Chronic Ischemic Heart Disease

Professor Yoseph Rozenman
The E. Wolfson Medical Center

Fellows course, November 2008

OUTLINE

- Pathophysiology
  - Atherosclerosis
  - Ischemia
- Therapy
  - Lifestyle
  - Pharmacology
  - Revascularization

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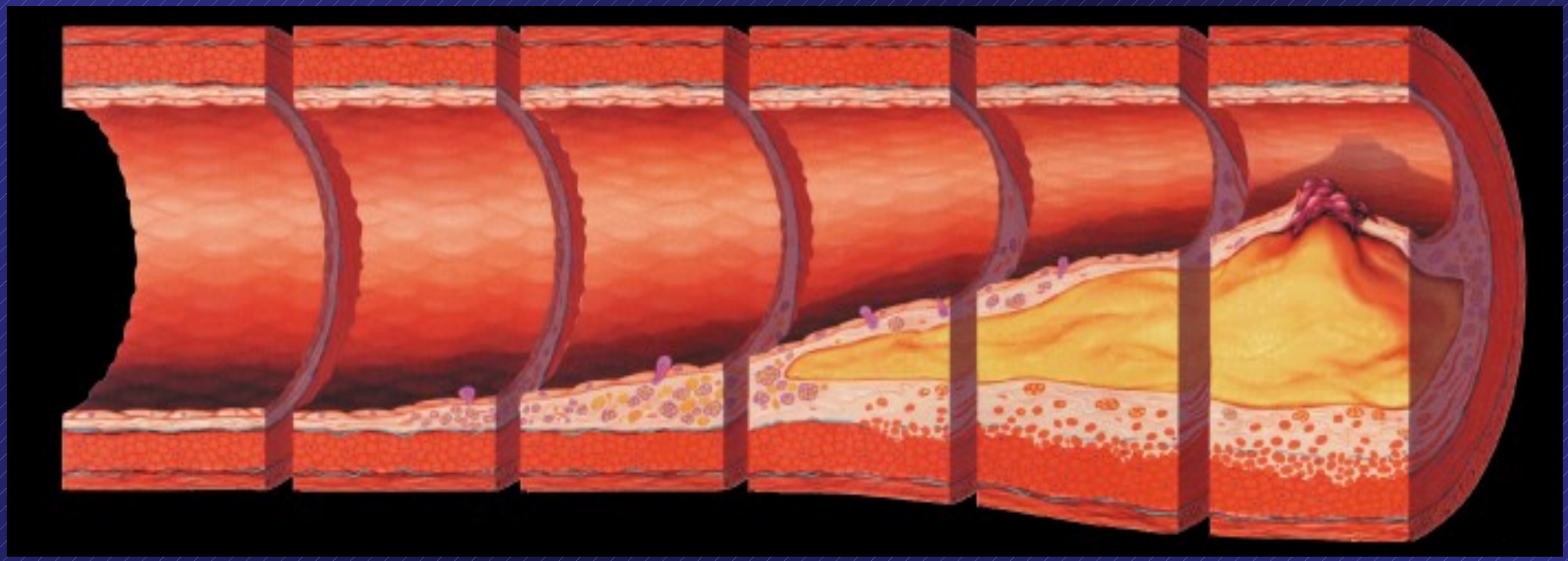
Atherosclerosis Timeline

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



Endothelial Dysfunction

From First Decade

From Third Decade

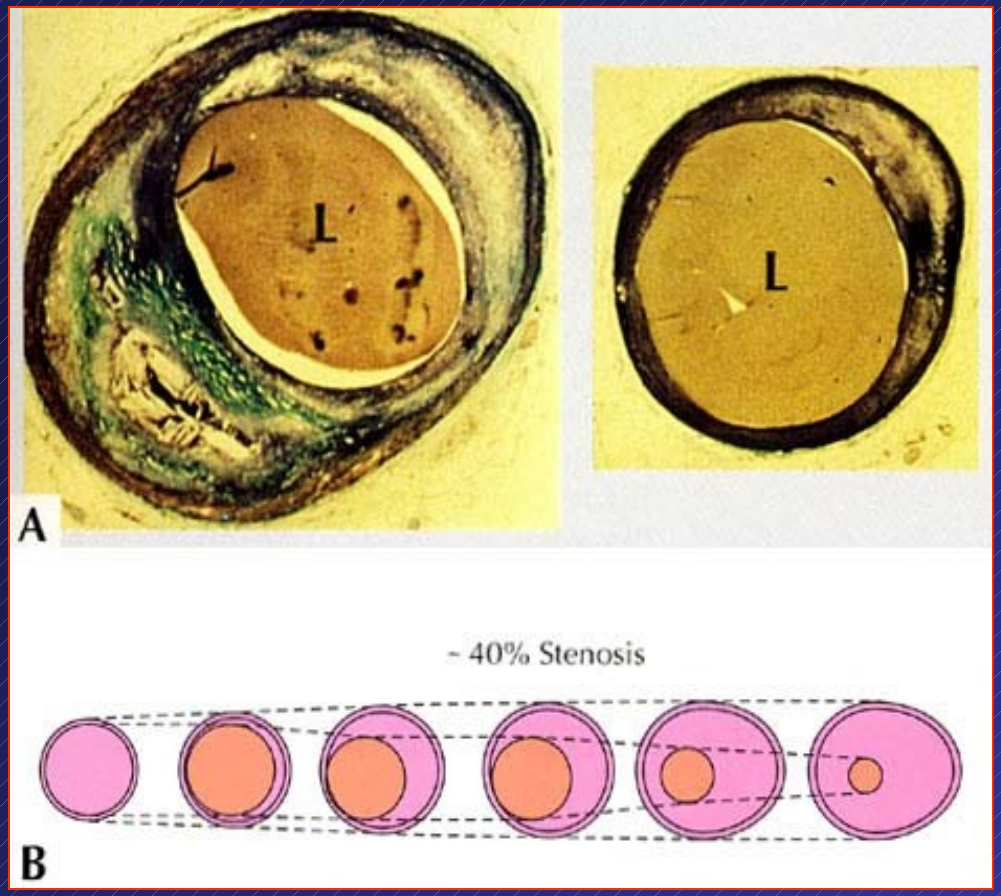
From Fourth Decade

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,

Myocardial Ischemia

- Oxygen demand
- Oxygen supply

Distribution and determinants of myocardial oxygen consumption

Components of myocardial oxygen consumption

Basal	20%	Volume work	15 %
Electrical	1 %	Pressure work	64 %

Effect of 50% increase on oxygen consumption

Wall stress	25%	Heart rate	50 %
Contractility	45 %	Volume work	4 %
Pressure work	50 %		

Increase in heart rate and pressure work are the main deteminants of oxygen consumption thus: Double product = HR X SBP is a good clinical estimate for myocardial oxygen demand

Oxygen Supply
myocardium vs other tissues

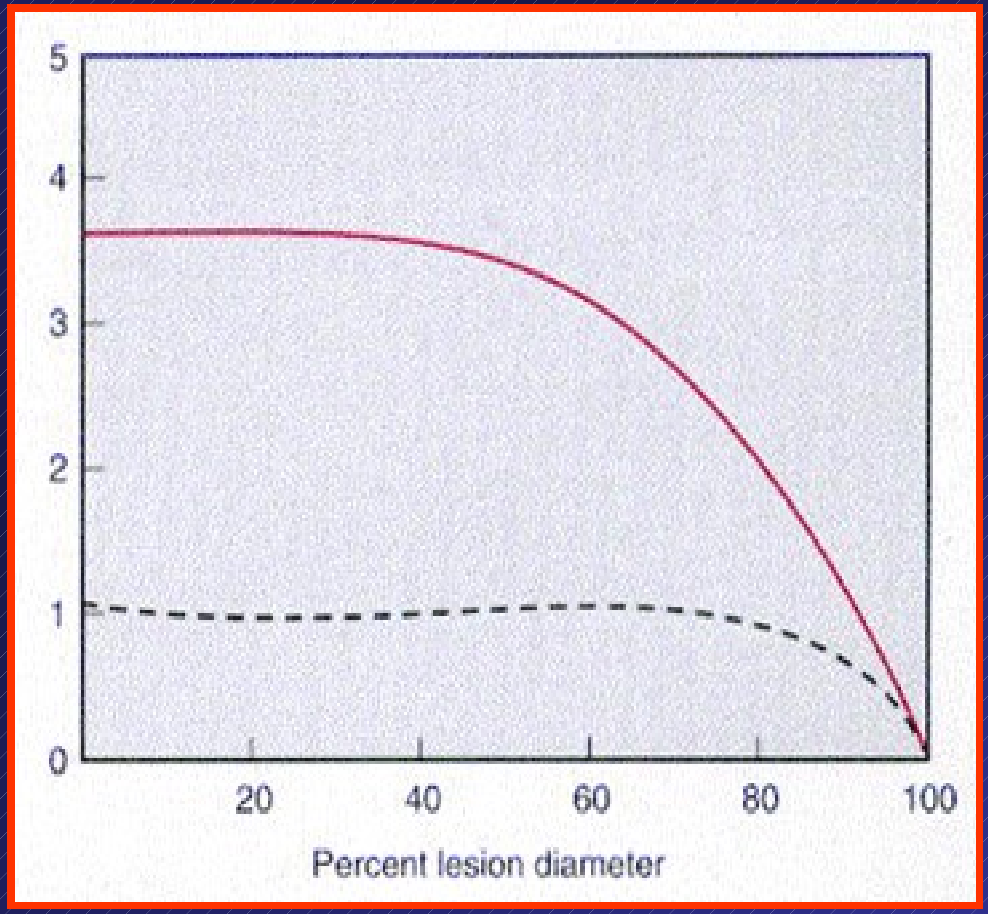
- O_2 Delivery
  - Coronary Blood Flow
  - Hemoglobin
  - Arterial O_2 saturation
- Myocardial (A-V) O_2 Difference

- 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.

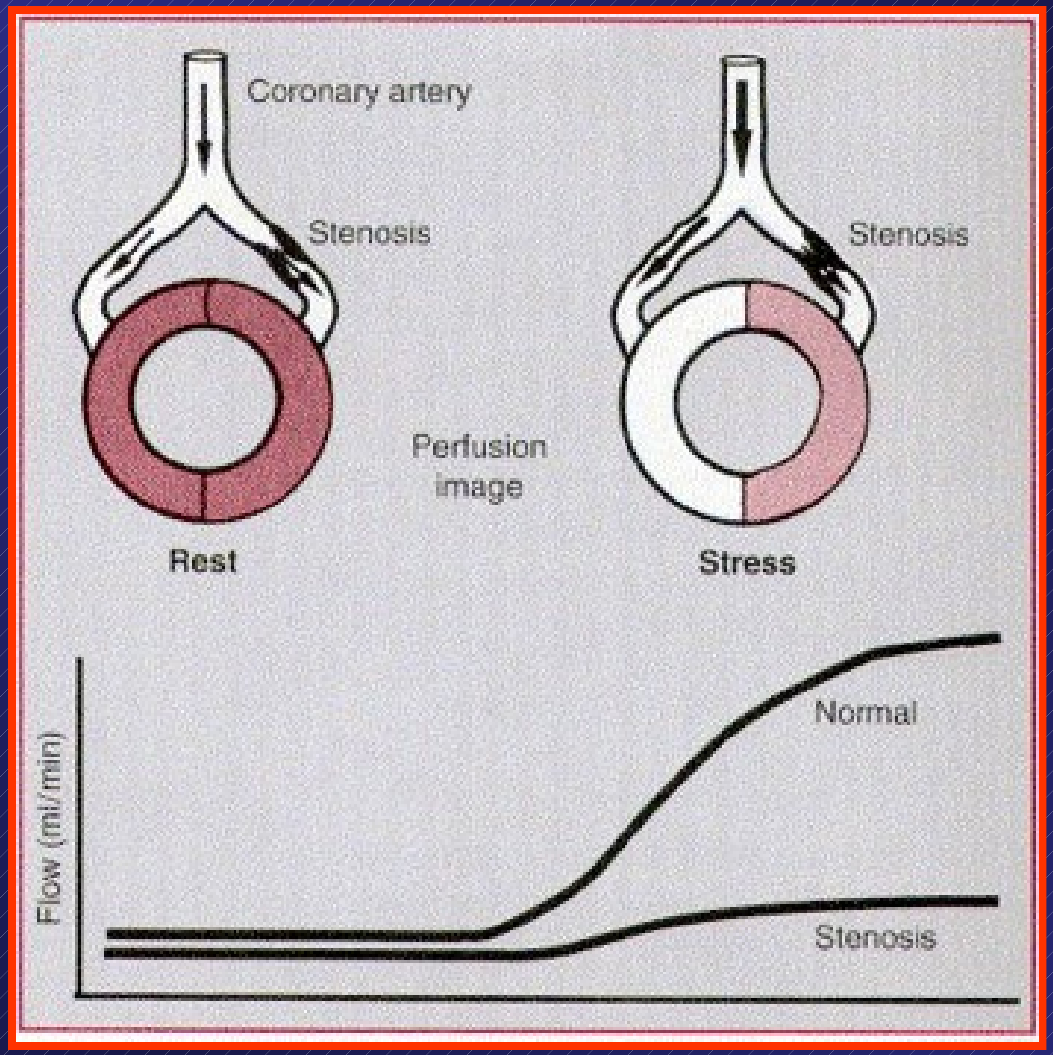
Impact of diameter stenosis on resting and maximal coronary flow (flow reserve)

Normalized flow reserve

Normalized resting flow

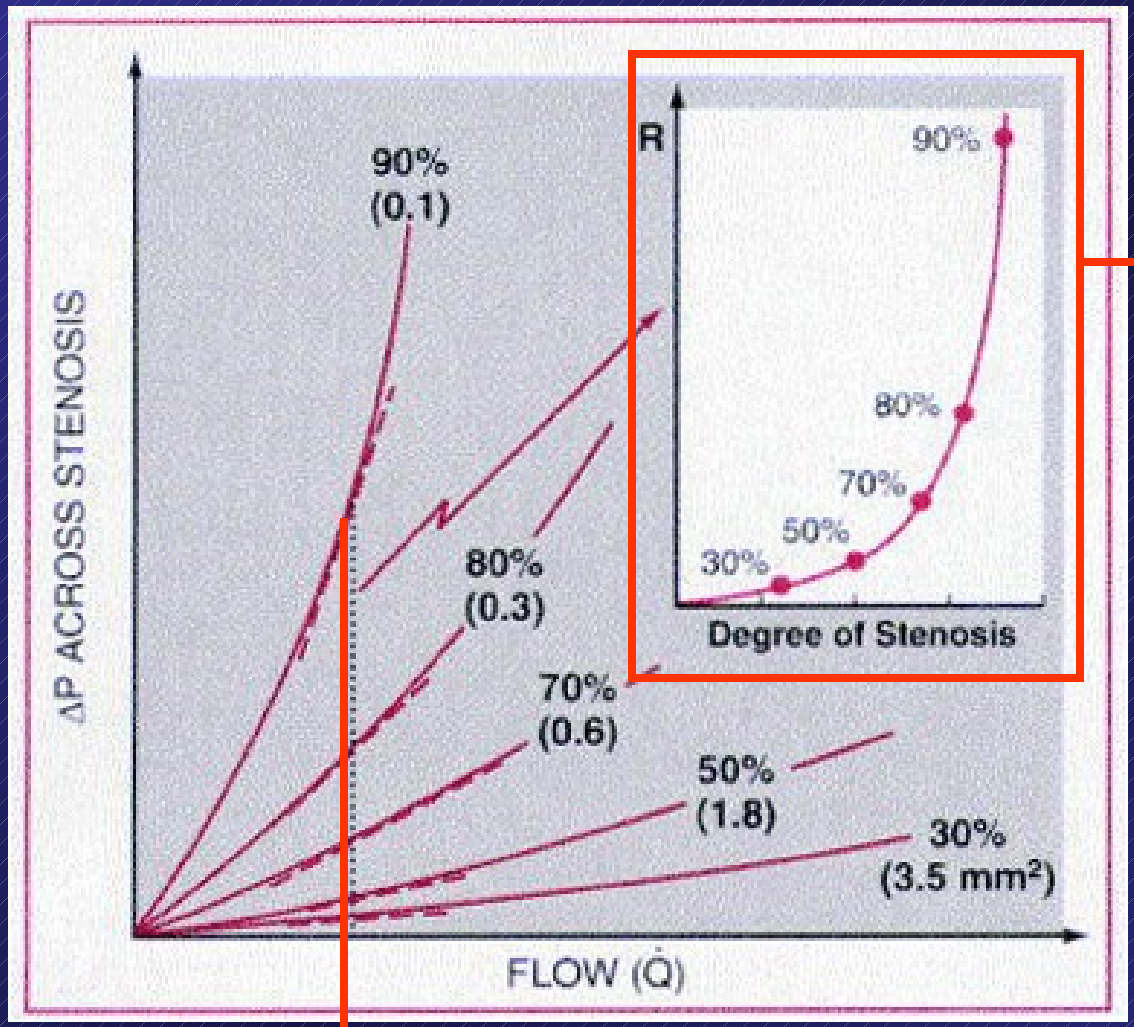


Mechanism of stress induced perfusion mismatch



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

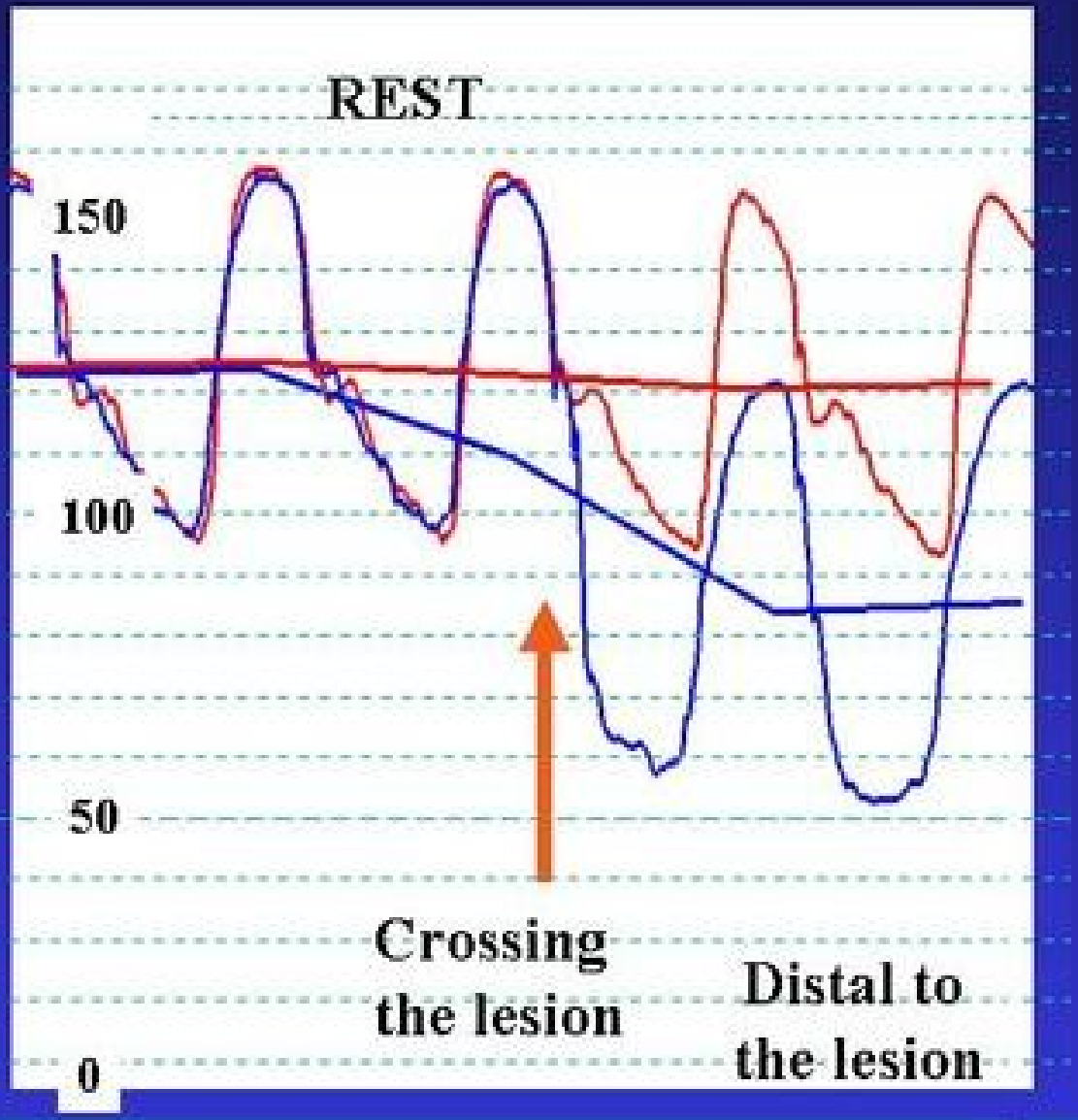
Relation between pressure gradient and flow for increasing % stenosis



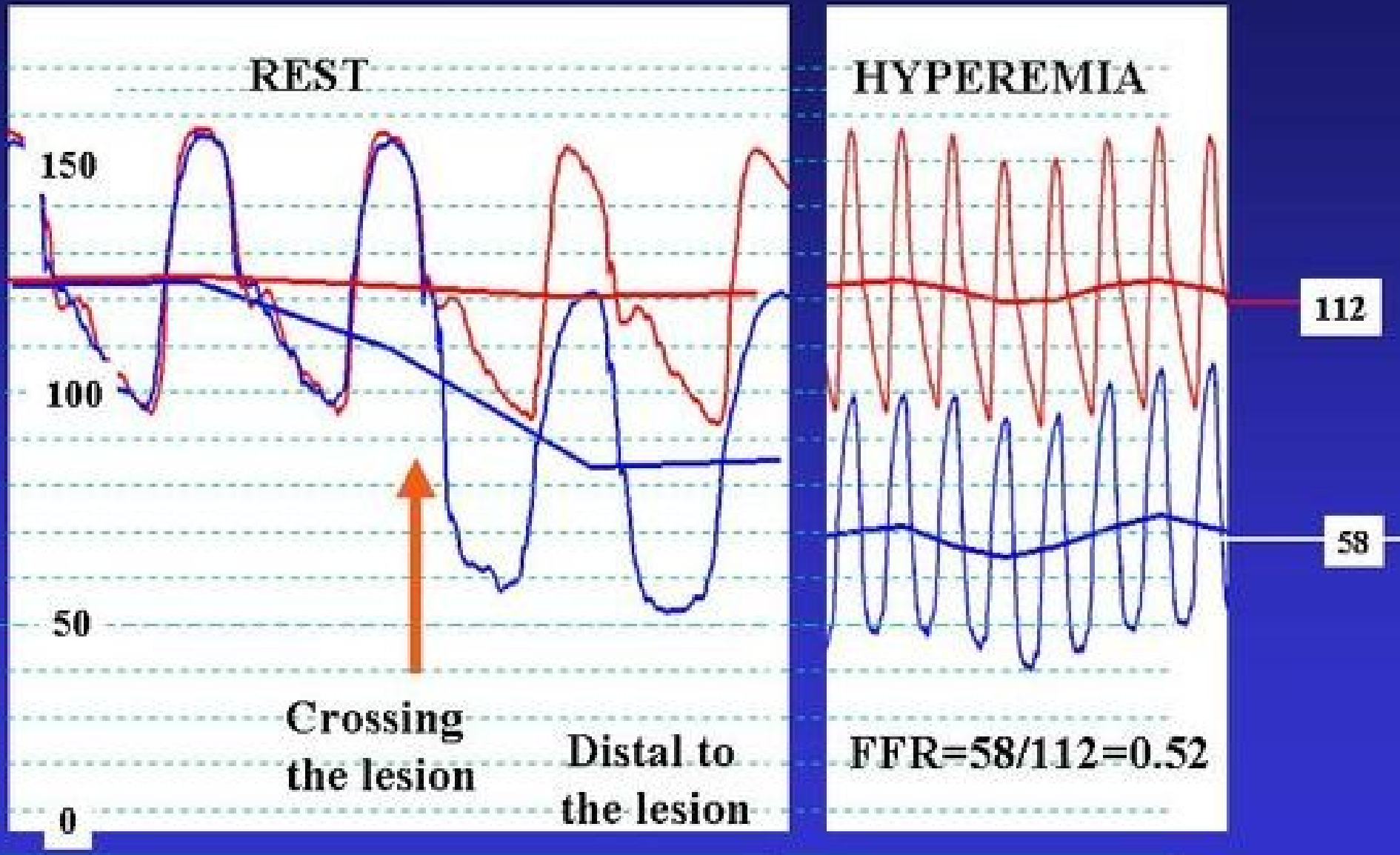
Resting flow

Resting flow

Fractional Flow Reserve in Clinical Practice



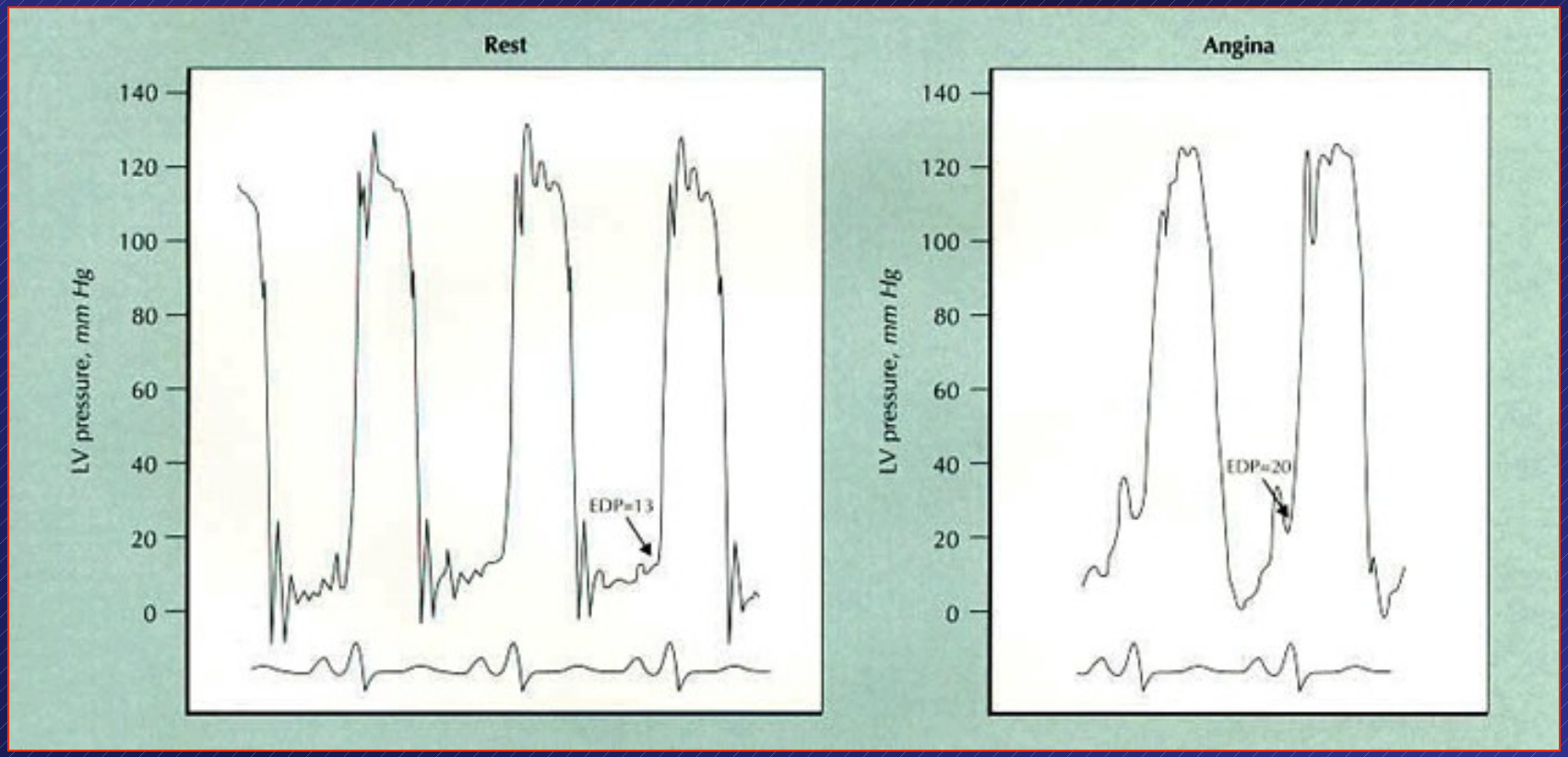
Fractional Flow Reserve in Clinical Practice



