Medical Management of Dyslipidemia

Focus on Atorvastatin & Rosuvastatin

Disclosures:

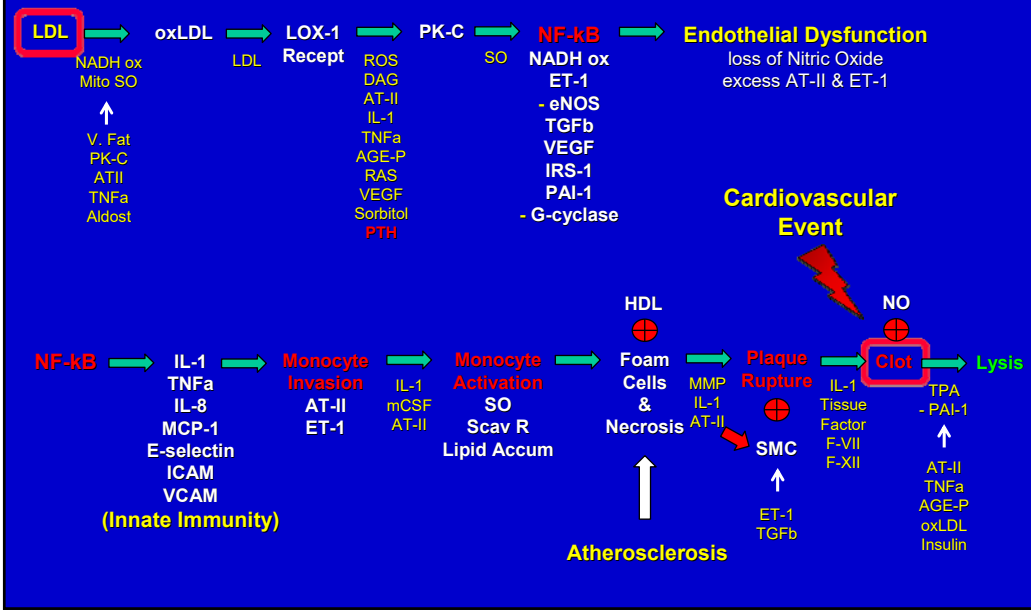
1. No financial conflicts
2. The opinions expressed in this discussion are my own and do not represent those of any group or organization

Objectives:

1. Do different statins have differing impacts on atherosclerosis?
2. Do different statins have differing impacts on CV events?
3. Do different statins have different adverse events?

Thomas A. Hughes, M.D.
Professor of Medicine – Retired
Division of Endocrinology, Metabolism, and Diabetes
University of Tennessee Health Science Center

Atherogenesis



LDL Targets vs Pleiotrophic Effects

- Observations:
  - oxLDL induces oxidation, inflammation, innate immunity, & atherosclerosis
  - Statins reduce both LDL and inhibit various steps of the oxidative & inflammatory pathways
- Do medications reduce atherosclerosis & prevent CV events?
- Do medications have clinically important effects independent of lowering LDL?
- Do different drugs within a class have different effects on CVD independent of their ability to lower LDL?
  - i.e. Do they have different Pleiotrophic effects?

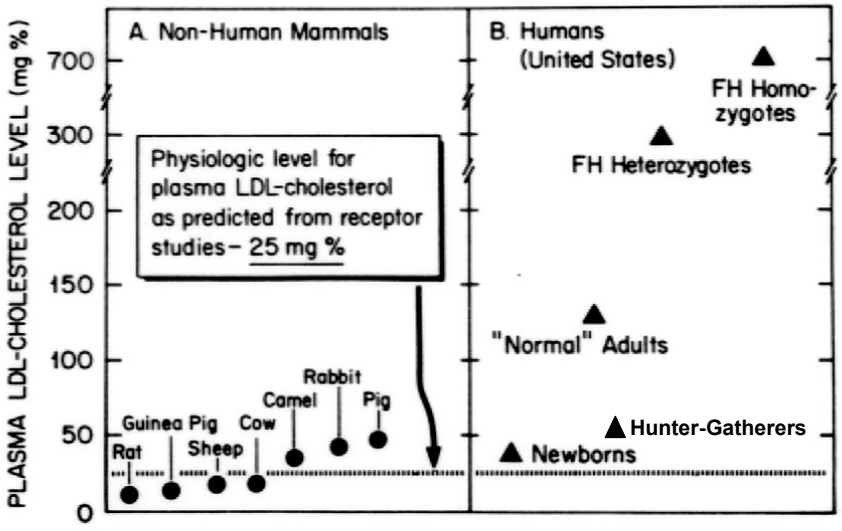
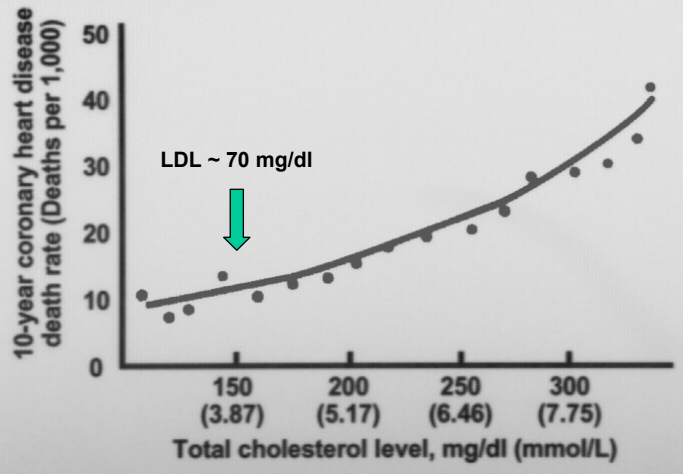


FIG. 9. Concentration of plasma LDL in various adult nonhuman mammalian species (panel **A**) as compared with that in normal newborns, normal human adults, and humans affected with the heterozygous and homozygous forms of FH (panel **B**). The estimated values for the adult nonhuman mammalian species were obtained from the data of Mills and Taylaur (35) and Calvert (14). The human values were obtained from the data of Fredrickson et al. (16).

The Relationship of Elevated Cholesterol to CHD Death Rate (MRFIT)



Adapted from National Cholesterol Education Program. *Arch Intern Med 151:*1071–1084, June 1991

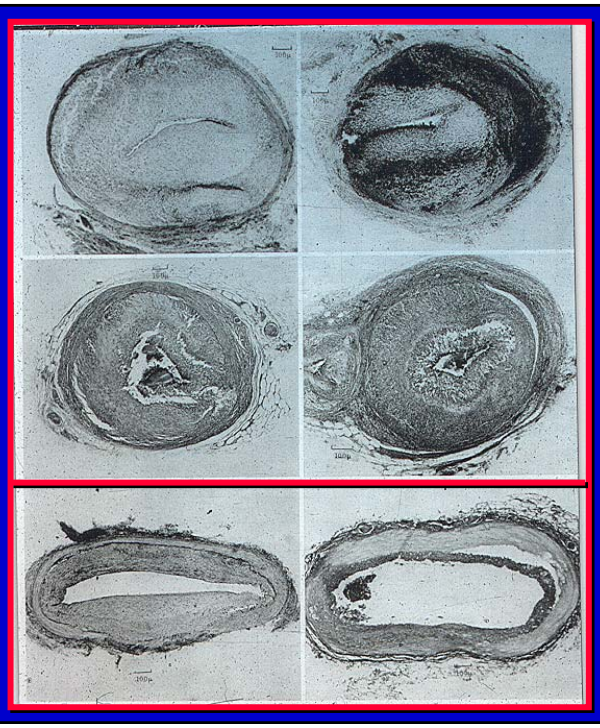
Experimental Atherosclerosis

Rhesis Monkeys
(Normal chol 140 mg/dl)

