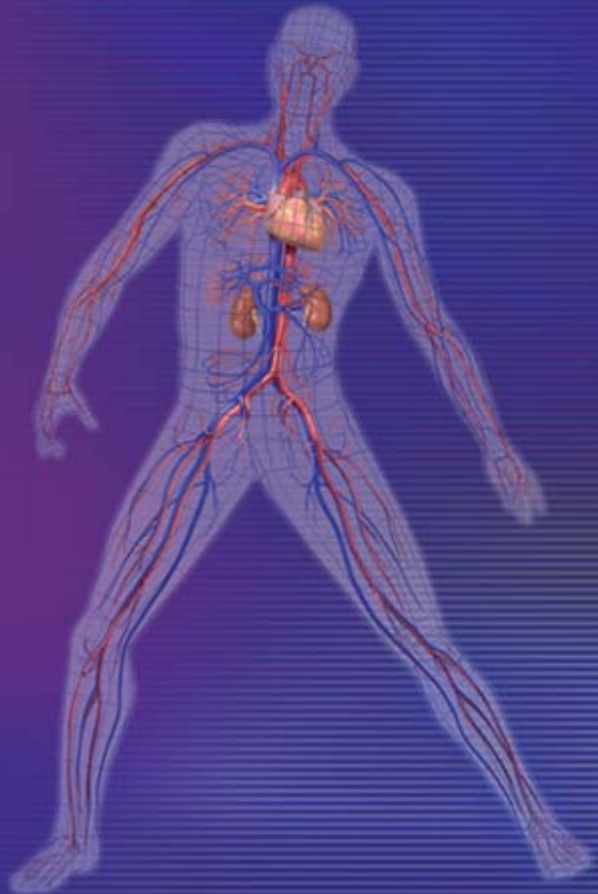


13th Annual Angioplasty Summit
TCT Asia Pacific
Seoul, Korea
April 25, 2008



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Carotid, Brachial Studies to Identify Vulnerable Patients

Michael R. Jaff, DO, FACP, FACC
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Michael R. Jaff, DO

Conflicts of Interest

- **Consultant**
 - Abbott Vascular
 - Atheromed
 - Bacchus Vascular, Inc
 - Baxter, Incorporated
 - FlexStent, Incorporated
 - Harvard Clinical Research Institute
 - Hypermed, Incorporated
 - I.C.Sciences, Incorporated
 - Micelle, Incorporated
 - Paragon IP
 - Pathway Medical
- **Equity**
 - Access Closure, Inc
 - Icon Interventional, Inc
 - Sadra Medical
 - Setagon
 - Square One, Inc
 - Vascular Therapies, Inc
- **Research Support**
 - Abbott Vascular
 - Genzyme
- **Board Member**
 - VIVA Physicians
 - www.vivapvd.com



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April, 2008



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How Does The Vascular Laboratory Predict Cardiovascular Risk?

- Ankle-Brachial Index
- Brachial Artery Reactivity
- Carotid Intima-Media Thickness

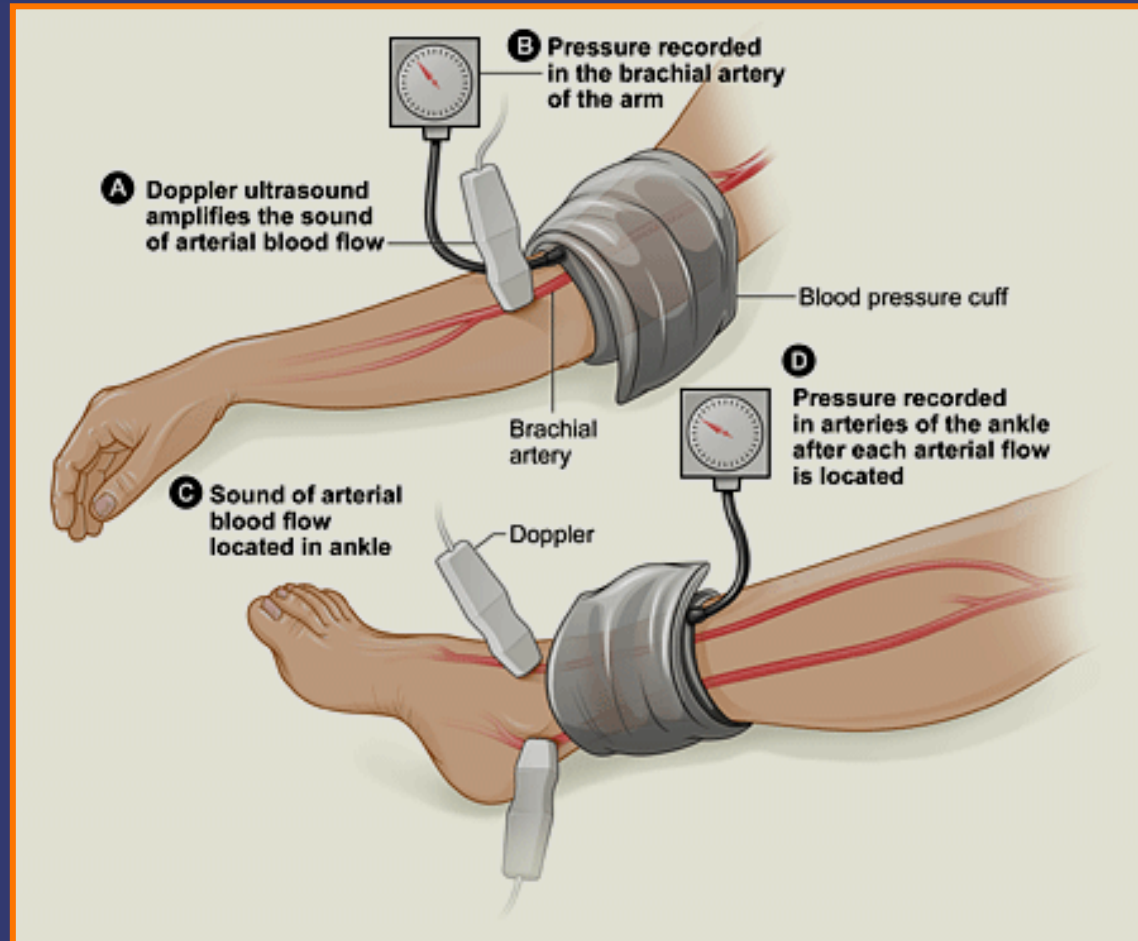


How Does The Vascular Laboratory Predict Cardiovascular Risk?

- Ankle-Brachial Index
- Brachial Artery Reactivity
- Carotid Intima-Media Thickness



Performance of the ABI



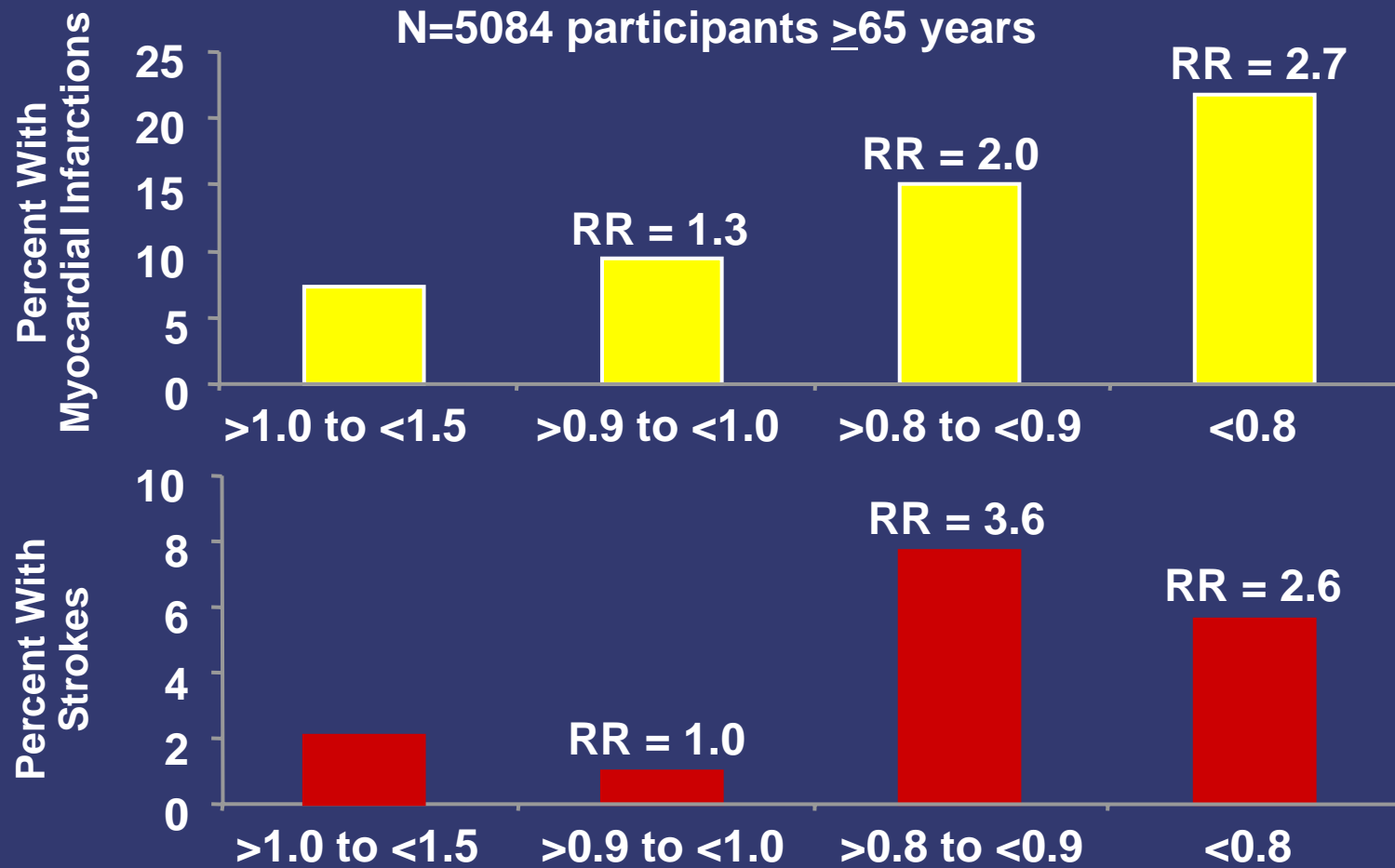
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http://www.nhlbi.nih.gov/health/dci/Diseases/pad/pad_diagnosis.html



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Cardiovascular Health Study: Ankle-Brachial Index as a Marker for Atherosclerosis



The HOPE Trial and PAD

- Large scale prospective multicenter trial evaluating patients at high risk of cardiovascular disease
 - Randomized to Ramipril (4645) or Placebo (4652)
- 8986 patients had ABI measured at baseline, 2 years, and at final visit
- 1715 patients enrolled due to symptomatic PAD
- 3099 patients had no symptoms with an abnormal ABI



