The "Vulnerable" Plaque- Pharmacological Approaches

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DISCLOSURES

Speaker honoraria - Roche, Menarini, Astra Zeneca, Boehringer, Servier

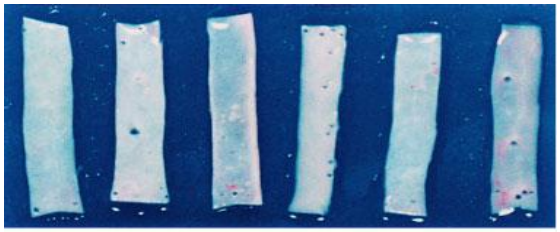
VULNERABLE PLAQUE STABILIZATION

Is it possible to stabilize (and regress) vulnerable plaques?

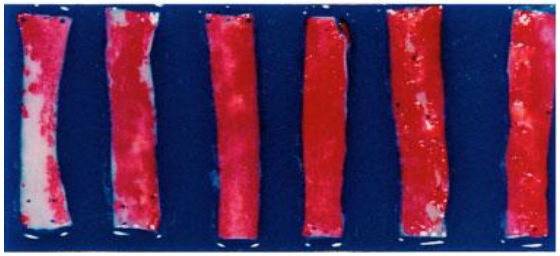
Role of pharmacological agents in plaque stabilization and regression

Plaque stabilization/ regression and CV events

ATHEROSCLEROTIC PLAQUE REGRESSION

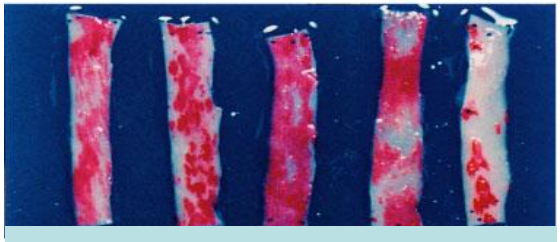


Normal Diet



High-cholesterol diet

High-cholesterol diet + Tra



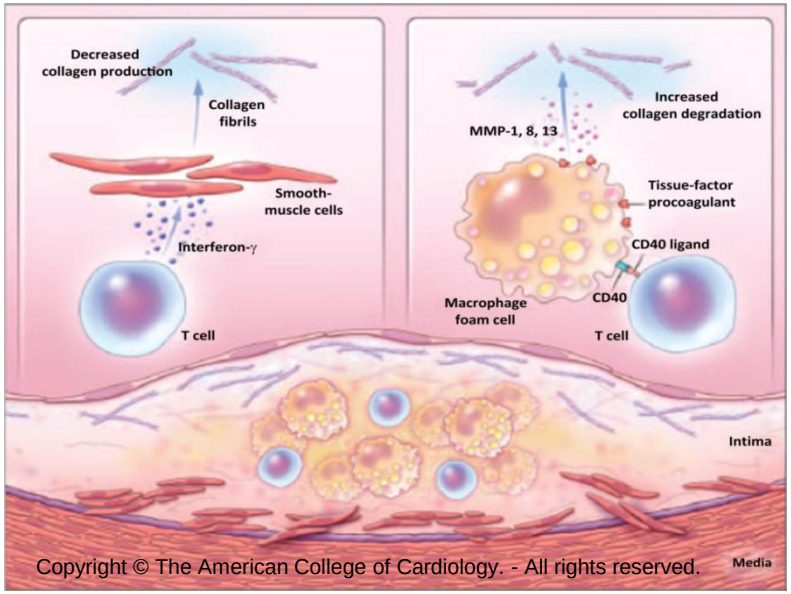
M Miyazaki, H Sakonjo & S Takai

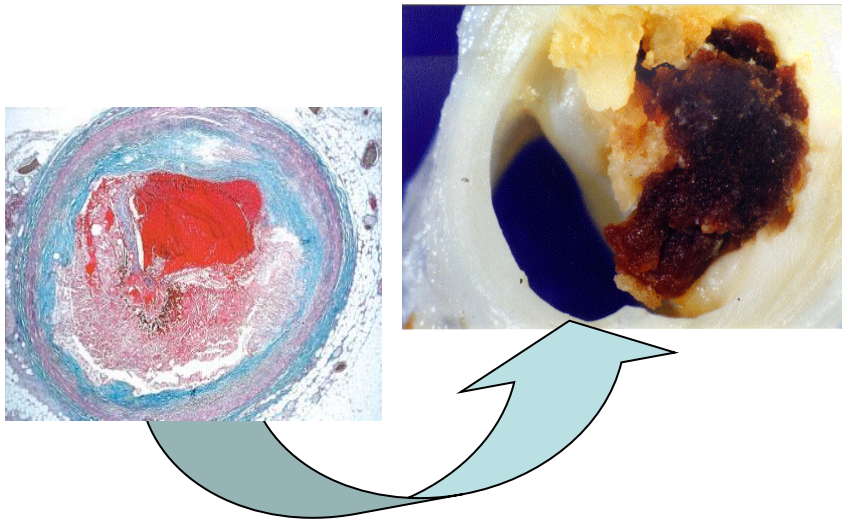
Regression of arterial lesions induced by high cholesterol diets after cessation of cholesterol feeding has been confirmed in many species i.e. rabbits, dogs, pigs, and nonhuman primates. *Malinow MR. Circ Res. 1980;46:311-320*

Regression is associated with low LDL-C, and higher HDL-C concentrations.

At the microscopic level, regression includes (1) restored integrity of the endothelium lining the plaques; (2) arrest of intimal cell proliferation; and (3) a decrease in the number of cells, in the amount of intracellular and interstitial lipid, and in the extent of necrotic and calcific foci in the plaques. *Malinow MR. Circ Res. 1980;46:311-320*

Inflammatory Pathways Leading to Plaque Rupture and Thrombosis



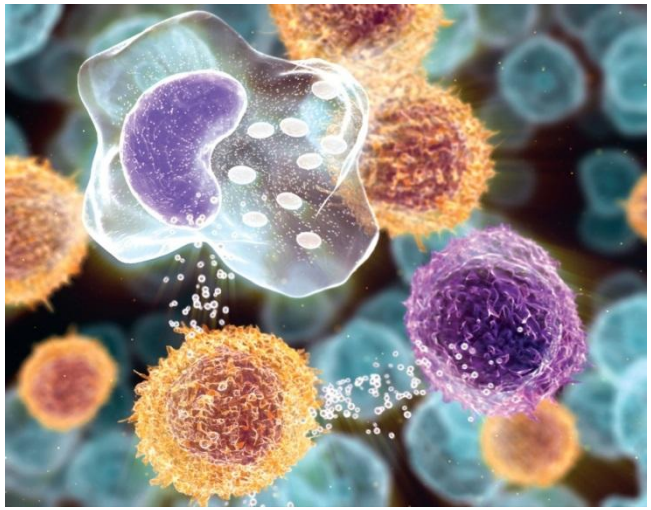


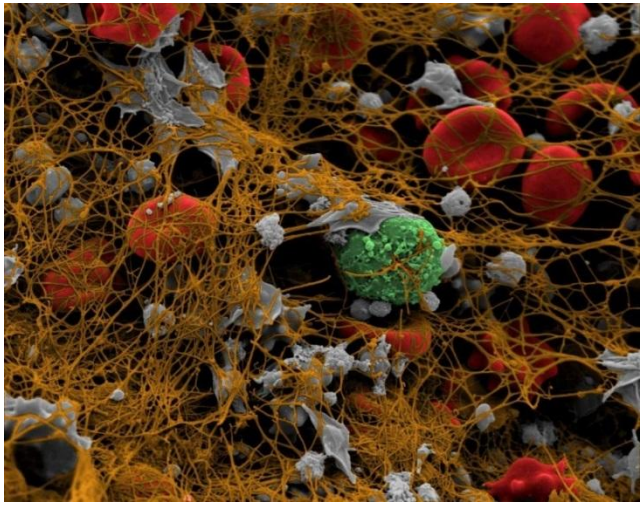
"Vulnerable" plaques (characterized by the instability of the fibrous cap), tend to progress rapidly and lead to ACS whereas stable plaques progress slowly *- Kaski et al. Circulation 2004.*

Libby described an updated model in terms of cellular and molecular pathways that underlie the pathogenesis of ACS, with a **central role for inflammation**, which drives plaque disruption and thrombosis **-** *Libby P, Ridker PM, Maseri A. Circulation 2002.*

How can we stabilize plaques (can we?) to slow progression and hopefully reduce coronary events?
FOCUS ON ANTI-INFLAMMATORY INTERVENTIONS

Inflammation – A Therapeutic Target





Corticosteroids – Lack of efficacy (OR: 0.95; 95% CI: 0.72-1.26)
Giugliano GR et al. Am J Cardiol 2003;91:1055–9.

NSAIDs - Except for aspirin, all NSAIDs increase AMI risk. In a Danish study of 99,187patients with first-time AMI, NSAID use was associated with increased mortality (HR: 1.63; 95% CI: 1.52-1.74) over a 5-year period.
Olsen AM et al. Circulation 2012;126:1955-63.

Colchicine – Anti-inflammatory actions on macrophages, neutrophils, and endothelial cells. Effective in gout and recurrent pericarditis.
Nidorf SM et al. J Am Coll Cardiol. 2013;61:404-10

Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease

Stefan M. Nidorf et al. J Am Coll Cardiol. 2013;61:404-410.

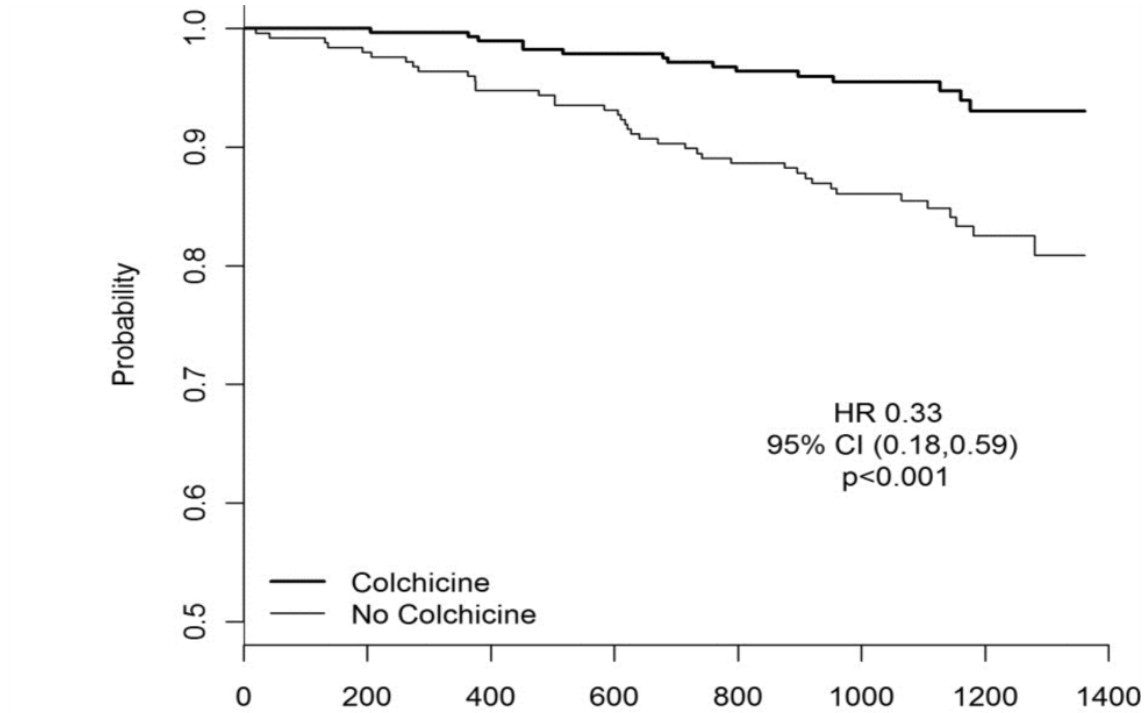
Methods Clinical trial with a PROBE design, 532 patients with stable CAD receiving aspirin and/or clopidogrel (93%) and statins (95%).

