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Inflammation: Novel Target for Cardiovascular Risk Reduction

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Why inflammation ?

- **Population-based studies:** low grade inflammation predicts CV events:
  - 1^0 prevention ("healthy"): leukocyte count, hsCRP, IL-18, Lp-PLA_2...
  - 2^0 prevention (e.g., ACS): hsCRP, IL-6, CD40L...
- **Pathology:** Inflammatory cells accompany all stages of atherosclerosis in humans:
  - macrophages, T cells
  - neutrophils (late stage)
- **Therapies:** emerging link between pharmacologic redeuction of inflammatory burden and CV events:
  - soluble biomarkers: e.g., hsCRP, CD40 ligand
  - cell-associated: e.g., chemokines, chemokine receptors

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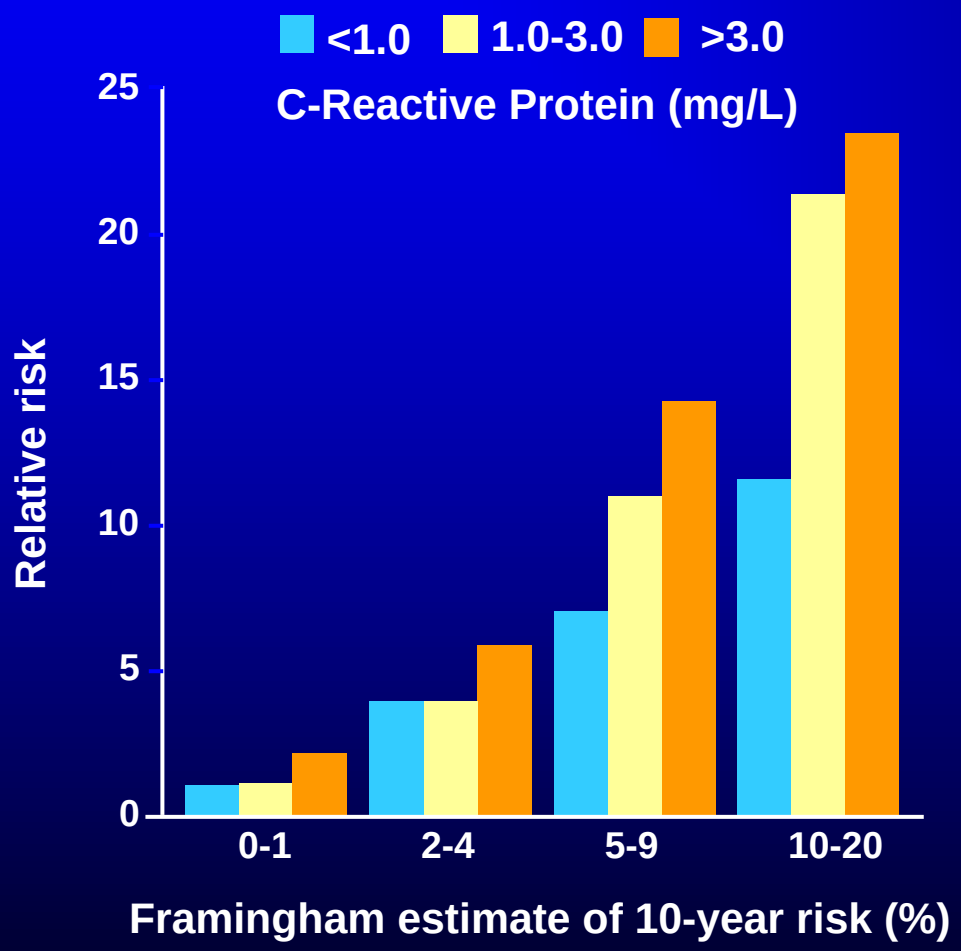
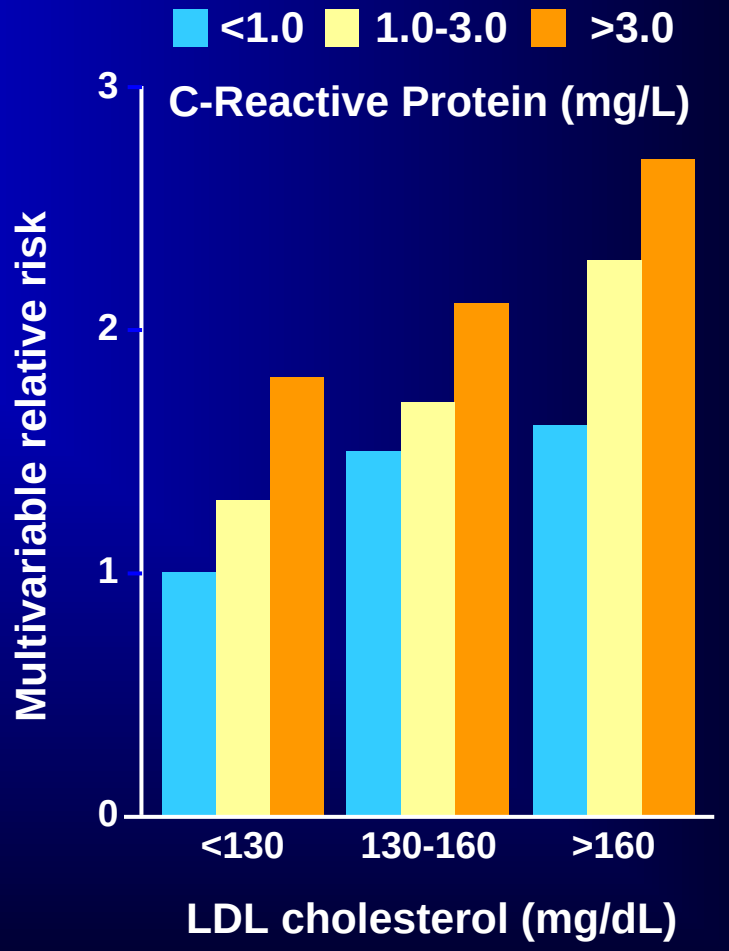
CRP adds prognostic information

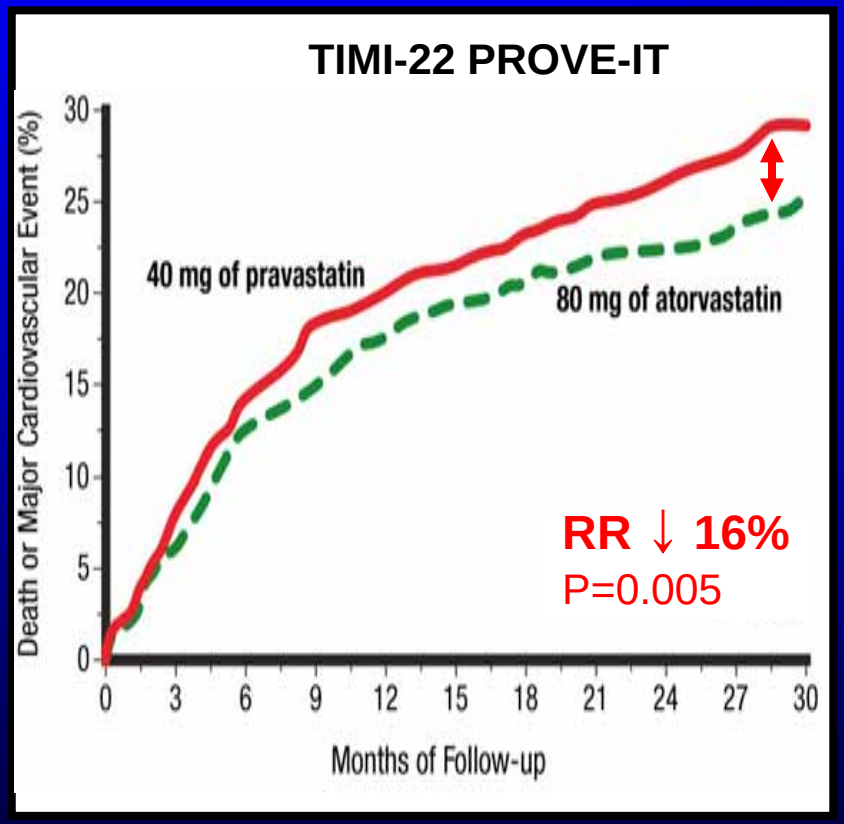




Ridker et al. *N Engl J Med* 2002;347:1557

- **Is there a need for additional treatments in patients at risk of CV events ?**
- What are potential therapeutic targets that are directed at inflammatory processes ?

