HYPERCHOLESTEROLEMIA
THE COMPLETE STORY

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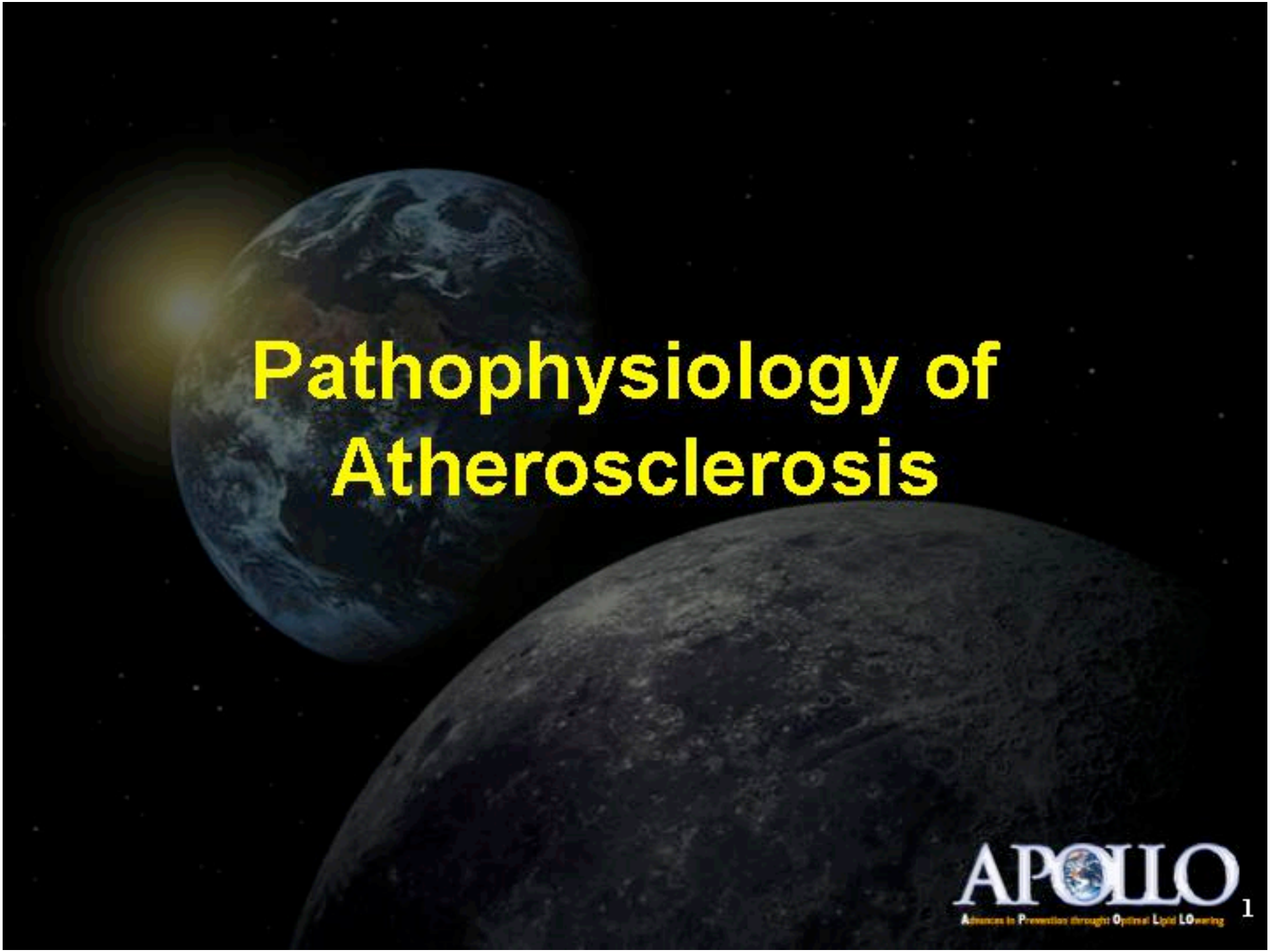
Pathophysiology of Atherosclerosis
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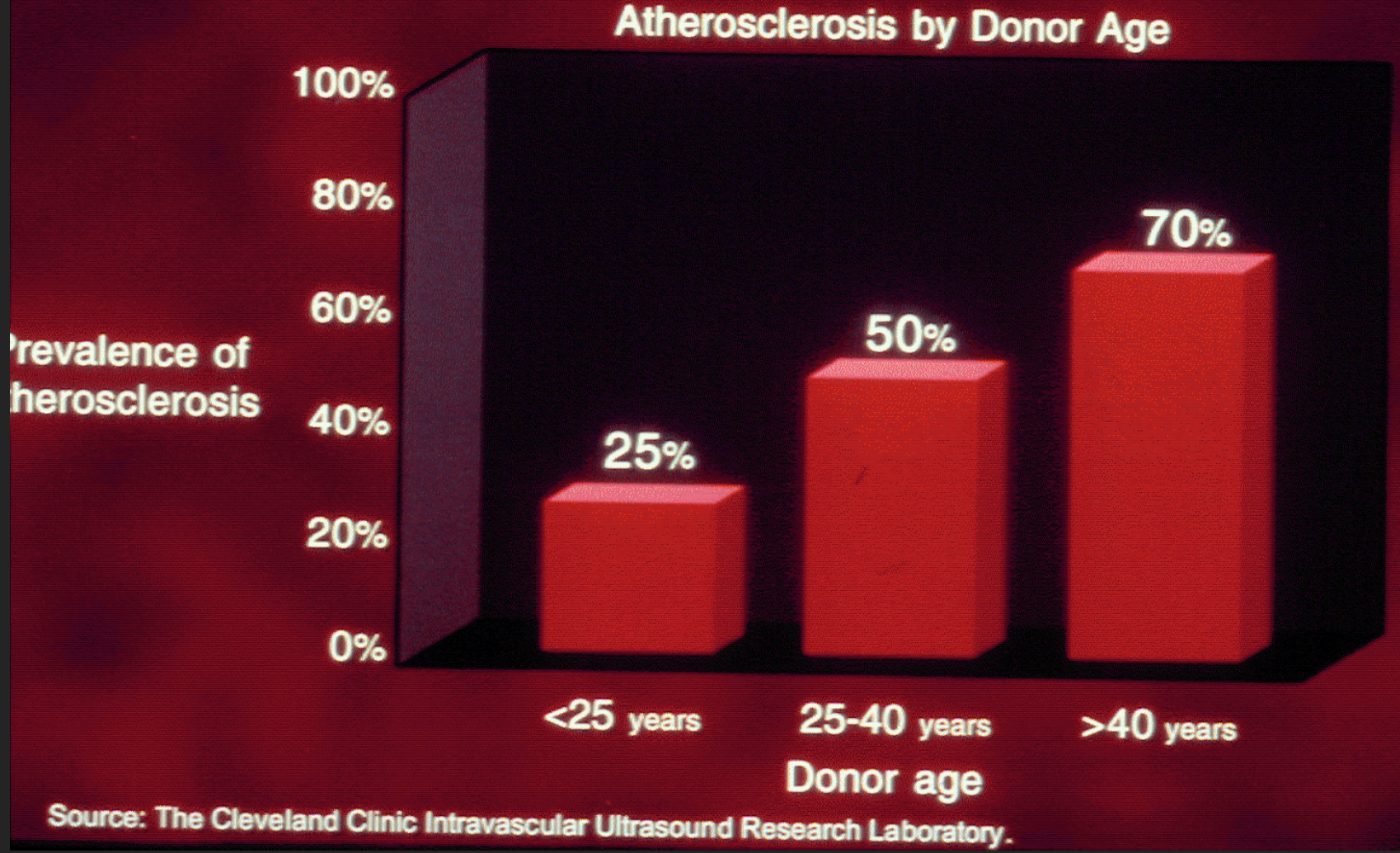
Advances in Prevention through Optimal Lipid LOwering

IVUS Reveals a Surprising Prevalence of Atherosclerosis



Source: The Cleveland Clinic Intravascular Ultrasound Research Laboratory.

Factors Contributing to Atherosclerosis

- High LDL-C
- Low HDL-C
- Obesity (abdominal, visceral)
- Diet
- Physical inactivity
- Hypertension
- Genetics
- Smoking
- Diabetes mellitus
- Environment

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol.

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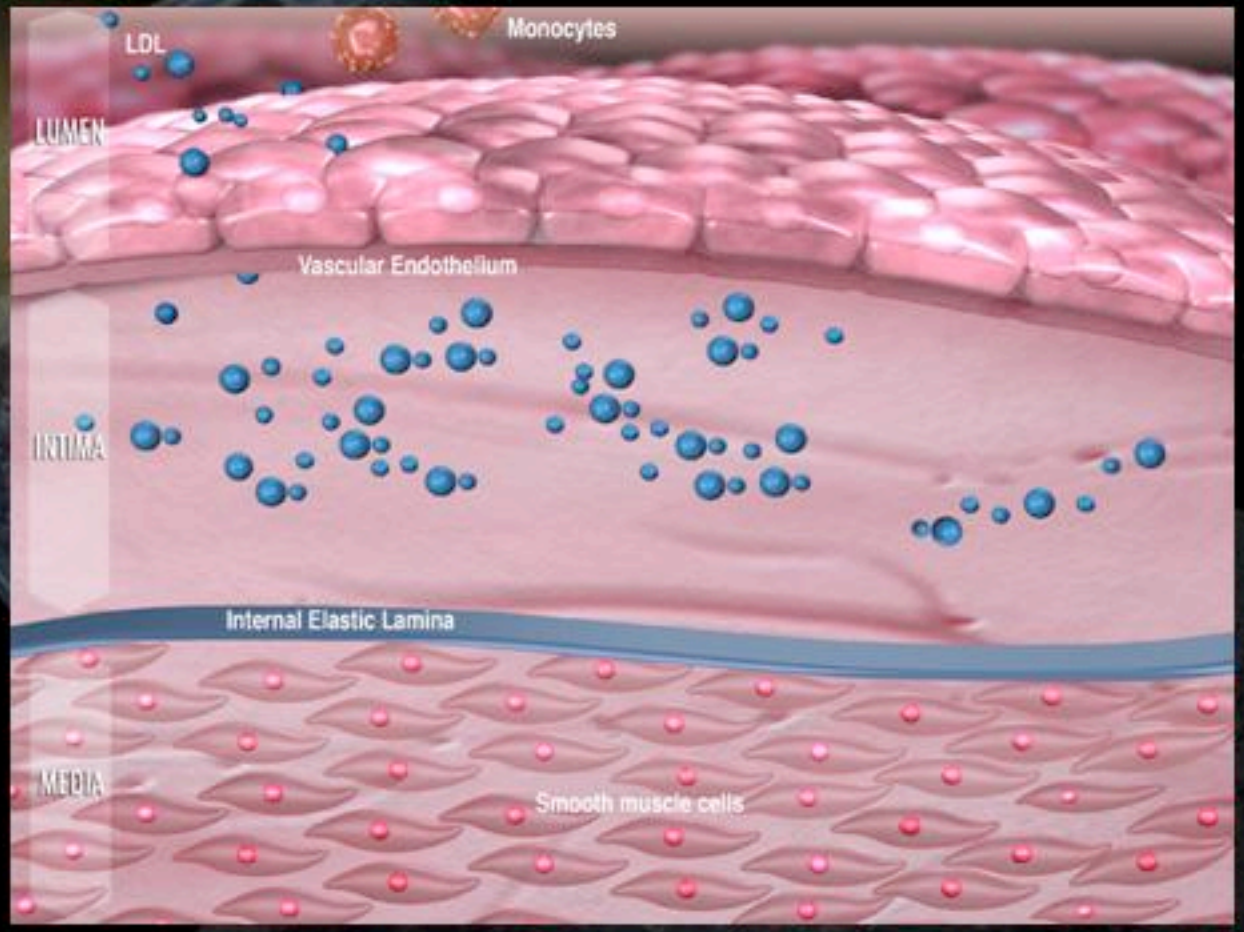
Atherosclerosis and Plaque Formation (1)



LDL = low-density lipoprotein.

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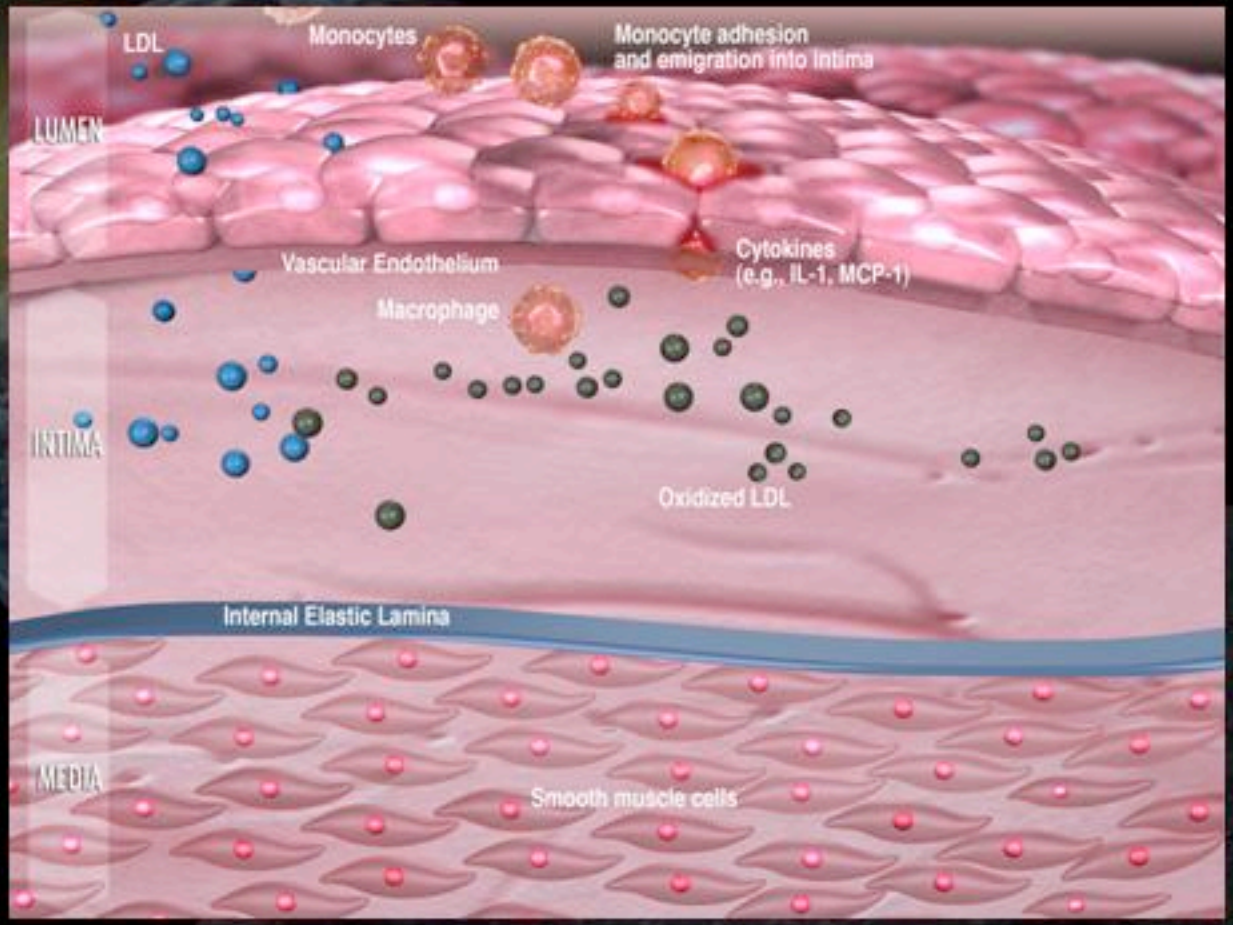
Atherosclerosis and Plaque Formation (2)



LDL = low-density lipoprotein; IL = interleukin; MCP = monocyte chemotactic protein.

