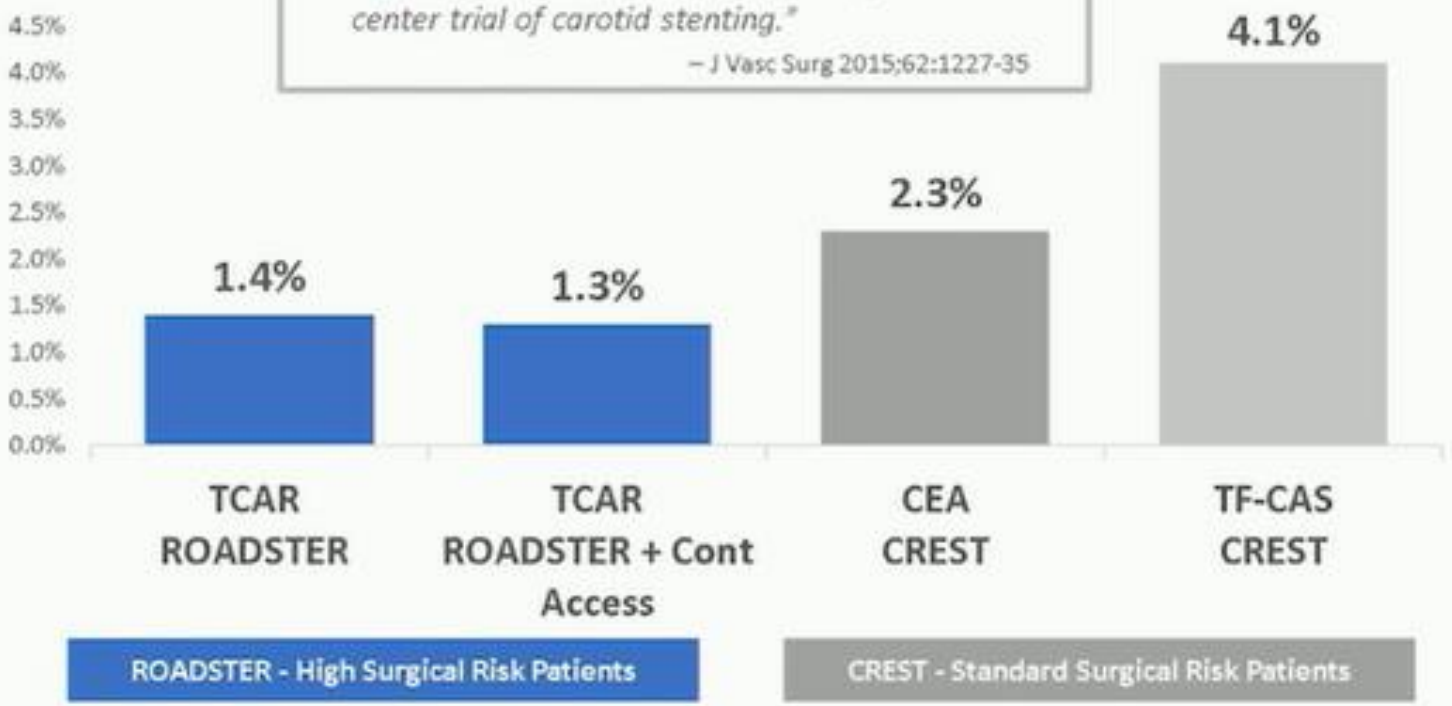
Imaging features with higher risk

Feature		Annual rate of ipsilat stroke
Silent infarction	Kakkos et al 2009	3.6%
Stenosis progression	Kakkos 2014	2%
Predominantly echolucent plaque	Gupta 2014	4%
Low GSM plaque/part of plaque	Kakkos 2015	5%
Large plaque area	Nicolaides 2010	4.6%
> 3 micro ulcers on plaque	Madani 2011	6%
MRI intraplaque hemorrhage	Singh 2009	OR 3.6
Emboli on TCD	Markus 2010	OR 6.6
Emboli + dark plaque	Topikain 2011	8.9%
Impaired cerebrovascular reserve	Gupta 2012	OR 3.9

Naylor, Schroeder & Sillesen, EJVES 2015

ROADSTER 1:
30 Day Stroke Outcomes vs Standard Risk in CREST

> *"The overall **stroke rate** of **1.4% is the lowest reported to date** for any prospective, multi-center trial of carotid stenting."*
> – J Vasc Surg 2015;62:1227-35



CREST Trial: N Engl J Med 2010;363:11-23

Which by CEA, which by CAS

- Type / Vulnerability of the plaque & Rate of stenosis
- Age and comorbidities (cardiac / renal)
- Anatomical complexity
- **Operative risks**

Severity of Asymptomatic Carotid Stenosis and Risk of Ipsilateral Hemispheric Ischaemic Events: Results from the ACSRS Study

A.N. Nicolaides,[1-4*] S.K. Kakkos,[1] M. Griffin,[1] M. Sabetai,[1] S. Dhanjil,[1] T. Tegos,[1] D.J. Thomas,[2] A. Giannoukas,[1] G. Geroulakos,[1-3] N. Georgiou,[4] S. Francis,[1] E. Ioannidou,[4] C.J. Doré[5] and For the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group

Objectives. *This study determines the risk of ipsilateral ischaemic neurological events in relation to the degree of asymptomatic carotid stenosis and other risk factors.*

Results. *The relationship between ICA stenosis and event rate is linear when stenosis is expressed by the ECST method, but S-shaped if expres… CI 1.21–2.15), history of contralate… % CI 1.23–3.65) were independent r… (7.3% annual event rate and 4.3%… stroke rate).*

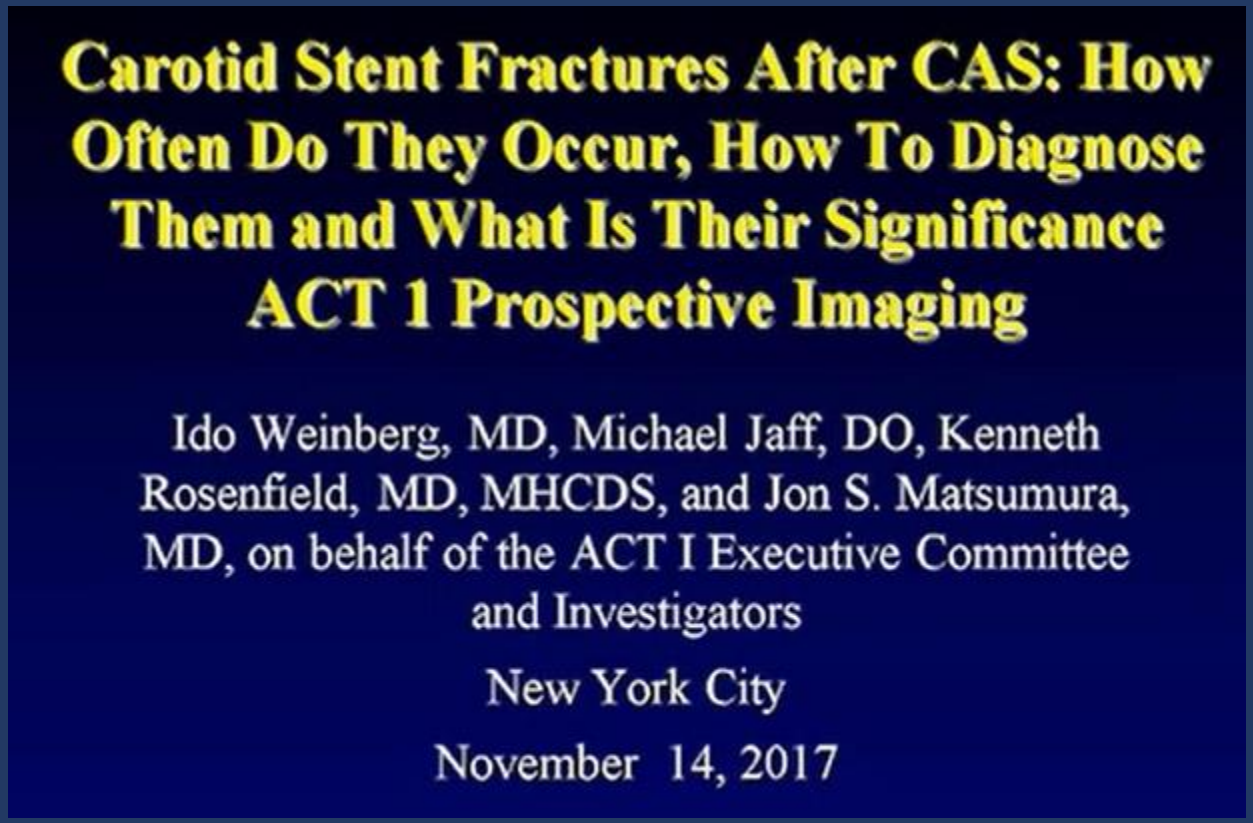
-3 risk factors:

- -ECST grade of stenosis
- -Hx of contralateral TIAs
- -Serum creatinine

-The combination of these three risk factors can identify a high-risk group (7.3% annual event rate and 4.3% annual stroke rate) and a low risk group (2.3% annual event rate and 0.7% annual stroke rate).

Eur J Vasc Endovasc Surg 30, 275–284 (2005)

Published in Circulation

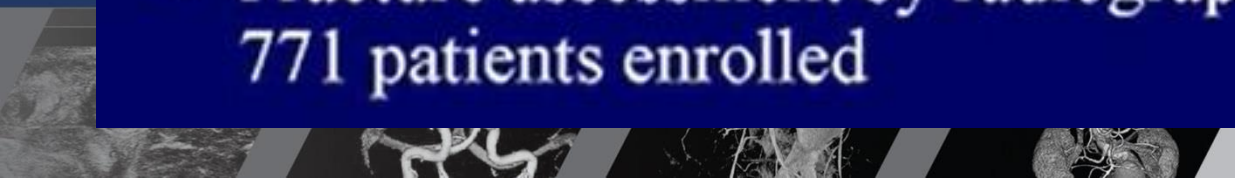


ACT 1
Study Design

- Prospective, randomized trial of asymptomatic, non-octogenarian patients (3:1 CAS:CEA)
- Strict investigator criteria by SMC and IMC
- Lead-in enrollment of up to 400 subjects with Xact® and Emboshield®, Abbott Vascular
- Prescribed contemporary medical therapy guidelines for all patients

1453 consented and enrolled subjects between March, 2005 and January 2013

- Fracture assessment by radiography added after 771 patients enrolled



How often do stent fx occur?

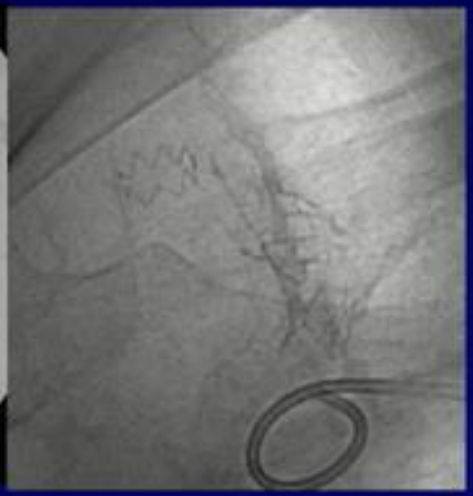
Table 3: Summary of Stent Fracture Related Data in Retrospective Series*				
Reference	**Number of Stents**	**X-ray Timing**	**Fracture Rate (%)**	**Comments**
Coppi G. [23]	323	12 months	3.4	Stent fractures were not associated with adverse outcomes
Eskandari MK [9]	73	N/A	5.5	X-ray protocol was not defined
Garcia-Toca M [16]	106	32 months	7.6	6/8 stent fractures were in arteries exhibiting dense calcifications; stent fractures were not associated with adverse outcomes
Chang CK [18]	116	4 years	4.0	Stent fractures were associated with dense calcifications; stent fractures were not associated with adverse outcomes
Ling AJ [24]	48	15 months	29.0	3/14 fractured stents also developed in-stent restenosis; X-ray protocol was not defined
* Case reports are not displayed in this table				

How to Diagnose Stent Fracture?

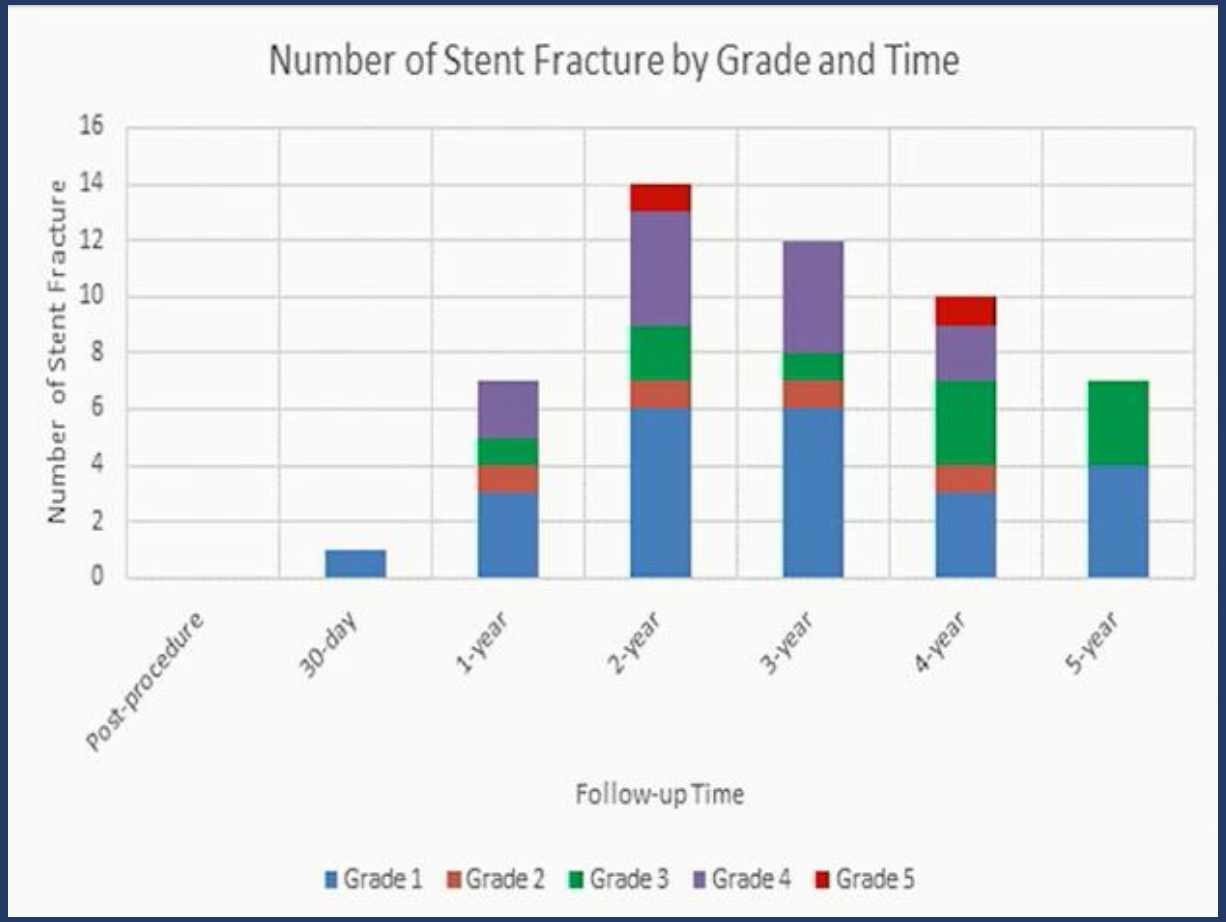
1) Routine imaging—corelab adjudication

2) Ultrasound surveillance detects restenosis or clinical symptoms develop

Angiogram performed and stent fracture identified



Peaks yrs 2-3 and does not increase w time



Summary
What is Their Significance?