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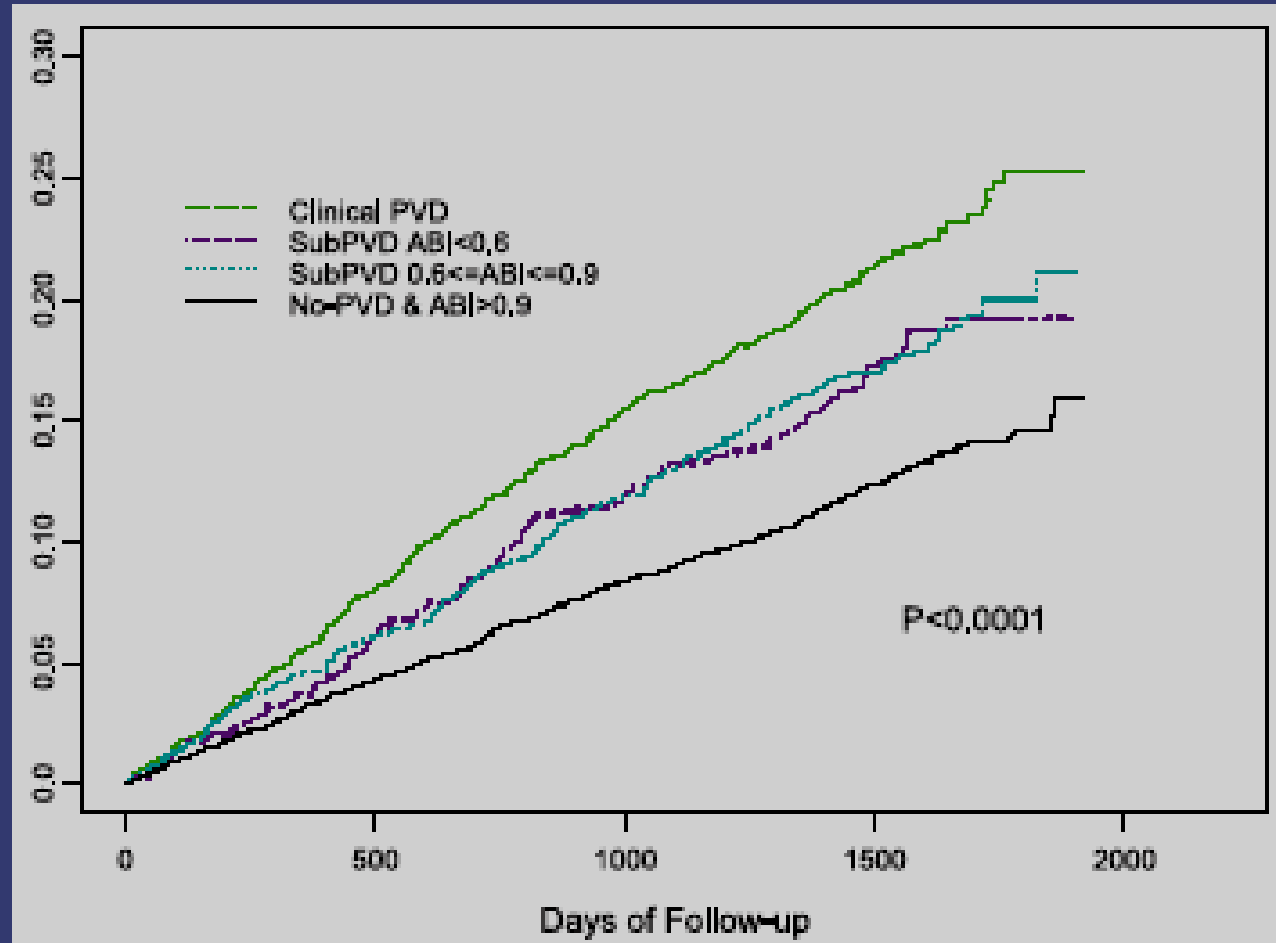
Eur Heart J 2004;25:17-24



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Primary Outcome

Primary Endpoint: MI, Stroke, Death



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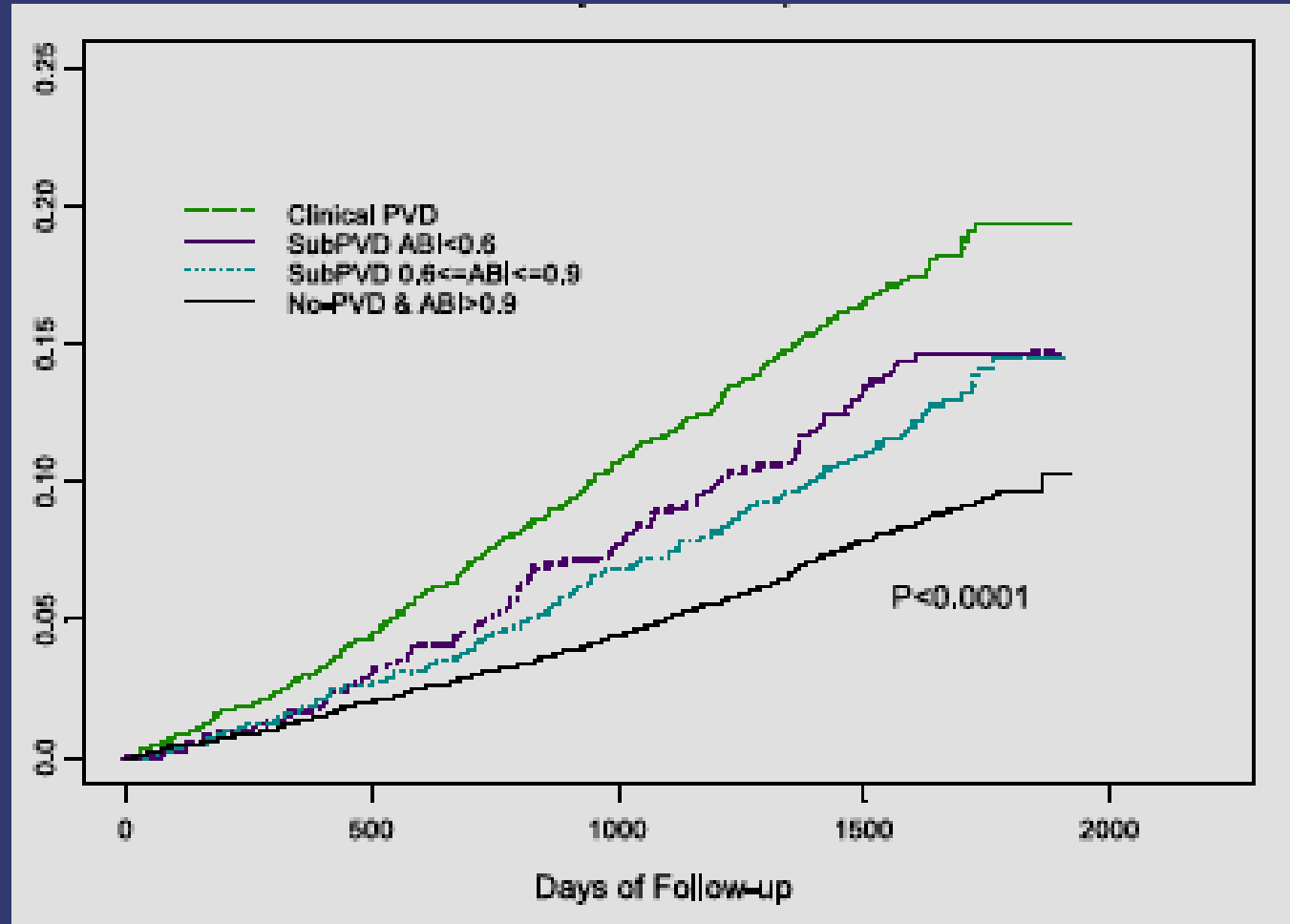
Eur Heart J 2004;25:17-24



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All Cause Mortality

All Cause Mortality



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Eur Heart J 2004;25:17-24



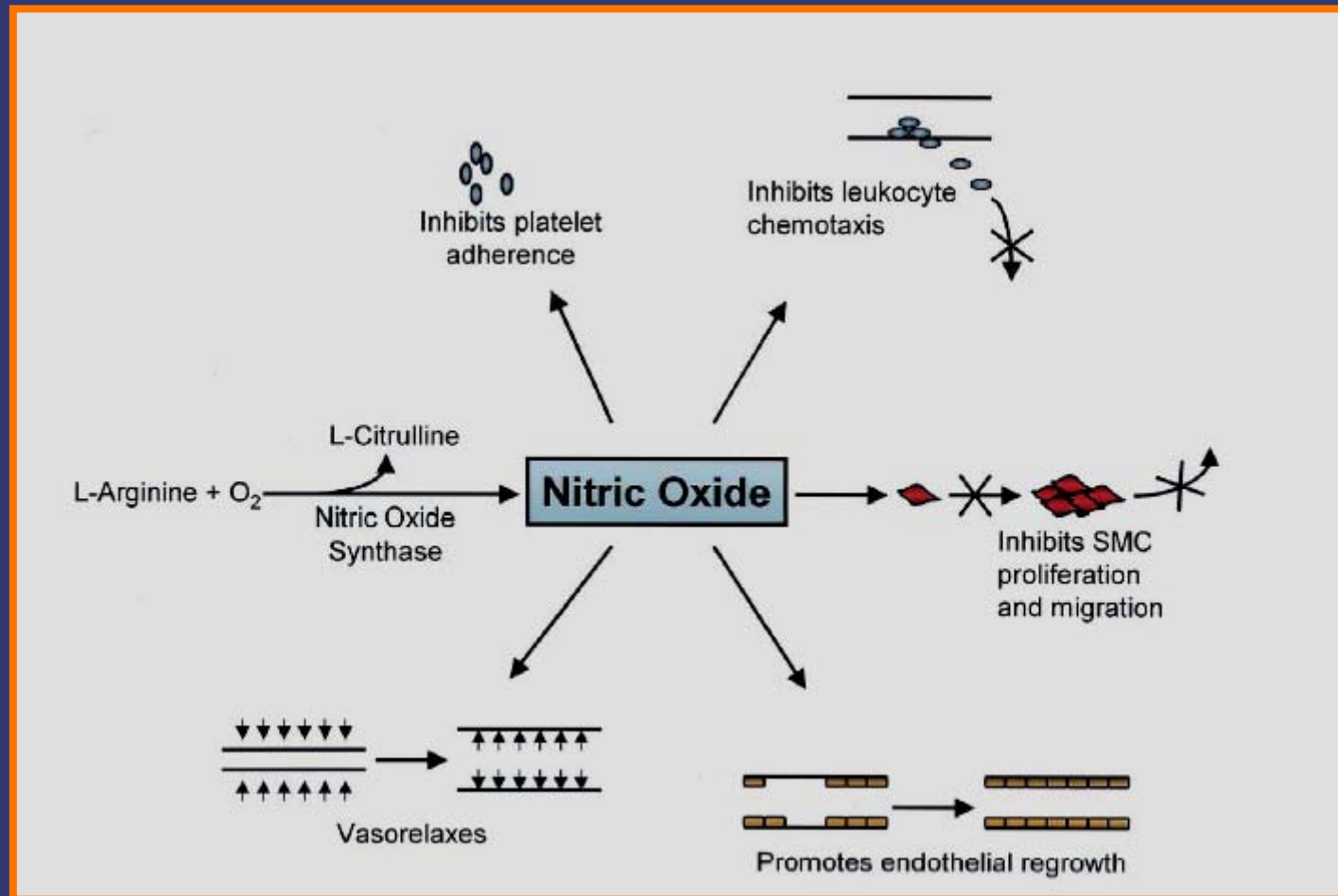
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How Does The Vascular Laboratory Predict Cardiovascular Risk?