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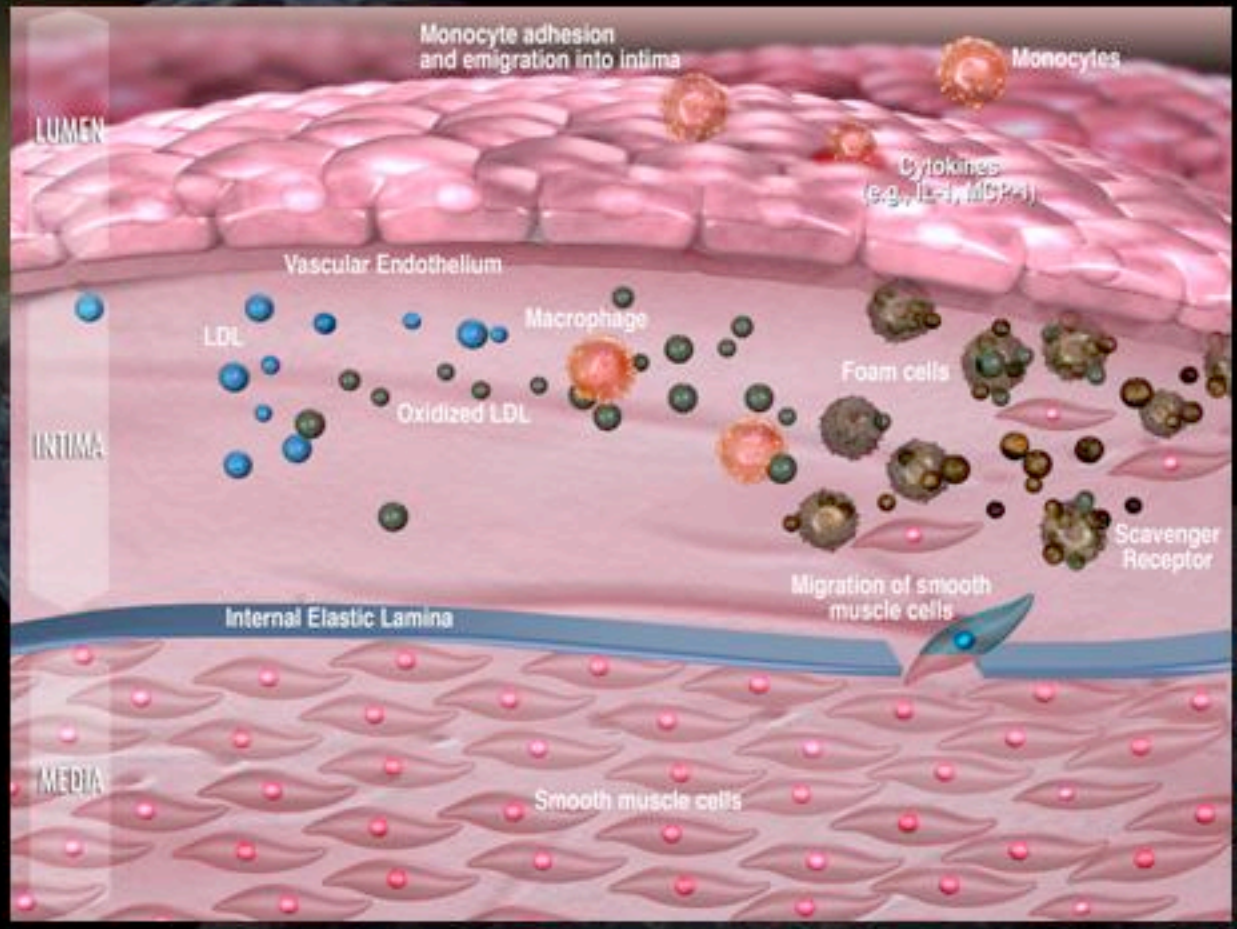
Atherosclerosis and Plaque Formation (3)



LDL = low-density lipoprotein; IL = interleukin; MCP = monocyte chemotactic protein.

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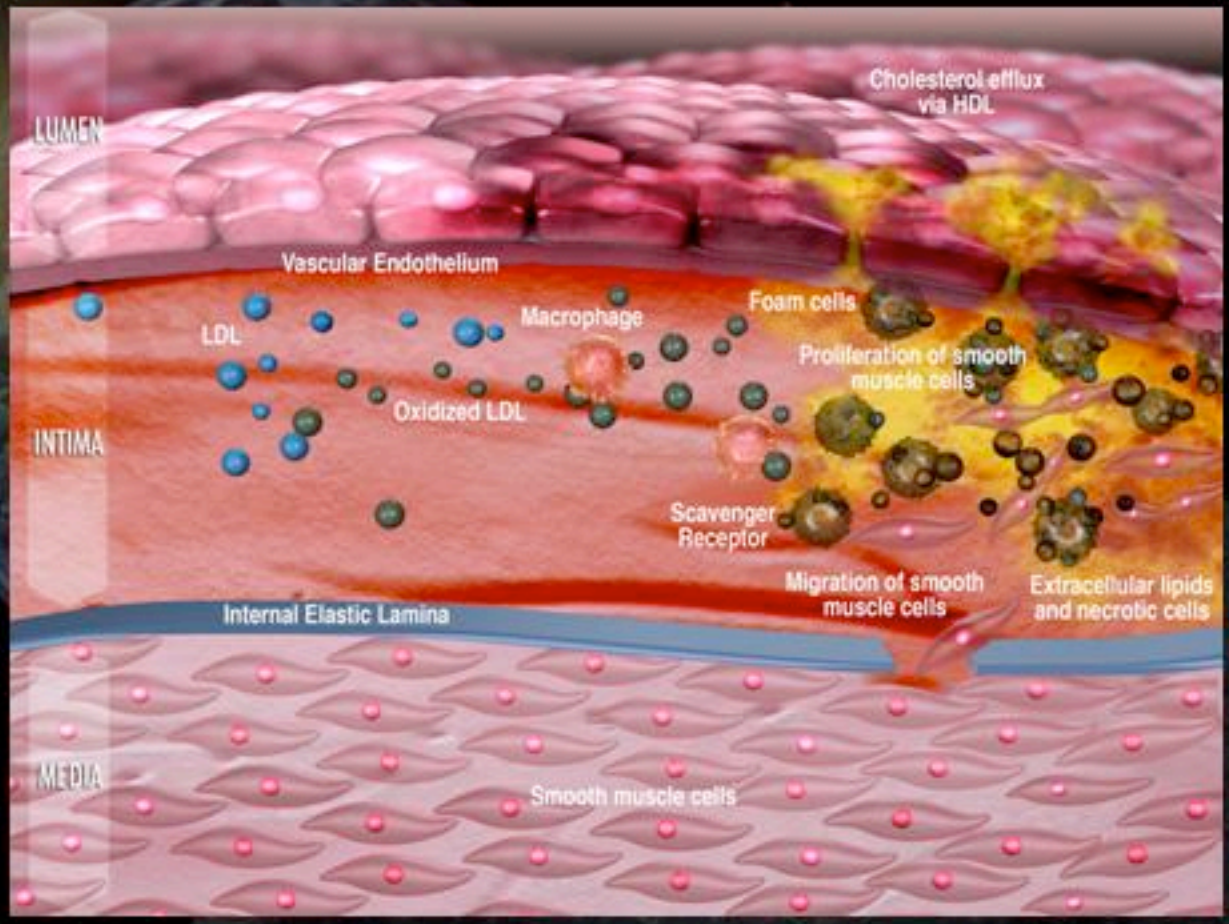
Atherosclerosis and Plaque Formation (4)



LDL = low-density lipoprotein; HDL = high-density lipoprotein.

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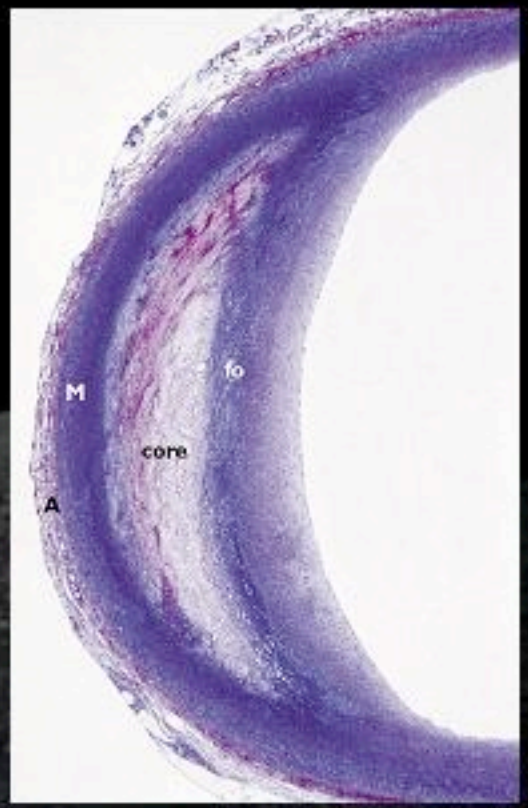
Classification of Atherosclerotic Lesions: Type IV

- Musculoelastic layer disrupted by extensive accumulation of extracellular lipid particles forming a lipid core
- Macrophages and macrophage foam cells appear in region between lipid core and endothelial surface
- No marked increase in smooth muscle cells or collagen fibers



fo = macrophage foam cells; M = media; A = adventitia.

Image from Stary HC. A Slide Atlas of Atherosclerosis Progression and Regression [atlas on CD-ROM]. New York, NY: Parthenon Publishing Group; 2002.

Complications of Atherosclerosis: Thrombosis

- Lumen occluded by fresh thrombus
- Lipid core of underlying lesion visible
- Previous thrombotic deposits within lesion indicated by brown and grey patches
- Occlusive thrombus (shown here) caused fatal myocardial infarction

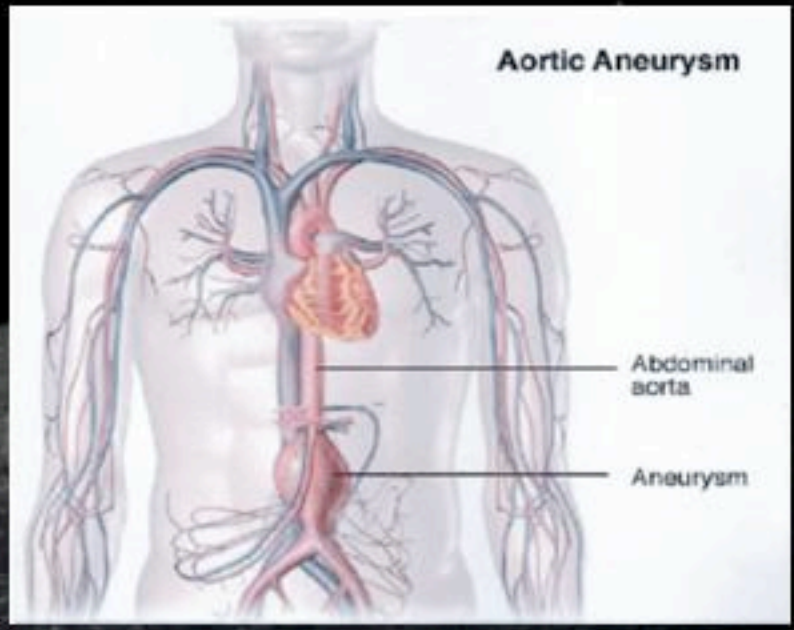
Image from Stary HC. A Slide Atlas of Atherosclerosis Progression and Regression [atlas on CD-ROM]. New York, NY: Parthenon Publishing Group; 2002.