CV Events: unmet medical needs



- **Maximizing therapy:** in ACS patients (PROVE-IT):
  - revascularization (~70%)
  - antiplatelet Rx (~100%)
  - early statin therapy (100%)
- **Aggressive atorvastatin Rx to new goals:**
  - on treatment LDL=62 mg/dL
- **Events continue to accrue:**
  - Death and CV events at 2 years: 22%

Cannon, C. P. et al. NEJM 2004;350:1495-1504

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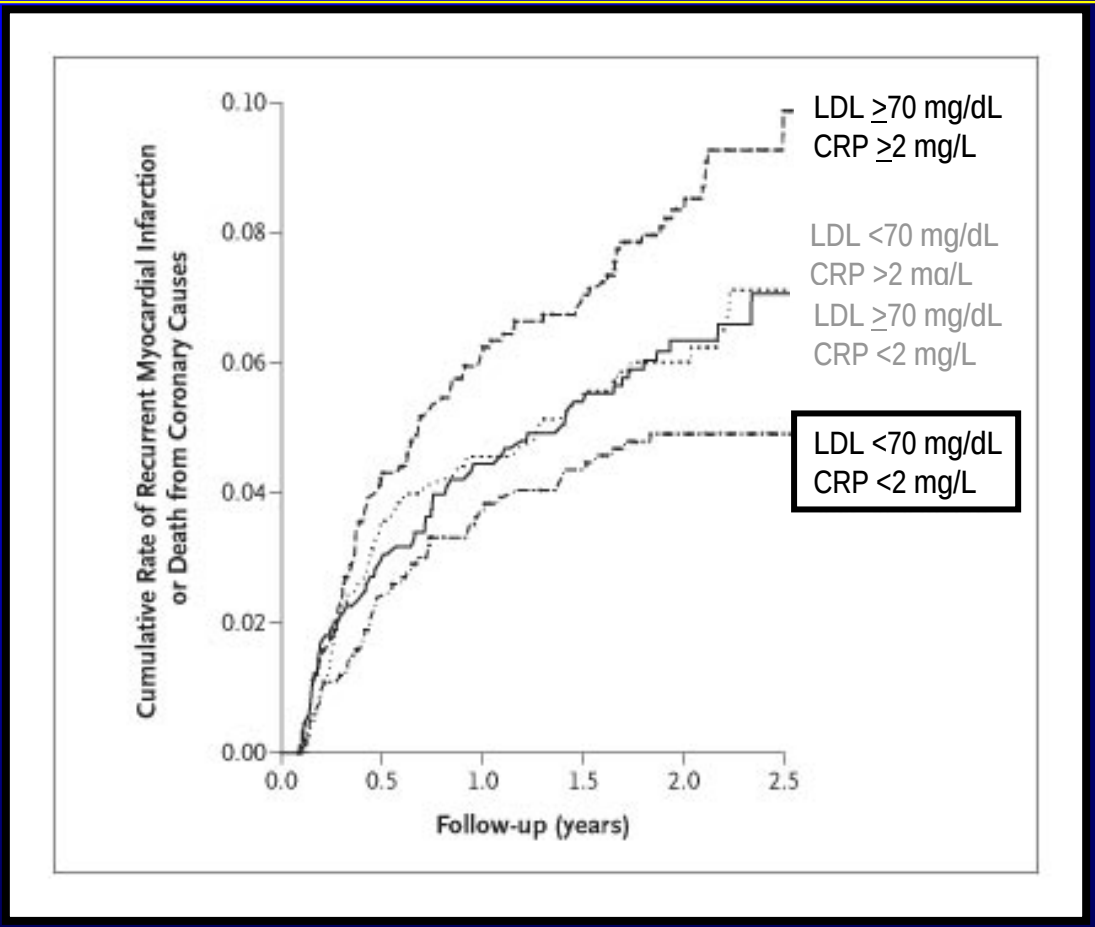
PROVE-IT: anti-inflammatory effect matters



- **PROVE-IT: Among patients with ACS, rapid reduction in CRP to <2mg/L is associated with fewer events at all levels of LDL cholesterol achieved**
- **A-to-Z trial: LDL lowering without CRP reduction has not conferred early clinical benefit**

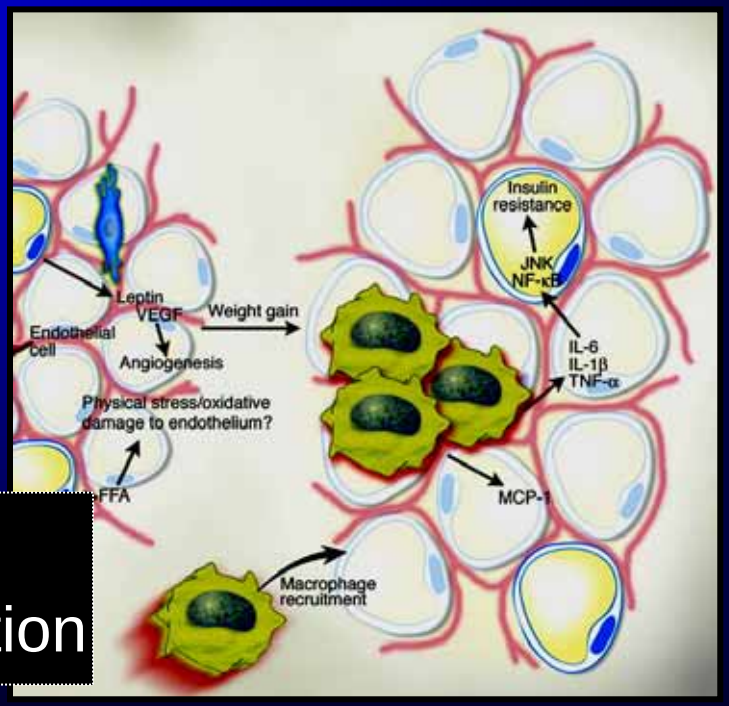
Ridker *N Engl J Med* 2005;352:20; Lemos *JAMA* 2004;292:1307

- Is there a need for additional treatments in patients at risk of CV events ?

