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Surrogate Markers of CHD – How Useful Are They?

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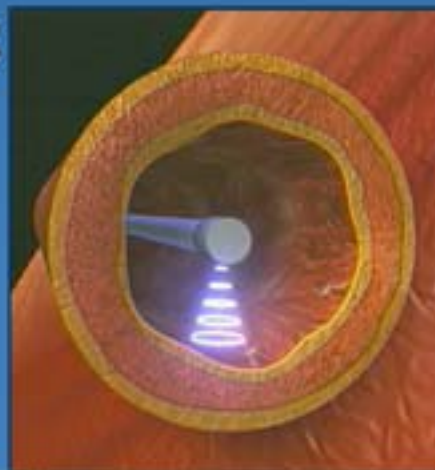


The Role of Surrogate Biomarkers in Identifying Cardiovascular Risk

Why Use Surrogate Markers?

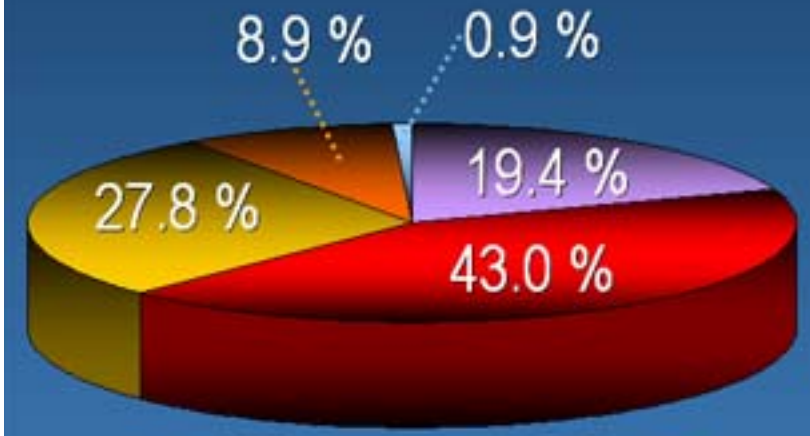
- ✓ Early detection of atherosclerosis and therefore early opportunity for therapeutic intervention
- ✓ End-points in clinical studies:
  - ✓ No need to wait for patients to have a major cardiovascular event
  - ✓ Studies require less time and resources to determine results
  - ✓ Relationship between intervention and its biological effects more easily studied

Which Surrogate Markers are Available?

- Blood Biomarkers
- Subclinical Disease

Prevalence of Major Risk Factors in Men With CHD

N=87,869



62.4%
0 to 1
major RF

4 major modifiable RF:
hypertension, smoking,
hypercholesterolemia, diabetes

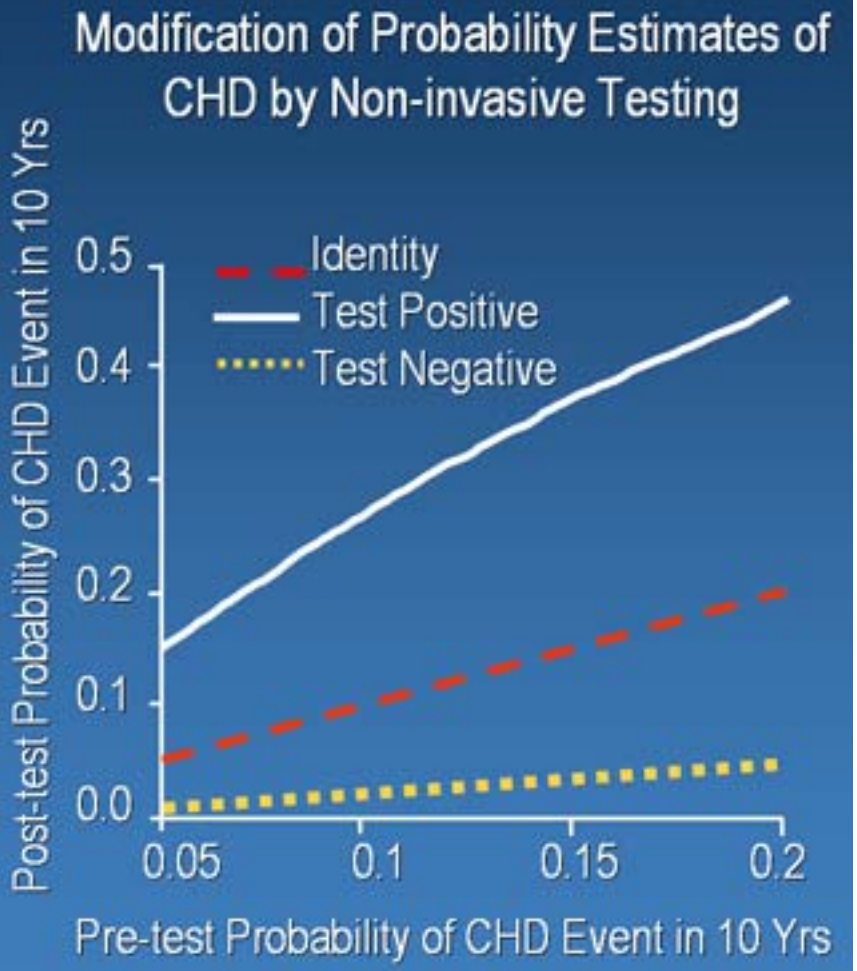
- ✓ Traditional risk factors (RF) are a useful first step in determining who could be at risk for a coronary event
- ✓ Exposure to one or more CHD risk factors is also highly prevalent in individuals who do not develop clinical CHD
- ✓ Less than 10% of patients have 3 or 4 major risk factors
- ✓ Secondary testing can be used to further stratify individuals for CHD risk

Khot et al. JAMA 2003;290:898-904

CHD Risk Assessment in Asymptomatic Patients: Selective Use of Noninvasive Testing

Low-Risk (~35 % of Pts)	Intermediate-Risk (~40% of Pts)	High-Risk (~25% of Pts)
<6%(10%)	6 (10%)-19 % over 10 years	≥20 %

- ✓ Assessment by multivariable statistical models: e.g. Framingham Risk Score, PROCAM Score, ESC SCORE
- ✓ Clear guidelines for high or low risk subjects, but not so for those at intermediate risk



modified after Greenland et al. Circulation 2001;104:1863-1867

Novel Risk Factors for Atherosclerotic Vascular Disease

Inflammatory Markers
C-reactive protein
Interleukins (e.g. IL-6, IL-18)
Vascular and cellular adhesion molecules
Soluble CD40 Ligand
Leukocyte count
Hemostasis/Thrombosis Markers
Fibrinogen
Von Willebrand factor antigen
Plasminogen activator inhibitor-1
Tissue-plasminogen activator
Factors V, VII and VIII
D-Dimer
Fibrinopeptide A
Prothrombin fragment 1+2
Platelet-Related factors
Platelet aggregation
Platelet activity
Platelet size and volume

Lipid-Related Factors
Small dense LDL
Lipoprotein (a)
Remnant lipoproteins
Apolipoproteins A1 and B
HDL subtypes
Oxidized LDL
Other Factors
Homocystein
Lipoprotein-associated phospholipase A_2
Microalbuminuria
Insulin resistance
PAI-1 genotypes
Angiotensin-converting enzyme genotype
Apo E genotype
Infectious agents: CMV, HSV, *Chlamydia pneumonia*, *Helicobacter pylori*
Psychosocial factors

Hackam & Anand. JAMA 2003;290:932-940

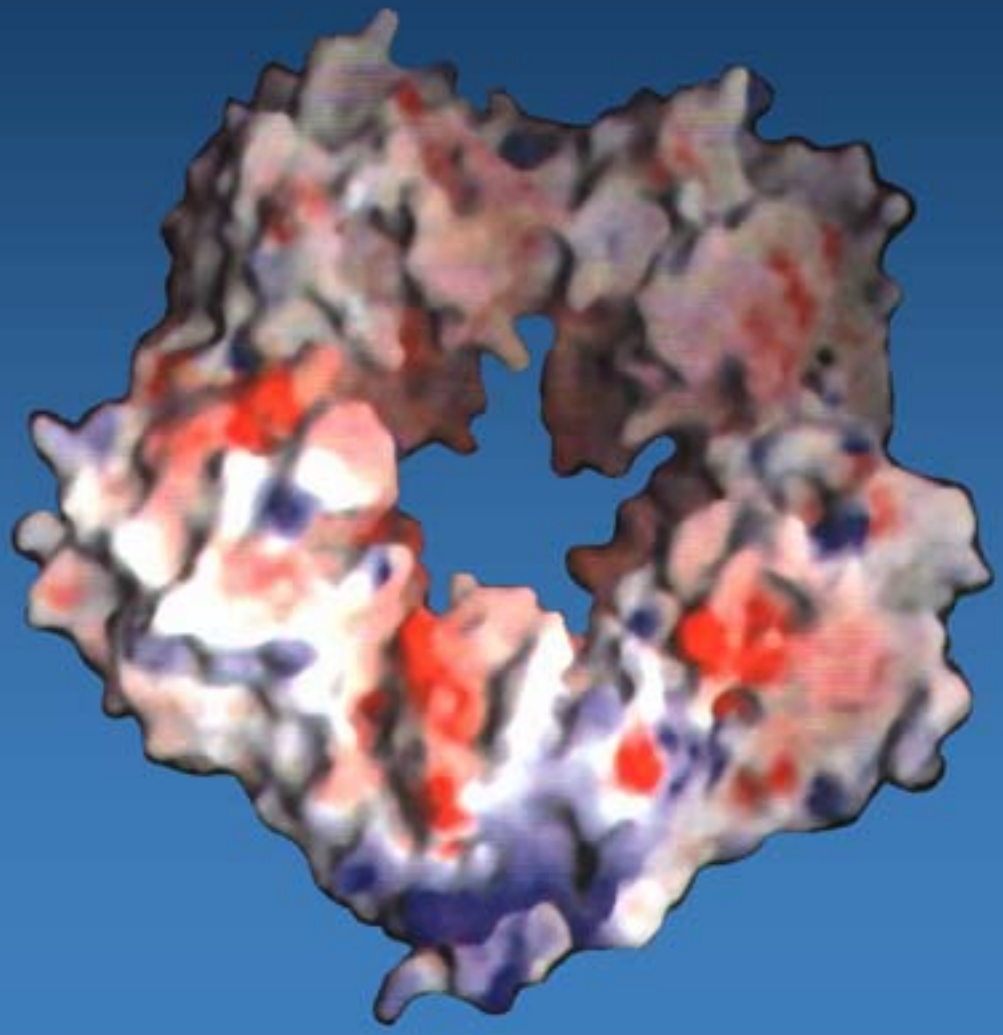
Evaluating Novel Cardiovascular Risk Factors

Does/Is the Risk Factor/Marker:

- ✓ Add independent information on risk or prognosis?
- ✓ Account for a clinically significant proportion of disease?
- ✓ Reliable and accurate?
- ✓ Provide good sensitivity, specificity and predictive value?
- ✓ Commercially available and practical for widespread application?

Stampfer et al. Circulation 2004;109 (Suppl IV):IV-3 – IV-5

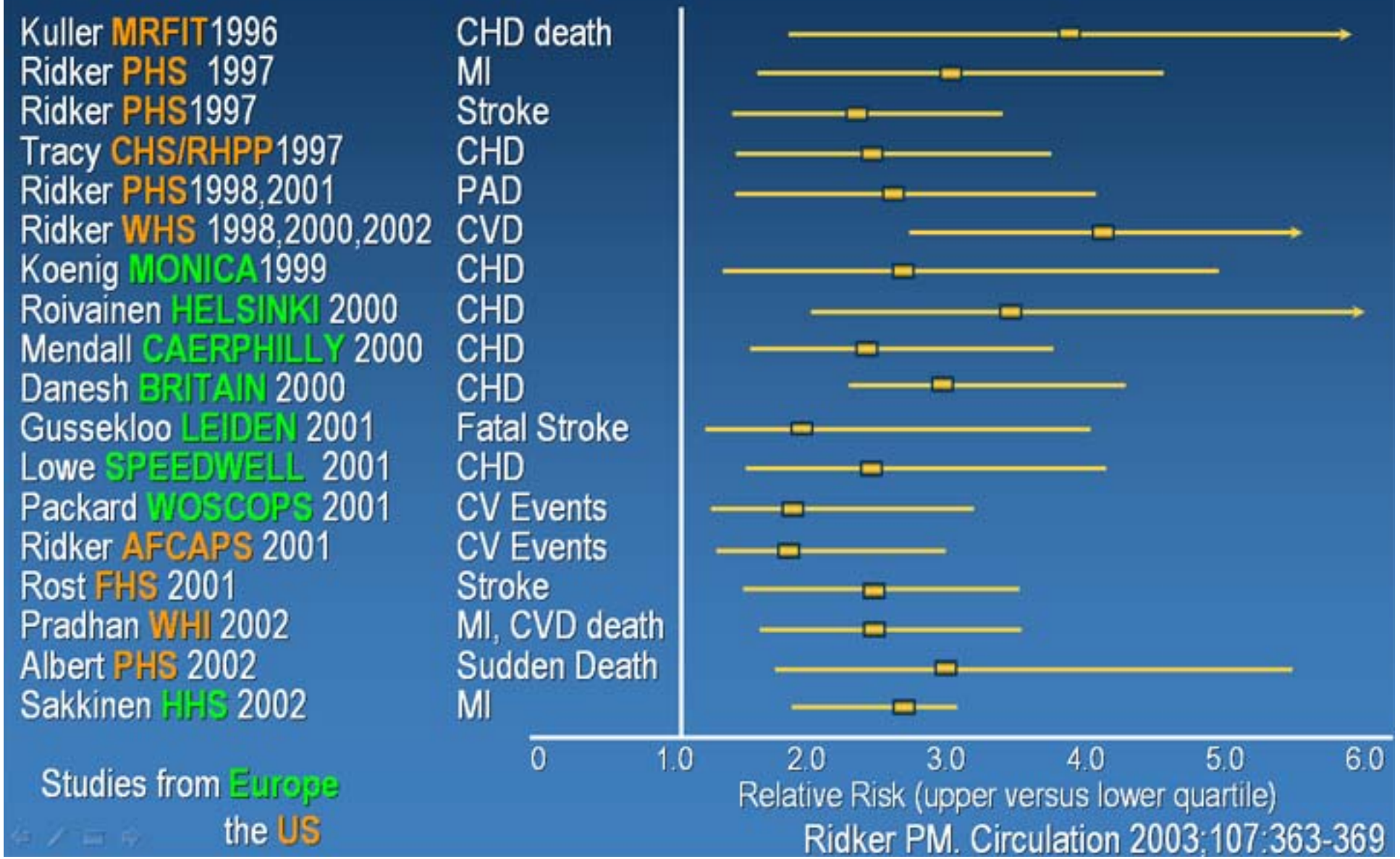
C-Reactive Protein (CRP)



The classical
acute phase protein

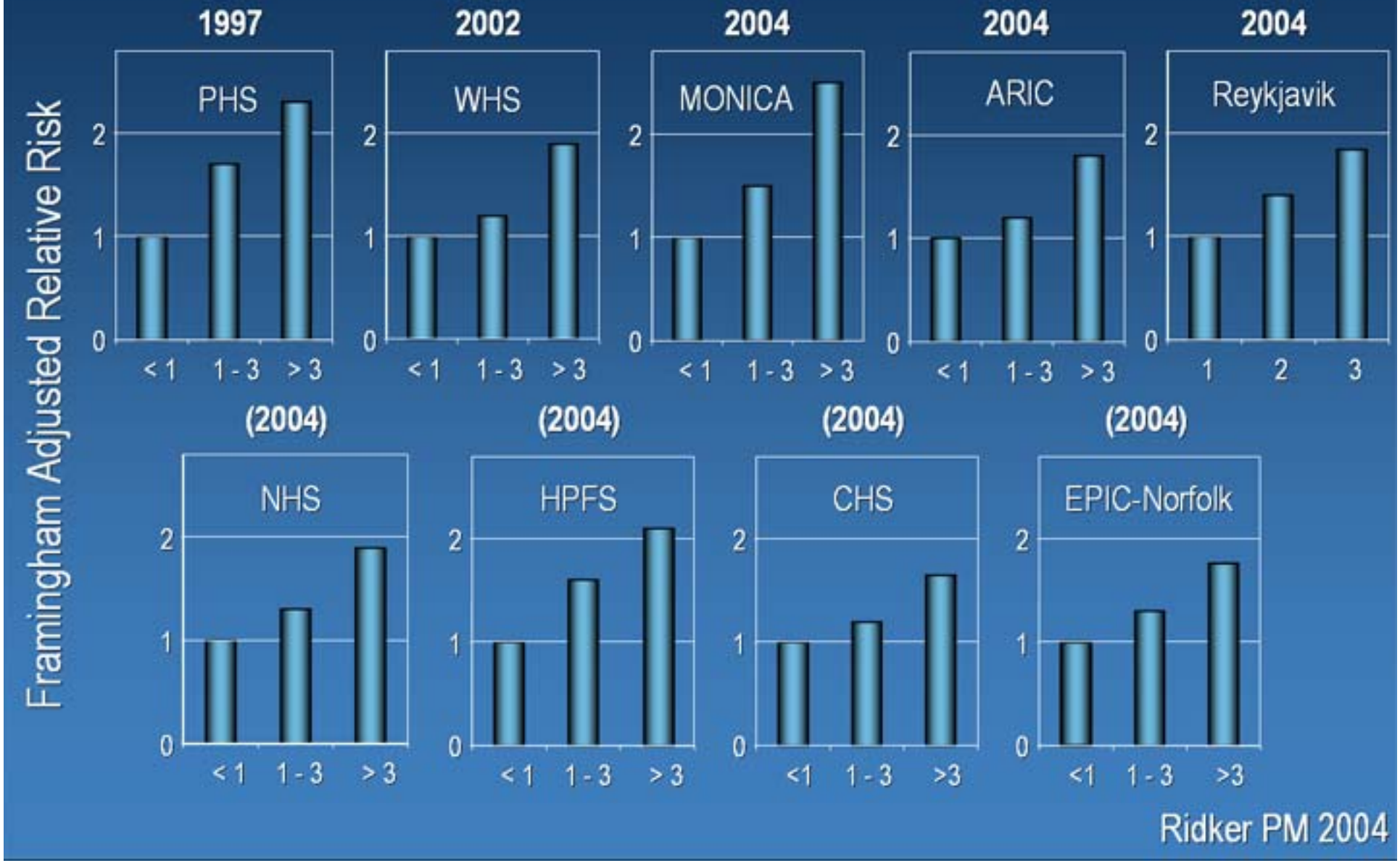
- ✓ hs-assay (CV < 6%)
- ✓ low cost
- ✓ good standardisation
- ✓ easy preanalytic sit.