Consequences of Atherosclerotic Lesion Formations

- Myocardial infarction (MI)
- Cerebrovascular accident
- Aortic aneurysm
- Sudden cardiac death
- Chronic ischemic heart disease
- Ischemic encephalopathy
- Gangrene of the legs
- Mesenteric occlusion

Complications of Atherosclerosis: Aortic Aneurysm

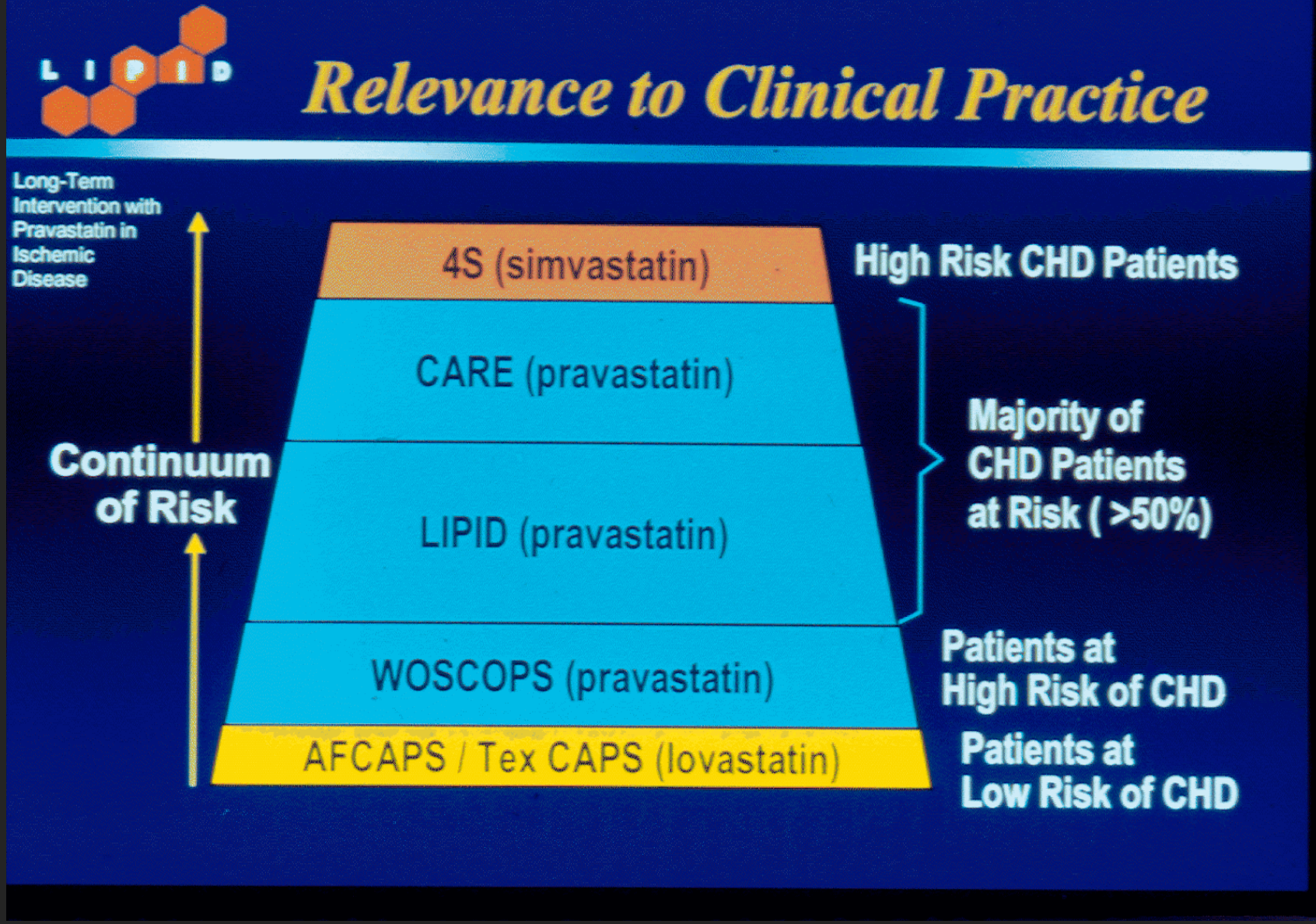
- Abdominal aortic aneurysm (AAA) is a localized dilation of the artery at least 1.5 times the normal arterial diameter[1]
- AAA growth appears to accelerate as diameter enlarges[2]
- In patients with AAA, aortic calcification correlated with atherosclerotic disease[3]
- Increases in atherosclerotic plaque area linked with significant decrease in thickness of abdominal aortic media[4]



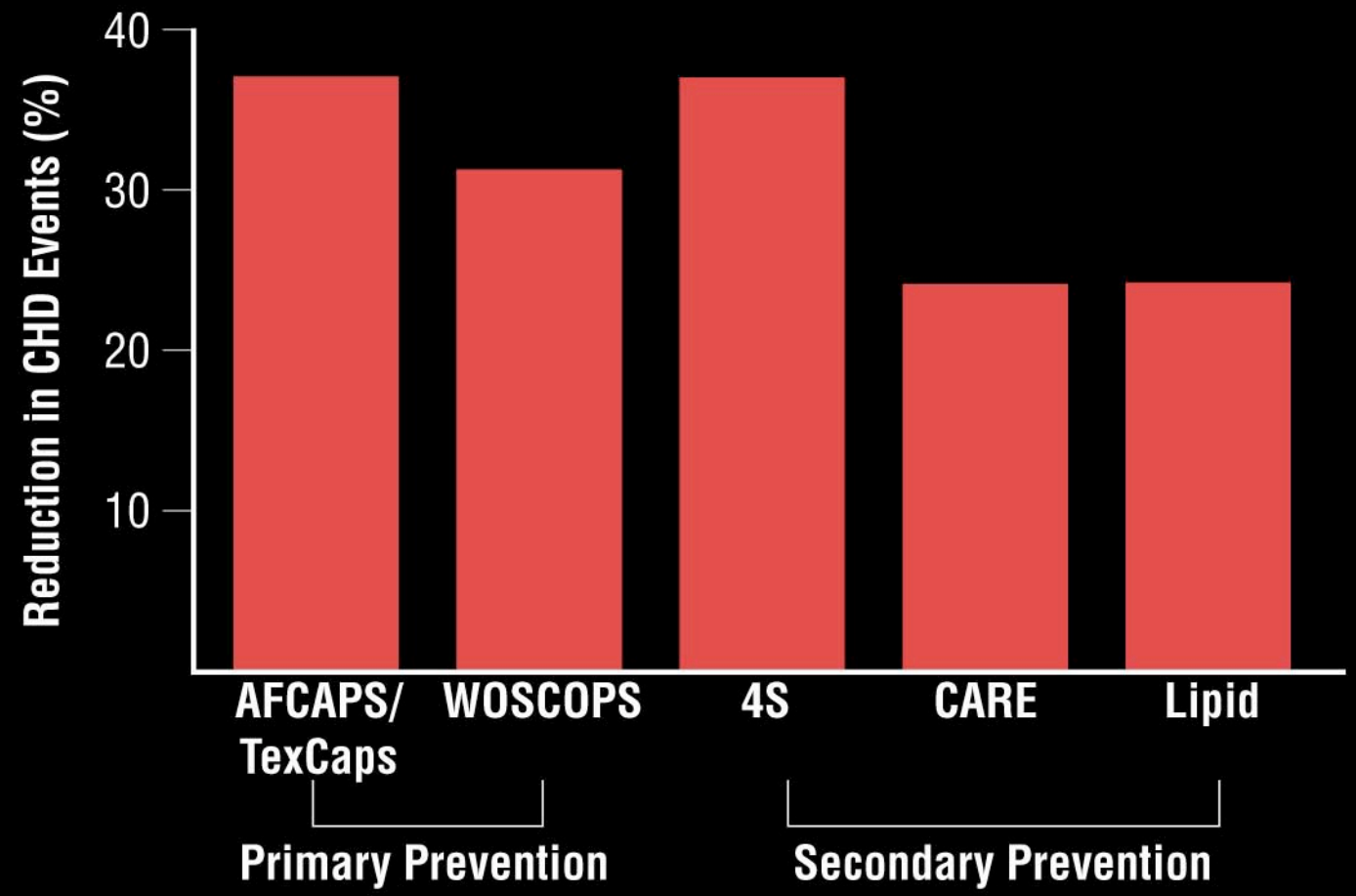
[1]Prisant LM, Mondy JS 3rd. *J Clin Hyperten*. 2004;6:85-89; [2]Brady AR, et al. *Circulation*. 2004;110:16-21; [3]Matsushita M, et al. *Int Angiol*. 2000;19:276-279; [4]Zarins CK, et al. *Atherosclerosis*. 2001;155:157-164.


MACRO
STORM

Relevance to Clinical Practice



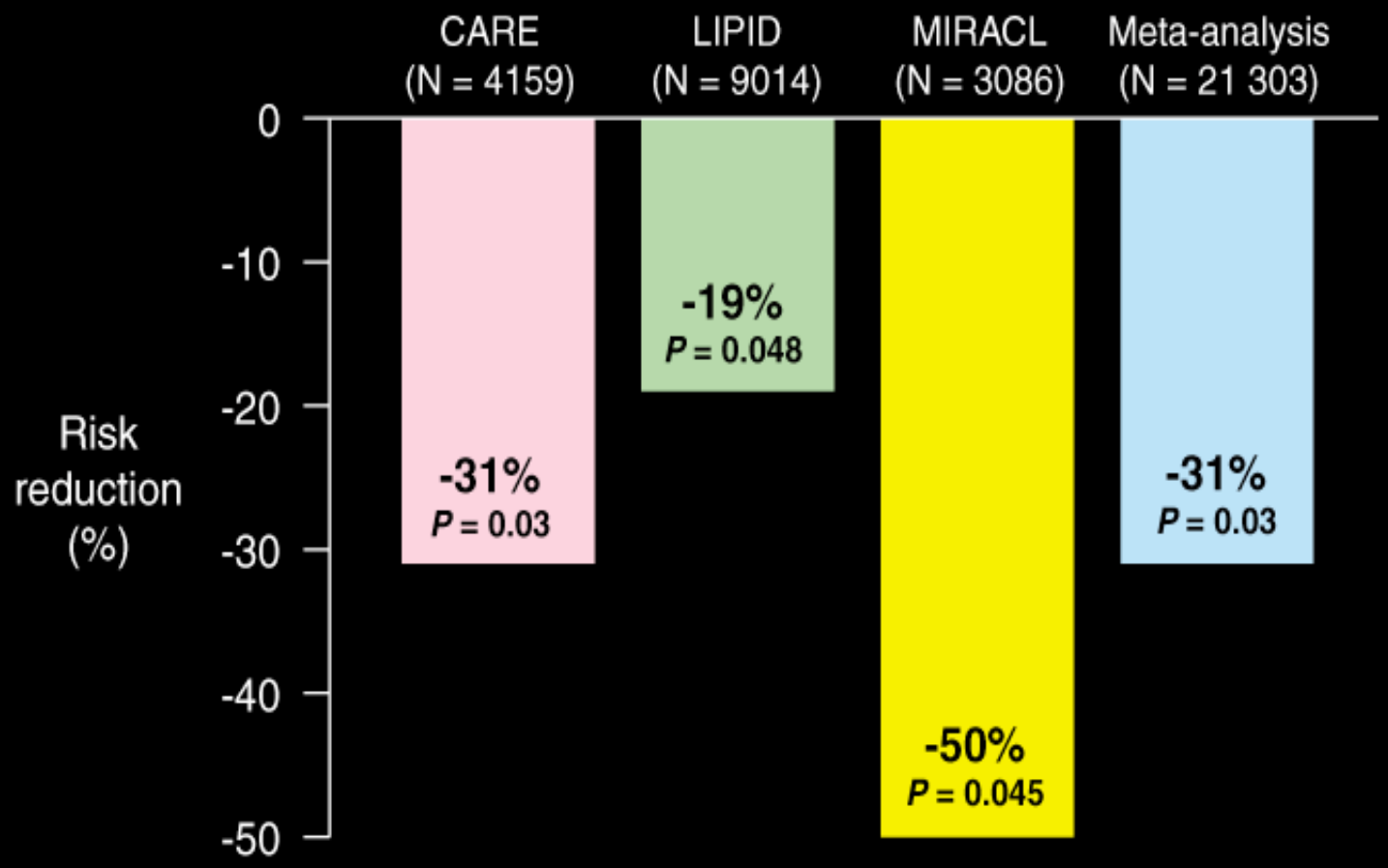
Lipid Lowering Reduces Coronary Events



Downs et al, *JAMA*, 1998; Shepherd et al, *N Engl J Med*, 1995; Scandinavian Simvastatin Survival Study Group, *Lancet*, 1994; Sacks et al, *N Engl J Med*, 1996; The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, *N Engl J Med*, 1998.

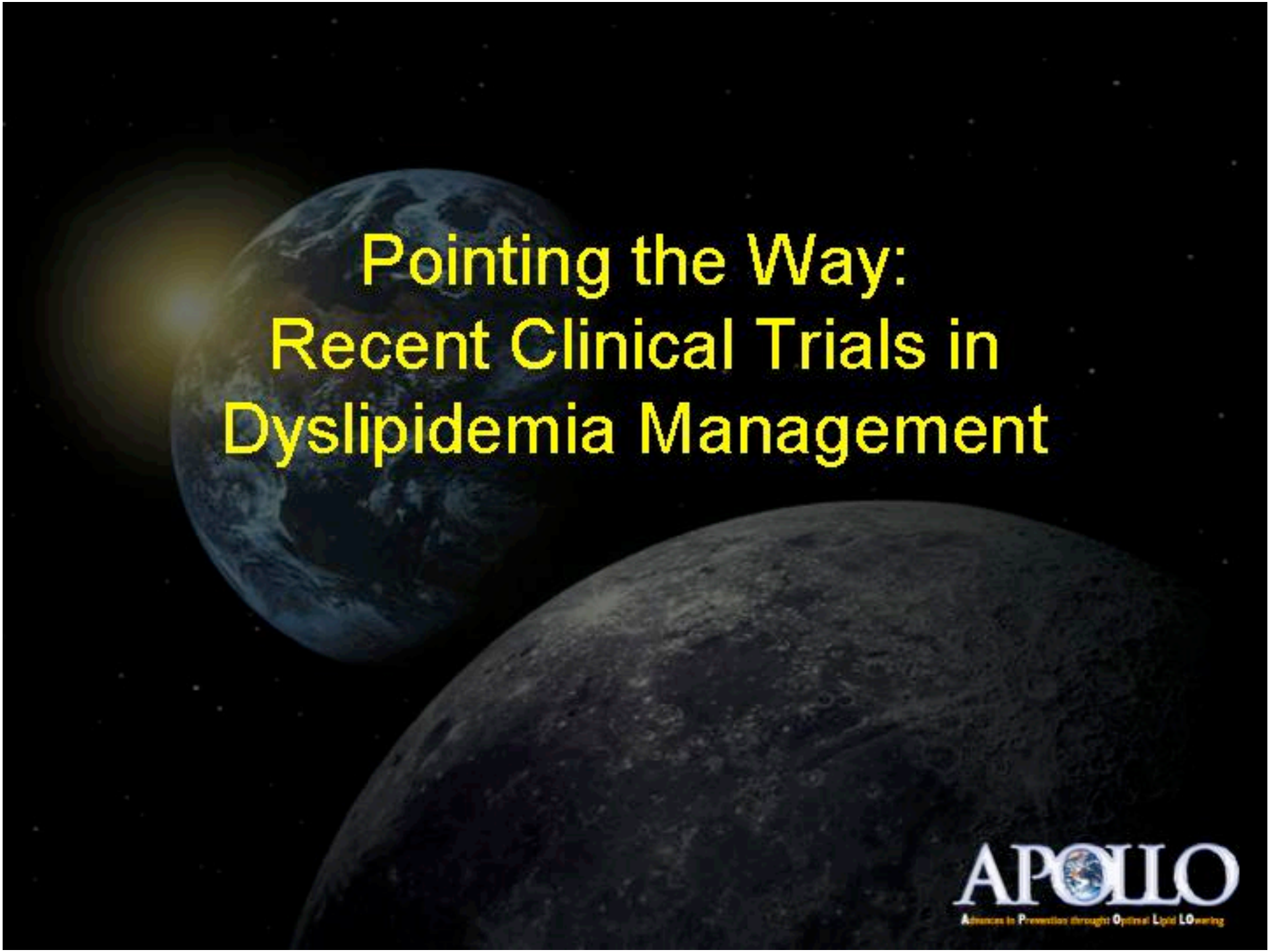
VBWG

Reduction in stroke risk with statin therapy



CARE: Pravastatin 40 mg; LIPID: Pravastatin 40 mg;
MIRACL: Atorvastatin 80 mg
Meta-analyses: Lovastatin 20/40 mg;
Pravastatin 15/20/40 mg; Simvastatin 20 mg

Sacks FM, et al. *N Engl J Med*. 1996;335:1001-1009.
The LIPID Study Group. *N Engl J Med*. 1998;339:1349-1357.
Schwartz GG, et al. *JAMA*. 2001;285:1711-1718.
Ross SD, et al. *Arch Int Med*. 1999;159:1793-1802.


