Treatment of Chronic Coronary Atherosclerosis

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The E. Wolfson Medical Center

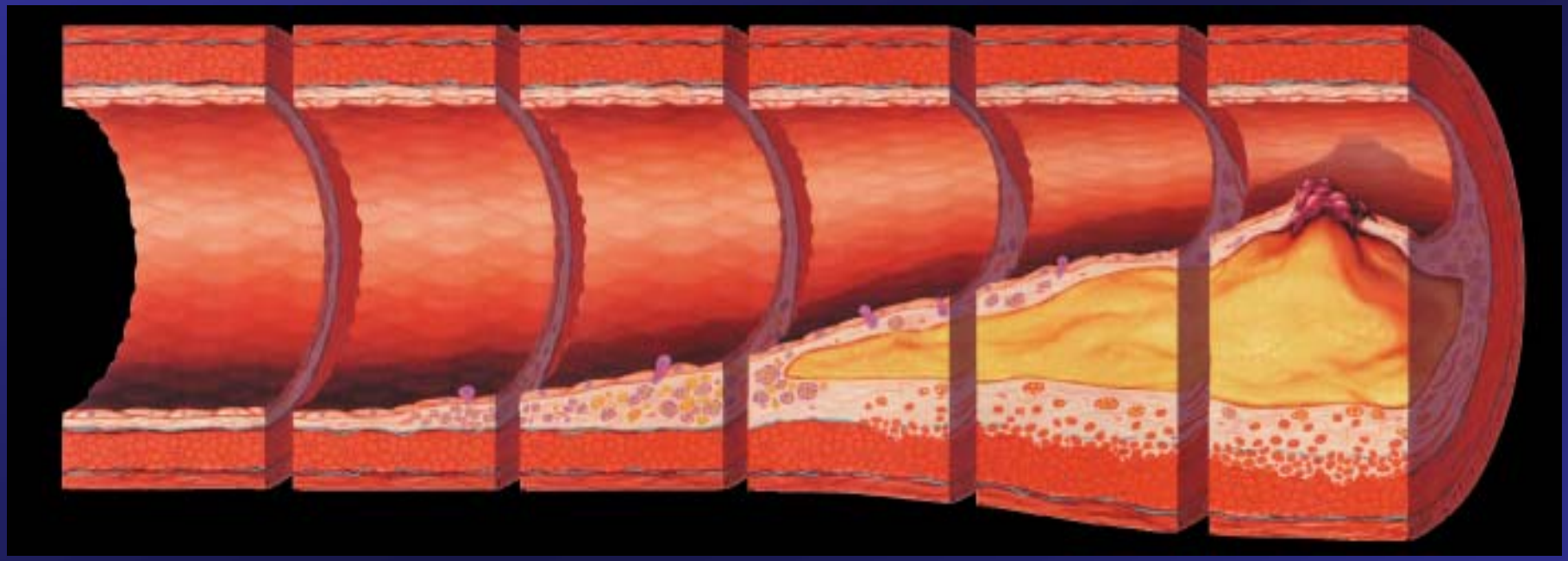
CME course, Cesaria 2010

OUTLINE

- Pathophysiology
  - Atherosclerosis
  - Ischemia
- Primary prevention – who should be treated
- Therapy
  - Lifestyle
  - Pharmacology
  - Revascularization

Atherosclerosis Timeline

Foam Cells | Fatty Streak | Intermediate Lesion | Atheroma | Fibrous Plaque | Complicated Lesion/ Rupture



Endothelial Dysfunction

From First Decade

From Third Decade

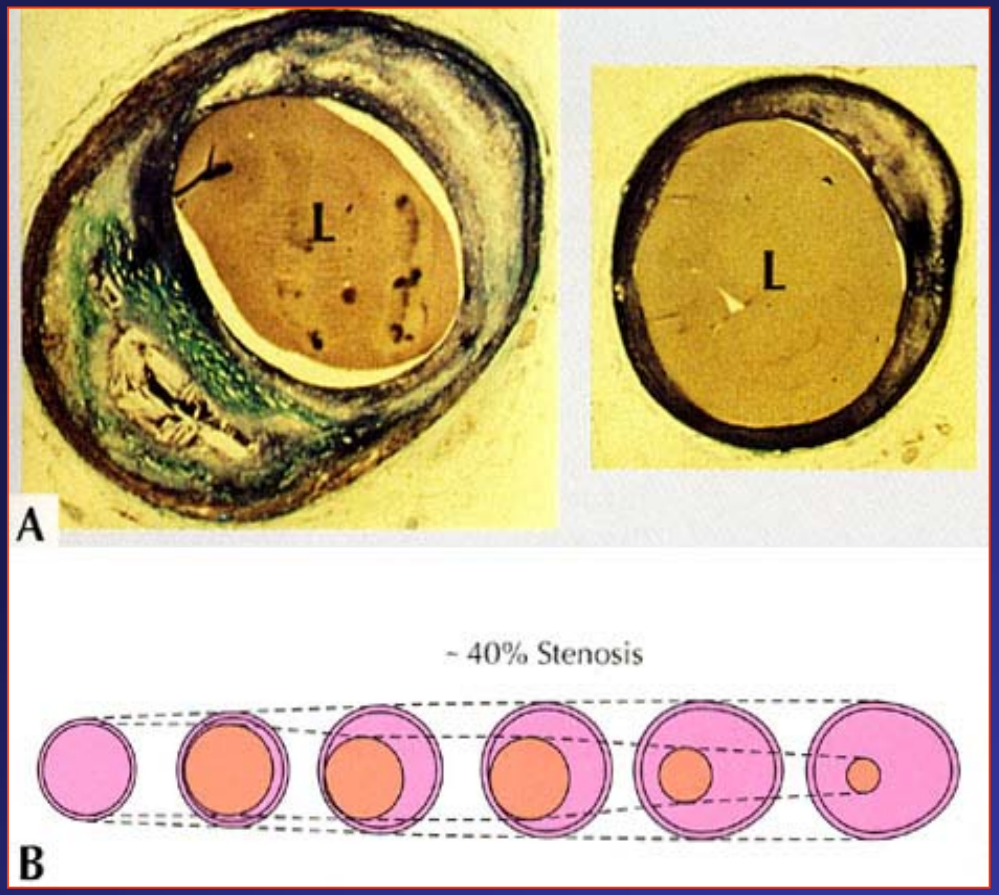
From Fourth Decade

Adapted from Pepine CJ. *Am J Cardiol.* 1998;82(suppl 104).

The Glagov Concept

Atherosclerosis progression and luminal narrowing

Similar luminal area despite marked variation in the volume of atheroma due to compensatory enlargement of the artery



Glagov S et al NEJM 316:1371, 1987,

Oxygen Supply
myocardium vs other tissues

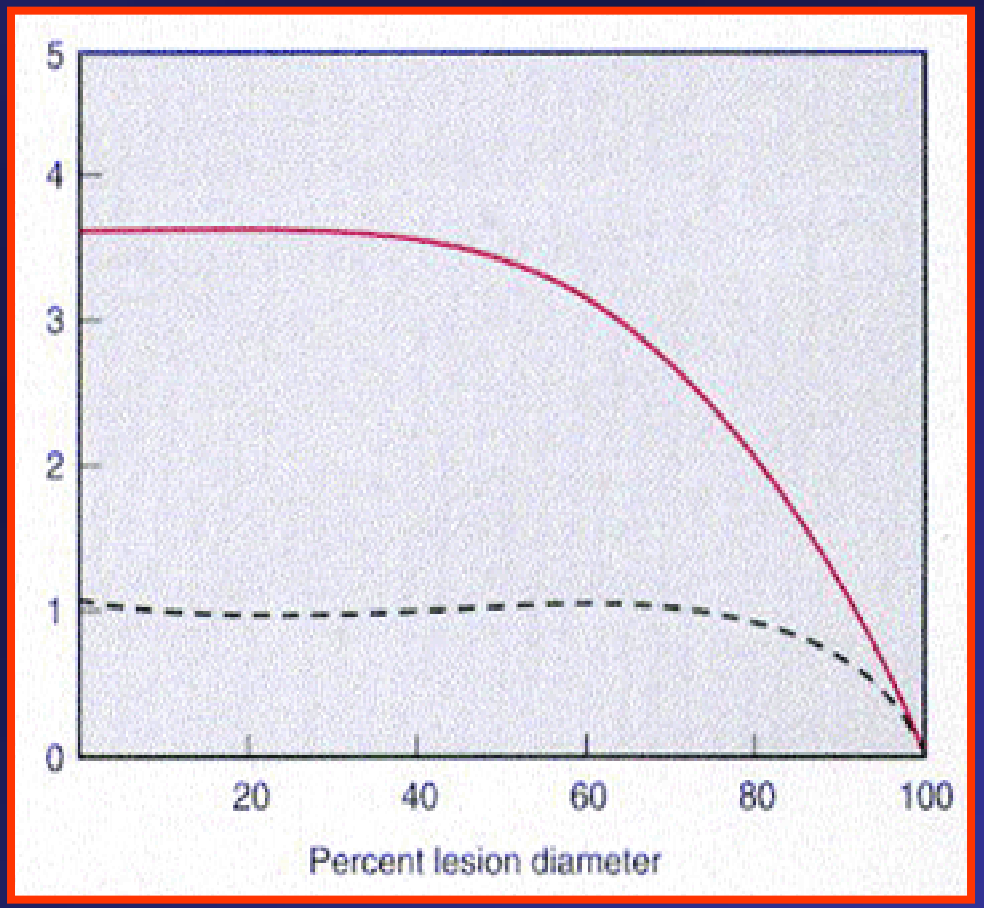
- O_2 Delivery
  - Coronary Blood Flow
  - Hemoglobin
  - Arterial O_2 saturation
- Myocardial (A-V) O_2 Difference

- In resting condition coronary sinus blood is desaturated thus oxygen supply to the myocardium during conditions of increased demand is dependent on coronary blood flow.

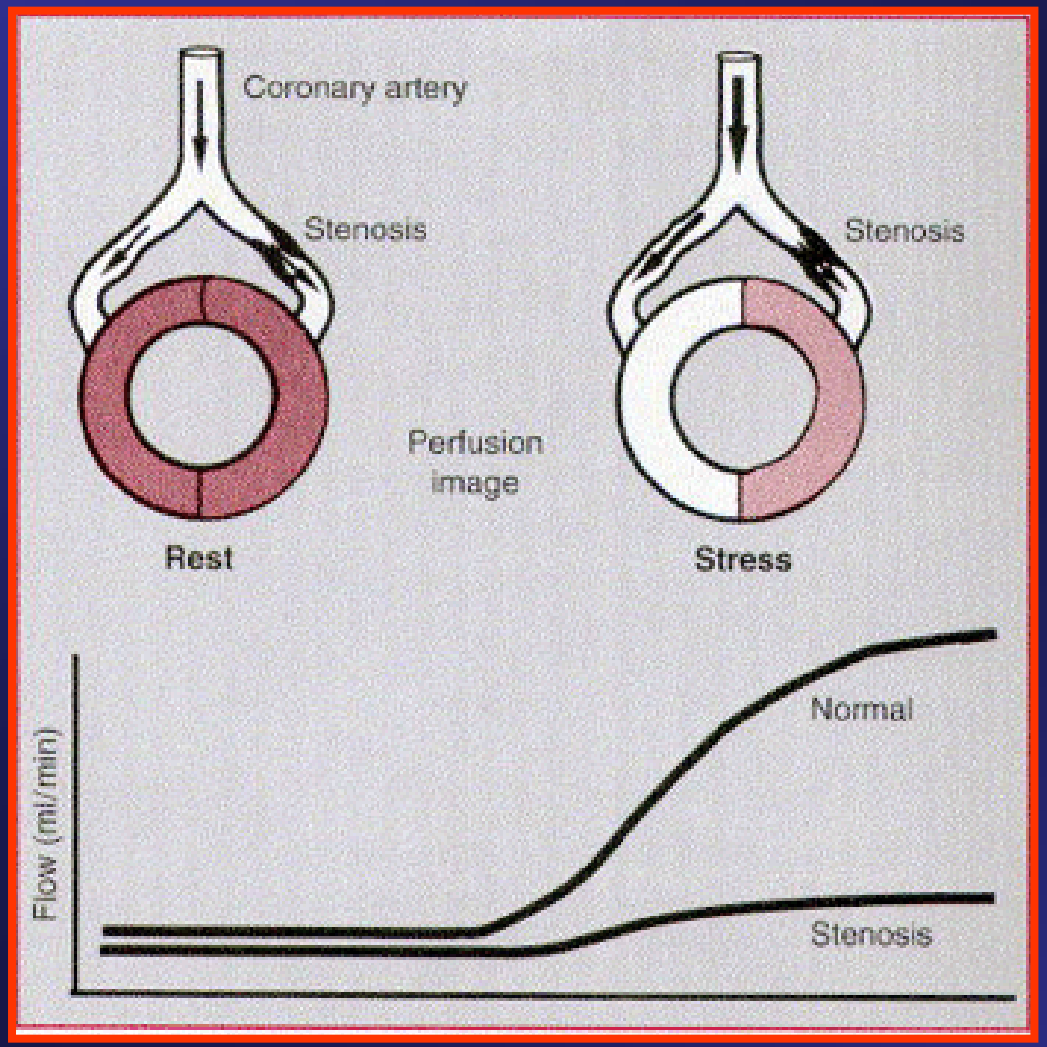
Impact of diameter stenosis on resting and maximal coronary flow (flow reserve)

Normalized flow reserve

Normalized resting flow

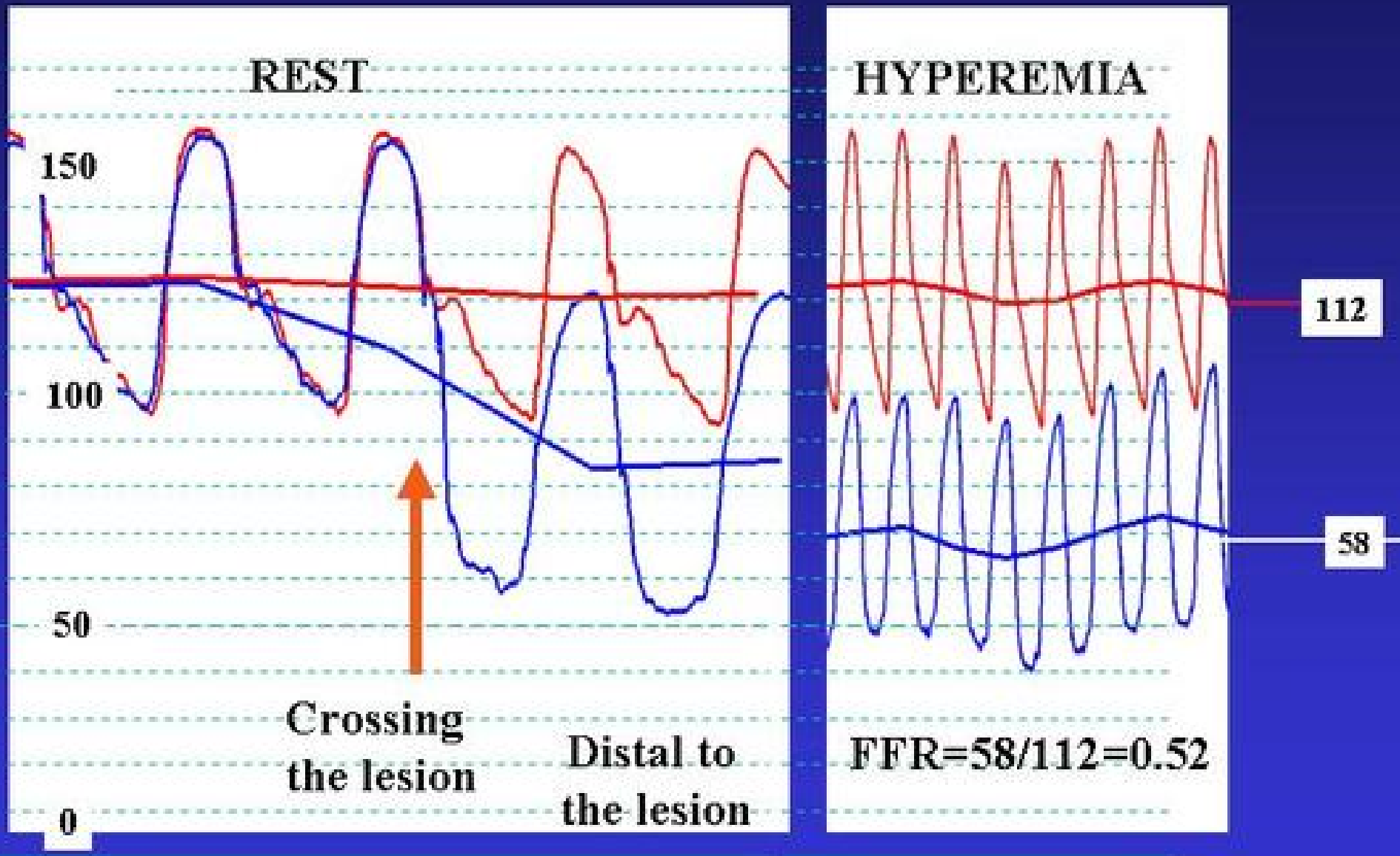


Mechanism of stress induced perfusion mismatch



Limited coronary flow reserve (CFR) in the territory supplied by the stenotic artery causing perfusion mismatch

Fractional Flow Reserve in Clinical Practice



Consequences of Acute Coronary Ischemia

- Typically causes ECG changes, myocardial dysfunction (diastolic and systolic) and symptoms of chest pain.
- Causes prolonged? dysfunction (stunning, occasional repetitive)
- Magnitude of effect modified by adaptive mechanisms (smart heart)
  - Hibernation (adaptation of mechanical function to flow limitation)
  - Preconditioning (protection from future ischemia by past ischemic episodes)

Unusual Presentations of Chronic Angina – Current Understanding

- Diurnal variation of angina
  - Coronary tone, preconditioning
- Angina disappears during walking
  - Coronary tone, preconditioning
- Prolonged fatigue after exertion
  - Myocardial stunning
- CHF symptoms without previous MI
  - Hibernation (repetitive stunning)

OUTLINE

- Pathophysiology
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- **Primary prevention – who should be treated**
- Therapy
  - Lifestyle
  - Pharmacology
  - Revascularization

בן 55 אסימפטומטי עם סיפור משפחתי של מחלת לב כלילית (LDL= 125mg/dl)

האם מומלץ להתחיל טיפול בסטטין?

1. כן
2. לא
3. תלוי ברמת הסיכון (שנקבעת על פי גורמי הסיכון) ובערך המטרה המתאים של LDL
4. תלוי בתוצאת מבחן מאמץ / מיפוי (אקו) תחת דחק
5. תלוי בנוכחות טרשת בכלי דם – בדיקת הדמיה של טרשת
6. תלוי ברמת CRP

Assessing CHD Risk in Men - Framingham

Step 1: Age

Years	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Step 2: Total Cholesterol

TC at (mg/dL)	Points at Age 20-39	Points at Age 40-49	Points at Age 50-59	Points at Age 60-69	Points at Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1

Step 3: HDL-Cholesterol

HDL-C (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Step 4: Systolic Blood Pressure

Systolic BP (mm Hg)	Points if Untreated	Points if Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Step 5: Smoking Status

	Points at Age 20-39	Points at Age 40-49	Points at Age 50-59	Points at Age 60-69	Points at Age 70-79

Step 6: Adding Up the Points

- Age
- Total cholesterol
- HDL-cholesterol
- Systolic blood pressure
- Smoking status
- Point total

Step 7: CHD Risk

Point Total	10 Year Risk	Point Total	10 Year Risk
<0	<1%	11	8%
0	1%	12	10%
1	1%	13	12%
2	1%	14	16%
3	1%	15	20%
4	1%	16	25%
5	2%	≥17	≥30%
6	2%		
7	3%		
8	4%		
9	5%		
10	6%		

Note: Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497.