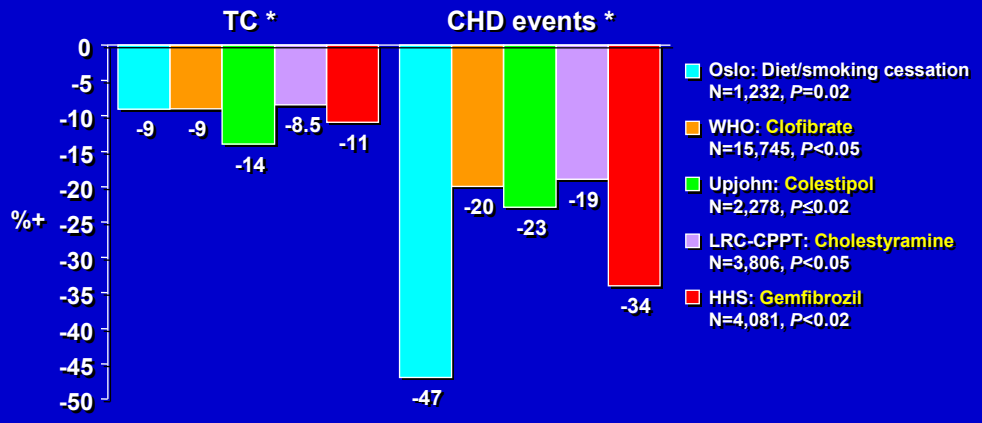
High fat diet 18 mths:
chol – 700 mg/dl

followed by
Low fat diet 24 mths:
chol – 140 mg/dl

Circ Res 27:59, 1970



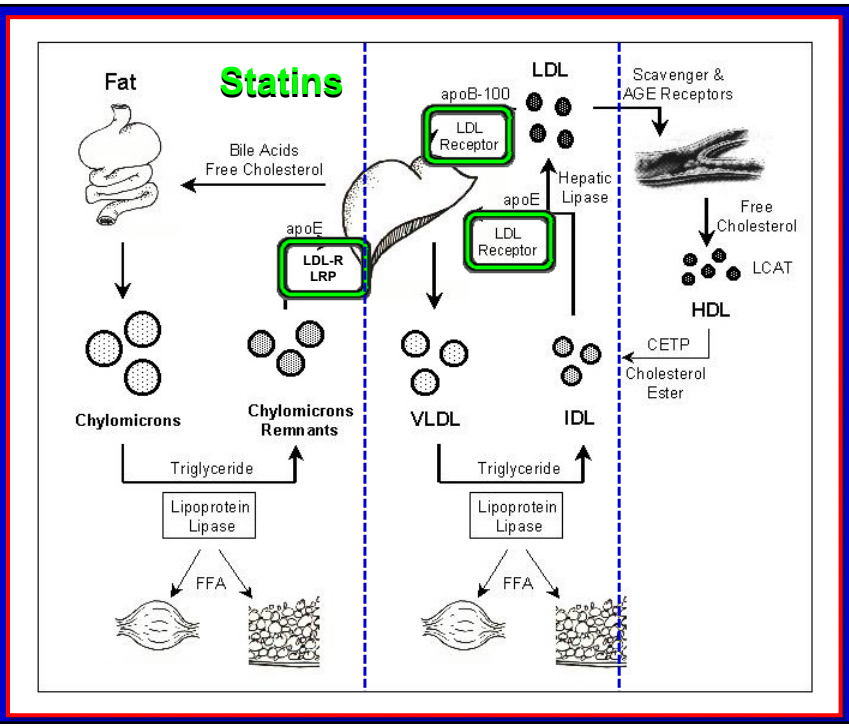
Early Primary-Prevention Trials: Overview
Other drugs that do reduce events



N=number enrolled.

* Net difference between treatment and control groups (*P* values are for events).

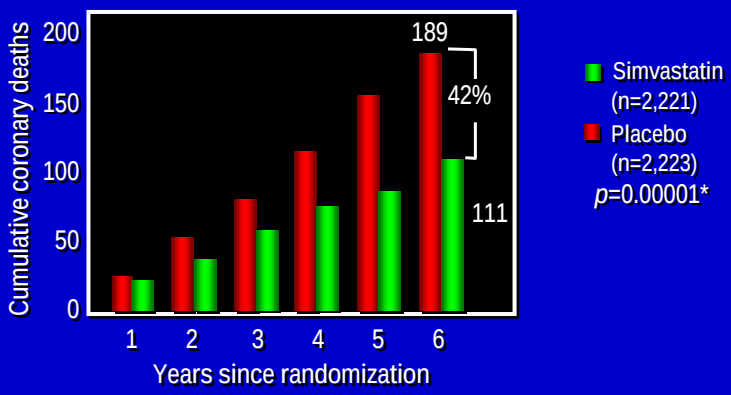
Adapted from Levine GN et al. *N Engl J Med.* 1995;332:512-521.



Scandinavian Simvastatin Survival Study:

"4S" - Coronary Mortality*

LDL
-180 mg/dL
Vs
-115 mg/dL
(35%)



*Coronary Mortality (secondary endpoint) was reduced by 42%

*Data on file, Merck & Co., Inc.

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

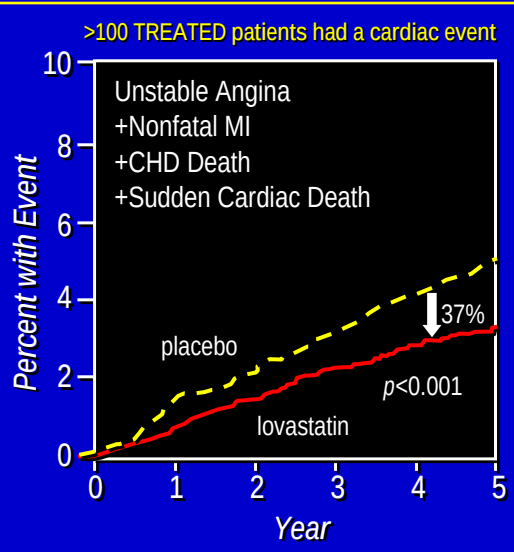
AFCAPS/TexCAPS

Primary Prevention

Low-Risk Subjects

LDL
~150 mg/dL
vs
~115 mg/dL

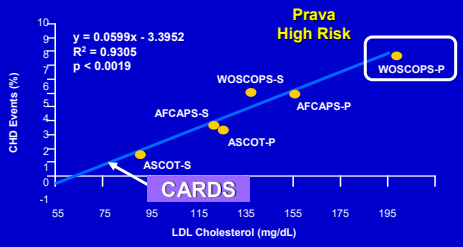
(Lovastatin – 24%)



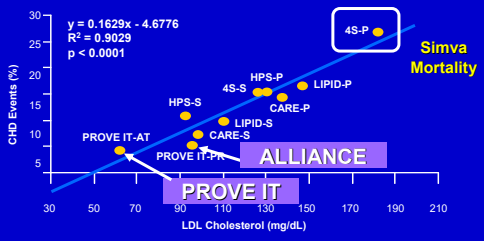
Downs JR et al. *JAMA*. 1998;279:1615-1622.

Lowering LDL: CV Events & Atherosclerosis

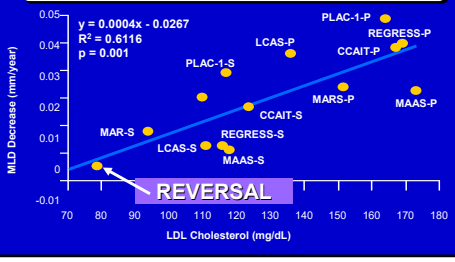
Primary Prevention Trials

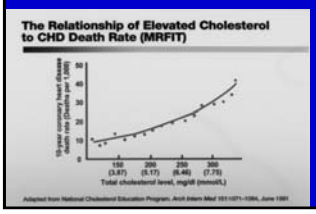


Secondary Prevention Trials



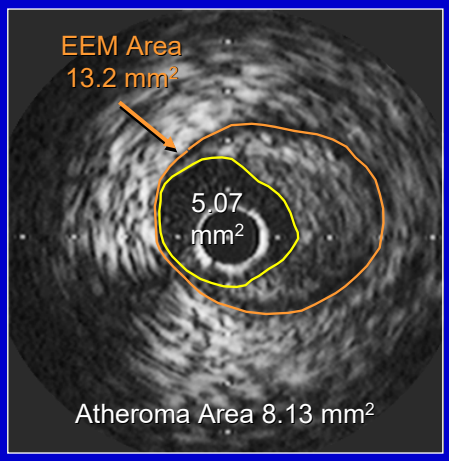
Regression Trials



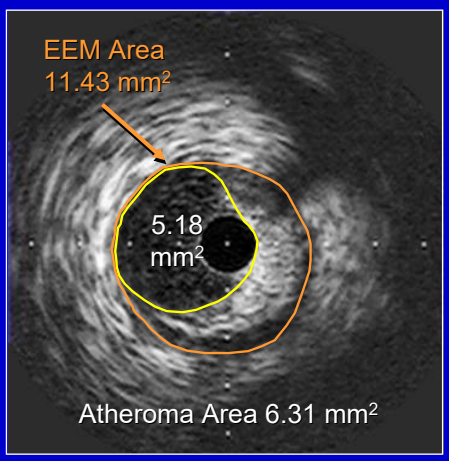


REVERSAL: Atheroma Regression

Pre-Statin



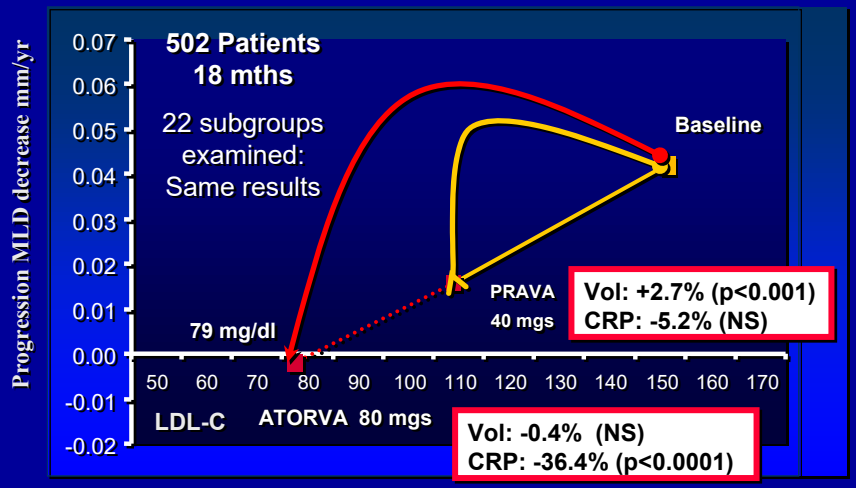
Post-Statin



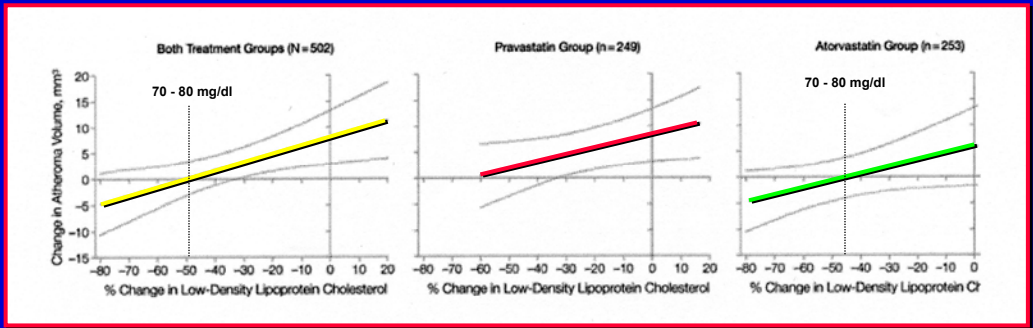
Adapted from Nissen SE, et al. *JAMA*. 2004;291:1071-1080.

