

Carotid Artery Disease and Stroke

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Conflicts of Interest

- **Consultant**

- Cordis Endovascular (Modest)
- Boston Scientific (Modest)
- Medtronic Vascular (Modest)
- Pathway Medical (Modest)
- Paragon IP (Modest)
- X-Tent, Inc (Modest)
- Harvard Clinical Research Institute (Modest)
- Bacchus Vascular, Inc (Modest)
- Baxter, Incorporated (Modest)
- ActivBiotics (Modest)

- **Equity**

- Access Closure, Inc (Modest)
- Square One, Inc (Modest)
- Vascular Therapies, Inc (Modest)
- Icon Interventional, Inc (Modest)
- Setagon (Modest)
- I.C.Sciences, Incorporated (Modest)

- **Speaker's Bureau**

- Bristol-Myers/Sanofi-Aventis Pharmaceuticals Partnership (Modest)

- **Research Support**

- Pfizer, Inc.
- Abbott Vascular
- Genzyme

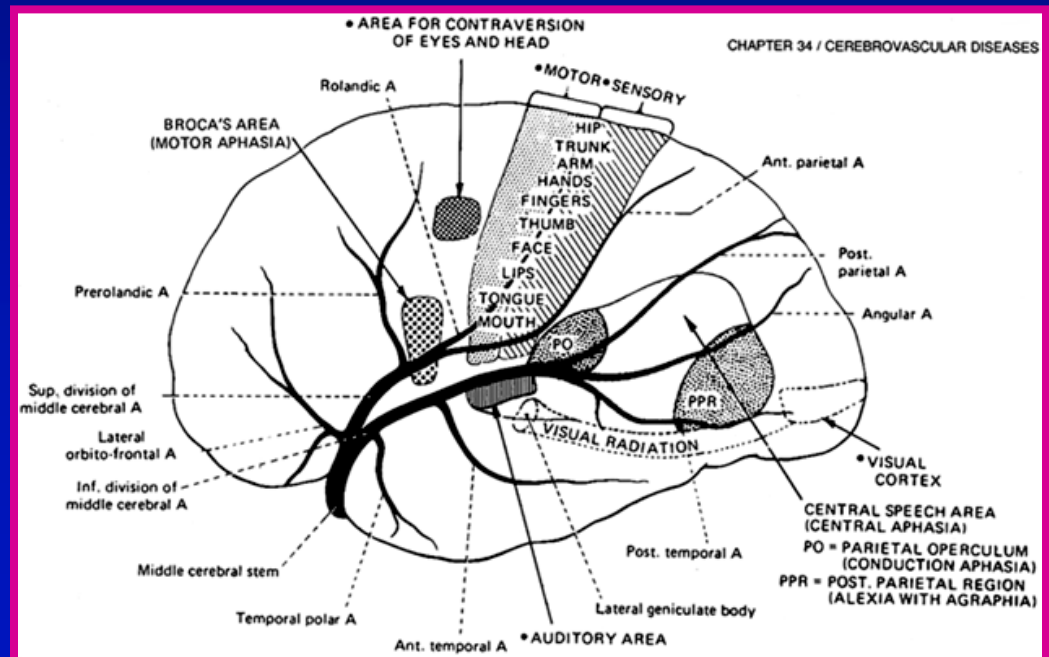
Burden of Stroke in the U.S.

- 1 stroke every 45 seconds (700,000 per year)
- 2.4 million non-institutionalized stroke survivors
- Stroke causes 1 in 15 deaths
- Approximately 30 % aged 70-80 have silent brain infarction
- Stroke cost= 58.8 billion/year



What is a Stroke?

- Reduction in arterial blood flow to the brain, resulting in ischemia to the brain itself
- The brain has geographic territories responsible for our higher functions



Transient Ischemic Attack (TIA)

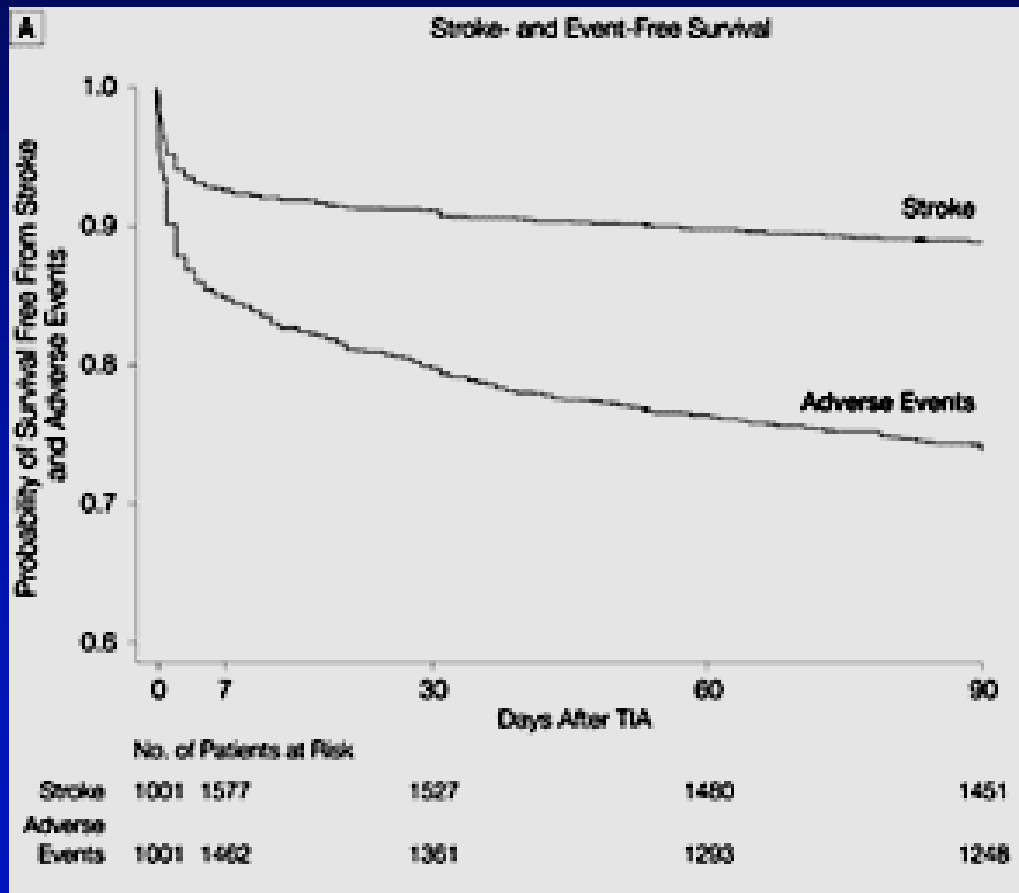
- 15% of all strokes are heralded by a TIA.
- 1/3 of TIAs would be infarction based on diffusion weighted MRI findings.
- Males and blacks have higher rates of TIA.
- Half fail to report TIA to their healthcare providers.
- 90-day risk of stroke is 3-17% after TIA, highest within the first 30 days.
- Carotid-associated TIA: 20% 90-day stroke risk

TIA Characteristics

- Duration <24 h, usually <15 min
- Symptoms:
 - motor and sensory dysfunction of contralateral limbs
 - pure sensory dysfunction
 - isolated aphasia/dysphasia
 - transient monocular blindness

TIAs Cause Early Stroke and Cardiovascular Events

Follow up of 1707 subjects diagnosed with TIA in ED



Risk Factors for Events:

	OR
Age > 60 y	1.8
Diabetes	2.0
>10 Min TIA	2.3
Weakness	1.9
Speech	1.5

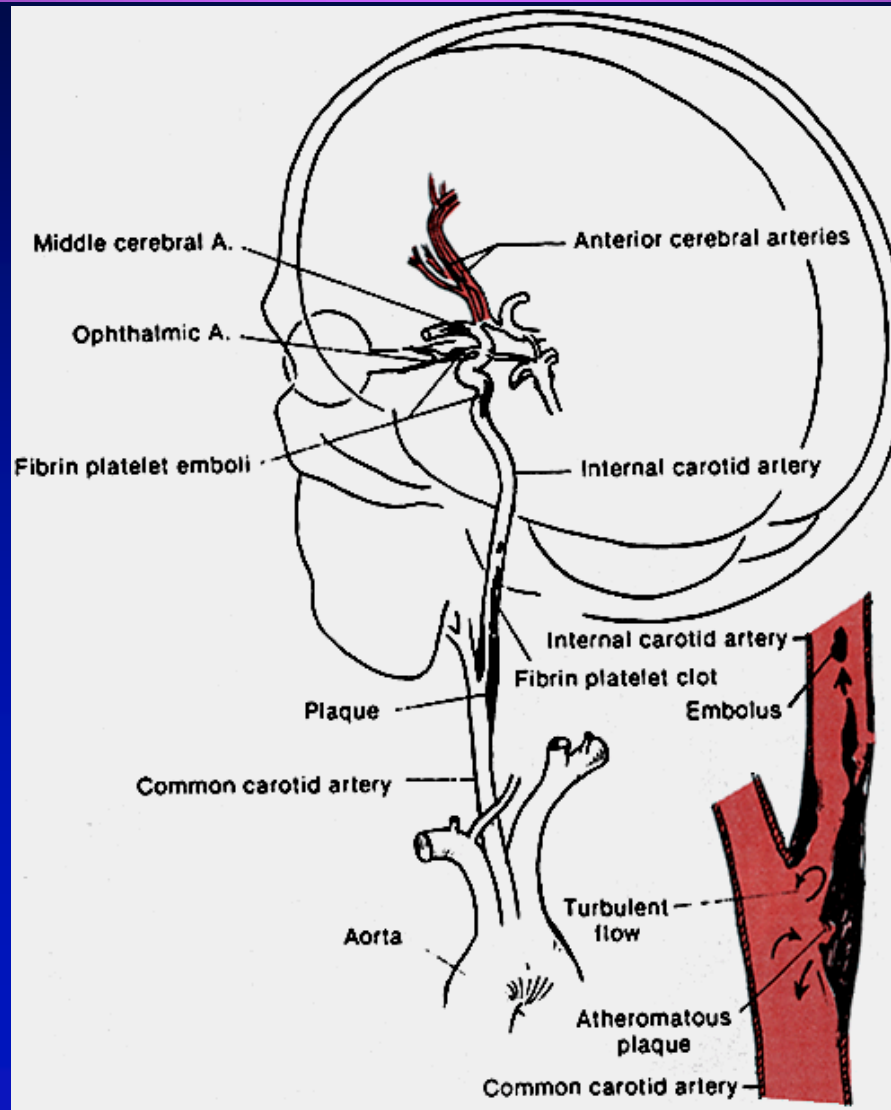
What Are The Common Causes of Ischemic Stroke?

TABLE 1. APPROXIMATE DISTRIBUTION OF MAJOR SUBTYPES OF ISCHEMIC STROKE.*

TYPE OF STROKE	PROPORTION OF STROKES (%)
Large-vessel atherothrombotic	15
Due to internal-carotid-artery stenosis	9
Small-vessel (lacunar)	25
Embolic	60
Due to atrial fibrillation	15
Other (due to dissection or other causes)	3

*The data are from the Stroke Data Bank of the National Institute of Neurological and Communicative Disorders and Stroke² and the Framingham Study.³The percentages do not total 100 because of a modification of the categories of stroke used.

Artery to Artery Embolism



Does Risk of Stroke Increase with Greater Degrees of ICA Stenosis?

- 696 Patients evaluated with Carotid Duplex Ultrasonography
- 369 Male/327 Female
 - Mean Age 64 years
- Mean Follow-Up 41 months
- Duplex Ultrasonography Categories
 - Mild <50% Stenosis
 - Moderate 50-75% Stenosis
 - Severe >75% Stenosis

Vascular Risk of Asymptomatic Carotid Stenosis

Category	N	TIA	CVA	Cardiac Event	Vascular Death
<50%	303	1	1.3	2.7	1.8
50-75%	216	3	1.3	6.6	3.3
>75%	177	7.2	3.3	8.3	6.5

75% of Events were Ipsilateral to the Stenosis

What Can the Physical Exam Tell You About the Etiology of Stroke?

