# Medical Management of Dyslipidemia
## Focus on LDL

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. Does treating lipoproteins reduce atherosclerosis & CV events?
2. Do different statins have differing impacts on CV events?
3. Do non-statins reduce CV events?
4. What are the roles of the <u>older</u> & newer therapies?

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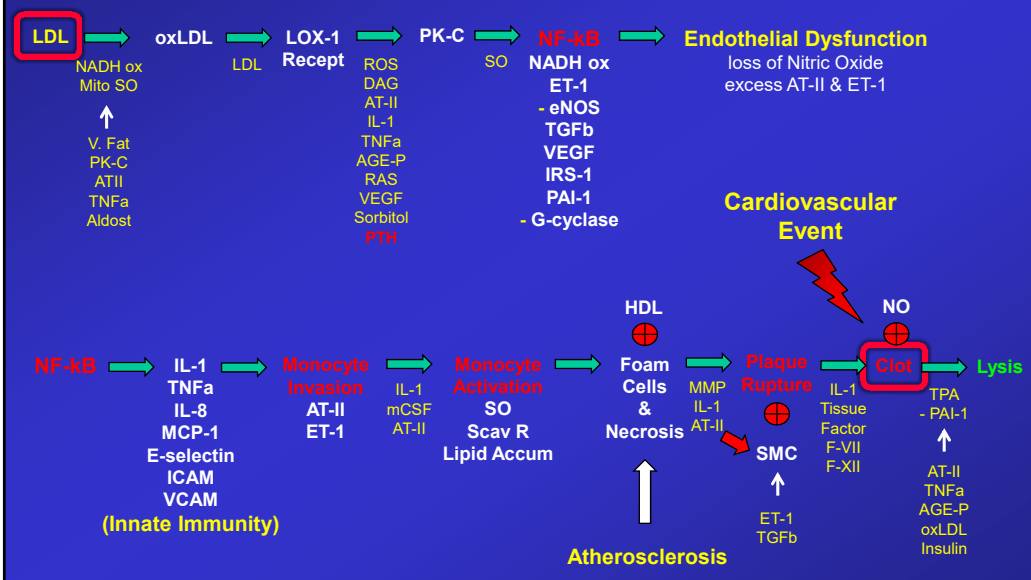
## Atherogenesis



# 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?

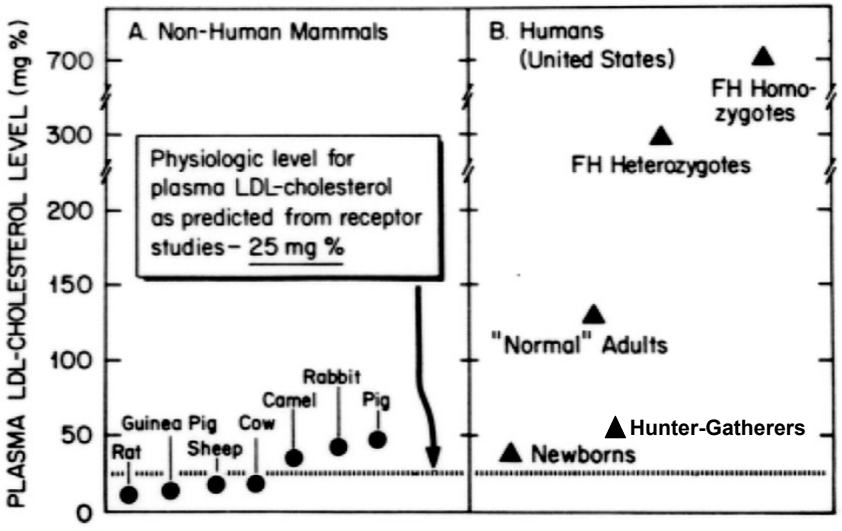
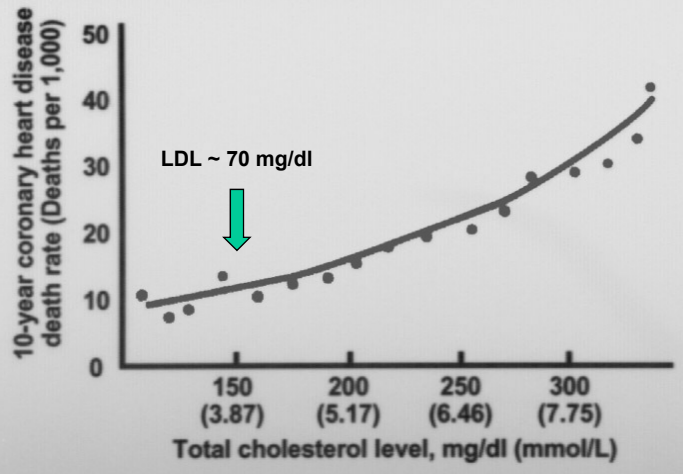



**FIG. 9.** Concentration of plasma LDL in various adult nonhuman mammalian species (panel **A**) as compared with that in normal newborns, normal human adults, and humans affected with the heterozygous and homozygous forms of FH (panel **B**). The estimated values for the adult nonhuman mammalian species 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

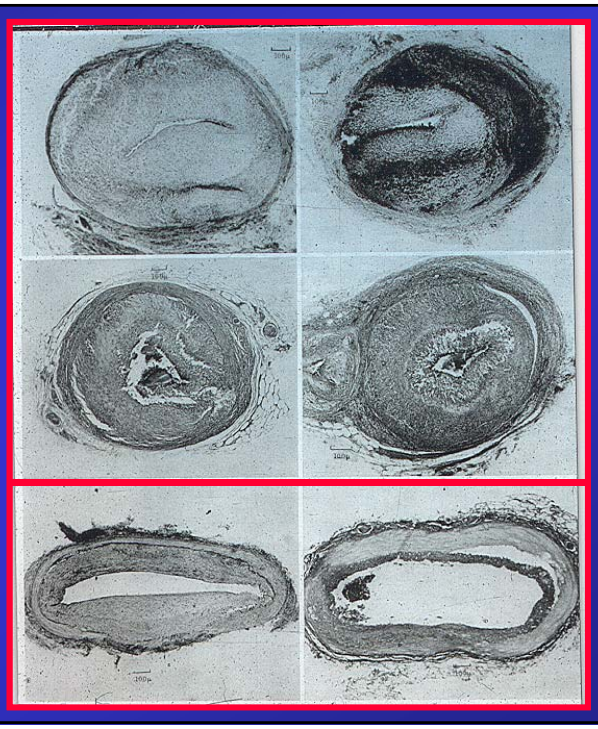
## Experimental Atherosclerosis

Rhesis Monkeys
(Normal chol 140 mg/dl)

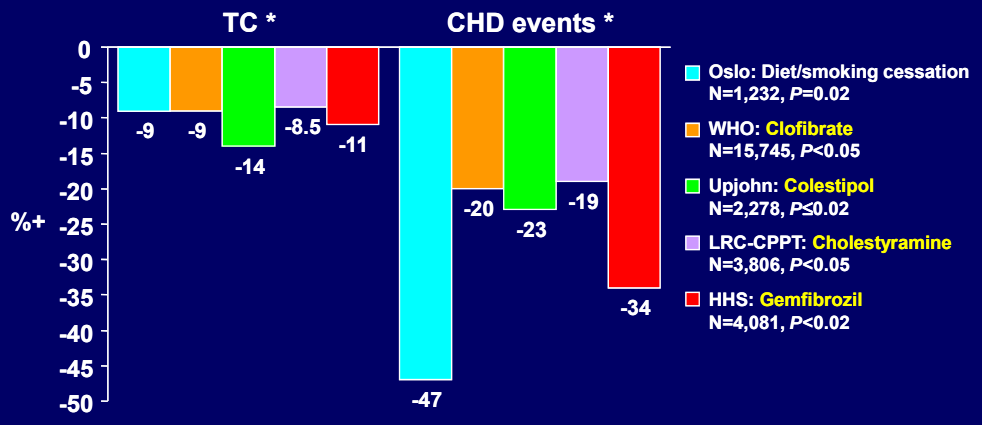
High fat diet 18 mths:
chol – 700 mg/dl

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

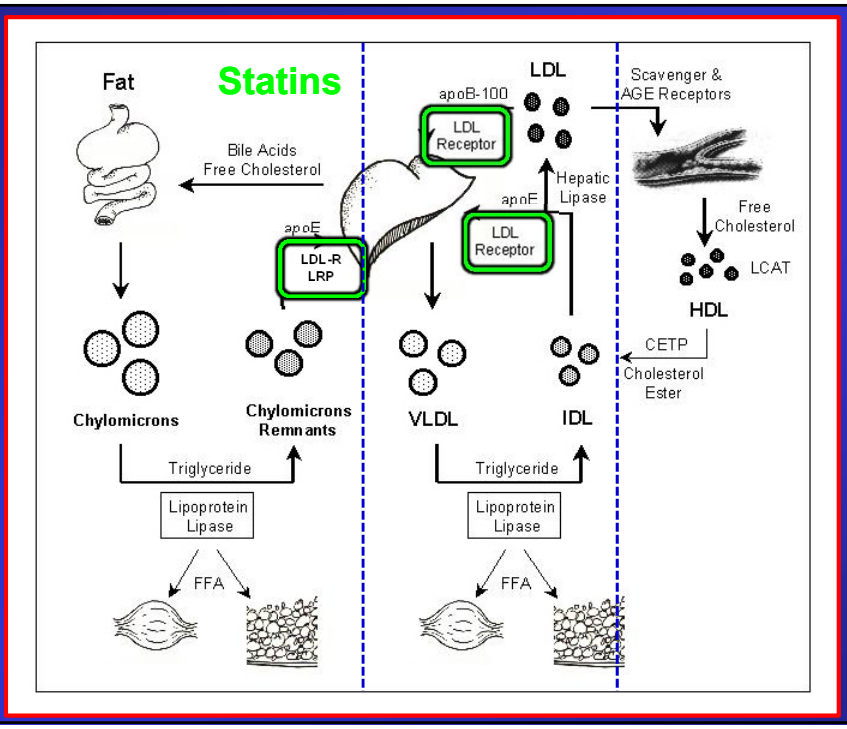



N=number enrolled.

* 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.