Consequences of Acute Coronary Ischemia

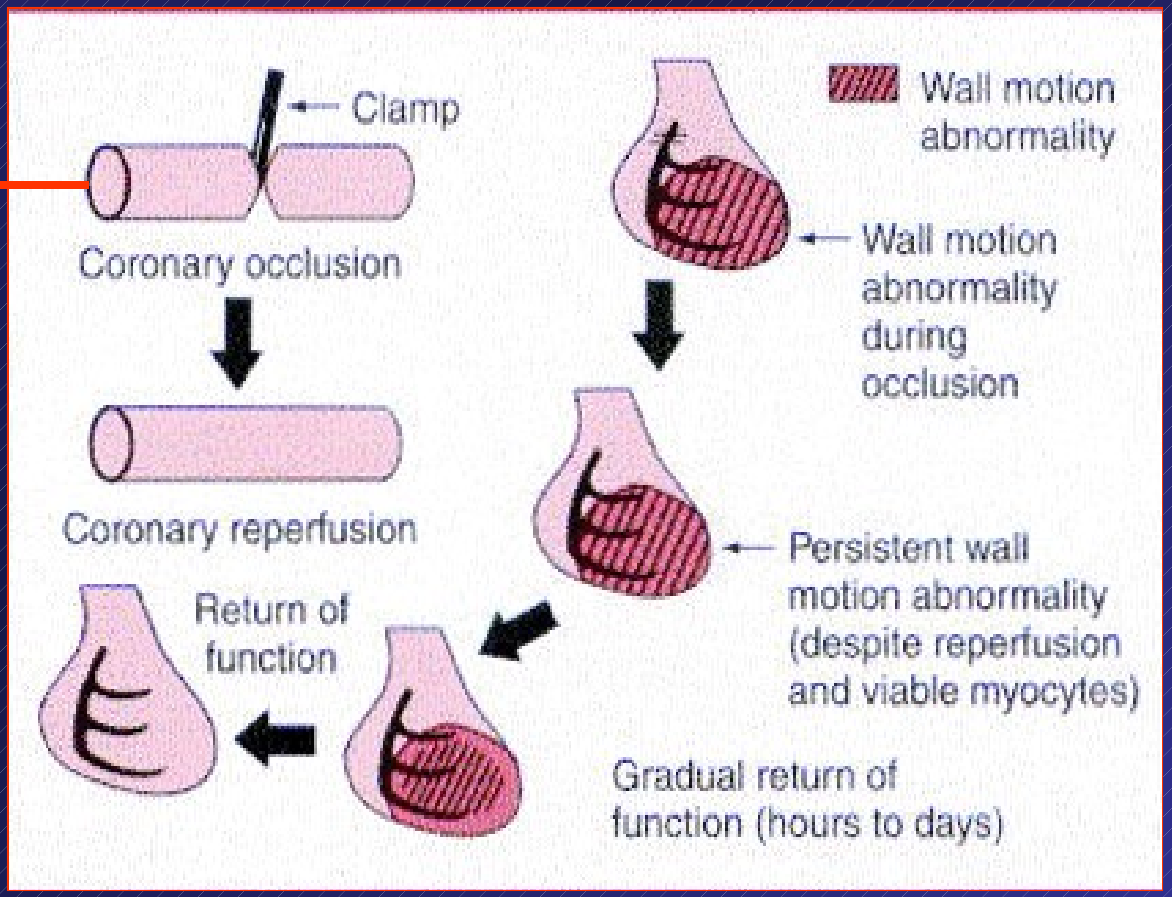
- Typically causes ECG changes, myocardial dysfunction (diastolic and systolic) and symptoms of chest pain.
- Causes prolonged? dysfunction (stunning)
- Magnitude of effect modified by adaptive mechanisms (smart heart)
  - Hybernation (adaptation of mechanical function to flow limitation)
  - Preconditioning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

LV pressure during ischemia



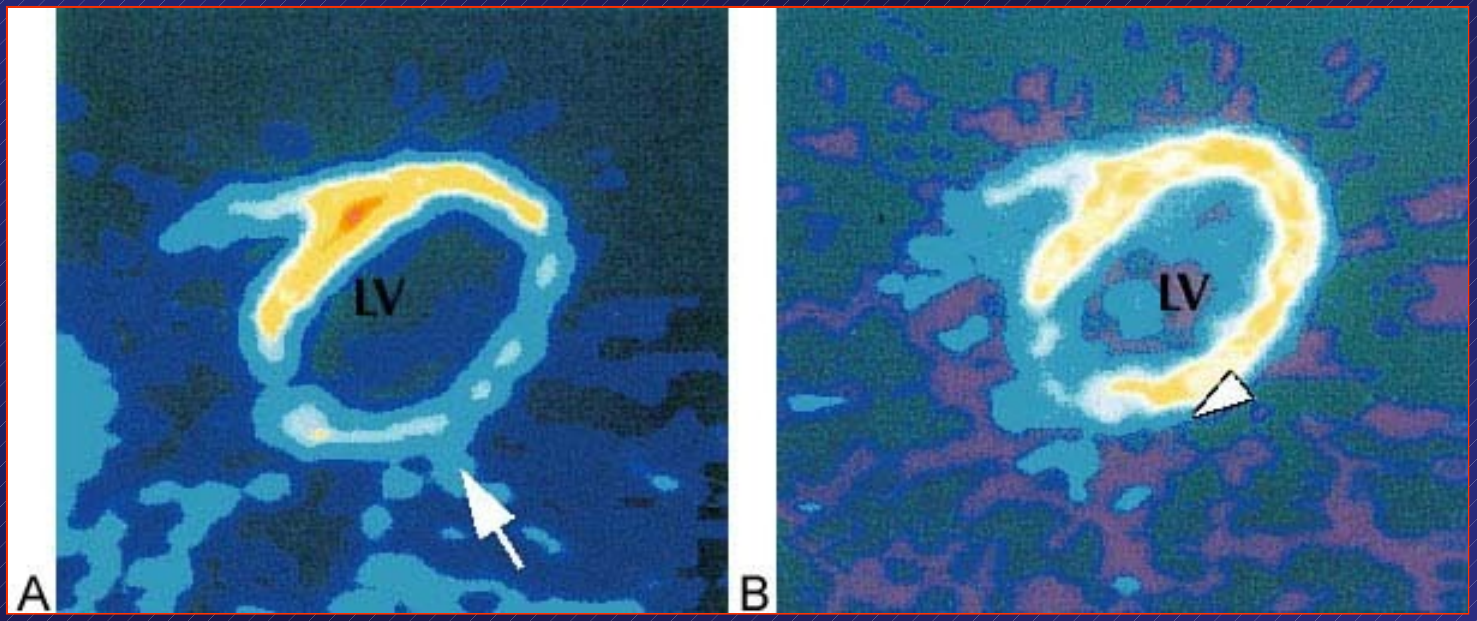
Myocardial Stunning

Can also be triggered by an episode of ischemia due to an increase in demand (e.g. post exercise)



Hibernating Myocardium (PET)

Perfusion **Metabolism**



[^{13}N]-ammonia scan demonstrates a large anterolateral perfusion defect

[^{18}F]-fluorodeoxyglucose image demonstrates preserved anterolateral metabolic activity

שאלה 1:חולה עם מחלה כלילית מתנגד לבצע מבחן מאמץ בטענה שמנסיונו בעבר גורם לו המבחן לחולשה וקוצר נשימה למשך יממה – מה ההסבר המתקבל ביותר על הדעת?

1. אין סיבה אורגנית
2. התקף לב בעקבות המאמץ
3. איסכמיה חריפה מתמשכת
4. Stunning
5. העדר preconditioning

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 (repeated stunning?)

OUTLINE

- Pathophysiology
  - Atherosclerosis
  - Ischemia
- Therapy
  - Lifestyle
  - Pharmacology
  - Revascularization

Aims of Treatment

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

Modes of Treatment General and Specific for CAD

- Life style modification
- Pharmacological therapy
- Non-pharmacological
  - Revascularization
    - Surgical, PCI
  - Others

Aims and Modes of Treatment
From the Guidlines

- **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 Guidlines

- **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

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

Therapy with Statins

Relation between atherosclerosis progression and clinical outcome

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

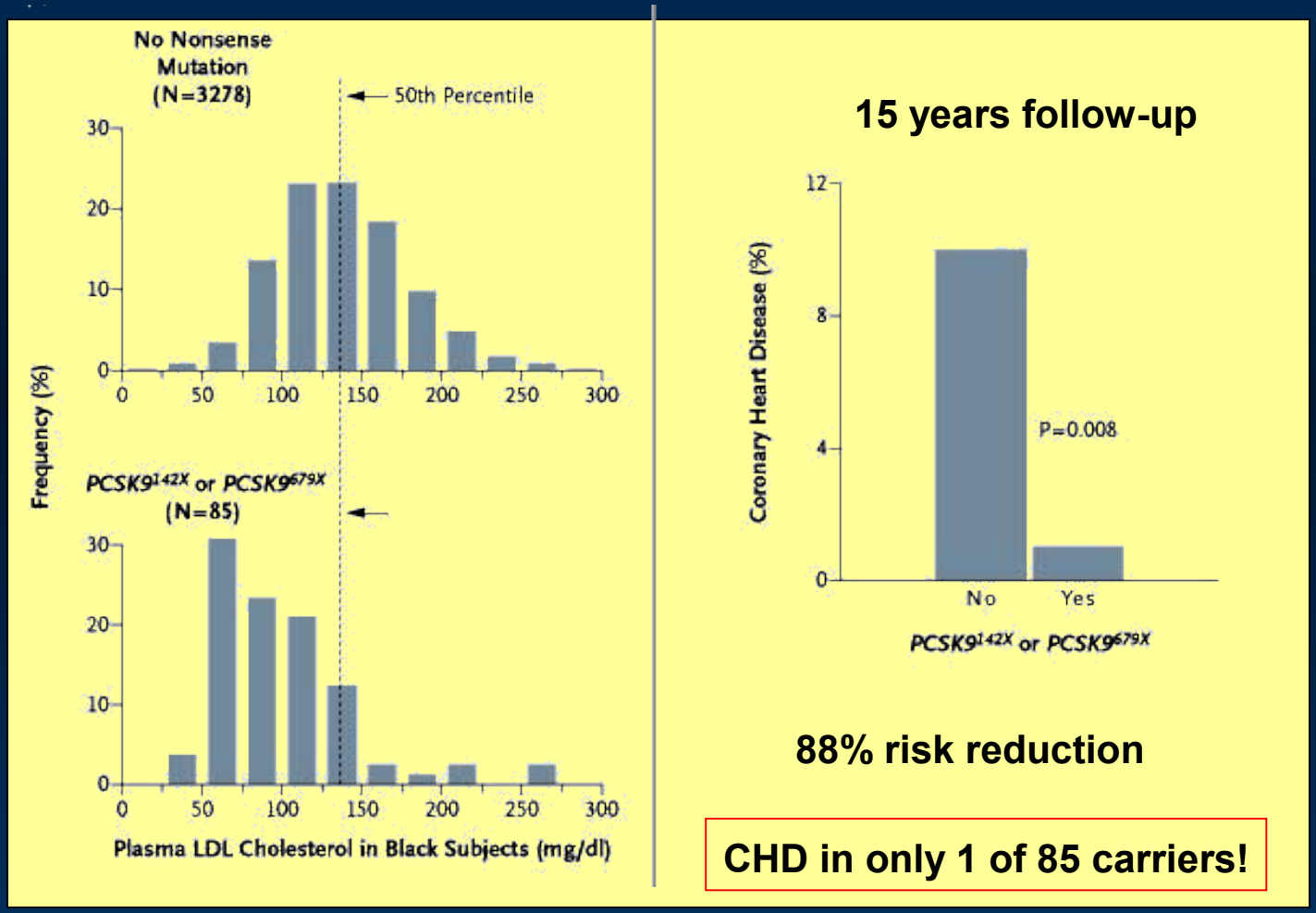
Cohen, J. et al. N Engl J Med 2006;354:1264-1272

- 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

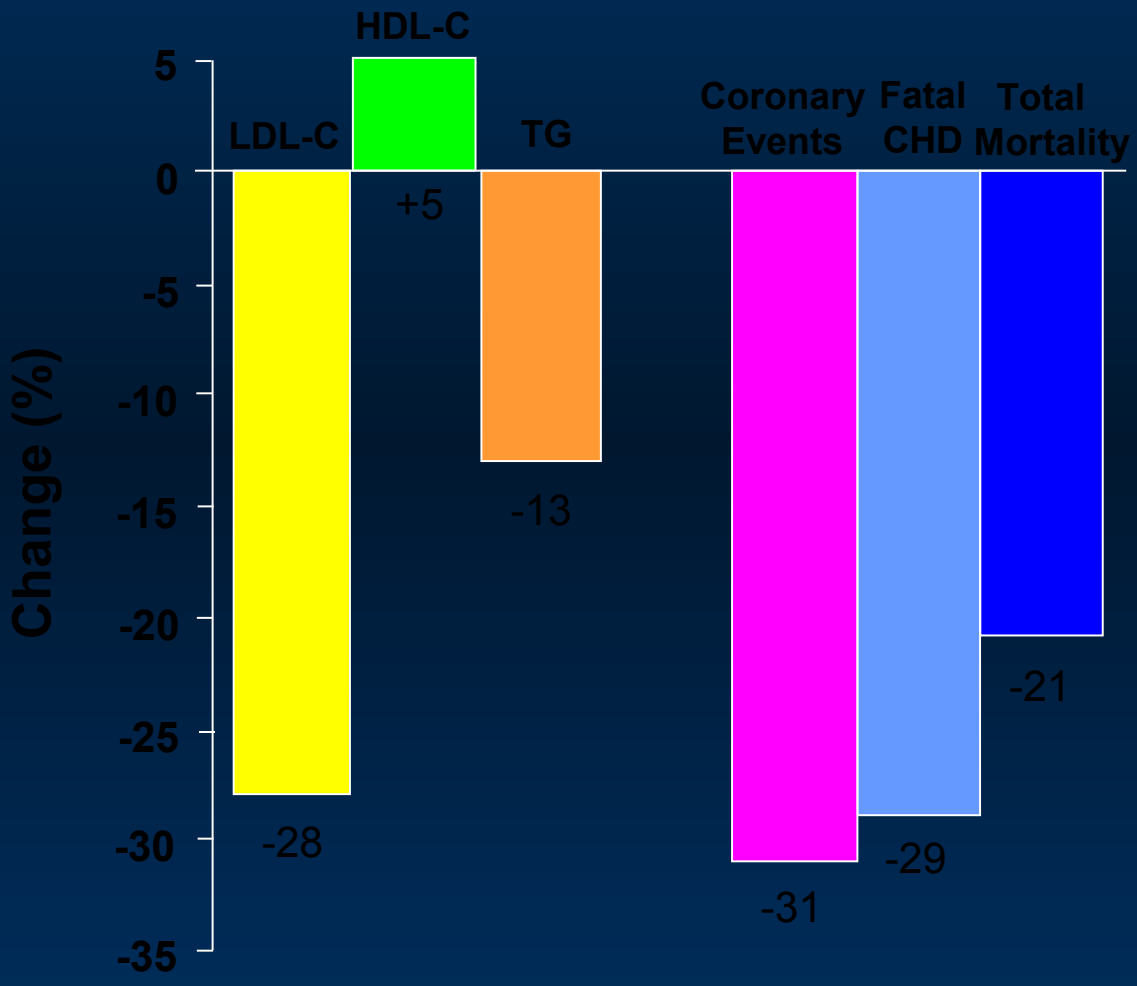
Carriers and noncarriers of PCSK9 nonsense mutation



Plasma LDL-C 28% lower in carriers

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

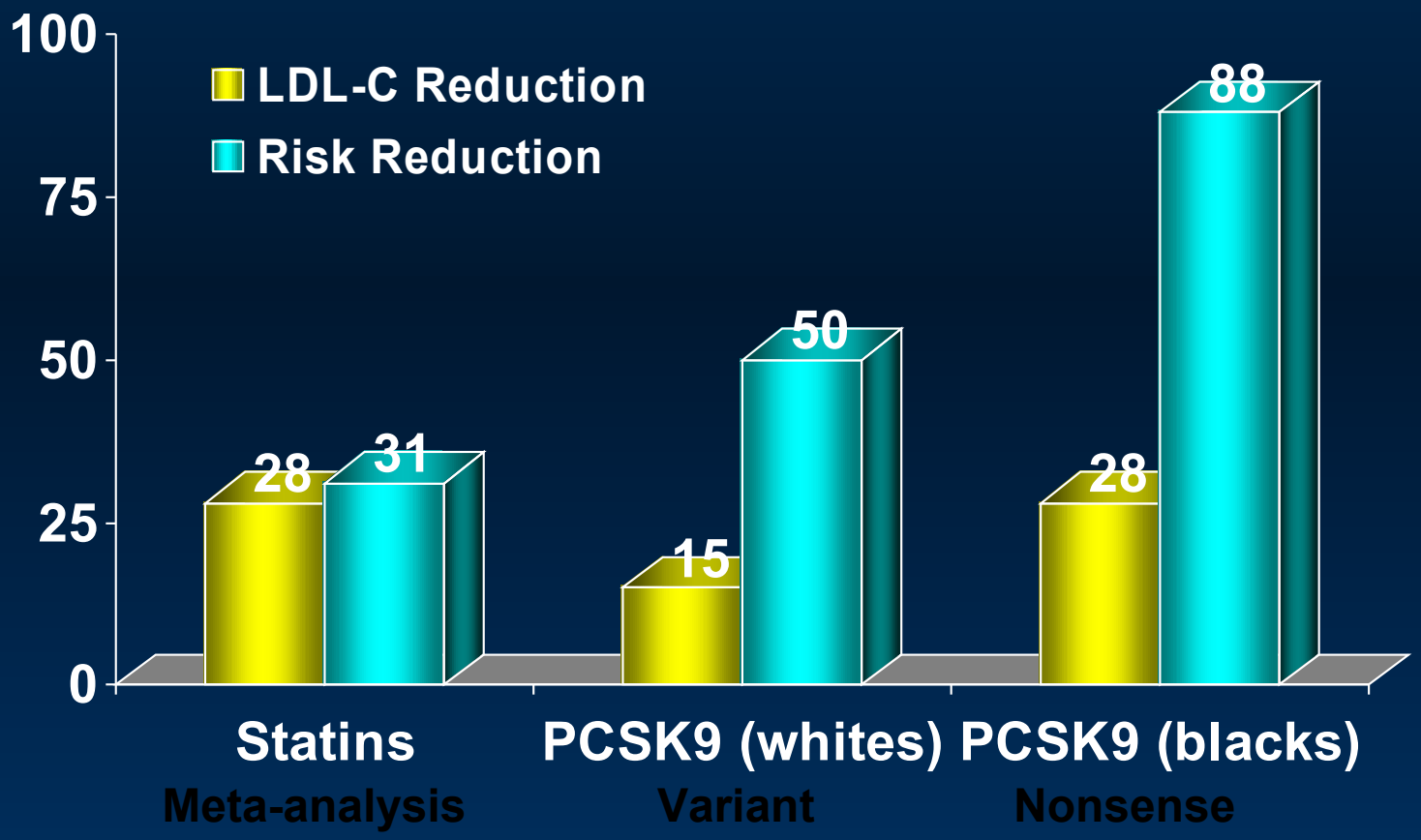
Meta-analysis of Statin Trials



LaRosa JC et al. *JAMA*. 1999;282:2340-2346.