Atrial Fib/Flutter, Bradycardia	Likely Cardiogenic Embolus
No pulse below knee	Recurrent systemic embolus
Carotid Bruit	Severe Extracranial Carotid Stenosis
Head/Orbital Bruit	AV Malformation
Fever and Acute CVA	Endocarditis and Cardiogenic Embolus
Stroke and Altered MS	Check Glucose, EtOH, Narcotics, O/D, other Toxins

Cervical Bruit

- Marker of systemic atherosclerosis
- Not indicative of severity of internal carotid artery stenosis
 - NASCET: Sensitivity 63%/Specificity 61%
- Frequency of Cervical Bruits
 - ~1-3% in adults aged 45-54 years
 - ~8% in adults ≥ 75 years

Causes of Cervical Bruit (Systolic, Diastolic, or Both)

- Carotid atherosclerosis
- Thyrotoxicosis
- Transmitted cardiac murmur
 - Aortic Stenosis (systolic)
 - Aortic Insufficiency (diastolic)
- Arteriovenous Fistula (systolic/diastolic)
- Venous Hum (systolic or systolic/diastolic)

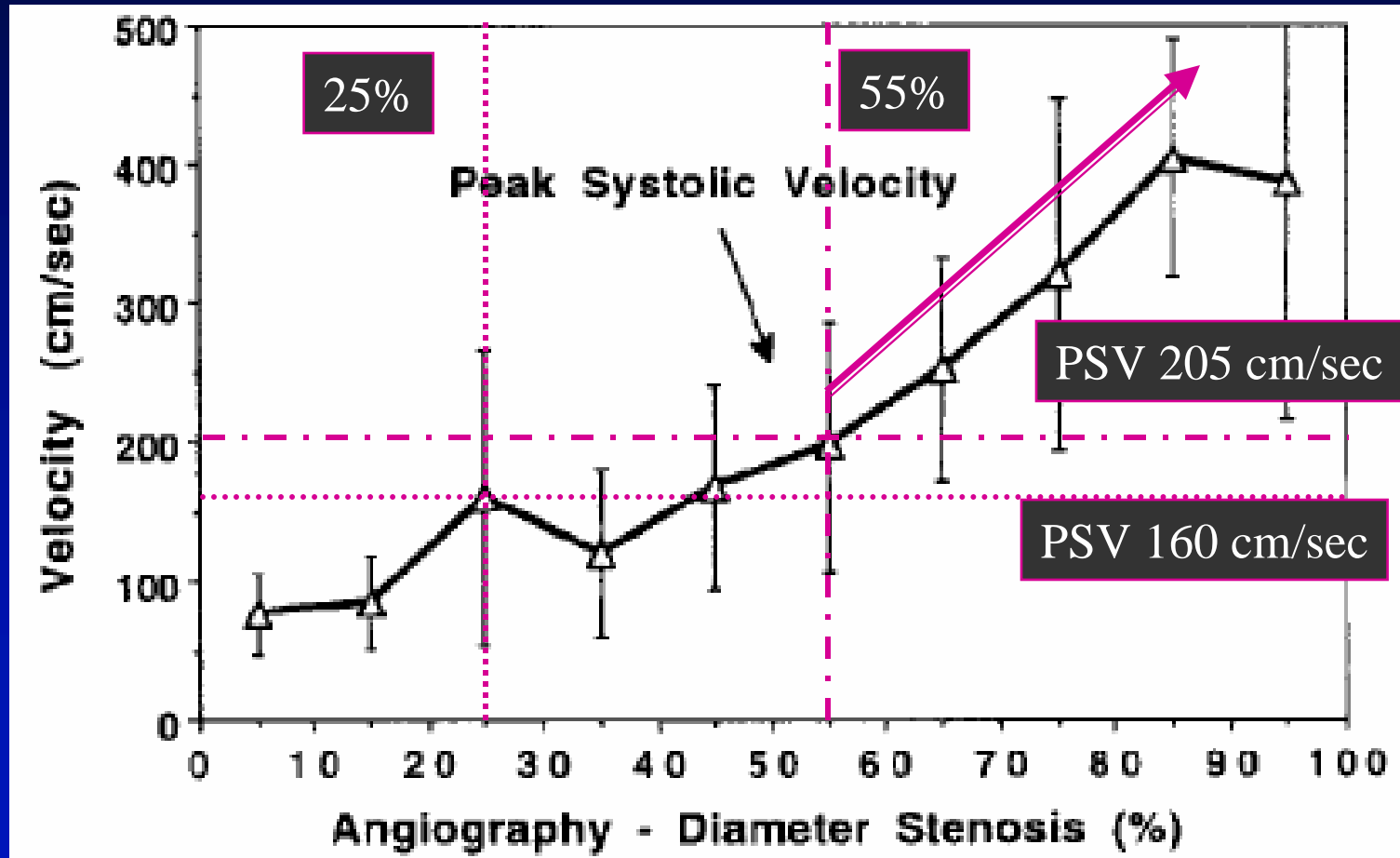
The Diagnosis of Carotid Artery Disease

- Complete neurologic history and physical examination
- Complete medical history and physical examination
- Carotid Duplex Ultrasonography
- (?) Magnetic Resonance Arteriography
- (?) CT Angiography
- (?) Arteriography

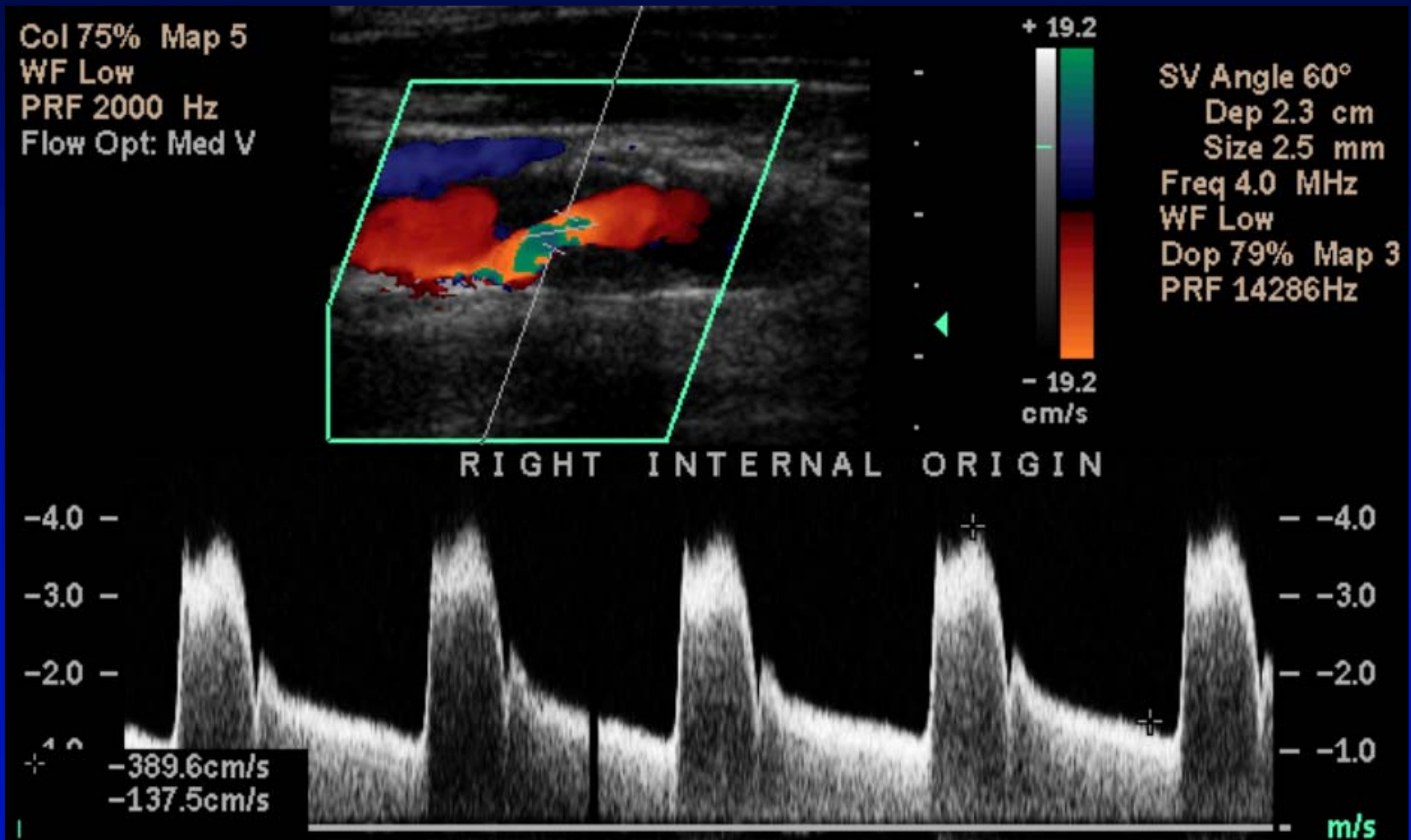
Indications for Carotid Duplex Ultrasonography

- Cervical bruit in an asymptomatic individual
- Amaurosis Fugax
- Transient Ischemic Attack
- Stroke in a potential candidate for CE or stent
- Follow-up of known stenosis (>20%) in asymptomatic individuals
- Follow-up after carotid endarterectomy or stent
- Intraoperative assessment of carotid endarterectomy
- Drop attacks (rare)

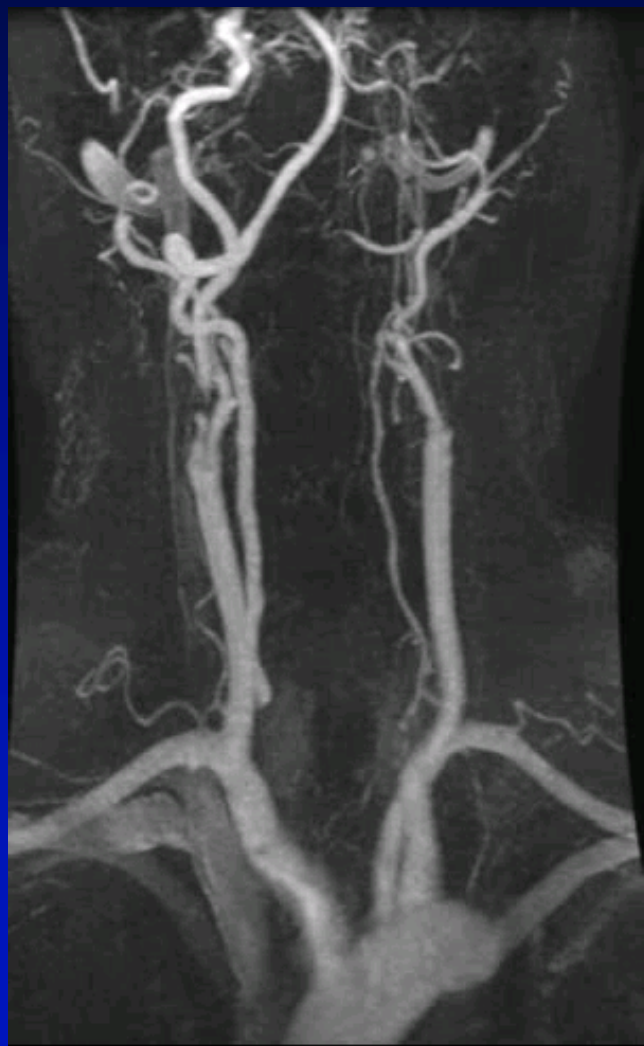
What is the Relationship Between PSV and Carotid Arteriographic Stenosis



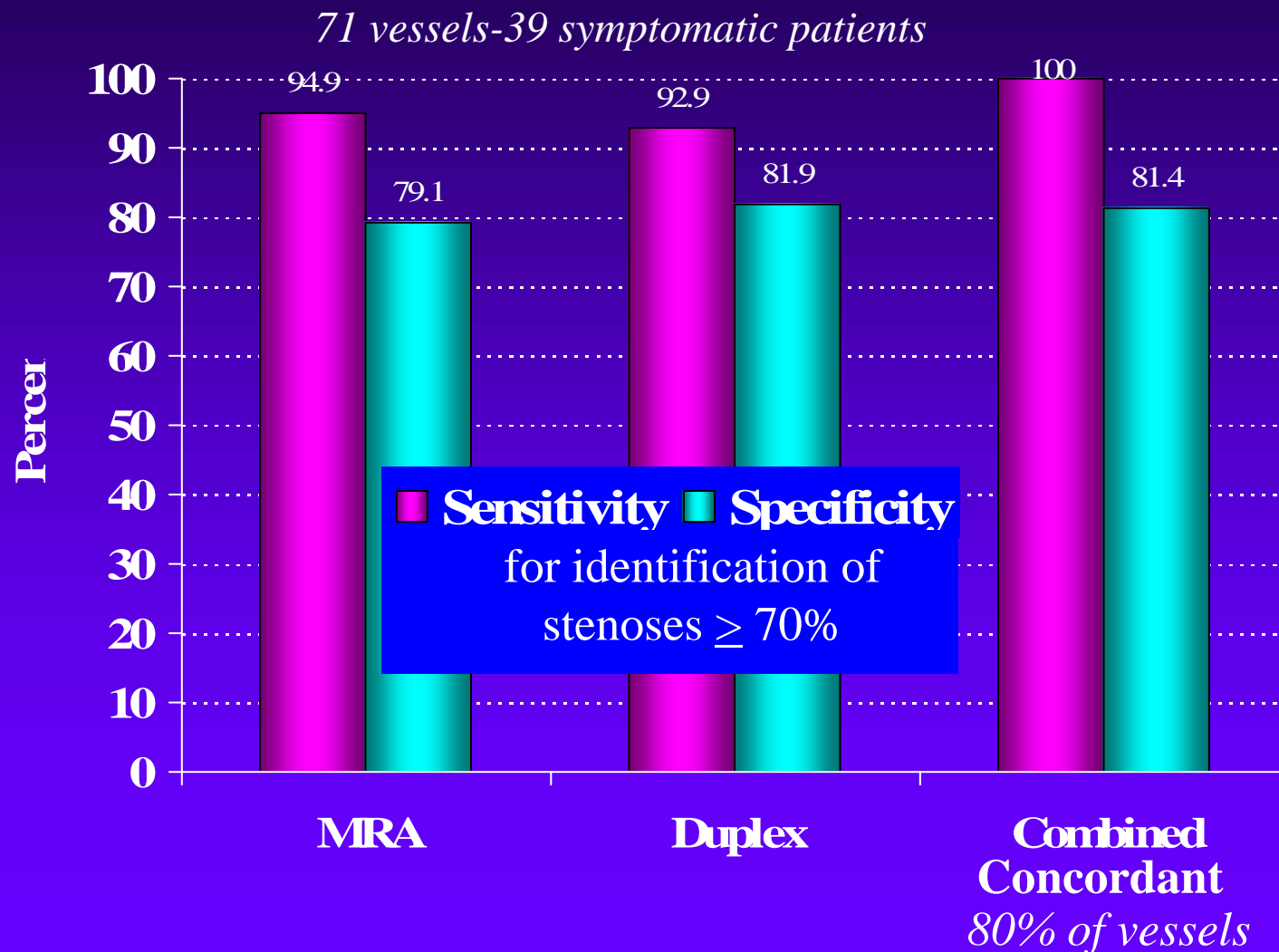
80-99% Internal Carotid Artery Stenosis



Carotid MRA



Preoperative Evaluation of Carotid Artery Stenosis: Comparison of Contrast-MR Angiography and Duplex Ultrasonography with Digital Subtraction Angiography

