Inflammation and Atherothrombosis: Where Are We Going?: The Cardiovascular Inflammation Reduction Trials

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Dr Ridker has received investigator-initiated research support from the NHLBI, NCI, American Heart Association, Donald W Reynolds Foundation, Leduc Foundation, Doris Duke Charitable Foundation, AstraZeneca, Novartis, and SanofiAventis.

Dr Ridker has served as a consultant to Vascular Biogenics, Merck, ISIS, and Genzyme.

Dr Ridker is listed as a co-inventor on patents held by the Brigham and Women’s Hospital (BWH) that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to Seimens and AstraZeneca. Dr. Ridker and the BWH receive royalties on sales of the hsCRP test. However, neither Dr. Ridker nor the BWH receives any royalties attributable to sales of the hsCRP test used in connection with the CIRT or CANTOS trials.
Is there evidence that individuals with elevated levels of inflammatory biomarkers are at high vascular risk even when other risk factors are acceptable? 1995-2002

Is there evidence that individuals identified at increased risk due to inflammation benefit from a therapy they otherwise would not have received? 2002-2008

Is there evidence that reducing inflammation per se will reduce vascular events? 2009 -
hsCRP and Risk of Future MI and CVA in Apparently Healthy Men

hsCRP and Risks of Future MI: Analysis Stratified by Year of Follow-Up

hsCRP, Aspirin, and Risks of Future Myocardial Infarction

Event-Free Survival According to Baseline Quintiles of hs-CRP and LDL Cholesterol

Quintiles of hsCRP

Quintiles of LDL

CVD Event-Free Survival Probability

Years of Follow-Up

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

Emerging Risk Factor Collaborators, Lancet January 2010
Meta-analysis of 54 Prospective Cohort Studies:
The magnitude of independent risk associated with inflammation is at least as large, if not larger, than that of BP and cholesterol.

<table>
<thead>
<tr>
<th>Risk Ratio (95%CI) per 1-SD higher usual values</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP</td>
</tr>
<tr>
<td>1.37 (1.27-1.48)</td>
</tr>
<tr>
<td>Systolic BP</td>
</tr>
<tr>
<td>1.35 (1.25-1.45)</td>
</tr>
<tr>
<td>Total cholesterol</td>
</tr>
<tr>
<td>1.16 (1.06-1.28)</td>
</tr>
<tr>
<td>Non-HDLC</td>
</tr>
<tr>
<td>1.28 (1.16-1.40)</td>
</tr>
</tbody>
</table>

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

Emerging Risk Factor Collaborators, Lancet January 2010
If you are healthy and without diabetes, the Reynolds Risk Score is designed to predict your risk of having a future heart attack, stroke, or other major heart disease in the next 10 years.

In addition to your age, blood pressure, cholesterol levels and whether you currently smoke, the Reynolds Risk Score uses information from two other risk factors, a blood test called hsCRP (a measure of inflammation) and whether or not either of your parents had a heart attack before they reached age 60 (a measure of genetic risk). To calculate your risk, fill in the information below with your most recent values. Click here for help filling the information.

As shown in the graph below, at Age 68, your chance of having a heart attack, stroke, or other heart disease event at some point in the next 10 years is 29 percent. This risk is approximately 3 times higher than that of a Man the same age who has optimal levels of all modifiable risk factors.

The graph above also compares your risk to that of a Man of age 68 who has optimal levels for all modifiable risk factors, and shows what your risk would be if you improved your individual risk factors. For young Men, risk may appear to be low over the next 10-years, yet can be very high over a lifetime. Thus, to see what your risk would be as you get older if your risk factors remain the same, click on the buttons above.
Comparison of the Framingham and Reynolds Risk Scores for Global Cardiovascular Risk Prediction in the Multiethnic Women’s Health Initiative

Nancy R. Cook, ScD; Nina P. Paynter, PhD; Charles B. Eaton, MD; JoAnn E. Manson, MD, DrPH; Lisa W. Martin, MD; Jennifer G. Robinson, MD, MPH; Jacques E. Rossouw, MD; Sylvia Wassertheil-Smoller, PhD; Paul M Ridker, MD

Background—Framingham-based and Reynolds Risk scores for cardiovascular disease (CVD) prediction have not been directly compared in an independent validation cohort.

