

# Statins, Inflammation and Atherosclerosis

## *Past, Present and Future*

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### Presenter Disclosure Information

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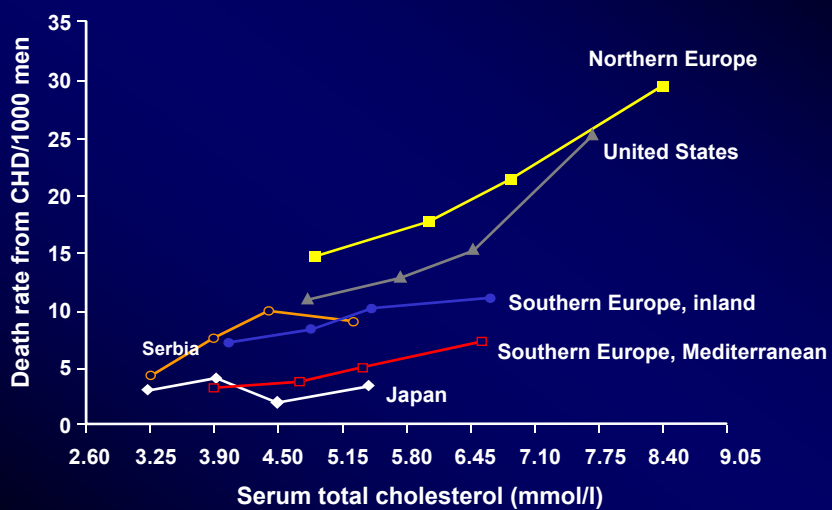
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Advisory Board	Vatera Capital	Significant
Board of Directors	Aegerion Pharmaceuticals, Arisaph Pharmaceuticals	Significant
Consultant	Kowa Pharmaceuticals, Merck	Significant
Consultant	AstraZeneca	Modest
Health Advisory Board	DuPont	Modest

## Statins, Inflammation and Atherosclerosis

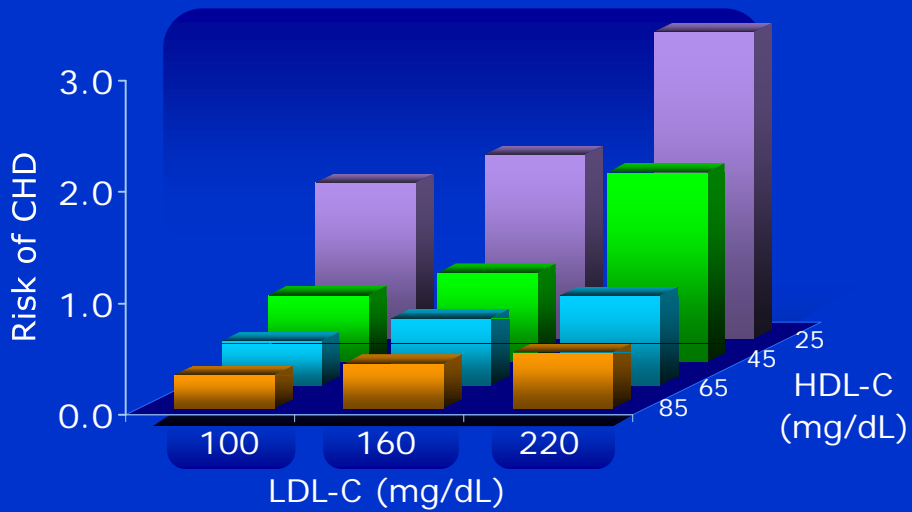
- The lipid hypothesis and “lower is better”
- Strategies to manage dyslipidemia
- Inflammation in atherosclerosis
- Future of cardiovascular prevention

### Relation of Serum Cholesterol to Mortality (25-yr follow-up of Seven Countries Study)



(Adapted from Verschuren *et al.*, *JAMA* 1995;274:131-6.  
Following the work of Ancel Keys in 1955)

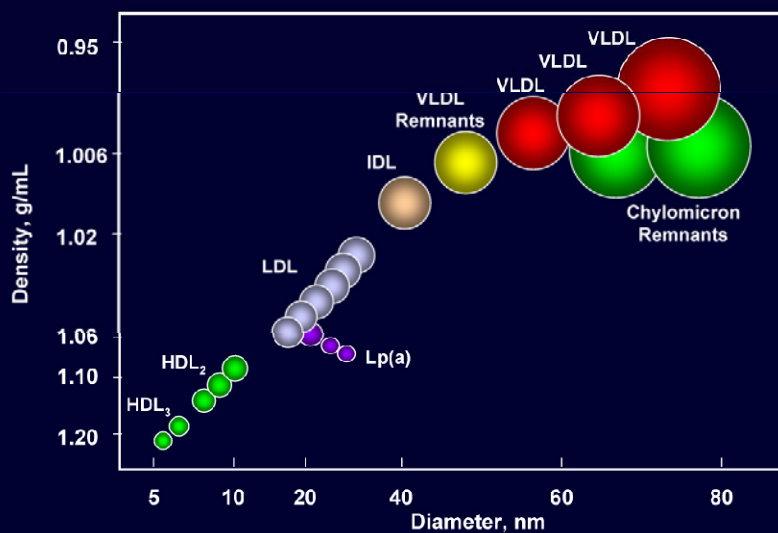
## Framingham: Low HDL-C and Elevated LDL-C Are Independent Predictors of CHD Risk



Gordon T et al. *Am J Med* 1977;62:707-714.

