



Stroke: Advances in Medical Therapy and Acute Stroke Intervention

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Disclosure

Relevant Financial Relationship(s)

KMB serves on the Executive Committee of the CREST-2 trial funded by the NINDS.

Off Label Usage

NONE

Objectives

- Review historical approach to stroke prevention in asymptomatic carotid stenosis
- Acknowledge current equipoise between intensive medical management and carotid revascularization for high-grade asymptomatic carotid occlusive disease
- Discuss emerging concepts in pre-hospital and remote stroke care



Case Vignette

- 67 y.o. man with history of HTN and ↑lipids seen for routine evaluation
- No history of stroke or transient neurologic deficits
- Meds: HCTZ (25mg daily), simvastatin (20mg daily), aspirin (81mg daily)
- Rare EtOH use; non-smoker

Case Vignette (cont.)

- BMI 27
- BP 140/85; P 72 regular
- Middle-pitched cervical bruit only in systole at the angle of the mandible
- Neurologic examination is normal
- Carotid duplex reveals 70-80% stenosis of the proximal RICA with irregular plaque and peak systolic velocity of 339cm/s. LICA reveals 20% stenosis

Which one of the following initial treatment options would be most appropriate for this patient?

1. Carotid endarterectomy
2. Carotid stenting
3. Medical management

Management Worldwide

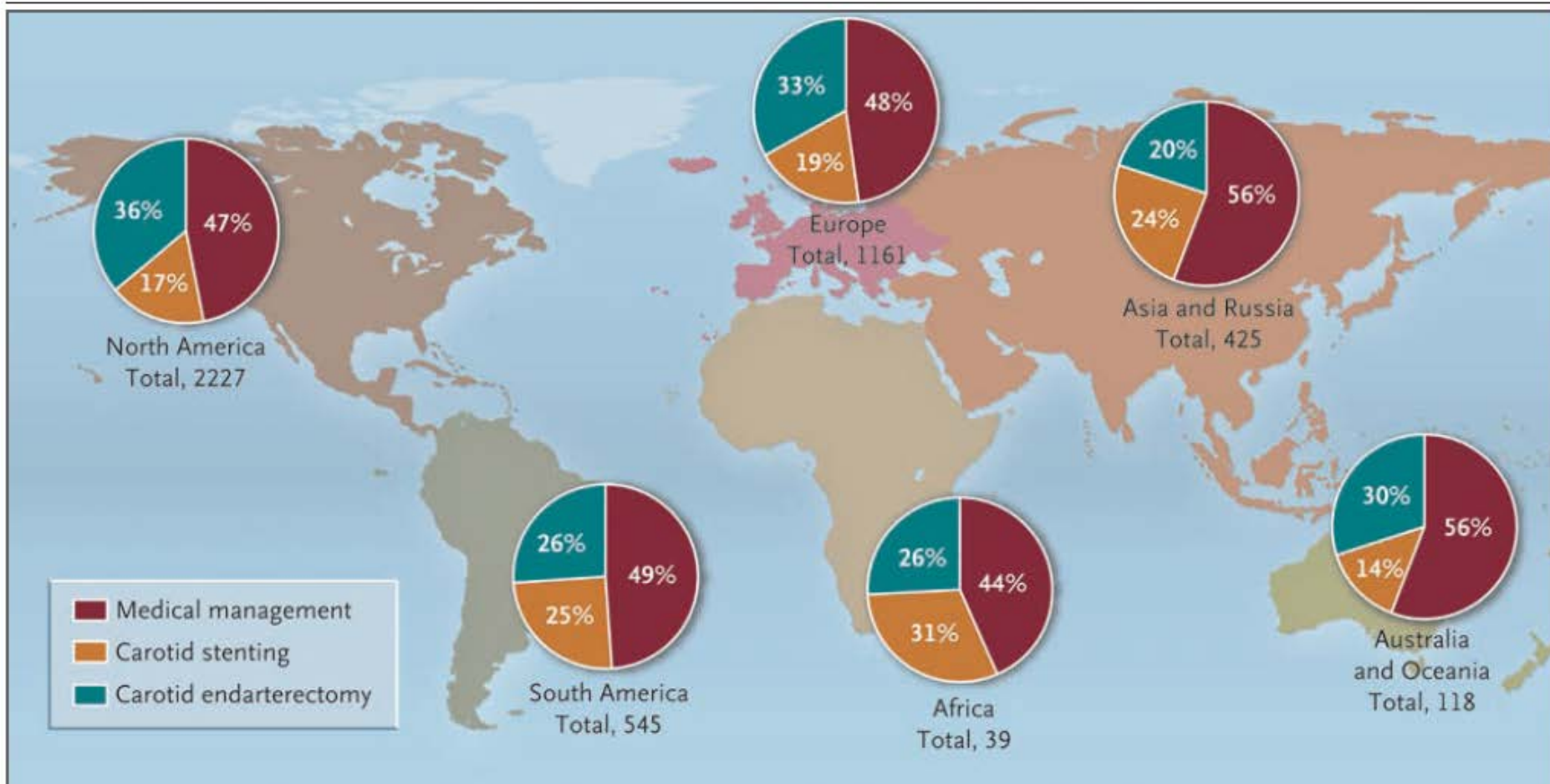
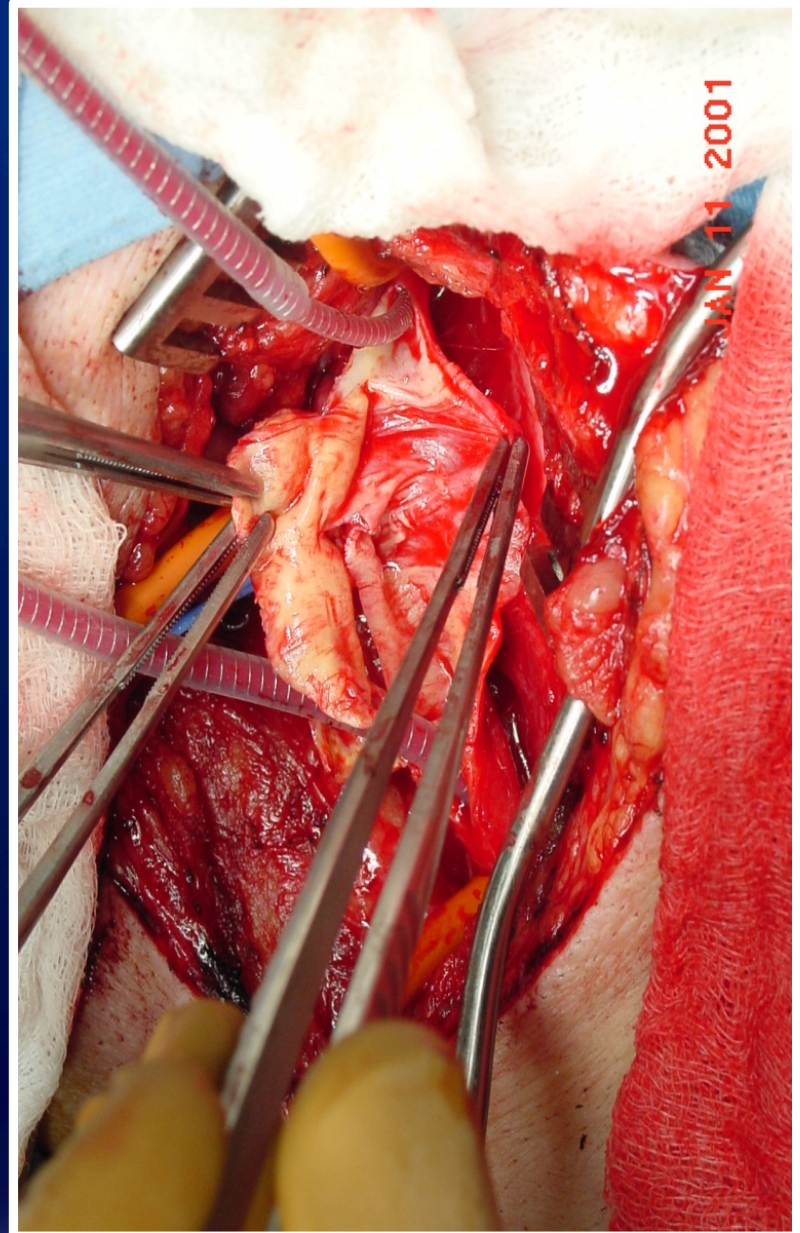
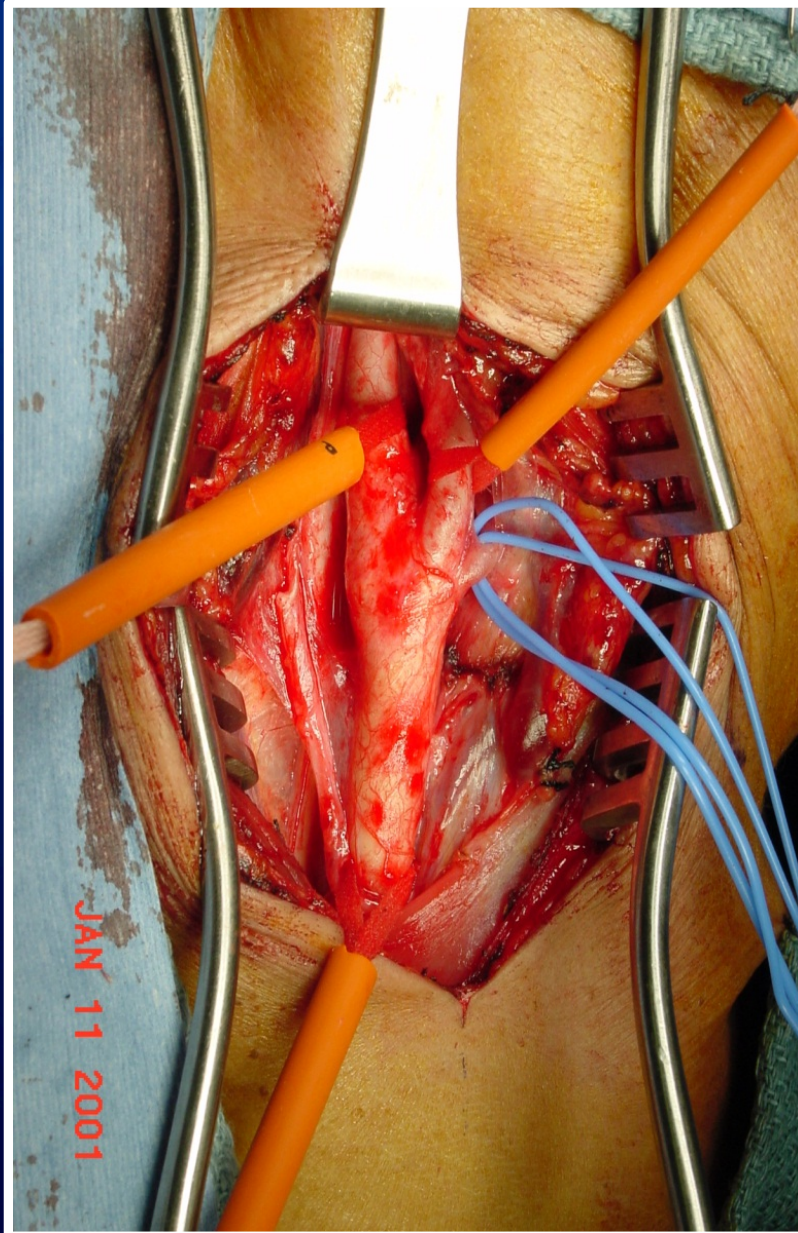