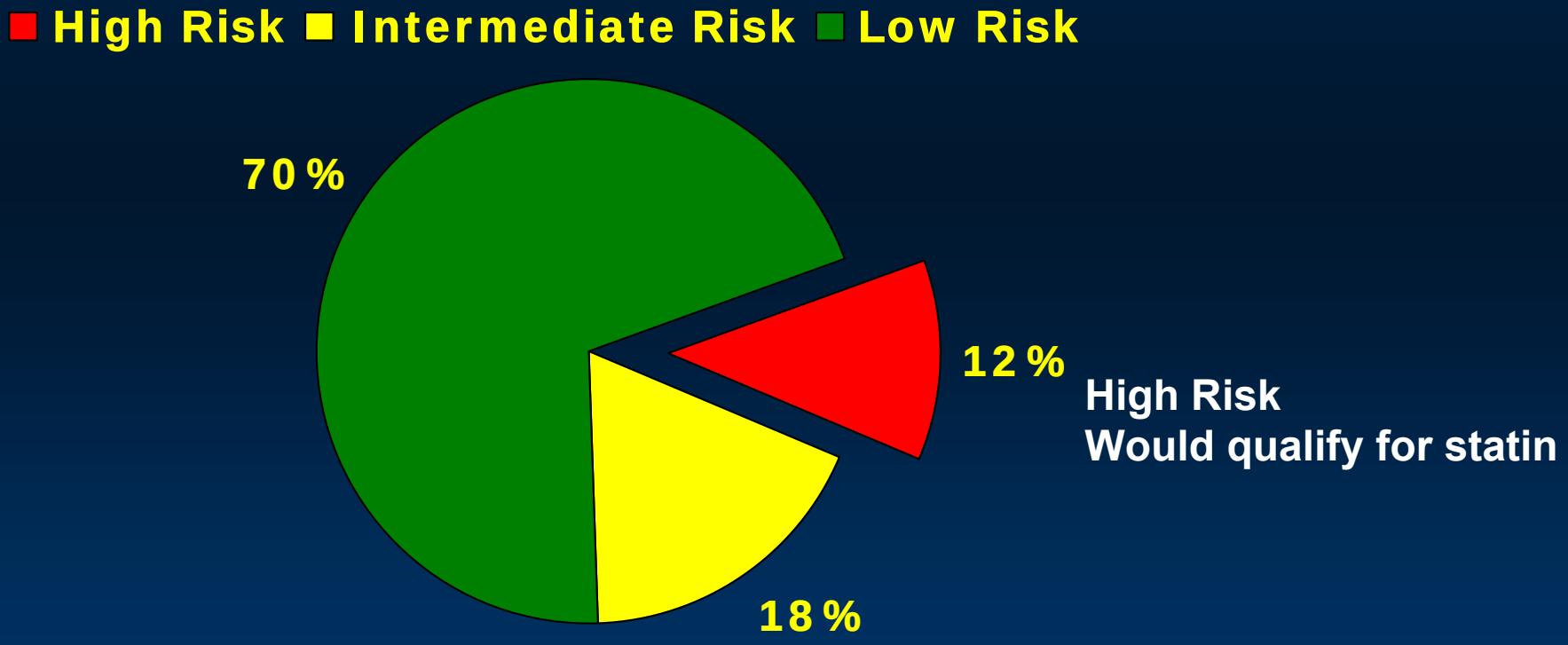
Risk subgroups

- LOW RISK designated as <0.6% CHD risk per year (<6% in 10 years)
- INTERMEDIATE RISK designated as a CHD risk of 0.6%-2.0% per year (6-20% over 10 years)
- HIGH RISK designated as a CHD risk of >2% per year (20% in 10 years) (CHD risk equivalent), including those with CVD, diabetes, and PAD

Target LDL and need for statin is determined by level of risk

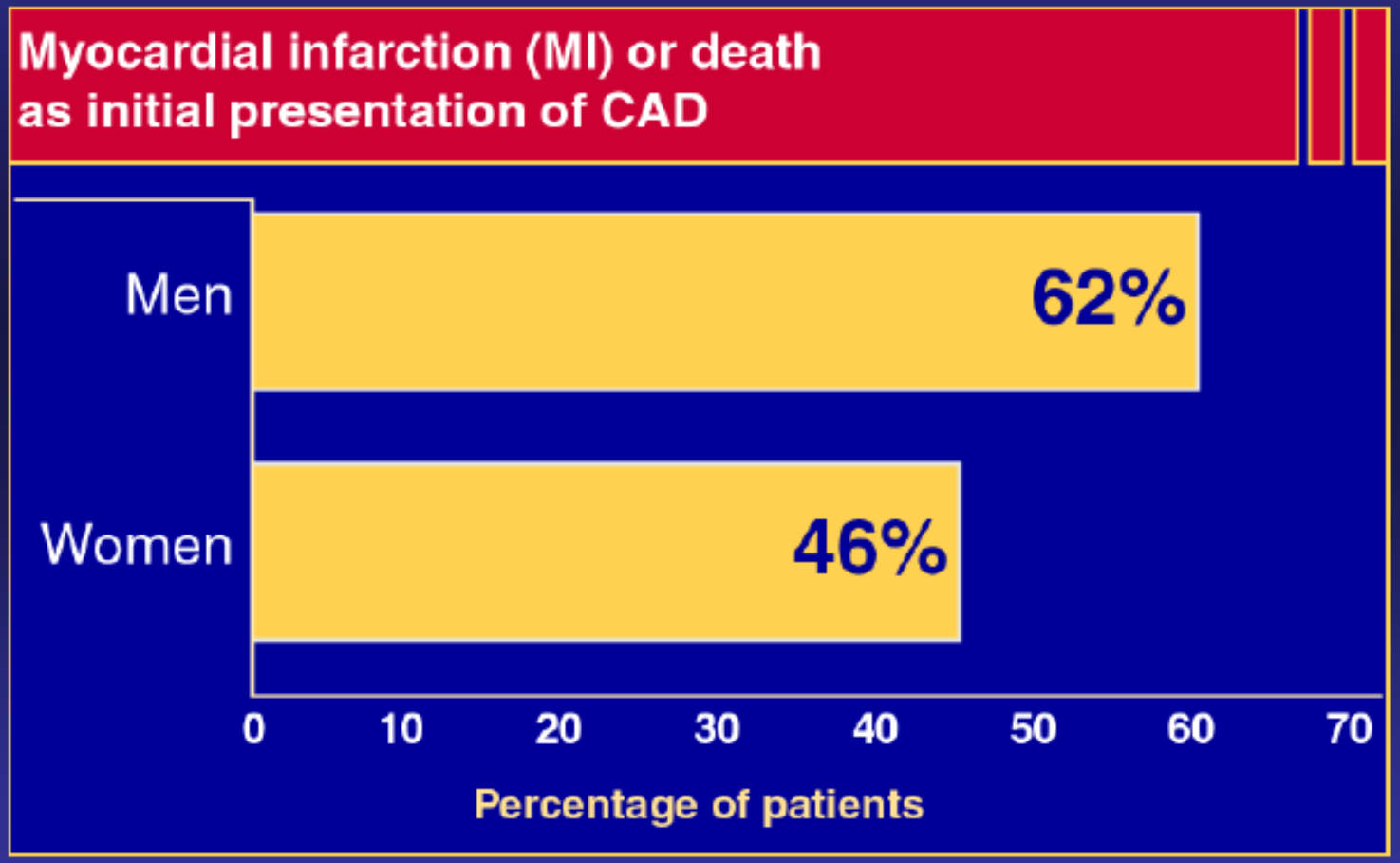
How Good Is NCEP III At Predicting MI in young?

222 patients with 1st acute MI, no prior CAD
men <55 y/o (75%), women <65 (25%), no DM



Akosah Et al, JACC 2003:41 1475-9

First Presentation is Frequently Sudden Death
might be preventable with early therapy

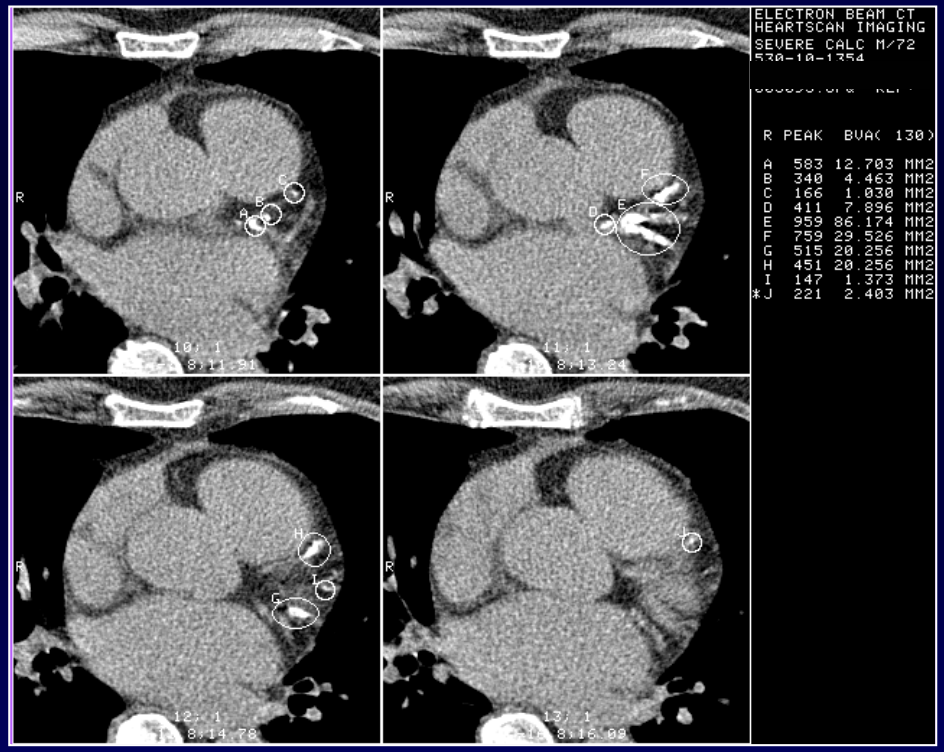


(Adapted from Levy et al.) Levy D et al in *Textbook of Cardiovascular Medicine*, 1998.

What should be done?
Who should be started on statin RX

- Everyone > 50 years old
- Only those at high risk for event
  - Risk predictors:
  - Calcium Score (CAC)
  - Carotid Intima–Media Thickness (CIMT)
  - C Reactive Protein (CRP)

How Is the Coronary Artery Calcium (CAC) Score Calculated?



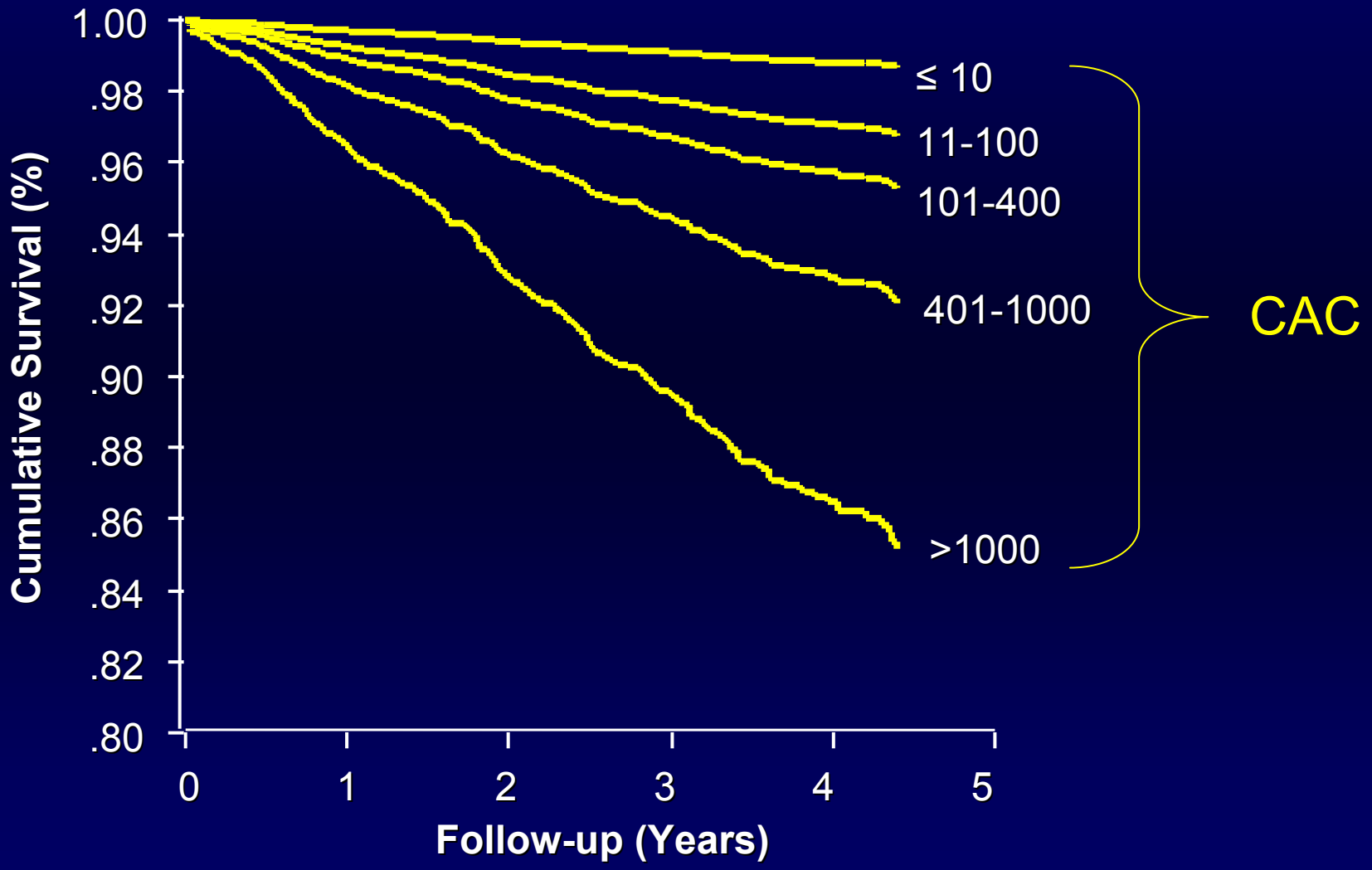
- Peak density and area in each location, in each coronary artery, are measured.

Hn (Agatston Scoring)	x-factor
130-199	1
200-299	2
300-399	3
>400	4

- CAC score = total of area and density of each calcified lesion

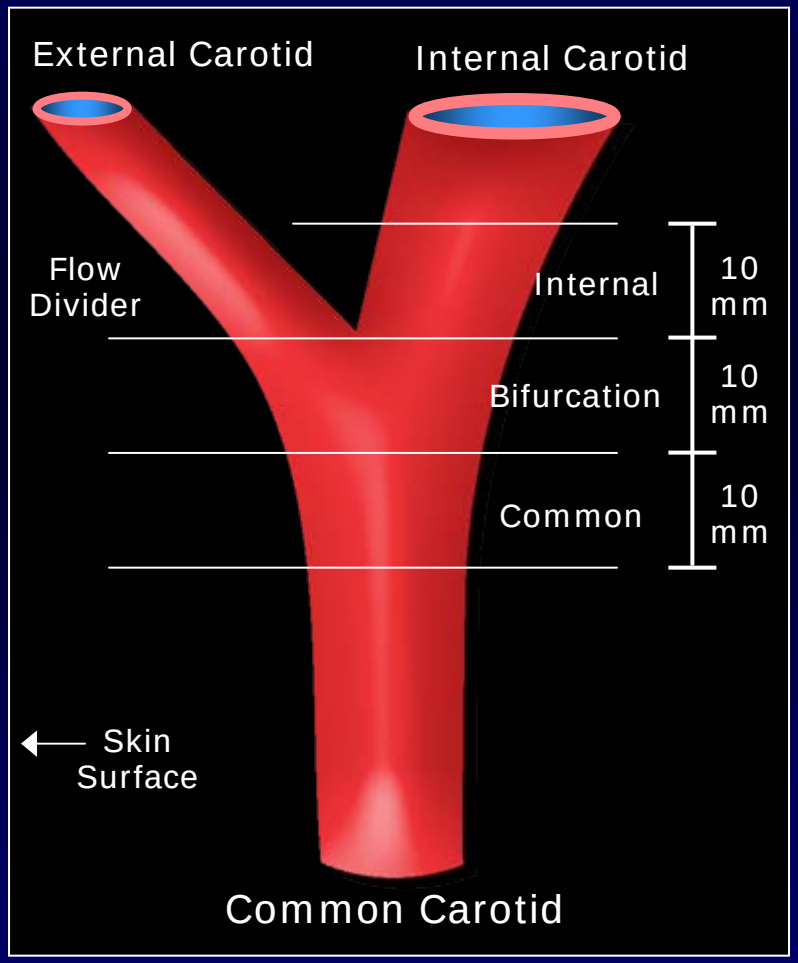
Images courtesy of Alan B. Zelinger, MD.

Coronary Artery Calcium (CAC) Score Can Predict Risk-Unadjusted All-Cause Mortality

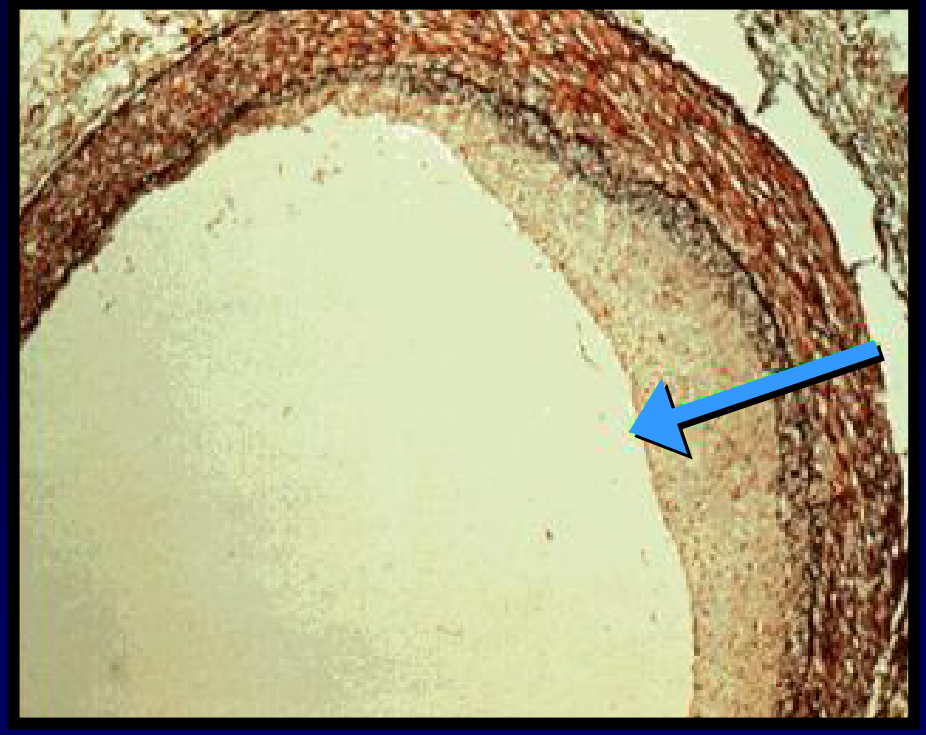


Shaw LJ, et al. *Radiology*. 2003;228:826-833.

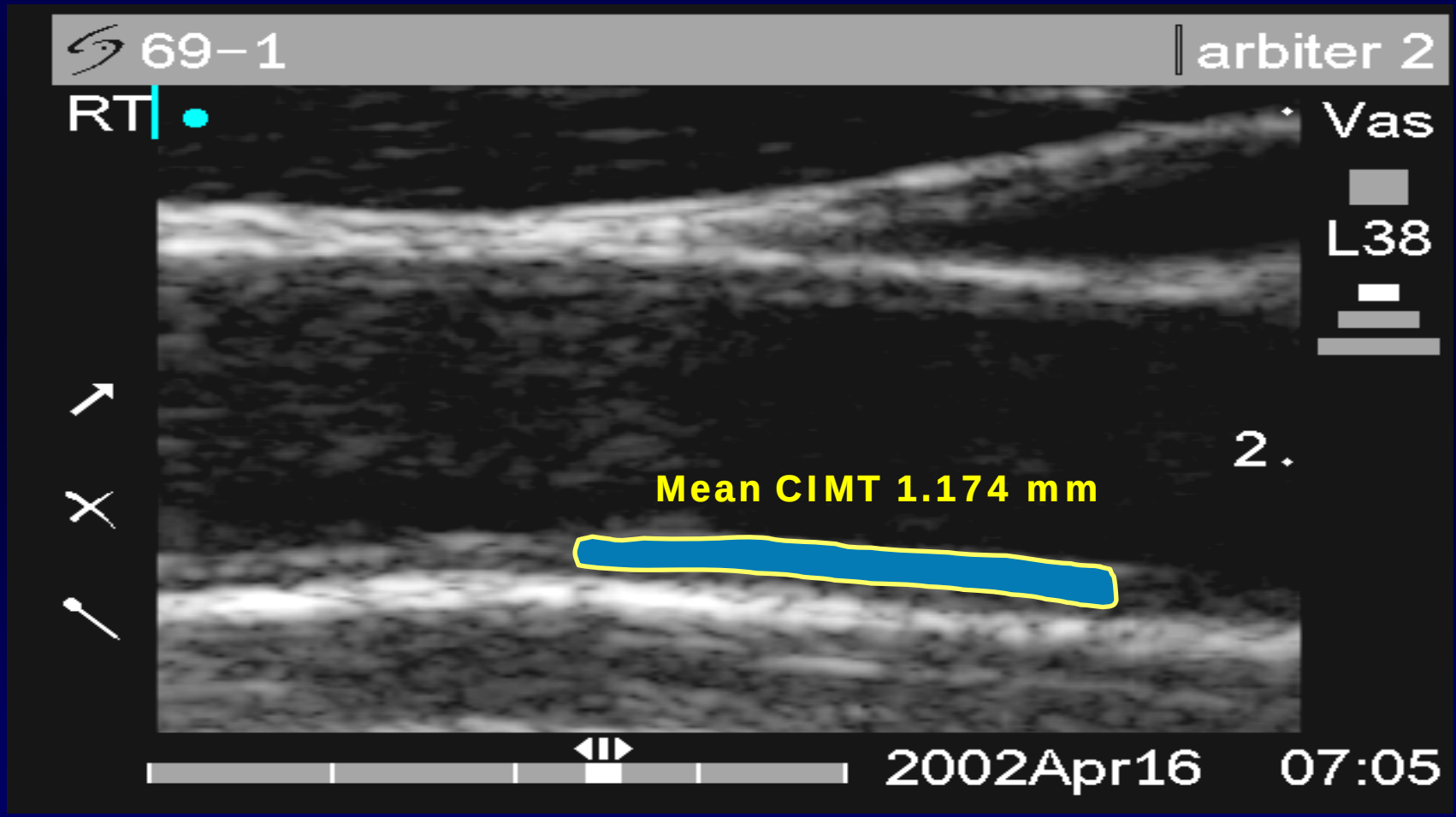
What is Carotid Intima–Media Thickness (CIMT)?



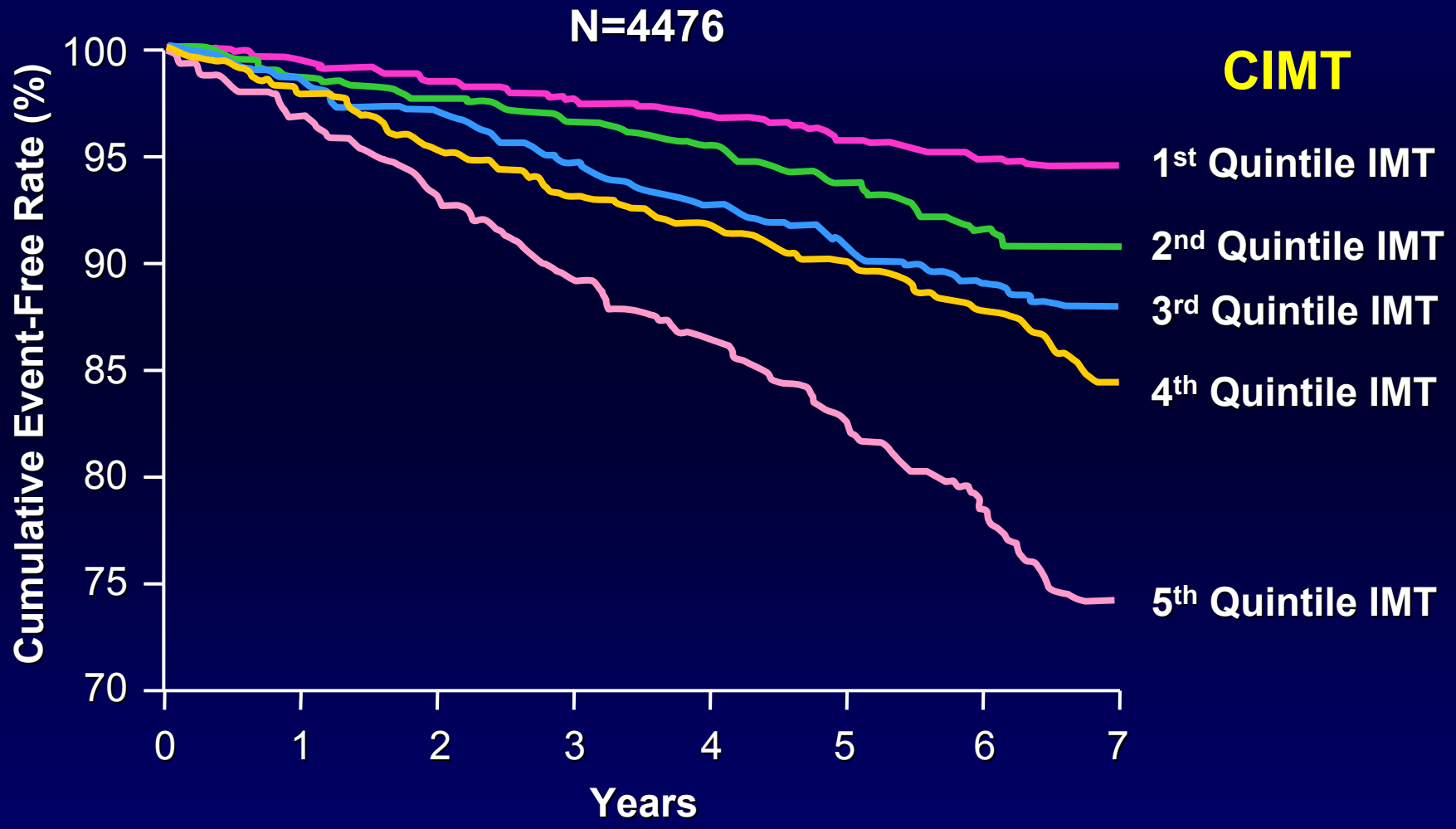
Normal and Diseased Arterial Histology



What is Carotid Intima–Media Thickness (CIMT)?