Slide Source  
Lipids Online Slide Library  
www.lipidsonline.org

## Multiple Lipid Factors Are Associated With CHD Risk



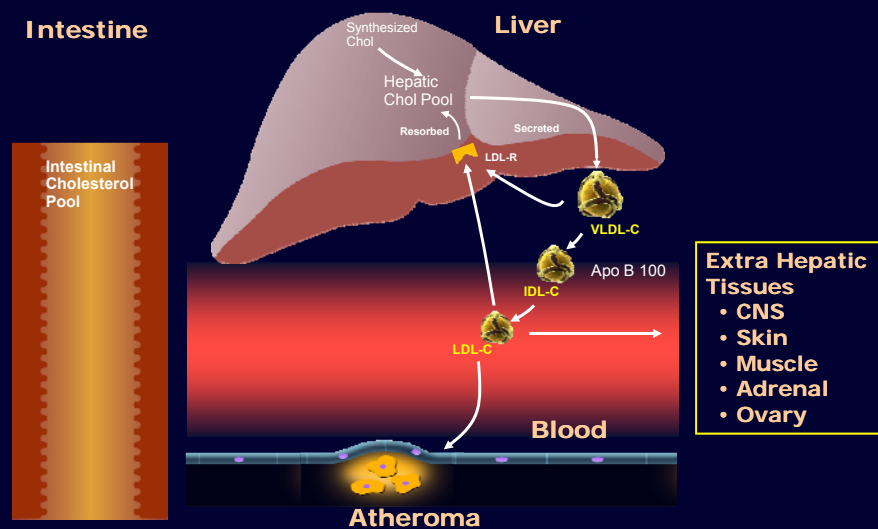
Adapted from Segrest JP et al. *Adv Protein Chem.* 1994;45:303-369.

## The Liver and the Intestine Are Key Organs Involved in Cholesterol Homeostasis

Cholesterol homeostasis is maintained by a complex balance between:

- Cholesterol synthesis
- Dietary intake
- Cholesterol absorption
- Excretion of cholesterol

### The Liver Synthesizes Cholesterol Endogenously, Takes It Up From the Circulation and Excretes It to the Intestine Via the Biliary System<sup>1-4</sup>



1. Shepherd J. *Eur Heart J Suppl.* 2001;3(suppl E):E2-E5. 2. Goldstein JL et al. *Science.* 2001;292:1310-1312.  
3. Davis HR Jr et al. *J Biol Chem.* 2004;279:33586-33592. 4. Yu KC-W et al. *Front Biosci.* 2001;6:D332-D354.

LDL BINDING → ENDO-CYTOSIS → LYSOSOMAL HYDROLYSIS → REGULATION OF MICROSOMAL ENZYMES

## Discovery of the LDL Receptor

### Michael Brown and Joseph Goldstein

Goldstein J and Brown M. Annu Rev Biochem 1977;46:897-930. Image on right from *Encyclopedia Britannica* online.

### The Small Intestine Helps Maintain Cholesterol Balance by Regulating Absorption and Excretion of Dietary and Biliary Cholesterol<sup>1-4</sup>

**Intestine**

25% Dietary chol

75% Biliary chol

Intestinal Cholesterol Pool

NPC1L1

ABCG5/8

Fecal sterols

**Liver**

Synthesized Chol

Excreted Chol

Hepatic Chol Pool

Bile Acids

Remnant receptors

**Extra Hepatic Tissues**

- CNS
- Skin
- Muscle
- Adrenal
- Ovary

**Blood**

CM-C

CMr-C

ApoB 48

**Atheroma**

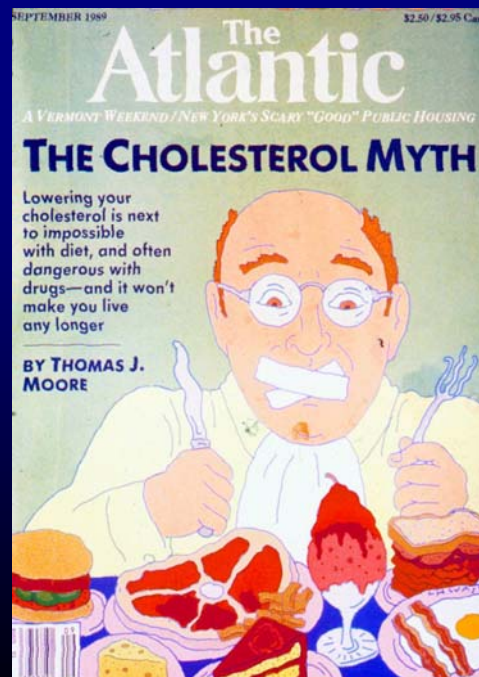
1. Shepherd J. *Eur Heart J Suppl.* 2001;3(suppl E):E2-E5. 2. Goldstein JL et al. *Science.* 2001;292:1310-1312. 3. Davis HR Jr et al. *J Biol Chem.* 2004;279:33586-33592. 4. Yu KC-W et al. *Front Biosci.* 2001;6:D332-D354.

## Isolation of HMG-CoA Reductase Inhibitor from Fungi



In 1976 biochemist Akira Endo demonstrated that compactin/mevastatin derived from *Penicillium citrinum* competitively inhibits HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis.

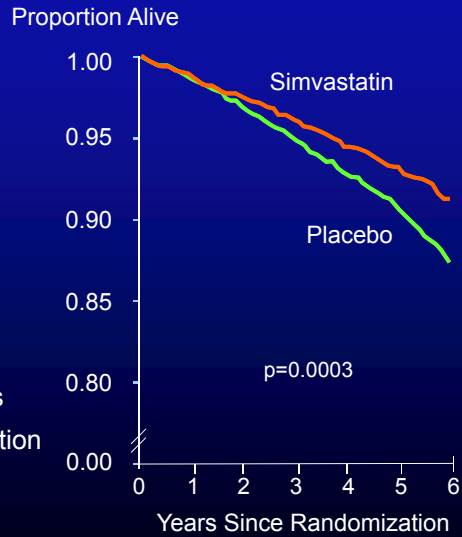
Image from Lasker Foundation, [www.laskerfoundation.org](http://www.laskerfoundation.org)