In the largest study of radiographic carotid stent assessment:

Fractures are uncommon (<6%)

Not associated with stroke

Not associated with restenosis

Not associated with retreatment

Routine radiographic surveillance is not indicated with this closed cell nitinol stent

Benefit conferred by CEA (CAS)

30-day risk ACAS 2.3% ACST 2.8%	stroke rate CEA	stroke rate BMT	Number of strokes prevented per 1000 CEAs	Unnecessary interventions at 5 years per 1000 ops
ACAS 5y	5.1%	11.0%	59@5yrs	941/1000 94%
ACST 5y	6.4%	11.8%	53@5yrs	947/1000 95%
ACST 10y	13.4%	17.9%	46@10yrs	954/1000 95%

AR Naylor Nature Rev Cardiol 2012

Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS)

N=1115

- Hx of contralateral sxs
- % Stenosis
- Plaque composition by duplex

Parameter	Annual risk of ipsilateral stroke (%)
History of contralateral TIA	
Yes	3.4
No	1.2
Stenosis (%)†	
50-69	0.8
70-89	1.4
90-99	2.4
Plaque type‡	
4	0.4
3	0.8
1 and 2	3.0
Plaque area (mm²)‖	
<40	1.0
40-80	1.4
>80	4.6
Aorta luminal black area (mm²)¶	
<4	0.4
4-8	1.4
8-10	3.2
>10	5.0
Gray-Scale Median#	
>30	0.6
15-30	1.6
<15	3.6

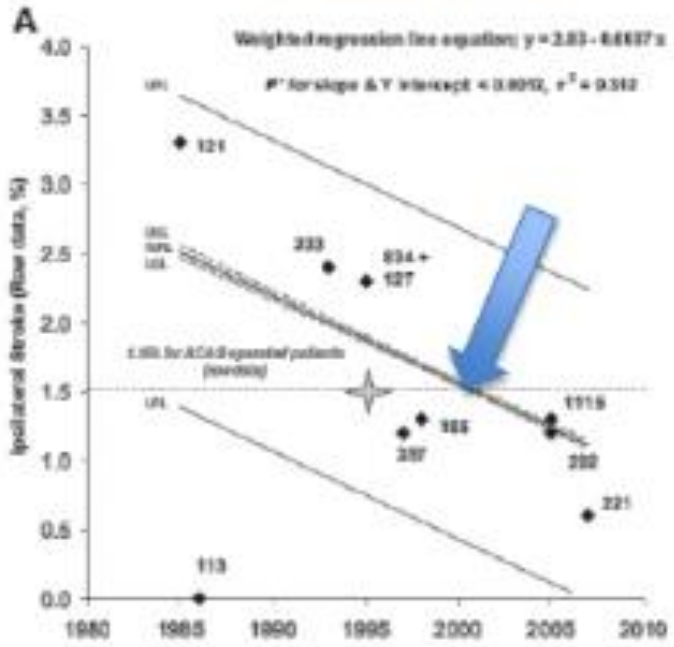
*Nicolaides AN, Kakkos SK, Kyriacou E, Griffin M, Sabetai M, et al; Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group. Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification. J Vasc Surg. 2010;52:1486-1496.e1-5.

†Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Cardiology, Naylor AR. Time to rethink management strategies in asymptomatic carotid artery disease. 2011 Oct 11;9(2):116-24. Copyright 2011.

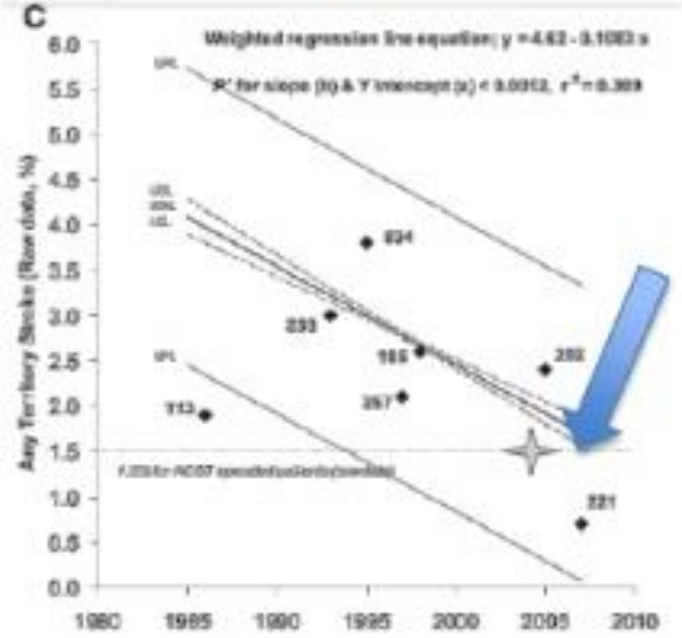
Annals of Internal Medicine | Beth Israel Deaconess Medical Center

What is the risk of stroke in Asymptomatic Carotid Stenosis?

ipsilateral stroke



any stroke



Abbott AL. Medical intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis. Stroke 2009;40:573-583

How to predict procedural stroke risk with CEA for asymptomatic carotid stenosis?

What percentage of such patients should undergo CEA or CAS?

Pooled Analysis of VA, ACAS, ACST-1 & GALA Trials

Dylan MORRIS, Hongchao PAN, Alison HALLIDAY, Richard BULBULIA
On behalf of the VA, ACAS, ACST-1 and GALA Collaborators