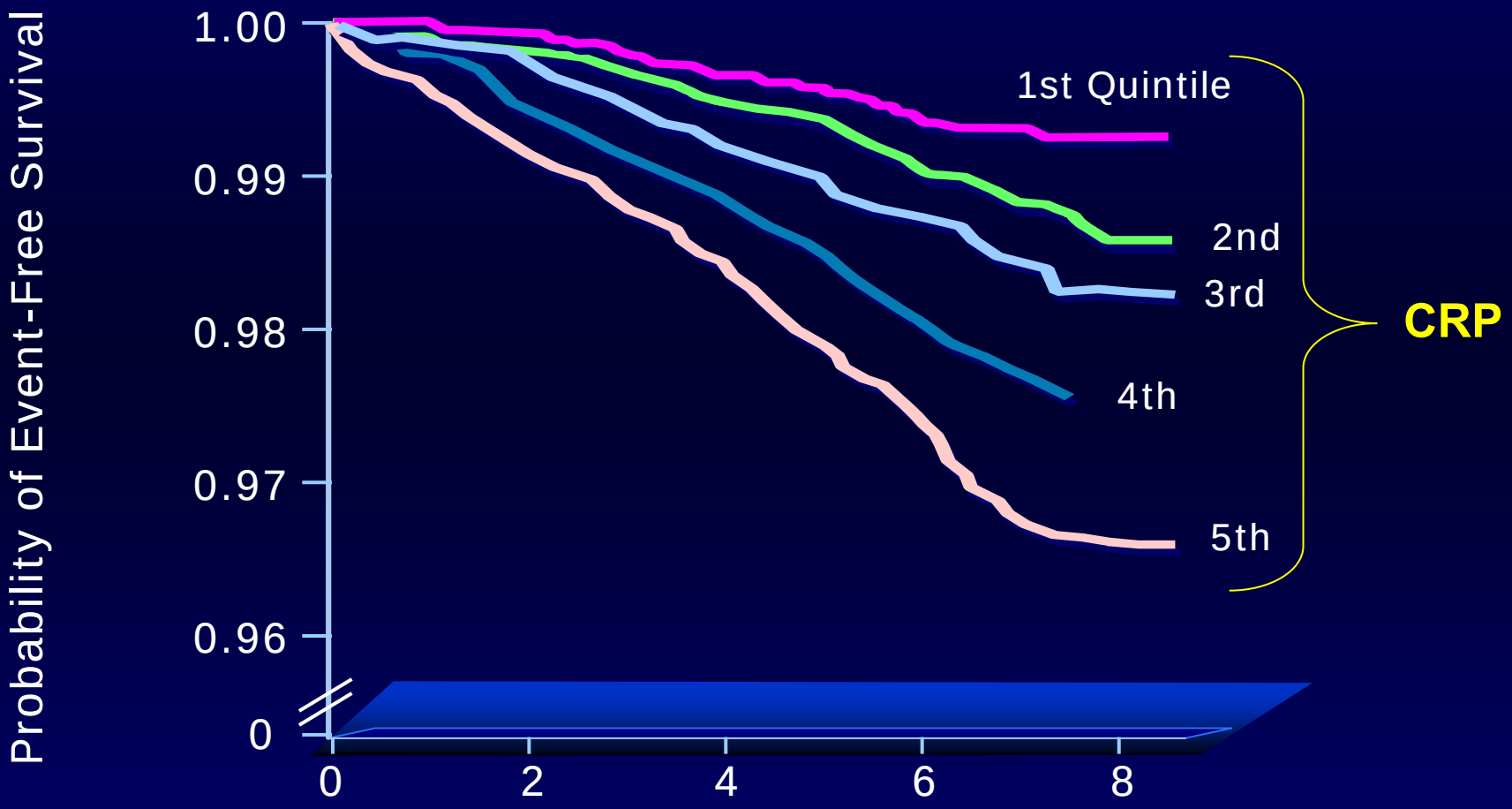


Carotid Disease as a Marker of Cardiovascular Risk: MI or Stroke



O'Leary, et al. *N Engl J Med*. 1999;340:14-22.

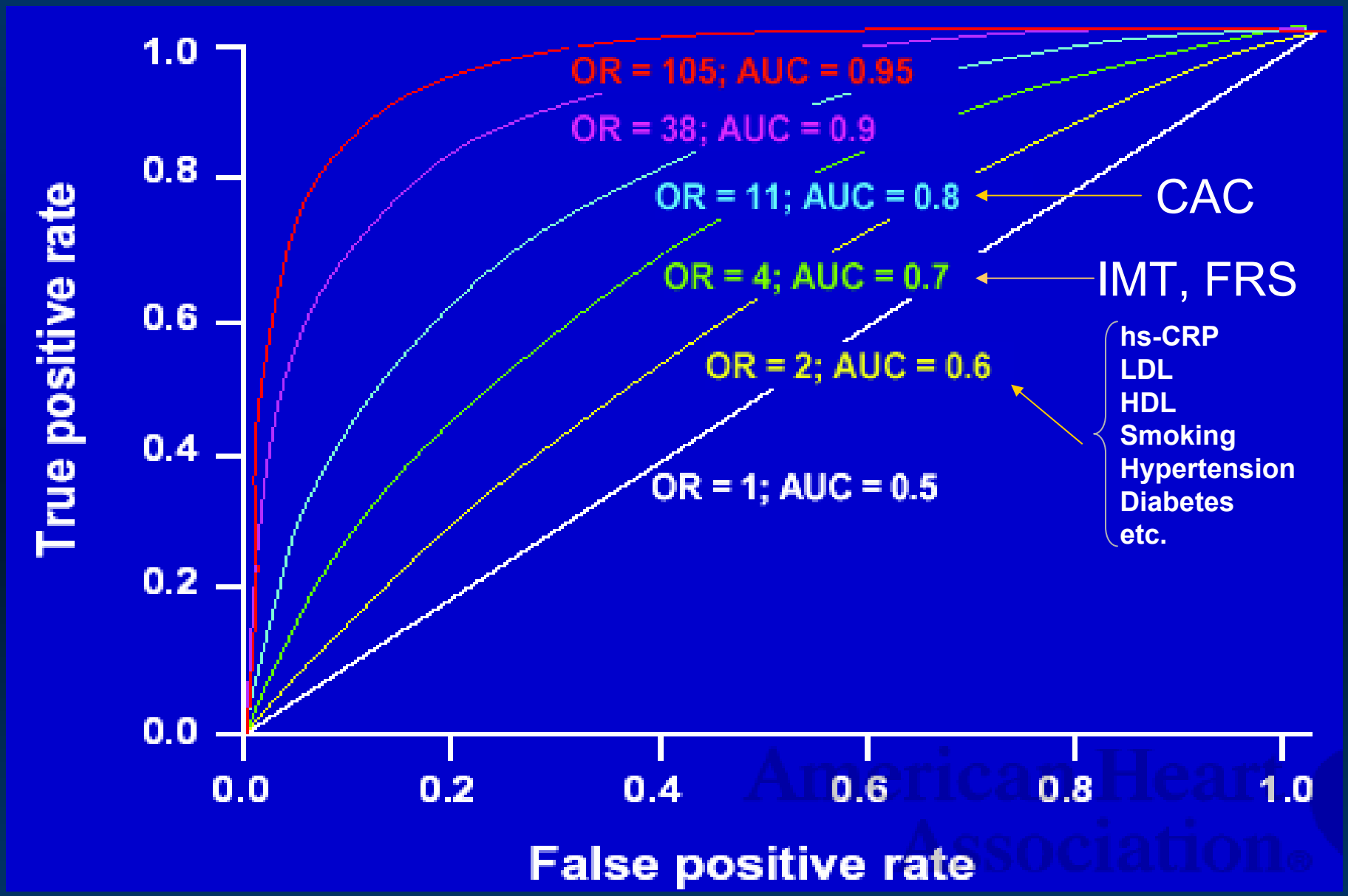
CVD Risk in the Women's Health Study According to Quintiles of CRP



Predictive utility of a screening test

- When making decisions about the predictive utility of new tests, the focus is not on relative risks.
- Rather, the best measure of the additional utility of a new test is to be found in comparing the areas under receiver operating characteristic curves (AUC).

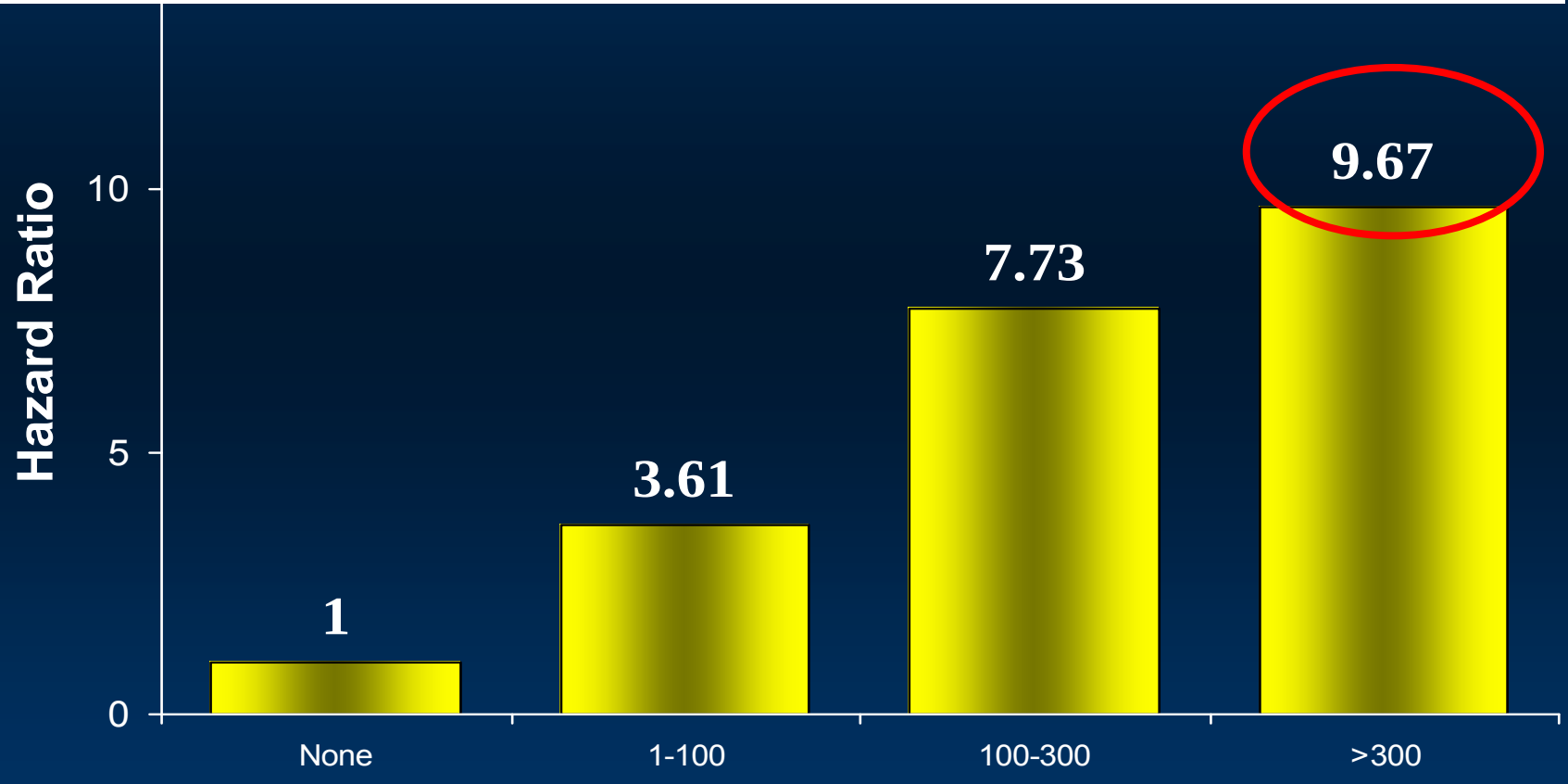
ROC Curve, its AUC and Corresponding Odds Ratio



Based on: Pepe e. al. Am J Epidemiol 2004; 159:882-890.

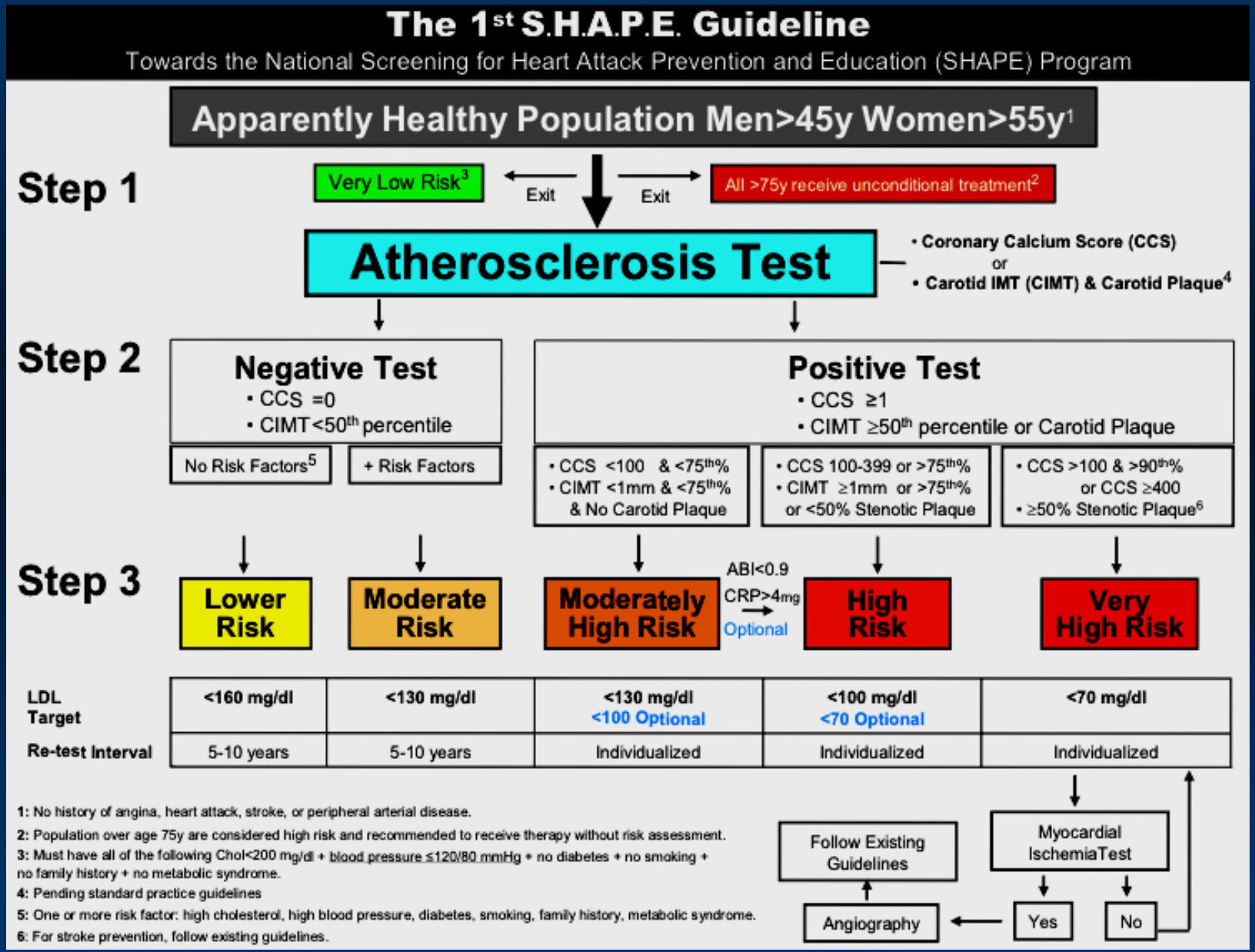
MESA Study – 6,814 Patients: 3.5 year follow-up

Risk of Coronary Events Associated with Increasing CAC after Adjustment for Standard Risk Factors

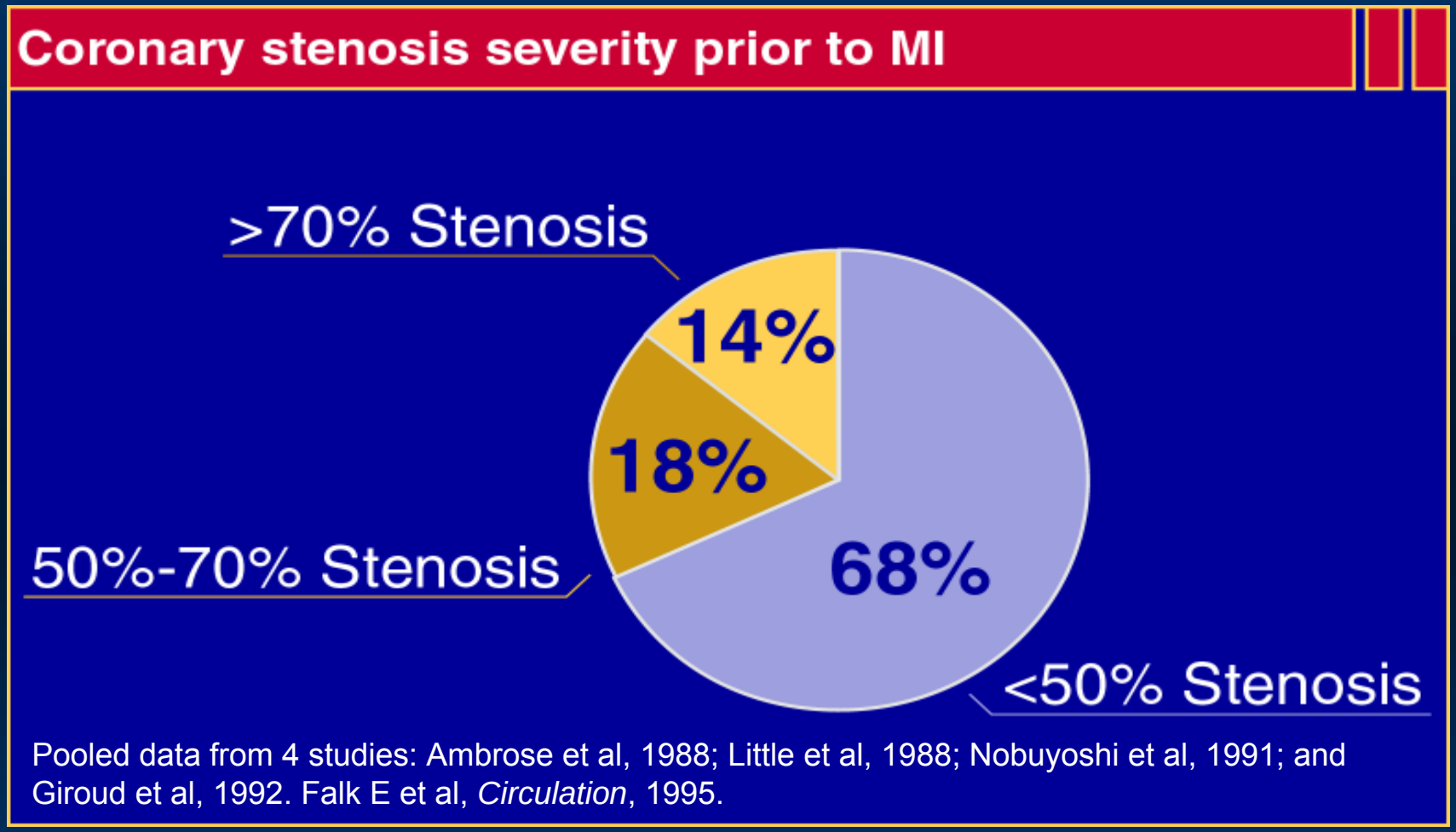


Fully adjusted – Detrano et al– *NEJM 2008*

Association for the Eradication of Heart Attacks



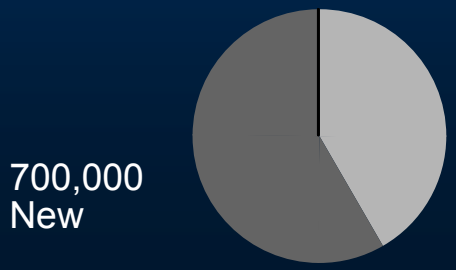
Most Myocardial Infarctions Are Caused by Low-Grade Stenoses:



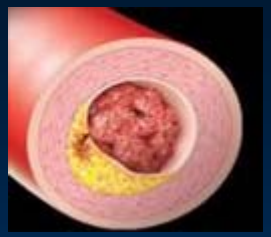
Failure rate of primary and secondary prevention is high even with statin therapy

Prediction and Prevention: The Vulnerable Plaque

Project Goal: Prevent heart attacks



- 700,000 new and 500,000 recurrent Myocardial Infarctions (MI) annually
- Vulnerable plaque causes most heart attacks



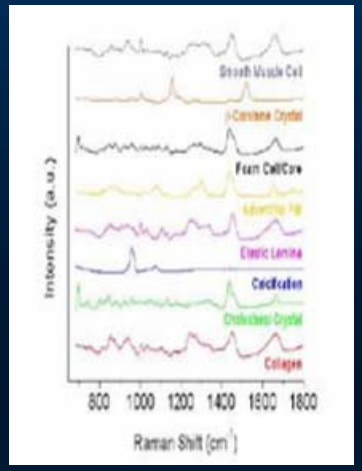
Current standard of primary & Secondary prevention