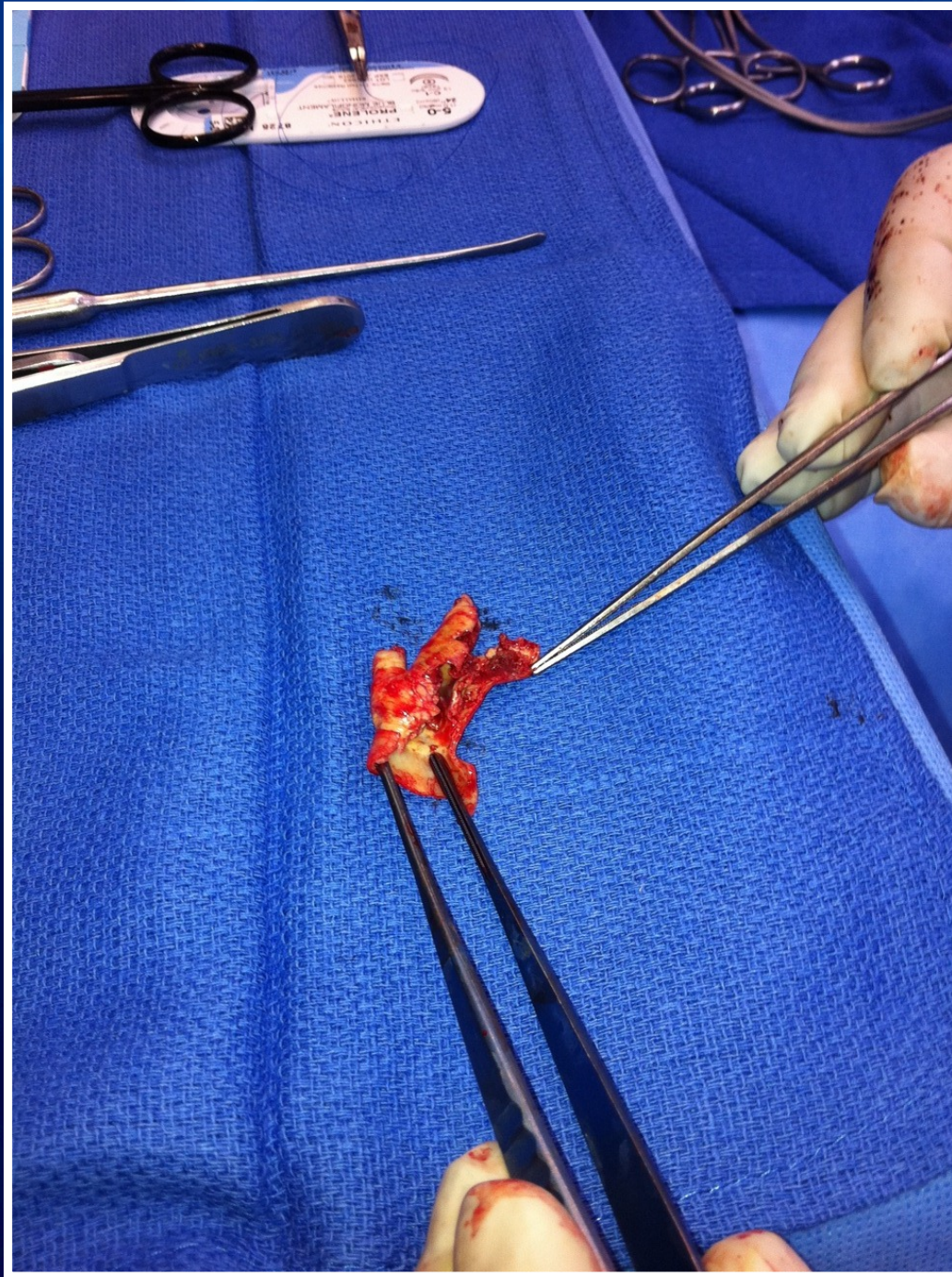
Figure 1. Percentage of Participants Choosing Each Treatment Option for the Management of Carotid Stenosis.

Carotid Disease & Stroke:

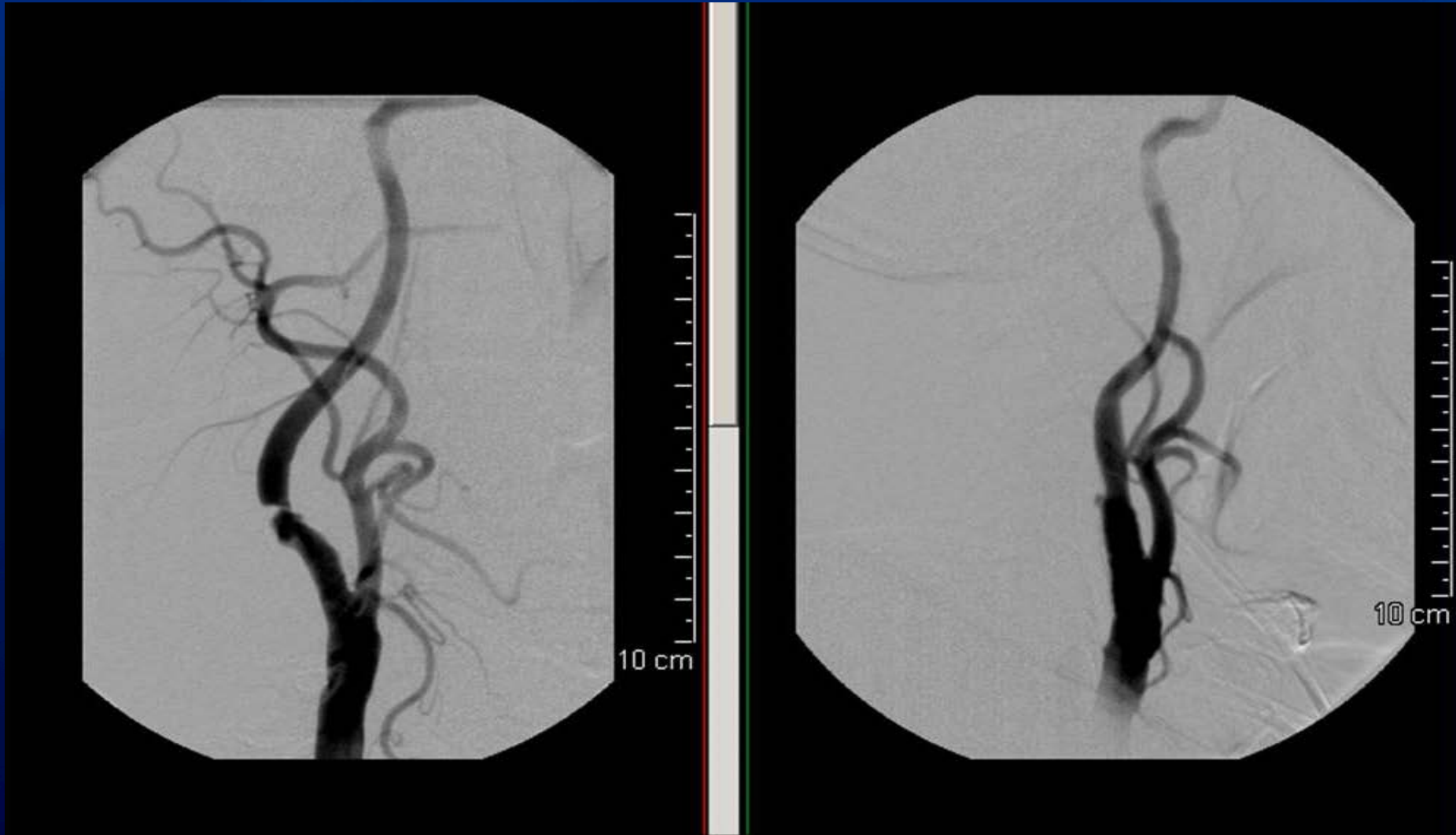
- Atherosclerotic narrowing of the extracranial internal carotid artery (ICA) is estimated to be causative in ~ 10-15% of strokes.
- ~5-10% of men and women (>65 y.o.) have carotid stenosis >50%
 - ~1% will have carotid stenosis >80%.

Carotid Endarterectomy (CEA)





Carotid Angioplasty & Stenting (CAS)



Carotid Revascularization

- ~ 140,000 carotid revascularizations yearly in the US (CEA and CAS).
- Annual US costs for CEA ~ \$21 Billion
 - CAS costs are comparable on a per case basis.



ACAS

(Asymptomatic Carotid Atherosclerosis Study)

- 1662 patients with $\geq 60\%$ stenosis
- 5-yr ipsilateral stroke rate plus any 30-day perioperative stroke or death:
 - Medical \rightarrow 11.0%
 - Surgical \rightarrow 5.1%
 - Absolute RR \rightarrow 5.9% (1.2%/yr)
- Number-needed-to-treat = 83



ACAS

- Exceedingly low perioperative complication rate (2.3%).
- Perioperative complications were higher among women than men (3.6% vs 1.7%).
- Benefits of surgery greater for men than women (66% vs 17% relative risk reduction).
- Benefit not associated with degree of stenosis

J Am Med Assoc 1995;273:1421-8

ACST

(Asymptomatic Carotid Surgery Trial)

- 3120 patients with $\geq 60\%$ stenosis
- 5-year combined risk of perioperative events and non-operative strokes:
 - Medical \rightarrow 11.8%
 - Surgical \rightarrow 6.4%
 - Absolute RR \rightarrow 5.4% (1.1%/yr)
- The ARR and NNT were almost identical to those achieved in ACAS

ACST

- Low 30-day stroke or death rate (3.1%)
- Benefit not associated with degree of stenosis
- Principal methodologic difference between ACAS and ACST was primary endpoint:
 - ACAS utilized ipsilateral stroke,
 - ACST included all strokes (ipsilateral, contralateral, and vertebrobasilar territory)

ACAS and ACST

- Results established CEA plus medical therapy as recommended treatment for selected patients with asymptomatic carotid stenosis.
- Benefit of CEA for asymptomatic carotid stenosis was highly dependent on surgical risk.



