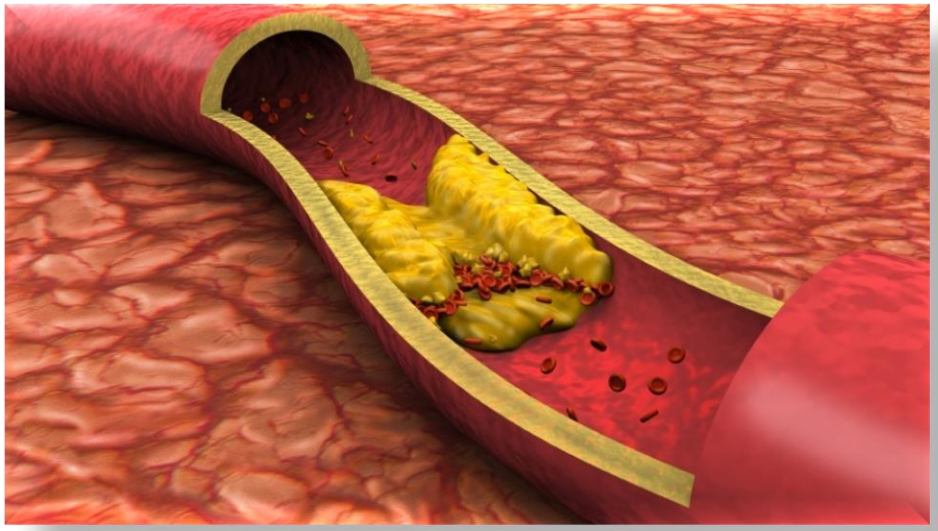
# Asymptomatic Carotid Disease: Sometimes you Should Intervene



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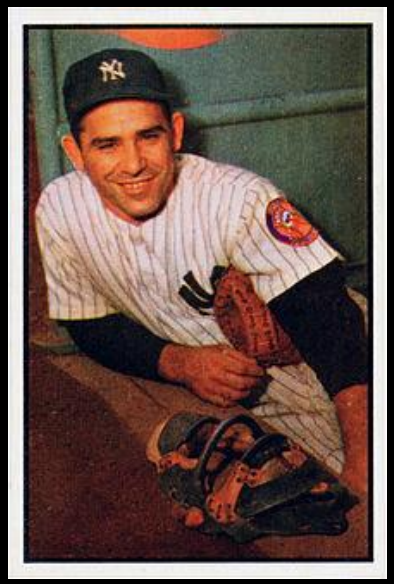
UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

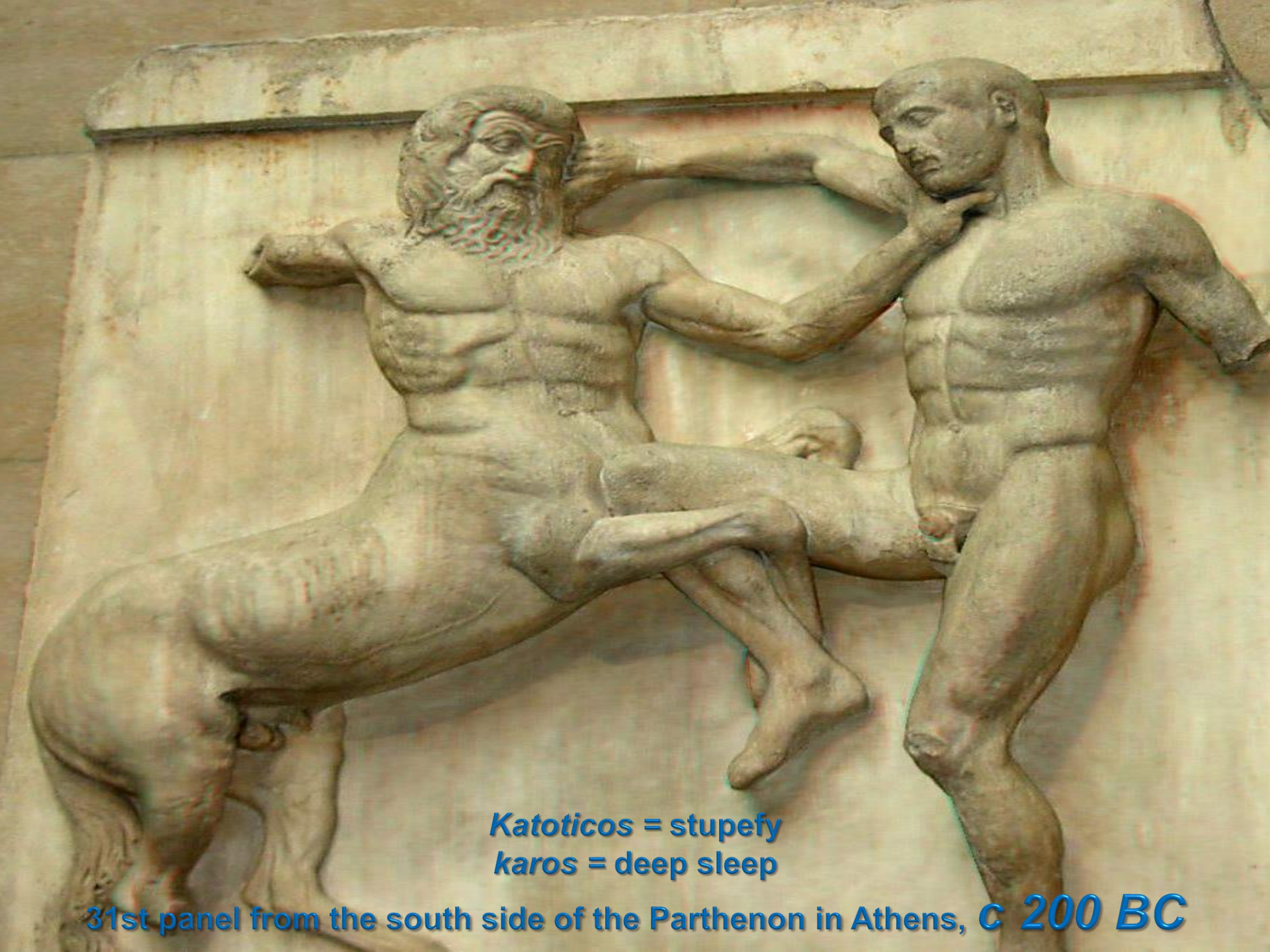
# Disclosures
# No Conflicts

| | |
|---|---|
| NIH | PI Management asymptomatic carotid stenosis (CREST-2) |
| NIH | PI Vascular Imaging Core Facility (VIC) |
| NIH/CMS/FDA/Industry | PI National Carotid Registry (C2R) |
| NIH (Admin Suppl) | PI Dental Carotid Cognitive Study (DCCS) |
| NIH (Admin Suppl) | PI Carotid- LifeLine Screening Study (C-LLS) |
| VA Merit | PI Cognitive Impairment in Carotid Disease-1 (ACCOF-2) |
| VA Merit | PI Flow mediated thrombus resolution in DVT (EFFORT-2) |
| MIPS-Maryland State | PI Novel targeted imaging for PAD |

