Inflammation, Plaque Stability Imaging, and Clinical Trials

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Features of Rupture Prone Plaque

Inflammation; **Macrophage,**
sICAM-1, Fibrinogen, CRP…

Thin cap

Large necrotic core

Angiogenesis

Intraplaque hemorrhage

Expansive remodeling

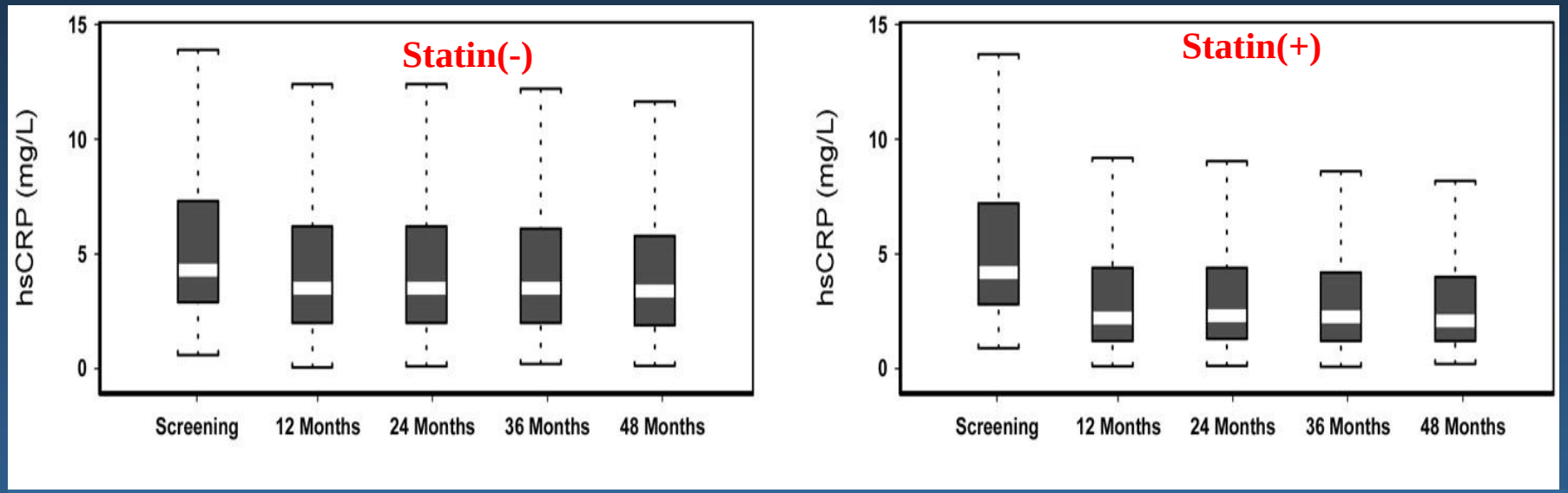
Spotty Calcification

CRP?

- **Reliability of hsCRP Measurements**
- **Epidemiologic Evidence**
- **In Vivo Evidence of Imaging Studies**
- **Causal Evidence of Genetic, Pathologic, and Clinical Studies**
- **Ongoing Studies Targeting Inflammation**

Tracking of High-Sensitivity C-Reactive Protein after an Initially Elevated Concentration: 8901 pts (JUPTER)

The distributions of hsCRP at the screening visit and at 12, 24, 36, and 48 months



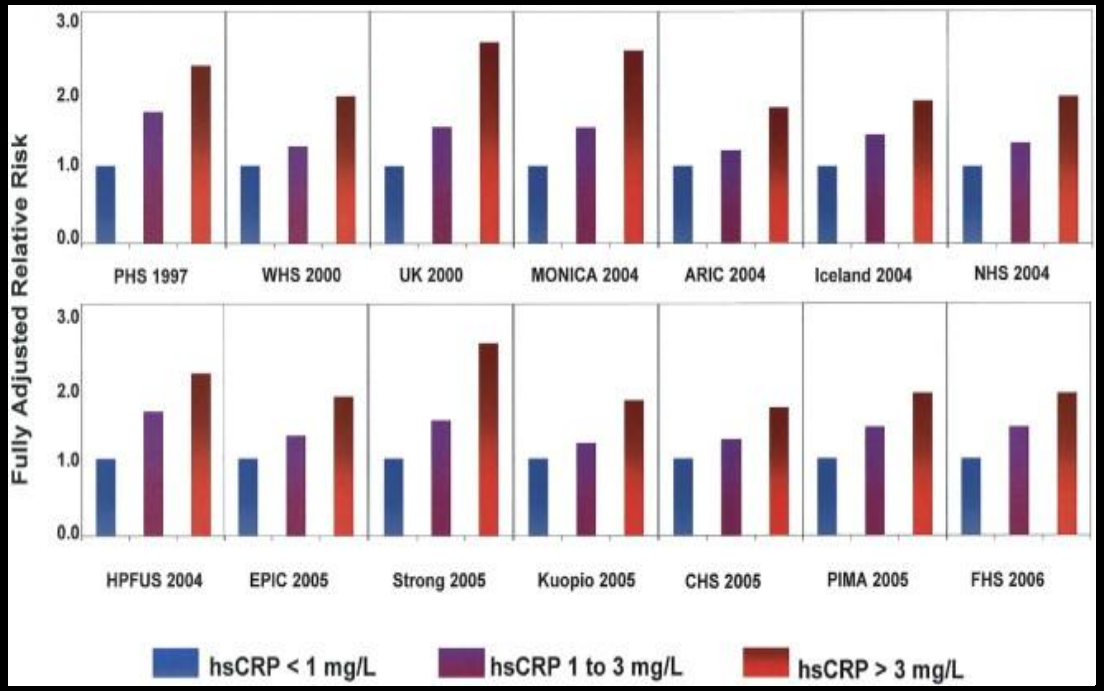
This study indicate temporal stability of hsCRP.

Tracking correlations for hsCRP over time were comparable to those for blood pressure and LDL cholesterol

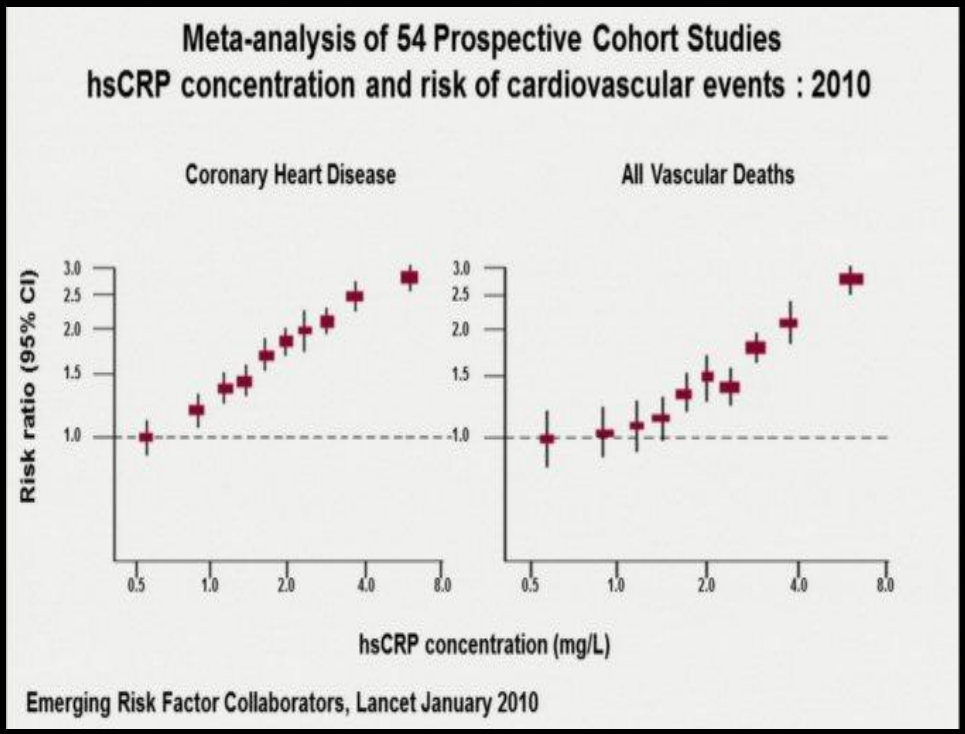
Glynn et al. Clinic chem 2009;55:305

Epidemiologic evidence linking inflammatory biomarkers such as C-reactive protein

The predictive value in 14 apparently healthy populations with baseline hsCRP levels of <1 mg/l, 1 to 3 mg/l, and >3 mg/l after adjustment for traditional risk factors