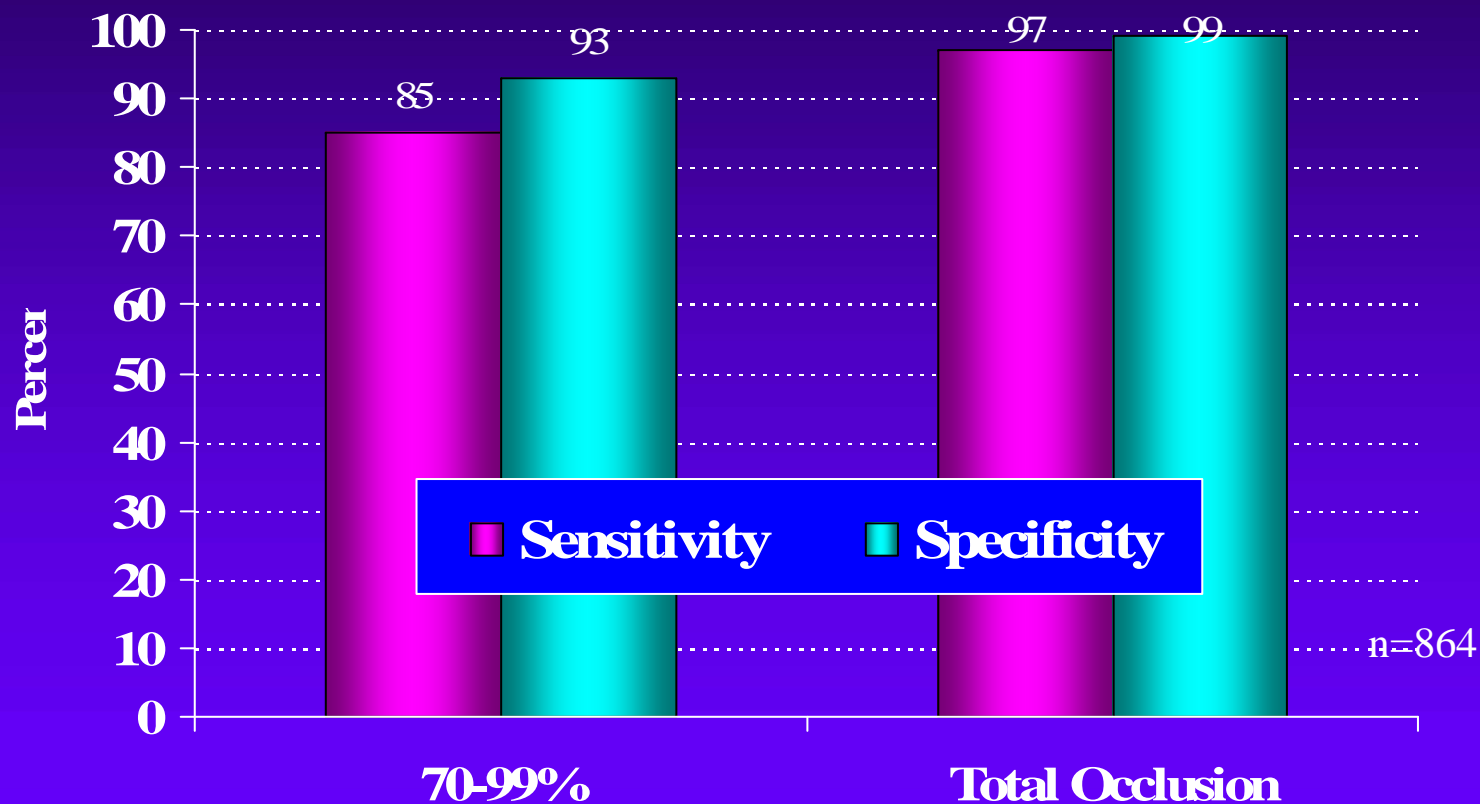


CT Angiography

- New and emerging technology
- Requires intravenous iodinated contrast
- Requires significant radiation exposure
- Allows for three dimensional wide field of view
- Able to detect and characterize calcification

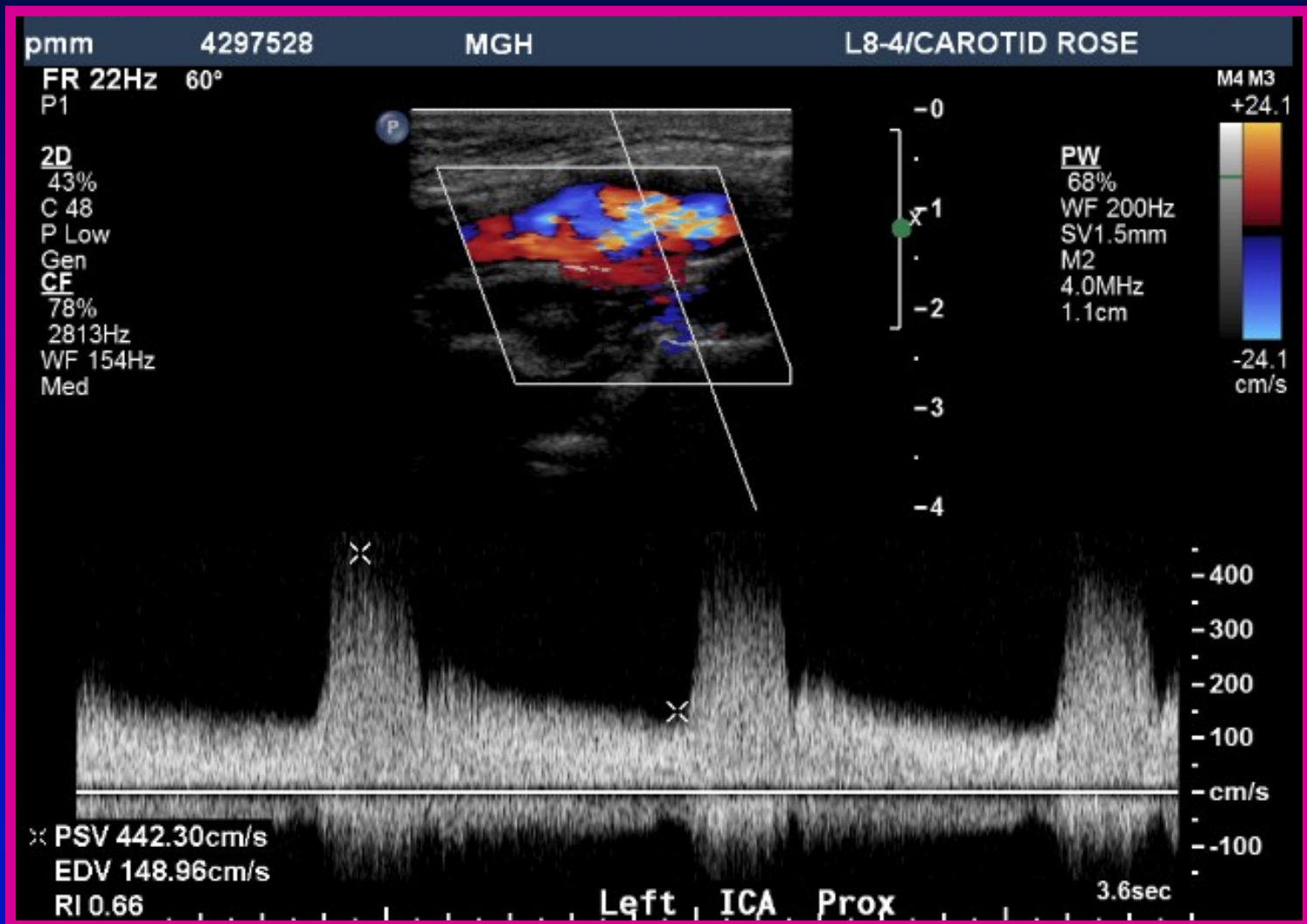
CTA for Assessment of Carotid Disease

meta-analysis of 28 studies



Carotid Duplex Ultrasonography

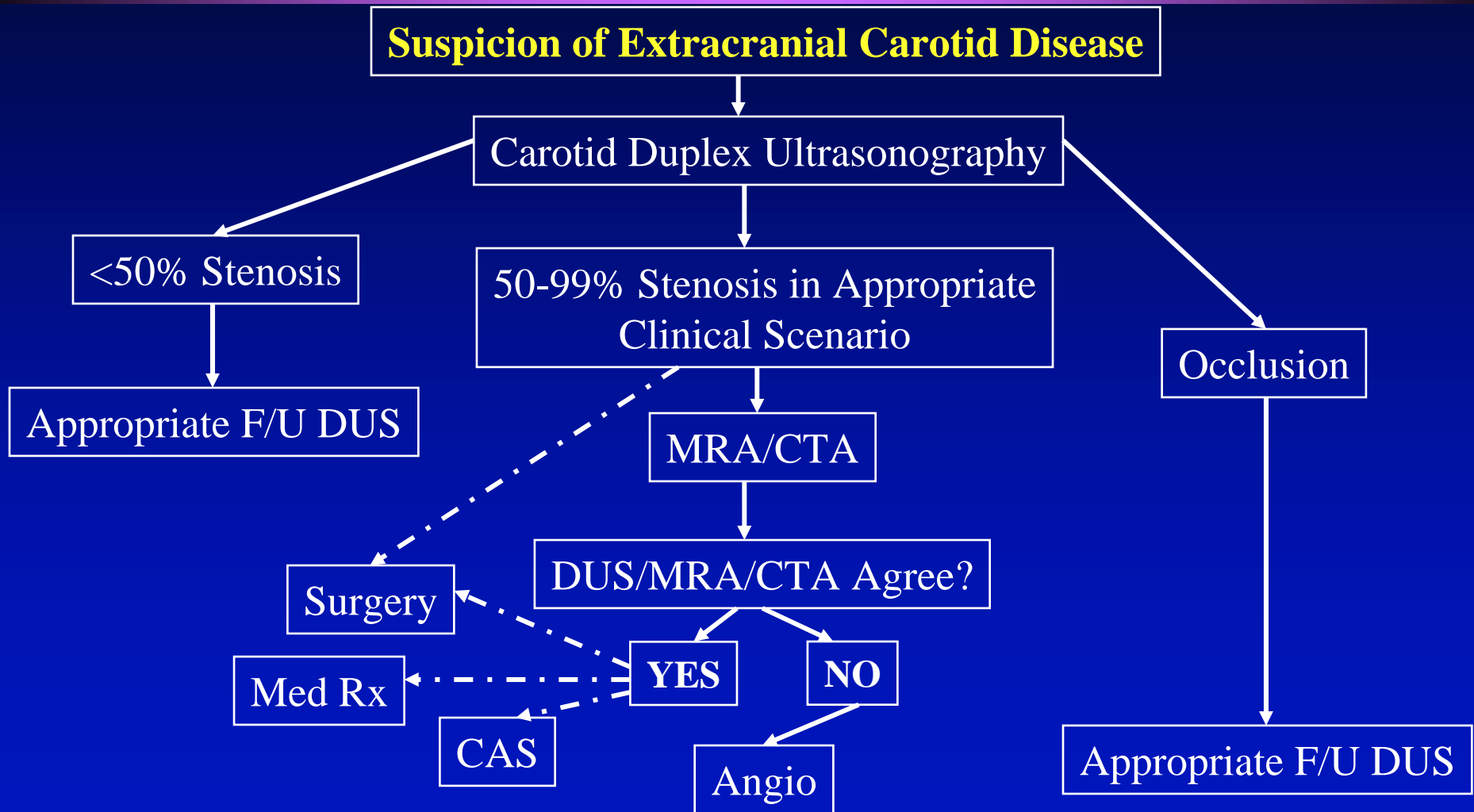
Ipsilateral to Bruit



CT Angiogram

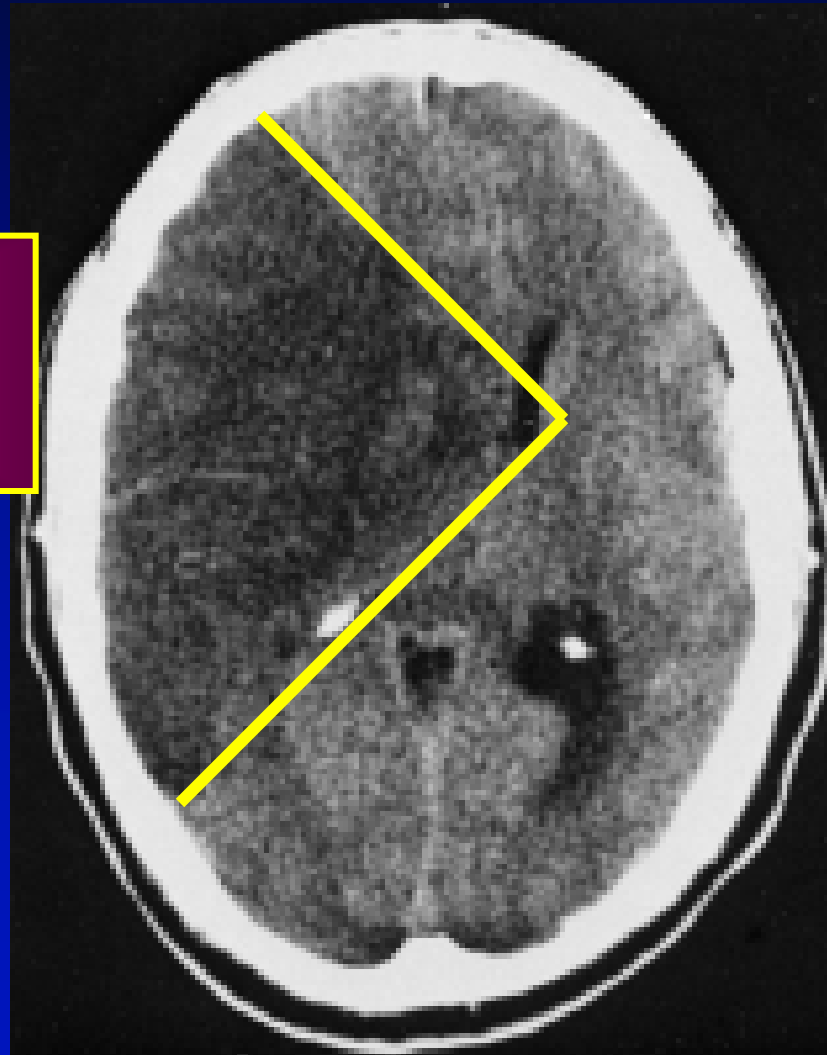


Modern Diagnostic Algorithm for Extracranial Carotid Disease



Once in an ED, You Must Get an Imaging Test IMMEDIATELY!

