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 Siemens and AstraZeneca. Dr. Ridker and the BWH receive royalties on sales of the hsCRP test. However, neither Dr. Ridker nor the BWH receive any royalties attributable to sales of the hsCRP test used in connection with the CIRT or CANTOS trials.
Event-Free Survival According to Baseline Quintiles of hs-CRP and LDL Cholesterol

CRP, IL-6 and the Risk for Developing Type-2 Diabetes in the Women's Health Study

CRP adds to the ATP-III Definition of the Metabolic Syndrome (N = 3,097 with ATP-III Metabolic Syndrome)
Linear Relationship of Inflammation to Vascular Risk Across a Very Wide Range of Values

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

Risk Ratio (95%CI) per 1-SD higher usual values

Why do we treat individuals with a persistent pro-inflammatory response with statin therapy?
Inflammation, Statin Therapy, and hsCRP: Initial Observations


Relative Risk Relative Risk

Pravastatin Placebo Pravastatin Placebo

Inflammation Absent Inflammation Present

Pravastatin Placebo Pravastatin Placebo

Median hsCRP (mg/dL)

-21.6% (P=0.004)

Baseline 5 Years

Clinical Relevance of Achieved LDL and Achieved CRP After ACS Treated with Statin Therapy


Clinical Relevance of Achieved LDL and Achieved CRP After ACS Treated with Statin Therapy

REVERSAL: Regression of Atherosclerosis On Statin Therapy Occurs Primarily Among Those with Both LDL and CRP Reduction

Nissen et al NEJM 2005; 352:29-38

JUPITER
Ridker et al NEJM 2008;359:2195-2207

Trial Design

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

No Prior CVD or DM
Men ≥40, Women ≥50
LDL <130 mg/dL
hsCRP >2 mg/L

Rosuvastatin 20 mg (N=8901)

Placebo (N=8901)

MI Stroke Unstable Angina Revascularization CVD Death CABG/PTCA

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 LDL C 104 mg/dL, Mean HDLC 50 mg/dL, hsCRP 4 mg/L

Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

HR 0.56, 95% CI 0.48-0.69
P < 0.00001

Number Needed to Treat (NNT) = 25

-44%

Number at Risk
Rosuvastatin: 8,901 8,631 8,412 6,508 3,865 1,963 1,333 955 534 174
Placebo: 8,901 8,631 8,412 6,508 3,865 1,963 1,333 955 534 174

Ridker et al NEJM 2008;359:2195-2207
JUPITER
Achieved LDL, Achieved hsCRP, or Both?

Is the large benefit observed in the JUPITER trial due to lipid lowering, to inflammation inhibition, or to a combination of these two processes?

JUPITER
Absolute Risk Reduction Increases With Increasing Levels of hsCRP

JUPITER
LDL reduction, hsCRP reduction, or both?
**C-Reactive Protein, but not Low-Density Lipoprotein Cholesterol Levels, Associate With Coronary Atheroma Regression and Cardiovascular Events After Maximally Intensive Statin Therapy**


**Hazard Ratio for Time to First MACE**

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>0.57 (0.37, 0.86)</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.0 (0.62, 1.56)</td>
</tr>
</tbody>
</table>

---

**JUPITER**

Total Venous Thromboembolism

Glynn et al NEJM 2010

**Figure:**

- Cumulative incidence of venous thromboembolism
- Placebo: 80/8901
- Rosuvastatin: 34/8901

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

---

**Can Targeted Anti-Inflammatory Therapy Reduce Cardiovascular Event Rates and Prolong Life?**
**Targeting Inflammatory Pathways for the Treatment of Cardiovascular Disease**

![Diagram of inflammatory pathways](image)

Ridker P Luscher T Eur Heart Journal 2014

---

**IL-6 and Risk of Future MI in Apparently Healthy Men**

![Graph showing relative risk of MI](image)