- **What are potential <u>new</u> therapeutic targets that are directed at inflammatory processes ?**

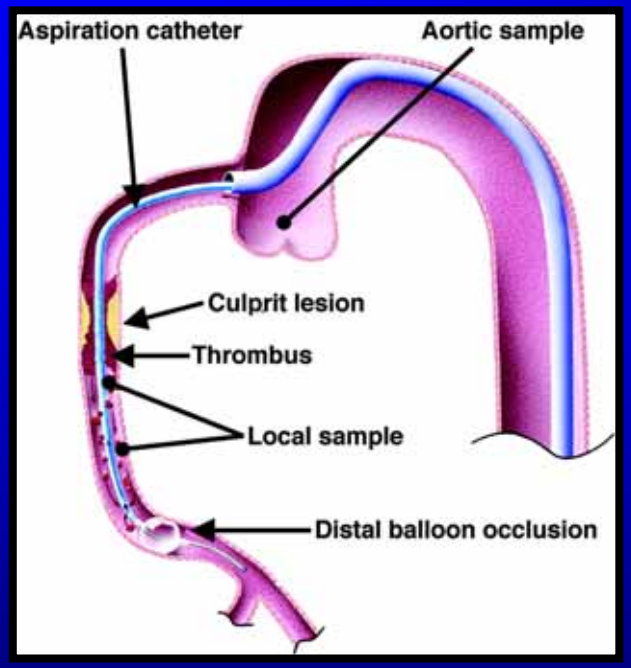
Inflammation: target for CV risk reduction

- Reverse cholesterol transport
- Oxidized LDL

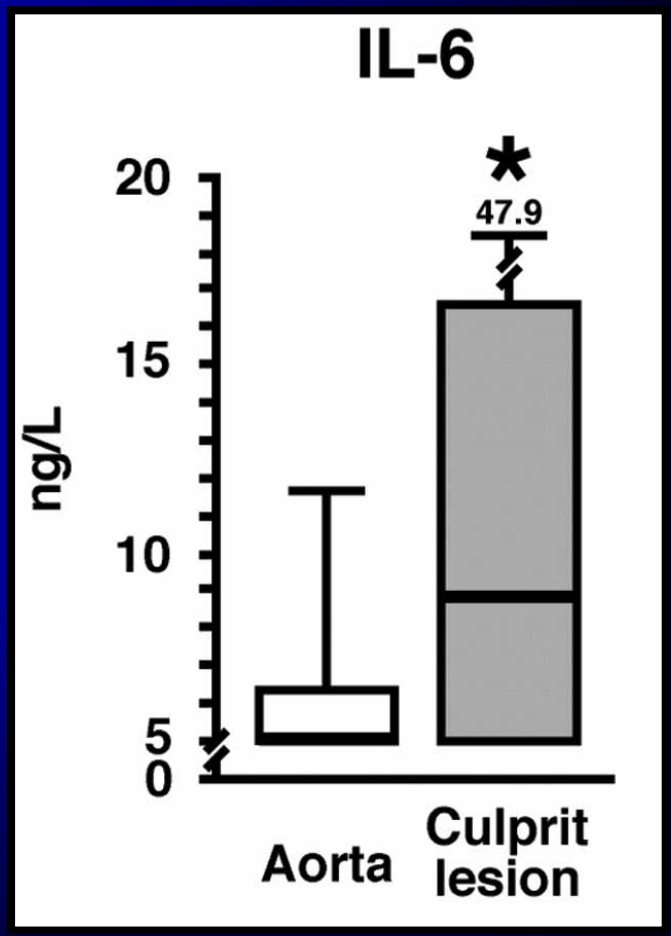


- Insulin resistance
- Local & systemic inflammation

Ruptured plaque releases inflammatory markers

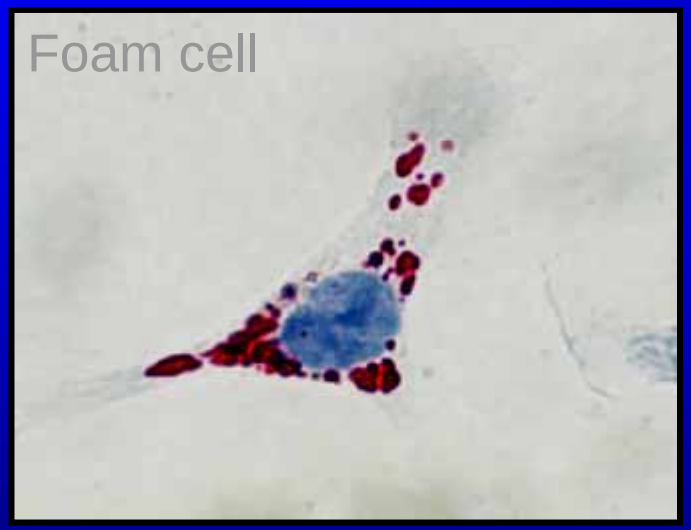


- **In patients with AMI, coronary levels IL-6, SAA are increased at the site of plaque rupture**