# “You can’t guess the future if you haven't seen the past”

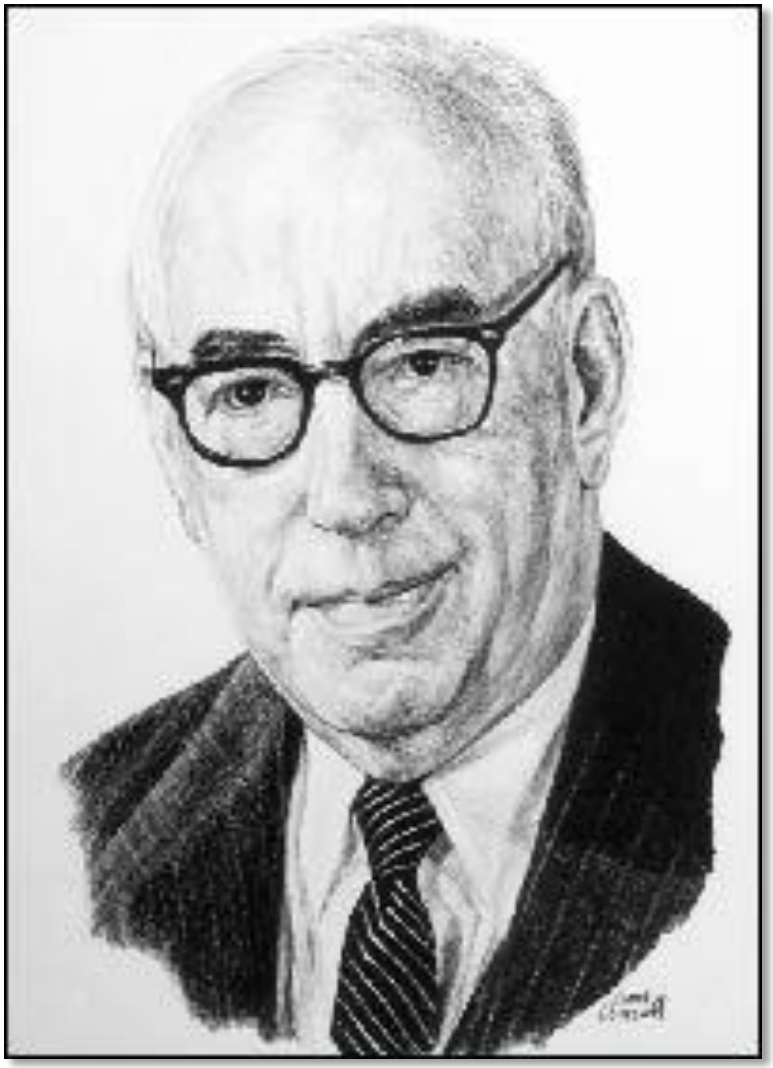


Yogi Berra



*Katoticos* = stupefy
*karos* = deep sleep

31st panel from the south side of the Parthenon in Athens, *C* 200 BC



**C Miller Fisher, Canadian Neurologist, 1951**
***Correlated carotid plaque with stroke***

JAMA®

The Journal of the American Medical Association

## Successful Carotid Endarterectomy For Cerebrovascular Insufficiency

### Nineteen-Year Follow-up

Michael E. DeBakey, MD

• This is believed to be the first successful case of thromboendarterectomy for cerebrovascular insufficiency caused by atherosclerotic occlusion of the carotid artery, as well as the longest follow-up study. At the time of the patient's death from coronary occlusion, 19 years after operation, he had no cerebrovascular symptoms, and there was clinical evidence of maintenance of the restored circulation in the carotid artery.

(*JAMA* 233:1083-1085, 1975)

palpable, whereas that on the left was only questionably palpable. The tendon reflexes on the right were hyperactive. Hoffmann, Babinski, and Chaddock signs were positive on the right. No evidence of cerebellar disturbance was observed on examination of the limbs. Sensation was normal on both sides. The right femoral, popliteal, and



THE LANCET

Volume 264, Issue 6846, 13 November 1954, Pages 994–996

## RECONSTRUCTION OF INTERNAL CAROTID ARTERY IN A PATIENT WITH INTERMITTENT ATTACKS OF HEMIPLEGIA

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*From the Medical and Surgical Units, St. Mary's Hospital, London*

IN 1914 Ramsay Hunt described the syndrome of internal carotid occlusion and prefaced his paper with the following observations:

"The object of the present study is to emphasise the importance of obstructive lesions of the main arteries of the neck, in the causation of softening of the brain, and more especially to urge the routine examination of these vessels in all cases presenting cerebral symptoms of vascular origin. In other words, the writer would advocate the same attitude of mind towards this group of cases as towards intermittent claudication, gangrene, and other vascular symptoms of the extremities, and never omit a detailed examination of the main arterial stem."

# Carotid Disease Management in the 20th Century

"Certainty Rules"

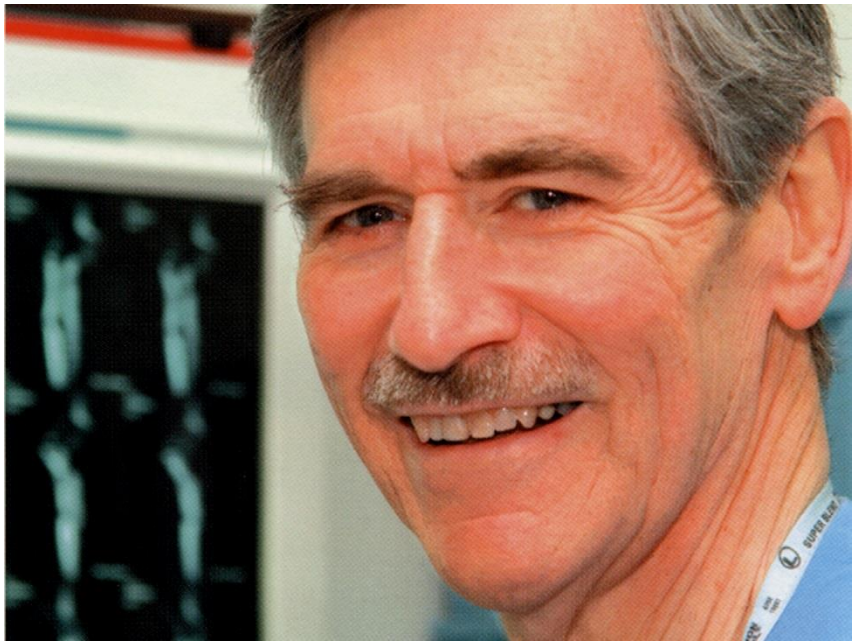
The New England
Journal of Medicine



Volume 328 JANUARY 28, 1993 Number 4

**EFFICACY OF CAROTID ENDARTERECTOMY FOR ASYMPTOMATIC CAROTID STENOSIS**

ROBERT W. HOBSON II, M.D., DAVID G. WEISS, PH.D., WILLIAM S. FIELDS, M.D., JERRY GOLDSTONE, M.D., WESLEY S. MOORE, M.D., JONATHAN B. TOWNE, M.D., CREIGHTON B. WRIGHT, M.D., AND THE VETERANS AFFAIRS COOPERATIVE STUDY GROUP*