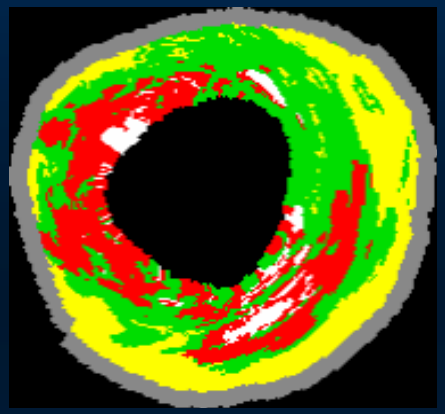
Predicting Vulnerability

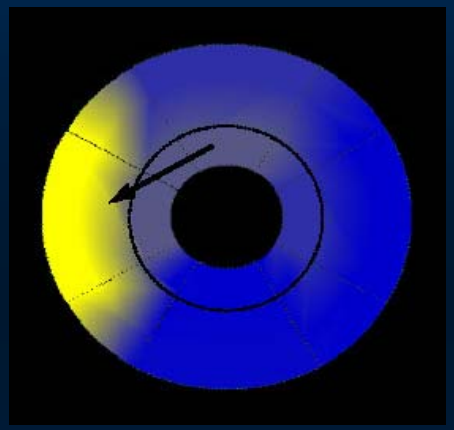
Preventing MI

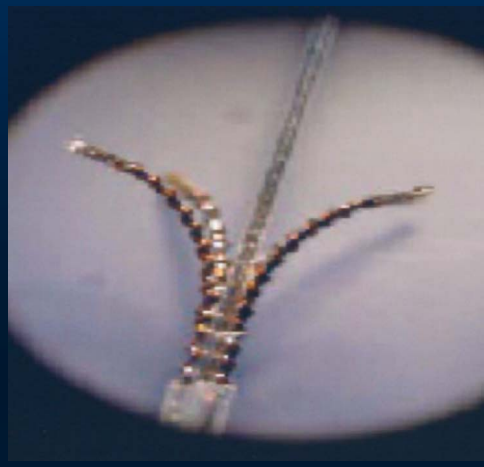
Detection of Vulnerable Plaque

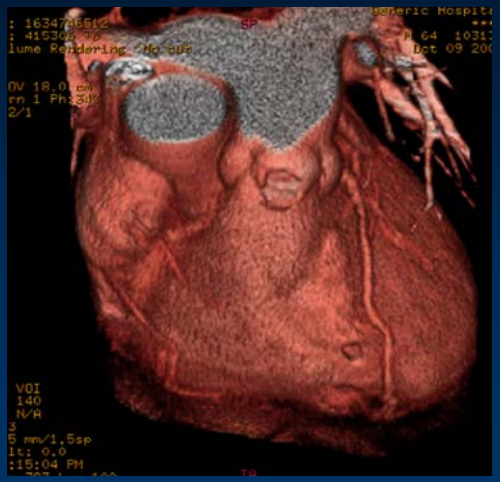
Catheter Base and Non-invasive techniques

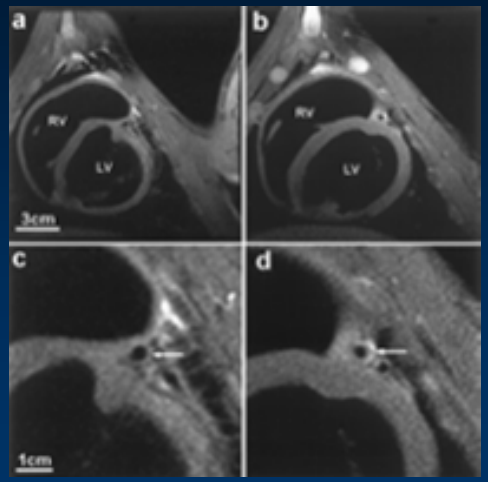






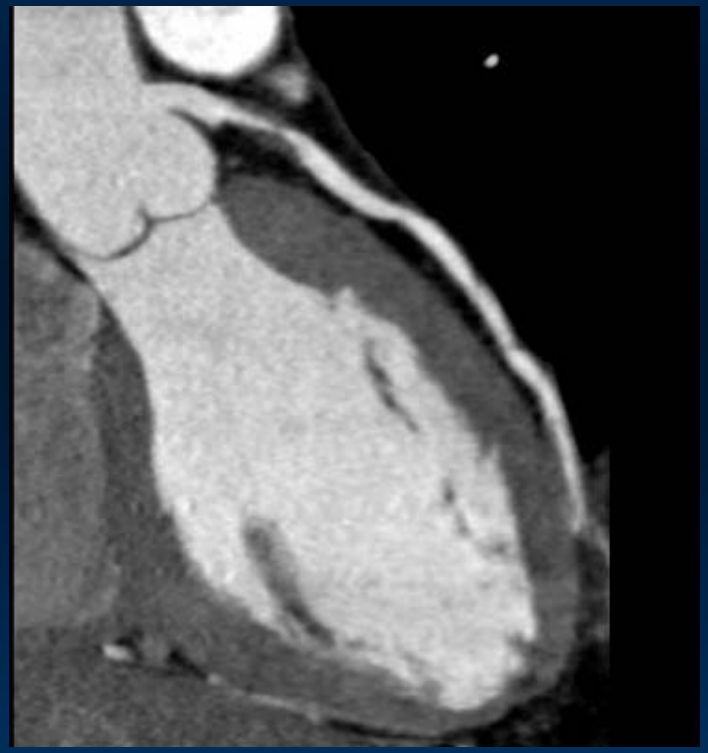




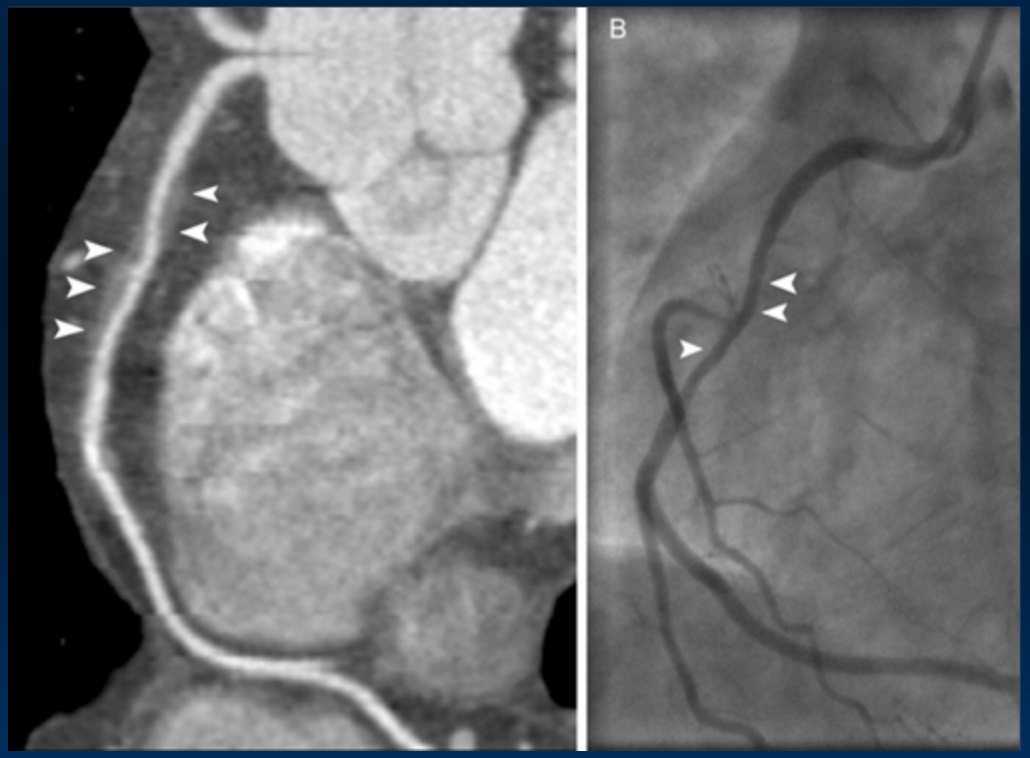


- Prediction should be reliable enough to justify invasive therapy (stent)
- Otherwise, patients with any plaques, should be on statins

Soft Plaque (CTA): A marker of vulnerability?



LAD: with narrowing



RCA: with minimal narrowing

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  - Revascularization

Aims of Treatment

- Improve prognosis
  - Prevention of death and myocardial infarction
- Improve quality of life
  - Prevent / minimize symptomatic ischemic events

Aims and Modes of Treatment
From the Guidelines

- **Improve prognosis**
  - **"Lifestyle changes and drug treatment play vital roles in modifying the atherosclerotic disease process and 'stabilising' coronary plaques ***"**
  - **"In certain circumstances, such as in patients with severe lesions in coronary arteries supplying a large area of jeopardised myocardium, revascularization offers additional opportunities to improve prognosis by improving existing perfusion or providing alternative routes of perfusion"**

ESC guidelines on the management of stable AP - 2006

Aims and Modes of Treatment
From the Guidelines

- **Improve quality of life**
  - **"Lifestyle changes, drugs, and revascularization all have a role to play in minimising or eradicating symptoms of angina, although not necessarily all in the same patient"**

ESC guidelines on the management of stable AP - 2006

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Explaining the Decrease in U.S. Deaths from Coronary Disease, 1980–2000

Earl S. Ford, M.D., M.P.H., Umed A. Ajani, M.B., B.S., M.P.H., Janet B. Croft, Ph.D., Julia A. Critchley, D.Phil., M.Sc., Darwin R. Labarthe, M.D., M.P.H., Ph.D., Thomas E. Kottke, M.D., Wayne H. Giles, M.D., M.S., and Simon Capewell, M.D.

- From 1980 to 2000, the age-adjusted mortality rate from CAD fell (per 100,000 population):
  - Men: from 542.9 to 266.8 (51%)
  - Women: from 263.3 to 134.4 (49%)
- A previously validated model was used to estimate the roles of specific cardiac treatments and changes in risk factors in this decline

N Engl J Med 2007;356:2388-98.

The NEW ENGLAND JOURNAL of MEDICINE

Sequence Variations in PCSK9*, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley Jr., Ph.D. and Helen H. Hobbs, M.D.

*proprotein convertase subtilisin/kexin type 9 serine protease gene

N Engl J Med Volume 354;12:1264-1272, March 23, 2006

Background: PCSK9 mutation and its effect on LDL-C level

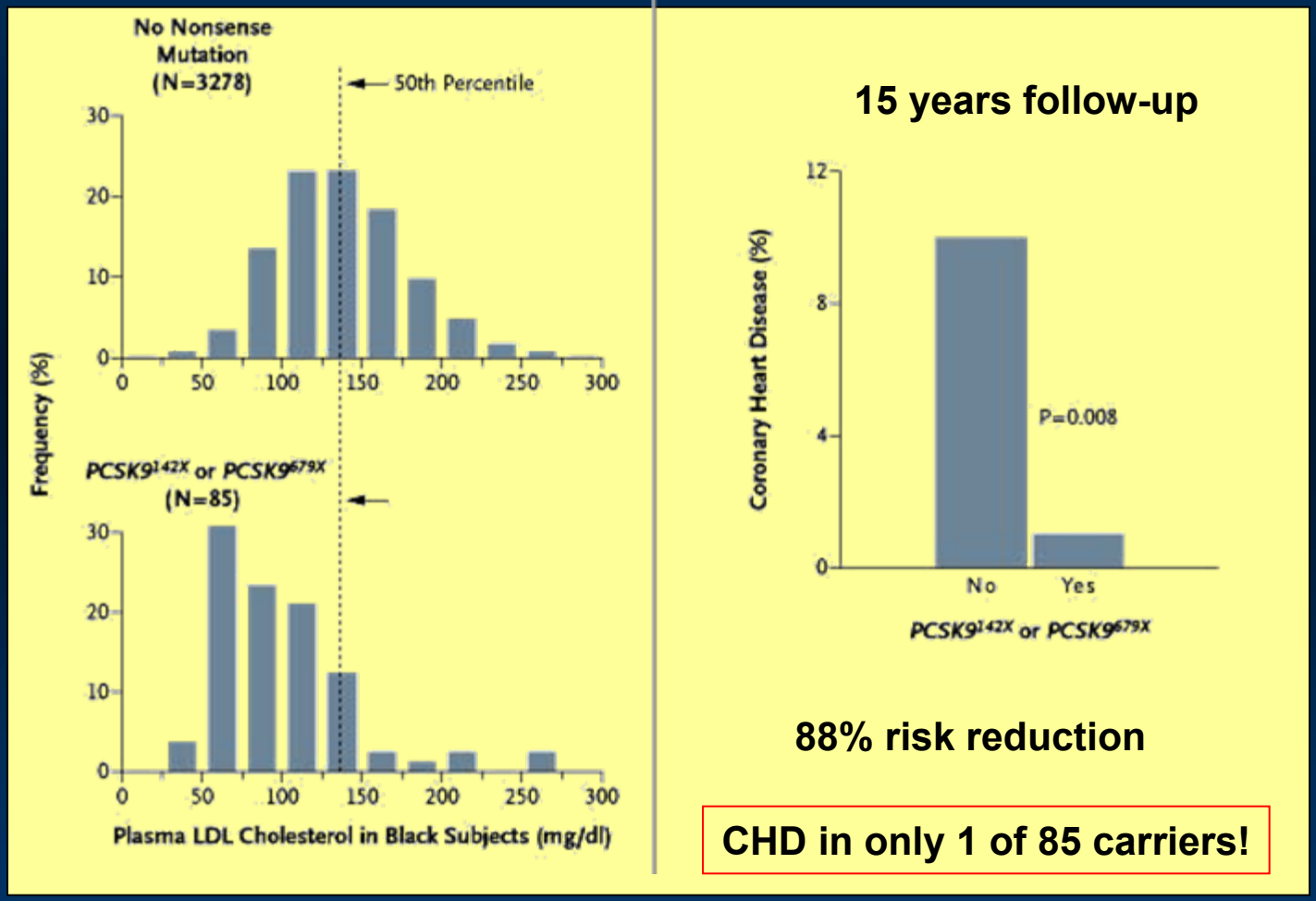
Cohen, J. et al. N Engl J Med 2006;354:1264-1272

- PCSK9 is responsible for degradation of LDL receptors in liver cells
- Various genetic variations are present in blacks (2%) and whites (3.2%)
  - Subjects have increased LDL receptor density (statin like effect)
  - associated with a 20-40 percent reduction in mean LDL cholesterol

- Clinical significance was determined in 15792 participants of ARIC: a prospective study of atherosclerosis in the community
- Data represents 15 years of follow-up

Distribution of Plasma LDL-C and Incidence of CHD among 3363 Black Participants in the Study

Carriers and noncarriers of PCSK9 nonsense mutation

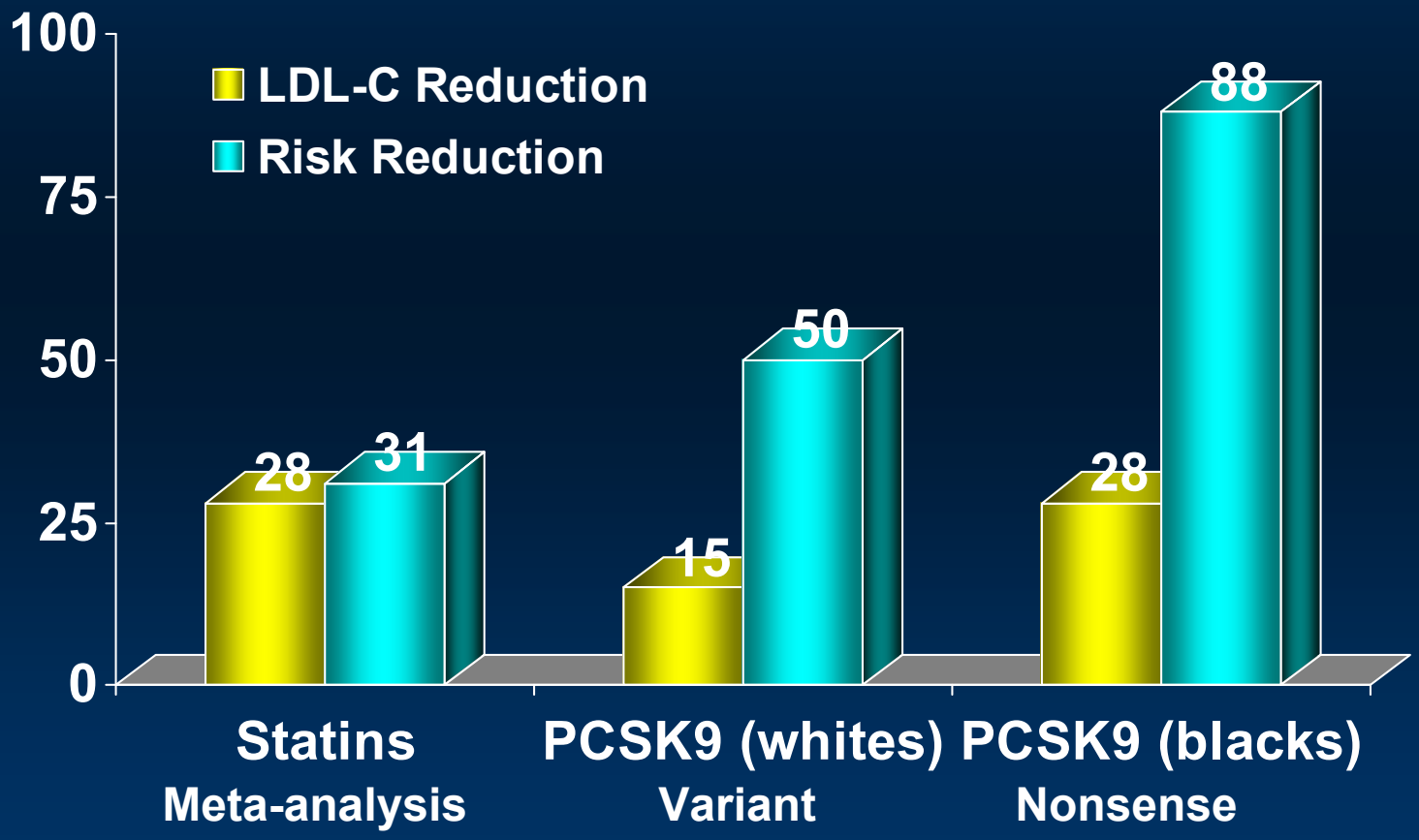


Plasma LDL-C 28% lower in carriers

Cohen, J. et al. N Engl J Med 2006;354:1264-1272

Relation Between Reduction of LDL-C and Cardiovascular Risk Reduction

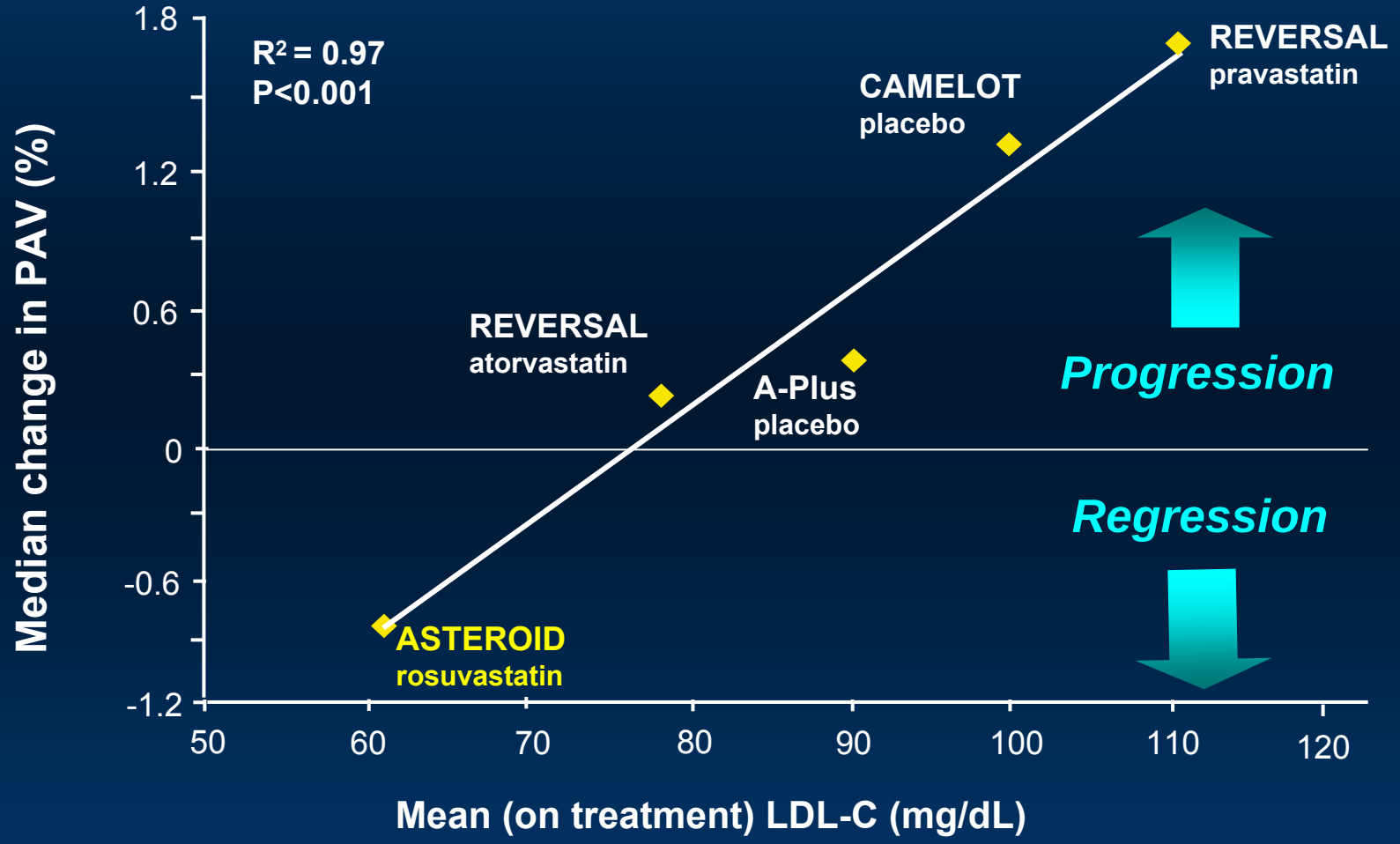
Statins as compared to PCSK9 mutation



Atherosclerosis Progression Implication for therapy

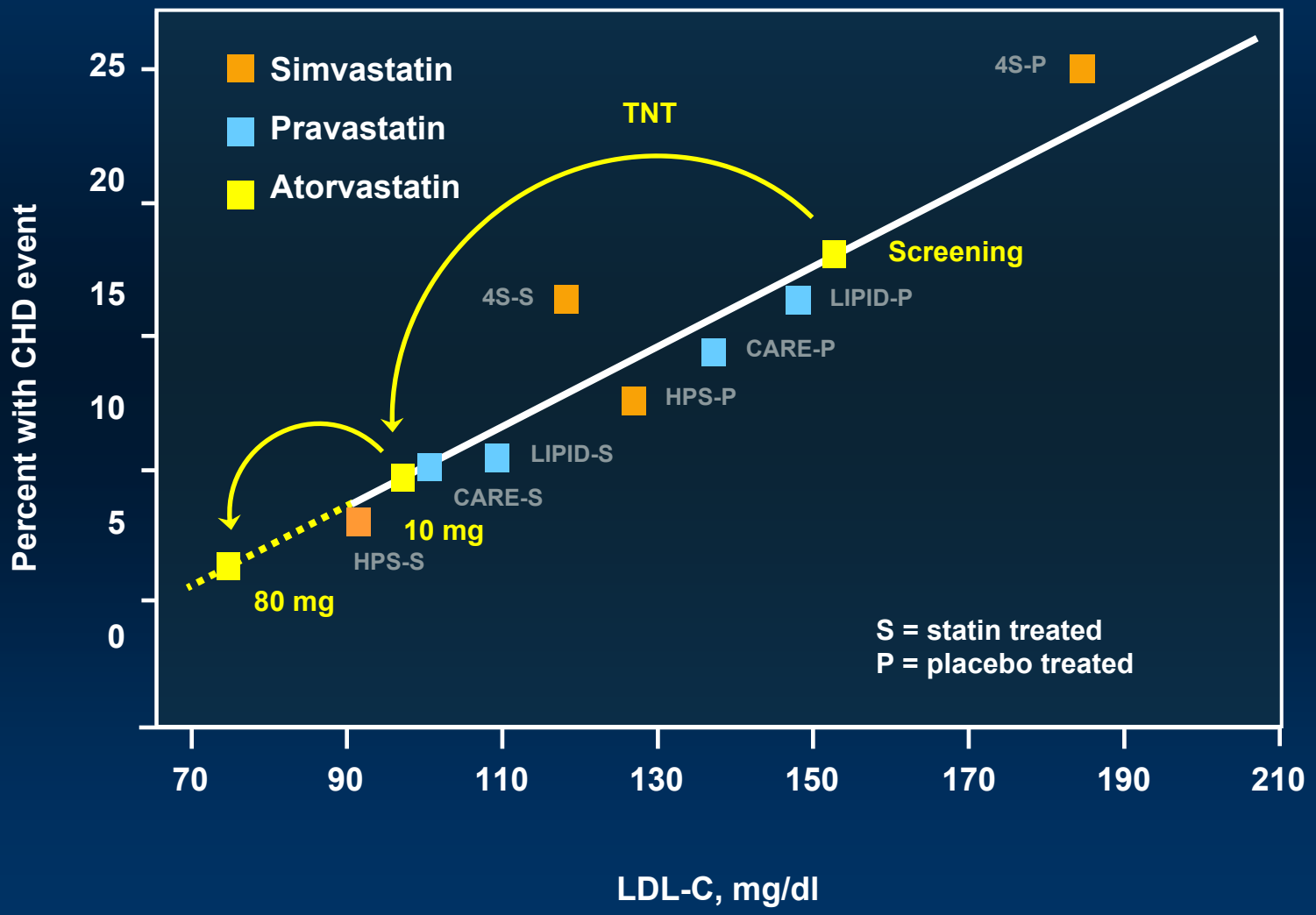
- Atherosclerosis is a slowly progressive disease
  - Disease starts at childhood but becomes clinically evident decades later
- It takes years until the maximal benefit of therapy is evident
  - 5 years (F/U time in many statin trials) are not enough to obtain the full benefit from therapy