Relation Between Reduction of LDL-C and Cardiovascular Risk Reduction

Statins as compared to PCSK9 mutation



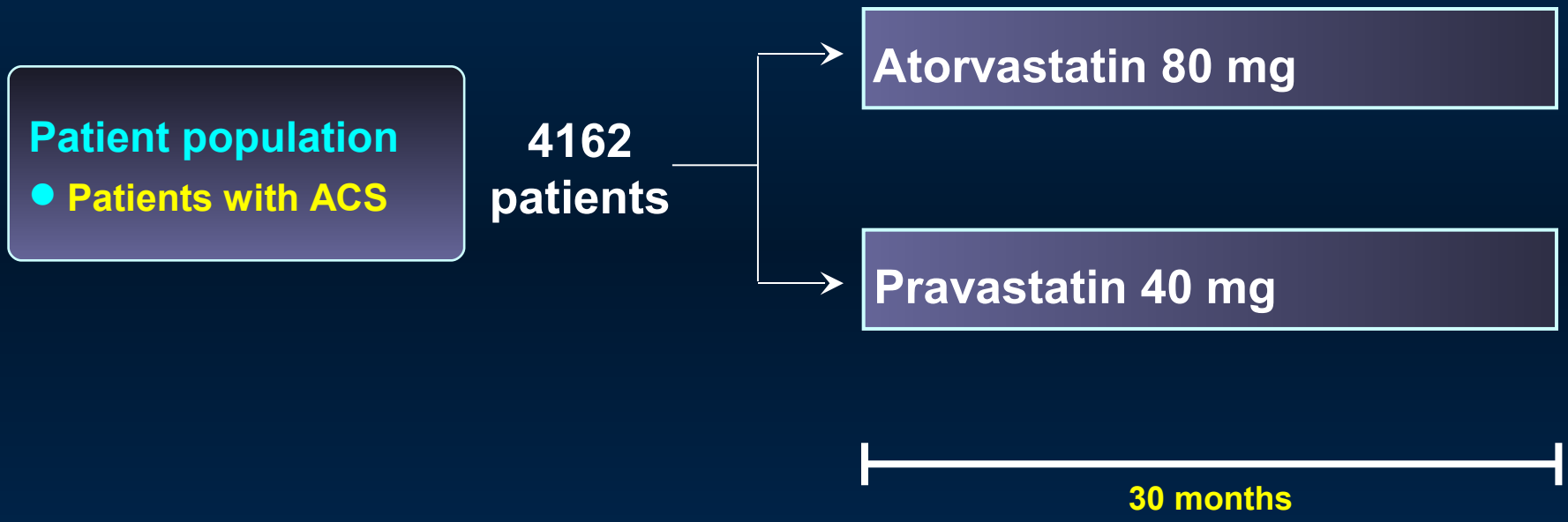
Atherosclerosis Progression Implication for therapy

- 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

Role of LDL reduction Correlation between Clinical Outcome and IVUS Data

- PROVE-IT
  - Clinical Outcome
- REVERSAL
  - IVUS data

PROVE-IT – TIMI 22

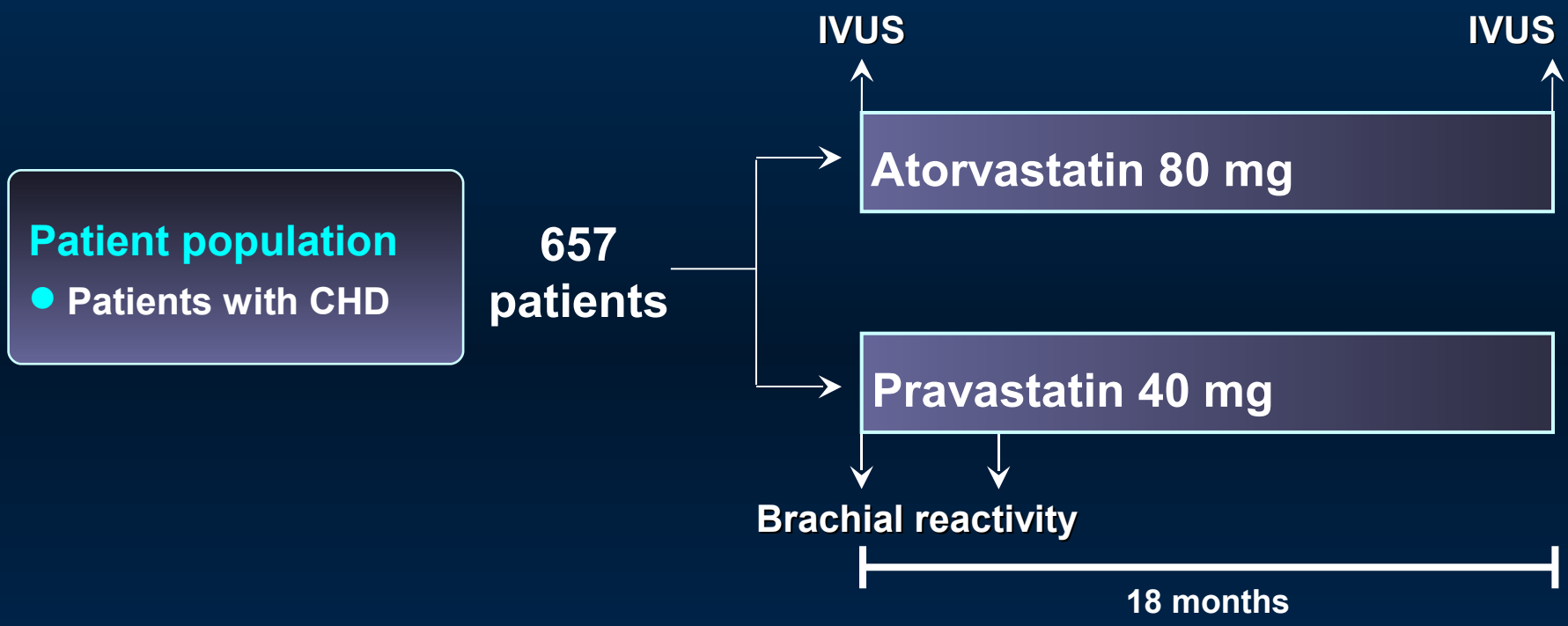


Primary endpoint:

- Death, MI, Documented UA requiring hospitalization, revascularization (> 30 days after randomization), or Stroke

REVERSAL

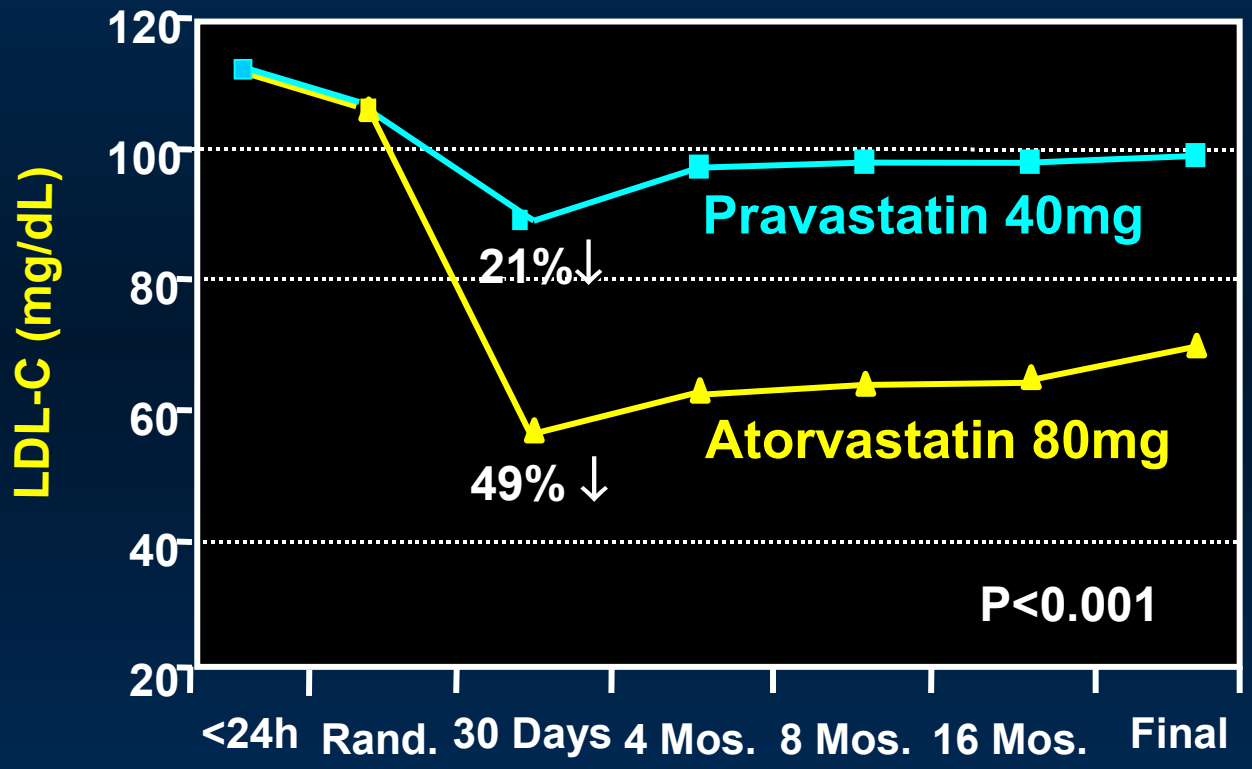
REVERSing Atherosclerosis with Aggressive Lipid Lowering



Primary endpoint:

- Change in coronary plaque volume by IVUS

Changes from (Post-ACS) Baseline in Median LDL-C

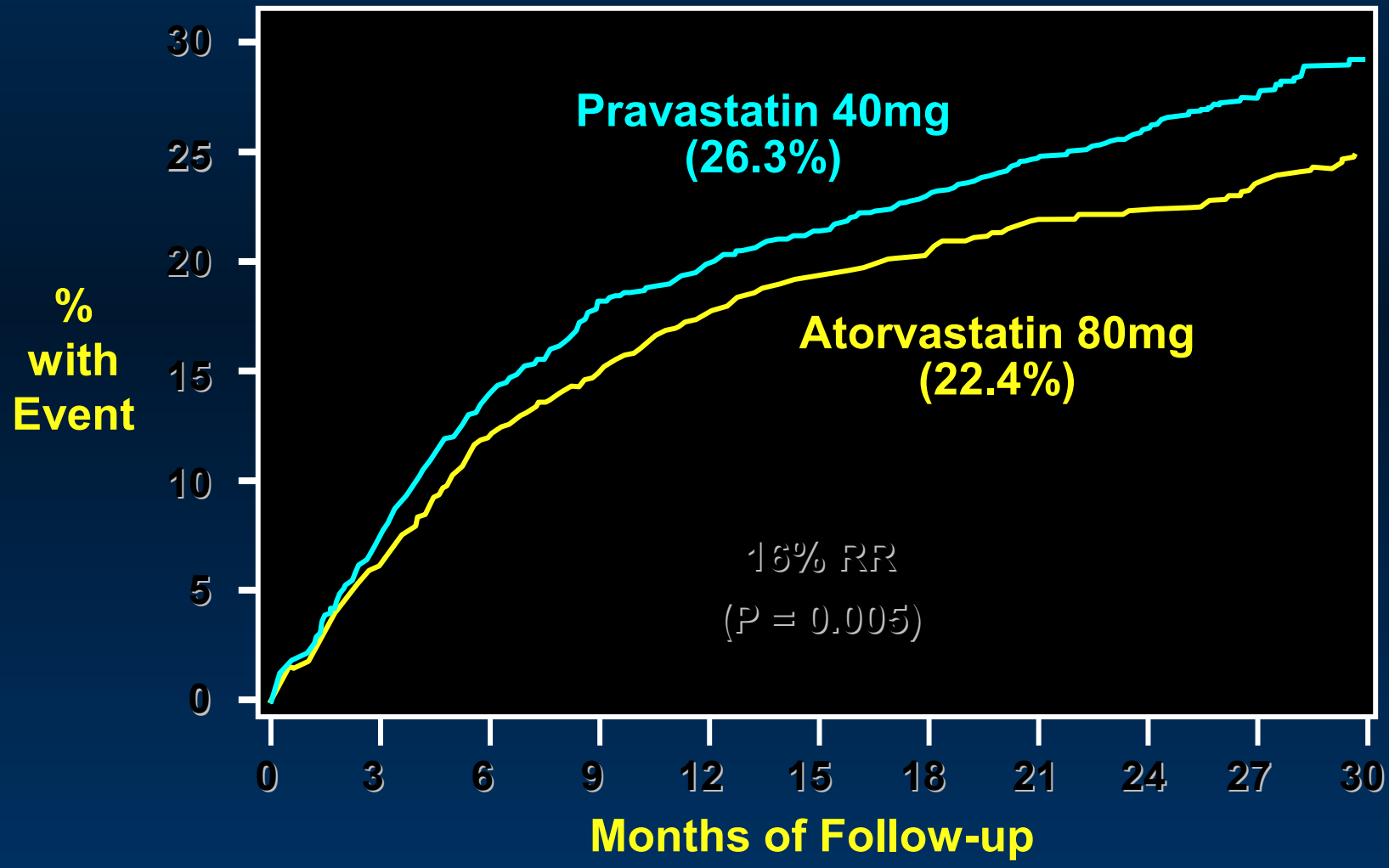


Median LDL-C (Q1, Q3)
95 (79, 113)
62 (50, 79)

Note: Changes in LDL-C may differ from prior trials:

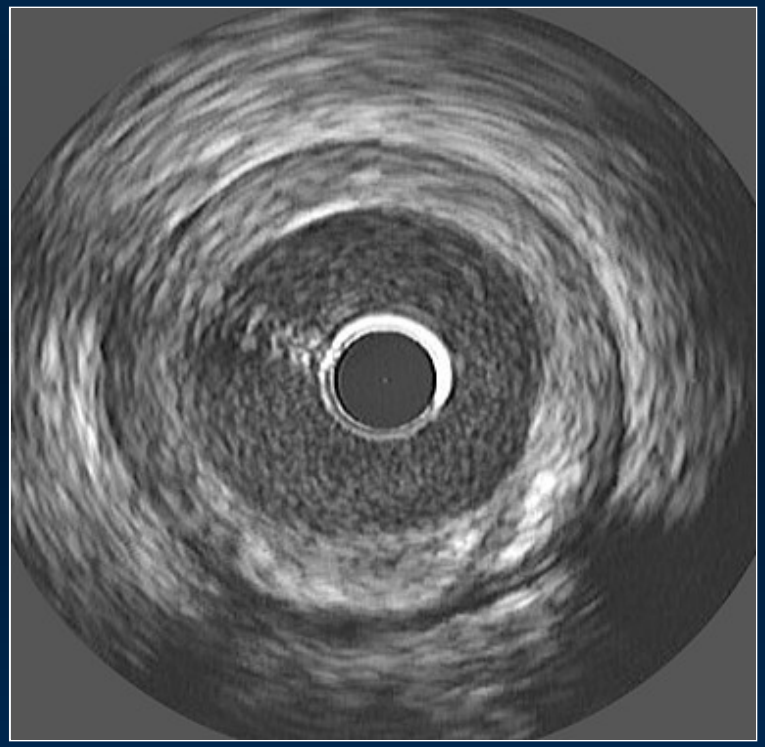
- **25% of patients on statins prior to ACS event**
- **ACS response lowers LDL-C from true baseline**

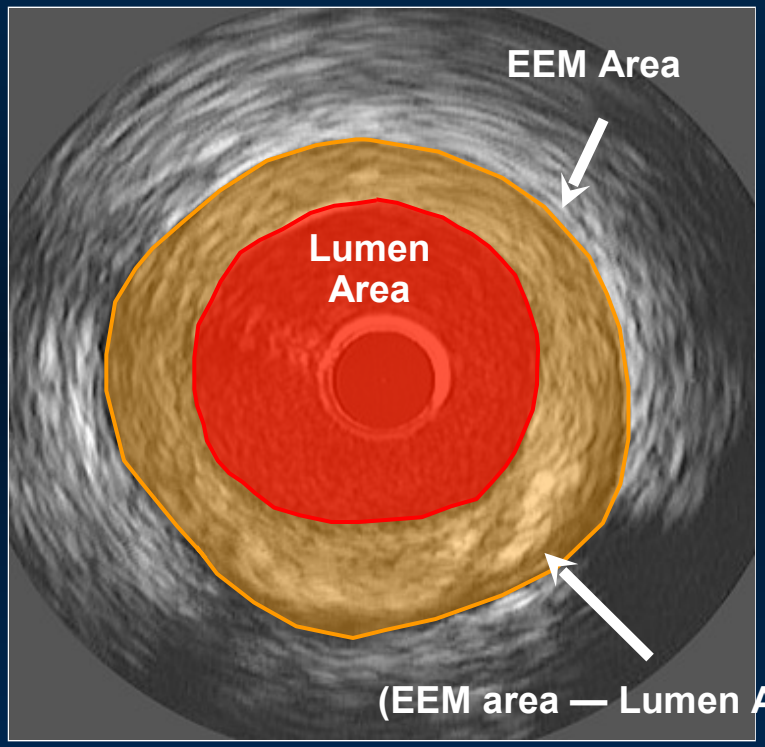
All-Cause Death or Major CV Events in All Randomized Subjects



REVERSAL: IVUS Determination of Atheroma Area

Precise Planimetry of EEM and Lumen Borders
allows calculation of Atheroma Cross-sectional Area





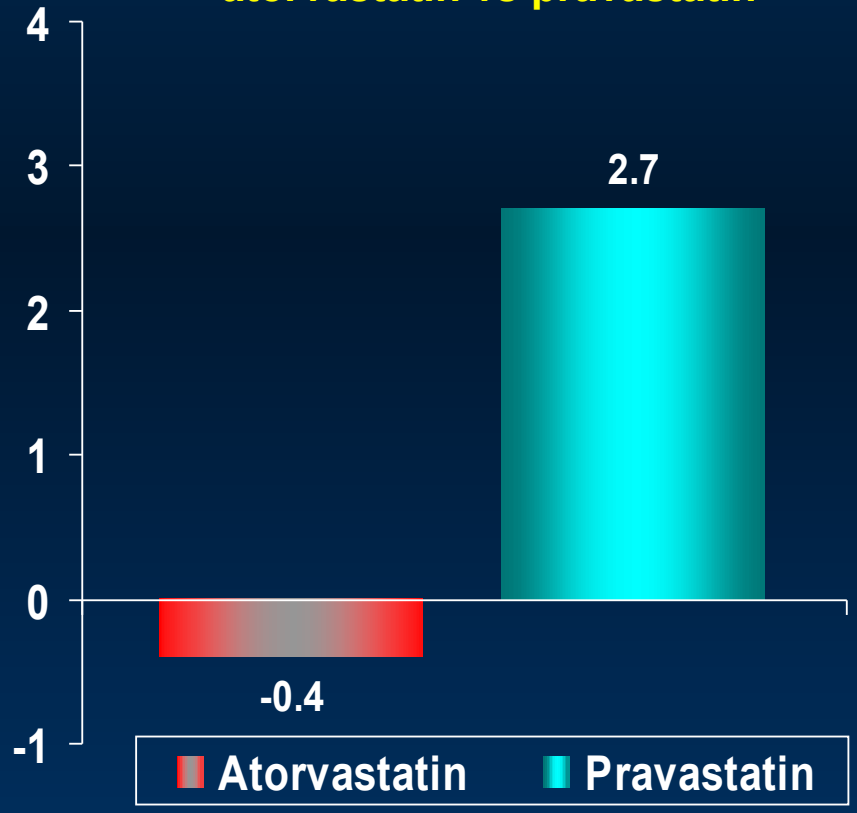
Images courtesy of Cleveland Clinic Intravascular Ultrasound Core Laboratory

EEM = External Elastic Membrane

REVERSAL Trial – IVUS analysis

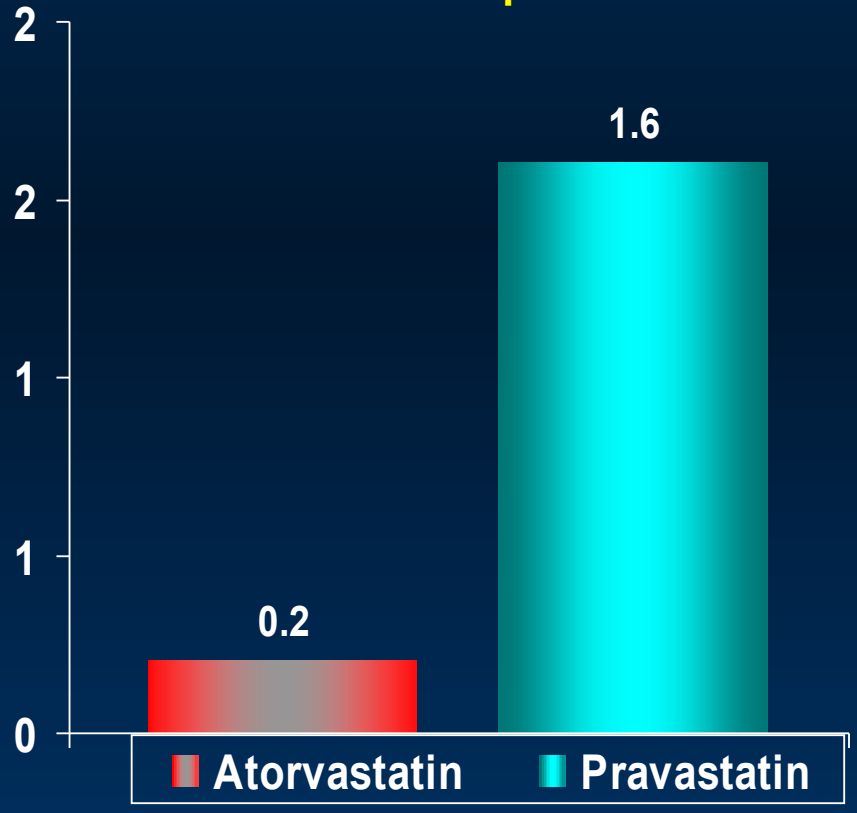
Change in total atheroma volume (TAV)

p=0.02 for change between atorvastatin vs pravastatin



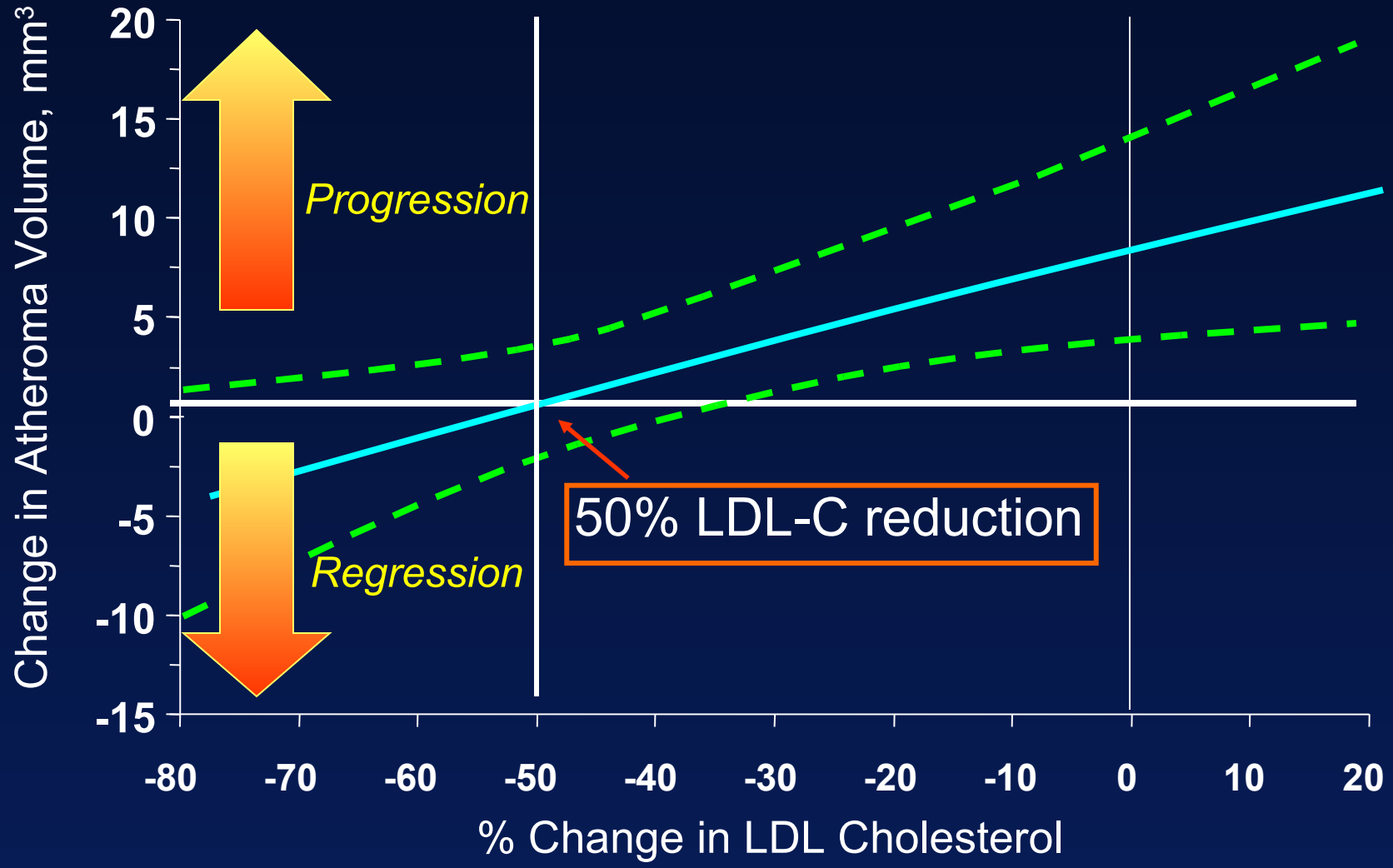
Change in percent obstruction volume

p=0.0002 for change between atorvastatin vs pravastatin



AHA 2003, Orlando, FL

REVERSAL: Continuous Relationship Between % Reduction in LDL-C and Change in Atheroma Volume: Both Treatment Groups (n=502)



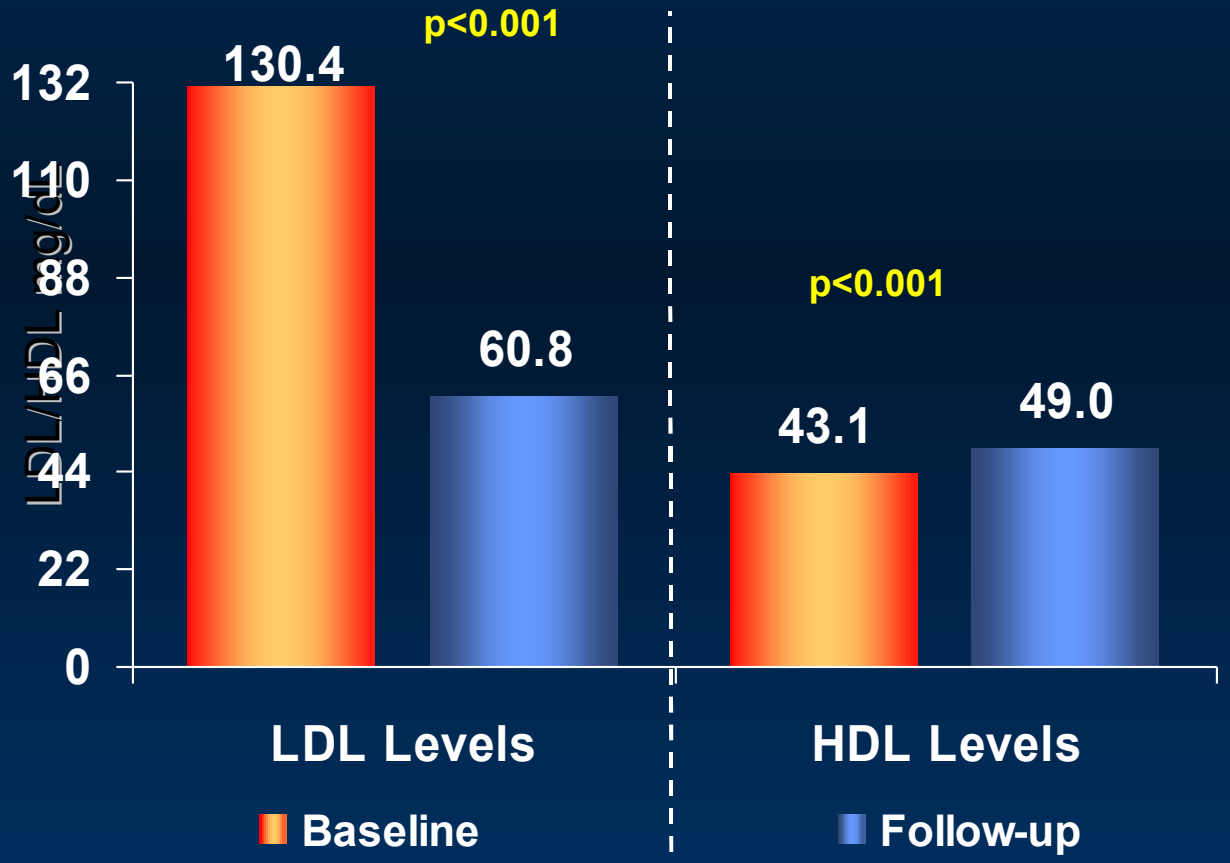
Adapted from Nissen S, et al., JAMA 2004; 291:1071-80.