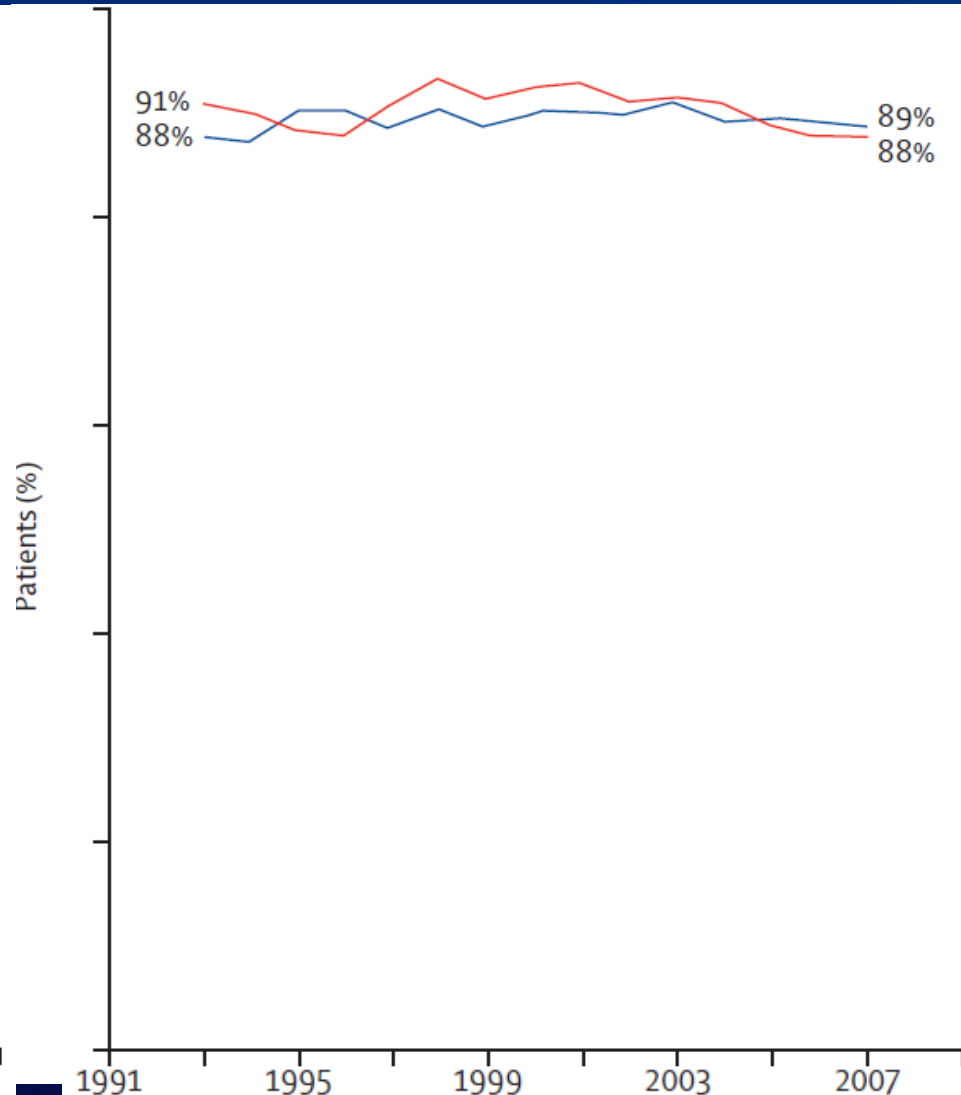
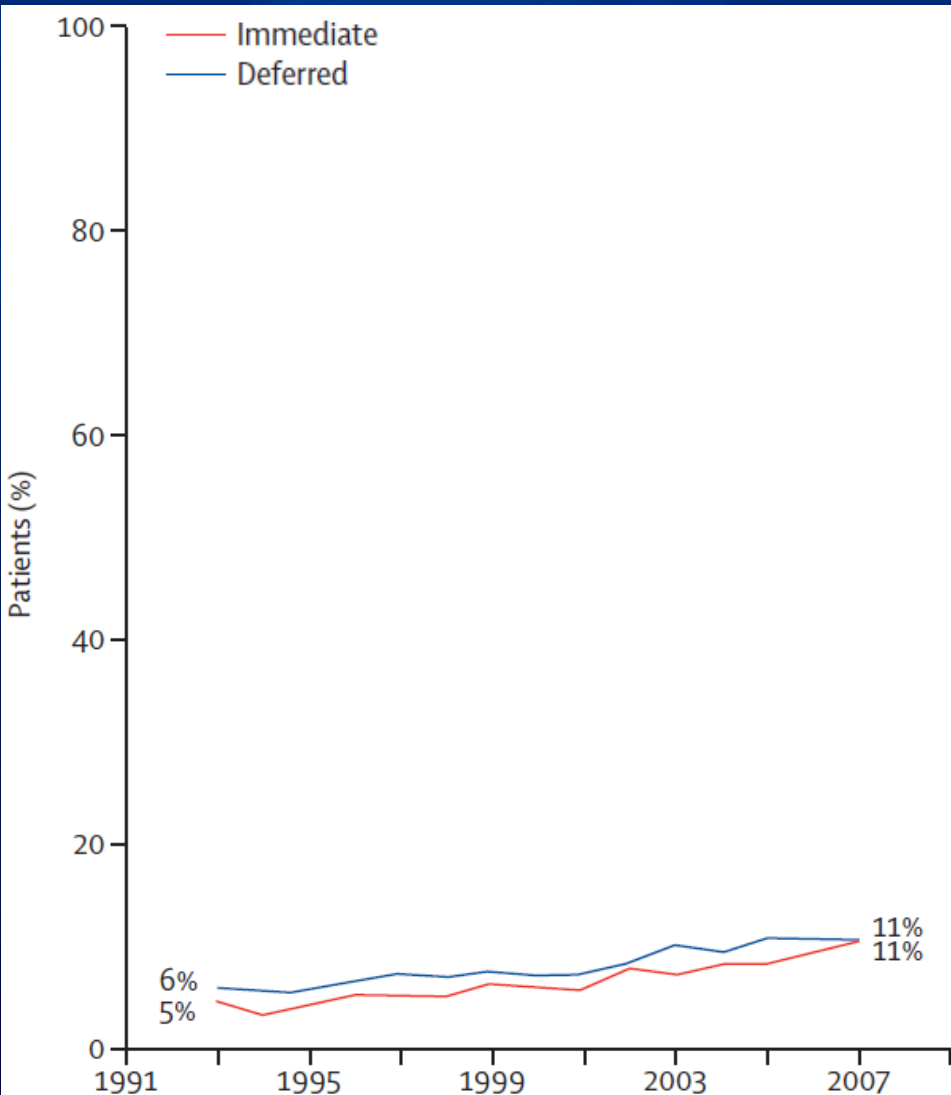
Evolution of Medical Therapy

- ACAS/VACS defined medical therapy as:
 - Aspirin
- Final ACST cohort compliance data:
 - 90% received anti-platelet
 - 81% anti-hypertensive therapy
 - 70% lipid-lowering therapy
- No data regarding degree of success

Medical Management in ACST

Anticoagulant drug use

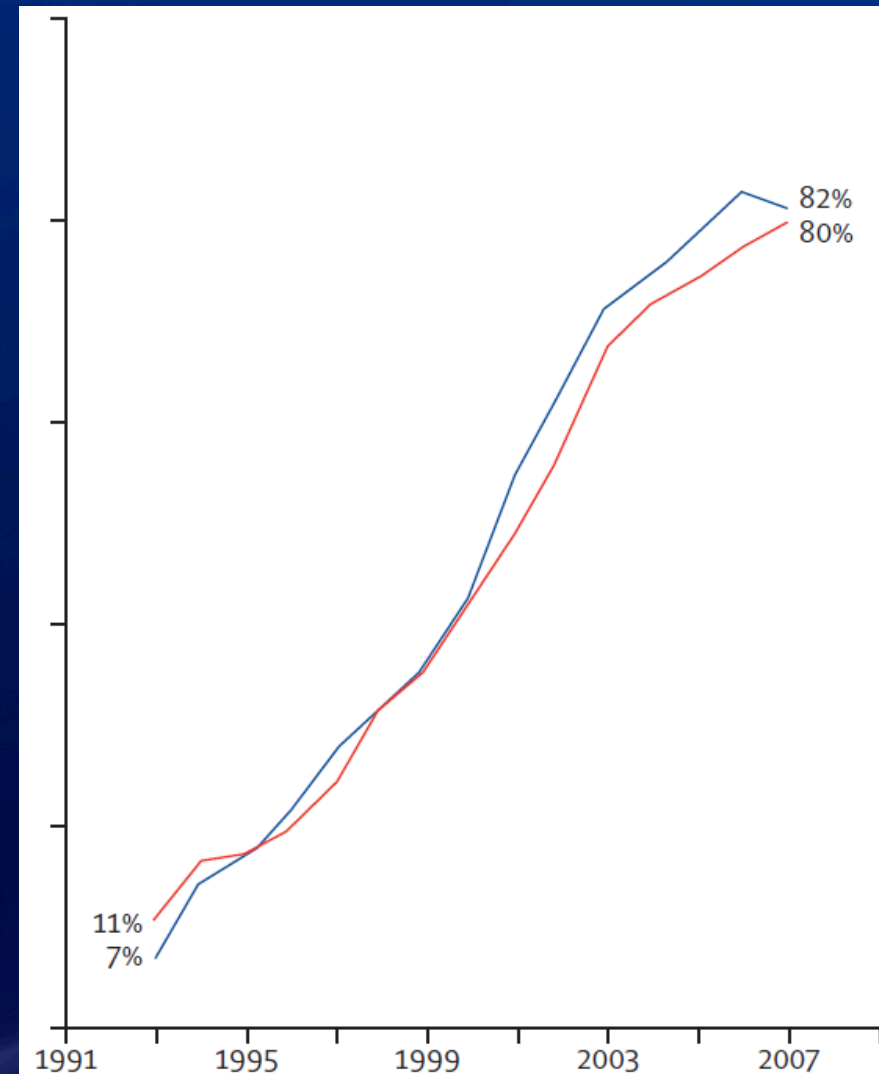
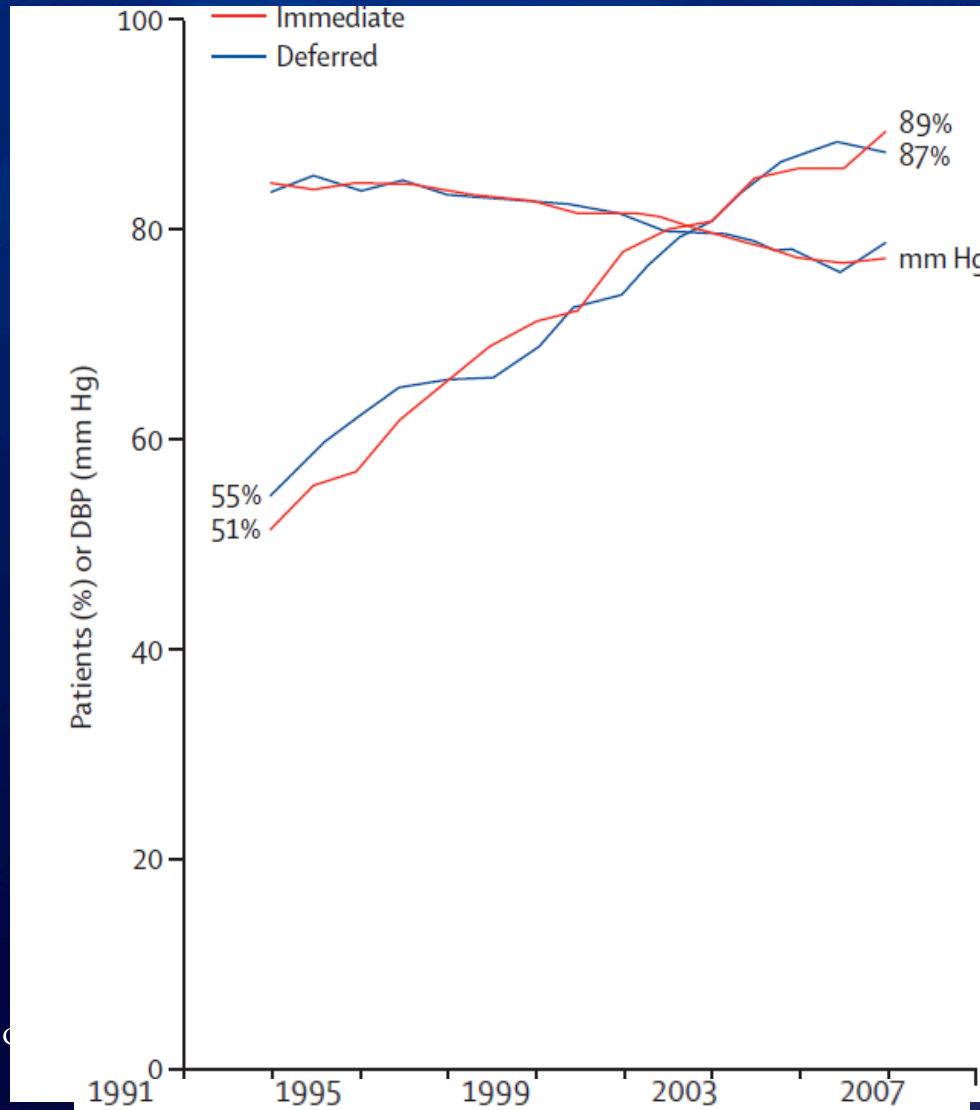
Antiplatelet drug use



