بسم الله الرحمن الرحيم

The Ideal Cholesterol: is the lower is better ?

By

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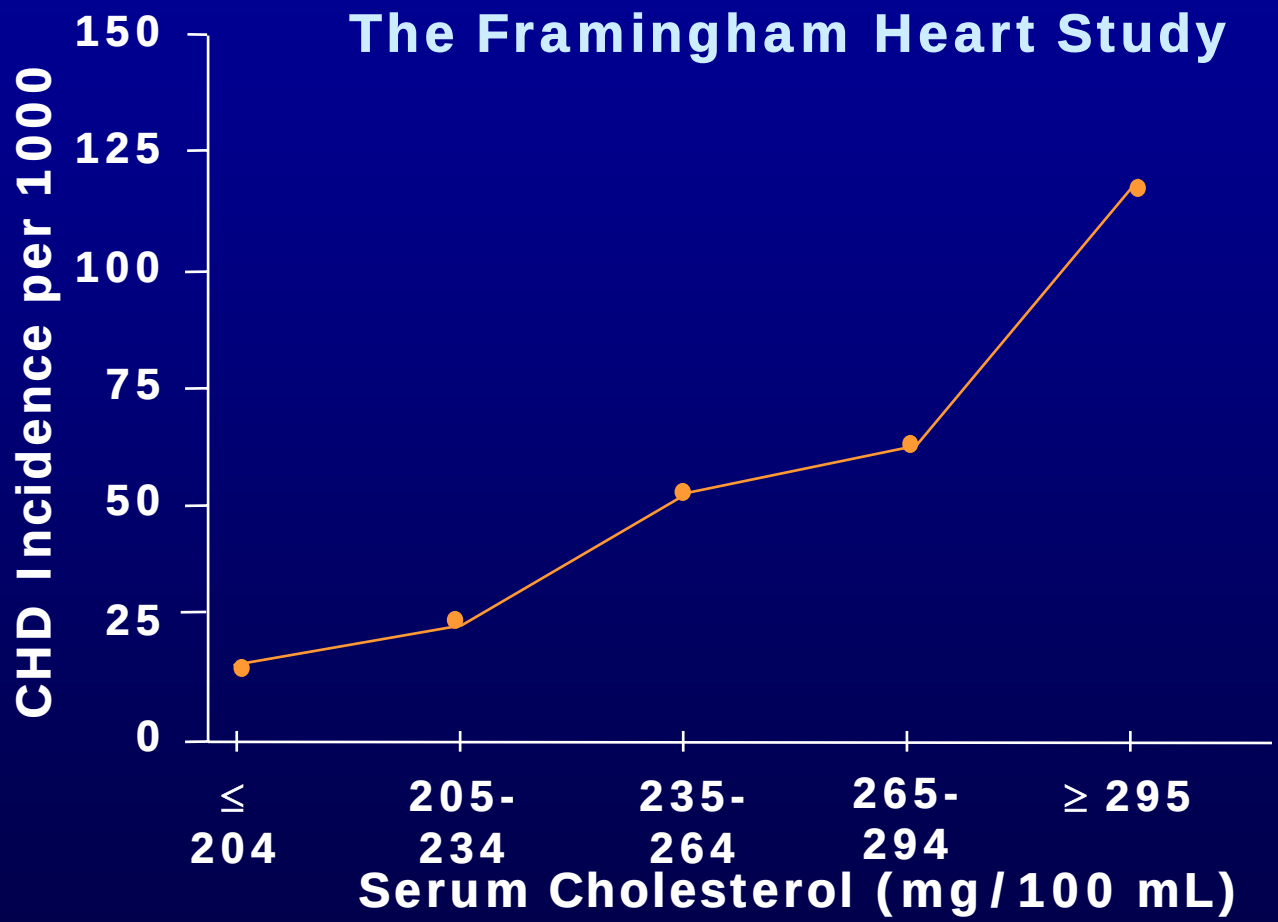
Cholesterol & atherogenesis

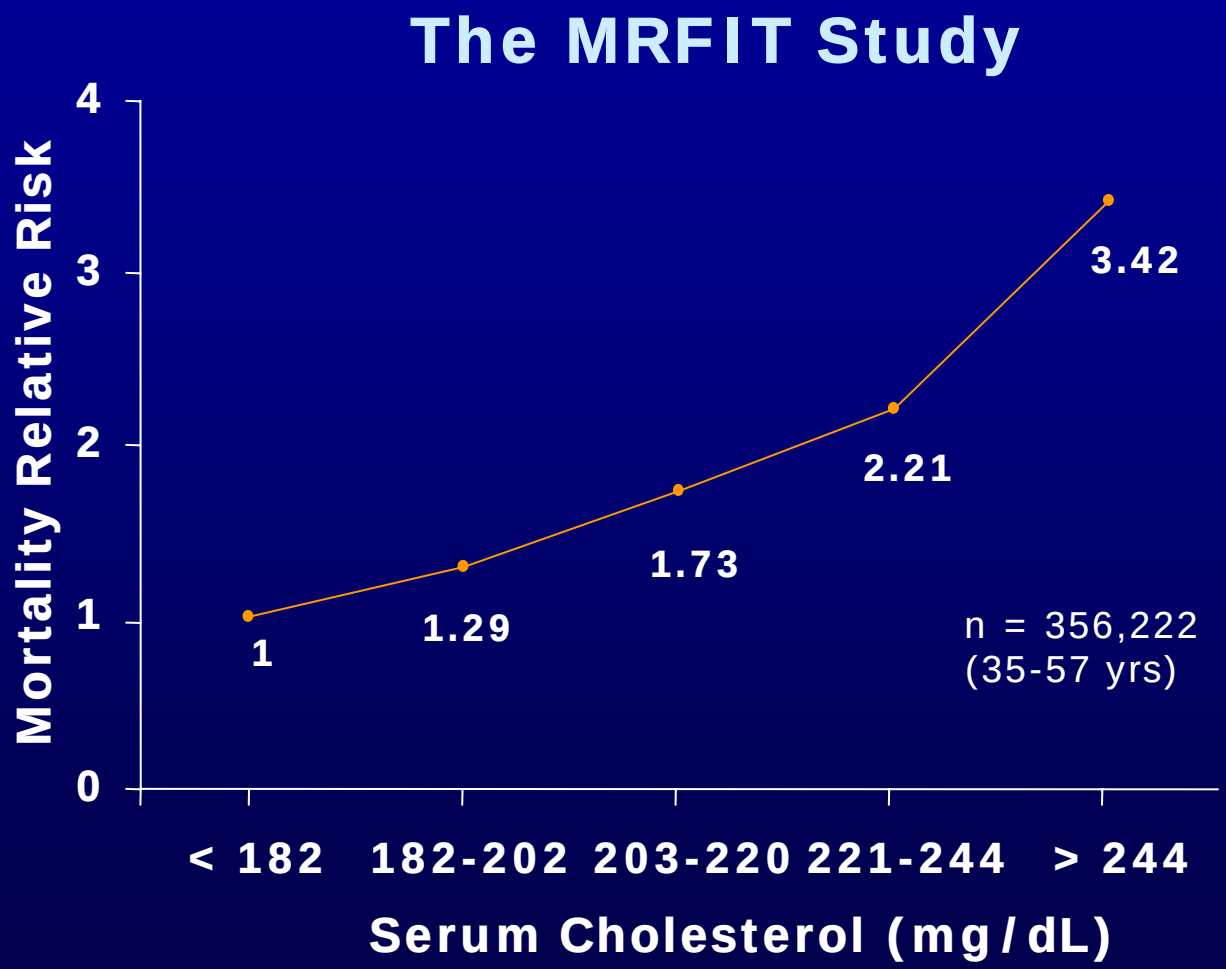
- Theoretical evidence
- Experimental evidence
- Epidemiological evidence
  - Large epidemiological trials
  - Regression trials

Lower Cholesterol Levels Associated With Lower CHD Risk



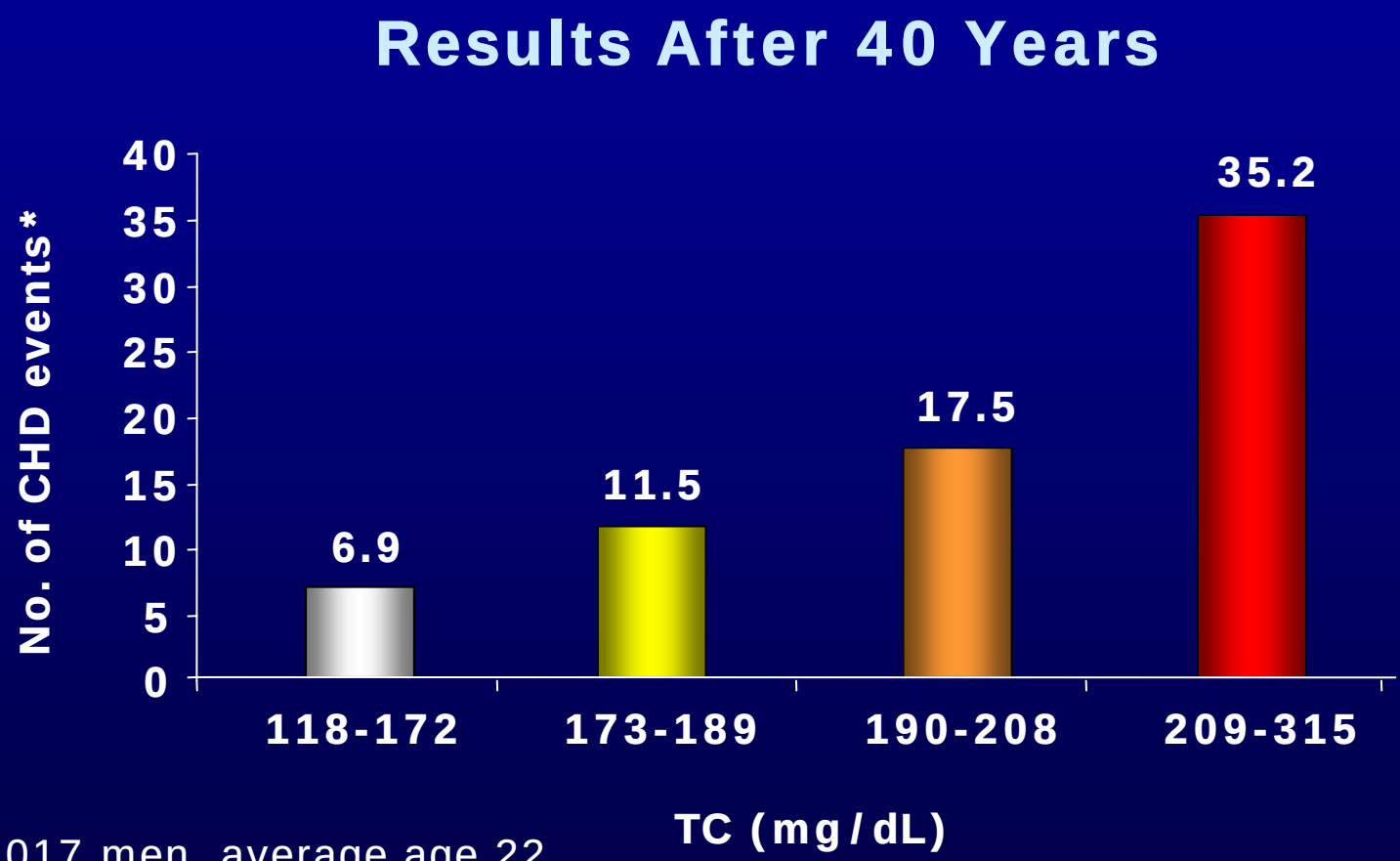
Castelli WP. Am J Med. 1984;76:4-12.

Relation of Serum Cholesterol to CHD Mortality



Stamler J, et al. JAMA. 1986;256:2823-2828.

Early High TC Levels Associated With Later CHD Events



*1017 men, average age 22

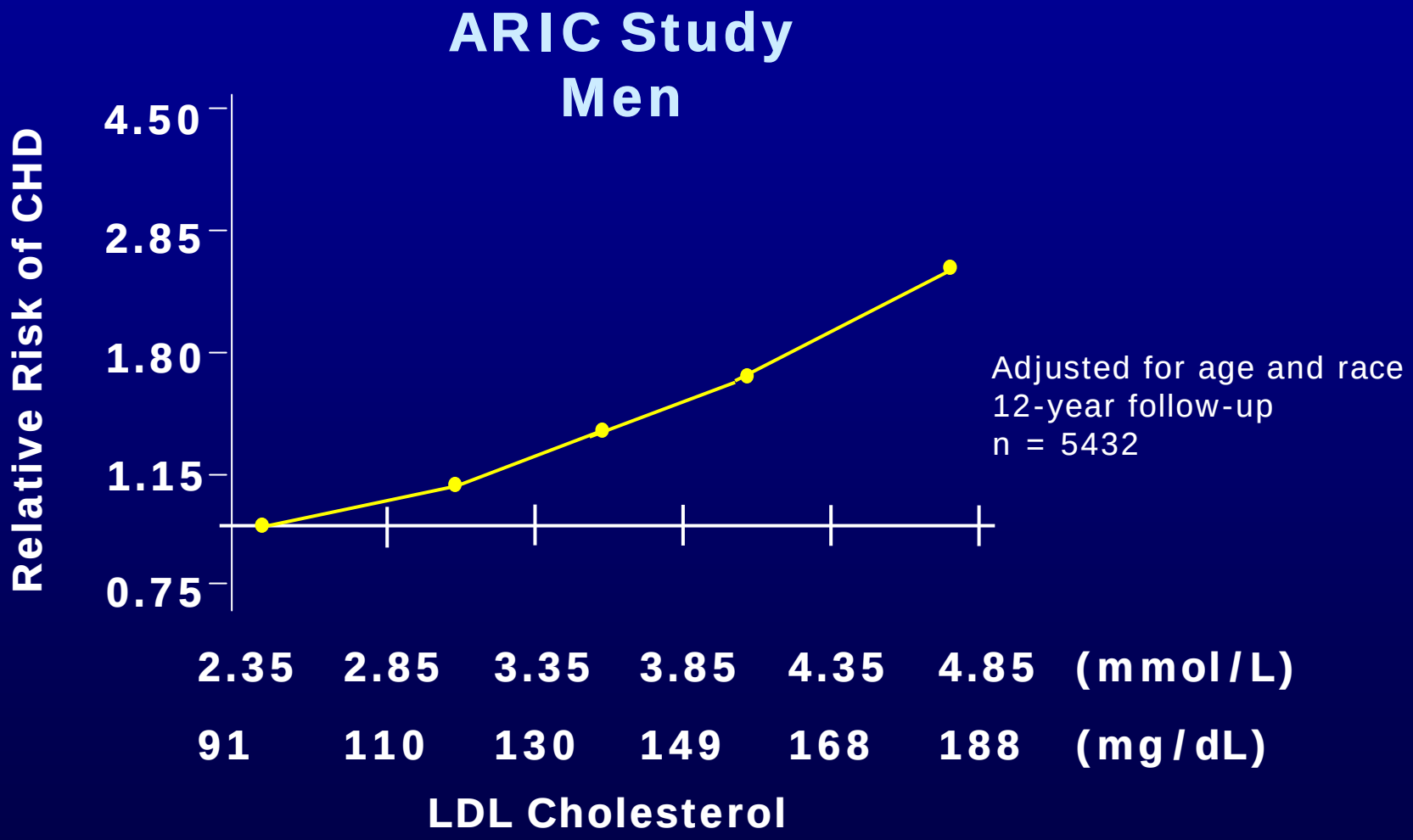
Adapted from Klag MJ, et al. *N Engl J Med*. 1993;328:313-318.

LDL Cholesterol

- Remains the cornerstone of dyslipidemia therapy[1]
- Strongly associated with atherosclerosis and CHD events[1]
- 10% increase results in a 20% increase in CHD risk[1]
- Most patients with elevated LDL untreated
  - Only 4.5 million out of 28.4 million treated[2,3]

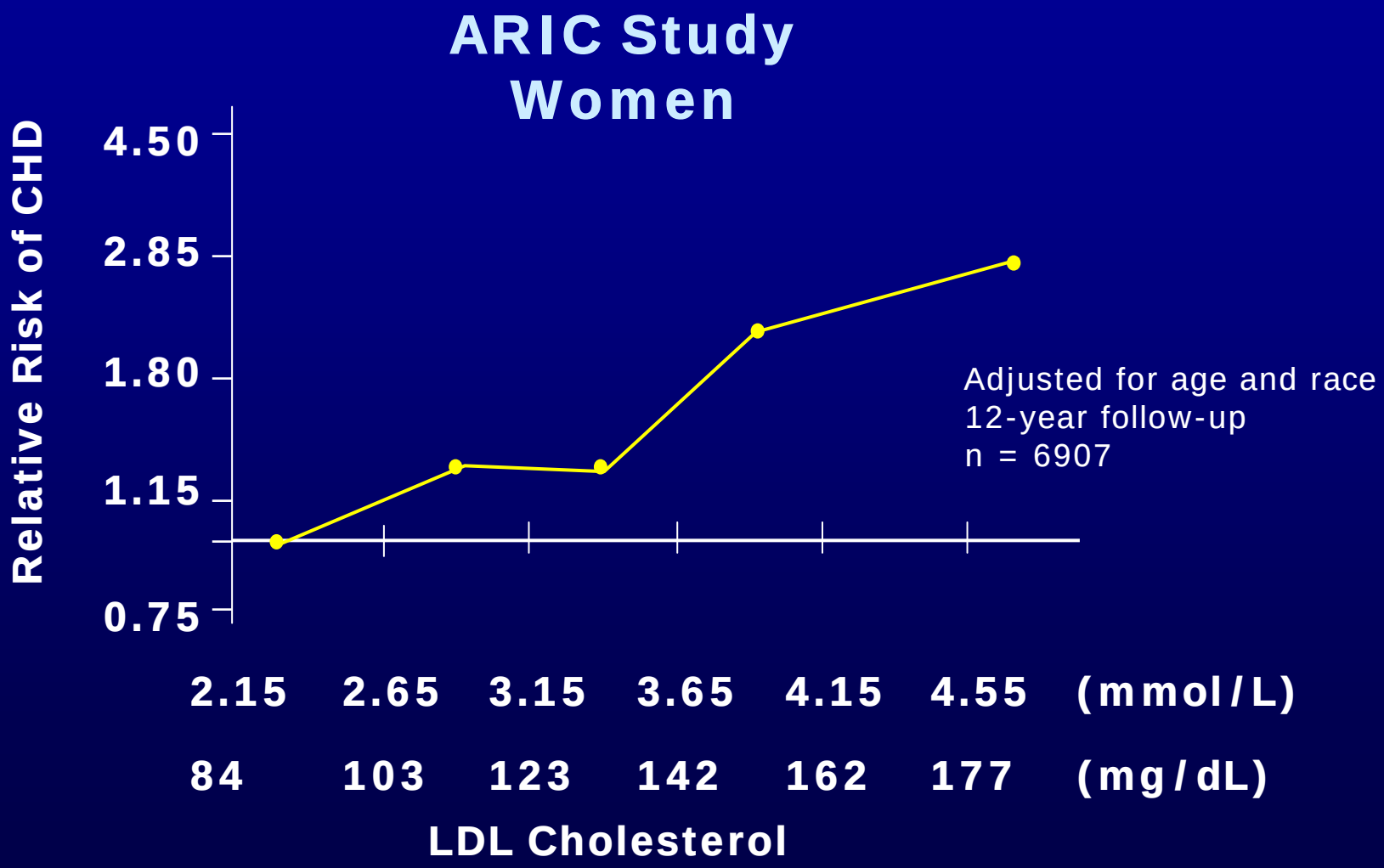
1. Wood D et al. *Atherosclerosis*. 1998;140:199-270.
2. National Centre for Health Statistics. *National Health and Nutrition Examination Survey* (III), 1994.
3. Jacobson TA, et al. *Arch Intern Med*. 2000;160:1361-1369.

Increased Relative Risk of CHD Associated With Increasing LDL Levels



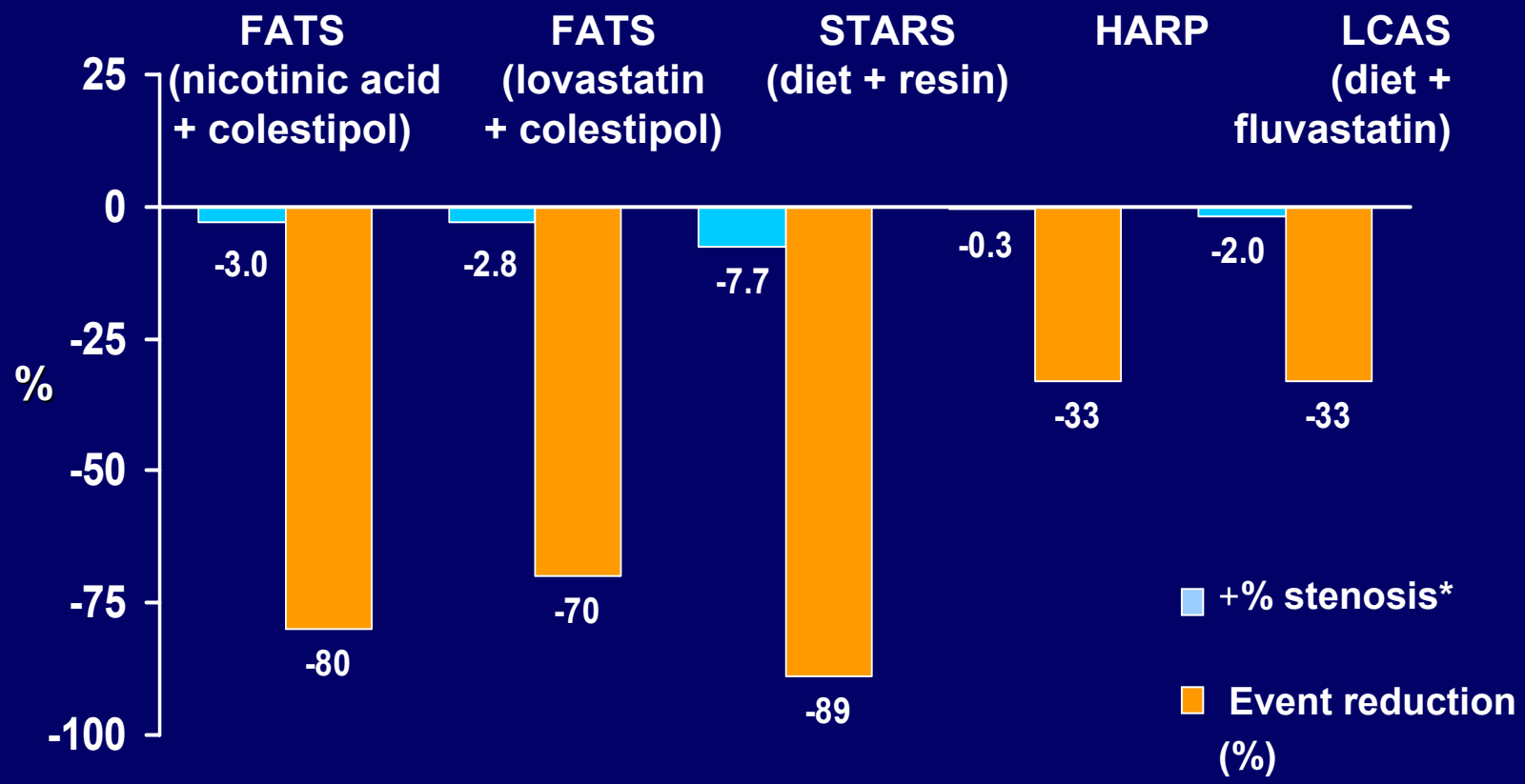
Adapted from Sharrett AR, et al. *Circulation*. 2001;104:1108-1113.