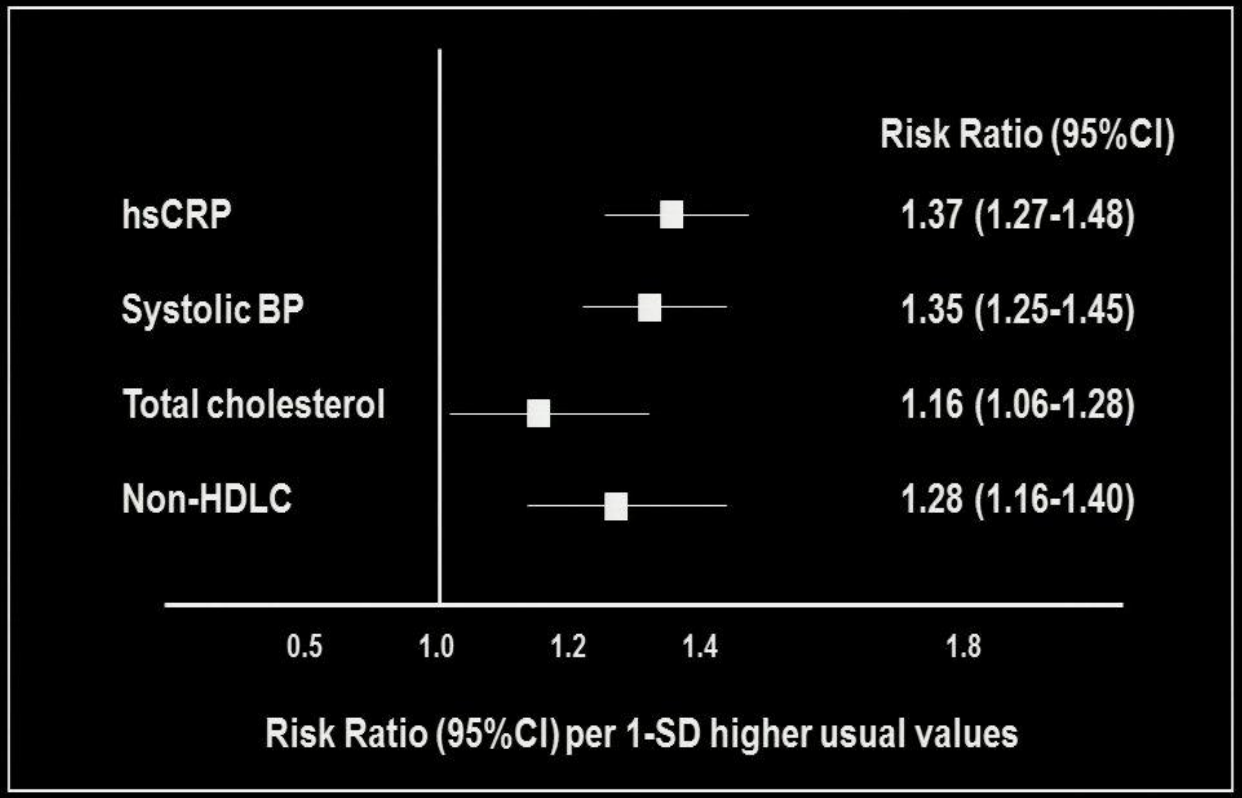


Inflammation is a strong and consistent of predictor of CV risk



Ridker PM. J Am Coll Cardiol 2007;49:2129–38

The magnitude of cardiovascular risk associated with a one standard deviation increase in hsCRP is at least as large as that associated with a one standard deviation increase of BP and cholesterol



Adjusted for age, gender, smoking, diabetes, BMI, triglycerides, alcohol, lipid levels, and hsCRP

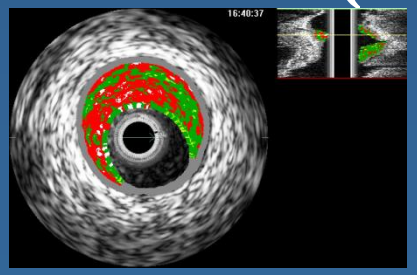
Emerging Risk Factor Collaborators, Lancet January 2010

Changes of Plaque Composition after Statin Therapy in Patients with Acute Coronary Syndrome;

Classification and Analysis by IntraVascular UltraSound-Virtual Histology:

Non-Culprit Plaque(n=54)

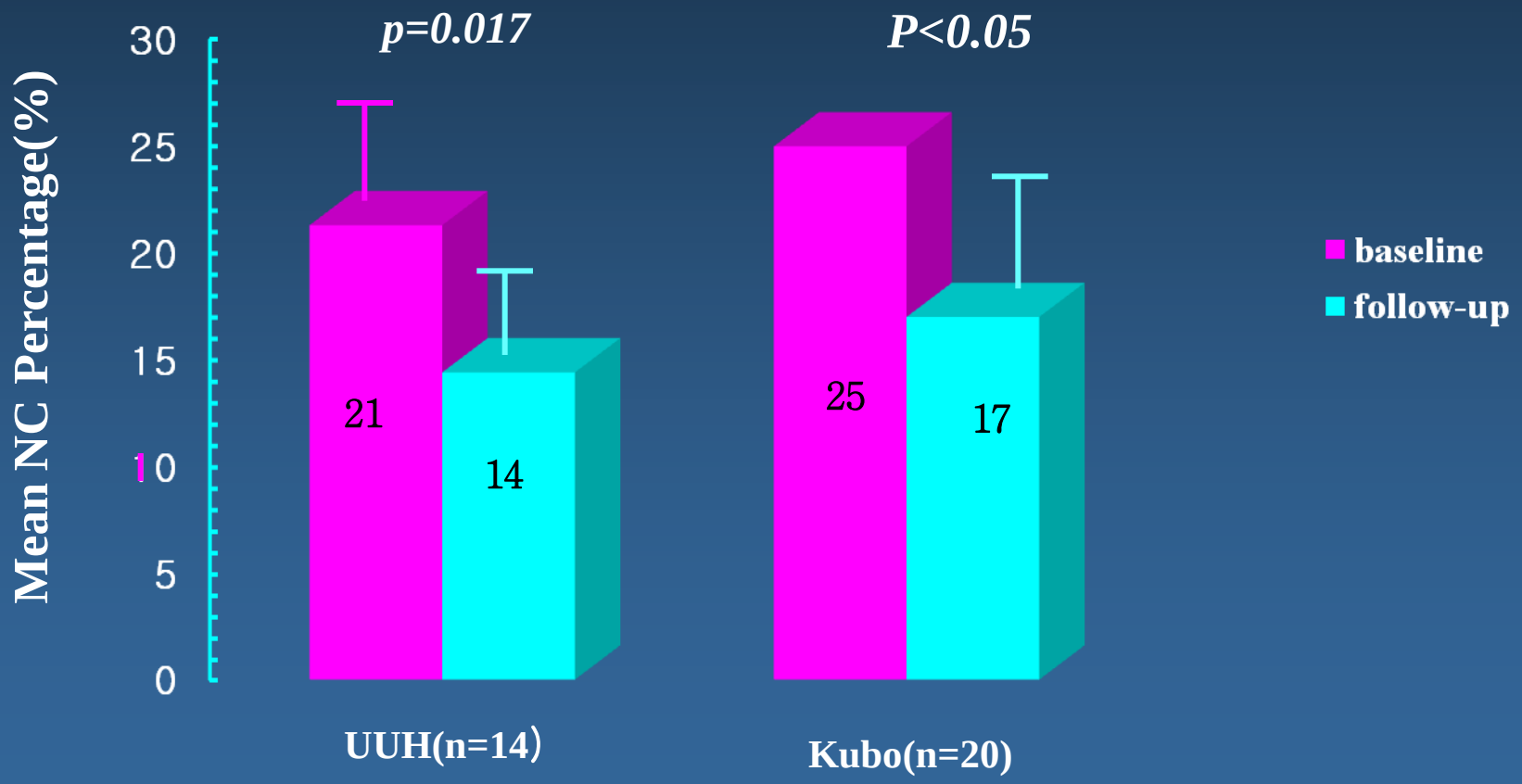
TCFA: n=14 (26%)