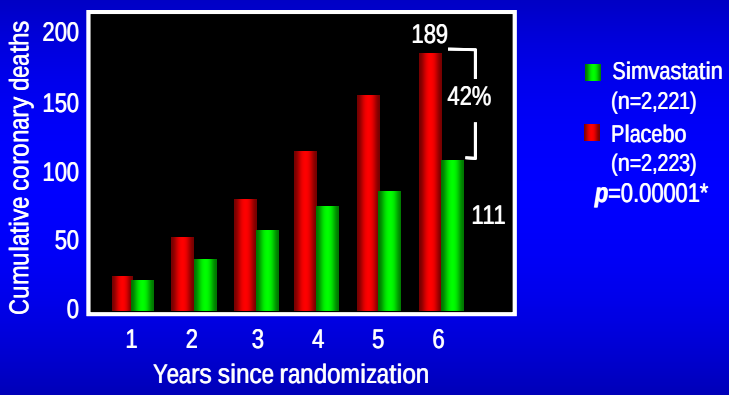




# Scandinavian Simvastatin Survival Study:

## "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.

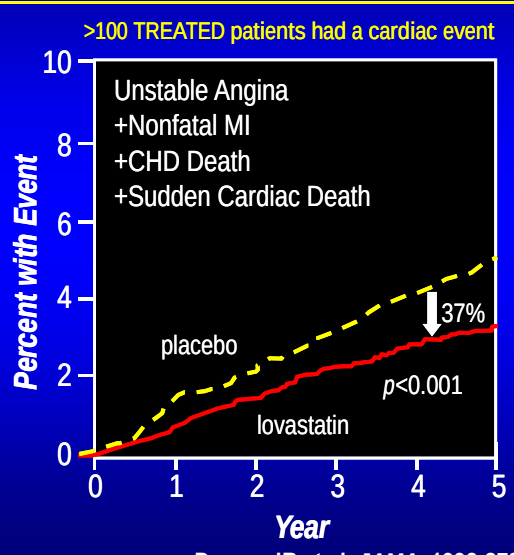
# AFCAPS/TexCAPS

Primary
Prevention

Low-Risk
Subjects

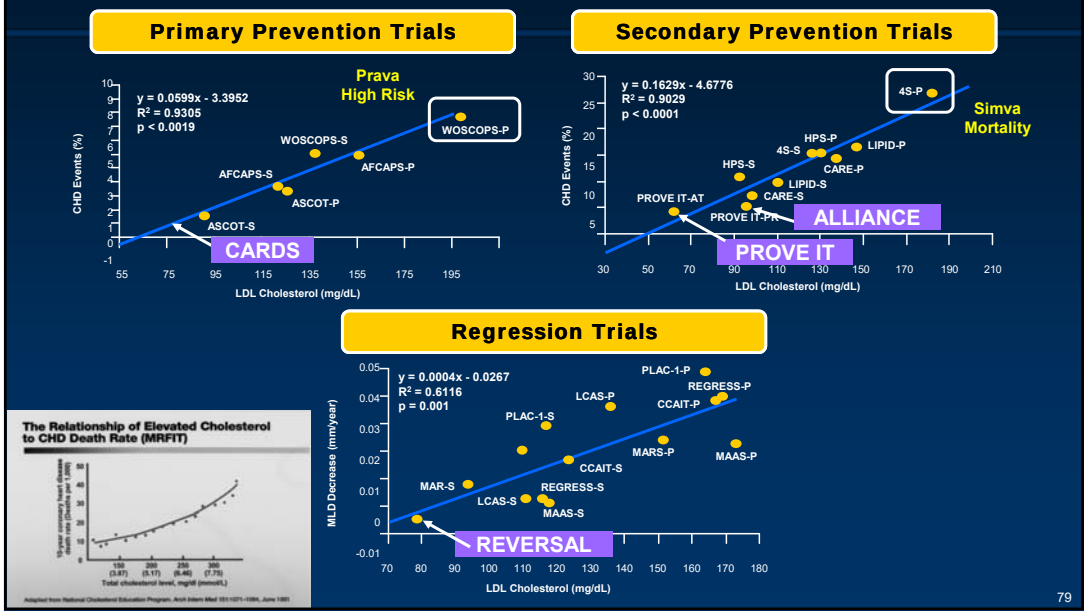
LDL
~150 mg/dL
vs
~115 mg/dL

(Lovastatin – 24%)



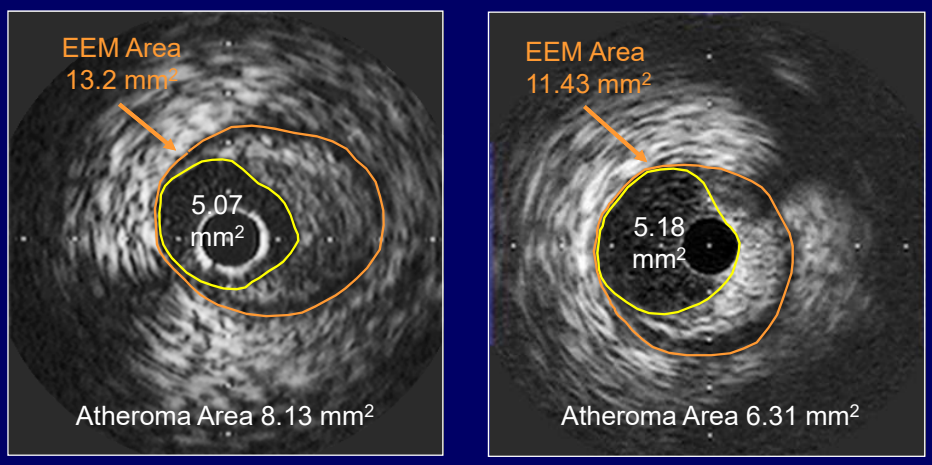

Downs JR et al. *JAMA*. 1998;279:1615-1622.

# Lowering LDL: CV Events & Atherosclerosis






# REVERSAL: Atheroma Regression

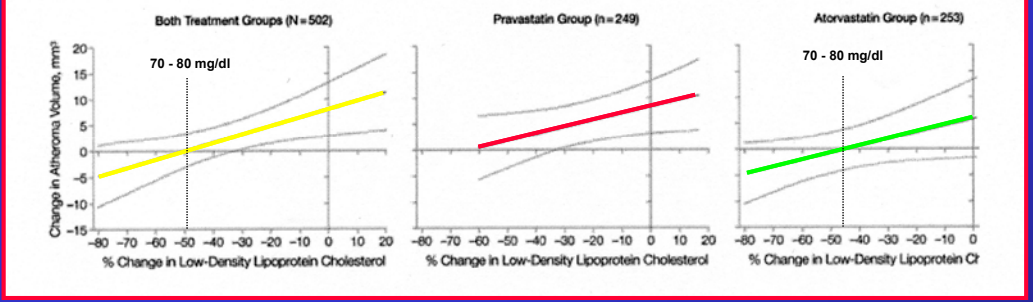



Adapted from Nissen SE, et al. *JAMA*. 2004;291:1071-1080.

# Intensive vs Moderate Lipid Lowering

## Coronary IV Ultrasound (Reversal Trial)

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



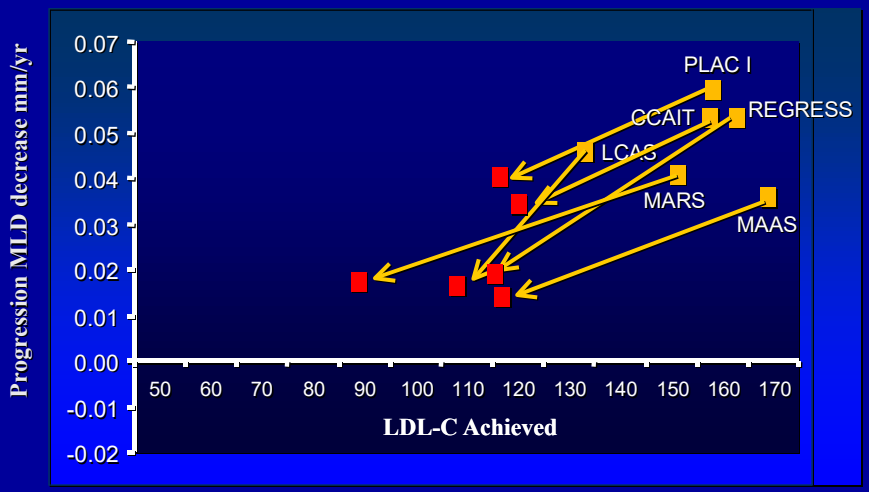

**502 Patients - 18 mths**
**Initial LDL 150 mg/dl**

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**

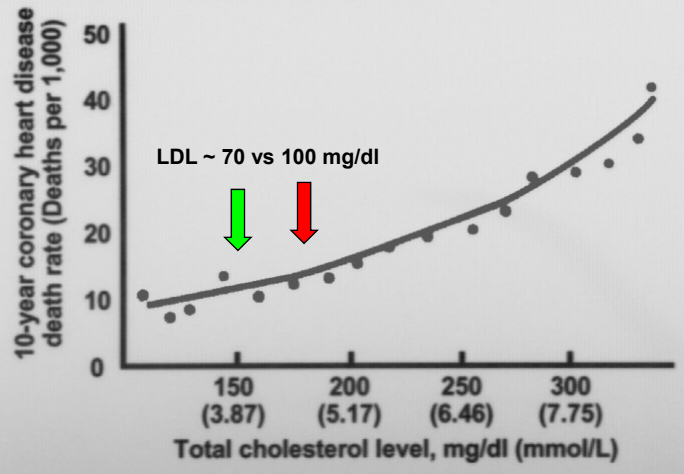
Carotid Ultrasound

## 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

## 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

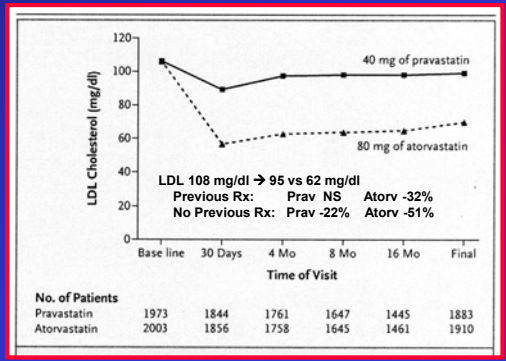
17.4% vs 14.8%, p=0.048 R.R=0.84
C.I.=0.701-0.999

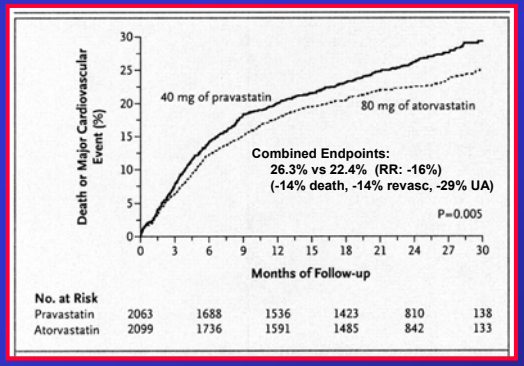
Worsening angina: 8.4% vs 6.4% p=0.02

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**

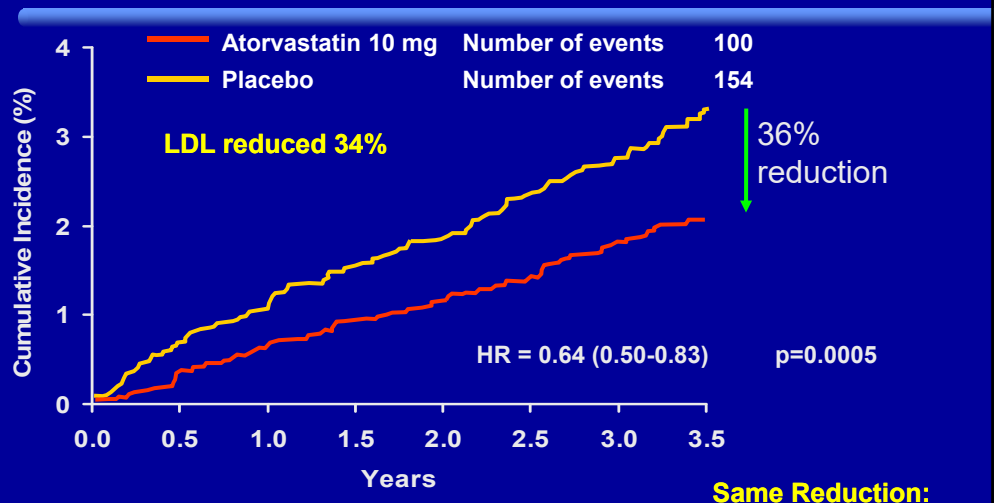
4162 pts: age 58, 78% M, 90% C, 50% HBP, 18% DM
LFTs: 1.1% prav, 3.3% ator
Myalgies: 2.7% prav, 3.3% ator