REVERSAL Study
Plaque Volume

Coronary IVUS
JAMA 291:1071-80, 2004



Intensive vs Moderate Lipid Lowering
Coronary IV Ultrasound (Reversal Trial)
Atorvastatin (80 mg) vs Pravastatin (40 mg)



502 Patients - 18 mths
Initial LDL 150 mg/dl

JAMA 291:1071-80, 2004

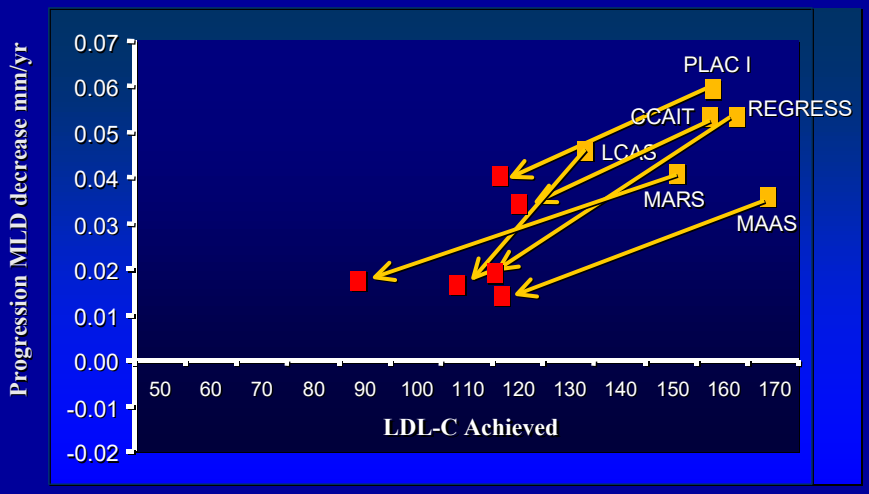
For every 10% reduction in LDL → ~1% reduction in Plaque Regression point ~ 70-80 mg/dl

Atorvastatin induced greater Plaque reduction at every LDL level
(Equivalent to an additional 20% LDL reduction??)

Similar Toxicity (Low)

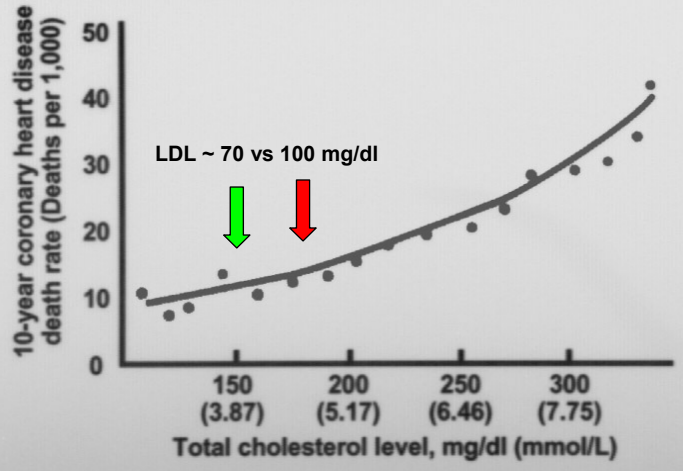
Carotid Ultrasound

More is Better - Regression Trials



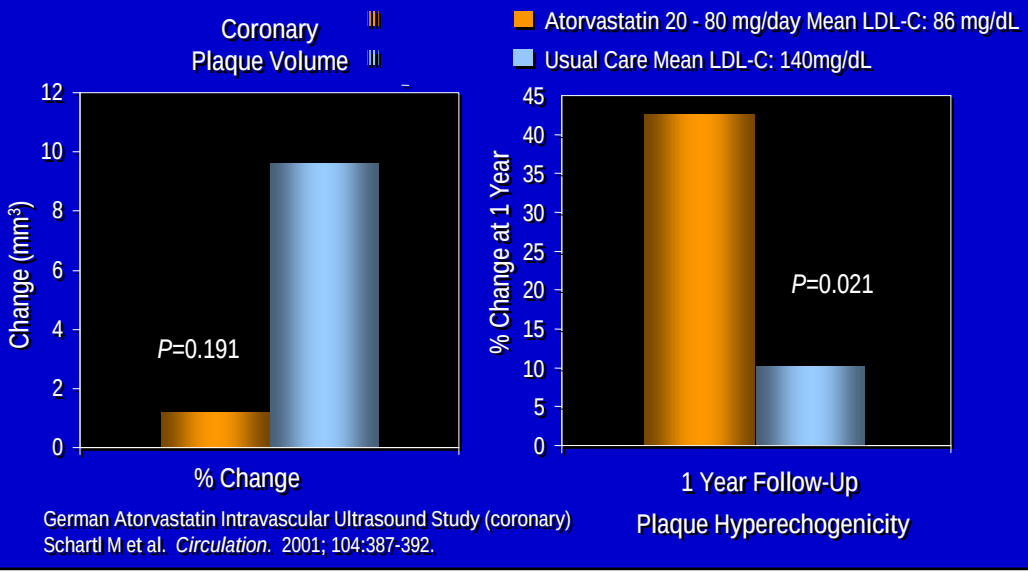
Ballantyne et al. Curr Opin Lipidol 1997;8:354-361.

The Relationship of Elevated Cholesterol to CHD Death Rate (MRFIT)



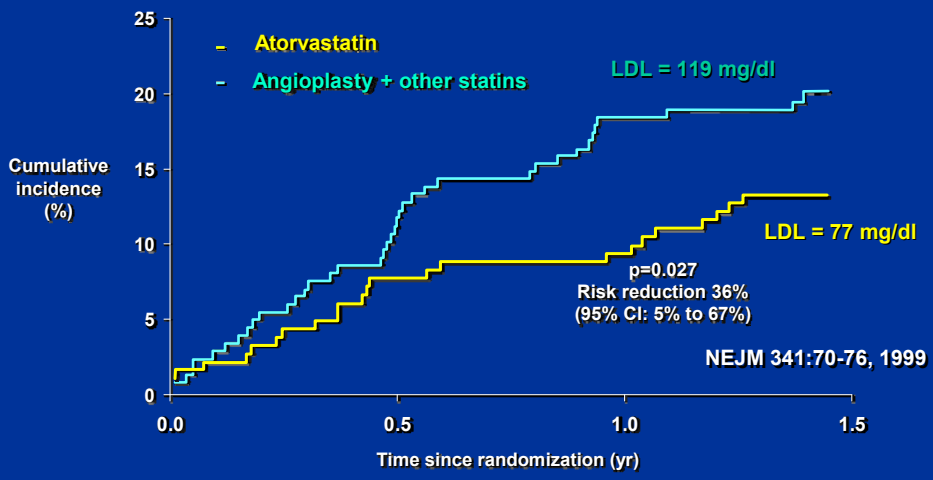
Adapted from National Cholesterol Education Program. *Arch Intern Med 151:*1071–1084, June 1991

Aggressive Lipid-Lowering (LDL-C <100 mg/dL) Slows Plaque Growth and Improves Plaque Stability



German Atorvastatin Intravascular Ultrasound Study (coronary)
Schartl M et al. *Circulation.* 2001; 104:387-392.

AVERT: Stable CAD Atorvastatin 80 mg vs angioplasty



1-2 vessal disease, mean stenosis 80%; EF = 61%; no ischemia at 4 min on ETT

MIRACL Study (JAMA 285:1711-8, April 4, 2001)

Patient Population

- Non-Q MI or UA
- randomized 24-96 hours from admission
- exclusions:
  - planned CABG / PTCA
  - prior Q-wave <28 days,
  - CABG <3 mo, PTCA <6 mo.,
  - IIIb/IV CHF,
  - TC>7 mmol.

ASA, nitrates, b-blockers, and heparin similar in both groups

4 months

3,000 Patients

- Usual Care + d/b PBO — LDL = 135, TG = 187
- atorvastatin 80 mg — LDL = 72, TG = 139

(HDL = 46 in both, no change)

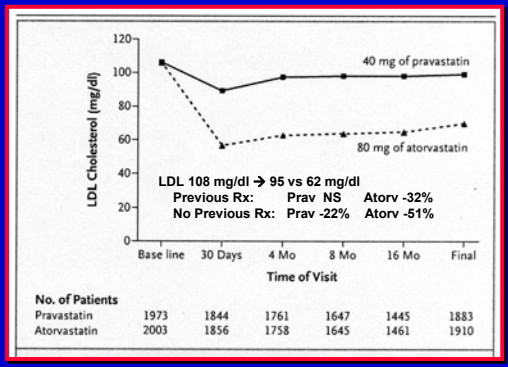
Primary Endpoint: time to ischemic events, CHD death, non-fatal MI, cardiac arrest, documented angina

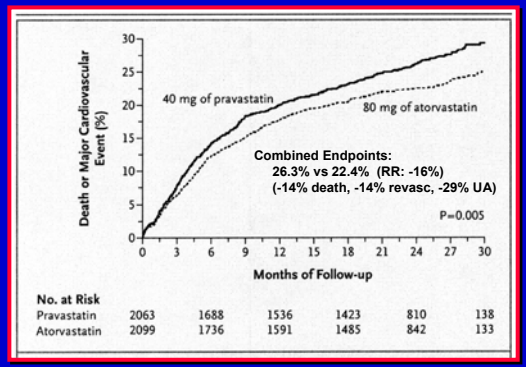
17.4% vs 14.8%, p=0.048 R.R=0.84
C.I.=0.701-0.999