Methods and Results—We selected a case-cohort sample of the multiethnic Women’s Health Initiative Observational Cohort, comprising 1722 cases of major CVD (752 myocardial infarctions, 754 ischemic strokes, and 216 other CVD deaths) and a random subcohort of 1004 women without major CVD. We estimated risk using the Adult Treatment Panel III criteria and the Reynolds Risk Score. The Reynolds Risk Score was better calibrated than the Framingham model in this large external validation cohort. The Reynolds score also showed improved discrimination overall in black and white women. Large differences in risk estimates exist between models, with clinical implications for statin therapy.

P=0.02), and positive integrated discrimination improvement (4.1%; P<0.0001) overall, excluding diabetics (NRI=4.2%; P=0.01), and in white (NRI=4.3%; P=0.04) and black (NRI=11.4%; P=0.13) women. The Reynolds (NRI=12.9%; P<0.0001) and ATP-III (NRI=5.9%; P=0.0001) models demonstrated better discrimination than the Framingham CVD model.

Conclusions—The Reynolds Risk Score was better calibrated than the Framingham-based models in this large external validation cohort. The Reynolds score also showed improved discrimination overall and in black and white women. Large differences in risk estimates exist between models, with clinical implications for statin therapy. (Circulation. 2012;125:1748-1756.)
Inflammation, Statin Therapy, and hsCRP: Initial Observations

**Relative Risk**

<table>
<thead>
<tr>
<th></th>
<th>Pravastatin</th>
<th>Placebo</th>
<th>Pravastatin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammation Absent</strong></td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Inflammation Present</strong></td>
<td>2.00</td>
<td>2.00</td>
<td>2.00</td>
<td>2.00</td>
</tr>
</tbody>
</table>

*P Trend = 0.005*

**Median hs-CRP (mg/dL)**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td>0.24</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Pravastatin</strong></td>
<td>0.18</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*P = 0.004*


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
JUPITER
Fatal or Nonfatal Myocardial Infarction

Ridker et al NEJM 2008;359:2195-2207

HR 0.45, 95%CI 0.30-0.70
P < 0.0002

Follow-up Years

Cumulative Incidence

Placebo

- 55 %

Rosuvastatin
JUPITER
Fatal or Nonfatal Stroke

Ridker et al NEJM 2008;359:2195-2207

Cumulative Incidence

HR 0.52, 95%CI 0.34-0.79
P = 0.002

Follow-up Years

Placebo
Rosuvastatin
- 48 %
JUPITER
Arterial Revascularization / Unstable Angina

HR 0.53, 95%CI 0.40-0.70
P < 0.00001

Placebo (N = 143)
Rosuvastatin (N = 76)

- 47 %

Ridker et al NEJM 2008;359:2195-2207
JUPITER
Secondary Endpoint – All Cause Mortality

HR 0.80, 95% CI 0.67-0.97
P = 0.02

Placebo 247 / 8901
Rosuvastatin 198 / 8901

- 20 %

Cumulative Incidence

Follow-up (years)

Number at Risk
Rosuvastatin 8,901 8,847 8,787 6,999 4,312 2,268 1,602 1,192 683 227
Placebo 8,901 8,852 8,775 6,987 4,319 2,295 1,614 1,196 684 246

NEJM 2008;359:2195-2207
JUPITER

Primary Endpoint – Understudied or “Low Risk” Subgroups

Understudied Subgroups
- Women
- Age > 70
- Black, Hispanic, Other

“Low Risk” Subgroups
- Framingham Risk ≤ 10 %
- BMI < 25 mg/m2
- No Hypertension
- No metabolic Syndrome
- All Participants