Ridker et al, Circulation 2000;101:1767-1772

---

**Relationship of IL-6 and Future Cardiovascular Events**

![Graph showing relationship](image)

Kaptoge et al, Eur Heart J 2013
Mendelian Randomization and the IL-6 Regulatory Pathway

Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies

Lancet 2012;379;1214-24

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

The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis

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

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

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

Swerdline et al, Lancet 2012;379;1214-24
### Differentiating Anti-Inflammatory Agents That Do and Do Not Target the Central IL-6 Signaling Pathway

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target Pathway</th>
<th>Trial/Study</th>
<th>Size</th>
<th>Sponsor</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Agents That Primarily Target the IL-6 Signaling Pathway</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canakinumab</td>
<td>IL-1β</td>
<td>CANTOS</td>
<td>10,000</td>
<td>Novartis</td>
<td>Enrolling</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>IL-6,TNF</td>
<td>CIRT</td>
<td>7,000</td>
<td>NHLBI</td>
<td>Enrolling</td>
</tr>
<tr>
<td>Azilsartine</td>
<td>IL-1Ra</td>
<td>IL-HEART</td>
<td>190</td>
<td>UK-MRC</td>
<td>Completed</td>
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<tr>
<td>Colchicine</td>
<td>multiple</td>
<td>LoDoCo</td>
<td>532</td>
<td>HRS, Aus</td>
<td>Positive</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>IL-6</td>
<td>ENTRACTE</td>
<td>3,080</td>
<td>Hoffmann</td>
<td>Enrolling</td>
</tr>
<tr>
<td>Infliximab</td>
<td>TNF</td>
<td>ENTRACTE</td>
<td>3,080</td>
<td>Hoffmann</td>
<td>Enrolling</td>
</tr>
<tr>
<td>B. Agents That Do Not Primarily Target the IL-6 Signaling Pathway</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succinobucol</td>
<td>Ox-LDL</td>
<td>ARISE</td>
<td>6,144</td>
<td>AtheroGenics</td>
<td>Negative</td>
</tr>
<tr>
<td>Varespladiab</td>
<td>sPLA2</td>
<td>VISTA-16</td>
<td>5,000</td>
<td>Amgen</td>
<td>Negative</td>
</tr>
<tr>
<td>Darapladab</td>
<td>LP-PLA2</td>
<td>STABILITY</td>
<td>15,000</td>
<td>GSK</td>
<td>Negative</td>
</tr>
<tr>
<td>Inclacumab</td>
<td>P-Selectin</td>
<td>SELECT-ACS</td>
<td>544</td>
<td>Roche</td>
<td>Completed</td>
</tr>
<tr>
<td>Inclacumab</td>
<td>P-Selectin</td>
<td>SELECT-CABG</td>
<td>380</td>
<td>Roche</td>
<td>Enrolled</td>
</tr>
</tbody>
</table>

---

### 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>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>↓↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>LDL</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>HDL</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>TG</td>
<td>←</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<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>

---

For More Information:
theCIRT.org  theCANTOS.org
Cardiovascular Inflammation Reduction Trial (CIRT) (Ridker PI) Primary Aims

- 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
Enrollment to Start June 2013
350 US and Canadian Sites