ASTEROID: Aggressive statin therapy can induce regression of atherosclerosis



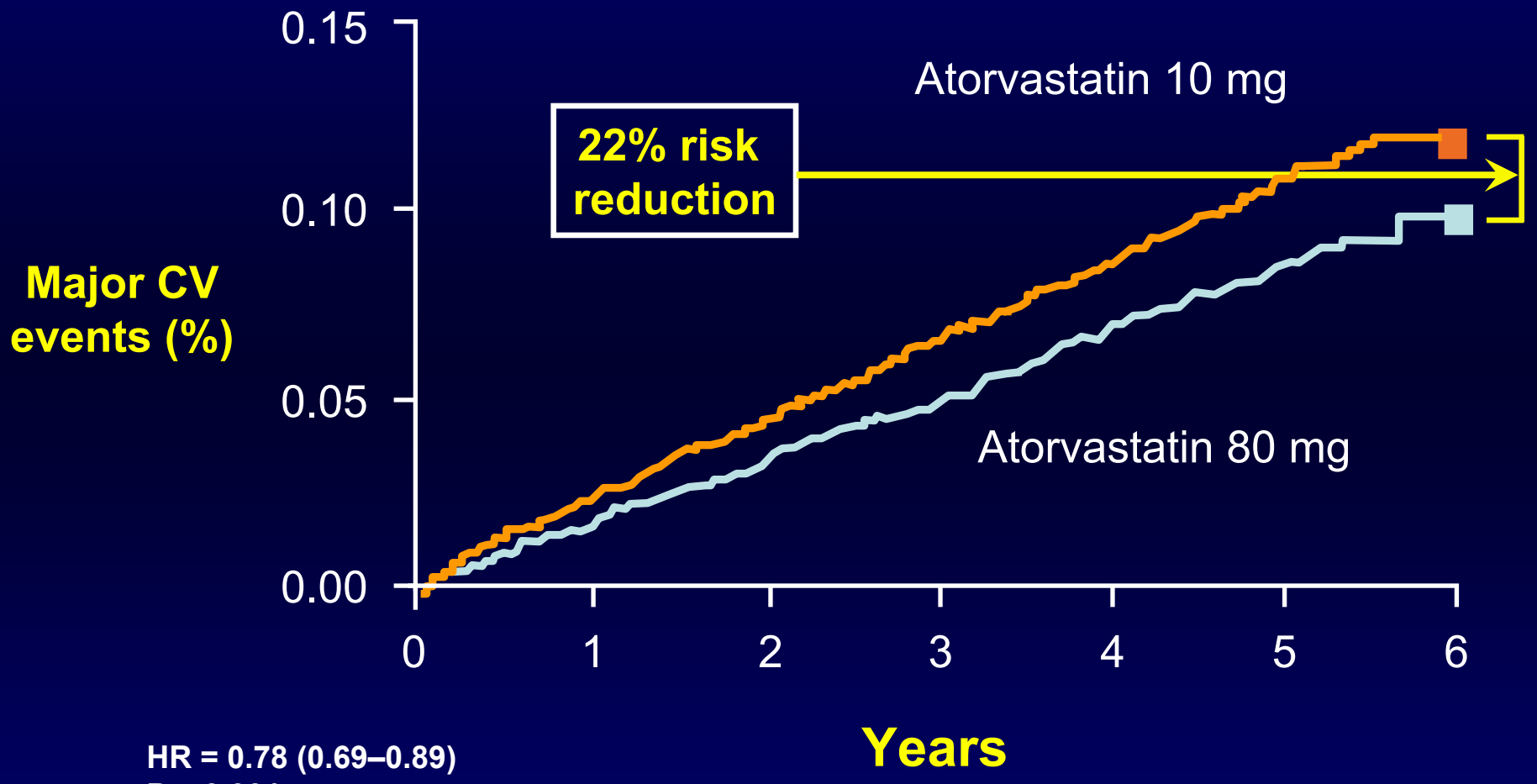
Ref: Nissen S *et al.* JAMA 2006; **295**: e-publication ahead of print

Treating to New Targets (TNT) trial: Rationale



Modified from Kastelein JJP. Atherosclerosis. 1999;143(suppl 1):S17-S21

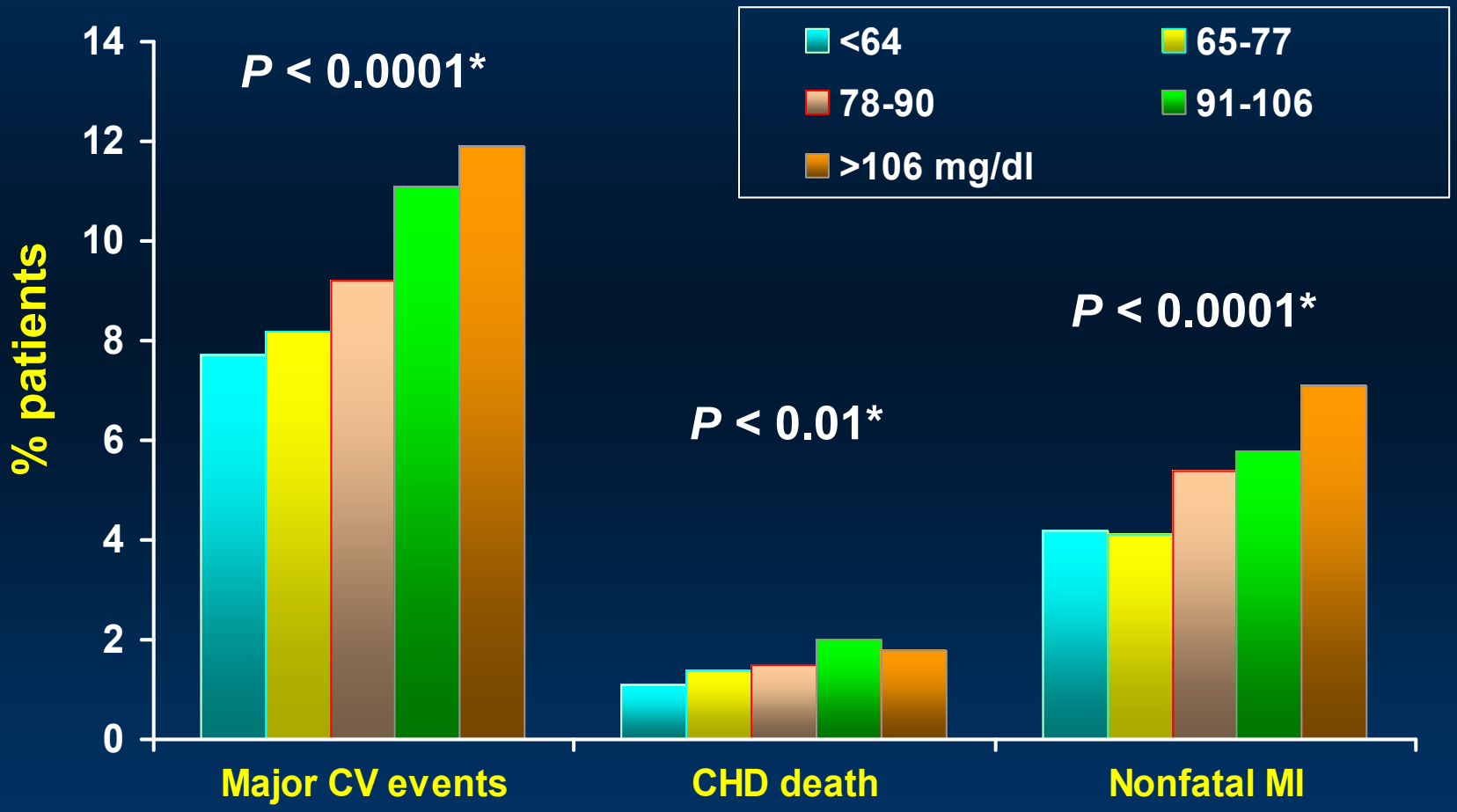
TNT: Treatment effects on primary outcome



HR = 0.78 (0.69–0.89)
P < 0.001

LaRosa JC et al. *N Engl J Med.* 2005;352.

Major CV Events Across Quintiles of Achieved LDL

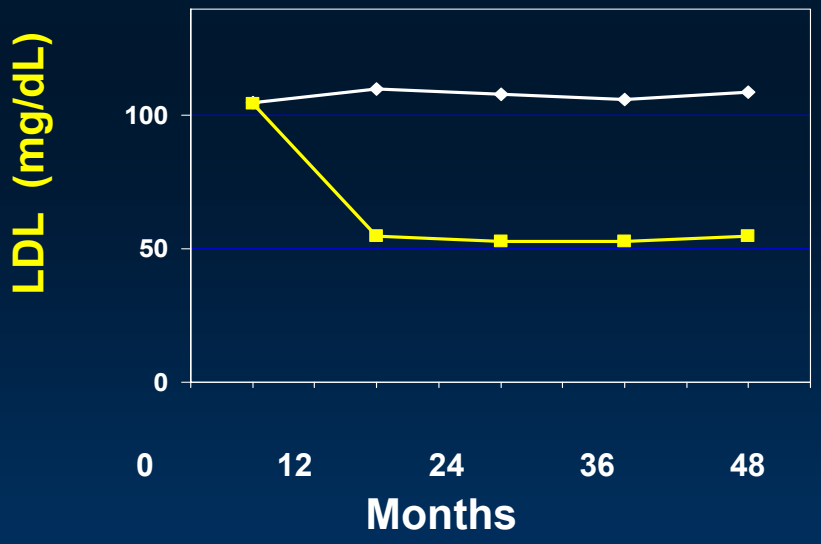


*P-value for trend across LDL-C

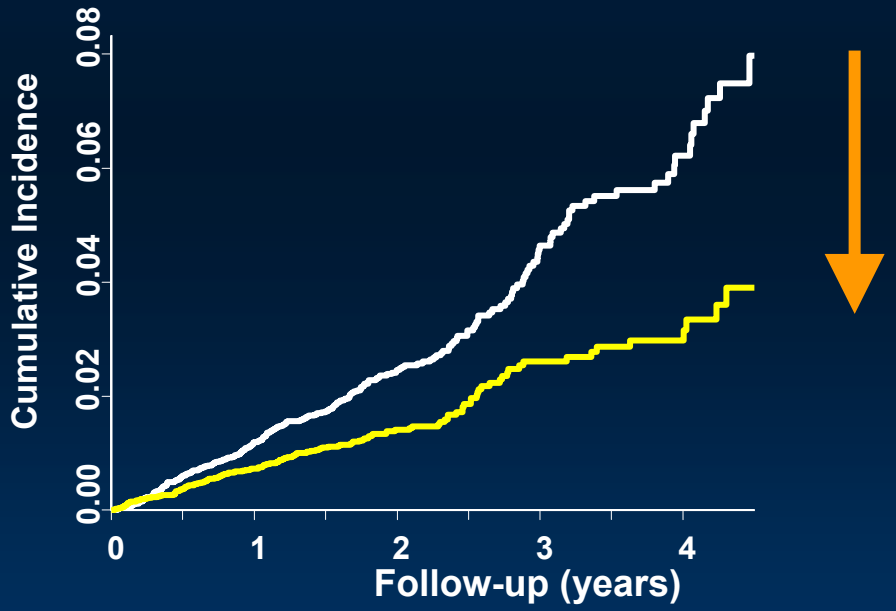
LaRosa JC. *AHA.* 2005

JUPITER Trial: LDL and event* reduction

LDL decrease 50 percent at 12 months



HR 0.56, 95% CI 0.46-0.69
P < 0.00001



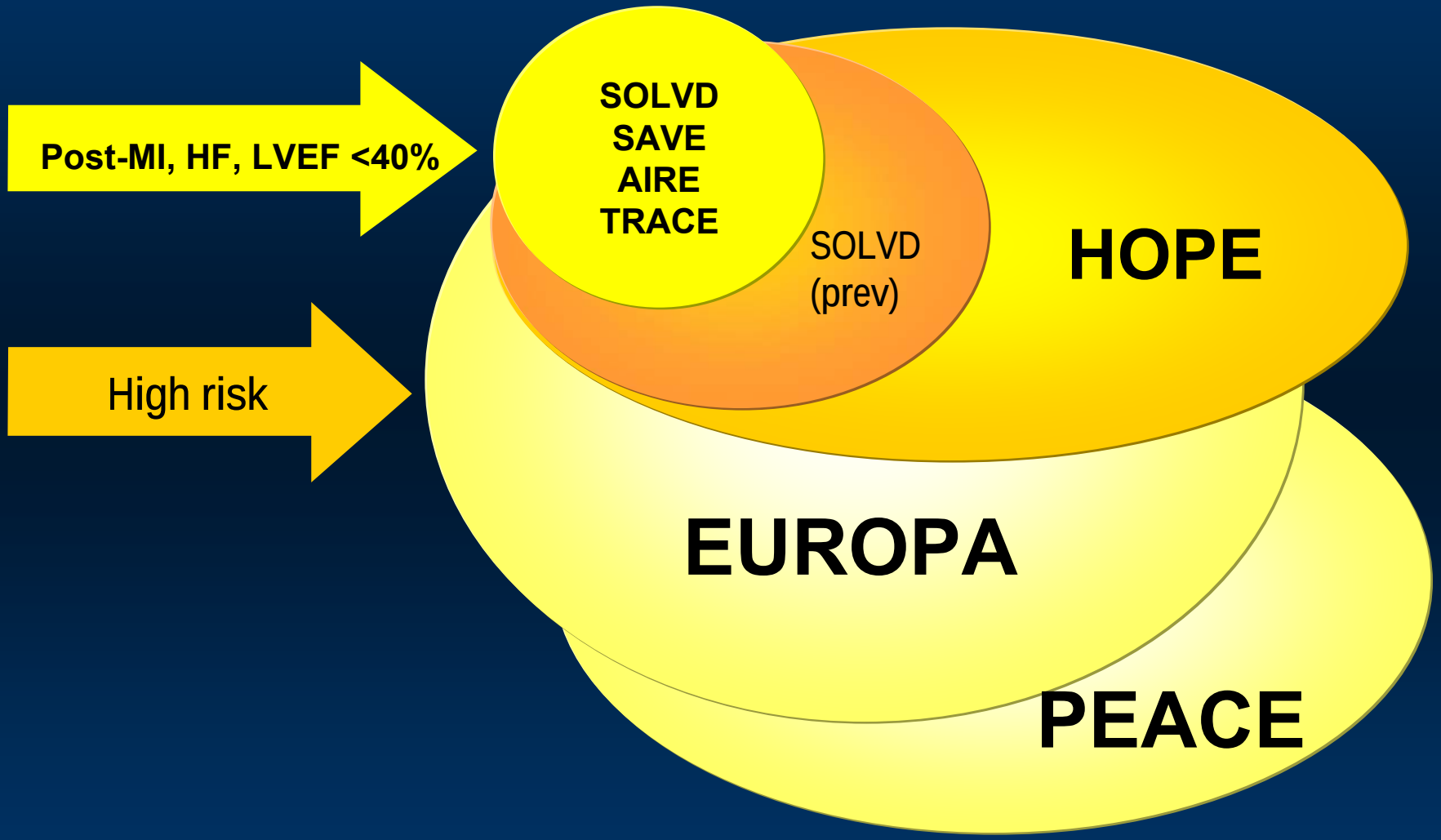
*Primary Trial Endpoint : MI, Stroke, UA/Revascularization, CV Death

Ridker et al NEJM 2008

Role of RAAS Modulation in CAD

Implications from recent clinical trials

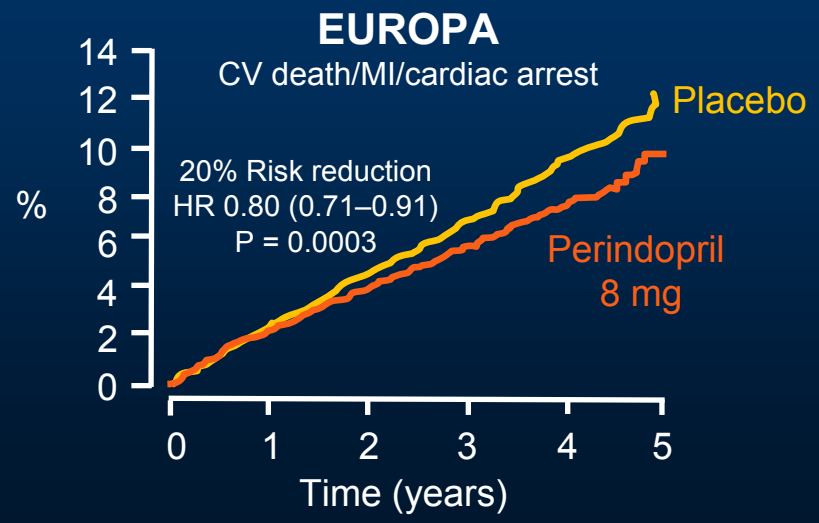
Benefit of ACE inhibition in CAD

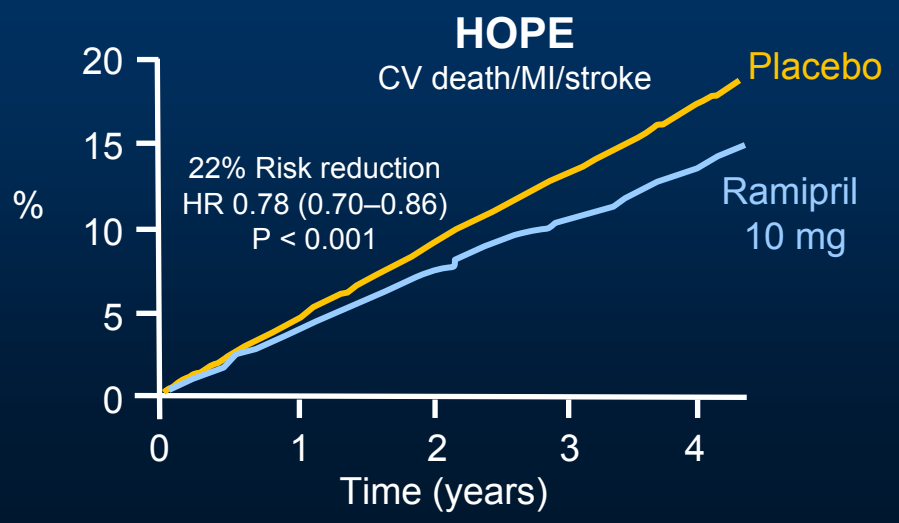


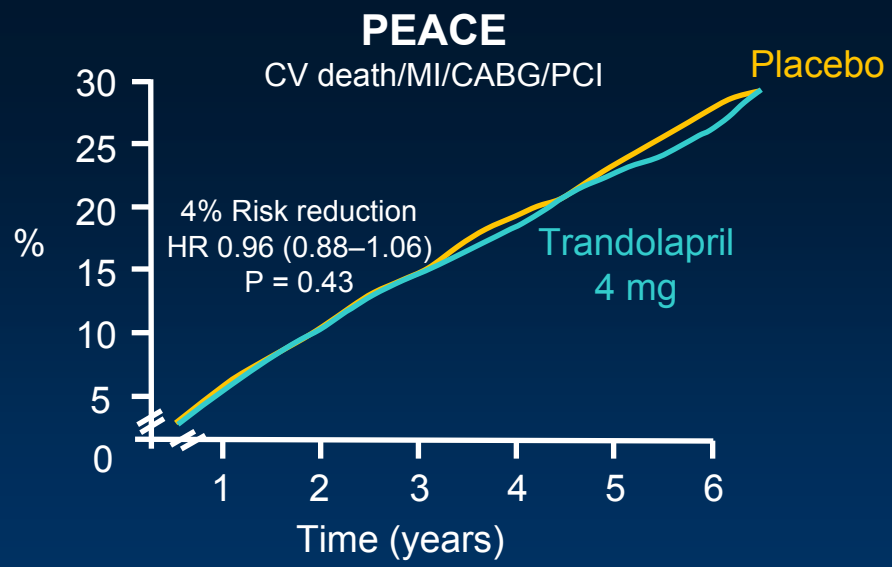
Bertrand ME. *Curr Med Res Opin.* 2004;20:1559-69.

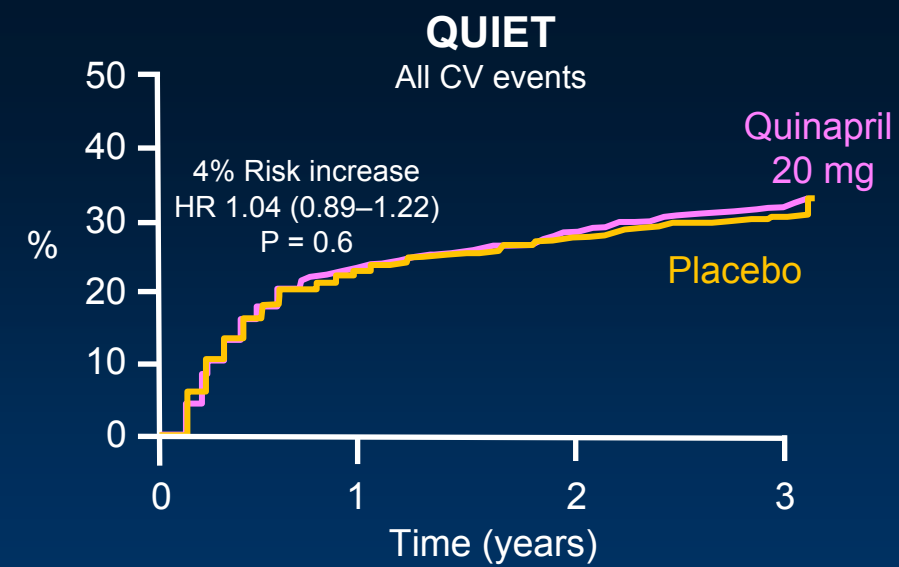
All CAD patients

ACEI trials in CAD without HF: Primary outcomes









EUROPA Investigators. *Lancet*. 2003;362:782-8.
PEACE Trial Investigators. *N Engl J Med.* 2004;351:2058-68.