CRP as a Risk Factor for Future CVD – Results from Population-Based Studies



Ridker PM. Circulation 2003;107:363-369

CRP Improves Prediction of CHD based on the Framingham Risk Score in ALL Cohort Studies



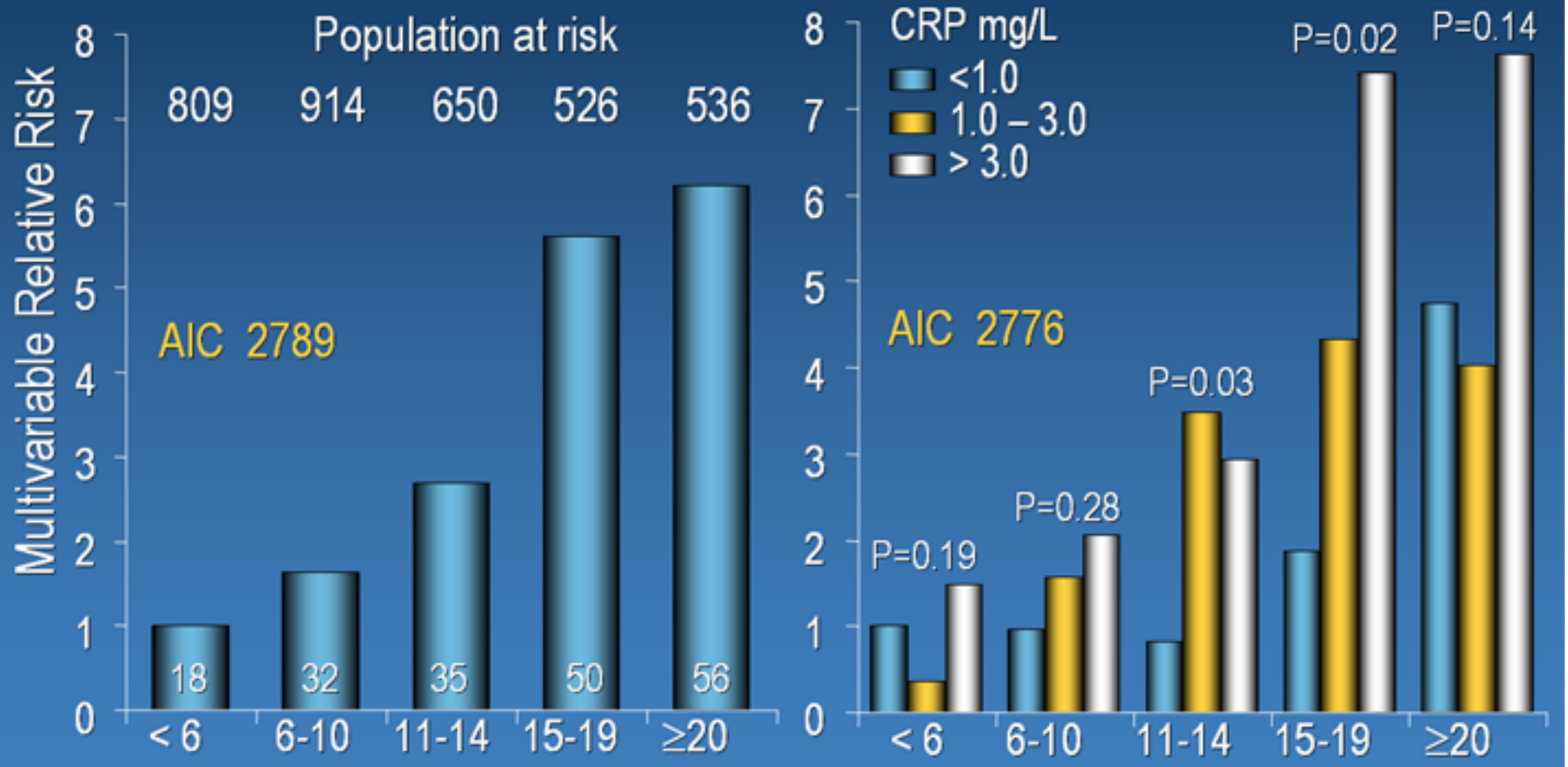
CRP and Prediction of Cardiovascular Risk: The Crucial Question is...

Does this biomarker add up to my usual risk assessment module: Framingham, PROCAM, ESC Score?

…is the incremental information worth it

RR of CHD According to the Estimated 10-Yr Risk Alone and in Combination with CRP: MONICA Augsburg Cohort

(N=3,435 Men, 45-74 Yrs; 191 Events, FU 6.6 Yrs)



Koenig et al. Circulation 2004;109:1349-1353

AHA/CDC Recommendations for Clinical and Public Health Practice

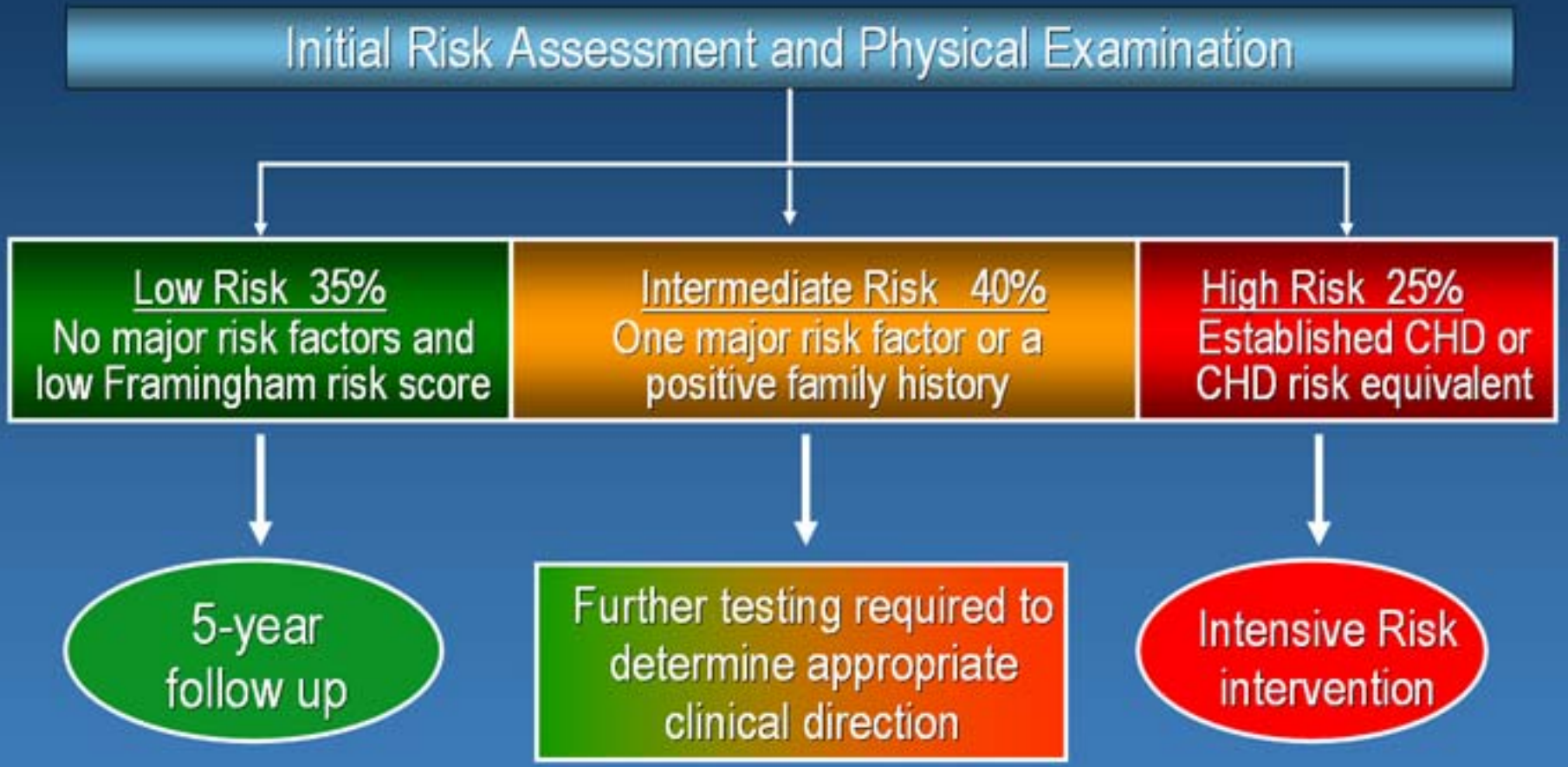
Class I: Should be performed
Class II: Conflicting evidence/opinion
  a: Weight in favor of usefulness/efficacy
  b: Usefulness/efficacy less well established
Class III: Should not be performed

Laboratory Tests

- ✓ Of current inflammatory markers identified, hs-CRP has the analyte & assay characteristics most conducive to use in practice (Class IIa, Level of Evidence B)
- ✓ Other inflammatory markers should not be measured for determination of CV risk in addition to hs-CRP (Class III, Level of Evidence C)

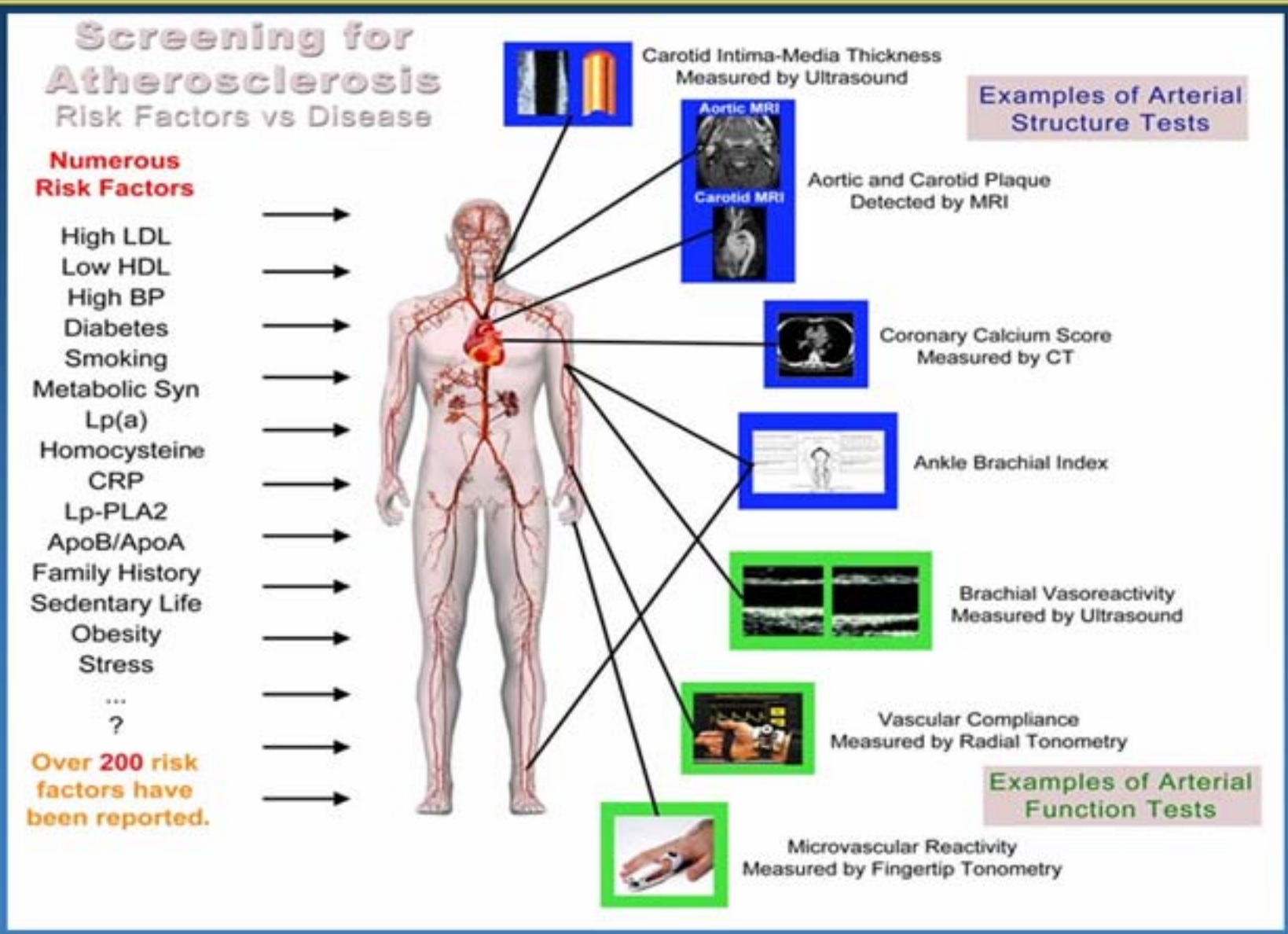
AHA/CDC Statement. Circulation 2003;107:499–511

Refining Cardiac Risk Assessment in Asymptomatic Patients

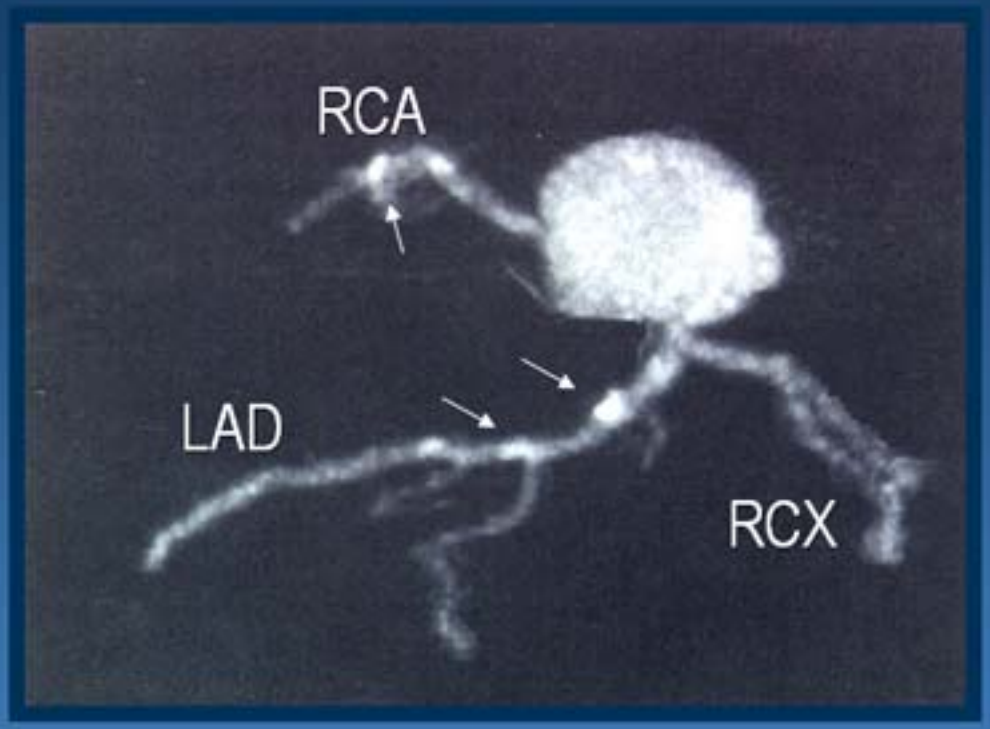


Greenland et al. Circulation 2001;104:1863-1867

Screening for Subclinical Atherosclerosis



Coronary Artery Calcium Scoring (EBT/MSCT)



A sufficiently evaluated diagnostic tool for cardiovascular risk assessment in primary prevention?

Coronary Artery Calcium Scoring Predicts CHD
INDEPENDENT OF STANDARD RISK FACTORS

1. South Bay Heart Watch (JAMA 2004)
2. Nashville EBT Registry (JACC 2004)
3. St. Francis Heart Study (JACC 2005)
4. PACC – Walter Reed Med Ctr. (JACC 2005)
5. Rotterdam Study (Circulation 2005)
6. Budoff – AHA Statement Update (Circulation 2005)
7. Greenland – ACC Statement Update (JACC 2006)

Recent Observational Cohort Studies Evaluating Prognostic Value of CACS, 2003-2005

Risk Subset	CAC Scores	N	Median % Annual CHD Events (Range)	Relative Risk (95% CI)
Low Risk	0	2,353	0.12 (0.05-0.6)	1.0
Mild Risk	1-100	4,832	0.37 (0.0-0.9)	2.2 (1.7-3.0)
Moderate Risk	101-299/399	3,327	0.71 (0.1-1.3)	4.2 (2.8-6.4)
High Risk	≥300 or ≥400	2,560	1.56 (0.5-3.3)	8.1 (5.6-11.6)
Very High Risk*	≥1,000	196	2.16 (-)	10.8 (4.2-27.7)
Summary RR for Mild – High Risk vs. Low Risk				4.5 (3.5-5.7)

Taylor et al. Am Coll Cardiol 2005;46(5):807-814
Arad et al. Am Coll Cardiol 2005;46:158-165
Greenland et al. JAMA 2004;291:210-215
Kondos et al. Circulation 2003;107:2571-2576
Vliegenthart et al. Circulation 2005;112: 572-527

Recent Observational Cohort Studies Evaluating Prognostic Value of CACS, 2003-2005

Author	Year	N	Historical or Measured RF Data	Univariable Relative Risk	Multivariable Relative Risk	Models Controlling for Additional Variables
Kondos	2003	8,855	Historical	0.001*	0.01	-
Greenland	2004	1,461	Measured	<0.001	<0.05**	-
Arad	2005	4,903	Measured	<0.0001	0.01	CRP
Taylor	2005	1,639	Measured	<0.0001	0.003	Family Hx of CHD
Vliegenthart	2005	1,795	Measured	<0.01	0.03	Family Hx-MI, BMI
LaMonte	2005	10,746	Historical	<0.0001	<0.05	
		3,619	Measured	<0.0001	<0.05	

* for men only

** for intermediate-high FRS

Taylor et al. Am Coll Cardiol 2005;46(5):807-814
Arad et al. Am Coll Cardiol 2005;46:158-165
Greenland et al. JAMA 2004;291:210-215
Kondos et al. Circulation 2003;107:2571-2576
Vliegenthart et al. Circulation 2005;112: 572-527
LaMonte et al. Am J Epidemiol. 2005;162:421-429

Future Needs for Screening Asymptomatic Subjects

- ✓ Do better with traditional risk factors!
- ✓ Identify the appropriate biomarker or their combinations for various clinical decision scenarios in addition to global risk scores
- ✓ Assess the value of a combination of blood biomarkers and non-invasive imaging (disease activity + burden!)
- ✓ Improve statistical approaches to assess the clinical utility of a biomarker (ROC, CART)
- ✓ Carry out clinical trials that show that changing the biomarker effectively changes clinical outcome

The Role of Surrogate Biomarkers in Identifying Cardiovascular Risk

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  - ✓ No need to wait for patients to have a major cardiovascular event
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Which Surrogate Markers are Available?