Randomly assigned colchicine 0.5 mg/day or no colchicine and followed for a median of 3 years.

Primary outcome: the composite incidence of ACS, cardiac arrest, or ischemic stroke.

Results 67% coronary event reduction!

Freedom From the Primary Outcome



Number at risk

Colchicine	282	281	277	272	249	192	83
No Colchicine	250	244	234	229	212	184	85

ONGOING TRIALS OF ANTI-INFLAMMATORY DRUGS IN ANGINA

The CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) trial will evaluate the effectiveness of a human monoclonal antibody to the inflammatory cytokine interleukin 1-beta in 17,200 stable patients post-MI, randomized to subcutaneous drug or placebo and followed over 4 years.

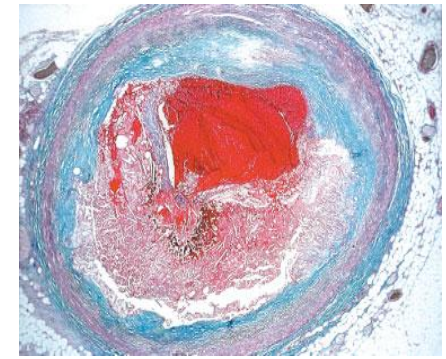
The CIRT (Cardiovascular Inflammation ReductionTrial) study will determine the effect of low-dose methotrexate (10 to 20 mg/week) on cardiovascular events in 7,000 patients with prior AMI, elevated CRP levels, and type 2 diabetes

Ridker PM, Thuren T, Zalewski A, Libby P. Interleukin-1 inhibition and the prevention of recurrent cardiovascular events: rationale and design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). Am Heart J 2011; 162:597– 605.

Ridker PM. Testing the inflammatory hypothesis of atherothrombosis:scientific rationale for the Cardiovascular Inflammation Reduction Trial. J Thromb Haemost 2009;7 Suppl 1:332–9.

Statins for Stabilisation of Atherosclerotic Plaques

Statins trigger marked reductions in circulating LDL-cholesterol concentrations and

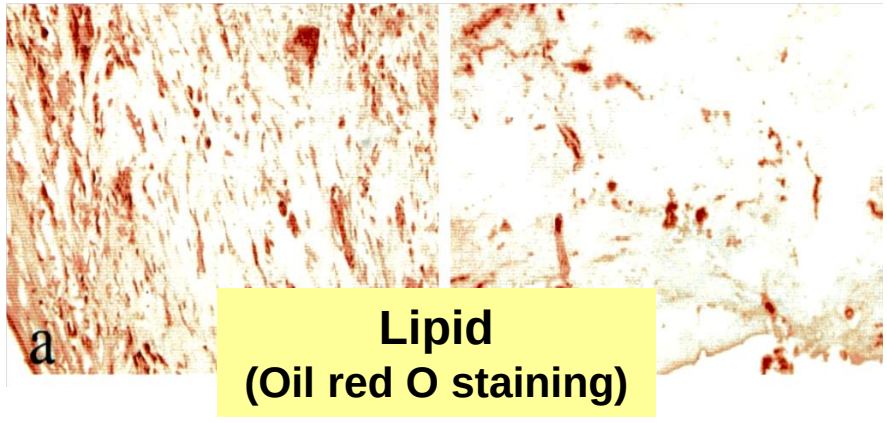


- ✓ **Reduce Ang II- and TNF-α induced NF-κB activation** *(attenuate CAM expression, inflammatory cell infiltration, EC activation,TF and MMP production, and cell proliferation)*
- ✓ **Reduce CRP levels**
- ✓ **Inhibit antigen dependent T-cell activation**
- ✓ **Enhance NO production**
- ✓ **Reduce platelet activation**

Statin Treatment Changes Atheromatous Plaque Composistion

Effects of pravastatin (40 mg/day for 3 months) on the composition of human carotid plaques removed during endarterectomy – Crisby M et al. Circulation 2001;103:926-933

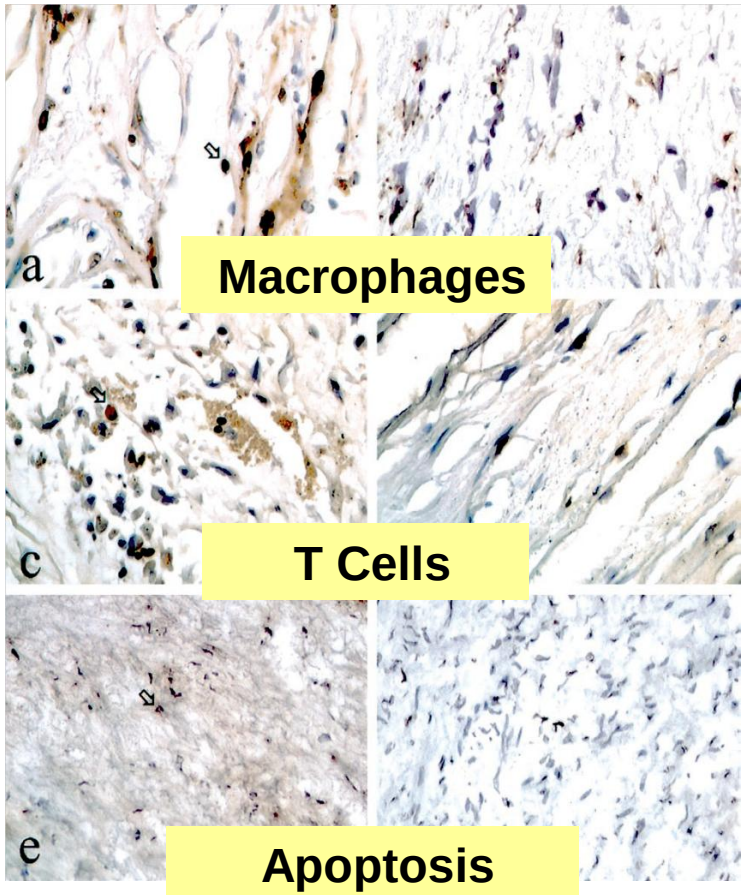
Placebo **Pravastatin**



Lipid
(Oil red O staining)

Oxidized LDL

Placebo **Pravastatin**



Macrophages

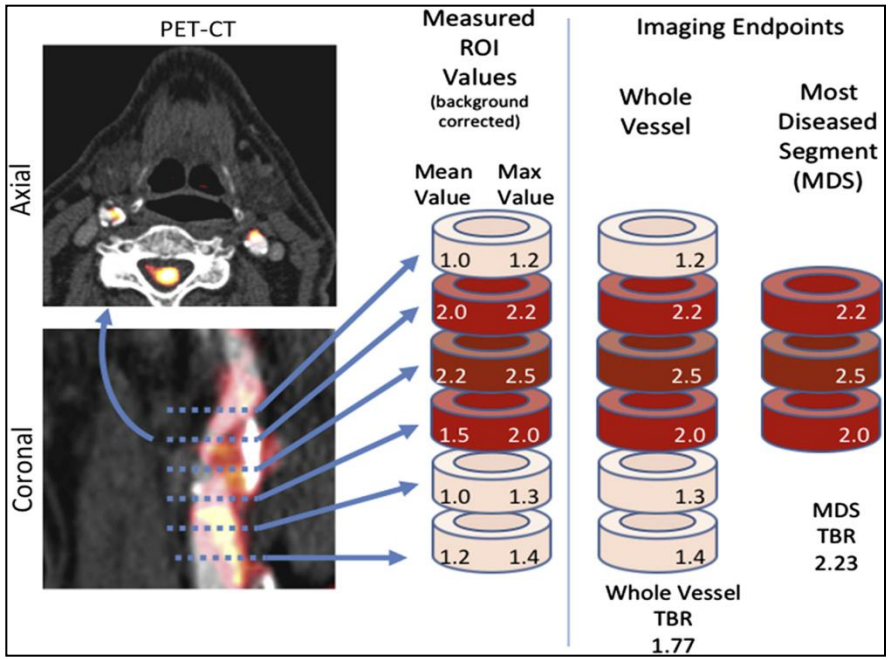
T Cells

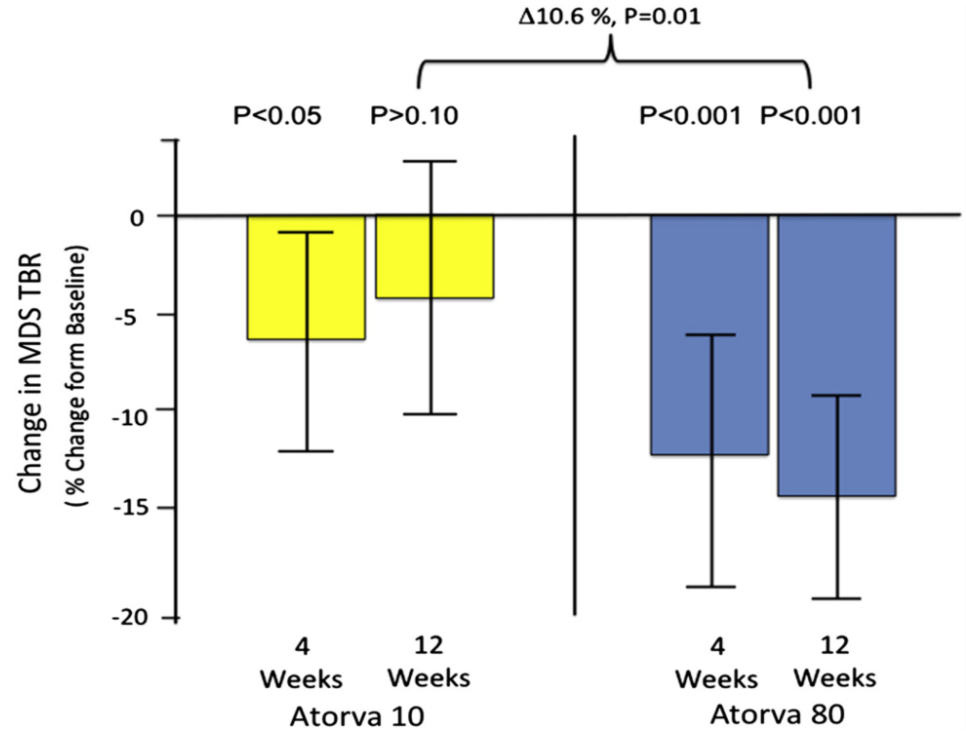
Apoptosis

Statin Treatment Reduces Plaque Inflammation

Adults (n = 83) with risk factors or established atherosclerosis, who were not taking high-dose statins, were randomized to atorvastatin 10 versus 80 mg in a double-blind, multicenter trial.