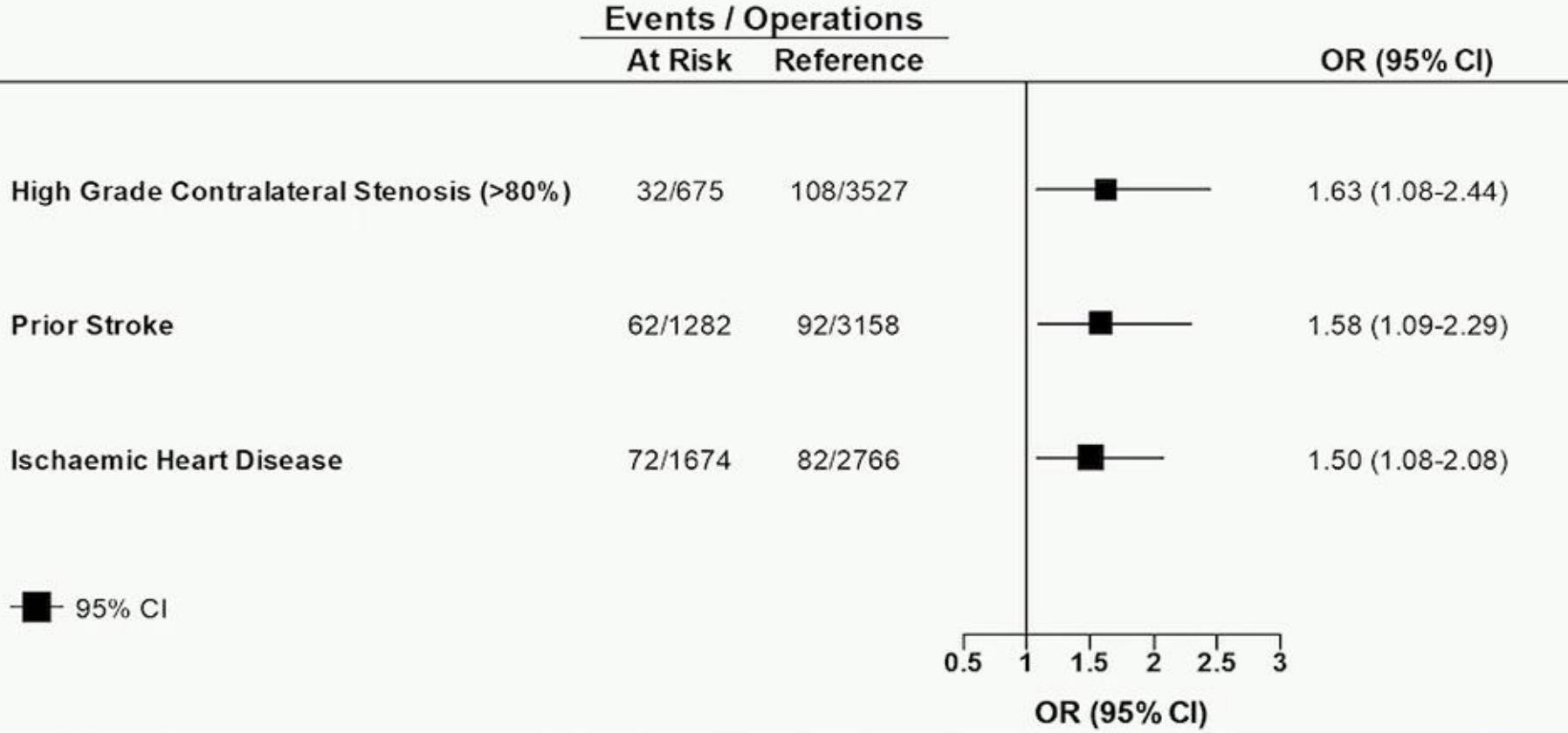
MRC Population Health Research Unit
Clinical Trial Service Unit & Epidemiological Studies Unit
University of Oxford

Types of Events

Event Type*	Number	Percent
Stroke	111	72.1%
MI	34	22.1%
Death	9	5.8%
Any Event	154	100%

*Note. If multiple events, stroke taken as main event

Important Risk Factors for Procedural MI, Stroke & Death (day 0-30)



Number of Risk Factors and Procedural Risk

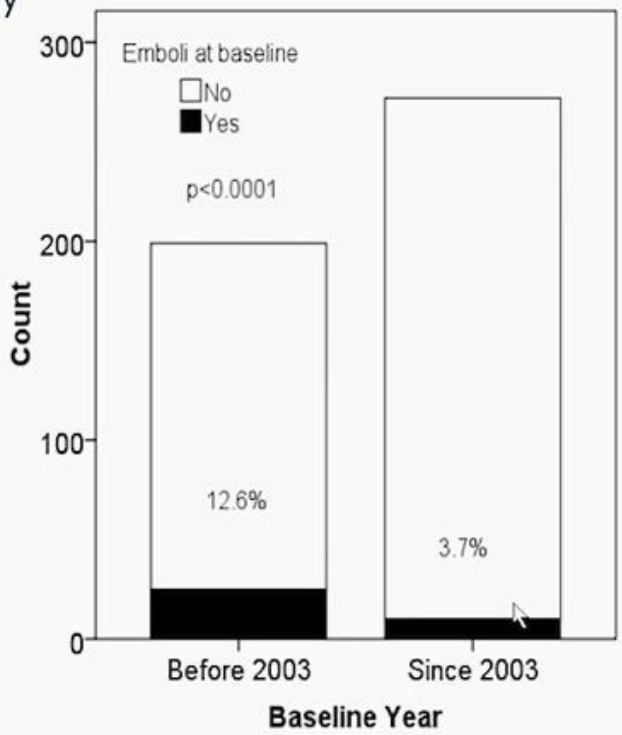
Number of Risk Factors	Events / Operations	Procedural Risk	OR (95% CI)
None	40 / 1819	2.2%	1.0 (0.73-1.37)
O			35)
T			0)
I			

Conclusion

<u>Simple characteristics</u> (contralateral stenosis, prior stroke, IHD) may identify asymptomatic patients with <u>higher risk of procedural complications</u>, thereby aiding selection

<5% benefit

Decline of microemboli with more intensive medical therapy



Probably the result of plaque stabilization

So < 5% can now benefit on the basis of microemboli

Spence JD et al. Arch Neurol. 2010;67:180-6

Asymptomatic Disease—Consensus Guidelines

- Class 1--Selection of asymptomatic patients for carotid revascularization 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 C)
- Class IIa--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 (Level A)
- Class IIb--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 (Level B)

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      - Fourth level
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ECST-2 Progress

- 32 centres enrolled
- 285 patients randomised to 15 Nov 2017
  - Number needed for MRI-based study=320 with 2 years follow-up
- 110 included with MR plaque imaging
  - Number needed for MR plaque imaging analysis=244 with 2 years follow-up
- New centres needed
- Please contact us on office@ecst2.com or via the website www.ecst2.com

- Click to edit Master text styles
  - Second level
    - Third level
      - Fourth level
        - » Fifth level

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 ... ociety of NeuroInte...

Developed ... Computed ...

	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: A
Stenting	Class I LOE: B	Class I LOE: B	Class IIb LOE: B

J Am Coll Cardiol 2011;57

Conclusion

Simple characteristics (contralateral stenosis, prior stroke, IHD)

may identify asymptomatic patients

with higher risk of procedural complications,

thereby aiding selection

Recent (post CREST) guidelines clearly show the need for ACST-2

AHA Carotid Disease Management Guidelines (2011)

It is *reasonable to perform CEA* in asymptomatic patients who have > 70% stenosis (Evidence Level: A)

Prophylactic *CAS might be considered* in highly selected patients with asymptomatic carotid stenosis (Evidence Level: B)

Society for Vascular Surgery Carotid Guidelines (2011)

Asymptomatic > 60% stenosis *should be considered for CEA* (Evidence Level: A)

CAS should not be performed except as part of an on-going clinical trial (Evidence Level: B)