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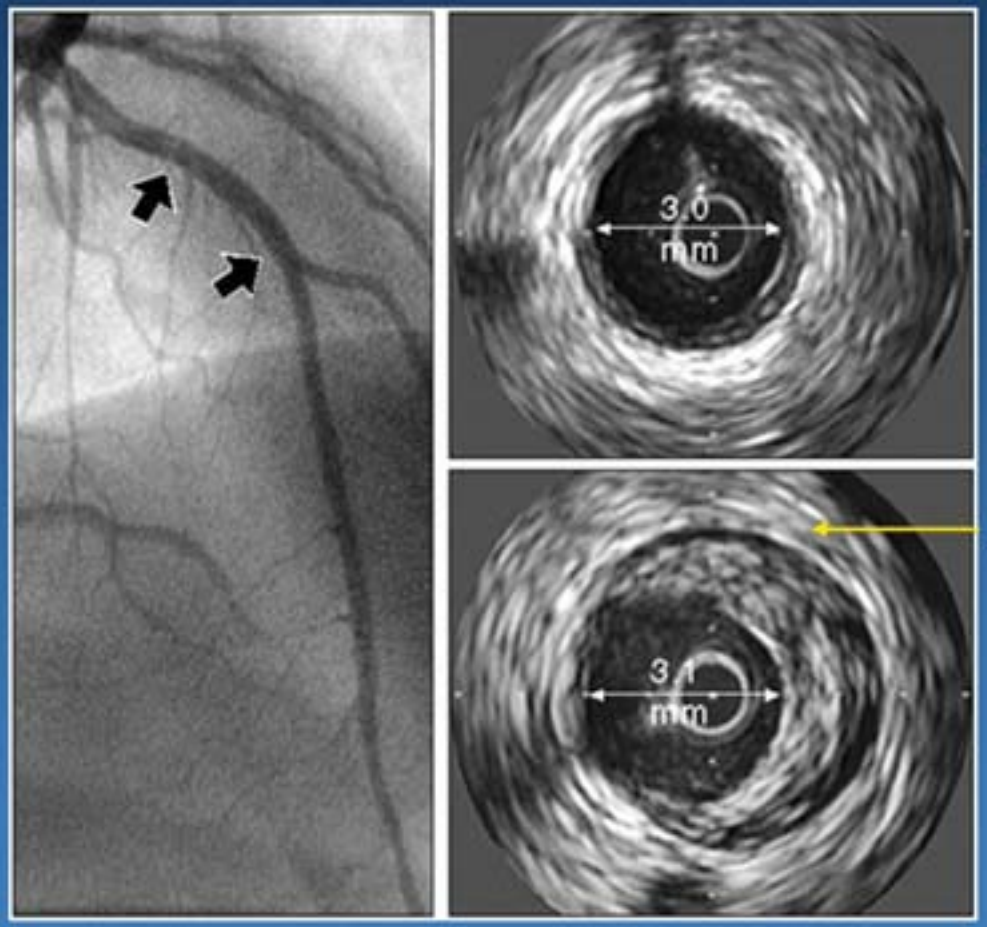
The IVUS Technique Can Detect Angiographically 'Silent' Atheroma

Angiogram

No evidence of disease



IVUS

Little evidence of disease

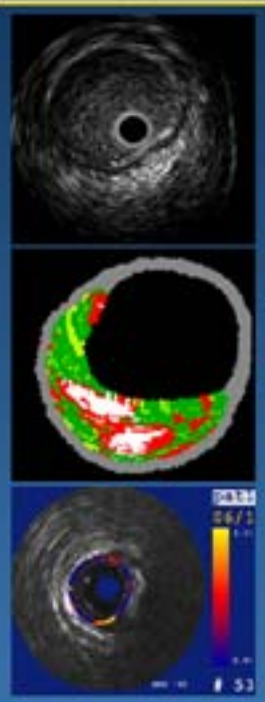
Atheroma

IVUS=intravascular ultrasound

Nissen S, Yock P. Circulation 2001; 103: 604–616

Extended Intravascular Imaging Modalities

Acquired with single pull back IVUS catheter at 0.5mm/sec.

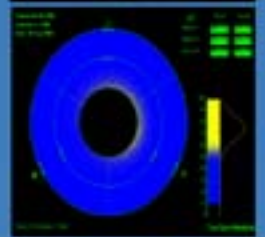


IVUS (gray scale; plaque size; echogenicity; Vasa vasorum)

Virtual Histology (plaque composition)

IVUS Palpography (mechanical properties)

Optical Coherence Tomography



Intravascular MRI

IBIS-2: Endpoints

PRIMARY

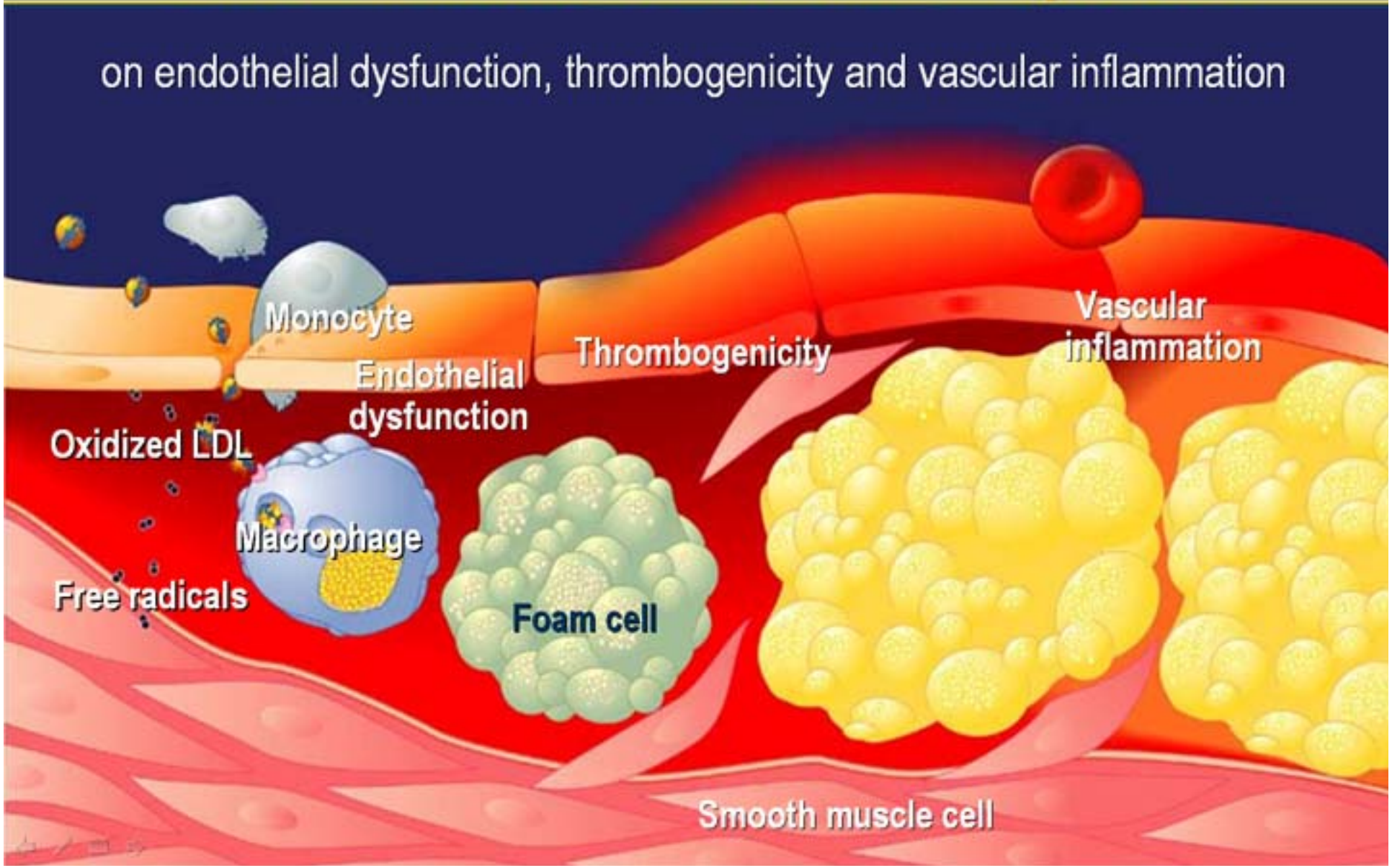
- ✓ Palpography: Index of plaque vulnerability
- ✓ hsCRP: Biomarker of systemic inflammatory burden

SECONDARY

- ✓ IVUS-VH: Compositional imaging
- ✓ Gray-scale IVUS: Plaque volume
- ✓ PAT: Endothelial function
- ✓ Biomarkers:

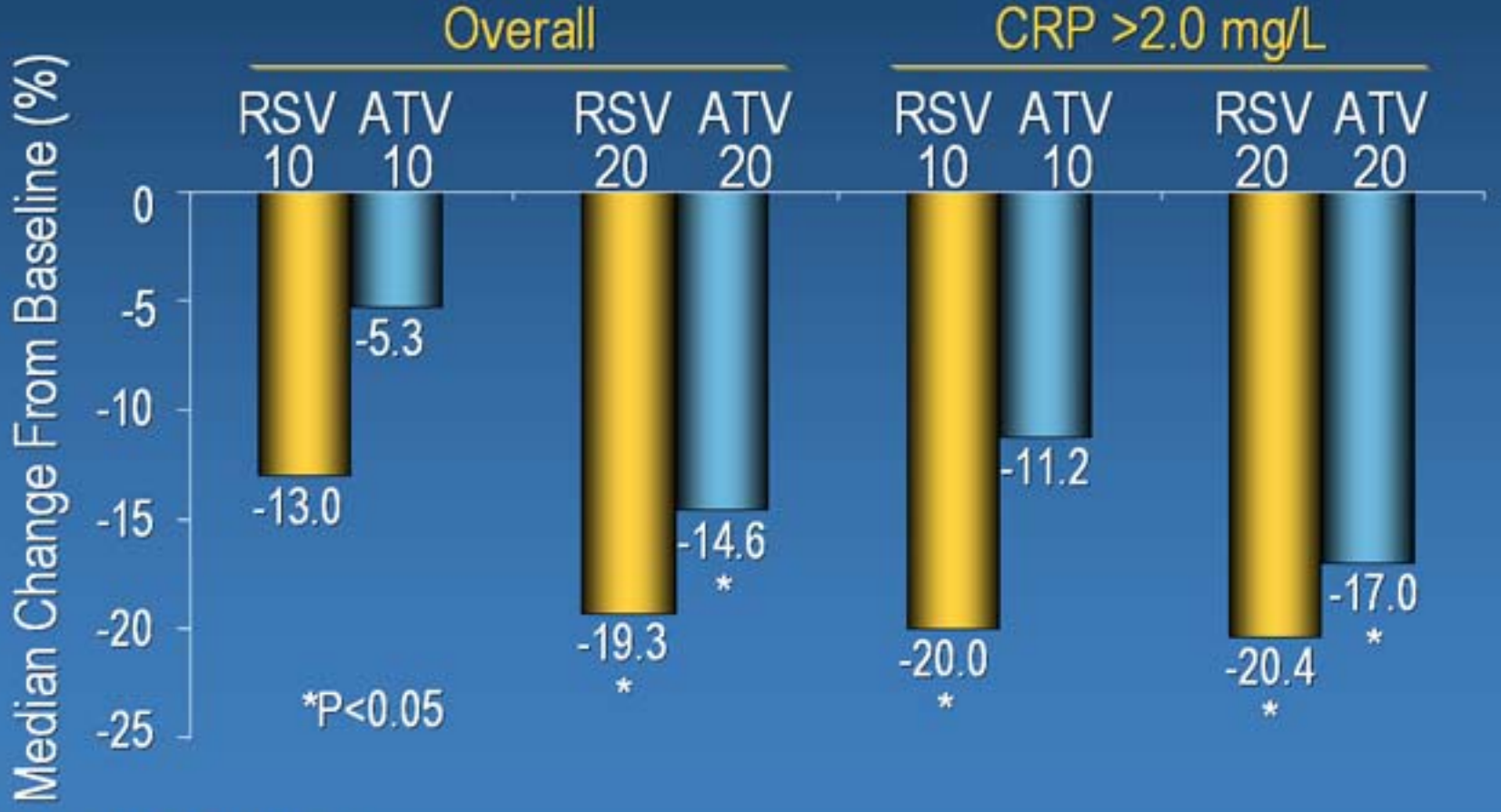
Inflammation-	IL-6, ICAM-1, CD40L, MPO
Plaque stability-	MMP-9
Target-	Lp-PLA_2, LysoPC, ox-LDL, ox-NEFA
Platelets-	P-selectin, sCD40L, u-11dehydroTBxB2

In Addition to Reducing LDL, Statins Show Other Antiatherosclerotic Properties



ARIES : Median Change in CRP

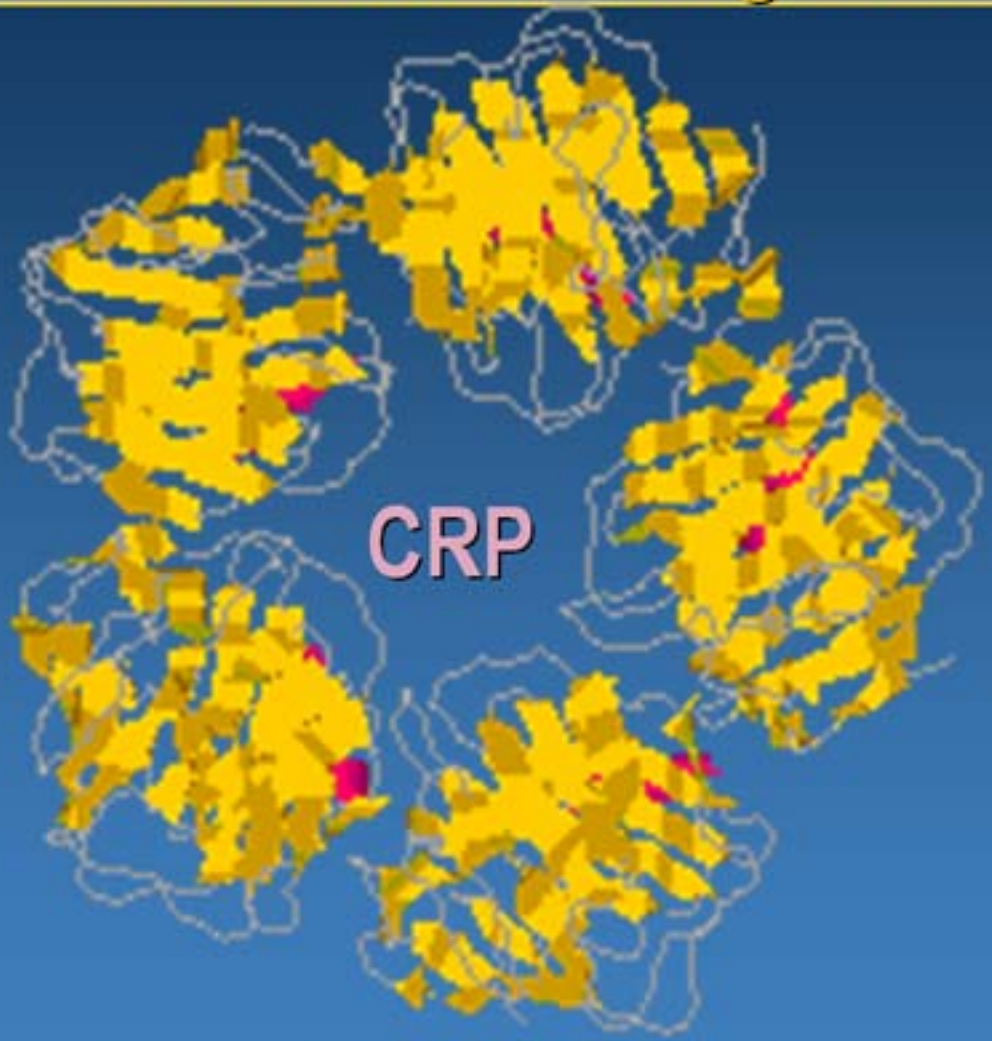
700 hypercholesterolemic adults randomized to rosuvastatin 10 or 20 mg or atorvastatin 10 or 20 mg for 6 weeks



Baseline CRP= 3.8 mg/L

Ferdinand et al. 2004

Beyond LDL-C – Clinical Evidence for Inflammation as a New Target for Therapy



As a Target for Statin Therapy?