FDG-PET/CT imaging of the ascending thoracic aorta and carotid arteries was performed at baseline, 4, and 12 weeks after randomization

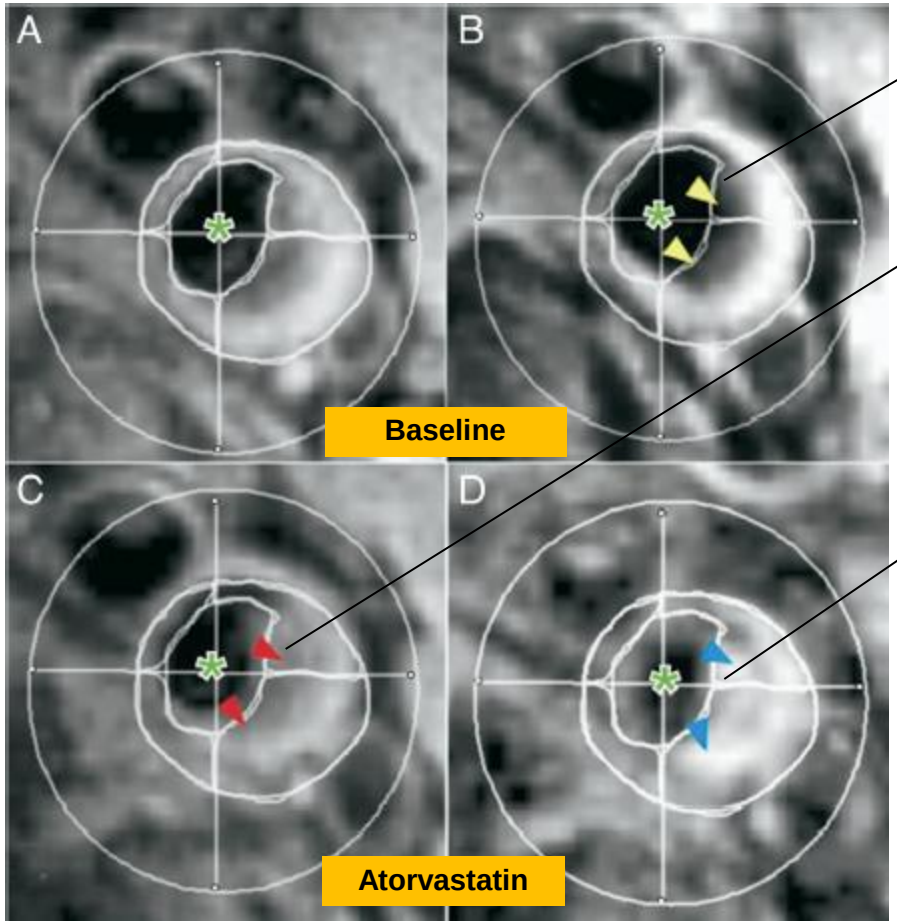




Intensification of Statin Therapy Results in a Rapid Reduction in Atherosclerotic Inflammation: Results of a Multicenter Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography Feasibility Study – Tawakol A et al. J Am Coll Cardiol. 2013;62(10):909-917.

The ATHEROMA (Atorvastatin Therapy: Effects on Reduction of Macrophage Activity) Study

T2*-weighted imaging of a right common carotid artery before and after ultrasmall super paramagnetic iron oxide (USPIO) infusion at 0 (A & B) and 12 weeks (C & D)



Tang et al. J Am Coll Cardiol 2009; 53:2039–50

USPIO (ultrasmall super paramagnetic iron oxide) uptake seen in the plaque at baseline

Sinerem has been cycled out of the plaque

Reduced USPIO uptake = reduced inflammation

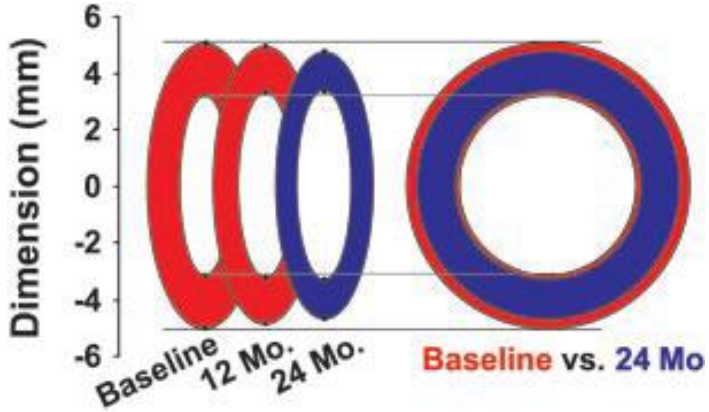
Aggressive lipid-lowering therapy (80 mg atorvastatin) over 3-months was associated with significant reduction in USPIO-defined inflammation

MRI - Plaque Regression with Simvastatin Treatment

21 hypercholesterolaemic subjects assessed by MRI at baseline, 6, 12, 18 and 24 months

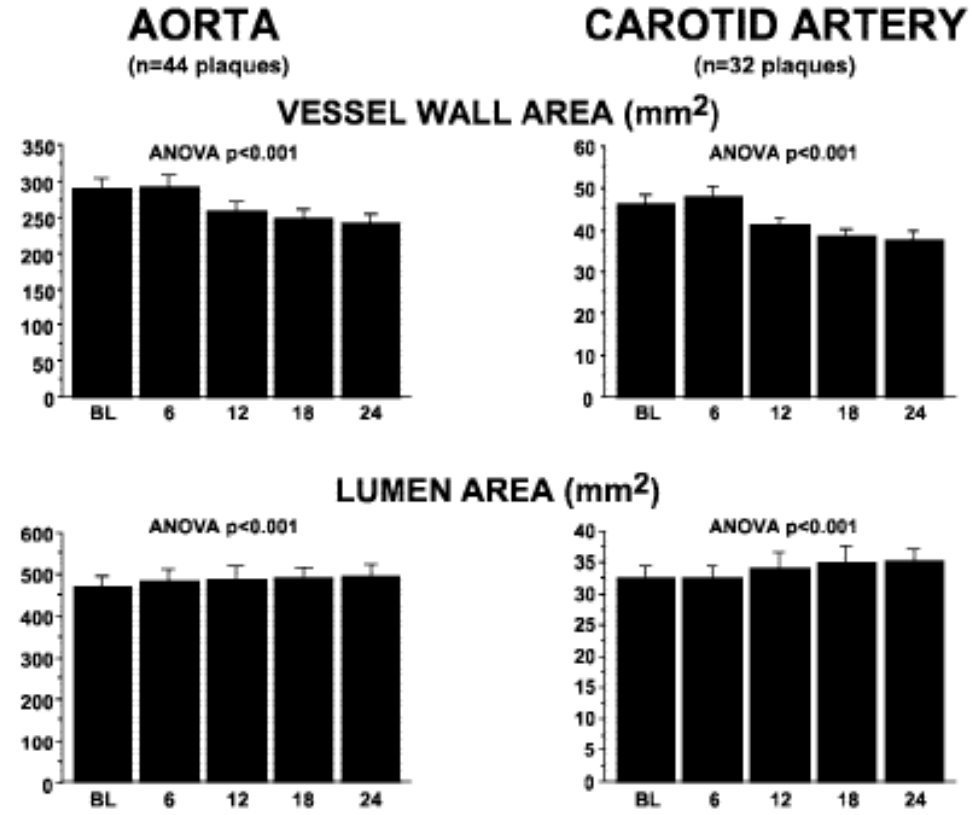
Total and LDL plasma cholesterol were reduced by simvastatin (by 23% & 38%, respectively; *P*<0.01 vs baseline) after 6 weeks

Significant (*P*<0.01) reductions in plaque size (maximal VWT and VWA) at 12 and 24 months

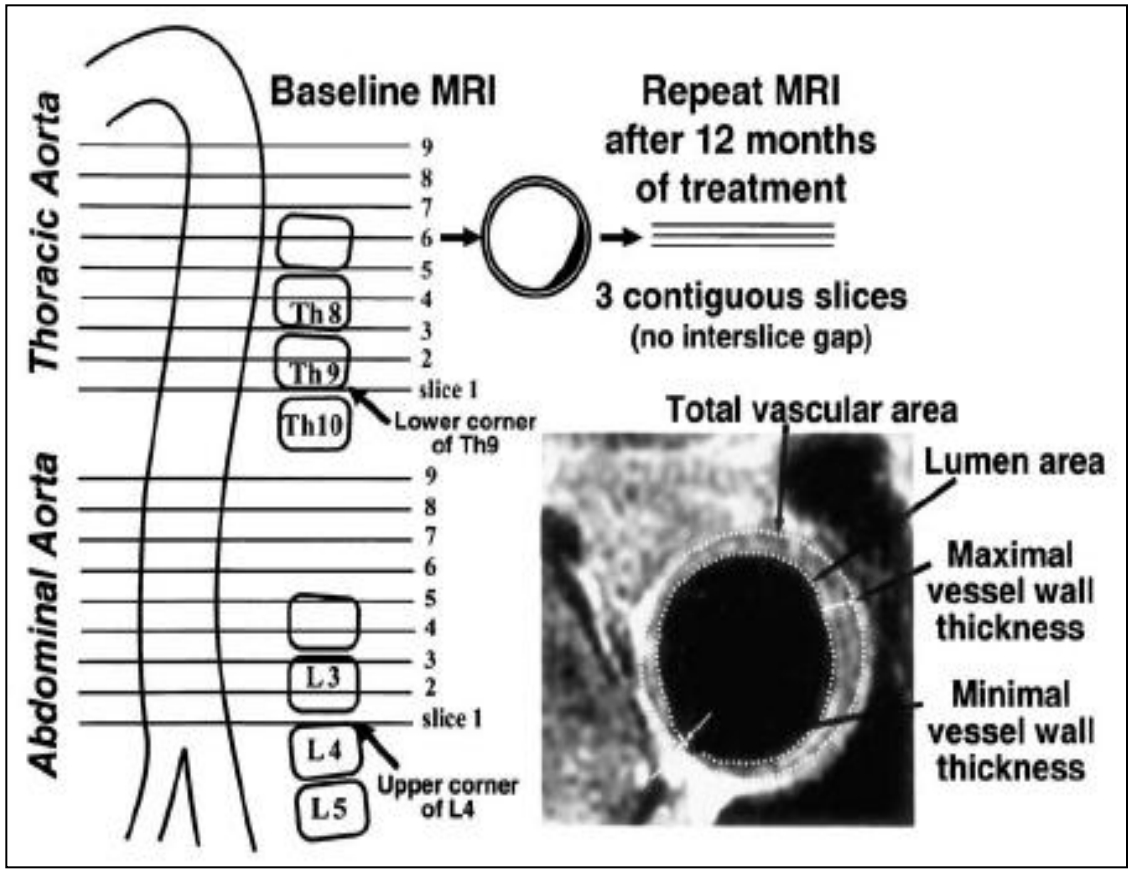


Comparison of plaque size at the end of the 24-month treatment period (blue) versus baseline (red)