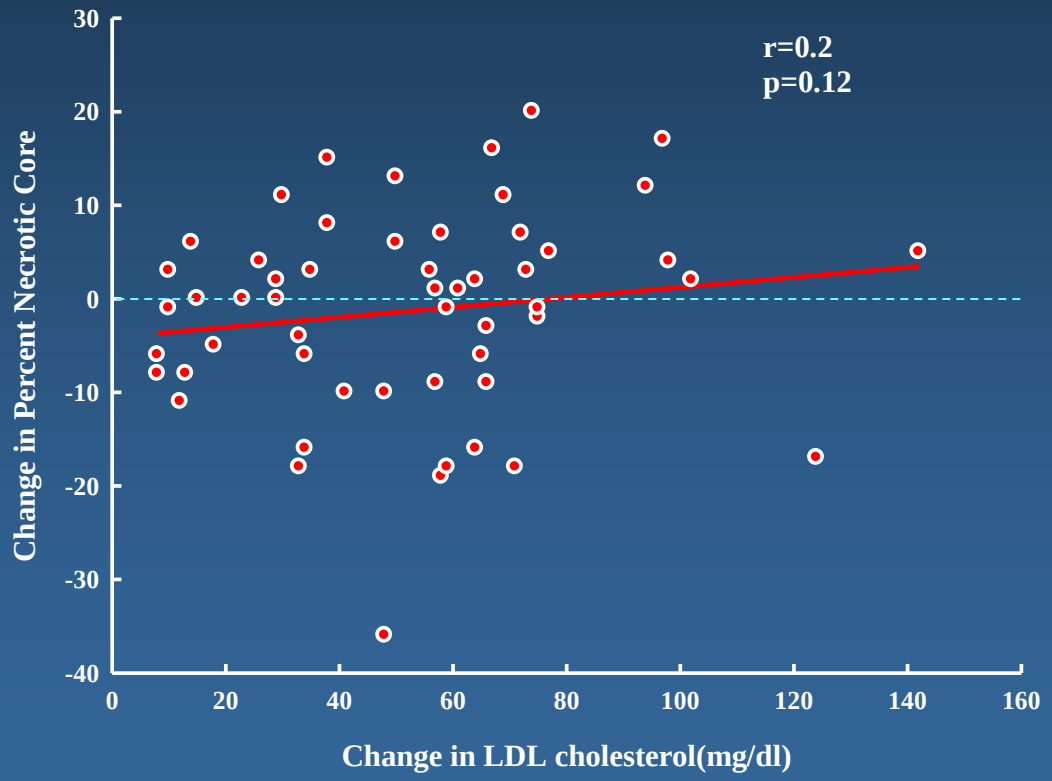
Non-TCFA: n=40 (74%)

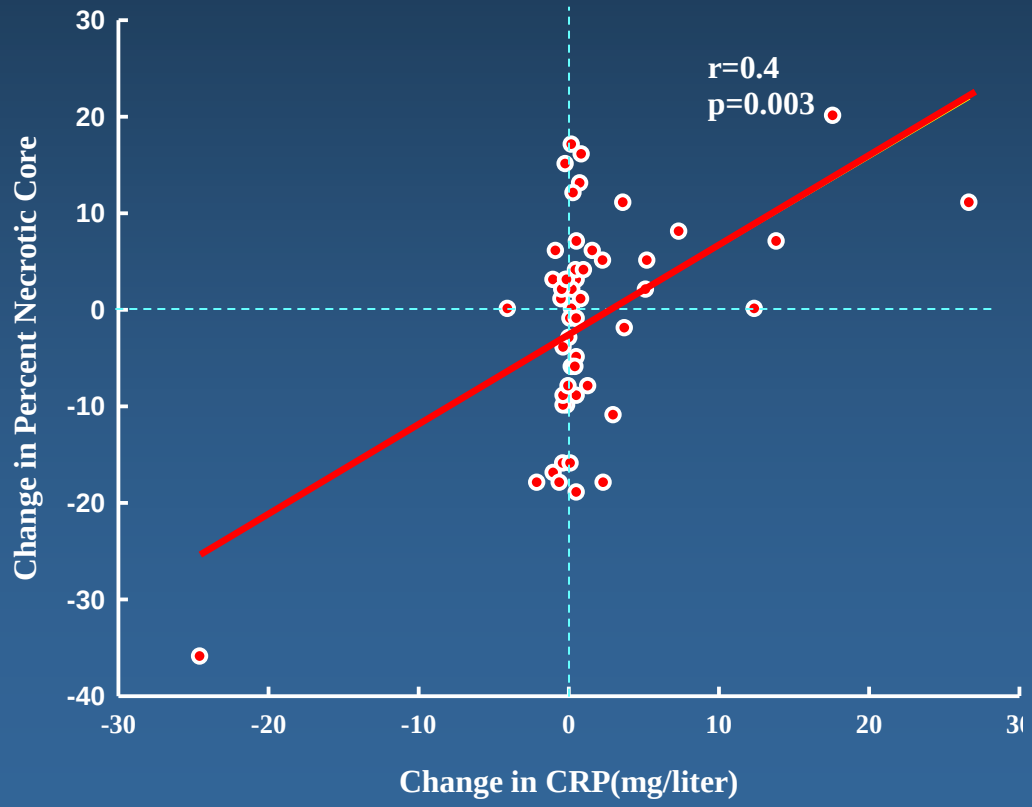
Lee SG et al. Y Med J 2013;54:336

Changes of percent necrotic core in VH-TCFA between Baseline and Follow-up



Correlation between change of necrotic core percentage and change of LDL-C and hsCRP level



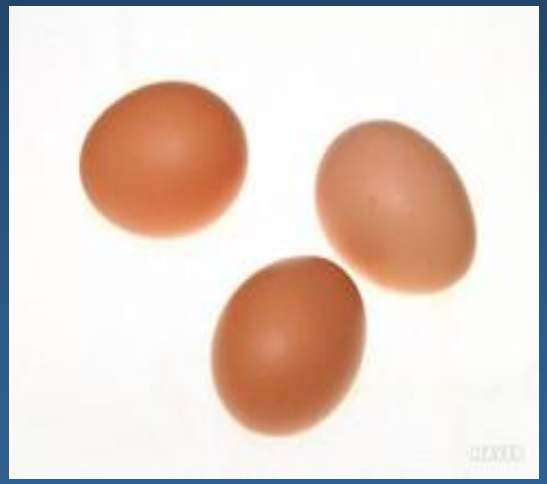


Effects of statin therapy on changes in TCFA

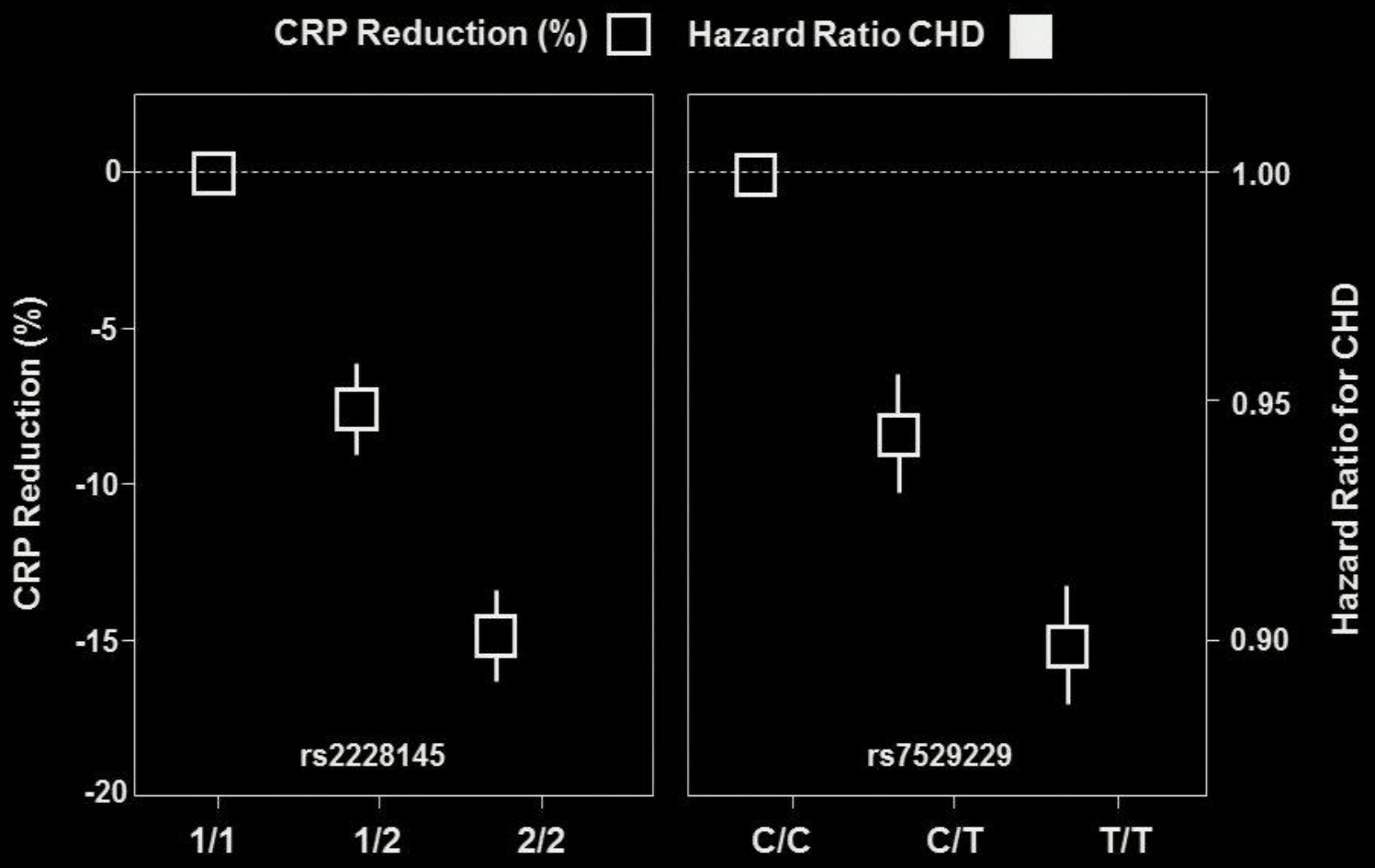
Study	Imaging tool	TCFA	hsCRP	correlation	p
SATURN (n=71)	VH-IVUS	%necrotic core	on-treatment hs CRP	r=0.25	0.03
Toyohashi (n=63)	OCT	fibrous cap thickness	change in hsCRP	r=0.42	0.001