The Atlantic Monthly  
1989

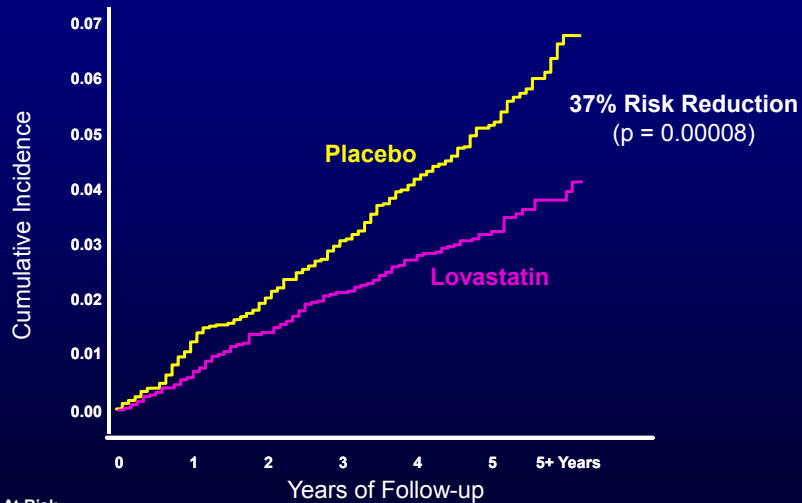
## Scandinavian Simvastatin Survival Study (4S)

- Secondary prevention
- 4444 patients
- Cholesterol:  $272 \pm 23$  mg/dL
- Simvastatin 20 mg/d
  - 40 mg/d in 37%
- LDL-C reduced 38%
- Survival and events
  - 30% decreased death rate
  - 34% decreased CHD events
- Subsequent secondary prevention trials



Scandinavian Simvastatin Survival Study Group. Lancet 1994;344: 1383-1389.

## AFCAPS/TexCAPS: First Acute Major Coronary Event

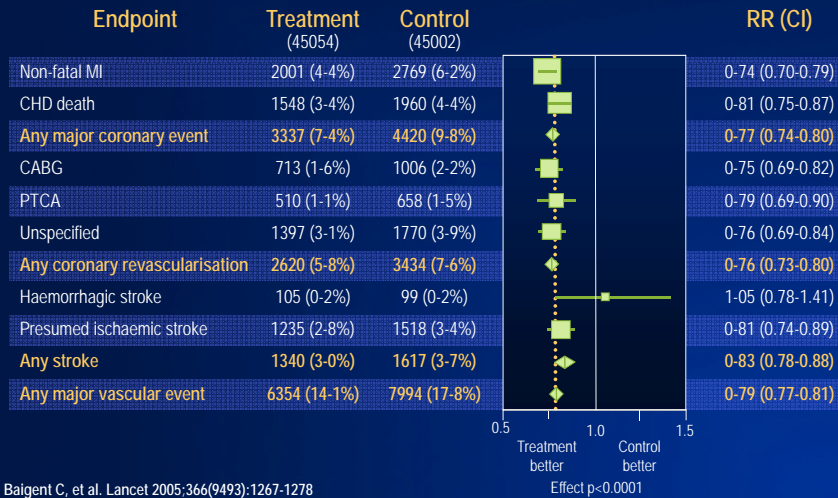


# At Risk						
Lovastatin	N=3304	N=3270	N=3228	N=3184	N=3134	N=1688
Placebo	N=3301	N=3251	N=3211	N=3159	N=3092	N=1644

Downs JR, et al. JAMA 1998;279:1615-22.

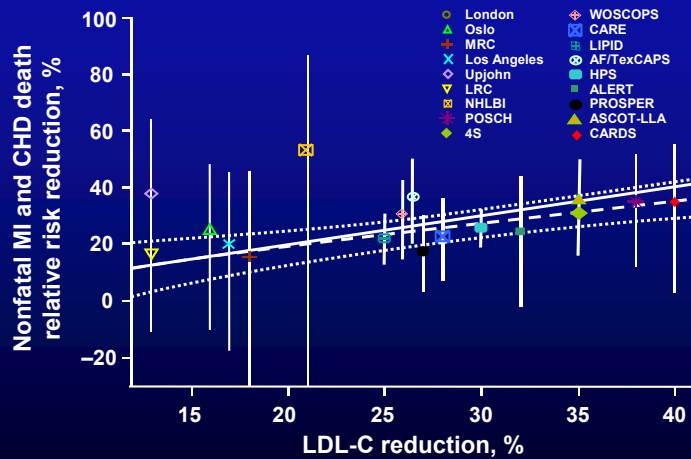
# CTT Meta-analysis

For every 1.0 mmol/L (39 mg/dL) reduction in LDL-C...



Baigent C, et al. Lancet 2005;366(9493):1267-1278

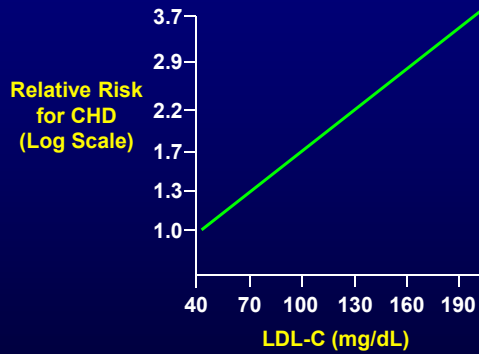
## 1:1 Relationship of LDL-C Reduction and CHD Risk Reduction Maintained between Statin and Non-Statin Trials



MI = myocardial infarction.

Adapted with permission from Robinson JG et al. *J Am Coll Cardiol.* 2005;46:1855-1862.