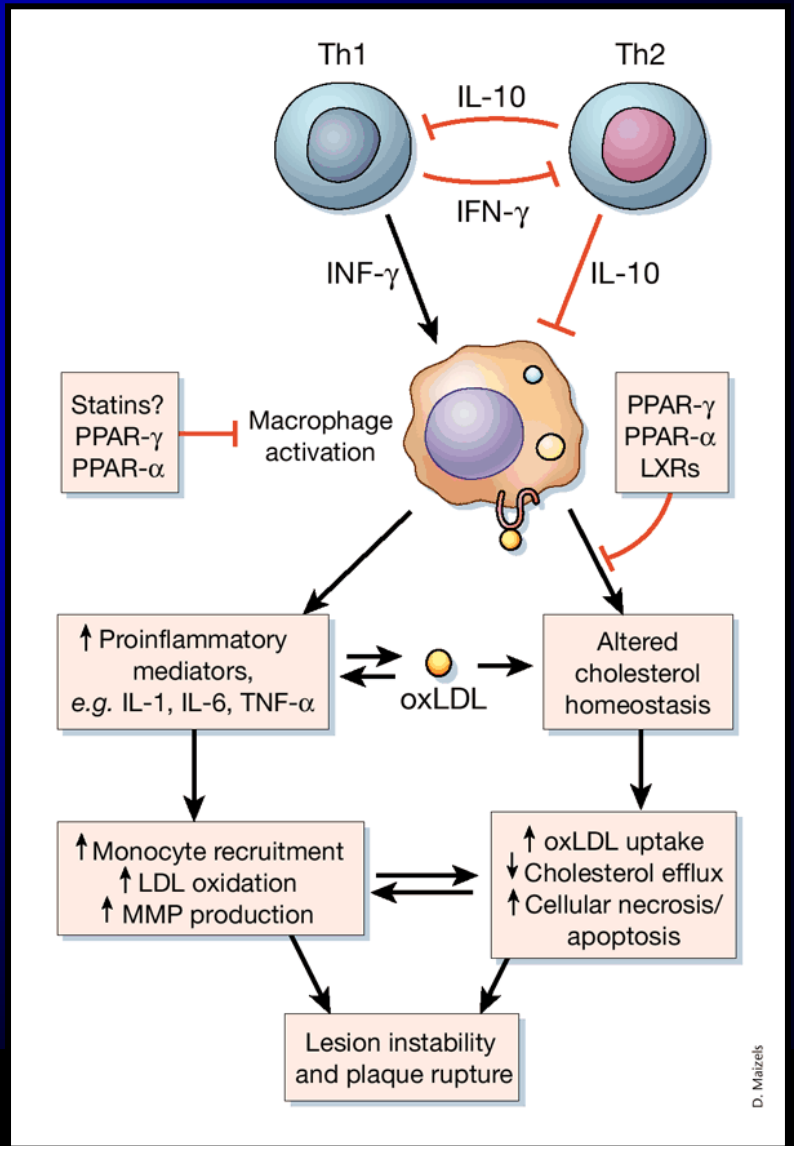


Maier *et al Circ* 2005;111:1355

Targeting macrophage foam cell

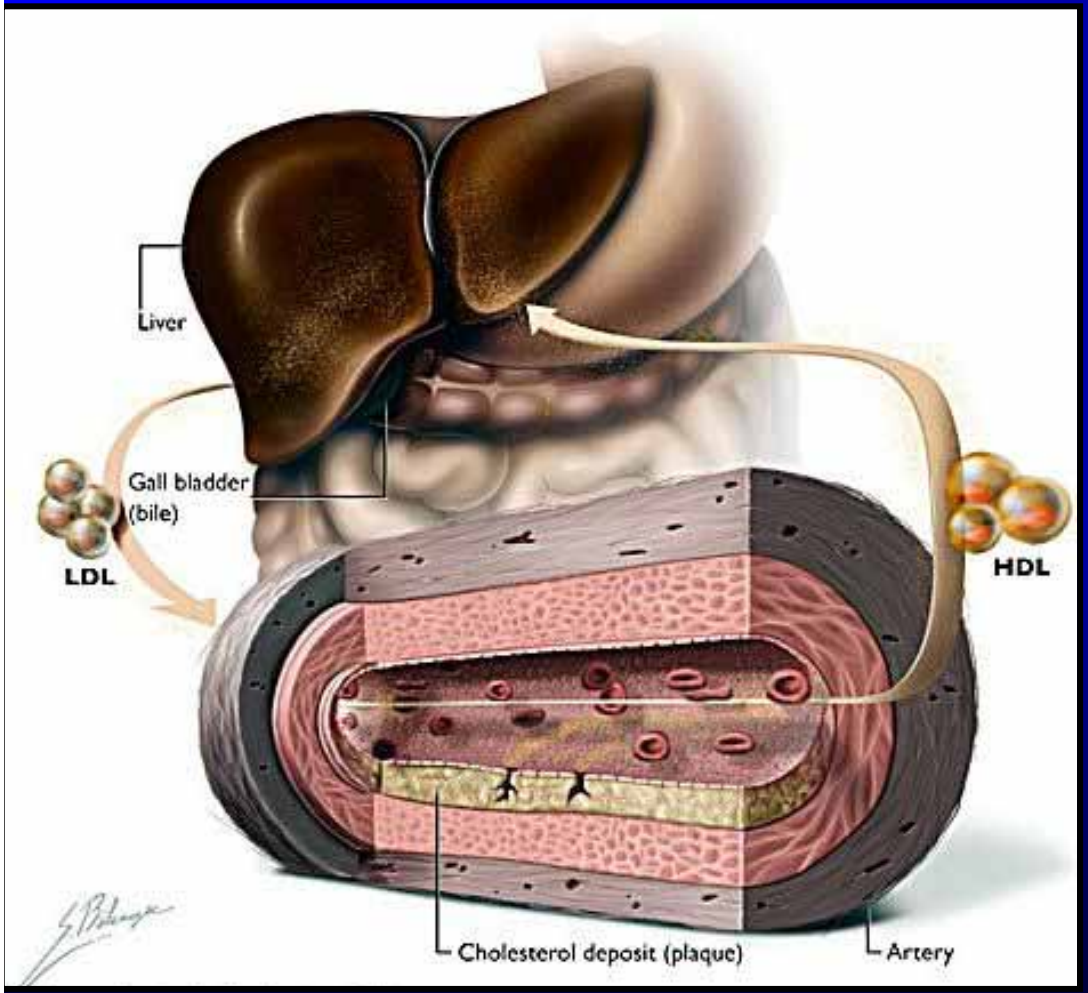


- **Cholesterol accumulation**
- **Inflammation**



Li and Glass. *Nat Med* 2002;8:1235

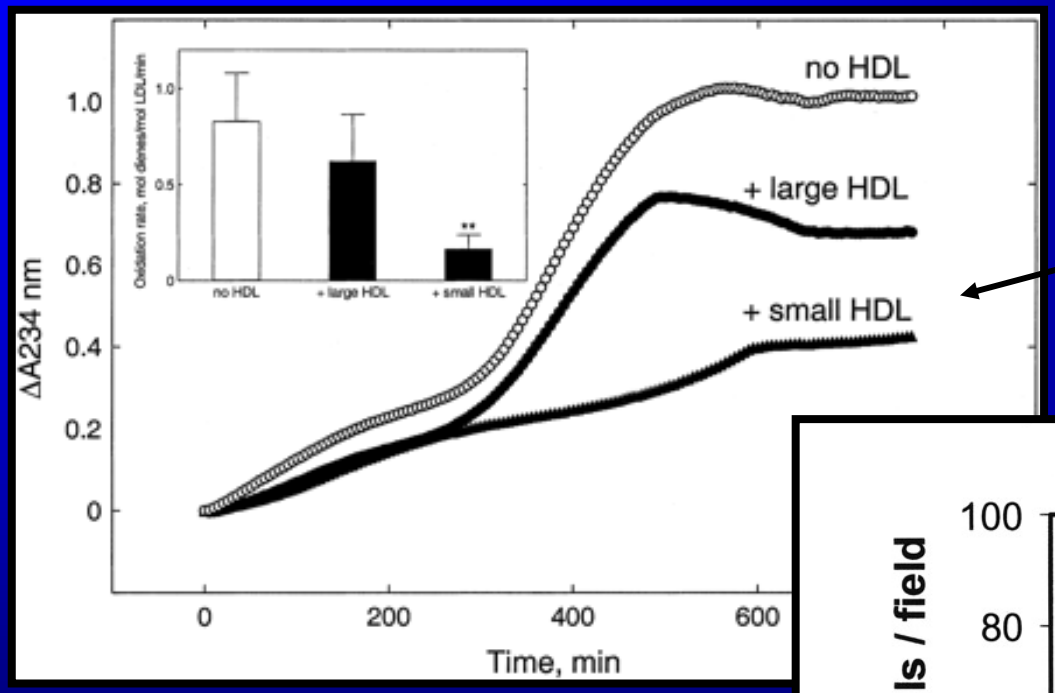
Reverse cholesterol transport



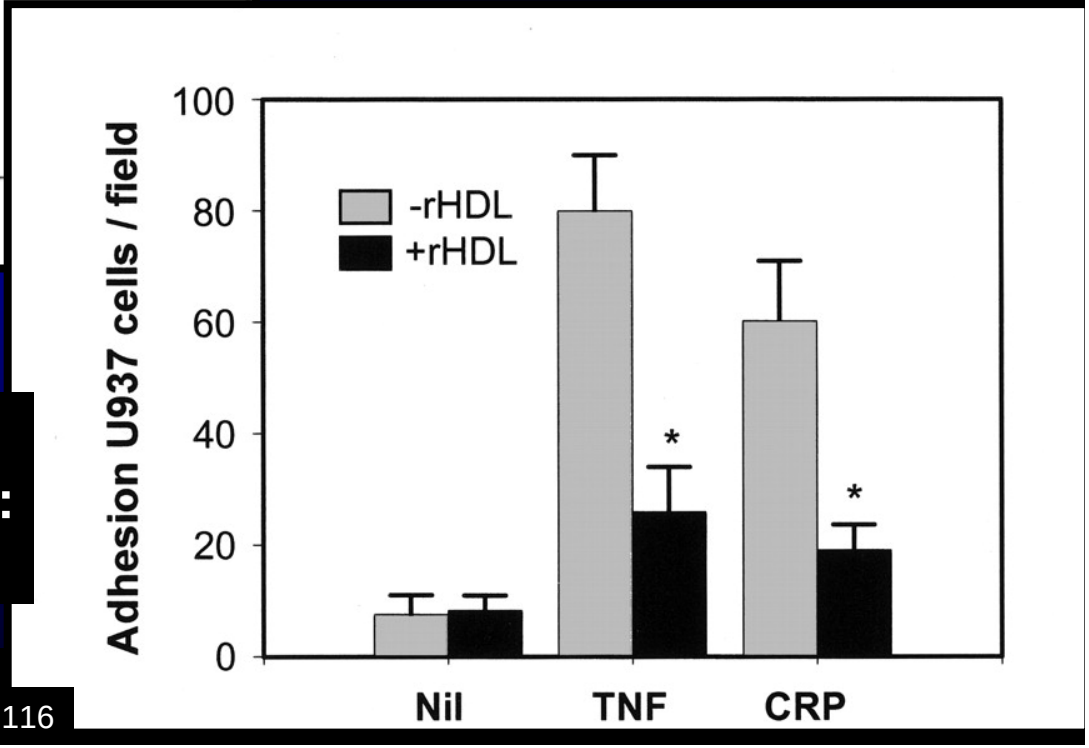
- **Removal of cholesterol**
  - activation of ABCA1 transporter (PPARs, LXR)
  - apoA-I acceptor (apoA-I_M/PL, apoA-I mimetics)
  - CE transfer to the liver (CETP inhibitor)
- **HDL effects**
  - inhibit adhesive molecules on EC (E-selectin, VCAM, ICAM-1)
  - protect LDL from oxidation
  - neutralize effects of CRP