Eur Heart J Cardiovasc Imaging 2014 ;15(4):380-8
Am J Cardiol 2014;113:580-587

Elevated CRP in Atherosclerosis- *Chicken or Egg?*



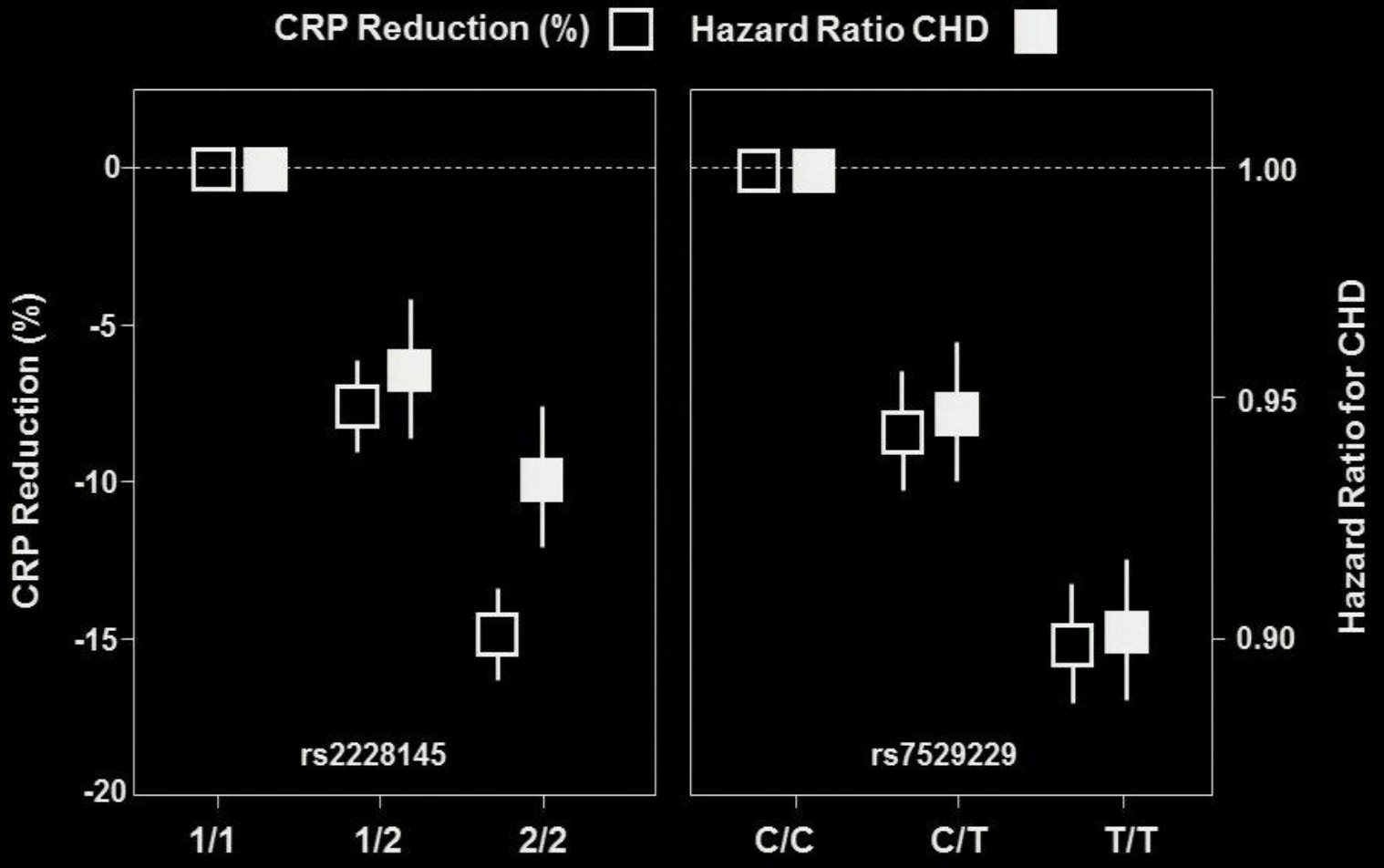
Effects on Polymorphism in the IL-6 receptor Signaling Pathway On downstream CRP Levels: *a collaborative meta-analysis of 82 studies*



Sawar N et al, Lancet 2012;379;1205-13

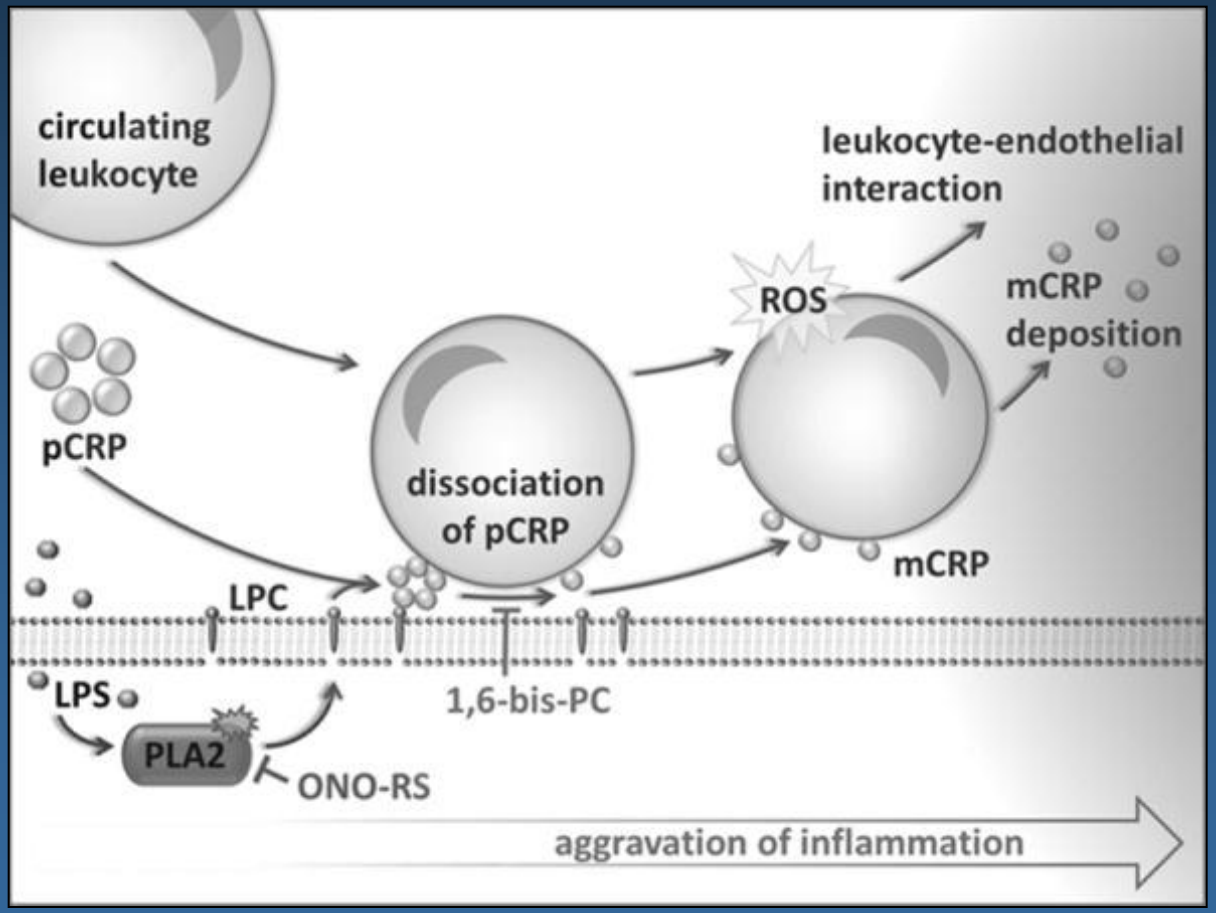
Swerdlow et al, Lancet 2012;379;1214-24

Effects on Polymorphism in the IL-6 receptor Signaling Pathway On Downstream CRP Levels and Risks of Coronary Heart Disease



Sawar N et al, Lancet 2012;379;1205-13 Swerdlow et al, Lancet 2012;379;1214-24

Proposed mechanism of phospholipase A2 (PLA2)-mediated lysophosphatidylcholine (LPC) generation and consecutive pentameric C-reactive protein (pCRP) dissociation in lipopolysaccharide (LPS)-induced inflammation.