Corti et al. Circulation 2002;106:2884-2887



Atorvastatin Treatment Induces Aortic Atheromatous Plaque Regression



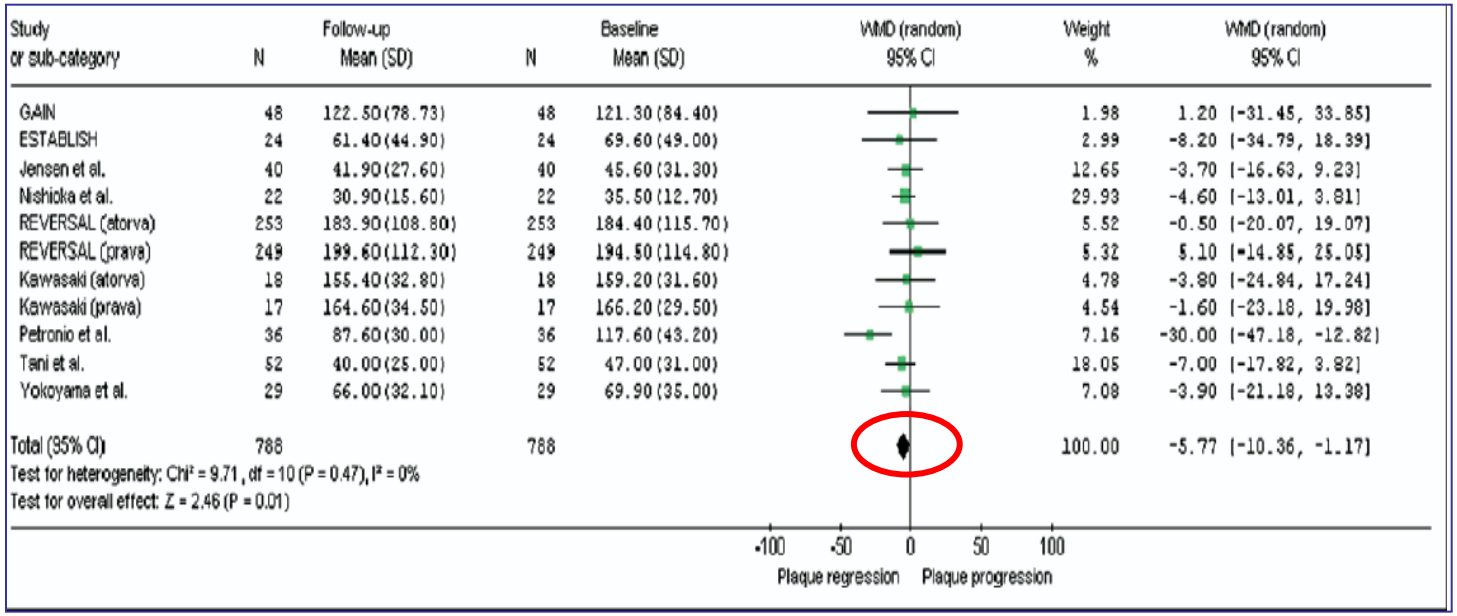
Yonemura et al. JACC 2005;45:733-42

1-year treatment with 20-mg atorvastatin induced regression of thoracic aortic plaques and stopped disease progression in the abdominal aorta

Good correlation found between LDL-cholesterol reduction and plaque regression

Effects of 20 mg versus 5 mg atorvastatin on thoracic and abdominal aortic atherosclerotic plaques in 40 asymptomatic hypercholesterolaemic patients

Plaque Regression with Statins - IVUS Studies



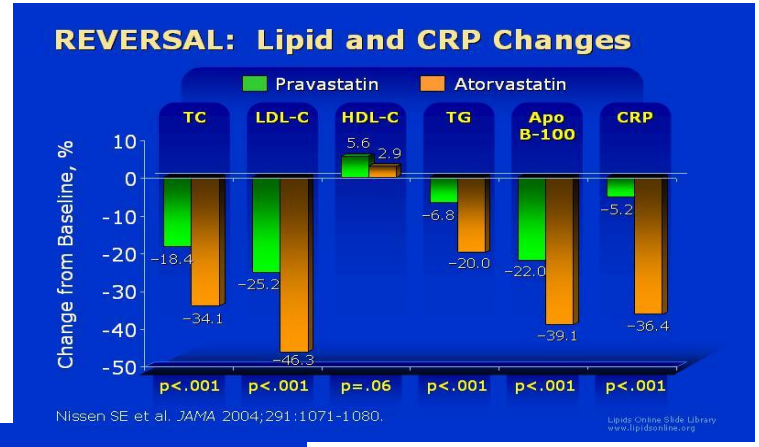
Am J Cardiol 2007;99:5–10

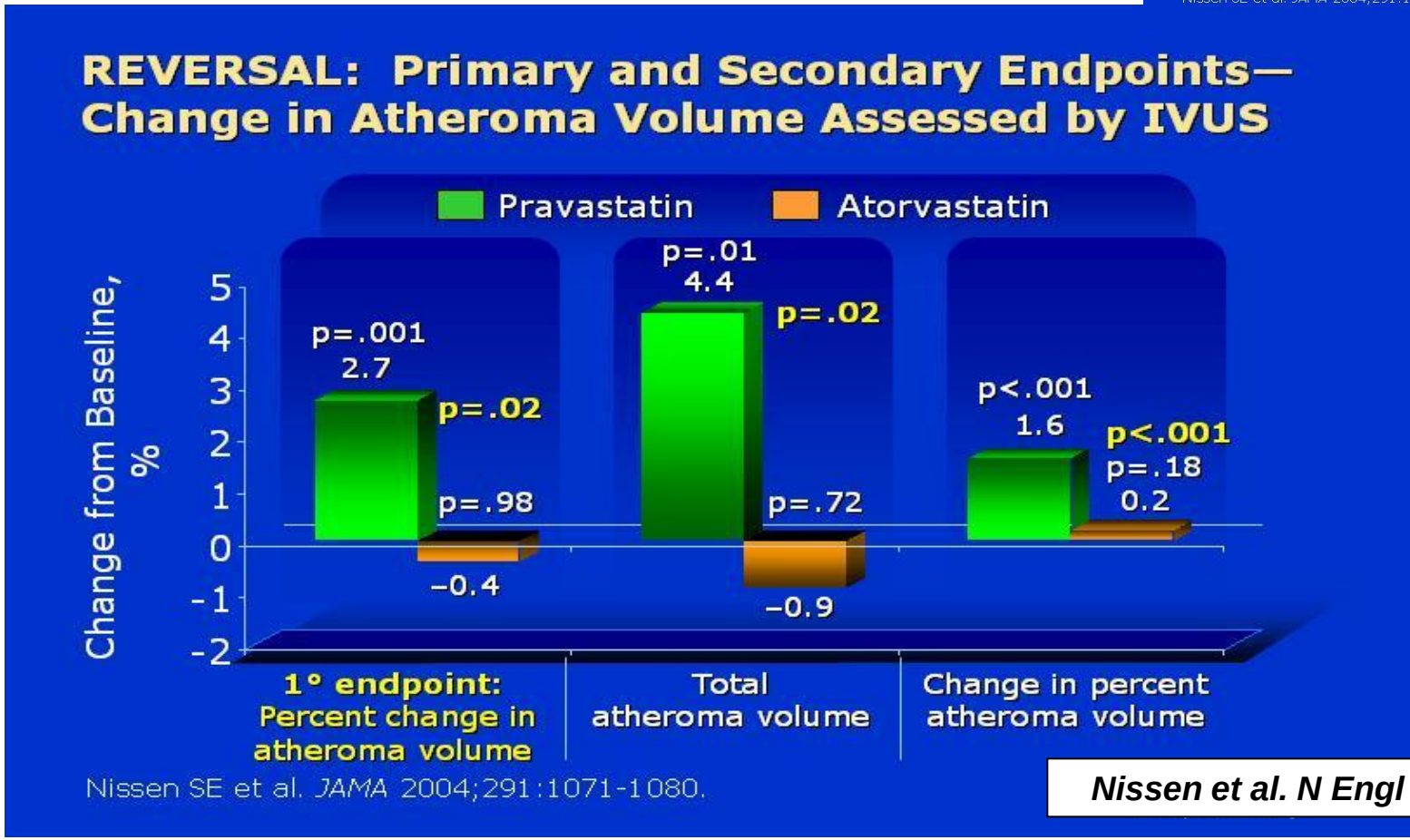
Studies in which the LDL cholesterol level was reduced to <100 mg/dl showed a stronger trend for plaque regression

Treatment with statins resulted in a decrease in coronary plaque volume over time (WMD 5.77 mm3, 95% CI 10.36 to 1.17, p <0.01), with no significant heterogeneity between studies (p=0.47)

REVERSAL trial

IVUS showed a reduced rate of stenosis progression in 502 CAD patients receiving atorvastatin 80 mg/d (v. pravastatin 40 mg/d) for 18 months





The reduced progression rate correlated with reductions in LDL-C, CRP, apo B-100, and non-HDL-C

Nissen et al. N Engl J Med 2005; 352:29.