Brewer HB. *ATVB* 2004;24:387; Kontusch *ATVB* 2003;23:1881; Wadham C et al. *Circulation* 2004;109:2116

"Anti-inflammatory" effects of HDL



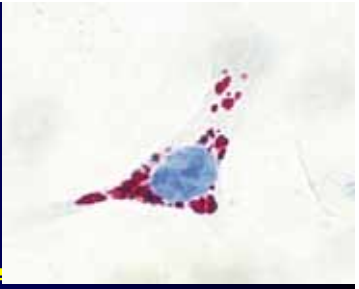
HDL protects LDL from oxidation: *"the size matters"*

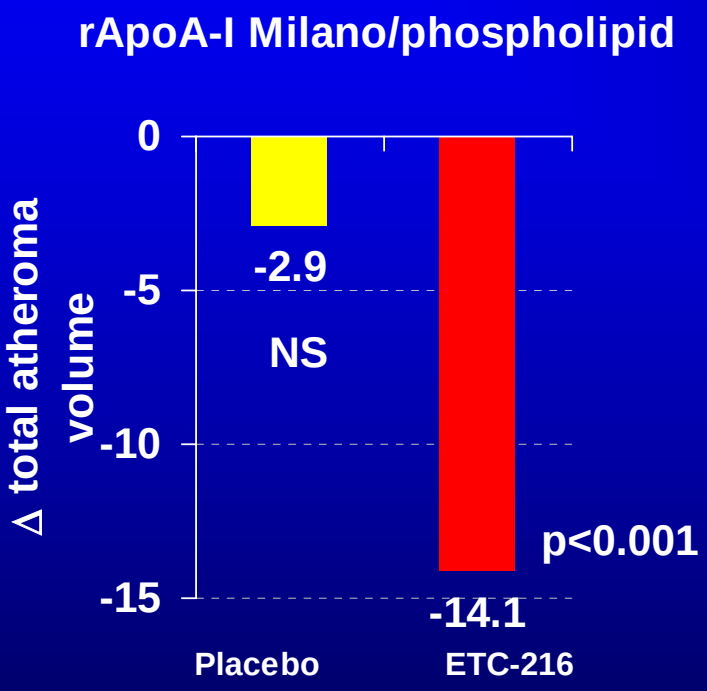


ApoA-I/PL prevents adhesion of monocytes to EC: *"composition matters"*

Kontush. *ATVB* 2003;23:1881; Wadham *Circ* 2004;109;2116

ApoA-I: reverse cholesterol transport





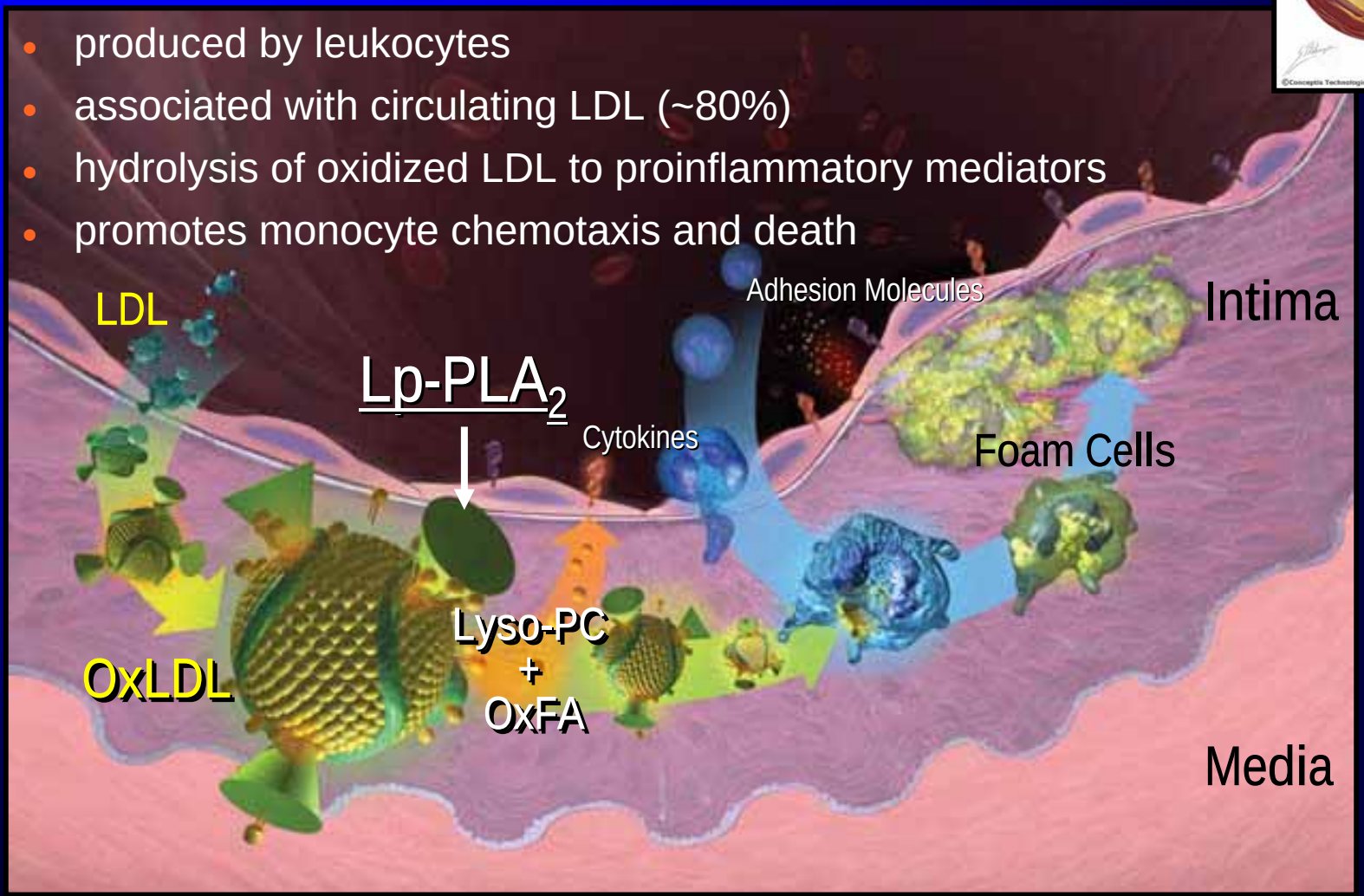
n=11 vs 36; f/u=5 wks

- **Lipid poor ApoA- I:** effective acceptor of free cholesterol
- **Medical genetics:** ApoA-I_M (Cys173Arg) variant → protection against CHD
- **Experimental biology:**
  - apoA-I_M/PL reduces
    - arterial cholesterol and
    - macrophage content (48 hrs)
- **Clinical experience:**
  - restoration of endothelial function (4 hrs)
  - apoA-I_M/PL suggestion of plaque regression by IVUS (5 weeks)