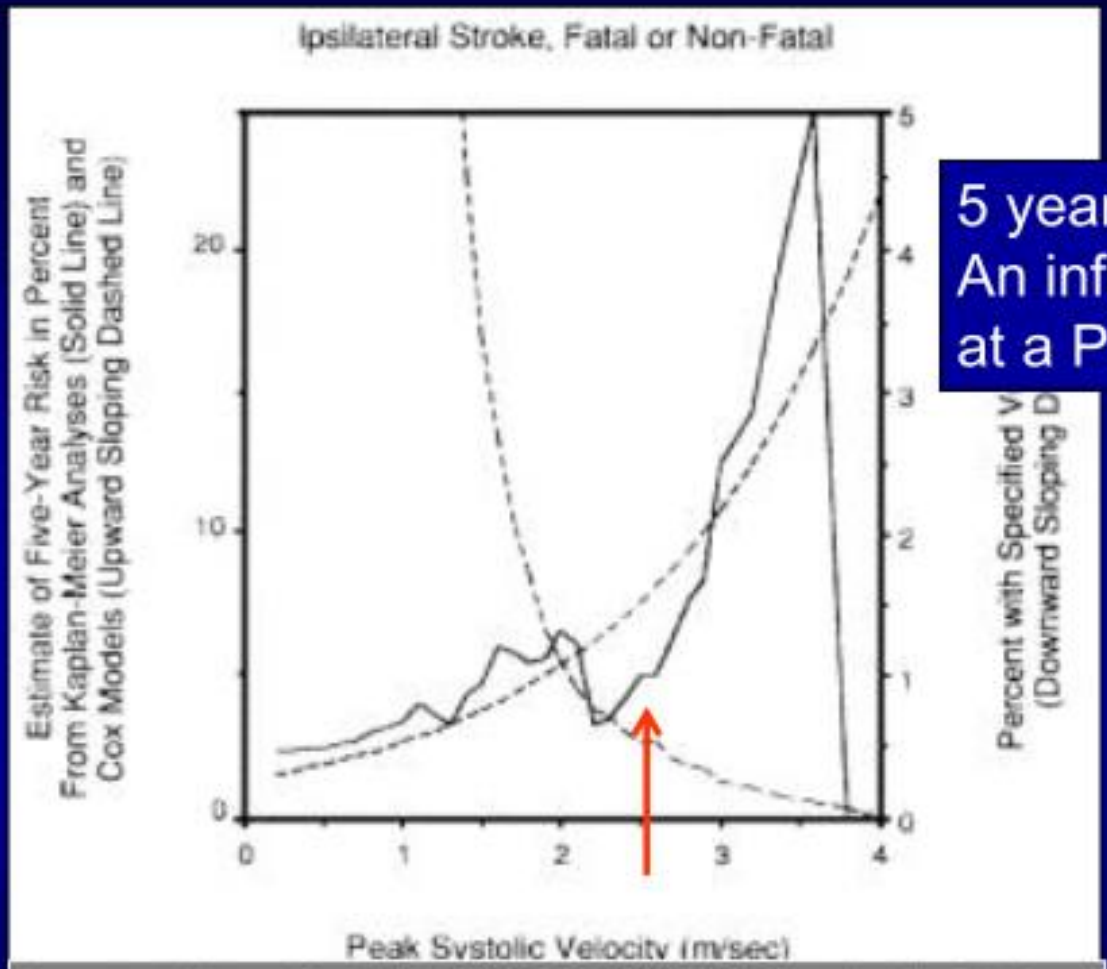
NICE Carotid Intervention Guidelines (2011)

"NICE encourages clinicians *either to enter patients into the ACST-2 trial*, or to submit data to the Endovascular Carotid Register"

RCP Stroke Guidelines (2012)

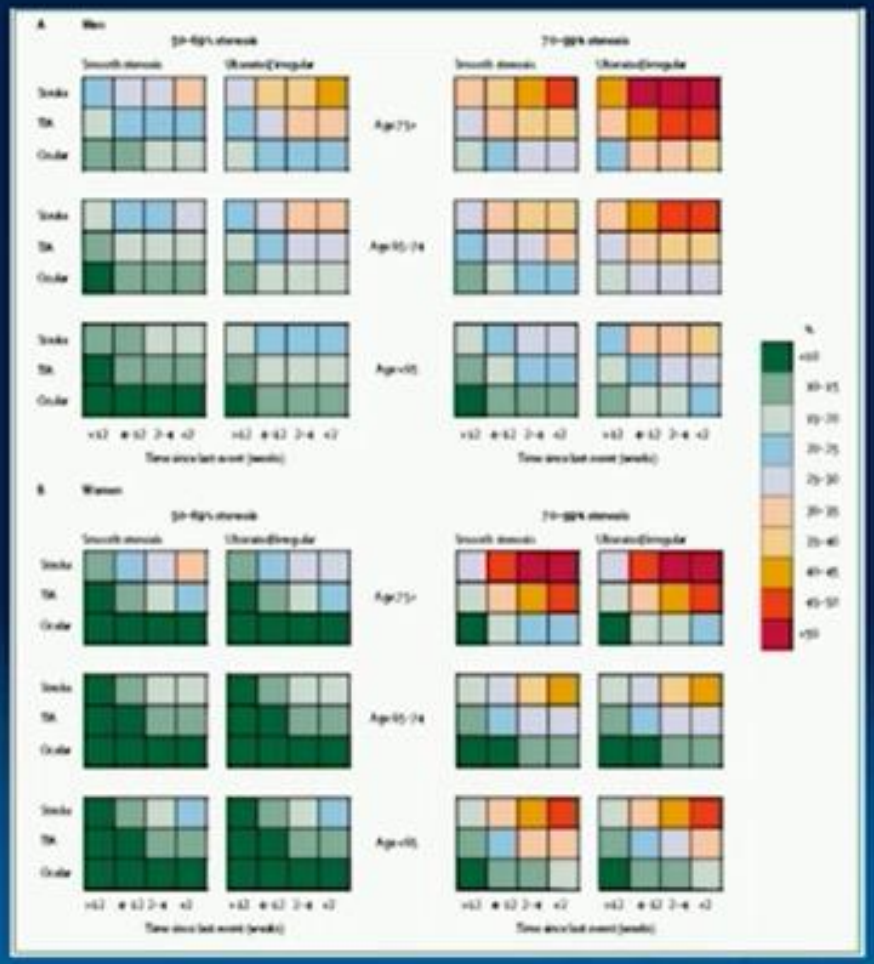
Surgery or stenting (CEA or CAS) for asymptomatic carotid artery stenosis should not routinely be performed unless as part of a randomised trial.

Where Do We Draw the Line?



5 year risk of stroke
An inflection point
at a PSV >250

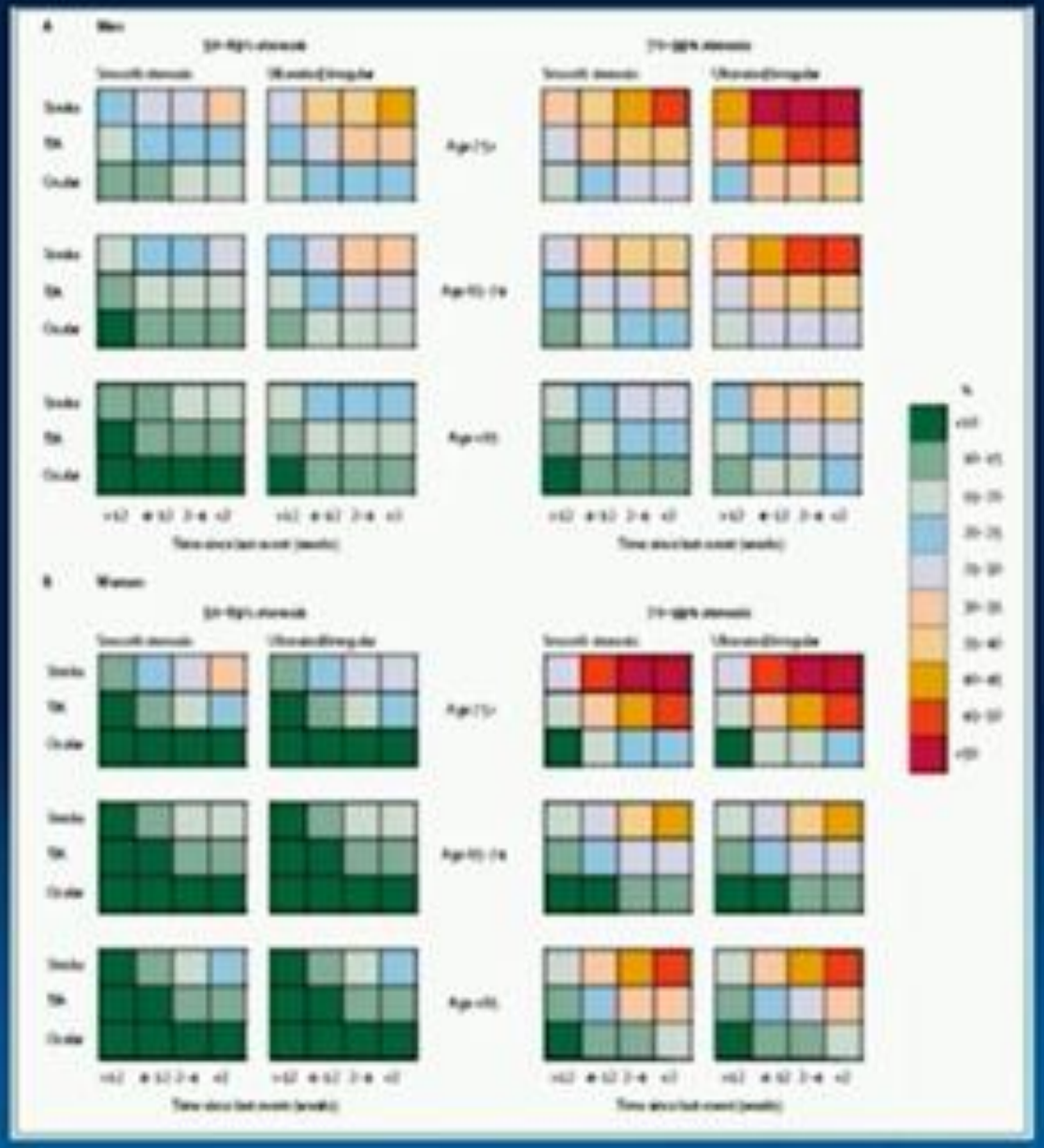
Asymptomatic Internal Carotid Artery Stenosis Defined by Ultrasound and the Risk of Subsequent Stroke in the Elderly: The Cardiovascular Health Study.
Longstreth et al Stroke. 29(11):2371-2376, November 1998.