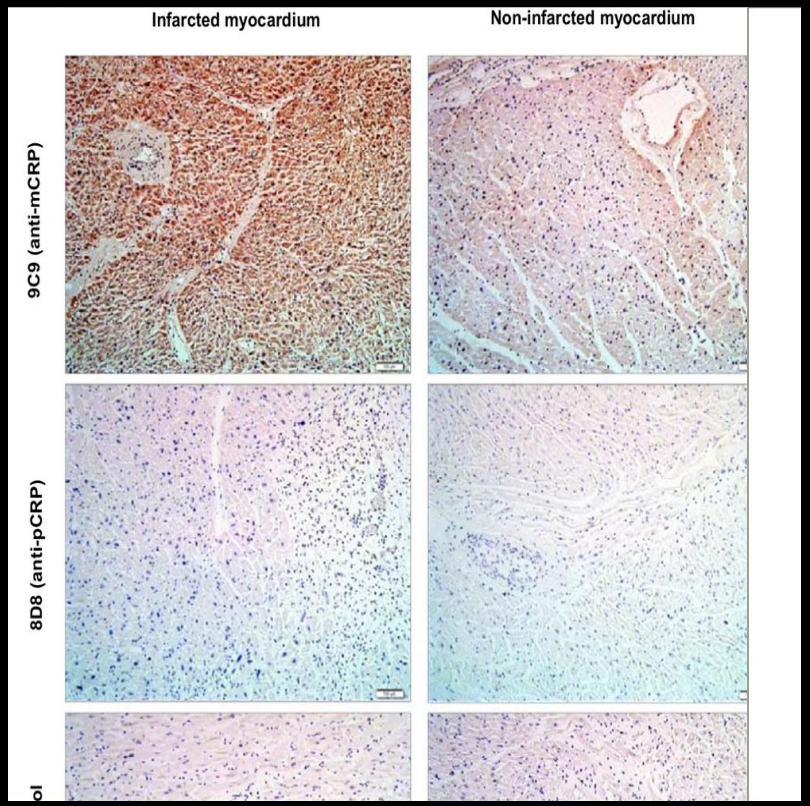
LPC is expressed on activated membranes via induction of PLA2 and mediates the dissociation of pCRP to mCRP

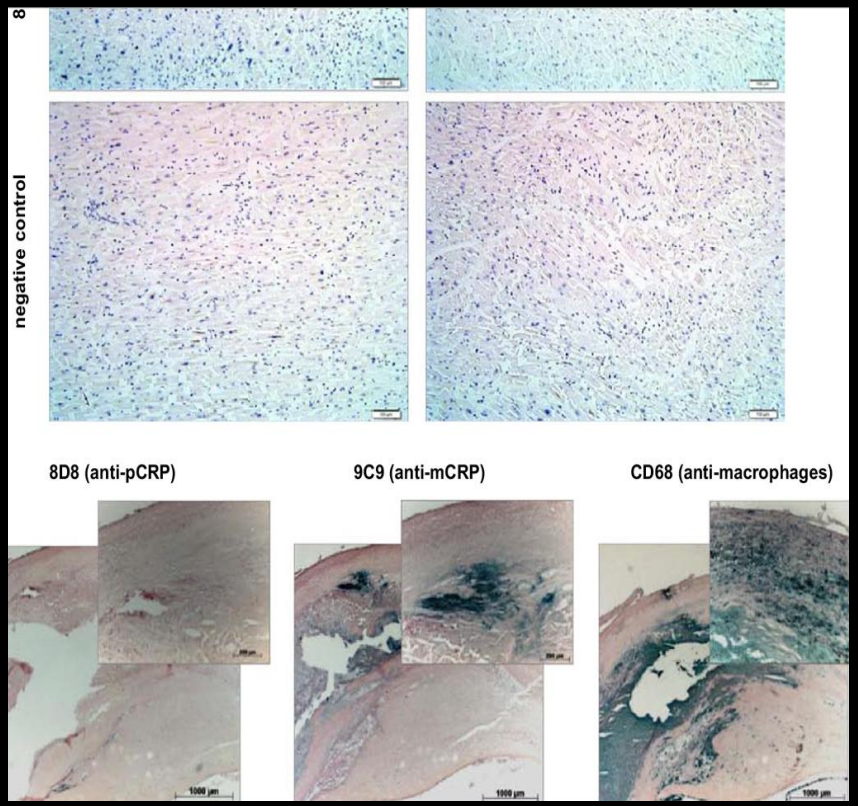
Monomeric subunit of C-reactive protein (mCRP) triggers leukocyte-endothelium interaction and is deposited in areas of inflammation.

Thiele et al. Circulation 2014;130:35

Dissociation of Pentameric to Monomeric C-Reactive Protein Localizes and Aggravates Inflammation: In Vivo Proof of a Powerful Proinflammatory Mechanism and a New Anti-Inflammatory Strategy

in vivo evidence for a novel mechanism that localizes and aggravates inflammation via phospholipase A2–dependent dissociation of circulating pCRP to mCRP





JUPITER

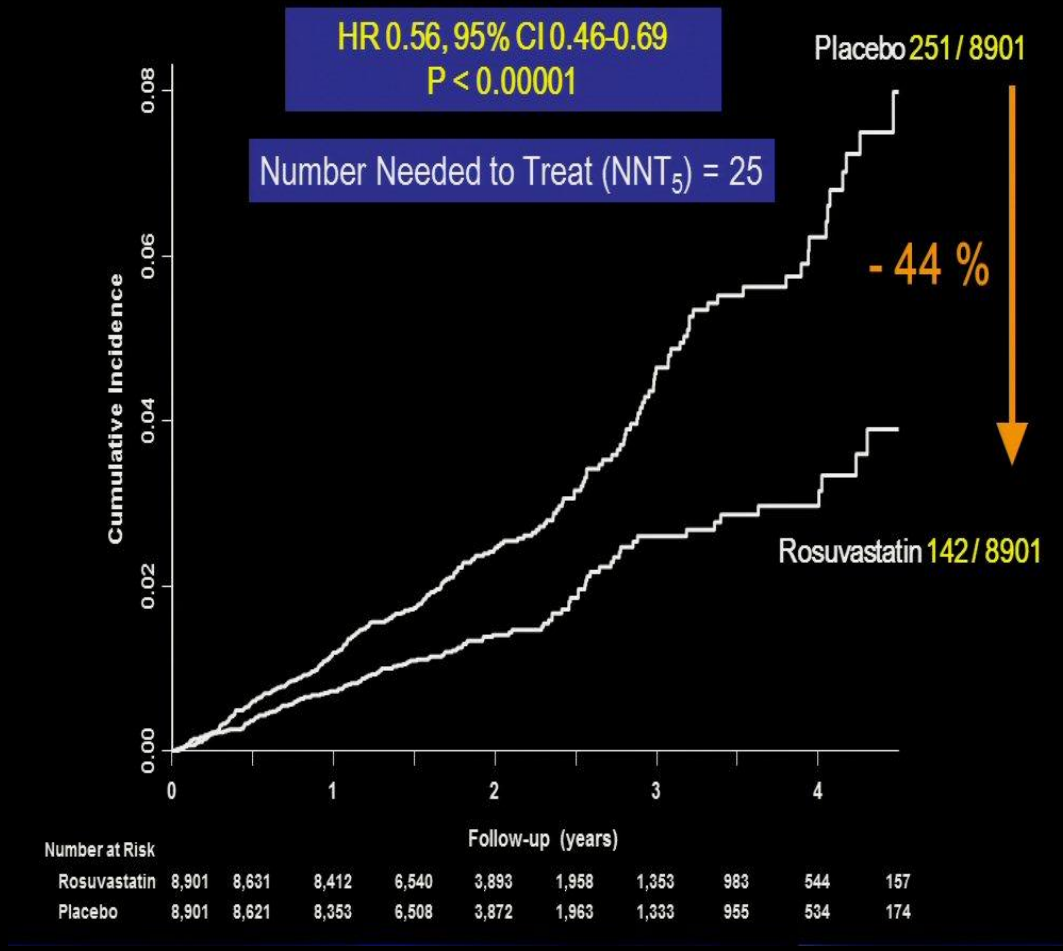
Primary Endpoint: MI, Stroke, UA/Revasc, CV death

