Inflammation as A Target for Therapy

Focus on “Residual Inflammatory Risk”

Paul M Ridker, MD
Eugene Braunwald Professor of Medicine
Harvard Medical School
Director, Center for Cardiovascular Disease Prevention
Brigham and Women’s Hospital, Boston MA
Residual inflammatory risk: addressing the obverse side of the atherosclerosis prevention coin

Paul M Ridker

Known Cardiovascular Disease
LDL 150 mg/dL
hsCRP 4.5 mg/L

High Intensity Statin

“Residual Cholesterol Risk”
LDL 110 mg/dL
hsCRP 1.8 mg/L

Additional LDL Reduction

“Residual Inflammatory Risk”
LDL 45 mg/dL
hsCRP 3.8 mg/L

Additional Inflammation Reduction
Can Targeted Anti-Inflammatory Therapy Reduce Cardiovascular Event Rates and Prolong Life?
**High Sensitivity C-Reactive Protein (hsCRP): A Test In Context**

- hsCRP
- 1 mg/L: Lower Risk
- 3 mg/L: Moderate Risk
- 10 mg/L: Higher Risk

Possible Acute Phase Response
Repeat in 2 to 3 weeks

Ridker PM. JACC 2016;16:67:712-23
Inflammation is a Strong and Consistent Predictor of CV Risk

Meta-analysis of 54 Prospective Cohort Studies
hsCRP concentration and risk of cardiovascular events: 2010

Emerging Risk Factor Collaborators, Lancet January 2010
The magnitude of independent risk associated with inflammation is at least as large, if not larger, than that of BP and cholesterol.

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

Emerging Risk Factor Collaborators, Lancet January 2010
PROVE-IT
Ridker et al, NEJM 2005;352:20-8

IMPROVE-IT
Bohula et al, Circulation 2015;132:1224-33

LDL >70 mg/dL
hsCRP > 2mg/L

LDL <70 mg/dL
hsCRP < 2mg/L

Neither Goal Achieved
LDL Goal Achieved
hsCRP Goal Achieved
Dual Goals Achieved

Ridker et al, Eur Heart J 2016;37:1729-22
Targeting Inflammatory Pathways for the Treatment of Cardiovascular Disease

Vessel Wall
- 5-LO Inhibitors
- FLAP Inhibitors
- Anti-CAMs
- SIRT activators
- CCR2 CCR5 Antagonists

Macrophage/Monocyte
- Leukotriene Function
- MMP-9
- ICAM-1
- VCAM
- P-selectin
- E-selectin

Adipose Tissue
- 5-LO Inhibitors
- FLAP Inhibitors
- Anti-CAMs
- SIRT activators
- CCR2 CCR5 Antagonists

NLRP3 Inflammasome
- TNF-α
- IL-1β
- IL-18
- Canakinumab
- Anakinra
- Colchicine

Upstream Targets and Biomarkers

Monocyte Recruitment
- Adalimumab
- Infliximab
- Tocilizumab
- Low Dose Methotrexate
- Darapladib
- Varespladib

Liver
- Lp-PLA2
- sPLA2
- CRP RNA - Antisense Anti-CRPs

Downstream Targets and Biomarkers
- PAI-1
- Fibrinogen
- SAA

Vascular risk hsCRP (mg/L)
- High: > 3 mg/L
- Intermediate: 1-3 mg/L
- Low: < 1 mg/L

Ridker PM, Luscher T. Eur Heart Journal 2014;35:1782-91
Effects of Polymorphism in the IL-6 Receptor Signaling Pathway On Downstream CRP Levels and Risks of Coronary Heart Disease

CRP Reduction (%) | Hazard Ratio CHD

| rs2228145 | rs7529229 |
| 1/1 | C/C | 1.00 |
| 1/2 | C/T | 0.95 |
| 2/2 | T/T | 0.90 |

Sawar N et al, Lancet 2012;379;1205-13
Swerdlow et al, Lancet 2012;379;1214-24
From CRP to IL-6 to IL-1: Moving Upstream to Identify novel Targets for Atheroprotection