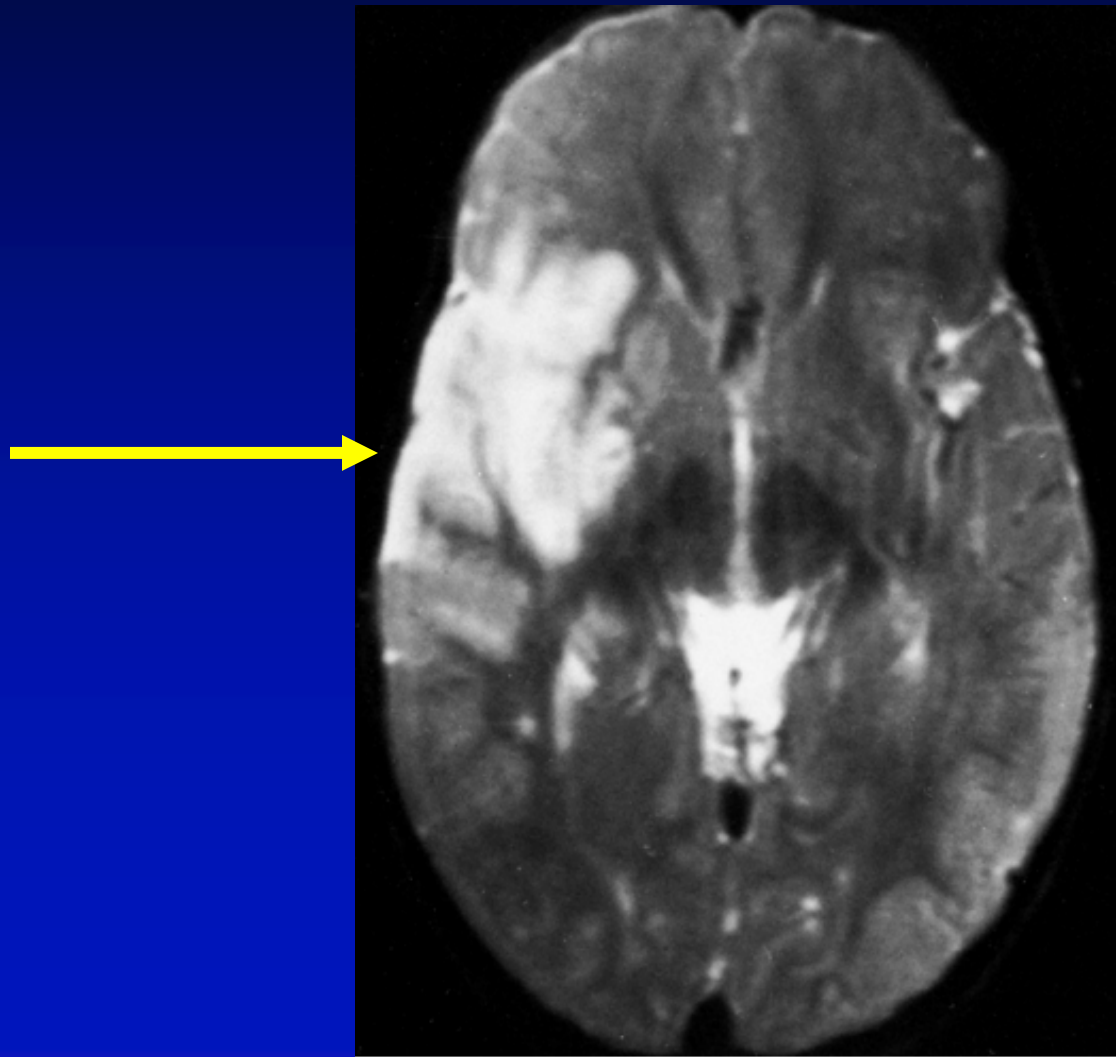
Classic Wedge-Shaped Acute Right MCA Stroke



Important Characteristics of the CT Scan

- Within 3 hours of onset of ischemia, the CT *without contrast* is virtually normal
- After 6-12 hours, there is evidence of hypodensity with brain edema
- Hemorrhage
 - Appearance will describe type
 - Subdural Hematoma: Crescent shape below dura
 - Subarachnoid Hemorrhage: Diffuse blood pattern along surface of brain in subarachnoid space
 - 5% of SAH have NORMAL CT!!! MUST perform Lumbar Puncture
 - Discern between SAH and traumatic LP
 - RBC Count in 4 tubes all similar
 - Xanthochromic Supernatant---old RBCs consistent with SAH

MRI Demonstrating Acute Right MCA CVA



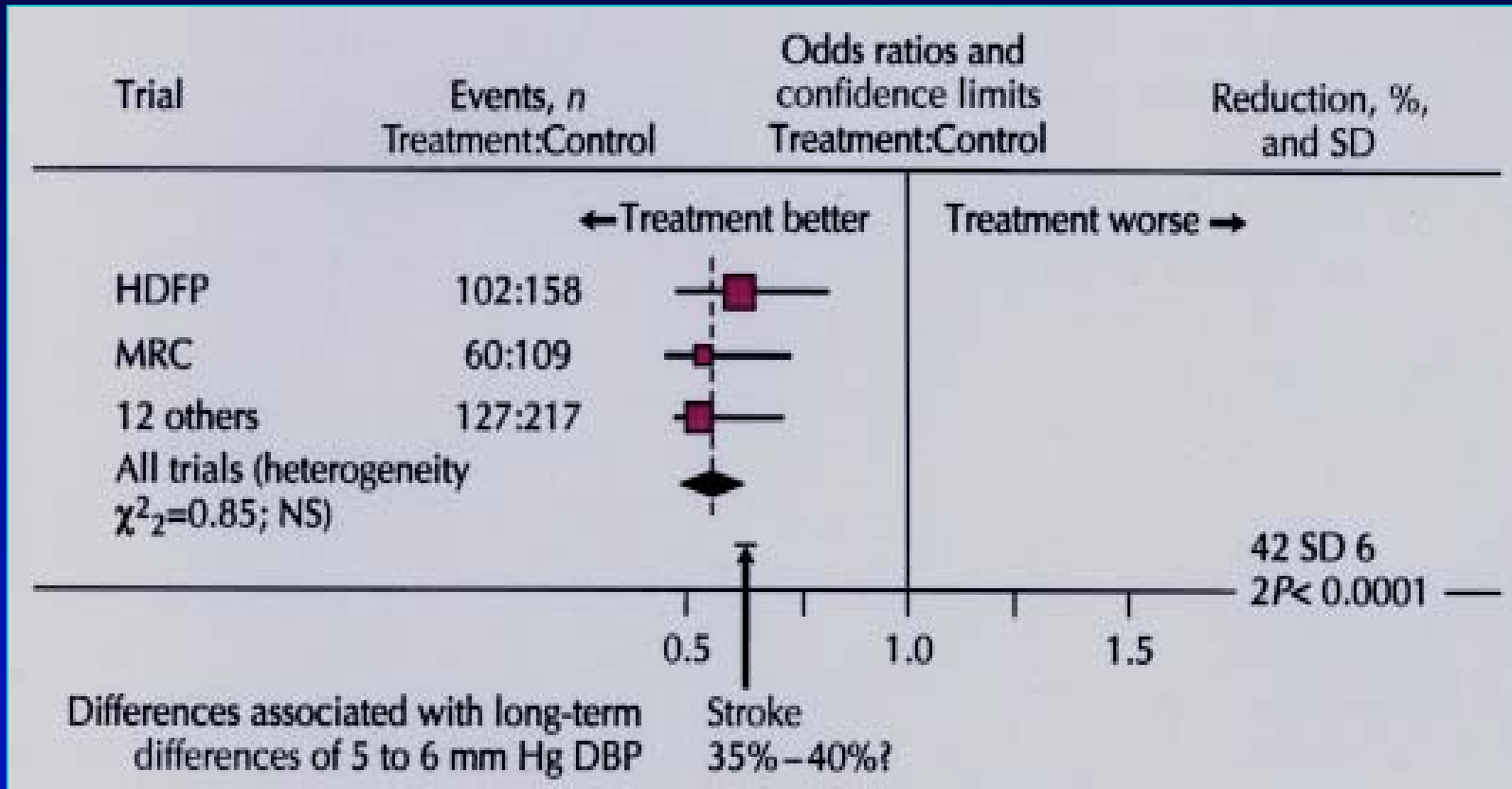
Stroke Prevention Strategies

- Reduction in Blood Pressure
- Cessation of Tobacco Use
- Reduction in Serum Cholesterol
- Aggressive Glycemic Control
- Antiplatelet Therapy
- Revascularization of Carotid Stenosis

Control of Hypertension

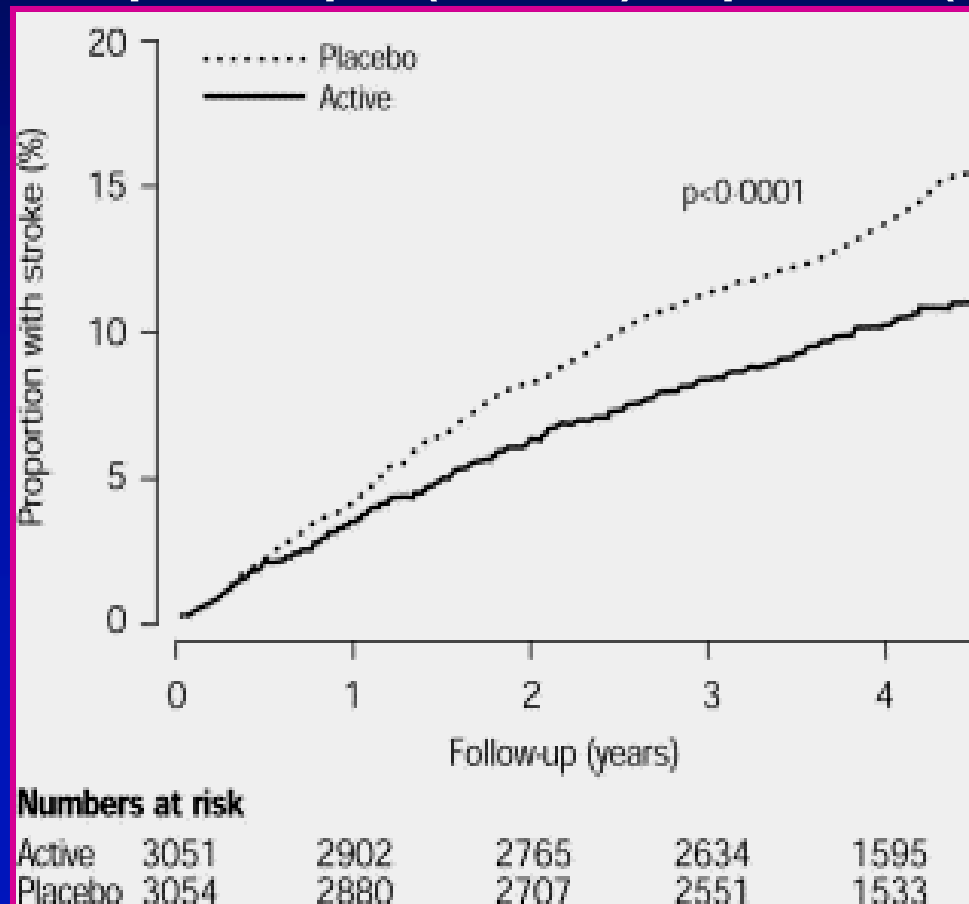
- The most potent risk factor for stroke
- A factor in nearly 70% of all strokes
- 10-12 fold increase in risk when comparing highest diastolic BP compared to the lowest

Effect of Diuretic Therapy on Risk of Stroke in Patients with Hypertension



ACE Inhibition Prevents Recurrent Stroke: *The Progress Trial*

6105 subjects with previous stroke randomly assigned to perindopril (n=3051) or placebo (n=3054).