Measurement of CRP Level for Targeting Statin Therapy in Primary Prevention (AFCAPS/TexCAPS)

LDL <median, CRP <median
(N=1,448)

LDL <median, CRP >median
(N=1,428)

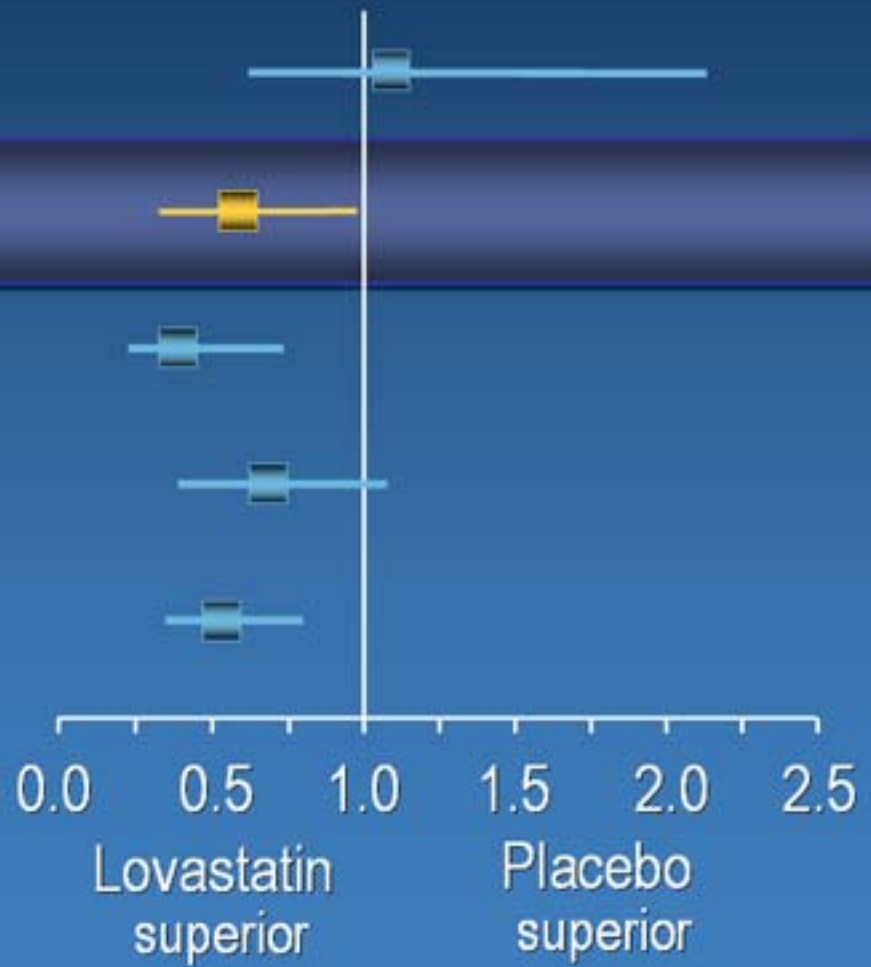
LDL >median, CRP <median
(N=1,420)

LDL >median, CRP >median
(N=1,446)

LDL <median, CRP>/< median
(N=2,866)

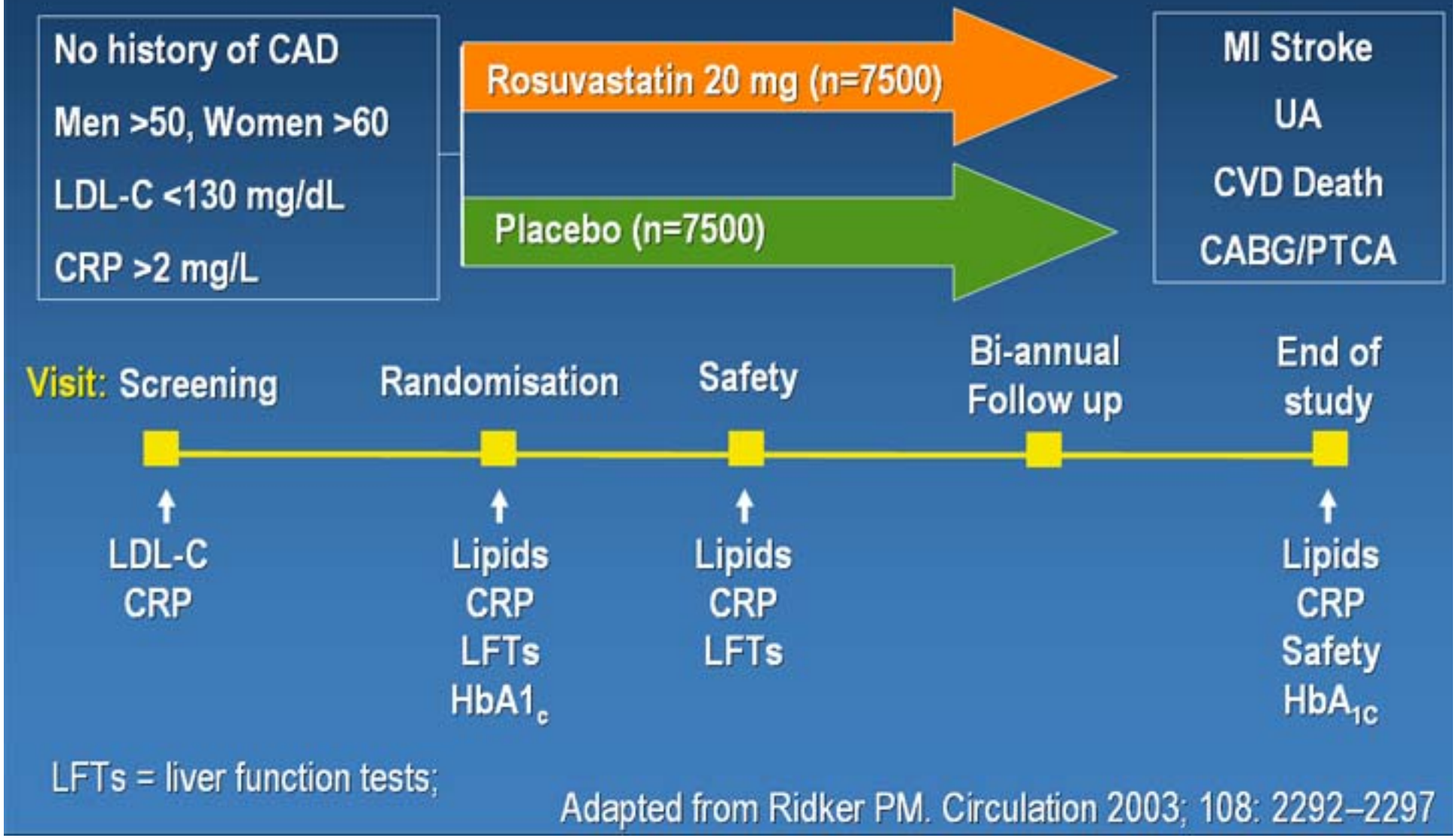
(AFCAPS/TexCAPS Study, Lovastatin)

LDL median: 159 mg/dL
CRP median:1.62 mg/L



Ridker et al. N Engl J Med 2001;344:1959-1965

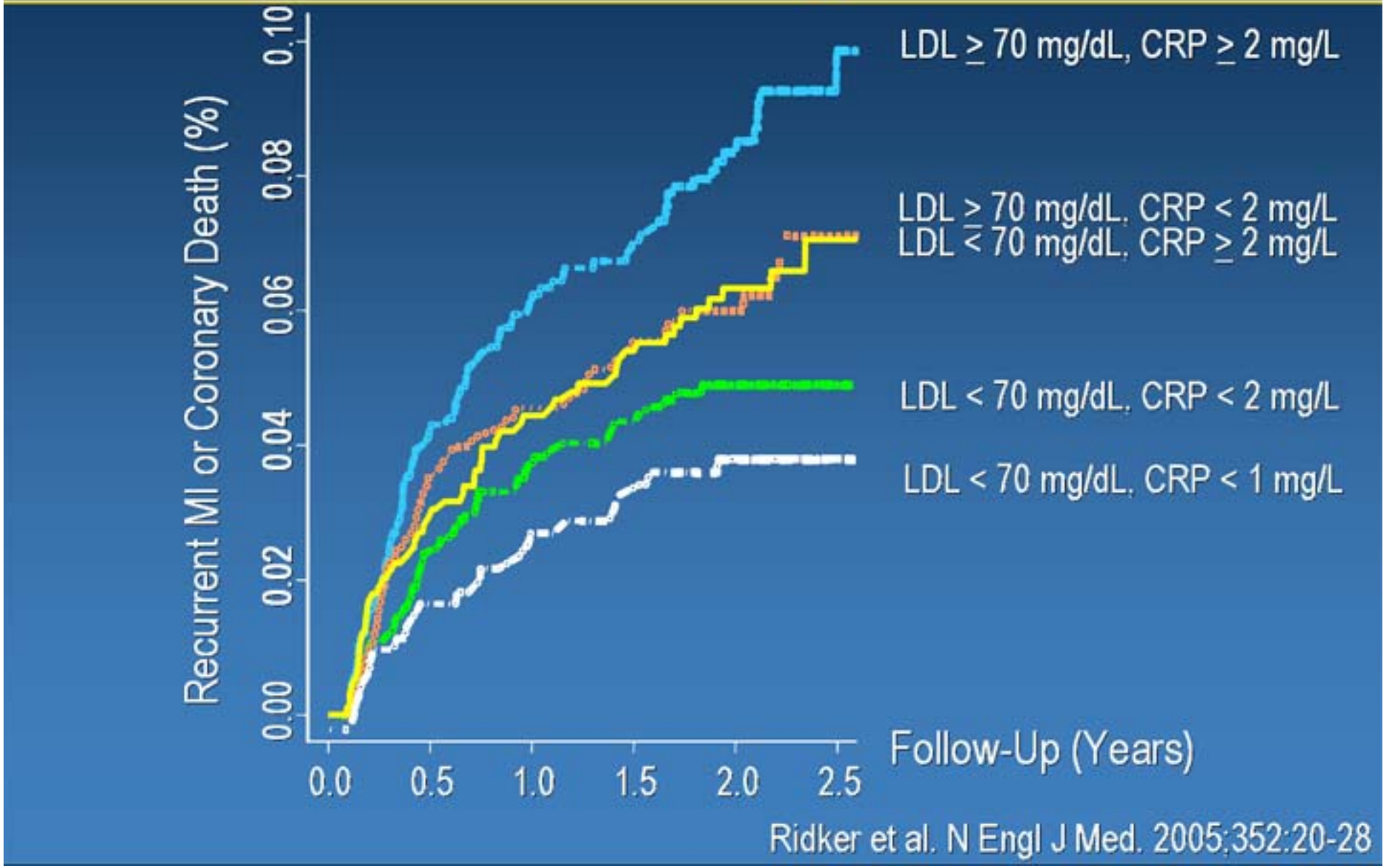
JUPITER – Study Design



LFTs = liver function tests;

Adapted from Ridker PM. Circulation 2003; 108: 2292–2297

Clinical Relevance of Achieved LDL and Achieved CRP After Rx With Statin Therapy: PROVE IT-TIMI 22

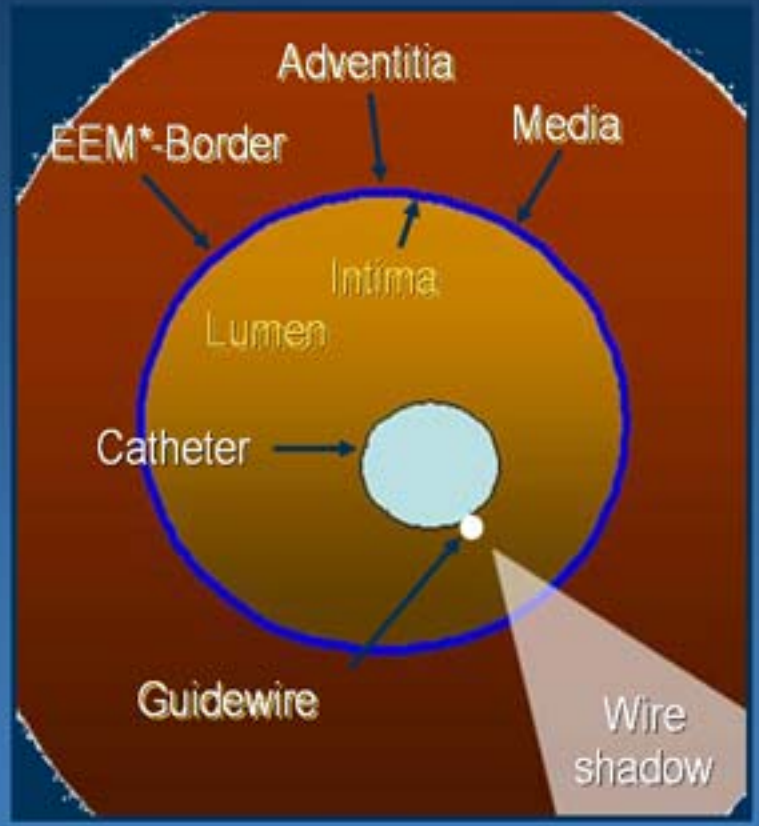


Ridker et al. N Engl J Med. 2005;352:20-28

Surrogate Markers of CHD - How Useful Are They?
Summary and Conclusions

- ✓ Markers of subclinical CHD and blood biomarkers enable early detection of atherosclerosis and therefore offer the opportunity for early therapeutic intervention
- ✓ Surrogate markers of CHD can de used as end-points in clinical studies ("proof of concept" studies)
- ✓ Statins, besides lowering LDL-C, reduce CRP and also affect other local mechanisms in the arterial vessel wall to change plaque volume and its phenotype
- ✓ Post-hoc analyses from several RCTs suggest that CRP may become a target for intervention which is presently being tested in the JUPITER trial

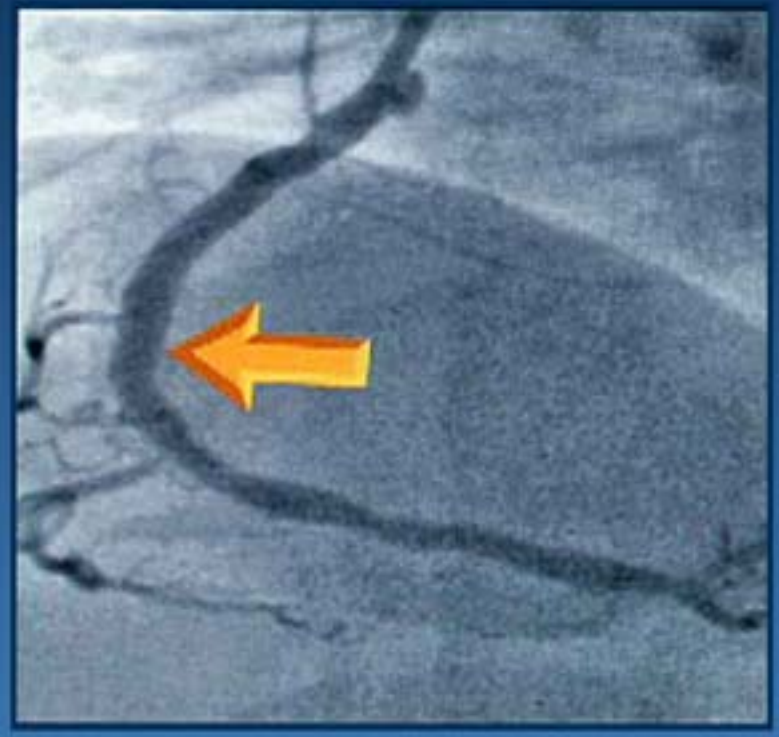
IVUS: Direct Imaging of Atherosclerosis



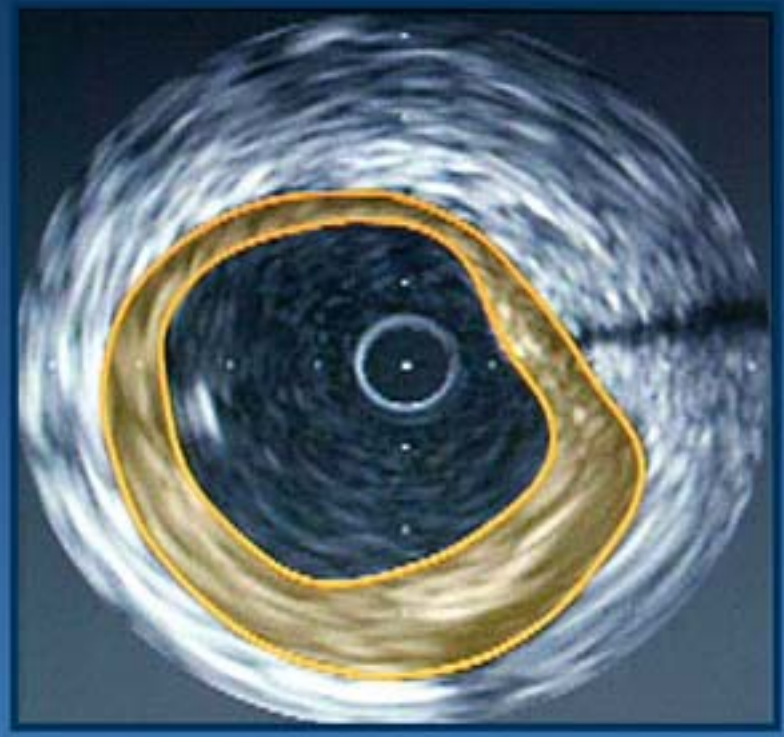
* EEM = external elastic membrane

mod. after Nissen S, American Heart Association (AHA), Scientific Sessions 2003, Orlando (USA)
Plenary Session XI: Late Breaking Trials, 12. November 2003