CAR Score*

- <5%
- 5-7%
- 8-10%
- 10-12%
- 13-15%
- 15-17%
- 18-20%
- 20-22%
- 23-25%
- >25%

*Recalibrated to take account of OMT



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- 13-15%
- 15-17%
- 18-20%
- 20-22%
- 23-25%
- >25%

*Recalibrated to take account of OMT

~ 85-90% of patients are better off with intensive medical therapy

Endarterectomy or stenting should not be done without evidence of high risk:

- Microemboli
- 3 or more Ulcers
- Reduced CBF reserve

In future, imaging of vulnerable plaques

…the longer term results : Lancet (*2014*)

4 year follow up

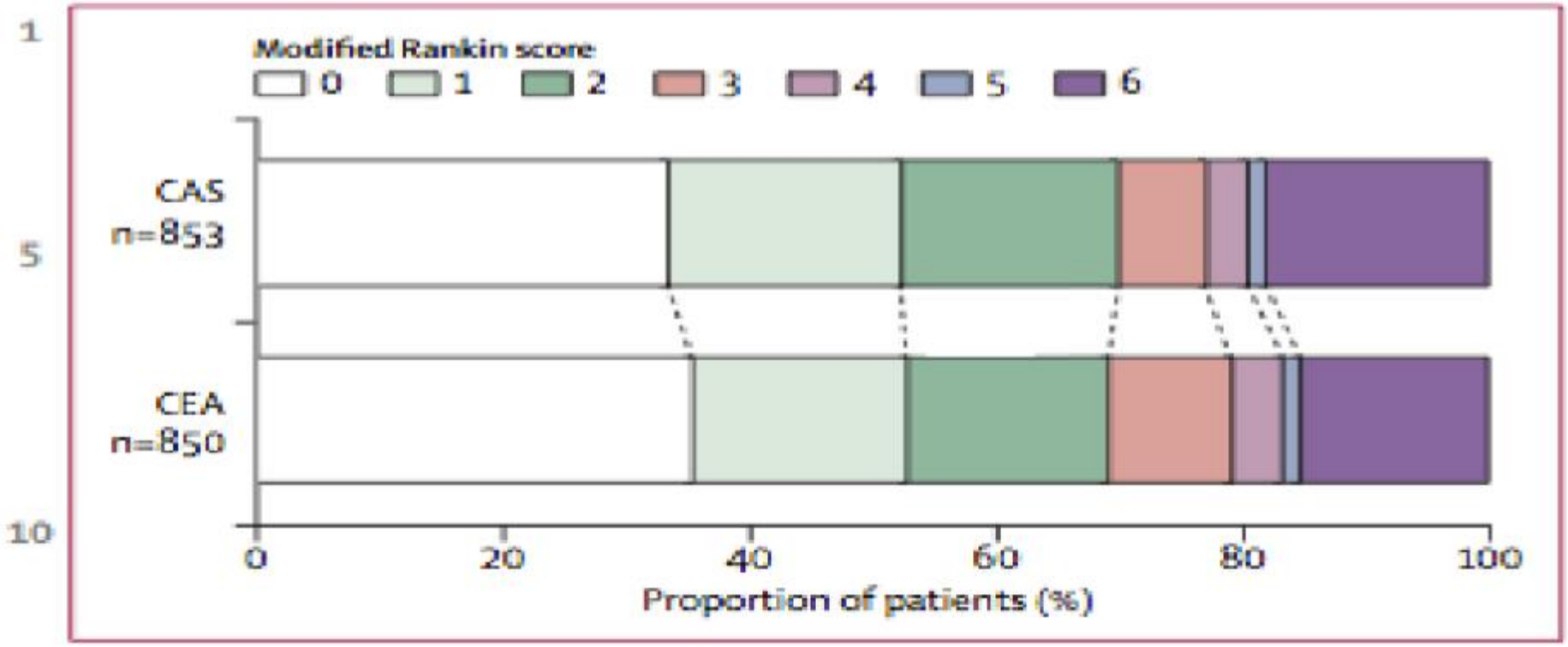


Figure 3: Functional ability measured by the modified Rankin Scale at the end of follow-up*

Medical Management

- CEA Trial: aspirin 325mg/d
- CAS Trial: dual antiplatelet therapy for ≥1 month post-procedure; then aspirin
- Both Trials: statin (PCSK9 inhibitors as needed)

Primary Risk Factor Targets

- Systolic BP <140 mm Hg
- LDL cholesterol <70 mg/dl

Secondary Risk Factor Targets

- Non-HDL cholesterol <100 mg/dl
- Hemoglobin A1c <7.0%
- Smoking cessation
- Targeted weight management
- >30 minutes of moderate exercise 3 times a week

ACST-2 and modern medical therapy At Trial Entry

85% lipid-lowering drugs

88% anti-hypertensive therapy

98% anti-thrombotic (anti-platelet / anti-coagulant)

Compliance remains good long-term

ACST-2: Blinded Procedural hazards 1500 patients (≤ 30 days)