Ridker et al NEJM 2008;359:2195-2207
JUPITER
Statins and the Development of Diabetes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Statin</th>
<th>HR</th>
<th>(95% CI)</th>
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</thead>
<tbody>
<tr>
<td>WOSCOPS</td>
<td>Pravastatin</td>
<td>0.70</td>
<td>(0.50–0.98)</td>
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<tr>
<td>(Hypothesis Generating Trial)</td>
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<tr>
<td>PROSPECT</td>
<td>Pravastatin</td>
<td>1.34</td>
<td>(1.06–1.68)</td>
</tr>
<tr>
<td>LIPID</td>
<td>Pravastatin</td>
<td>0.91</td>
<td>(0.72–1.18)</td>
</tr>
<tr>
<td>HPS</td>
<td>Simvastatin</td>
<td>1.20</td>
<td>(0.98–1.35)</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>Atorvastatin</td>
<td>1.20</td>
<td>(0.91–1.44)</td>
</tr>
<tr>
<td>PROVE-IT</td>
<td>Atorvastatin</td>
<td>1.11</td>
<td>(0.67–1.83)</td>
</tr>
<tr>
<td>VS Pravastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CORONA</td>
<td>Rosuvastatin</td>
<td>1.13</td>
<td>(0.86–1.50)</td>
</tr>
<tr>
<td>JUPITER</td>
<td>Rosuvastatin</td>
<td>1.25</td>
<td>(1.05–1.54)</td>
</tr>
<tr>
<td>(Hypothesis Testing Trials)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR: Hazard Ratio
CI: Confidence Interval
JUPITER
Incident Diabetes Limited to Those With Impaired Fasting Glucose

Fasting Glucose Level (mg/dL)

- <100
- 100-104
- 105-109
- 110-114
- 115-119
- 120-125

Incidence Rate (per 100 person years)

- Placebo
- Rosuvastatin

- (51) (62)
- (18) (43)
- (39) (38)
- (34) (53)
- (34) (29)
- (39) (45)

- (45)
JUPITER

Statin Highly Effective in All Patients – Primary Endpoint

**Impaired Fasting Glucose**

HR 0.69, 95% CI 0.49-0.98

**Normal Fasting Glucose**

HR 0.51, 95% CI 0.40-0.67
## JUPITER
Cardiovascular Benefits of Statin Therapy In All High Risk Groups for Diabetes

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>N</th>
<th>Nonfatal MI + Stroke</th>
<th>Revascularization + Unstable Angina</th>
<th>VTE</th>
<th>Mortality</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic Syndrome          Y</td>
<td>7,316</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>10,278</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FG &gt;100 mg/dL               Y</td>
<td>5,504</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>12,170</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &gt; 30 kg/m²              Y</td>
<td>6,637</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>11,042</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c &gt;6 %                  Y</td>
<td>3,008</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>14,615</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Risk Factor             Y</td>
<td>11,508</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>6,095</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Rosuvastatin Superior
- Rosuvastatin Inferior
Cardiovascular Benefits and Diabetes Risks of Statin Therapy in Primary Prevention: The JUPITER Trial

- In absolute terms for those without a major diabetes risk factor, 65 vascular events or death were avoided by statin therapy with no excess cases of diabetes diagnosed.
- In absolute terms for those with a major diabetes risk factor, 93 vascular events or deaths were avoided by statin therapy for every 54 new cases of diabetes diagnosed.
- **Conclusion:** In primary prevention, the cardiovascular and mortality benefits of statin therapy exceed the diabetes hazard, including among individuals at high risk for developing diabetes. Long-term microvascular effects unknown.
“The initial step in risk assessment in individual patients involves the ascertainment of a global risk score (Framingham, Reynolds, etc) and the elucidation of a family history of atherosclerotic CVD. These Class I recommendations which are simple and inexpensive determine subsequent strategies to be undertaken”