CIRT
CARDIOVASCULAR INFLAMMATION REDUCTION TRIAL

CANTOS
Canakinumab Anti-inflammatory Thrombosis Outcomes Study
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Group</th>
<th>HR* (95% CI)</th>
<th>Endpoint</th>
<th>Exposure</th>
</tr>
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<tbody>
<tr>
<td>Wichita</td>
<td>RA</td>
<td>0.4 (0.2 - 0.8)</td>
<td>Total Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.3 (0.2 - 0.7)</td>
<td>CV Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.4 (0.3 - 0.8)</td>
<td>CV Mortality</td>
<td>LDM &lt; 15 mg/wk</td>
</tr>
<tr>
<td>Netherlands</td>
<td>RA</td>
<td>0.3 (0.1 - 0.7)</td>
<td>CVD</td>
<td>LDM only</td>
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<tr>
<td></td>
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<td>0.2 (0.1 - 0.5)</td>
<td>CVD</td>
<td>LDM + SSZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 (0.1 - 1.2)</td>
<td>CVD</td>
<td>LDM + HCQ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 (0.1 - 0.5)</td>
<td>CVD</td>
<td>LDM + SSZ + HCQ</td>
</tr>
<tr>
<td>Miami VA</td>
<td>PsA</td>
<td>0.7 (0.6 - 0.9)</td>
<td>CVD</td>
<td>LDM</td>
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<tr>
<td></td>
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<td>0.5 (0.3 - 0.8)</td>
<td>CVD</td>
<td>LDM &lt; 15 mg/wk</td>
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<tr>
<td></td>
<td>RA</td>
<td>0.8 (0.7 - 1.0)</td>
<td>CVD</td>
<td>LDM</td>
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<td>0.6 (0.5 - 0.8)</td>
<td>CVD</td>
<td>LDM &lt; 15 mg/wk</td>
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<tr>
<td>CORRONA</td>
<td>RA</td>
<td>0.6 (0.3 - 1.2)</td>
<td>CVD</td>
<td>LDM</td>
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<tr>
<td>Solomon 2008</td>
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<td>0.4 (0.2 - 0.8)</td>
<td>CVD</td>
<td>TNF-inhibitor</td>
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<tr>
<td>QUEST-RA</td>
<td>RA</td>
<td>0.85 (0.8 - 0.9)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td>Narango 2008</td>
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<td>0.82 (0.7 - 0.9)</td>
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<td>LDM</td>
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<tr>
<td></td>
<td></td>
<td>0.89 (0.8 - 1.0)</td>
<td>Stroke</td>
<td>LDM</td>
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<tr>
<td>UK Norfolk</td>
<td>RA, PsA</td>
<td>0.6 (0.4 - 1.0)</td>
<td>Total Mortality</td>
<td>LDM</td>
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<tr>
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<td></td>
<td>0.5 (0.3 - 1.1)</td>
<td>CV Mortality</td>
<td>LDM</td>
</tr>
</tbody>
</table>
Methotrexate Inhibits Atherogenesis in Cholesterol-fed Rabbits

Bulgarelli et al, J Cardiovasc Pharmacol 2012;59:308-14
To directly test the inflammatory hypothesis of atherothrombosis

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

N = 7,000  NHLBI-Sponsored
350 US and Canadian Sites
The Balance of IL-1 and IL-1Ra: Key Regulatory Proteins for Innate Immunity

Pro-Inflammatory

IL-1α
IL-1β

IL-1R

Anti-Inflammatory

IL-1Ra
NLRP3 Cryopyrin Inflammasome, Caspase-1, and IL-1β Maturation
Endogenous Danger Signals in Vascular Biology?

NLRP3 Inflammasome, Caspase-1, and IL-1β Maturation
Role of Cholesterol Crystals
Clinical update

Cholesterol crystal induced arterial inflammation and destabilization of atherosclerotic plaque

Abed Janoudi¹, Fadi E. Shamoun², Jagadeesh K. Kalavakunta¹,³, and George S. Abela¹,⁴*

¹Department of Medicine, Division of Cardiology, Michigan State University, East Lansing, MI, USA; and ²Department of Physiology, Dartmouth College, Hanover, NH, USA.

Received 3 August 2015; revised 28 October 2015; accepted 16 November 2015.

Evolution of plaque that is prone to rupture is characterized by increased cell and matrix turnover in the sub-intima provides esterified cholesterol (ESC) and free cholesterol (FRC). Membrane-bound cholesterol ester hydrolases (CEHs). Membrane-bound transport function and altered composition can lead to increased intracellular FRC accumulation. Saturation of FRC binding capacity between ESC and FRC can impact foam cell and cholesterol esterification. Inflammation and cholesterol esterification leading to interleukin-1β (IL-1β) production and associated inflammation destabilize the plaque. Thus, inflammation and foam cell formation may stabilize vulnerable plaques.