Pointing the Way:
Recent Clinical Trials in
Dyslipidemia Management
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Heart Protection Study (HPS): Cholesterol Lowering With Simvastatin

Randomized, controlled, multicenter study of whether size of risk reduction from lowering LDL-C is determined by patients' overall risk for CVD rather than initial lipid concentration

Primary objective

- Assess the long-term effects of LDL-C–lowering statin therapy on vascular and nonvascular mortality and major morbidity in patients with occlusive arterial disease or diabetes

Therapeutic interventions and targets

- 20,536 men and women, aged 40-80 years, with coronary or other occlusive arterial disease or diabetes
- Randomized to simvastatin 40 mg/d or placebo for 5 years

Primary study endpoints

- Overall mortality and fatal or nonfatal vascular events for subcategory analyses

LDL-C = low-density lipoprotein cholesterol; CVD = cardiovascular disease.

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

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HPS Study Results

- All-cause mortality significantly reduced to 12.9% vs. 14.7% (*P*=.0003)
  - Coronary death rate significantly reduced 18% (*P*=.0005)
- 1st event rate for nonfatal MI or coronary death; nonfatal or fatal stroke; and coronary or noncoronary revascularization highly significantly reduced ≈25% (*P*<.0001)
- First event rate for occurrence of any major vascular event reduced 24% (*P*<.0001)
- After first year, highly significant reduction in major vascular events in high-risk patients, including those with CVD, peripheral artery disease, or diabetes, or aged >70
- Significant reductions even in those with initial LDL-C <116 mg/dL or TC <193 mg/dL
- Largest benefit in patients at higher risk from arterial occlusion, diabetes, or age

MI = myocardial infarction; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol.

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

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The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)

Randomized, controlled trial of prevention of CAD and other vascular events by blood pressure lowering and by cholesterol lowering (factorial design)

- Lipid-lowering arm (LLA)
  - Primary objective
    - Compare the effects on the combined outcome of nonfatal MI (including silent MI) and fatal CAD of atorvastatin 10 mg/d with those of placebo in hypertensive patients with TC levels of ≤6.5 mmol/L (≤250 mg/dL)

CAD = coronary artery disease; MI = myocardial infarction; TC = total cholesterol.

Sever PS, et al, for the ASCOT Investigators. *Lancet*. 2003;361:1149-1158.

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ASCOT-LLA Design

Therapeutic interventions and targets (LLA)

- Atorvastatin 10 mg/d vs placebo
- No fixed lipid-lowering target

Eligibility criteria

- SBP ≥160 mm Hg and/or DBP ≥100 mm Hg (untreated) or SBP ≥140 mm Hg and/or DBP ≥90 mm Hg (treated)
- TC ≤6.5 mmol/L (250 mg/dL) and TGs ≤4.5 mmol/L (400 mg/dL)
- 40-79 years of age
- 3+ CVD risk factors
- No history of CAD

ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; LLA = Lipid-Lowering Arm; CAD= coronary artery disease; CVD = cardiovascular disease; DBP = diastolic blood pressure; SBP = systolic blood pressure; TC = total cholesterol; TG = triglyceride.

Sever PS, et al, for the ASCOT Investigators. *Lancet*. 2003;361:1149-1158.

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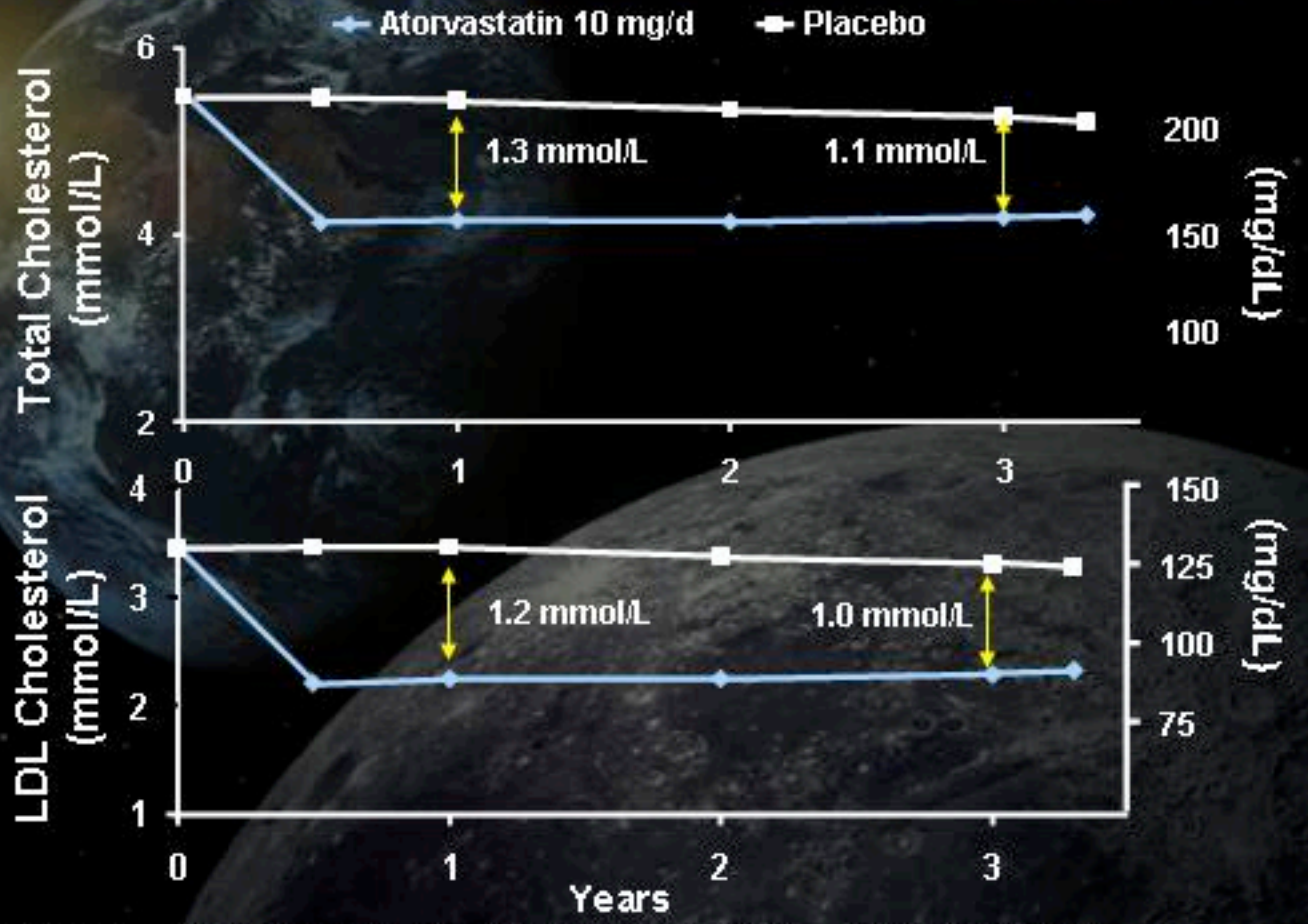
ASCOT-LLA Reductions in Total and LDL Cholesterol



ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; LLA = Lipid-Lowering Arm; LDL = low-density lipoprotein.

Sever PS, et al, for the ASCOT Investigators. *Lancet*. 2003;361:1149-1158.

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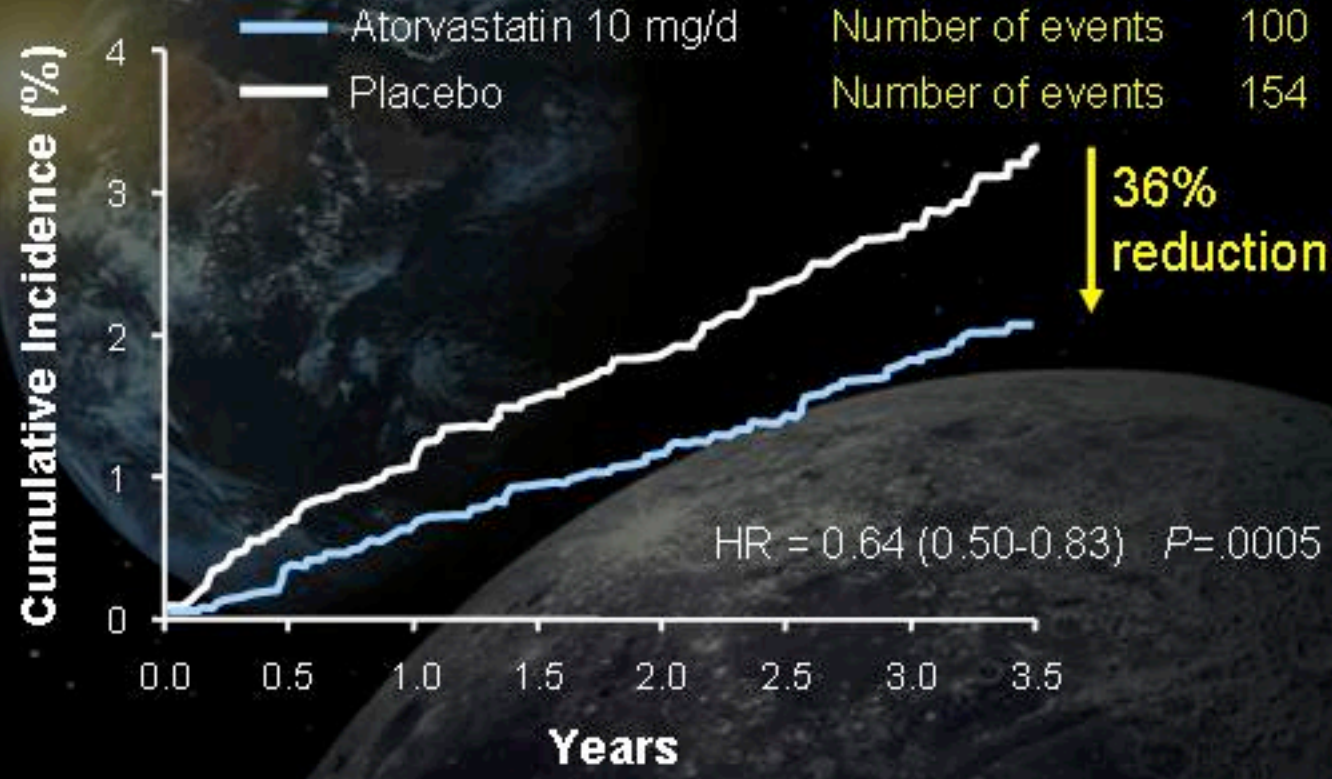
ASCOT-LLA Primary Endpoint: Nonfatal MI and Fatal CAD



ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; LLA = Lipid-Lowering Arm; MI = myocardial infarction; CAD = coronary artery disease; HR = hazard ratio. Events = nonfatal MI and fatal CAD.

Sever PS, et al, for the ASCOT Investigators. *Lancet.* 2003;361:1149-1158.

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PRavastatin or AtOrVastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction (PROVE-IT–TIMI 22) Study Design

Randomized, double-blind, parallel-group, multicenter trial of intensive vs usual statin therapy in optimal lipid lowering in ACS patients

Primary objective

- Compare clinical benefit of intensive vs usual statin treatment in preventing death or major CV events in hospitalized ACS patients

Therapeutic interventions and targets

- 4162 patients aged ≥18 years hospitalized for ACS within previous 10 days
- Randomized to atorvastatin 80 mg/d (intensive dose) or pravastatin 40 mg/d (usual dose)
- After 14 days and for 2 weeks + 10 days each month thereafter, gatifloxacin 400 mg/d or placebo
- Follow-up visit on day 30 and every 4 months thereafter for ≥18 months (average 2 years)

ACS = acute coronary syndrome; CV = cardiovascular.

Cannon CP, et al. *N Engl J Med.* 2004;350:1495-1504.

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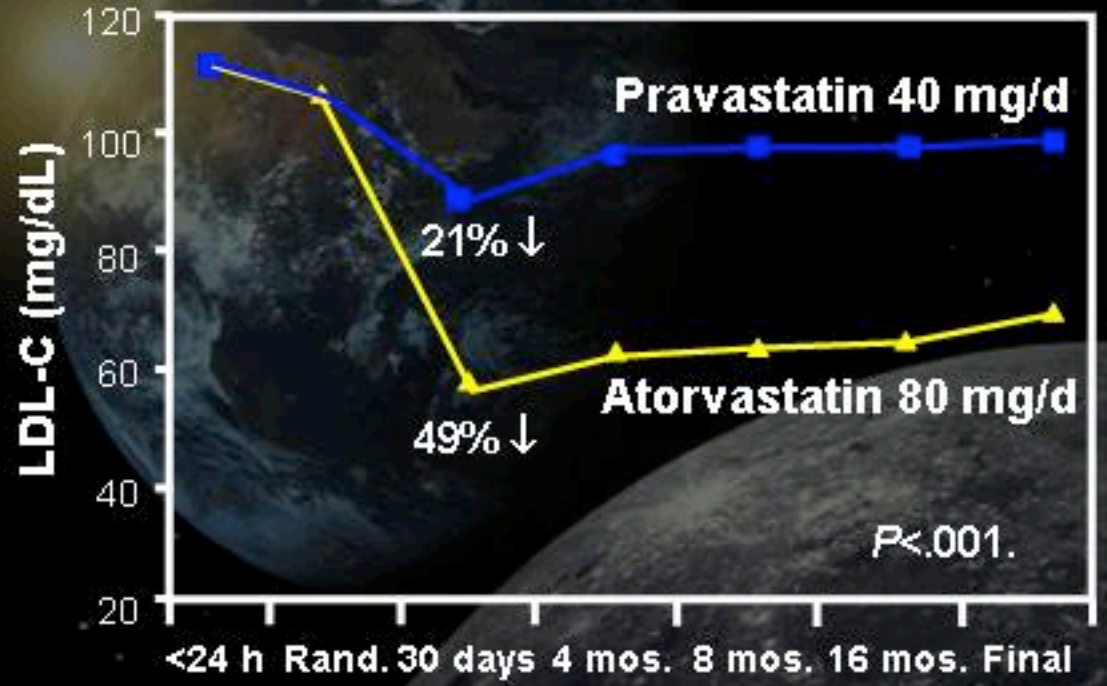
PROVE-IT Study: Changes From (Post-ACS) Baseline in Median LDL-C



Median LDL-C (Q1, Q3)

95 (79, 113)

62 (50, 79))

Changes in LDL-C may differ from previous trials

PROVE-IT = Pravastatin or AtOrVastatin Evaluation and Infection Therapy; LDL-C = low-density lipoprotein cholesterol; ACS = acute coronary syndrome.