Medical Management in ACST

Antihypertensive drug use & mean DBP

Lipid-lowering drug use




Evolution of Medical Therapy

- Interval release of guidelines demonstrating the benefit of stringent risk factor control for reducing cardiovascular outcomes
- SAMMPRIS demonstrated that event rates could be significantly reduced in patients with intracranial atherosclerosis using protocol-driven intensive medical therapy:

	<u>30d</u>	<u>1y</u>
• WASID	10%	25%
• SAMMPRIS	6%	8%

Modern Concept of Medical Therapy

- Synergistic approach including:
 - Anti-platelet treatment
 - Blood pressure control
 - Statins for hyperlipidemia
 - Glycemic control for diabetes
 - Lifestyle interventions to reduce tobacco use, obesity, and increase physical activity



Low Risk of Ipsilateral Stroke in Patients With Asymptomatic Carotid Stenosis on Best Medical Therapy

- Population-based Oxford Vascular Study
- Of 1155 consecutively imaged patients presenting with stroke or TIA, 101 (8.8%) had $\geq 50\%$ asymptomatic carotid stenosis (near age 75 yrs)
- During 301 patient-years of follow-up (mean, 3 yrs), there were 6 ischemic events in the territory of an asymptomatic stenosis
- Average annual event rate on medical treatment was 0.34% (95% CI, 0.01 to 1.87) for any ipsilateral stroke

Primary Aims

- Assess in patients with high-grade asymptomatic stenosis:
 - The treatment differences between medical management and CEA
 - The treatment differences between medical management and CAS
- Primary endpoint:
 - The proportion of patients who experienced any stroke or death within 44 days of randomization or ipsilateral ischemic stroke thereafter up to 4 years.

Cognitive Outcomes in CREST-2

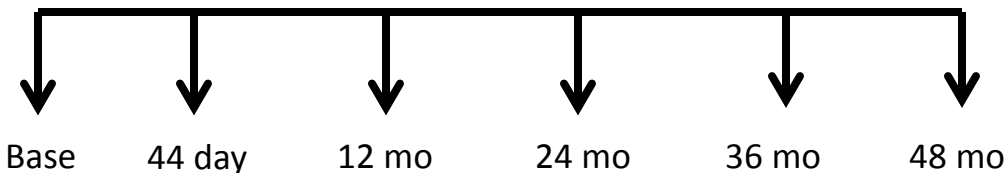
Secondary Aim

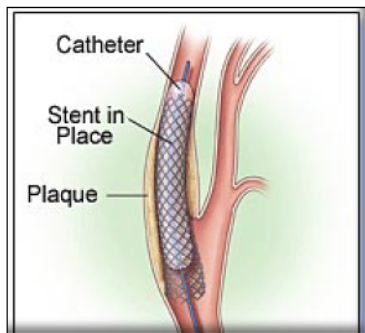
- To compare the changes of cognitive function from baseline to 48 mo. among those in the revascularized cohort with those in the non-revascularized cohort.

Testing

- Word list learning
- SF-12
- Word list learning (recall)
- Letter fluency
- Animal naming
- Digit span – forward and backward
- CES-D-4 Depression scale

Timeline Schedule





Plus



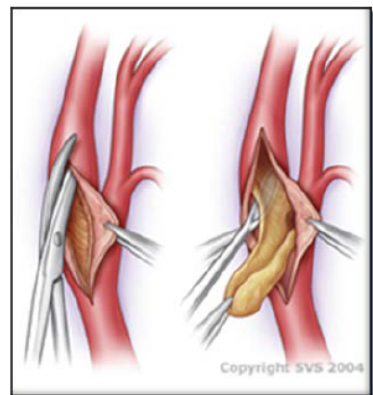
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versus



n=620

and



Plus



n=620

versus

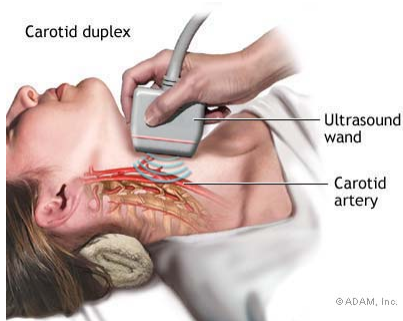


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Endpoint

4 Years

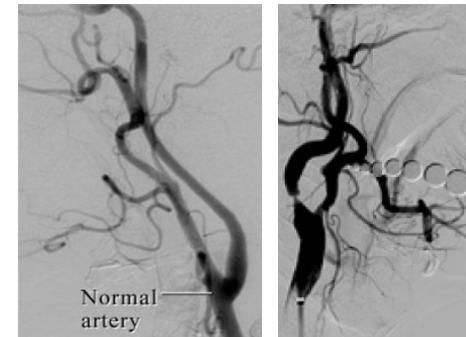
Trial Definition of High-Grade Stenosis



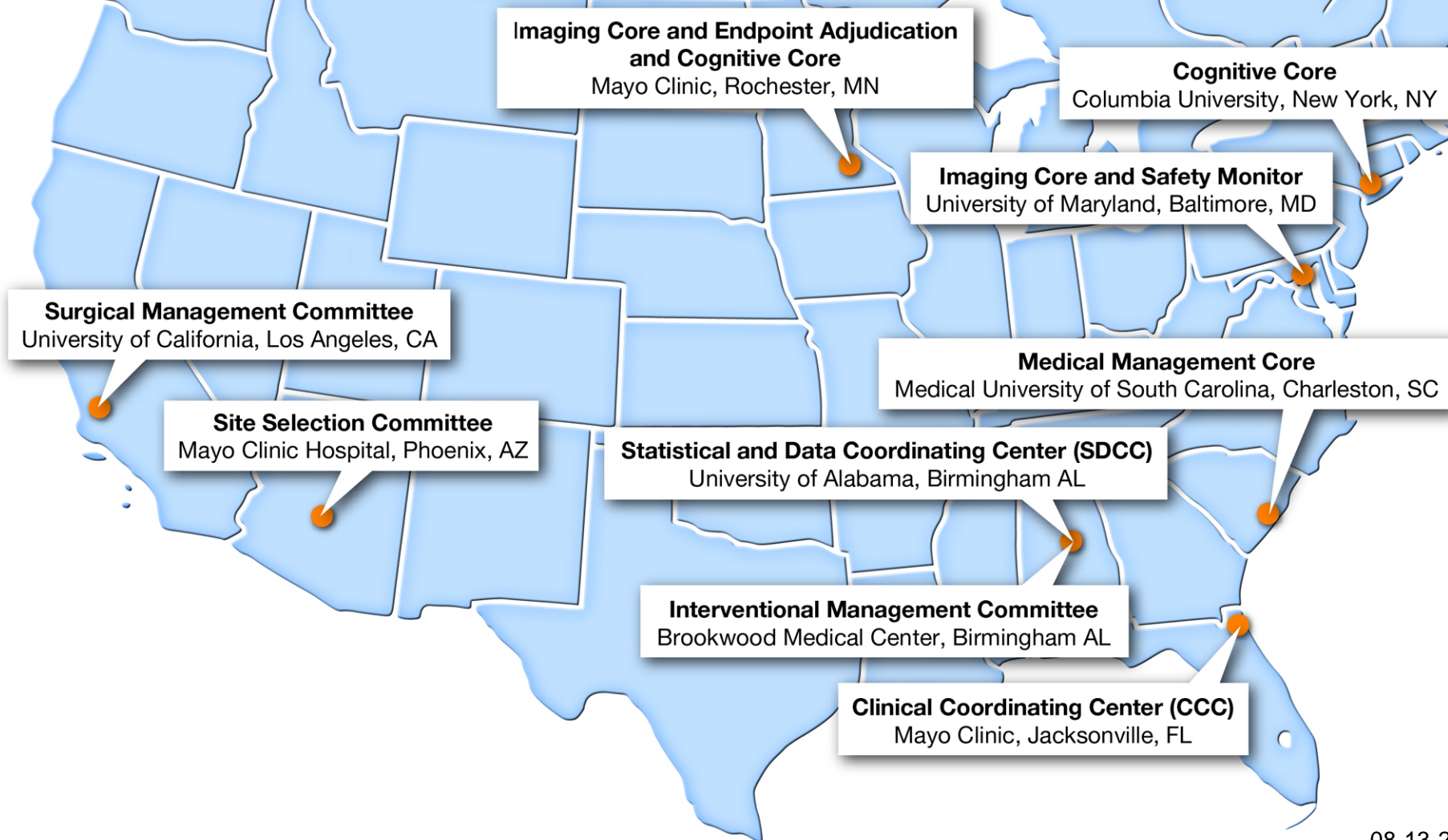
➤ Peak systolic velocity ≥ 230 cm/sec on Duplex ultrasound *and*

➤ At least one of the following:

- End diastolic velocity ≥ 100 cm/sec or
- IC/CC peak systolic velocity ratio ≥ 4.0
- $\geq 70\%$ stenosis on MR angiogram
- $\geq 70\%$ stenosis on CT angiogram