Stroke Prevention Strategies

- Reduction in Blood Pressure
- **Cessation of Tobacco Use**
- Reduction in Serum Cholesterol
- Aggressive Glycemic Control
- Antiplatelet Therapy
- Revascularization of Carotid Stenosis

Risk of CVA Among Women Who Smoke and Have Partners Who Smoke

5379 Women Who Smoke Followed for 8.5 Years

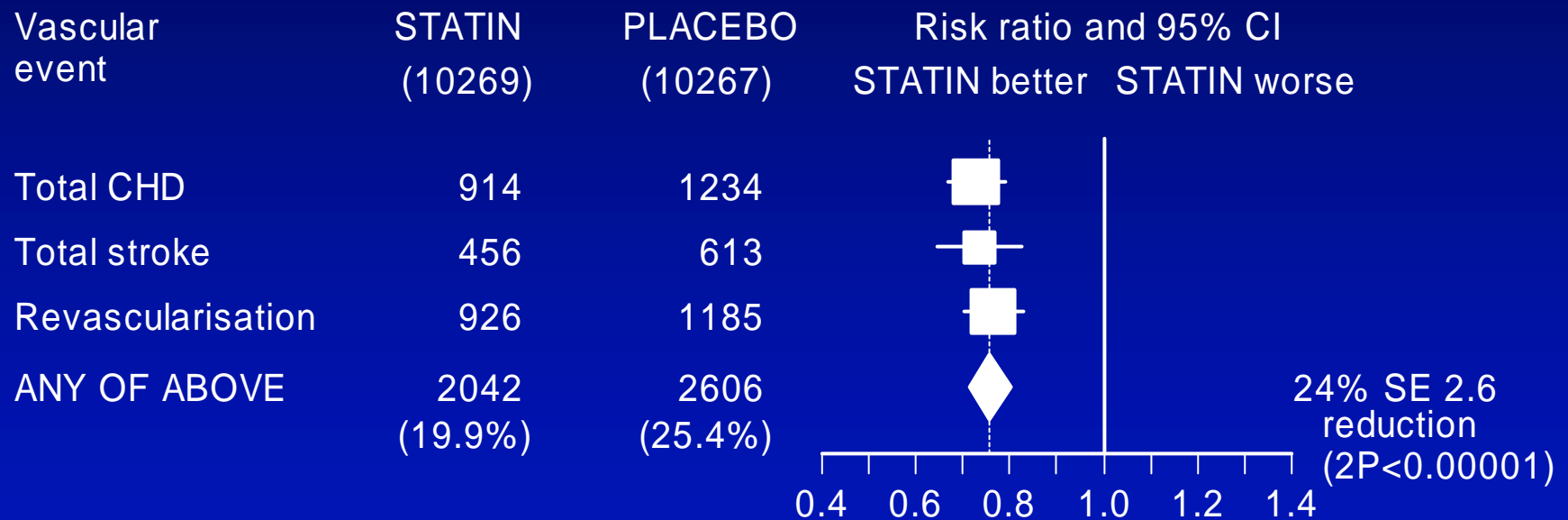
Participants	Sample Size	No. of Events	Event Rate/100	Age-Adjusted RR (95% CI)	Multivariate-Adjusted RR (95% CI)	<i>P</i>
Cardiovascular diseases						
Cigarette-smoking women with nonsmoking spouse	443	28	6.3	Reference	Reference	Reference
Cigarette-smoking women with cigarette-smoking spouse	1904	174	9.1	1.4 (0.95–2.1)	1.4 (0.9–2.0)	0.1
All strokes						
Cigarette-smoking women with nonsmoking spouse	443	2	0.5	Reference	Reference	Reference
Cigarette-smoking women with cigarette-smoking spouse	1904	49	2.6	5.7 (1.4–24)	5.7 (1.4–24)	0.02
Ischemic stroke						
Cigarette-smoking women with nonsmoking spouse	443	2	0.5	Reference	Reference	Reference
Cigarette-smoking women with cigarette-smoking spouse	1904	43	2.3	5.1 (1.2–21)	4.8 (1.2–20)	0.03

Stroke Prevention Strategies

- Reduction in Blood Pressure
- Cessation of Tobacco Use
- **Reduction in Serum Cholesterol**
- Aggressive Glycemic Control
- Antiplatelet Therapy
- Revascularization of Carotid Stenosis

Statins Decrease the Risk of Stroke in High Risk Patients: *Heart Protection Study*

SIMVASTATIN: MAJOR VASCULAR EVENTS

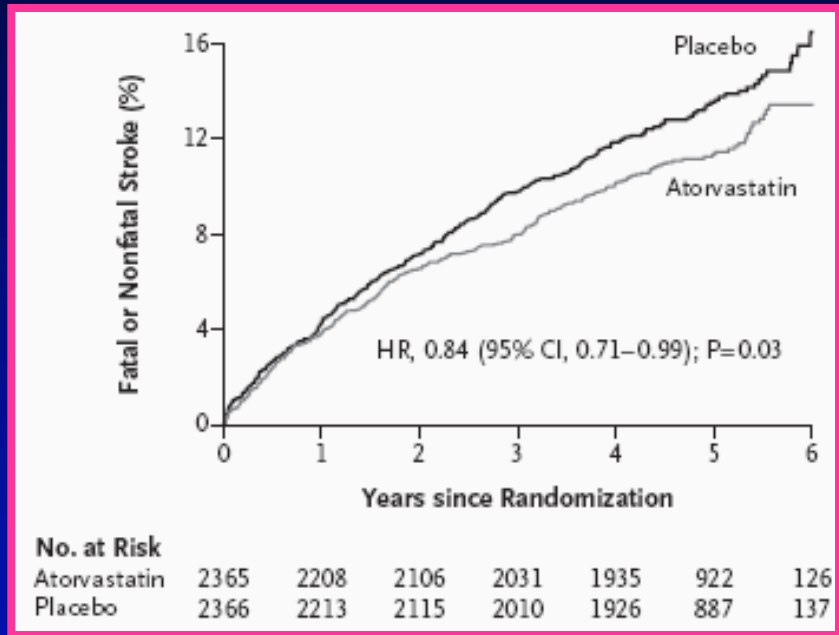


50% reduction in CEA or angioplasty
(simvastatin 42 [0.4%] vs placebo 82 [0.8%]; P=0.0003)

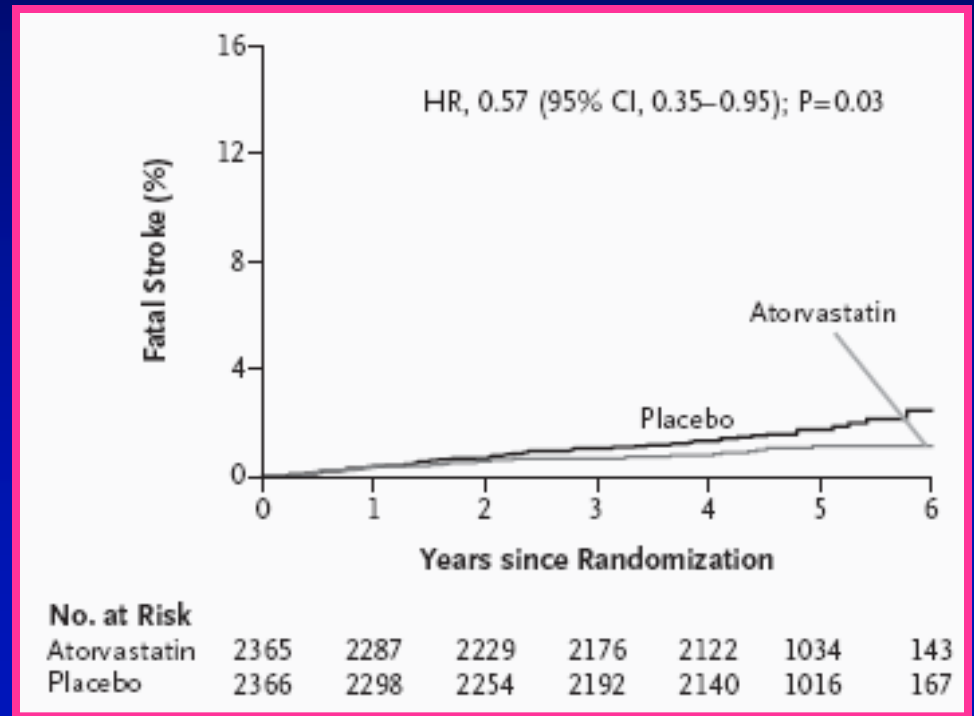
SPARCL

- 4731 patients with recent CVA/TIA (1-6 months before randomization)
- NO KNOWN CAD
- LDL-C 100-190 mg/dL
- Randomized to Placebo vs Atorvastatin 80 mg/d
- Primary Endpoint:
First non-fatal or fatal stroke

SPARCL



Primary Endpoint



Fatal Stroke

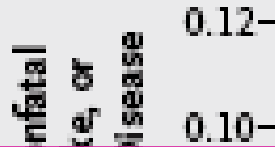
Stroke Prevention Strategies

- Reduction in Blood Pressure
- Cessation of Tobacco Use
- Reduction in Serum Cholesterol
- **Aggressive Glycemic Control**
- Antiplatelet Therapy
- Revascularization of Carotid Stenosis

Diabetes Control and CV Events

- The DCCT (**D**iabetes **C**ontrol and **C**omplications **T**rial)
 - 1441 patients with Type 1 DM (1983-1993)
 - Randomized to conventional vs intensive glycemc control
 - Treated for mean of 6.5 years
 - 93% followed until February 2005
- CV Disease defined as: Non-Fatal MI, CVA, Death due to CV Disease, Angina, Need for CABG/PCI)

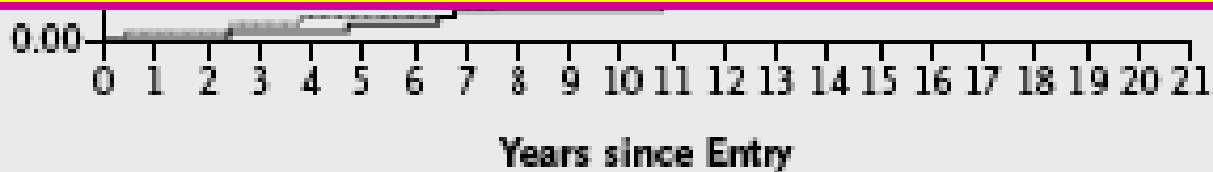
Cumulative Incidence of Non-Fatal MI, CVA, CV Death



nonfatal
MI, CVA,
or CV death

Intensive Treatment:

- Reduced Risk of ANY CV Event by **42%**
- Reduced Risk of Non-Fatal MI, CVA, CV Death by **57%**
- Reduction in HbA1C explained vast majority of benefit



0.00

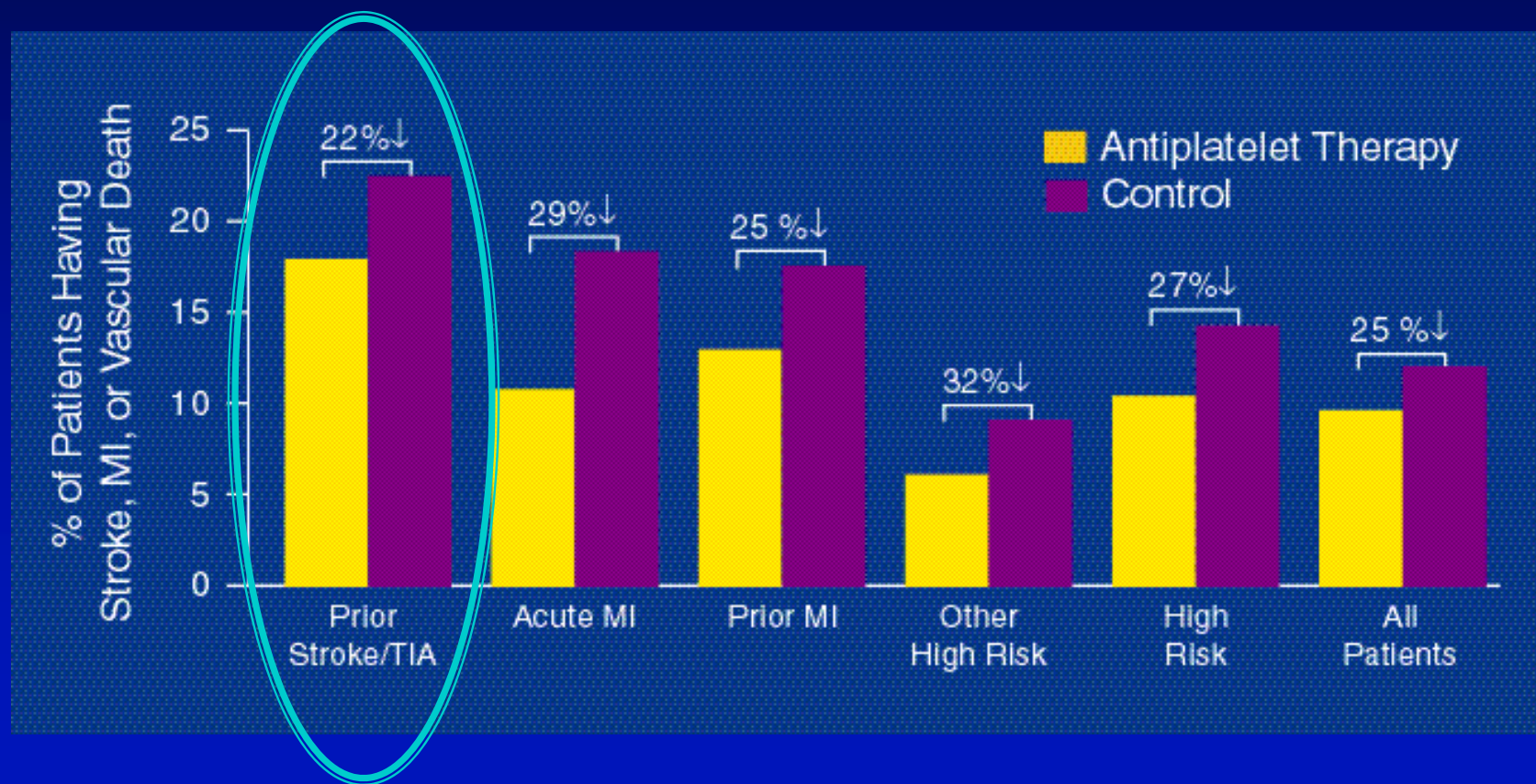
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21

Years since Entry

Stroke Prevention Strategies

- Reduction in Blood Pressure
- Cessation of Tobacco Use
- Reduction in Serum Cholesterol
- Aggressive Glycemic Control
- **Antiplatelet Therapy**
- Revascularization of Carotid Stenosis

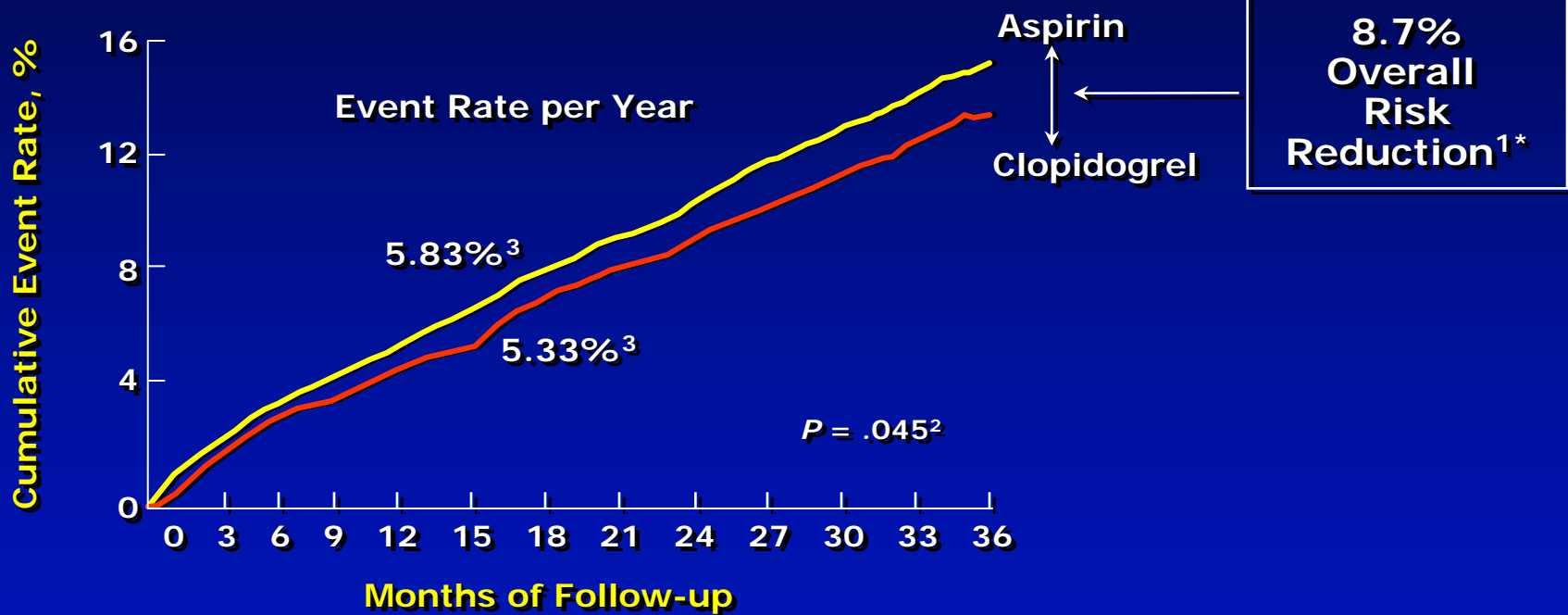
Antiplatelet Trialists' Collaboration Efficacy in Prevention of Ischemic Events



Antiplatelet Trialists' Collaboration. *BMJ*. 1994;308:81–106.