Increased Relative Risk of CHD Associated With Increasing LDL Levels



Adapted from Sharrett AR, et al. *Circulation*. 2001;104:1108-1113.

Event Reduction in Angiographic Plaque Regression Trials

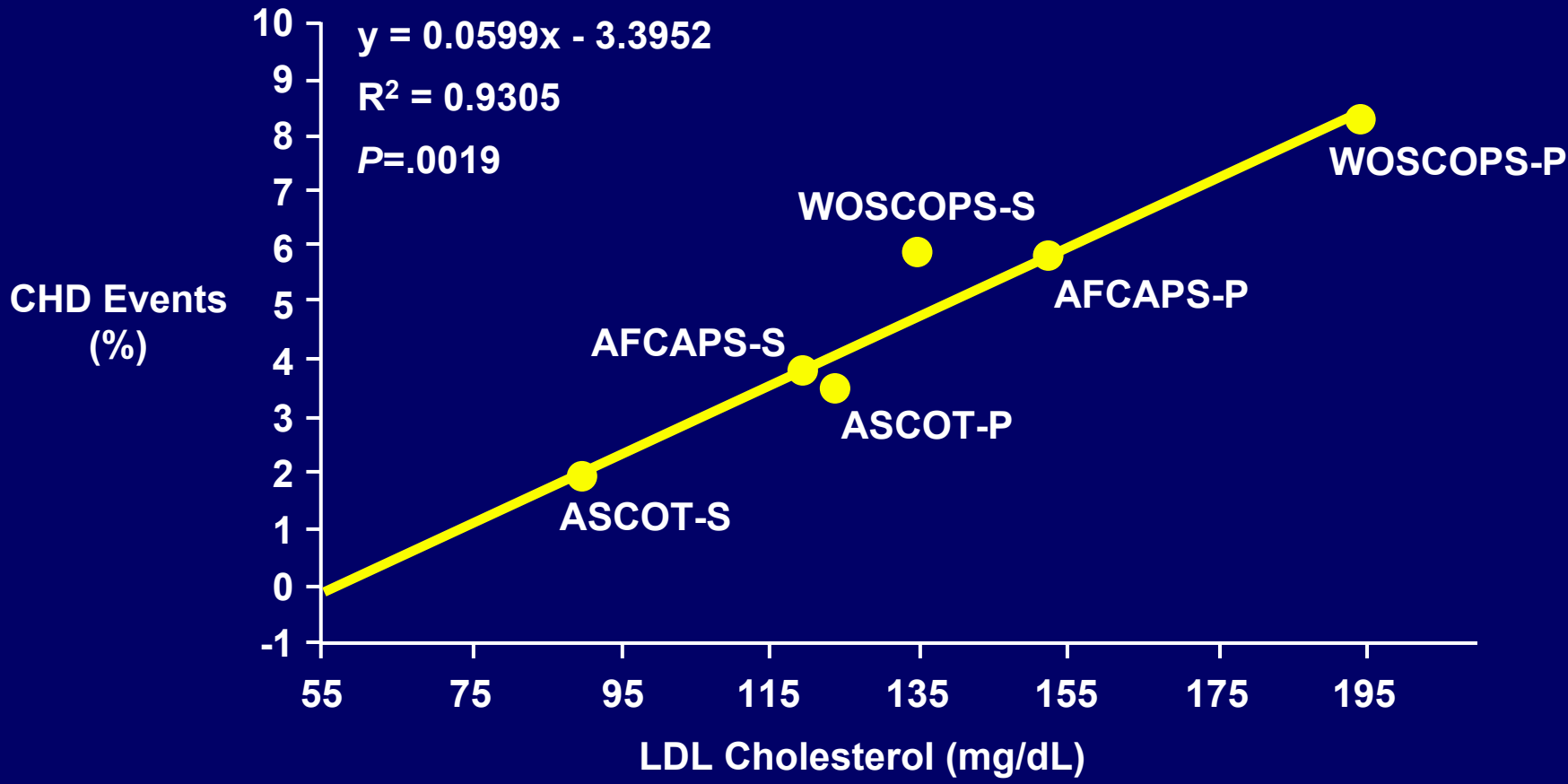


* As defined by the comparison between the change in the treated group vs the change in the control.

Brown BG et al. Circulation. 1993;87:1781-1791.

Clinical Events Correlate Directly With On-Treatment LDL-Cholesterol Levels

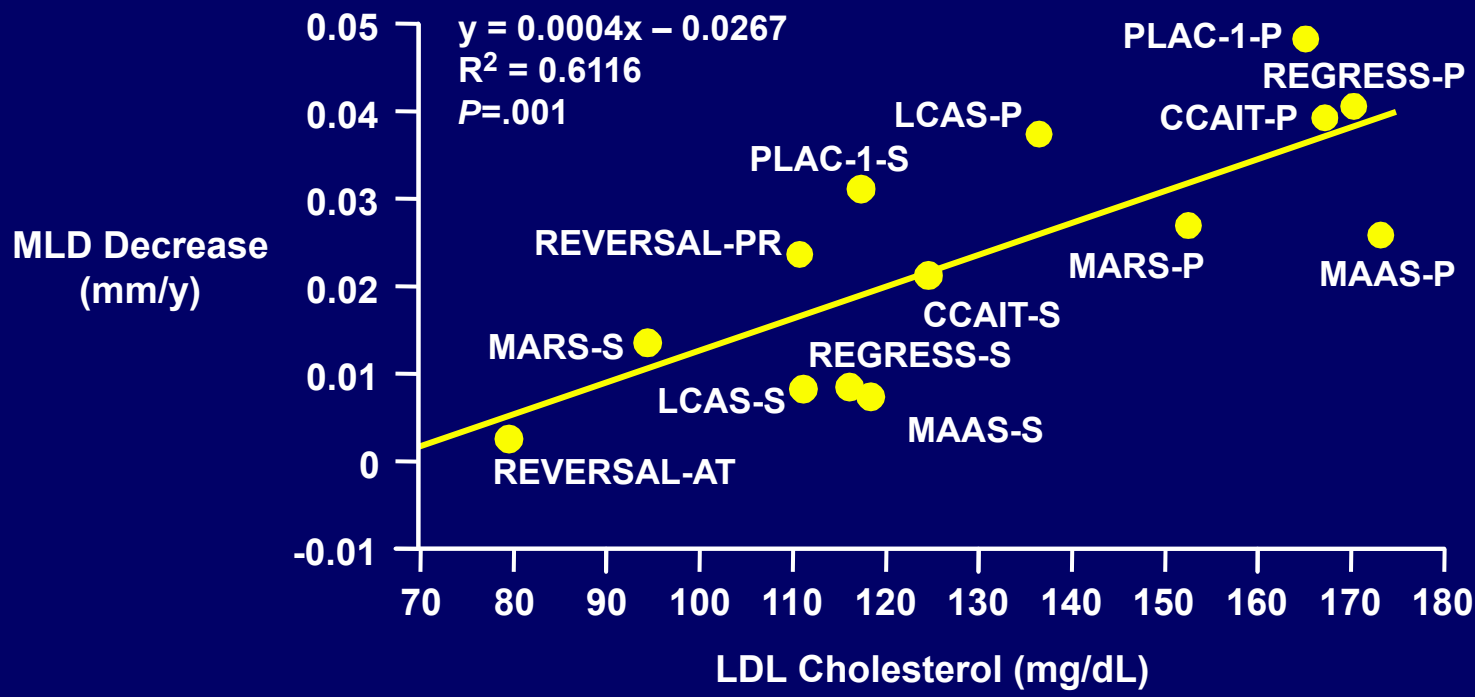
TIME TO BENEFIT in Lipid-Lowering Trials



P = placebo; S = statin.

O'Keefe et al. *J Am Coll Cardiol*. 2004;43:2142

Atherosclerosis Progression Varies Directly With On-Treatment LDL Cholesterol Levels



AT = atorvastatin; CCAIT = Canadian Coronary Atherosclerosis Intervention Trial; LCAS = Lipoprotein and Coronary Atherosclerosis Study; MAAS = Multicentre Anti-Atheroma Study; MARS = Monitored Atherosclerosis Regression Study; MLD = mean lumen diameter; PLAC = Pravastatin Limitation of Atherosclerosis in the Coronary Arteries study; PR = pravastatin; REGRESS = Regression Growth Evaluation Statin Study; REVERSAL = Reversal of Atherosclerosis with Aggressive Lipid Lowering.

O'Keefe et al. *J Am Coll Cardiol*. 2004;43:2142

Gotto. *Am J Cardiol*. 2005;96(suppl):34F.

Proposed Mechanisms of Event Reduction by Lipid-Lowering Therapy

- Improved endothelium-dependent vasodilation
- Stabilization of atherosclerotic lesions
  - especially nonobstructive, vulnerable plaques
- Reduction in inflammatory stimuli
  - lipoproteins and modified lipoproteins
- Prevention, slowed progression, or regression of atherosclerotic lesions

Libby P. *Circulation*. 1995;91:2844-2850.

Intermolecular Similarities And Differences Of Statins

- Intermolecular similarities
  - all statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase
  - all statins share a common dihydroxy group necessary for HMG-CoA reductase enzyme inhibition
- Intermolecular difference
  - substituents on pharmacophore moiety are responsible for pharmacokinetic and pharmacodynamic differences, which in turn affect efficacy, safety, and pleiotropic effects

Mason et al. *Am J Cardiol*. 2005;96(suppl):11F.

Chemical Structures Of Statins

TIME TO BENEFIT
in Lipid-Lowering Trials

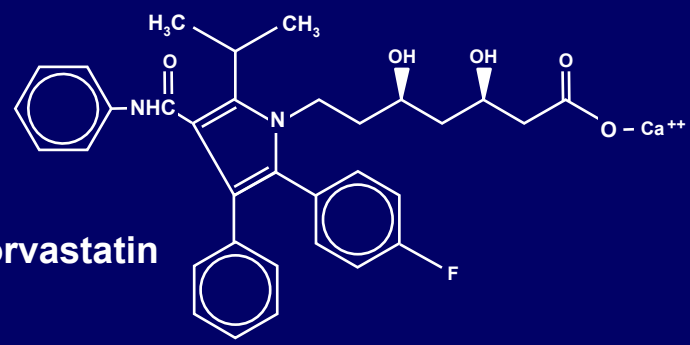
Natural Or Fungal-Derived

Lovastatin

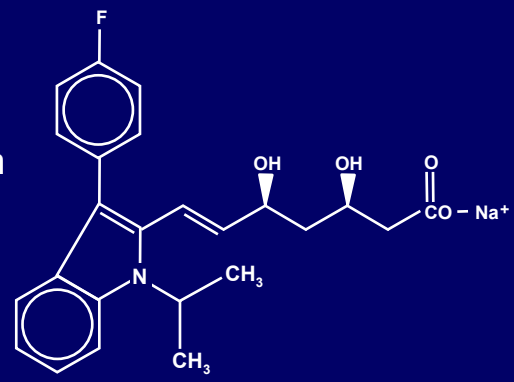
Simvastatin

Pravastatin

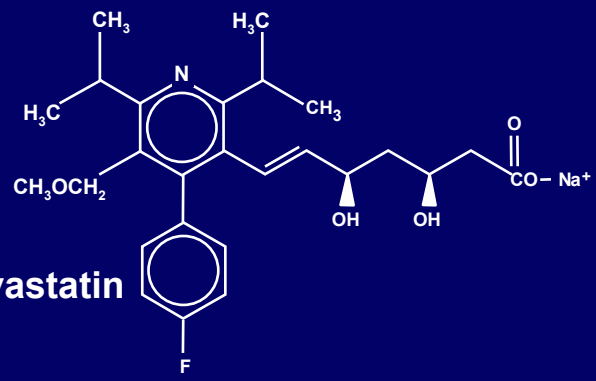
Synthetic



Atorvastatin

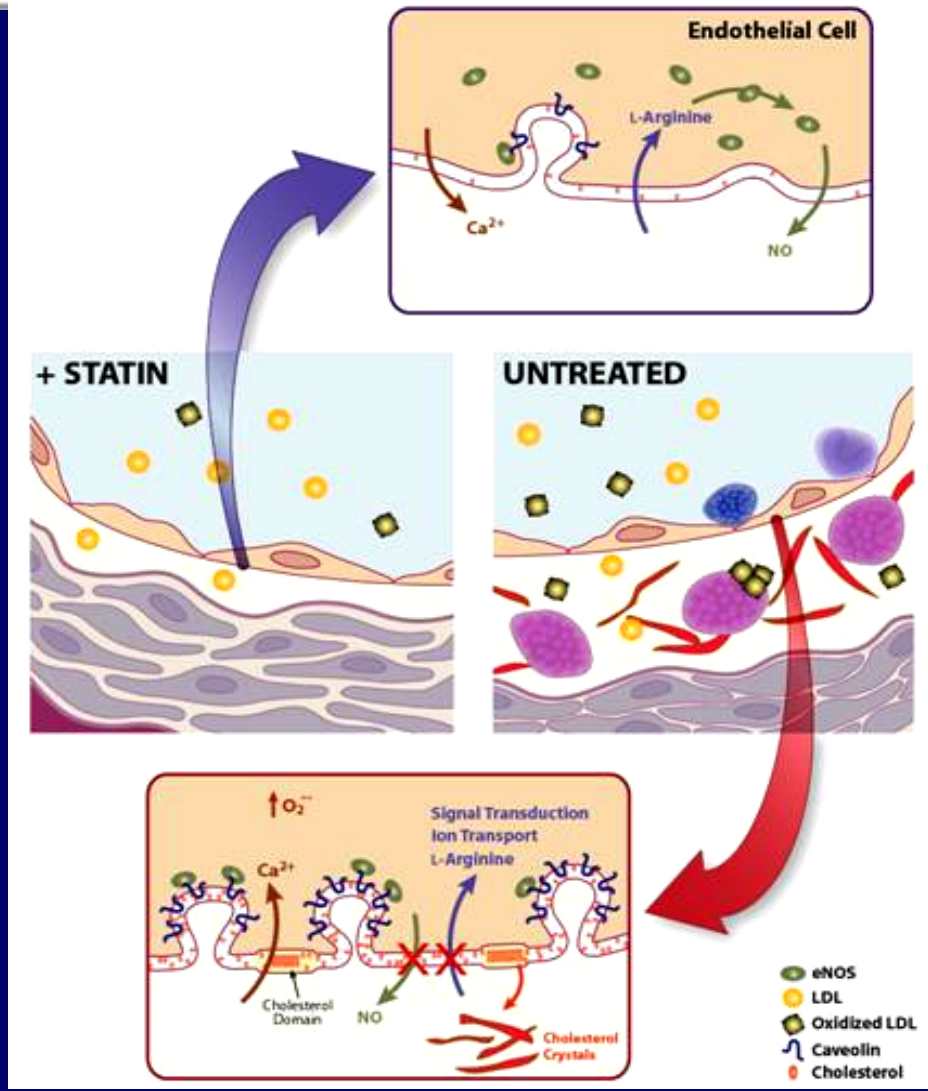


Fluvastatin



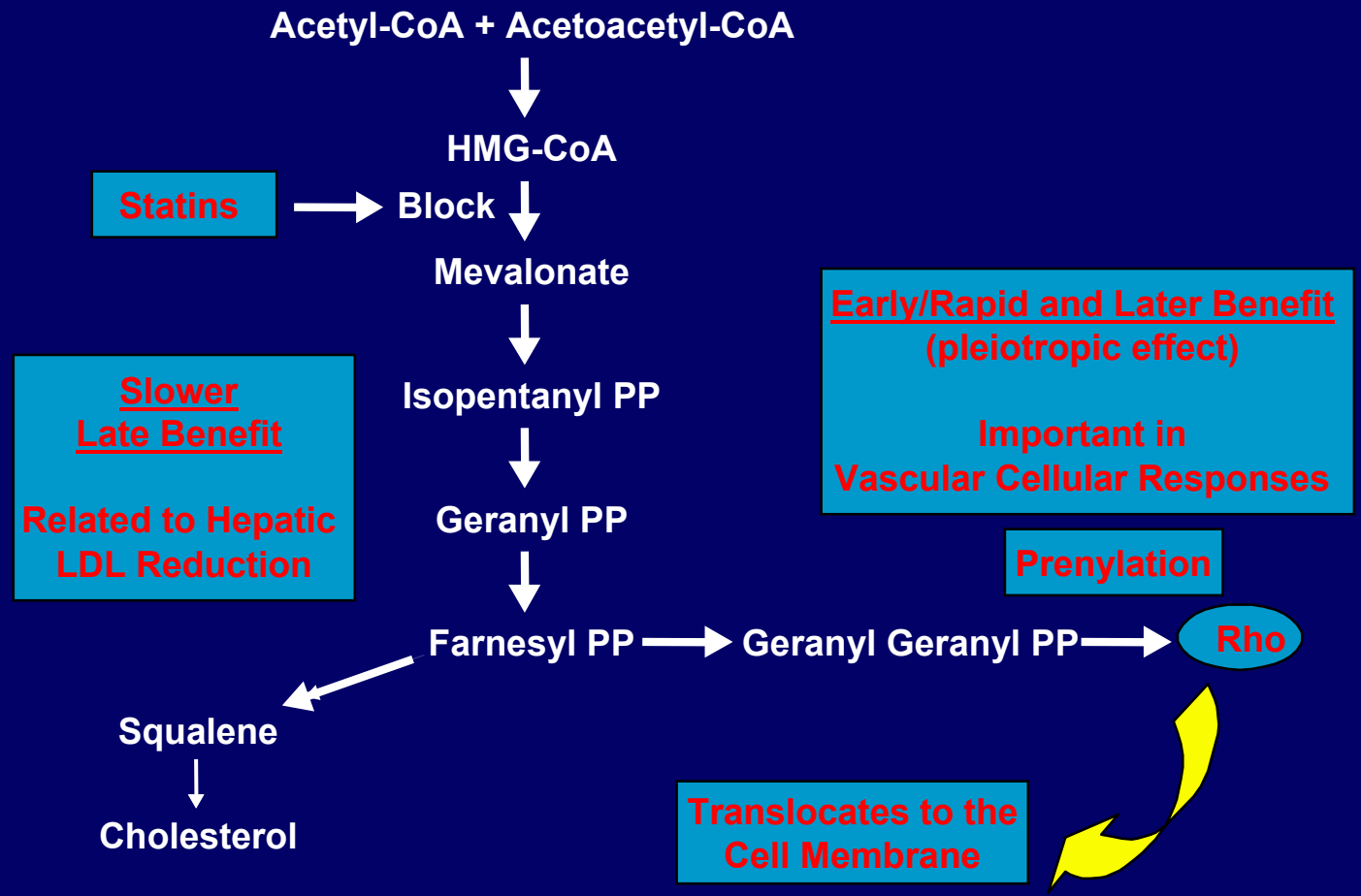
Cerivastatin

Vessel Wall And Endothelial Cell Membrane Changes With Atherogenesis



Mason et al. *Am J Cardiol*. 2005;96(suppl):11F.