VA Cooperative Study Protocol 167

# Increasing Enthusiasm for CEA

JAMA
The Journal of the American Medical Association

Joint Study of Extracranial Arterial Occlusion

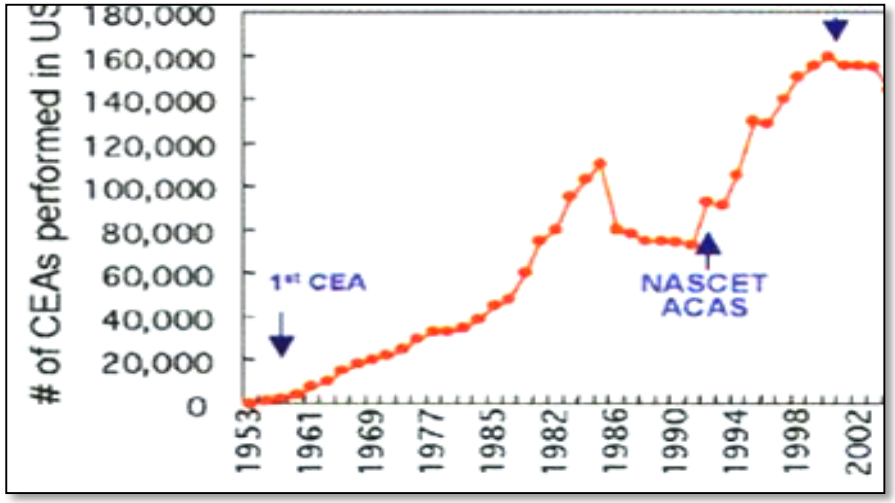
X. Internal Carotid Artery Occlusion

William S. Fields, MD, Noreen A. Lemak, MD

JAMA
The Journal of the American Medical Association

Endarterectomy for Asymptomatic Carotid Artery Stenosis

Executive Committee for the Asymptomatic Carotid Atherosclerosis Study




The NEW ENGLAND JOURNAL of MEDICINE

Volume 325:445-453 August 15, 1991 Number 7

Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators

The NEW ENGLAND JOURNAL of MEDICINE

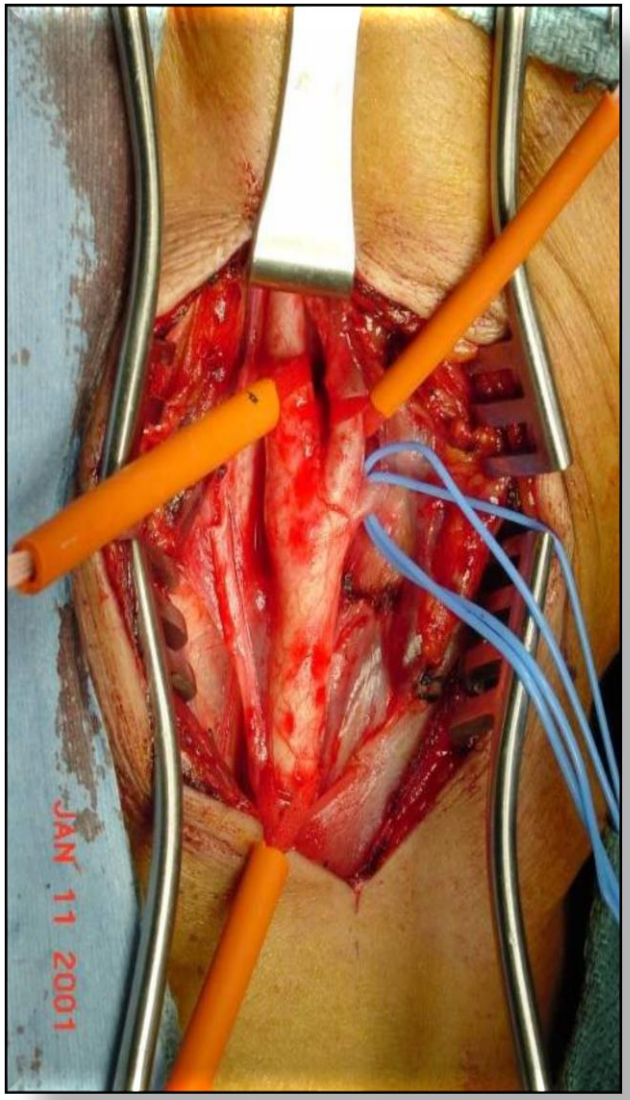
Volume 339:1415-1425 November 12, 1998 Number 20

Benefit of Carotid Endarterectomy in Patients with Symptomatic Moderate or Severe Stenosis

Henry J.M. Barnett, M.D., D. Wayne Taylor, M.A., Michael Eliasziw, Ph.D., Allan J. Fox, M.D., Gary G. Ferguson, M.D., R. Brian Haynes, M.D., Richard N. Rankin, M.D., G. Patrick Clagett, M.D., Vladimir C. Hachinski, M.D., David L. Sackett, M.D., Kevin E. Thorpe, M.Math., Heather E. Meldrum, B.A., J. David Spence, M.D., for The North American Symptomatic Carotid Endarterectomy Trial Collaborators

# CEA becomes the standard of care for severe carotid stenosis

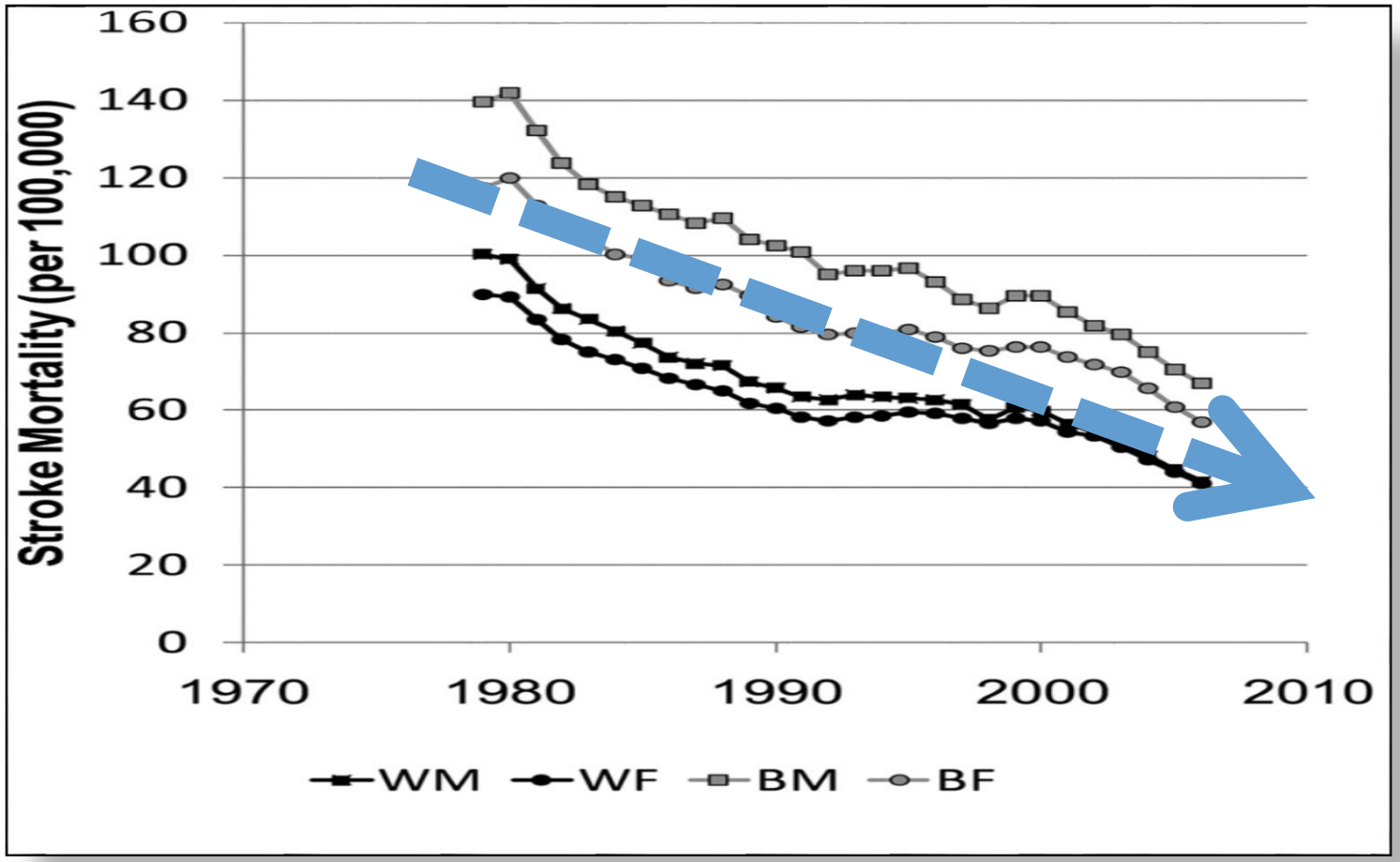
One of the most frequently performed vascular surgery procedures



# “When did medicine get so messy?”

Intern in Gray’s Anatomy

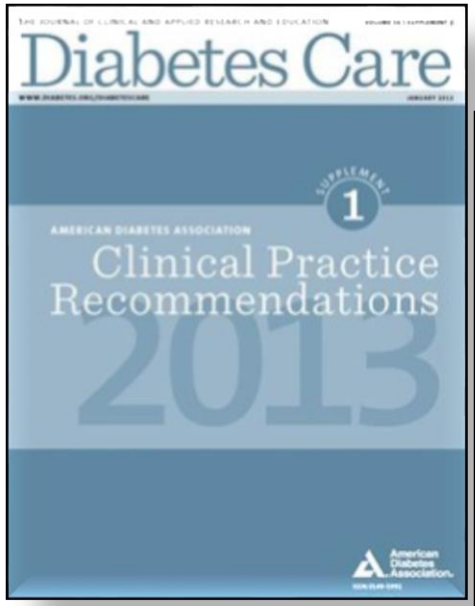
# 1. Stroke rates ….. are declining




Age-adjusted stroke **mortality** for blacks and whites aged ≥45 years

**Stroke drops to #5 cause of death in 2014**

# 2. Medical risk-factor management ….. is more comprehensive and guideline-driven





AACE Guidelines

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS' GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF ATHEROSCLEROSIS

*Paul S. Jellinger, MD, MACE; Donald A. Smith, MD, FACE; Ath E. Mehta, MD, FRCPC), FACE; Om Ganda, MD, FACE; Yehuda Handelsman, MD, FACP, FACE; Helena W. Rodbard, MD, FACP, MACE; Mark D. Shepherd, MD, FACE; John A. Seibel, MD, MACE; the AACE Task Force for Management of Dyslipidemia and Prevention of Atherosclerosis*

*American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health care professionals in medical decision-making for specific clinical conditions, but are in no way a substitute for a medical professional's independent judgment and should not be considered medical advice. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied.*