REVERSAL and PROVE-IT
Duality of IVUS and Clinical outcomes

- Significant reduction and lower achieved level of LDL-cholesterol leads to:
  - Attenuation of coronary atherosclererosis progression (regression)
  - Reduction of cardiovascular morbidity and mortality

ASTEROID Trial: Principal Findings

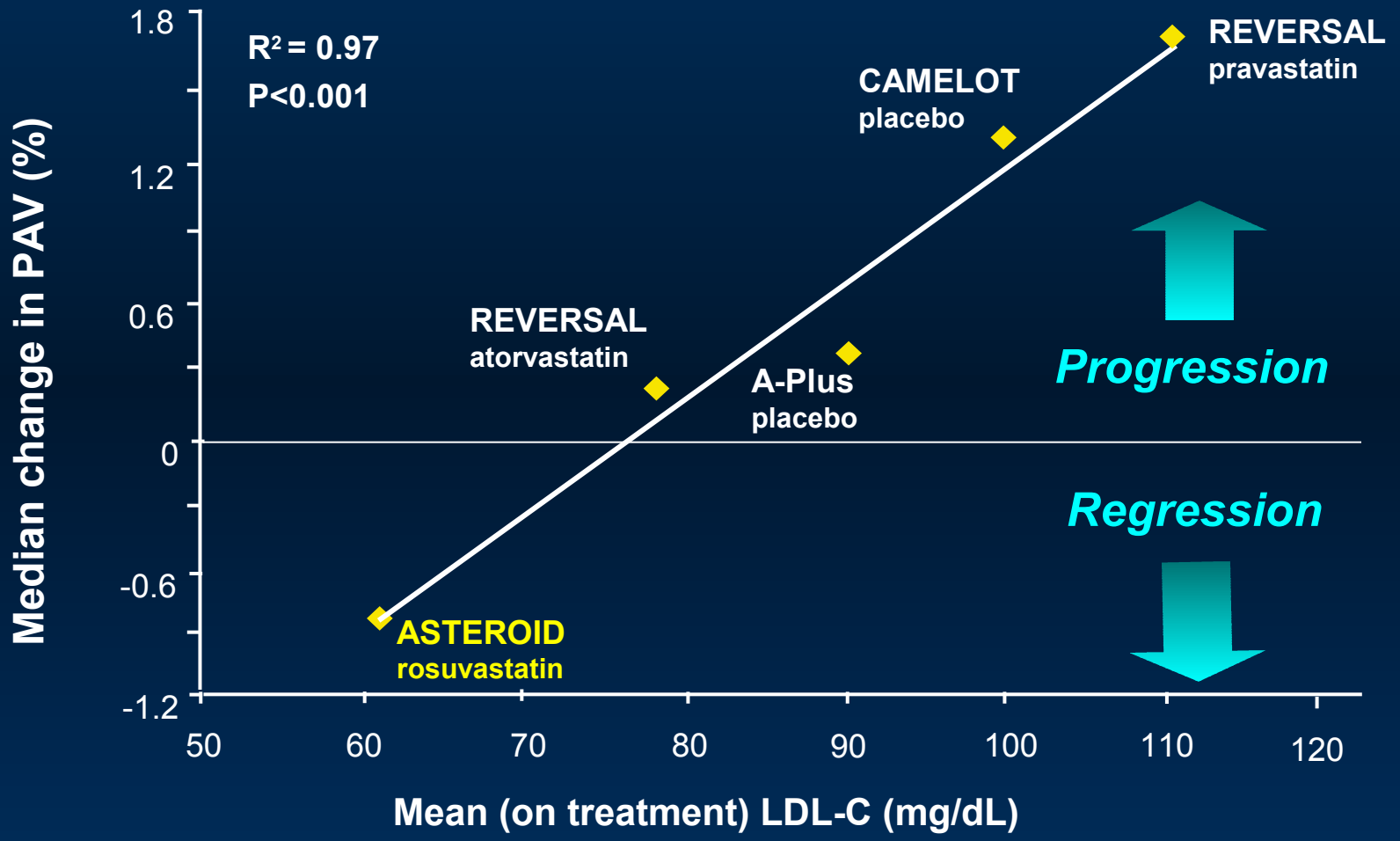
Mean LDL level decrement and HDL level increment (mg/dL)



75% of patients achieving an LDL <70 mg/dL.

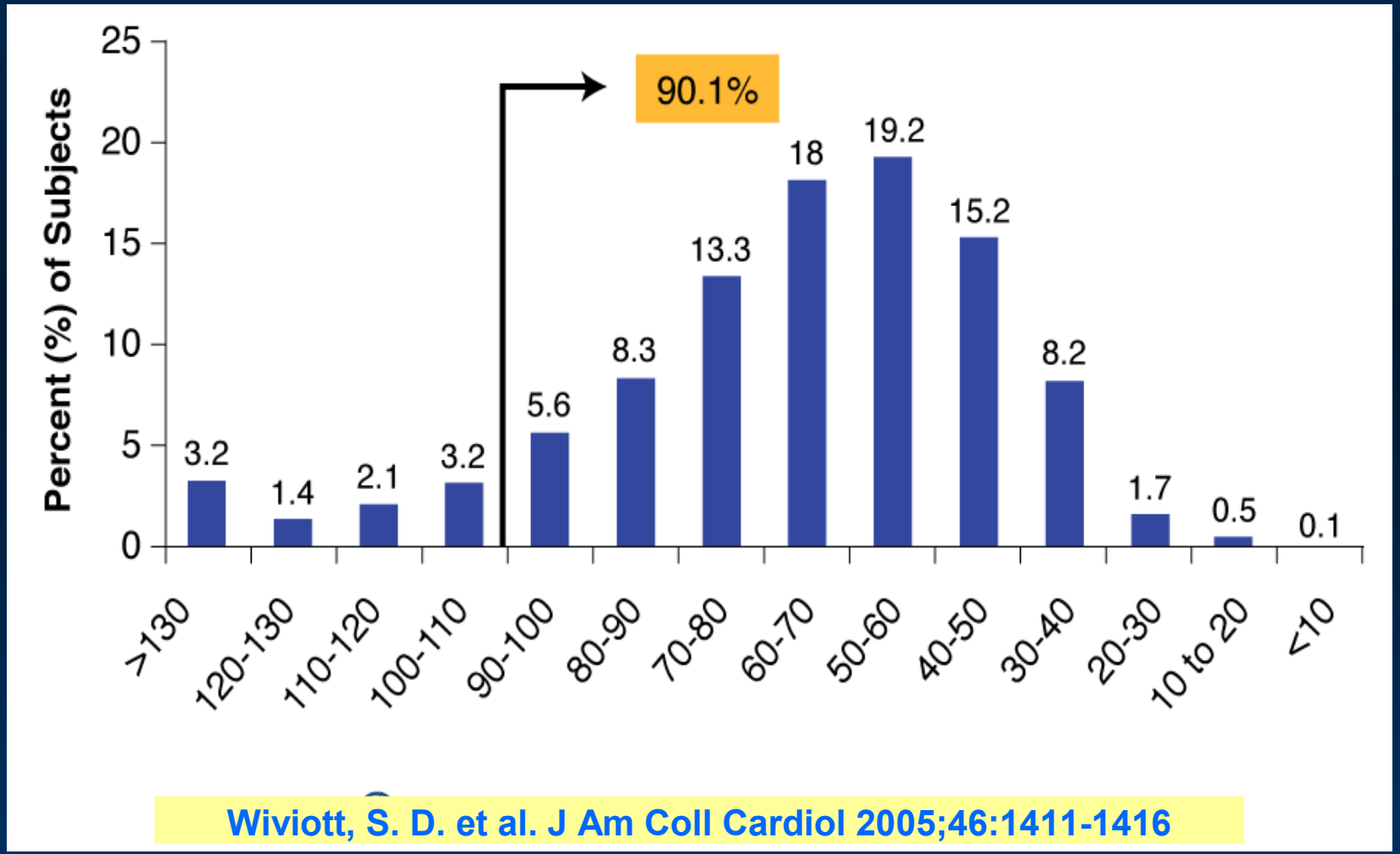
Presented at ACC 2006

ASTEROID: Aggressive statin therapy can induce regression of atherosclerosis



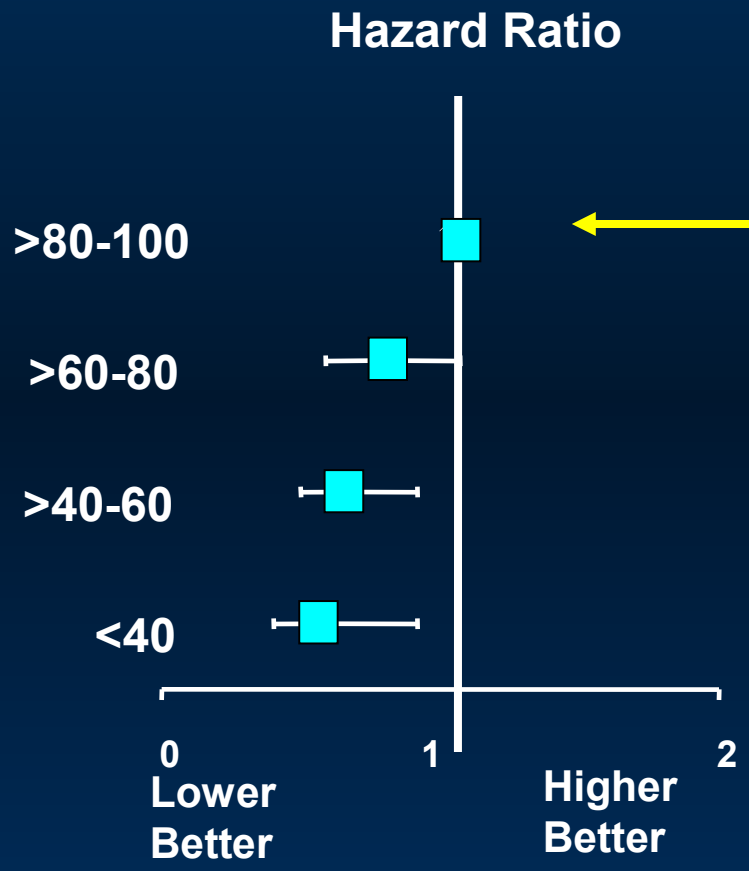
Ref: Nissen S *et al.* JAMA 2006; **295**: e-publication ahead of print

PROVE-IT - Distribution of four-month LDL level
Atorvastatin subgroup



Wiviott, S. D. et al. J Am Coll Cardiol 2005;46:1411-1416

PROVE-IT: Primary End Point By 4-Month *(LDL Level (Multivariable Adjustment



Referent

0.80 (0.59, 1.07)

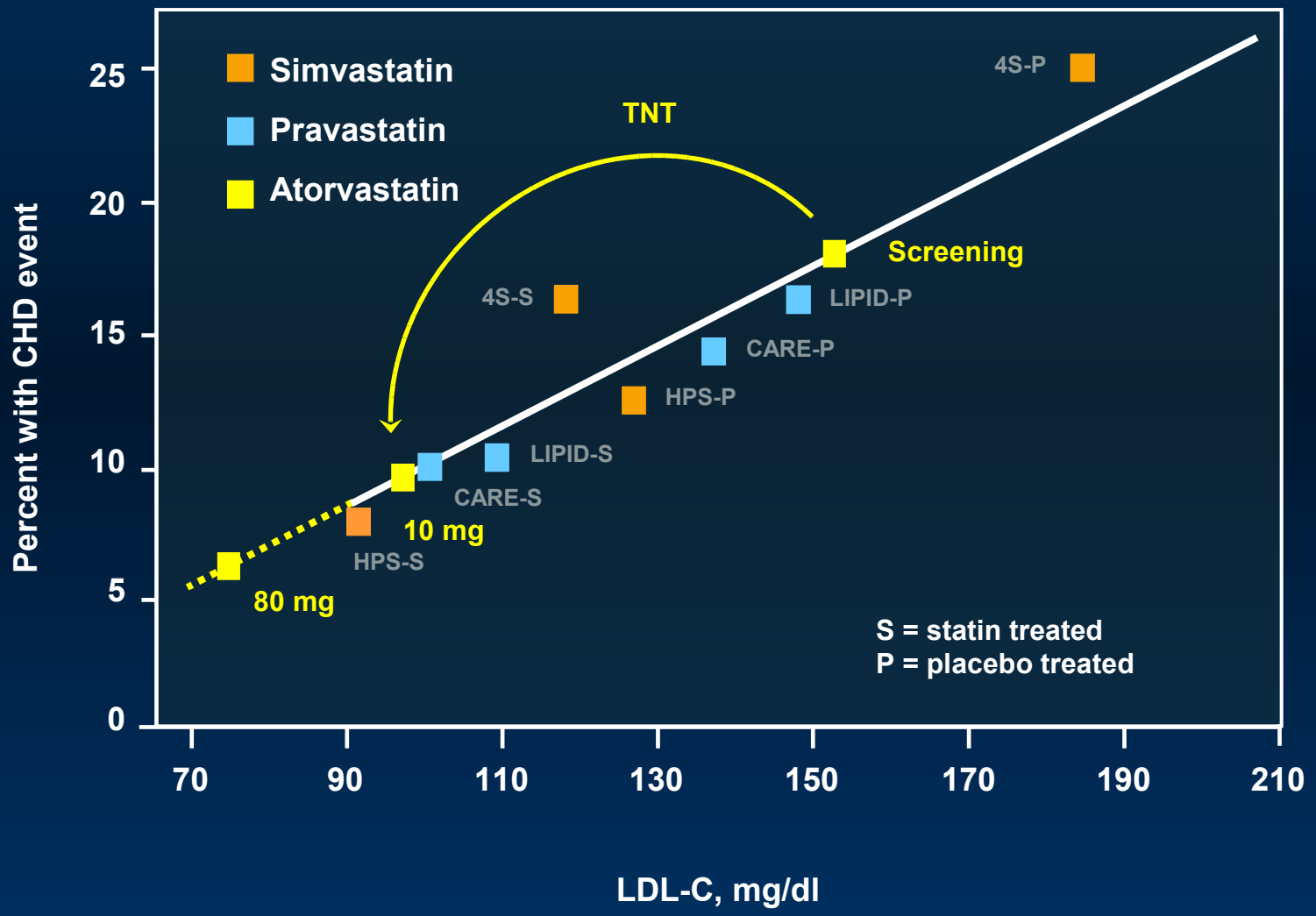
0.67 (0.50, 0.92)

0.61 (0.40, 0.91)

*Age, gender, DM, prior MI, baseline LDL.

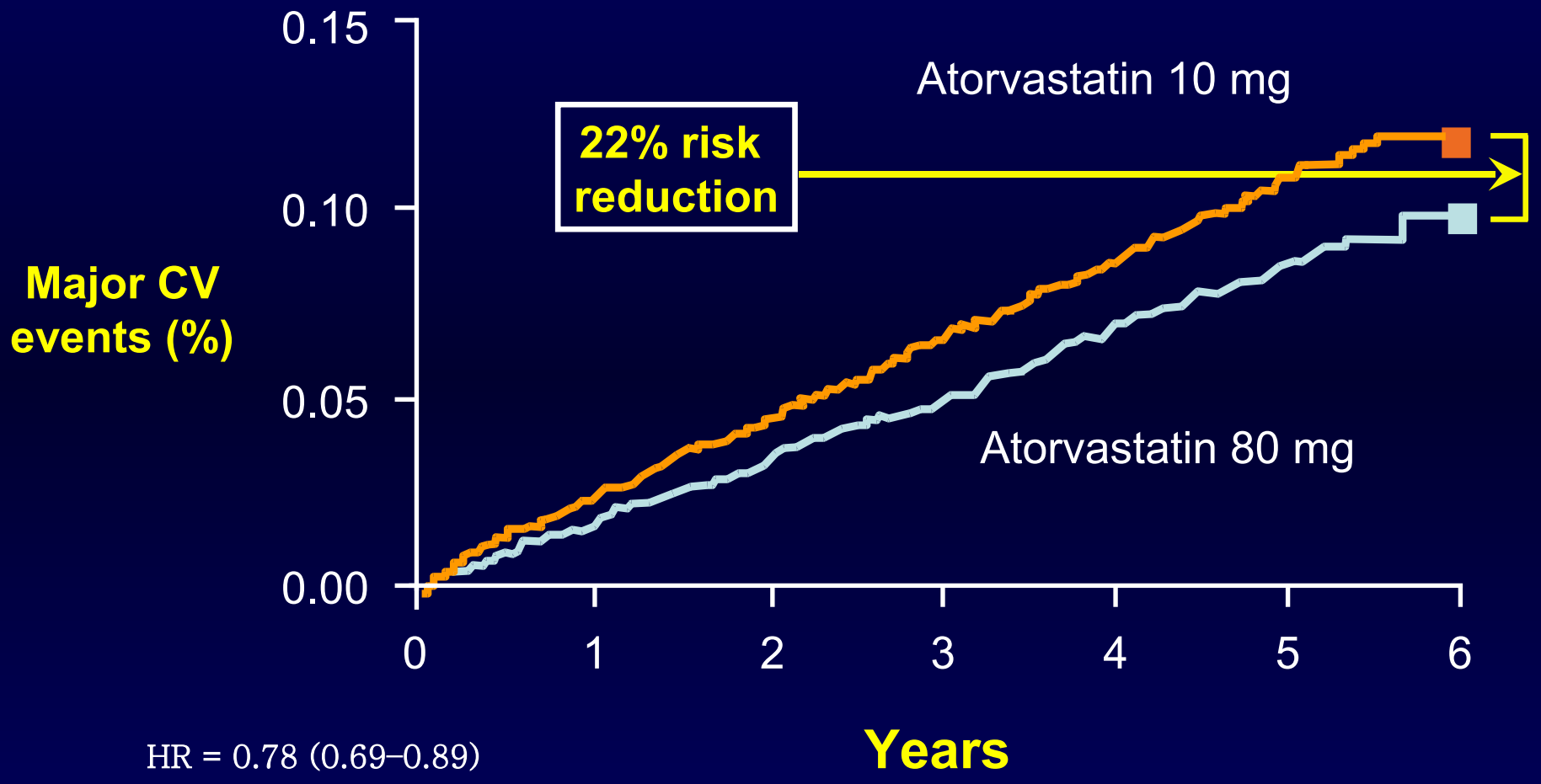
Wiviott SD, et al. *Circulation*. 2004;110:III-498. Abstract 2340.

Treating to New Targets (TNT) trial: Rationale



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

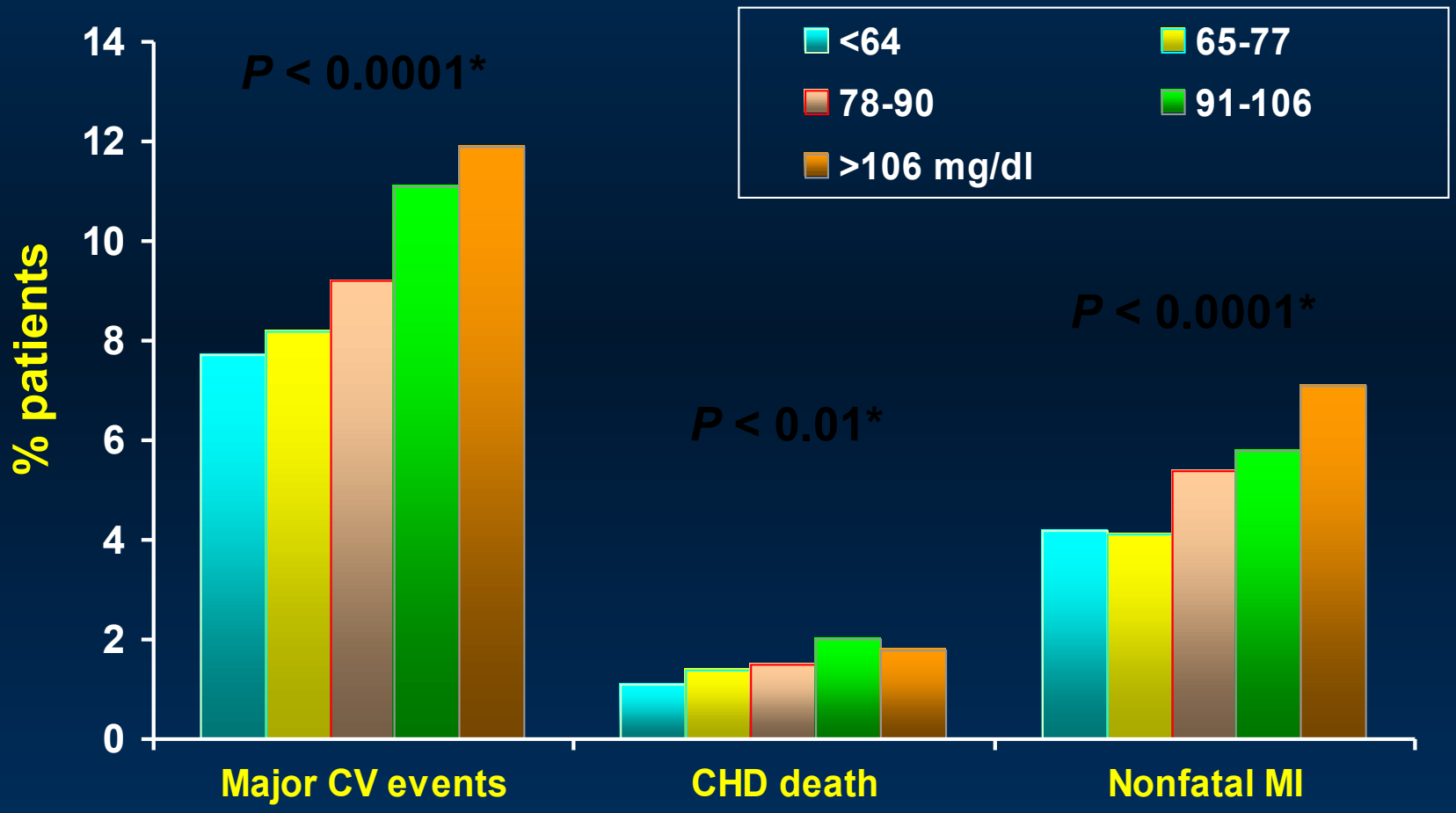
TNT: Treatment effects on primary outcome