Reynolds = Framingham + hsCRP + family history
## 2009 Canadian Cardiovascular Society (CCS) Guidelines for the Diagnosis and Treatment of Dyslipidemia and Prevention of Cardiovascular Disease in the Adult

<table>
<thead>
<tr>
<th>Level</th>
<th>Risk Factors</th>
<th>LDL Goal</th>
<th>Treatment Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>CAD, CVA, PVD&lt;br&gt;Most pts with Diabetes&lt;br&gt;FRS &gt; 20%&lt;br&gt;RRS &gt; 20%</td>
<td>&lt;2mmol/L or 50% reduction</td>
<td>Class I Level A</td>
</tr>
<tr>
<td>Moderate</td>
<td>FRS 10-19%&lt;br&gt;RRS 10-19%&lt;br&gt;LDL &gt; 3.5 mmol/L&lt;br&gt;TC/HDL C &gt; 5.0&lt;br&gt;hsCRP &gt; 2 in&lt;br&gt;men &gt; 50 yr&lt;br&gt;women &gt; 60 yr</td>
<td>&lt;2mmol/L or 50% reduction</td>
<td>Class IIA Level A</td>
</tr>
<tr>
<td>Low</td>
<td>FRS &lt; 10%</td>
<td>&lt;5mmol/L</td>
<td>Class IIA Level A</td>
</tr>
</tbody>
</table>

**Secondary Targets:** TC/HDL C < 4, non HDLC < 3.5 mol/L, hsCRP < 2 mg/L, TG < 1.7 mol/L, ApoB/A < 0.8

The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)†

567 References - No mention of the JUPITER trial, No Change in Practice at all
JUPITER
Achieved LDLC, Achieved hsCRP, or Both?

The **Real Controversy:**
Is the large benefit observed in the JUPITER trial due to lipid lowering, to inflammation inhibition, or to a combination of these two processes?
Inflammation and Thrombosis

- Resting Endothelial Cell
- Activated Endothelial Cell
- Activated Macrophage
- Resting Platelet
- Activated Degranulating Platelet
- Resting Smooth Muscle Cell
- Proliferating Modulated Smooth Muscle Cell
- Thrombin

Pro-inflammatory Mediators (e.g., CD40L, RANTES, IL-6)

- Reactive Oxygen Species
- Tissue Factor Procoagulant
- Pro-inflammatory Cytokines
- Lipid mediators Of inflammation
Venous Endothelium- *transmission electron micrograph*
JUPITER
Total Venous Thromboembolism

HR 0.57, 95% CI 0.37-0.86
P = 0.007

Placebo 60 / 8901
- 43%

Rosuvastatin 34 / 8901

Number at Risk
Rosuvastatin 8,901 8,648 8,447 6,575 3,927 1,986 1,376 1,003 548 161
Placebo 8,901 8,652 8,417 6,574 3,943 2,012 1,381 993 556 182
JUPITER
Absolute Risk Reduction Increases With Increasing Levels of hsCRP

Baseline hsCRP

<table>
<thead>
<tr>
<th>Baseline hsCRP</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10 mg/L</td>
<td>2,503</td>
</tr>
<tr>
<td>&gt;9 mg/L</td>
<td>3,071</td>
</tr>
<tr>
<td>&gt;8 mg/L</td>
<td>3,839</td>
</tr>
<tr>
<td>&gt;7 mg/L</td>
<td>4,723</td>
</tr>
<tr>
<td>&gt;6 mg/L</td>
<td>5,897</td>
</tr>
<tr>
<td>&gt;5 mg/L</td>
<td>7,425</td>
</tr>
<tr>
<td>&gt;4 mg/L</td>
<td>9,726</td>
</tr>
<tr>
<td>&gt;3 mg/L</td>
<td>12,939</td>
</tr>
<tr>
<td>&gt;2 mg/L</td>
<td>17,802</td>
</tr>
</tbody>
</table>
**JUPITER**