*These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with, and not as a replacement for, their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.*

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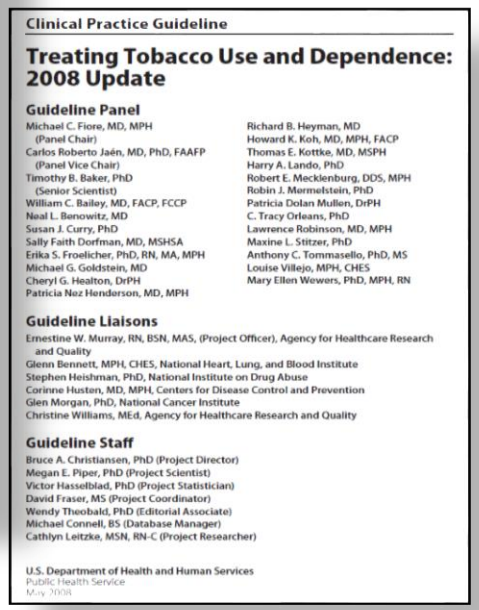
Clinical Practice Guideline

## Treating Tobacco Use and Dependence: 2008 Update

### Guideline Panel

Michael C. Fiore, MD, MPH (Panel Chair)
Carlos Roberto Jaén, MD, PhD, FAAFP (Panel Vice Chair)
Timothy B. Baker, PhD (Senior Scientist)
William C. Bailey, MD, FACP, FCCP
Neal L. Benowitz, MD
Susan J. Curry, PhD
Sally Faith Dorfman, MD, MSHSA
Erika S. Froelicher, PhD, RN, MA, MPH
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Cheryl G. Healton, DrPH
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Wendy Theobald, PhD (Editorial Associate)
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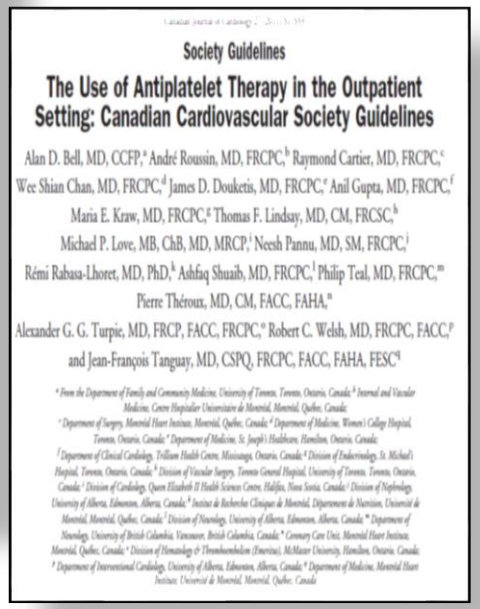
Cathlyn Leitzke, MSN, RN-C (Project Researcher)

U.S. Department of Health and Human Services
Public Health Service
May 2008


Society Guidelines

## The Use of Antiplatelet Therapy in the Outpatient Setting: Canadian Cardiovascular Society Guidelines

Alan D. Bell, MD, CCFP,[a] André Roussin, MD, FRCPC,[b] Raymond Cartier, MD, FRCPC,[c] Wee Shian Chan, MD, FRCPC,[d] James D. Douketis, MD, FRCPC,[e] Anil Gupta, MD, FRCPC,[f] Maria E. Kraw, MD, FRCPC,[g] Thomas F. Lindsay, MD, CM, FRCSC,[h] Michael P. Love, MB, ChB, MD, MRCP,[i] Neesh Pannu, MD, SM, FRCPC,[j] Rémi Rabasa-Lhoret, MD, PhD,[k] Ashfaq Shuaib, MD, FRCPC,[l] Philip Teal, MD, FRCPC,[m] Pierre Théroux, MD, CM, FACC, FAHA,[n] Alexander G. G. Turpie, MD, FRCP, FACC, FRCPC,[o] Robert C. Welsh, MD, FRCPC, FACC,[p] and Jean-François Tanguay, MD, CSPQ, FRCPC, FACC, FAHA, FESC[q]

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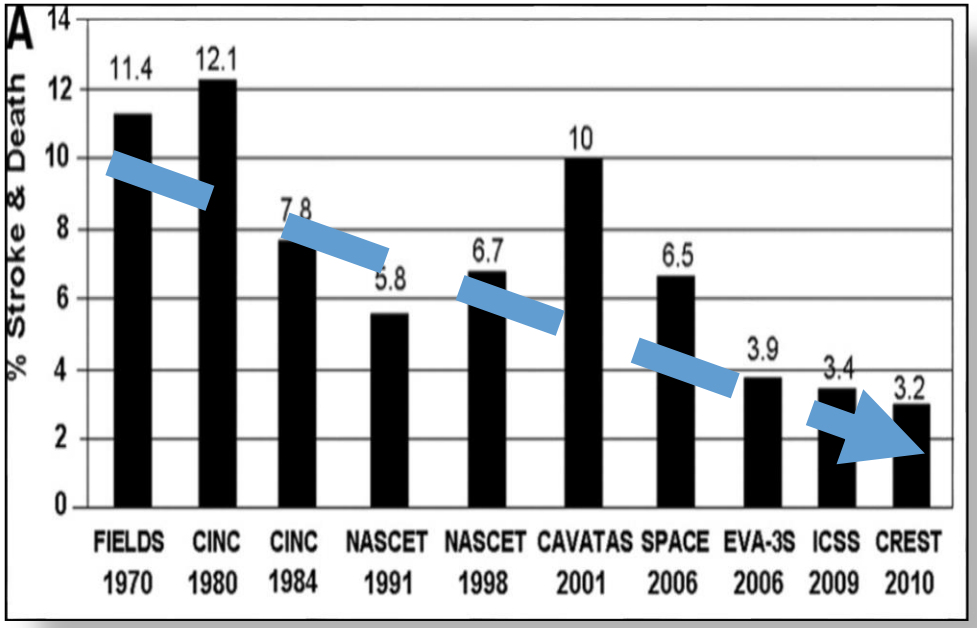
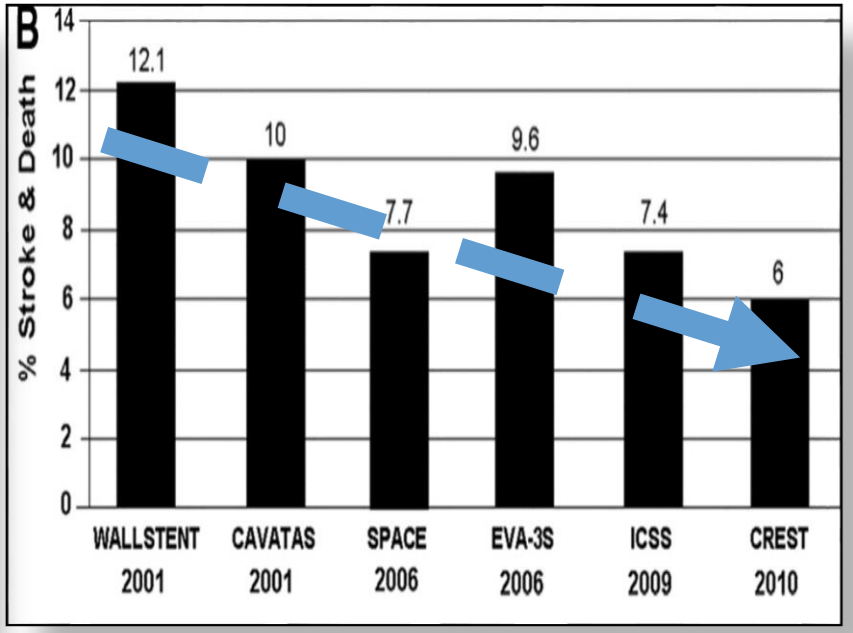
# 3. Technical expertise ….. is improving dramatically