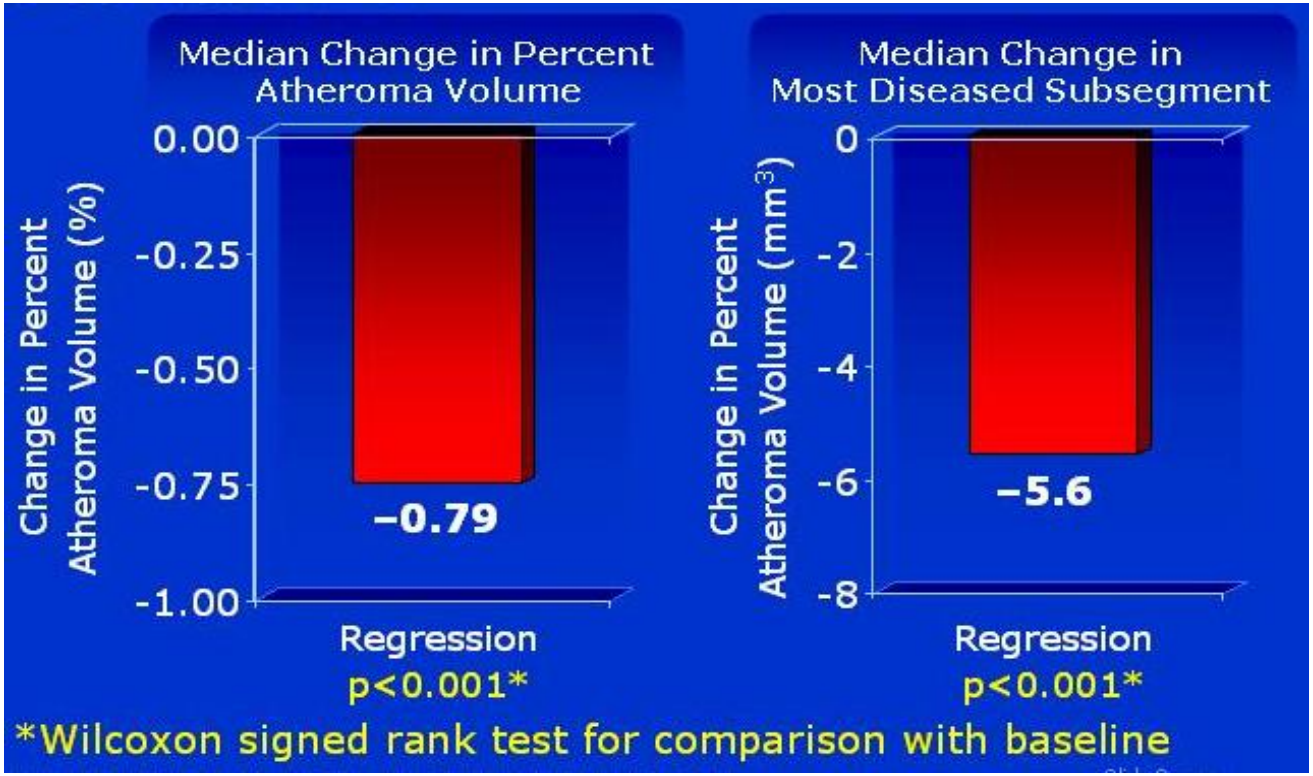
ASTEROID – A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound - Derived Coronary Atheroma Burden

507 patients on no statin therapy undergoing coronary angiography - Mean LDL-C: 130 mg/dL

Target vessel (IVUS) >50% stenosis

Rosuvastatin 40 mg v. placebo

Baseline IVUS and repeat IVUS (n=349) at 2 years



53% reduction in LDL-Chol and 14.7% increase in HDL-Chol. **Only patients with LDL-C < 70 mg/dl showed significant regression**

Nissen S et al. *JAMA* 2006. 295:1556-65

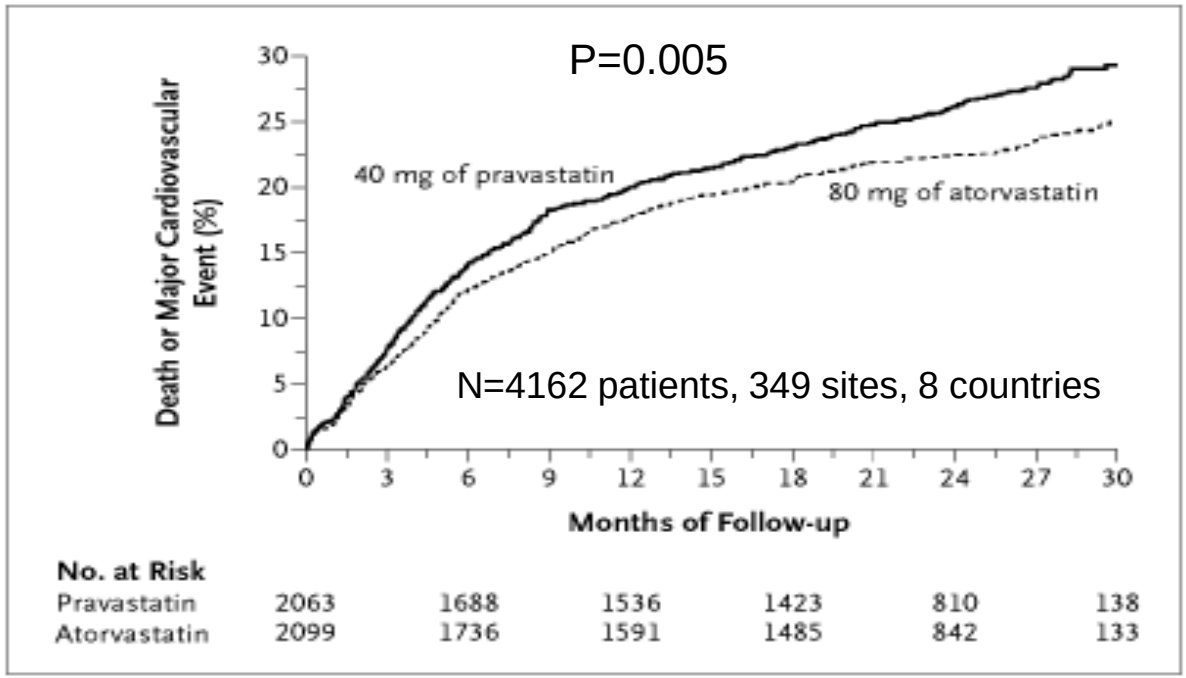
PROVE IT TIMI 22 - Early Statin Therapy in ACS

LDL-C (mg/dL) = 62 vs. 95

The primary end point (death, AMI, unstable angina requiring rehospitalization, revascularization, or stroke) occurred in: **22.4% (atorva) vs. 26.3% (prava)**

(p=0.005)

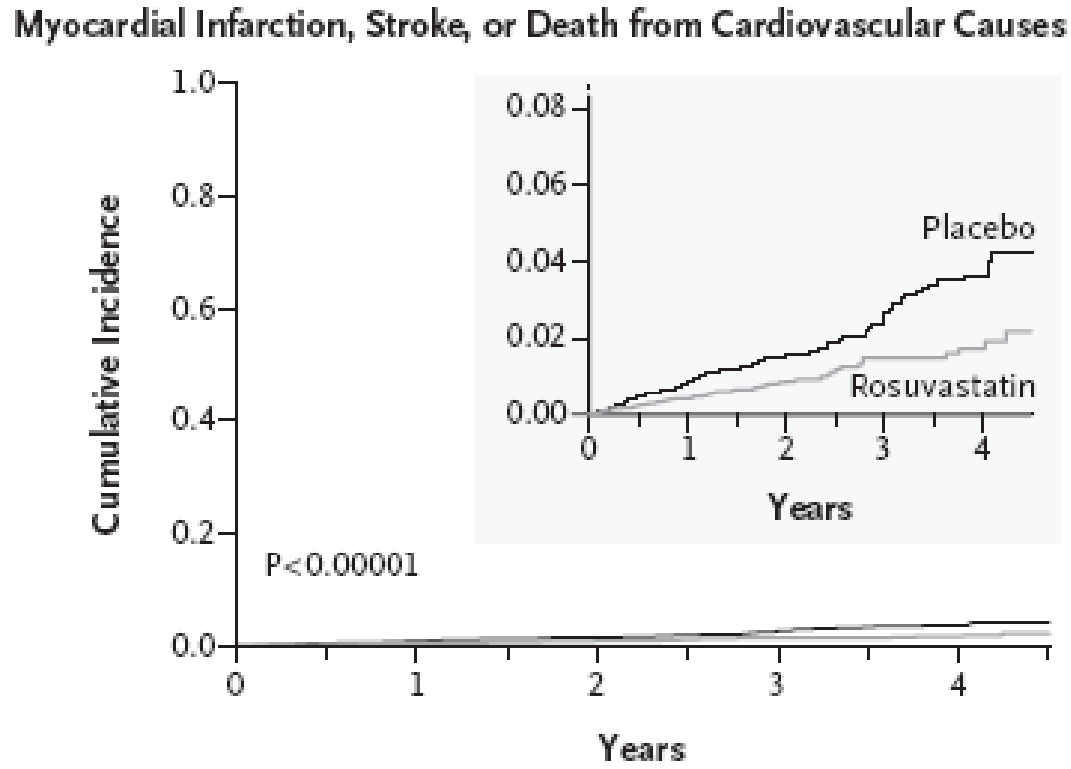
Head-to-head comparison: high-dose potent statin (atorvastatin 80 mg) vs. moderate-dose, less potent statin (pravastatin 40 mg) - Follow-up: 24 months



PROVE IT TIMI 22 (The Pravastatin or Atorvastatin Evaluation and Infection Therapy) ***NEJM 2004; 350: 1495-1504***

JUPITER - Justification for the Use of statins in Primary prevention: an International Trial Evaluating Rosuvastatin

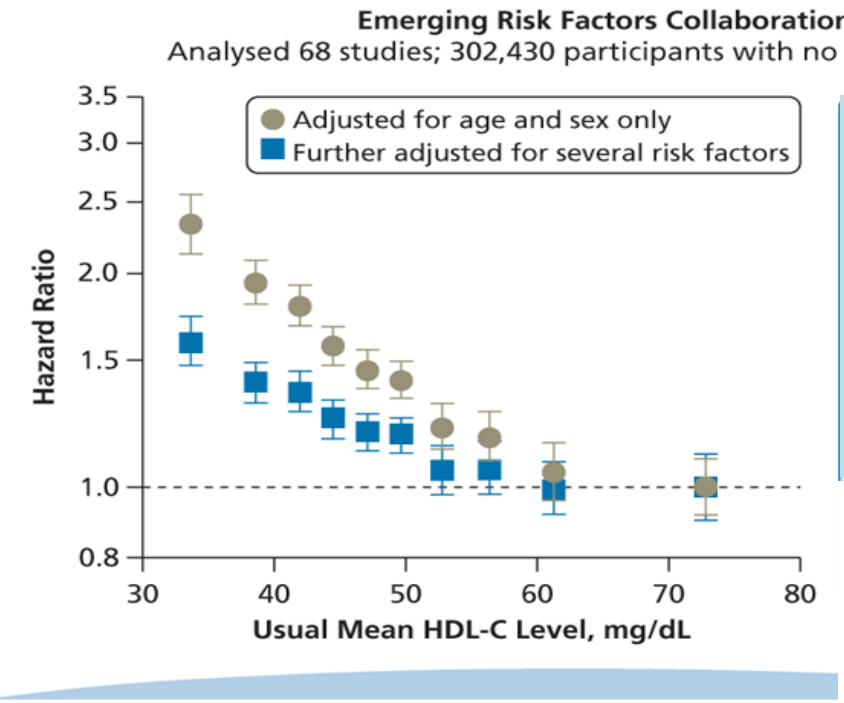
- **Intensive statin therapy prevented cardiovascular events in apparently healthy subjects with LDL-C <130 mg/dL but elevated levels of hsCRP**
- **NNT to prevent 1 end-point= 25**