JUPITER

Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP

Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

Mean LDLC 104 mg/dL, Mean HDLC 50 mg/dL, hsCRP 4 mg/L

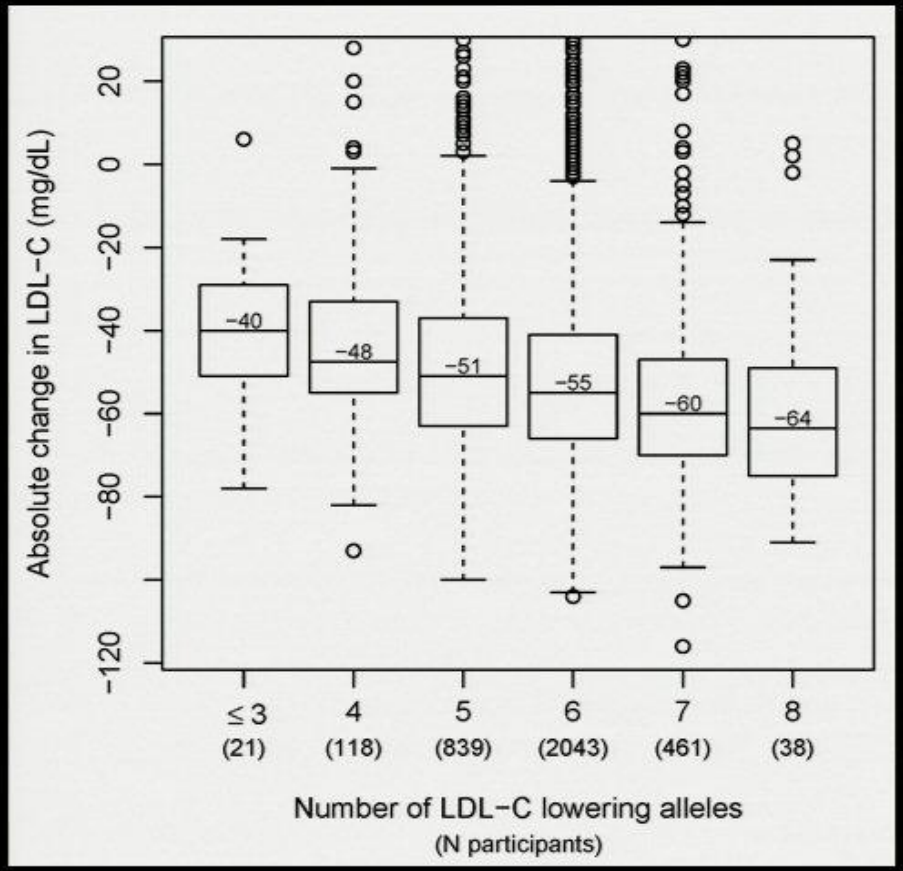


Ridker et al NEJM 2008;359:219

JUPITER
LDL reduction, hsCRP reduction, or both

The genetic determinants of rosuvastatin-induced LDL-C reduction do not predict rosuvastatin-induced CRP reduction

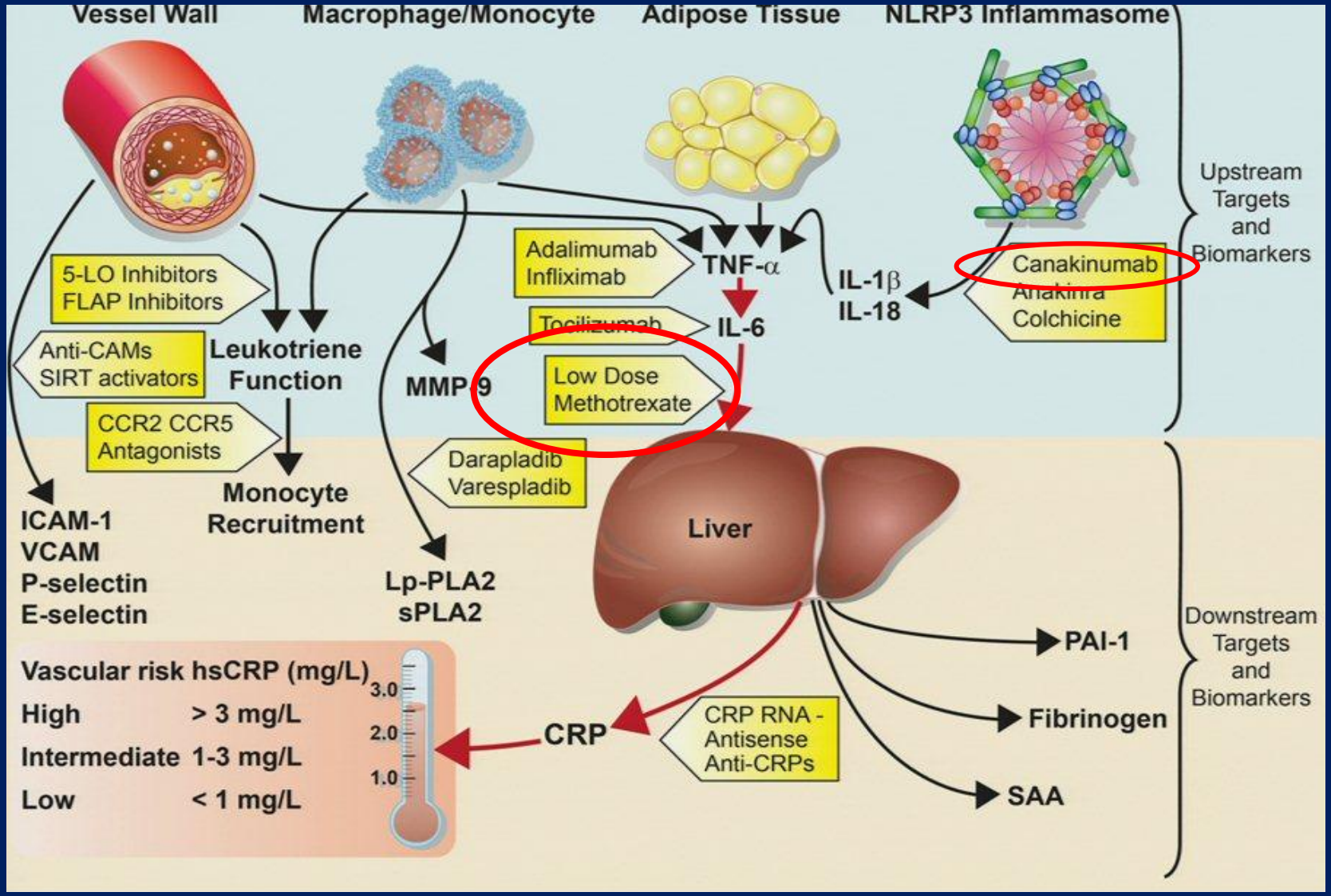
The genetic determinants of rousvastatin-induced CRP reduction do not predict rosuvastatin-induced LDL-C reduction