HOPE Study Investigators. *N Engl J Med.* 2000;342:145-53.
Pitt B et al. *Am J Cardiol*. 2001;87:1058-63.

EUROPA, HOPE, PEACE, QUIET: Totality of trial evidence

Pepine CJ, Probstfield JL. *Vasc Bio Clin Pract.* CME Monograph; UF College of Medicine. 2004;6(3).

ACE inhibitors: ESC guidelines on the management of stable AP - 2006

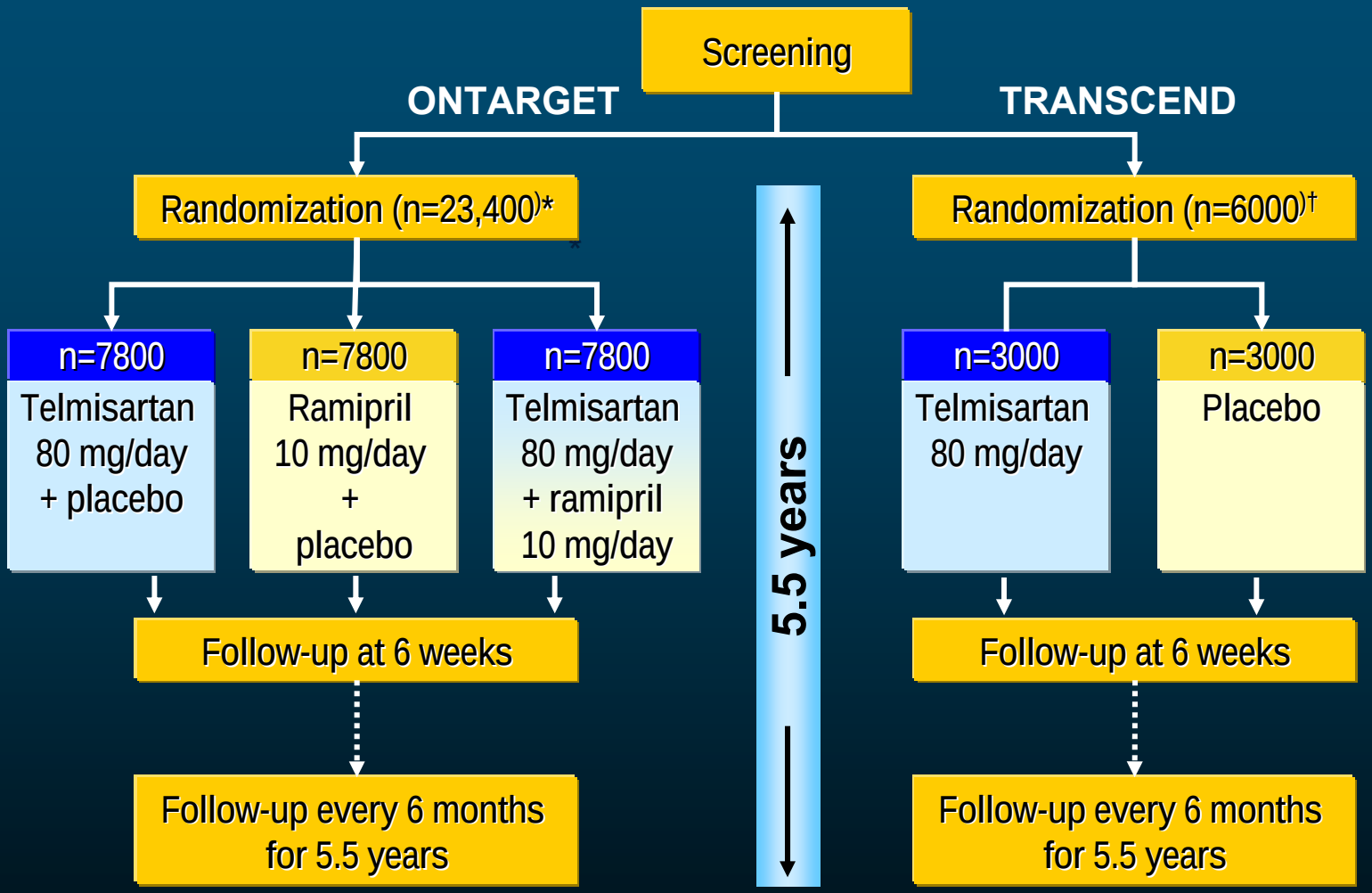
Class I

- ACE-inhibitor therapy in patients with coincident indications for ACE-inhibition, such as hypertension, heart failure, LV dysfunction, prior MI with LV dysfunction, or diabetes
  - level of evidence A

Class IIa

- ACE-inhibitor therapy in all patients with angina and proven coronary disease
  - level of evidence B

Role of ARB's: The ONTARGET Program



*Planned. Actual=25,620; †Planned. Actual=5926.

The ONTARGET/TRANSCEND Investigators. *Am Heart J*. 2004;148:52-61.

The ONTARGET Trial

Inclusion Criteria

- Age ≥55 years
- At high risk of developing a CVD event, with a history of
  - Coronary artery disease
  - Peripheral arterial occlusive disease (PAOD)
  - Cerebrovascular event
  - Diabetes mellitus with end organ disease
- Intolerant to ACE inhibitors (TRANSCEND)

Criteria similar to HOPE trial

The ONTARGET/TRANSCEND Investigators. *Am Heart J*. 2004;148:52-61.

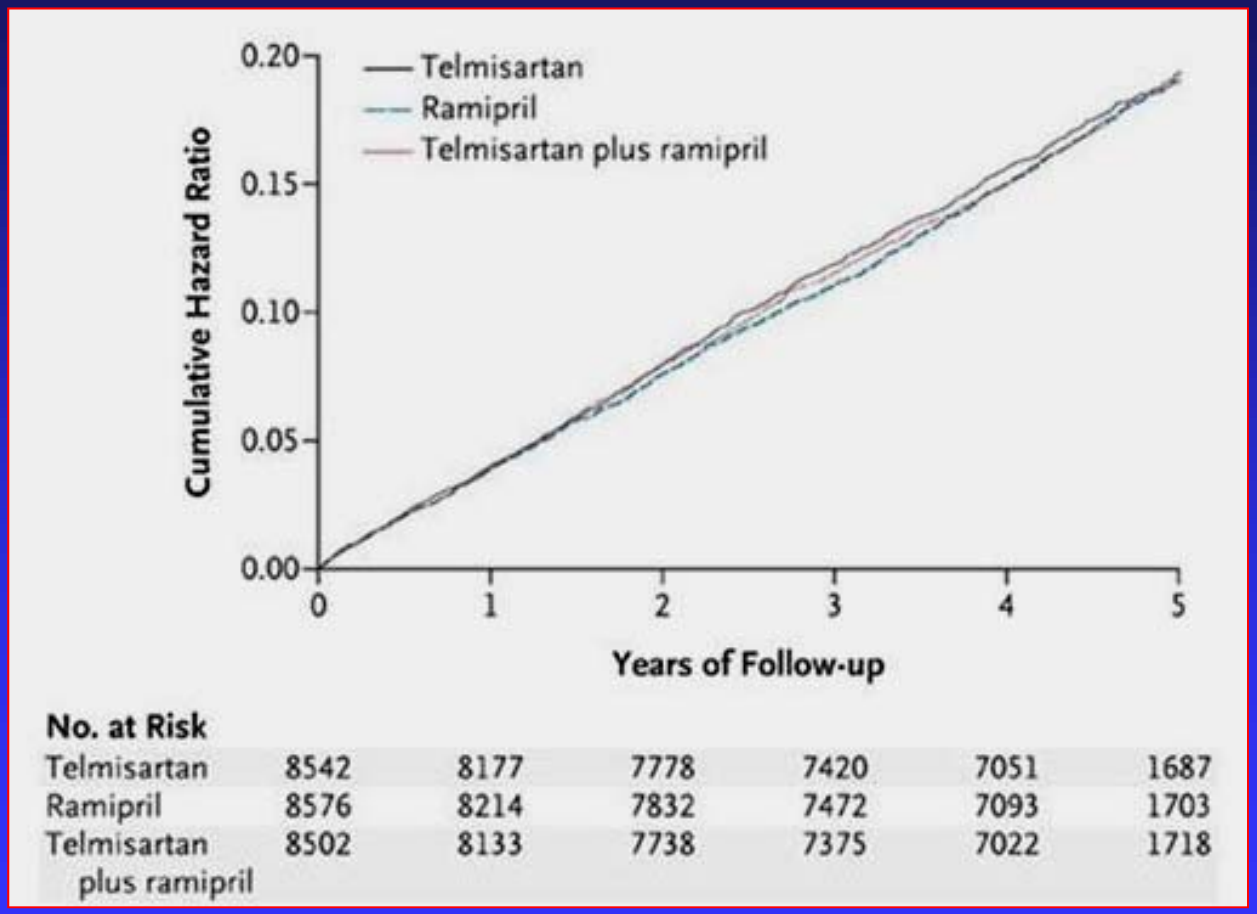
ONTARGET

Change in BP (mmHg)

	Ramipril	Telmisartan	Combination
Systolic	-6.0	-6.9	-8.4
Diastolic	-4.6	-5.2	-6.0

ONTARGET

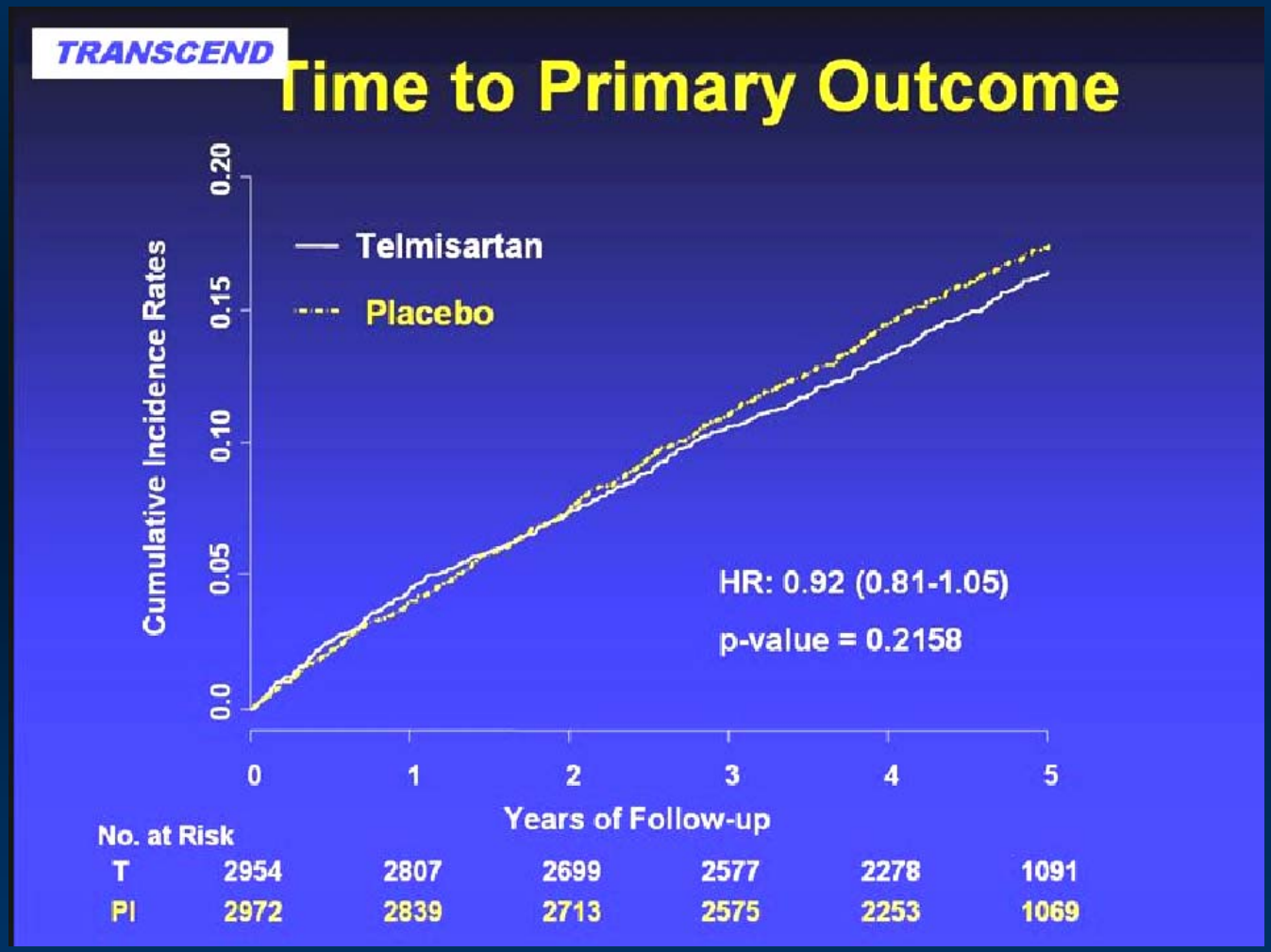
Time to Primary Outcome



No. at Risk						
Telmisartan	8542	8177	7778	7420	7051	1687
Ramipril	8576	8214	7832	7472	7093	1703
Telmisartan plus ramipril	8502	8133	7738	7375	7022	1718

NEJM 2008: 358; 1547-1559

Telmisartan vs. Placebo in ACE intolerant patients



ESC: SEP 2008

ONTARGET

Implications

- Telmisartan is as effective as ramipril, with a slightly better tolerability.
- Combination therapy is not superior to ramipril, and has increased side effects.
- Telmisartan is not better than placebo in ACE intolerant patients

How can Telmisartan be as effective as Ramipril (HOPE population) and at the same time not be better than placebo????

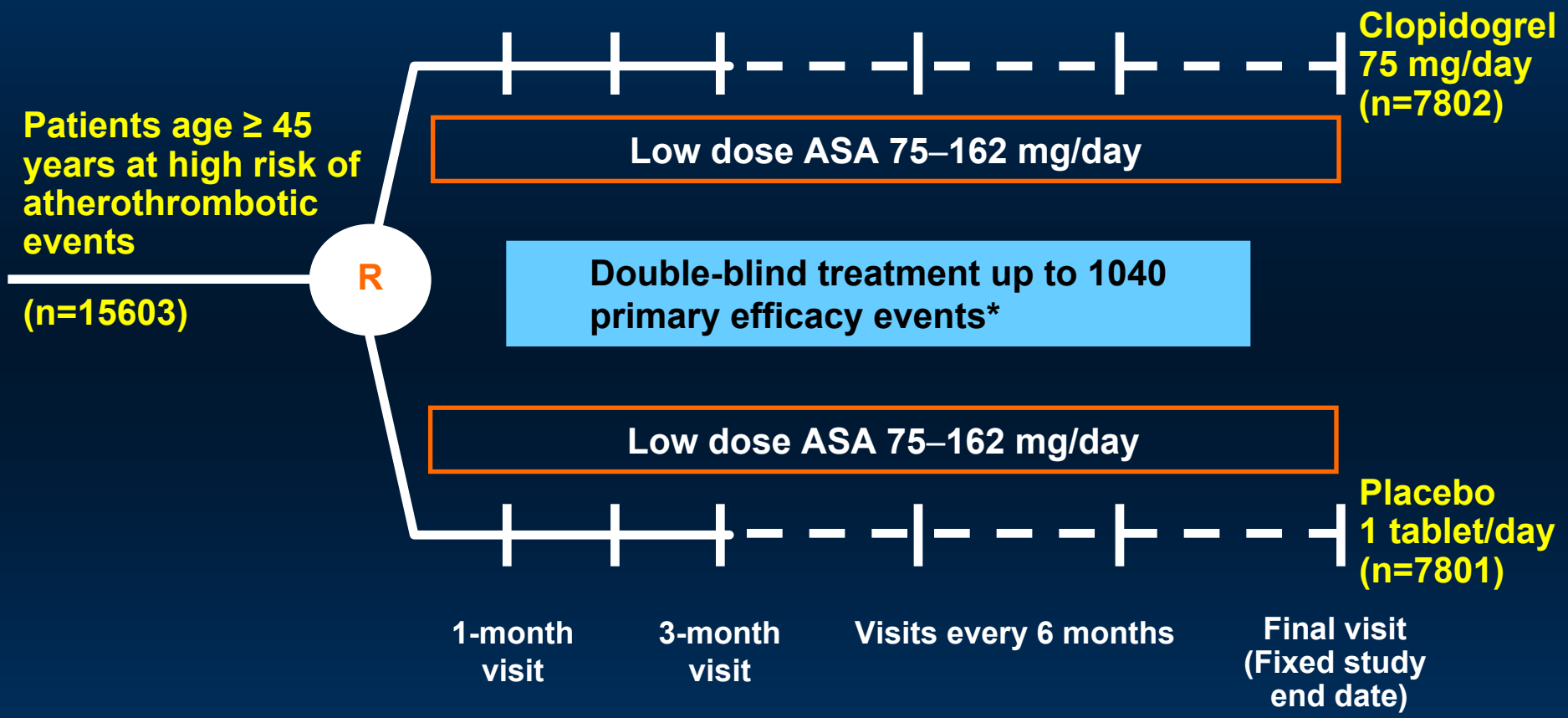
Antiplatelet Therapy

Antiplatelet therapy – beyond aspirin

- Aspirin is a weak antiplatelet agent
- Role of aspirin in treatment in patients with ACS and in stable CAD is proven beyond doubt
- Addition of clopidogrel to aspirin is helpful to improve outcome in ACS
- Is there benefit to combination therapy (aspirin and clopidogrel) in stable CAD?

Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA)

Study Design



* MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death; event-driven trial

Bhatt DL, Topol EJ, et al. Am Heart J 2004; 148: 263–268.

CHARISMA

Inclusion criteria

Must include

Signed Written Informed Consent

Patients aged ≥45 years

At least one of four criteria

1. Documented cerebrovascular disease
2. Documented coronary disease
3. Documented symptomatic PAD
4. 2 major or 1 major and 2 minor or 3 minor risk factors

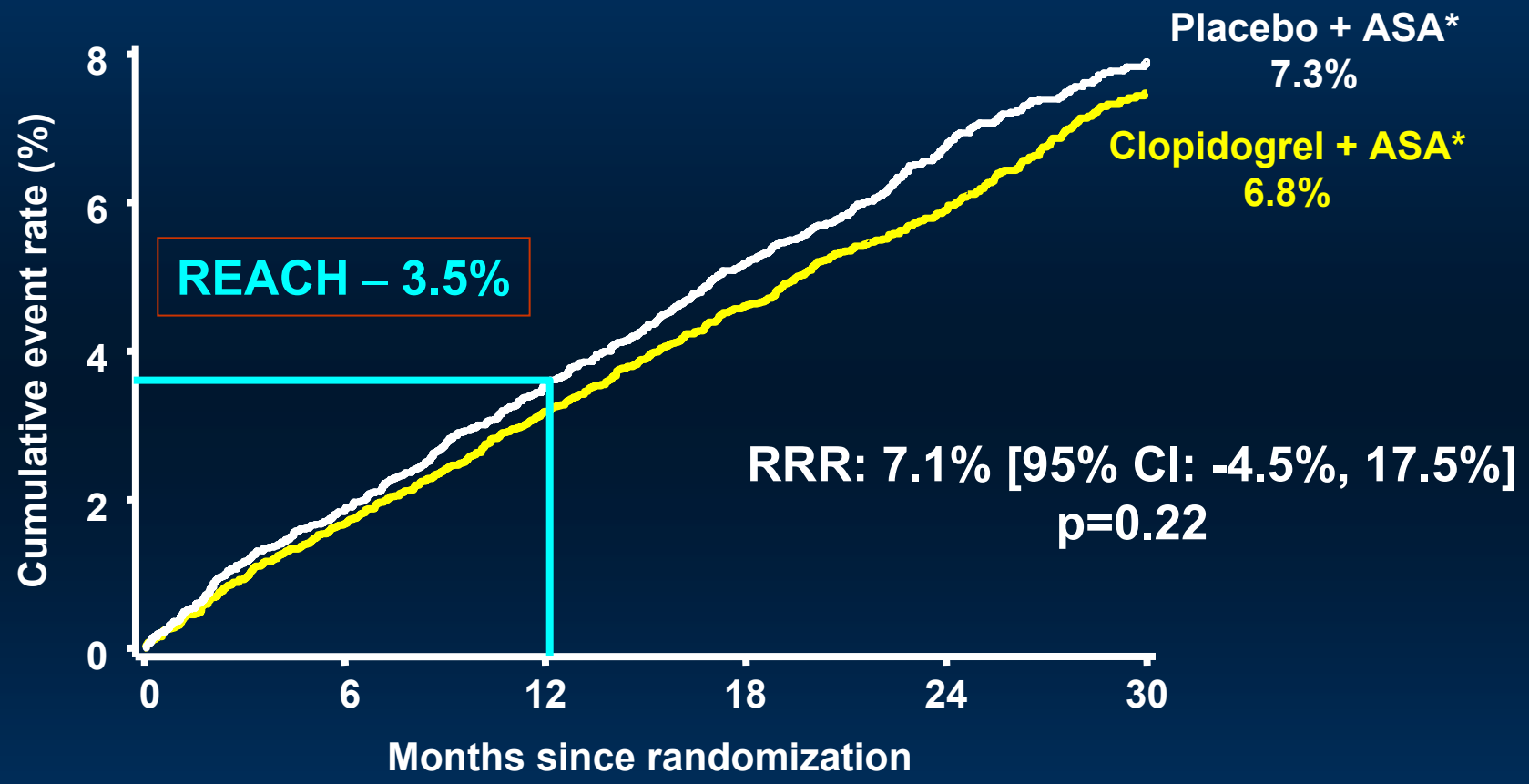
Major Risk Factors

- Type I or Type II diabetes
- Diabetic nephropathy
- Ankle Brachial Index <0.9
- Asymptomatic carotid stenosis > 70%
- Presence of at least one carotid plaque

Minor Risk Factors

- SBP ≥150 mm Hg (despite therapy)
- Hypercholesterolemia
- Current smoking >15 cigarettes/day
- Male ≥65 years or female ≥70 years

Overall Population: Primary Efficacy Outcome (MI, Stroke, or CV Death)†



† First Occurrence of MI (fatal or non-fatal), stroke (fatal or non-fatal), or cardiovascular death

*All patients received ASA 75-162mg/day

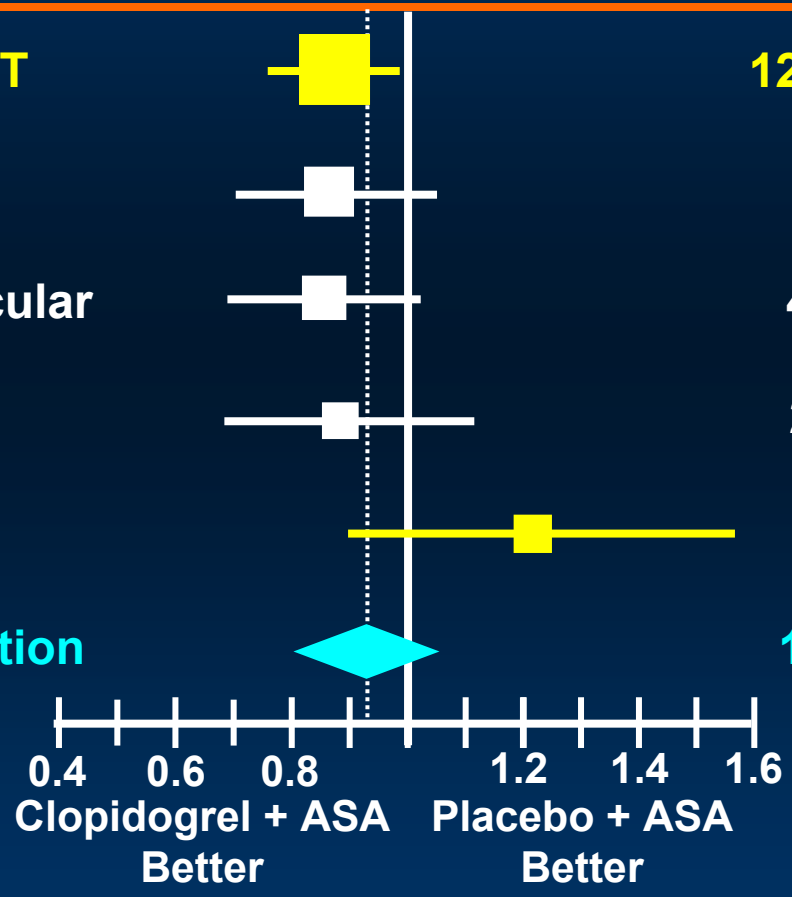
Median follow-up was 28 months

Bhatt DL, Fox KA, Hacke W, et al. *NEJM* 2006 – In press

CHARISMA

Primary Efficacy Results (MI/Stroke/CV Death)* by Category of Inclusion Criteria

Population	N	RR (95% CI)	p value
Documented AT	12,153	0.88 (0.77, 0.998)	0.046
Coronary	5,835	0.86 (0.71, 1.05)	0.13
Cerebrovascular	4,320	0.84 (0.69, 1.03)	0.09
PAD	2,838	0.87 (0.67, 1.13)	0.29
Multiple RF	3,284	1.20 (0.91, 1.59)	0.20
Overall Population	15,603	0.93 (0.83, 1.05)	0.22



* First Occurrence of MI (fatal or not), Stroke (fatal or not), or CV Death
RF= Risk Factors, AT= Atherothrombosis

Bhatt DL. Oral presentation at ACC 2006.