Data from Cannon CP, et al. *N Engl J Med.* 2004;350:1495-1504.

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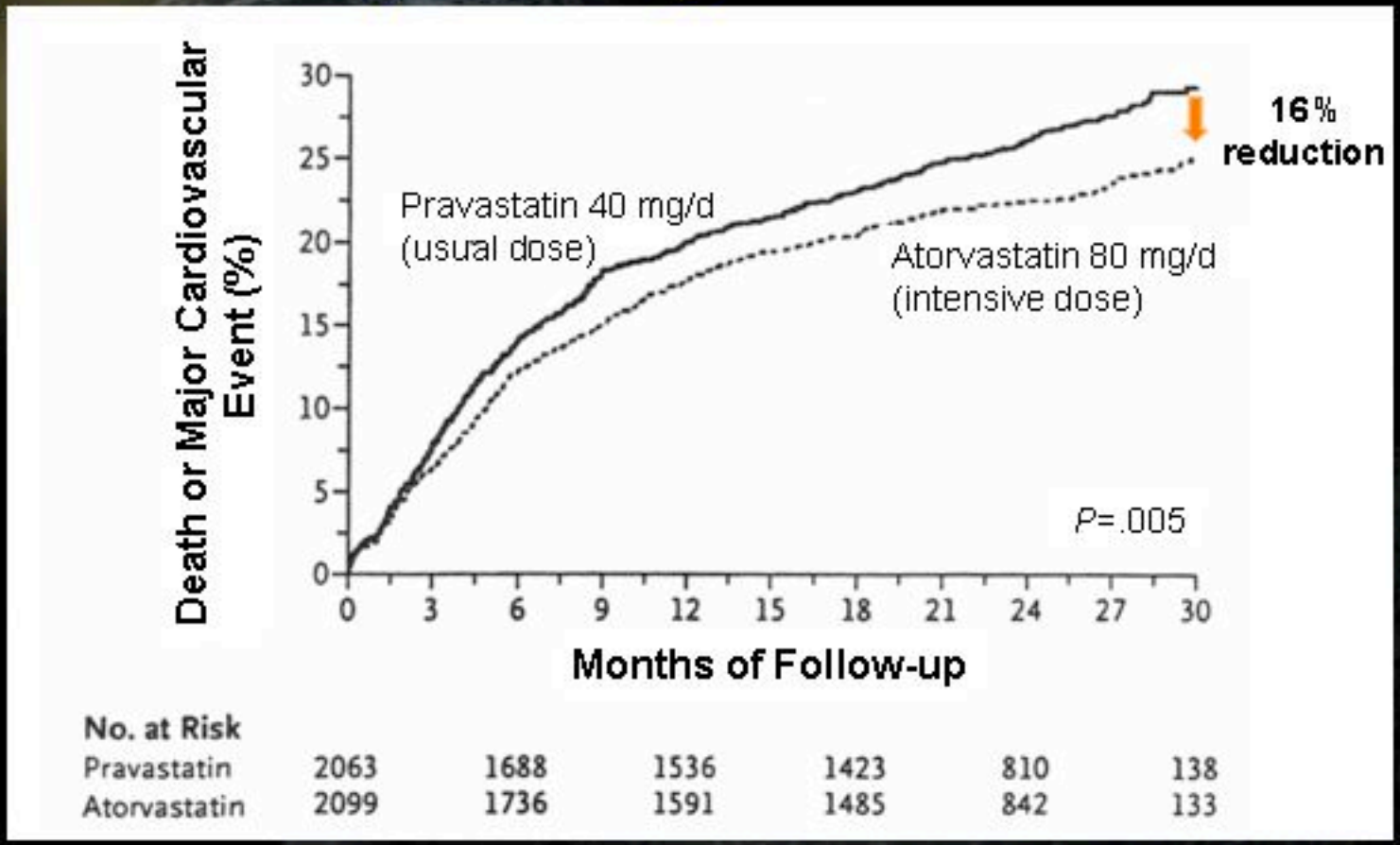
PROVE-IT Study: All-Cause Death, or Major CV Events



PROVE-IT = Pravastatin or AtOrVastatin Evaluation and Infection Therapy; CV = cardiovascular.

Cannon CP, et al. *N Engl J Med.* 2004;350:1495-1504.

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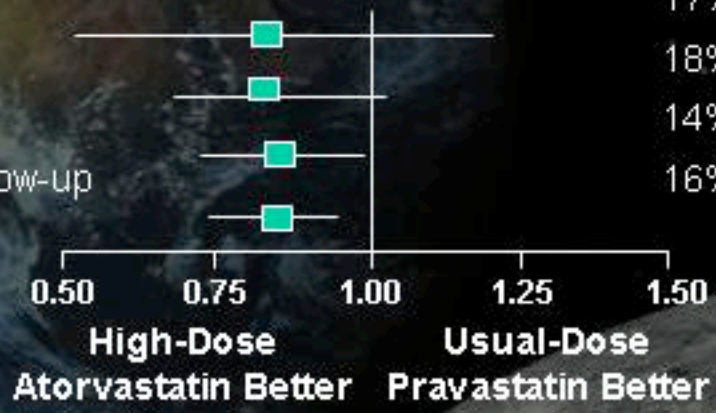
PROVE-IT Study: Primary Endpoint Over Time

Censoring Time	Hazard Ratio (95% CI)	Risk Reduction	Event Rates	
			Atorvastatin 80 mg/d	Pravastatin 40 mg/d
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%*



*2-year event rates.

Hazard ratio for the primary endpoint of death from any cause or a major cardiovascular event at 30, 90, and 180 days and at the end of follow-up in the high-dose atorvastatin group, as compared with the usual-dose pravastatin group

Event rates are Kaplan-Meier estimates censored at the timepoints indicated with the use of the average duration of follow-up (2 years) (*P*=.005).

PROVE-IT = Pravastatin or AtOrVastatin Evaluation and Infection Therapy.

Cannon CP, et al. *N Engl J Med.* 2004;350:1495-1504.

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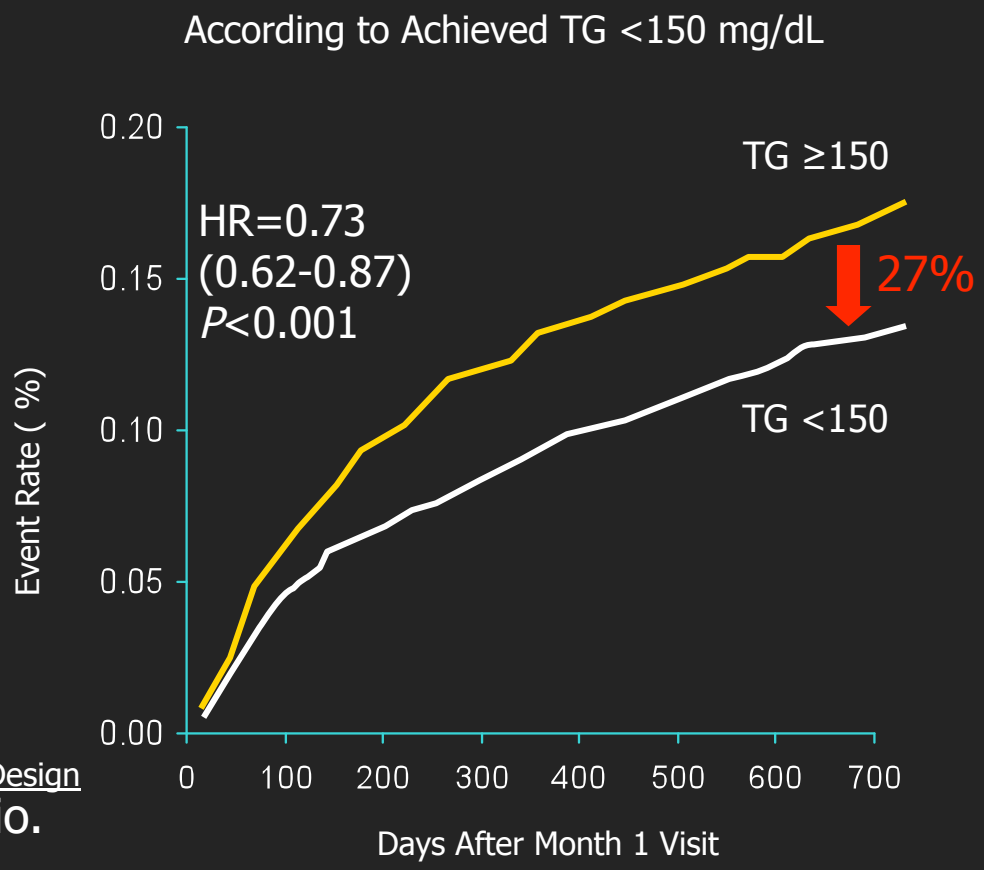
PROVE IT-TIMI 22: Subanalysis[3]

Relationship Between TG and Events in Patients After Acute Coronary Syndrome (ACS)

Estimates of Death, MI, and Recurrent ACS
Between 30 Days and 2 Years of Follow-up



PROVE IT-TIMI 22 Study Design

HR=hazard ratio.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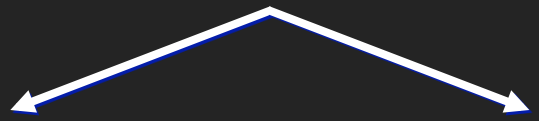
TNT Trial

10,003 patients with stable coronary heart disease

Age 35-75 years, LDL between 130 and 250 mg/dL, triglyceride ≤ 600 mg/dL

19% female, mean age 60.3 years

All received atorvastatin 10 mg during 8 week open-label run-in period



Atorvastatin 80 mg
n=4,995

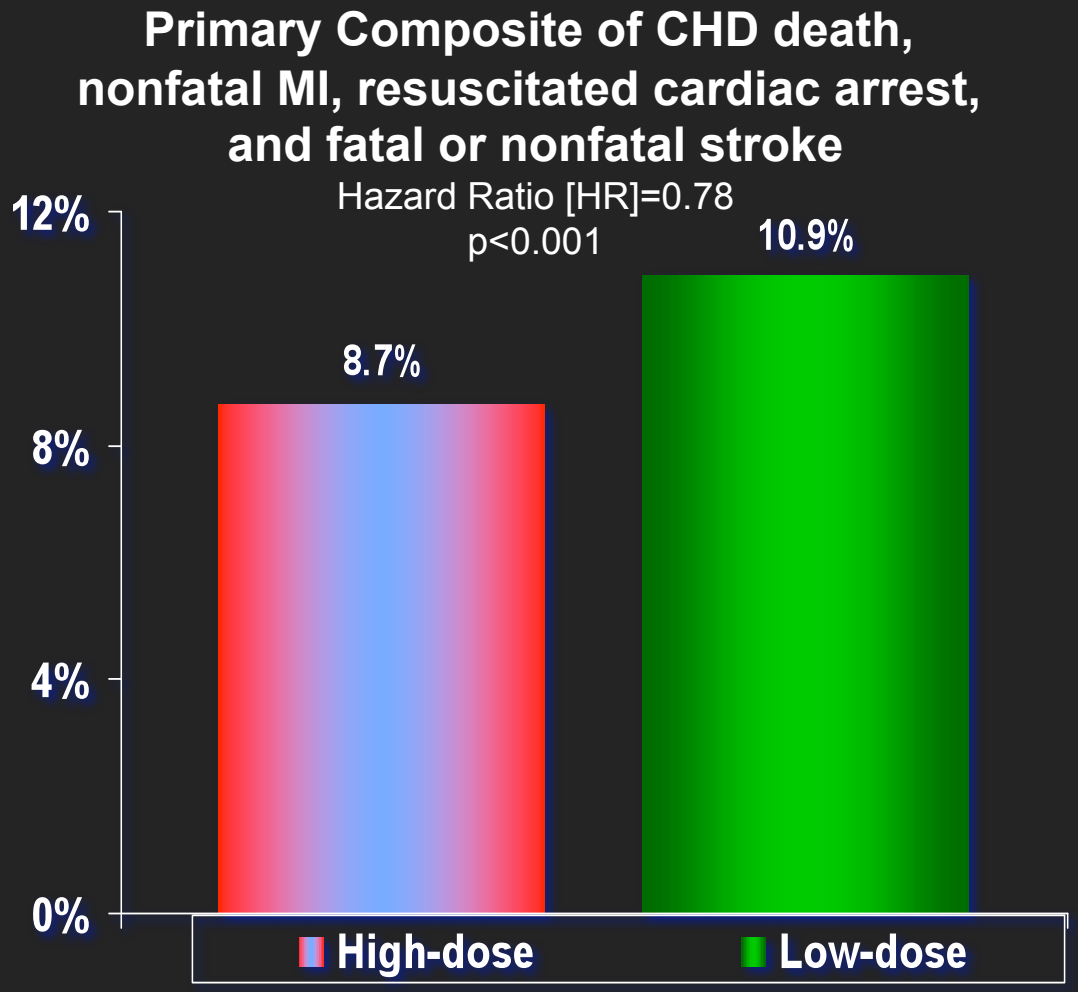
Atorvastatin 10 mg
n=5,006

Primary Endpoint: Major cardiovascular event defined as coronary heart death (CHD) , nonfatal M, resuscitated cardiac arrest, and fatal or nonfatal stroke at a mean follow-up of 4.9 years.