HR = 0.78 (0.69–0.89)
P < 0.001

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

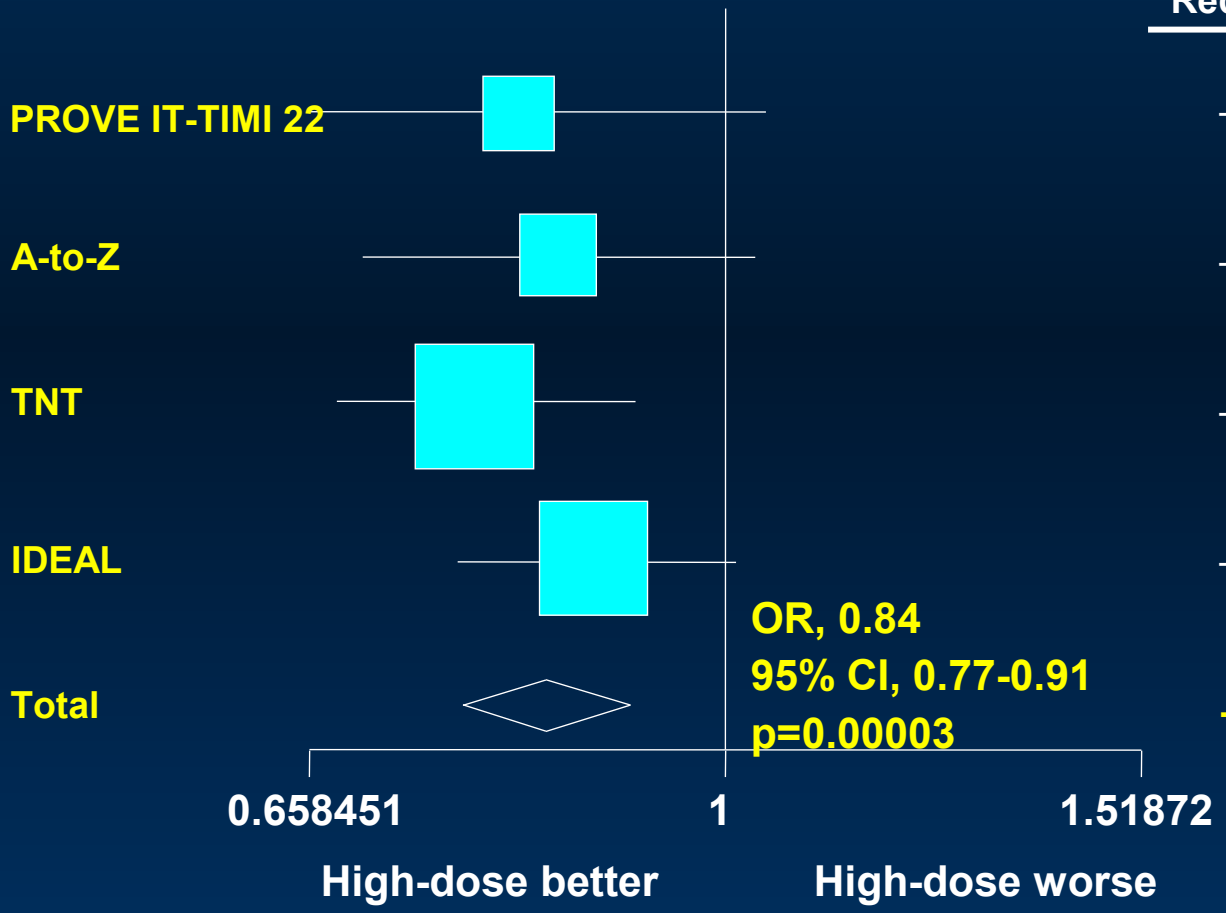
Major CV Events Across Quintiles of Achieved LDL



*P-value for trend across LDL-C

LaRosa JC. *AHA.* 2005

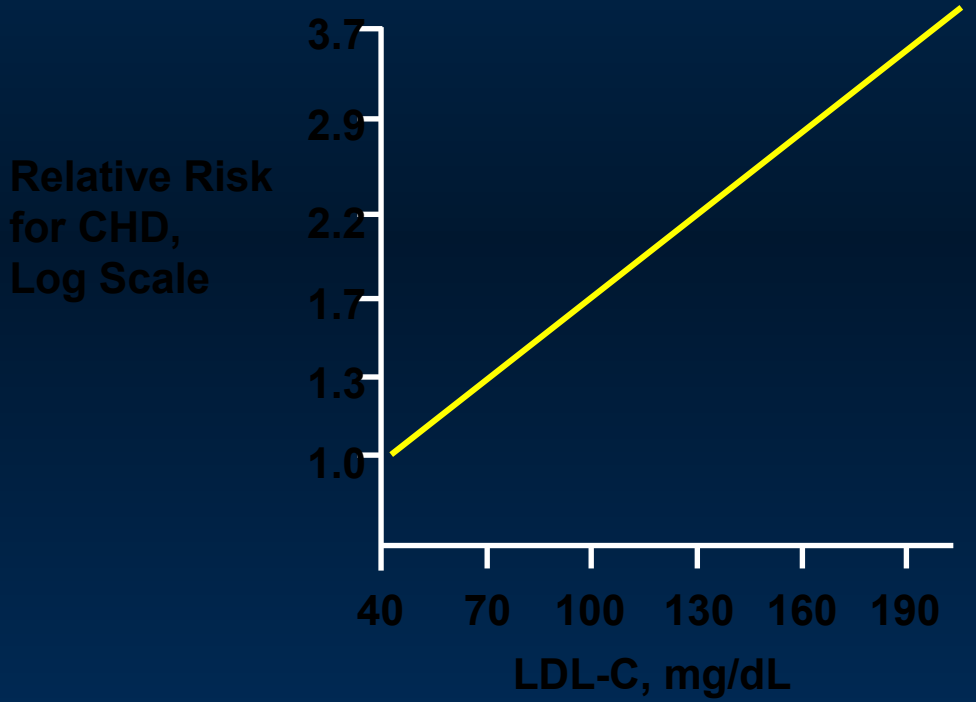
Meta-Analysis of Intensive Statin Therapy Coronary Death or MI



	Odds Reduction	Event Rates No./Total (%) High Dose	Std Dose
PROVE IT-TIMI 22	-17%	147/2099 (7.0)	172/2063 (8.3)
A-to-Z	-15%	205/2265 (9.1)	235/2232 (10.5)
TNT	-21%	334/4995 (6.7)	418/5006 (8.3)
IDEAL	-12%	411/4439 (9.3)	463/4449 (10.4)
Total	**-16%**	**1097/13798 (8.0)**	**1288/13750 (9.4)**

Cannon CP, et al.

Log-Linear Relationship Between LDL-C Levels and Relative Risk for CHD



- This relationship is consistent with a large body of epidemiologic data and data available from clinical trials of LDL-C–lowering therapy.
- These data suggest that for every 30-mg/dL change in LDL-C, the relative risk for CHD is changed in proportion by about 30%.
- The relative risk is set at 1.0 for LDL-C = 40 mg/dL.

Reprinted with permission from Grundy SM, Cleeman JI, Merz CNB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation.* 2004;110:227–239.

Prediction of LDL-C target in 5 years

- An LDL-C of 50 mg/dL in a high-risk population
- An LDL-C of 75 mg/dL in a lower-risk population

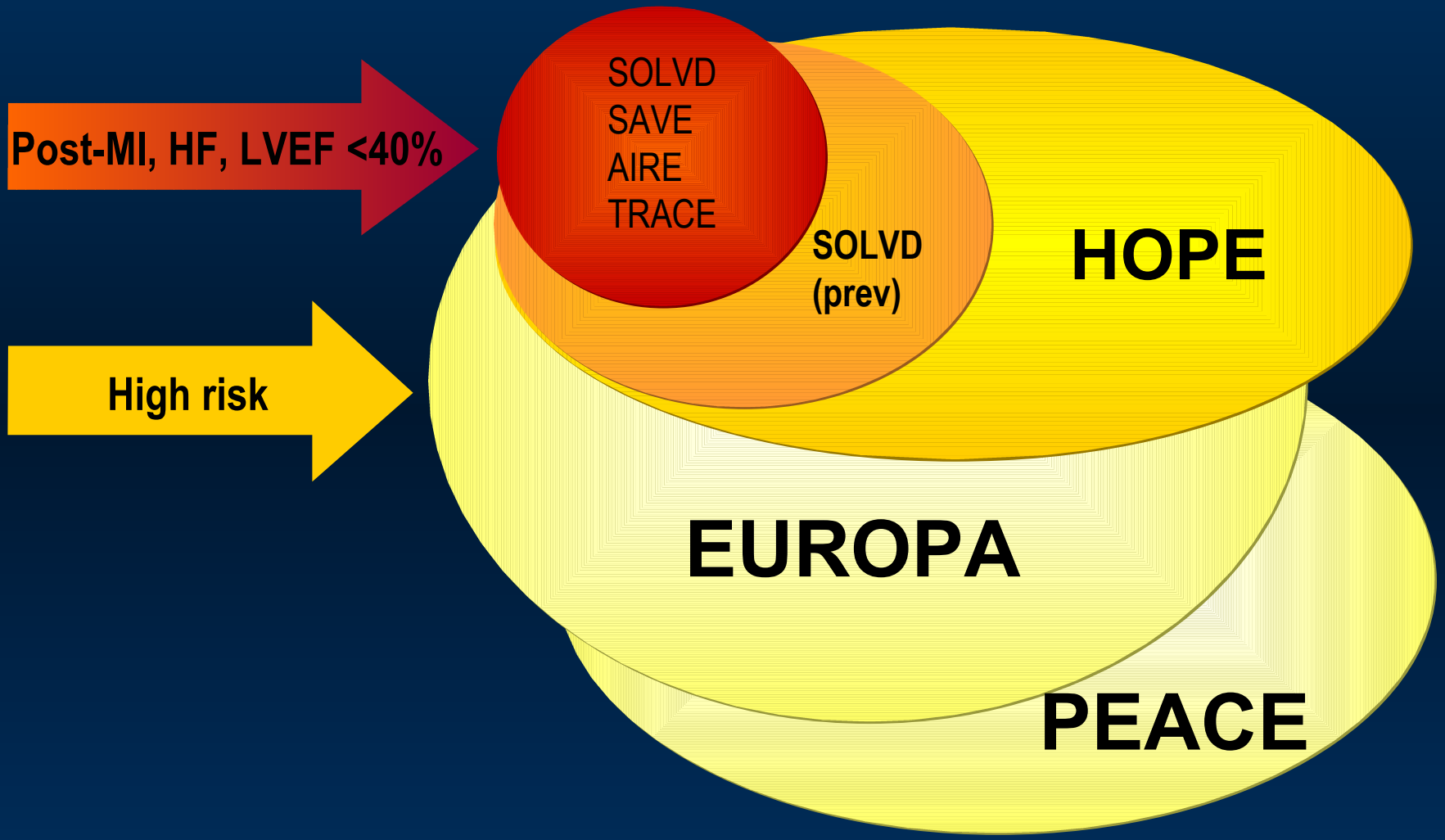
Christopher Cannon

Valentin Fuster

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

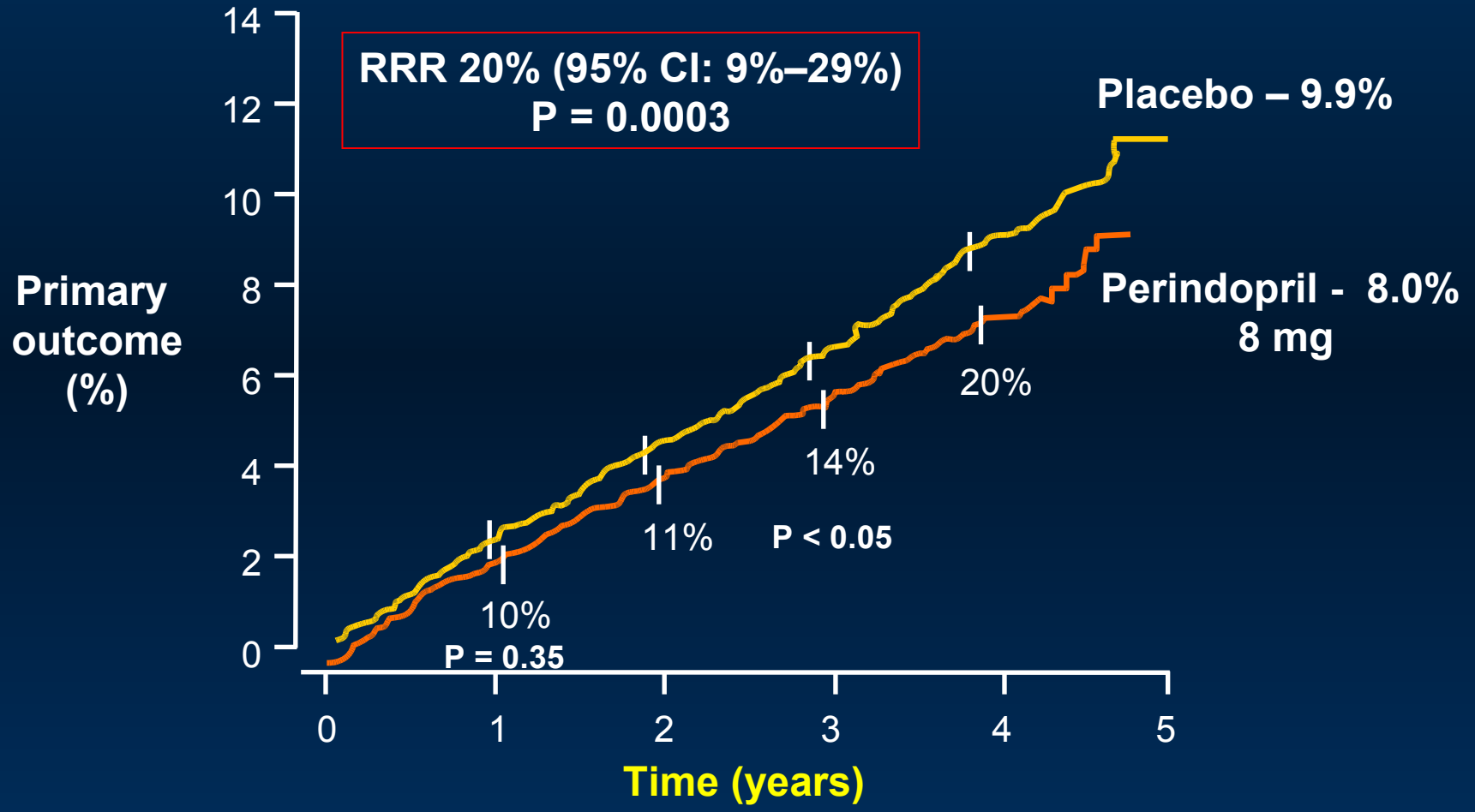
EUROPA: EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease

Objective:	Assess effects of the ACEI perindopril on CV risk in a broad-spectrum population with stable CAD and without HF
Design:	N = 12,218, age ≥18 years, with CAD/without HF at randomization
Treatment:	Perindopril 8 mg or placebo
Follow-up:	4.2 years
Primary outcome:	CV death, nonfatal MI, cardiac arrest

EUROPA Investigators. *Lancet.* 2003;362:782-8.

EUROPA: Primary outcome

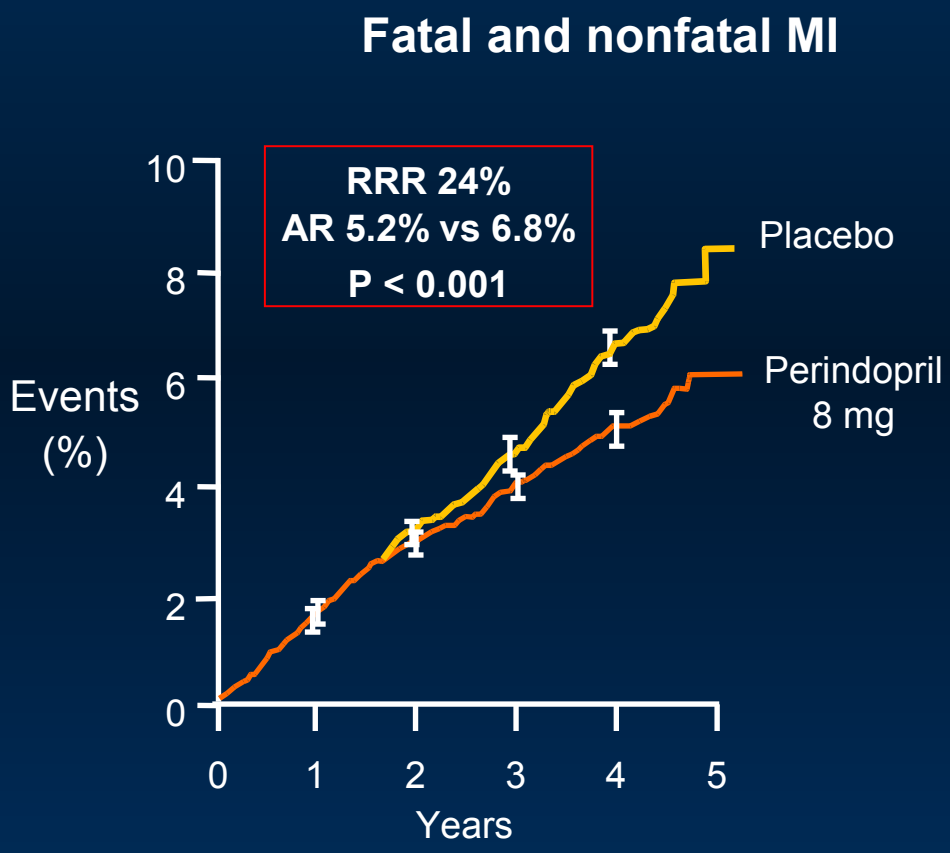
CV death, MI, cardiac arrest

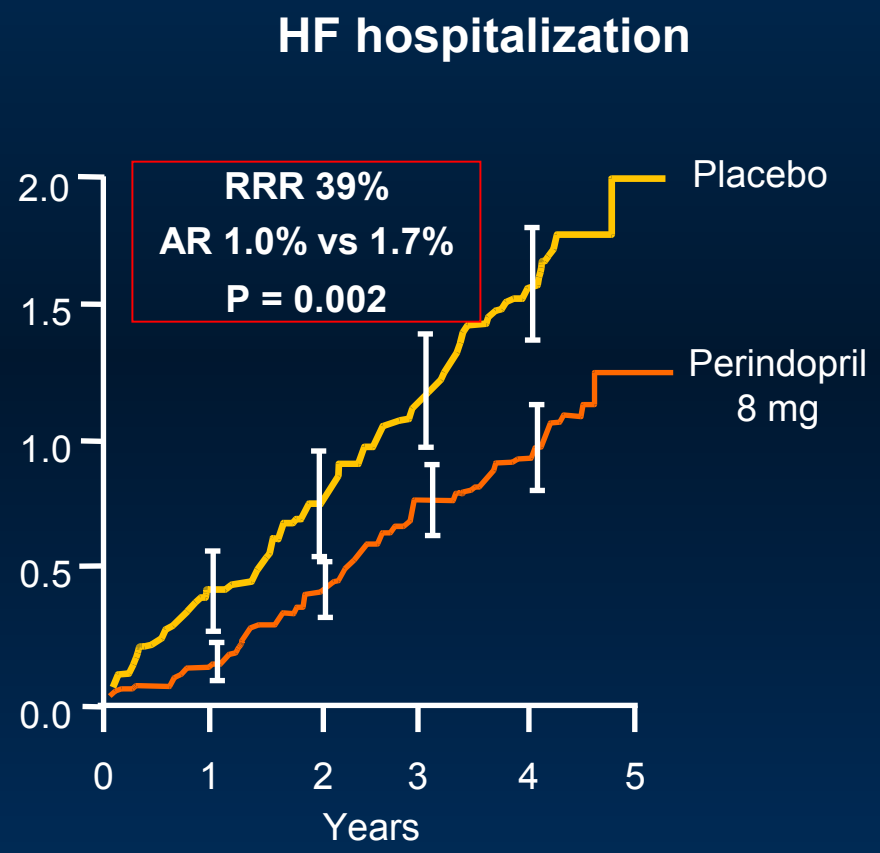


EUROPA Investigators. *Lancet*. 2003;362:782-8.

Fox KM. *Br J Cardiol*. 2004;11:195-204.

EUROPA: Effect of ACEI on fatal/nonfatal MI and HF hospitalizations





AR = absolute risk (perindopril vs placebo)

EUROPA Investigators. *Lancet*. 2003;362:782–8.

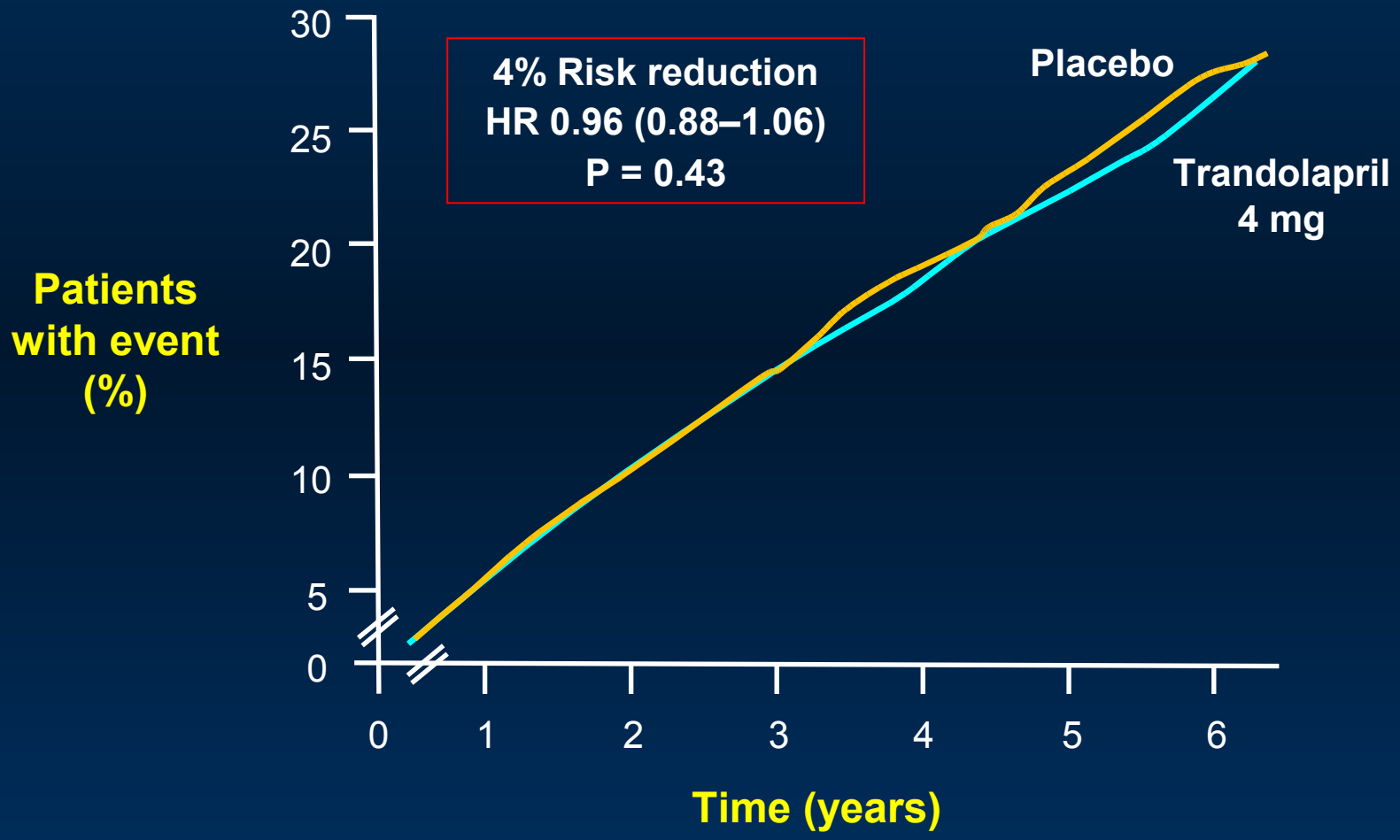
PEACE: Prevention of Events with Angiotensin Converting Enzyme inhibition

Objective:	Assess effect of ACEI in patients with stable CAD and normal/slightly reduced LV function
Design:	N = 8290 randomized
Treatment:	Trandolapril 4 mg or placebo
Follow-up:	4.8 years
Primary outcome:	CV death, nonfatal MI, CABG, PCI

PEACE Trial Investigators. *N Engl J Med.* 2004;351:2058-68.