**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

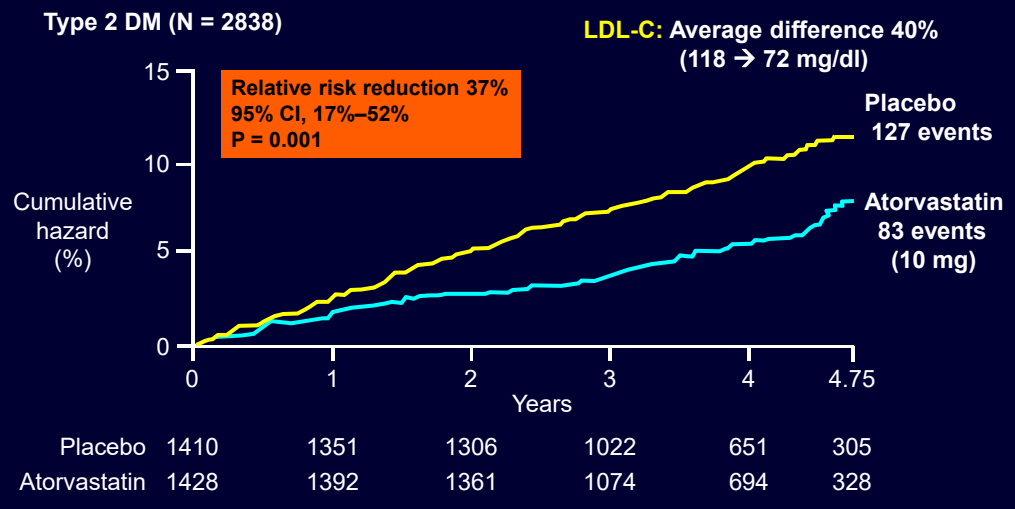



**Same Reduction: Pts > < 60 yrs**

*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)




**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 Lipid Lowering w/ Atorvastatin in Stable CVD: TNT

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

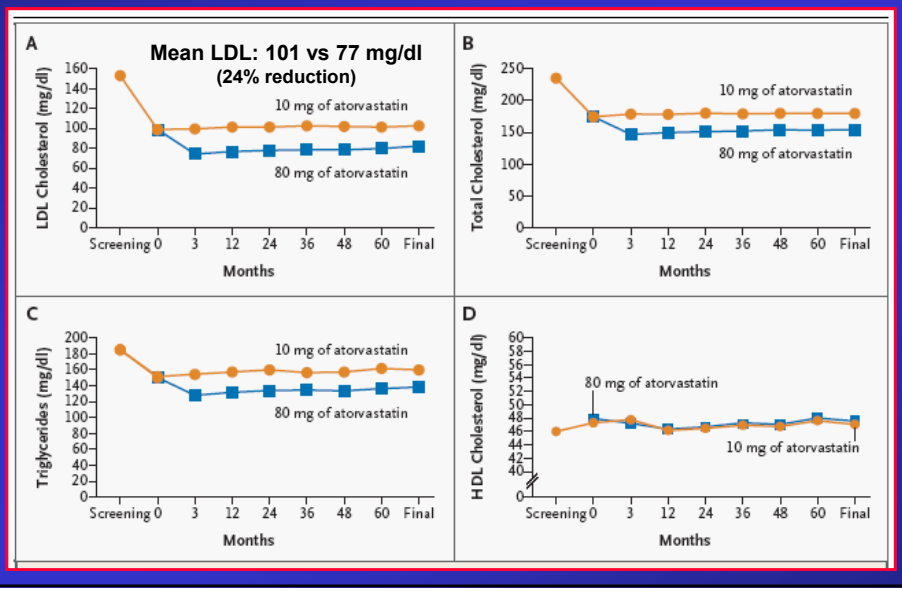
Compare
CV Events
LDL ~ 100
vs ~ 70
In Patients
with Advanced
Lesions

**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 |

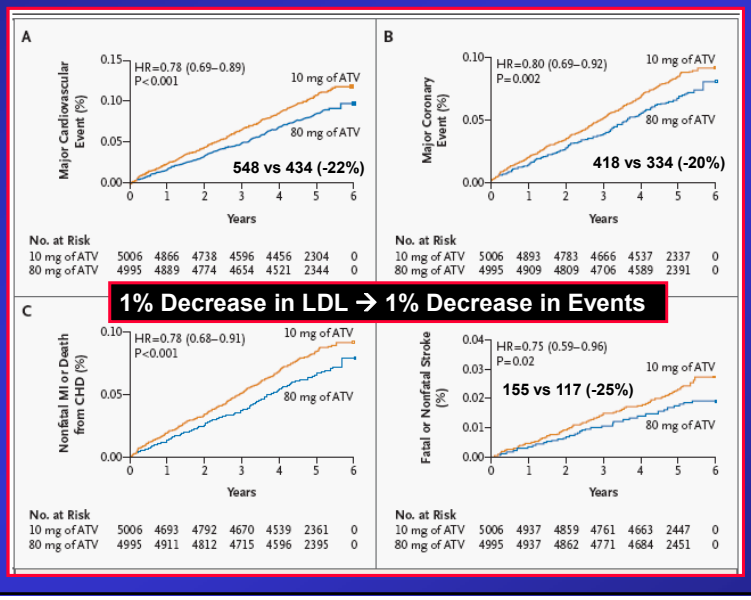
## Intensive Lipid Lowering w/ Atorvastatin in Stable CVD: TNT

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?**

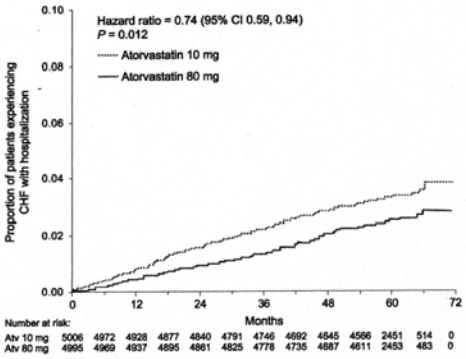



**Figure 1.** Proportion of patients in the 10- and 80-mg arms of TNT hospitalized with HF during follow-up. CI indicates confidence interval.

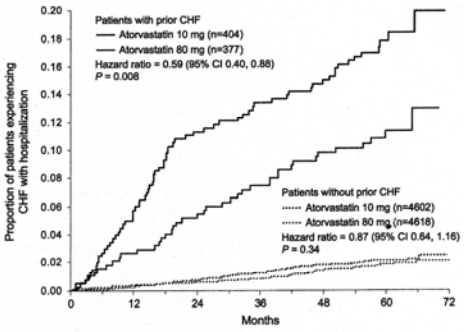


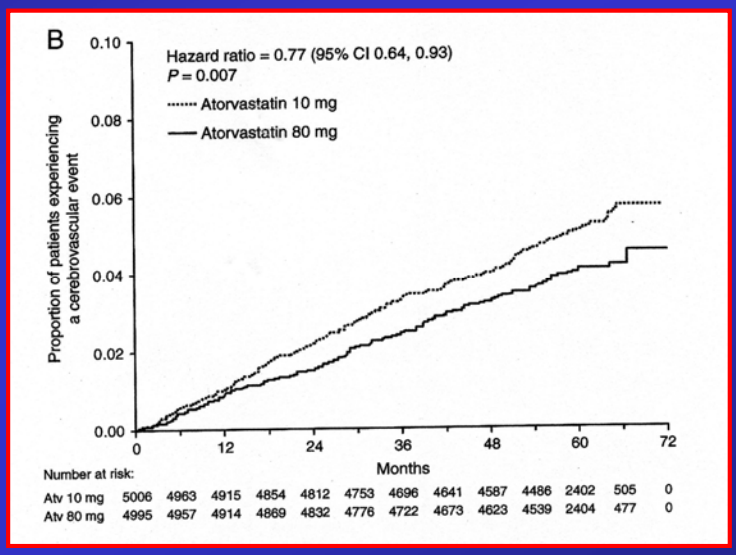

**Figure 2.** Proportion of patients with and without a history of HF in the 10- and 80-mg arms of TNT experiencing hospitalization for HF during follow-up. CI indicates confidence interval.

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)

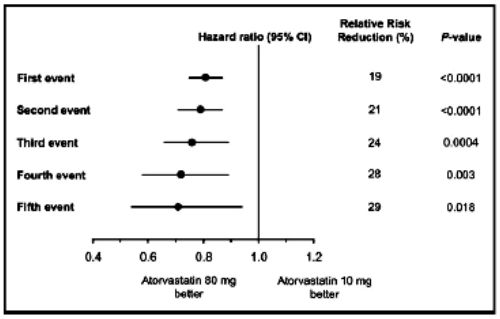



Figure 1. Risk decrease in cardiovascular events.

Amer J Cardiol 105:283–287, 2010

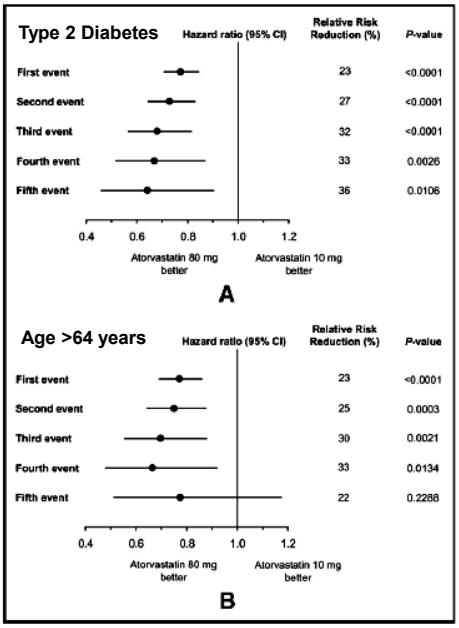
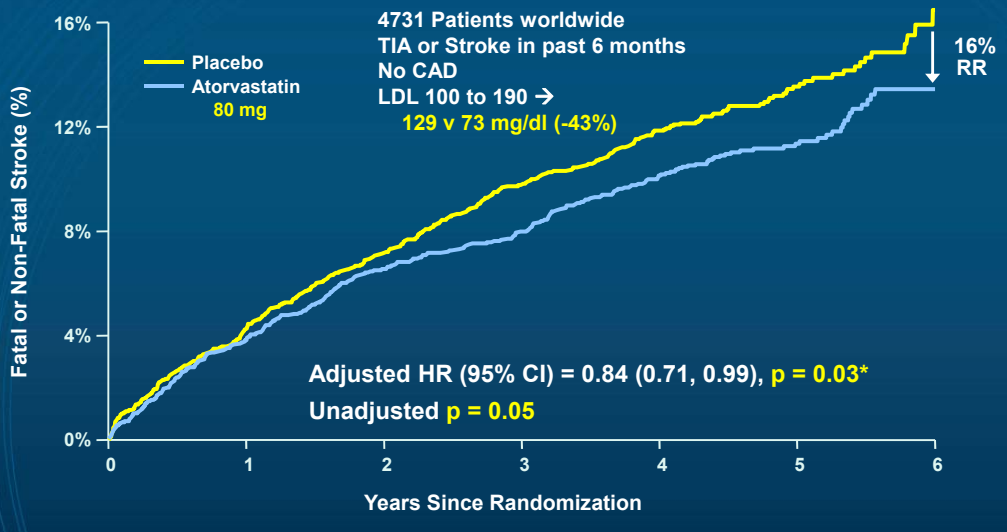


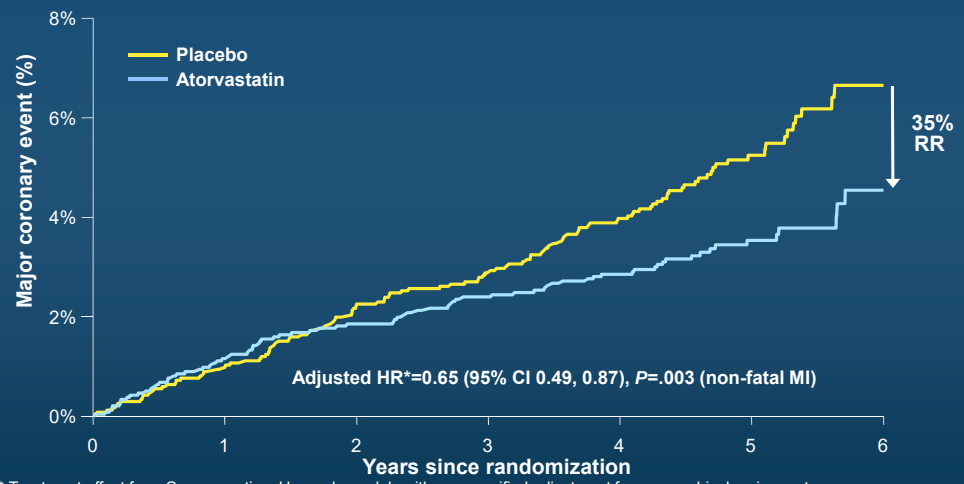

Figure 2. Risk decrease in cardiovascular events in patients (*A*) with type 2 diabetes and/or metabolic syndrome and (*B*) ≥65 years of age.