Worsening angina: 8.4% vs 6.4% p=0.02
Stroke (fatal or nonfatal): 24 vs 12 events
p=0.045 R.R.=0.50

Intensive vs Moderate Lipid Lowering with Acute Coronary Syndrome

Atorvastatin (80 mg) vs Pravastatin (40-80 mg)





Atorva reduces PAI-1 and Factor VII within 1 month

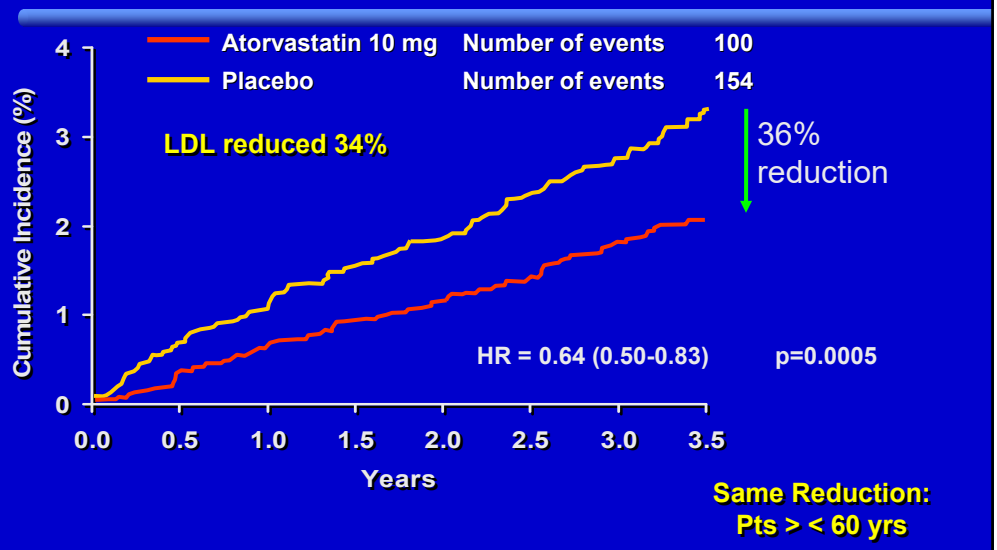
4162 pts: age 58, 78% M, 90% C, 50% HBP, 18% DM
LFTs: 1.1% prav, 3.3% ator
Myalgies: 2.7% prav, 3.3% ator

Effect evident after just 30 days
Effect greatest if initial LDL > 125

NEJM 350: (online 3/12/04) April 8, 2004

ASCOT: Hypertensive Patients (multiple risk factors)

Primary End Point - Nonfatal MI and Fatal CHD



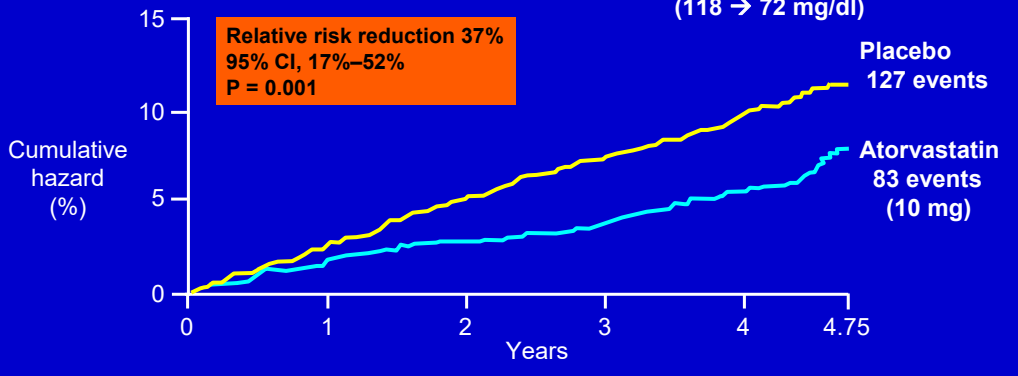
Sever PS, Dahlöf B, Poulter N, Wedel H, et al, for the ASCOT Investigators. Lancet. 2003;361:1149-58

VBWG

CARDS: Type 2 Diabetes (37% Reduction in primary outcome)

Type 2 DM (N = 2838)

LDL-C: Average difference 40%
(118 → 72 mg/dl)



Placebo	1410	1351	1306	1022	651	305
Atorvastatin	1428	1392	1361	1074	694	328

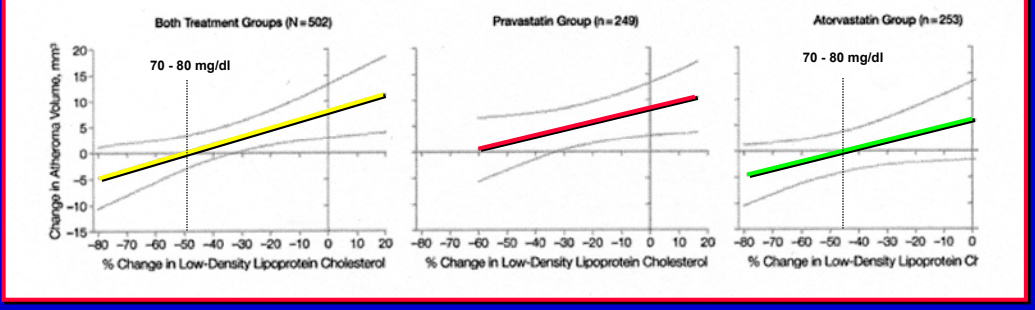
Primary outcome: Composite of major coronary events, revascularizations, unstable angina, resuscitated cardiac arrest, and stroke

Colhoun HM et al. *Lancet*. 2004;364:685-96.

Intensive vs Moderate Lipid Lowering

Coronary IV Ultrasound (Reversal Trial)

Atorvastatin (80 mg) vs Pravachol (40 mg)



502 Patients - 18 mths
Initial LDL 150 mg/dl

For every 10% reduction in LDL → ~1% reduction in Plaque
Regression point ~ 70-80 mg/dl
Atorvastatin induced greater Plaque reduction at every LDL level
(Equivalent to an additional 20% LDL reduction??)
Similar Toxicity (Low)

JAMA 291:1071-80, 2004

Intensive Lipid Lowering w/ Atorvastatin in Stable CVD: TNT

LaRosa et al.
www.nejm.org
March 14, 2005

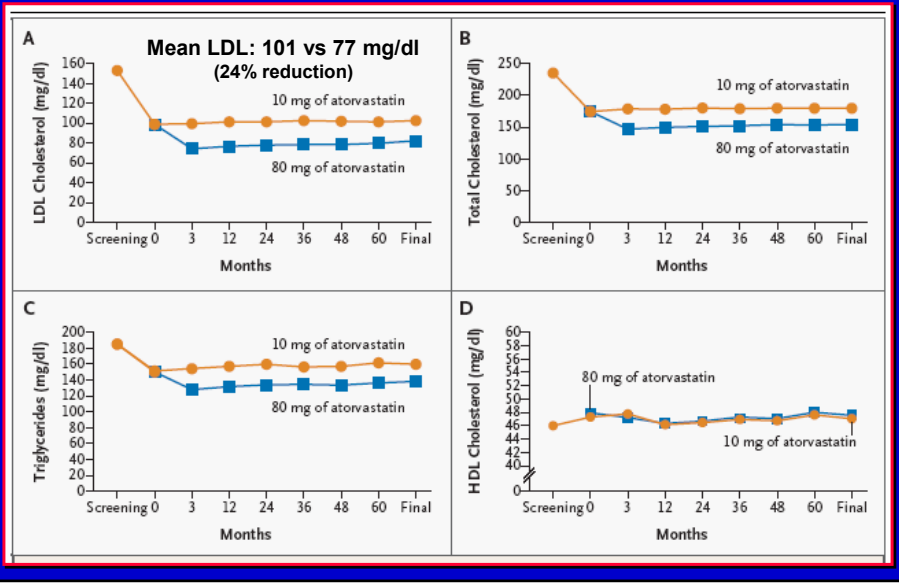
Compare CV Events LDL ~ 100 vs ~ 70 In Patients with Advanced Lesions

Table 1. Baseline Characteristics of the Patients.*

Characteristic	10 mg of Atorvastatin (N=5006)	80 mg of Atorvastatin (N=4995)
Age — yr	60.9±8.8	61.2±8.8
Male sex — no. (%)	4045 (80.8)	4054 (81.2)
White race — no. (%)†	4711 (94.1)	4699 (94.1)
Systolic blood pressure — mm Hg	131±17	131±17
Diastolic blood pressure — mm Hg	78±10	78±10
Body-mass index‡	28.6±4.7	28.4±4.5
Cardiovascular history — no. (%)		
Current smoker	672 (13.4)	669 (13.4)
Former smoker	3167 (63.3)	3155 (63.2)
Systemic hypertension	2721 (54.4)	2692 (53.9)
History of diabetes mellitus	753 (15.0)	748 (15.0)
Myocardial infarction	2888 (57.7)	2945 (59.0)
Angina	4067 (81.2)	4084 (81.8)
Cerebrovascular accident	263 (5.3)	255 (5.1)
Peripheral-artery disease	570 (11.4)	603 (12.1)
Congestive heart failure	404 (8.1)	377 (7.6)
Arrhythmia	927 (18.5)	907 (18.2)
Coronary revascularization		
Angioplasty	2719 (54.3)	2688 (53.8)
Bypass	2338 (46.7)	2317 (46.4)
Lipids — mg/dl§		
LDL cholesterol	98±18	97±18
Total cholesterol	175±24	175±24
Triglycerides **Baseline ~180 mg/dl**	151±72	151±70
HDL cholesterol	47±11	47±11