Rye and Barter ATVB 2004;24:421; Spieker Circ 2002;105:1399; Shah *Circ* 2001;103:3047; Nissen *JAMA* 2003;290:2292

Lipoprotein-associated PLA_2

- produced by leukocytes
- associated with circulating LDL (~80%)
- hydrolysis of oxidized LDL to proinflammatory mediators
- promotes monocyte chemotaxis and death



Macphee *Biochem J* 1999,338:479; Zaleweski and Macphee *ATVB* 2005;25:1

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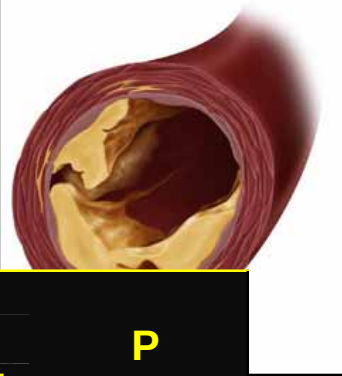
Lp-PLA$_2$: CV events

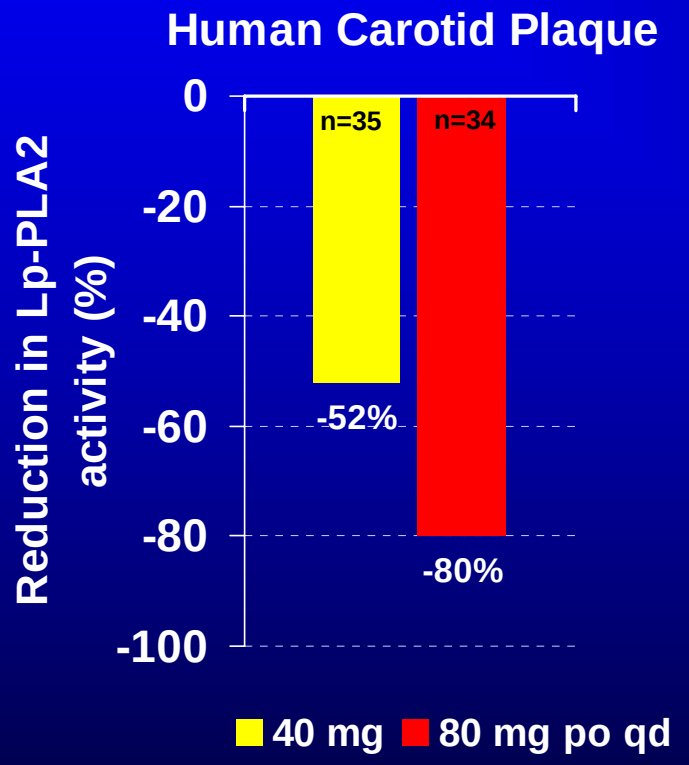


Study	Endpoint	Difference in mean Lp-PLA$_2$ levels	Multivariate-adjusted risk*	P
WOSCOPS	CV death, MI, revasc.	Yes	Yes	**0.005**
WHS	CV death, MI, stroke	Yes	No	**NS**
MONICA	CV death, MI, sudden death	Yes	Yes	**0.04**
ARIC	CV death, MI, revasc.	Yes	LDL <130 mg/dL	**0.05**
ARIC	Stroke	Yes	Yes	**0.015**
Rotterdam	CV death, MI, revasc., VFib, CHF	Yes	Yes	**0.02**
Rotterdam	Stroke	Yes	Yes	**0.04**

* Covariates: age, gender/race (where appropriate), DM, smoking, BMI, systolic BP, LDL, HDL, TG and/or total cholesterol. Several studies further adjusted for WBC and/or CRP and/or fibrinogen.

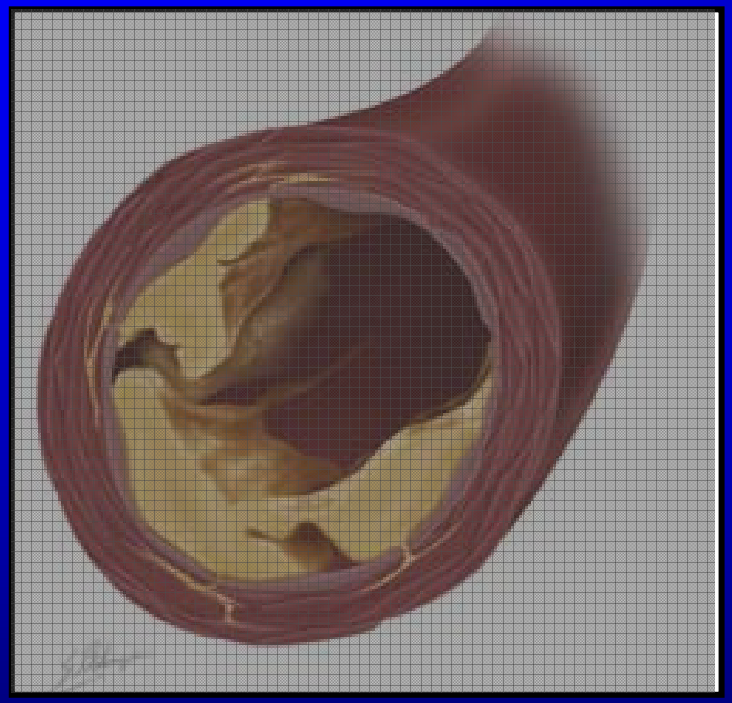
Packard *NEJM* 2000; Blake *JACC* 2001; Konig *Circ* 2004; Ballantyne *Circ* 2004; Oei *Circ* 2005

Lipoprotein-associated PLA_2

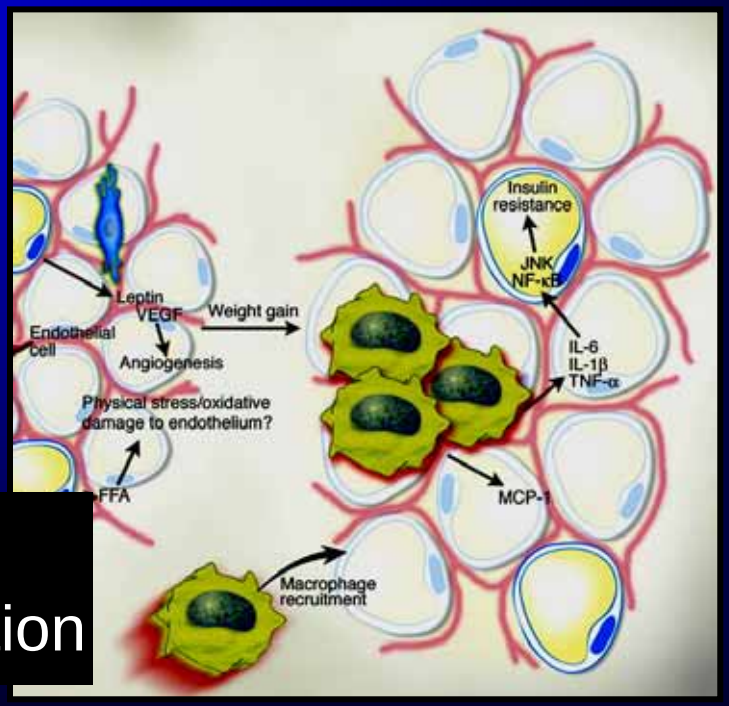


- **Localization:** elevated expression in human plaques (macrophage/T cells);
- **Association:** Lp-PLA_2 expression correlates with genes that confer increased CV risk (MMP-9, 5-LO);
- **Clinical trials:** selective inhibitors reduce Lp-PLA_2 activity in human plasma/plaque