Chu et al Circ Cardiovasc Genet. 2012;5:58

Targeting Inflammatory Pathways for the Treatment of Cardiovascular Disease

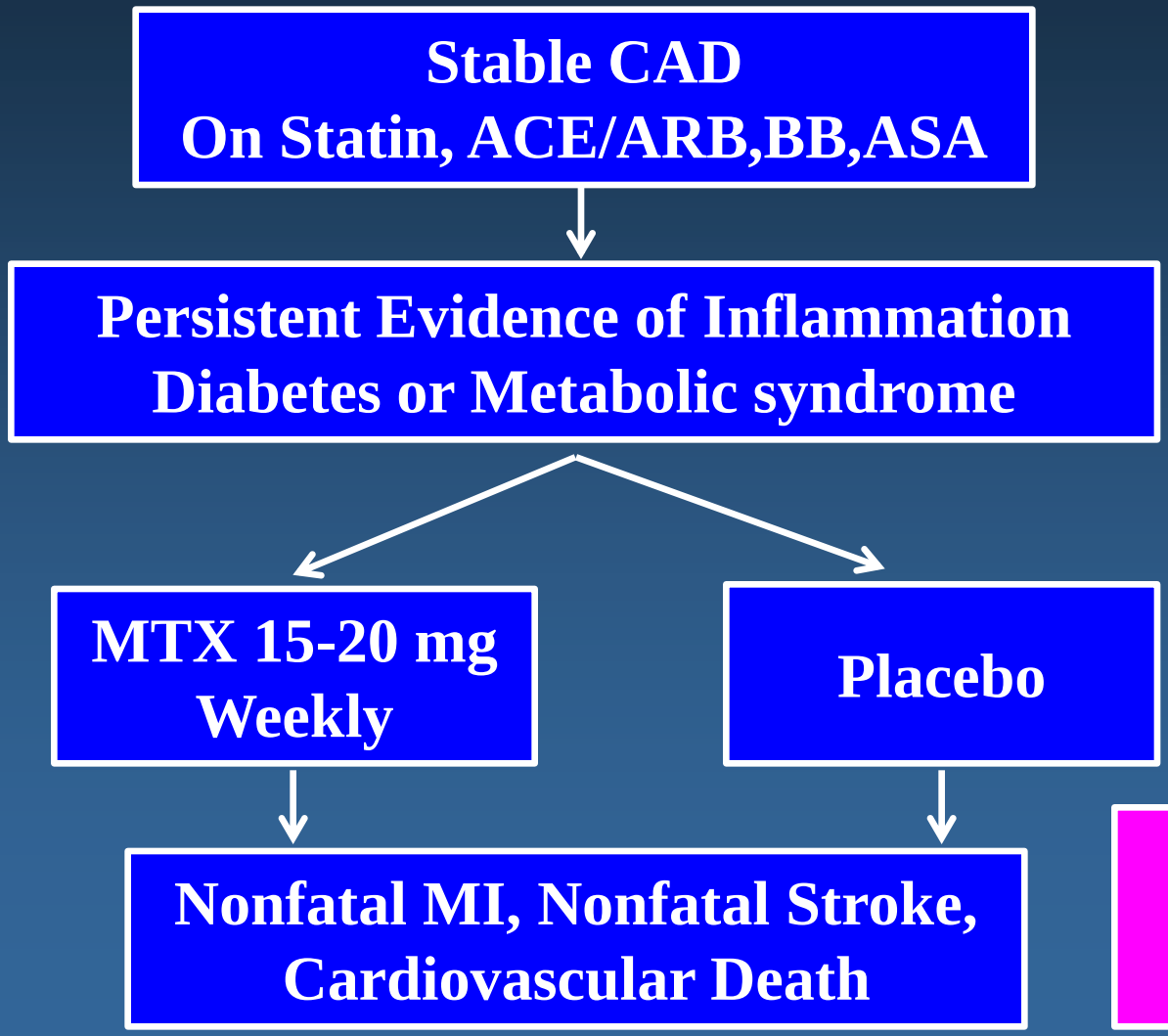
JCR 2014



Low Dose Methotrexate and CVD: Observational Evidence

cohort	Group	HR* (95% CI)	Endpoint	Exposure
Wichita Choi 2002	RA	0.4 (0.2-0.8) 0.3 (0.2-0.7) 0.4 (0.3-0.8)	Total Mortality CV Mortality CV Mortality	LDM LDM LDM
Netherlands Van Helm 2006	RA	0.3 (0.1-0.7) 0.2 (0.1-0.5) 0.2 (0.1-1.2) 0.2 (0.1-0.5)	CVD CVD CVD CVD	LDM LDM LDM LDM
Miami VA Pradanovich 2005	RA	0.8 (0.7-1.0) 0.6 (0.5-0.8)	CVD CVD	LDM LDM
CORRONA solomon 2008	RA	0.6 (0.3-1.2) 0.3 (0.2-0.8)	CVD CVD	LDM TNF-inhibitor
QUEST-RA Narango 2008	RA	0.85 (0.8-0.9) 0.82 (0.7-0.9) 0.89 (0.8-1.0)	CVD MI Stroke	LDM LDM LDM

Cardiovascular Inflammation Reduction Trial(CIRT)



- To evaluate in a randomized, double-blind, placebo-controlled trial whether MTX given at a target dose of 20mg po weekly over a three year period will reduce rates of recurrent myocardial infarction , stroke, or cardiovascular death among patents with coronary atherosclerosis and either type 2 diabetes or metabilic syndrome.

N=7,000 NHLBI-Sponsored
Enrollment to Start June 2013
350 US and Canadian Sites

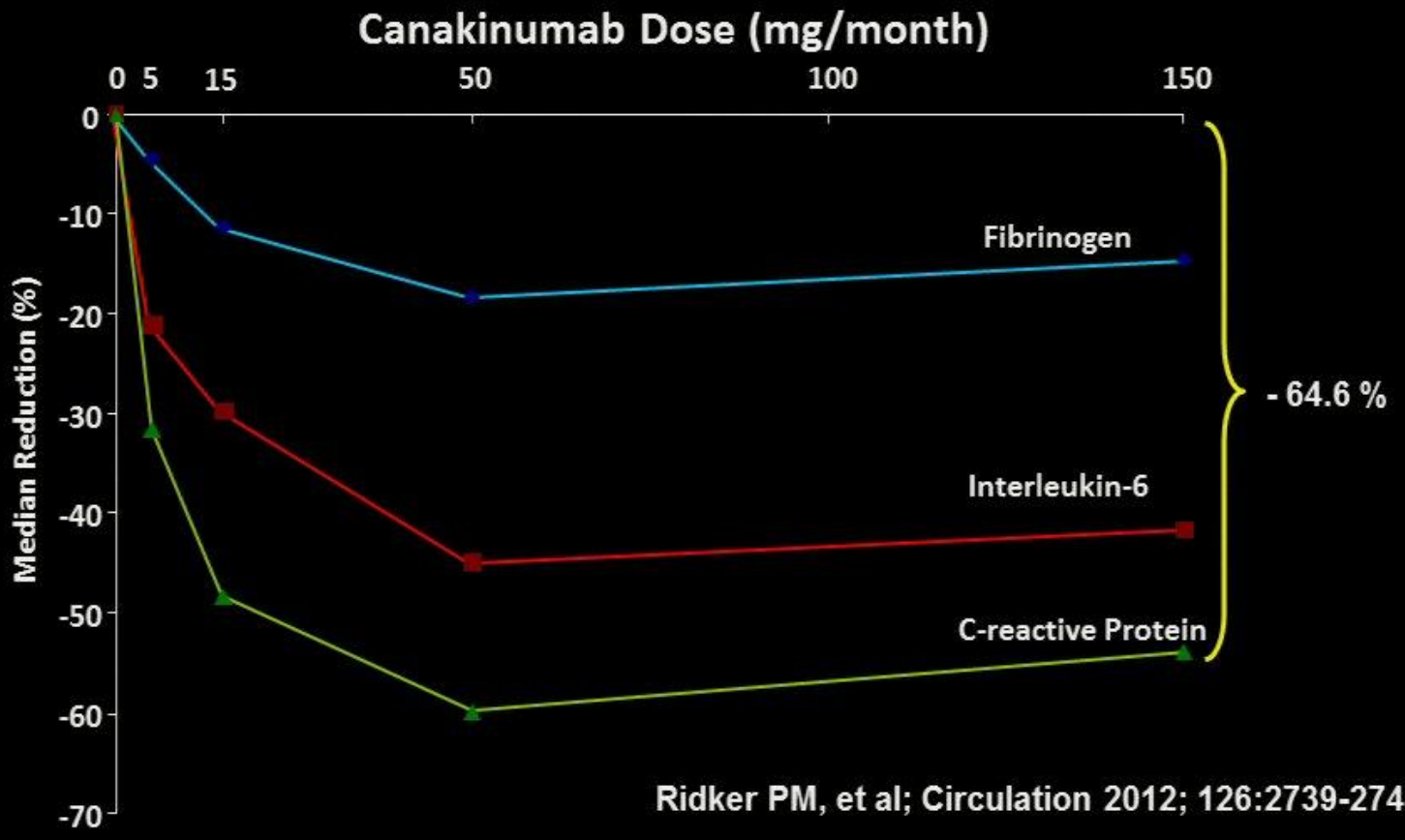
Canakinumab

- **High affinity human monoclonal anti-human IL-1 beta antibody**
- **Designed to bind to human IL-1 beta and functionally neutralize the bioactivity of this pro-inflammatory cytokine**
- **Long half life(4-8weeks)with CRP and IL-6 reduction for up to 3 months**

Effects of Interleukin-1β Inhibition With Canakinumab on Hemoglobin A1c, Lipids, C-Reactive Protein, Interleukin-6, and Fibrinogen