Clopidogrel vs Aspirin to Prevent Recurrent Ischemic Events

Primary Analysis of MI, Ischemic Stroke, or Vascular Death

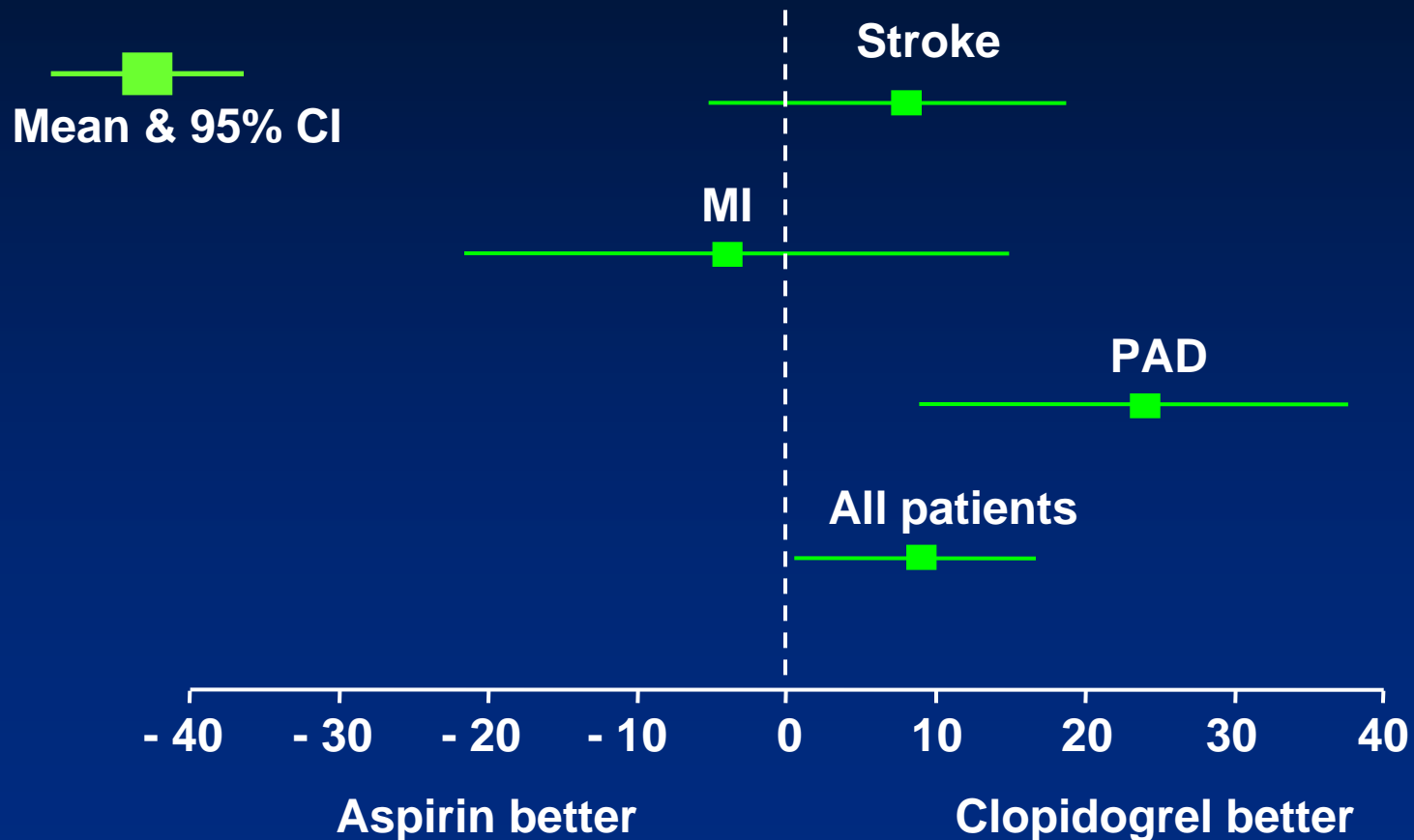


* ITT analysis.

¹ CAPRIE Steering Committee. *Lancet*. 1996;348:1329-1339.

CAPRIE Study

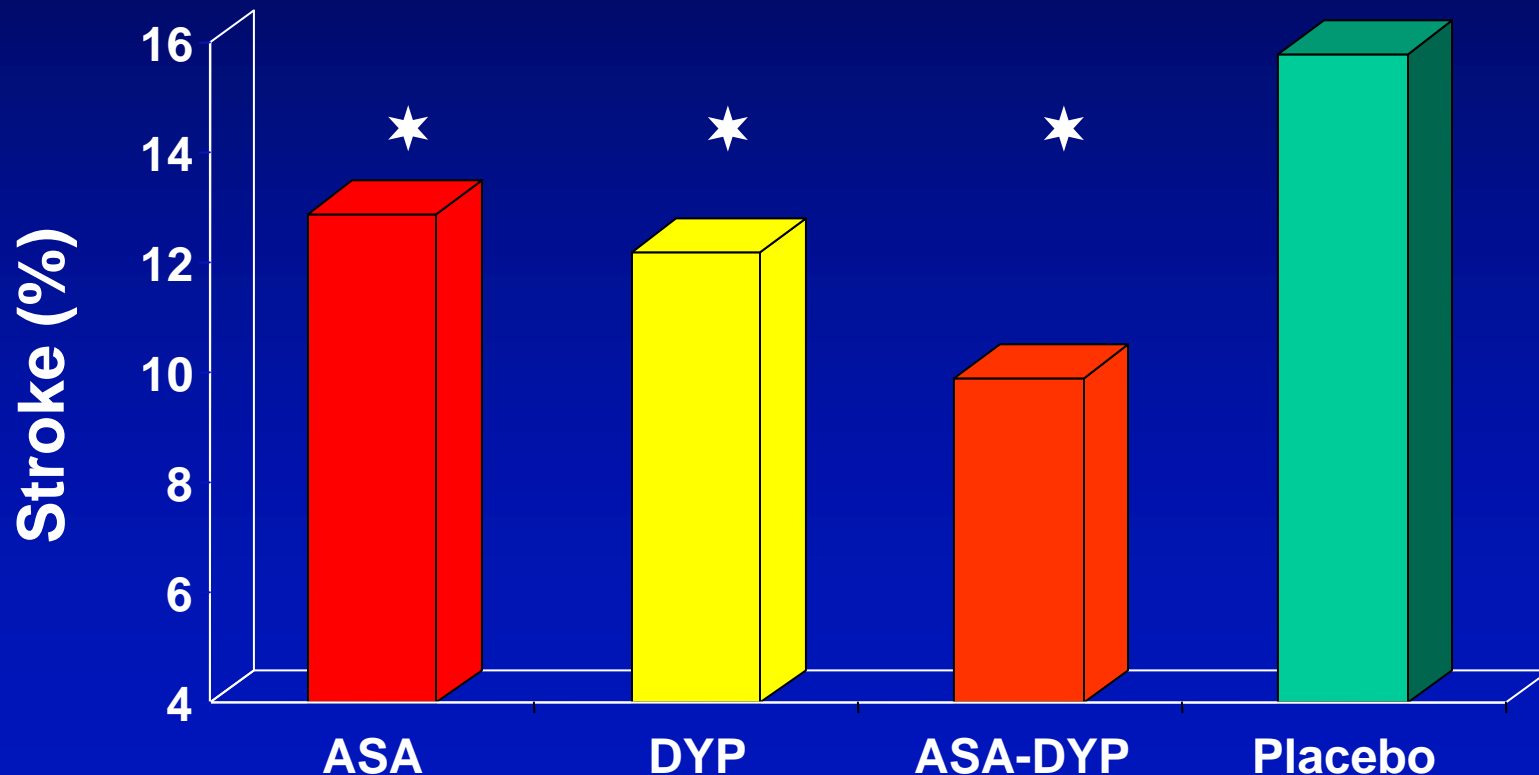
Outcome by Subgroup



Aspirin & Dipyridamole Decreases Stroke after TIA

European Stroke Prevention Study

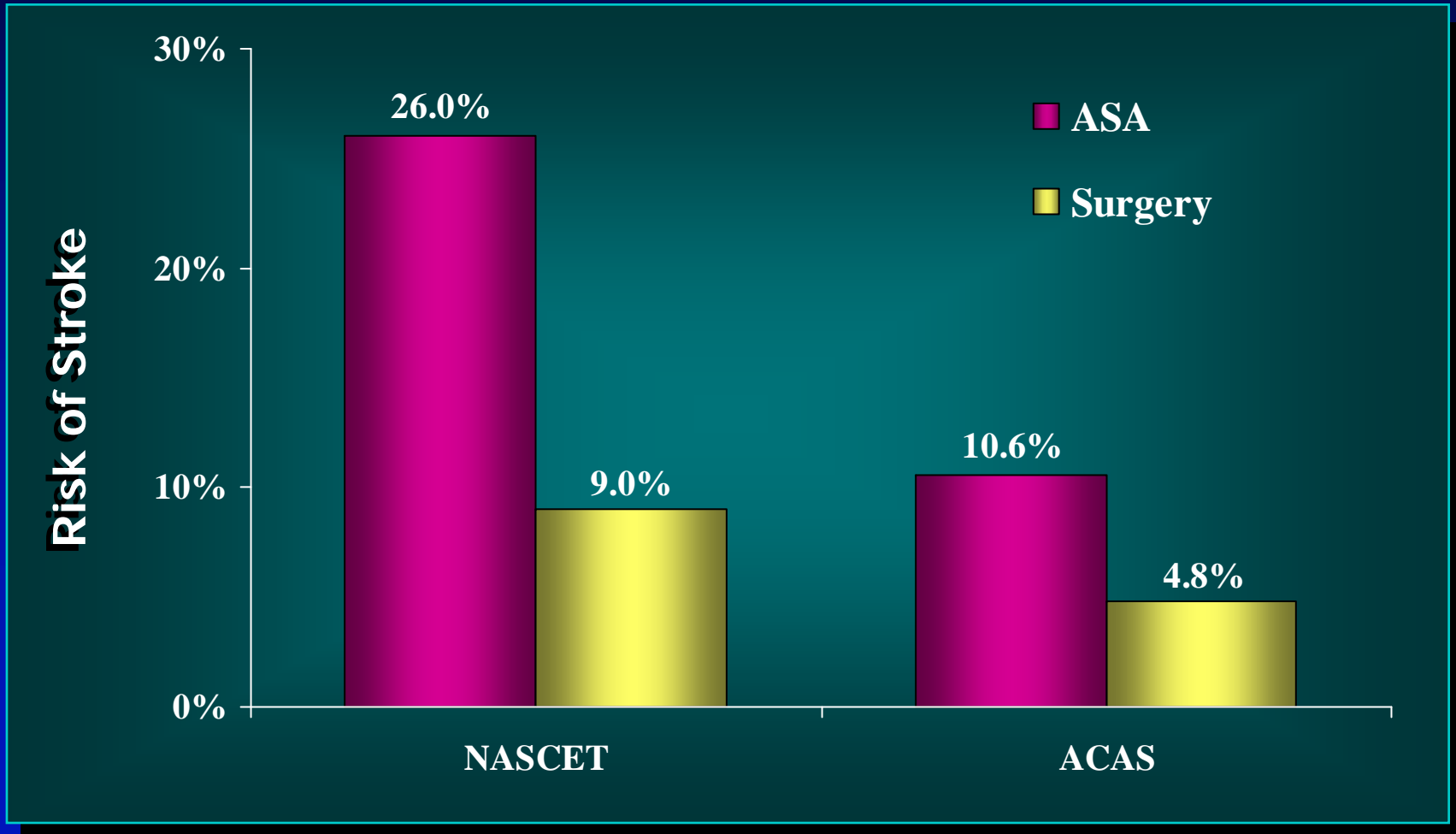
6602 pts with recent TIA or CVA followed for 2 years



So, What Works in Preventing Stroke?