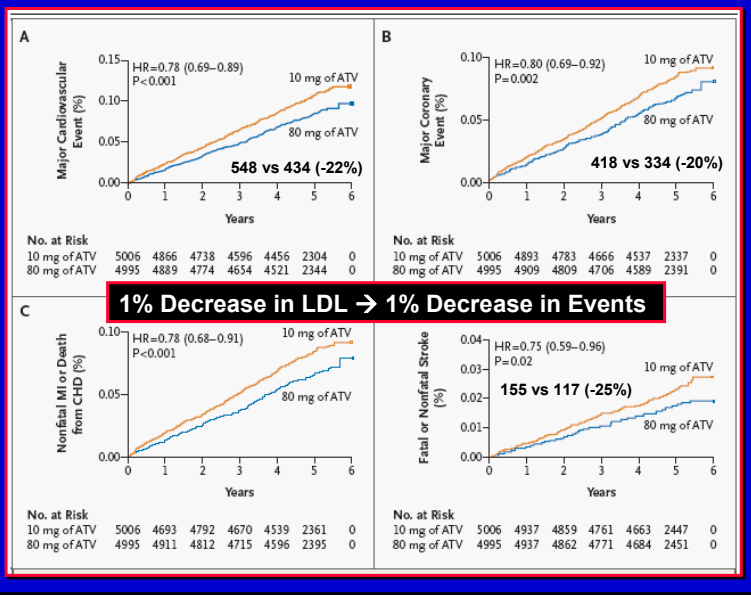
Intensive Lipid Lowering w/ Atorvastatin in Stable CVD: TNT

LaRosa et al., www.nejm.org, March 14, 2005



Intensive Lipid Lowering w/ Atorvastatin in Stable CVD: TNT

LaRosa et al., www.nejm.org, March 14, 2005



Effect of High-Dose Atorvastatin on Hospitalizations for Heart Failure: TNT

Direct anti-inflammatory, anti-oxidant, and/or anti-fibrosis effect?

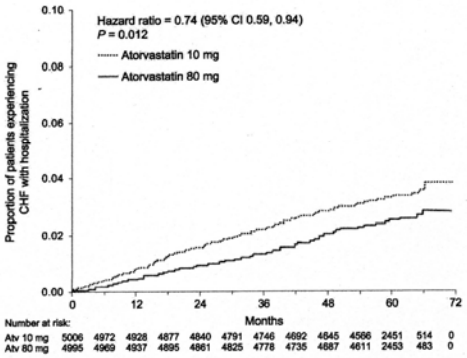


Figure 1. Proportion of patients in the 10- and 80-mg arms of TNT hospitalized with HF during follow-up. CI indicates confidence interval.

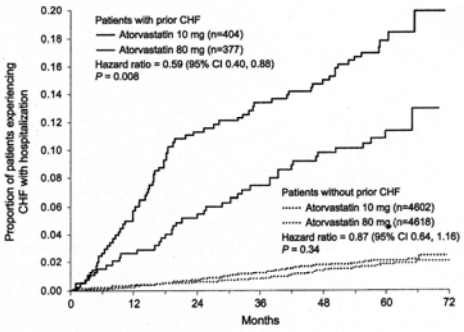


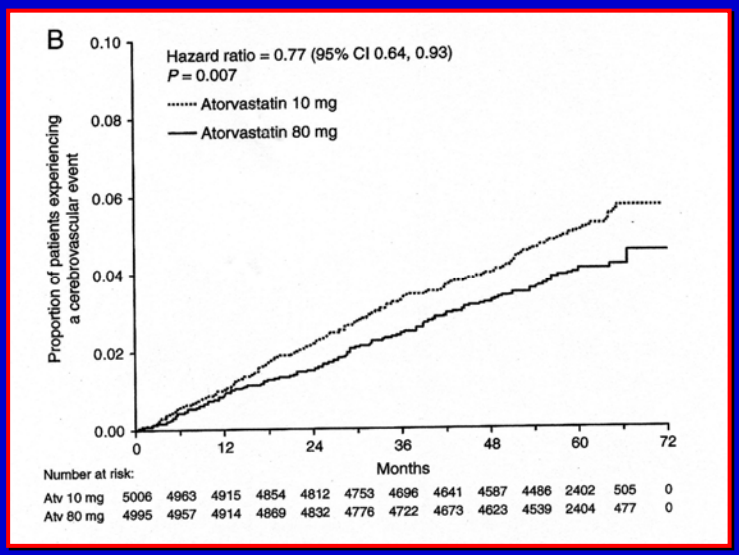
Figure 2. Proportion of patients with and without a history of HF in the 10- and 80-mg arms of TNT experiencing hospitalization for HF during follow-up. CI indicates confidence interval.

Khush et al., Circ 115:576-583, 2007

Effect of High-Dose Atorvastatin on Cerebrovascular Events: TNT

Types:

Total	155 vs 117
Embolic	44 vs 29
Ischemic	90 vs 68
Hemorr	18 vs 16
Unknown	15 vs 11



Waters et al., JACC 48:1793-9, 2006

Comparison of 80 vs 10 mg of *Atorvastatin* on Occurrence of CV Events after 1st Event (TNT)

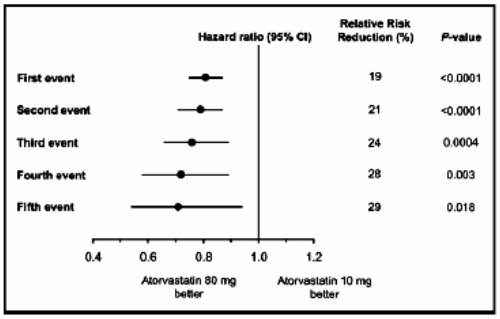


Figure 1. Risk decrease in cardiovascular events.

Amer J Cardiol 105:283–287, 2010

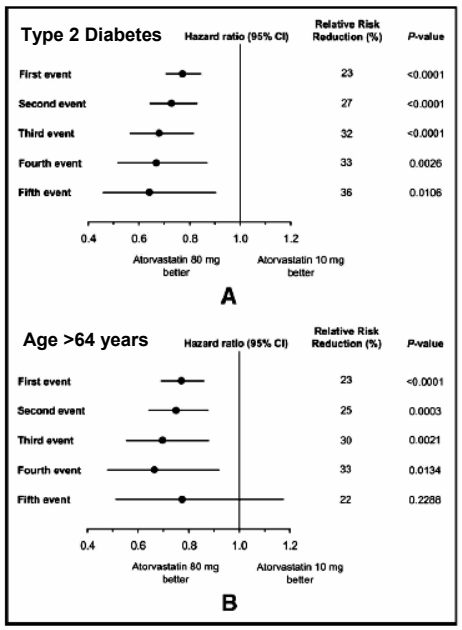
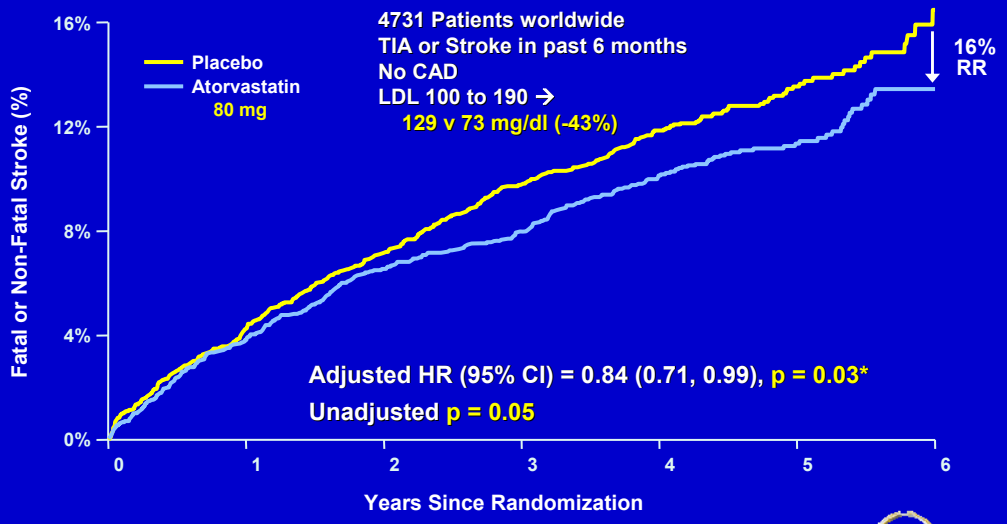


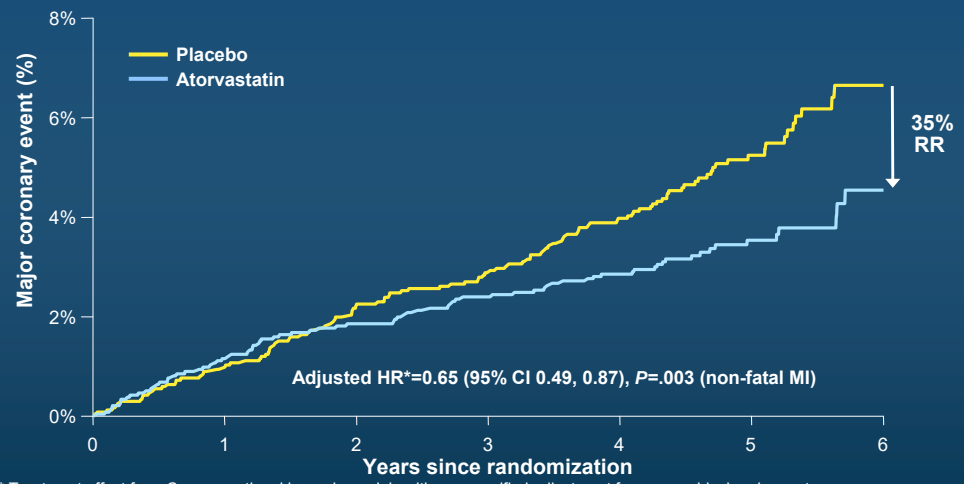
Figure 2. Risk decrease in cardiovascular events in patients (*A*) with type 2 diabetes and/or metabolic syndrome and (*B*) ≥65 years of age.