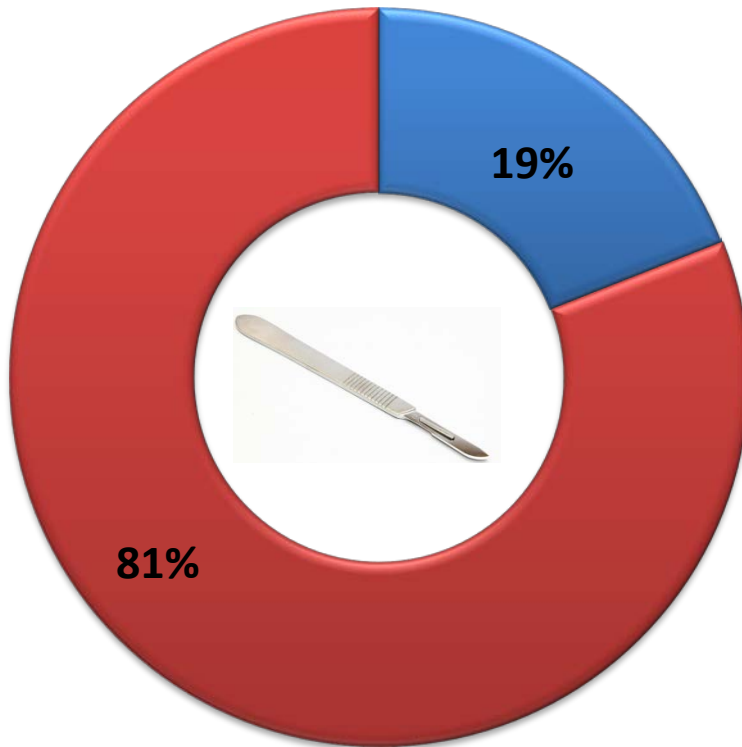


CREST-2 Coordinating Centers

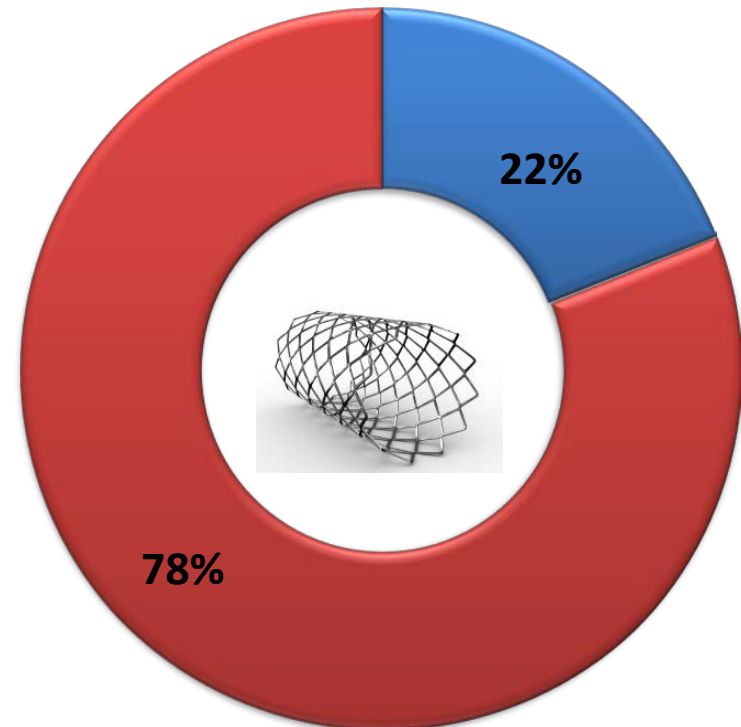


Percent of Target Enrollment by Procedure

CEA



CAS



As of March 7, 2017



Informing clinical judgement

Based on CREST:

- For ages 50-74 years, no favored procedure
- For ages <50 years, CAS is the favored procedure
- For ages >74 years, CEA is the favored procedure
- In CREST asymptomatic patients had few events, so there were wide confidence intervals

So, the choice of CEA or CAS cannot be mandated in CREST-2.

Individual patient characteristics and preferences may supersede guidelines.

Selected CEA Exclusions



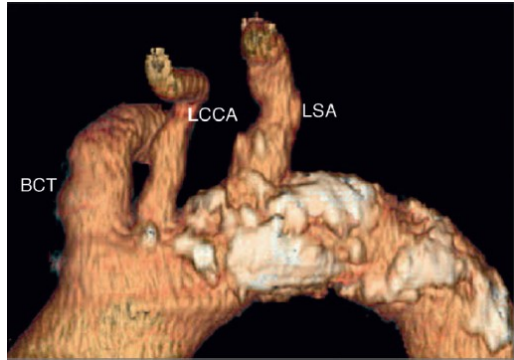
Neck
dissection



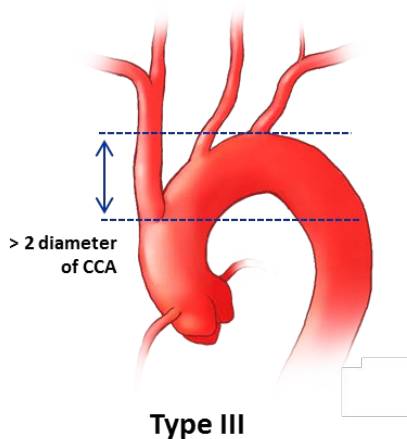
Tracheostomy
stoma

- Radical neck dissection
- Surgically inaccessible lesions
- Neck anatomy limiting surgical exposure
- Tracheostomy stoma
- Laryngeal nerve palsy contralateral to target vessel

Selected CAS Exclusions



- Severe atherosclerosis of the aortic arch or origin of the innominate or common carotid arteries



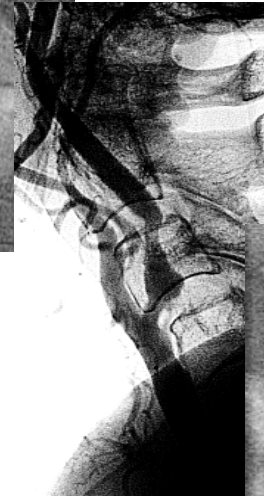
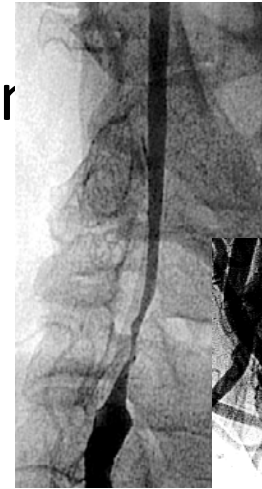
- Type III, calcified aortic arch anatomy



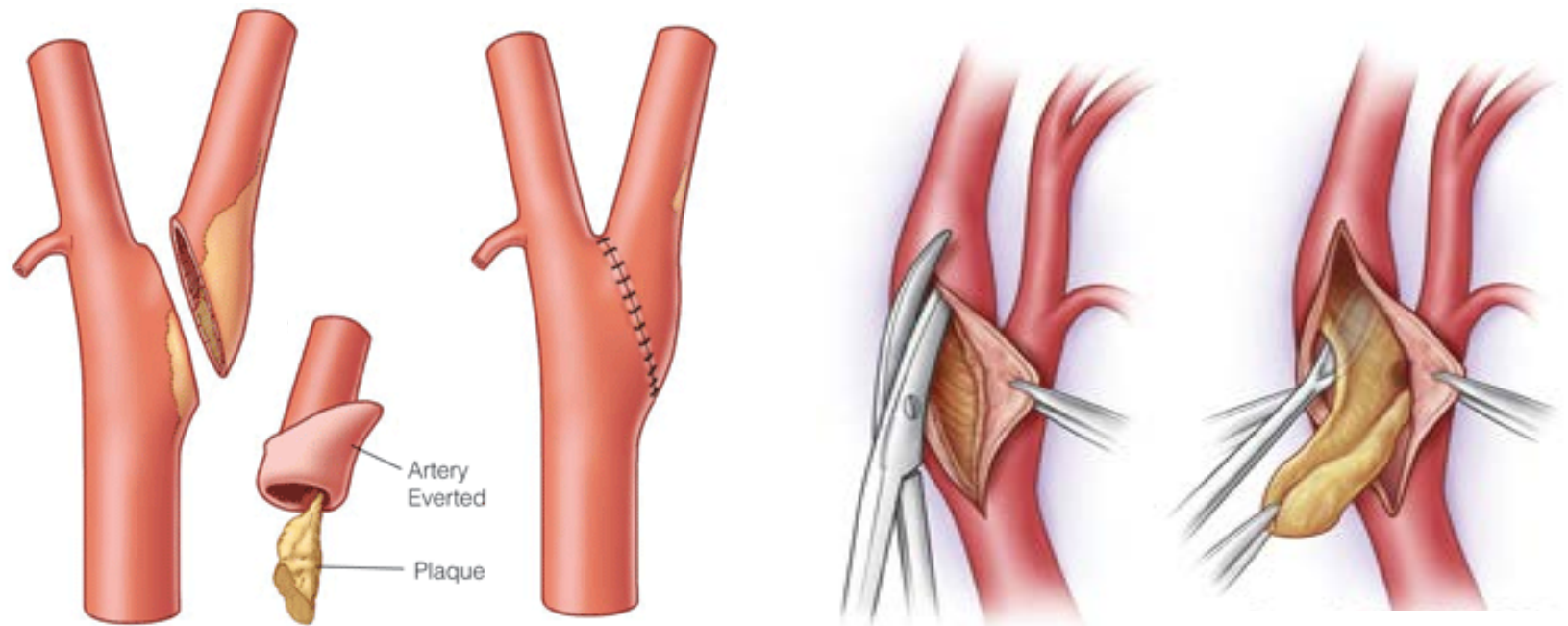
- Angulation or tortuosity ($\geq 90^\circ$) of the innominate, common or internal carotid artery

Selected CAS Exclusions

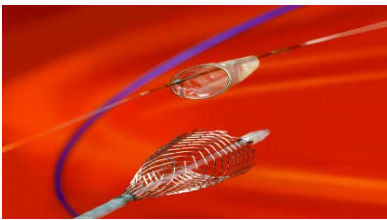
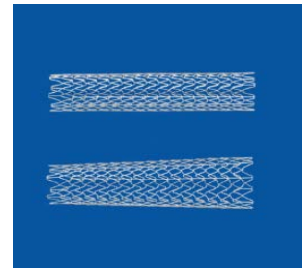
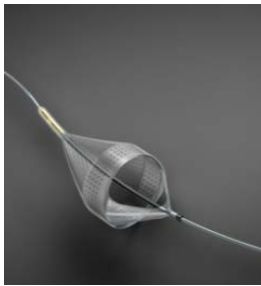
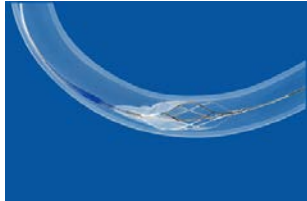
- Excessive or circumferential calcification of the stenotic lesion
- Lesions >30 mm in length, sequential lesions, and narrow-mouth ulcers
- Inability to deploy or utilize an FDA-approved Embolic Protection Device (EPD)



Surgeons given latitude on approach to endarterectomy



Stenters given some latitude on devices



Company	Stent	Embolic Protection Device
Abbott	RX Acculink [®]	RX Accunet [®]
	Xact Stent	Emboshield Nav ⁶
Boston Scientific	Carotid WALLSTENT [™]	FilterWire EZ [™]
Cordis-a Cardinal Health Company	PRECISE PRO RX [®] Nitinol Stent	ANGIOGUARD [®] RX Emboli Capture Guidewire
Medtronic/Covidien	Protege [®] RX	SpiderFX [®] MO.MA [®] Ultra

Medical Management

- Patients in both trials will take aspirin 325mg/d for the entire follow-up period (CAS patients will be on DAP pre- and 1 month post-procedure).
- Primary risk factors: systolic blood pressure and LDL cholesterol
 - Target systolic BP <140 mm Hg
 - Target LDL <70 mg/dl
 - Managed by the study neurologist or internist

Medical Management

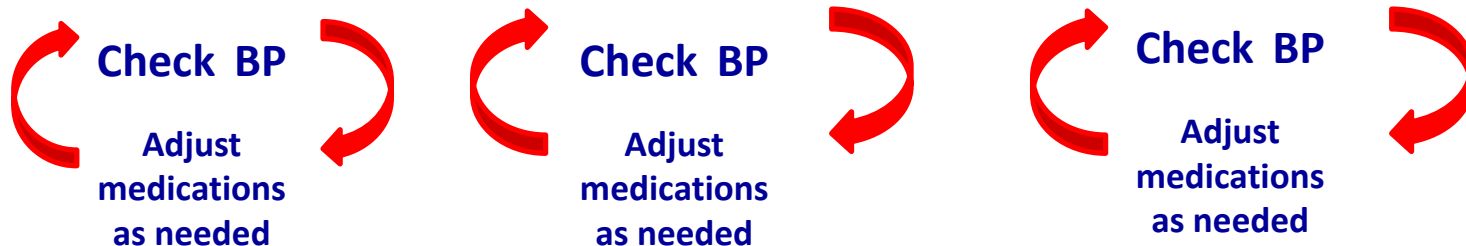
- Secondary risk factor targets:
 - <100 mg/dl non-HDL cholesterol
 - <7.0% hemoglobin A1C
 - >30 min. moderate exercise 3x/ week
 - Smoking cessation
 - Targeted weight management

Covered Medications

- Antiplatelet agents
 - Clopidogrel
- Statin
 - Atorvastatin
- Anti-hypertensive Rx
 - One drug from each major class will be available: diuretic, ACE inhibitor, potassium-sparing diuretic, angiotensin receptor blocker, beta blocker, vasodilator, central alpha agonist, long-acting calcium channel antagonist



BP Management Algorithm



OMRON HEM-705CP Auto Blood Pressure Monitor-Printer Bundle



+ atenolol, felodipine,
or spironolactone
based on k^+ and HR

+ chlorthalidone 12.5
mg

lisinopril
10 – 40 mg

No
medications

Lifestyle Coaching in CREST-2

- Lifestyle management and cardiovascular disease risk reduction will be done using INTERVENT.
- Incorporates SAMMPRIS targets and national guidelines.
- Provides individualized risk factor counseling telephone sessions at regular intervals:
 - twice a month for 12 weeks.
 - monthly thereafter.
- Case Managers at INTERVENT call center, Savannah, GA.