- Reduction in Blood Pressure
- Cessation of Tobacco Use
- Reduction in Serum Cholesterol
- Aggressive Glycemic Control
- Antiplatelet Therapy
- **Revascularization of Carotid Stenosis**

Surgery for Carotid Stenosis



Early vs Deferred Carotid Endarterectomy in Asymptomatic Patients with >70% ICA Stenosis

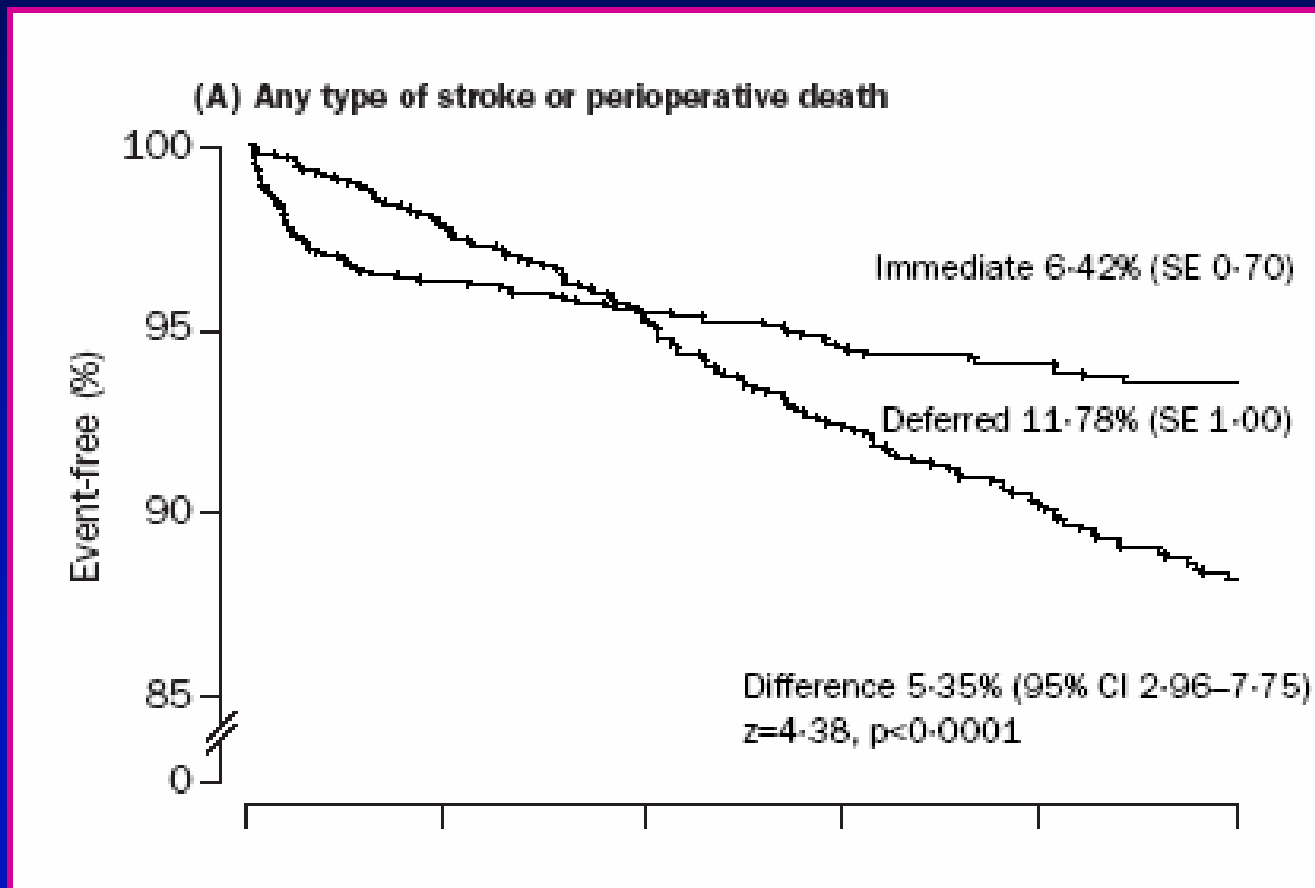
- Prospective randomized multicenter trial in Europe
 - 126 hospitals in 30 Countries
 - Surgeons with documented perioperative CVA/Death rate <6% in prior 50 CEAs
- 3120 asymptomatic patients with asymptomatic ICA stenosis >60%
- Randomized to
 - Immediate CEA
 - Indefinite deferral of CEA
- Followed for up to 5 years (mean 3.4 y)

Early vs Deferred Carotid Endarterectomy in Asymptomatic Patients with >70% ICA Stenosis

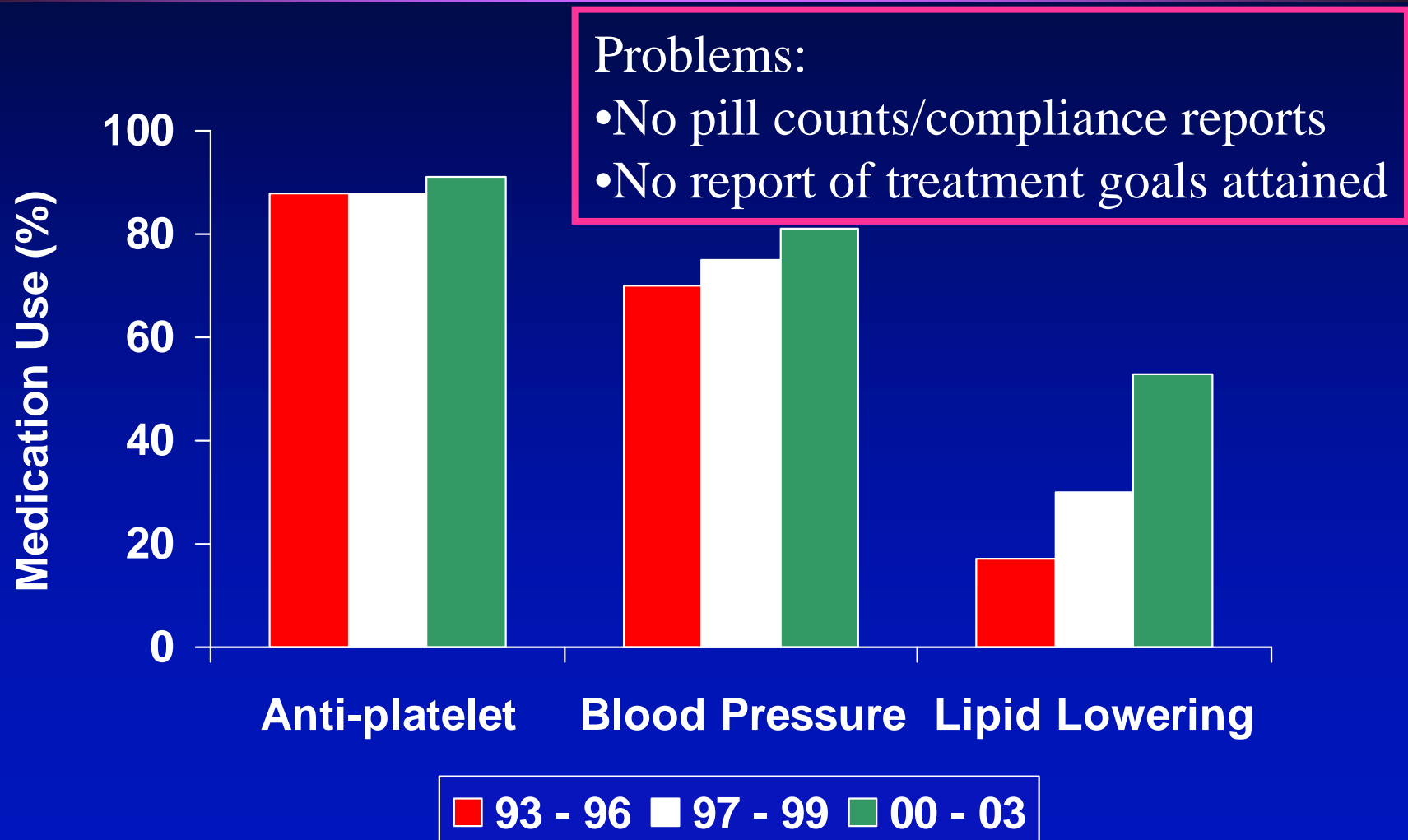
- Risk of CVA/Death within 30 days of CEA
 - 3.1%
- 5-year CVA risk
 - 3.8% immediate CEA
 - 11% deferred CEA ($p < 0.0001$)
 - Half of all CVAs were disabling
- Combining peri-op and non-peri-op CVA
 - 5-year CVA risk
 - 6.4% vs 11.8% ($p < 0.0001$)

Early vs Deferred Carotid Endarterectomy in Asymptomatic Patients with >70% ICA Stenosis

Any Stroke or Perioperative Death



MRC Asymptomatic Carotid Surgery Trial (ACST): Medical RX



Carotid Endarterectomy

- **Complications**

- Wound Complications

- Hematoma 0.7-1.5%
- Infection/Pseudoaneurysm 0.15%
- Cranial Nerve Dysfunction
 - Hypoglossal Nerve 5-8%
 - All other Cranial Nerves <2%
- Perioperative Stroke
 - Cleveland Clinic
 - 1.5% Asymptomatic
 - 2.7% Prior TIA
 - 3.8% Prior CVA

Carotid Artery Stenting

Why Carotid Stenting?

- Potential Advantages
 - Less Invasive Technique
 - More Widely Accepted by Patients
 - Less Discomfort
 - Faster Recovery Time
 - Less Expensive
 - Treat Difficult Lesions
 - Post Radiation ICA Stenosis
 - Restenosis after Endarterectomy
 - High Bifurcation Stenosis
 - Serious Co-Morbid Medical Conditions



Who Will Be Covered?

- Patients at **high risk for CEA** with a SYMPTOMATIC carotid artery stenosis $\geq 70\%$
- Patients at **high risk for CEA** with a SYMPTOMATIC carotid artery stenosis between 50% and 70% AND are enrolled in a Category B IDE Clinical Trial
- Patients at **high risk for CEA** with an ASYMPTOMATIC carotid artery stenosis $\geq 80\%$ AND are enrolled in a Category B IDE Clinical Trial

Unchanged in April 2007

Decision Memo for Percutaneous Transluminal Angioplasty (PTA) of the Carotid Artery Concurrent with Stenting (CAG-00085R3)

Decision Memo

TO: Administrative File: CAG 00085R3
Percutaneous Transluminal Angioplasty (PTA) of the Carotid Artery Concurrent with Stenting

FROM: Steve Phurrough, MD, MPA
Director, Coverage and Analysis Group

Marcel Salive, MD, MPH
Director, Division of Medical and Surgical Services

Sarah McClain, MHS
Lead Analyst

Joseph Chin, MD, MS
Lead Medical Officer

Rosemarie Hakim, PhD, MS
Epidemiologist

SUBJECT: Coverage Decision Memorandum for Percutaneous Transluminal Angioplasty (PTA) of the Carotid Artery Concurrent with Stenting

DATE: April 30, 2007

What is “High Risk”?

- **Serious Co-Morbid Medical Condition**

- Congestive heart failure (class III/IV) and/or known severe left ventricular dysfunction
LVEF <30%
- Open heart surgery needed within six weeks
- Recent MI (>24 hrs. and <4 weeks)
- Unstable angina (CCS class III/IV)
- Severe pulmonary disease

- **Anatomic Challenges**

- Contralateral carotid occlusion
- Contralateral laryngeal nerve palsy
- Radiation therapy to neck
- Previous CEA with recurrent stenosis
- High cervical ICA lesions or CCA lesions below the clavicle
- Severe tandem lesions
- Age > 80 years

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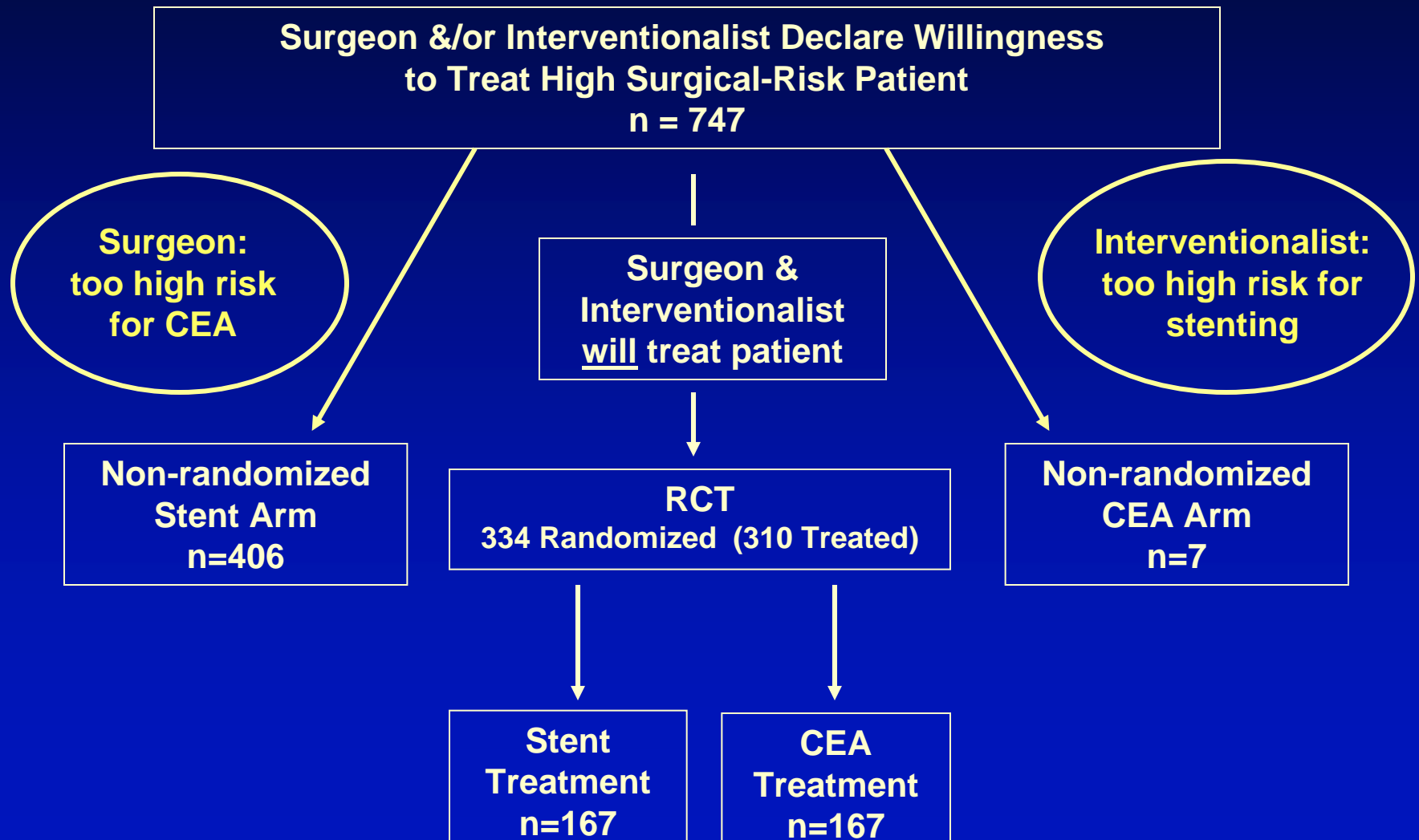
OCTOBER 7, 2004