## 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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## 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+%

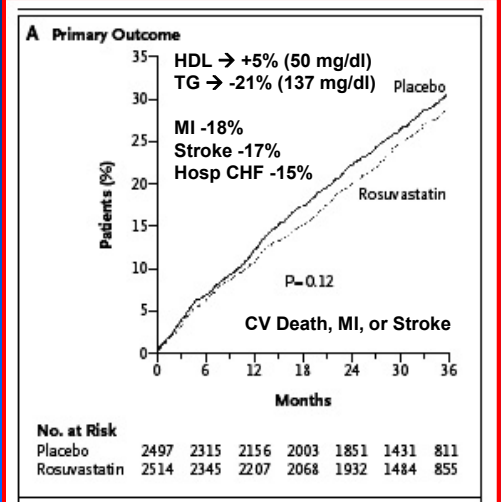
Many Renal Insuff

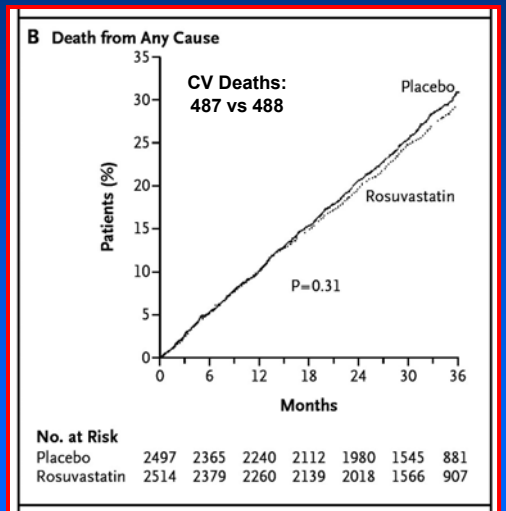
High hsCRP

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)



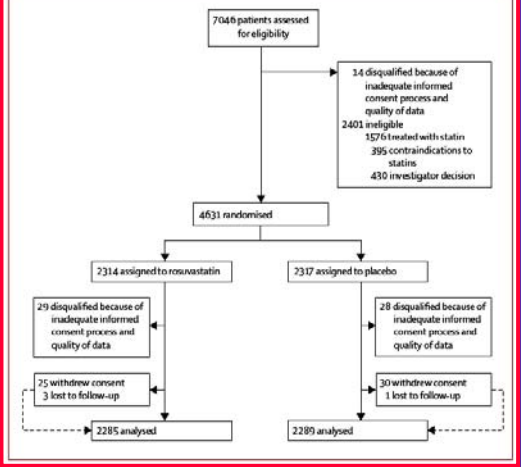




**45% difference in LDL → ~138 vs ~76 mg/dl**

## 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%) |

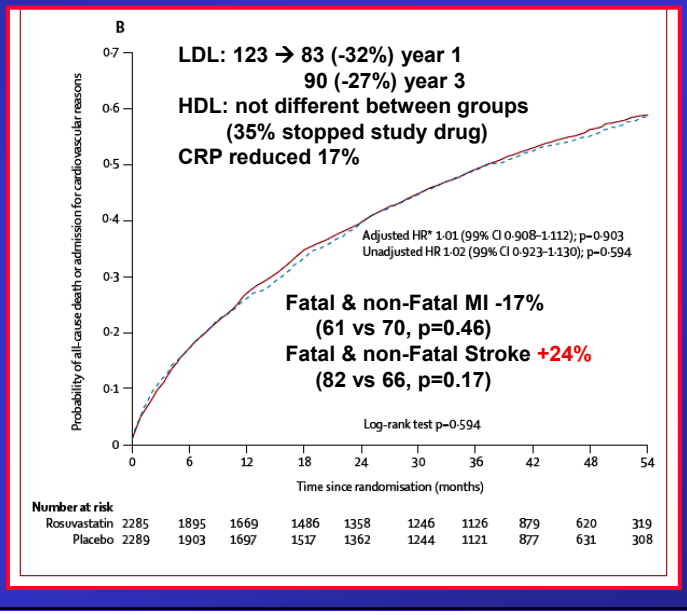
## GISSI-HF: Rosuvastatin in CHF

Age 68 ± 11
Men 77%

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

BP ~127/77

High hsCRP (2.71)

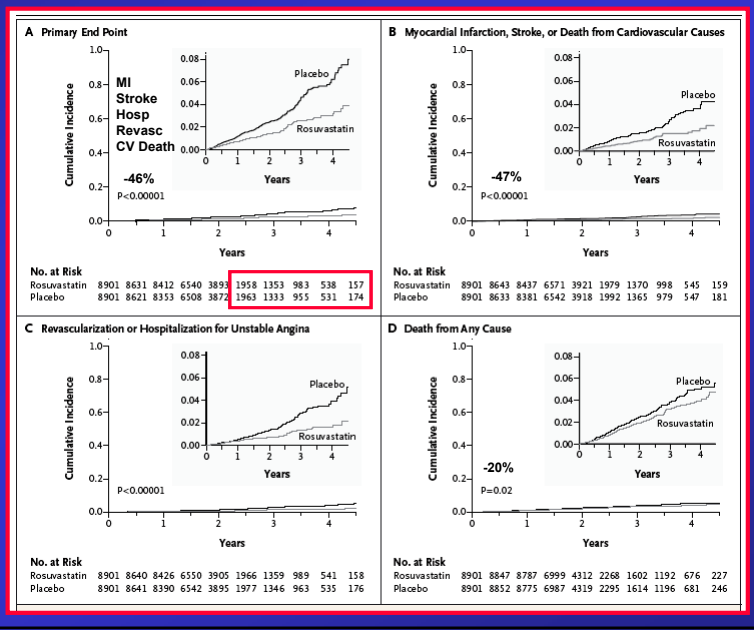


# **Jupiter:** Rosuvastatin 20 mg w/ CRP >2.0

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

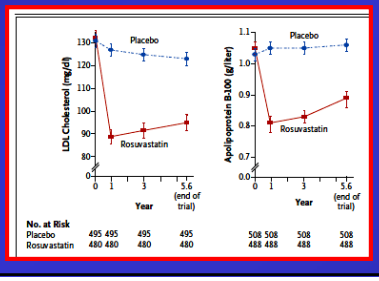



# **HOPE-3:** Rosuvastatin 10 mg - Intermediate CV Risk

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)



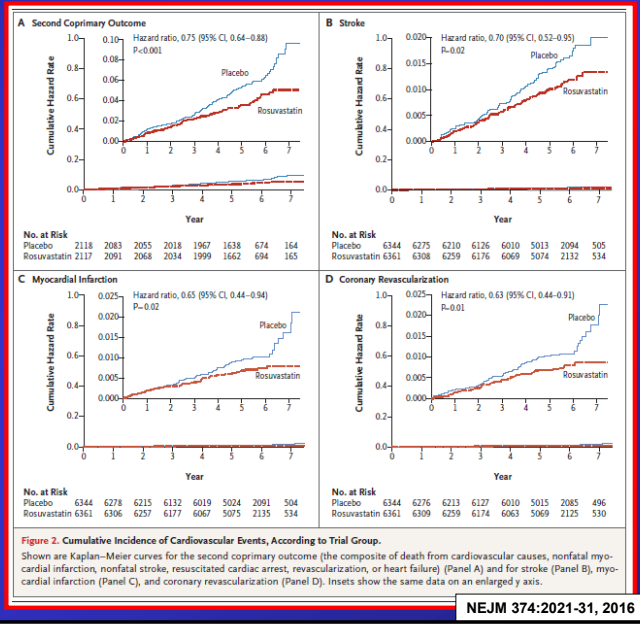




Figure 2. Cumulative Incidence of Cardiovascular Events, According to Trial Group.
Shown are Kaplan–Meier curves for the second coprimary outcome (the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, revascularization, or heart 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:**

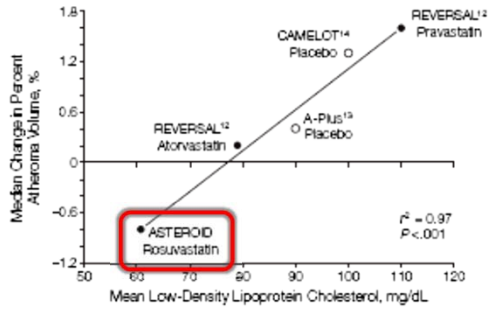
No control group
349 completed
125 dropped

LDL 130 → 61
-53%

HDL 43 → 49
+14%

TG 152 → 121
-20%

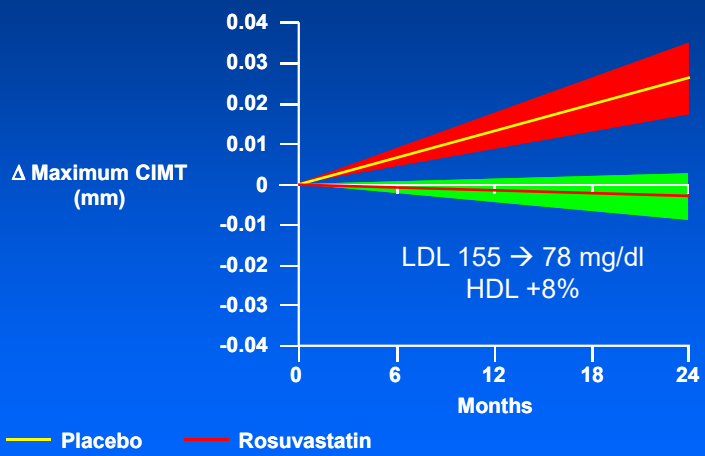
**Figure 3.** Relationship Between Mean Low-Density Lipoprotein Cholesterol Levels and Median Change in Percent Atheroma Volume for Several Intravascular Ultrasound Trials




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

## 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)**

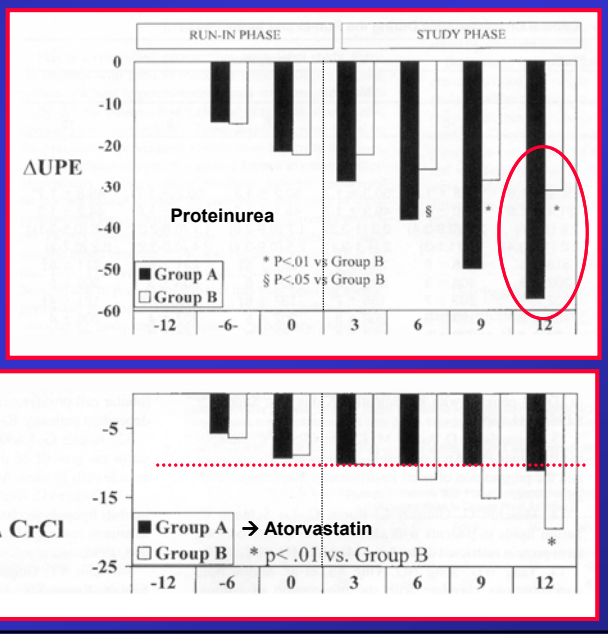
| | |
|---|---|
| Age | 55.6 yrs |
| CrCl | 50.4 ml/min |
| UPE | 2.2 g/day |
| LDL | 198 mg/dl → 121 |
| HDL | 36 mg/dl |
| Trig | 174 mg/dl → 132 |
| Album | 3.3 g/dl |