Disabling/fatal stroke or fatal MI
much lower than in symptomatic trials

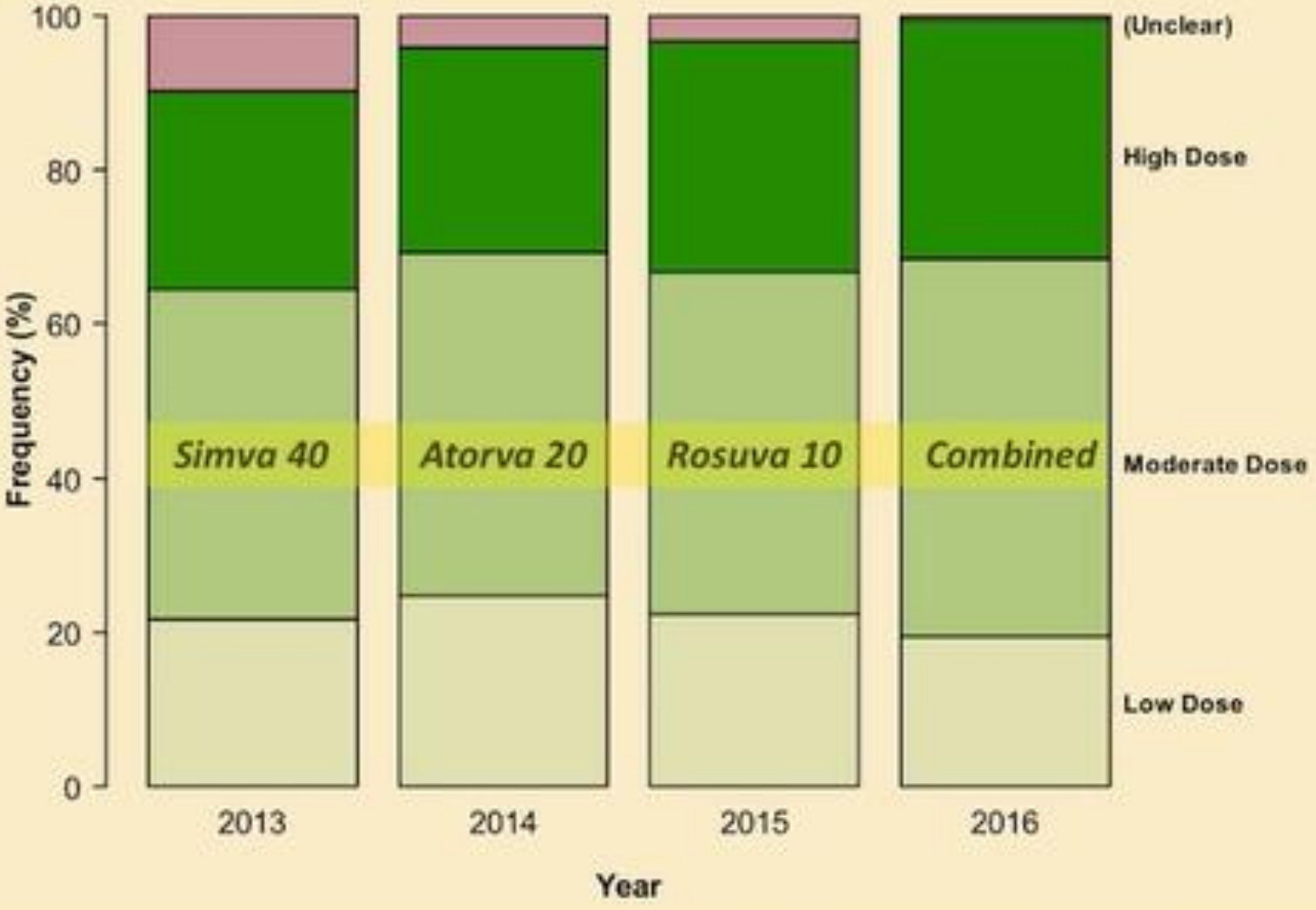
Lower than ACST-1 (CEA) 1.7%

Despite increasing age, and more risk factors for stroke compared with ACST-1;

ACST-2 procedural risk (CEA and CAS)

1.0%

>75% on good (or very good) statin regimens



Event Rates in Patients With ASX Carotid Artery Stenosis Managed Without Revascularization

ACAS 1995	**1662**	**ASX**	**>60%**	**5 yrs**	**ASA**	**Ipsi stroke or death**	**11% or 2.2% / yr**
ACST 1994	3120	ASX	>60%	5 yrs	ASA	Any stroke	11.8% or 2.4% / yr
VA 1993	444	ASX	>50%	4 yrs	ASA	Ipsi stroke	9.4% or 2.4% / yr
Abbott 2005	**202**	**ASX**	**60-90%**	**34 m**	**multiple**	**cva / tia**	**3% or 1% / yr**
Goessens 2007	2684	ASX	>50%	3.6 yrs	Multiple	cva / death	Death 2.5%, cva .54%

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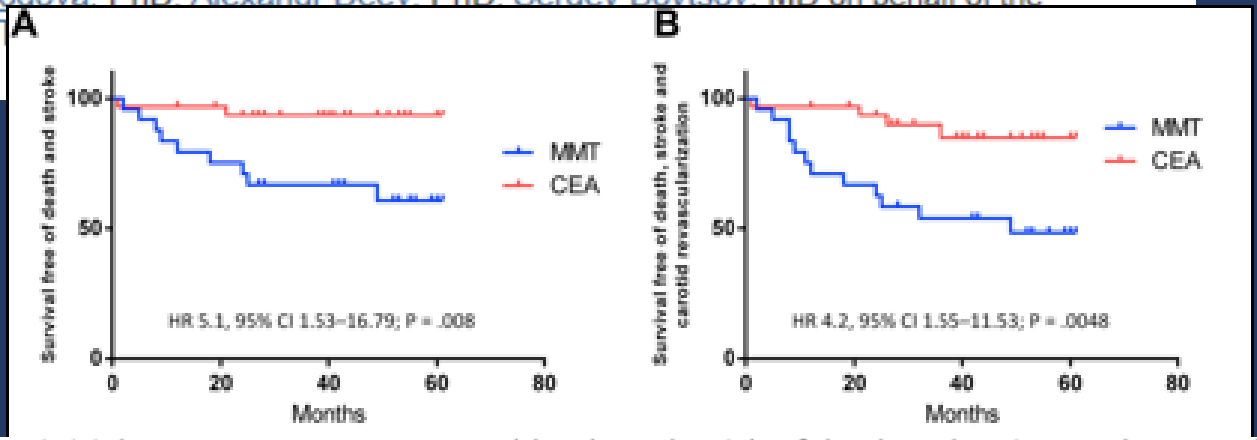
Modern medical treatment with or without carotid endarterectomy for severe asymptomatic carotid atherosclerosis

JVS

October 2015 Volume 62, Issue 4, Pages 914–922

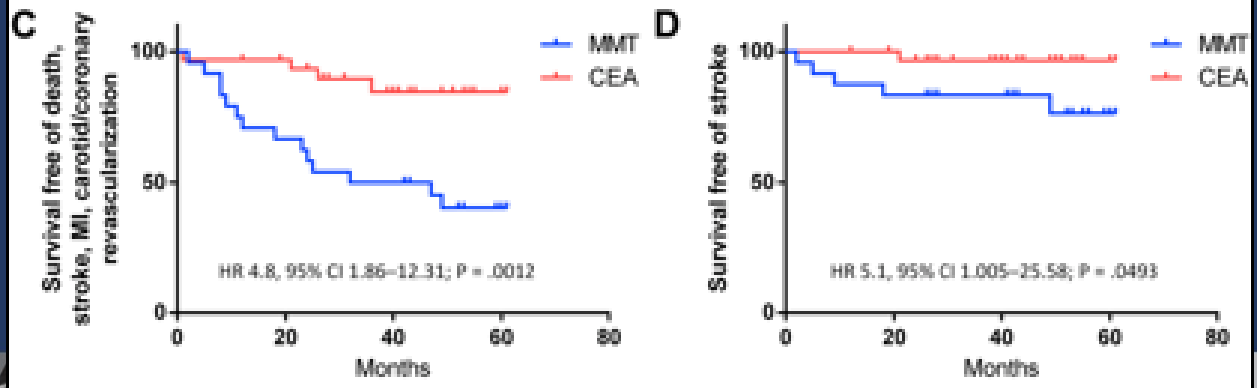
Igor Kolos, PhD, Alexandr Troitskiy, MD, Tatiana Balakhonova, MD, Merab Shariya, PhD, Denis Skrypnik, Tatiana Tvorogova, PhD, Alexandr Deev, PhD, Sergey Boytsov, MD on behalf of the Aggressive Medical T... Group



Conclusions: CEA as an initial management strategy could reduce the risk of death and major cerebrovascular events when added to MMT. (J Vasc Surg 2015;62:914-22.)

MMT	31	25	23	22
CEA	24	22	22	22

MMT	31	23	20	19
CEA	24	22	20	20



No. at Risk	Baseline	20 months	40 months	60 months
MMT	31	23	19	17
CEA	24	22	20	20

No. at Risk	Baseline	20 months	40 months	60 months
MMT	31	27	27	26
CEA	24	23	23	23

Texture-based classification of atherosclerotic carotid plaques

Coars.=21.6, Entropy=0.421, Median=22.0	Coars.=12.0, Entropy=0.326, Median=25.5

NIHR HTA/BUPA Foundation/University of Oxford

Asymptomatic Carotid Surgery Trial (ACST-2)

The Asymptomatic Carotid Surgery Trial-2 (ACST-2): an ongoing randomised controlled trial comparing carotid endarterectomy with carotid artery stenting to prevent stroke.