Relative hazard reductions in the rosuvastatin group were similar for women (46%) and men (42%) and were observed in every subgroup evaluated (age, ethnic group, status re. traditional risk factors, and Framingham risk score)

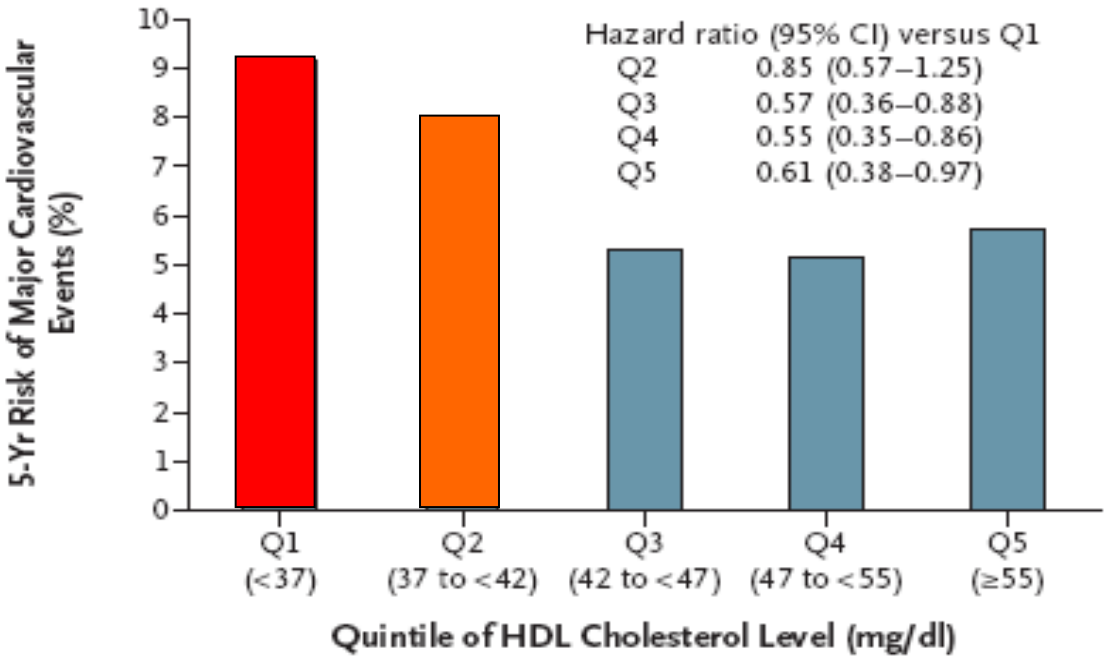
Ridker P et al. NEJM 2008

Low HDL-Cholesterol is Strongly Associated with Increased Cardiovascular Risk



http://www.peervoice.com/o1/pvr25

Increased 5 year risk of major cardiovascular events in patients with low HDL-C despite low LDL cholesterol levels



Experimental and epidemiological studies support an anti-atherogenic effect and vasculo-protective actions of HDL-C

Barter PJ et al. NEJM 2007

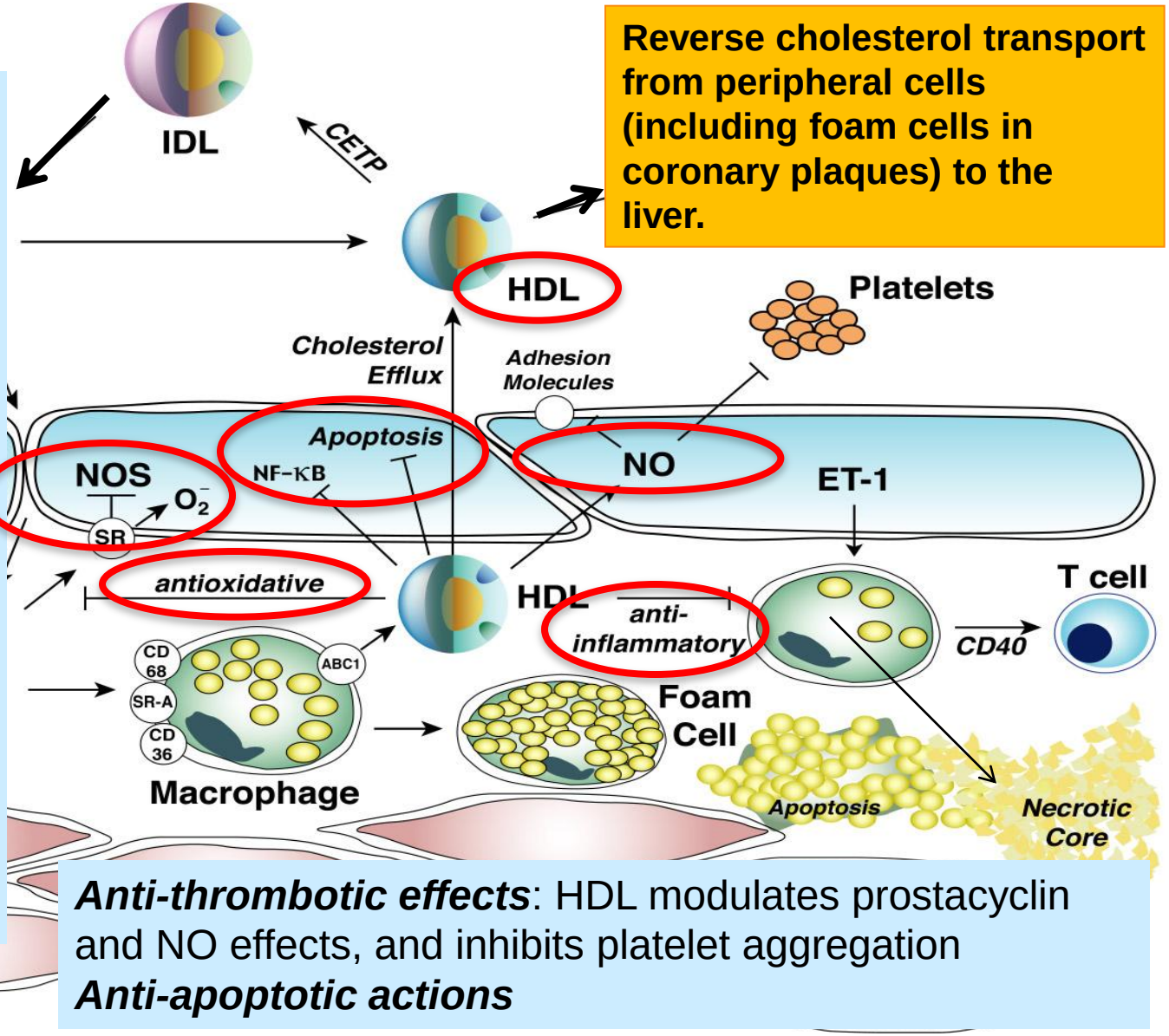
Anti-atherogenic Effects of HDL

Anti-inflammatory properties:

HDL increases eNO synthase expression, NO release & bioavailability

Increases flow-mediated dilatation (FMD) in hyper-cholesterolemic patients

Reduces monocyte transmigration and increases M2 polarization



Anti-thrombotic effects: HDL modulates prostacyclin and NO effects, and inhibits platelet aggregation
Anti-apoptotic actions

Spieker et al. Curr Drug Targets Immune Endocr Metabol Disord. 2004

Table. Selected HDL and ApoAI Regression Studies

The preclinical data convincingly demonstrate the ability of functional HDL and lipid-poor apoAI particles to promote the regression of atherosclerosis by effects on both the number and the inflammatory state of plaque macrophages

Nissen et al[58]	Human	$apoAI_{Milano}$ (ETC 216)	15 and 45 mg/kg	IV weekly >5 wk	Coronary artery (assessed by IVUS)	Combined rHDL groups vs baseline (median): Change in total atheroma volume: –13.3 mm^3 ($P<0.001$) Change in atheroma volume: –4.2% Change in percent atheroma volume (PAV): –0.81% ($P=0.02$)
Tardif et al (ERASE)[59]	Human (ACS)	rHDL (CSL-111)	40 and 80 mg/kg (80 mg/kg dosage discontinued because of liver function test abnormalities)	IV weekly >4 wk	Coronary artery (assessed by IVUS)	rHDL vs placebo group (median): Change in total plaque volume: –5.3 vs –2.3 mm^3 (NS) Change in atheroma volume: –3.4% vs –1.6% (NS) Significant improvement of plaque characterization index and coronary score
Shaw et al[60]	Human (PAD)	rHDL (CSL-111)	80 mg/kg	IV	SFA (after atherectomy 5–7 d after infusion)	Lipid content ↓ Macrophages cell size ↓ VCAM-1 expression ↓

Increased HDL Concentrations and Plaque Regression

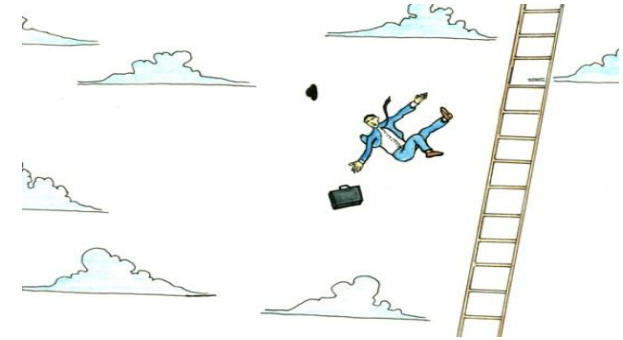
The major clinical studies of niacin that have included effects on plaques are:

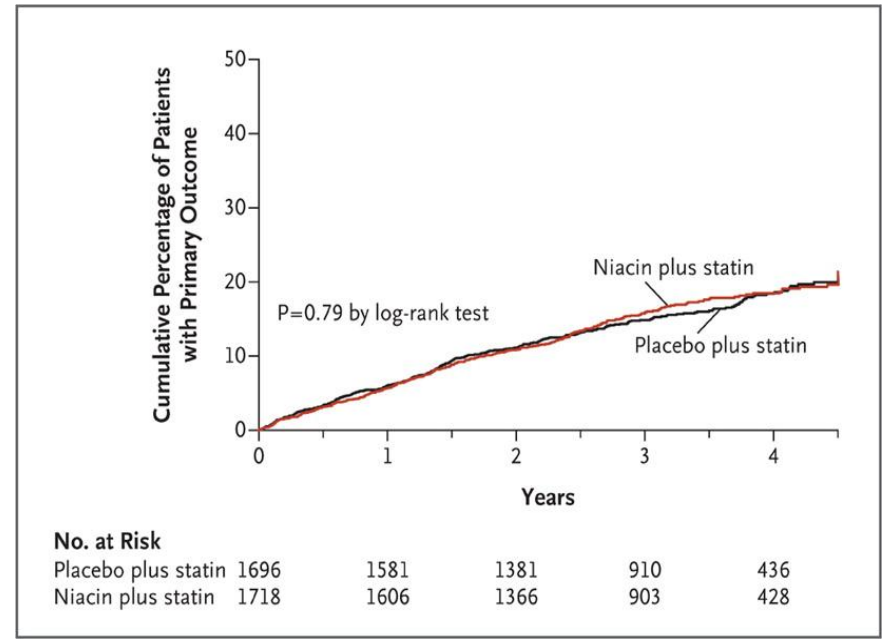
- The Familial Atherosclerosis Treatment Study **(FATS)**
- The Cholesterol-Lowering Atherosclerosis Study **(CLAS)**
- The HDL-Atherosclerosis Treatment Study **(HATS)**
- The Arterial Biology for the Investigation of Treatment Effects of Reducing Cholesterol **(ARBITER)**
- The Niaspan Oxford Study.