**LDL reduction, hsCRP reduction, or both?**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>7832</td>
<td>1.11</td>
</tr>
<tr>
<td>LDL &gt; 70mg/dL, hsCRP &gt; 2 mg/L</td>
<td>1384</td>
<td>1.11</td>
</tr>
<tr>
<td>LDL &lt; 70mg/dL, hsCRP &gt; 2 mg/L</td>
<td>2921</td>
<td>0.62</td>
</tr>
<tr>
<td>LDL &gt; 70mg/dL, hsCRP &lt; 2 mg/L</td>
<td>726</td>
<td>0.54</td>
</tr>
<tr>
<td>LDL &lt; 70mg/dL, hsCRP &lt; 2 mg/L</td>
<td>2685</td>
<td>0.38</td>
</tr>
</tbody>
</table>

**Full Adjusted Hazard Ratio**

0.21, 95% CI 0.09-0.52, P < 0.0001

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Ridker et al Lancet 2009;373:1175-82
JUPITER
LDL reduction, hsCRP reduction, or both?

JUPITER GWAS:
The genetic determinants of rosuvastatin-induced LDL-C reduction do not predict rosuvastatin-induced CRP reduction.
The genetic determinants of rosuvastatin-induced CRP reduction do not predict rosuvastatin-induced LDL-C reduction.

Chasman et al, 2012 Circulation Cardiovascular Genetics
Chu et al, 2012 Circulation Cardiovascular Genetics
Can Targeted Anti-Inflammatory Therapy Reduce Cardiovascular Event Rates and Prolong Life?
Cardiovascular Inflammation Reduction Trial (CIRT)

Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA

Persistent Evidence of Inflammation

How to define?

Anti-Inflammatory Intervention
Placebo

Nonfatal MI, Nonfatal Stroke, Cardiovascular Death, Incident T2DM

Ridker PM. Thromb Haemost 2009
## Issues in the Selection of Anti-inflammatory Agents for Trials of Cardiovascular Inflammation Inhibition

<table>
<thead>
<tr>
<th></th>
<th>Statins</th>
<th>TNF Inhibition</th>
<th>IL-6 Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>LDL</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>HDL</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>TG</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Chylo</td>
<td>↔</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>CRP / IL-6</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>
Issues in the Selection of Anti-inflammatory Agents for Trials of Cardiovascular Inflammation Inhibition