- Ankle-Brachial Index
- **Brachial Artery Reactivity**
- Carotid Intima-Media Thickness



Vascular Effects of Nitric Oxide



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J Vasc Surg 2004;40:187-93



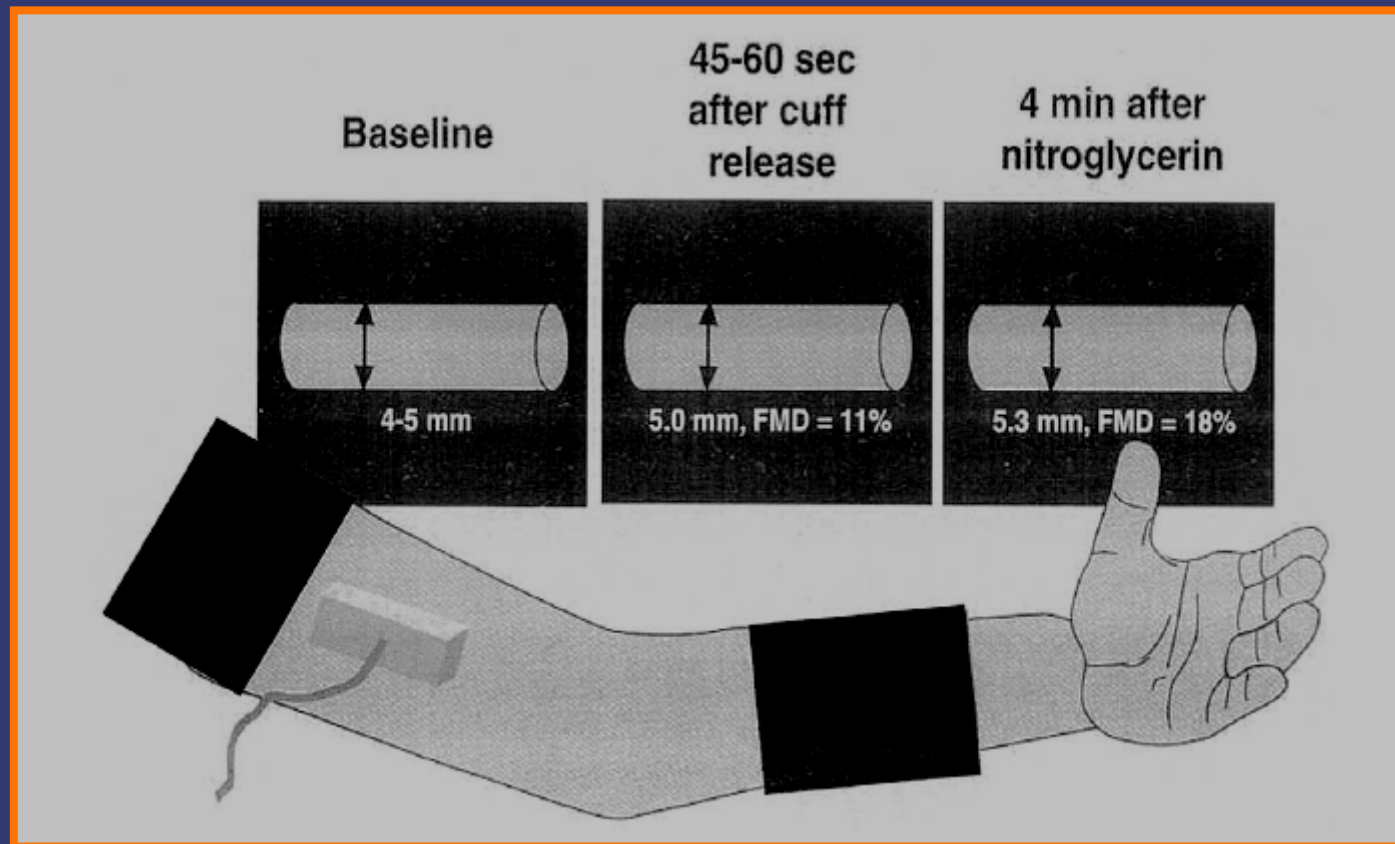
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Brachial Artery Reactivity (Flow Mediated Vasodilation)

- Blood flow through brachial artery increases in response to hyperemia
 - Blood pressure cuff on upper arm
- With sudden release, brachial artery vasodilates
 - Thought to be due to release of NO from endothelial cells
- Healthy brachial arteries
 - Increase diameter 5-15%
 - 5-6 fold increase in brachial artery flow
- Impaired endothelial function
 - Blunting of vasodilatory response
 - Actual abnormal vasoconstriction



Concept of BAFMD



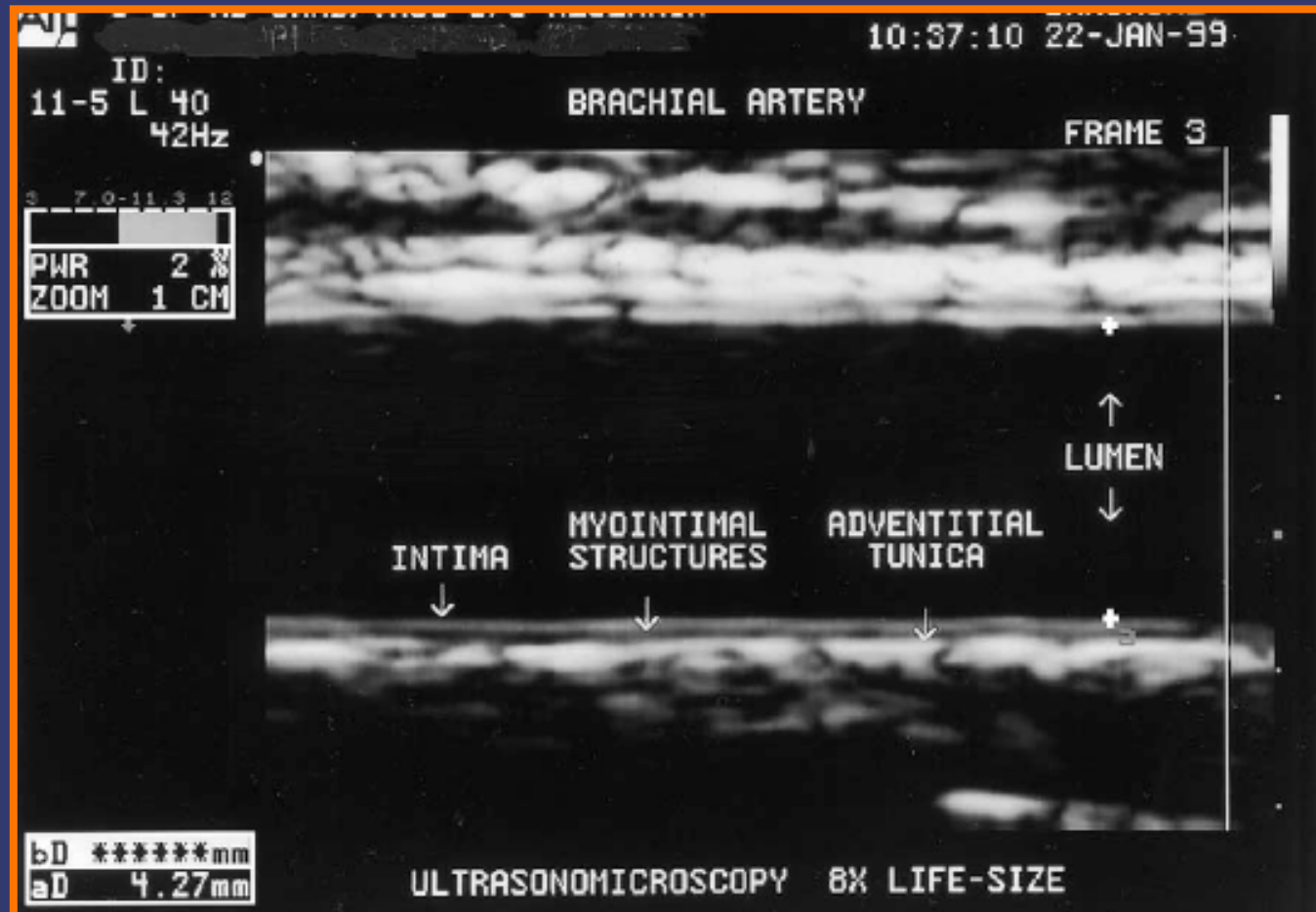
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J Am Coll Cardiol 2002;39:257-65



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Brachial Artery High Resolution Duplex Ultrasonography



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J Am Coll Cardiol 2002;39:257-65



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Clinical Value of BAFMD

- Strong association between abnormal Coronary Artery Endothelial Function and abnormal BAFMD

Am J Cardiol 1998;82:1535-9

- Impaired BAFMD strongly associated with multiple cardiovascular risk factors
 - Tobacco, DM, Hyperlipidemia, Age

J Am Coll Cardiol 1994;24:1468-74



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Digital Tonometry--- A Surrogate for BA Reactivity?



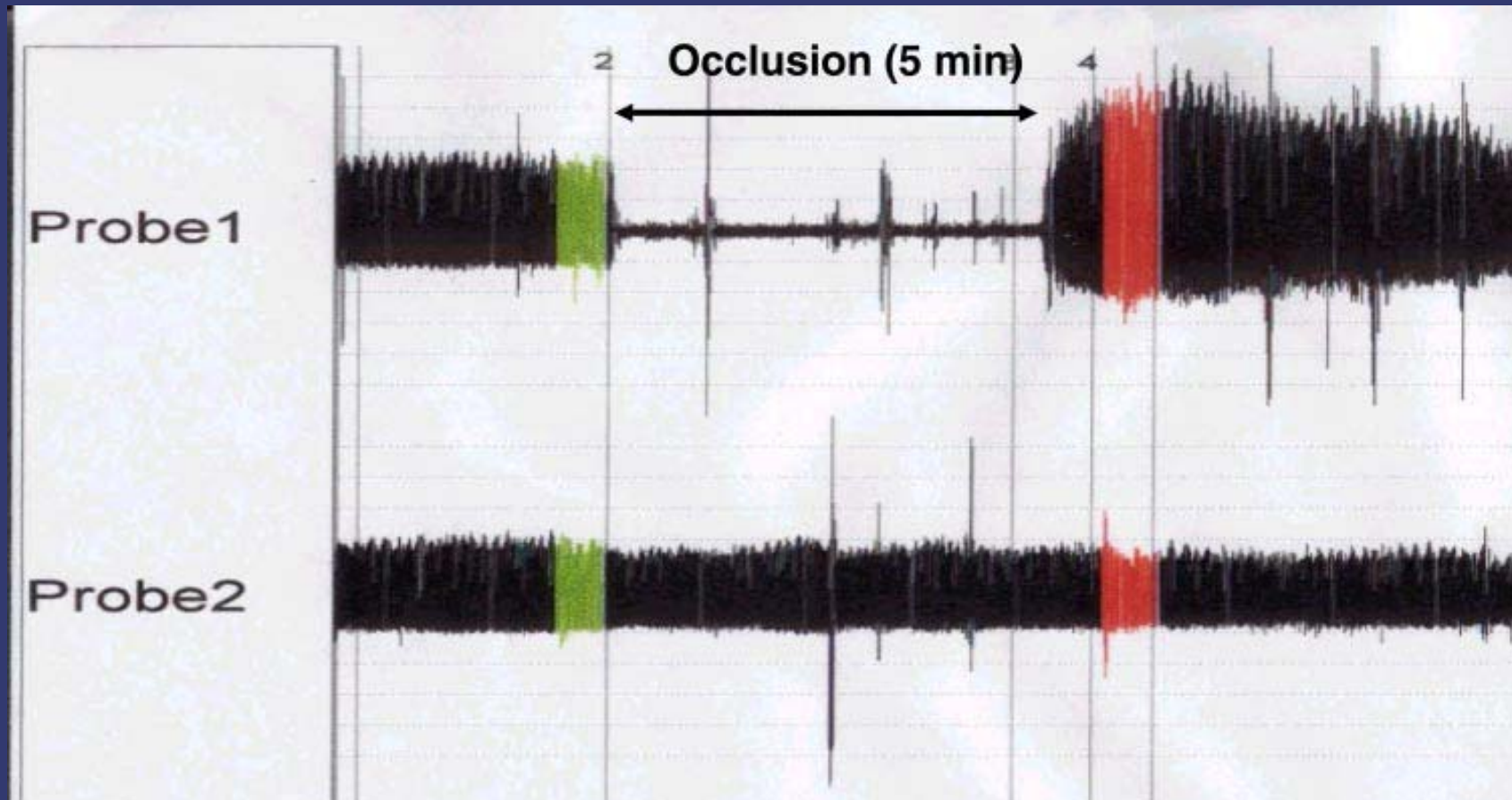
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Digital Pulse Volume Amplitude