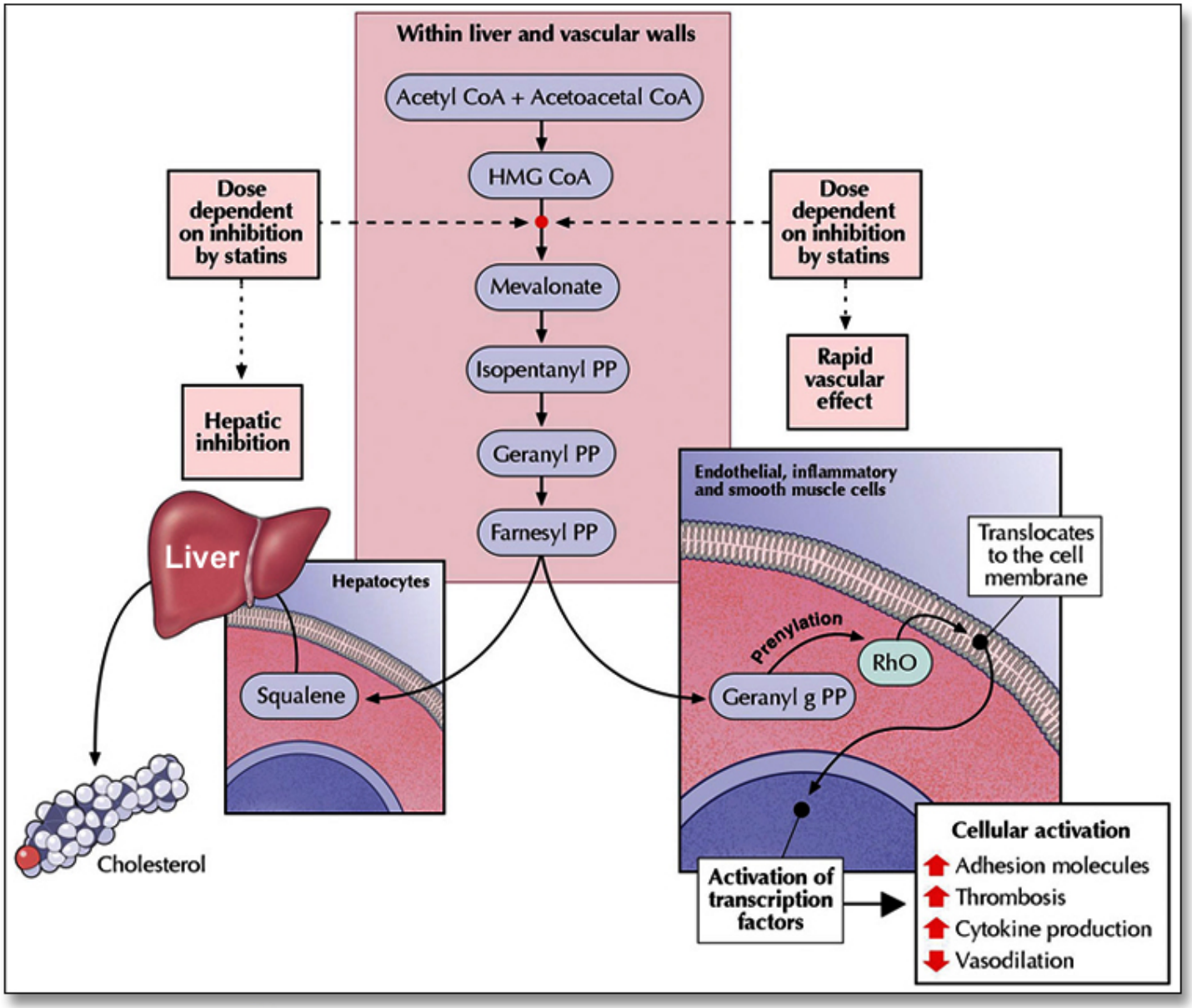
Metabolic Pathways Blocked By Statins



PP = pyrophosphate.

Ray and Cannon. *Am J Cardiol*. 2005;96(suppl):54F.

Hepatic and Extra-hepatic (Pleiotropic Effects) of Statins

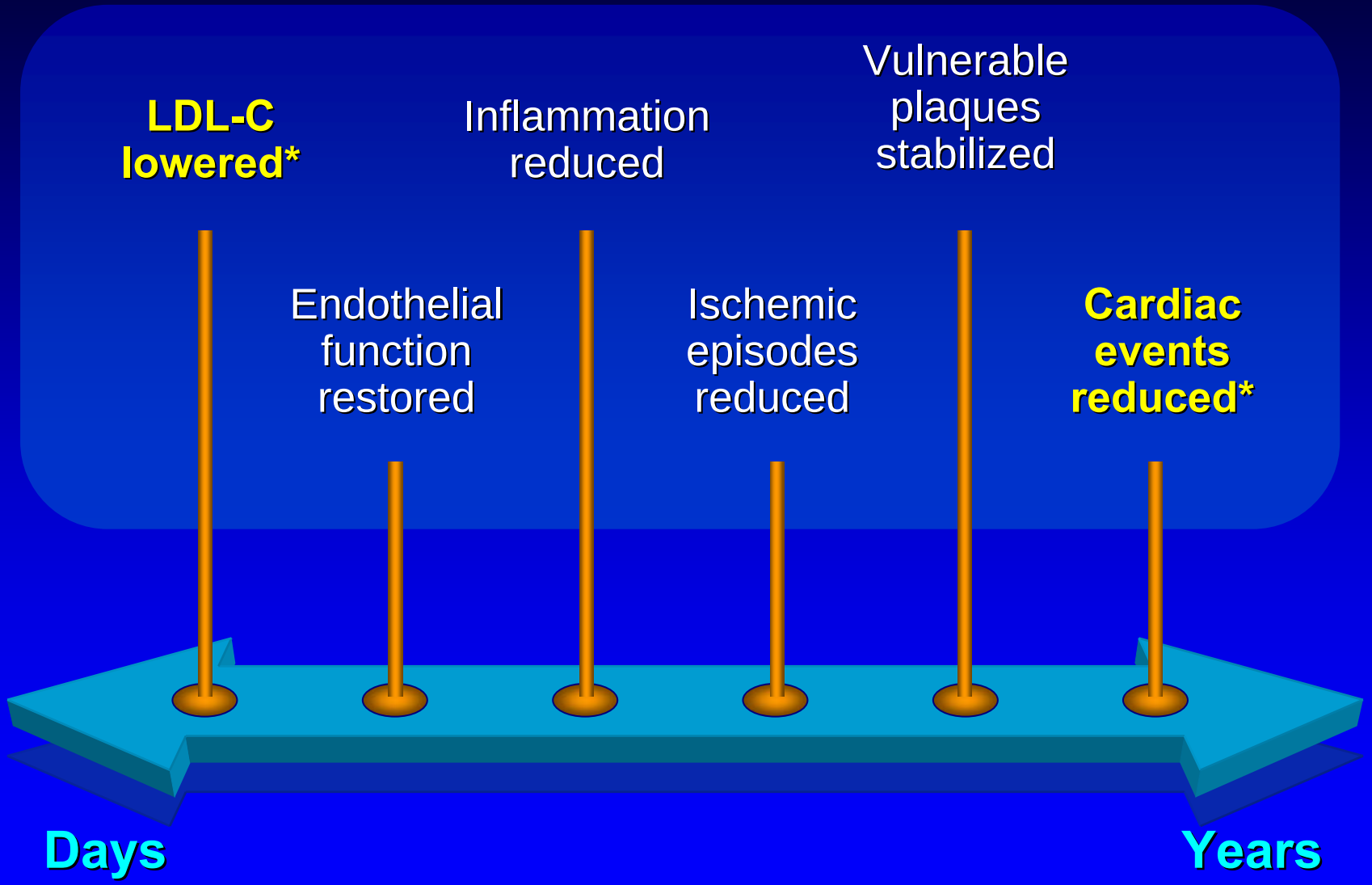


PLEIOTROPIC EFFECTS OF STATINS

- **Antiatherosclerotic effects on:**
  - **Endothelial dysfunction**
  - **Inflammation (inhibition of adhesion molecules)**
  - **plaque stability (inhibition of MMP)**
  - **LDL oxidation and density**
  - **SMC proliferation**
  - **Cholesterol esterification and accumulation**
- **Antithrombotic effects on:**
  - **Tissue Factor**
  - **Platelet aggregation**
  - **Blood viscosity and fibrinogen**
  - **fibrinolysis**

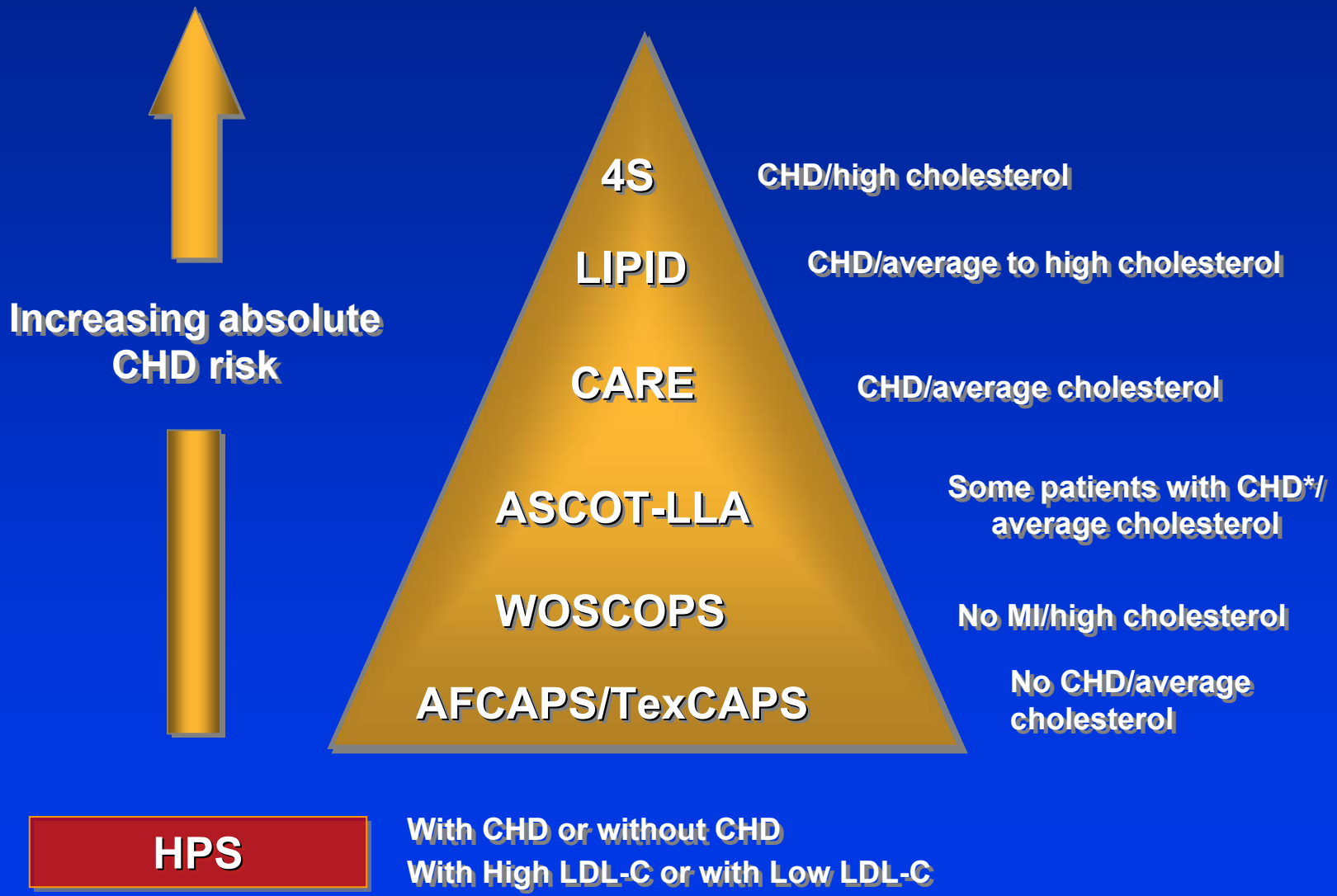
Corsini, Int J Clin Prat 2004 494-503

Potential Time Course of Statin Effects



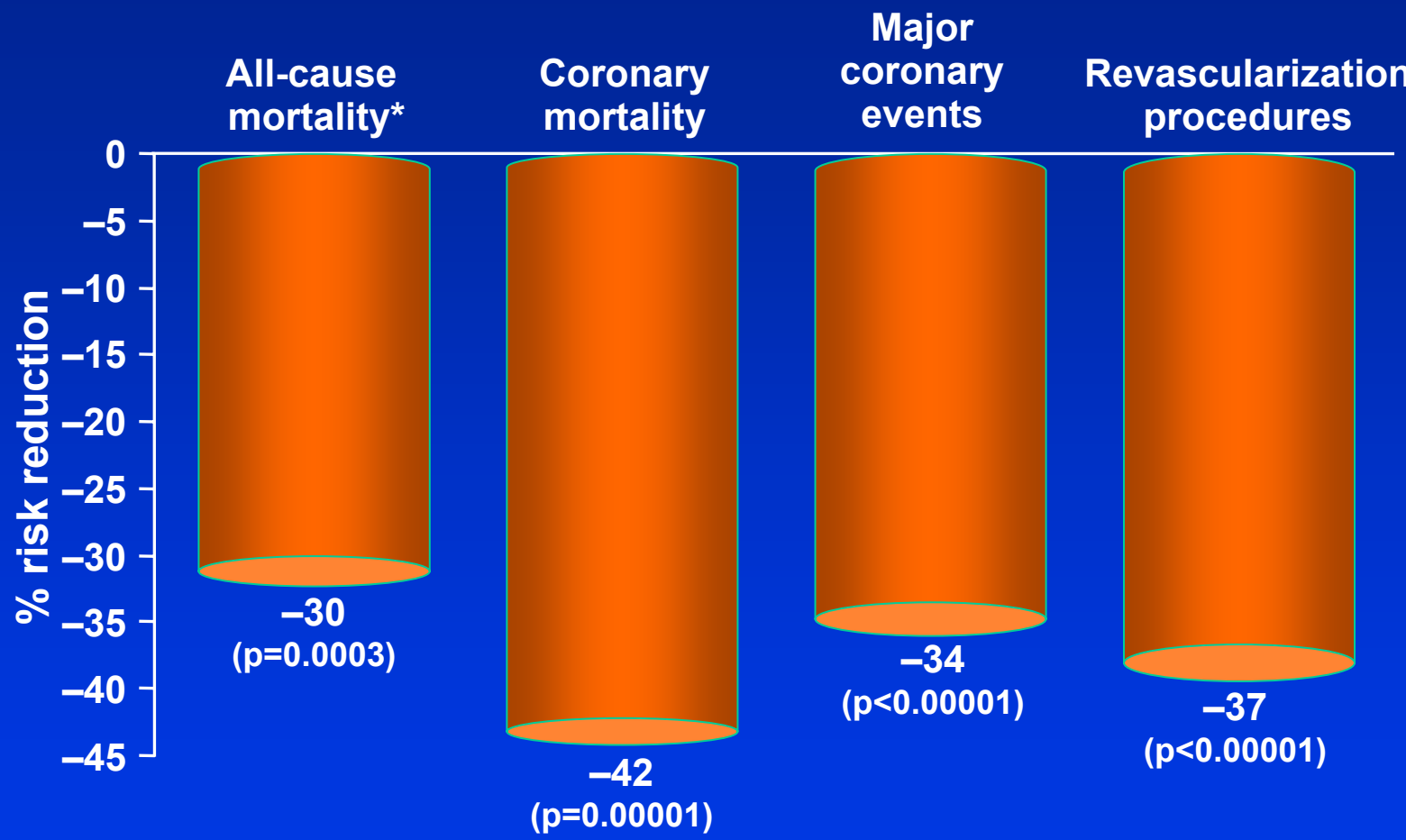
* Time course established

Key Statin Trials and Spectrum of Risk



*CHD risk equivalent, e.g. diabetes

4S Study: Provided Hard Evidence for the Use of Simvastatin 20-40mg in CHD Patients

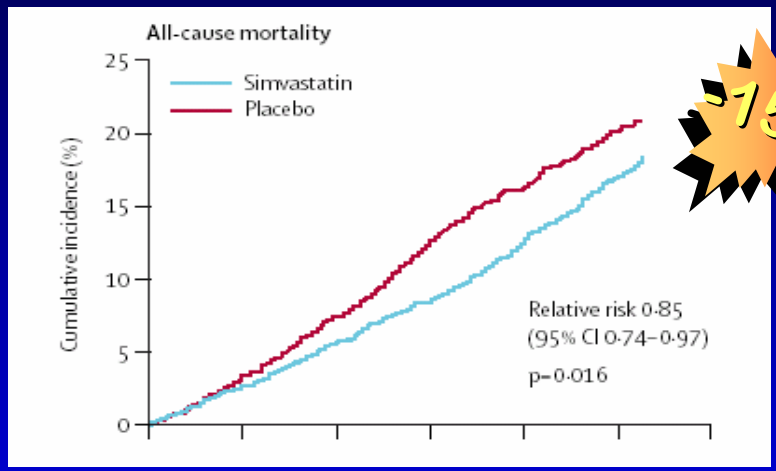


*Primary endpoint

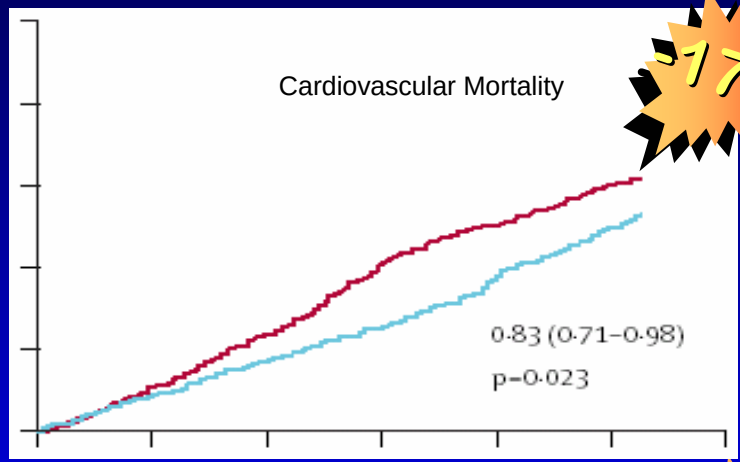
Adapted from Scandinavian Simvastatin Survival Study Group *Lancet* 1994;344(8934):1383-1389; Kjekshus J et al *Am J Cardiol* 1995;76:64C-68C.

4S Study: 10-year follow-up

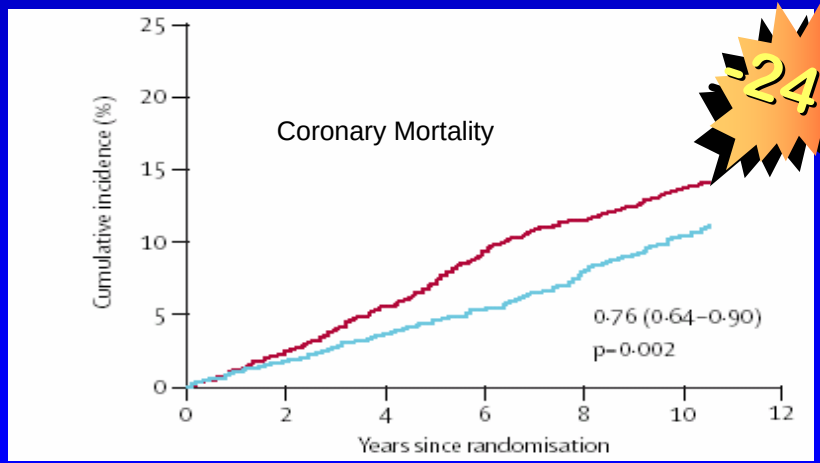
The survival benefits that pts allocated to simvastatin accrued during the double-blind period of 4S persisted during long-term follow-up (10.4 years)