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







## LDL Targets vs Pleiotrophic Effects

### Acute Coronary Syndrome

The ultimate in advanced lesions

Obviously unstable

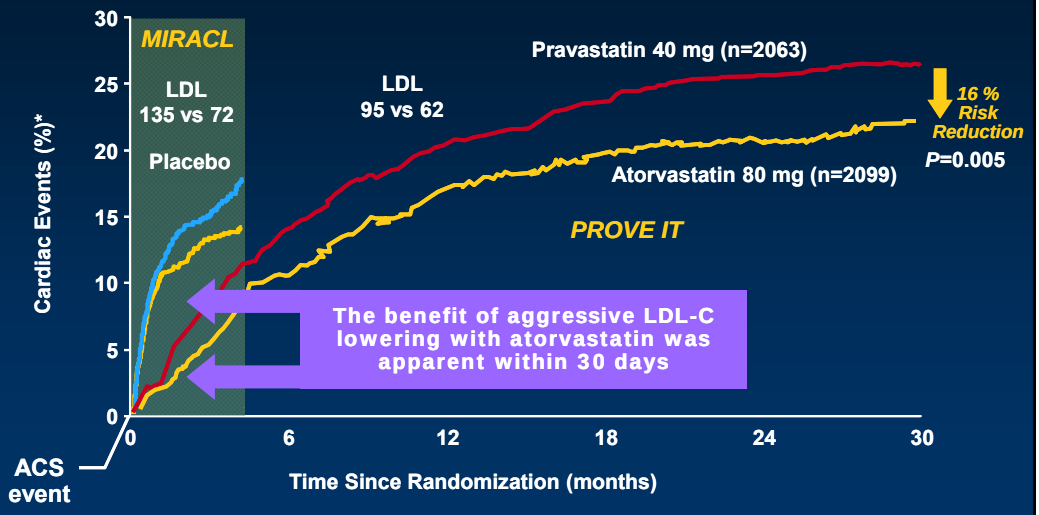
Major coagulation involvement

(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.

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## Early Intensive vs Delayed Conservative Simvastatin Strategy in Patients with ACS

Phase Z of the A to Z Trial

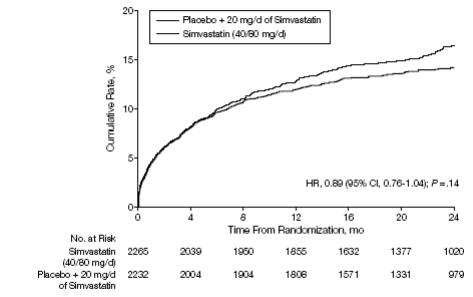

James A. de Lemos, MD
Michael A. Blazing, MD
Stephen D. Wiviott, MD
et al
for the A to Z Investigators


**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**

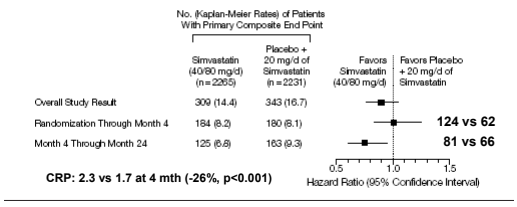

JAMA, Sept 15, 2004, Vol 292, No. 11 p **1307**


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



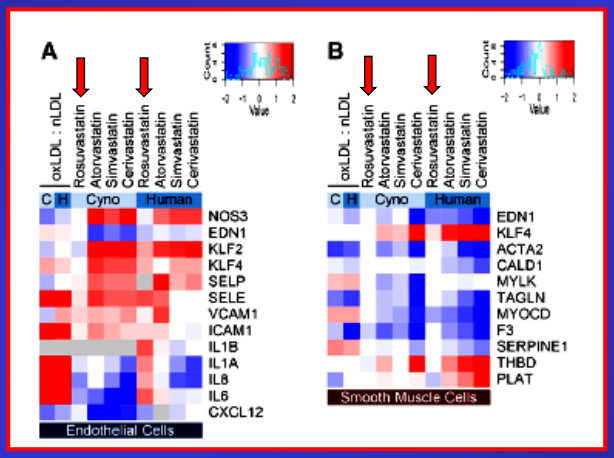

The primary end point is cardiovascular death, myocardial infarction, readmission for acute coronary syndrome, or stroke. CI indicates confidence interval; HR, hazard ratio.

**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)**

## 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

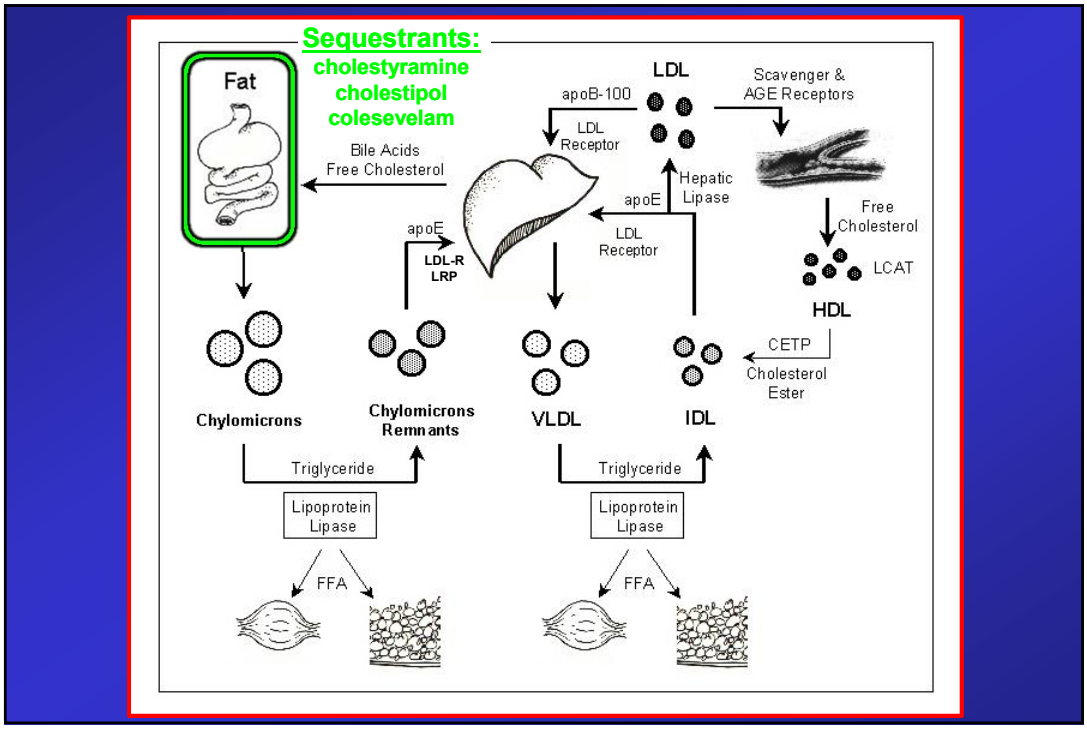
6k to 10k patients - follow for 4 to 12 months

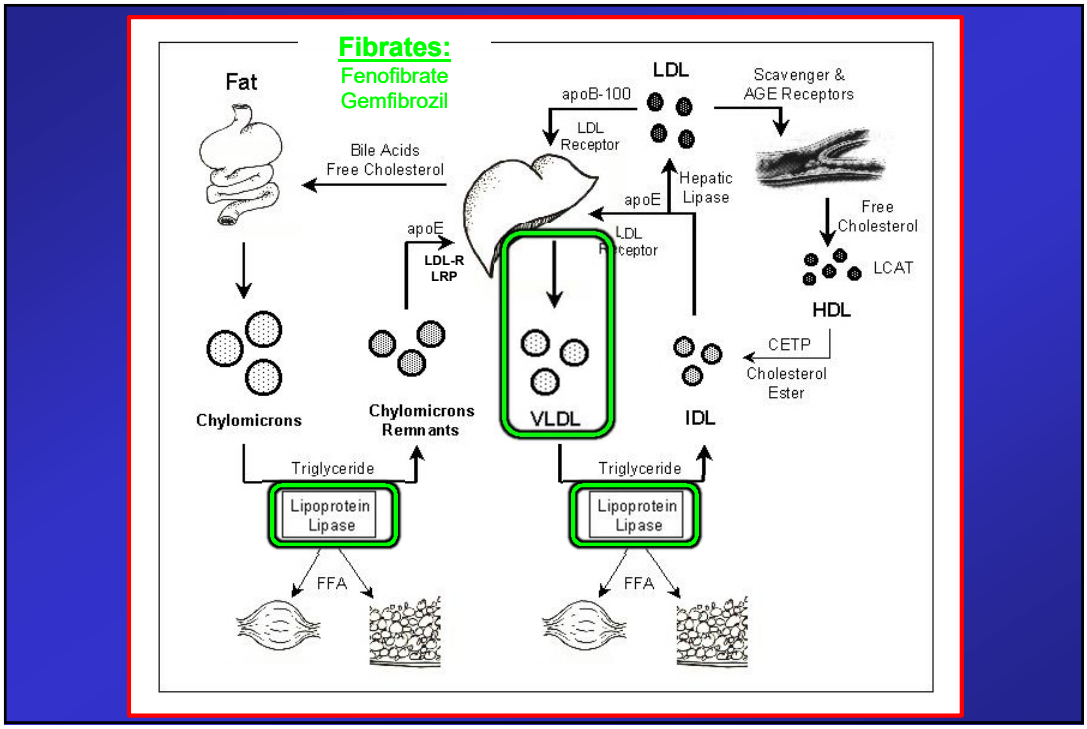
Randomize: Atorva 40 vs Simva 80 vs Rosuva 10

(40-50% reduction in LDL)

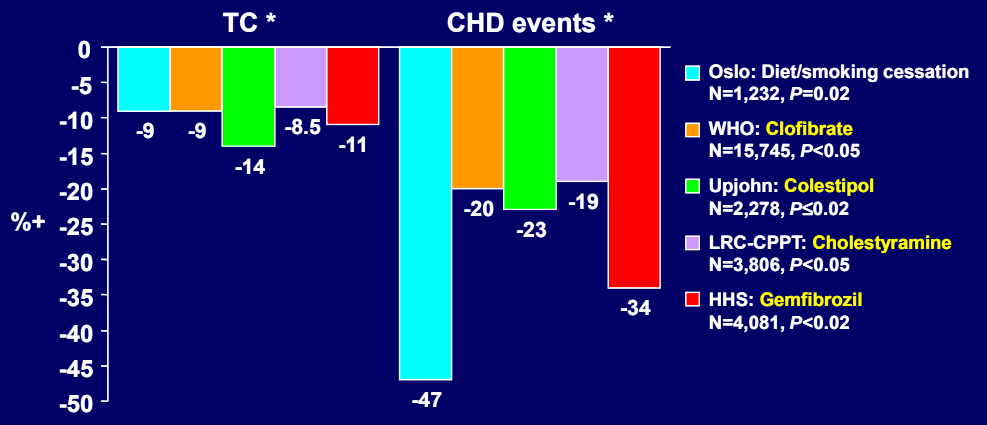
Endpoint: Non-fatal MI, Stroke, CV Death

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


Sequestrants:
cholestyramine
cholestipol
colesevelam
Fat
Bile Acids
Free Cholesterol
apoE
LDL-R
LRP
LDL
apoB-100
LDL
Receptor
Hepatic
Lipase
apoE
LDL
Receptor
Scavenger &
AGE Receptors
Free
Cholesterol
LCAT
HDL
CETP
Cholesterol
Ester
Chylomicrons
Chylomicrons
Remnants
VLDL
IDL
Triglyceride
Lipoprotein
Lipase
FFA
Triglyceride
Lipoprotein
Lipase
FFA


Fibrates:
Fenofibrate
Gemfibrozil
Fat
Bile Acids
Free Cholesterol
apoE
LDL-R
LRP
LDL
apoB-100
LDL
Receptor
Hepatic
Lipase
apoE
LDL
Receptor
Scavenger &
AGE Receptors
Free
Cholesterol
LCAT
HDL
CETP
Cholesterol
Ester
Chylomicrons
Chylomicrons
Remnants
VLDL
IDL
Triglyceride
Lipoprotein
Lipase
FFA
Triglyceride
Lipoprotein
Lipase
FFA

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




N=number enrolled.