Cognitive Outcomes in CREST-2

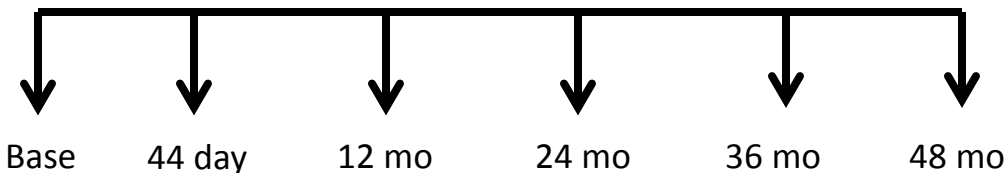
Secondary Aim

- To compare the changes of cognitive function from baseline to 48 mo. among those in the revascularized cohort with those in the non-revascularized cohort.

Testing

- Word list learning
- SF-12
- Word list learning (recall)
- Letter fluency
- Animal naming
- Digit span – forward and backward
- CES-D-4 Depression scale

Timeline Schedule



Imaging of Possible Stroke Endpoints

- Sites are encouraged to evaluate all patients with possible stroke or TIA endpoint with brain MRI unless contraindicated, in which case CT is acceptable.
- Brain imaging should be done as close to symptom onset as possible, preferably within the first 2-7 days.
- Brain imaging should be completed even if symptoms resolve within 24 hours.
- Stroke evaluation should also include a NIHSS.

Common MRI Contraindications

- Metal implant
- Surgical/aneurysm clip
- Deep brain stimulator wire
- Cardiac pacemaker
- Cochlear implant
- Claustrophobia

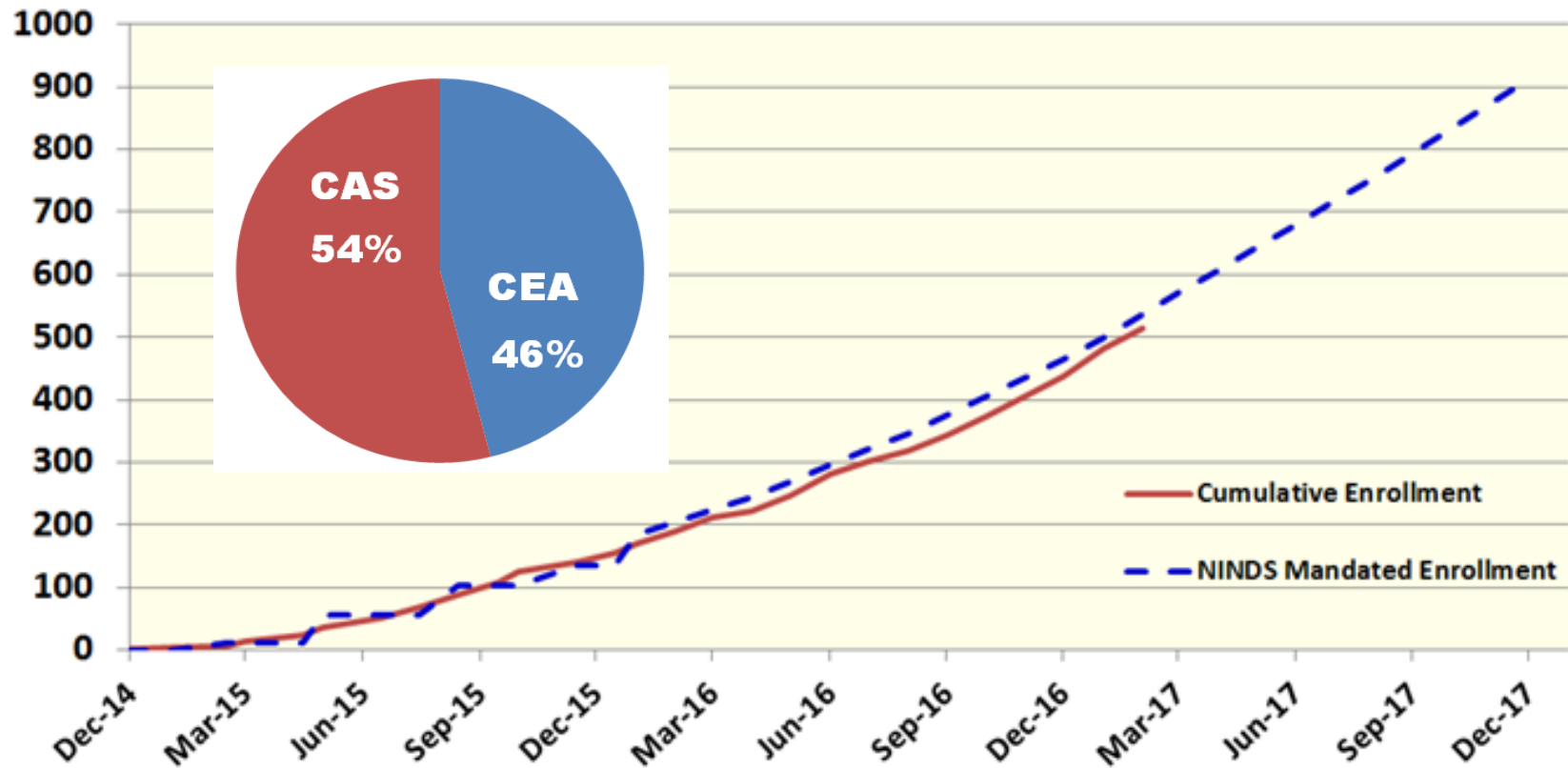
Stroke Endpoint Adjudication

- Sites will send digital copies of CT and/or MRI and any relevant medical records.
 - Admission note; Neurology consult; ED admission/triage; ECG; echocardiogram; NIHSS; discharge summary, laboratory reports; physical, occupational and speech therapy notes
 - Studies will be centrally read by neuroradiologist at Mayo Clinic Rochester blinded to treatment group assignment.

Stroke Adjudication

- Centralized (Mayo Clinic Rochester).
- Blinded to treatment assignment.
- Uses modern definitions of ischemic stroke and TIA.
- Classifies subtypes of stroke by inferred mechanism.
- Abstraction of information related to stroke severity and in-hospital outcomes.