Inflammation: target for CV risk reduction



- Reverse cholesterol transport
- Oxidized LDL



- Insulin resistance
- Local & systemic inflammation

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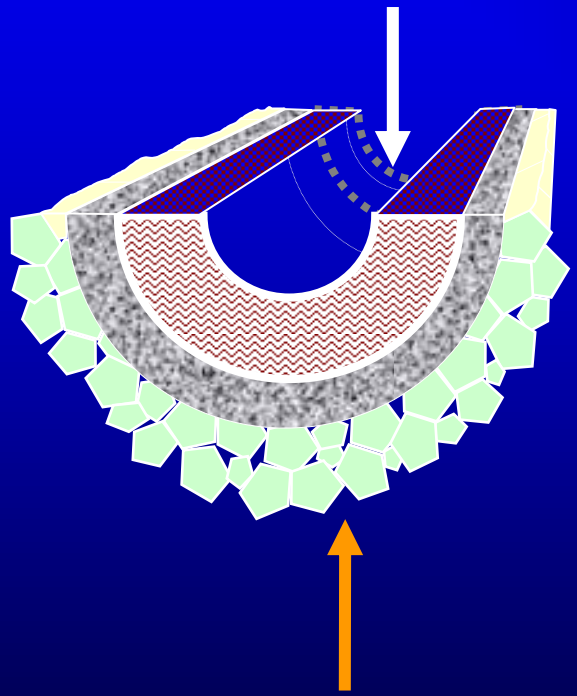
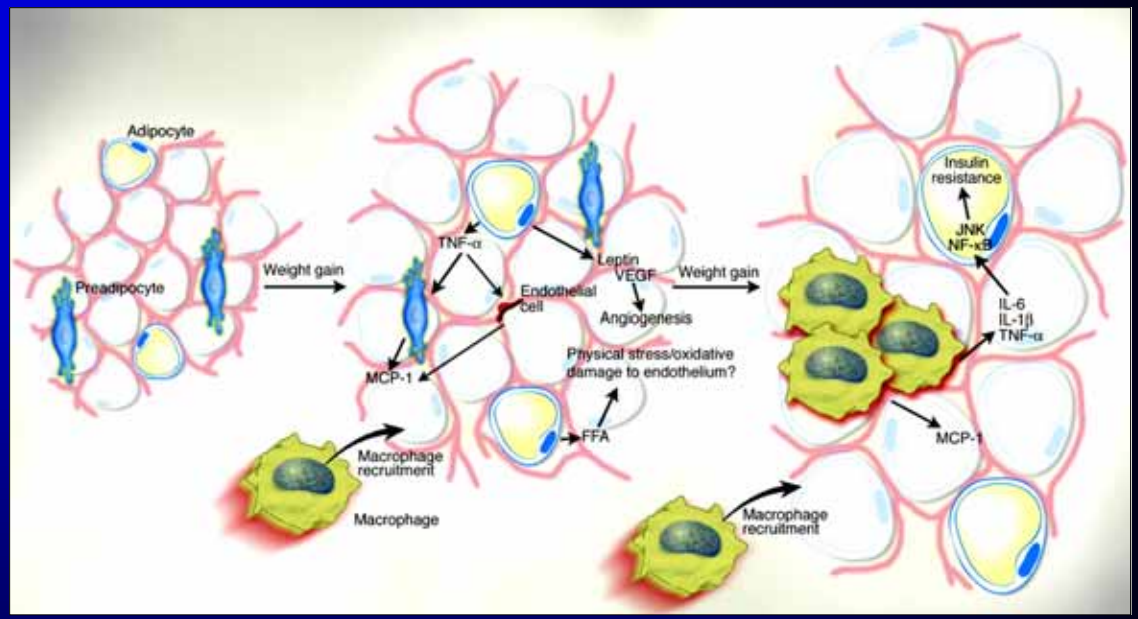
Adipose tissue signaling

Endothelial activation





Perivascular inflammation: "outside-to-inside" signaling (?)

Zalewski *Circ Res* 2002, Mazurek *Circ* 2003;108:2460

Wellen and Hotamisligil *JCI* 2003;112:1785

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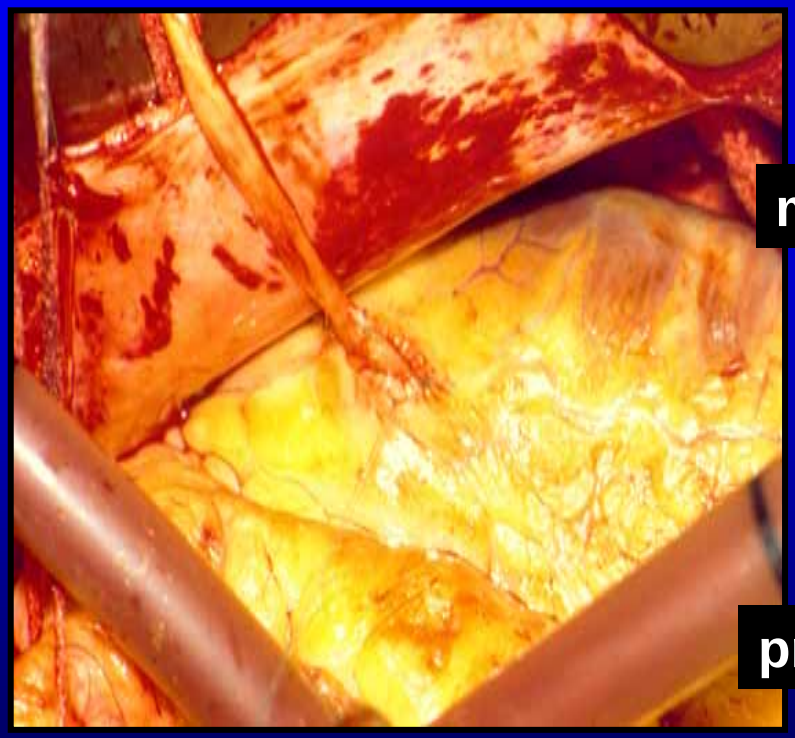
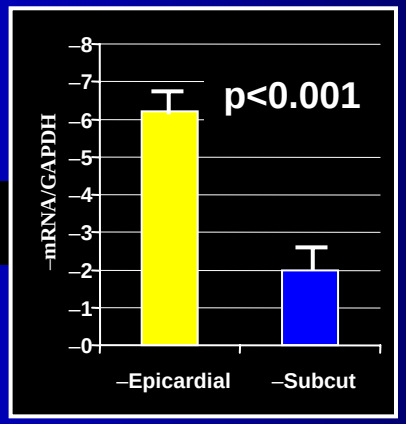
Epicardial fat inflammation in CAD