SPARCL: Primary Endpoint
Time to Fatal or Non-Fatal Stroke



* Treatment effect from Cox proportional hazards models with pre-specified adjustment for geographical region, entry event, time since entry event, gender, and baseline age.

Secondary Endpoint: Time to Major Coronary Event



* Treatment effect from Cox proportional hazards models with pre-specified adjustment for geographical region, entry event, time since entry event, gender, and baseline age.

RR, risk reduction; HR, hazard ratio; CI, confidence interval.

The SPARCL Investigators. *N Engl J Med*. 2006;355:549-559.

The NEW ENGLAND JOURNAL of MEDICINE

Online Nov., 2007

ORIGINAL ARTICLE

Rosuvastatin in Older Patients with Systolic Heart Failure

John Kjekshus, M.D., Ph.D., Eduard Apetrei, M.D., Ph.D., Vivencio Barrios, M.D., Ph.D., Michael Böhm, M.D., Ph.D., John G.F. Cleland, M.D., Jan H. Cornel, M.D., Ph.D., Peter Dunselman, M.D., Ph.D., Cândida Fonseca, M.D., Assen Goudev, M.D., Ph.D., Peer Grande, M.D., Ph.D., Lars Gullestad, M.D., Ph.D., Åke Hjalmarson, M.D., Ph.D., Jaromir Hradec, M.D., Ph.D., András Jánosi, M.D., D.Sc., Gabriel Kamenský, M.D., Ph.D., Michel Komajda, M.D., Jerzy Korewicki, M.D., Ph.D., Timo Kuusi, M.D., Ph.D., François Mach, M.D., Vyacheslav Mareev, M.D., Ph.D., John J.V. McMurray, M.D., Naresh Ranjith, M.D., Maria Schaufelberger, M.D., Ph.D., Johan Vanhaecke, M.D., Ph.D., Dirk J. van Veldhuisen, M.D., Ph.D., Finn Waagstein, M.D., Ph.D., Hans Wedel, Ph.D., and John Wikstrand, M.D., Ph.D., for the CORONA Group*

Rosuvastatin: Older Patients w/ CHF (Corona - NEJM 11/07)

Age 73 ± 7
Men 76%

LDL ~ 138 mg/dl
HDL ~ 48 mg/dl
Trig ~ 176 mg/dl

98% Class II or III
EF ~31%
CAD 75+%

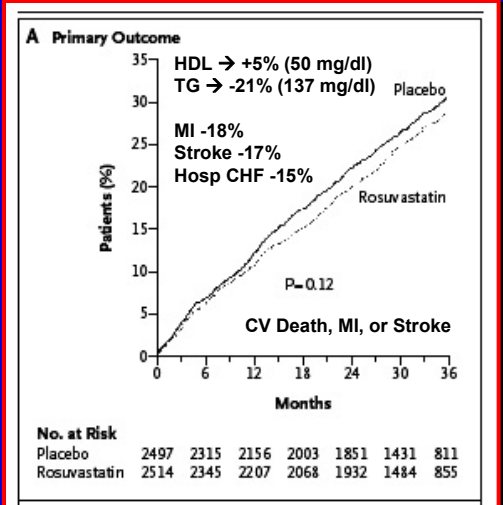
Many Renal Insuff

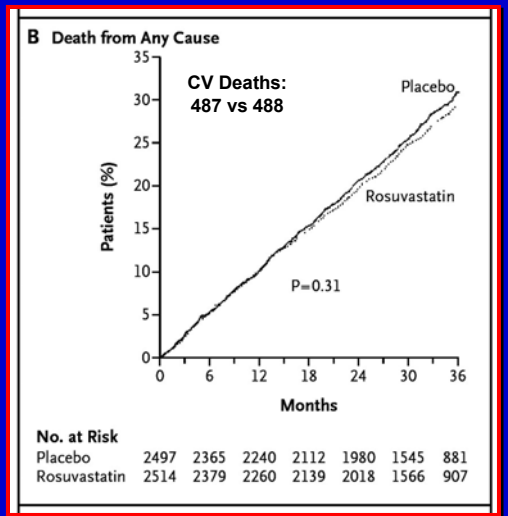
High hsCRP

Table 1. (Continued.)

Variable	Placebo (N=2497)	Rosuvastatin (N=2514)	P Value
Laboratory measurements			
Cholesterol — mmol/liter			
Total	5.35±1.06	5.36±1.11	0.77
Low-density lipoprotein	3.56±0.93	3.54±0.95	0.60
High-density lipoprotein	1.23±0.34	1.24±0.36	0.23
ApoB:ApoA-I ratio	0.87±0.24	0.87±0.25	0.60
Triglycerides — mmol/liter	1.99±1.23	2.01±1.33	0.65
Serum creatinine			
Mean	115±28	115±28	0.66
>130 μmol/liter — no. (%)	593 (24)	570 (23)	0.35
Estimated GFR			
Mean	58±15	58±15	0.99
<60 ml/min/1.73 m² — no. (%)	1432 (57)	1418 (57)	0.98
NT-pro-BNP — pmol/liter†			0.13
Median	166	180	
Interquartile range	71–350	74–384	
hsCRP — mg/liter			0.68
Median	3.5	3.5	
Interquartile range	1.6–7.8	1.6–7.2	

Rosuvastatin: Older Patients w/ CHF (Corona - NEJM 11/07)



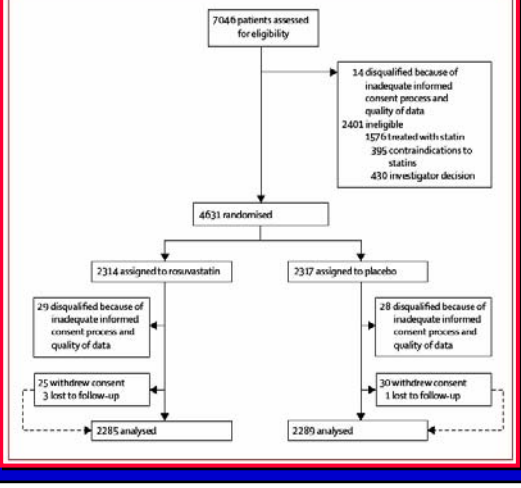


45% difference in LDL → ~138 vs ~76 mg/dl

Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial

GISSI-HF investigators*

Lancet 2008; 372: 1231–39



	Rosuvastatin (N=2285)	Placebo (N=2289)
Patients' characteristics		
Age (years)	68 (11)	68 (11)
Age >70 years	1002 (43·9%)	1012 (44·2%)
Women	543 (23·8%)	489 (21·4%)
Heart disease risk factors		
BMI (kg/m²)	27·1 (4·6)	27·1 (4·4)
SBP (mm Hg)	127 (18)	127 (18)
DBP (mm Hg)	77 (10)	77 (10)
Heart rate (beats per min)	73 (14)	73 (13)
Current smoking	323 (14·1%)	321 (14·0%)
History of hypertension	1260 (55·1%)	1224 (53·5%)
NYHA class		
II	1398 (61·2%)	1462 (63·9%)
III	828 (36·2%)	771 (33·7%)
IV	59 (2·6%)	56 (2·4%)
LVEF (%)	33·4% (8·8)	33·1% (8·7)
LVEF >40%	236 (10·3%)	225 (9·8%)

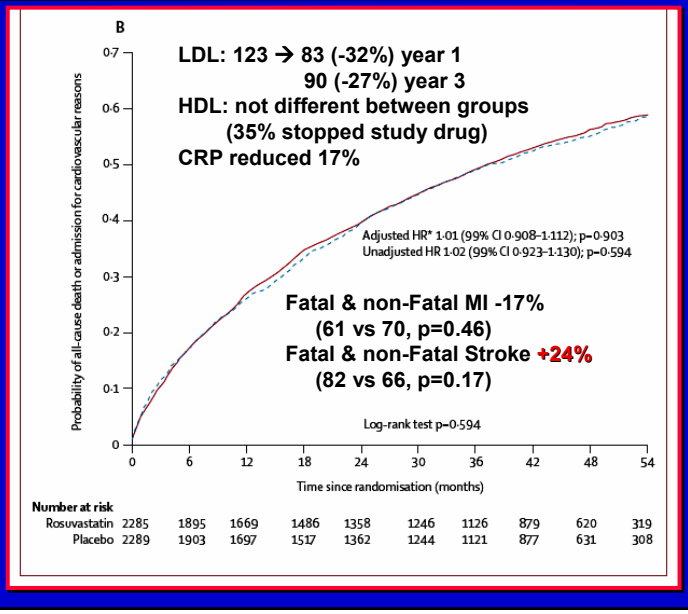
GISSI-HF: Rosuvastatin in CHF

Age 68 ± 11
Men 77%

96% Class II or III
EF ~33%
CAD 50+%

BP ~127/77

High hsCRP (2.71)