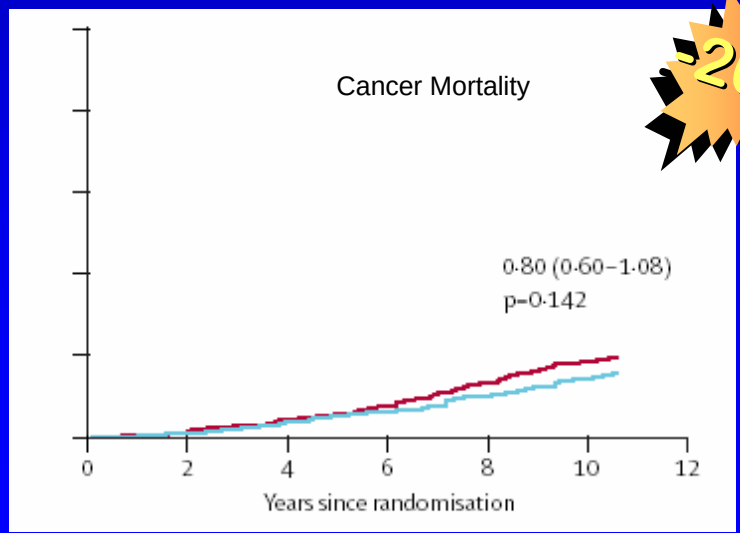
-15%



-17%



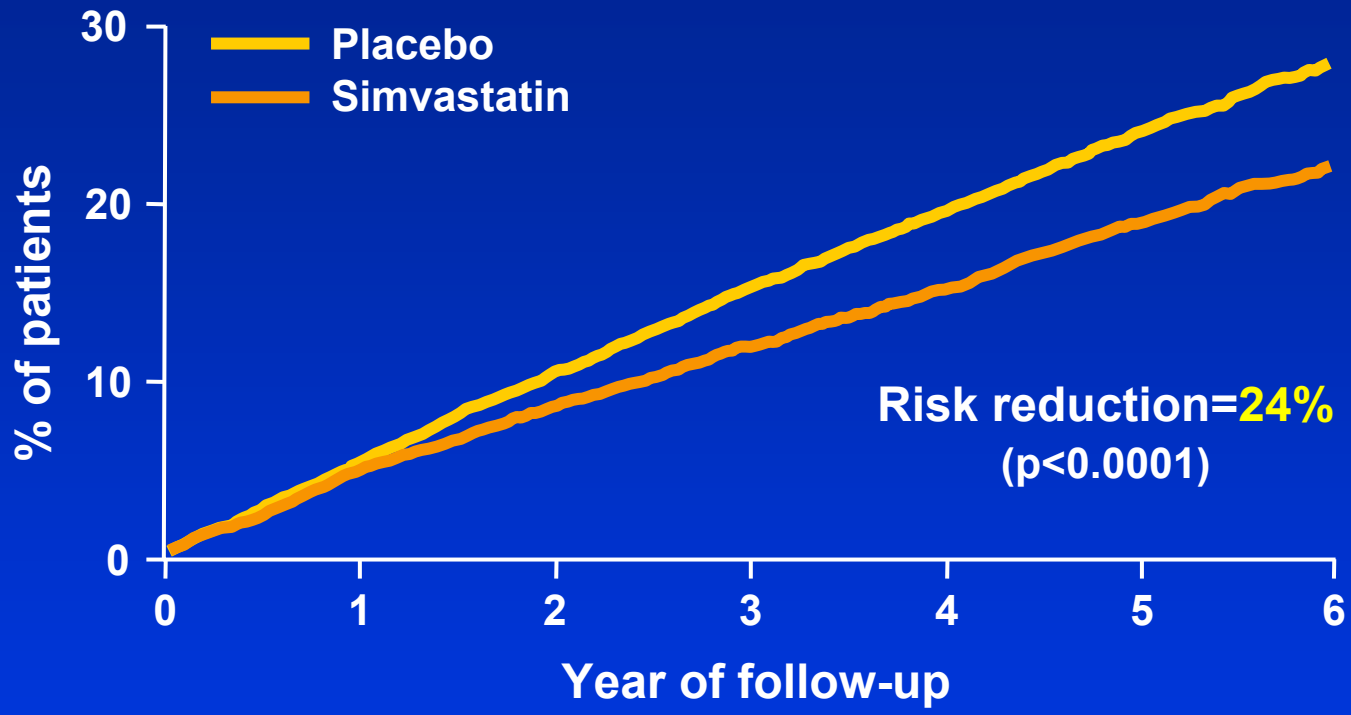
-24%



-20%

T.E.. Strandeberg et al. LANCET 2004; 364: 771–777

Heart Protection Study
Major Vascular Events Over Time



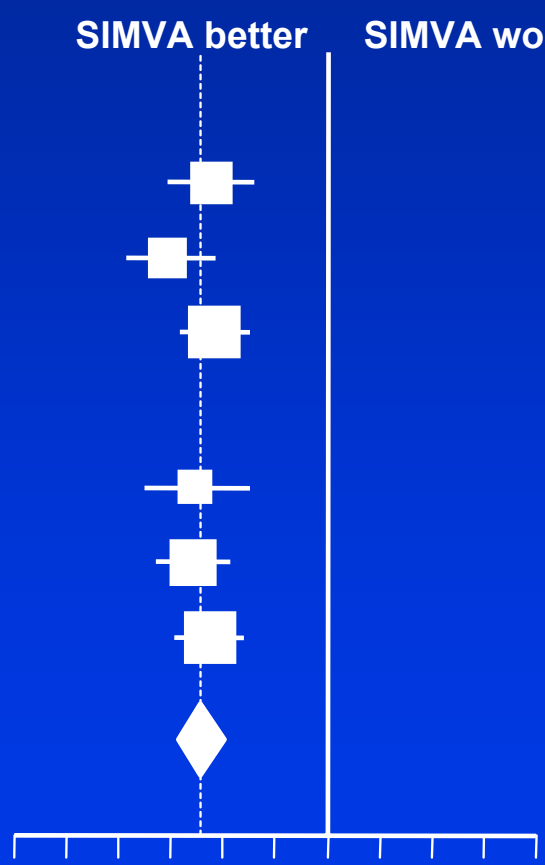
Benefit (mean ± SE) per 1000 patients allocated to simvastatin	5 ± 3	20 ± 4	35 ± 5	46 ± 5	54 ± 7	60 ± 18

SE=standard error of the mean

Adapted from Heart Protection Study Collaborative Group *Lancet* 2002;360:7-22.

Simvastatin 40mg
Vascular Events by Prior Lipid Levels

Baseline features	SIMVA (10269)	PLACEBO (10267)
LDL (mmol/l)		
< 3.0 (116 mg/dl)	602	761
> 3.0 < 3.5	483	655
> 3.5 (135 mg/dl)	957	1190
Total cholesterol (mmol/l)		
<5.0 (193 mg/dl)	361	476
>5.0 < 6.0	746	965
>6.0 (232 mg/dl)	935	1165
ALL PATIENTS	2042 (19.9%)	2606 (25.4%)



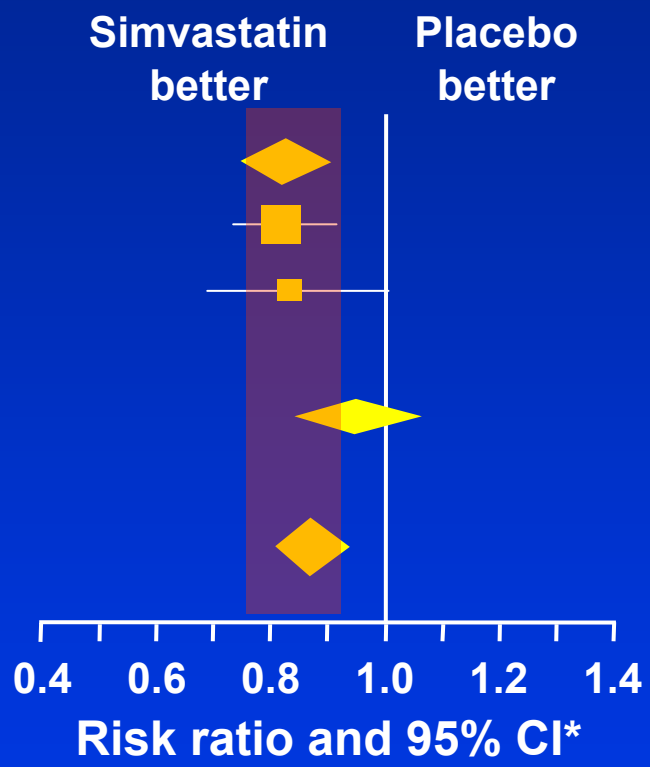
Het χ^2_2 = 3.0

Het χ^2_2 = 0.5

24%SE 2.6
reduction
(2P<0.00001)

Heart Protection Study
Impact of Simvastatin on Mortality

Consistency Across End Points



Cause of death	
Vascular events	**17% risk reduction** p<0.0001
Coronary	
Other vascular	
Nonvascular events	**p=NS**
ALL CAUSES	**13% risk reduction** p=0.0003

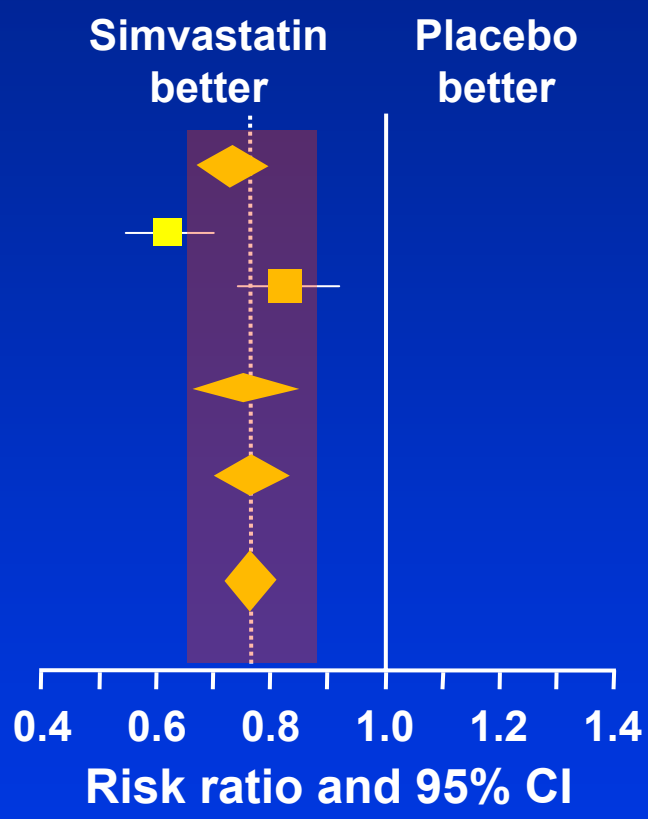
*Areas of the symbols are proportional to the amount of statistical information in each subdivision

Adapted from Heart Protection Study Collaborative Group *Lancet* 2002;360:7-22.

Impact of Simvastatin in Heart Protection Study
Major Vascular Events

Consistency Across End Points

Vascular event*	
Major coronary event	**27%** risk reduction, p<0.0001
Nonfatal MI	
Coronary death	
Stroke	**25%** risk reduction, p<0.0001
Revascularization**	**24%** risk reduction, p<0.0001
ANY MAJOR VASCULAR EVENT	**24%** risk reduction, p<0.0001

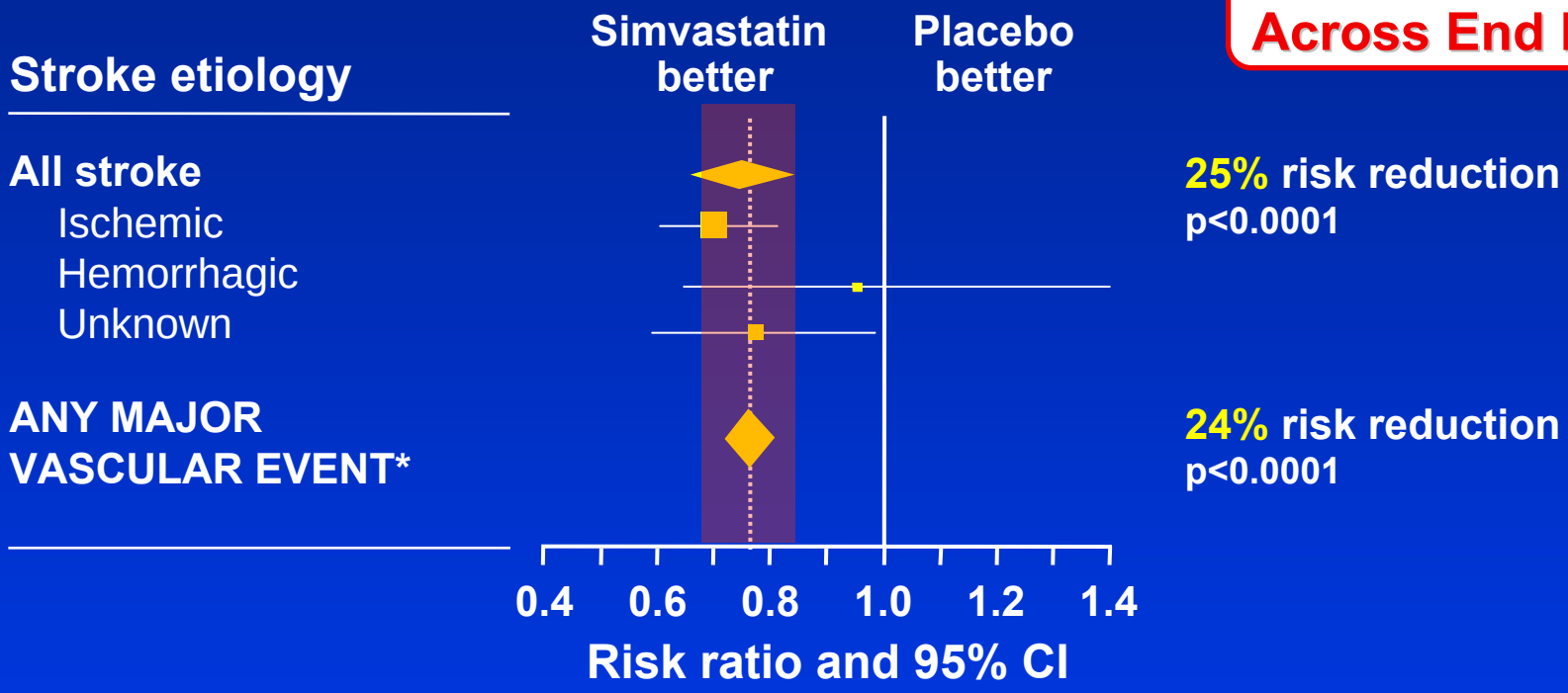


*Patients could be in more than one vascular event category.
**Includes coronary and noncoronary revascularizations.

Adapted from Heart Protection Study Collaborative Group *Lancet* 2002;360:7-22.

Heart Protection Study
Impact of Simvastatin on Stroke

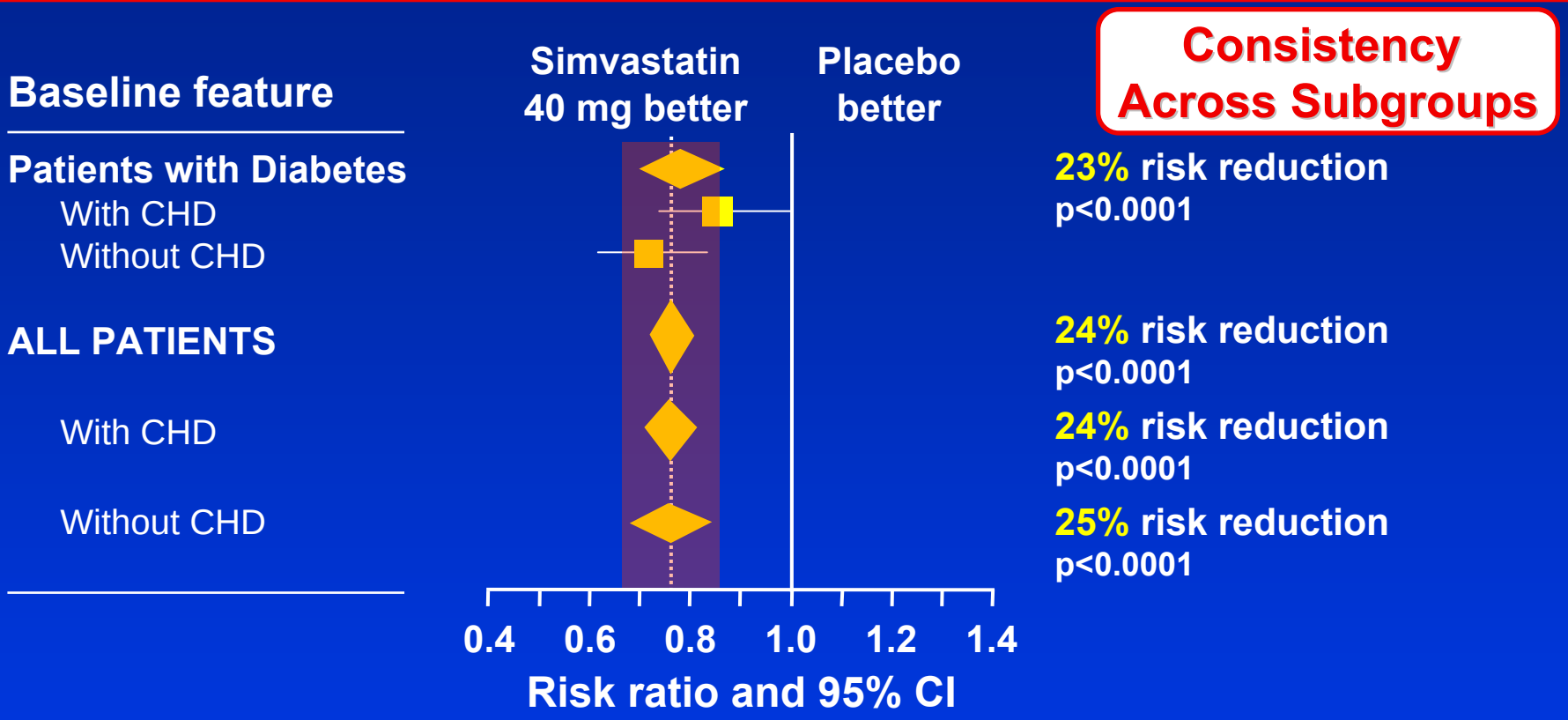
Consistency Across End Points



*Major vascular events included nonfatal MI, coronary death, revascularization, and stroke.

Adapted from Heart Protection Study Collaborative Group *Lancet* 2002;360:7-22.

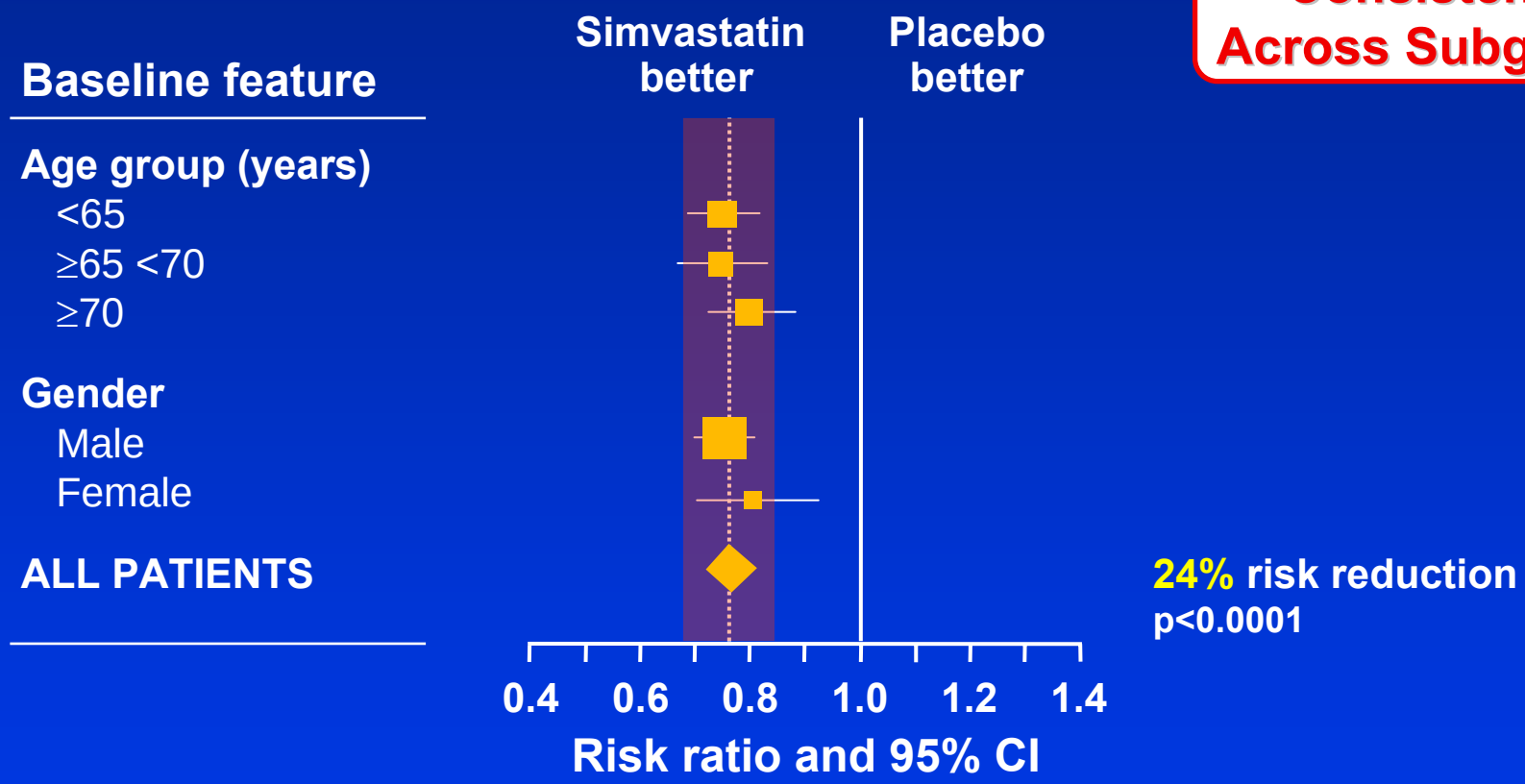
Impact of Simvastatin on Major Vascular Events
Patients with Diabetes



Adapted from Heart Protection Study Collaborative Group *Lancet* 2002;360:7-22; HPS Group communication.

Impact of Simvastatin on Major Vascular Events
By Age and Gender

Consistency Across Subgroups



24% risk reduction
p<0.0001

Adapted from Heart Protection Study Collaborative Group *Lancet* 2002;360:7-22.

Post-CABG: Impact of Aggressive vs Moderate Lowering of LDL-C on Atherosclerosis

Study group characteristics

- Sample size: 1,351 (M/F)
- 1 to 11 yr post-CABG
- LDL-C 130-174 mg/dL after diet

Treatment

- Randomized, blinded to
  - lovastatin 40-80 mg + cholestyramine 8 g/day (if needed)
  - lovastatin 2.5-5 mg + cholestyramine 8 g/day (if needed)
  - aggressive LDL-C target: ≤85 mg/dL
  - moderate LDL-C target: 130-140 mg/dL

Monitoring

- Quantitative coronary angiography

Post-CABG Trial Investigators. N Engl J Med. 1997;336:153-162.

Post-CABG: End Points, Results, Conclusions

- Primary end point: Mean per-patient percentage of grafts with significant progression in SVG (≥0.6 mm change)
- Secondary end point: New occlusions, new lesions, lumen narrowing
- Results:
  - aggressive treatment group: significantly less (P<0.001) progression, fewer new occlusions and lesions, and ↓ mean lumen diameter
  - revascularization rate ↓ 29% (P=0.03)
- Conclusions: Mean LDL-C levels of 95 mg/dL associated with greater benefit than mean LDL-C of 135 mg/dL

Post-CABG Trial Investigators. N Engl J Med. 1997;336:153-162.