Secondary Endpoint: Major coronary events, cerebrovascular events, hospitalization for congestive heart failure (CHF), all-cause mortality, peripheral artery disease, any cardiovascular event, any coronary event

Presented at ACC 2005

TNT Trial: Primary endpoint

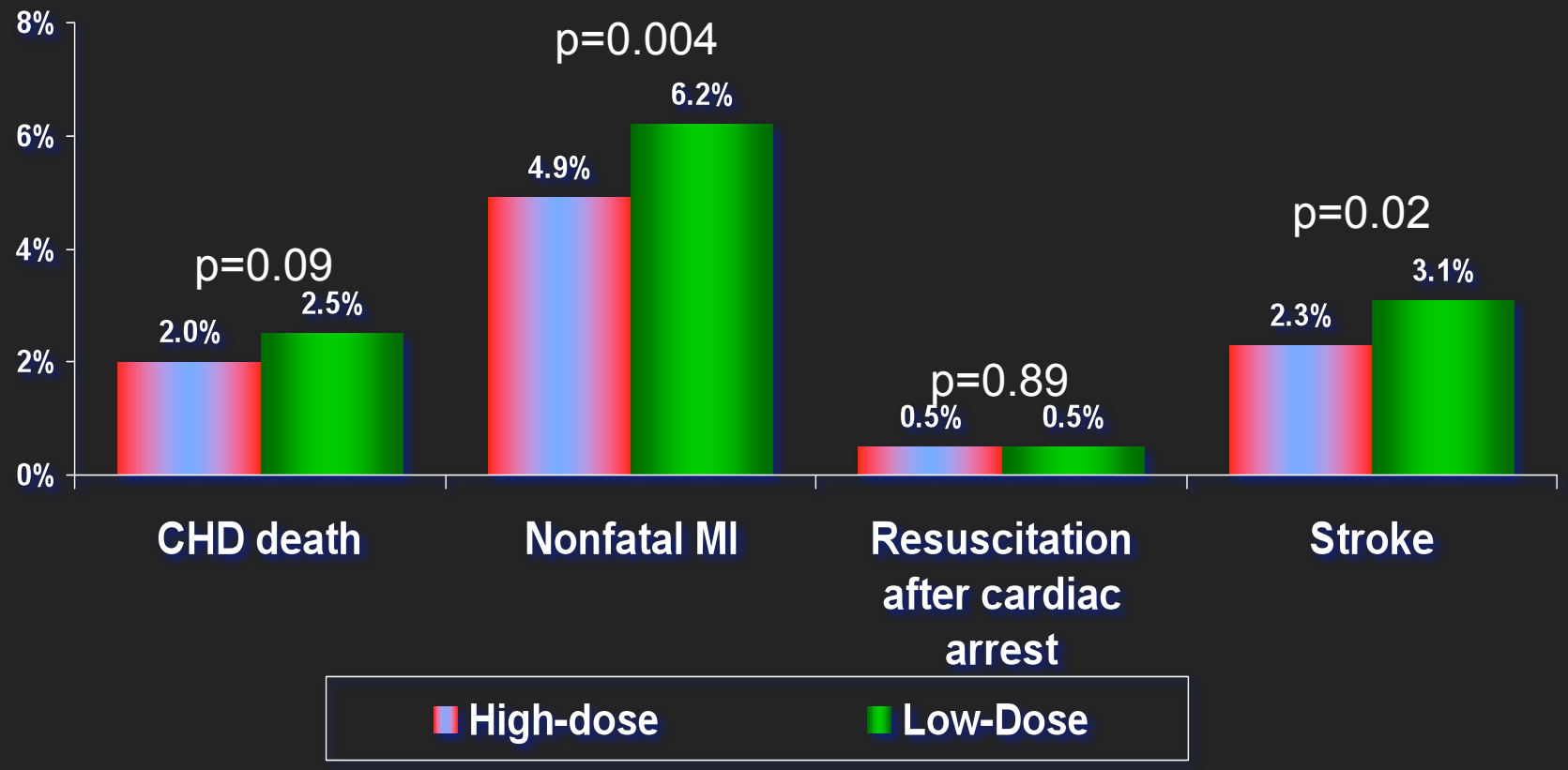


- The primary composite endpoint of CHD death, nonfatal MI, resuscitated cardiac arrest, and fatal or nonfatal stroke was lower in the high-dose atorvastatin 80 mg group at a mean follow-up of 4.9 years.

Presented at ACC 2005

TNT Trial: Primary Endpoint

The individual components of the primary endpoint were also lower or tended to be lower in the high-dose group compared to the low-dose group with the exception of resuscitation after cardiac arrest, which was the equal in both groups.

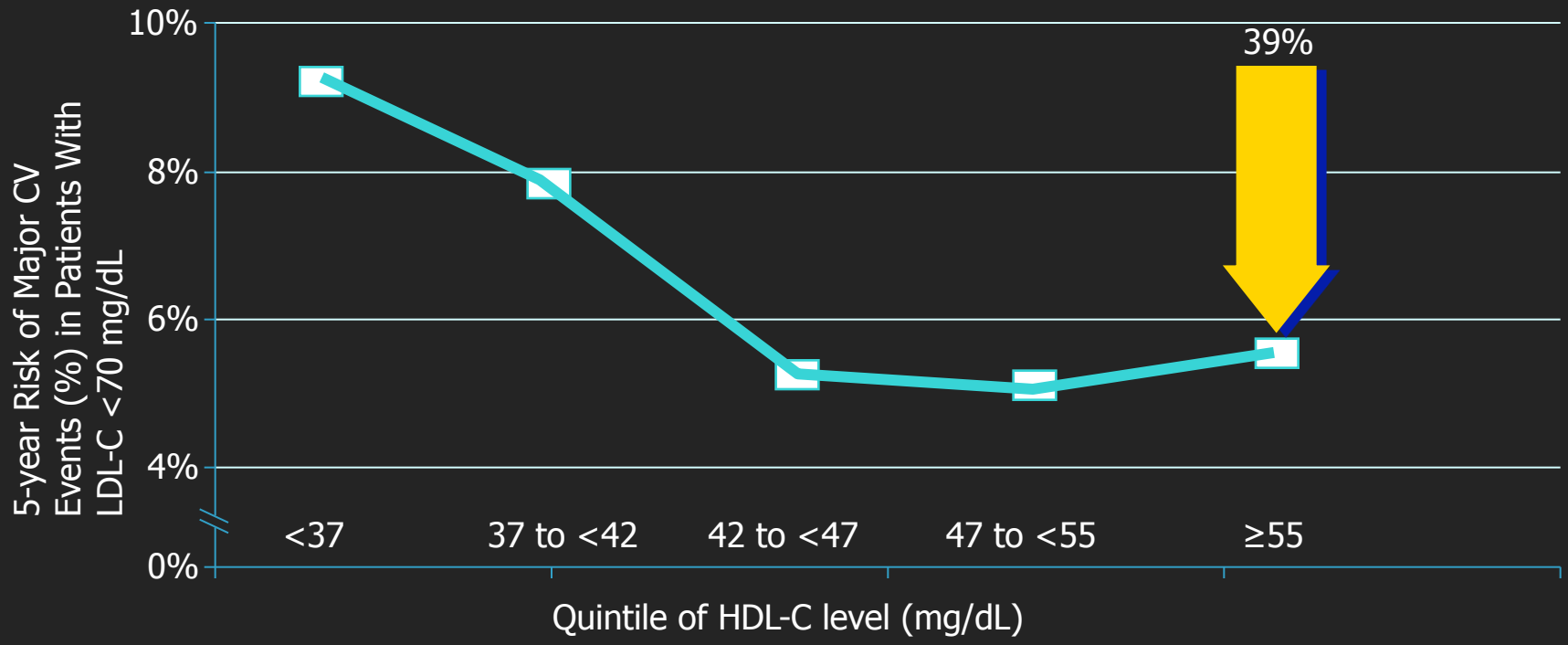


Presented at ACC 2005

TNT Study: Post Hoc Analysis[1]

HDL-C Levels and Associated CV Events After Aggressive LDL-C Lowering to <70 mg/dL

Relationship Between HDL-C and Risk of Major CV Events at 5 Years in Patients With LDL-C Levels <70 mg/dL in TNT Study

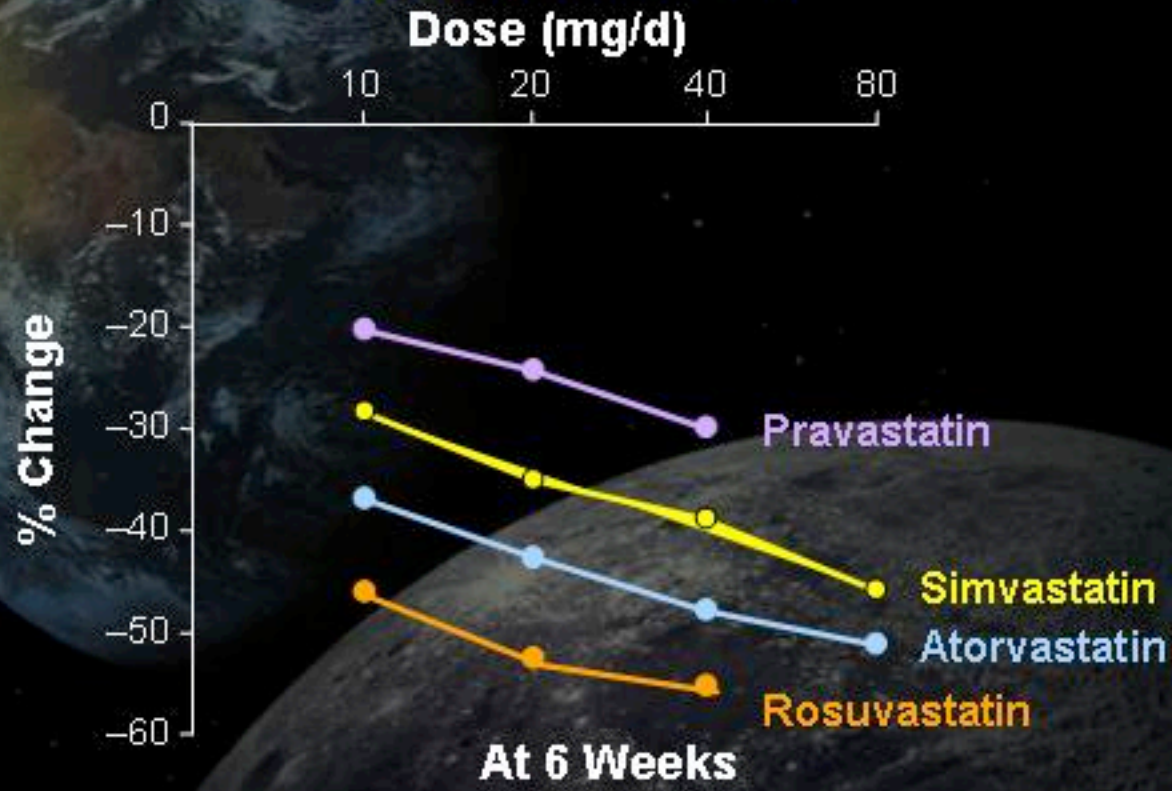


	Q1	Q2	Q3	Q4	Q5
No. of events	575034	3435			
No. of patients	473525	550569	544		

Hazard ratio for the risk of major CV events (95% CI) vs Q1: Q2=0.85 (0.57-1.25); Q3=0.57 (0.36-0.88); Q4=0.55 (0.35-0.86); Q5=0.61 (0.38-0.97), demonstrating that patients with LDL-C <70 mg/dL and HDL-C ≥55 mg/dL had a 39% lower risk of major CV events at 5 years

TNT Study Design

STELLAR: LDL-C—Percentage Change From Baseline, Rosuvastatin 10-40 mg/d vs Comparators



P<.001 vs. comparators for matching doses.
Data presented as least-squares means.

STELLAR = Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin.

Adapted from Jones PH, et al. *Am J Cardiol.* 2003;93:152-160.

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JUPITER
Primary Objectives

Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin

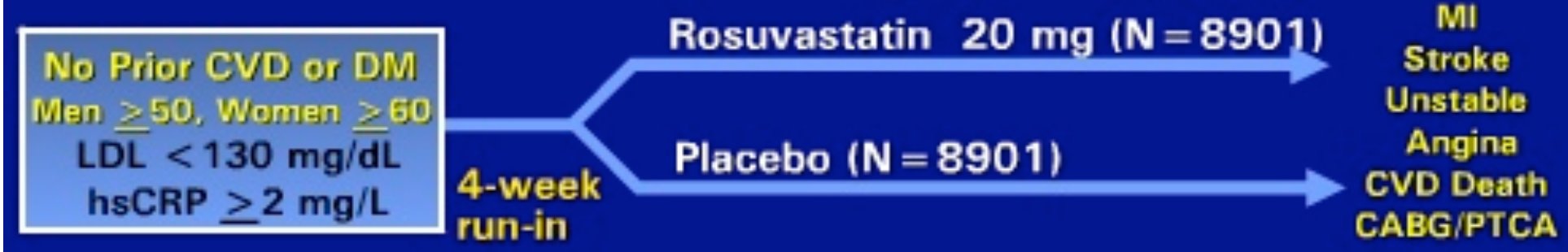
To investigate whether rosuvastatin 20 mg compared to placebo would decrease the rate of first major cardiovascular events among apparently healthy men and women with LDL < 130 mg/dL (3.36 mmol/L) who are nonetheless at increased vascular risk on the basis of an enhanced inflammatory response, as determined by hsCRP ≥ 2 mg/L.

To enroll large numbers of women and individuals of Black or Hispanic ethnicity, groups for whom little data on primary prevention with statin therapy exists.

JUPITER
Trial Design

JUPITER

Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP



Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

Ridker et al, Circulation 2003;108:2292-2297.

JUPITER

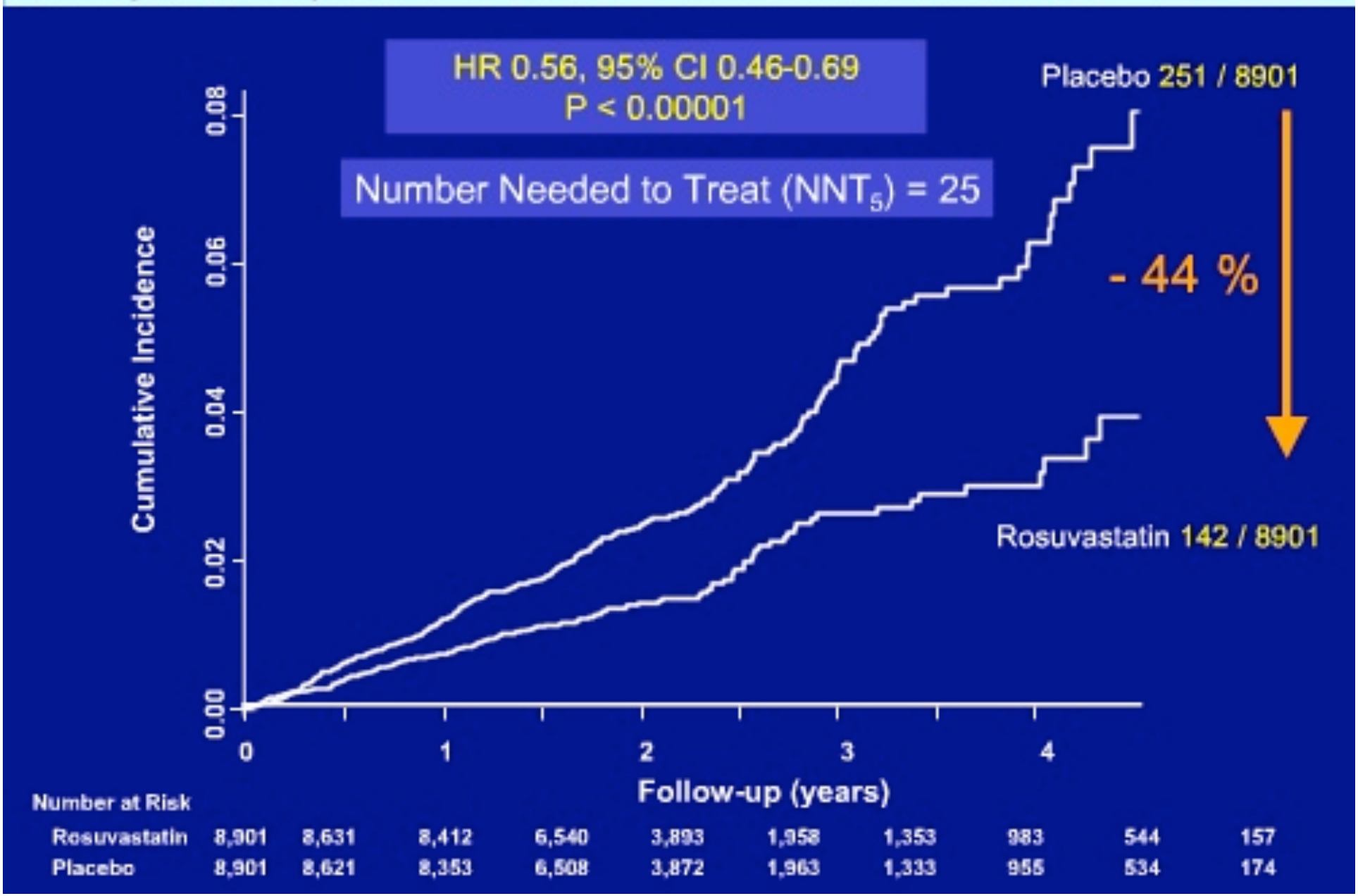
Baseline Blood Levels (median, interquartile range)