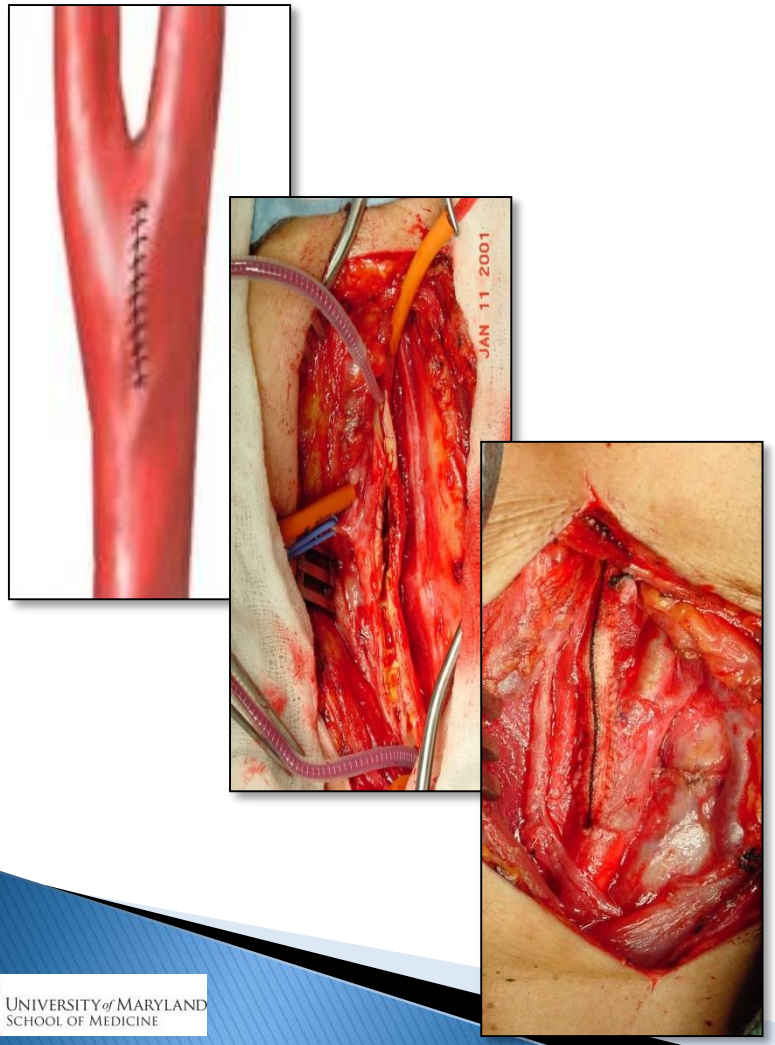

Perioperative stroke and death rate for **CEA** in **symptomatic** patients




Perioperative stroke and death rate for **CAS** in **symptomatic** patients

# 4. Revascularization Technology ….. is getting better and better

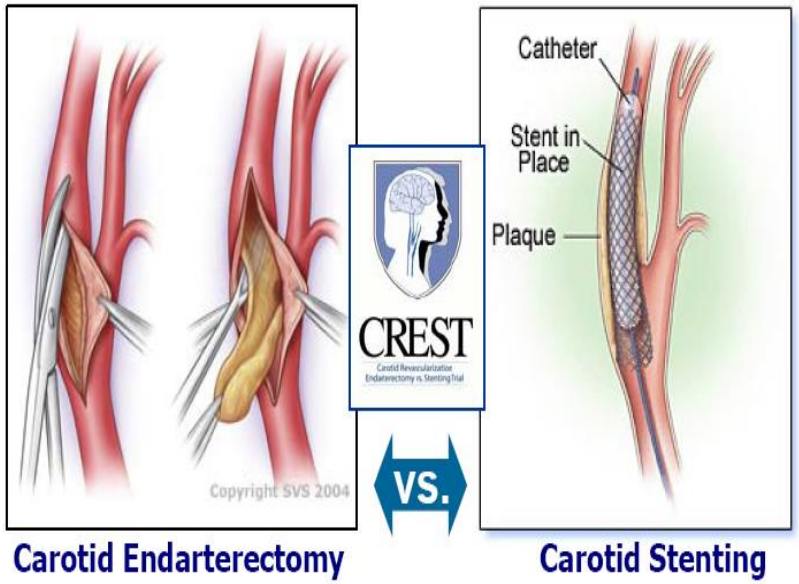
## Endarterectomy




- Protecting cerebral perfusion during carotid clamping
  - Blood pressure
  - Shunts
  - Neural monitoring
- Carotid patching
  - ↓ stroke (OR 0.31)
  - ↓ perioperative arterial occlusion (OR 0.18)
  - ↓ restenosis (OR 0.24)

*Cochrane Database of Systematic Reviews, 2009*

# Carotid Revascularization, Endarterectomy vs Stent Trial (CREST-1)




- In preventing any **stroke, MI, and all-cause mortality** during peri-procedural period, and
- In maintaining durable patency over the follow-up period

| CAS vs. CEA | | Hazard Ratio, 95% CI | P-Value |
|---|---|---|---|
| **7.2** vs. **6.8%** | | HR = 1.11; 95% CI: 0.81-1.51 | 0.51 |
| Stroke | **4.1** vs. **2.3%** | HR = 1.79; 95% CI: 1.14-2.82 | 0.01 |
| MI | **1.1** vs. **2.3%** | HR = 0.50; 95% CI: 0.26-0.94 | 0.03 |

*Hobson RW et al, JACS 2002*
*Brott TG et al, NEJM 2010*
*Lal BK & Brott TG, J Vasc Surg 2011*

# 5. Revascularization technology ….. is getting better and better

## Carotid artery stenting

- Embolic protection
  - Filter
  - Flow reversal
- Stent designs
  - Open cell
  - Closed cell
  - Hybrid- Open-closed
- Hybrid designs
  - Stent-mesh
  - Stent-filter-balloon
  - Double filter

*Lal BK et al JVS 2003*
*Bosiers M et al, 2007*

# Carotid Disease in the 21st century

Do we have Equipoise?

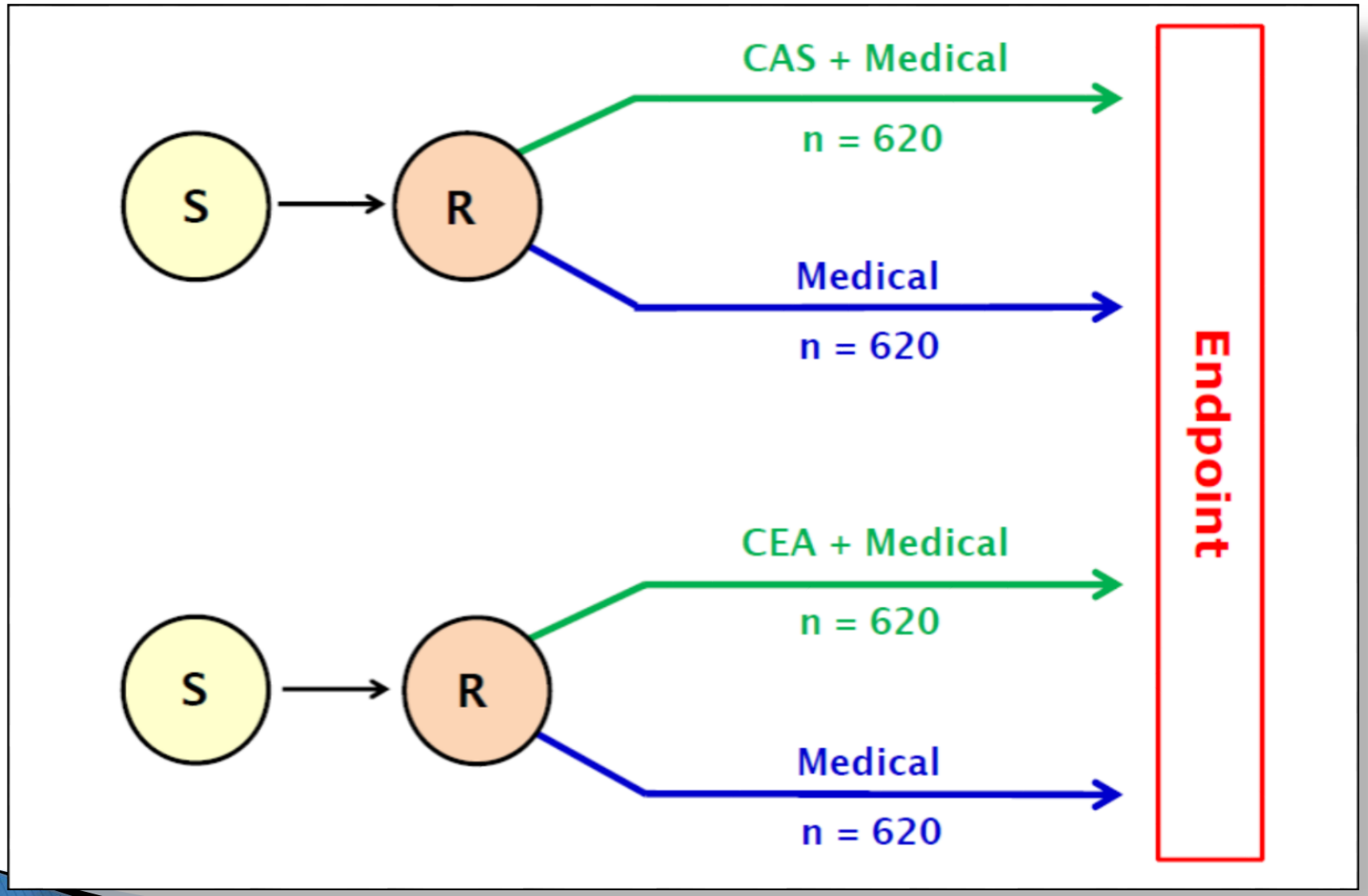
# Carotid Revascularization for Primary Prevention of Stroke Trial (CREST-2)