REVERSAL: An IVUS Study Comparing Atorvastatin and Pravastatin



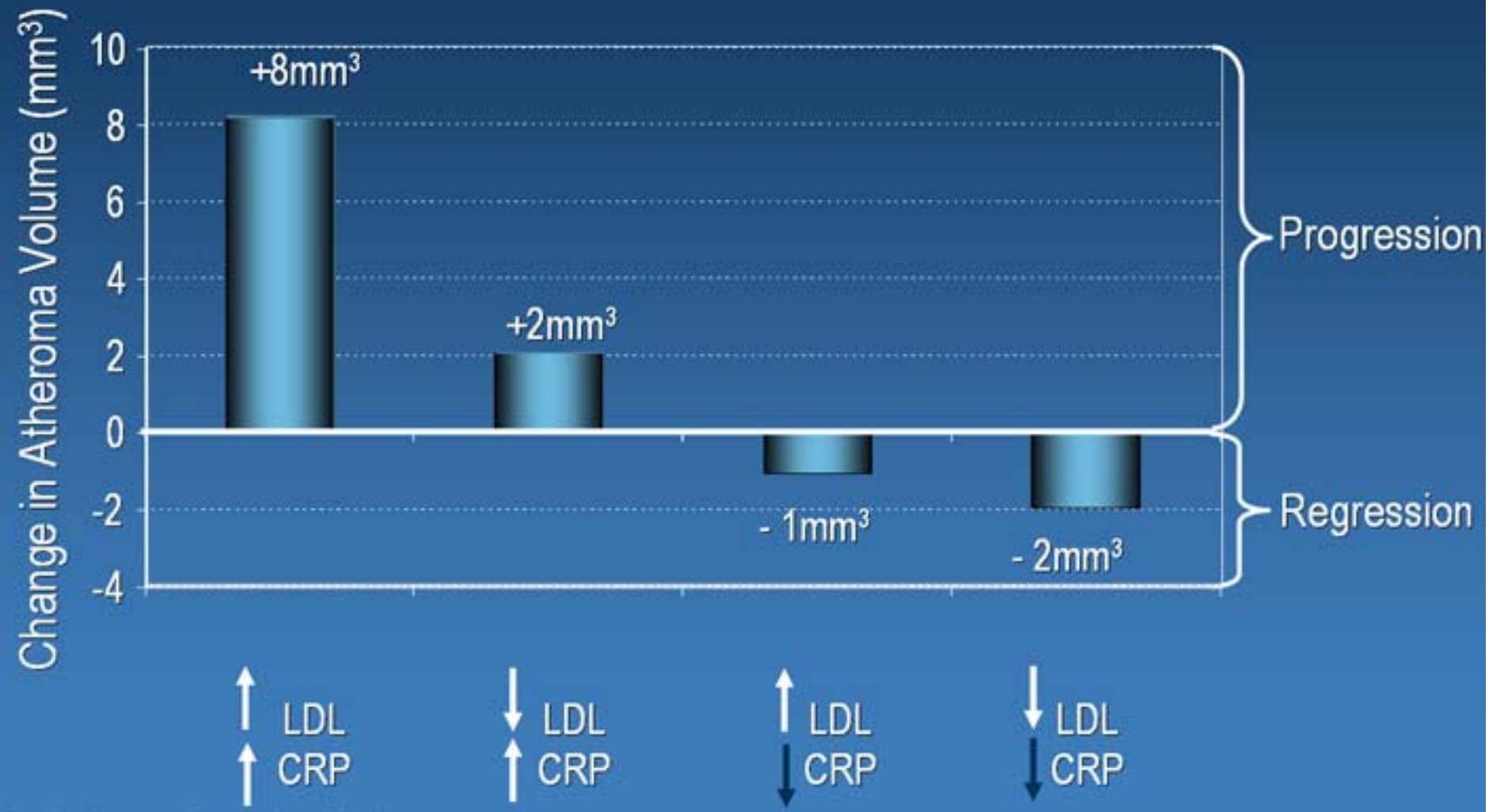
Coronary angiogram: No abnormalities, no lumen narrowing



Intravascular ultrasound (IVUS): Massive atherosclerotic plaque

mod. after Nissen S. AHA 2003, Orlando (USA)

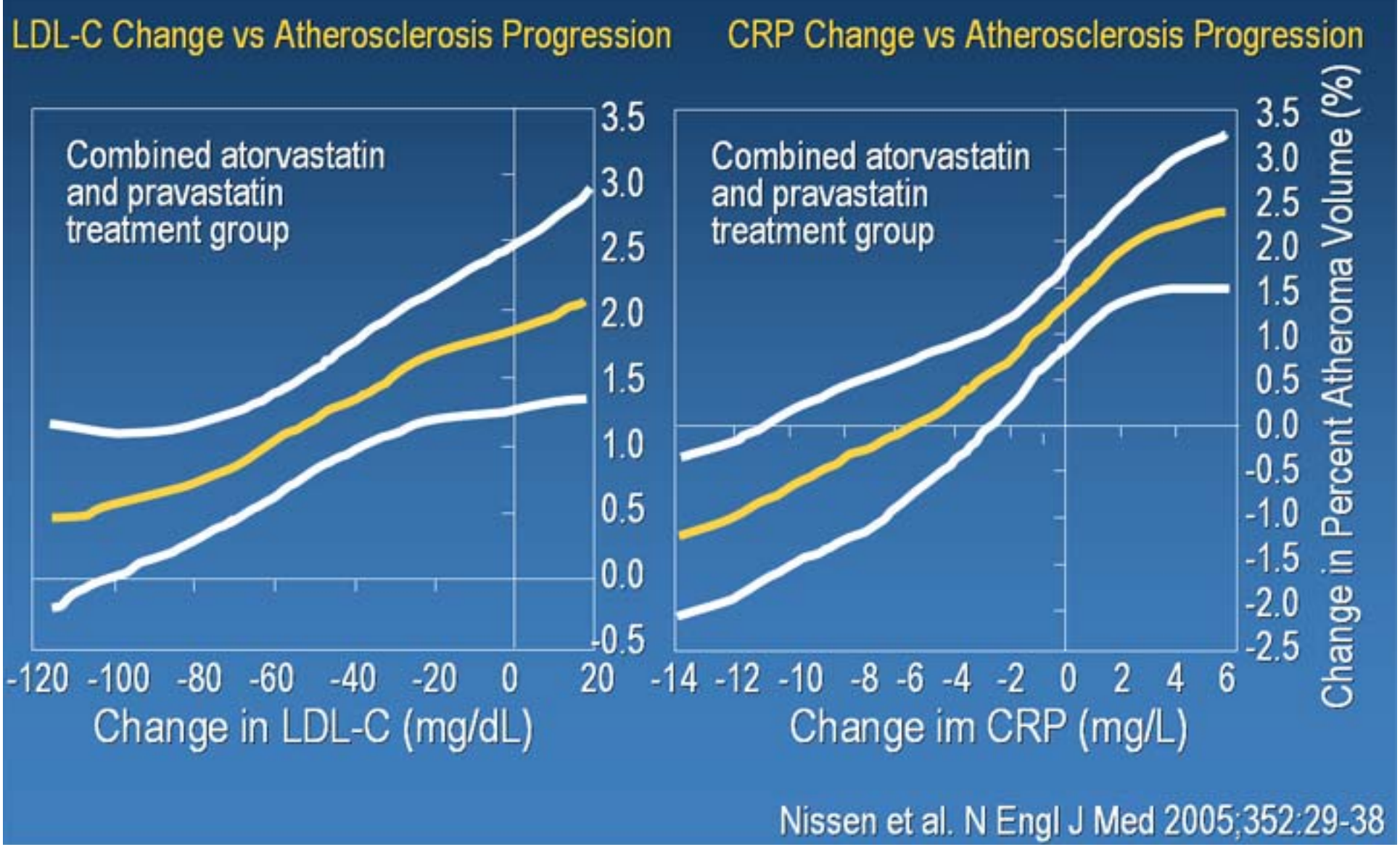
REVERSAL: Regression of Atherosclerosis On Statin Therapy Only Occurs Among Those with CRP Reduction



Reductions >/< median % change:
LDL -37.1%, CRP -21.4%

Nissen et al. N Engl J Med 2005;352:29-38

Effects of LDL and CRP Reduction on CAD Progression Measured By IVUS: REVERSAL

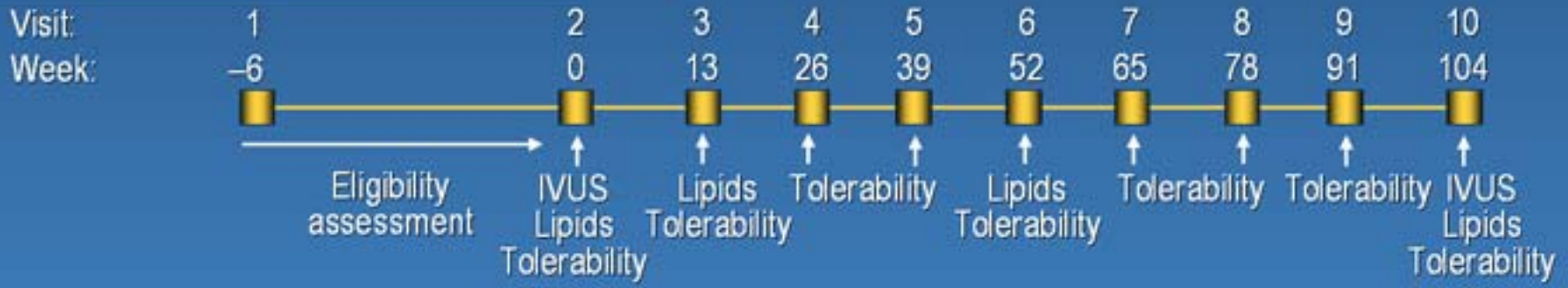


Nissen et al. N Engl J Med 2005;352:29-38

ASTEROID – Study Design

Patients
CAD, undergoing coronary angiography
Target coronary artery: ≤50% reduction in lumen diameter of ≥40 mm segment
No cholesterol entry criteria
≥18 years

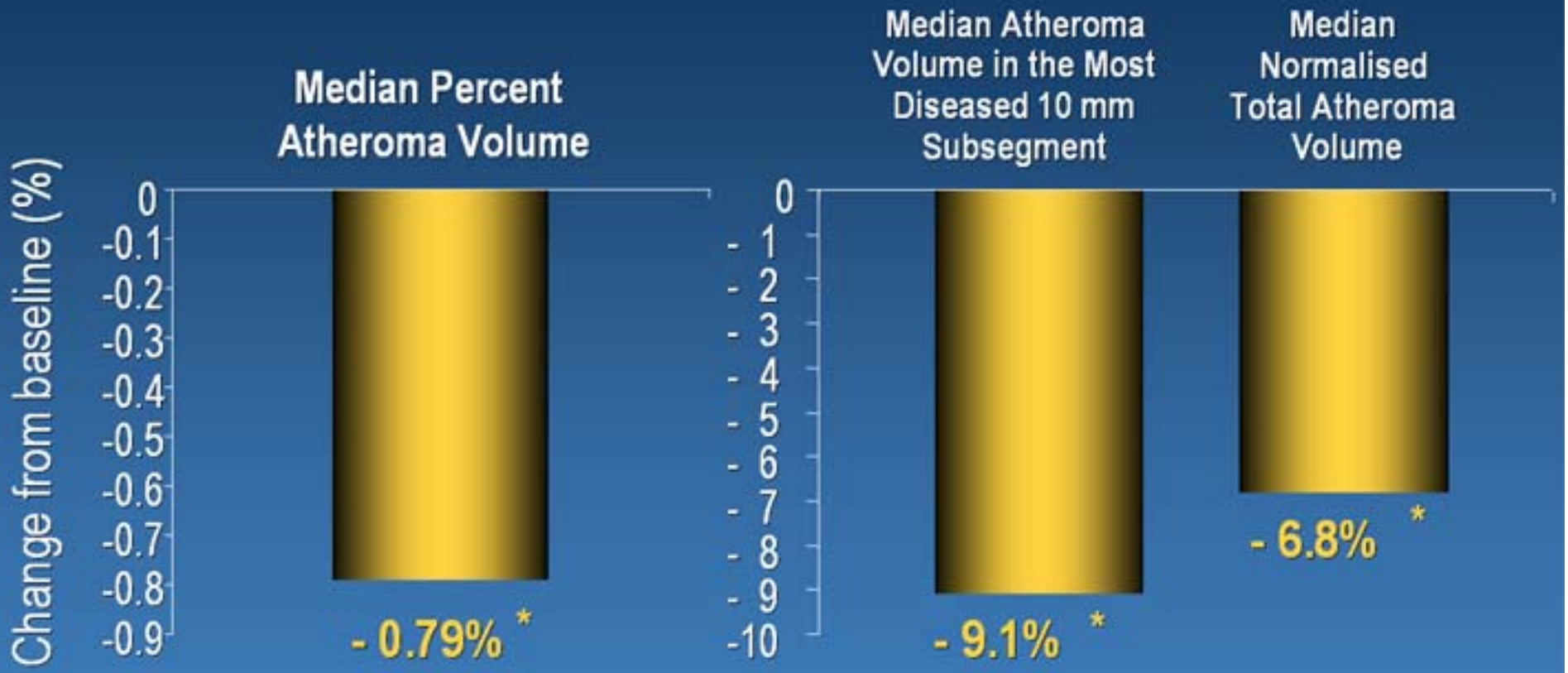
Rosuvastatin 40 mg
(n=349 evaluated serial IVUS examinations)



CAD=coronary artery disease;
PCI=percutaneous coronary intervention;
IVUS=intravascular ultrasound

Nissen et al. JAMA 2006;295:1556-1565

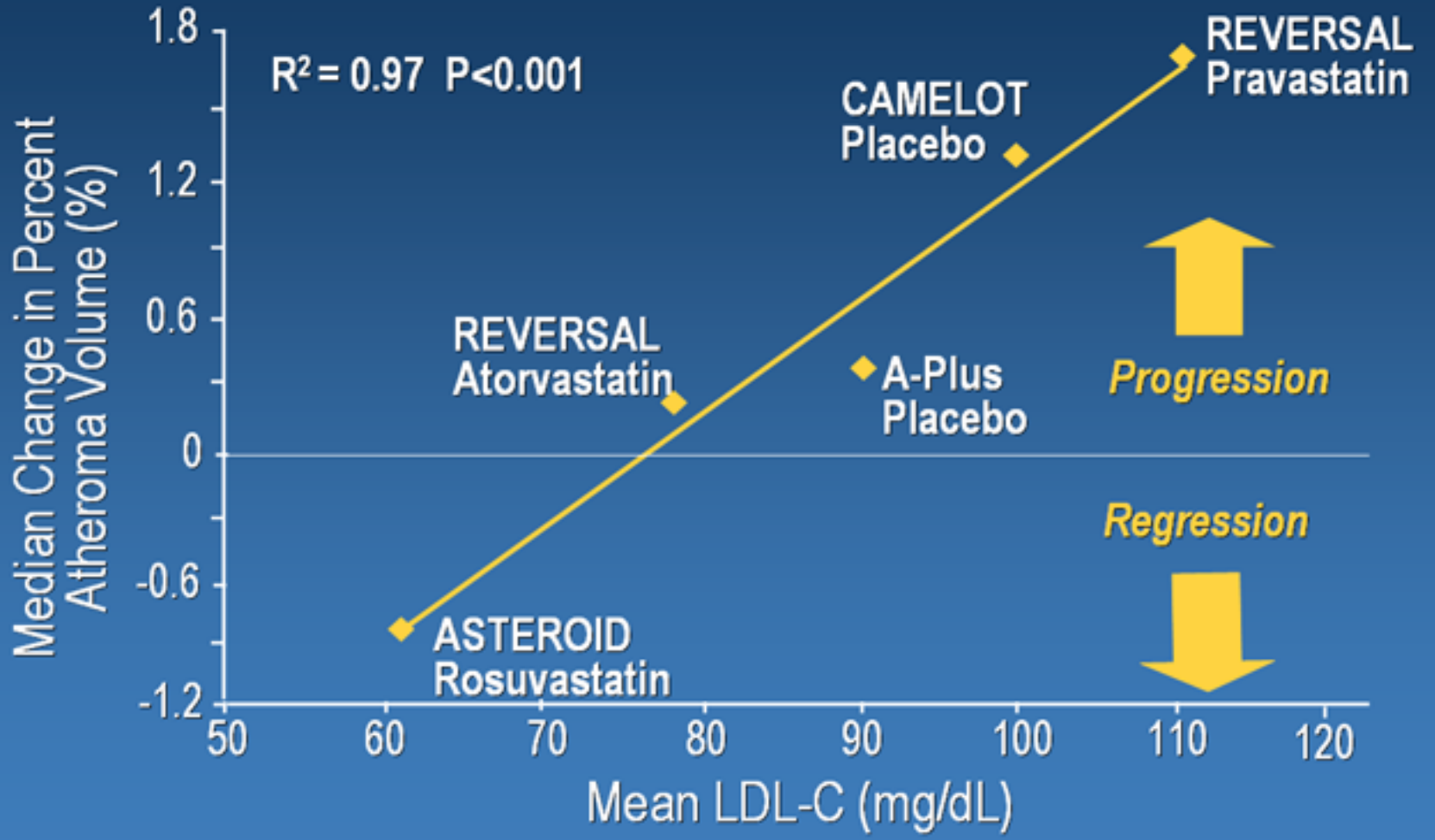
Endpoint Analysis: Change in Key IVUS Parameters



* p<0.001 for difference from baseline values. Wilcoxon signed rank test

Nissen et al. JAMA 2006;295:1556-1565

Relationship between LDL-C Levels and Change in Percent Atheroma Volume for Several IVUS Trials



CAMELOT: Comparison of Amlodipine vs Enalapril to Limit Outcome of Thrombosis
A-Plus: Avasimibe and Progression of Lesions on IVUS

Nissen et al. JAMA 2006;295:1556-1565

ASTEROID

Tolerability of Rosuvastatin

- In ASTEROID, rosuvastatin 40mg was taken by more than 500 patients in this 2 year study.
- Rosuvastatin 40mg was well tolerated with a safety profile consistent with the existing extensive safety database
- Increases in ALT* were low (0.2%)
- There were no clinically significant increases in CK# observed in the core laboratory and there were NO cases of rhabdomyolysis
- The number of clinical events in the study was too small for any meaningful analysis of the relationship between progression rate and morbidity or mortality