Keywords
Atherosclerosis • Cholesterol ester hydrolases • Inflammation • Foam cells
Canakinumab (Ilaris, Novartis)

- high-affinity human monoclonal anti-human interleukin-1β (IL-1β) antibody currently indicated for the treatment of IL-1β driven inflammatory diseases (Cryopyrin-Associated Period Syndrome [CAPS], Muckle-Wells Syndrome)
- designed to bind to human IL-1β and functionally neutralize the bioactivity of this pro-inflammatory cytokine
- long half-life (4-8 weeks) 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 et al, Circulation 2012; 126:2739-2748
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

Stable CAD (post MI)  
On Statin, ACE/ARB, BB, ASA  
Persistent Elevation of hsCRP (> 2 mg/L)

Randomized  
Canakinumab 50 mg  
SC q 3 months

Randomized  
Canakinumab 150 mg  
SC q 3 months

Randomized  
Canakinumab 300 mg  
SC q 3 months

Randomized  
Placebo  
SC q 3 months

Primary Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death

Secondary Endpoints: Total Mortality, New Onset Diabetes, Other Vascular Events

Exploratory Endpoints: DVT/PE; SVT; hospitalizations for CHF; PCI/CABG; biomarkers

N = 10,064  
Novartis
Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease

Stefan M. Nidorf, MD, MBBS,* John W. Eikelboom, MBBS,† Charley A. Budgeon, BSc (Hons),‡ Peter L. Thompson, MD§
Perth, Australia; and Hamilton, Ontario, Canada

What About inflammation Inhibition in Acute Coronary Syndromes?

The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study

Effect of a single dose of the interleukin-6 receptor antagonist tocilizumab on inflammation and troponin T release in patients with non-ST-elevation myocardial infarction: a double-blind, randomized, placebo-controlled phase 2 trial

Ola Kleveland¹,², Gabor Künszt⁴,⁶, Marte Bratlie⁴,⁵,⁶, Thor Ueland⁵,⁶,⁷,⁸, Kaspar Broch⁴,⁸, Espen Holte¹,², Annika E. Michelsen⁵,⁶, Bjørn Bendz⁴, Brage H. Amundsen¹,², Terje Espevik³, Svend Aakhus²,⁴, Jan Kristian Damás³, Pål Aukrust⁵,⁶,⁷, Rune Wiseth¹,², and Lars Gulgestad⁴,⁶,⁸,⁹

Anti-inflammatory treatment of acute coronary syndromes: the need for precision medicine

Filippo Crea* and Giovanna Liuzzo

Institute of Cardiology, Catholic University, Rome, Italy

N = 117
Tnt effect in PCI subgroup only
The selective NLRP3-inflammasome inhibitor MCC950 reduces infarct size and preserves cardiac function in a pig model of myocardial infarction

Gerardus P.J. van Hout†‡, Lena Bosch†‡, Guilielmus H.J.M. Ellenbroek†, Judith J. de Haan†, Wouter W. van Solinge‡, Matthew A. Cooper‡, Fatih Arslan†, Saskia C.A. de Jager†, Avril A.B. Robertson†, Gerard Pasterkamp†,‡, and Imo E. Hoefer†,‡

1Experimental Cardiology Laboratory (Room G02.523), University Medical Center Utrecht, Utrecht, the Netherlands. Clinical Chemistry and Hematology, University Medical Center Utrecht, Utrecht, the Netherlands.

Received 20 May 2015; revised 28 February 2016; accepted 29 April 2016.
Effect of Losmapimod (Map-Kinase Inhibition) on CV Outcomes Following Acute MI

Hazard ratio, 1.16 (95% CI, 0.91-1.47)
Log-rank $P = .24$

Cumulative Incidence of Primary End Point, %

No. at risk
<table>
<thead>
<tr>
<th>Losmapimod</th>
<th>Placebo</th>
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<td>1731</td>
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<td>1583</td>
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</table>

Waiting For CANTOS (1997 – 2017)
A Twenty Year Clinical Journey from CRP to IL-6 to IL-1

The New England Journal of Medicine

VOLUME 336
APRIL 3, 1997
NUMBER 14

INFLAMMATION, ASPIRIN, AND THE RISK OF CARDIOVASCULAR DISEASE IN APPARENTLY HEALTHY MEN

PAUL M. RIDKER, M.D., MARY CUSHMAN, M.D., MEIR J. STAMPFER, M.D., RUSSELL P. TRACY, PH.D., AND CHARLES H. HENNEKENS, M.D.

[Graphs and data showing relative risk of myocardial infarction across quartiles of plasma C-reactive protein and years of study follow-up.]
Known Cardiovascular Disease
LDL 150 mg/dL
hsCRP 4.5 mg/L
TG 240 mg/dL

High Intensity Statin

Residual Cholesterol Risk
LDL 110 mg/dL
hsCRP 1.8 mg/L
TG 180 mg/dL
Additional LDL Reduction

Residual Inflammatory Risk
LDL 60 mg/dL
hsCRP 3.8 mg/L
TG 180 mg/dL
Additional Inflammation Reduction

Residual Triglyceride Risk
LDL 60 mg/dL
hsCRP 1.8 mg/L
TG 220 mg/dL
Additional TG Reduction