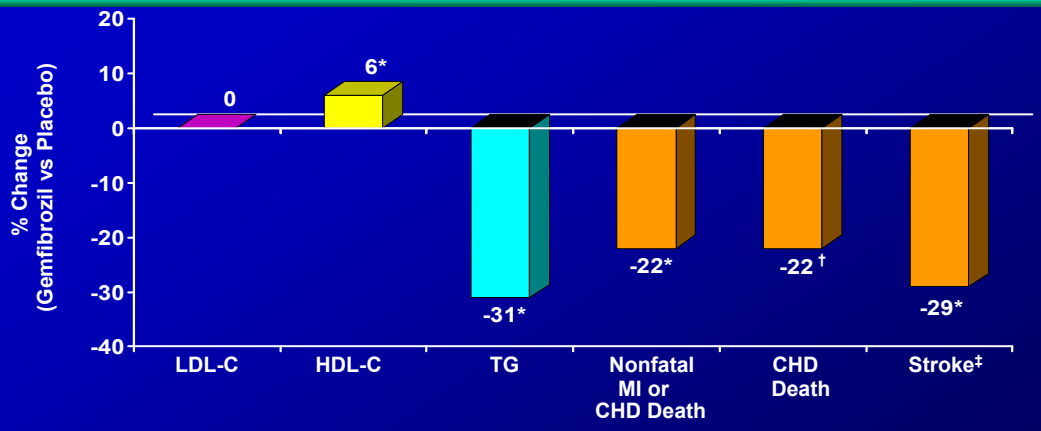
* Net difference between treatment and control groups (*P* values are for events).

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

NLEC™



# VA-HIT: Treating Dyslipidemia Beyond LDL-C Improves Clinical Outcomes




VA-HIT = Veterans Affairs High-Density Lipoprotein Intervention Trial.

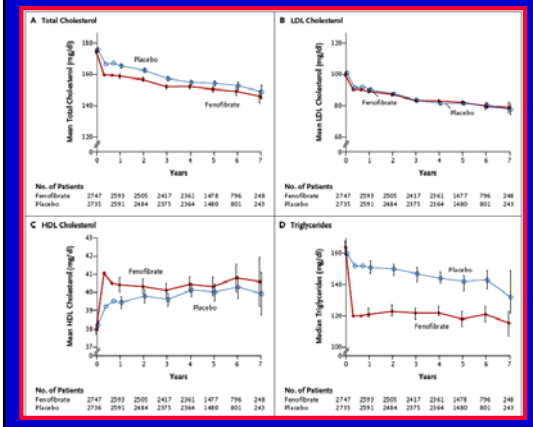
*$p \leq 0.05$. †$p = 0.07$. ‡Investigator-designated.

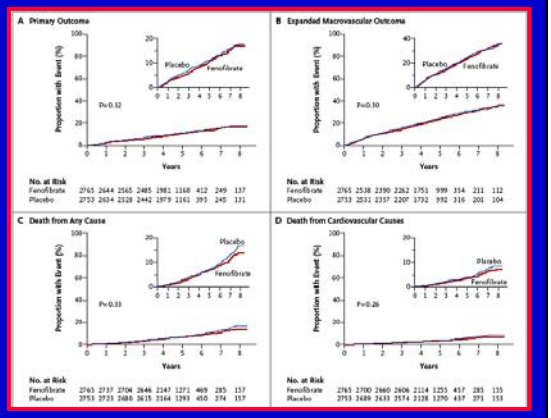
2531 men with CHD, HDL ≤40 mg/dL, and LDL ≤140 mg/dL were randomized to gemfibrozil (1200 mg/d) or placebo, and followed for a median of 5.1 years.

Rubins HB et al. *N Engl J Med*. 1999;341:410-418.

# Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus

The ACCORD Study Group*



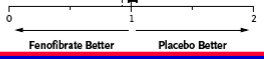

**5518 Diabetics:** 62 yo, 70% male, 68% cauc, BMI 32
CVD 37%, HgbA1c 8.3%, Statins 60%

NEJM: March 14, 2010

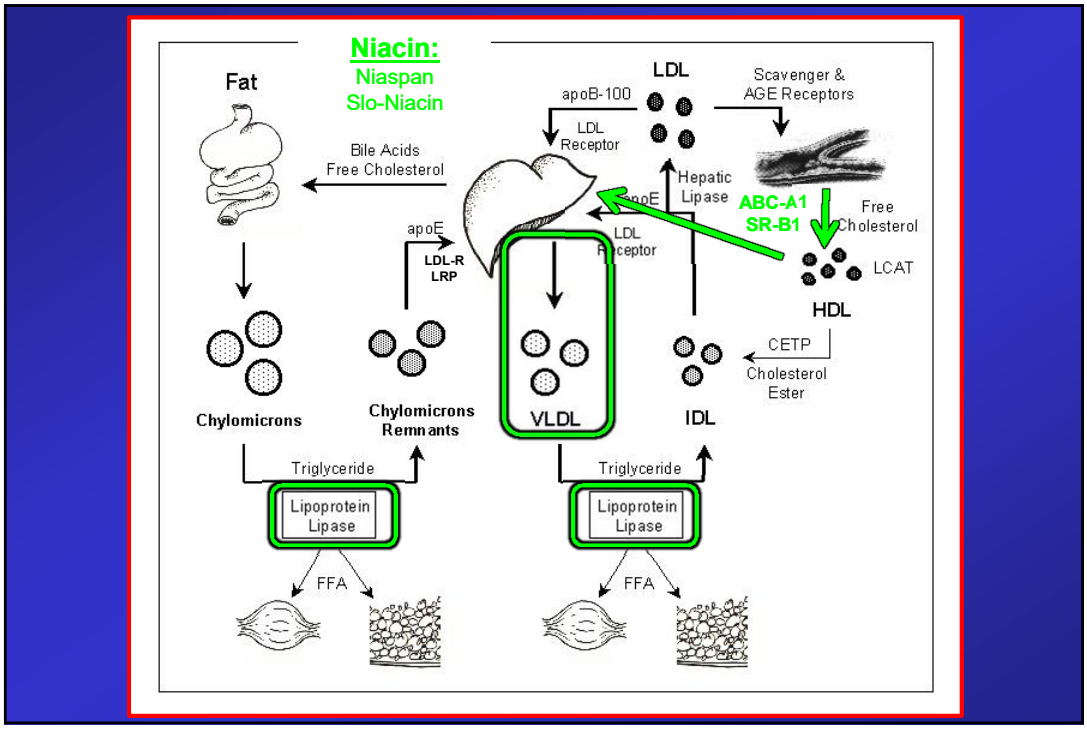
## Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus

ACCORD Study Group

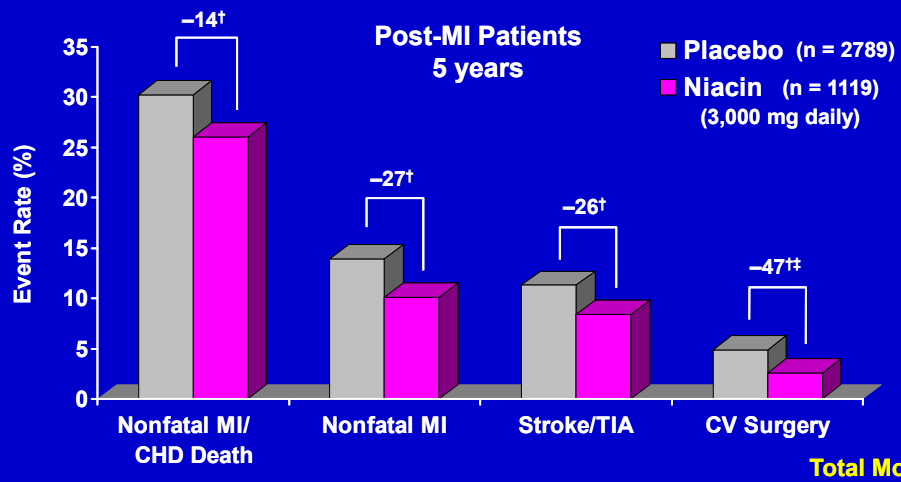
| Subgroup | Fenofibrate | Placebo | Hazard Ratio (95% CI) | P Value for Interaction |
|---|---|---|---|---|
| | % of events (no. in group) | | | |
| Overall | 10.52 (2765) | 11.26 (2753) | | |
| Sex | | | | 0.01 |
| Female | 9.05 (851) | 6.64 (843) | | |
| Male | 11.18 (1914) | 13.30 (1910) | | |
| Age | | | | 0.25 |
| <65 yr | 8.11 (1838) | 9.50 (1822) | | |
| ≥65 yr | 15.32 (927) | 14.72 (931) | | |
| Race | | | | 0.09 |
| Nonwhite | 9.70 (856) | 8.22 (888) | | |
| White | 10.90 (1909) | 12.71 (1865) | | |
| Previous cardiovascular disease | | | | 0.45 |
| No | 7.29 (1757) | 7.34 (1745) | | |
| Yes | 16.17 (1008) | 18.06 (1008) | | |
| Glycemia group | | | | 0.36 |
| Standard therapy | 10.14 (1391) | 11.61 (1370) | | |
| Intensive therapy | 10.92 (1374) | 10.92 (1383) | | |
| LDL cholesterol | | | | 0.12 |
| ≤84 mg/dl | 9.38 (938) | 12.23 (891) | | |
| 85–111 mg/dl | 9.85 (934) | 11.17 (922) | | |
| ≥112 mg/dl | 12.43 (877) | 10.57 (927) | | |
| HDL cholesterol | | | | 0.24 |
| ≤34 mg/dl | 12.24 (964) | 15.56 (906) | | |
| 35–40 mg/dl | 10.12 (860) | 9.47 (866) | | |
| ≥41 mg/dl | 9.08 (925) | 8.99 (968) | | |
| Triglycerides | | | | 0.64 |
| ≤128 mg/dl | 9.88 (891) | 11.29 (939) | | |
| 129–203 mg/dl | 10.50 (924) | 9.86 (913) | | |
| ≥204 mg/dl | 11.13 (934) | 12.84 (888) | | |
| Triglyceride–HDL cholesterol combination | | | | 0.06 |
| Triglyceride ≥204 mg/dl and HDL ≤34 mg/dl | 12.37 (485) | 17.32 (456) | | |
| All others | 10.11 (2264) | 10.11 (2284) | | |
| Glycated hemoglobin | | | | 0.20 |
| ≤8.0% | 8.69 (1324) | 10.56 (1335) | | |
| ≥8.1% | 12.20 (1435) | 11.94 (1415) | | |




NEJM: March 14, 2010




# Coronary Drug Project (CDP):
## Niacin - Clinical Outcomes*

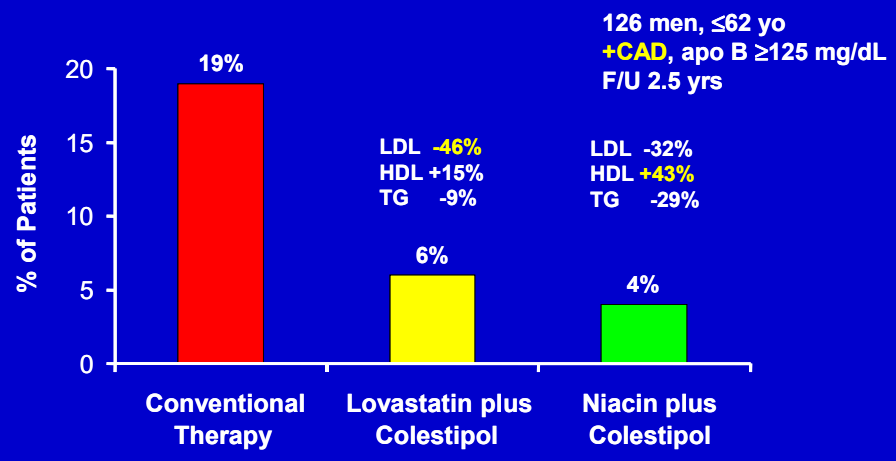



Total Mortality
15 yrs: -11%
p=0.0004

*Total follow-up, adjusted for baseline characteristics. †$p<0.05$. ‡ 5-yr rate.