Nissen et al. JAMA 2006;295:1556-1565

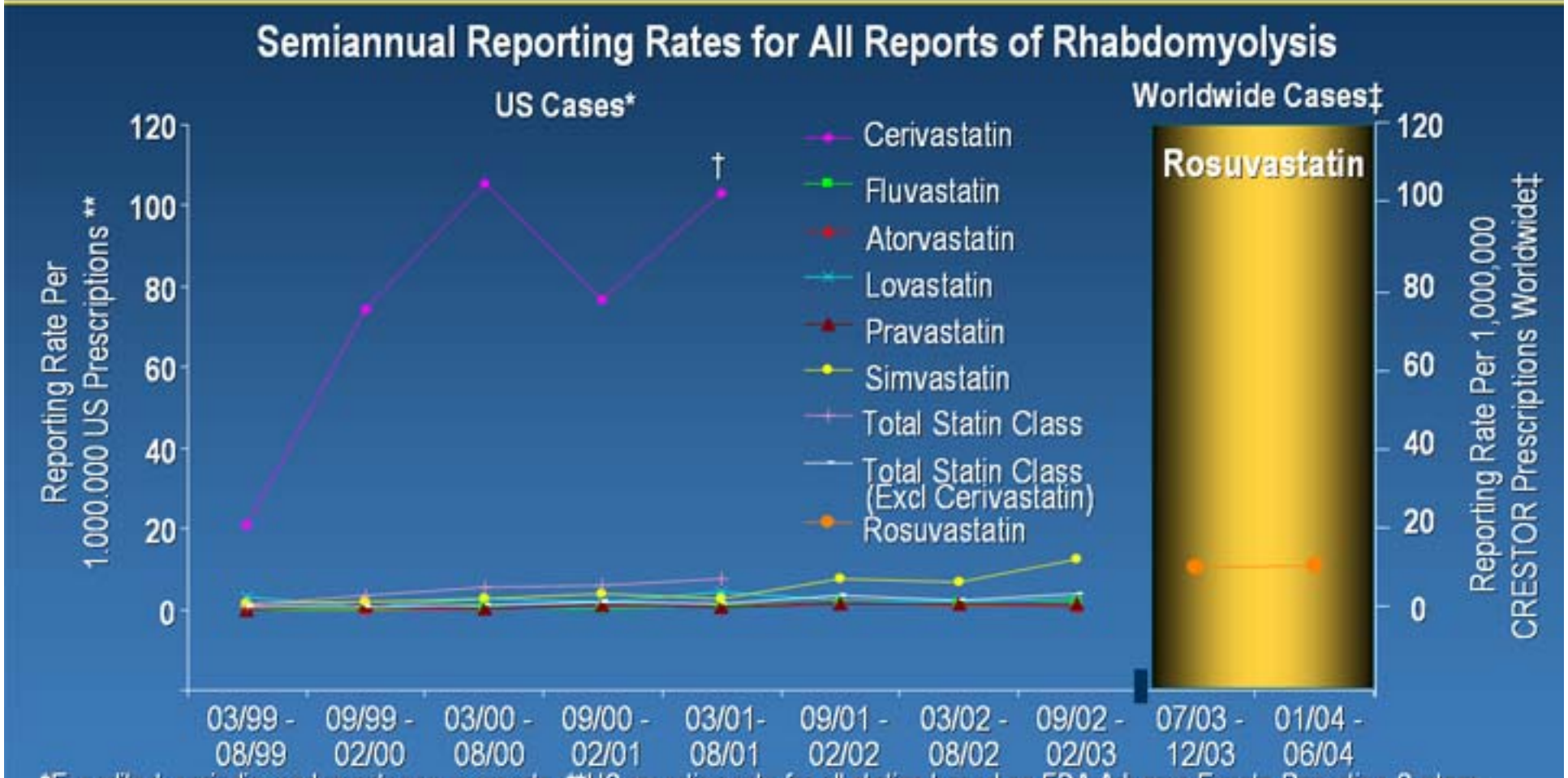
ASTEROID

Clinical Implications

- ✓ Rosuvastatin is the first and only statin that has been shown to reduce atheroma and reverse established atherosclerosis in a major clinical study; rosuvastatin 40 mg produced significant regression of atherosclerosis for all three IVUS measures assessed
- ✓ While other statins have tried to demonstrate this effect, only rosuvastatin has produced this unprecedented reduction in plaque volume in a large clinical trial
- ✓ These landmark results, backed by established superiority in lowering LDL-C and raising HDL-C, further confirm rosuvastatin as an effective and well-tolerated product for the treatment of high cholesterol

Nissen et al. JAMA 2006;295:1556-1565

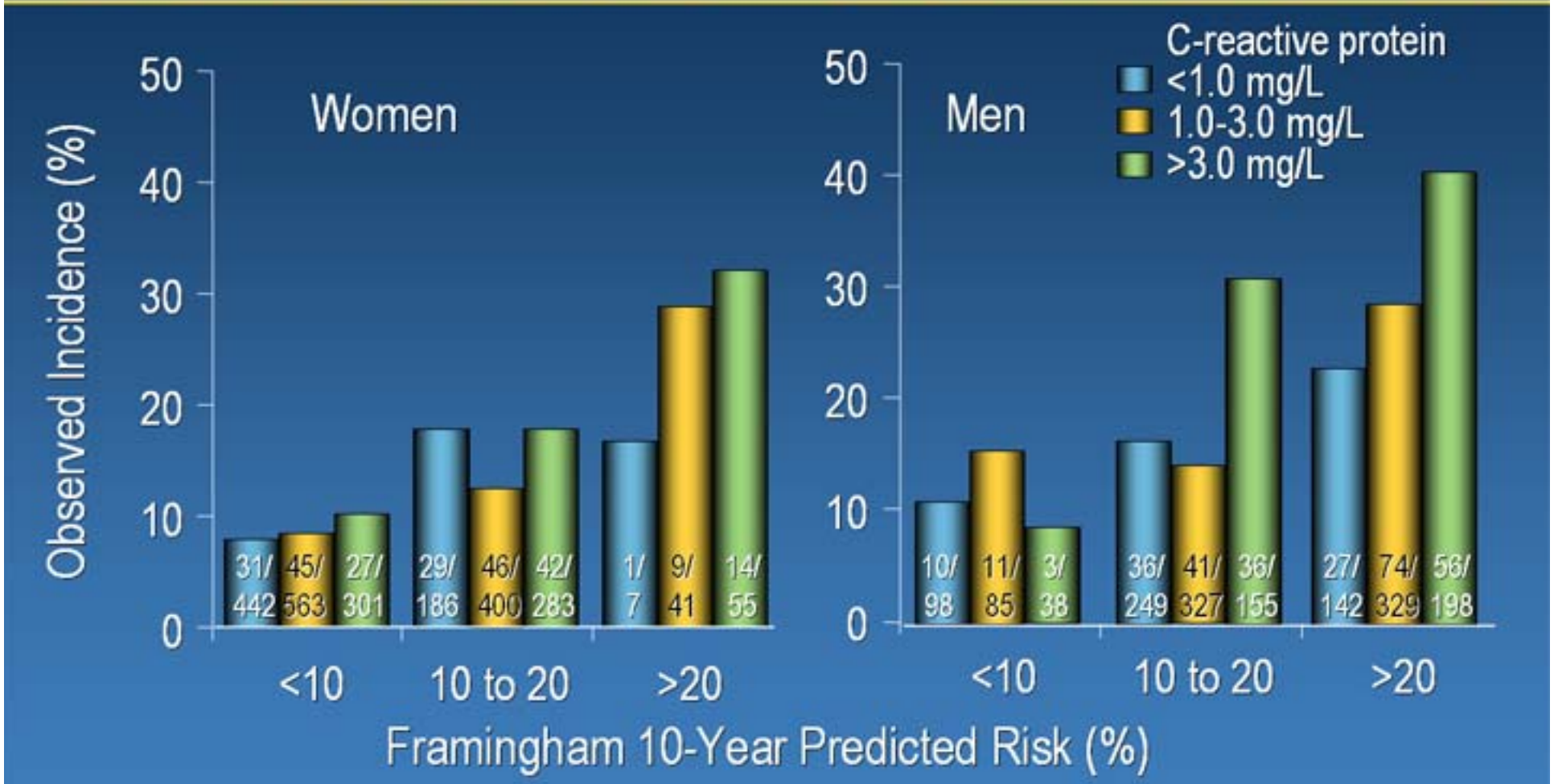
Reporting Rates of Rhabdomyolysis With Statin Therapy



*Expedited, periodic, and spontaneous reports. **US reporting rate for all statins based on FDA Adverse Events Reporting System made available through Freedom of Information Act divided by US prescribing data supplied by IMS through February 2003. †Cerivastatin reports received after September 1, 2001, are excluded. ‡Global reporting rate for rosuvastatin based on case counts of rhabdomyolysis within AstraZeneca global drug safety database divided by estimated worldwide prescriptions to the end of June 2004. Total prescriptions based on IMS data from US, Canada, UK, France, Italy and The Netherlands; rest of world prescriptions based on actual sales calculations.

Update: 06 August 2004

CRP and the 10-Year Incidence of Coronary Heart Disease in *Older* Men and Women: CHS



Observed incidence based on categories of CRP was determined within each category of Framingham-predicted risk. For each category, numbers across top represent number of events per number at risk in that group

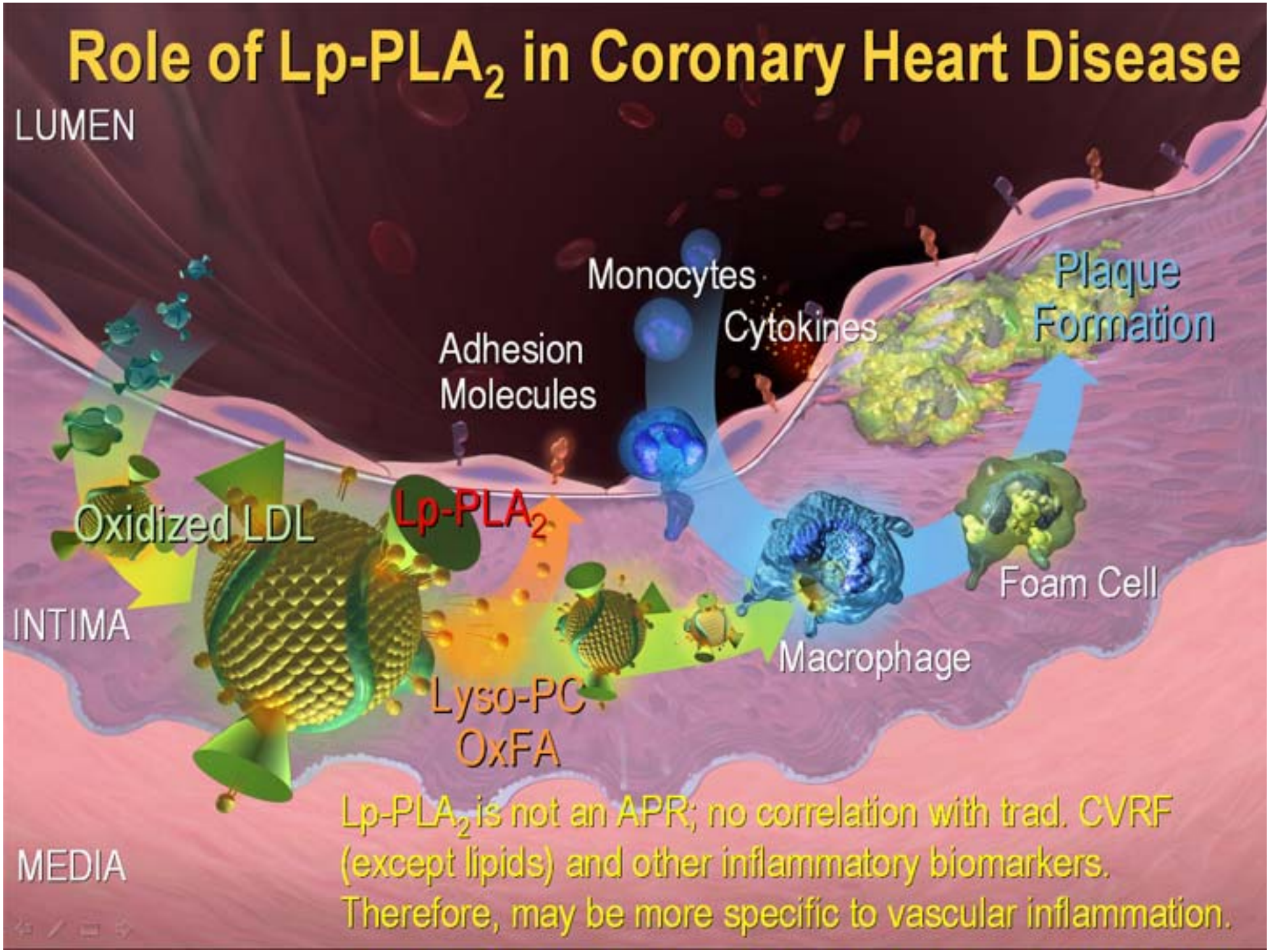
Cushman et al. Circulation 2005;112:25-31

Trial of Atorvastatin in Rheumatoid Arthritis (TARA): Double-Blind, Randomised Placebo-Controlled Trial

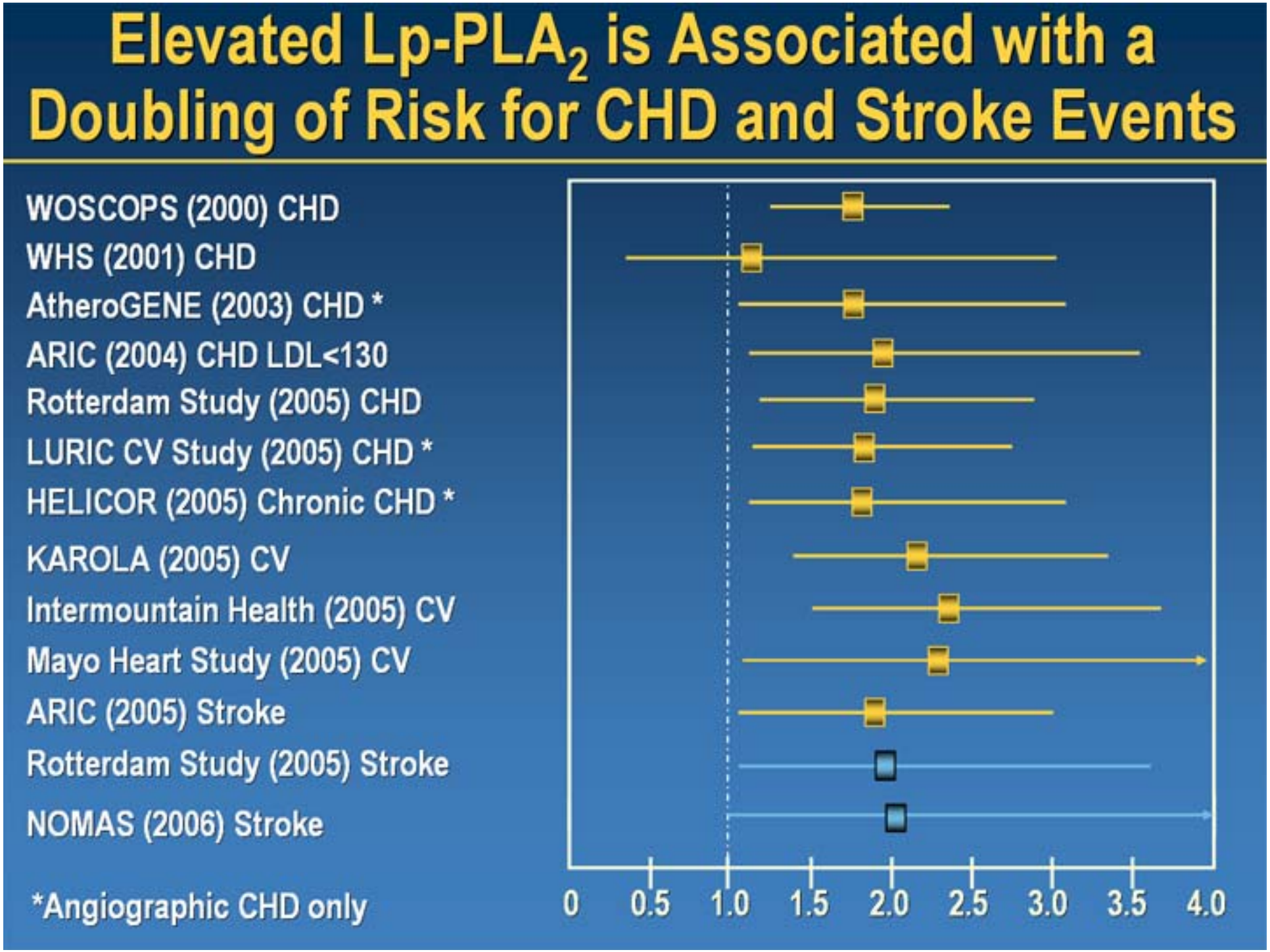
	Atorvastatin (n=58)	Placebo (n=58)	p
Primary outcome measure			
Disease activity score	- 0.50 (- 0.75 to - 0.25)	0.03 (- 0.23 to 0.28)	0.004
Secondary outcome measure			
CRP (log mg/L)	- 0.46 (- 0.64 to - 1.67)	0.12 (- 0.09 to 0.34)	<0.0001
LDL-C (mmol/L)	- 1.40 (- 1.63 to - 1.17)	- 0.07 (- 0.23 to 0.10)	<0.0001
HDL-C (mmol/L)	0.03 (- 0.03 to 0.09)	- 0.04 (- 0.10 to 0.02)	0.097
Fibrinogen (g/L)	- 0.38 (- 0.69 to - 0.07)	0.00 (0.19 to - 0.20)	0.041
Plasma viscosity (mPa•s)	- 0.05 (- 0.06 to - 0.03)	- 0.00 (- 0.02 to 0.01)	0.0004
VWF (IU/dL)	- 8.5 (- 20.6 to 3.58)	- 4.53 (-16.7 to 7.60)	0.64
ICAM-1 (ng/mL)	-22.6 (- 41.6 to - 3.70)	2.37 (-18.2 to 22.90)	0.076
Interleukin-6 (pg/mL)	-6.6 (-13.2 to 0.01)	3.84 (- 2.85 to 10.50)	0.028