	Rosuvastatin (N = 8901)		Placebo (n = 8901)	
hsCRP, mg/L	4.2	(2.8 - 7.1)	4.3	(2.8 - 7.2)
LDL, mg/dL	108	(94 - 119)	108	(94 - 119)
HDL, mg/dL	49	(40 – 60)	49	(40 – 60)
Triglycerides, mg/L	118	(85 - 169)	118	(86 - 169)
Total Cholesterol, mg/dL	186	(168 - 200)	185	(169 - 199)
Glucose, mg/dL	94	(87 – 102)	94	(88 – 102)
HbA1c, %	5.7	(5.4 – 5.9)	5.7	(5.5 – 5.9)

All values are median (interquartile range). [Mean LDL = 104 mg/dL]

JUPITER

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

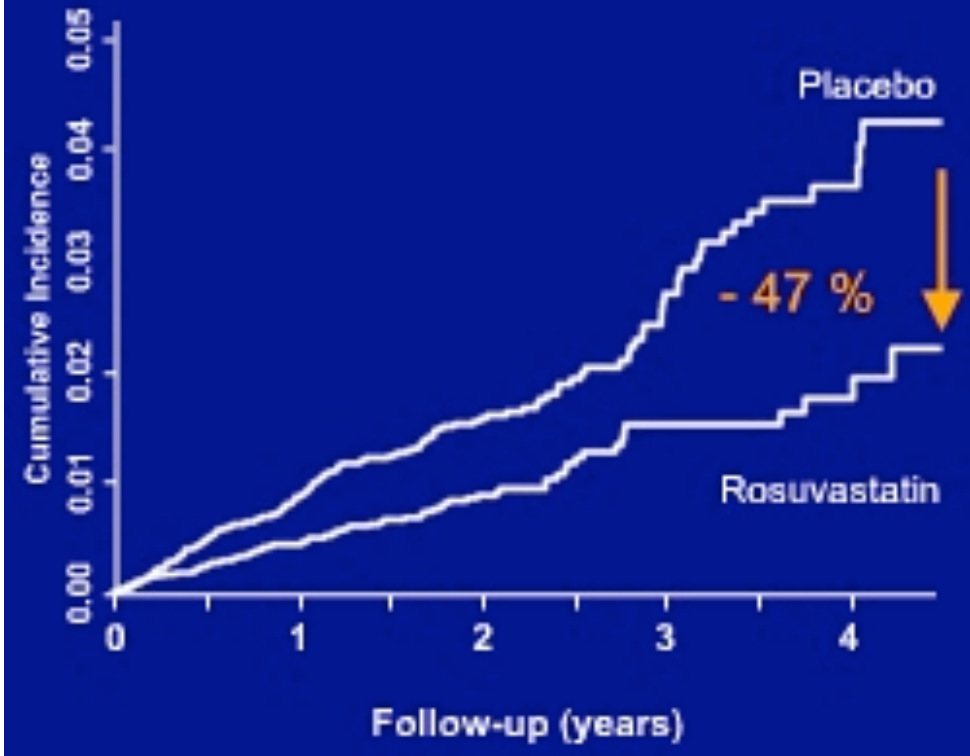


JUPITER

Grouped Components of the Primary Endpoint

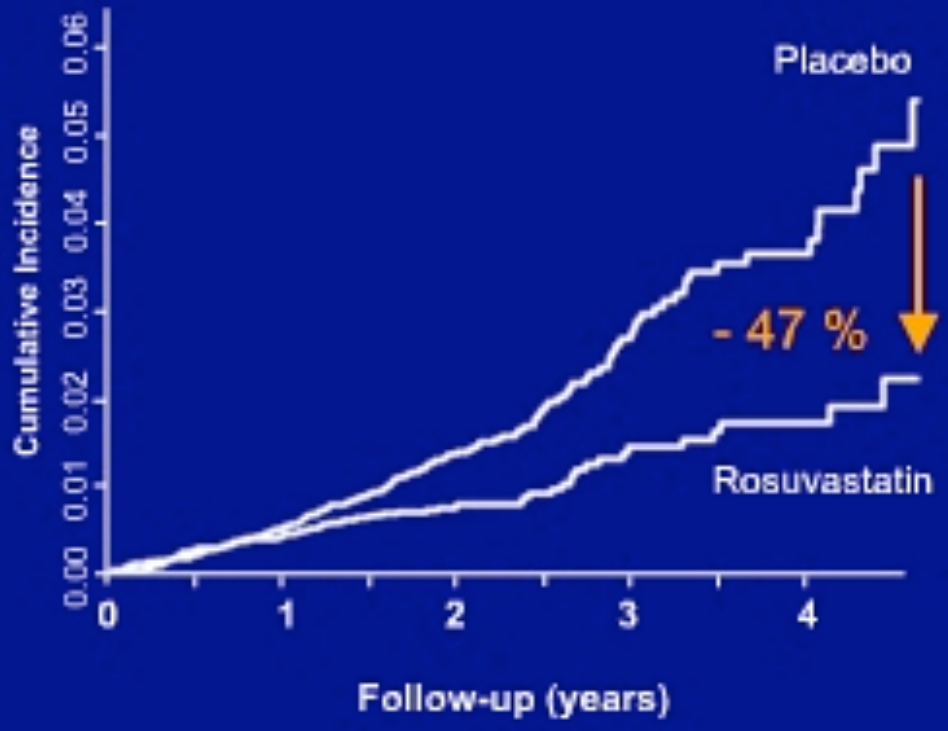
Myocardial Infarction, Stroke, or Cardiovascular Death

HR 0.53, CI 0.40-0.69
P < 0.00001



Arterial Revascularization or Hospitalization for Unstable Angina

HR 0.53, CI 0.40-0.70
P < 0.00001



Goals of Lipid-Lowering Therapy

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ATP III Lipid and Lipoprotein Classification

HDL Cholesterol (mg/dL)

<40	Low
≥60	High

ATP III Classification of Triglycerides

• Normal triglycerides	<150 mg/dL (1.7 mmol/L)
• Borderline-high triglycerides	150-199 mg/dL (1.7-2.2 mmol/L)
• High triglycerides	200-499 mg/dL (2.3-5.6 mmol/L)
• Very high triglycerides	≥500 mg/dL (5.6 mmol/L)

NCEP Adult Treatment Panel III. *JAMA.* 2001;285:2486-2497.

NCEP ATP III Current Guidelines Provide Direction on How to Treat Patients With Dyslipidemia[4,5]

- The first priority of treatment is to lower LDL-C
  - The first line of drug therapy to manage LDL-C is statins
  - In high-risk patients, the LDL-C goal is <100 mg/dL
  - Optional goal of LDL-C to <70 mg/dL for patients considered to be at very high risk
- If LDL-C at goal but TG ≥200 mg/dL
  - Non-HDL-C is a second target of therapy
  - Combining a fibrate or nicotinic acid with an LDL-C-lowering drug can be considered
- TG ≥150 mg/dL defined as borderline high and should be addressed
- A specific goal for HDL-C is not specified
  - HDL-C <40 mg/dL is defined as low
  - Treatment of low HDL-C should be considered for high-risk patients

NCEP ATP III Guidelines: LDL-C Cut Points, Risk, and Goals for TLC and Drug Therapy

	LDL-C (mg/dL)		
Risk Category	**Goal**	**Level for Initiation of TLC**	**Level for Consideration of Drug Therapy**
CAD or CAD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)
2+ risk factors (10-year risk ≤20%)	<130	≥130	≥130 if 10-year risk is 10%–20% ≥160 if 10-year risk is <10%
0-1 risk factor	<160	≥160	≥190 (160-189: LDL-C–lowering drug optional)

NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; LDL-C = low-density lipoprotein cholesterol; TLC = therapeutic lifestyle change(s); CAD = coronary artery disease.

NCEP ATP III. *Circulation*. 2002;106:3143-3421.

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Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines

Scott M. Grundy; James I. Cleeman; C. Noel Bairey Merz; H. Bryan Brewer, Jr; Luther T. Clark; Donald B. Hunninghake; Richard C. Pasternak; Sidney C. Smith, Jr; Neil J. Stone; for the Coordinating Committee of the National Cholesterol Education Program

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Implications of Recent Clinical Trials for NCEP ATP III Guidelines

Revised risk category definitions

- Very high risk: established CAD plus
  - Multiple major risk factors (especially types 1 and 2 diabetes mellitus)
  - Severe and poorly controlled risk factors, eg, continued smoking
  - Metabolic syndrome (especially with TG ≥200 mg/dL, plus non–HDL-C ≥130 mg/dL and HDL-C <40 mg/dL)
  - Acute coronary syndromes

NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; CAD = coronary artery disease; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol.

Grundy SM, et al. *Circulation.* 2004;110:227-239.

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Implications of Recent Clinical Trials for the NCEP ATP III Guidelines

- High risk
  - CAD (10-year risk >20%)
  - CAD equivalent: PAD, AAA, carotid artery disease, diabetes, 2+ risk factors with 10-year risk for hard CAD >20%
- Moderately high risk: 2+ risk factors (10-yr risk 10%-20%)
- Moderate risk: 2+ risk factors (10-year risk <10%)
- Lower risk: 0-1 risk factor

NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; CAD = coronary artery disease; PAD = peripheral arterial disease; AAA = abdominal aortic aneurysm.

Grundy SM, et al. *Circulation.* 2004;110:227-239.

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Implications of Recent Clinical Trials for NCEP ATP III Guidelines

Goals and Thresholds

Risk Category	CAD	CAD Risk Equivalents	CAD Risk Factors	10-Year Risk (%)	LDL-C Threshold (mg/dL)		LDL-C Goal (mg/dL)
					Initiate TLC	Initiate Medication	
Very high	Yes	Yes	Yes*	>20	≥100	≥100	<100
						<100 (optional†)	<70 (optional)
High	Yes	Yes	2+	>20	≥100	≥100	<100
Moderately high	No	No	2+	10-20		≥130	<130
						100-129 (optional)	<100 (optional)
Moderate	No	No	2+	<10	≥130	≥160	<130
Lower	No	No	0-1	NA	≥160	≥190	<160
						160-189 (optional)	

R = risk assessments; N = additions and revisions.

*Multiple risk factors (especially diabetes): severe, poorly controlled risk factors (especially smoking); multiple metabolic syndrome risk factors (especially triglycerides ≥200 mg/dL and non–HDL-C ≥130 mg/dL with HDL-C <40 mg/dL); acute coronary syndrome.

†It is advised that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction of LDL-C.

NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; CAD = coronary artery disease; LDL-C = low-density lipoprotein cholesterol; TLC = therapeutic lifestyle change(s); HDL-C = high-density lipoprotein cholesterol.

Grundy SM, et al. *Circulation.* 2004;110:227-239.

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AHA Recommendations for Omega-3 FA Intake

Population	Recommendation
Patients without documented CHD	Eat a variety of (preferably oily) fish at least twice a week. Include oils and foods rich in α-linolenic acid (flaxseed, canola, and soybean oils; flaxseeds; and walnuts)
Patients with documented CHD	Consume ~1 g of EPA+DHA per day, preferably from oily fish. EPA+DHA supplements could be considered in consultation with the physician
Patients needing triglyceride lowering	2–4 grams of EPA+DHA per day provided as capsules under a physician's care

Kris-Etherton PM et al. *Circulation* 2002;106:2747-2757.

FENOFIBRATES

- TRILIPIX™ (fenofibric acid) delayed-release capsules is a new fenofibric acid molecule that is indicated as an adjunct to diet in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.
- **Limitations of Use: No incremental benefit of TRILIPIX on cardiovascular morbidity and mortality over and above that demonstrated for statin monotherapy has been established.**
- Combination therapy with TRILIPIX and statins:
  - Significantly reduces TG, raises HDL-C when compared with statin monotherapy
  - Significantly reduces LDL-C when compared with TRILIPIX monotherapy
- No cases of rhabdomyolysis were reported in up to 64 weeks of statin plus TRILIPIX combination therapy
  - **Fibrate and statin monotherapy increase the risk of myositis or myopathy and have been associated with rhabdomyolysis. Data from observational studies suggest that the risk for rhabdomyolysis is increased when fibrates are coadministered with a statin (with a significantly higher rate observed for gemfibrozil). The risk for serious muscle toxicity appears to be increased in elderly patients and in patients with diabetes, renal failure, or hypothyroidism.**

Please see Indications and Important Safety Information on slides 42-45.
Full Prescribing Information available from your representative.


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Lipid-Lowering Therapy With Statins: Safety Considerations and Education
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Safety Concerns in Perspective: Consequences of CAD

Prevention is necessary

- In 2004, about 1.2 million people will have a cardiac event*
- Event frequency in 2001
  - New or recurrent MI (estimated) = 865,000
  - Total CAD-related deaths = 502,189 or about 42%
  - Death from CAD prior to hospitalization = 340,000 or about 68%
- Rate of post-MI complications
  - Death within 1 month of hospitalization 10%
  - Death within 1 month of heart failure (HF) 33%
  - 1-year death rate for HF patients 21%
  - Recurrent MI within 5 years 30%

*Hospitalizaiion with definite or probable MI or fatal CAD, but not including silent MIs.