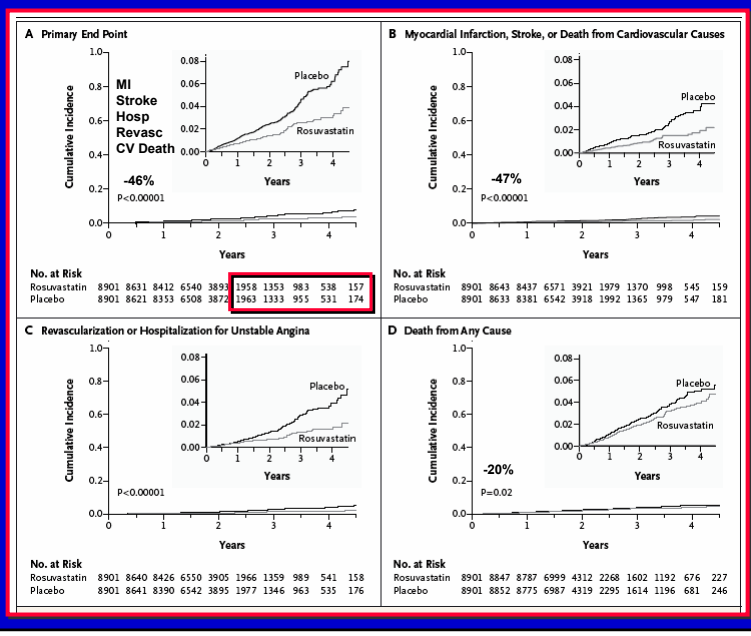


Jupiter: Rosuvastatin 20 mg w/ CRP >2.0

Age 66
Men 63%
Caucasian 71%
Healthy
Subjects: 17,800

BP ~134/80

hsCRP 4.3 → 1.8
LDL 108 → 53
HDL 49 → 52
TG 118 → 99

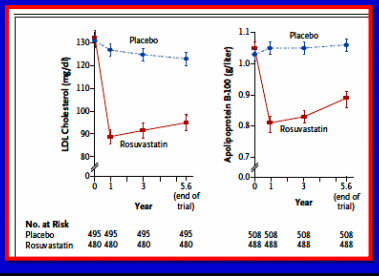


HOPE-3: Rosuvastatin 10 mg - Intermediate CV Risk

Age ~66 Men 54%
Caucasian 20%
Hispanic 28%
Chinese 29%
South Asian 15%

Intermediate Risk
Subjects: 12,705
BP ~138/82
LDL 128 → ~95 (26.5%)

Events: 3.7 v 4.8% (-24%, p=0.002)



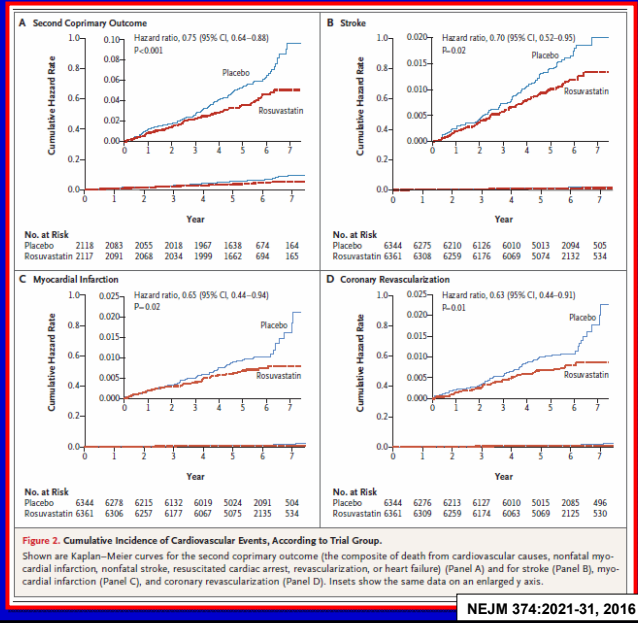


Figure 2. Cumulative Incidence of Cardiovascular Events, According to Trial Group.
Shown are Kaplan–Meier curves for the second coprimary outcome (the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, revascularization, or heart failure) (Panel A) and for stroke (Panel B), myocardial infarction (Panel C), and coronary revascularization (Panel D). Insets show the same data on an enlarged y axis.

NEJM 374:2021-31, 2016

Statin Effects on IVUS

Asteroid:

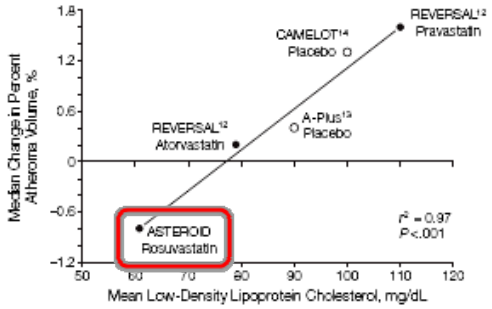
No control group
349 completed
125 dropped

LDL 130 → 61
-53%

HDL 43 → 49
+14%

TG 152 → 121
-20%

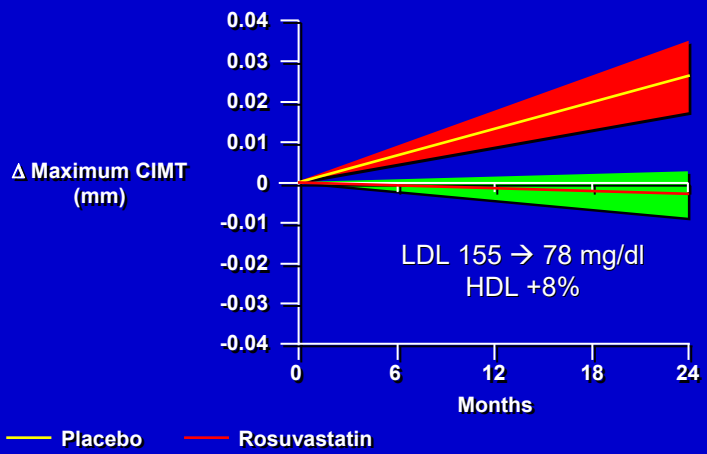
Figure 3. Relationship Between Mean Low-Density Lipoprotein Cholesterol Levels and Median Change in Percent Atheroma Volume for Several Intravascular Ultrasound Trials



There is a close correlation between these 2 variables (r^2=0.97). REVERSAL indicates Reversal of Atherosclerosis With Aggressive Lipid-Lowering[12]; CAMELOT, Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis[14]; A-Plus, Avasimibe and Progression of Lesions on Ultrasound[13]; and ASTEROID, A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden.

Changes in CIMT with rosuvastatin (40 mg) vs placebo

METEOR Trial



No CVD
Middle Aged (~57 yrs)
60% men
94% caucasian
Mildly obese (~20% obese)
Small %: HBP, MS, DM,
low HDL, smokers
~1/3 with multiple risk factors

Shading indicates 95% CI

Crouse JR III et al. *JAMA*. 2007;297:1344-53.

CS-114

Proportion of Patients With Proteinuria ≥ 96 weeks of Rosuvastatin Treatment

Combined All Controlled/Uncontrolled and RTLD Pool

Rosuva Dose	N	Any time n (%)	Last visit n (%)	Creatinine increase > 30%, n		
				Hematuria*		% Rhabdo*
5 mg	261	3 (1.1)	0		0	
10 mg	838	17 (2.0)	4 (0.5)	1	0	0.2
20 mg	112	5 (4.5)	1 (0.9)	1	0	0.2
40 mg	100	4 (4.0)	2 (2.0)	6	0	0.4
80 mg	590	99 (16.8)	37 (6.3)	13 (≥1+)	7	1.9 (CK ≥ 10x)
≥ 40 mg†	807	136 (16.9)	10 (1.2)		0	

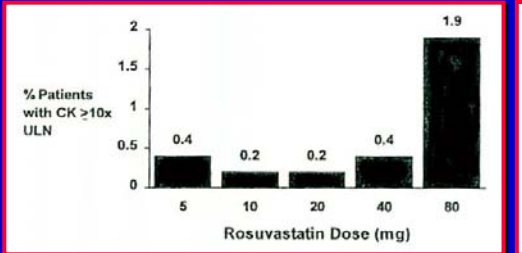
* Includes shorter treatment times

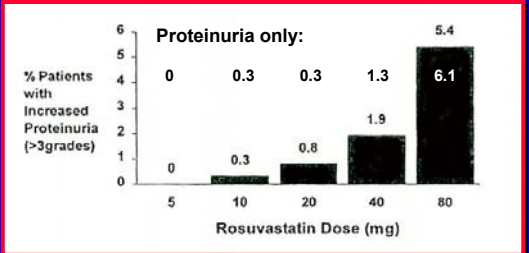
Proteinuria: "none or trace" to "2+ or greater"

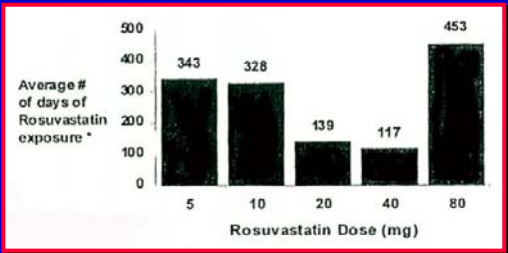
† Includes patients who back-titrated from the 80-mg dose

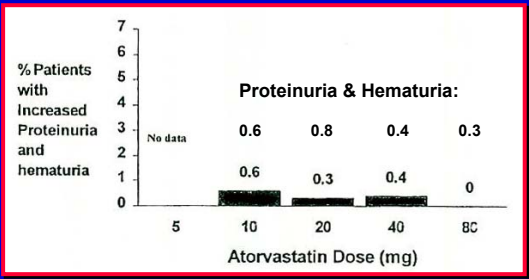
AstraZeneca

Crestor Adverse Events









<8.4% (20mg) and <6.5% (40mg) Rx'ed > 48 wks
Median time to Rhabdo 80mg: 35 wks

Crestor Adverse Events

FDA Advisory Panel - Recommended:

- Monitor S.Creat, urine protein/creat ratio &/or complete UA w/40 mg (or, at least, dipstick); maybe for 20 mg
- Monitoring Frequency – at baseline & every 6 -12 mths
- Reserve 40 mg for LDL > 190 mg/dl
- Further study – both animal and human (with biopsies)

FDA:

- Did not recommend monitoring
- But did not allow the 40 mg to be stocked in Pharmacies
- Limited to 5 mg with Cyclosporin & 10 mg with gemfibrozil (Fenofibrate OK)
- Reduce dosage by ½ in Asians and Renal Disease
- Adjust INR

Effects of Atorvastatin on Proteinurea & Progression of Renal D.