EndoPAT Device



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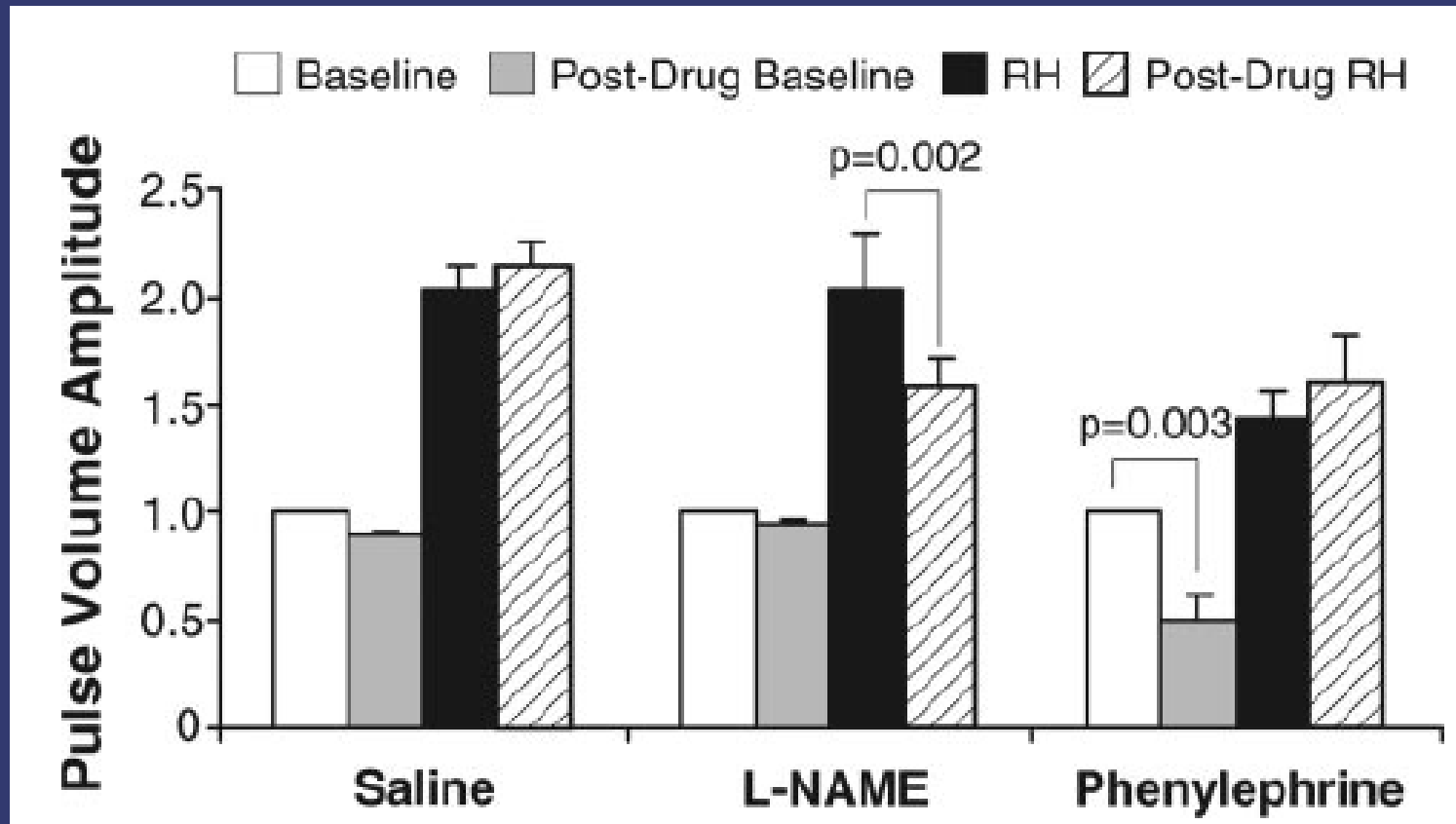
J Applied Physiol 2006;101:545-8.



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Digital Pulse Volume Amplitude

EndoPAT Device



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J Applied Physiol 2006;101:545-8.



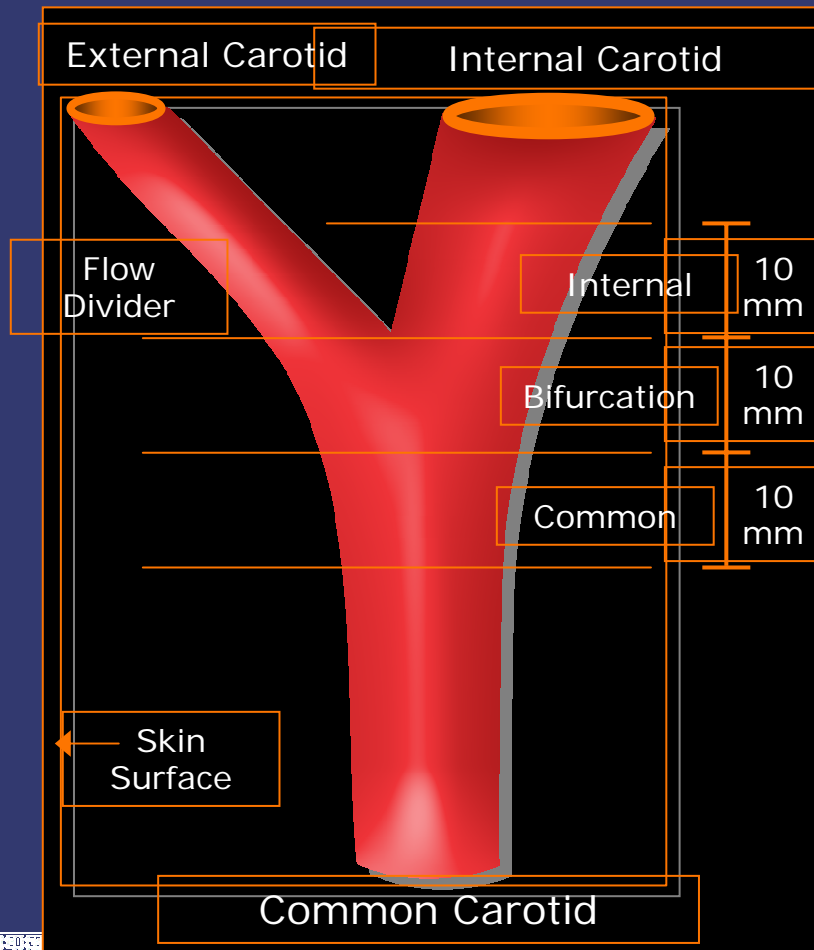
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How Does The Vascular Laboratory Predict Cardiovascular Risk?

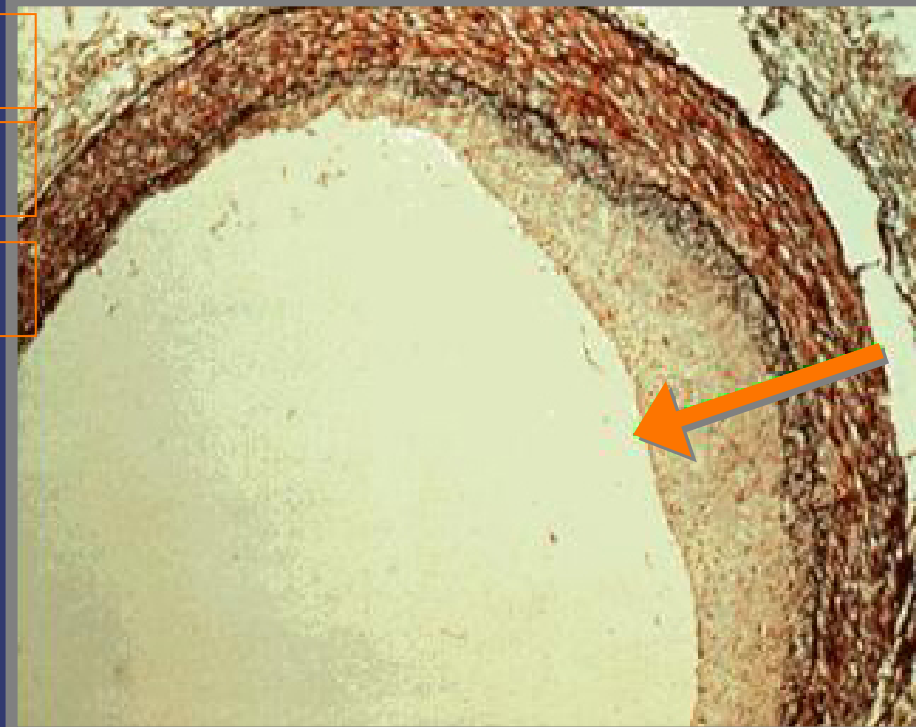
- Ankle-Brachial Index
- Brachial Artery Reactivity
- Carotid Intima-Media Thickness



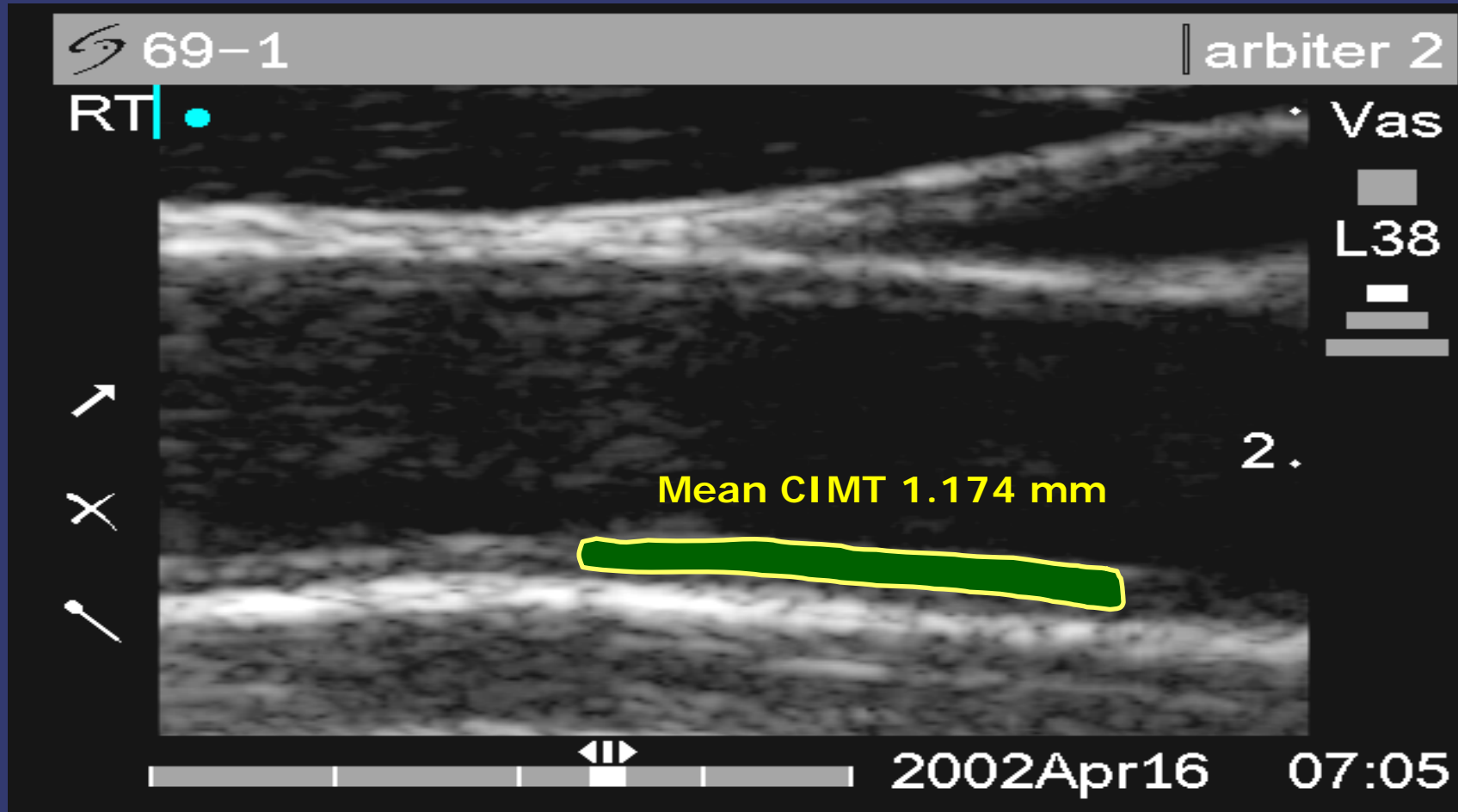
What is Carotid Intima–Media Thickness (CIMT)?