These studies showed a modest reduction in plaque burden. The patient population sizes in all were small (71–162 patients).

AIM-HIGH and HPS2-Thrive

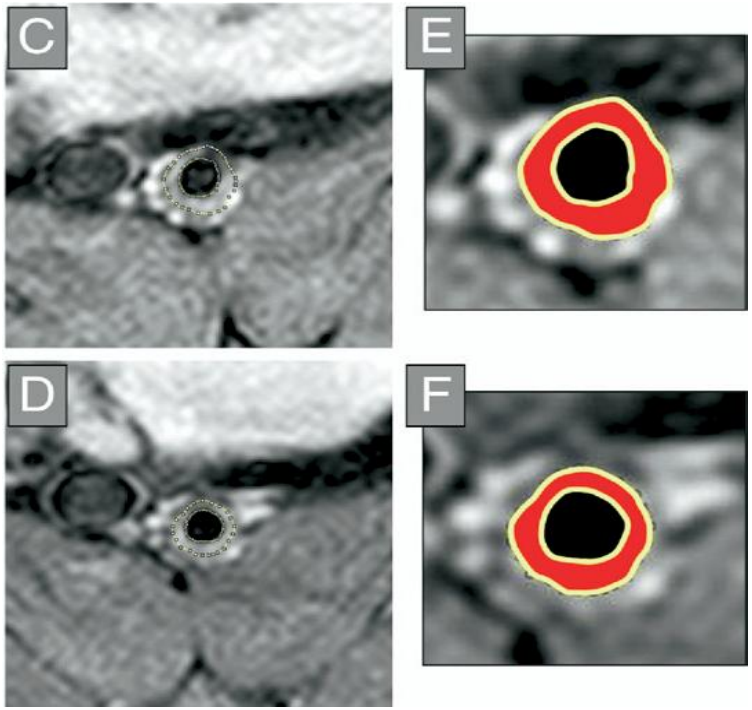
The lack of efficacy of niacin to reduce cardiovascular events – despite increases in HDL-C- in the large **AIM-HIGH** study (*Athero-thrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides*) (3,414 subjects) (NEJM 2011) and the **Heart Protection Study 2-Thrive** *(Treatment of HDL to Reduce the Incidence of Vascular Events)* using ER niacin 2 g + laropiprant 40 mg od (25,673 patients) (EHJ 2013) has been disappointing.





The AIM-HIGH Investigators. N Engl J Med 2011;365:2255-2267.

Apo AI_{Milano} (ETC-216) – MRI Assessment



Reduction in plaque macrophage density and a significant down-regulation in gene and protein expression of tissue factor, MCP1, cyclooxygenase-2, and a marked decrease in gelatinolytic activity

40 New Zealand White rabbits randomized to placebo or apoAI Milano (ETC-216), 2 infusions 4 days apart

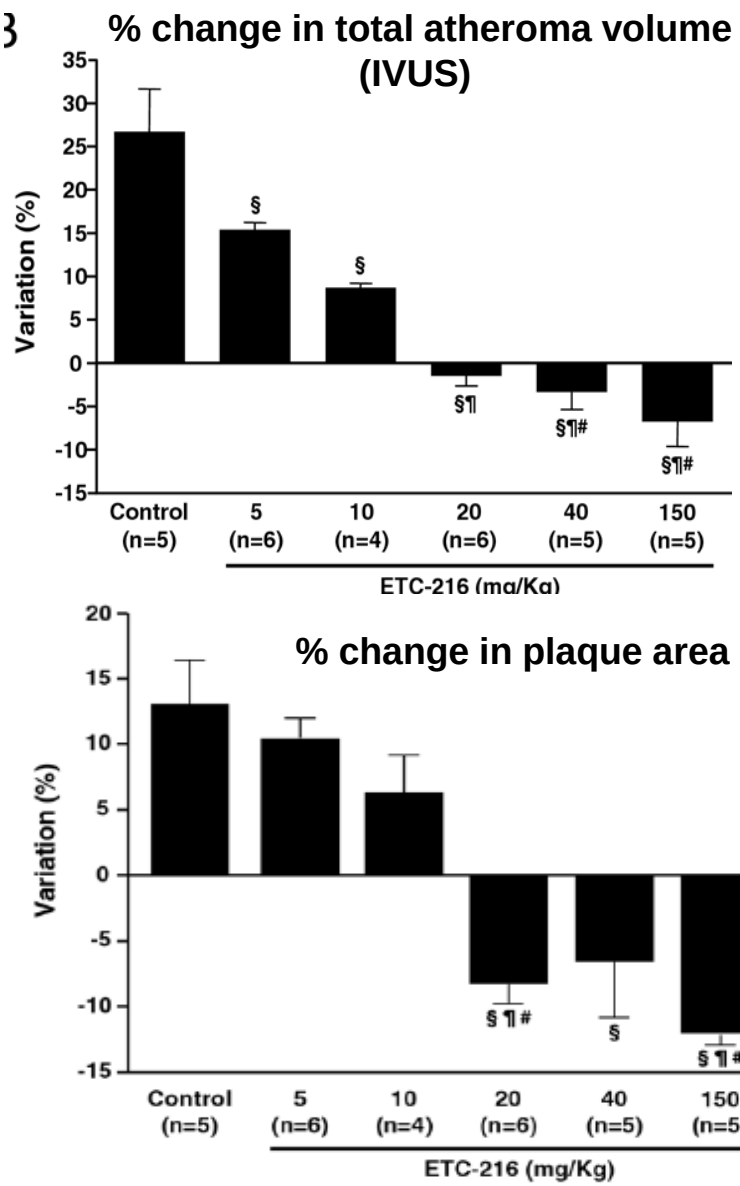
Plaque regressed by 20.5% after 2 doses of apoA-I Milano

Plaque regression was associated with a change in the molecular footprint of the atherosclerotic lesions, suggesting a change into a more stable phenotype