Differences after 6 months of treatment

McCarey et al. Lancet 2004; 363: 2015–2021


Role of Lp-PLA2 in Coronary Heart Disease
LUMEN
Monocytes
Cytokines
Plaque Formation
Adhesion Molecules
Oxidized LDL
Lp-PLA2
Foam Cell
INTIMA
Macrophage
Lyso-PC
OxFA
Lp-PLA2 is not an APR; no correlation with trad. CVRF (except lipids) and other inflammatory biomarkers. Therefore, may be more specific to vascular inflammation.
MEDIA

Elevated Lp-PLA$_2$ is Associated with a Doubling of Risk for CHD and Stroke Events



Established and Emerging Modalities for Measuring Subclinical Cardiovascular Disease

Technique	Measure	Availability	Incremental Predictive Value over Office- Based Risk Assessment	Evidence Showing Relation to Clinical Events	Reproducibility
Carotid Ultrasound	Intima Media Thickness (IMT)	Widely available	Yes	Excellent	Good
Computer Tomography	Coronary calcium score, volume	Moderately (EBCT) to widely (MSCT) available	Some data	Very Good	Good
Ankle-Brachial Index	ABI ratio	Widely available (office-based)	Yes	Excellent	Very Good
Magnetic Resonance	Plaque cross-sectional area, plaque components	Limited available of centers asseseing atherosclerotic plaque	No data	No data	Very Good to Excellent
Brachial Ultrasound	Flow mediated dilatation	Widely available but requires spec. training	No data	Good	Fair

Noninvasive Tests of Atherosclerotic Burden

- ✓ Ankle-brachial blood pressure index (ABI)
  AHA recommended
- ✓ Carotid ultrasonography
  AHA recommended
- ✓ EBCT
  (AHA: not recommended at present)
- ✓ Multislice CT
  (AHA: not recommended at present)
- ✓ MRI
  (AHA: not recommended at present)
- ✓ Determination of endothelial function
  (AHA: no recommended at present)

Prevention Conference V Circulation 2000;101:e16-e22

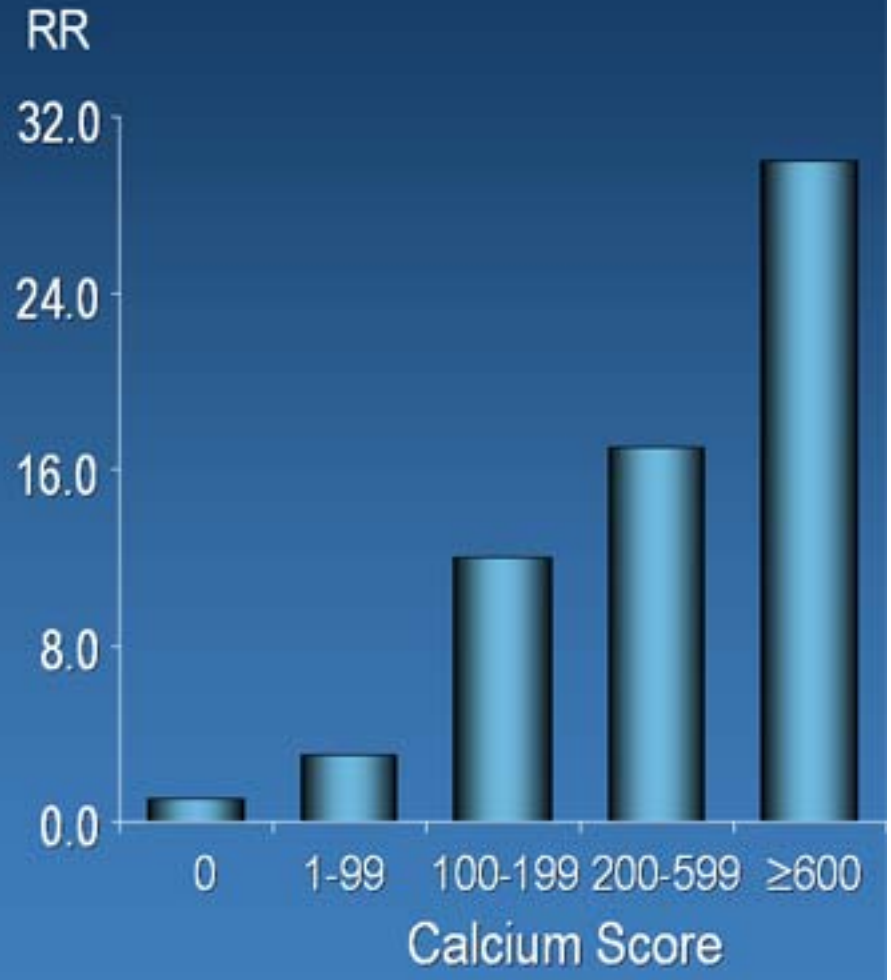
Prediction of CVD Events by Coronary Calcium Score: St. Francis Heart Study

- ✓ Baseline Calcium Score and CVD Events:

Event	584 ± 775	p < 0.0001
No event	142 ± 381	

- ✓ Coronary Calcium Score (≥100 vs <100) and CVD Events:

Events	N	RR (95% CI)
All CVD	122	9.5 (6.5-13.8)
All coronary	105	10.7 (7.1-16.3)
MI/coronary death	43	9.9 (5.2-18.9)

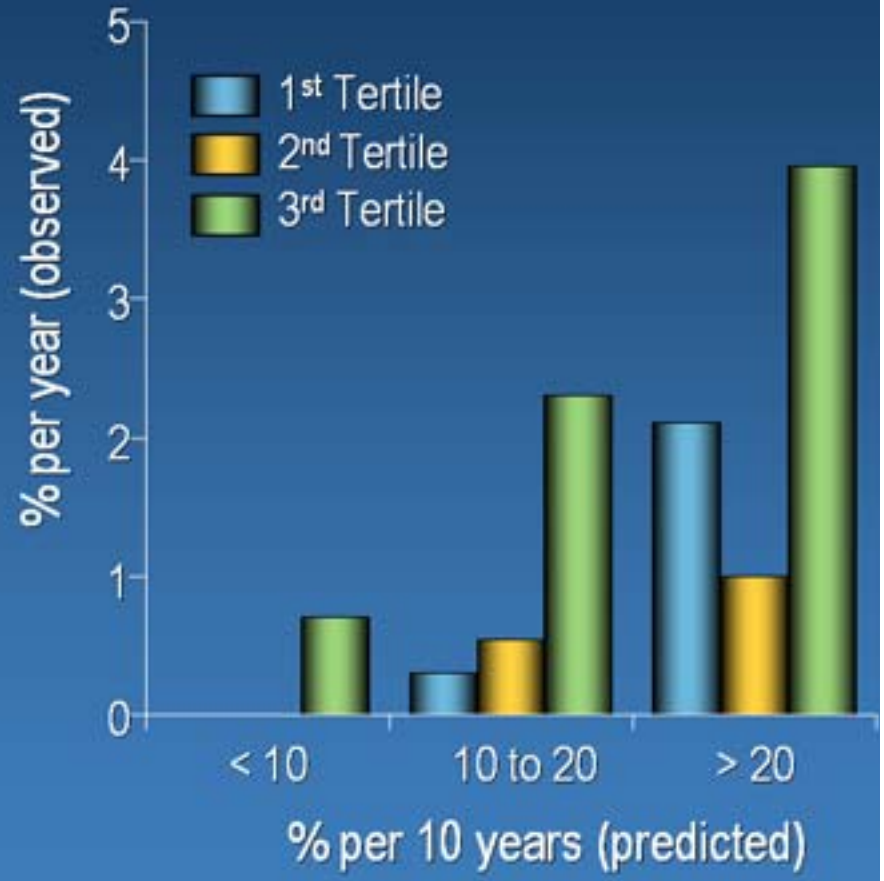


Arad et al. ACC, Chicago 2003

Prediction of CVD by Coronary Calcium Score vs Framingham Score: St. Francis Heart Study

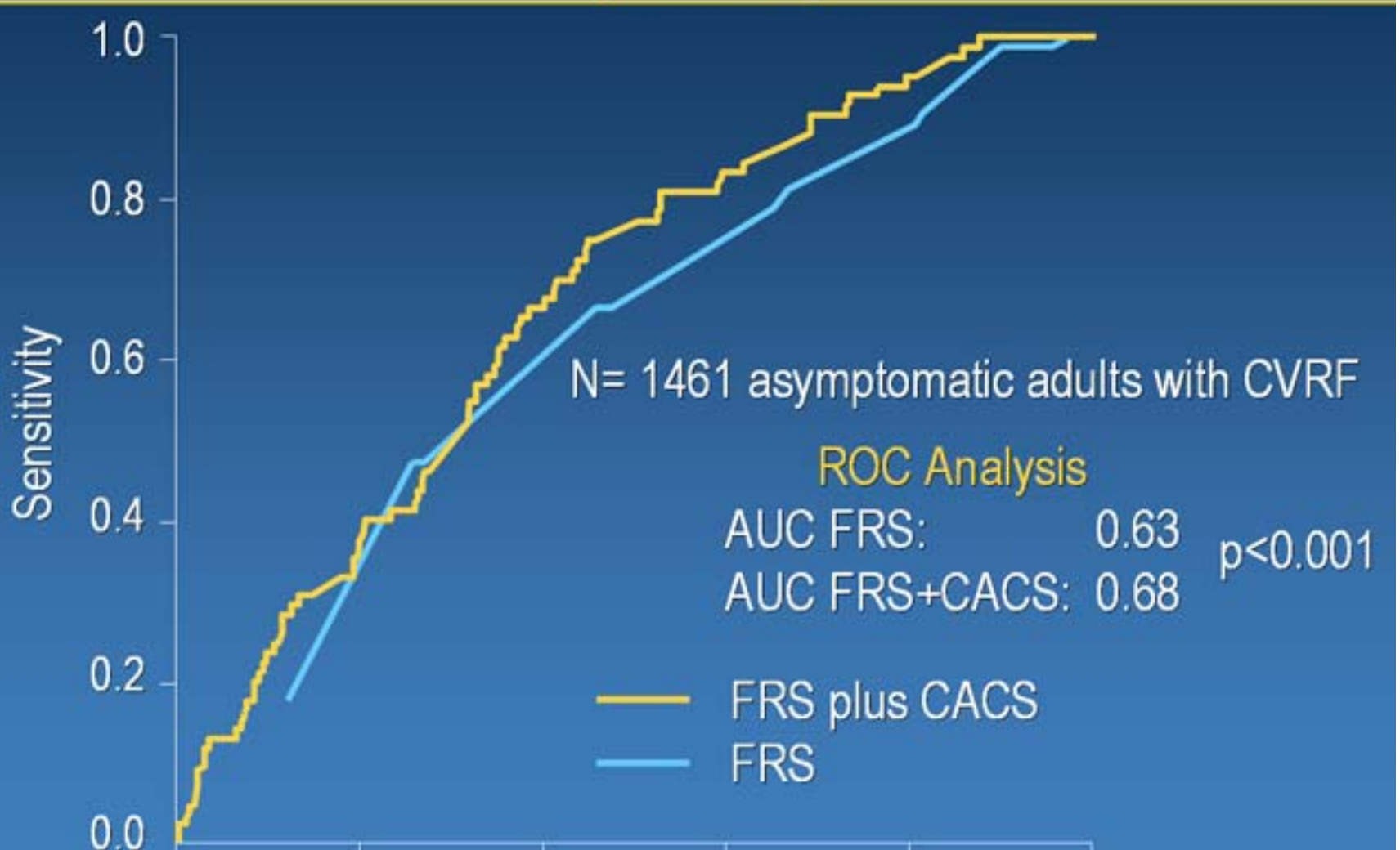
Calcium score vs
Framingham risk index prediction
of coronary events

	Area under ROC curve	P-value
Calcium score	0.81 ± 0.03	< 0.01
Framingham	0.71 ± 0.03	



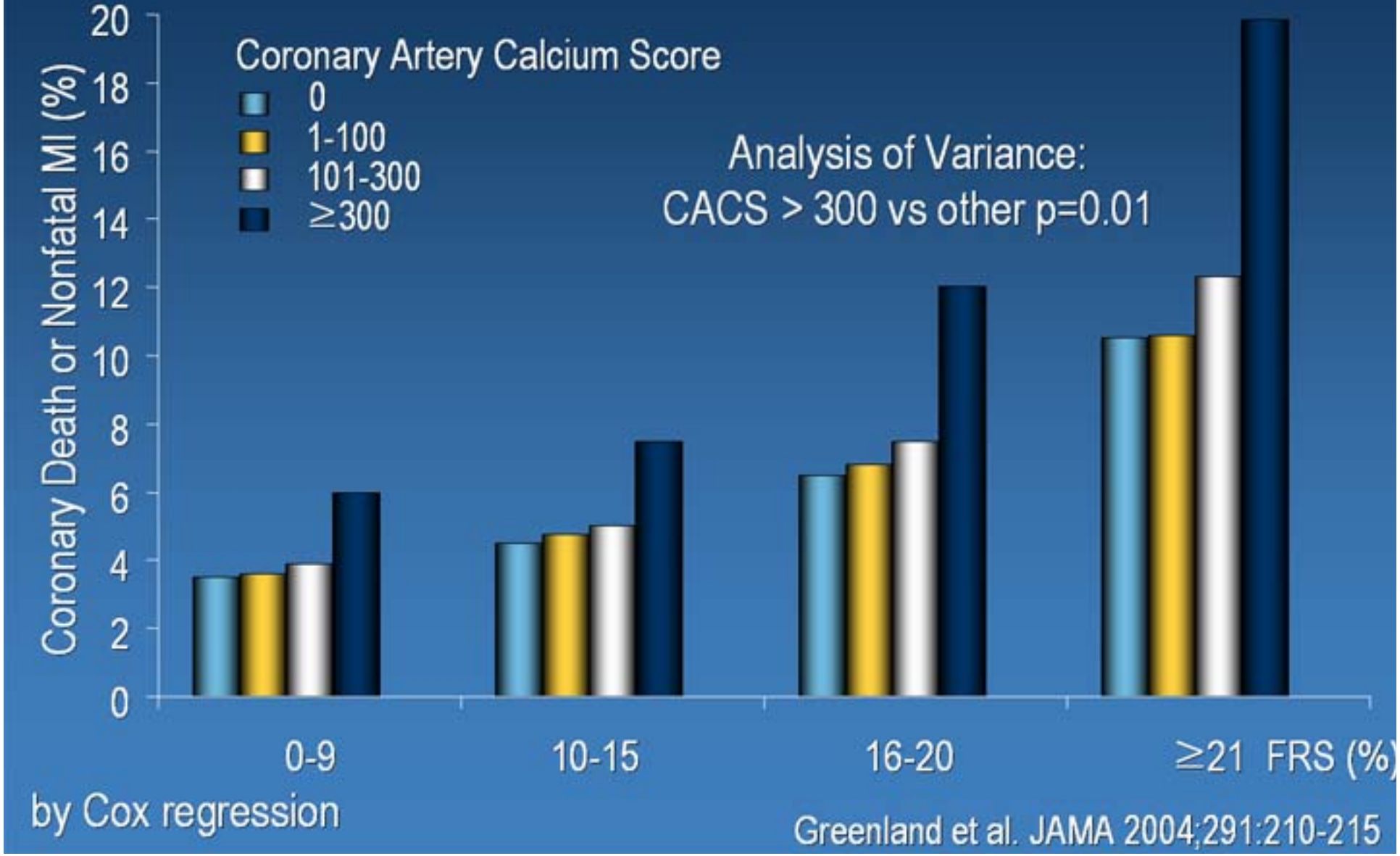
Arad et al. ACC, Chicago 2003

Predicted Coronary Death or Nonfatal MI for FRS w/o and With Coronary Artery Calcium Score