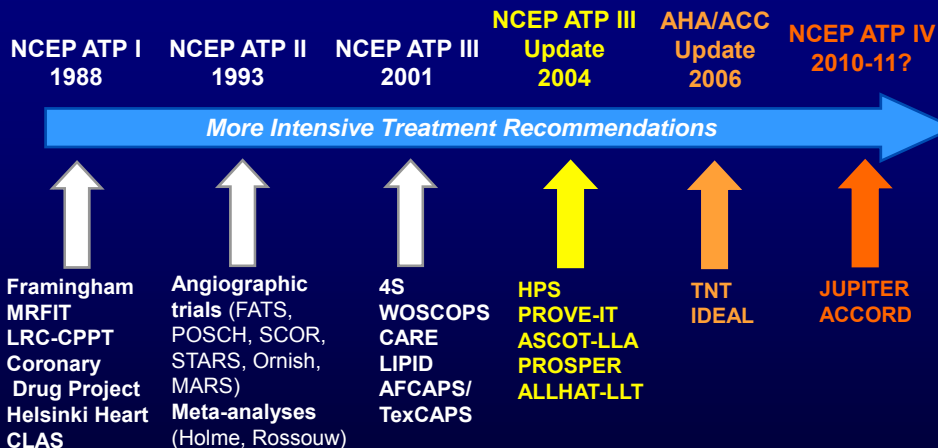
## Log-Linear Relationship Between LDL-C Levels and Relative Risk for CHD



- This relation is consistent with a large body of epidemiologic data available from clinical trials of LDL-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

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

## Evolution of NHLBI Supported Guidelines



NHLBI = National Heart, Lung, and Blood Institute.  
 NCEP ATP = National Cholesterol Education Panel Adult Treatment Panel.  
 AHA = American Heart Association.  
 ACC = American College of Cardiology.

## Where Do We Stand?

- Atherosclerosis was once thought to be an irreversible, inevitable consequence of aging.
- The recognition of dyslipidemia as a major modifiable risk factor introduced the possibilities of both treatment and prevention.
- The “lipid hypothesis” is now confirmed. Over the last decade, research has exposed new areas involving other lipoprotein fractions and inflammation, raising new opportunities.

## Statins, Inflammation and Atherosclerosis

- The lipid hypothesis and “lower is better”
- **Strategies to manage dyslipidemia**
- Inflammation in atherosclerosis
- Future of cardiovascular prevention

## Risk Assessment

- Obtain fasting lipid profile (every 5 years in adults  $\geq 20$  yr)
- Determine presence/absence of CHD and CHD risk equivalents
  - Other atherosclerotic disease (PAD, AAA, carotid artery disease)
  - Diabetes
  - At least 2 major risk factors with 10-year risk for CHD  $>20\%$
- Identify major risk factors other than LDL-C

Expert Panel. *JAMA*. 2001;285:2486-2497.

## Major CHD Risk Factors (Exclusive of LDL-C)

- Cigarette smoking
- Hypertension (BP  $\geq 140/90$  mmHg or on antihypertensive medication)
- Low HDL cholesterol ( $<40$  mg/dL)<sup>†</sup>
- Family history of premature CHD
  - CHD in male first-degree relative  $<55$  years
  - CHD in female first-degree relative  $<65$  years
- Age (men  $\geq 45$  years; women  $\geq 55$  years)

<sup>†</sup> HDL cholesterol  $\geq 60$  mg/dL counts as a “negative” risk factor; its presence removes one risk factor from the total count.

Expert Panel. *JAMA*. 2001;285:2486-2497.

## Risk Stratification

- Patients with CHD or CHD risk equivalents are high risk
- For patients with at least 2 risk factors, calculate Framingham risk score to identify 10-yr risk for CHD
  - Online version (at NHLBI website) and cell phone apps are available
- Patients with 0-1 risk factor are low risk

Expert Panel. *JAMA*. 2001;285:2486-2497.



NATIONAL CHOLESTEROL EDUCATION PROGRAM  
Third Report of the Expert Panel on  
Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

### Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)

The [risk assessment tool](#) below uses recent data from the Framingham Heart Study to estimate 10-year risk for "hard" coronary heart disease outcomes (myocardial infarction and coronary death). This tool is designed to estimate risk in adults aged 20 and older who do not have heart disease or diabetes. Use the calculator below to estimate 10-year risk.

Age:  years  
Gender:  Female  Male  
[Total Cholesterol:](#)  mg/dL  
[HDL Cholesterol:](#)  mg/dL  
[Smoker:](#)  No  Yes  
[Systolic Blood Pressure:](#)  mm/Hg  
Currently on any medication to treat high blood pressure.  No  Yes

Calculate 10-Year Risk

<http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm>

## Lifestyle and Emerging Risk Factors

- Obesity
  - Physical inactivity
  - Atherogenic diet
  - Lipoprotein(a)
  - CRP
  - Prothrombotic factors
  - Impaired fasting glucose (100-125 mg/dL)
  - Evidence of subclinical atherosclerosis
- Encourage lifestyle changes
- Can use to guide treatment decisions

Expert Panel. *JAMA*. 2001;285:2486-2497.

## LDL-C is the Primary Target

- Primary and secondary prevention focuses on achieving LDL-C goals first
  - Exception: TG  $\geq$ 500 mg/dL
- Therapeutic lifestyle changes (TLC) are essential to lipid management
- Note: rule out possible causes of secondary dyslipidemia in individuals with elevated LDL-C
  - Diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, medications

Expert Panel. *JAMA*. 2001;285:2486-2497.

## ATP 2004 Update: LDL-C Therapy by Risk Categories

Risk Category	LDL-C Goal	Initiate Therapeutic Lifestyle Changes (TLC)	Consider Drug Therapy
<b>High risk:</b> CHD or CHD risk equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥100 mg/dL
<b>Very high risk</b>	Optional: <70 mg/dL		
<b>Moderately high risk:</b> ≥2 risk factors (10-year risk 10%–20%)	<130 mg/dL (Optional: <100 mg/dL)	≥130 mg/dL	≥130 mg/dL (consider drug if LDL-C 100–129 mg/dL)
<b>Moderate risk:</b> ≥2 risk factors (10-year risk <10%)	<130 mg/dL	≥130 mg/dL	>160 mg/dL
<b>Low risk:</b> ≤1 risk factor	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (consider drug if LDL-C 160–189 mg/dL)

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

## Characteristics of the Metabolic Syndrome (A Secondary Target)

Risk Factor (≥3)	Defining Level
Abdominal obesity	Waist circumference*
Triglycerides	≥150 mg/dl
HDL-C	<40 mg/dl in men; <50 mg/dl in women
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dl

\*In US: men >40 in (102 cm); women >35 in (88 cm)

Expert Panel. *JAMA*. 2001;285:2486–2497;  
Enas EA, et al. *JCMS* 2007;2:267–75.