AHA. *Heart Disease and Stroke Statistics—2004 Update*. Dallas, Tex: AHA; 2004.
Spencer FA, et al. *J Am Coll Cardiol*. 1999;34:1378-1387.

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Safety Concerns in Perspective

- Of the estimated 1.2 million people who will have a cardiac event in 2004, 42% will die within the year (≈1 in every 5 deaths overall)
- NCEP ATP III
  - LDL-C lowering with a statin could reduce CAD events 25% to 35% in 5 years
  - Although 36 million are candidates for statin therapy, only 12.5 million people in the US take a statin

American Heart Association. *Heart Disease and Stroke Statistics–2004 Update*. Dallas, Tex: American Heart Association; 2004. NCEP ATP III. *Circulation*. 2002;106:3143-3421.

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Statins and Low-dose Aspirin

Statins

- Reduces risk of CAD events by about **30%**[1]
  - Long-term at doses of 40 mg/day, up to **61%**[2]
- Reduces the risk of stroke by about **17%**[2]
- Severe myopathy **.08-.09%**[5]
- Elevated ALTs **.5-2%**[3]

Aspirin

- Reduces risk of CAD by **28%**[3]
  - MI by **44%**[4]
- Increases the risk of hemorrhagic stroke **.002%**[4]
- Major GI bleeding events **.002-.012%**[4]

1. Grundy SM, et al. Implication of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227-39.
2. Law MR, et al. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ*. 2003;326:1423.
3. US Preventive Services Task Force. Aspirin for the Primary Prevention of Cardiovascular Events: Recommendations and Rationale. Guidelines from Guide to Clinical Preventive Services: 3rd ed. (2000-2003). January 1, 2002.
4. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. *N Engl J Med*. 1989;321:129-135.
5. Pasternak RC, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol*. 2002;567-572. Available at: http://www.nhlbi.nih.gov/guidelines/cholesterol/statins.pdf.

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ACC/AHA/NHLBI Advisory Regarding Statins

Statements about liver function

- "Whether transaminase elevation with statin therapy constitutes true hepatotoxicity has not been determined. Progression to liver failure specifically due to statins is exceedingly rare if it ever occurs."
- "Reversal of transaminase elevation is frequently noted with a reduction in dose, and elevations do not often recur with either re-challenge or selection of another statin."

Pasternak RC, et al. *Circulation*. 2002;106:1024-1028.

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ACC/AHA/NHLBI Advisory Regarding Statins

Statements about muscle toxicity

- "Statins carry a small but definite risk of myopathy (<1%)"
- "A common complaint is nonspecific muscle aches or joint pains that are generally not associated with significant increases in creatine kinase"
- "Myositis* … occurs more frequently when statins are used in combination with a variety of medications"
- With myositis, "failure to discontinue drug therapy can lead to rhabdomyolysis, myoglobinuria, and acute renal necrosis"

*Muscle symptoms with increased CK levels.

Pasternak RC, et al. *Circulation*. 2002;106:1024-1028.

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What to Do if Patient Develops Myopathy

- Obtain CK at baseline and if the patient reports muscle symptoms
- Minor elevations common in statin users and nonusers alike. Testing alone is not diagnostic
- Encourage patients at high risk for a vascular event who develop minor myalgias to continue treatment
- Discontinue statin if serious myalgias or muscle weakness occurs
- Discontinue statin if CK >10 × ULN with myalgias because diagnostic of myositis

Pasternak RC, et al. *J Am Coll Cardiol.* 2002;40:567-572.

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What to Do if Patient Develops Myopathy (Cont'd)

Rule out common causes of myopathy

Drug-induced	Eg, procainamide, D-penicillamine, glucocorticoids, alcohol, colchicines, amphetamines, sodium, calcium, magnesium, or phosphorus; AZT, steroids; B_2 adrenergics; androgens
Infections	Eg, influenza and Coxsackievirus (associated with high CK levels in children); brucellosis; AIDS; cysticercosis; schistosomiasis
Neoplasm and paraneoplastic syndromes	
Other	Overusage (myotonia, strenuous work or exercise, neural overactivity), thyroid disease, dehydration, electrolyte imbalance

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What to Do if Patient Develops Myopathy (Cont'd)

- Use lowest statin dose possible to achieve adequate lipid lowering
- If combination is required, use niacin or fibrate (but not gemfibrozil)
- Increased incidence of myalgia is associated with risk factors of advanced age, small frame, renal or hepatic impairment, multiple medications, diabetes, hypothyroidism

Pasternak RC, et al. *J Am Coll Cardiol.* 2002;40:567-572.
Thompson P, et al. *JAMA.* 2003;289:1681-1690.

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Statins and the Liver

- On initiating statin therapy, evaluate ALT/AST at baseline and at 12 weeks, then annually or as indicated
  - Rely on ALT to document possible hepatotoxicity because of nonspecificity of AST levels (may be elevated in muscle or liver injury)
- Risk factors for elevated LFTs include use of near-maximum statin dose or concomitant CYP3A4 inhibitors, combination lipid-lowering therapy, advanced age, or impaired renal function
- Statins contraindicated in patients with active or chronic liver disease
- Most minor enzyme elevations resolve spontaneously with continued treatment

Parra JL, Reddy KR. *Clin Liver Dis.* 2003;7:415-433.
Knopp RH. *N Engl J Med.* 1999;341:498-511.

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Effect of Grapefruit Juice (3A4 Inhibition) on Statin Kinetics in Humans

Statin	AUC	C_{max}
Atorvastatin*	↑ 2.5x	1.0x
Fluvastatin	–	–
Lovastatin*	↑ 15.0x	↑ 12.0x
Pravastatin	1.0x	
Rosuvastatin	–	–
Simvastatin*	↑ 16.0x	↑ 9.0x

*Concomitant use with >1 qt/day of grapefruit juice should be avoided or the dose of statin reduced.

Williams D, Feely J. *Clin Pharmacokinet.* 2002;41:343-370; Lilja KK, et al. *Clin Pharmacol Ther.* 1999;66:118-127; Kantola T, et al. *Clin Pharmacol Ther.* 1998;63:397-402; Lilja KK, et al. *Clin Pharmacol Ther.* 1998;64: 477-483.

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Drugs That May Interfere With Statin Metabolism Via CYP450

CYP3A4 substrates

Atorvastatin, lovastatin, simvastatin

CYP3A4 inhibitors

Triazole antifungals	Clotrimazole, fluconazole, itraconazole, ketoconazole, lansoprazole, miconazole, omeprazole
Macrolide antibiotics	Clarithromycin, erythromycin
HIV protease inhibitors	Indinavir, nelfinavir, ritonavir, saquinavir
Fluoroquinolones	Ciprofloxacin, norfloxacin
Misc. anti-infectives	Metronidazole, troleandomycin
Psychiatric medications:	Clomipramine, fluoxetine, fluvoxamine, nefazodone, norfluoxetine, paroxetine, sertraline, venlafaxine
Calcium channel blockers	Diltiazem, verapamil
Antiarrhythmics	Amiodarone, quinidine
Miscellaneous	

Williams D, Feely J. *Clin Pharmacokinet*. 2002;41:343-370.

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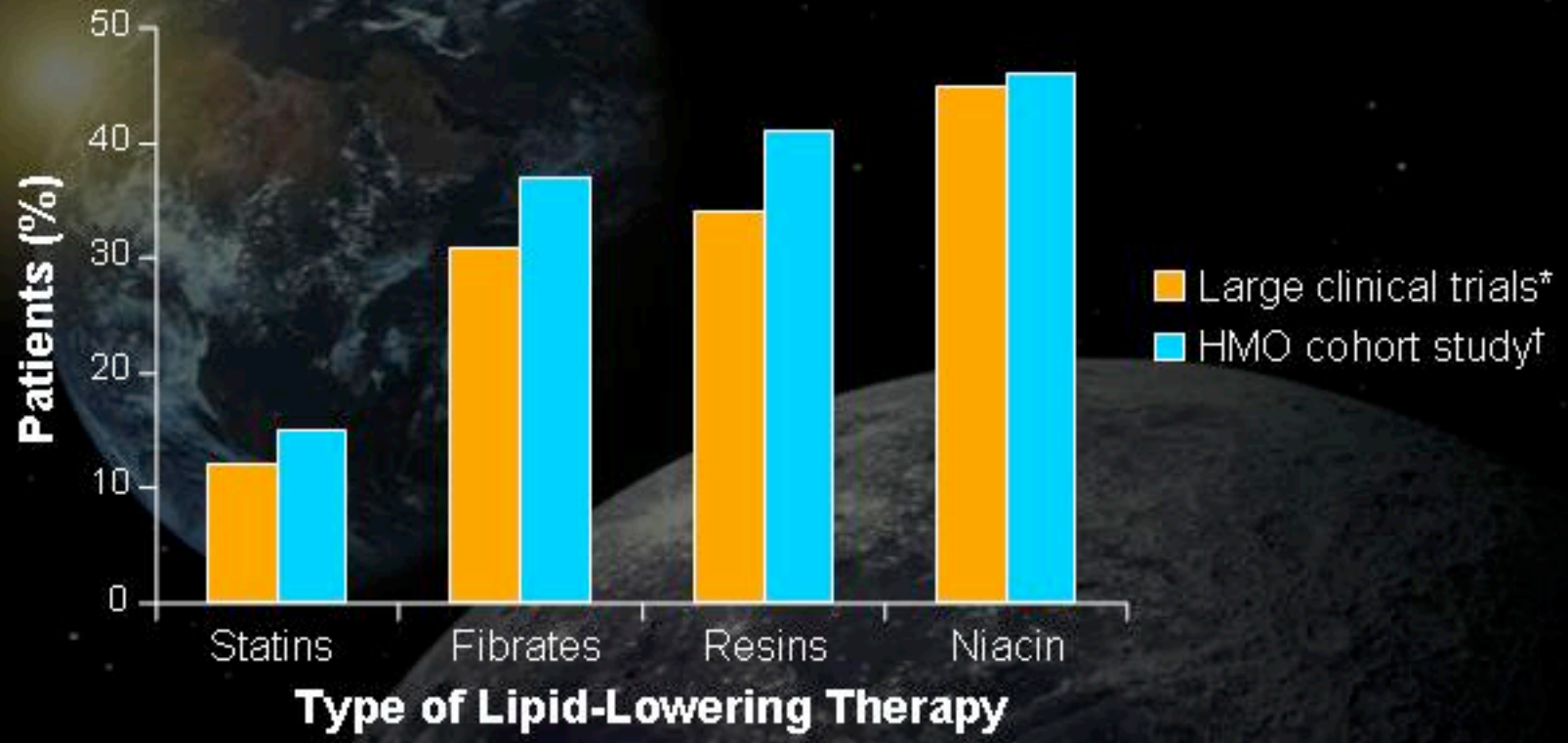
Discontinuation Rates With Lipid-Lowering Therapies



*Bars represent the high end of the range for 8 large clinical trials; N >23,000.
†From 2 HMO studies, n=2369.

Adapted from Braunstein JB, et al. *Chest*. 2001;120:979-988.
Andrade SE, et al. *N Engl J Med*. 1995;332:1125-1131.

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Conclusions

- Statins reduce the incidence of major coronary events, coronary procedures, and strokes in high-risk patients
- Statins are safe. The rare toxicities that do occur are reversible
- All potential liver and muscle toxicities can be prevented with a good understanding of the pharmacodynamic and pharmacokinetic properties of these agents

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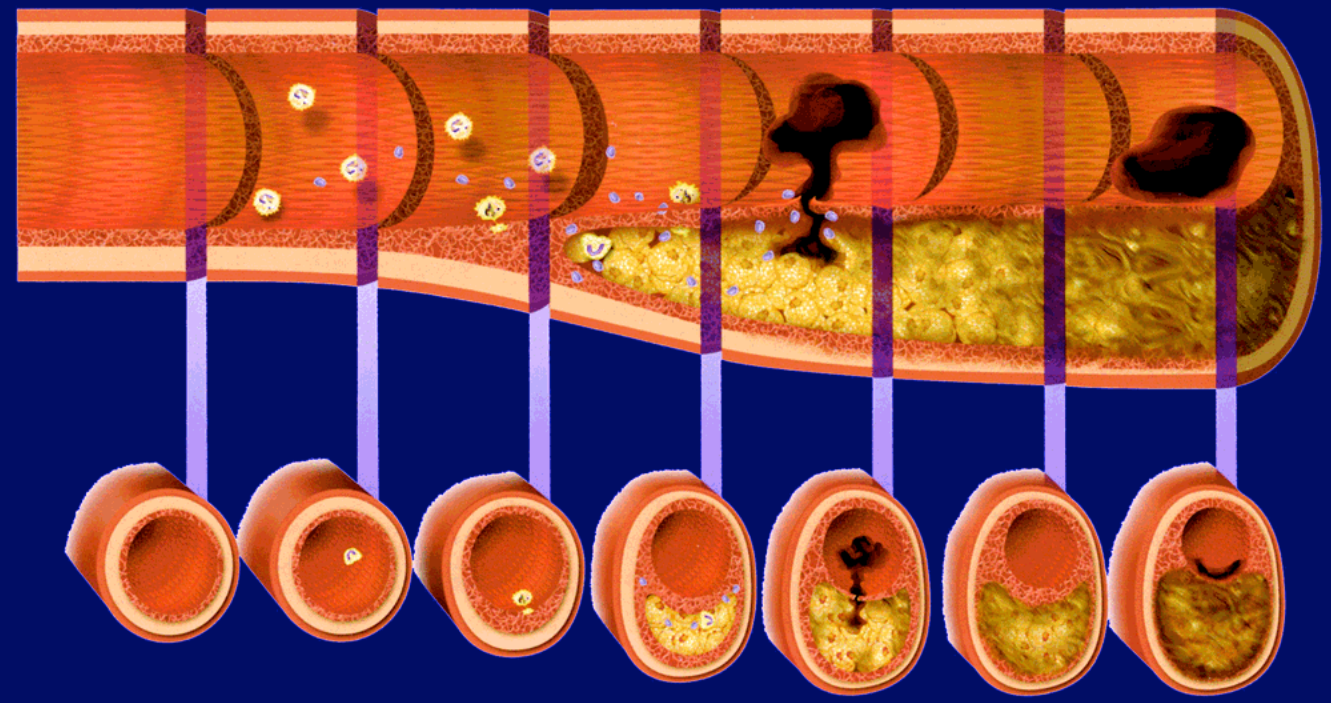
Progression of Coronary Atherosclerotic Plaque

Development of Atherosclerosis and Vulnerable Plaque

Acute Coronary Syndrome

Secondary Prevention



Ischemic Heart Disease

Cerebrovascular Disease

Peripheral Vascular Disease

Adapted from Libby P. *Circulation*. 2001;104:365-372.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