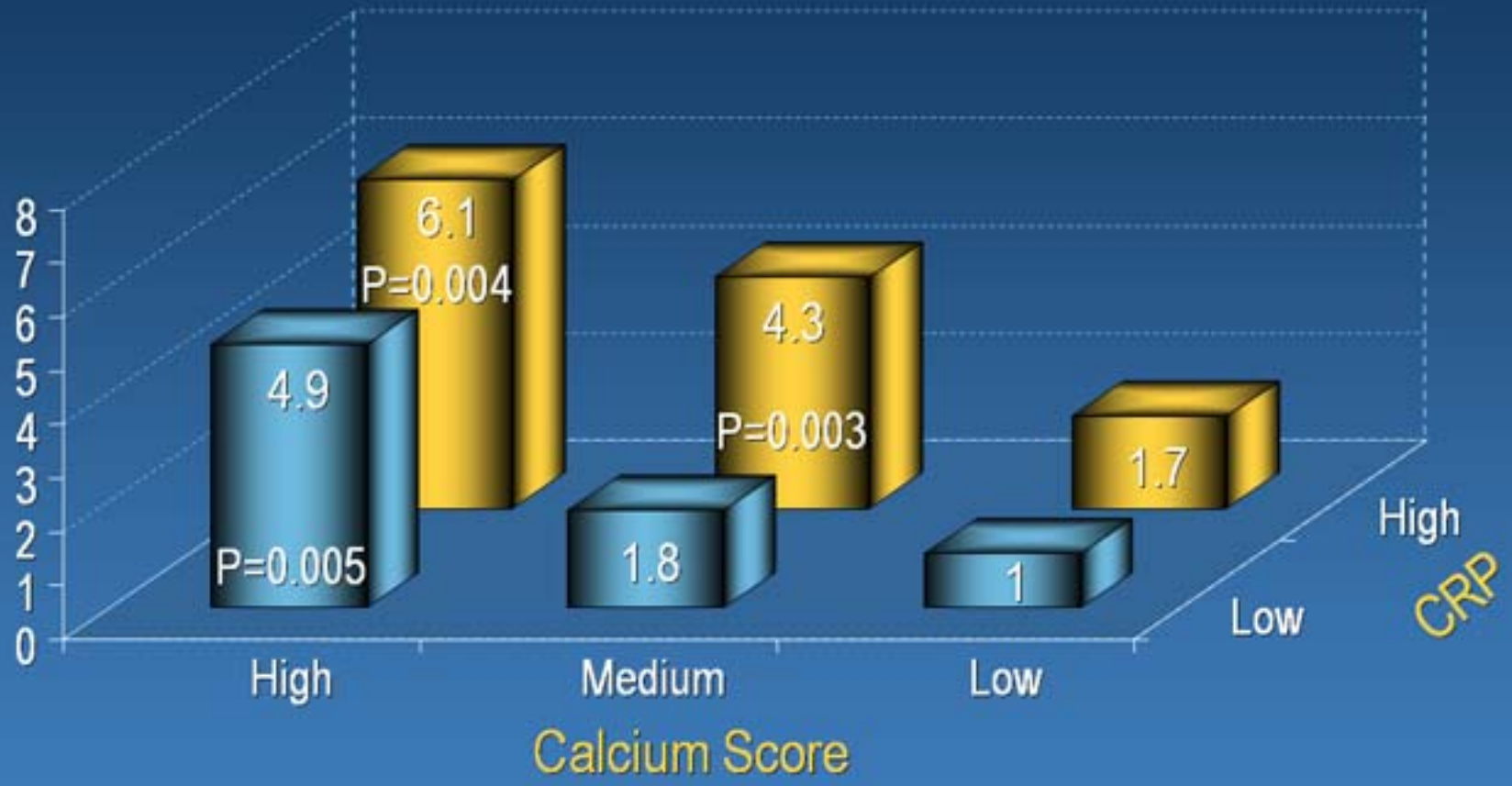


Greenland et al. JAMA 2004;291:210-215

Predicted 7-Y Event Rates for CHD Death or Nonfatal MI for Categories of FRS or CACS*



Risk Stratification by Means of Coronary Calcium Score (CT) and CRP Levels



Risk for myocardial infarct and coronary death in relation to coronary calcium score and CRP level

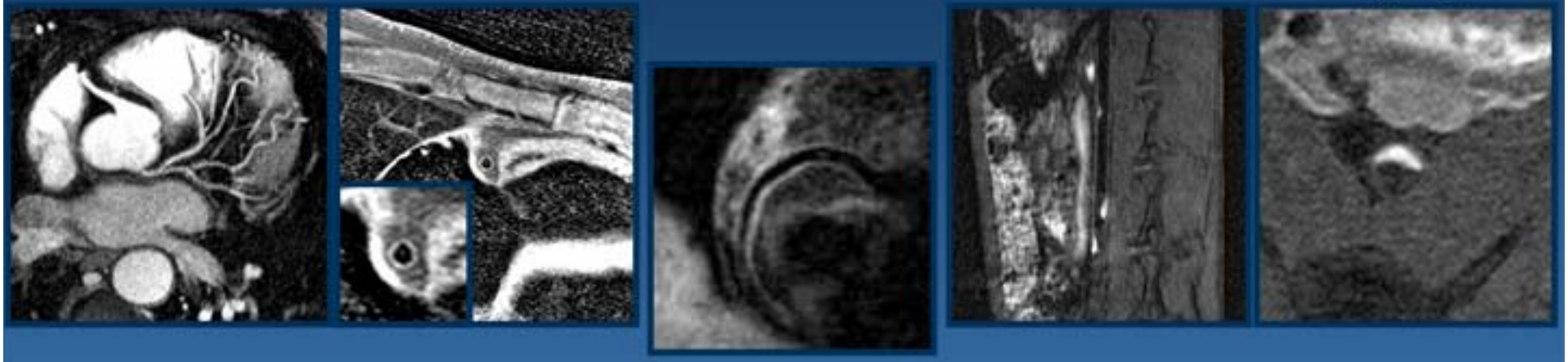
Park et al. Circulation 2002;106:2073-2077

Coronary Artery Calcium and Prediction of CHD

- ✓ CACS is highly predictive of major CHD events; independent of traditional risk factors including the FRS, BMI, Family hx CHD, and CRP.
- ✓ Missing validation research:
  - ✓ MSCT for risk stratification
  - ✓ Gender and ethnic subsets
- ✓ Intermediate FRS + High Risk CACS = CHD Risk Equivalent Status
- ✓ Monitoring progression results are preliminary!
- ✓ Don't forget about established modalities including evidence on selective screening with SPECT.
- ✓ Multi-marker approach – quite helpful identify "at risk"
  - ✓ Functional capacity + …
  - ✓ CT + SPECT …

Carotid, Aortic, Coronary MRI: The Future ?

Lumen → Vessel Wall → Molecular Imaging



- ✓ Morphology, function, molecular/cellular processes
- ✓ Provision of new information
  Early diagnosis of "unstable" plaque
- ✓ Provision of tools for basic research
  local drug delivery, gene therapy, stem cell research, angiogenesis

Statins and Cardiovascular Protection

↓ Lesion initiation
- restores endothelial dysfunction
- antioxidant effect
- ↓ endothelial permeability
- ↑ endothelial cell migration

↓ Lesion progression
- ↓ Lipid core
- ↓ **Inflammation**
- ↓ Foam cell formation
- ↓ SMC transmigration
- ↓ Platelet aggregation

↑ Myocardial perfusion
- ↑ NO production
- ↓ endothelin-1
- ↓ blood / plasma viscosity

↓ Myocardial damage
- Troponin T
- CK-MB
- ↓ Blood pressure
- ↓ LV hypertrophy
- ↓ Heart failure
- ↓ Aortic stenosis

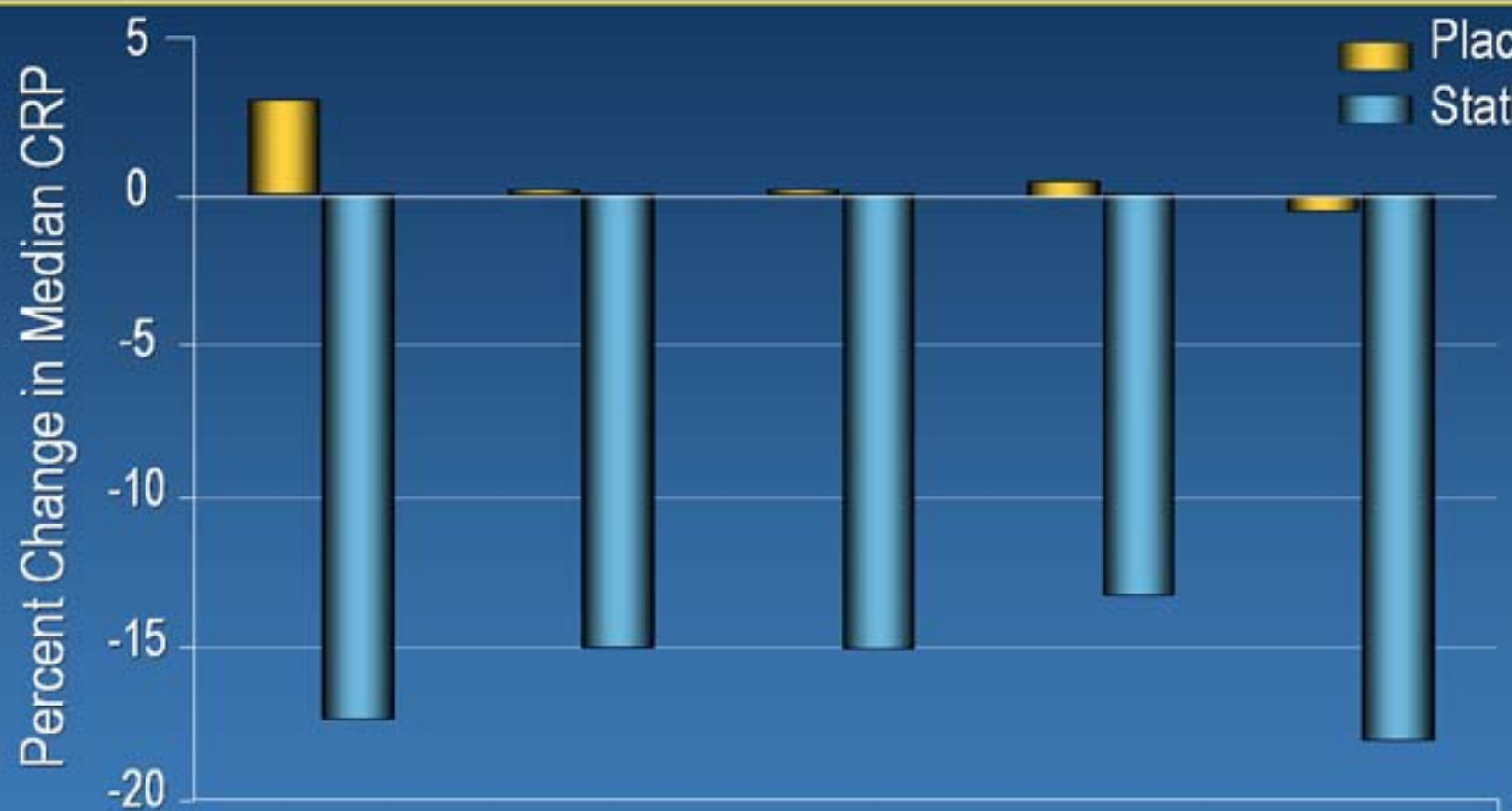
↑ Myocardial repair
- EPC recruitment

↓ Ischemic burden
- AS regression
- ↑ angiogenesis

↑ Survival post transplantation
- Immunosuppression
- ↓ Inflammation

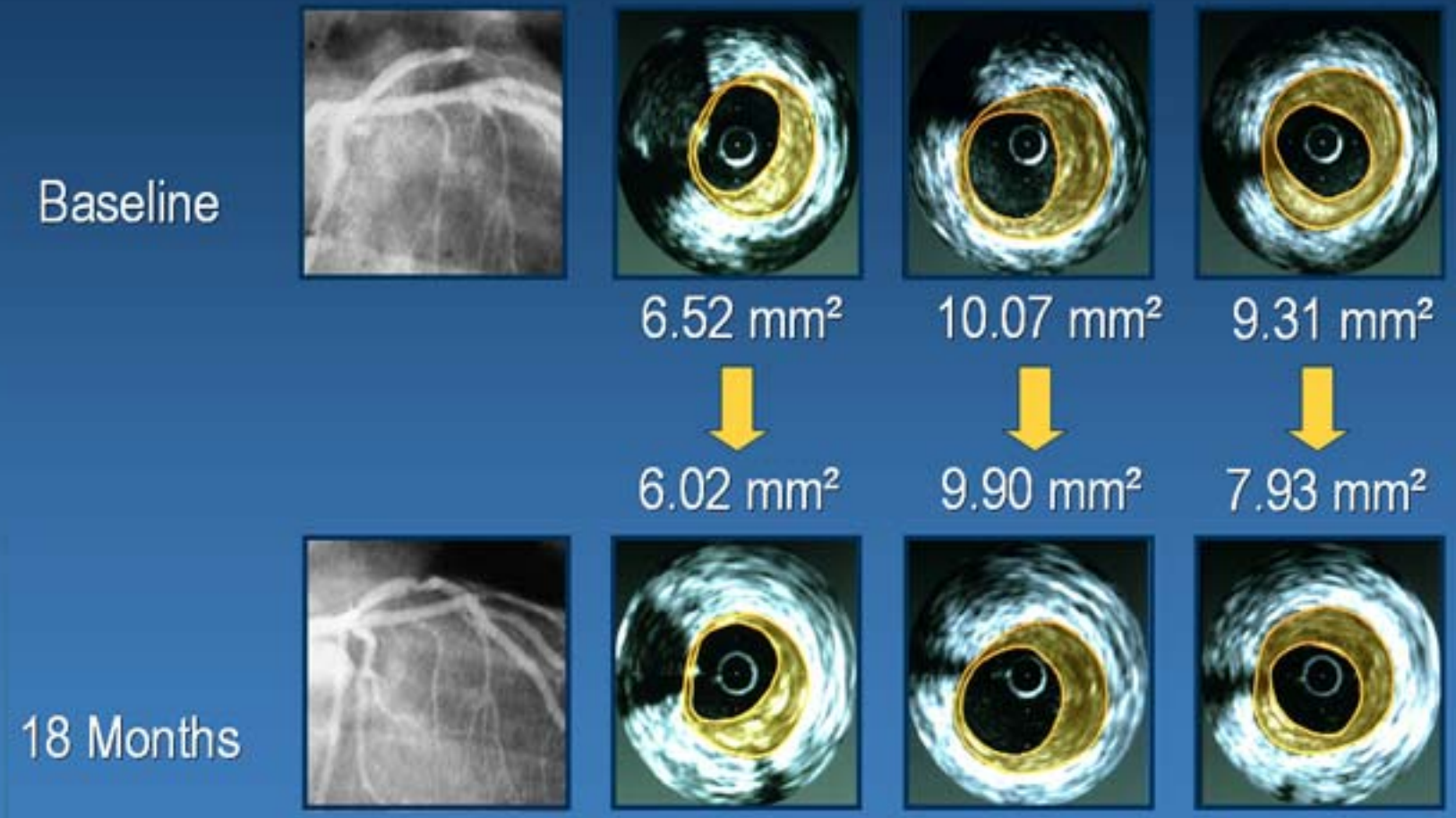
after Davignon 2003

Effects of Statin Therapy on CRP



Ridker P. 2004

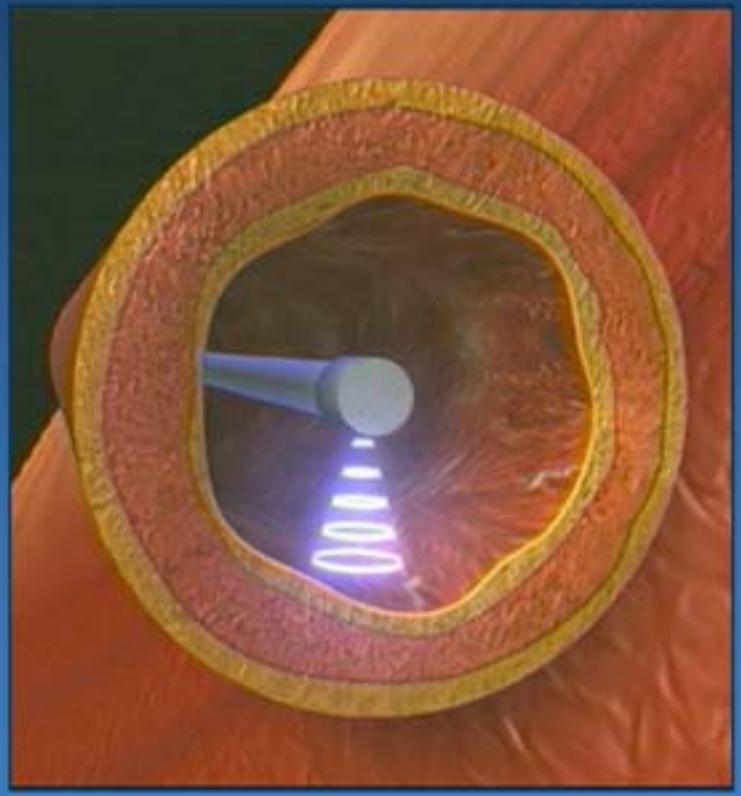
Clinical Implications from REVERSAL: Atorvastatin – no Progression



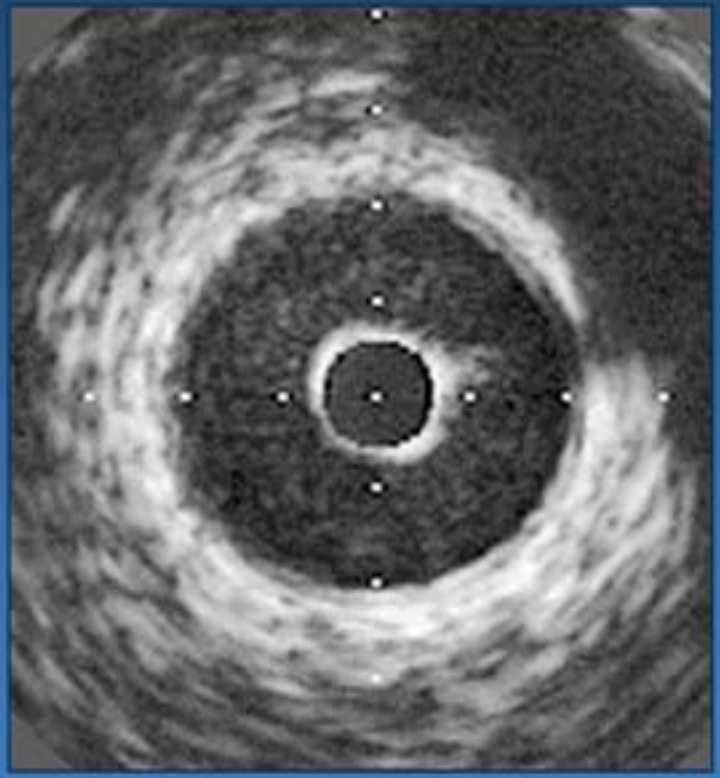
mod. after Nissen S, American Heart Association (AHA), Scientific Sessions 2003, Orlando (USA)
Plenary Session XI: Late Breaking Trials, 12. November 2003

The IVUS Coronary Imaging Technique

Rotating transducer



Normal coronary anatomy



Images courtesy of Cleveland Clinic Intravascular Ultrasound Core Laboratory