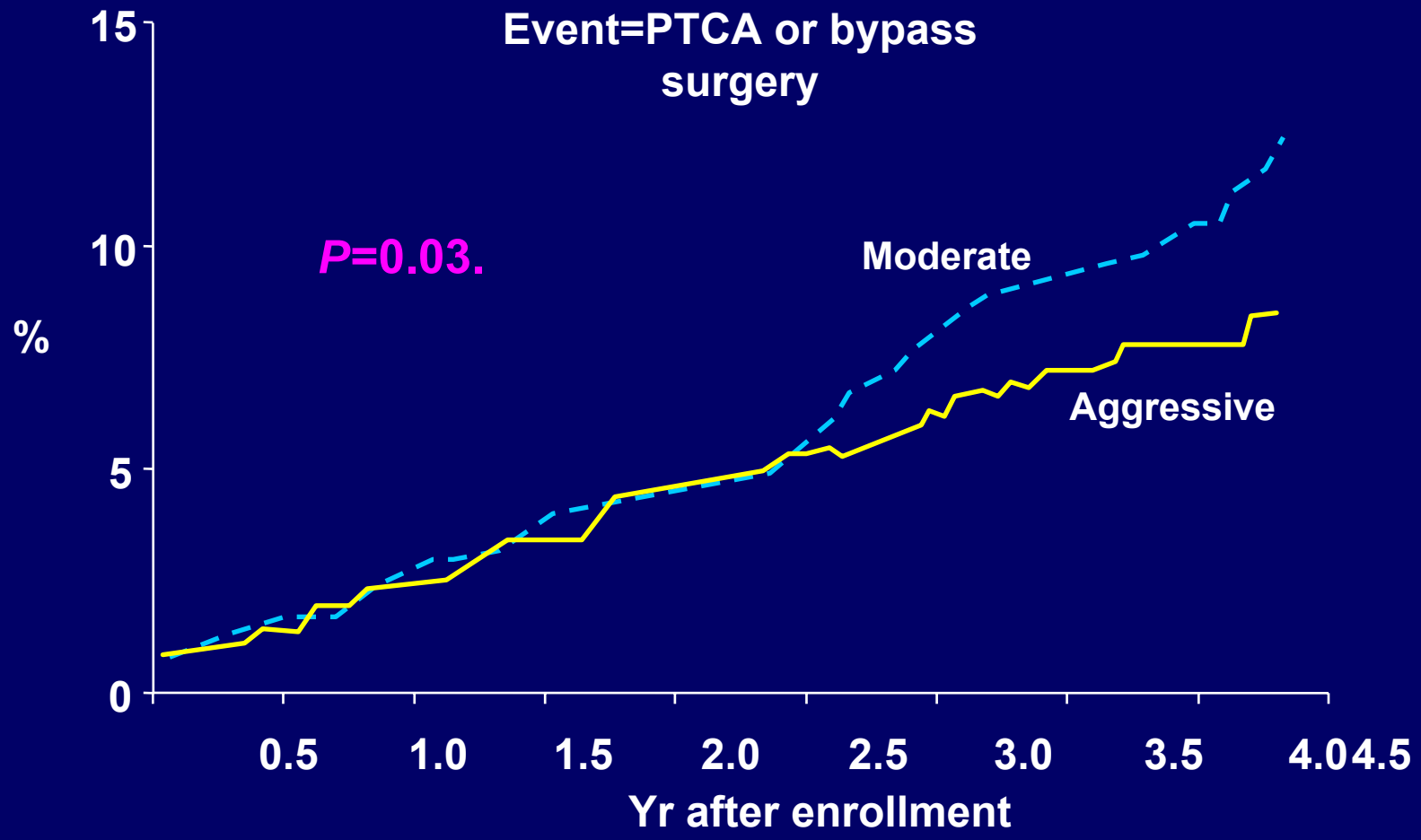
Post-CABG Angiographic Outcomes

	MRE		Difference	
	Moderate	Aggressive	%	*P* value
Progression	39	28	28	<0.001
New occlusions	16	10	40	<0.001
New lesions	21	10	52	<0.001
	Mean lumen change in mm			
Minimum diameter	-0.38	-0.20	48	<0.001
Mean diameter	-0.34	-0.16	52	<0.001

MRE=Mean per-patient percentage of grafts.

Post-CABG Trial Investigators. N Engl J Med. 1997;336:153-162.

Post-CABG: Event Rates by Cholesterol Group



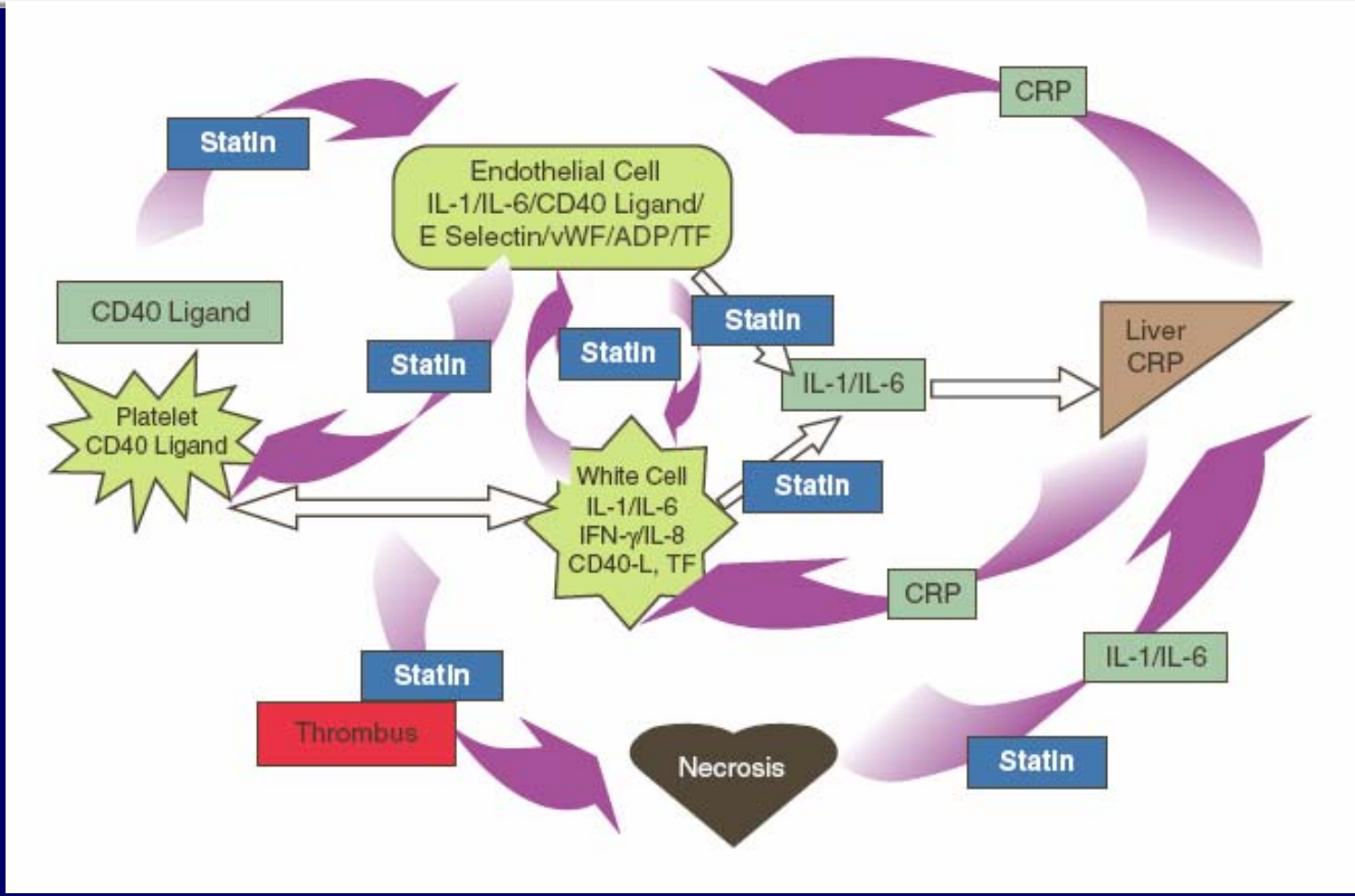
Post-CABG Trial Investigators. N Engl J Med. 1997;336:153-162.

Rationale For Statins In ACS

- Revascularization procedures do not modify underlying pathophysiology and only modestly reduce the risk of subsequent events
- Statins contribute to plaque stability and/or regression through a number of lipid-dependent and -independent (pleiotropic) mechanisms (eg, ↓ inflammation)
- Small differences in therapeutic efficacy can result in significant differences in events

Schwartz and Olsson. Am J Cardiol. 2005;96(suppl):45F.

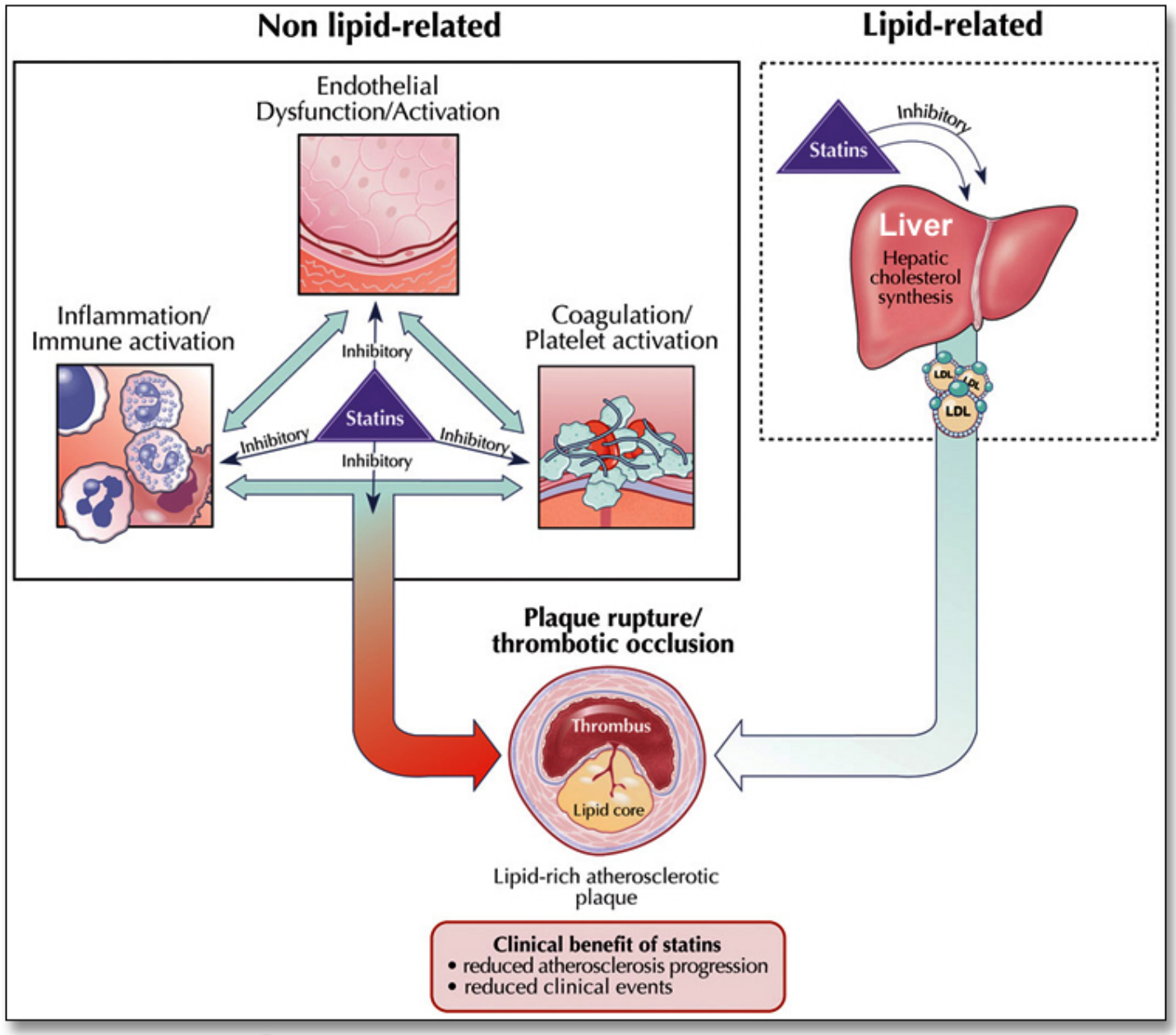
Role Of Statins In ACS: Non-Lipid Effects



ADP = adenosine diphosphate; CD40-L = CD40 ligand; IFN = interferon; IL = interleukin; vWF = von Willebrand factor.

Cannon and Ray. *Am J Cardiol*. 2005;96:54F.

Pathobiology of Lipid and non-Lipid mechanisms in ACS



Randomized Trials Of Statins In ACS

Trial (year published)	Treatment	Duration	Number Of Patients
MIRACL (2001)	Placebo versus atorvastatin 80 mg	4 months	3086
FLORIDA (2002)	Placebo versus fluvastatin 80 mg	1 year	540
PROVE-IT (2004)	Pravastatin 40 mg versus atorvastatin 80 mg	2 years	4162
A to Z (2004)	Placebo for 4 months followed by simvastatin 20 mg versus simvastatin 40 mg for 1 month followed by simvastatin 80 mg	2 years	4496
PACT (2004)	Placebo versus pravastatin 20-40 mg	1 month	3408
PRINCESS (presented 2004)	Placebo versus cerivastatin 0.4 mg	3 months*	3605

*Study was designed with a subsequent 18-month period in which both groups were to be treated with cerivastatin 0.4-0.8 mg/dL. However, this was not accomplished due to early termination of study.

Schwartz and Olsson. *Am J Cardiol*. 2005;96(suppl):45F

PROVE IT - TIMI 22: Study Design

4,162 patients with an Acute Coronary Syndrome < 10 days

ASA + Standard Medical Therapy

Double-blind

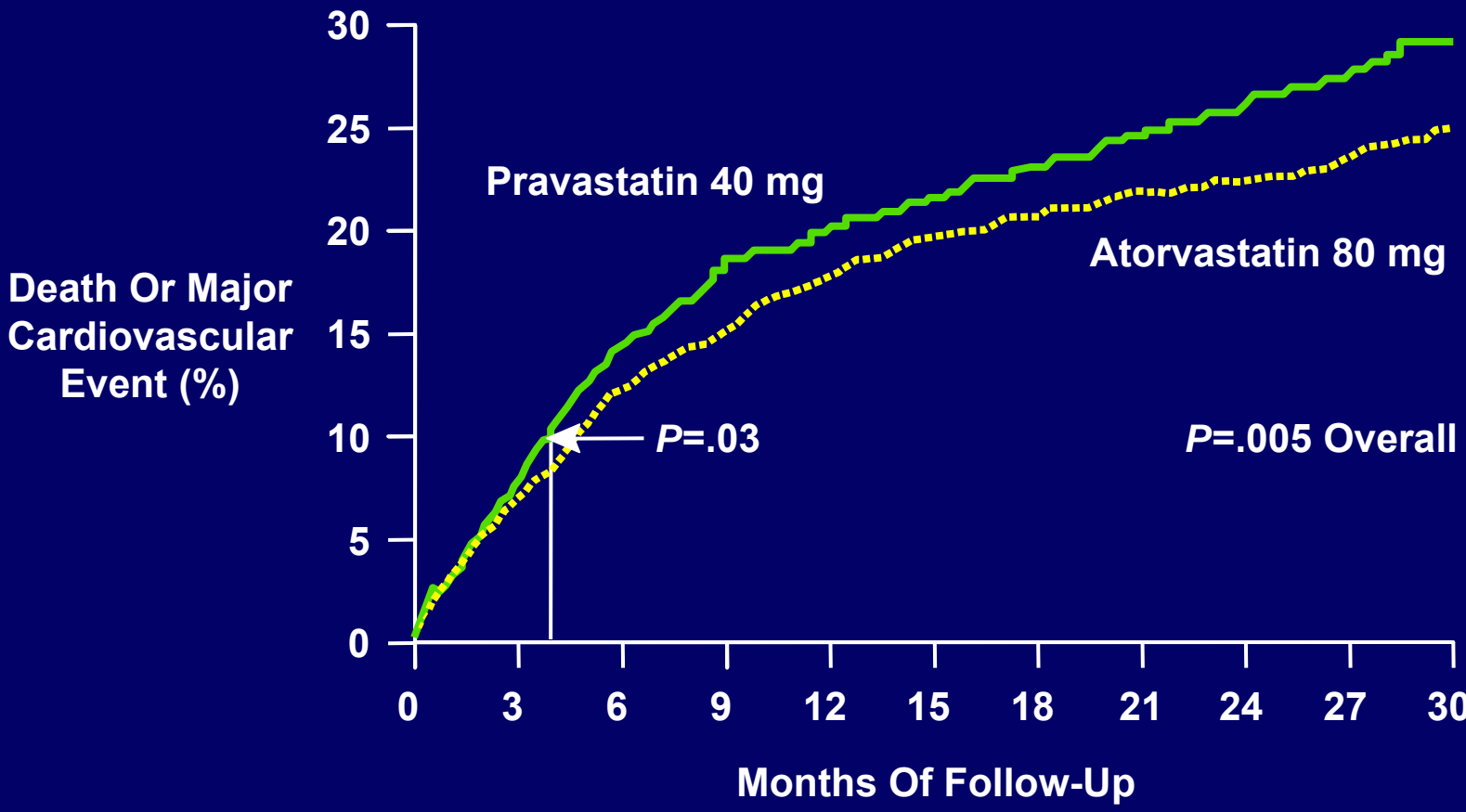
- **Standard Therapy (Pravastatin 40 mg)**
- **Intensive Therapy (Atorvastatin 80 mg)**

Duration: Mean 2 year follow-up (1001 events)

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

PROVE IT-TIMI 22: A Major Cardiovascular Event Or Death From Any Cause

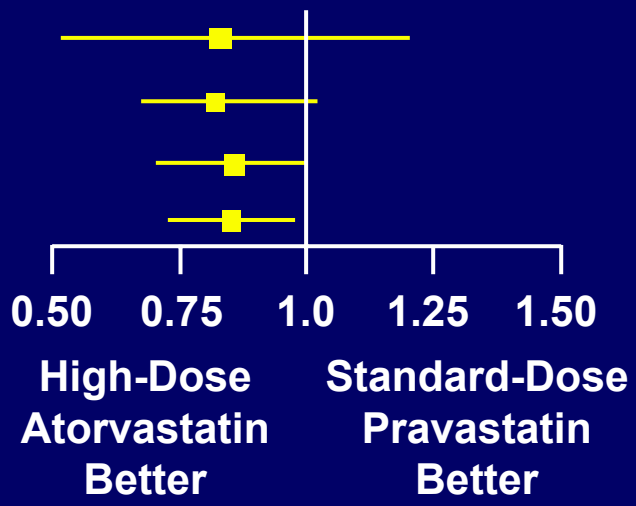
Primary End Point



Cannon et al. N Engl J Med. 2004;350:1495

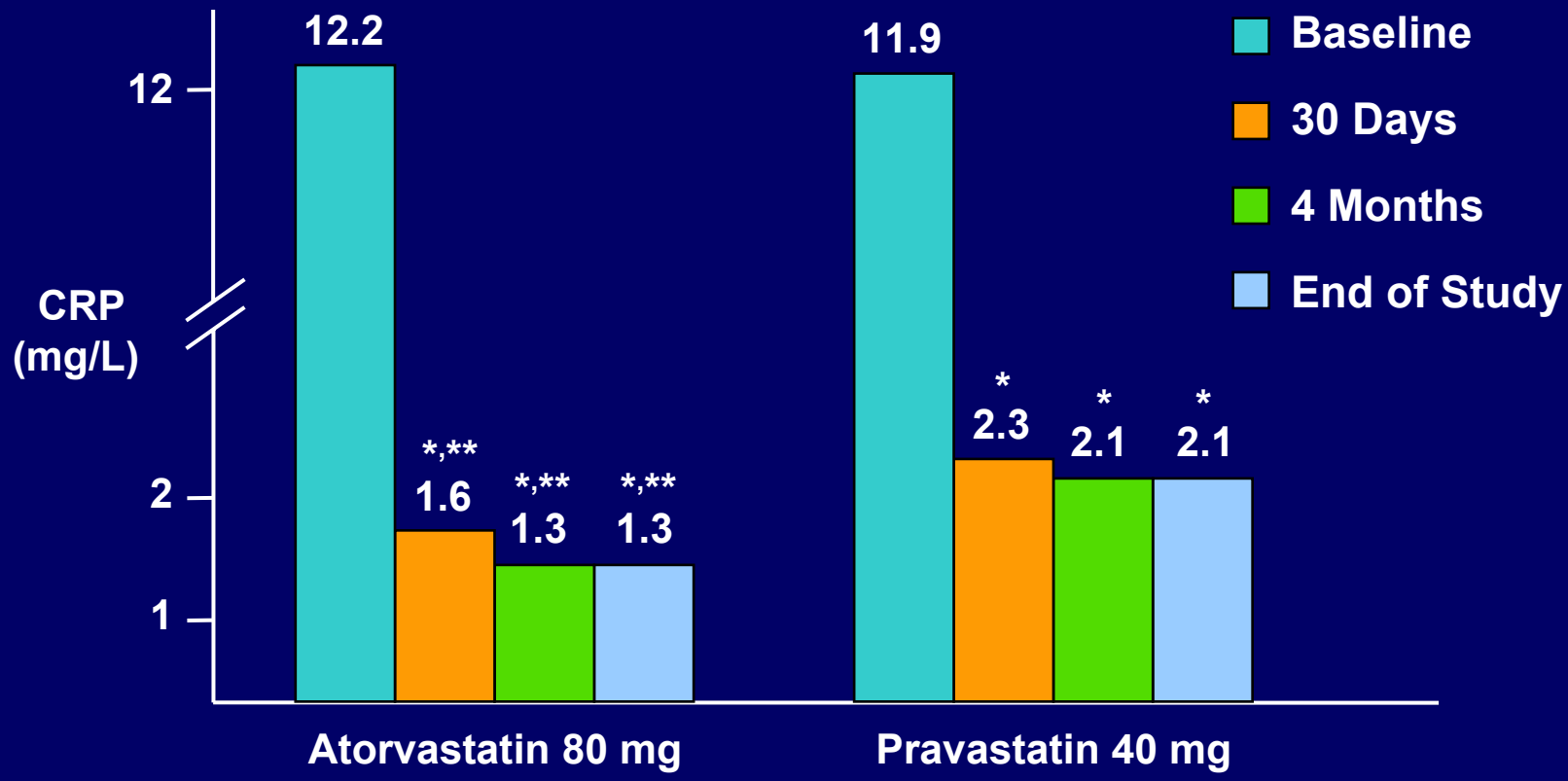
PROVE IT-TIMI 22: A Major Cardiovascular Event Or Death From Any Cause At Different Censoring Times