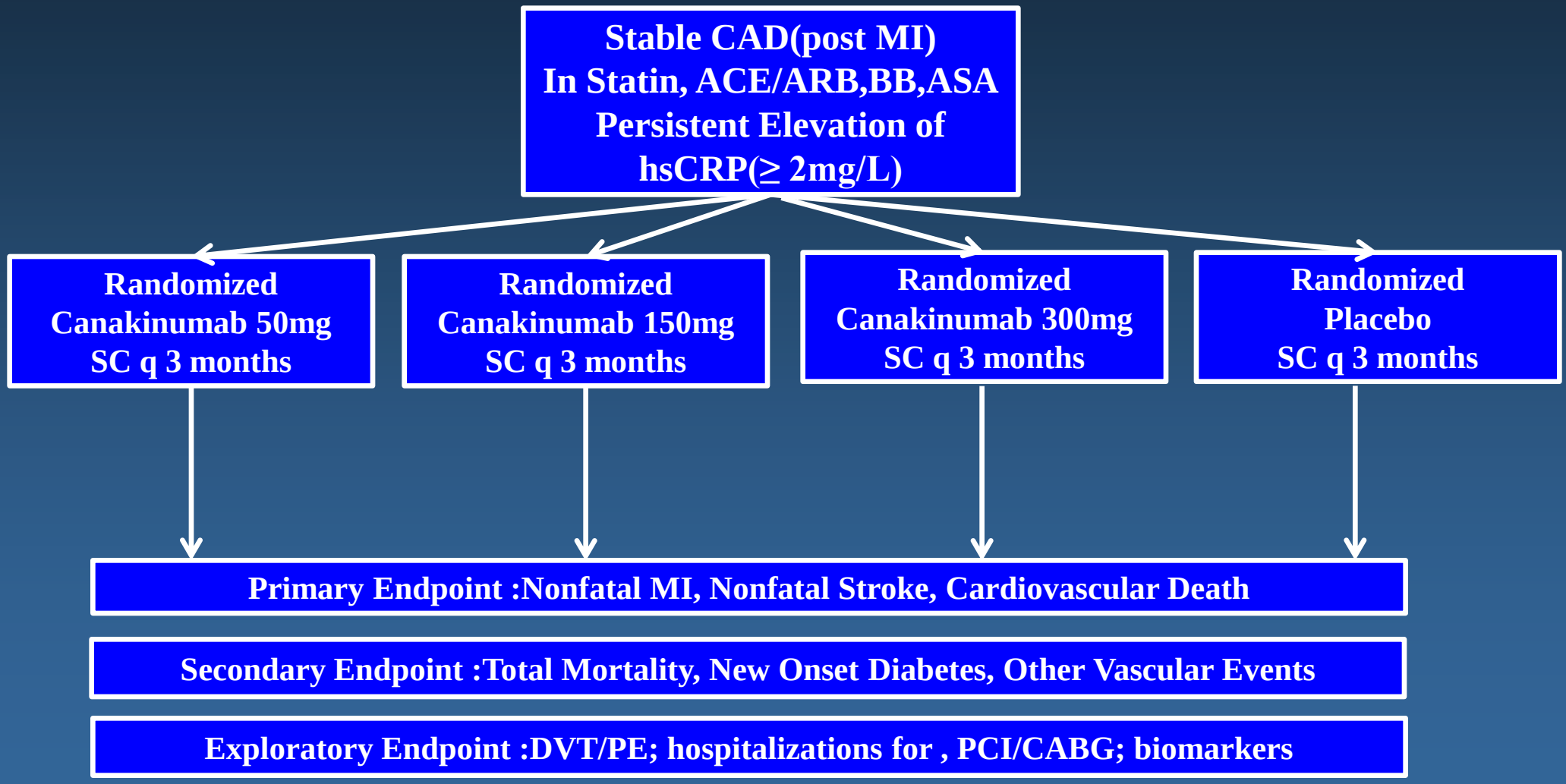
A Phase IIb Randomized, Placebo-Controlled Trial

Paul M Ridker, MD, MPH; Campbell P. Howard, MD; Verena Walter, Dipl Math (FH); Brendan Everett, MD; Peter Libby, MD; Johannes Hensen, MD; Tom Thuren, MD, PhD, on behalf of the CANTOS Pilot Investigative Group



Ridker PM, et al; Circulation 2012; 126:2739-2748

Canakinumab Anti-inflammatory Thrombosis Outcomes Study(CANTOS)



Summary

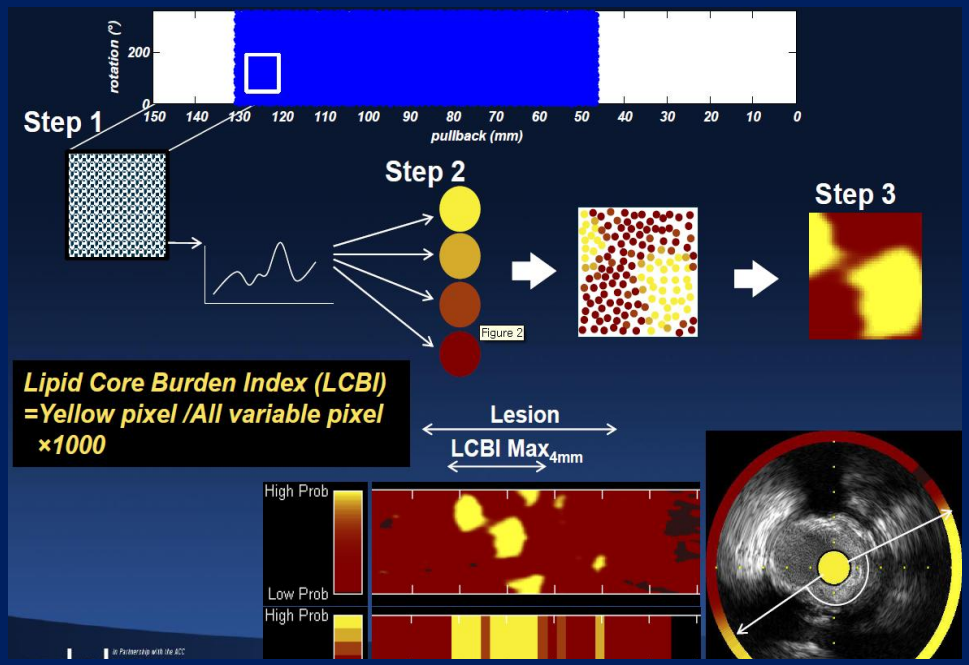
1. **hsCRP is a reliable inflammatory biomarker due to its ease of measurement and temporal stability.**

2. **Many epidemiologic evidence shows that elevated CRP level is a strong and consistent predictor of CV risk.**

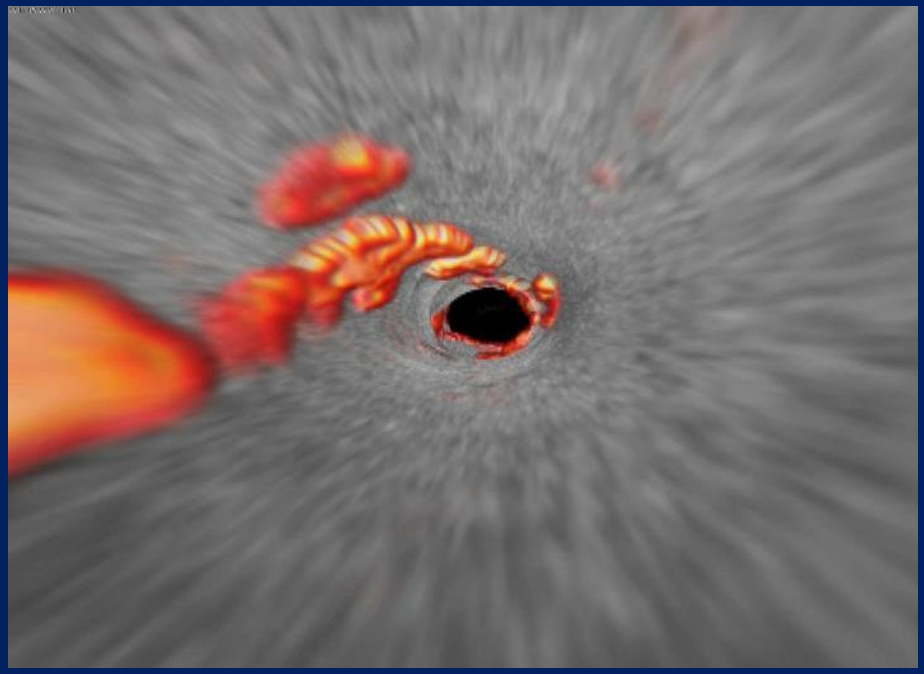
3. **A reduction of percent necrotic core and fibrous cap thickness using imaging studies showed a significant correlation with high-sensitivity CRP levels .**

4. **Recent genetic and pathologic studies provide in-vivo evidence and a direct causal role of CRP in inflammation.**

5. **Ongoing clinical trials targeting CRP will provide critical safety and efficacy data on long-term inhibition of inflammation.**



Near InfraRed Spectroscopy(NIRS)



Dual-Modal NIRF-OFDI


Thank you for your attention!