Actual & Projected Cumulative Enrollment



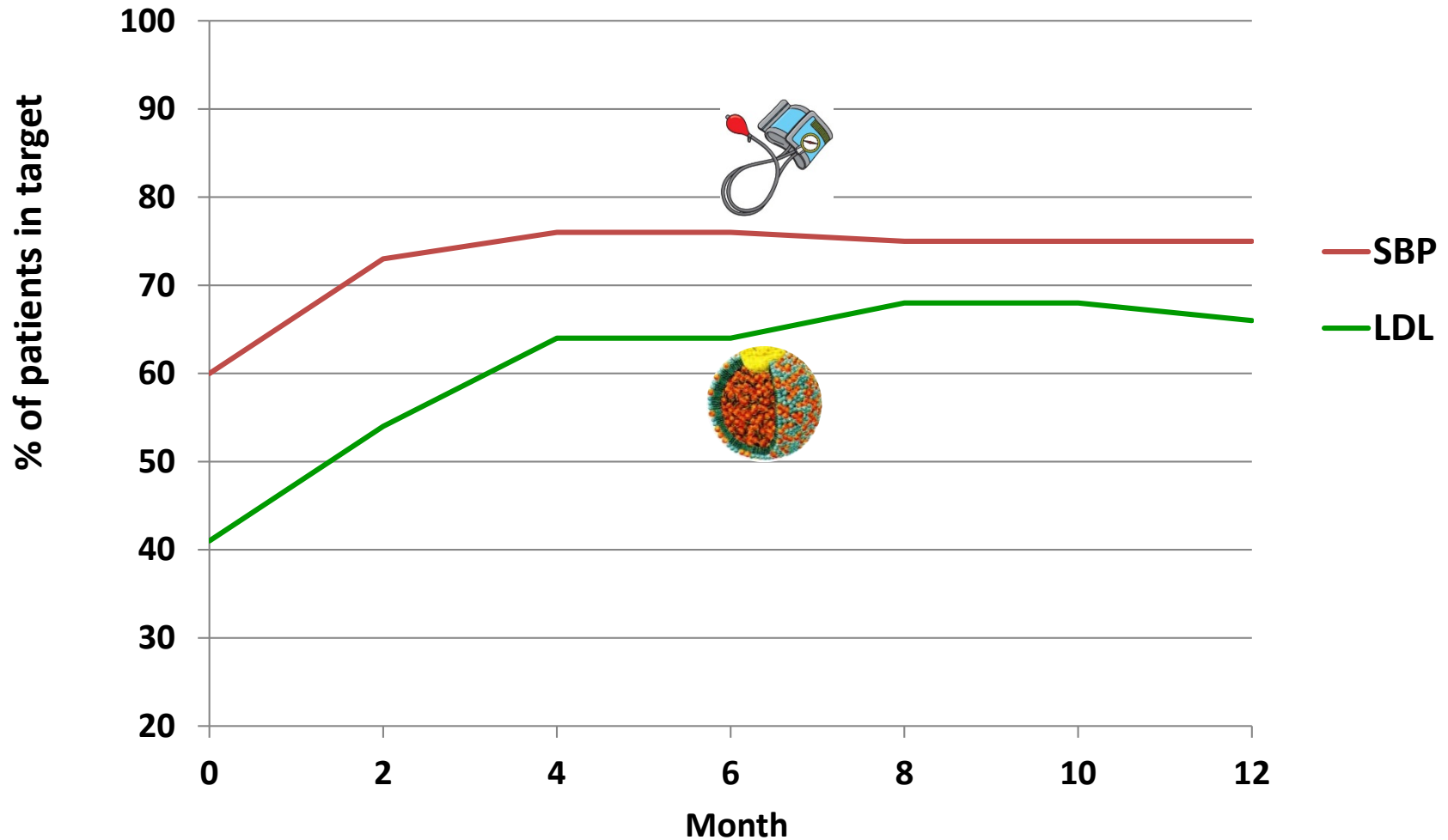
As of March 7, 2017

Top CREST-2 Sites

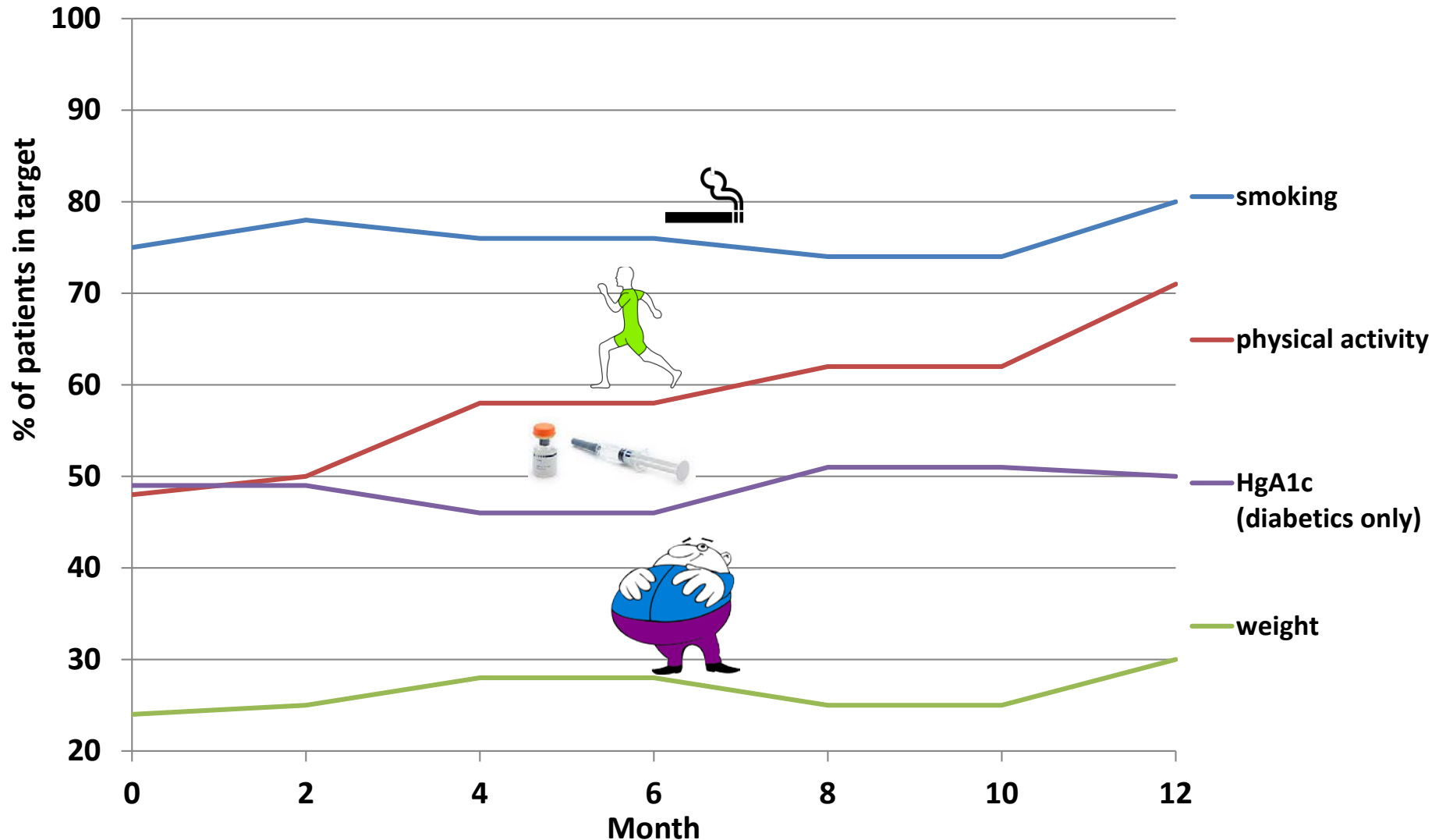
Site Name	# Enrolled
Baptist Health, Lexington, KY	33
Novant Health, Winston-Salem, NC	27
Cardiovas Assoc/Brookwood, Birmingham, AL	19
Johns Hopkins Medical Institution, Baltimore, MD	18
Tennova Healthcare, Knoxville, TN	17
Mercy Hospital, St. Louis, MO	17
UPMC Presbyterian, Pittsburgh, PA	16
Ochsner Health System, New Orleans, LA	15
Columbia University Medical Center, New York, NY	14
Washington Adventist Hospital, Takoma Park, MD	14
North Carolina Heart and Vascular, Raleigh, NC	12
Prairie Heart/St. John's Hospital, Springfield, IL	12
Maine Medical Center, Portland, ME	11
Massachusetts General Hospital, Boston, MA	10

As of March 7, 2017

% of patients meeting PRIMARY risk factor targets in CREST-2



% of patients meeting SECONDARY risk factor targets in CREST-2



Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): a prospective observational study

Hugh S Markus, Alice King, Martin Shipley, Raffi Topakian, Marisa Cullinane, Sheila Reihill, Natan M Bornstein, Arjen Schaafsma

Summary

Background Whether surgery is beneficial for patients with asymptomatic carotid stenosis is controversial. Better methods of identifying patients who are likely to develop stroke would improve the risk–benefit ratio for carotid endarterectomy.

- Embolic signals detected in 77/467 (16.5%)
- Absolute annual risk of ipsilateral stroke was 3.62% for those with embolic signals vs. 0.70% for those without embolic signals

Findings Of 467 patients with asymptomatic carotid stenosis, 77 (16.5%) had embolic signals on TCD. The absolute annual risk of ipsilateral stroke or transient ischaemic attack between baseline and 2 years was 7.13% in patients with embolic signals and 3.04% in those without, and for ipsilateral stroke was 3.62% in patients with embolic signals and 0.70% in those without. The hazard ratio for the risk of ipsilateral stroke and transient ischaemic attack for patients who had embolic signals on the recording preceding the next 6-month follow-up compared with those who did not was 2.63 (95% CI 1.01–6.88; $p=0.049$), and for ipsilateral stroke alone the hazard ratio was 6.37 (1.59–25.57; $p=0.009$). Controlling for antiplatelet therapy, degree of stenosis, and other risk factors did not alter the results.

Interpretation Detection of asymptomatic embolisation on TCD can be used to identify patients with asymptomatic carotid stenosis who are at a higher risk of stroke and transient ischaemic attack, and also those with a low absolute stroke risk. Assessment of the presence of embolic signals on TCD might be useful in the selection of patients with asymptomatic carotid stenosis who are likely to benefit from endarterectomy.

Acute Ischemic Stroke Intervention

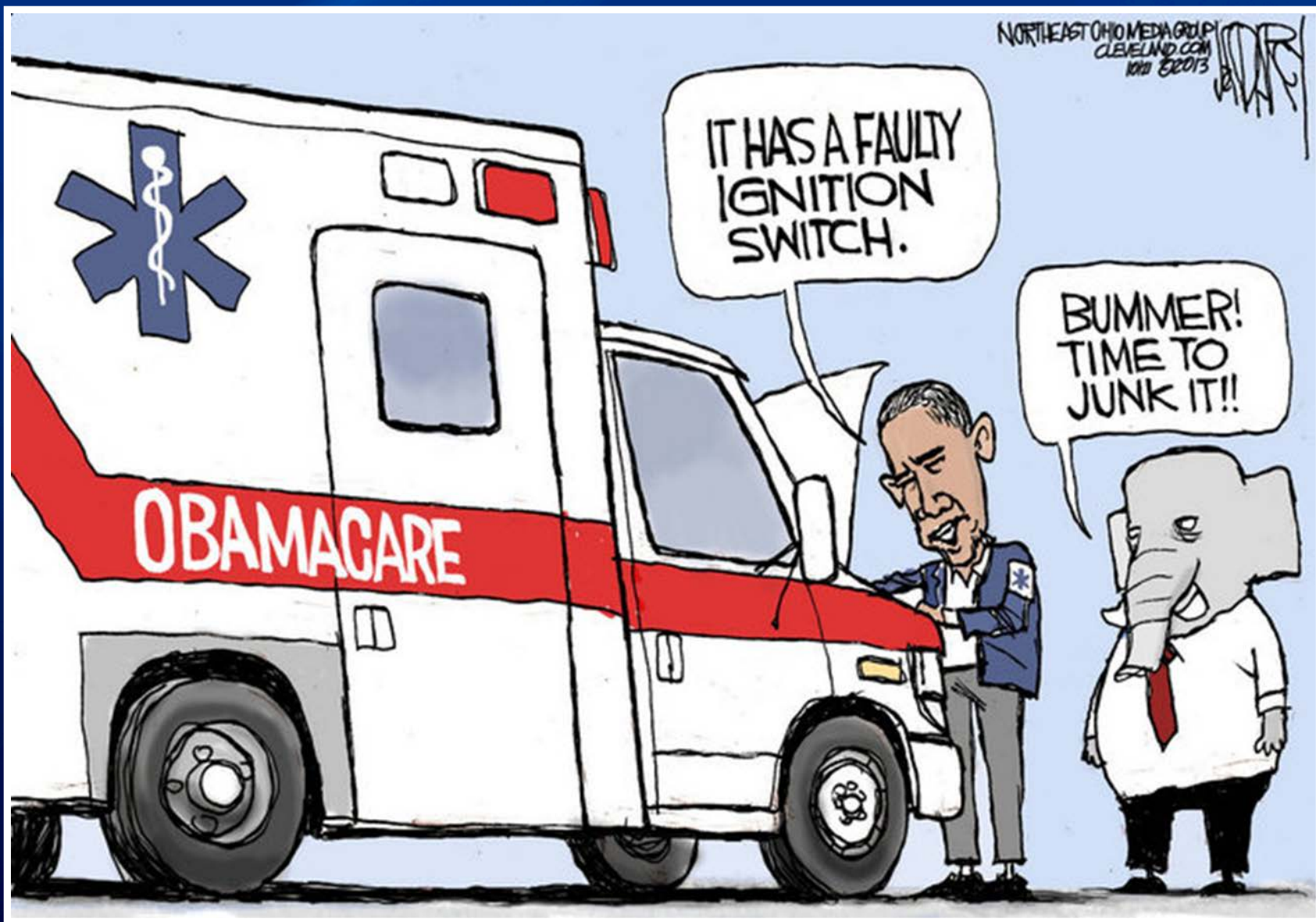
- Approximately 800,000 incident and recurrent strokes in the U.S. each year
- Stroke is the second leading cause of death worldwide
- 1996 IV rtPA received FDA approval for treatment of stroke within a 3 hour window
- ECASS III extended the window to 4.5 hours and was supported by the AHA/ASA however has not received FDA approval



AHA/ASA Guidelines

- In patients eligible for intravenous rtPA, benefit of therapy is time dependent, and treatment should be initiated as quickly as possible. The door-to-needle time (time of bolus administration) should be within 60 minutes from hospital arrival (*Class I; Level of Evidence A*).