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

- The treatment differences between medical management and **CEA**
- The treatment differences between medical management and **CAS**
- **Stroke & Death at 4 years**

*Lal BK et al, Semin Vasc Surg 2017*

# Dual Trial Design



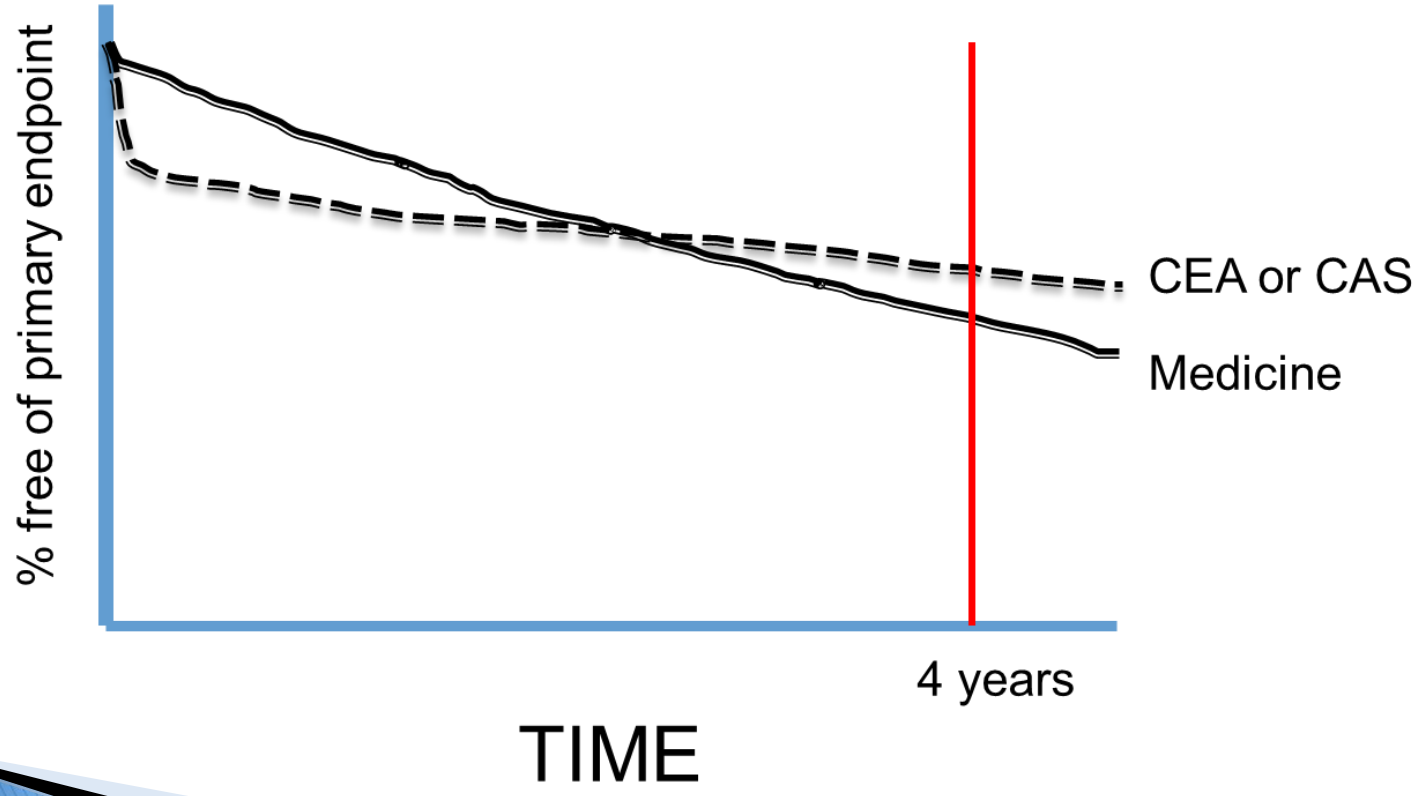

*Lal BK et al, Endov Today 2013*

# “CREST-2 is the best treatment for asymptomatic carotid stenosis”

Walter Koroshetz, MD, Director NINDS

# CREST-2 Primary Aims

- Peri-procedural stroke and death
- Post-procedural ipsilateral stroke (4 years)



# Risk of stroke based on demographic characteristics

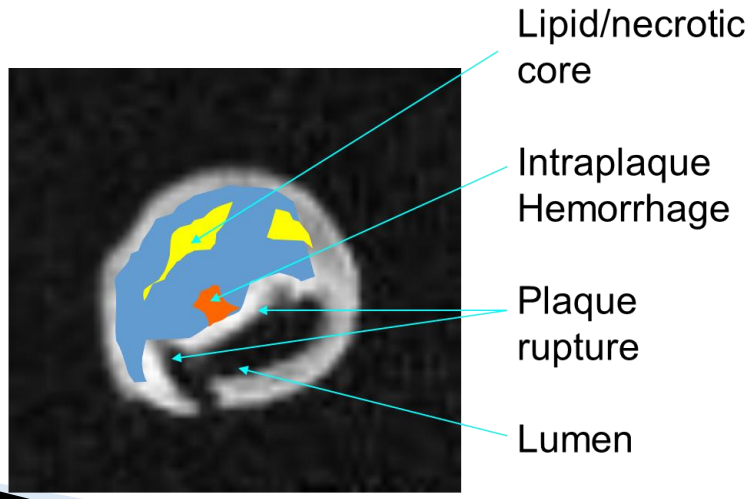
| Risk factor | HR (95% CI) | P value |
|---|---|---|
| Stenosis (per 10%) | 1.18 (1.10–1.25) | <0.0001 |
| Near occlusion | 0.49 (0.19–1.24) | 0.1309 |
| Male sex | 1.19 (0.81–1.75) | 0.3687 |
| Age (per 10 years) | 1.12 (0.89–1.39) | 0.3343 |



*Rothwell P et al, Lancet 2004*

# Risk of stroke based on plaque characteristics

| | No. of studies | Total population | Follow-up period (mean) | HR/OR [95% CI] |
|---|---|---|---|---|
| **Intraplaque hemorrhage** | | | | |
| Saam et al 2013 (HR)[20] | 8 | 689 | 1–38 (20) months | 5.7 [3.0–10.9] |
| Gupta et al 2013 (HR)[21] | 7 | 678 | 9–38 (20) months | 4.6 [2.9–7.2] |
| Hosseini et al 2013 (OR)[22] | 7 | 667 | 9–38 months | 10.0 [5.5–18.4] |
| **Lipid-rich necrotic core** | | | | |
| Gupta et al 2013 (HR)[21] | 4 | 403 | 12–38 (24) months | 3.0 [1.5–5.9] |
| **Thin or ruptured fibrous cap** | | | | |
| Gupta et al 2013 (HR)[21] | 4 | 363 | 12–38 (22) months | 5.9 [2.7–13.2] |




*Liem MI et al, Circ J, 2017*
*Lal BK et al, Stroke 2003*
*Lal BK et al, IEEE Bioeng*. 2004
*Lal BK et al, Ann Vas Sur 2006*
*AlMuhanna et al, J Vasc Surg 2014*