CHARISMA

Multiple Risk Factor Population: Secondary Efficacy Results

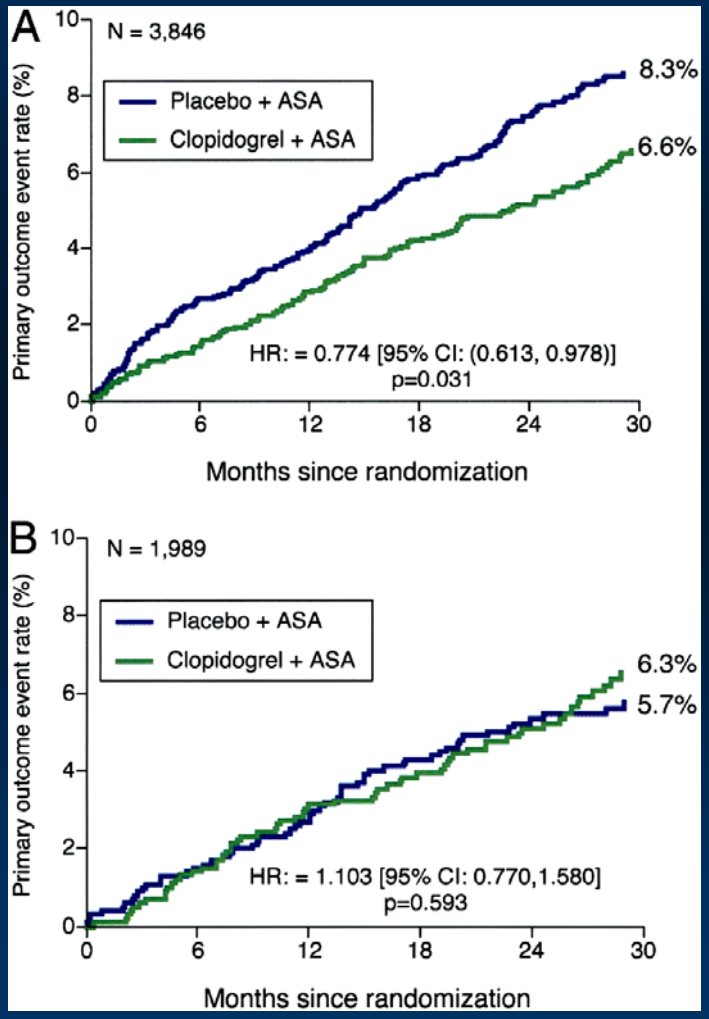
Endpoint* – N (%)	Clopidogrel (n=1659)	Placebo + ASA (n=1625)	+ ASA RR (95% CI)	p value
Principal Secondary Endpoint†	224 (13.5)	216 (13.3)	1.01 (0.84, 1.22)	0.88
All Cause Death	89 (5.4)	62 (3.8)	1.41 (1.02, 1.95)	0.04
Cardiovascular Death	64 (3.9)	36 (2.2)	1.74 (1.16, 2.62)	0.01
Myocardial Infarction	40 (2.4)	33 (2.0)	1.19 (0.75, 1.89)	0.45
Ischemic Stroke	27 (1.6)	29 (1.8)	0.91 (0.54, 1.54)	0.73
Stroke	35 (2.1)	36 (2.2)	0.95 (0.60, 1.52)	0.84
Hospitalization‡	140 (8.4)	147 (9.0)	0.93 (0.74, 1.18)	0.55

*Intention to treat analysis
†First occurrence of MI (fatal or not), stroke (fatal or not), cardiovascular death (including hemorrhagic death), or hospitalization‡
‡For UA, TIA, or revascularization

Bhatt DL. Oral presentation at ACC 2006.

CHARISMA

CHARISMA – post hoc subgroup analysis cardiovascular death, MI, or stroke

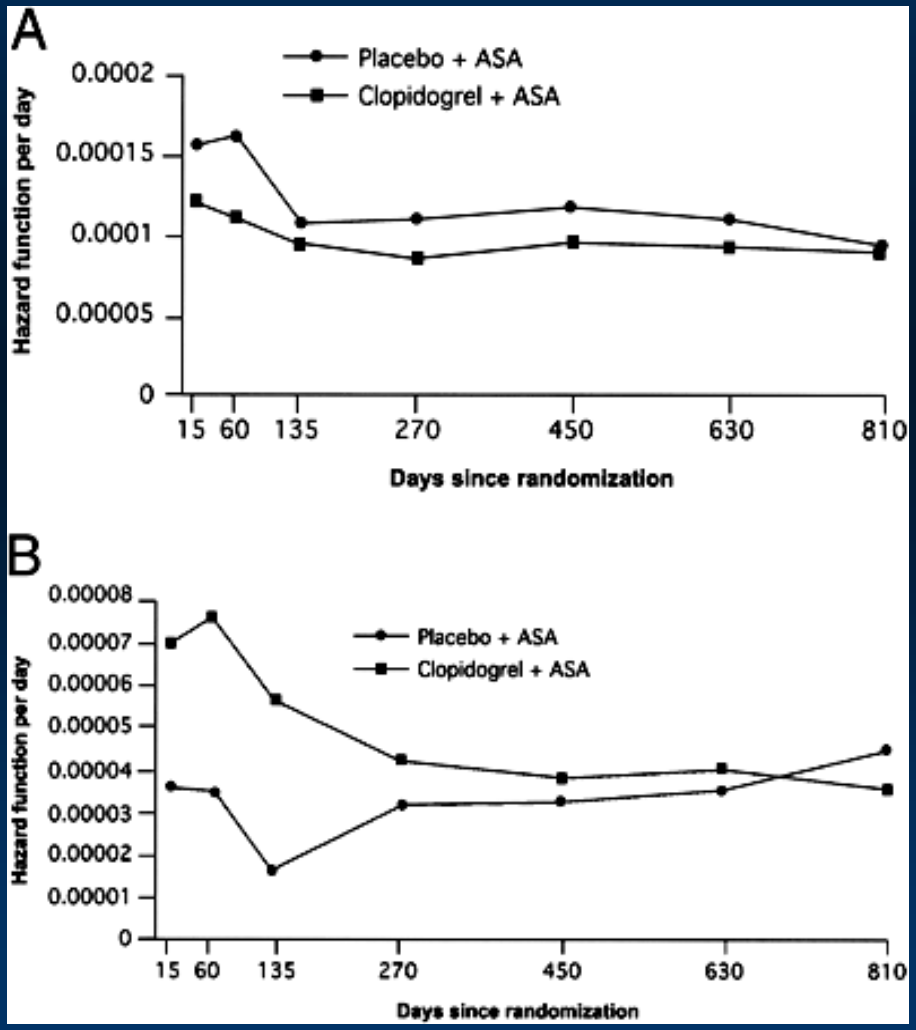


Patients with prior MI

Validity of subgroup analysis in a negative trial?

Patients with CAD Without prior MI

CHARISMA – time dependence of daily hazard



Ischemic event

Bleeding

Recommendations for pharmacological therapy to improve prognosis

Class I

- **Aspirin** 75 mg daily in **all** patients without specific contraindications (ie active GI bleeding, aspirin allergy or previous aspirin intolerance) **(level of evidence A)**
- **Statin** therapy for **all** patients with coronary disease **(level of evidence A)**
- **ACE-inhibitor** therapy in patients with coincident indications for ACE-inhibition, such as **hypertension, heart failure, LV dysfunction, prior MI with LV dysfunction, or diabetes (level of evidence A)**
- **Oral beta blocker** therapy in patients **post-MI or with heart failure (level of evidence A)**

ESC guidelines on the management of stable AP - 2006

Recommendations for pharmacological therapy to improve prognosis

Class IIa

- ACE-inhibitor therapy in all patients with angina and proven coronary disease (level of evidence B)
- Clopidogrel as an alternative antiplatelet agent in patients with stable angina who cannot take aspirin eg Aspirin allergic (level of evidence B)
- High-dose statin therapy in high risk (>2% annual CV mortality) patients with proven coronary disease (level of evidence B)

Class IIb

- Fibrate therapy in patients with low HDL and high triglycerides who have diabetes or the metabolic syndrome (level of evidence B)

ESC guidelines on the management of stable AP - 2006

pharmacological therapy to improve symptoms and/or reduce ischaemia

- Beta Blockers
- Nitrates
  - Short, long acting
- Ca Channel Blockers
  - Dihydropyridines, Non-dihydropyridines
- Others
  - K channel opener - Nicorandil
  - Sinus node inhibitor – Ivabradine
  - Metabolic modifiers – Trimetazidine, Ranolazine

OUTLINE

- Pathophysiology
  - Atherosclerosis
  - Ischemia
- Primary prevention – who should be treated
- Therapy
  - Lifestyle
  - Pharmacology
  - Revascularization

COURAGE

Clinical **O**utcomes **U**tilizing

Revascularization and

Aggressive **G**uideline-Driven

Drug **E**valuation

Hypothesis

PCI + Optimal Medical Therapy

will be Superior to

Optimal Medical Therapy Alone

Optimal Medical Therapy

Pharmacologic

- Anti-platelet: aspirin; clopidogrel in accordance with established practice standards
- Statin: simvastatin ± ezetimibe or ER niacin
- ACE Inhibitor or ARB: lisinopril or losartan
- Beta-blocker: long-acting metoprolol
- Calcium channel blocker: amlodipine
- Nitrate: isosorbide 5-mononitrate

Lifestyle

- Smoking cessation
- Exercise program
- Nutrition counseling
- Weight control

Applied to Both Arms by Protocol and Case-Managed

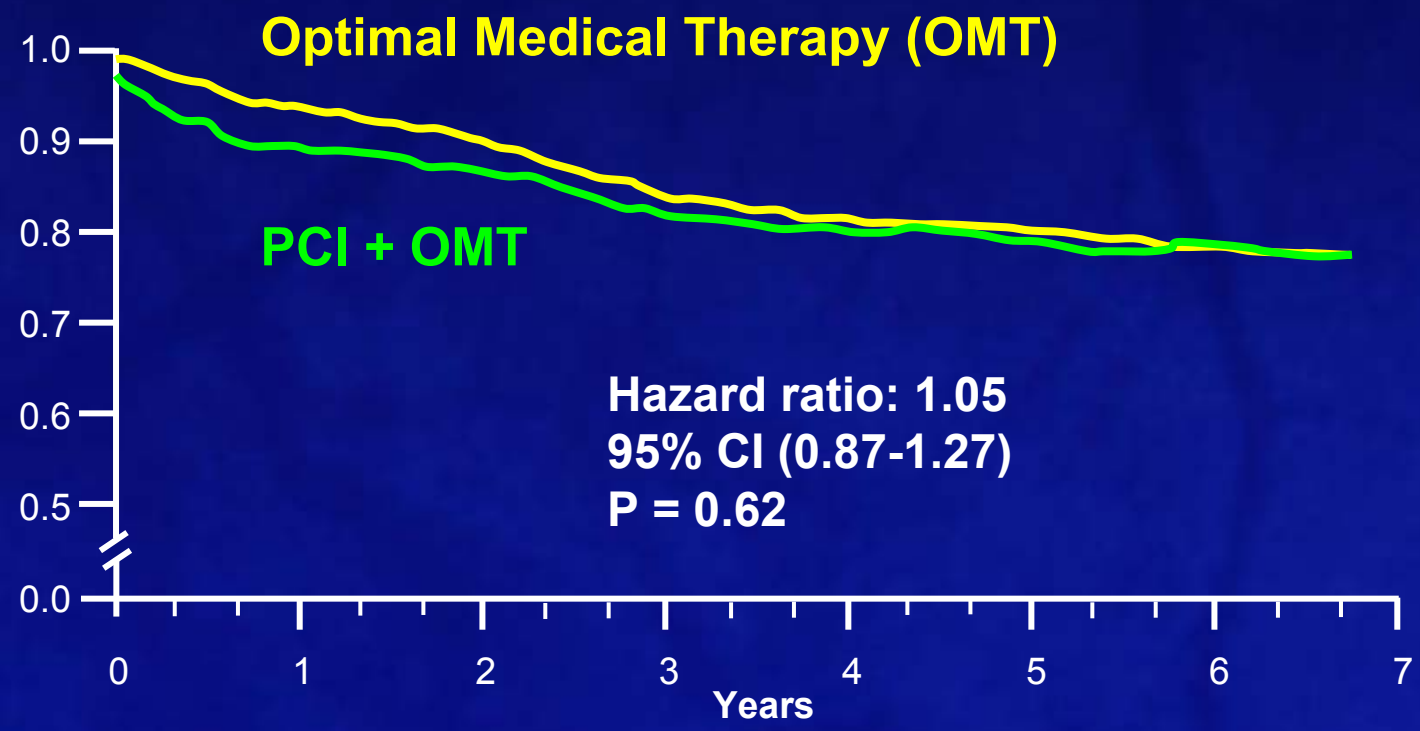
Risk Factor Goals

Variable	Goal
Smoking	Cessation
Total Dietary Fat / Saturated Fat	<30% calories / <7% calories
Dietary Cholesterol	<200 mg/day
LDL cholesterol (primary goal)	60-85 mg/dL
HDL cholesterol (secondary goal)	>40 mg/dL
Triglyceride (secondary goal)	<150 mg/dL
Physical Activity	30-45 min. moderate intensity 5X/week
Body Weight by Body Mass index	Initial BMI / Weight Loss Goal 25-27.5 / BMI <25 >27.5 / 10% relative weight loss
Blood Pressure	<130/85 mmHg
Diabetes	HbAlc <7.0%

Long-Term Improvement in Treatment Targets (Group Median ± SE Data)

Treatment Targets	Baseline		60 Months	
	PCI +OMT	OMT	PCI +OMT	OMT
SBP	131 ± 0.77	130 ± 0.66	124 ± 0.81	122 ± 0.92
DBP	74 ± 0.33	74 ± 0.33	70 ± 0.81	70 ± 0.65
Total Cholesterol mg/dL	172 ± 1.37	177 ± 1.41	143 ± 1.74	140 ± 1.64
LDL mg/dL	100 ± 1.17	102 ± 1.22	71 ± 1.33	72 ± 1.21
HDL mg/dL	39 ± 0.39	39 ± 0.37	41 ± 0.67	41 ± 0.75
TG mg/dL	143 ± 2.96	149 ± 3.03	123 ± 4.13	131 ± 4.70
BMI Kg/M^2	28.7 ± 0.18	28.9 ± 0.17	29.2 ± 0.34	29.5 ± 0.31
Moderate Activity (5x/week)	25%	25%	42%	36%

Survival Free of Death from Any Cause and Myocardial Infarction



Number at Risk

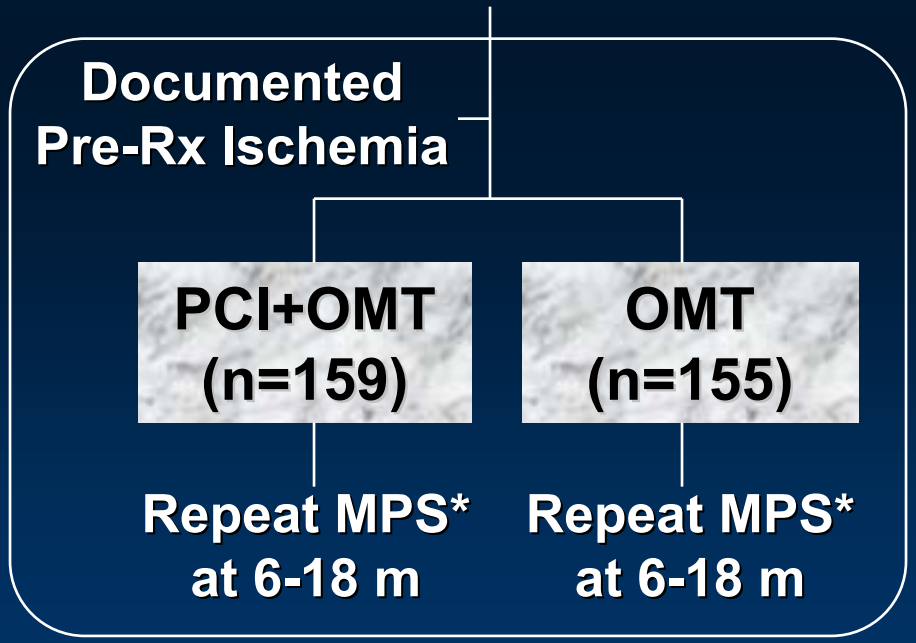
Medical Therapy	1138	1017	959	834	638	408	192	3
PCI	1149	1013	952	833	637	417	200	3

Nuclear Substudy (n=314/2,287)

Hypothesis: Reduction in Ischemia will be greater for patients randomized to PCI+OMT than for those randomized to OMT

Serial Rest/Stress Myocardial Perfusion SPECT (MPS)
To compare patient management strategy for ischemia reduction

- Pre-Rx = Off Meds
- 6-18m = On Meds



*Timing chosen to occur beyond window of in-stent restenosis & delayed to allow effects of medical Rx to be observed

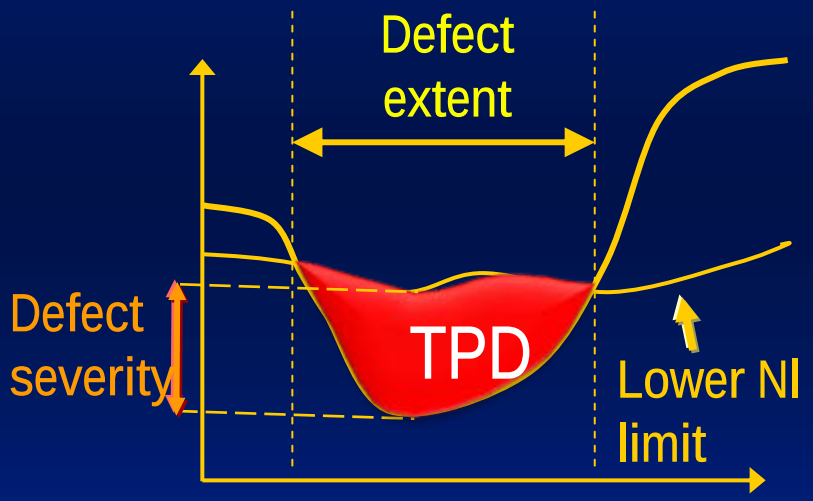
Shaw et al: J Nucl Cardiol 2006; 13:685-98

Mean = 374±50 days

Quantification of extent and severity of ischemia by nuclear perfusion study: total perfusion deficit (TPD)

% ischemic myocardium:
(stress TPD-rest TPD)