Normal and Diseased Arterial Histology



What is Carotid Intima–Media Thickness (CIMT)?



Mannheim Intima-Media Thickness Consensus Conference

- Where to Measure?
 - Region free of plaque at a point where a double line pattern is observed
 - Must note whether this is in the CCA, bulb, or ICA
 - Far wall is preferable
 - Measure a minimum of 10 mm vessel length
- How to Measure?
 - High resolution B-mode system with linear array transducer above 7 MHz, depth of focus 30-40 mm, frame rate >15 Hz



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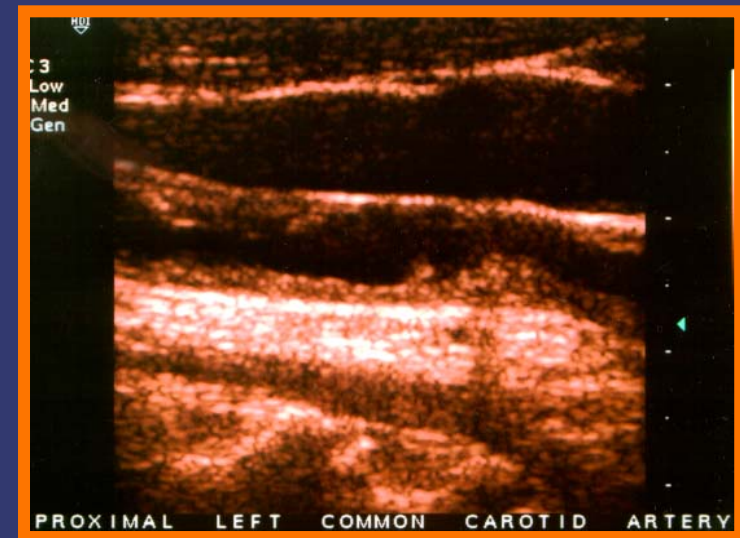
Cerebrovasc Dis 2004;18:346-9



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Carotid Artery Intima-Media Thickness and Risk for Myocardial Infarction and Stroke

- Duplex Ultrasonographic measurements of Common and Internal Carotid Artery intima-media thickness
- 4476 patients \geq 65 years with *NO CLINICAL CARDIOVASCULAR DISEASE*
- Primary End Points
 - New Myocardial Infarction/Stroke



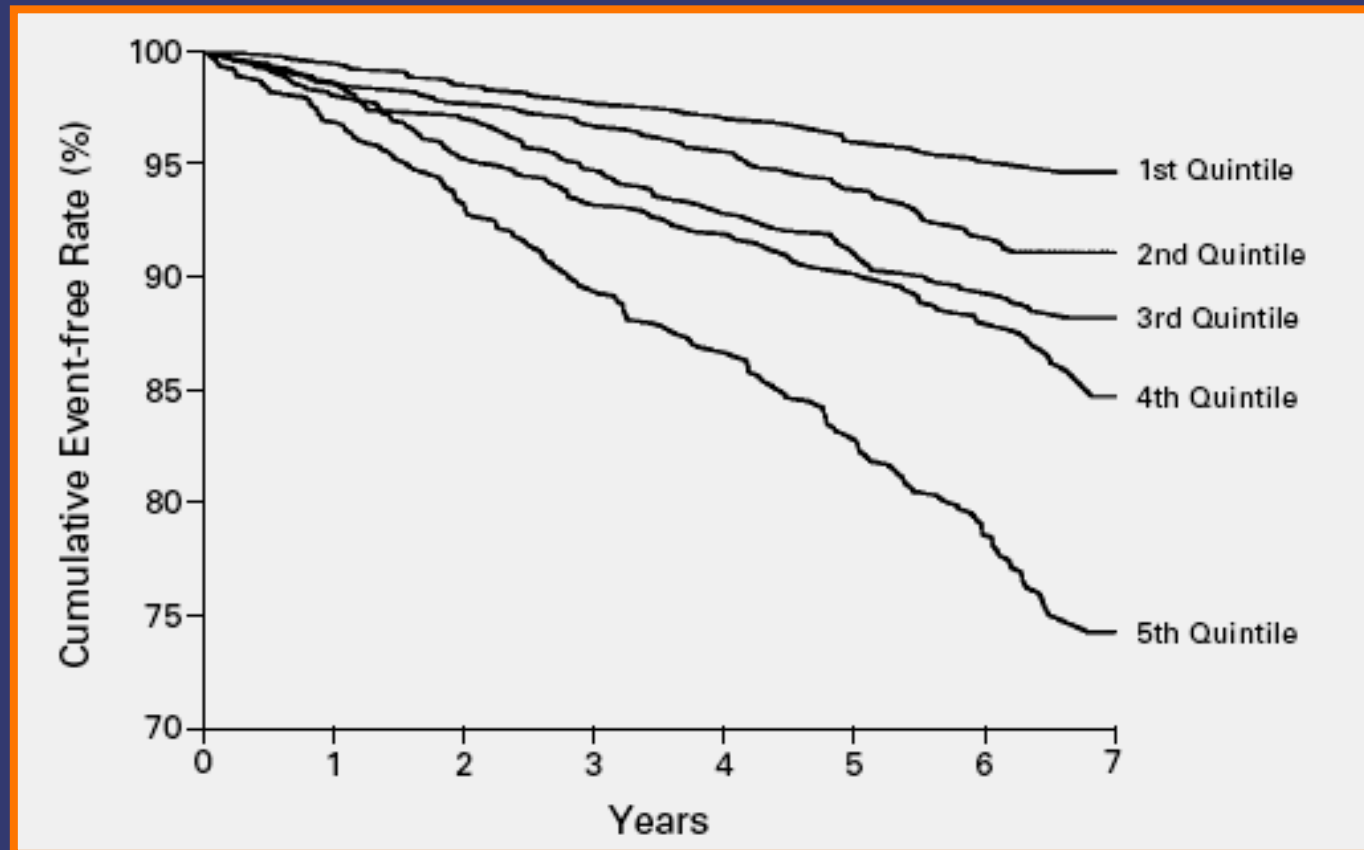
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N Engl J Med 1999;340;14-22



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Carotid IMT and Mortality



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N Engl J Med 1999;340:14-22



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Subclinical Atherosclerosis in Young Patients
with Metabolic Syndrome—
The Bogalusa Heart Study

- Of 507 pts in the Bogalusa Heart Study
 - 67 (13%) had the Metabolic Syndrome as defined by NCEP
 - 65 (13%) had the Metabolic Syndrome as defined by WHO



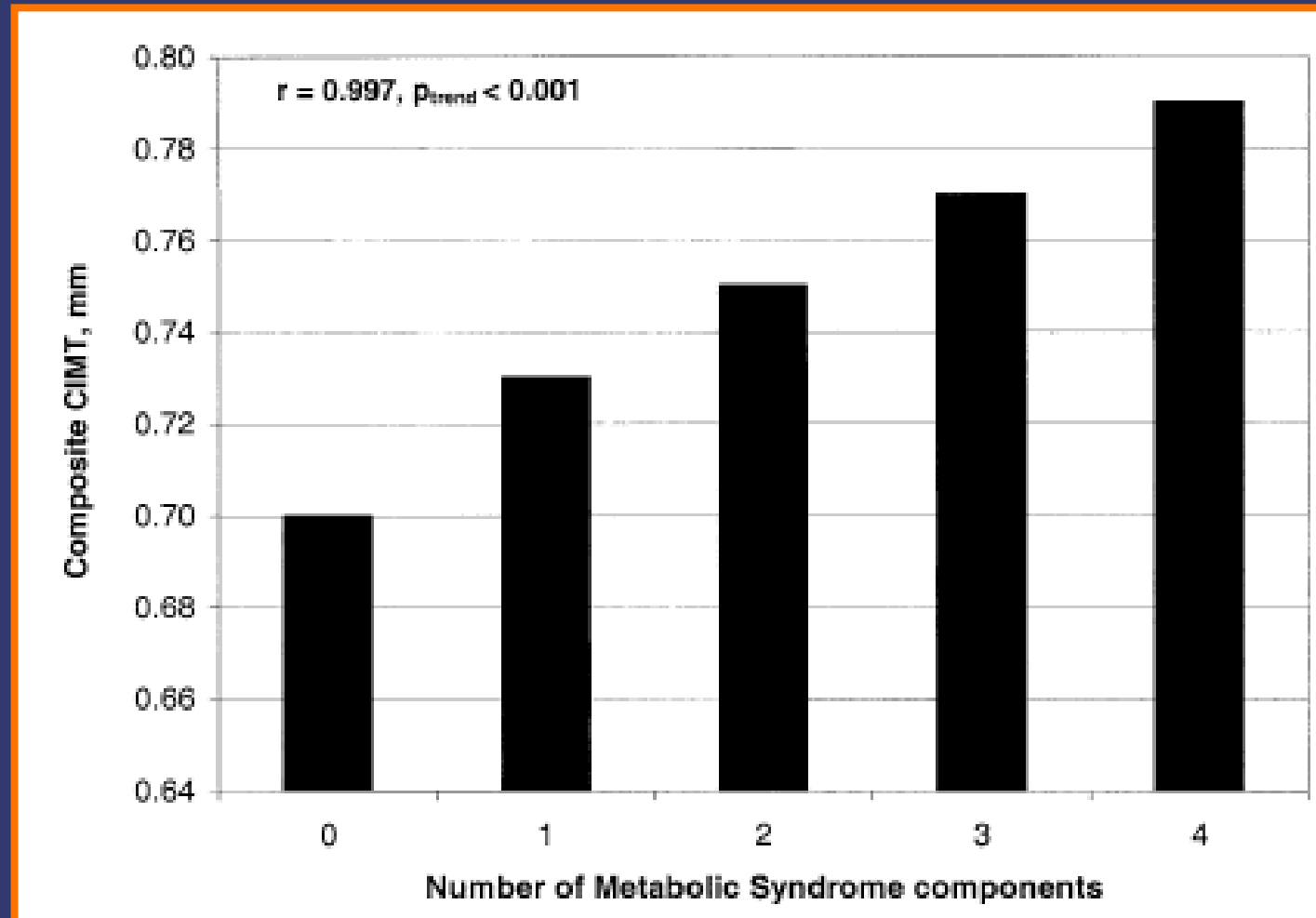
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J Am Coll Cardiol 2005;46:457-63



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Subclinical Atherosclerosis in Young Patients with Metabolic Syndrome— The Bogalusa Heart Study



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Intensive Therapy for Type 1 DM: Impact on Carotid IMT (EDIC Trial)

- Epidemiology of Diabetes Interventions and Complications (EDIC) Trial
- 1229 patients underwent carotid IMT at 1 and 6 years
 - 611 patients assigned to conventional DM therapy
 - 618 patients assigned to intensive DM therapy