PEACE: Primary outcome

CV death, MI, CABG/PCI; N = 8290



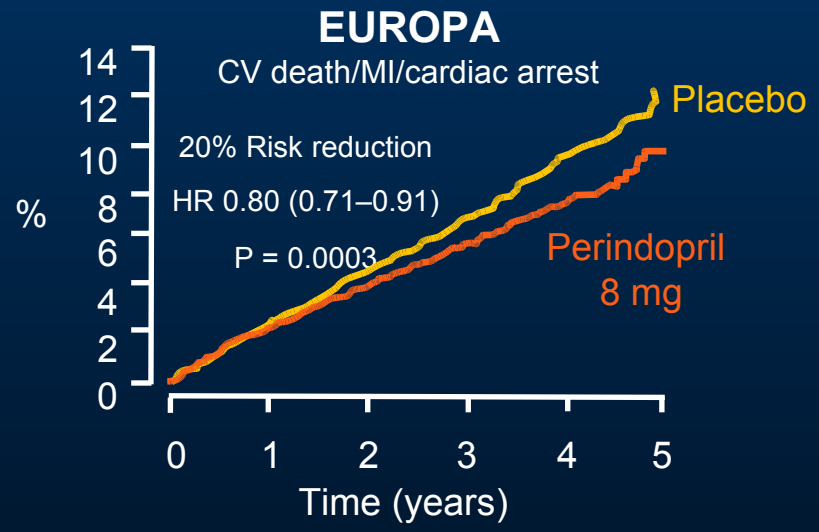
PEACE Trial Investigators. *N Engl J Med.* 2004;351:2058-68.

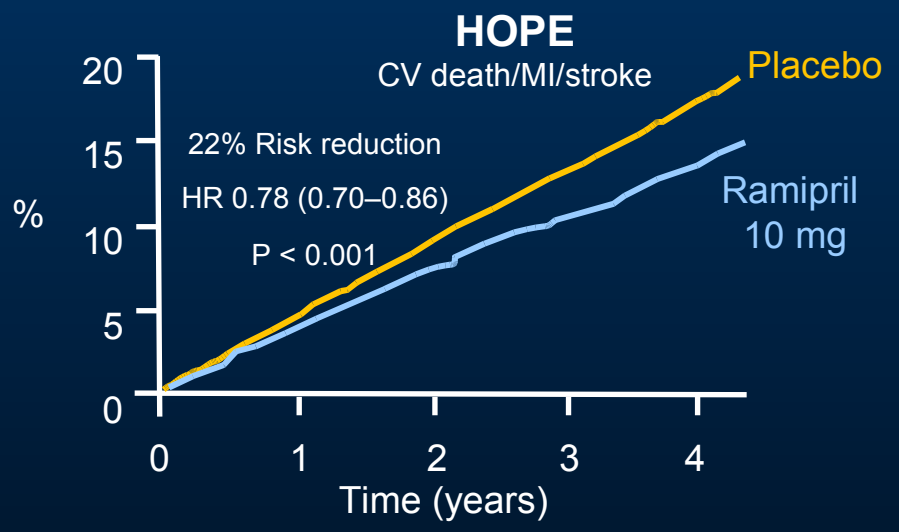
ACEI trials in CAD patients without HF: Key baseline characteristics

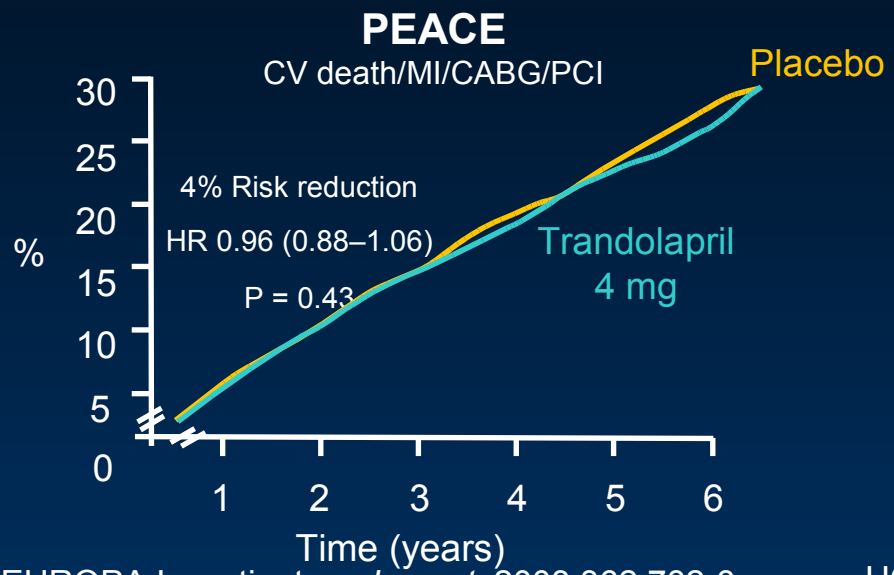
	EUROPA	HOPE	PEACE	QUIET
N	**12,218**	**9297**	**8290**	**1750**
Follow-up (yrs)	4.2	4.5	4.8	2.3
ACEI/dose (mg)	P-8	R-10	T-4	Q-20
Age (yrs)	60	66	64	58
Men (%)	85	73	82	82
CAD/Cor rev (%)	100/55	80/44	100/72	100/100
Diabetes (%)	12	39	17	16
Hypertension (%)	27	47	46	47
Prior MI (%)	65	53	55	49
Ejection fraction (%)	NA	NA	58	59
PVD (%)	7	43	NA	NA

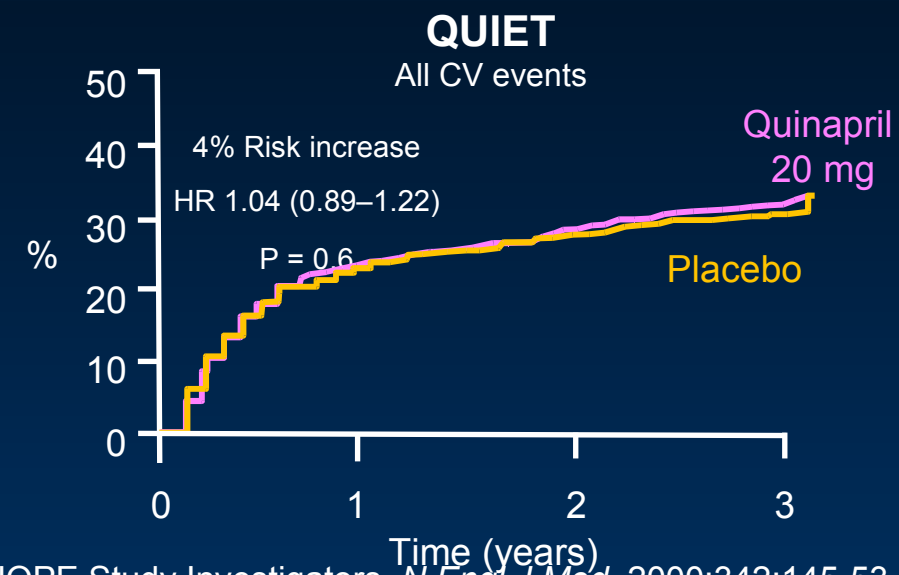
EUROPA Investigators. *Lancet*. 2003;362:782-8.
HOPE Study Investigators. *N Engl J Med*. 2000;342:145-53.
PEACE Trial Investigators. *N Engl J Med*. 2004;351:2058-68.
Pitt B et al. *Am J Cardiol*. 2001;87:1058-63.

ACEI trials in CAD without HF: Primary outcomes









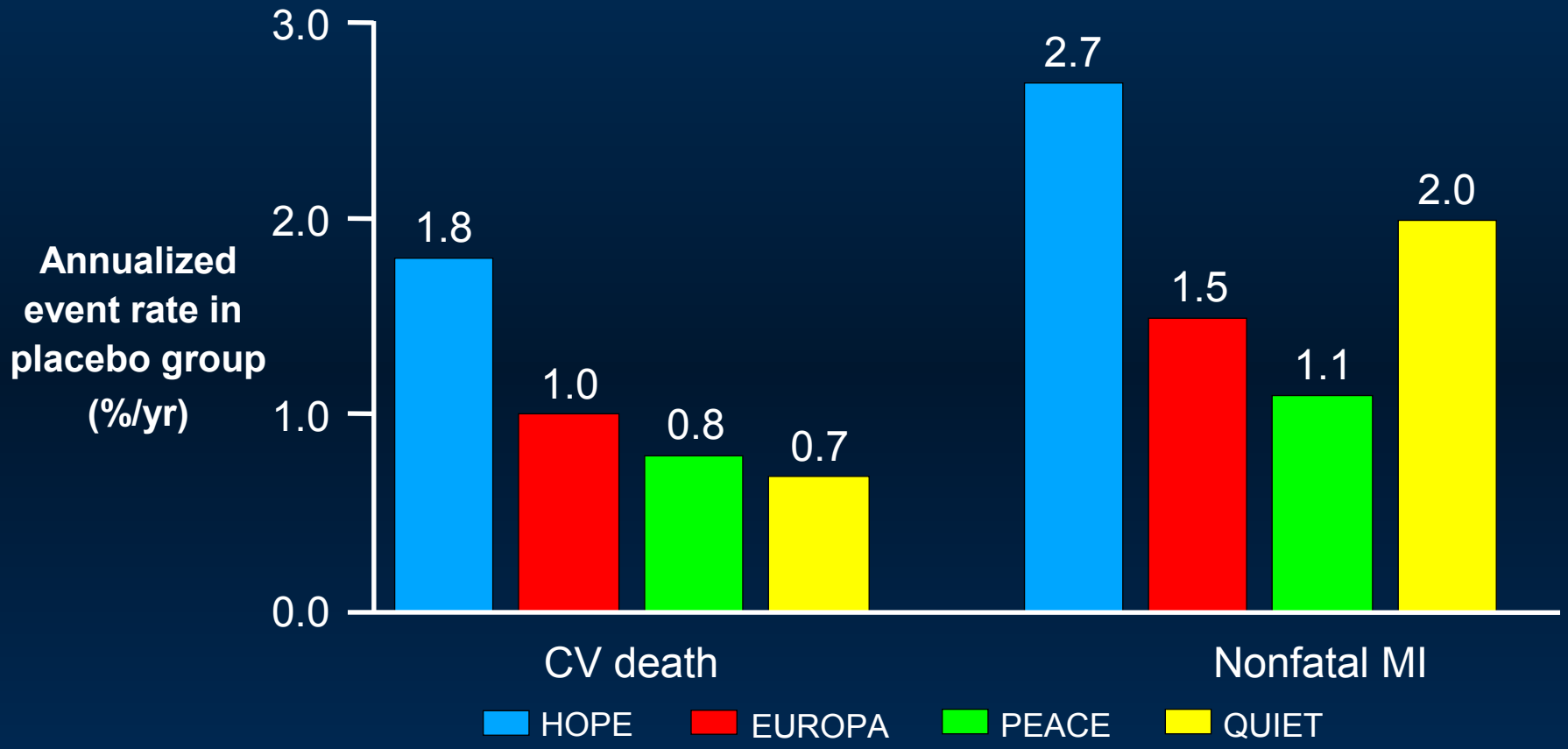
EUROPA Investigators. *Lancet*. 2003;362:782-8.

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.

HOPE, EUROPA, PEACE, QUIET: Differences in baseline CV risk



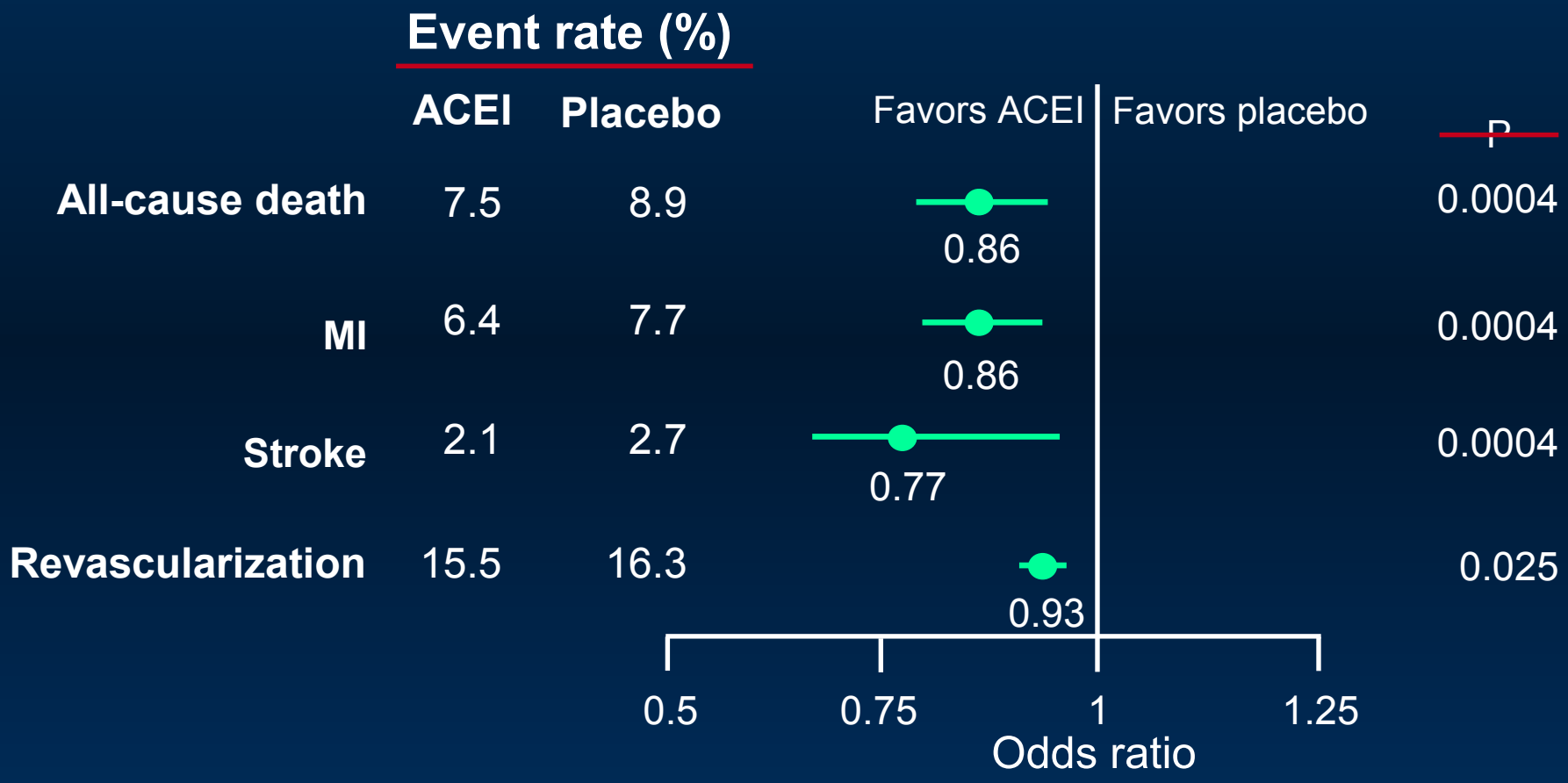
HOPE Study Investigators. *N Engl J Med*. 2000;342:145-53.

EUROPA Investigators. *Lancet*. 2003;362:782-8.

PEACE Trial Investigators. *N Engl J Med*. 2004;351:2058-68.

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

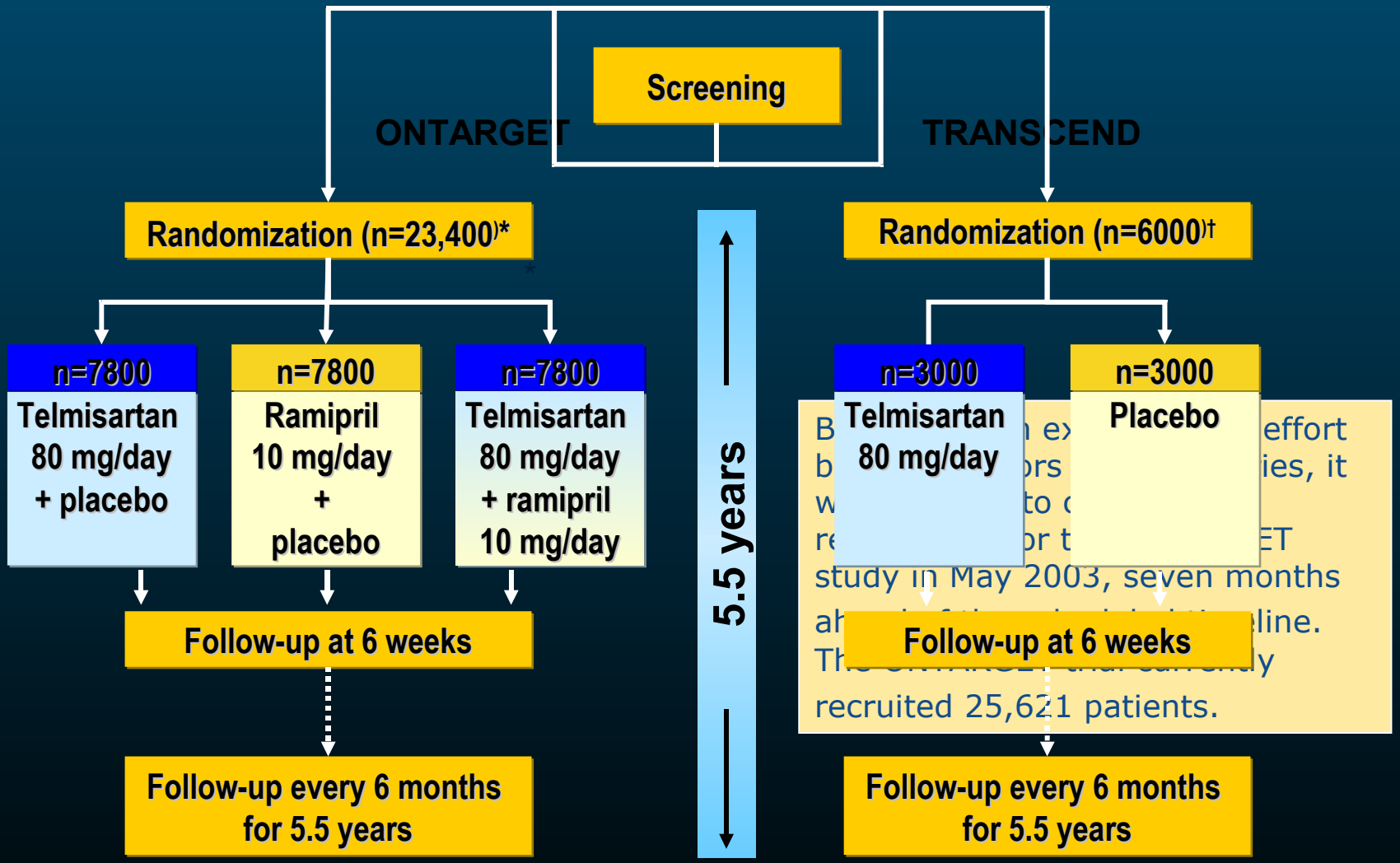
Class IIa

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

שאלה 2: טיפול ב ARB (כתוספת לטיפול במעכבי ACE) הוכח כיעיל במחקר:

1. VALIANT
2. ONTARGET
3. CHARM
4. כל הנ"ל
5. אף אחד מהנ"ל

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.

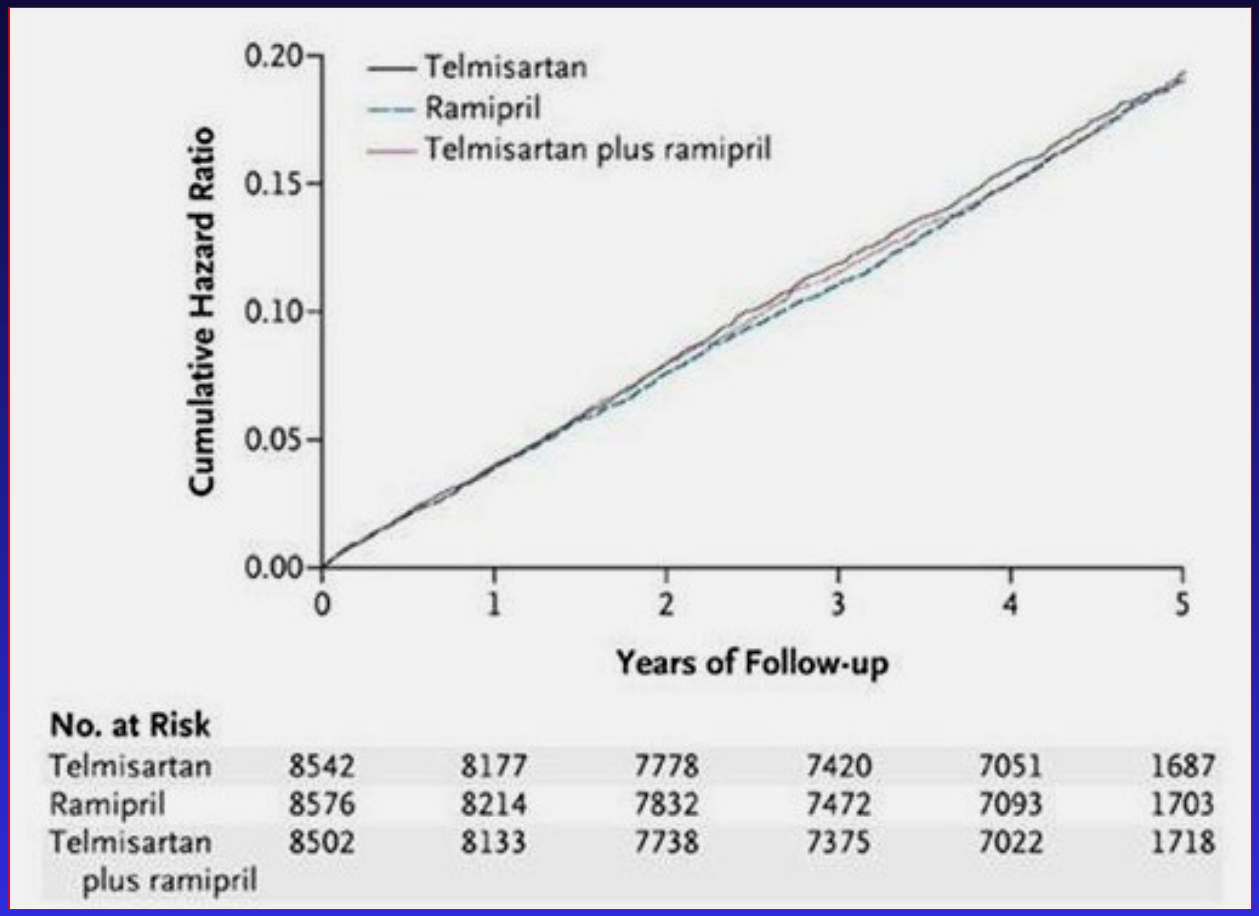
ONTARGET

Change in BP (mmHg)

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

ONTARGET

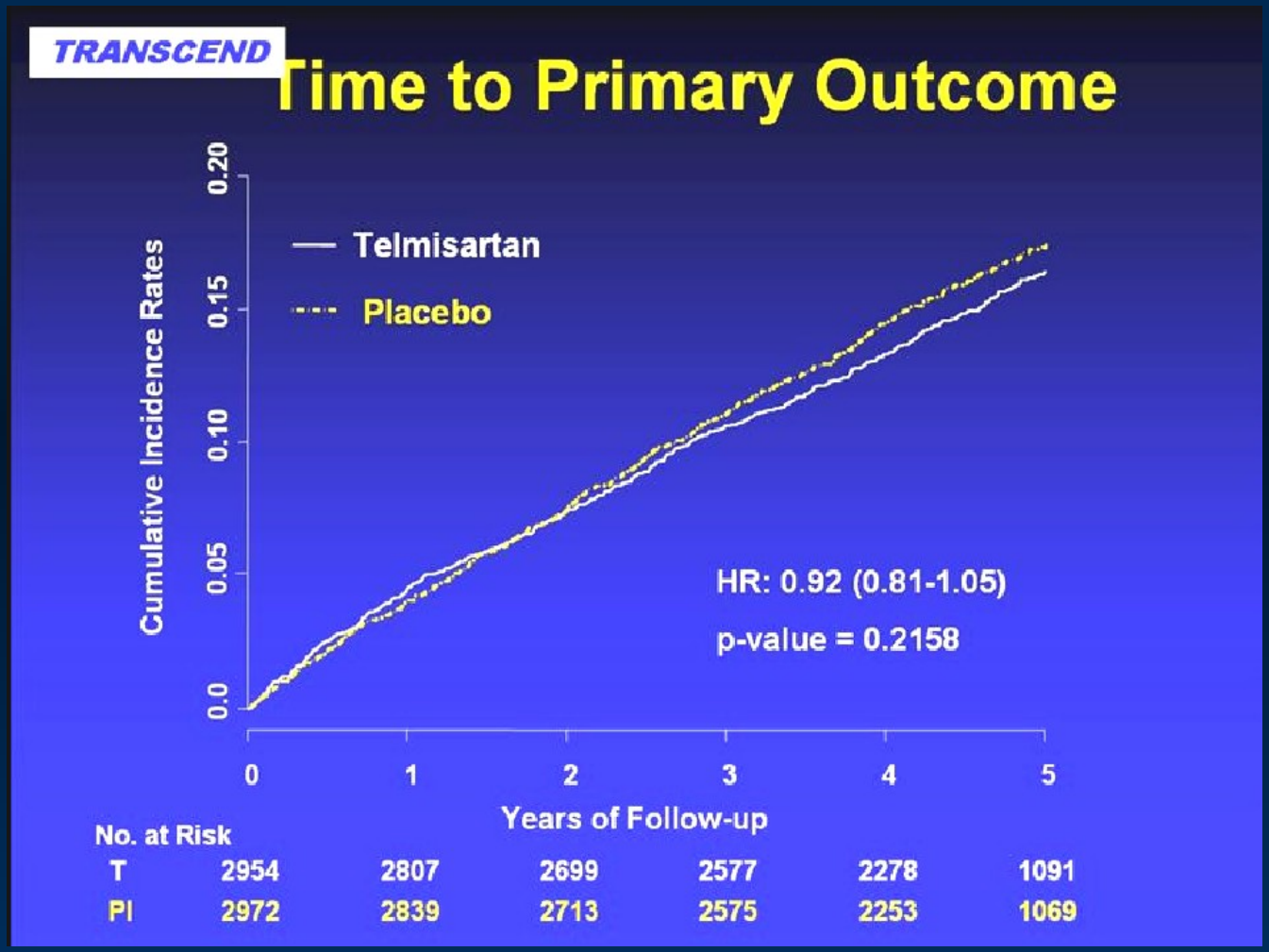
Time to Primary Outcome



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????