<table>
<thead>
<tr>
<th></th>
<th>Statins</th>
<th>TNF inhibition</th>
<th>IL-6 Inhibition</th>
<th>LDM</th>
<th>IL-1β inhibition</th>
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</tr>
<tr>
<td>LDL</td>
<td>↓↓</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>--</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chylo</td>
<td>--</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP / IL-6</td>
<td>↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td></td>
<td>↓</td>
</tr>
</tbody>
</table>
A randomized, double-blind, placebo-controlled, event-driven trial of weekly low-dose methotrexate (LDM) in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with type 2 diabetes or metabolic syndrome.
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Group</th>
<th>HR* (95 % CI)</th>
<th>Endpoint</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wichita RA 0.4</td>
<td>(0.2 - 0.8)</td>
<td>Total Mortality</td>
<td>LDM</td>
<td></td>
</tr>
<tr>
<td>Choi 2002 0.3</td>
<td>(0.2 - 0.7)</td>
<td>CV Mortality</td>
<td>LDM</td>
<td></td>
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<tr>
<td></td>
<td>0.4</td>
<td>(0.3 – 0.8)</td>
<td>CV Mortality</td>
<td>LDM &lt; 15 mg/wk</td>
</tr>
<tr>
<td>Netherlands RA 0.3</td>
<td>(0.1 – 0.7)</td>
<td>CVD</td>
<td>LDM only</td>
<td></td>
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<tr>
<td>van Helm 2006 0.2</td>
<td>(0.1 – 0.5)</td>
<td>CVD</td>
<td>LDM + SSZ</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>(0.1 – 1.2)</td>
<td>CVD</td>
<td>LDM + HCQ</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>(0.1 – 0.5)</td>
<td>CVD</td>
<td>LDM + SSZ + HCQ</td>
</tr>
<tr>
<td>Miami VA RA 0.7</td>
<td>(0.6 – 0.9)</td>
<td>CVD</td>
<td>LDM</td>
<td></td>
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<tr>
<td>Pradanovich 2005 0.5</td>
<td>(0.3 – 0.8)</td>
<td>CVD</td>
<td>LDM</td>
<td></td>
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<tr>
<td></td>
<td>0.8</td>
<td>(0.7 – 1.0)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>(0.5 – 0.8)</td>
<td>CVD</td>
<td>LDM &lt; 15 mg/wk</td>
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<tr>
<td>CORRONA RA 0.6</td>
<td>(0.3 – 1.2)</td>
<td>CVD</td>
<td>LDM</td>
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<td>Solomon 2008 0.4</td>
<td>(0.2 – 0.8)</td>
<td>CVD</td>
<td>TNF-inhibitor</td>
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<tr>
<td>QUEST-RA RA 0.85</td>
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<td>CVD</td>
<td>LDM</td>
<td></td>
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<td>Narango 2008 0.82</td>
<td>(0.7 – 0.9)</td>
<td>MI</td>
<td>LDM</td>
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<tr>
<td></td>
<td>0.89</td>
<td>(0.8 - 1.0)</td>
<td>Stroke</td>
<td>LDM</td>
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<tr>
<td>UK Norfolk RA, PsA 0.6</td>
<td>(0.4 – 1.0)</td>
<td>Total Mortality</td>
<td>LDM</td>
<td></td>
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<tr>
<td>2008</td>
<td>0.5</td>
<td>(0.3 – 1.1)</td>
<td>CV Mortality</td>
<td>LDM</td>
</tr>
</tbody>
</table>
MTX Inhibits Atherogenesis in Cholesterol-Fed Rabbits

Hematoxylin-eosin

Anti-VSMC

Anti-rabbit macrophage

Anti-rabbit MMP-9

Bulgarelli et al, J Cardiovasc Pharmacol 2012;59:308-14
MTX Inhibits Atherogenesis in Cholesterol-Fed Rabbits

Bulgarelli et al, J Cardiovasc Pharmacol 2012;59:308-14
Cardiovascular Inflammation Reduction Trial (CIRT)

Primary Aims

- To directly test the inflammatory hypothesis of atherothrombosis by evaluating in a randomized, double-blind, placebo-controlled trial whether LDM given at a target dose of 20 mg po weekly over a three to four 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.

- To determine in a randomized, double-blind, placebo-controlled setting whether LDM will reduce the rate of new onset type 2 diabetes among those with metabolic syndrome but not diabetes at study entry.

N = 7,000  NHLBI-Sponsored
Enrollment to Start February 2013
350 US and Canadian Sites
## Issues in the Selection of Anti-inflammatory Agents for Trials of Cardiovascular Inflammation Inhibition

<table>
<thead>
<tr>
<th>Statins</th>
<th>TNF inhibition</th>
<th>IL-6 Inhibition</th>
<th>LDM</th>
<th>IL-1β inhibition</th>
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<tr>
<td>TC</td>
<td>↓↓</td>
<td>↑</td>
<td>↑</td>
<td>←→</td>
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<tr>
<td>LDL</td>
<td>↓↓</td>
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<td>TG</td>
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<td>←→</td>
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<tr>
<td>Chylo</td>
<td>←→</td>
<td>↑</td>
<td>↑</td>
<td>←→</td>
</tr>
<tr>
<td>CRP / IL-6</td>
<td>↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓</td>
</tr>
</tbody>
</table>
The Balance of IL-1 and IL-1Ra: Key Regulatory Proteins for Innate Immunity