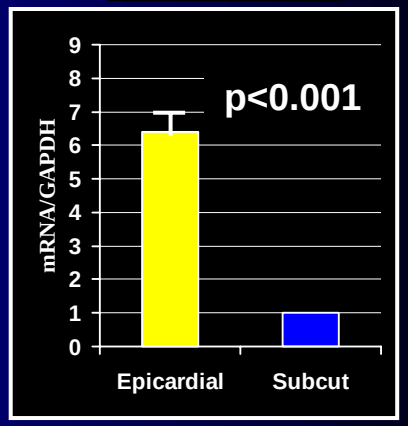
mRNA

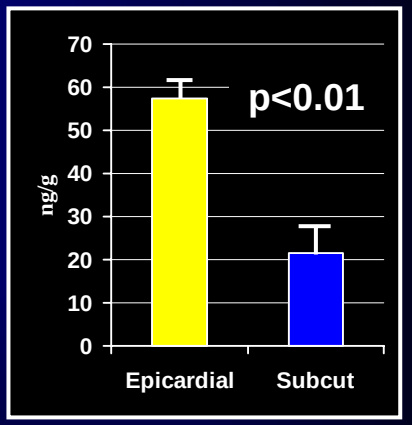
protein

IL-6



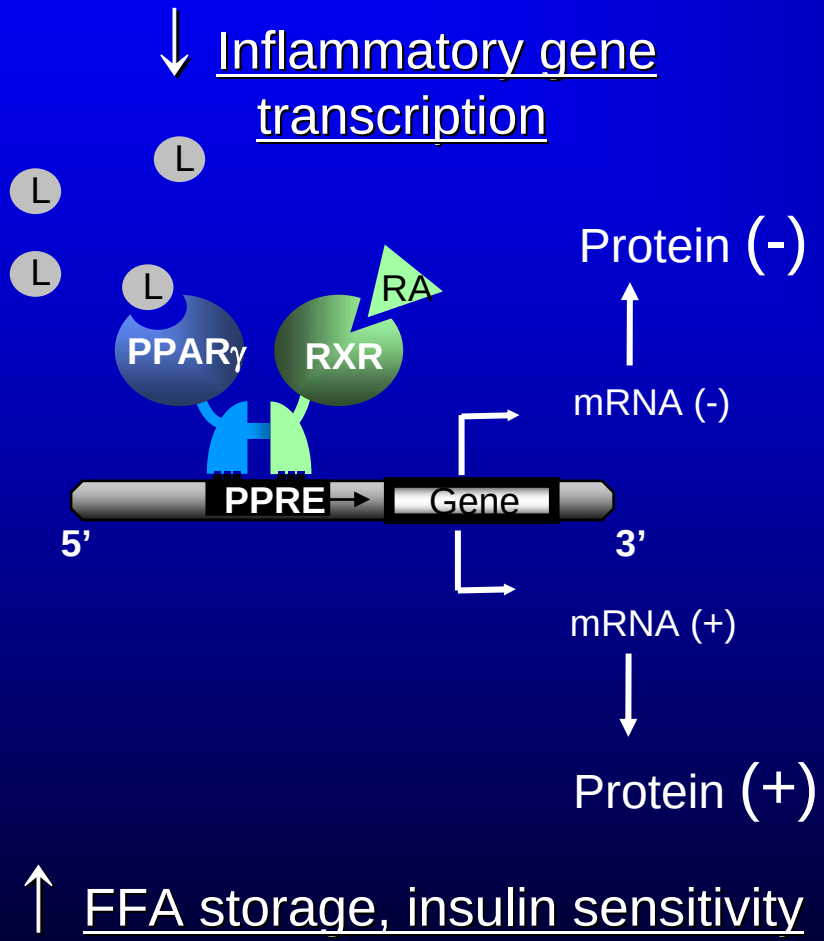
MCP-1





Mazurek et al *Circ* 2003;108:2460

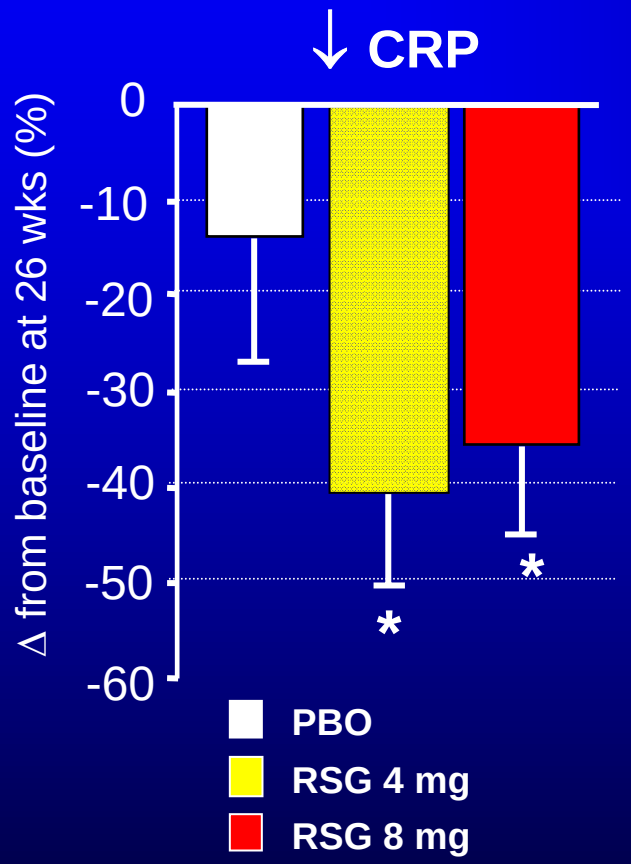
PPAR-γ agonists: "from the belly to the heart"



- **Downregulate inflammation:**
  - adipose tissue (TNFα, FFA)
  - monocytes (cytokines, iNOS)
  - vessel wall (TNFα, MMPs, adhesion molecules)
- **Restore insulin sensitivity:**
  - ≥50% of CHD patients have metabolic syndrome;
  - >60% of post-MI patients have abnormal glucose metabolism;
  - relationship between glucose metabolism and severity of CAD

van Wijk, Rabelink *ATVB* 2004;24:798; Olijhoek *EHJ* 2004;25:342; Norhammar *Lancet* 2002;359:2140; Sasso *JAMA* 2004;291:1857

PPAR γ activation: "from the fat to the heart"

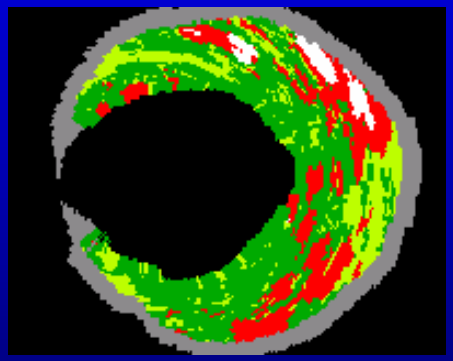


- **Plasma biomarkers:**
  - ↓ inflammatory biomarkers
    - T2DM: CRP, CD40L, MMP-9;
    - non-T2DM: CRP, vWF, E-selectin
- **Atherosclerosis progression:**
  - carotid IMT: CHICAGO (pioglitazone)
  - coronary IVUS: APPROACH (rosiglitazone), PERISCOPE (pioglitazone);
- **CV outcomes:**
  - PROactive=5,000,
  - RECORD; n=4200,
  - BARI-2D: n=2800, f/u 5-6 yrs.

Haffner *Circ* 2002;106:679; Sidhu *JACC* 2003;42:1757; Raji *Diab Care* 2003;26:172; Sidhu *ATVB* 2004;24:930

Quo vadis: inflammation and beyond….

- **Human tissue studies**
  - mechanisms of disease
  - novel targets → more effective Rx (?)



- **Clinical index of risk** (intermediate endpoints)
  - plaque imaging: structural vs compositional
  - plasma biomarkers & global approach…omics

- **Outcome studies:** closing therapeutic gap in "post HPS/PROVE-IT era":
  - high risk populations: post ACS, metabolic syndrome/diabetes, renal impairment….