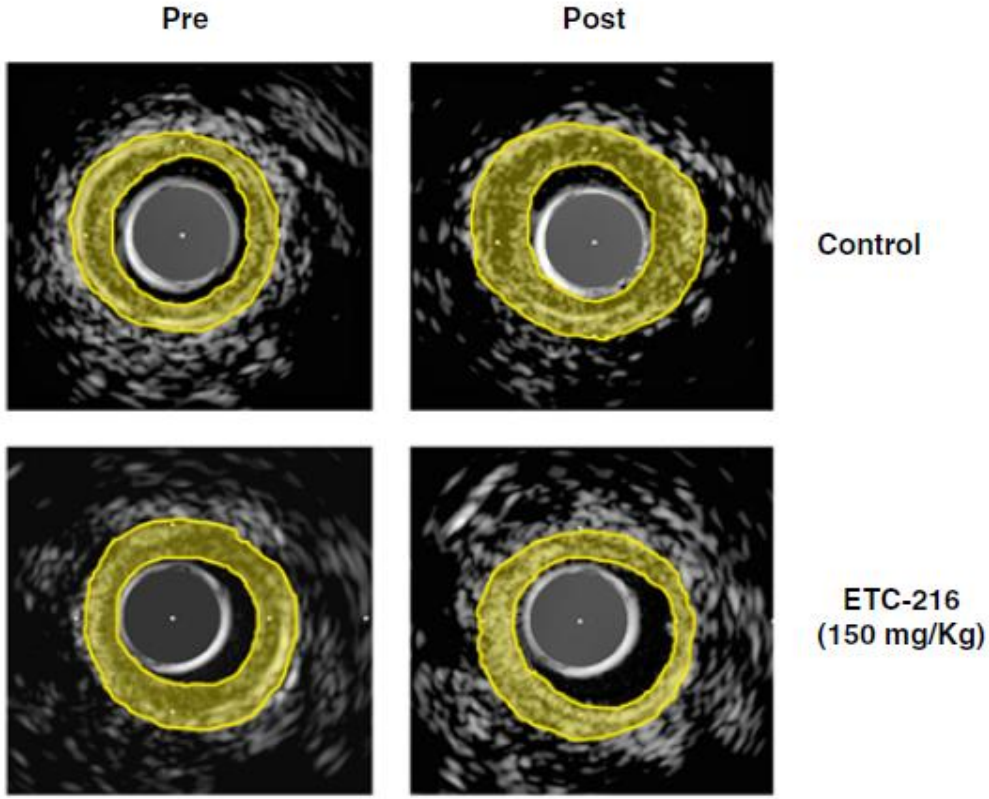
Ibañez et al. JACC 2008;51:1104-09

Plaque Regression with Apo AI_{Milano} Treatment

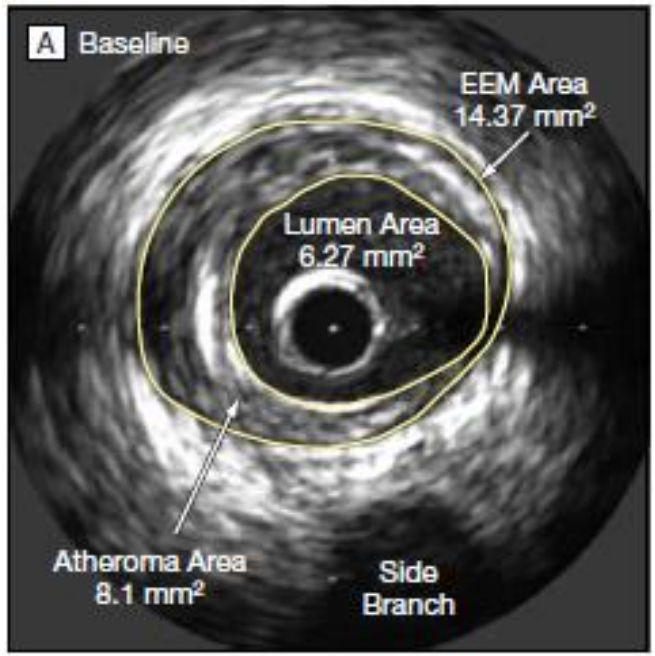
Parolini et al. JACC2008; 51:1198-103

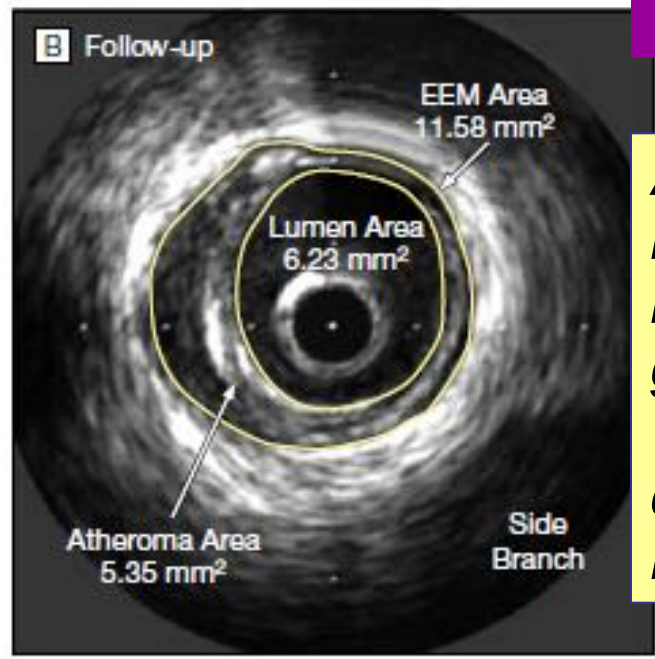


36 New Zealand White rabbits randomly divided into 6 groups and treated with vehicle or ETC-216 at 5, 10, 20, 40, and 150 mg/kg every 4 days



Recombinant Apolipoprotein AI_{Milano} (ETC-216)





Plaque regression

Absolute reduction in atheroma volume in the treatment group was −14.1mm3 or a 4.2 % decrease from baseline (P<.001).

57 ACS patients randomly assigned to 5 weekly infusions of placebo or ETC-216 (15 mg/kg or 45 mg/kg)

IVUS carried out within 2 weeks from ACS and repeated after 5 weekly treatments

Nissen et al. JAMA 2003; 290:2292-2300

ERASE - Effect of rHDL on Atherosclerosis-Safety and Efficacy

An IVUS study to investigate the effects of reconstituted HDL (CSL-111), on plaque burden (i.e. atheroma volume)

Patients 183 patients had a baseline IVUS examination and 145 had evaluable IVUS examinations after 6 weeks. 60 patients randomly received 4 weekly infusions of placebo, 111 pts 40 mg/kg of reconstituted HDL and 12 pts 80 mg/kg of CSL-111.

Main Outcome Measures % change in atheroma volume and coronary score on QCA.

Results - Change in atheroma volume was −3.4% with CSL-111 and −1.6% for placebo (*P* = .48 between groups, *P*<.001 vs baseline for CSL-111).

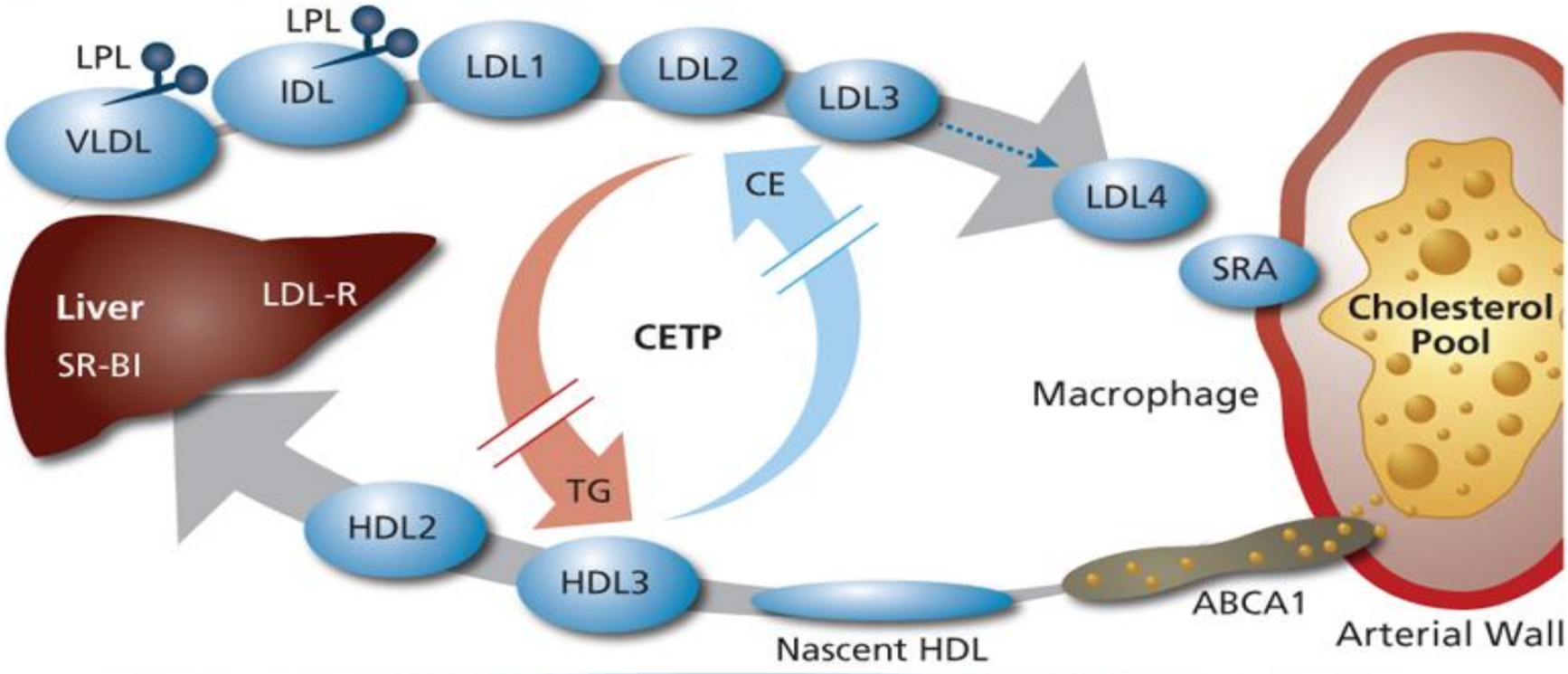
Conclusions rHDL resulted in a significant improvement in markers of coronary plaque burden

Tardiff J-C et al. JAMA. 2007;297:1675-1682

Plasma Cholesteryl Ester Transport Protein (CETP): A Therapeutic Target

CETP plays a key role in HDL metabolism

- Removes cholesterol from HDL to ApoB-containing lipoproteins like VLDL; enriches HDL with triglycerides
- Net result is to lower HDL
- Inhibiting or modulating CETP may increase HDL



Drugs which increase HDL-C can provide an opportunity to reduce CV events further

CETP Inhibition and Events

In the **ILLUMINA Study, Torcetrapib** increased death and cardiovascular events *(Barter P et al. NEJM 2007)*

In **Dal-Vessel, Dalcetrapib** significantly reduced CETP activity and increased HDL-C with neutral action on endothelial function, BP and CRP

In the dal-OUTCOMES trial (ACS patients) dalcetrapib increased HDL-C but did not reduce the risk of recurrent cardiovascular events *(Schwartz GG et al. NEJM 2012)*

REVEAL (anacetrapib, 30,000 patients) completed recruitment and **ACCELERATE (**evacetrapib) is still recruiting.

Reasons for the Disconnect Between Experimental and Clinical Studies

- ✓ **Statins lower LDL-C aggressively thus making it difficult for the increase in HDL-C to result in further benefit.**
- ✓ **Improvements in plaque characteristics may not translate into reduced event rates**
- ✓ **Increases in plasma HDL-C may not necessarily affect plaque biology if the protective functions of HDL are not present**

HDL-C and Atherosclerosis Regression: The Clinical Controversy

The presumption (clearly wrong) has been that the increases in HDL-C would reflect the actions of an increased supply of functional HDL and lipid-poor apoAI particles, which would be expected to have beneficial effects on plaque size, plaque composition, and CVD risk

Reasons for the Discrepancy Between Experimental and Clinical Data

In contrast to what is observed in plasma, the vast majority of apoAI (>95%) within normal and atherosclerotic human arterial tissue was found to be predominantly lipid-poor and to not to reside on an HDL particle *(Fisher ED et al. ATVB 2012)*

Most of apoAI within arterial tissues was found to be extensively oxidized and cross-linked resulting in reduced protective effects (with pro-inflammatory action)

ApoAI recovered from human aorta was found to be dysfunctional, with 80% to 90% reductions in cholesterol efflux activity and ability to activate lecithin–cholesterol acyltransferase when incorporated into reconstituted HDL particles

Examination of the relatively lipid-poor fraction of apoAI in the circulation was found to be substantially more oxidatively cross-linked than the apoAI recovered in circulating HDL (*Fisher ED et al. ATVB 2012; Undurti A et al. J Biol Chem 2009)*

Thus in addition to the plasma level of HDL-C not necessarily being functionally relevant, even studies that focus on biological activities of apoAI recovered from plasma or serum HDL may not reflect the biology of apoAI within the artery wall

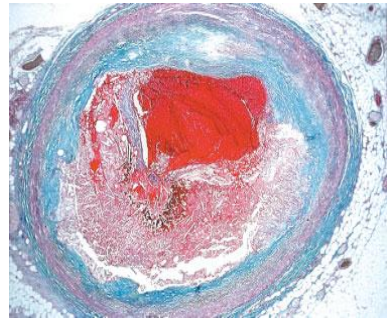
Feig JE et al. Circ Res 2014;114:201-213

Conclusions – *HDL can regress plaques but…*

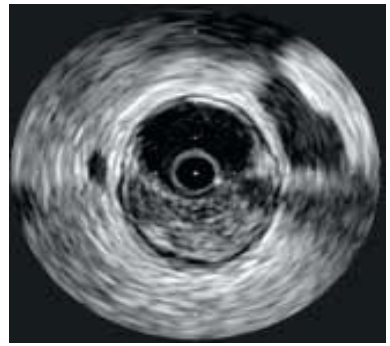
- More research is needed regarding basic mechanisms and to establish whether changes translate clinically to reduced cardiovascular events
- Recent clinical trial results do not eliminate HDL from consideration as an atheroprotective agent but rather highlights the important distinction between HDL **function** and **plasma levels** of HDL-C

Conclusions

Plaque stabilization and atherosclerosis regression have been documented in experimental and clinical studies with statin treatment



Statins improve clinical outcomes



Beneficial effects of HDL in experimental studies have not translated into clinical benefits in large trials so far

New anti-inflammatory interventions (i.e. colchicine) have shown promise and large studies of novel anti-inflammatory agents are currently ongoing