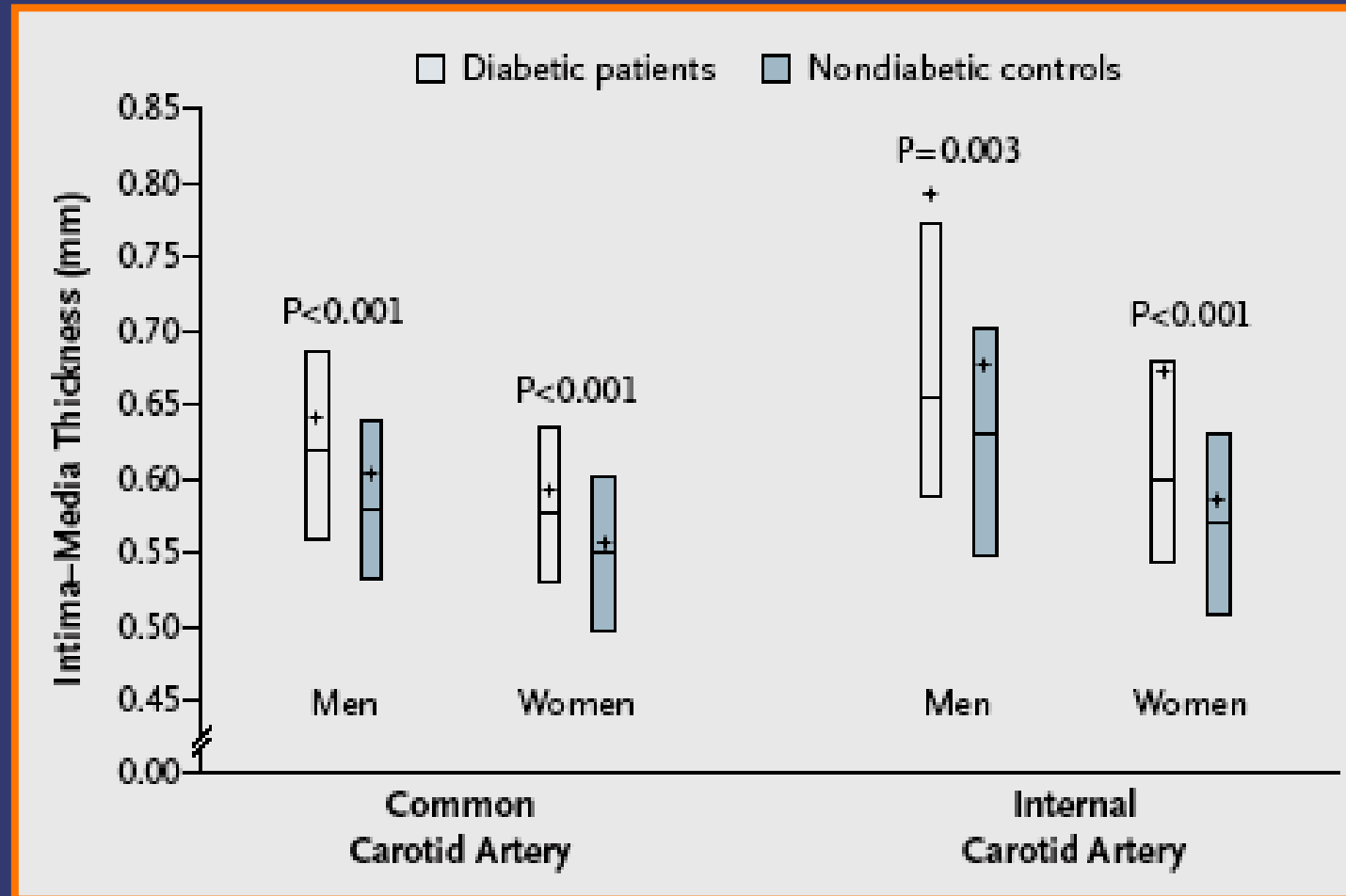
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N Engl J Med 2003;348:2294-303



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Intensive Therapy for Type 1 DM: Impact on Carotid IMT (EDIC Trial)



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N Engl J Med 2003;348:2294-303



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Intensive Therapy for Type 1 DM: Impact on Carotid IMT (EDIC Trial)

Variable	Change in Intima–Media Thickness of Common Carotid Artery		Change in Combined Intima–Media Thickness	
	Least-Squares Mean (95% CI)	P Value	Least-Squares Mean (95% CI)	P Value
	<i>mm</i>		<i>mm</i>	
Conventional treatment	0.046 (0.023 to 0.068)		0.007 (–0.277 to 0.292)	
Intensive treatment	0.032 (0.010 to 0.055)		–0.155 (–0.440 to 0.131)	
Difference between treatment groups	0.013 (0.003 to 0.024)	0.01	0.162 (0.031 to 0.293)	0.02



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ARBITER 2

- **Objective**
 - Compare effects of niacin ER 1000 mg/d with placebo on carotid intima–media thickness (primary endpoint) over 12 months
- **Study population**
 - Patients with known CHD with good LDL-C on statin therapy
- **Design**
 - Randomized, double-blind, placebo-controlled, single-center, investigator-initiated study
- **Timeline**
 - Enrollment: December 2001 through May 2003
 - Final follow-up: May 2004



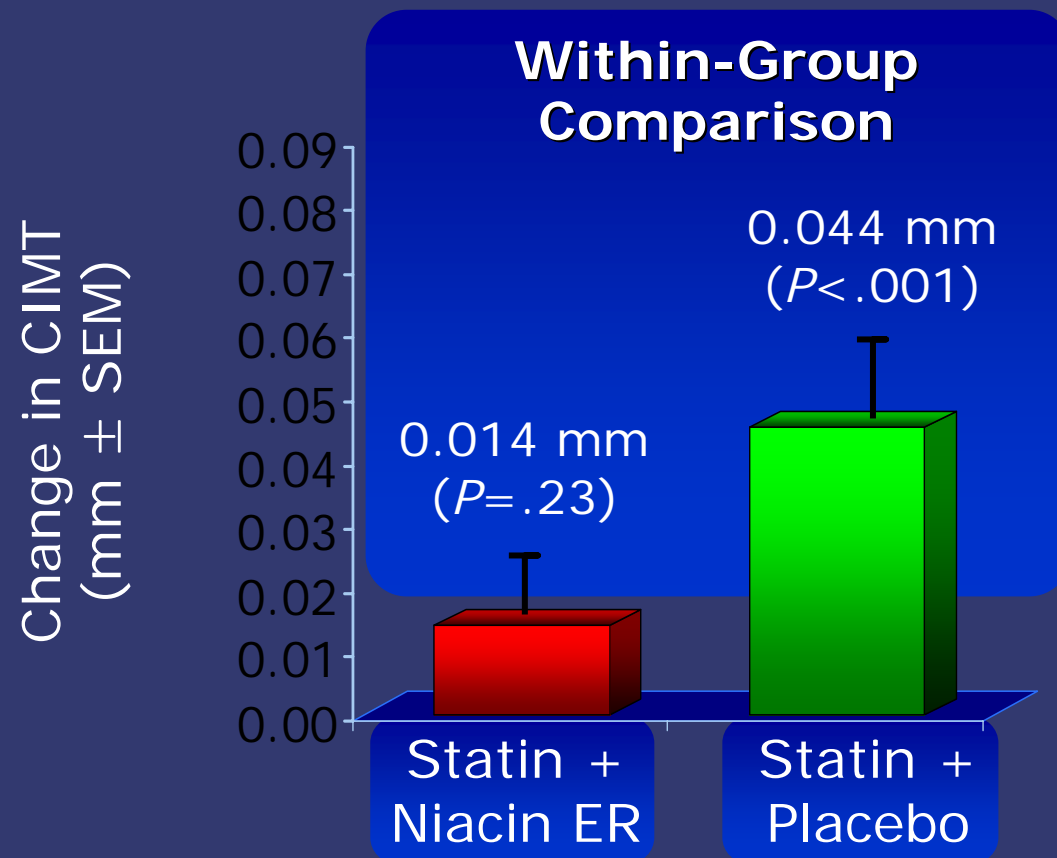
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Taylor AJ et al. *Circulation* 2004;110:3512-3517.



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ARBITER 2: Δ CIMT at 12 Months versus Baseline



Statin + Niacin ER

- Safe
- Flushing common, occurred in 2/3 of patients
- Adherence >90%

Between-group comparison: $P = .08$, intent-to-treat analysis of placebo > niacin ER, $P = .048$.

Effect of Rosuvastatin on Progression of Carotid Intima-Media Thickness in Low-Risk Individuals With Subclinical Atherosclerosis

The METEOR Trial

- 984 patients
- Age as sole CHD risk factor (mean 57 years) OR
- FHS score <10th percentile
- Moderate CIMT
- LDL cholesterol mean 154 mg/dL
- Randomized to
 - Rosuvastatin 40 mg/d
 - Placebo
- Followed for 4 years



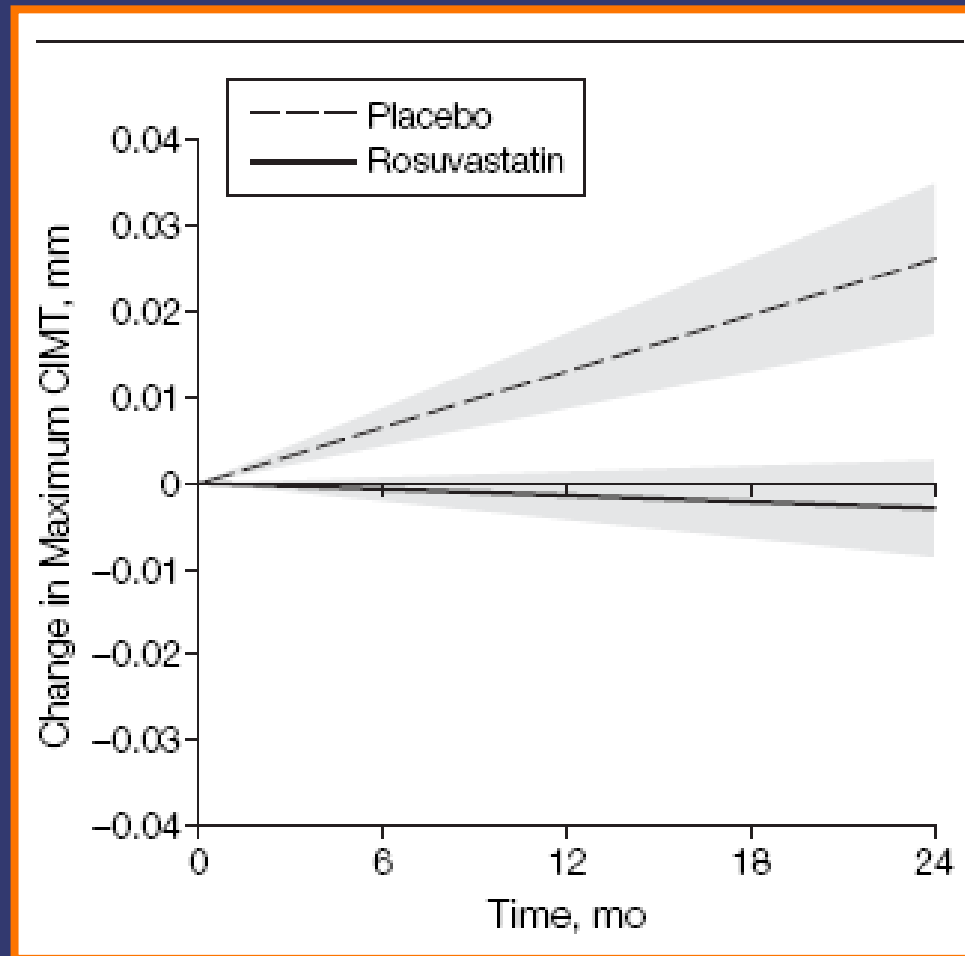
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Effect of Rosuvastatin on Progression of Carotid Intima-Media Thickness in Low-Risk Individuals With Subclinical Atherosclerosis

The METEOR Trial



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Carotid IMT Is Now The Test of Choice... For Wall Street!!!!