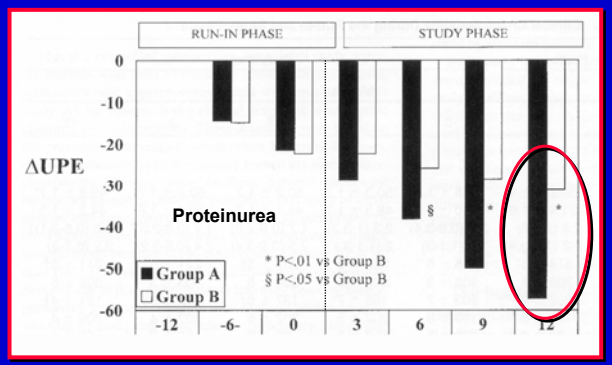
Glomerulonephritis (n = 56)

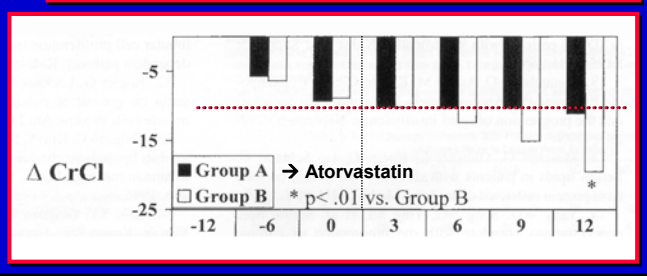
Age	55.6 yrs
CrCl	50.4 ml/min
UPE	2.2 g/day
LDL	198 mg/dl → 121
HDL	36 mg/dl
Trig	174 mg/dl → 132
Album	3.3 g/dl

One year Rx HBP
- ACEI 96%
- CCB 45%
- ASA 66%

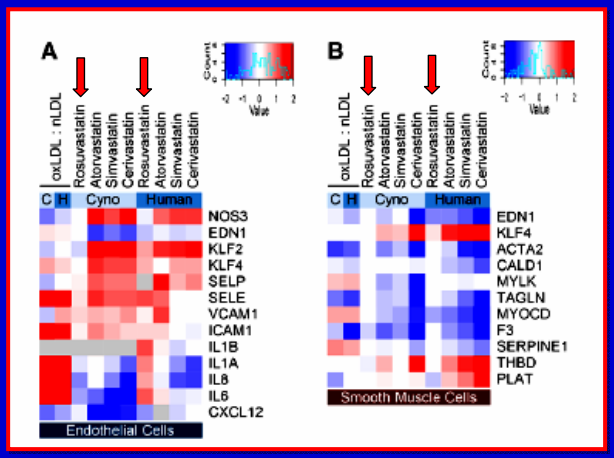
Goal:
- LDL < 120 mg/dl or ↓ 40%
- Dose: 10 - 40 mg/d

Bianchi et al;
Amer J Kid D 41:565-570, 2003





An In Vitro Cynomolgus Vascular Surrogate System for Preclinical Drug Assessment and Human Translation



Cole et al: *Arterioscler Thromb Vasc Biol* 35:2185-2195, 2015. DOI: 10.1161/ATVBAHA.115.306245.

LDL Targets vs Pleiotrophic Effects

To Test Hypothesis

Acute Coronary Syndrome

6k to 10k patients - follow for 4 to 12 months

Randomize: Atorva 40 vs Simva 80 vs Rosuva 10

(40-50% reduction in LDL)

Endpoint: Non-fatal MI, Stroke, CV Death

(Secondary: Death, CHF, CV Procedures & Hosp)

LDL Targets vs Pleiotrophic Effects

Acute Coronary Syndrome

The ultimate in advanced lesions

Obviously unstable

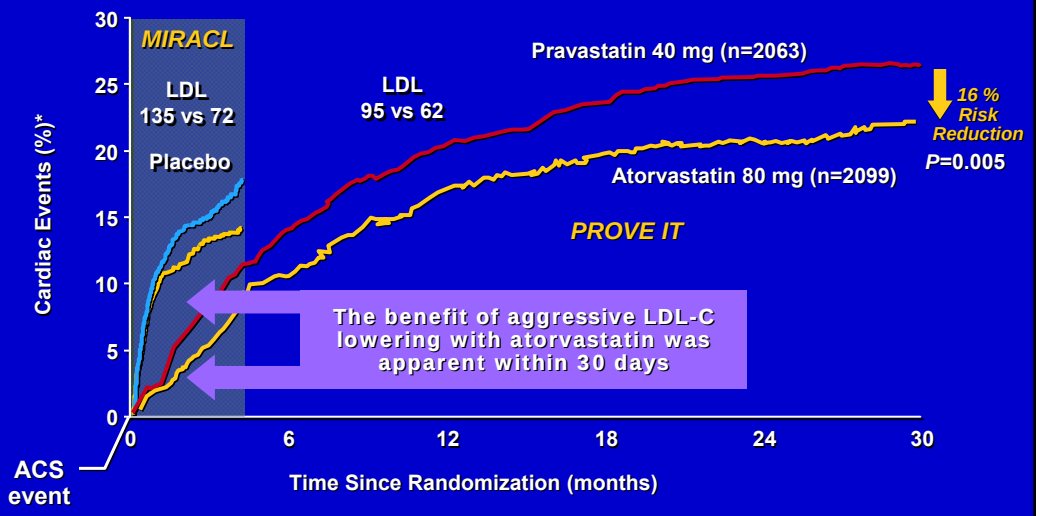
Major coagulation involvement

(Aspirin)

High mortality

Acute Coronary Syndrome (ACS)

Atorvastatin: Effect within 30 days vs placebo or pravastatin



Schwartz GG, et al. *JAMA.* 2001;285:1711-1718. Cannon CP, et al. *N Engl J Med.* 2004;350:1495-1504.

Early Intensive vs Delayed Conservative Simvastatin Strategy in Patients with ACS

Phase Z of the A to Z Trial

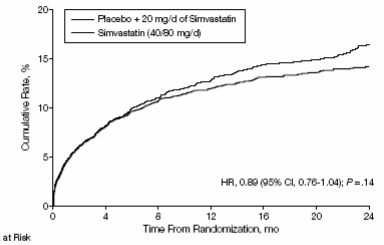
James A. de Lemos, MD
Michael A. Blazing, MD
Stephen D. Wiviott, MD
et al
for the A to Z Investigators

No effect on CV events at 4 months
Despite reduction in CRP
And similar reduction in LDL

Subsequent drop in events may be related to early diff in LDL

JAMA, Sept 15, 2004, Vol 292, No. 11 p **1307**

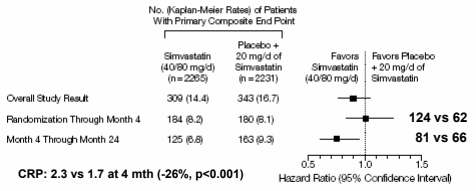
Figure 2. Estimates of the Rate of the Primary End Point



No. at Risk							
Simvastatin (40/80 mg/d)	2265	2039	1950	1855	1632	1377	1020
Placebo + 20 mg/d of Simvastatin	2232	2004	1904	1808	1571	1331	979

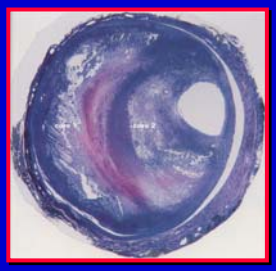
The primary end point is cardiovascular death, myocardial infarction, readmission for acute coronary syndrome, or stroke. CI indicates confidence interval; HR, hazard ratio.

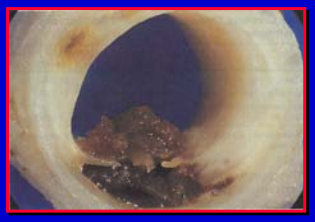
Figure 3. Estimates of Hazard Ratio for the Primary End Point Within the First 4 Months After Randomization and Between Months 4 and 24



CRP: 2.3 vs 1.7 at 4 mth (-26%, p<0.001)

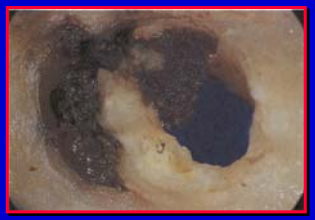
Atherosclerosis: Plaque Rupture → Thrombosis





Intraluminal

Intramural



Occlusive → Infarct