Censoring Time	Hazard Ratio (95% CI)	Risk Reduction (%)	Event Rate (%)	
			Atorvastatin	Pravastatin
30 days		17	1.9	2.2
90 days		18	6.3	7.7
180 days		14	12.2	14.1
End of follow-up		16	22.4	26.3



Cannon et al. N Engl J Med. 2004;350:1495

PROVE IT-TIMI 22: CRP Levels At Enrollment And During Follow-Up

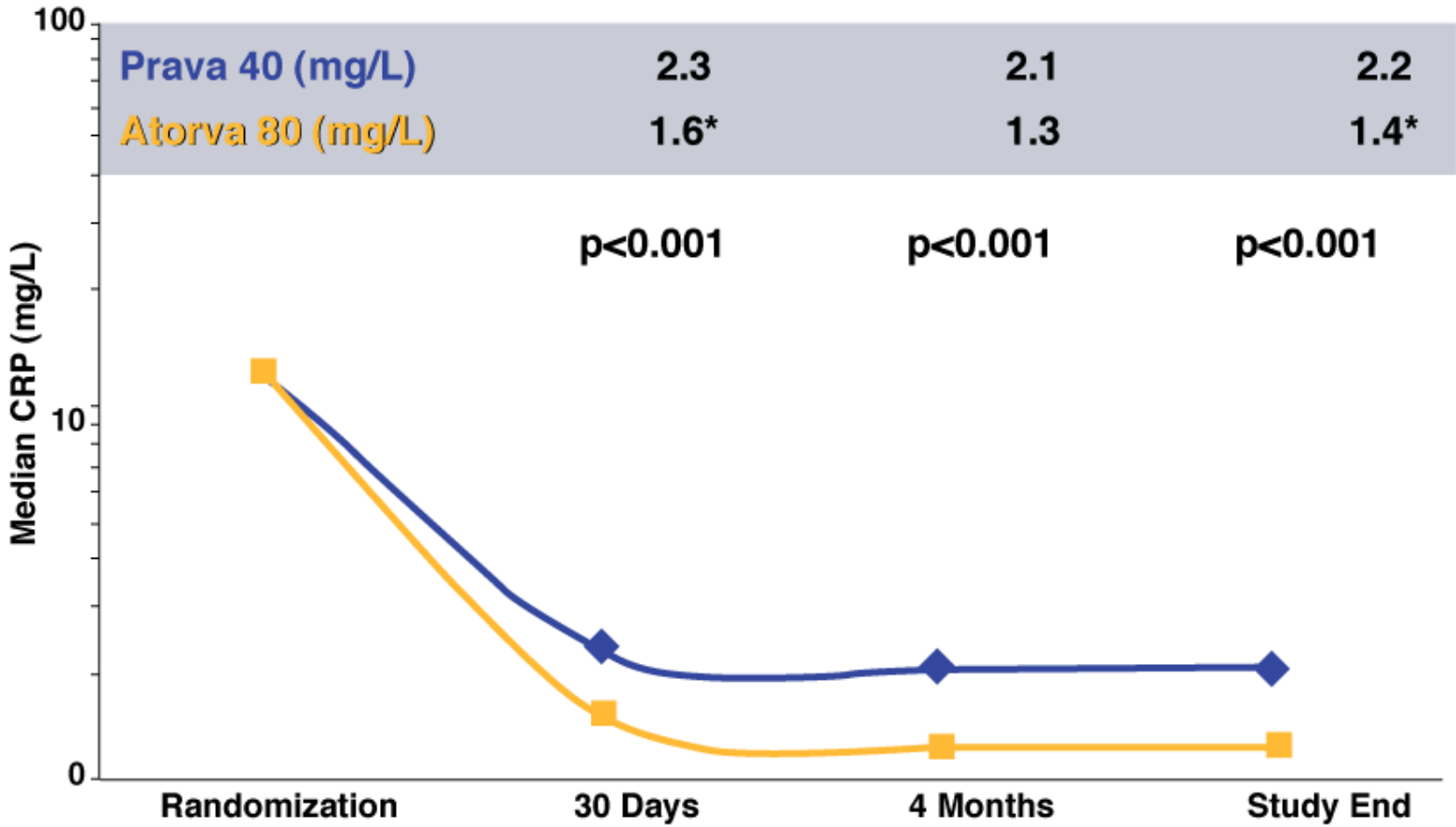


* *P*<.001 vs baseline.

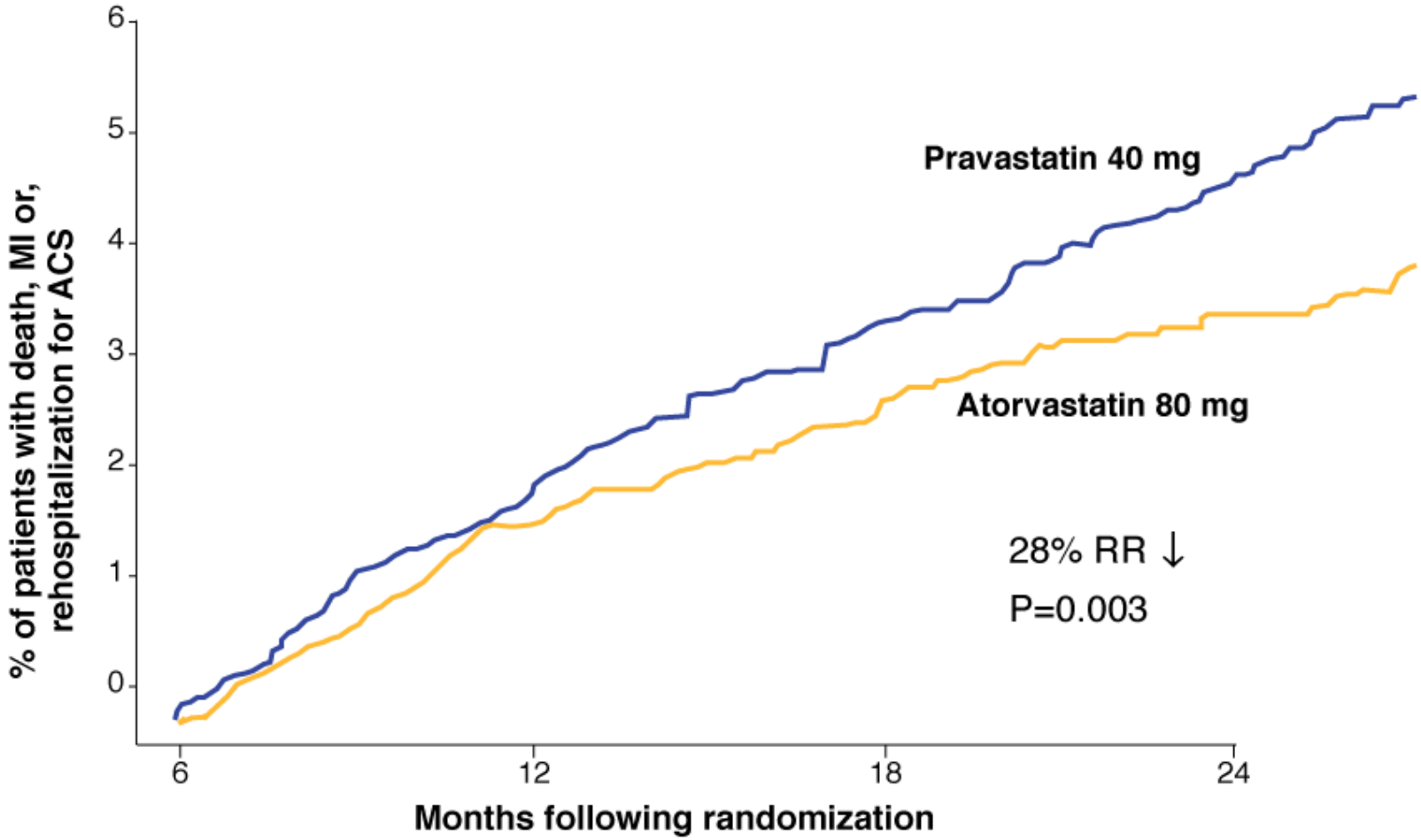
** *P*<.001 vs pravastatin.

Ridker et al. *N Engl J Med*. 2005;350:20..

Achieved CRP With Intensive Versus Standard Statin Therapy

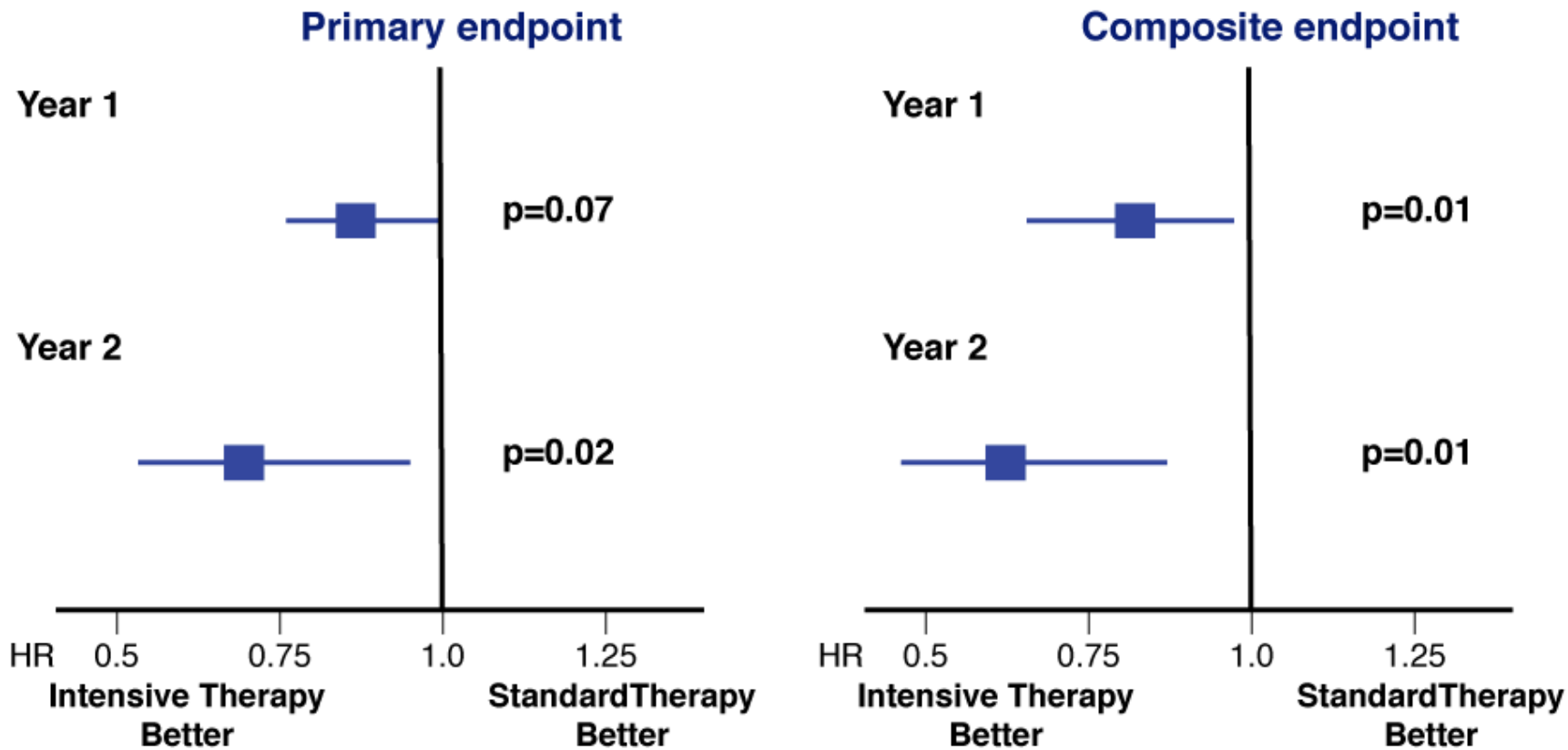


Death, MI or ACS Rehospitalization (Late Phase)



Ray et al. JACC 2005

Conditional Hazard Ratio of Intensive vs Standard Therapy



Ray et al. JACC 2005

Conclusions

- Benefits of intensive therapy occur within weeks, a time window consistent with the early pleiotropic effects

- Continuing high-dose statin therapy in more stable patients beyond the acute phase is associated with similar long-term benefit

  →Two “windows of cardioprotection”

- ACS patients should be started in-hospital on intensive statin therapy and should be continued long-term

AHA/CDC Panel: Recommendations for hs-CRP Laboratory Testing

- **Measurements of hs-CRP:**
  - Should be performed twice (2 weeks apart)
  - Results averaged, expressed as mg/L
  - Fasting or nonfasting, in metabolically stable patients
  - If level >10 mg/L, test should be repeated, patient examined for sources of infection or inflammation
- **Relative risk categories for hs-CRP levels:**
  - Low <1 mg/L
  - Average 1.0–3.0 mg/L
  - High >3.0 mg/L

Pearson TA et al. *Circulation.* 2003;107:499-511.

Implications of recent statin trials on ATP III guidelines

- **Risk categories definitions:**
  - **Very high risk:**
    1. **Multiple risk factors especially DM**
    2. **Uncontrolled risk factors**
    3. **Metabolic syndrome**
    4. **ACS**
  - **High risk**
    1. **CAD**
    2. **CAD equivalent e.g. PAD, Carotid atheroma, AAA, DM, 2 Risk factors (10y risk > 20%)**

Implications of recent statin trials on ATP III guidelines

- Moderate high risk:

  2 risk factors (10y risk 10-20%)

- Moderate risk

  2 risk factors (10y risk < 10%)

- Low risk

  0-1 risk factors

- Change in LDL-C Galls:
  - Very high risk LDL-C < 70mg/dl
  - High risk LDL-C < 100mg/dl

Implications of recent statin trials on ATP III guidelines

- Moderate high risk LDL-C < 130 mg/dl
- Moderate and low risk recommendations unchanged

- Statin doses that can achieve 30-40% reduction in LDL-C are:

Atorvastatin	10mg
Simvastatin	20-40 mg
Lovastatin	40mg
Pravasatin	40 mg
Fluvastatin	40-80 mg
Rosuvastatin	5-10 mg

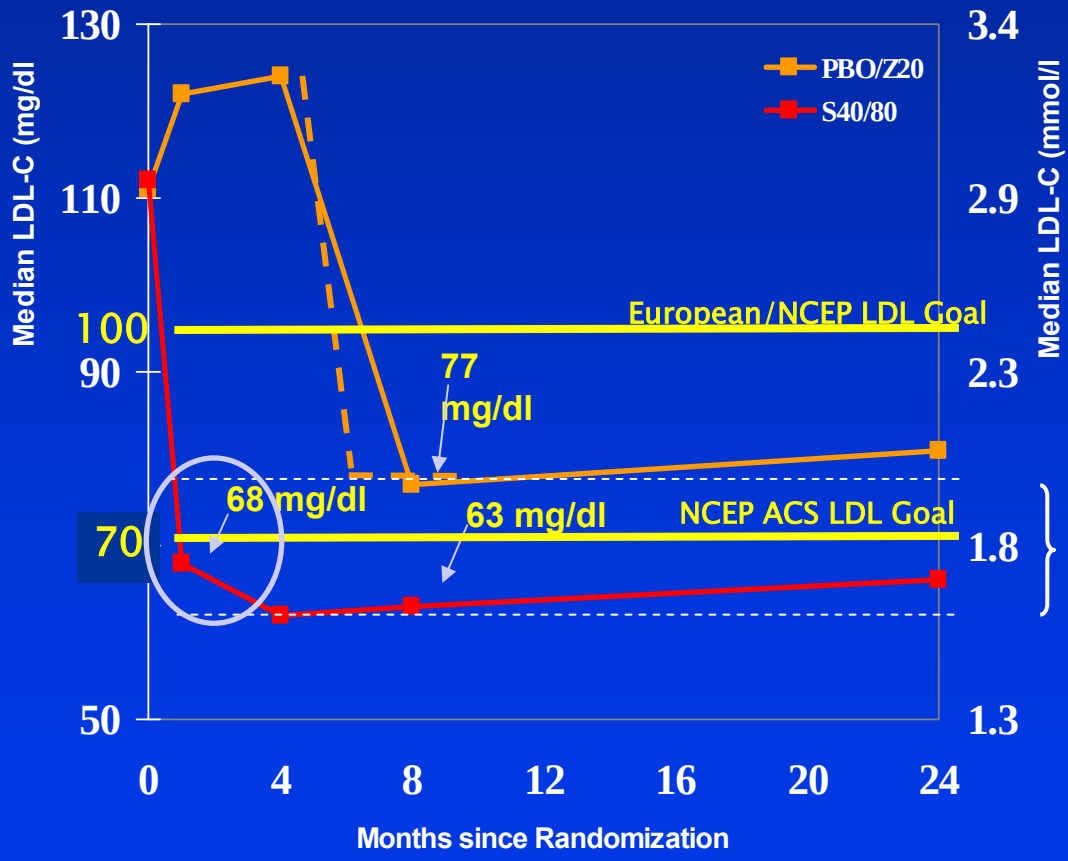
ATP III New Galls

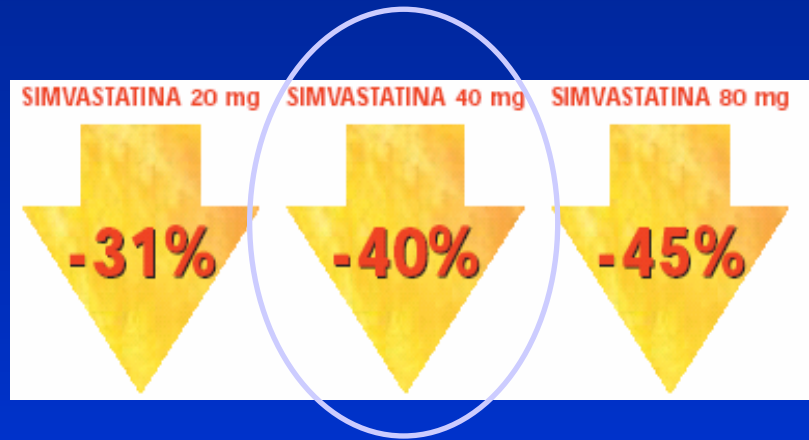
TABLE 2. ATP III LDL-C Goals and Cutpoints for TLC and Drug Therapy in Different Risk Categories and Proposed Modifications Based on Recent Clinical Trial Evidence

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy**
High risk: CHD* or CHD risk equivalents† (10-year risk >20%)	<100 mg/dL (optional goal: <70 mg/dL)‖	≥100 mg/dL#	≥100 mg/dL†† (<100 mg/dL: consider drug options)**
Moderately high risk: 2+ risk factors‡ (10-year risk 10% to 20%)§§	<130 mg/dL¶	≥130 mg/dL#	≥130 mg/dL (100–129 mg/dL; consider drug options)‡‡
Moderate risk: 2+ risk factors‡ (10-year risk <10%)§§	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk: 0–1 risk factor§	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)

A-to-Z Phase Z: Lipid Results

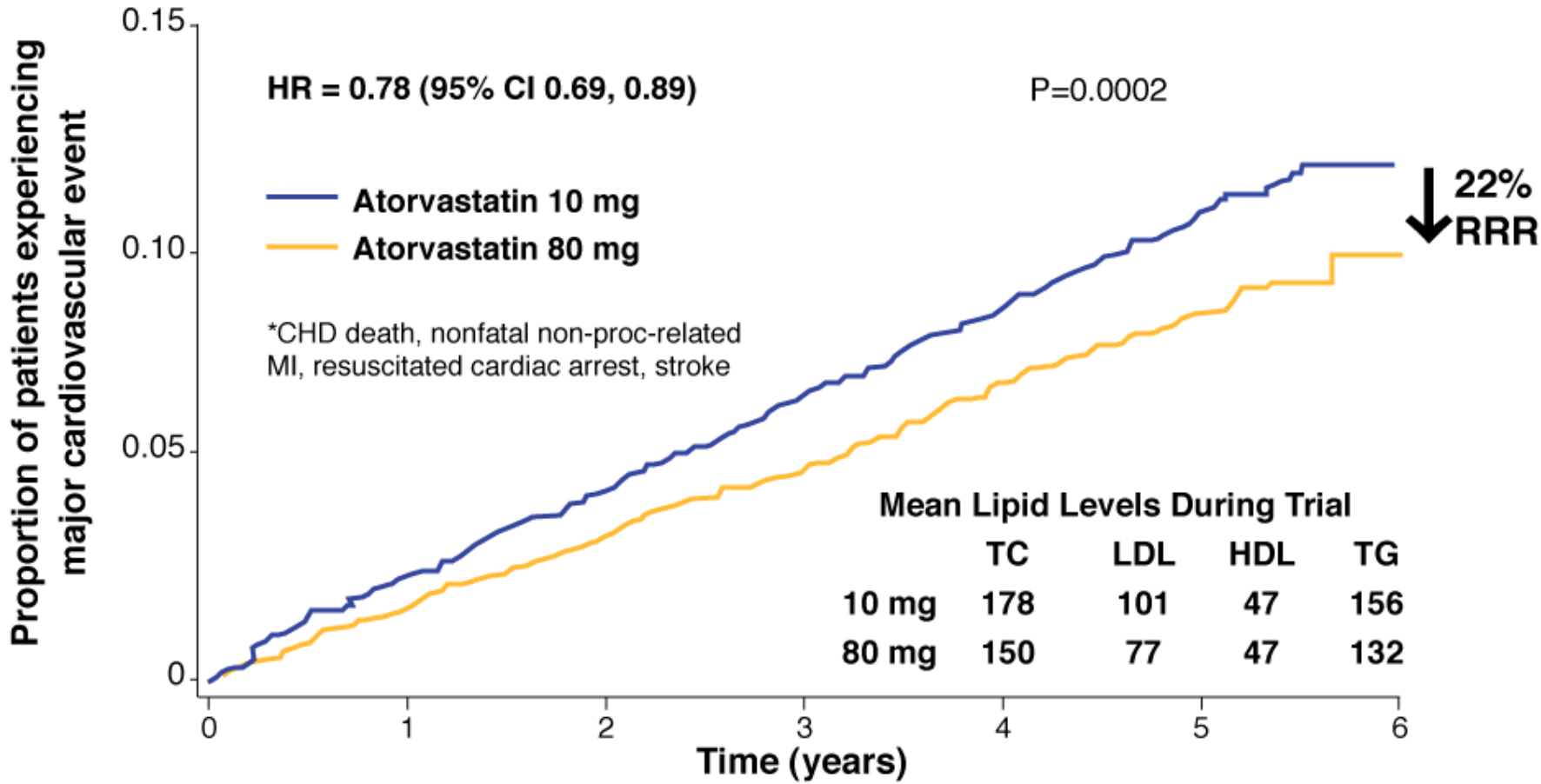
ALL of the ACS pts treated with Simvastatin 40mg achieved the new LDL treatment goal (70mg/dl) based upon the revised U.S. Guidelines (NCEP-ATPIII)





de Lemos et al. *JAMA* 2004;292:1307-1316

Primary Efficacy Outcome Measure: First Major Cardiovascular Event*



IDEAL

Incremental **D**ecrease in
Endpoints through
Aggressive **L**ipid **L**owering

IDEAL Study Design…

- Multi-center (190 centers in Northern Europe) prospective, randomized, open-label blinded endpoint classification (PROBE Design)
- Patients with CHD who had experienced a MI
- Received atorvastatin 80 mg/per day or simvastatin 20 mg/per day (approximately 20% of which were increased to 40 mg/day at week 24 in patients whose total cholesterol remained greater than 190 mg/dL or whose LDL-C remained greater than 115 mg/dL).
- Median Duration: 5.5 years
- The Study was designed to have 90% power to detect an anticipate 21% relative risk reduction in primary endpoint