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

APRIL 3, 2008

VOL. 358 NO. 14

Simvastatin with or without Ezetimibe
in Familial Hypercholesterolemia



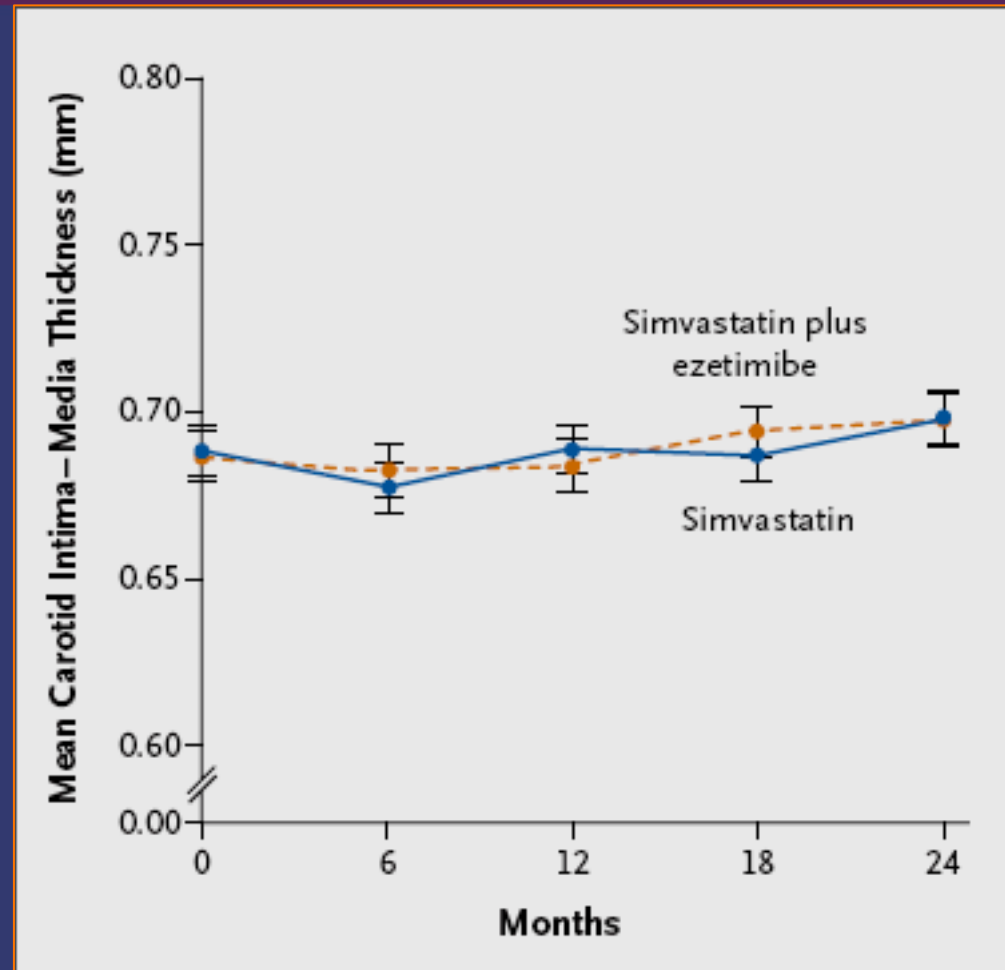
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N Engl J Med 2008;358:1431-43



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ENHANCE: Primary Endpoint: Change in CIMT



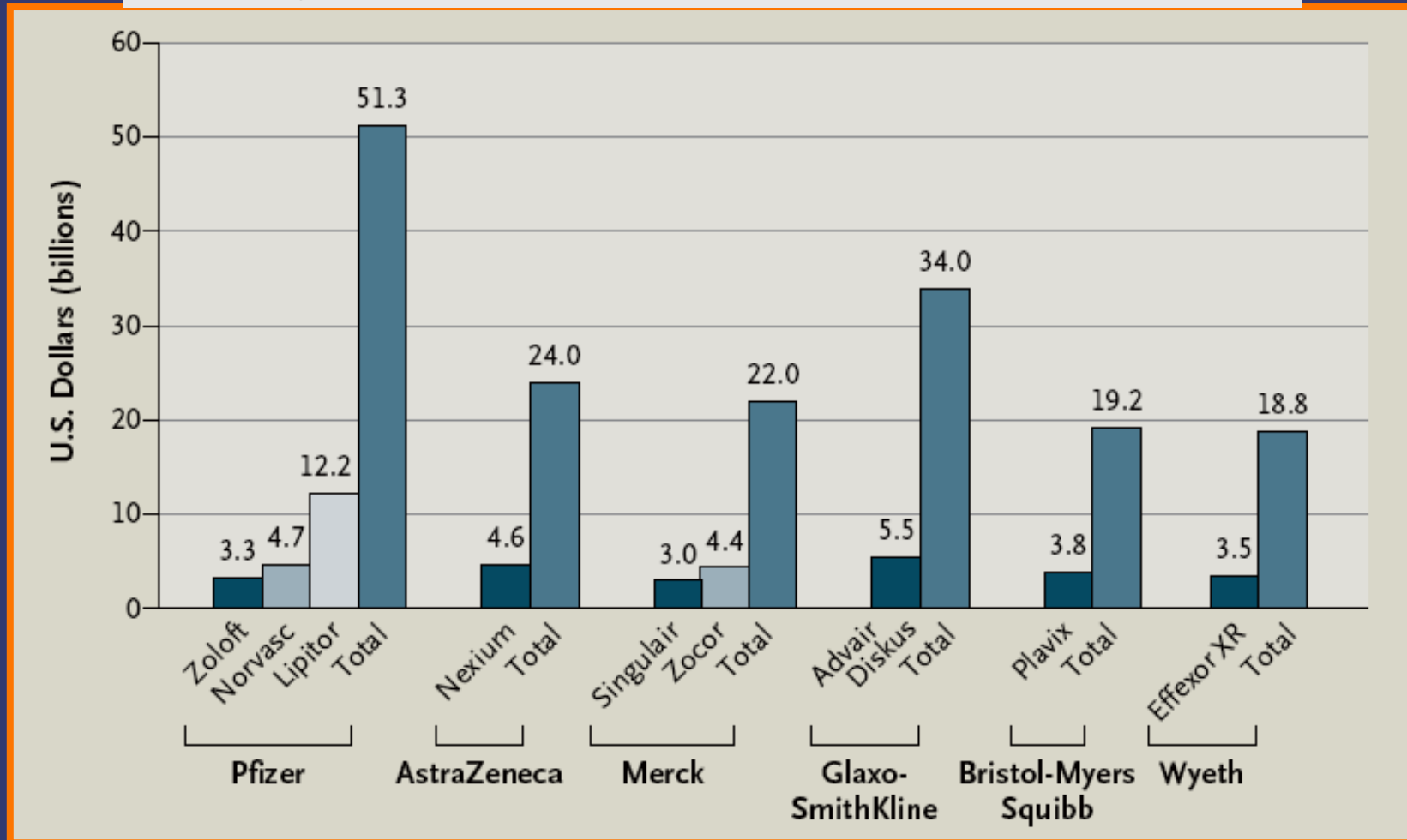
Failure of ENHANCE and Loss of Potential Revenue

PERSPECTIVE

THE DEMISE OF THE BLOCKBUSTER?

The Demise of the Blockbuster?

David M. Cutler, Ph.D.



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Prediction of Stroke with CAS— The ICAROS Trial

- 496 CAS procedures worldwide evaluated pre-intervention with duplex-US derived Gray Scale Median (GSM) scores
- 415 cases actually underwent CAS
 - 219 cases with embolic protection devices
- CAS Complications
 - 13 TIAs
 - 9 Minor CVAs
 - 6 Major CVAs
 - 0 Deaths



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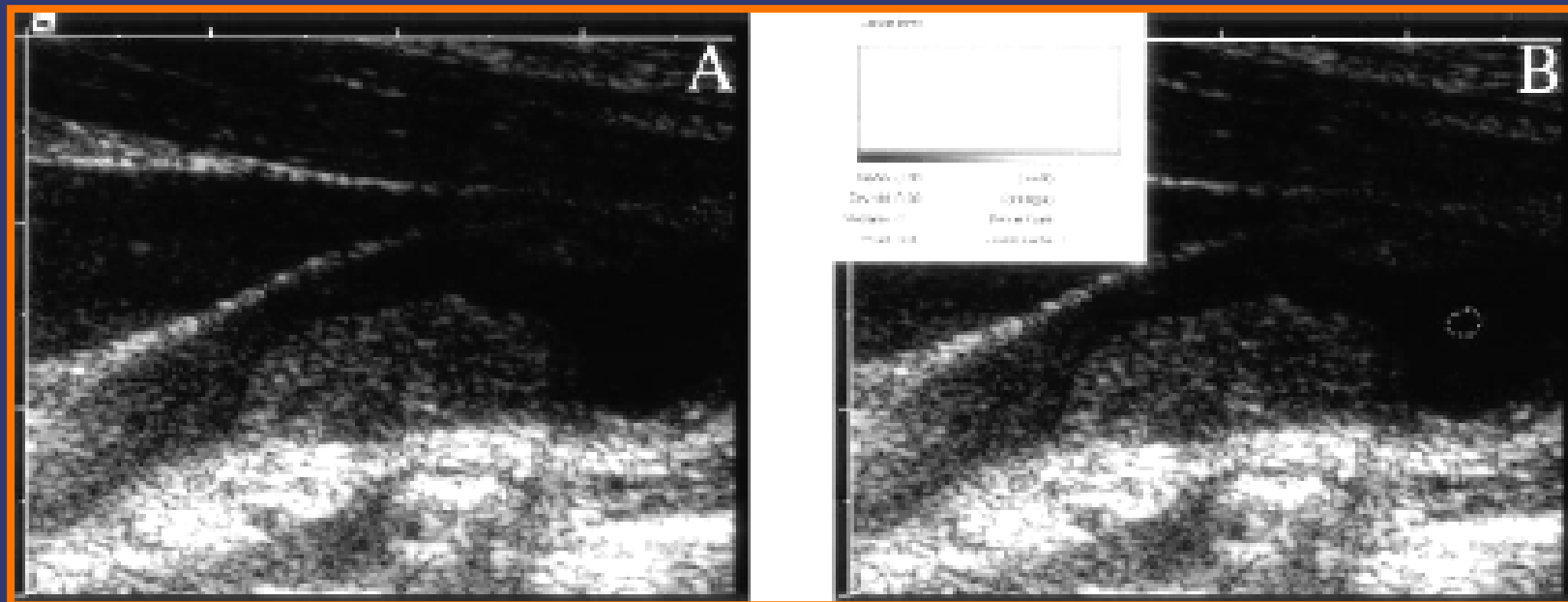
Circulation 2004;110:756-62



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Prediction of Stroke with CAS— The ICAROS Trial

Gray Scale Median: Based on notion that echolucent plaques have higher embologenic potential than echodense plaques