שאלה 3: טיפול בדיהידרופיריידין (אמלודיפין):

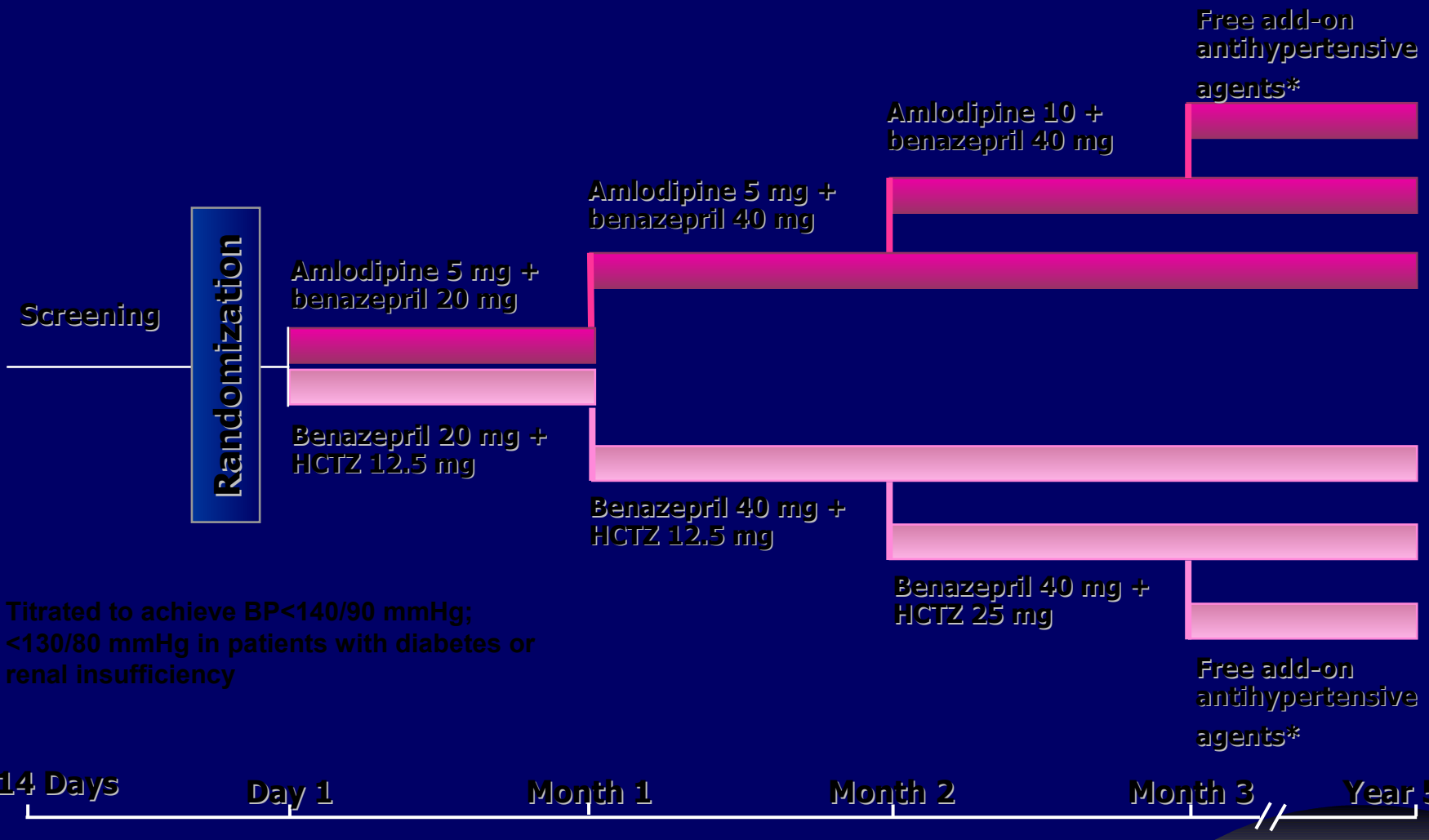
1. קשור בשיעור נמוך יותר של תעוקת חזה (בחולים עם מחלה כלילית יציבה) בהשוואה למעכב ACE
2. אינו נופל ממעכב ACE במיתון פרוגרסיה של טרשת כלילית (בבדיקת IVUS)
3. בשילוב עם ACE/ARB עדיף על טיפול דיורטי בהקטנת תחלואה ותמותה וסקולריים בחולים היפרטנסיביים
4. כל הנ"ל
5. אף אחד מהנ"ל

Avoiding Cardiovascular Events through COMbination Therapy in Patients LIving with Systolic Hypertension

Kenneth Jamerson[1], George L. Bakris[2], Bjorn Dahlof[3], Bertram Pitt[1], Eric J. Velazquez[4], and Michael A. Weber[5] for the ACCOMPLISH Investigators

University of Michigan Health System, Ann Arbor, MI[1]; University of Chicago-Pritzker School of Medicine, Chicago, IL[2]; Sahlgrenska University Hospital, Gothenburg, Sweden[3]; Duke University School of Medicine, Durham, NC[4]; SUNY Downstate Medical College, Brooklyn, NY[5]

ACCOMPLISH: Design

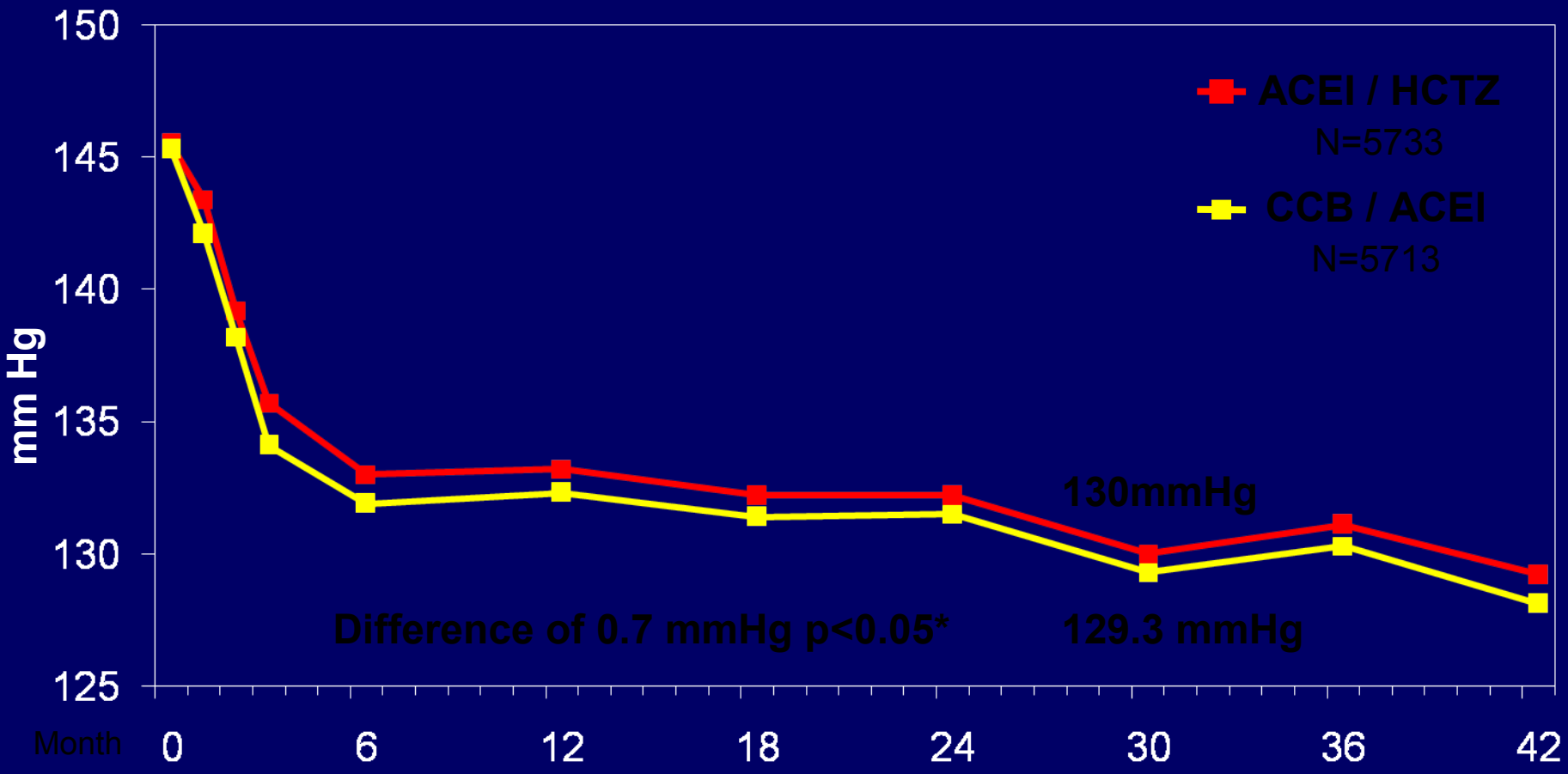


*Beta blockers; alpha blockers; clonidine; (loop diuretics).

Jamerson KA et al. *Am J Hypertens*. 2003;16(part2)193A

ACCOMPLISH

Systolic Blood Pressure Over Time

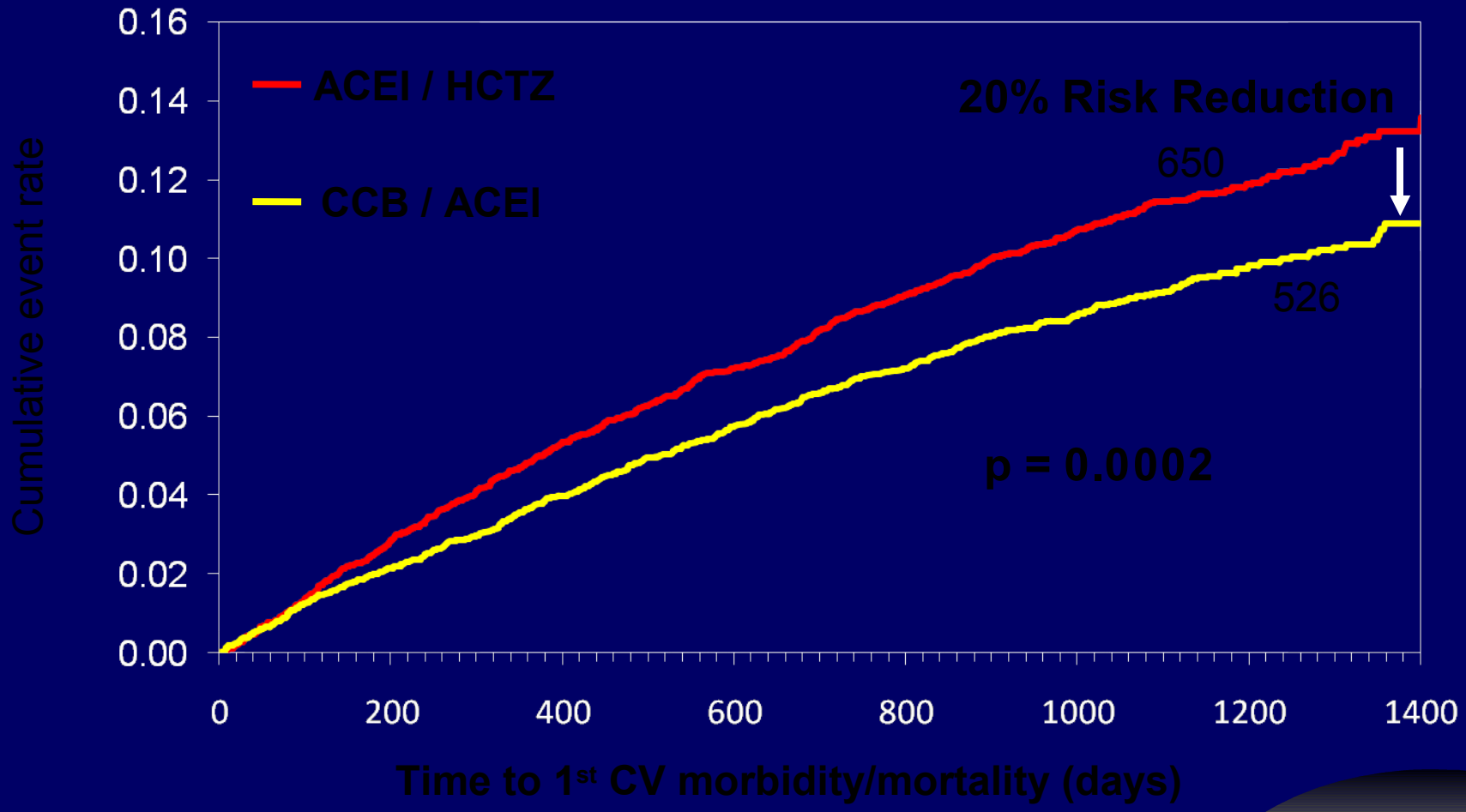


*Mean values are taken at 30 months F/U visit

DBP: 71.1 DBP: 72.8

ACCOMPLISH

Kaplan Meier for Primary Endpoint



HR (95% CI): 0.80 (0.72, 0.90)

INTERIM RESULTS Mar 08

ACCOMPLISH

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?

REGISTRY
REduction of Atherothrombosis for Continued Health

One-Year Cardiovascular Event Rates in a Global Contemporary Registry of >68,000 Outpatients with Atherothrombosis: *the REduction of Atherothrombosis for Continued Health (REACH) Registry Results*

Ph.G Steg*, DL. Bhatt, PWF.Wilson, EM.Ohman, J. Röther,
CS. Liau, AT. Hirsch, JL. Mas, S. Goto,
on behalf of the REACH Registry Investigators

*AP-HP, Hôpital Bichat-Claude Bernard, Paris, France

Presented at the ACC – Atlanta 2006

REACH REGISTRY
REduction of Atherothrombosis for Continued Health

Inclusion criteria

Must include

Signed Written Informed Consent

Patients aged ≥45 years

1 At least of four criteria

- Documented cerebrovascular disease Ischemic stroke or transient ischemic attack
- Documented coronary disease Angina, MI, angioplasty/ stent/bypass
- Documented historical or current intermittent claudication associated with ABI <0.9

At least **3** atherothrombotic risk factors

- Male ≥65 years or female ≥70 years
- Current smoking >15 cigarettes/day
- Type I or Type II diabetes
- Hypercholesterolemia
- Diabetic nephropathy
- Hypertension
- Ankle Brachial Index (ABI) <0.9 in either leg at rest
- Asymptomatic carotid stenosis ≥70%
- Presence of at least one carotid plaque

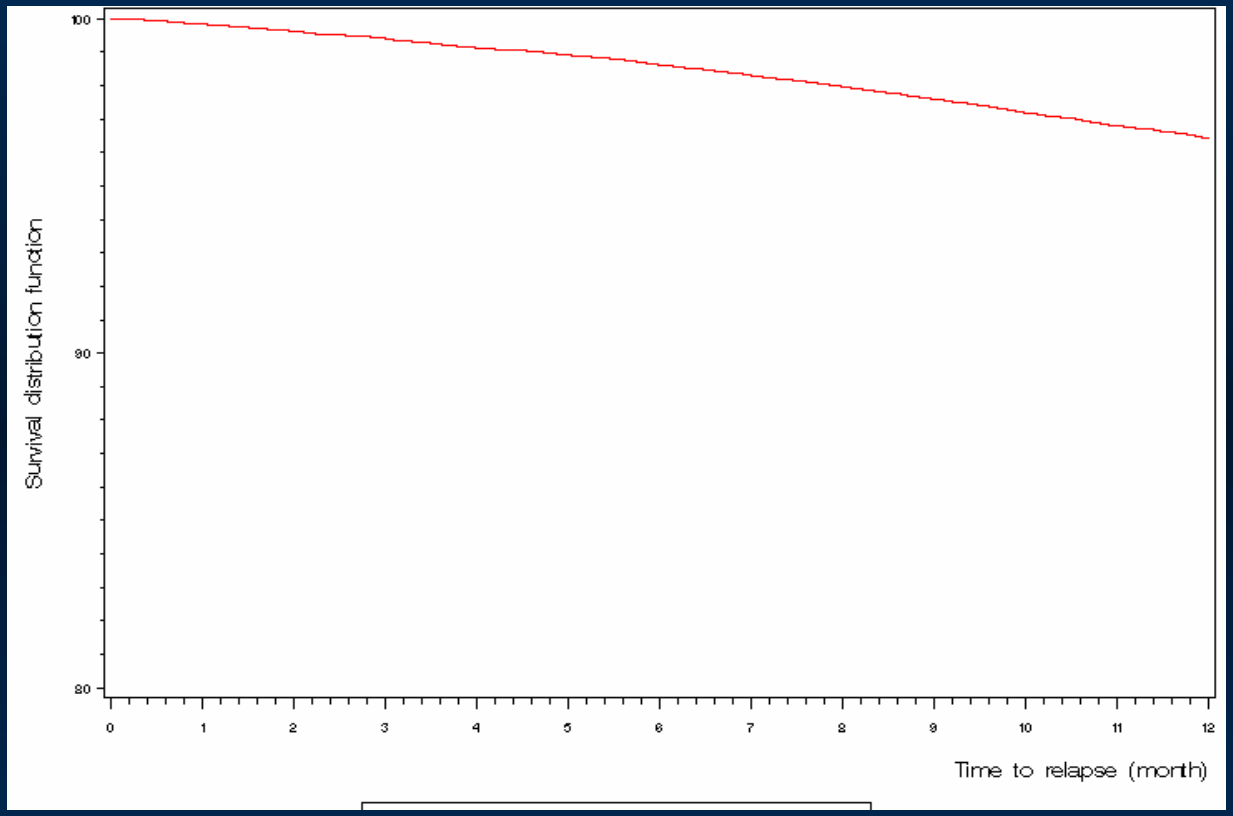
REACH REGISTRY
REduction of Atherothrombosis for Continued Health

1-year results

Unless otherwise specified, event rates have been adjusted for age, hypertension, diabetes, smoking and cholesterol

REach REGISTRY
REduction of Atherothrombosis for Continued Health

CV death / MI / stroke



Constant slope is a marker of stability – chronic phase

REach REGISTRY
REduction of Atherothrombosis for Continued Health

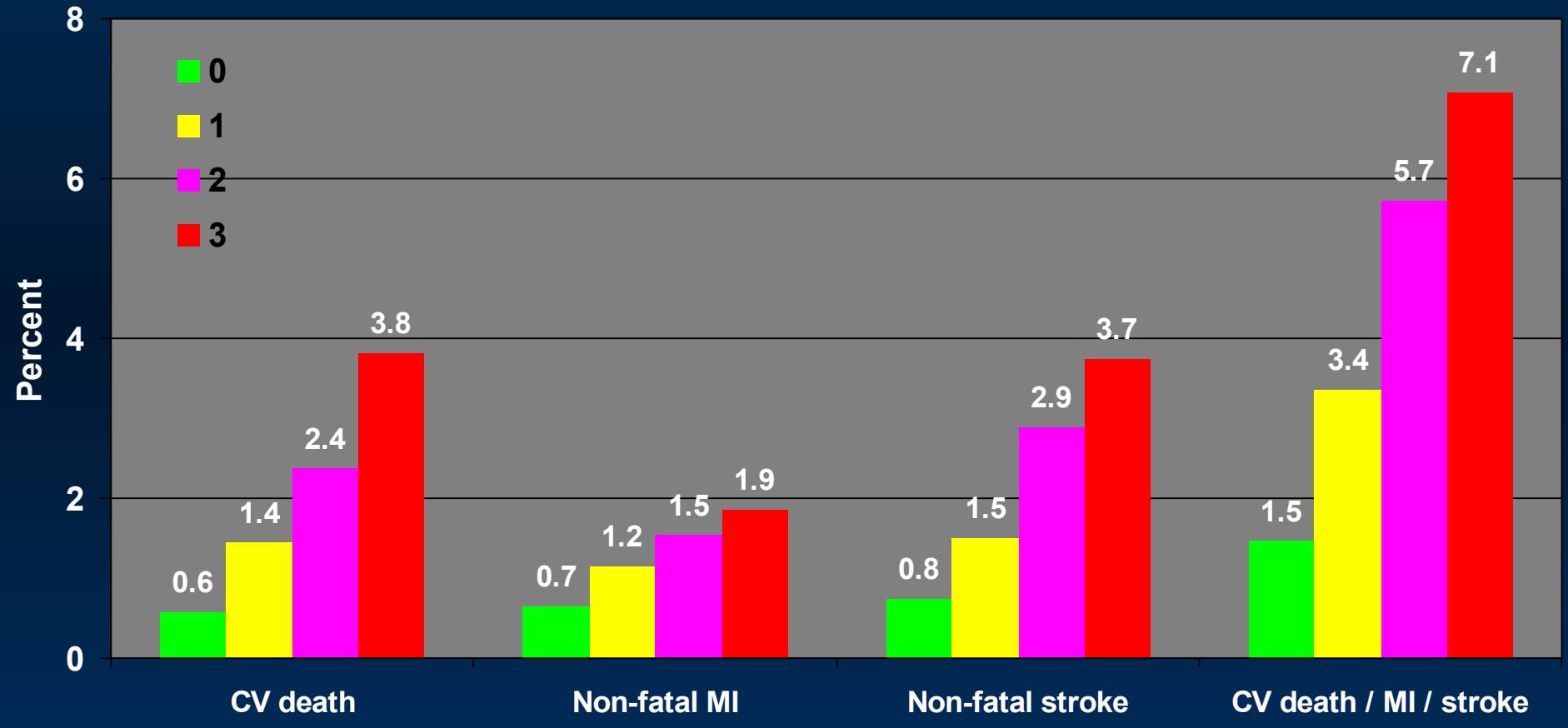
Major adverse cardiovascular event rates at one year (unadjusted)

	Total (N=63,129)	Symptomatic (N=51,685)	Multiple RF only (N=11,444)
CV death	1.5	1.7	0.6
Non-fatal MI	1.2	1.2	0.8
Non-fatal stroke	1.6	1.8	0.8
CV death/MI/ stroke	3.5	3.9	1.7
CV death/MI/ stroke/ hospitalization for atherothrombotic events*	12.9	14.5	5.4

*TIA, unstable angina, other ischemic arterial event including worsening of peripheral arterial disease
RF=risk factor

REACH REGISTRY
REduction of Atherothrombosis for Continued Health

1-year cardiovascular event rates as function of number of symptomatic disease locations*



