What do I do with CRP?

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Disclosures

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Overview hsCRP

- What is it?
- What is it not
- Placing it in context
- Summary
Inflammatory Markers of Coronary Risk

Proinflammatory Risk Factors (oxLDL, infectious agents, etc)
Vascular and Extravascular Sources

Primary Proinflammatory Cytokines (eg, IL-1, TNF-α)

ICAM-1
Selectins, HSPs, etc

Endothelium and Other Cells

IL-6
“Messenger” Cytokine

CRP
SAA

Liver

Circulation

CRP and Inflammation

- Acute phase marker - immune response protein
- Downstream marker of overall cytokine activation
- Long half life
- Stable levels in blood without circadian variations
- Easily measured in outpatient setting – fresh, stored, frozen plasma

Libby et al, Circulation 2002; 105:1135
Prevalence of Inflammation in Acute Coronary Syndrome

Frequency of CRP >3.0 mg/L

- Normals: <10%
- Chronic stable angina: ~20%
- Unstable angina: >65%
- Acute infarction preceded by unstable angina: >90%
- Acute infarction not preceded by unstable angina: <50%

Liuzzo et al NEJM 1994; 331:417
Biasucci et al Ital. HT 2001; 2:164
Libby et al Circulation 2002; 105:1135
HS-CRP Marker or Mechanism?

CRP localizes in atherosclerotic but not normal intima

CRP induced complement activation

CRP induced production of cell adhesion molecules, MCP-1, ET-1

CRP attenuates NO production decreases eNOS expression

CRP induced PAI-1 expression stabilizes PAI-1 mRNA

CRP triggered oxidation of LDL cholesterol

CRP mediated LDL uptake by macrophages

CRP dependent monocyte recruitment into arterial wall

CRP induced production of tissue factor in monocytes

CRP based blunting of endothelial vasoreactivity

Ridker et al: Circulation 2003; 108:2292
CRP for as a marker for population risk

Trial cut points – LDL 70mg/dL

PROVE IT–TIMI 22

From lipidsonline.org

CRP and risk in a primary prevention population

Ridker, et al; NEJM 2002; 347:1557

Nurses Health Study
CRP as a risk factor

Risk factors for future cardiovascular events: WHS

Lipoprotein(a)  Homocysteine  IL-6  TC  LDL-C  sICAM-1  SAA  Apo B  TC: HDL-C  hs-CRP  hs-CRP + TC: HDL-C

Relative risk of future cardiovascular events

WHS = Women’s Health Study; IL-6 = interleukin-6; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; sICAM-1 = soluble intercellular adhesion molecule-1; SAA = serum amyloid A; Apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; hs-CRP = high-sensitivity C-reactive protein.

Source: Ridker PM, et al.12

CRP as a target - JUPITER

Study Design
Randomized Trial of Rosuvastatin 20 mg po qd in the Primary Prevention of Cardiovascular Events Among Individuals with Low Levels of LDL-C and Elevated Levels of CRP

- No History of CAD
  - Men >55, Women > 65
  - LDL-C <130 mg/dL
  - CRP >2 mg/L

- Rosuvastatin 20 mg (N = 7500)
- Placebo (N = 7500)

Visit Timeline:
- Screening Visit
- Randomization Visit
- Safety Visit
- Bi-Annual Follow-Up Visits
- End of Study Visit

- LDL
- CRP
- FHS

- Lipids
- hs-CRP
- LFTs
- HbA$_{1c}$

- MI
- Stroke
- Unstable Angina
- CVD Death
- CABG/PTCA
Outcomes from JUPITER

A Primary End Point

Cumulative incidence

Years

No. at Risk
Rosuvastatin 8901 8621 8313 6958 1353 963 538 157
Placebo 8901 8621 8313 6958 1353 963 538 157

P<0.00001

B Myocardial Infarction, Stroke, or Death from Cardiovascular Causes

Cumulative incidence

Years

No. at Risk
Rosuvastatin 8901 8643 8437 6971 3921 1979 1170 998 545 159
Placebo 8901 8633 8301 6142 3918 1992 1165 979 547 181

P<0.00001

C Revascularization or Hospitalization for Unstable Angina

Cumulative incidence

Years

No. at Risk
Rosuvastatin 8901 8649 8426 6550 3895 1977 1346 963 535 158
Placebo 8901 8641 8390 6542 3895 1977 1346 963 535 176

P<0.00001

D Death from Any Cause

Cumulative incidence

Years

No. at Risk
Rosuvastatin 8901 8847 8737 6999 4312 2258 1602 1192 676 227
Placebo 8901 8652 8775 6967 4319 2235 1614 1196 681 246

P=0.02

Ridker et al NEJM 359; 2008
What is CRP not?

• It is not a prognostic tool for individual risk
Why it not useful in an individual

Too much overlap between values found in those with and without events results in a low sensitivity for the marker when used as a predictive tool

Ware  NEJM 2006
To make it useful in an individual

The separation of the mean values for the marker between those who will have an event and those who will not, must be large enough to result in minimal overlap at the right tail. For this example the resulting odds ratio for the marker is > 200 for persons at the 90th percentile in the event free group relative to those at the 10th percentile.

Ware  NEJM 2006
What is CRP not?

- It is not a prognostic tool for individual risk

hsCRP does not have sufficient association with coronary event outcomes to be used as a basis for early diagnosis or prediction for individual patients

Nor do LDL, HDL, Smoking, or Diabetes for that matter

Ware NEJM 2006
hsCRP as a CRF for risk models - Pro

• Bayes Information Criteria, Brier score, Yates slope, and entropy have demonstrated large and clinically important differences between prediction models with and without hsCRP.

• This turns out to be of greatest importance for reclassifying individuals at intermediate global risk using ATP-III criteria.
hsCRP as a CRF for risk models - Con

• The Framingham Offspring Study, PROSPER (Prospective Study of Pravastatin in the Elderly at Risk), and the multi-ethnic Dallas Heart Study, have found hsCRP provided only modest or no incremental information compared with traditional risk factors.

• Large meta-analysis found
  – CRP did not perform better than the Framingham risk equation for discrimination.
  – The improvement in risk stratification or reclassification from addition of CRP to models based on established risk factors was small and inconsistent.

Arterial Wall and the Plaque

Lumen

endothelium

NO*

Lipid

Collagen

basement membrane

Smooth Muscle
Initial Phases of Damage: Repair versus Degradation

Lumen

endothelium

Fibrous cap

basement membrane

Smooth Muscle

NO*
The Perilous Plaque – Blister

Degradation > repair

Lumen

Adhesion molecules

P

NO*

MP’s

Lipid pool

endothelium

Thinned Fibrous cap

basement membrane

Smooth Muscle

TPA
The Stable Plaque - Callous

Repair >> Destruction

- Lumen
- endothelium
- Fibrous cap
- Lipid pool
- basement membrane
- Smooth Muscle
- NO*
- Mac
- Mac
- Mac
Summary

• hsCRP is a CRF with discrimination on par to perhaps better than individual lipid measures – it is another piece of information but not the piece

• hsCRP can be a target
  – Primary prevention for reduced events with relatively large NNT values
  – In secondary preventions as a secondary target for dose

• It makes for a good story and can be a motivational tool but it is not a good individual risk measure due to overlap and non-specificity of the marker