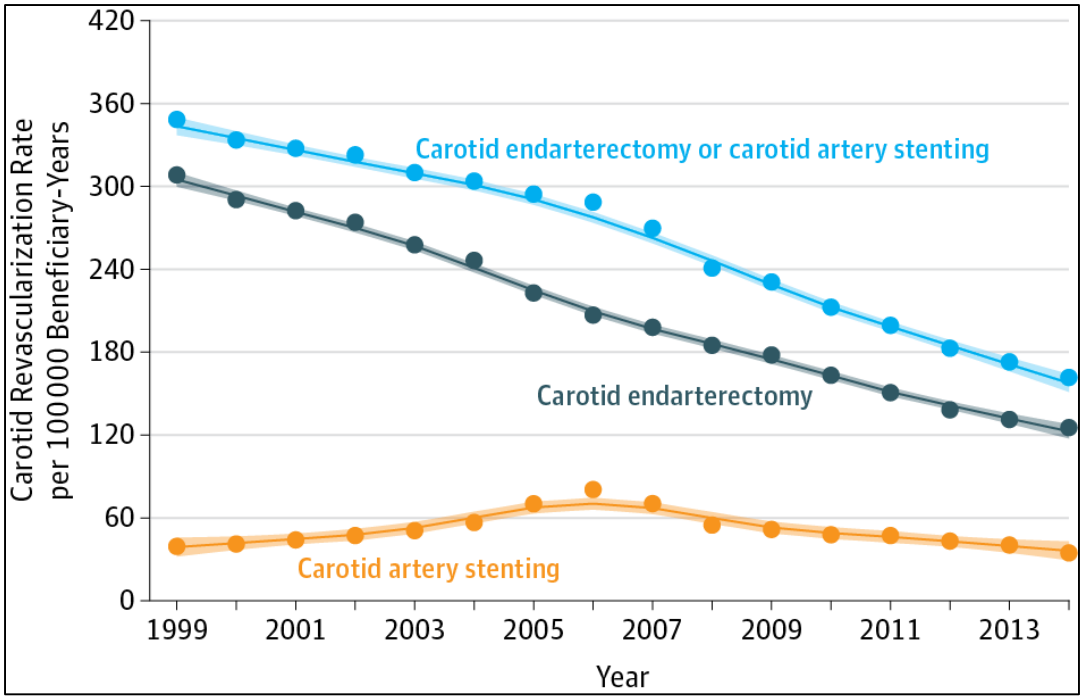
# Risk of stroke based on transcranial Doppler HITs

| Study | Year | n | MES positive | Follow-up | No. of events | OR (95% CI) |
|---|---|---|---|---|---|---|
| **Symptomatic patients** | | | | | | |
| Markus et al[31] | 2005 | 200 | 89 (44.5%) | 3 months | 31 (15.5%) | 4.67 (1.99–11.01) |
| Censori et al[33] | 2000 | 50 | 20 (40%) | 0.6 months | 7 (14%) | 12.43 (1.36–113.41) |
| Altaf et al[34] | 2014 | 123 | 46 (37.4%) | Median 36 days (IQR 15–87) | 37 (30%) | HR 3.28 (1.68–6.42) |
| Molloy et al[35] | 1999 | 67 | 20 (42%) | 0.8 months | 9 (13%) | 12.12 (2.24–65.55) |
| **Asymptomatic patients** | | | | | | |
| Markus et al[30] | 2010 | 467 | 77 (16.5%) | 24 months | 32 (6.9%) | 2.50 (1.13–5.51) |
| Abbott et al[36] | 2005 | 231 | 60 (26%) | 70.8 months | 18 (7.8%) | 1.47 (0.4–4.48) |
| Spence et al[37] | 2005 | 319 | 32 (10%) | 12 months | 16 (5%) | 15.65 (5.34–45.88) |
| Siebler et al[38] | 1995 | 64 | 8 (12.5%) | 16.8 months | 5 (7.8%) | 31 (3–302) |

# Let's not throw the baby out with the bathwater !

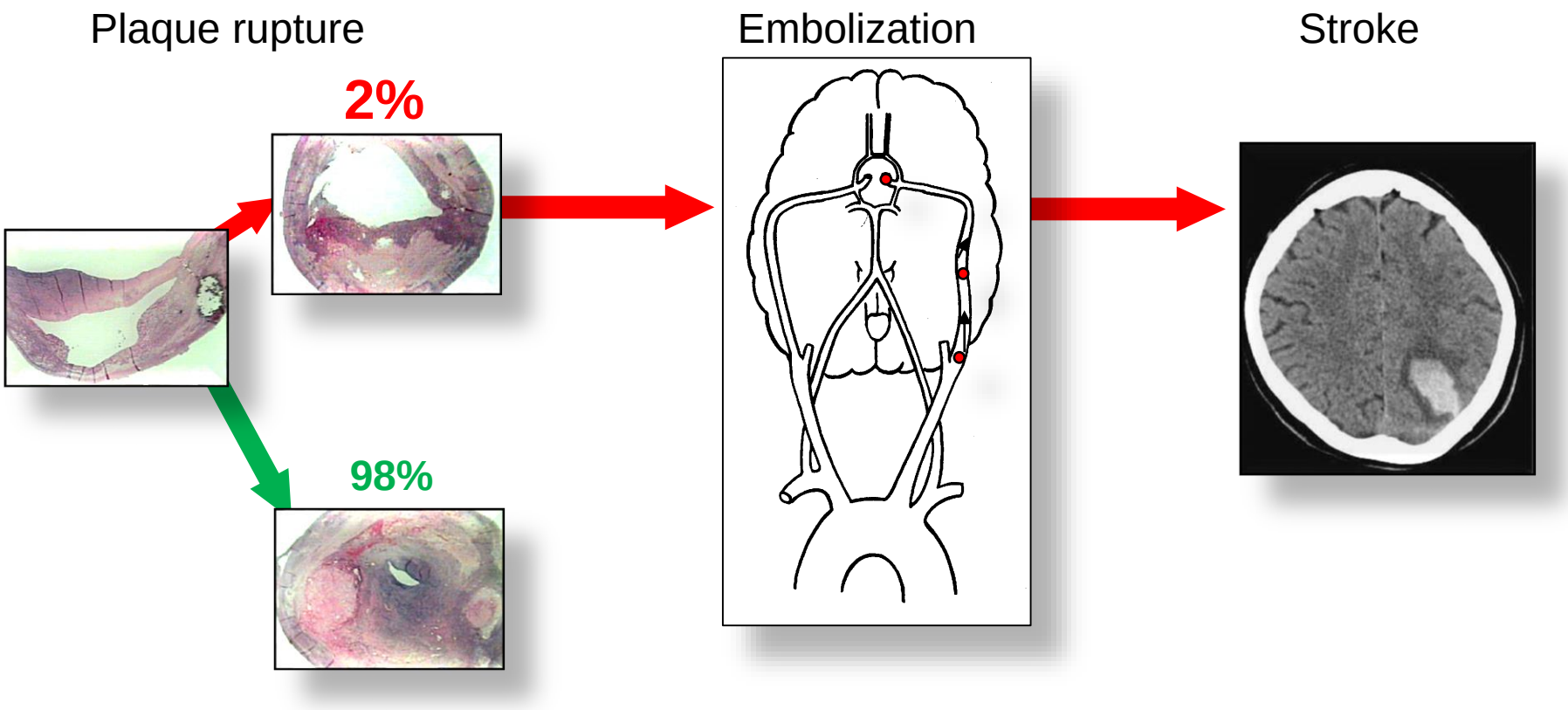
Appeal to the Enlightened,
Thomas Murner, 1512