Pro-Inflammatory

IL-1α
IL-1β

Anti-Inflammatory

IL-1Ra

IL-1R
Application of IL-1β promotes arterial intimal thickening in porcine coronary artery

Shimokawa et al. (1996) J Clin Invest 97:769
Lack of IL-1β decreases severity of atherosclerosis in ApoE-deficient mice

NLRP3 Cryopyrin Inflammasome, Caspase-1, and IL-1β Maturation Endogenous Danger Signals in Vascular Biology?
Genetic Determinants of Plasma CRP Level

Dehgman et al, Circulation 2011;123:731-8
NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals

Peter Duewell¹,³*, Hajime Kono²*, Katey J. Rayner⁴,⁵, Cherilyn M. Sirois¹, Gregory Vladimer¹, Franz G. Bauernfeind⁶, George S. Abela⁸, Luigi Franchi⁹, Gabriel Núñez⁹, Max Schnurr³, Terje Espevik¹⁰, Egil Lien¹, Katherine A. Fitzgerald¹, Kenneth L. Rock², Kathryn J. Moore⁴,⁵, Samuel D. Wright¹¹, Veit Hornung⁵* & Eicke Latz¹,⁷,¹⁰*

Cholesterol Crystals Activate the NLRP3 Inflammasome in Human Macrophages: A Novel Link between Cholesterol Metabolism and Inflammation

Kristiina Rajamäki¹*, Jani Lappalainen¹, Katariina Öörni¹, Elina Välimäki², Sampsa Matikainen², Petri T. Kovanen¹, Kari K. Eklund¹

¹ Wihuri Research Institute, Helsinki, Finland, ² Finnish Institute of Occupational Health, Helsinki, Finland
Cholesterol crystals activate the caspase-1-activating NLRP3 inflammasome to generate IL-1β and initiate atherosclerosis.

**Diagram Description:**
- **Endogenous Danger Signal:** Cholesterol crystals; Modified LDL
- **Phagosome**
- **Lysosome**
- **Phagolysosome**
- **NLRP3 Inflammasome**
- **ASC**
- **Cardinal**
- **Pro-caspase-1**
- **Caspase-1**
- **IL-1β**
- **Pro-IL-1β**
- **IL-1B mab or IL-1rA**
- **IL-6**
- **Liver**
- **Vascular inflammation ↑ hsCRP**
IL-6 and Risk of Future MI in Apparently Healthy Men

\[ P = 0.01 \]

\[ P = 0.003 \]

\[ P = 0.3 \]

\[ \text{Quartile of IL-6 (range, pg/dL)} \]

\[ 1 \leq 1.04 \]

\[ 1.04 - 1.46 \]

\[ 1.47 - 2.28 \]

\[ \geq 2.28 \]

\[ P \text{ Trend} = 0.001 \]

\[ \text{Relative Risk of MI} \]

\[ \text{Ridker et al, Circulation 2000;101:1767-1772} \]
Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies

IL6R Genetics Consortium and Emerging Risk Factors Collaboration

Summary
Background Persistent inflammation has been proposed to contribute to various stages in the pathogenesis of cardiovascular disease. Interleukin-6 receptor (IL6R) signalling propagates downstream inflammation cascades. To assess whether this pathway is causally relevant to coronary heart disease, we studied a functional genetic variant known to affect IL6R signalling.
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
Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA
Persistent Elevation
of hsCRP (> 2 mg/L)

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 = 17,200
Novartis
(>2000 currently)
Inflammation, Atherothrombosis, and Vascular Prevention: Three Crucial Questions

Is there evidence that individuals with elevated levels of inflammatory biomarkers are at high vascular risk even when other risk factors are acceptable? Yes

Is there evidence that individuals identified at increased risk due to inflammation benefit from a therapy they otherwise would not have received? Yes

Is there evidence that reducing inflammation per se will reduce vascular events and slow progression of diabetes? TINSAL, CIRT, CANTOS – Let’s find out