Coronary Drug Project Research Group: *JAMA* 231:360-381, 1975

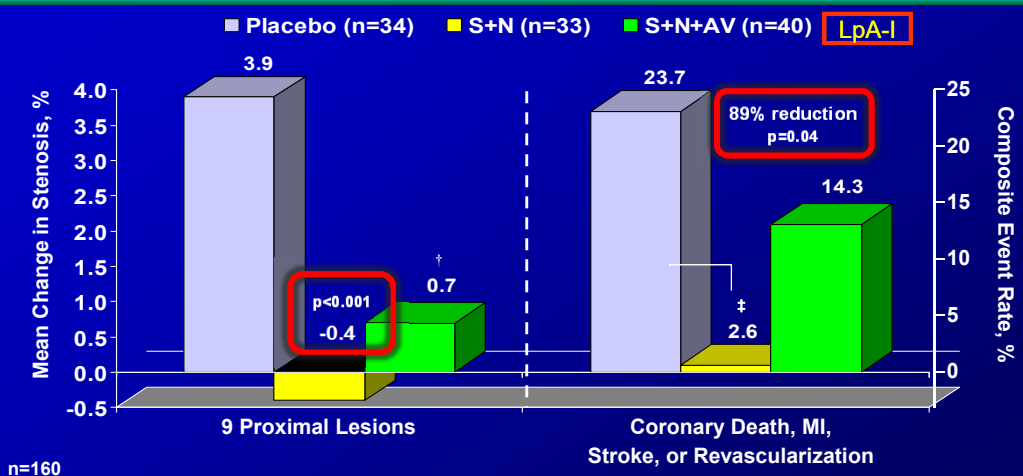
# FATS: Cardiac Events*



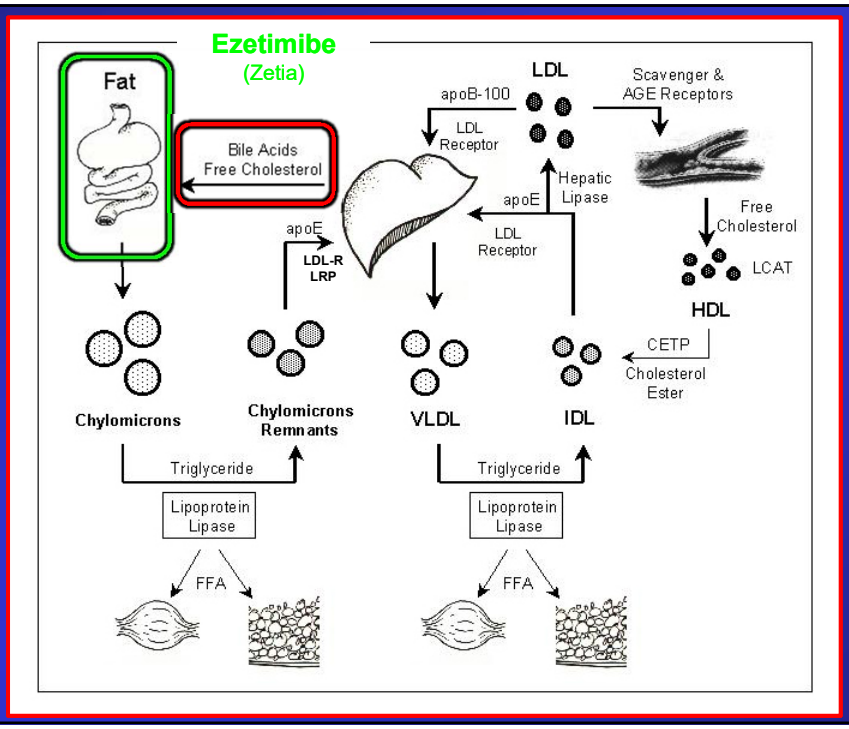

p= 0.01 for drug-treated versus conventional therapy.
*Includes death, MI, and revascularization.

*N Engl J Med* 323:1289-1298, 1990.

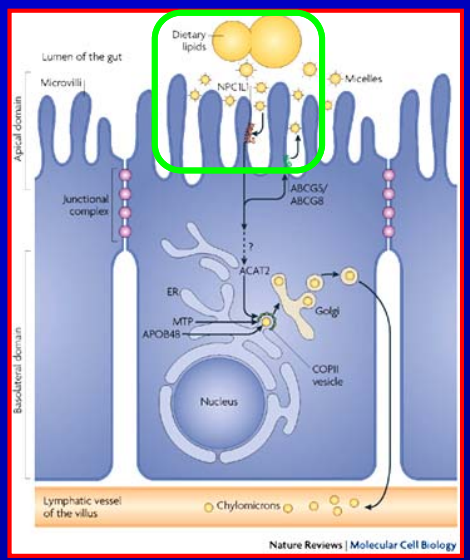
# HATS: Angiographic and Clinical Endpoints After 3 Years

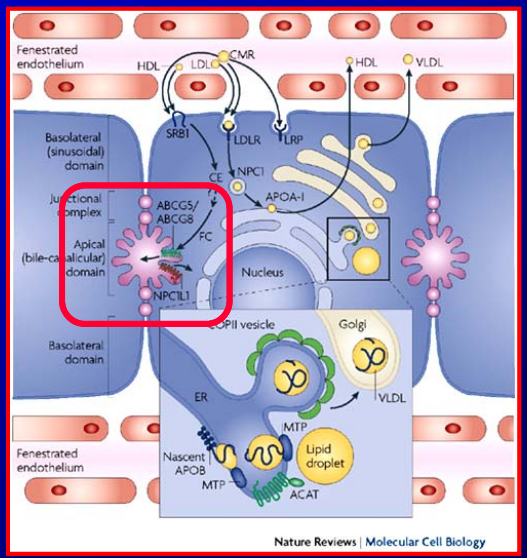



n=160
HATS = HDL-Atherosclerosis Treatment Study; S = simvastatin; N = niacin; AV = antioxidant vitamins.
*$p$<0.001 vs. placebo; †$p$<0.005 vs. placebo; ‡$p$=0.04 vs. placebo.
Brown BG, et al. *N Engl J Med.* 2001;345:1583-1592.




# NPC1L1 (Niemann–Pick C1-Like-1) protein




Ezetemibe inhibits NPC1L1 activity → reduces LDL-C ~20% & biliary cholesterol 'in vivo'

# ENHANCE: Familial Hypercholesterolemia → Zetia

| Baseline LDL 319 mg/dl<br>706 pts | Ezeti/simva 10/80<br>LDL - 58% (134) | Simva 80 mg<br>LDL - 41% (188) | 24 mths<br>80% prior statins |
|---|---|---|---|
| Change in mean CIMT (mm) | + 0.0111 | + 0.0058 | p = 0.29 |
| Baseline mean CIMT (mm) | 0.68 | 0.69 | |

| | | |
|---|---|---|
| CV Deaths | 2/357 | 1/363 |
| Non-fatal MI | 3/357 | 2/363 |
| Non-fatal Stroke | 1/357 | 1/363 |
| Revascularizations | 6/357 | 5/363 |
| Elevated CPK's (> 10x ULN) | 4/356 (1.1%) | 8/360 (2.2%) |

Merck/Schering-Plough Press Release – Jan 14, 2008

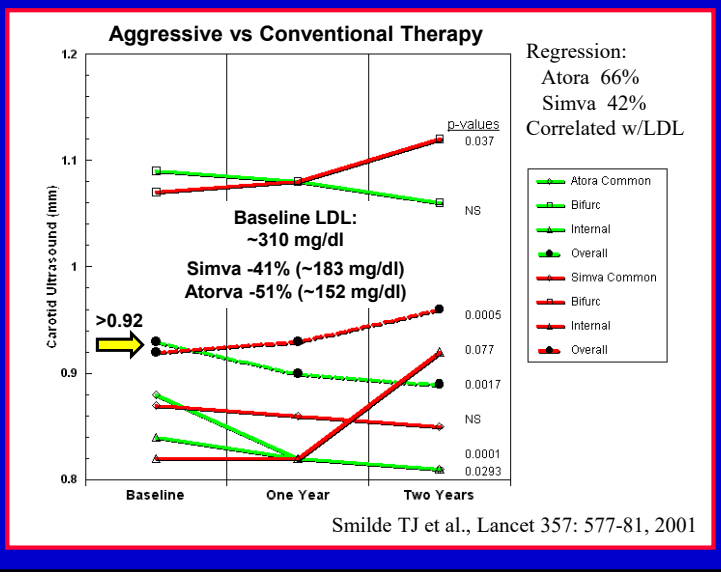
# ASAP: Carotid Ultrasound

Atorvastatin (80 mg) vs Simvastatin (40 mg)

**Familial Hyperchol:**
- Pt#: 160 vs 165
- Age 48±10
- BMI 26±3
- SBP 131±16
- DBP 78±8
- CVD 31%
- Smokers 32%
- Previous Rx 71%
  - **8 wk placebo run-in**
  - **14% dropout**
  - **80% compliance**

Myalgias: 16 vs 17
No severe +CPK
Mild GI Sxs: 18 vs 16

Resins used (LDL>309):
Atorva 4 vs Simva 25




Smilde TJ et al., Lancet 357: 577-81, 2001

# ENHANCE: Familial Hypercholesterolemia

| Baseline LDL 319 mg/dl<br>706 pts | Ezeti/simva 10/80<br>LDL - 58% (134) | Simva 80 mg<br>LDL - 41% (188) | 24 mths<br>80% prior statins |
|---|---|---|---|
| Change in mean CIMT (mm) | + 0.0111 | + 0.0058 | p = 0.29 |
| Baseline mean CIMT (mm) | 0.68 | 0.69 | |

| | | |
|---|---|---|
| CV Deaths | 2/357 | |
| Non-fatal MI | 3/357 | |
| Non-fatal Stroke | 1/357 | |
| Revascularizations | 6/357 | 5/363 |
| Elevated CPK's (> 10x ULN) | 4/356 (1.1%) | 8/360 (2.2%) |

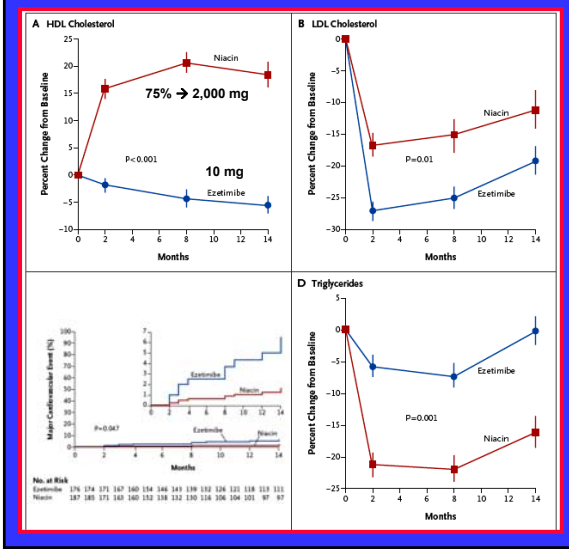
**Theories:**

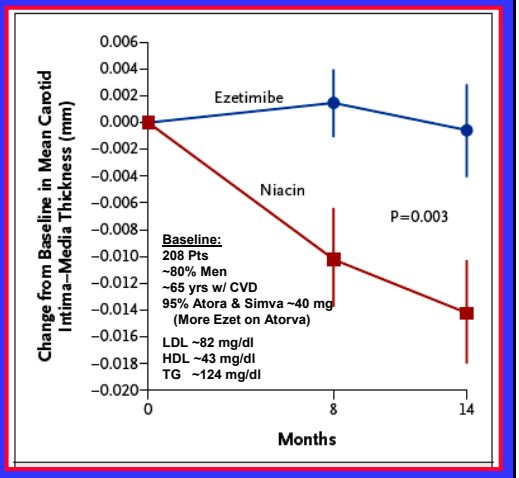
1. **Lipid Hypothesis is wrong**
2. **This is LDL-resistant population**
3. **An adverse effect countered LDL**

Merck/Schering-Plough Press Release – Jan 14, 2008

## Extended-Release Niacin or Ezetimibe and Carotid Intima–Media Thickness

Allen J. Taylor, M.D., Todd C. Villines, M.D., Eric J. Stanek, Pharm.D., Patrick J. Devine, M.D., Len Griffen, M.D., Michael Miller, M.D., Neil J. Weissman, M.D., and Mark Turco, M.D.