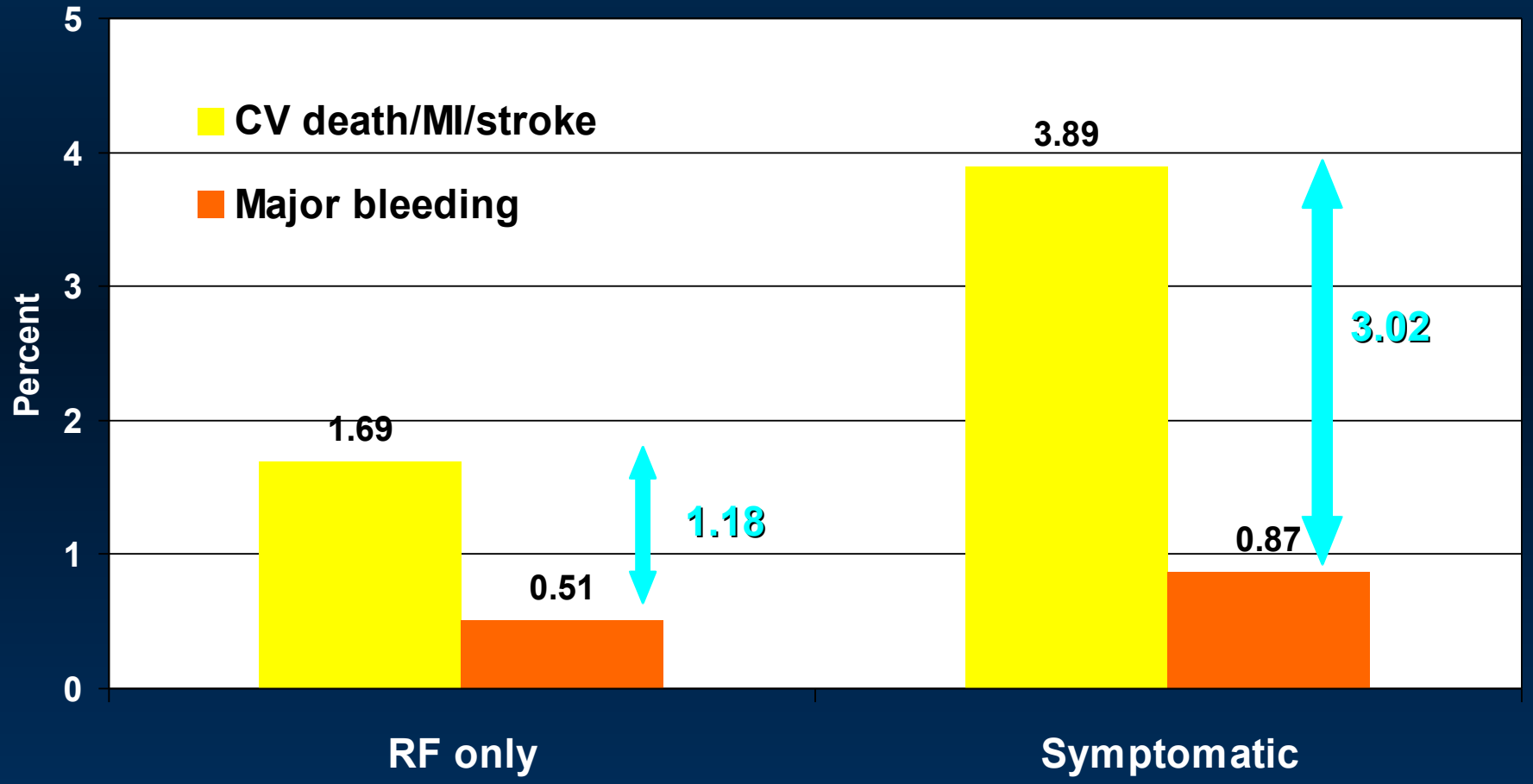
All p values <0.001

*Pts with ≥3 risk factors but no symptoms are counted as 0, even in the presence of asymptomatic carotid plaque or reduced ABI

**TIA, unstable angina, other ischemic arterial event including worsening of peripheral arterial disease

REACH REGISTRY
REduction of Atherothrombosis for Continued Health

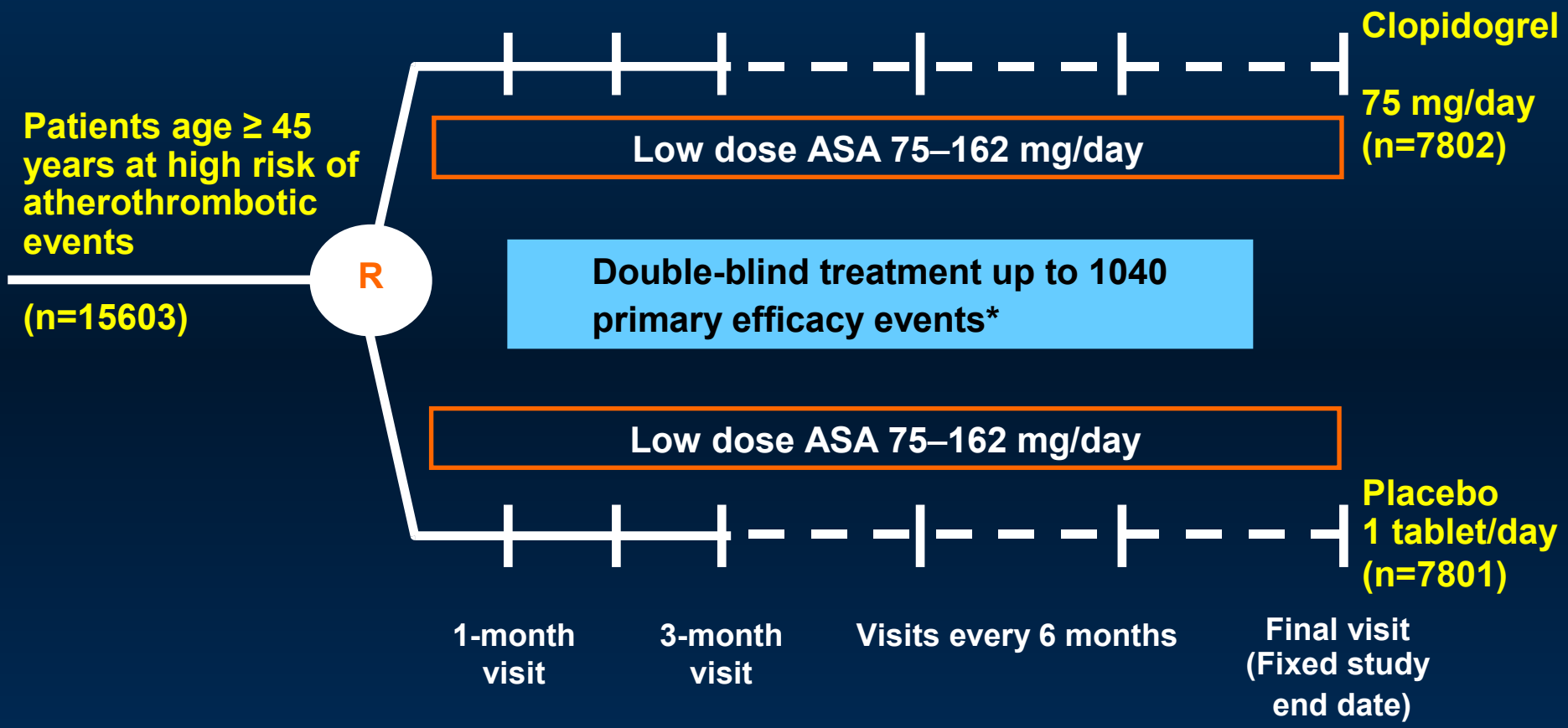
CV death/MI/stroke vs bleeding* : symptomatic vs RF only (unadjusted)



*: requiring hospitalization or transfusion

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

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

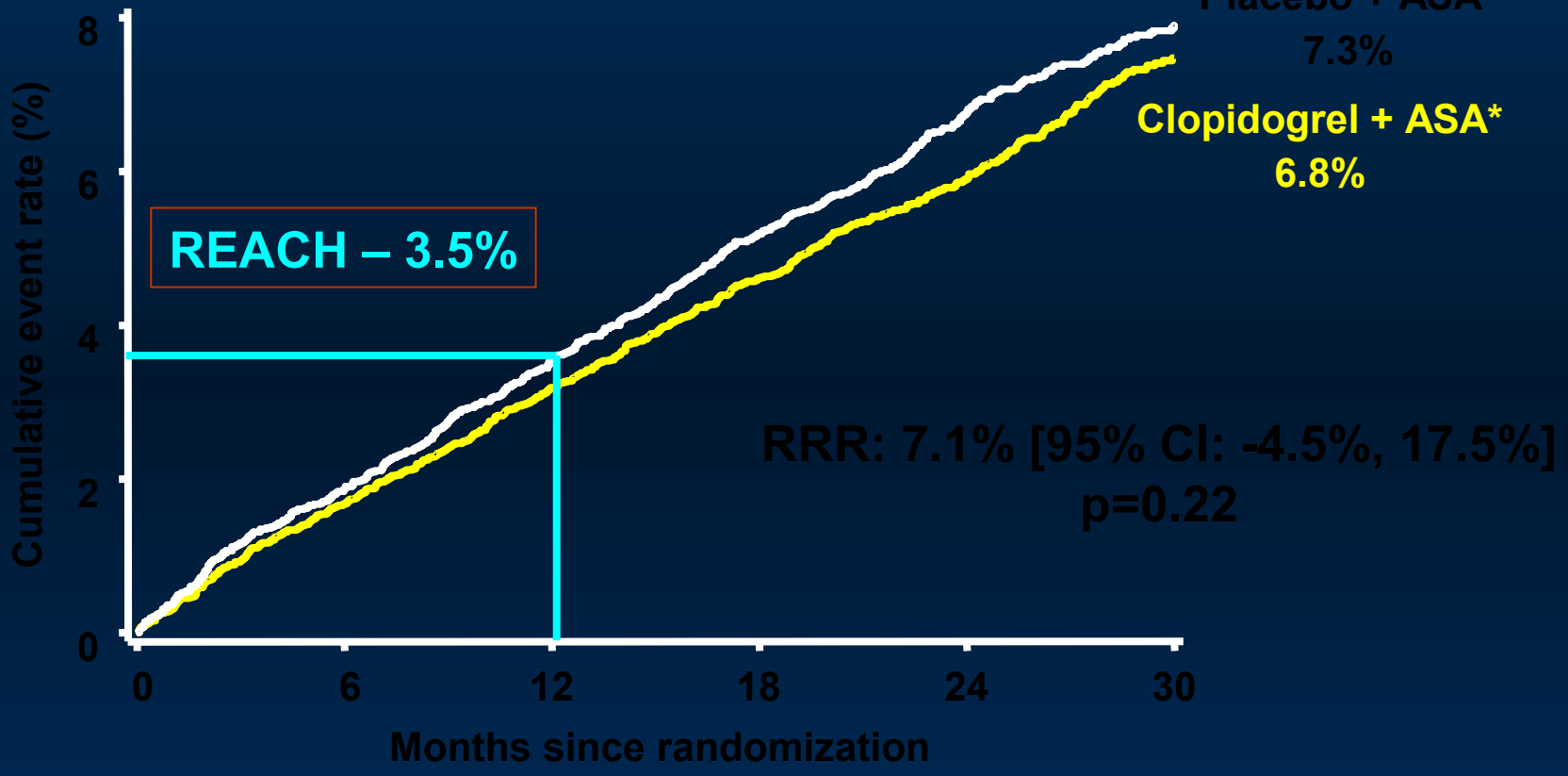
Major Risk Factors

- 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

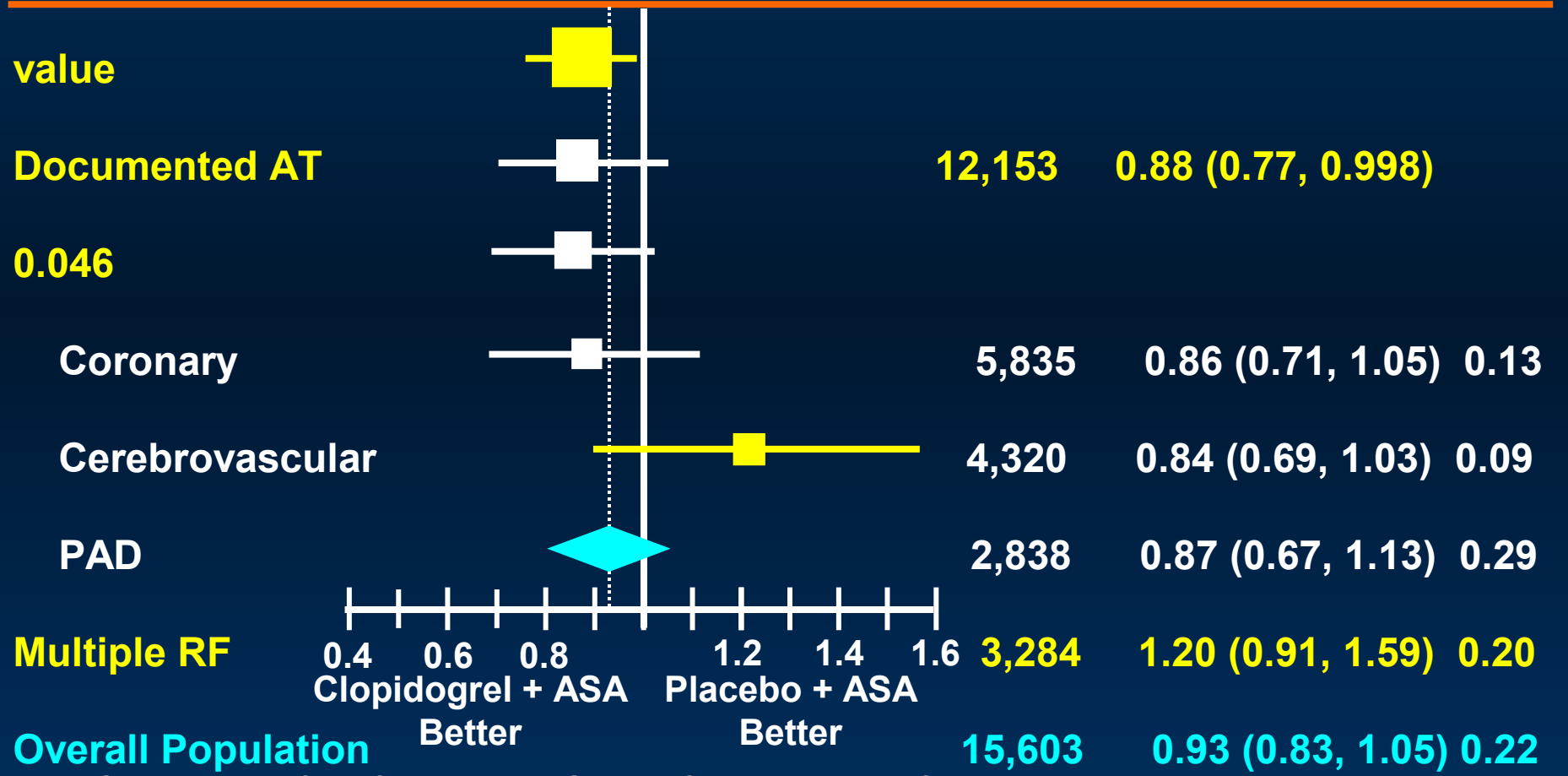
*All patients received ASA 75-162mg/day

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



* First Occurrence of MI (fatal or not), Stroke (fatal or not), or CV Death

RF= Risk Factors, AT= Atherothrombosis

CHARISMA

Bhatt DL. Oral presentation at ACC 2006.

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 Death64 (3.9)	36 (2.2)	1.74 (1.16, 2.62)	0.01	
Myocardial Infarction40 (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

CHARISMA

Bhatt DL. Oral presentation at ACC 2006.

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

OUTLINE

- Pathophysiology
  - Atherosclerosis
  - Ischemia
- Therapy
  - Lifestyle
  - Pharmacology
  - Revascularization

COURAGE

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

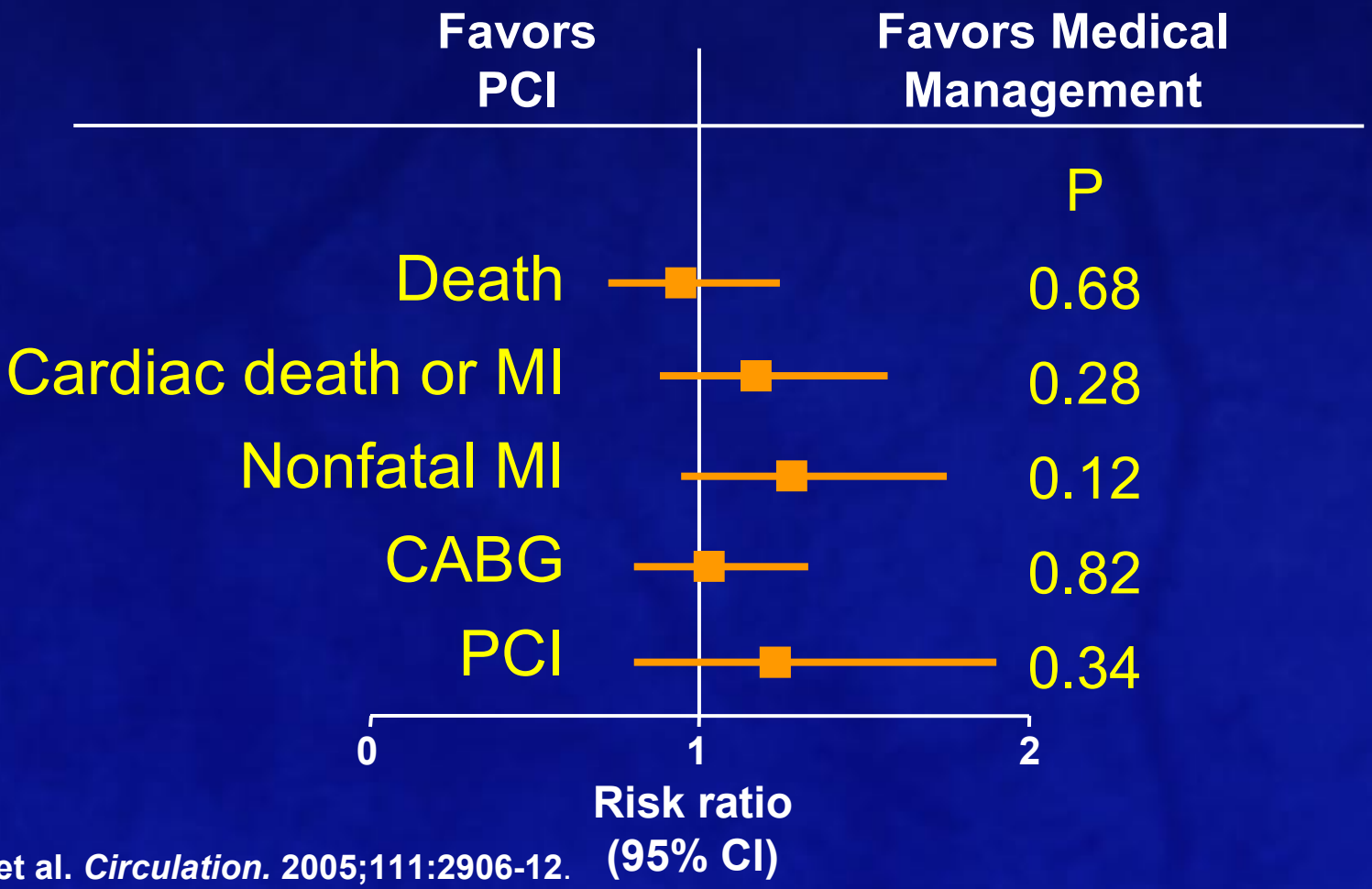
Revascularization and

Aggressive **G**uideline-Driven

Drug **E**valuation

Stable CAD: PCI vs Conservative Medical Management

Meta-analysis of 11 randomized trials; N = 2,950



Katritsis DG et al. *Circulation.* 2005;111:2906-12.

Hypothesis

PCI + Optimal Medical Therapy

will be Superior to

Optimal Medical Therapy Alone

Inclusion/Exclusion Criteria

Inclusion

- Men and Women
- 1, 2, or 3 vessel disease
  (> 70% visual stenosis of proximal coronary segment)
- Anatomy suitable for PCI
- CCS Class I-III angina
- Objective evidence of ischemia at baseline, ECG or imaging
- ACC/AHA Class I or II indication for PCI

Exclusion

- Uncontrolled unstable angina
- Complicated post-MI course
- Revascularization within 6 months
- Ejection fraction <30%
- Cardiogenic shock/severe heart failure
- History of sustained or symptomatic VT/VF

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

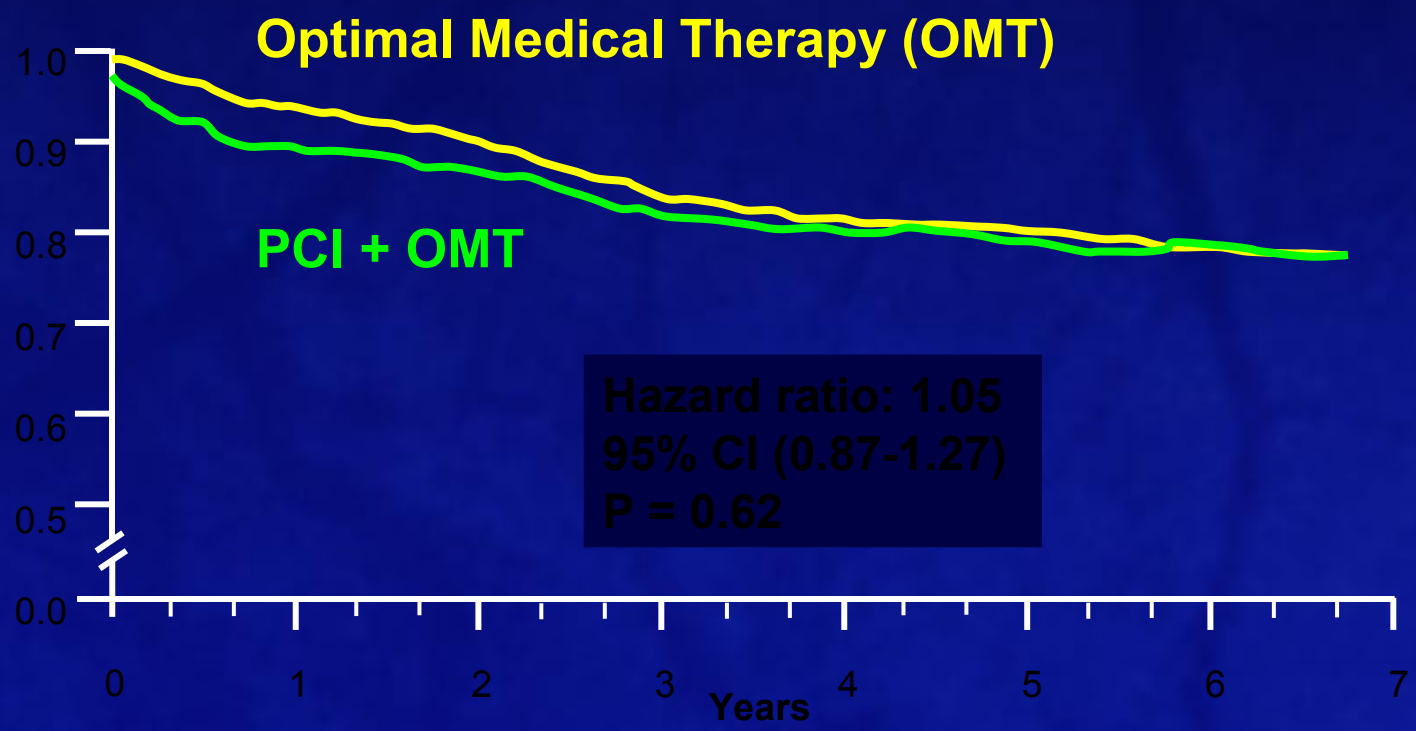
Risk Factor Goals

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

Freedom from Angina By CCS Class During Long-Term Follow-up

Characteristic	PCI + OMT	OMT
CLINICAL		
Angina free – no.		
Baseline	12%	13%
1 Yr	66%	58%
3 Yr	72%	67%
5 Yr	74%	72%

The comparison between the PCI group and the medical-therapy group was significant at 1 year (P<0.001) and 3 years (P=0.02) but not at baseline or 5 years.

Recommendations for pharmacological therapy to improve symptoms and/or reduce ischaemia

Class I

- Provide **short-acting nitroglycerin** for acute symptom relief and situational prophylaxis, with appropriate instructions on how to use the treatment **(level of evidence B)**

- Test the effects of a **beta-1 blocker, and titrate to full dose**; consider the need for 24 h protection against ischaemia **(level of evidence A)**

- In case of beta-blocker intolerance or poor efficacy attempt monotherapy with a **calcium channel blocker (level of evidence A), long acting nitrate (level of evidence C),** or **nicorandil (level of evidence C)**

- If the effects of **beta-blocker** monotherapy are insufficient, add a **dihydropyridine** calcium channel blocker **(level of evidence B)**

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Recommendations for pharmacological therapy to improve symptoms and/or reduce ischaemia

Class IIa

- In case of beta-blocker intolerance try **sinus node inhibitor** (level of evidence B)

- If CCB monotherapy or combination therapy (CCB with beta-blocker) is unsuccessful, substitute the CCB with a **long-acting nitrate or nicorandil**. Be careful to avoid nitrate tolerance (level of evidence C)

Class IIb

- **Metabolic agents may be used** where available as add on therapy, or as substitution therapy when conventional drugs are not tolerated (level of evidence B)

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