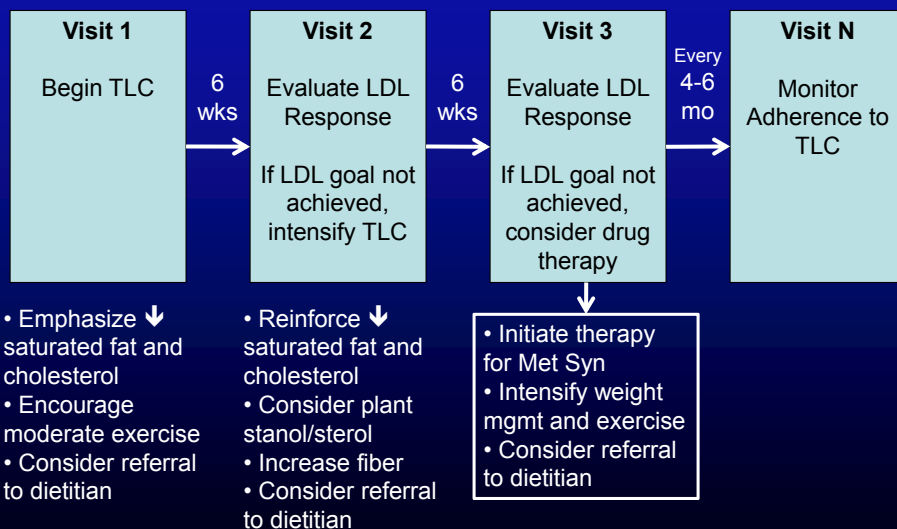
## AHA Dietary and Lifestyle Guidelines



- Balance calorie intake and exercise ( $\geq 30$  min/d on most days) to maintain desirable weight
- Include a variety of fruits, vegetables, whole grains, low-fat or nonfat dairy products, fish, legumes, poultry, lean meats
- Limit excess consumption of salt, added sugars, and alcohol
- Limit foods high in saturated fat ( $< 7\%$  of calories), *trans* fat ( $< 1\%$ ), and cholesterol ( $< 300$  mg/d)

Lichtenstein et al. *Circulation* 2006;114:82-96.

## Steps in TLC (if not immediately initiating drug therapy)

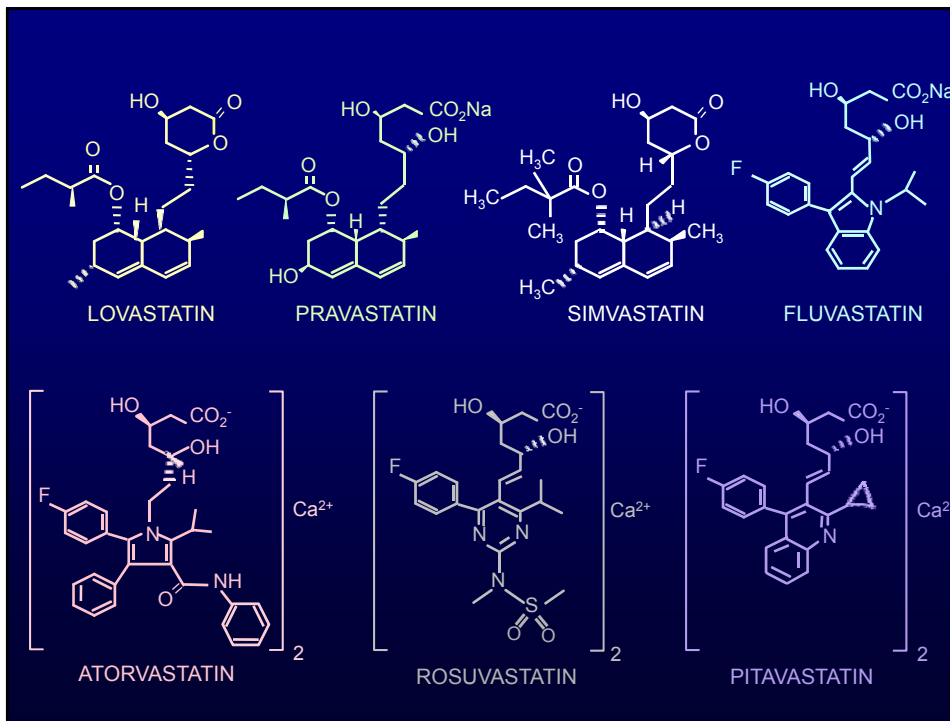


NCEP ATP III. *JAMA*. 2001;285:2486-2497.

## Effects of Drug Classes on Serum Lipids

Drug Class	TC	LDL	HDL	TG
Resins	↓ 20%	↓ 15%–30%	↑ 3%–5%	Variable
CAI	↓ 13%	↓ 19%	↑ 3%	↓ 8%
Nicotinic acid	↓ 25%	↓ 5%–25%	↑ 15%–35%	↓ 20%–50%
Fibrates	↓ 15%	Variable	↑ 10%–20%	↓ 20%–50%
n-3 fatty acids	<-->	<-->	<-->	↓ 35-50%
Statins	↓ 15%–60%	↓ 18%–60%	↑ 5%–15%	↓ 7%–30%

Adapted from Gotto AM Jr, Pownall HJ, eds. *Manual of lipid disorders*. 3<sup>rd</sup> ed. Baltimore: Williams & Wilkins; 2003.