IDEAL Study Objective & Endpoints…

Objective:

- To determine whether an incremental decrease in the risk of CHD can be achieved by a greater decrease in LDL-C in patients with CHD who had experienced an MI

Primary Endpoint:

1. Major Coronary event :Coronary death, hospitalization for Non fatal acute MI, or Cardiac arrest with resuscitation

Secondary Endpoints:

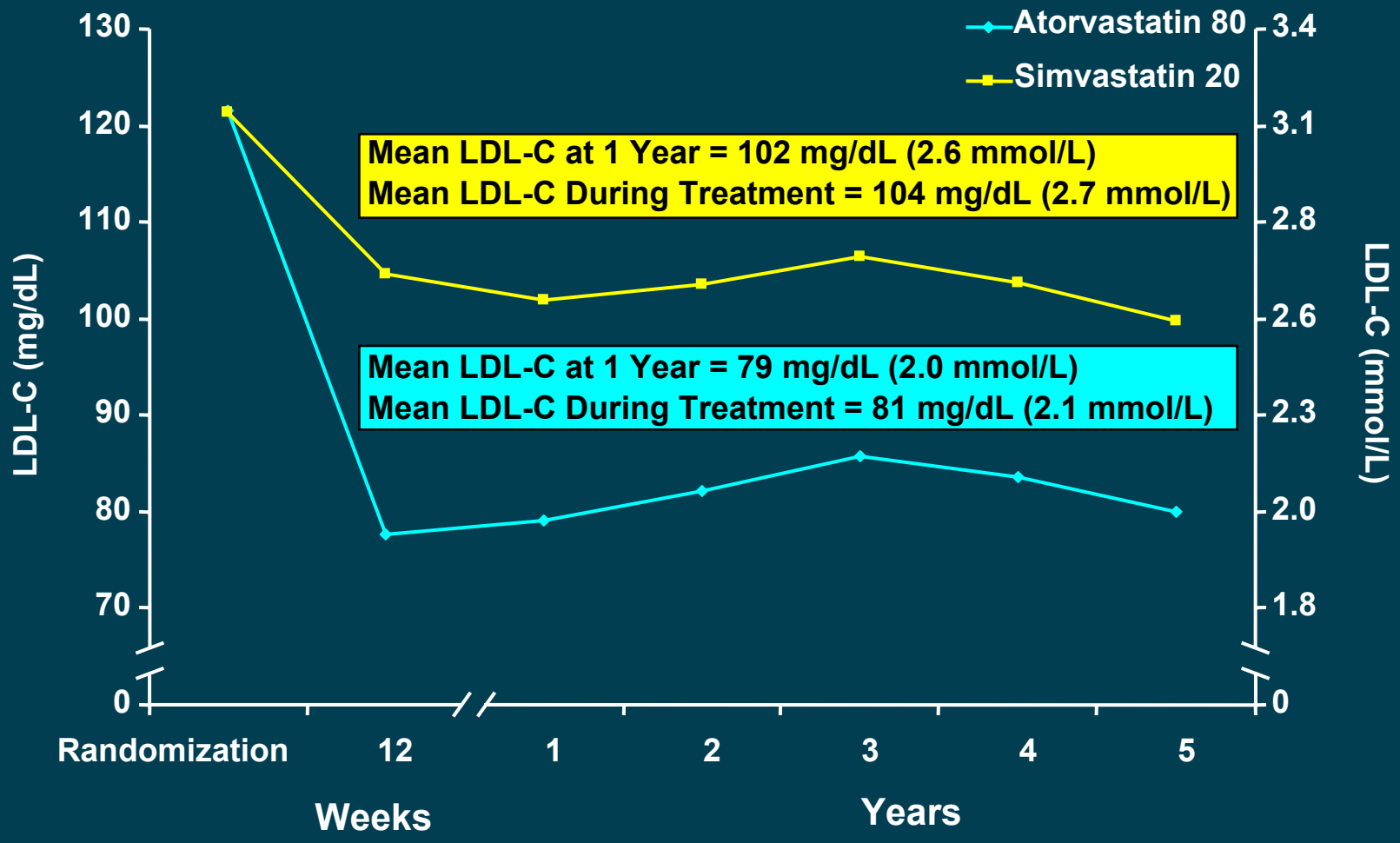
1. Major CV event :Any primary event plus Stroke
2. Any Coronary Heart Disease event: Any primary event , any coronary revascularization procedure, or hospitalization for Unstable Angina.
3. Any Cardiovascular events: Any of the former plus hospitalization with 1ry diagnosis of CHF and PAD.
4. Individual components of the composite endpoints
5. All cause Mortality

IDEAL Study Patients Characteristics…

8,888 patients with CHD who had experienced a myocardial infarction aged of 80 years or younger. The randomized patients had the following characteristics:

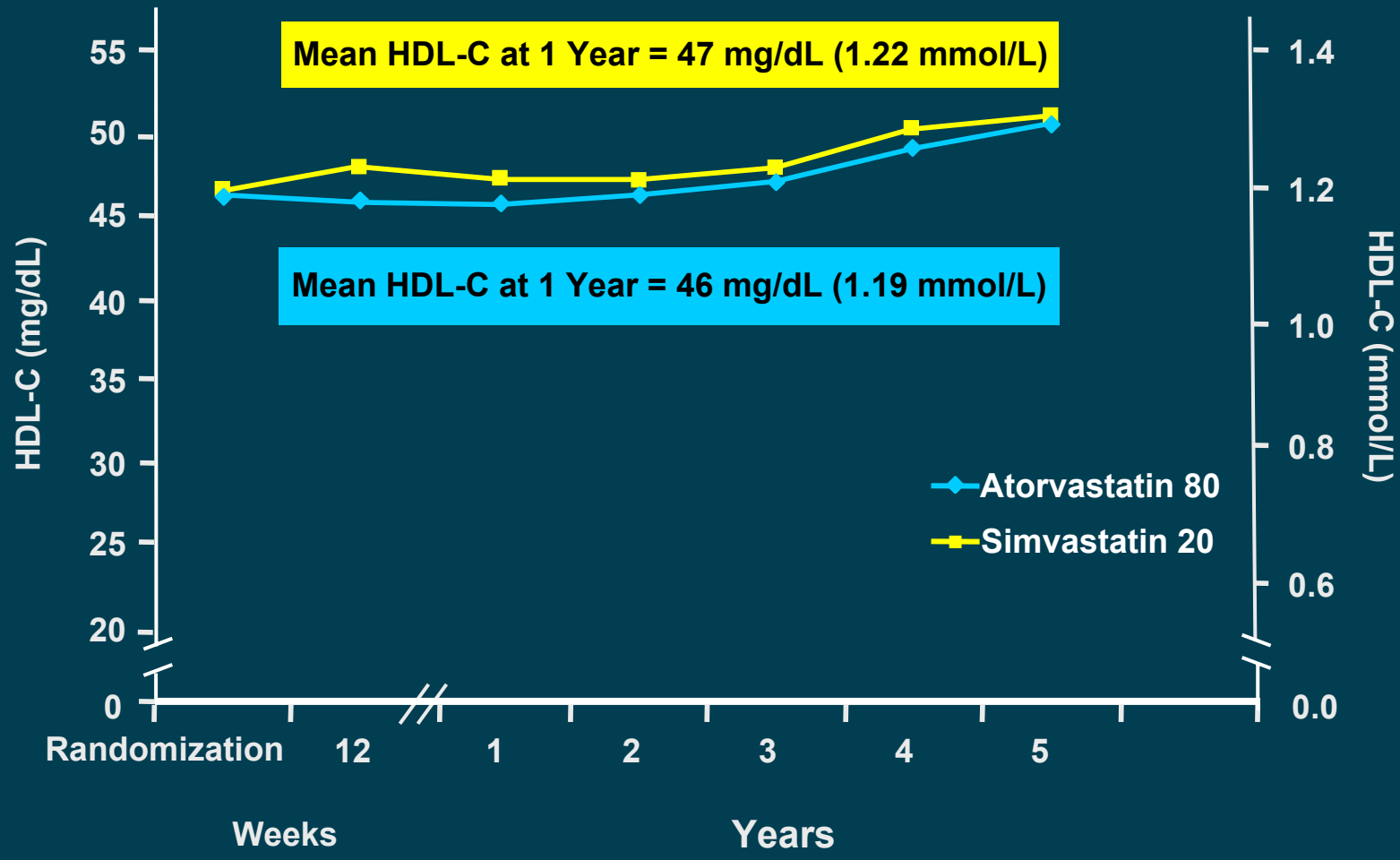
- Mean age: 61.7 and +/- 9.5 years
- 19.1% women (mean age 64 +/- 9.5 years)
- Mean baseline Total C: 196 mg/dL
- Mean baseline LDL-C: 122 mg/dL
- Mean baseline HDL-C: 46 mg/dL

Reductions in LDL-C by Treatment Group



Pedersen TR et al. *JAMA*. 2005;294:2437-2445.

Reductions in HDL-C by Treatment Group

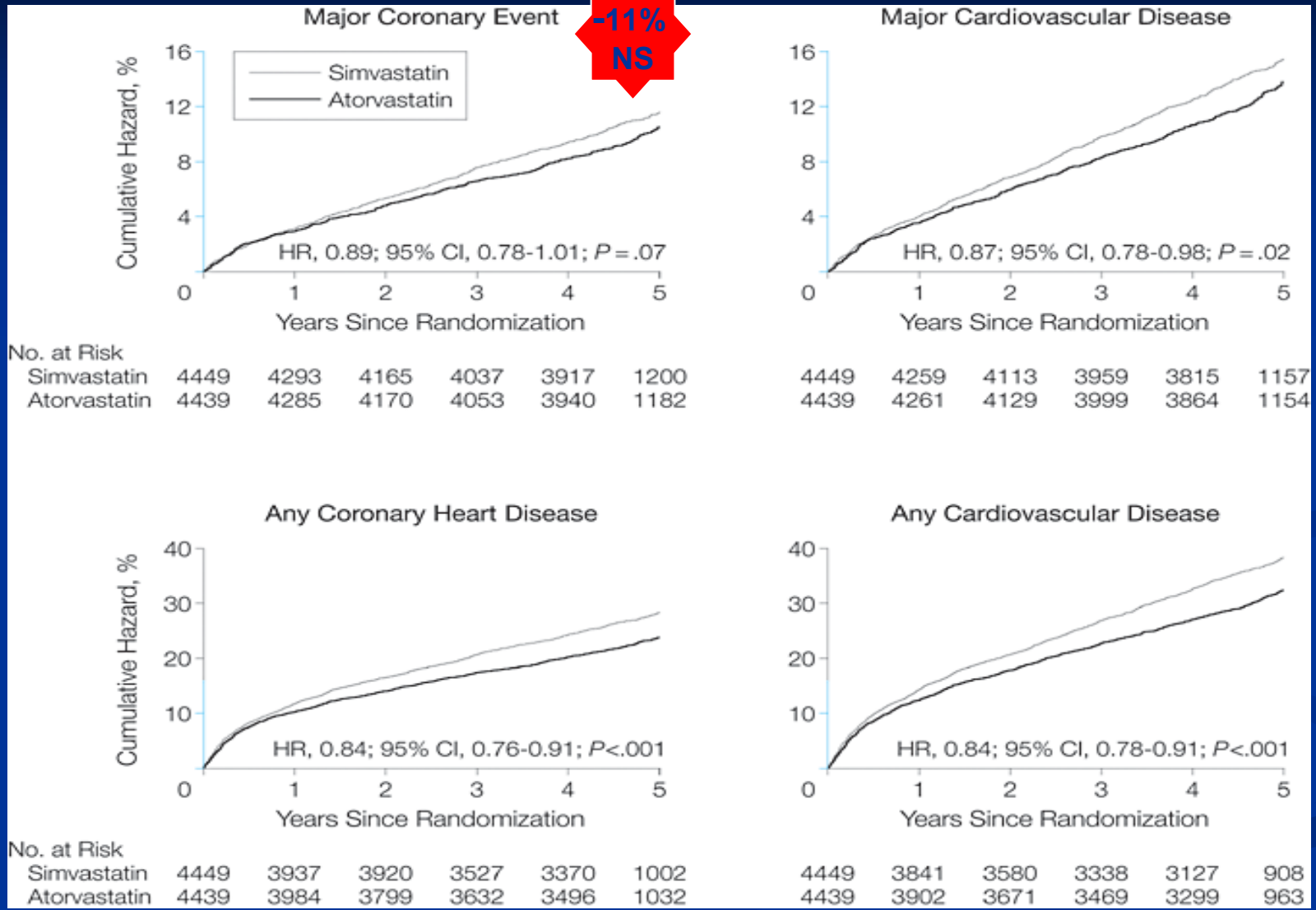


Pedersen TR et al. *JAMA*. 2005;294:2437-2445.

IDEAL: Primary outcome

Outcome (%)	Simvastatin (n=4449)	Atorvastatin (n=4439)	HR	P
Major coronary event	10.4	9.3	0.89	0.07
CHD death	4.0	3.9	0.99	0.90
Nonfatal MI	7.2	6.0	0.83	0.02
Cardiac arrest with resuscitation	0.2	0.2	NA	NA

Cumulative Hazard of Cardiovascular Disease



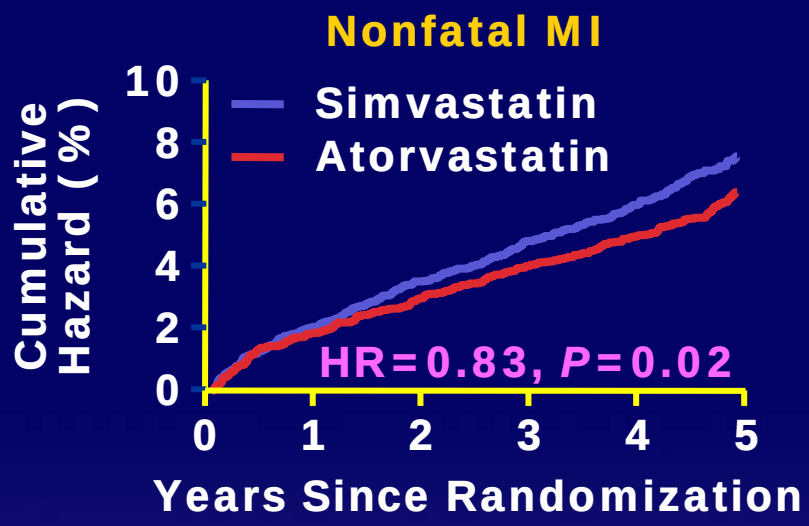
Pedersen, T. R. et al. JAMA 2005;294:2437-2445.

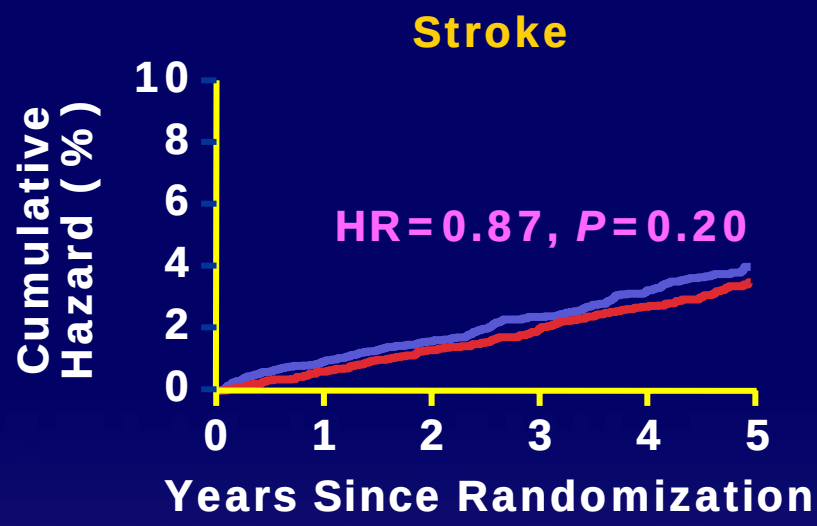
IDEAL: Secondary outcomes

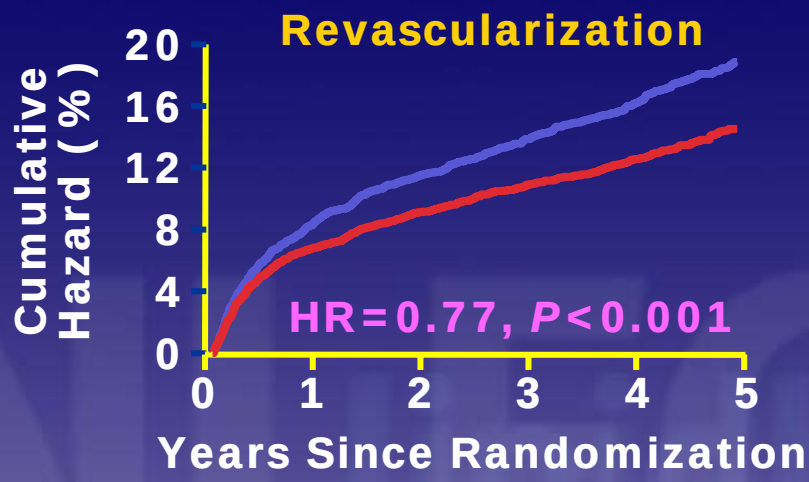
Outcome (%)	Simvastatin (n=4449)	Atorvastatin (n=4439)	HR	P
Any CHD event	23.8	20.2	0.84	<0.001
Coronary revascularization	16.7	13.0	0.77	<0.001
Hospitalization for U/A	5.3	4.4	0.83	0.06
Fatal or nonfatal stroke	3.9	3.4	0.87	0.20
Major CV event	13.7	12.0	0.87	0.02

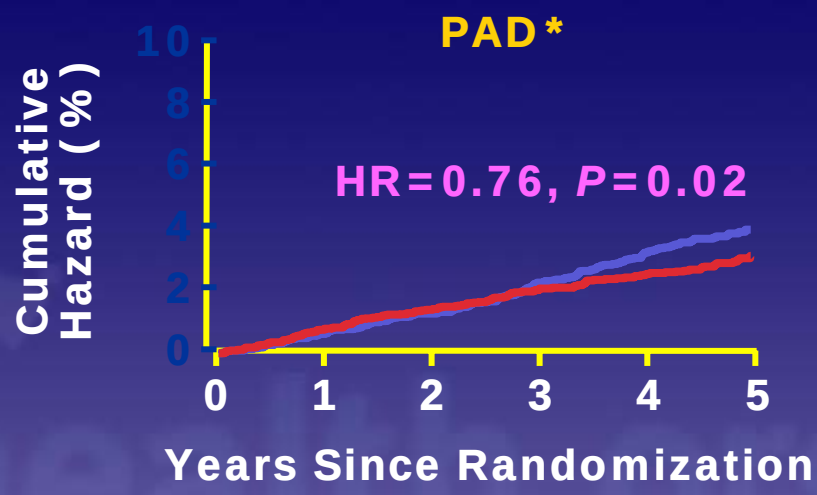
IDEAL Study:

Secondary End Points









*Newly diagnosed or requiring hospitalization.

Adapted from Pedersen TR et al. *JAMA*. 2005;294:2437-2445.