# Carotid revascularization has become more selective and rates have declined



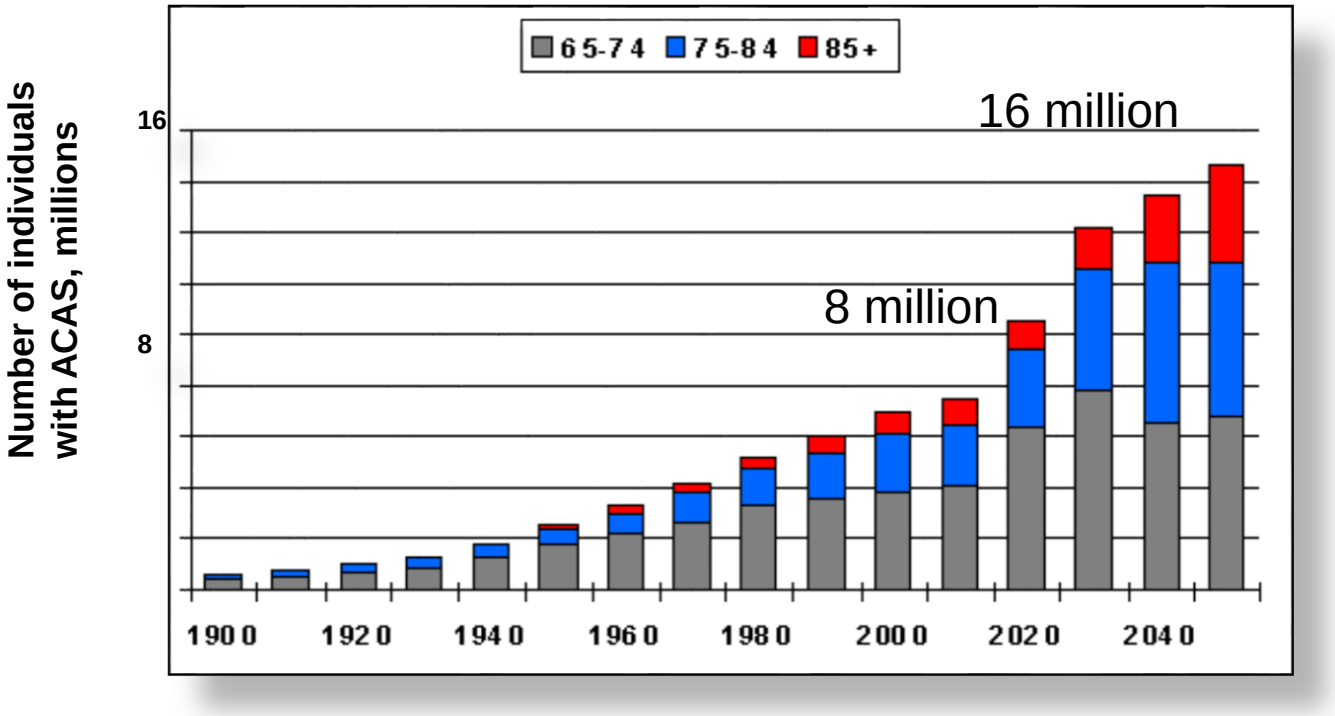

*Lichtman J & Lal BK et al, JAMA, 2017*

# Carotid artery stenosis
## Mechanism of end-organ damage




*Lal BK & Hobson RW, JSCV Dis 2006*

# “Asymptomatic” carotid artery stenosis




**10-15% of adults ≥65 years**

# Stroke is devastating
# And expensive to treat

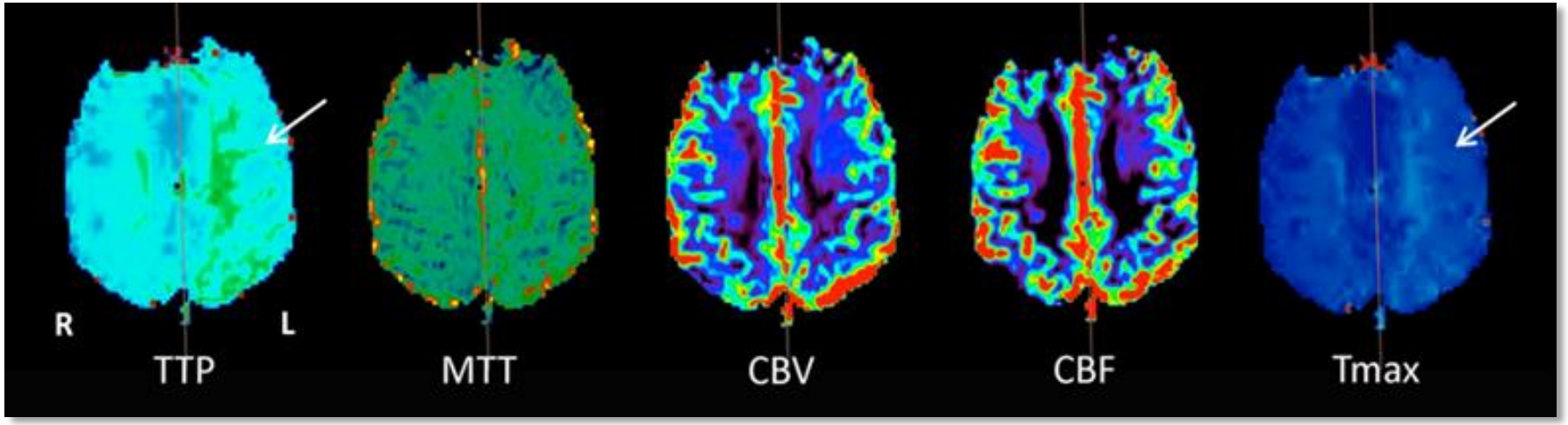
- Someone in the United States has a stroke every **40 seconds**
- Every **4 minutes**, someone dies of a stroke
- Stroke costs $34 billion per year

# Let's be part of the solution and not stand by the sidelines!

# CREST- H (Hemodynamics)

- **Goal**: To determine whether a subset of CREST-2 patients with cerebral **hemodynamic impairment** and mild **cognitive impairment** will benefit from revascularization

- **Additional testing**: MRI perfusion scan to look for hemodynamic flow failure at baseline



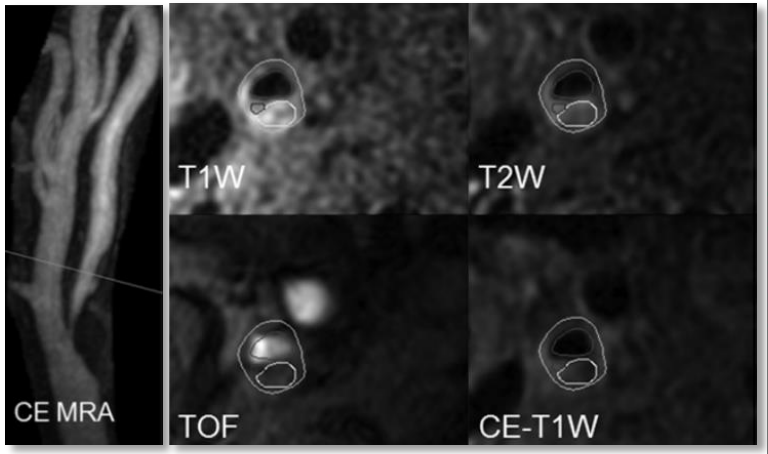


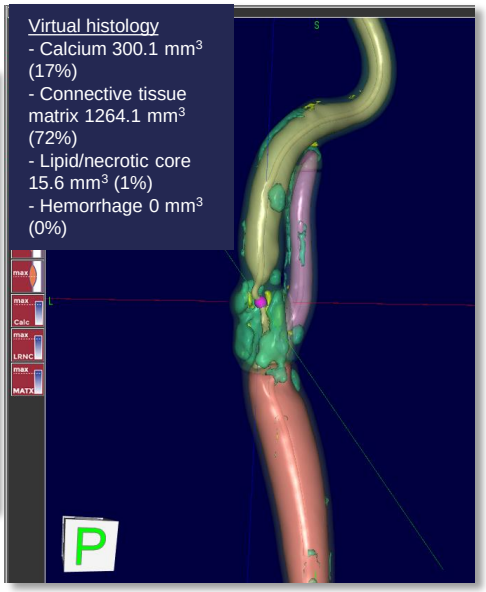

*Marshall R, Lazar R & Lal BK, NIH, 2018*

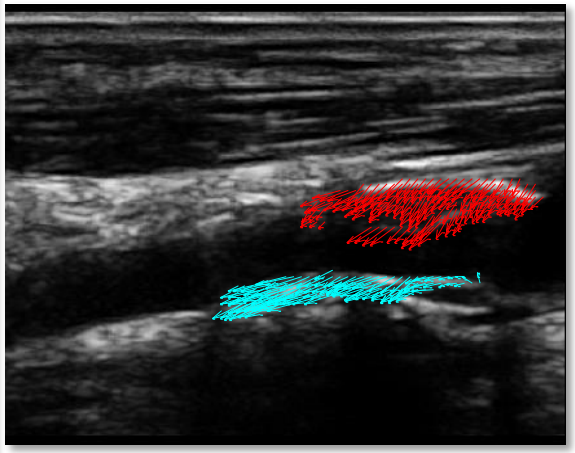
# CREST-M (Imaging)

- **Goal**: To determine whether carotid plaque disruption and stroke may be influenced by plaque **geometry**, plaque **histologic components**, plaque **biomechanical forces.**

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



*Lal BK and Huston J, NIH, 2018*

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