## Combination Therapy

Consider combination therapy if:

- LDL-C goals are not achieved (ezetimibe, resin)
  - Ezetimibe as add-on to statin reduces LDL-C additional 25%
- Higher statin doses are not tolerated (ezetimibe, resin)
- A high-risk patient has high triglycerides ( $\geq 200$  mg/dL) or low HDL-C ( $< 40$  mg/dL)
  - May add nicotinic acid or fibrate to statin
  - Caution: can increase risk of myotoxicity

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

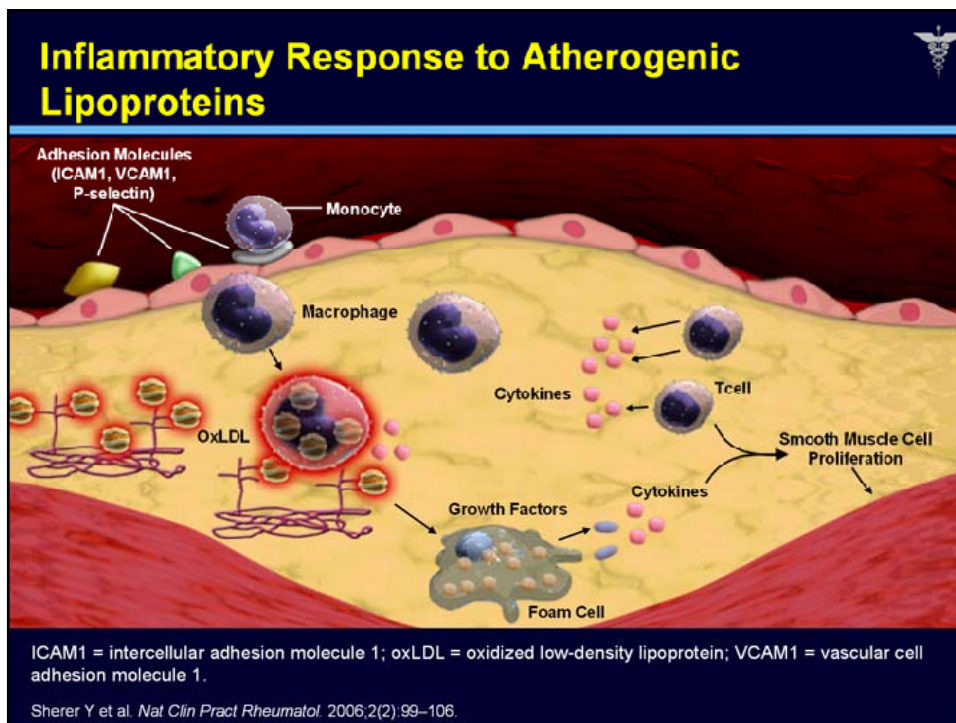
## Other Lipid Targets

- **Non-HDL-C** in high-risk patients with TG  $\geq 200$  mg/dL
  - Target is 30 mg/dL higher than corresponding LDL-C goal
  - Add fibrate or nicotinic acid to statin
- **TG  $\geq 500$  mg/dL** - must treat immediately
  - Nicotinic acid, fibrates, prescription omega-3 fatty acids
- **HDL-C** – no specific target
- **Metabolic Syndrome**
  - Weight reduction and physical activity will improve underlying risk factors

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

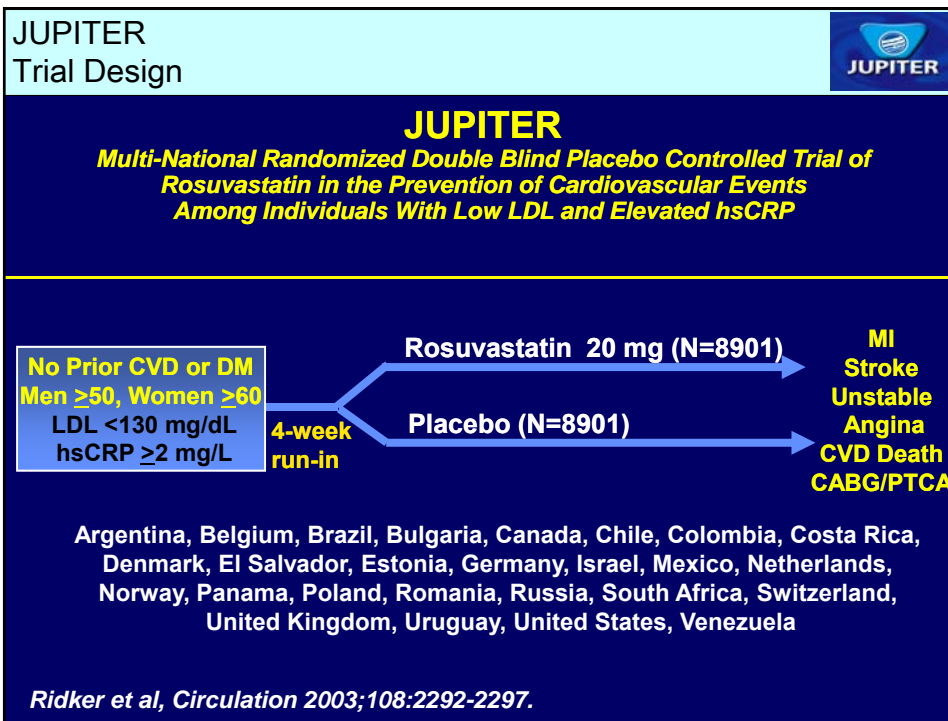
## Statins, Inflammation and Atherosclerosis

- The lipid hypothesis and “lower is better”
- Strategies to manage dyslipidemia
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## Atherosclerosis is an Inflammatory Disorder

- Key points
  - Inflammation is involved in atherogenesis
  - Inflammatory cells (leukocytes, mediators) are critical in development of atheroma
  - Microbial infection may play a role
  - Benefits of anti-inflammatory agents (except ASA) in therapy of atherosclerosis remains speculative