Bulbulia R[1], Halliday A[2].

OBJECTIVES: The second Asymptomatic Carotid Surgery Trial (ACST-2) compares carotid endarterectomy (CEA) with carotid artery stenting (CAS) directly, randomising patients with asymptomatic carotid stenosis for whom a carotid procedure is considered definitely necessary; both procedures seem anatomically feasible, and there is substantial uncertainty as to which of the two would be better for such individuals. Although it will compare procedural risks, the trial's primary aim is to compare the long-term durability of protection against strokes occurring in the years post procedure due to any remaining or recurrent carotid disease.

DESIGN: Randomised controlled trial comparing CEA with CAS.

SETTING: Hospitals in the UK and worldwide, in which carotid procedures are common.

PARTICIPANTS: Men and women with severely stenotic atherosclerotic carotid artery disease, with or without previous stroke but with no recent symptoms from the randomised artery.

INTERVENTIONS: CEA and CAS.

OUTCOMES: (1) Periprocedural risk defined as myocardial infarction, stroke or death within 30 days after the randomised procedure and (2) long-term rates of disabling or fatal stroke during follow-up of patients.

MEASUREMENT OF COSTS AND OUTCOMES: Measurement of intervention costs and stroke costs (periprocedural and during follow-up) and of quality of life [EuroQol-5 Dimensions (EQ-5D®)] for patients in the top six recruiting countries (UK, Italy, Belgium, Germany, Serbia and Sweden), who currently constitute 85% of those randomised.

PROGRESS SO FAR: By the end of March 2016, ACST-2 had included 2125 patients, nearly two-thirds of the planned recruitment of 3600; 1061 were randomly allocated to CEA and 1064 to CAS.

CONCLUSIONS: Further funding has been secured and recruitment continues, with completion anticipated by the end of 2019. ACST-2 will report initial results in 2021.

ACST-2
Surgery vs Stenting

Asymptomatic patients with tight stenosis requiring intervention:

Which procedure is generally better (in addition to good medical treatment)?

carotid surgery (CEA)
or
carotid stenting (CAS)?

Hypothesis of the ECST-2 Trial

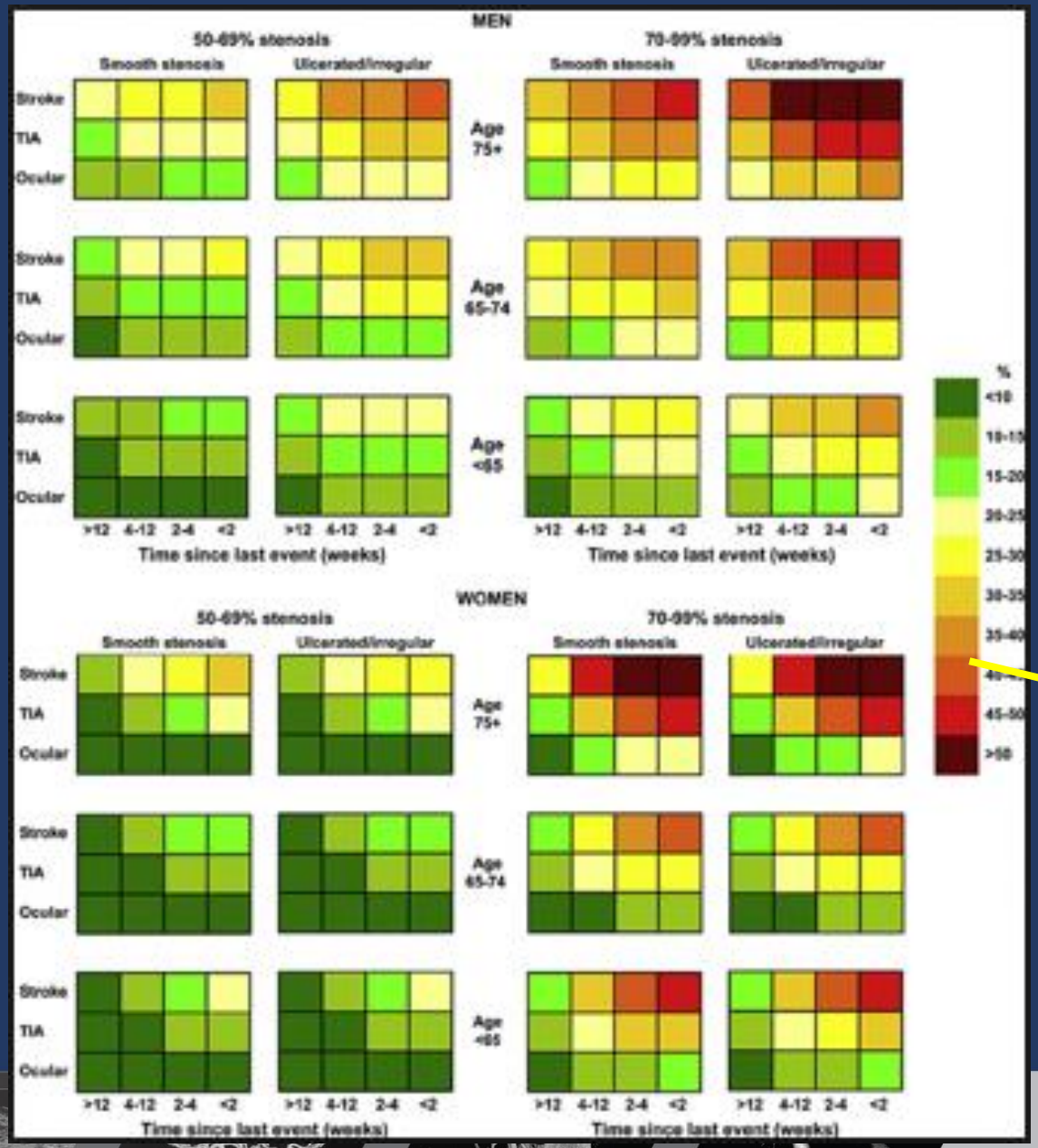
We hypothesise that the routine use of modern optimised medical treatment (OMT) in patients with carotid stenosis will halve the risk of recurrent stroke

Patients with a predicted risk of stroke in the next 5 years <20% will not benefit from intervention (CEA or CAS)

CAR Score

- Oxford Risk Prediction Tool recalibrated to include asymptomatic patients and the predicted benefit of modern optimised medical therapy

- Risk factors used to assess CAR score are:
  - Gender: male or female
  - Severity of presenting events: stroke, TIA or ocular
  - Degree of stenosis: 50-69% or 70-99%
  - Plaque morphology: smooth or ulcerated/irregular
  - Age: <65, 65-74 or >75
  - Time since last event: >12, 4-12, 2-4 or <2 weeks



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- 10-12%
- 13-15%
- 15-17%
- 18-20%
- 20-22%
- 23-25%
- >25%

*Recalibrated to take account of OMT

Which Patients With Real Carotid Disease Are at Increased Risk?

- Assume PSV 275-325cm/sec
- ≥5% annual risk
  - Gray scale median <15
  - Juxtaluminal black area >8mm^2
  - Plaque area >80mm
  - Contralateral stroke or occlusion
  - Silent cerebral emboli (CT or MRI)
  - TCD hits

Nicolaides et al. J Vasc Surg 2010;52:1486
Topakian et al. ACES Study Neurology 2011;77:751-58
Kakkos et al. J Vasc Surg 2013;57:609

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