- < 5%: minimal ("no ischemia")
- 5.0%-9.9%: mild
- ≥ 10%: moderate-to-severe

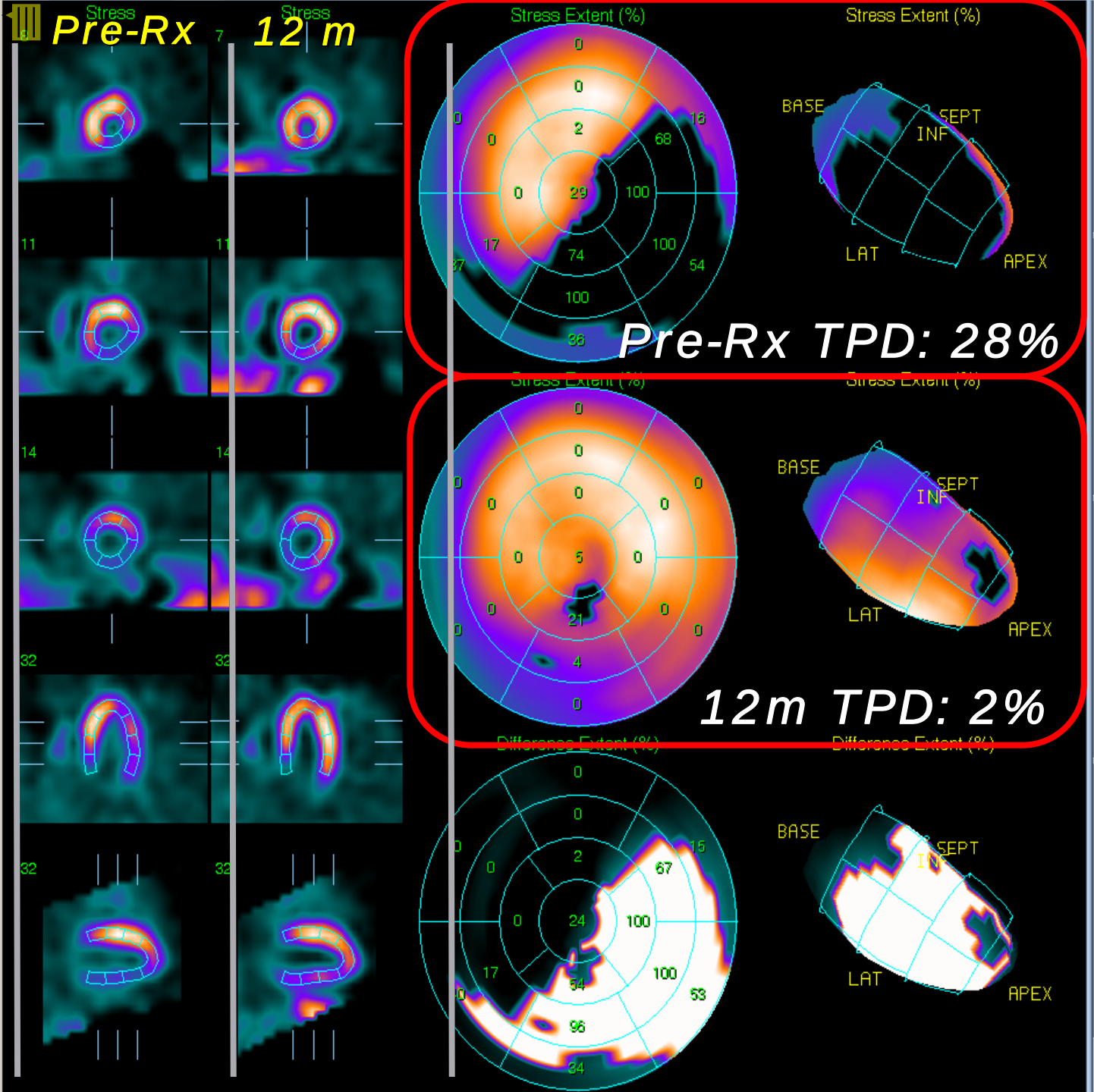


Significant reduction in ischemia:

- ≥5% reduction in ischemic myocardium*

*threshold exceeds test repeatability

Slomka et al. *J Nucl Cardiol* 2005;12:66-77

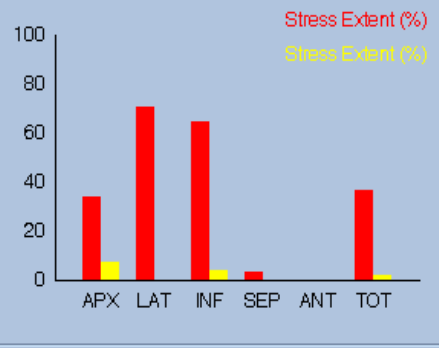


Name	Hidden 01
Pat ID	Hidden 01
Sex	MALE
Limits	--
TID	--
LHR	--
Change	--

SSS	24	SSS	6	SDS	18
SS%	35	SS%	9	SD%	26

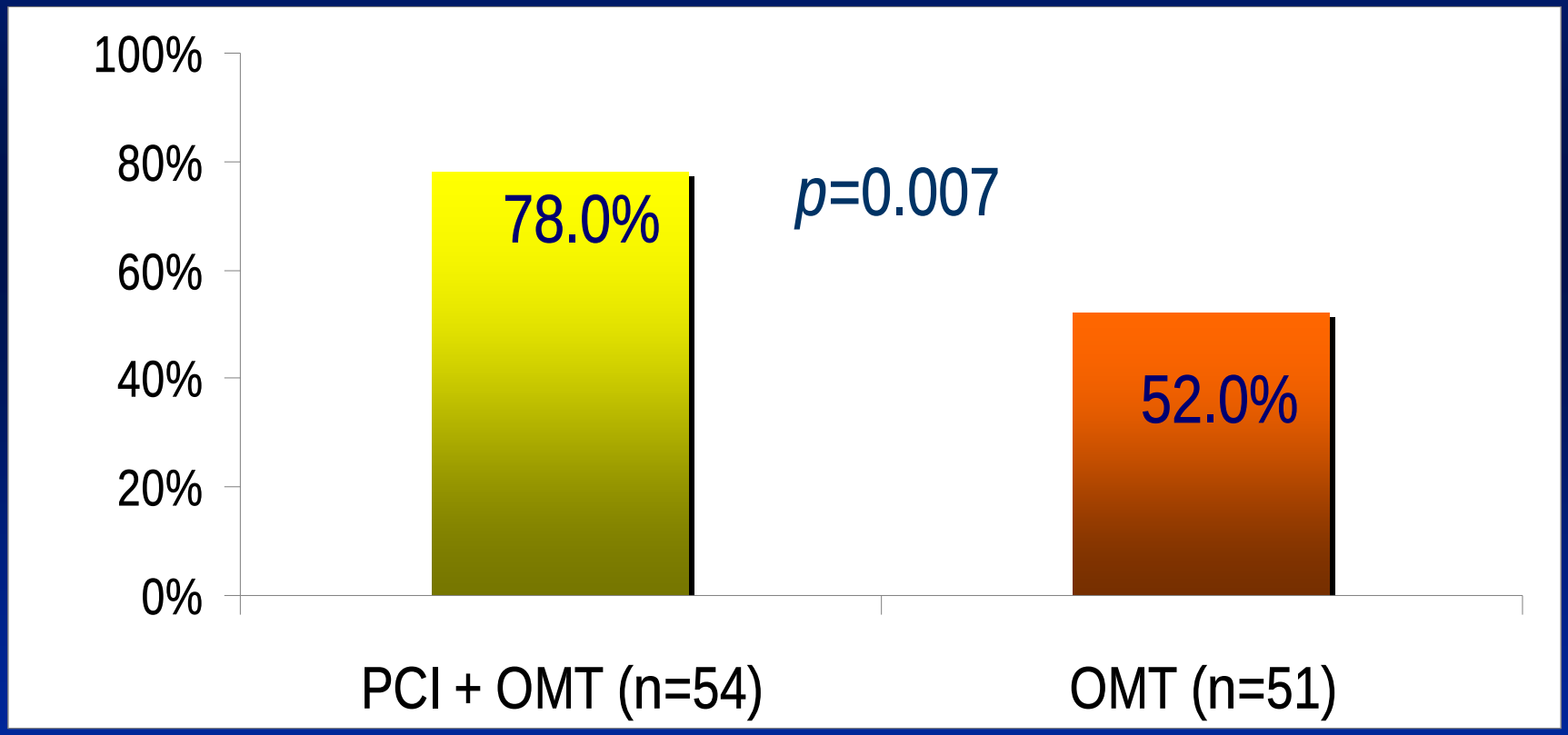
Study	STR ADENO MIBI
Dataset	Stress SAX 1
Date	0000-00-00
Limits	MaleStressMB
Volume	70ml
Wall	144ml
Defect	53ml
Extent	37%
TPD	28%
Shape	0.53 [SI], 0.86 [Ecc]

Study	STR ADENO MIBI
Dataset	Stress SAX 2
Date	2001-01-31 13:22
Limits	MaleStressMB
Volume	75ml
Wall	141ml
Defect	3ml
Extent	2%
TPD	2%
Shape	0.51 [SI], 0.88 [Ecc]

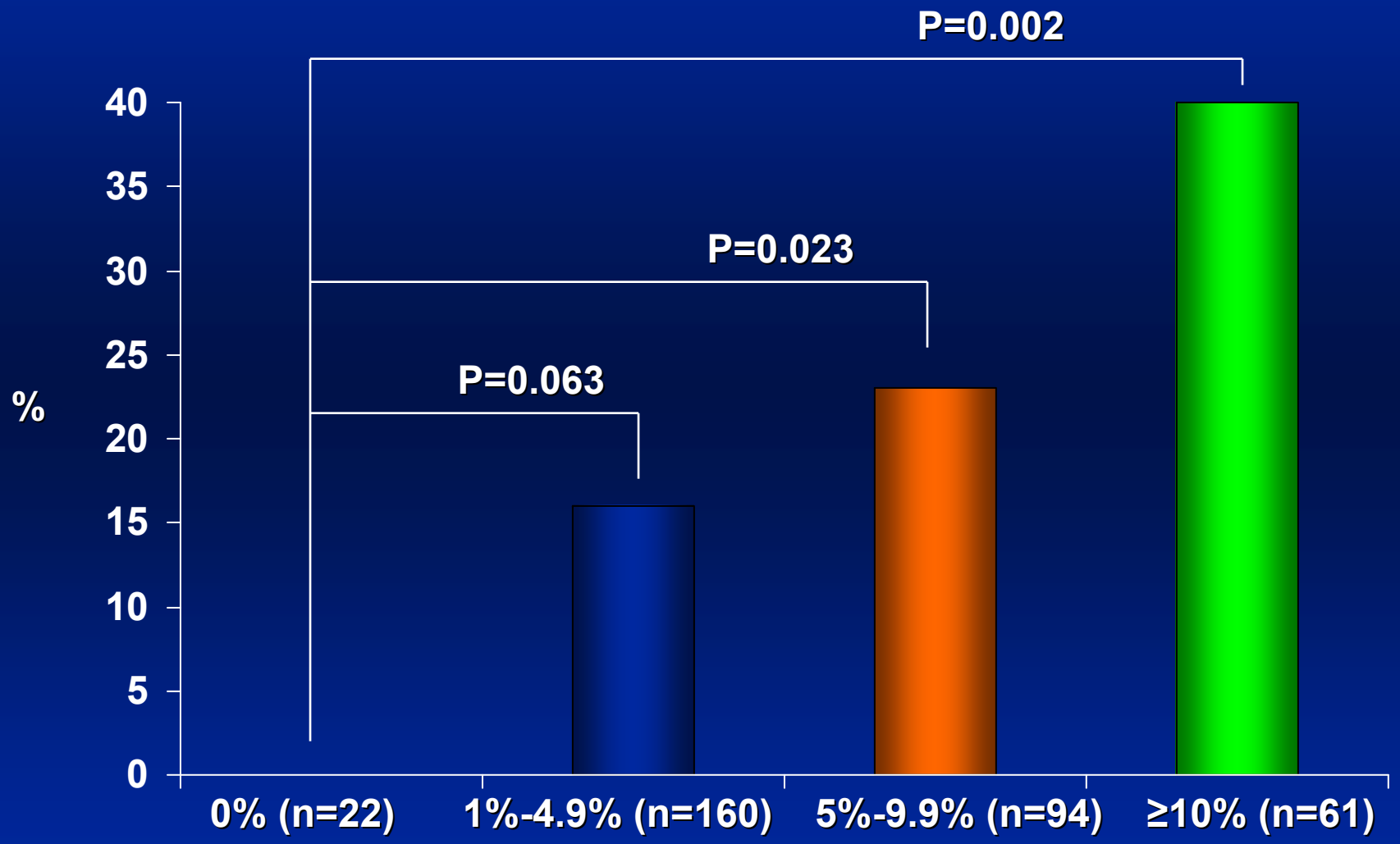


% with ischemia reduction ≥5% myocardium

(n=105 moderate-to-severe pre-Rx ischemia)

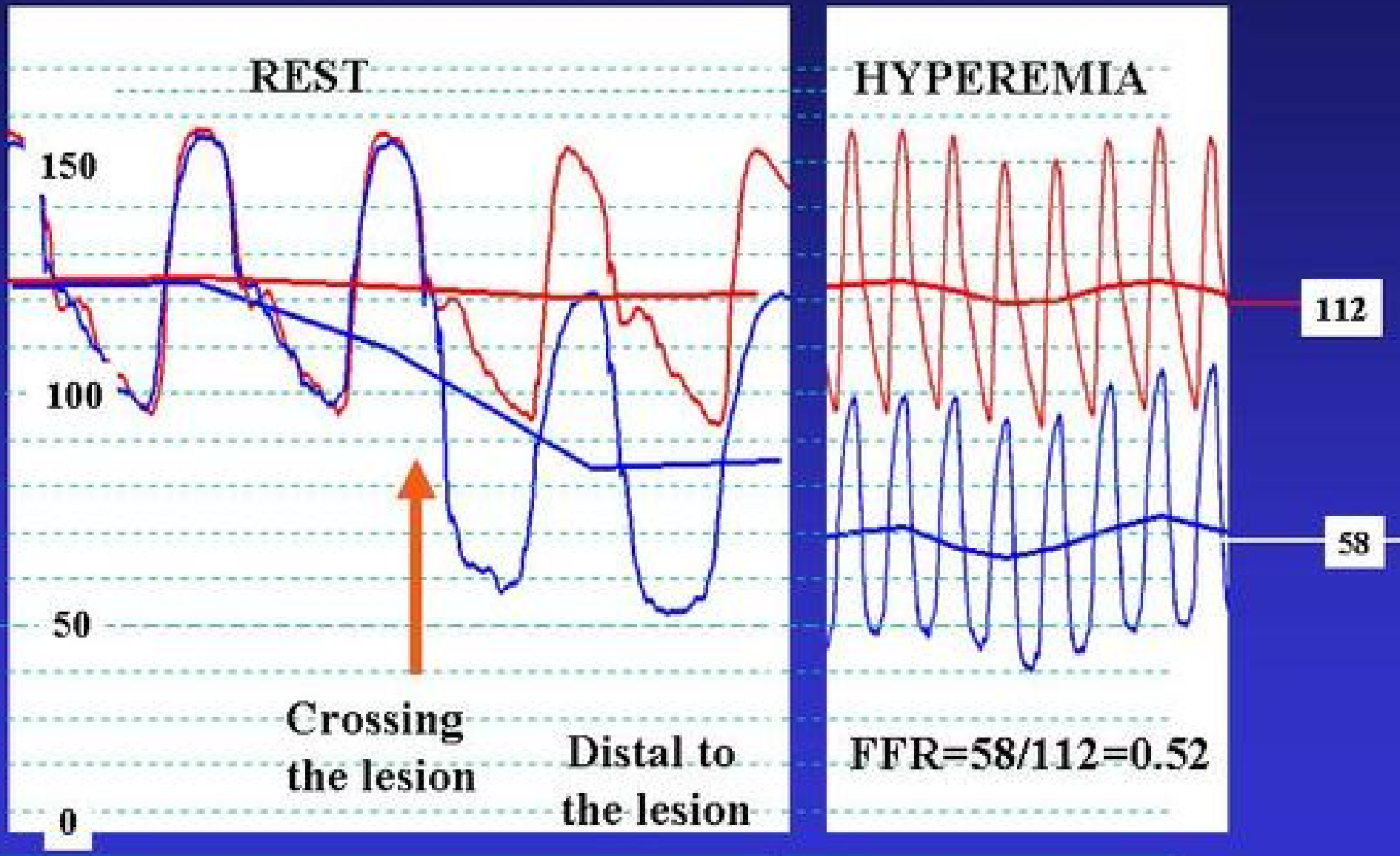


Rates of Death or MI by Residual Ischemia

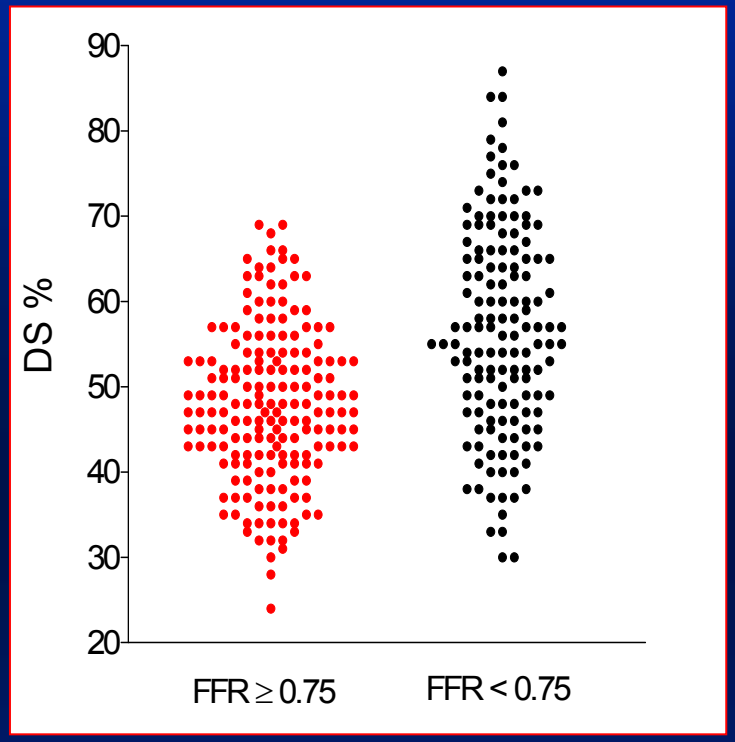


COURAGE Trial

Fractional Flow Reserve in Clinical Practice



Diameter Stenosis versus FFR



- Diameter stenosis is the main determinant of coronary stenosis

However

- Resistance is also influenced by lesion length and the 3D morphology of the stenosis

- Anatomical assessment is not accurate enough to determine physiological significance
- Coronary angiography provides only the anatomical data

FAME study: HYPOTHESIS

FFR guided Percutaneous Coronary Intervention (PCI) in multivessel disease, is superior to current angiography guided PCI

FAME study: Baseline Characteristics (2)

	ANGIO-group N=496	FFR-group N=509	P-value
# indicated lesions per patient	2.7±0.9	2.8±1.0	0.34
Reference diameter (mm)	2.5±0.6	2.5±0.7	0.81
% stenosis severity	61±17	60±18	0.24
MLD (mm)	1.0±0.4	1.0±0.5	0.35
50-70% narrowing, No (%)	550 (41)	624 (44)	-
70-90% narrowing, No (%)	553 (41)	530 (37)	-
90-99% narrowing, No (%)	207 (15)	202(14)	-
Total occlusion, No (%)	40 (3)	58 (4)	-
Patients with ≥1 total occlusion (%)	7.5	10.6	0.08

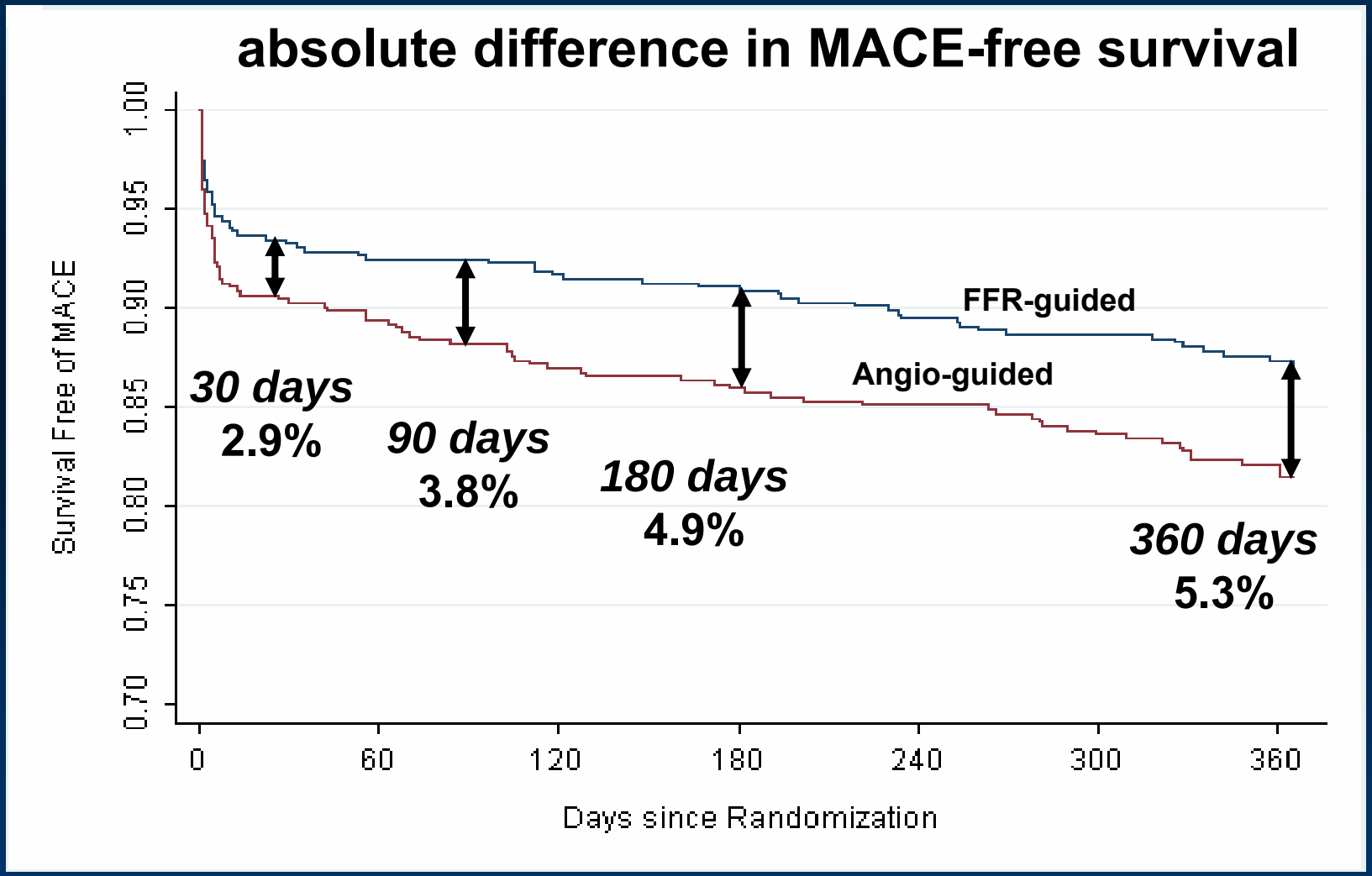
FAME study: Procedural Results (1)

	ANGIO-group N=496	FFR-group N=509	P-value
# indicated lesions per patient	**2.7 ± 0.9**	**2.8 ± 1.0**	0.34
FFR results			
Lesions succesfully measured, No (%)	-	**1329 (98%)**	-
Lesions with FFR ≤ 0.80 ,No (%)	-	**874 (63%)**	-
Lesions with FFR > 0.80 ,No (%)	-	**513 (37%)**	-

FAME study: Procedural Results (1)

	ANGIO-group N=496	FFR-group N=509	P-value
# indicated lesions per patient	2.7 ± 0.9	2.8 ± 1.0	0.34
FFR results			
Lesions succesfully measured, No (%)	-	1329 (98%)	-
Lesions with FFR ≤ 0.80 ,No (%)	-	874 (63%)	-
Lesions with FFR > 0.80 ,No (%)	-	513 (37%)	-
stents per patient	2.7 ± 1.2	1.9 ± 1.3	<0.001
Lesions succesfully stented (%)	92%	94%	-
DES, total, No	1359	980	-

FAME study: Event-free Survival



Impact of revascularization on outcome - controversial

- Anatomic obstruction with documented ischemic physiology
  - Long term outcome is **better** with PCI compared to OMT
    - COURAGE nuclear substudy, FAME
- Anatomic obstruction without documented ischemic physiology
  - Long term outcome is **worse** with PCI compared to OMT
    - DEFER, FAME

תודה רבה