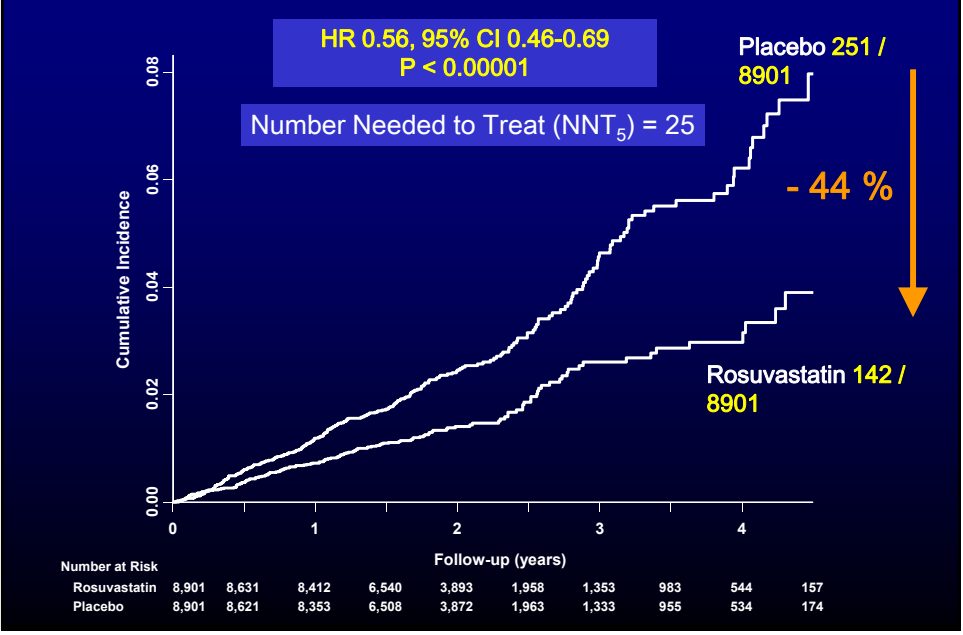


# JUPITER

Ridker et al NEJM 2008



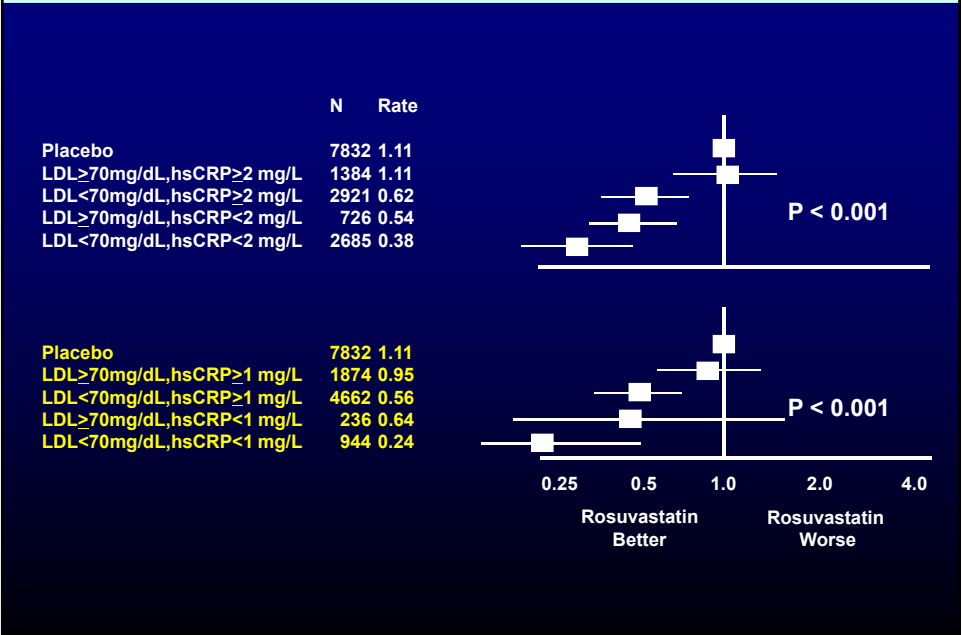
Primary Trial Endpoint : MI, Stroke, UA/Revascularization, CV Death



# JUPITER

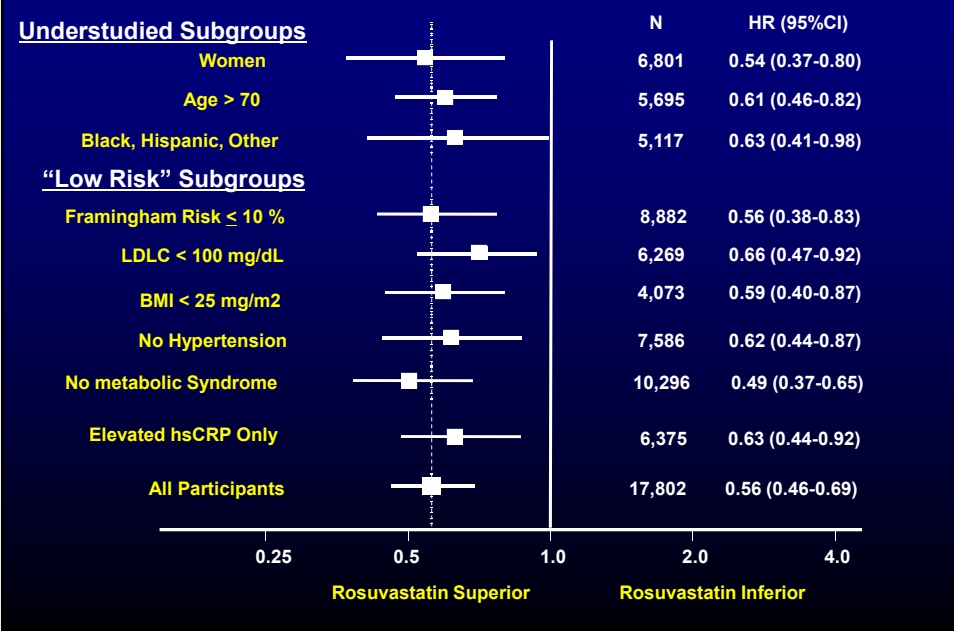


LDL reduction, hsCRP reduction, or both?