Jauch EC, *Stroke* 2013





Pre-hospital Stroke Care

- Potential Benefits

- Reducing time to rtPA treatment
- Earlier start of general stroke treatment, i.e. neuroprotectants
- Earlier start of stroke subtype-specific treatment beyond rtPA, i.e. warfarin reversal or BP lowering in intracerebral hemorrhage
- Routing of patients suitable for endovascular or neurosurgical therapies to appropriate receiving hospitals
- Comprehensive pre-notification of in-hospital facilities
- Effective management of “golden hour” trials in acute stroke

Audebert H et al. *Neurology* 2013

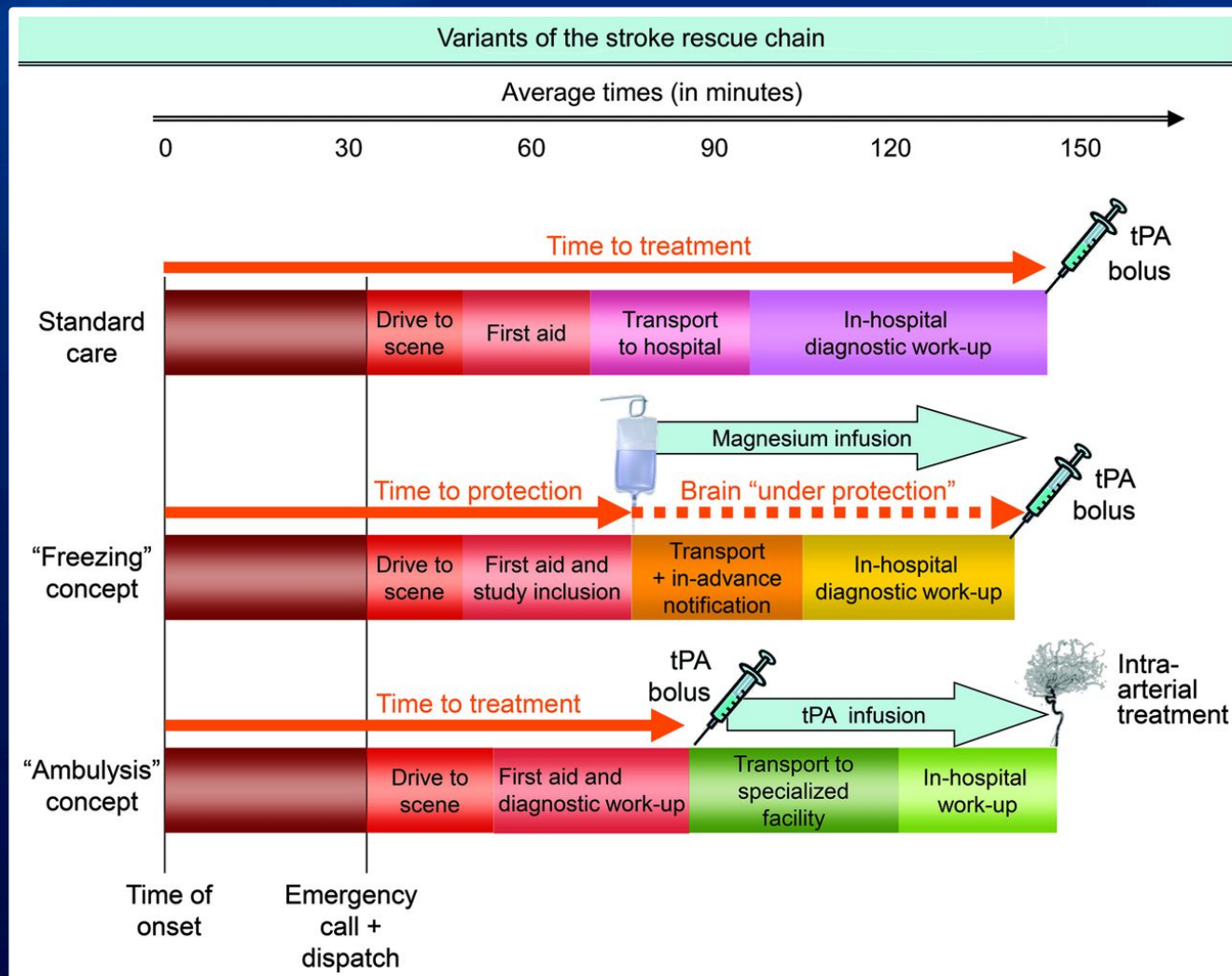
Pre-hospital Stroke Care

- Limitations

- Recognition of stroke patients at dispatcher level is desirable but limited by scarce information in emergency calls
- Major infrastructural changes needed, i.e. training of dispatchers and paramedics, significant modifications of rescue algorithms
- Diagnostic accuracy may be weakened by the short observation times
- High costs for advanced ambulances (investing and staffing) require frequent use, thus limiting utilization in rural areas
- Cost-effectiveness of current approaches not yet been demonstrated

Audebert H et al. *Neurology* 2013

Approaches to pre- and in-hospital stroke management



Audebert H et al. *Neurology* 2013

Stroke emergency mobile unitCT scanner



Stroke emergency mobile unitCT scanner



Prehospital Acute Neurological Treatment and Optimization of Medical care in Stroke Study (PHANTOM-S)

- Objective to determine if starting thrombolysis in a specialized ambulance reduces delays in treatment
- Randomly assigned weeks with and without STEMO availability
- Intervention was initiation of thrombolysis prior to hospital arrival if ischemic stroke confirmed and contraindications excluded

PHANTOM-S Catchment

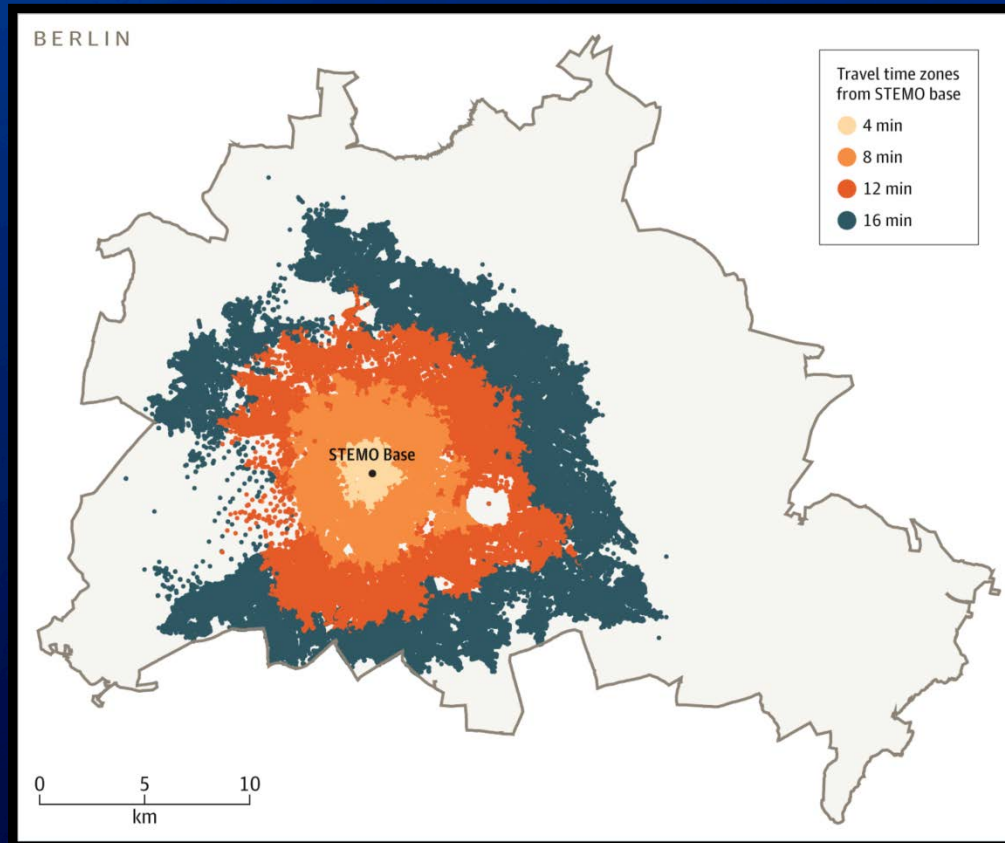


Figure Legend:

Map of Berlin, Germany, With Color-Coded STEMO Catchment Area Around STEMO Base The Stroke Emergency Mobile (STEMO) catchment area (colored zones) is defined by a 75% probability of reaching the emergency site within 16 minutes from base (Fire Station 3400, Berlin-Wilmersdorf). Courtesy of the Berliner Feuerwehr.



PHANTOM-S Results

- Reduction of 25 minutes [95% CI, 20-29; $p < 0.001$] for patients treated in STEMO
- Thrombolysis rates were 33% with STEMO vs. 21% during control weeks ($p < 0.001$)
- No increased risk of sICH during STEMO weeks
- Compared to usual care, ambulance-based thrombolysis resulted in decreased time to treatment without an increase in adverse events

Teleneurosonology (TCD)



Rubin, MN et al. *J Stroke Cerebrovasc Dis*, 2015

Teleneurosonology (Carotid Duplex)



Rubin, MN et al. *J Stroke Cerebrovasc Dis*, 2015

TeleTCD – Integrated Control Station



Rubin, MN et al. *J Stroke Cerebrovasc Dis*, 2015

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Alteplase (IV rtPA) Prescribing Information

- Alteplase full Prescribing Information has been updated to reflect the FDA Physician Labeling Rule (PLR) for human drug and biological products:
 - Provides a standardized format with uniform presentation
 - Reinforces clear section definitions for the appropriate categorization of prescribing information

Alteplase (IV rtPA) Prescribing Information

- The most significant changes have been made to *Contraindications* and *Warnings & Precautions*
- Contraindications - A drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards, **and not theoretical possibilities**, can be the basis for a contraindication

Alteplase (IV rtPA) Prescribing Information

- Dosage and Administration (Section 2)

“Administer Activase as soon as possible but within 3 hours after onset of symptoms” was added

“During and following Activase administration for the treatment of acute ischemic stroke, frequently monitor and control blood pressure”

“In patients without recent use of oral anticoagulants or heparin, Activase treatment can be initiated prior to the availability of coagulation study results.

Discontinue Activase if the pretreatment International Normalized Ratio (INR) is greater than 1.7 or the activated partial thromboplastin time (aPTT) is elevated [*see Contraindications (4.1)*]

Alteplase (IV rtPA) Prescribing Information

- Contraindications (Section 4)
 - Previous stroke was removed
 - Seizure at the onset of stroke was removed
 - Severe uncontrolled hypertension remains a contraindication. However, specific examples of hypertension cutoff levels were removed:
 - Blood pressure >185 mm Hg systolic or >110 mm Hg diastolic
 - Bleeding diathesis remains a contraindication; however, specific examples were removed:
 - Current use of oral anticoagulants (eg, warfarin sodium) or an International Normalized Ratio (INR) >1.7 or a prothrombin time (PT) >15 seconds
 - Platelet count <100,000/mm³

Alteplase (IV rtPA) Prescribing Information

- Warnings and Precautions (Section 5)
 - Blood glucose level warnings (ie, <50 mg/dL or >400 mg/dL) were removed
 - Recent intracranial hemorrhage was added
 - Severe neurological deficit (NIHSS >22) was removed
 - Major early infarct signs was removed
 - Minor neurological deficit or rapidly improving symptoms was removed
 - Orolingual angioedema is now located in its own subsection of Warnings and Precautions

Conclusions

- There is equipoise with respect to optimal treatment for stroke prevention in high grade asymptomatic carotid stenosis
- Systems of care are beginning to focus on pre-hospital diagnosis and treatment initiation to reduce onset to treatment times



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