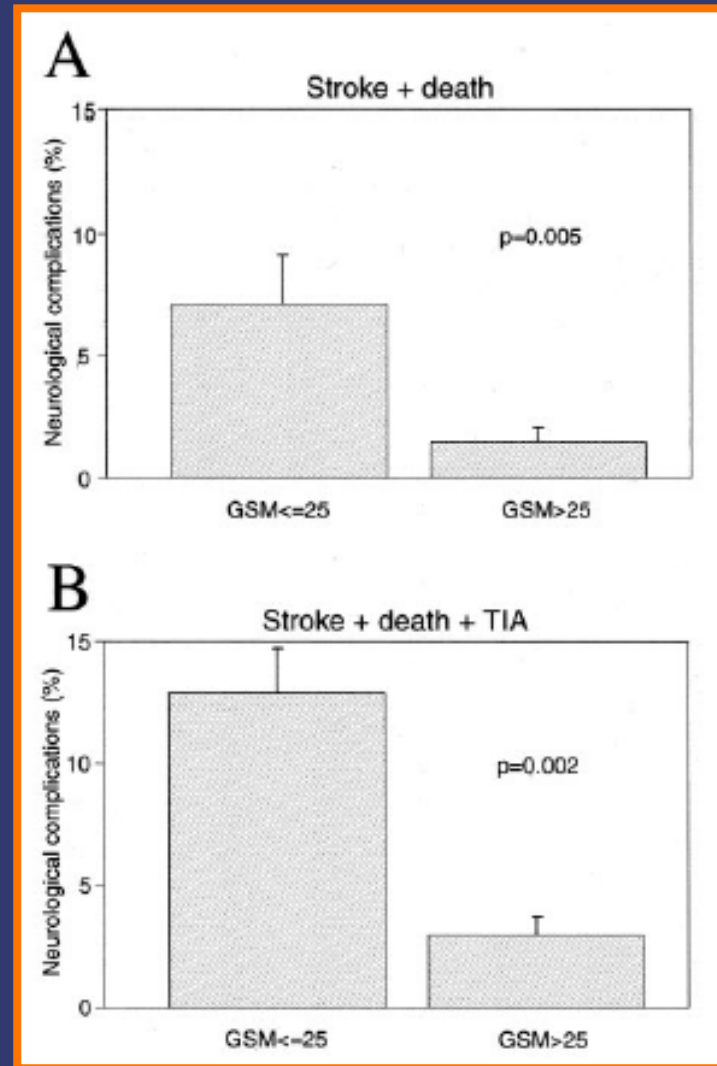
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Circulation 2004;110:756-62



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Prediction of Stroke with CAS— The ICAROS Trial



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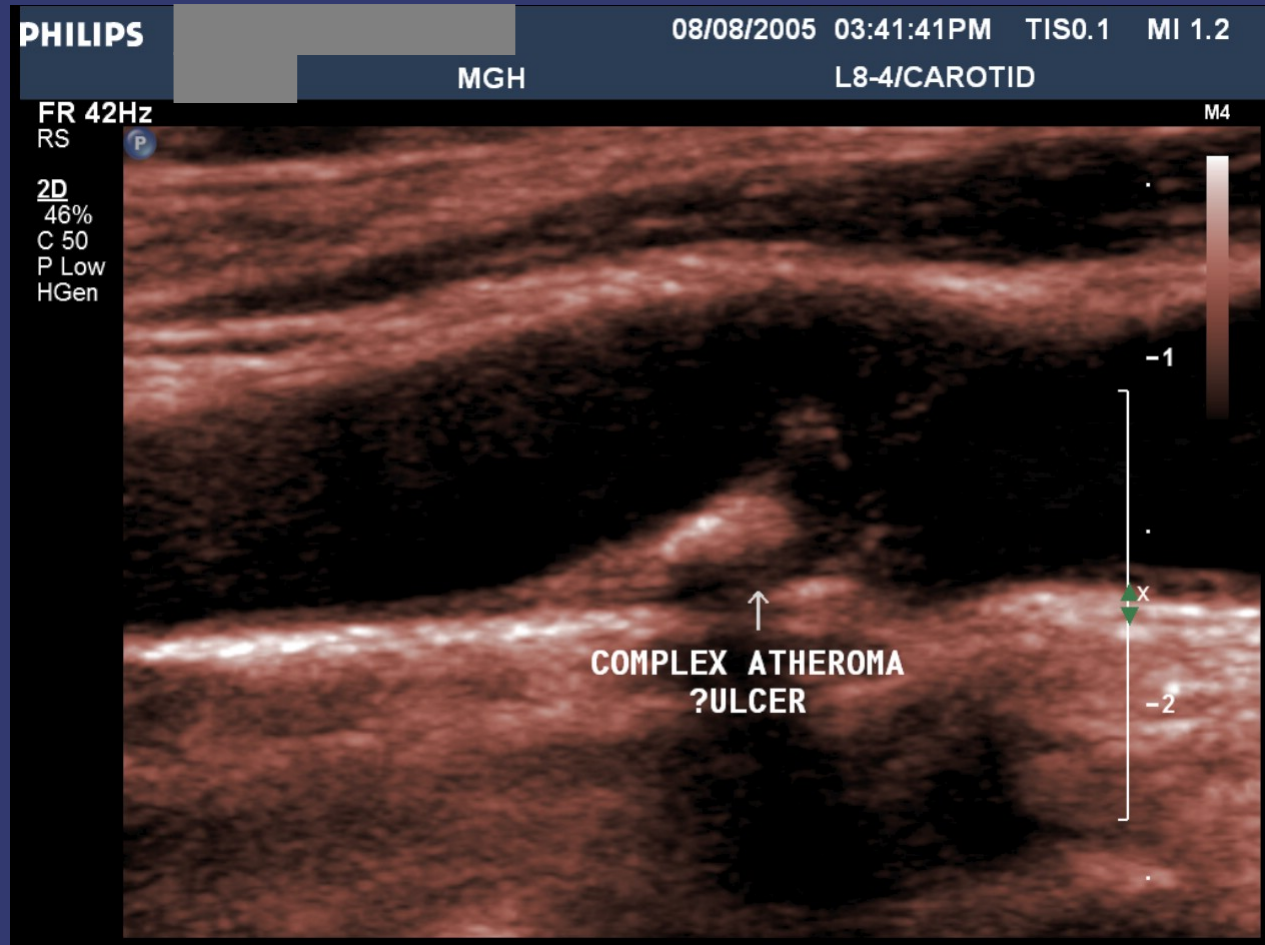
Prediction of Stroke with CAS— The ICAROS Trial

Multiple Logistic Regression Analysis Odds Ratio of Stroke

	OR	P	95% CI
GSM			
≤25 vs >25	7.11	0.002	2.06–24.57
Stenosis, %			
≥85 vs <85	5.76	0.010	1.51–21.91
Symptomatology			
Symptomatic vs asymptomatic	2.92	0.061	0.95–8.93
Brain CT			
Positive vs negative	2.54	0.099	0.84–7.47



Can Carotid Duplex Ultrasonography Detect Vulnerable Plaque?



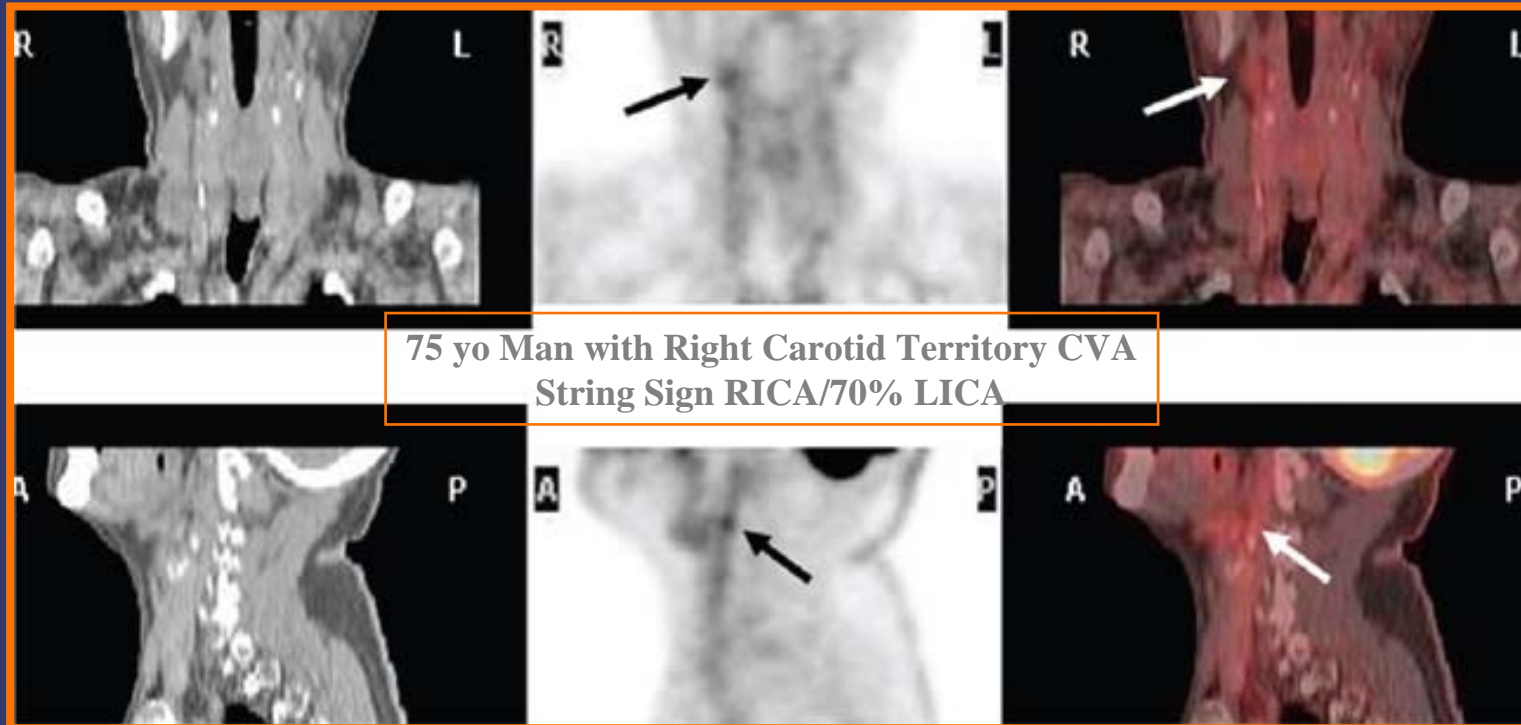
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PET/CT and MMP Content in Carotid Plaque

- 25 patients with carotid plaque and 22 patients with normal carotid arteries



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PET/CT and MMP Content in Carotid Plaque

All patients with carotid stenosis (<i>n</i> = 25)			
Baseline	SUVmax > 2.0 (<i>n</i> = 18)	SUVmax ≤ 2.0 (<i>n</i> = 7)	<i>P</i>
hs-CRP (mg/dL)	2.0 ± 1.6	2.4 ± 1.3	NS
MMP-1 (ng/mL)	9.3 ± 6.0	1.4 ± 3.1	0.01
Leukocyte count (1,000/μL)	6.4 ± 1.5	6.3 ± 0.9	NS
Patients who underwent stenting (<i>n</i> = 19)			
Parameter	SUVmax > 2.0 (<i>n</i> = 14)	SUVmax ≤ 2.0 (<i>n</i> = 5)	<i>P</i>
hs-CRP (mg/dL)			
Baseline	2.1 ± 1.6	2.6 ± 1.4	NS
After stenting	2.1 ± 1.7	2.7 ± 1.5	NS
MMP-1 (ng/mL)			
Baseline	7.6 ± 6.7	1.9 ± 1.2	0.02
After stenting	14.1 ± 8.8	6.6 ± 0.5	0.03
Leukocyte count (1,000/μL)			
Baseline	6.5 ± 1.9	5.8 ± 0.7	NS
Second day	8.4 ± 1.9	7.2 ± 1.6	NS



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J Nucl Med 2007;48:227-33



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Identification of Vulnerable Patients with Vascular Imaging

- Ankle Brachial Index predicts cardiovascular events and mortality
- Brachial Artery Reactivity/Digital Tonometry assesses endothelial function
- Carotid IMT associated with CV events/mortality, and is used as a surrogate for pharmaceutical trial effect