Arbiter 6 - NEJM 361: Nov 15, 2009

## Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes

**Cannon et al: NEJM 372(25): 2387-97, 2015**

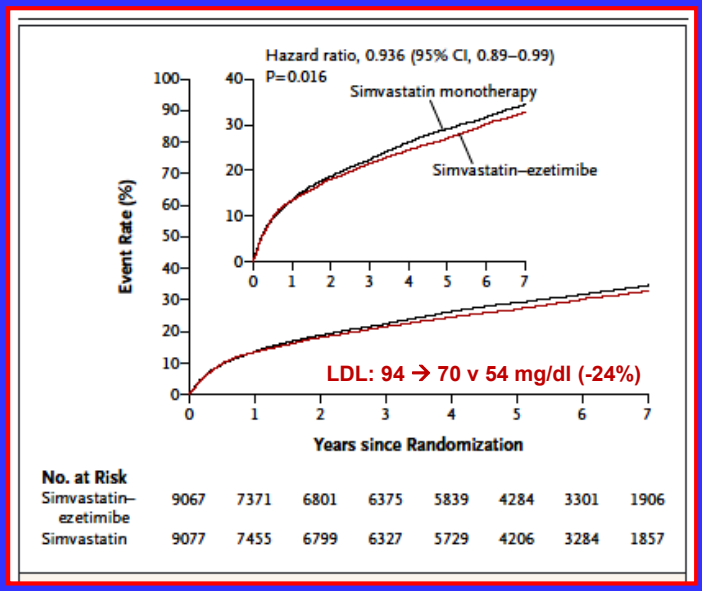
**Acute Coronary Syndrome**
75% AMI, 25% Unstable Angina
9,000+ per group

Age ~64 yrs
Male ~76%
BMI ~28
Diabetic ~27%
Smokers ~33%

Past Events:
MI ~21%
PCI ~20%
CABG ~9%

Individual Events:
Any MI: → 13% p=0.002
Ischemic Stroke: → 21% p=0.008
Urgent Revasc: → 19% p=0.001
CV Death: → 10% p=0.003

Safety Endpoints: NS

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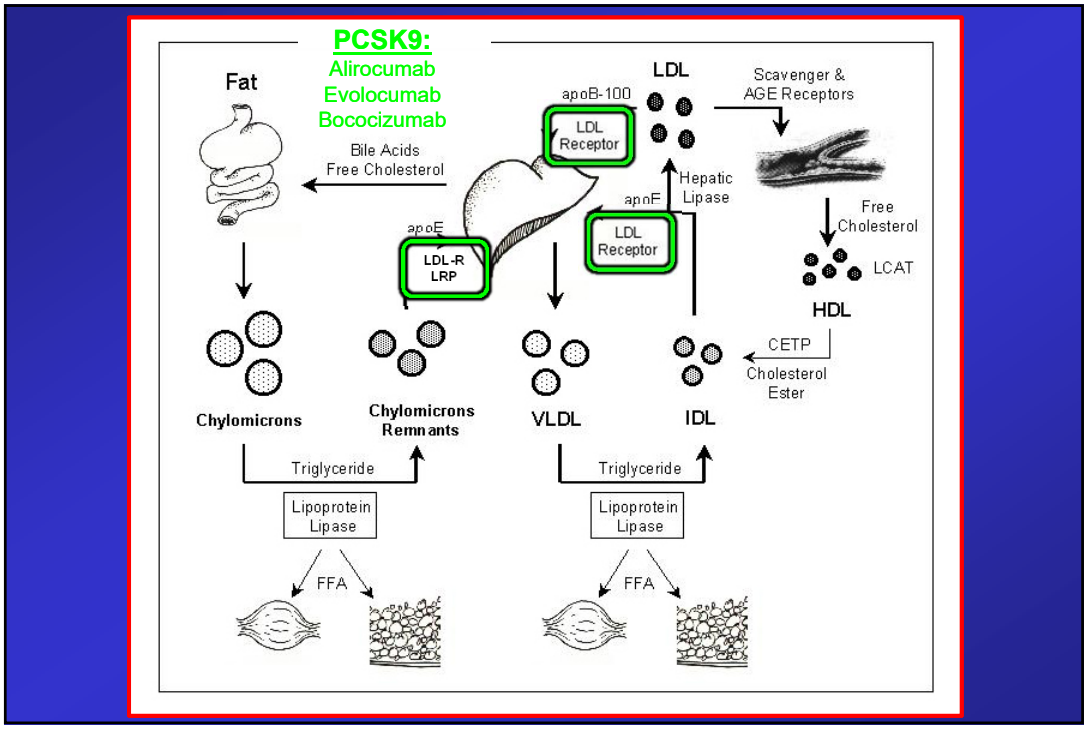
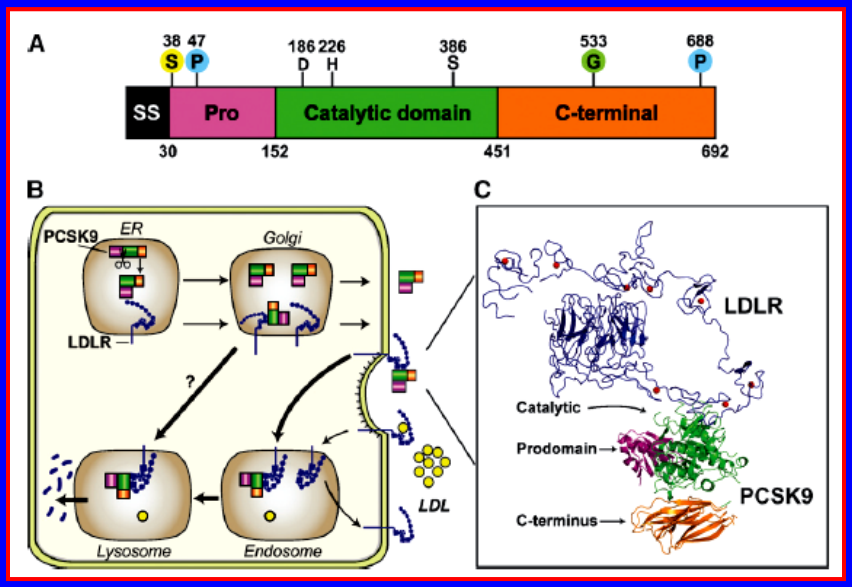
Safety Endpoints: NS

| Characteristic | Total Patients | KM % at 7 years SIMVA/EZE | KM % at 7 years SIMVA | Hazard Ratio (95% CI) | Interaction *P*-Value |
|---|---|---|---|---|---|
| Diabetes | | | | | |
| Yes | 4933 | 40.04 | 45.51 | 0.856 (0.779, 0.939) | 0.023 |
| No | 13202 | 30.16 | 30.84 | 0.977 (0.915, 1.044) | |
| Gender | | | | | |
| Male | 13728 | 33.26 | 34.87 | 0.952 (0.895, 1.012) | 0.267 |
| Female | 4416 | 31.01 | 34.02 | 0.885 (0.791, 0.991) | |
| Age Group 1 (years) | | | | | |
| <65 | 10173 | 29.94 | 30.79 | 0.975 (0.904, 1.051) | 0.098 |
| ≥65 | 7971 | 36.35 | 39.94 | 0.890 (0.824, 0.961) | |
| Age Group 2 (years) | | | | | |
| <75 | 15346 | 31.67 | 32.46 | 0.971 (0.915, 1.031) | 0.005 |
| ≥75 | 2798 | 38.95 | 47.60 | 0.797 (0.704, 0.902) | |

**Older, Diabetic Women**




## Antibody to PCSK9 in Primary Hypercholesterolemia

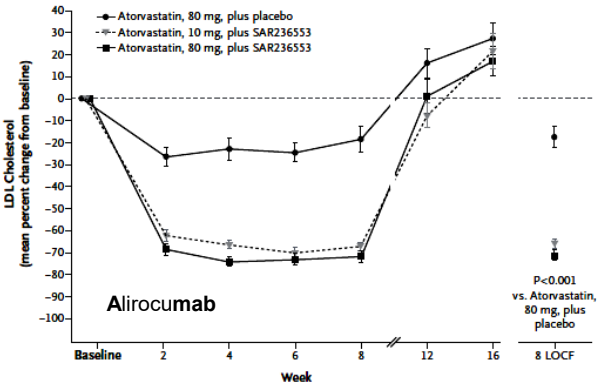



Horton et al: J Lipid Res 50: S172–S177, 2009

# Antibody to PCSK9 in Primary Hypercholesterolemia

**90 Day Cost:**
**$1,335.40**
**w/ discount**

**Atorvastatin**
**80 mg**
**$18.38**
**+**
**Slo-Niacin**
**2,000 mg**
**$46.80**
**or**
**Ezetimibe**
**10 mg**
**$21.21**




| No. of Patients | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Atorvastatin, 80 mg, plus placebo | 29 | 29 | 27 | 25 | 24 | 25 | 21 | 29 |
| Atorvastatin, 10 mg, plus SAR236553 | 29 | 29 | 26 | 26 | 27 | 27 | 24 | 29 |
| Atorvastatin, 80 mg, plus SAR236553 | 30 | 29 | 28 | 28 | 28 | 27 | 27 | 30 |

**Figure 1. Mean Percent Change from Baseline in Low-Density Lipoprotein (LDL) Cholesterol Levels, According to Treatment Group.**

N Engl J Med 367:1891-1900, 2012

# Medical Management of Dylipidemia

- Observations:
  - oxLDL induces oxidation, inflammation, innate immunity, & atherosclerosis
  - Statins reduce both LDL and inhibit various steps in the oxidative, inflammatory, and coagulation pathways
- Lowering LDL does reduce AS and CV events
  - Exceptions: Ezetimide failed to show an impact on carotid atherosclerosis (x2)
  - (Did reduce CV events in one study)
  - Rosuvastatin failed to reduce CV events in 3 of 5 studies
  - (Does reduce plaques by ultrasound)
- Atorvastatin may be uniquely beneficial in:
  - Advanced disease, ACS, & CHF (compared to simvastatin, pravastatin, rosuvastatin)
- Therapy: Statins (At > Si > Pr > Pi > Ro) → Niacin &/or Fibrate ($24.44) (TGs) →
  - Cholestryramine (Questran $162), Colestipol (Cholestid), or Colesevelam (Welchol $197)
  - Ezetimibe (Zetia): inferior to niacin
  - PCSK9 Inhibitors (A-mab or E-mab): reduces CV events (expensive)

Goal LDL: Everyone <100 mg/dl  Patients with risk factors <70 mg/dl