Protected Carotid-Artery Stenting versus Endarterectomy
in High-Risk Patients

Jay S. Yadav, M.D., Mark H. Wholey, M.D., Richard E. Kuntz, M.D., M.Sc., Pierre Fayad, M.D., Barry T. Katzen, M.D., Gregory J. Mishkel, M.D., Tanvir K. Bajwa, M.D., Patrick Whitlow, M.D., Neil E. Strickman, M.D., Michael R. Jaff, D.O., Jeffrey J. Popma, M.D., David B. Snead, Ph.D., Donald E. Cutlip, M.D., Brian G. Firth, M.D., Ph.D., and Kenneth Ouriel, M.D., for the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators*

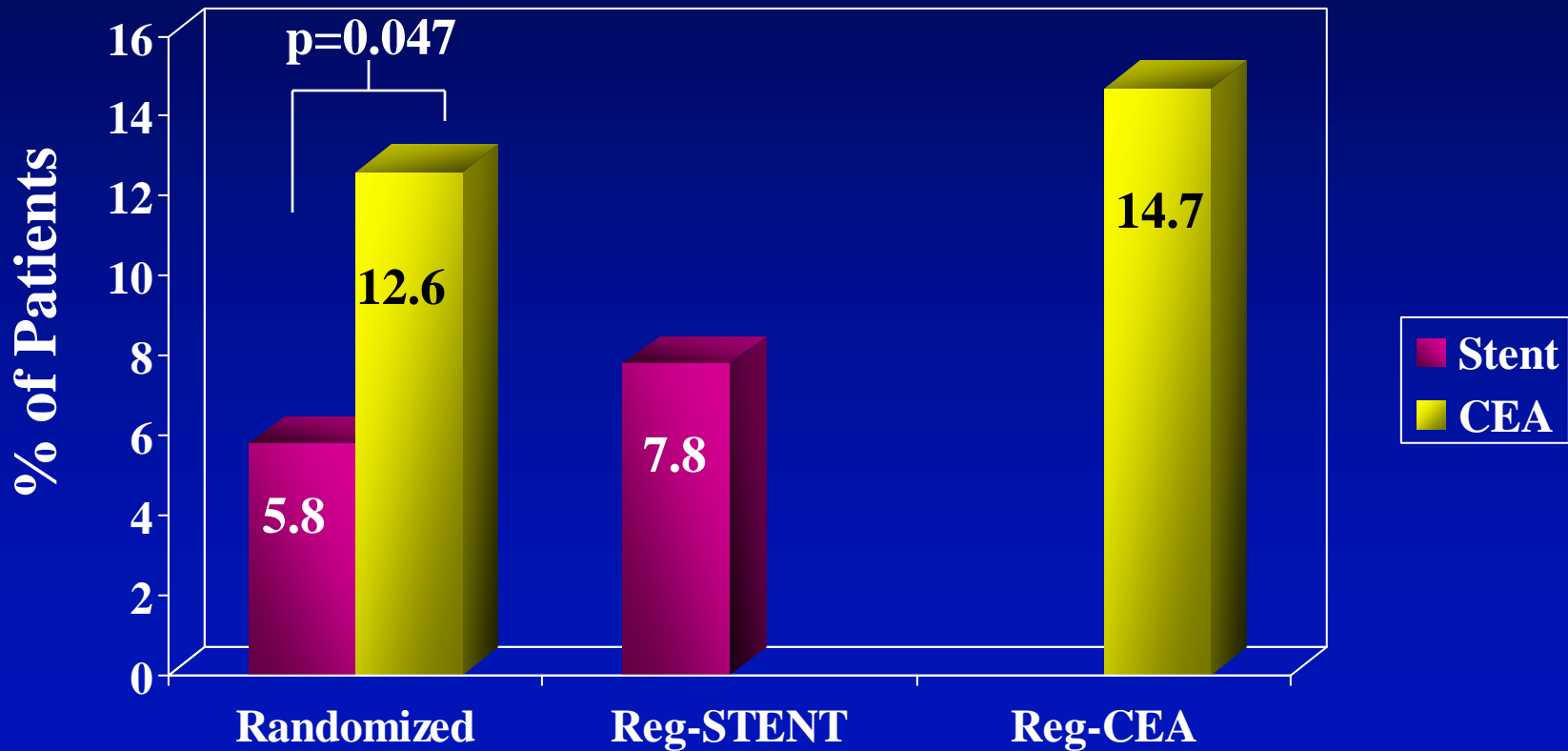
SAPPHIRE STUDY

Trial Design and Patient Flow



The SAPPHERE Trial

Primary Endpoint: Stroke, MI, Death at 30 Days



SAPPHIRE Data

Event	Intention-to-Treat Analysis			Actual-Treatment Analysis		
	Stenting (N=167) no. (%)	Endarterectomy (N=167) no. (%)	P Value	Stenting (N=159) no. (%)	Endarterectomy (N=151) no. (%)	P Value
Death	12 (7.4)	21 (13.5)	0.08	11 (7.0)	19 (12.9)	0.08
Stroke	10 (6.2)	12 (7.9)	0.60	9 (5.8)	11 (7.7)	0.52
Major ipsilateral	1 (0.6)	5 (3.3)	0.09	0	5 (3.5)	0.02
Major nonipsilateral	1 (0.6)	2 (1.4)	0.53	1 (0.6)	1 (0.7)	0.97
Minor ipsilateral	6 (3.7)	3 (2.0)	0.34	6 (3.8)	3 (2.2)	0.37
Minor nonipsilateral	3 (1.9)	4 (2.7)	0.64	3 (2.0)	3 (2.1)	0.89
Myocardial infarction	5 (3.0)	12 (7.5)	0.07	4 (2.5)	12 (8.1)	0.03
Q-wave	0	2 (1.2)	0.15	0	2 (1.3)	0.15
Non-Q-wave	5 (3.0)	10 (6.2)	0.17	4 (2.5)	10 (6.7)	0.08
Cranial-nerve palsy	0	8 (4.9)	0.004	0	8 (5.3)	0.003
Target-vessel revascularization	1 (0.6)	6 (4.3)	0.04	1 (0.7)	6 (4.6)	0.04
Conventional end point (stroke or death at 30 days plus ipsilateral stroke or death from neurologic causes within 31 days to 1 yr)	9 (5.5)	13 (8.4)	0.36	8 (5.1)	11 (7.5)	0.40
Primary end point (death, stroke, or myocardial infarction at 30 days plus ipsilateral stroke or death from neurologic causes within 31 days to 1 yr)	20 (12.2)	32 (20.1)	0.05	19 (12.0)	30 (20.1)	0.05

The CREATE Trial

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Interventional Cardiology

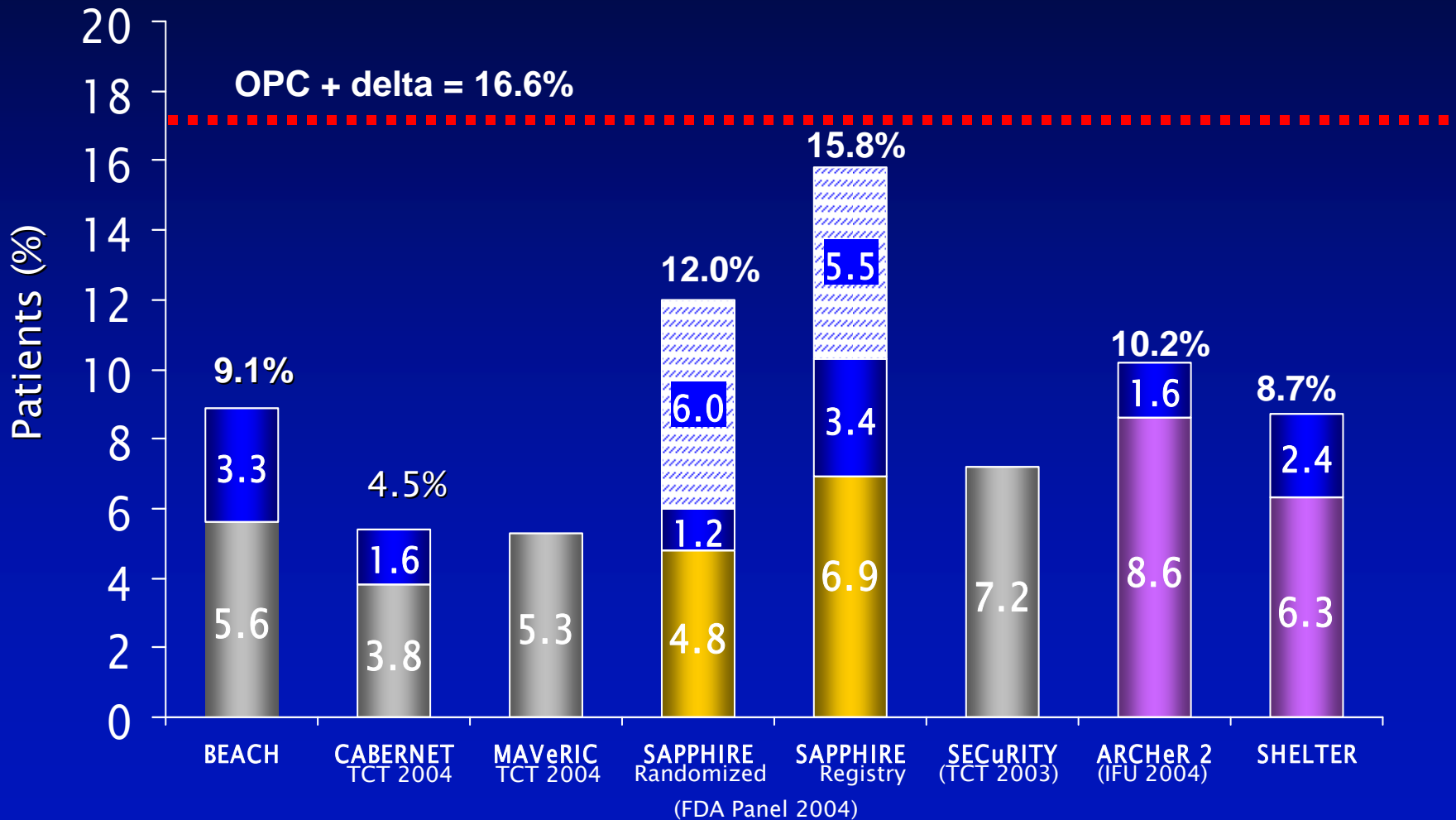
Protected Carotid Stenting in High-Risk Patients With Severe Carotid Artery Stenosis

Robert D. Safian, MD,* John F. Bresnahan, MD,† Michael R. Jaff, DO,‡ Malcolm Foster, MD,§
J. Michael Bacharach, MD,|| Brijeshwar Maini, MD,¶ Mark Turco, MD,# Subbarao Myla, MD,**
Gustav Eles, MD,†† Gary M. Ansel, MD,‡‡ on behalf of the CREATE Pivotal Trial Investigators

CREATE

- Prospective non-randomized registry of 419 high-risk patients for CEA
- Technical success 97.4%
- Primary Endpoint
 - Death 8 (1.9%)
 - Nonfatal CVA 14 (3.3%)
 - Nonfatal MI 4 (1%)
- Independent Predictors of CVA/Death at 30 Days
 - Symptomatic Status
 - Duration of Filter Dwell Time
 - Baseline Renal Function

1 Year Composite MAE Endpoint Carotid Stenting Trials



Lancet 2006;368:1239-47

30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial

*The SPACE Collaborative Group**

N Engl J Med 2006;355:1660-71

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Endarterectomy versus Stenting in Patients
with Symptomatic Severe Carotid Stenosis

What Are The Benefits of rtPA in Acute Ischemic Stroke?

- 30% more likely to have no/minimal residual deficit compared to patients who received placebo
- Risk: 10-fold risk of intracerebral or any hemorrhagic complication

Thrombolytic Therapy in Acute Ischemic Stroke

Duration	<3 h from onset
CT brain	No hemorrhage or clear infarction
Laboratory studies	Hematocrit, platelets, PT/PTT
If above are negative or normal, treat with intravenous tPA	
Administer tPA, 0.9 mg/kg: 10% in 1 min; remainder in 60 min	
Perform hourly neurologic examinations × 6, then every 2 h for first 24 h	
Repeat CT and blood studies at day 2	

Who Benefits from Carotid Therapy Today?

- Symptomatic patients with >70% ipsilateral carotid artery stenosis deserve revascularization
 - High Risk for CEA: Candidate for CAS
- **The jury (CMS) remains out on ANYONE else**
- Symptomatic patients with 50-69% ipsilateral carotid artery stenosis
 - Candidates for CEA (CAS if high risk and in trial)
- Asymptomatic patients with >60% carotid stenosis
 - ??? CEA
 - Trial to evaluate CAS
 - Optimize medical therapy?
 - Enroll in TACIT?
- EVERYONE gets optimal
 - Antiplatelet Therapy
 - Antihypertensive Therapy
 - Lipid Lowering Therapy
 - Strategies to Stop Smoking
 - Tight Glycemic Control