Other Results

- No difference in total mortality
- More nonserious adverse events resulting in drug discontinuation in the atorvastatin group and a greater proportion of patients developing liver-enzyme elevation with atorvastatin 80 mg
- Benefit of atorvastatin in line with achieved LDL cholesterol reduction

Frequency of Adverse Events and Most Relevant Liver Enzyme Elevations

Table 4. Frequency of Adverse Events and Most Relevant Liver Enzyme Elevations

	Simvastatin, No. (%) (n = 4449)	Atorvastatin, No. (%) (n = 4439)	*P* Value*
Any adverse event	4202 (94.4)	4204 (94.7)	.62
Any serious adverse event	2108 (47.4)	2064 (46.5)	.42
Any adverse event resulting in permanent discontinuation of study drug	186 (4.2)	426 (9.6)	<.001
Adverse events resulting in permanent discontinuation of study drug with incidence ≥0.5% in either treatment group			
Myalgia	51 (1.1)	97 (2.2)	<.001
Diarrhea	9 (0.2)	38 (0.9)	<.001
Abdominal pain	10 (0.2)	37 (0.8)	<.001
Nausea	6 (0.1)	22 (0.5)	.004
Investigator-reported myopathy	11 (0.25)	6 (0.14)	.33
Investigator-reported rhabdomyolysis (subset of coded myopathy)	3 (0.07)	2 (0.05)	>.99
AST >3 × ULN at 2 consecutive measurements	2 (0.04)	18 (0.41)	<.001
ALT >3 × ULN at 2 consecutive measurements	5 (0.11)	43 (0.97)	<.001
Myopathy defined as CPK >10 × ULN at 2 consecutive measurements with muscle symptoms	0	0	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; ULN, upper limit of normal.
*P values were calculated by 2-sided χ^2 test.

Pedersen, T. R. et al. JAMA 2005;294:2437-2445.

Statin Advisory: Definitions of Muscle Toxicity

- ***Myopathy*** — a general term referring to any disease of muscles; myopathies can be acquired or inherited and can occur at birth or later in life
- ***Myalgia*** — muscle ache or weakness without creatine kinase (CK) elevation
- ***Myositis*** — muscle symptoms with increased CK levels
- ***Rhabdomyolysis*** — muscle symptoms with marked CK elevation (>10x the upper limit of normal [ULN]) and creatinine elevation (usually with brown urine and urinary myoglobin)

Pasternak RC et al. *J Am Coll Cardiol*. 2002;40:568-573.
Pasternak RC et al. *Circulation*. 2002;106:1024-1028.

Statin Advisory: Monitoring Parameters, Follow-Up Schedule

Headache, dyspepsia	Evaluate baseline symptoms, 6–8 wk after initiating therapy, then at each follow-up visit
Muscle soreness, tenderness, or pain	Evaluate baseline muscle symptoms and CK levels; muscle symptoms 6–12 wk after initiating therapy and at each follow-up visit; CK measurement when muscle soreness, tenderness, or pain present
ALT, AST	Evaluate baseline ALT/AST, 12 wk after initiating therapy, then annually or as indicated

ALT=alanine transferase; AST=aspartate transferase.

Pasternak RC et al. *J Am Coll Cardiol*. 2002;40:568-573.
Pasternak RC et al. *Circulation*. 2002;106:1024-1028.

Statin Advisory: Clinical Precautions When Prescribing Statin Therapy

- Myopathy more likely to occur at higher doses
- Doses should not exceed those required to attain ATP III goals
- Attention should be paid to factors that may increase risk for myopathy

Pasternak RC et al. *J Am Coll Cardiol*. 2002;40:568-573.
Pasternak RC et al. *Circulation*. 2002;106:1024-1028.

Statin Advisory: Risk Factors for Statin-Associated Myopathy

- **Concomitant medications:**
  - Fibrates
  - Nicotinic acid (rarely)
  - Cyclosporine
  - Azole antifungals
    Itraconazole, ketoconazole
  - Macrolide antibiotics
    Erythromycin, clarithromycin
  - HIV protease inhibitors
  - Nefazodone (antidepressant)
  - Verapamil
  - Amiodarone
  - Large quantities of grapefruit juice (>1 qt/d)
  - Alcohol abuse

- **Other considerations:**
  - Advanced age (especially >80 yr; women more than men)
  - Small body frame, frailty
  - Multisystem disease (eg, chronic renal insufficiency, especially due to diabetes)
  - Multiple medications
  - Perioperative periods

Pasternak RC et al. *J Am Coll Cardiol*. 2002;40:568-573.
Pasternak RC et al. *Circulation*. 2002;106:1024-1028.

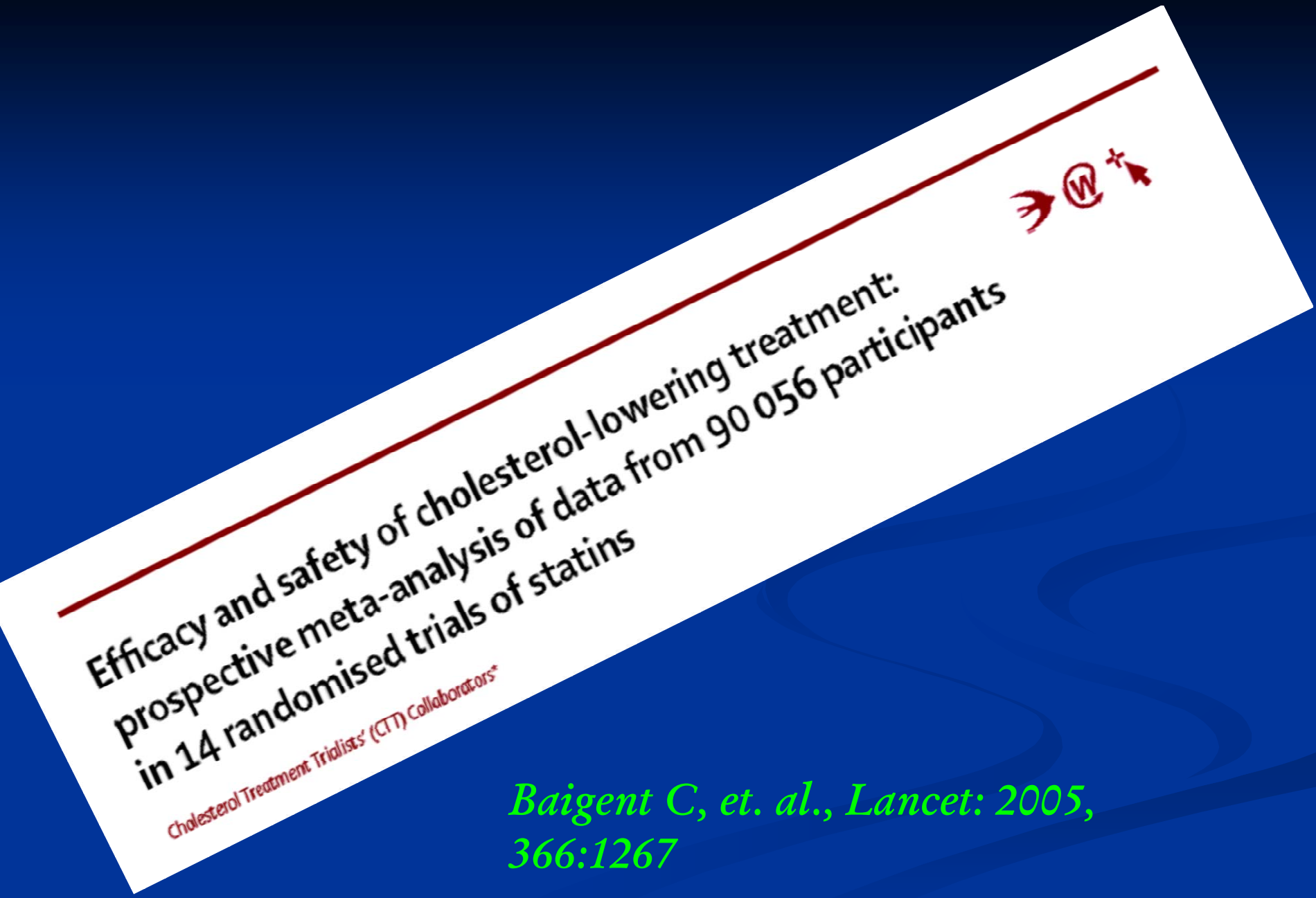
Statin Advisory: Conclusions

- Statins reduce the incidence of major coronary events, coronary procedures, and stroke in high-risk patients
- This potential is not fully realized due to underuse in clinical practice
- Statins are safe in the vast majority of patients
- Statins should be used with appropriate caution, particularly in selected patients

Pasternak RC et al. *J Am Coll Cardiol*. 2002;40:568-573.
Pasternak RC et al. *Circulation*. 2002;106:1024-1028.

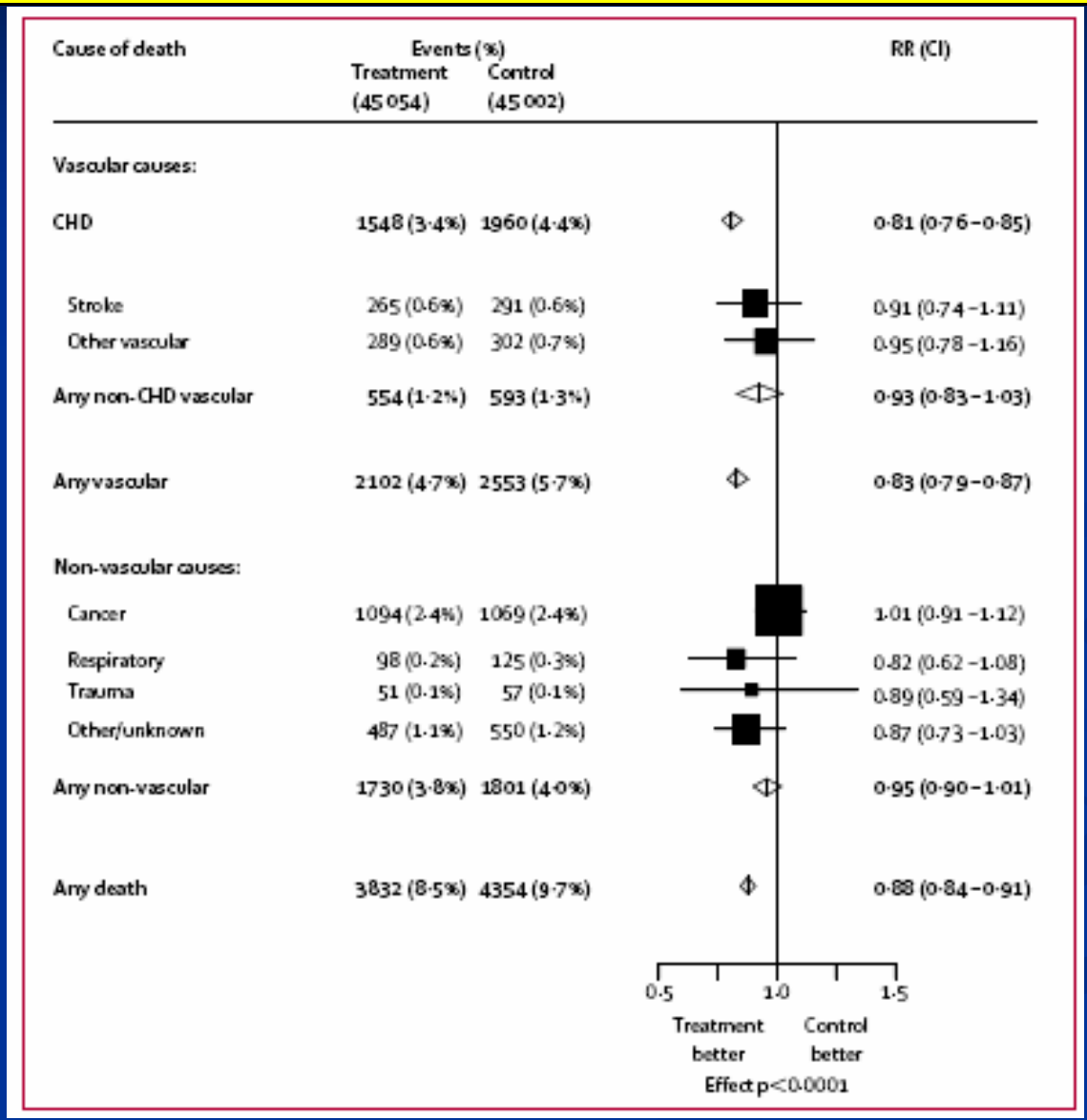
Clinical Outcome Trials Testing Intensive Vs Standard Statin Therapy

Trial	Population	N	Duration Years	LDL-C reduction Mg/dl	Risk reduction %	Risk reduction in CAD death or MI
PROVE IT-TIMI22	ACS	4162	2	33	16	16
A-Z	ACS	4497	2	14	11	15
TNT	Stable CAD	10000	5	24	22	21
IBEAL	Stable CAD	8888	5	23	11	11

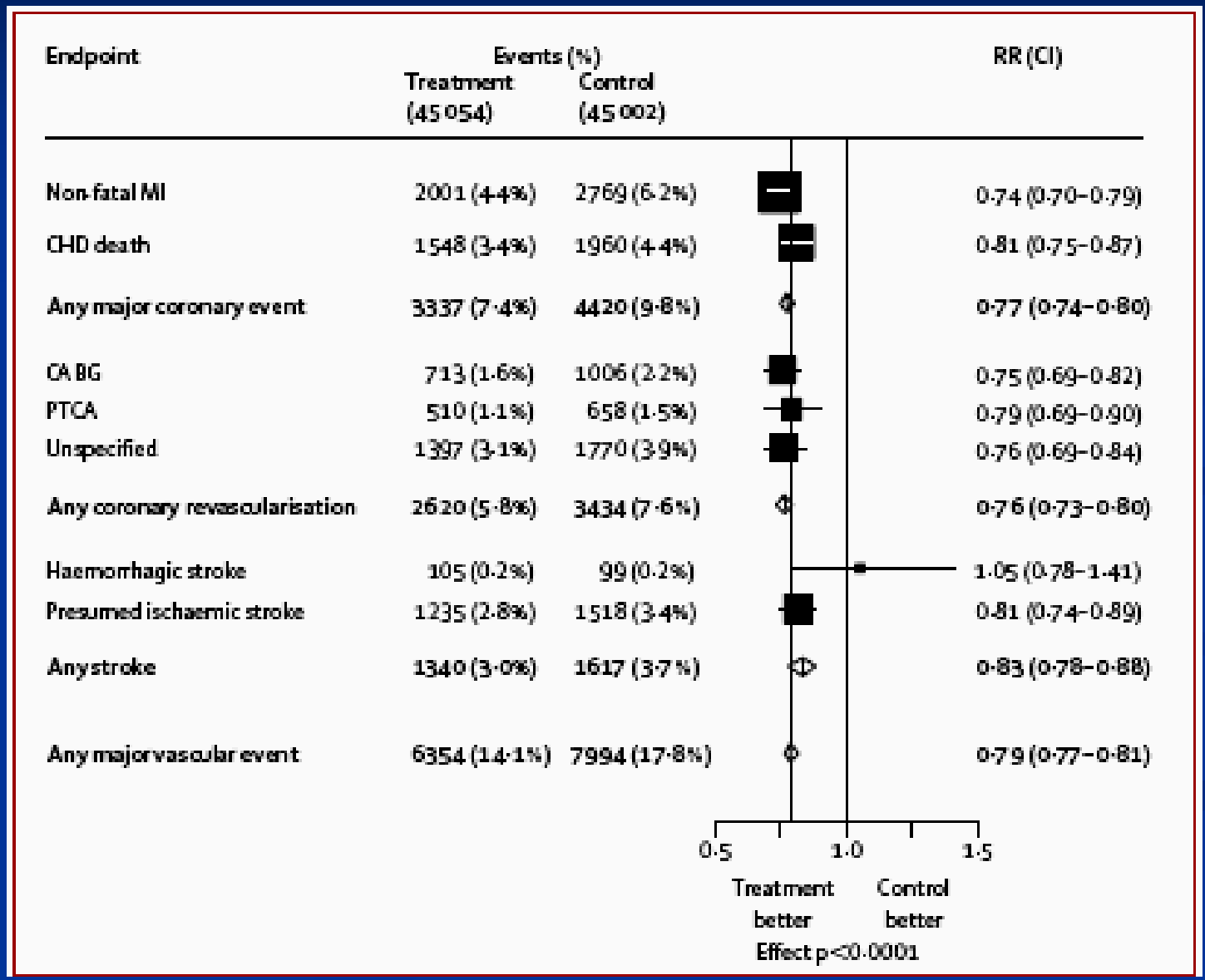


Baigent C, et. al., Lancet: 2005, 366:1267

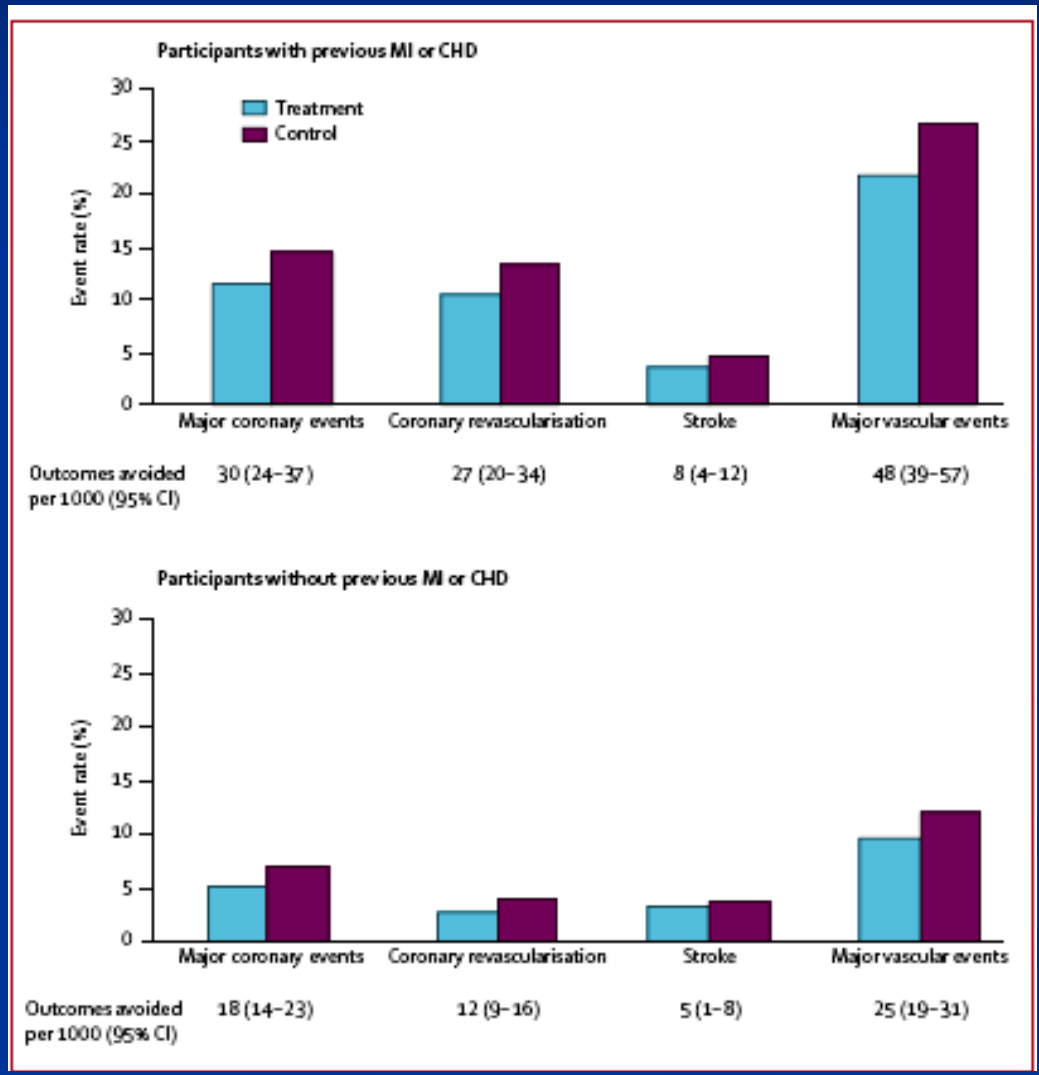
Proportional effects on cause-specific mortality per mmol/L LDL cholesterol reduction



Proportional effects on major vascular events per mmol/L LDL cholesterol reduction



5-year absolute benefits on vascular outcomes per mmol/L LDL- C reduction in participants with and without previous MI or CHD



Implications

- The present meta-analysis indicate that the proportional reductions in the incidence of major coronary events, coronary revascularisations, and strokes were approximately related to the absolute reductions in LDL -C achieved with the statin regimens studied

Implications

- the proportional reductions in such major vascular events per mmol/L LDL-C reduction were similar irrespective of the pretreatment cholesterol concentrations or other characteristics (eg, age, sex, or pre-existing disease) of the study participants.
- Current treatment guidelines are based on lowering LDL-C to particular target levels, with somewhat lower targets for people at higher risk of coronary events.

Implications

- The results of this meta-analysis suggest, however, that this strategy may not realise the full potential of such treatment.
  - First, assessment of baseline risk should be based on any type of occlusive vascular event (rather than on coronary events alone), since lowering LDL cholesterol with a statin lowers the risks not just of coronary events but also of revascularisation procedures and of ischaemic strokes.
  - Secondly, treatment goals for statin treatment should aim chiefly to achieve substantial absolute reductions in LDL-C (rather than to achieve particular target levels of LDL-C), since the risk reductions are proportional to the absolute LDL-C reductions.

Implications

- Full compliance with available statin regimens can reduce LDL -C by at least 1 ·5 mmol/L in many circumstances, and hence might be expected to reduce the incidence of major vascular events by about one third. Ensuring that patients at high 5-year risk of any type of occlusive major vascular event achieve and maintain a substantial reduction in LDL-C would result in major clinical and public health benefits.

Take Home Messages

- Aggressive LDL-C lowering reduce CV events and NCEP 2004 Update to be fully adopted
- Physicians must follow the guidelines regarding indications and dose
- Patients already on statins must reduce their LDL-C to the new target
- The messages to the patients are:
  - For the bad cholesterol "the lower is better" for preventing MI, Stroke, need for revascularization and death

Take Home Messages

- Statins are safe overall even for patients with extremely low LDL-C levels, however side effects are more (up to 5%) but reversible
- Need to monitor their LDL-C & HDL-C
- Appropriate diet and exercise programs are essential

- Need for new therapeutic modalities "Beyond Statins"

Thank You