Methotrexate Inhibits Atherogenesis in Cholesterol-fed Rabbits

Bulgarelli et al, J Cardiovasc Pharmacol 2012;59:308-14

LDM and CVD: Observational Evidence

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Group</th>
<th>HR</th>
<th>(95% CI)</th>
<th>Endpoint</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wichita</td>
<td>RA</td>
<td>0.4</td>
<td>(0.2 - 0.8)</td>
<td>Total Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.3</td>
<td>(0.2 - 0.7)</td>
<td>CV Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6</td>
<td>(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</td>
<td>(0.1 - 0.7)</td>
<td>CVD</td>
<td>LDM only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2</td>
<td>(0.1 - 0.5)</td>
<td>CVD</td>
<td>LDM + SSZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2</td>
<td>(0.1 - 0.5)</td>
<td>CVD</td>
<td>LDM + HCQ</td>
</tr>
<tr>
<td></td>
<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</td>
<td>PsA</td>
<td>0.7</td>
<td>(0.6 - 0.9)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6</td>
<td>(0.3 - 0.8)</td>
<td>CVD</td>
<td>LDM &lt; 15 mg/wk</td>
</tr>
<tr>
<td></td>
<td>RA</td>
<td>0.6</td>
<td>(0.3 - 1.0)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6</td>
<td>(0.5 - 0.8)</td>
<td>CVD</td>
<td>LDM &lt; 15 mg/wk</td>
</tr>
<tr>
<td>CORRONA</td>
<td>RA</td>
<td>0.6</td>
<td>(0.3 - 1.2)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td>PsA</td>
<td>0.4</td>
<td>(0.2 - 0.6)</td>
<td>CVD</td>
<td>TNF-Inhibitor</td>
</tr>
<tr>
<td>ORALIS</td>
<td>RA</td>
<td>0.6</td>
<td>(0.3 - 1.0)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td>PsA</td>
<td>0.6</td>
<td>(0.3 - 1.0)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td>PsA</td>
<td>0.6</td>
<td>(0.3 - 1.0)</td>
<td>M</td>
<td>LDM</td>
</tr>
<tr>
<td>UK Norfolk</td>
<td>RA, PsA</td>
<td>0.6</td>
<td>(0.4 - 1.0)</td>
<td>Total Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6</td>
<td>(0.3 - 1.1)</td>
<td>CV Mortality</td>
<td>LDM</td>
</tr>
</tbody>
</table>
Cardiovascular Inflammation Reduction Trial (CIRT)
theCIRT.org website

The Balance of IL-1 and IL-1Ra: Key Regulatory Proteins for Innate Immunity

IL-1Ra
IL-1R

Pro-Inflammatory Anti-Inflammatory

IL-1α IL-1β

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
Kiril et al. (2003) Atherosclerosis Thrombosis 25:256

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

**Crystals activate the NLRP3 inflammasome**

- Exogenous particles: Alum, Silica, Asbestos, endogenous material: Cholesterol, Uric acid

*Courtesy Eicke Latz  Phase transition from soluble to crystalline as a “danger signal”*
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 Homoglobin A1c, Lipids, C-Reactive Protein, Interleukin-6, and Fibrinogen
A Phase Ib Randomized, Placebo-Controlled Trial
Paul M Ridker, MD, MPH, Campbell P. Hovind, MD, Venosa Robert, MD, Mark FH, Randozta Federico, MD, Pinto Enrique, MD, Aboush Mounir, MD, Tom Doan, MD, TGX on behalf of the CANTOS Film Investigator Group

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) (Ridker PI)

Stable CAD (post MI) On Statin, ACE/ARB, BB, ASA Persistent Elevation of hsCRP (>2 mg/L)
N = 10,000 Novartis

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
The challenges in targeting inflammation in any chronic inflammatory disease lie in three properties that are critical for evolutionary survival: redundancy, compensation, and necessity.

Monitor for infection, TB, cancer

Balance potential vascular benefits with probable risks

hsCRP, Aspirin, and Risks of Future Myocardial Infarction


Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease

Are the anti-inflammatory effects of lipid-lowering relevant for clinical practice?

<table>
<thead>
<tr>
<th>Agent</th>
<th>Event Reduction</th>
<th>LDL-Lowering</th>
<th>CRP-Lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ezetimibe + Statin</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fibrates</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Niacin</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>CETP-inhibitors</td>
<td>No/*</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>HRT</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>PCSK9-inhibitors</td>
<td>??</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

For More Information:
theCIRT.org
pridker@partners.org
Elaine Zaharris (617) 278-0893