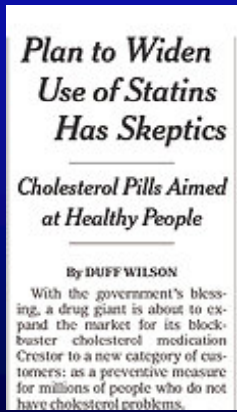
# JUPITER

Primary Endpoint – Understudied or “Low Risk” Subgroups



## New Indication for Rosuvastatin

For primary prevention “in individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥50 years old in men and ≥60 years old in women, hsCRP ≥ 2 mg/L, and the presence of at least one additional CVD risk factor”

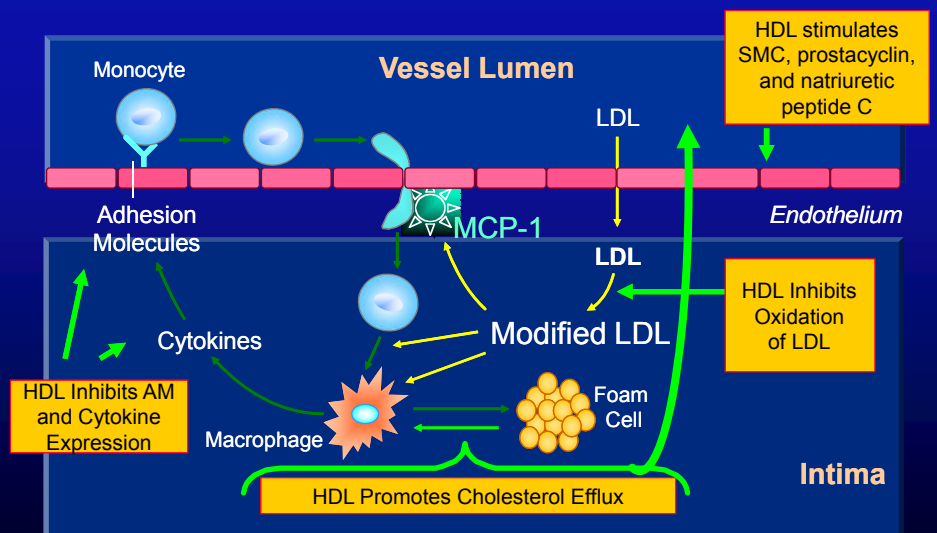


*New York Times*  
Front page  
March 31, 2010

## Statins, Inflammation and Atherosclerosis

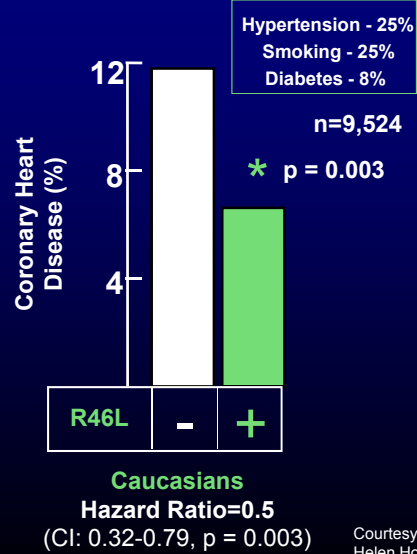
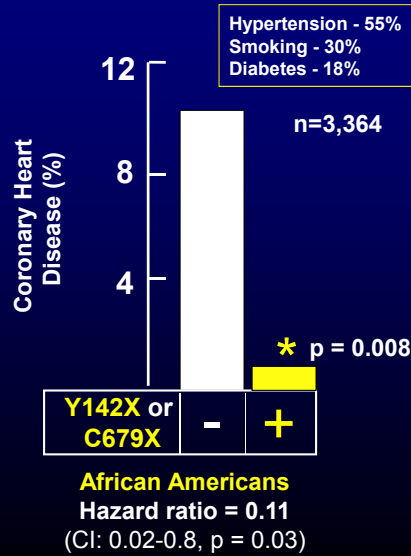
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## Mechanisms of HDL Protection



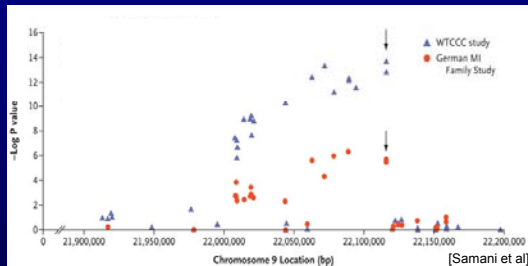
Adapted from Barter, 2004

## PCSK9 Alleles Decrease LDL-C by 28% in African Americans and 15% in Caucasians



Courtesy of Helen Hobbs

## Genome-Wide Association Studies Link Chromosome 9p21 to Increased CHD Risk



- Replicated in 3 separate studies (n>45,000) with Caucasian subjects
- Risk allele not associated with major risk factors
- Chromosomal locus of risk not associated with any known genes
- Adjacent to tumor suppressor genes CDKN2A and CDKN2B

- ~20-25% of population are homozygotes
  - ~30-40% increased CHD risk (McPherson et al)
  - ~1.64 times increased MI risk, ~2.02 times increased early-onset MI risk (Helgadottir et al)
- Heterozygotes (50% of population) associated with ~15-20% increased CHD risk (McPherson et al)

Samani NJ, et al. *NEJM* 2007;357(5):443-53; McPherson R, et al. *Science* 2007;316:1488-91; Helgadottir A, et al. *Science* 316:1491-93.

## Conclusion

- The development of statins has helped confirm the lipid hypothesis and has revolutionized the field of cardiovascular prevention.
- LDL-C is the primary target of therapy.
- CRP helps target otherwise low-risk patients who would benefit from lipid-lowering therapy.
- The specific roles of inflammation, HDL-C, and other non-HDL-C components (VLDL, IDL, chylomicron remnants) in CV prevention and treatment remains to be determined.