May 8th, 9:00 AM - 10:00 AM

Inflammation and Atherothrombosis: Where Have We Been? Where Are We Going? Why Perform the CIRT and CANTOS Trials? From Bench to Bedside to Population and Back: A Story of Clinical Translation

Paul M. Ridker
Harvard Medical School

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Inflammation and Atherothrombosis: Where have we been? Where Are We Going? Why Perform the CIRT and CANTOS Trials?

From Bench to Bedside to Population and Back: A Story of Clinical Translation

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
What is translational research? How does an integrated health care system support it?

Bench → Bedside → Population

Affiliated Network Hospitals Clinics

T1, T2, T3
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.
Inflammation, Atherothrombosis, and Vascular Prevention: Three Translational Questions

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

Quartile of IL-6 (range, pg/dL)

- Quartile 1: ≤1.04
- Quartile 2: 1.04-1.46
- Quartile 3: 1.47-2.28
- Quartile 4: ≥2.28

Relative Risk of MI

- Quartile 1: P=0.3
- Quartile 2: P=0.003
- Quartile 3: P=0.01

P Trend = 0.001

Ridker et al, Circulation 2000;101:1767-1772
hsCRP and Risk of Future MI and CVA in Apparently Healthy Men

Quartile of hs-CRP

Relative Risk of MI

$P$ Trend $<0.001$

Relative Risk of Stroke

$P$ Trend $<0.01$

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

Markers of Inflammation in the Prediction of Cardiovascular Disease in Women

Ridker et al NEJM. 2000;342:836–43.
Markers of Inflammation in the Prediction of Cardiovascular Disease in Women

Ridker et al NEJM. 2000;342:836–43.
CRP, IL-6 and the Risk for Developing Type-2 Diabetes in the Women’s Health Study

Pradhan et al JAMA 2001; 286:327-34
Linear Relationship of Inflammation to Vascular Risk Across a Very Wide Range of Values

Relative Risk of Future CV Events

- "lower risk" < 1 mg/L
- "moderate risk" 1 – 3 mg/L
- "higher risk" > 3 mg/L

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

Emerging Risk Factor Collaborators, Lancet January 2010
Direct Comparison of Lipid Markers and hsCRP in 166,596 Individuals Followed For First-Onset Cardiovascular Disease (ERFC NEJM 2012;367:1310-1320)

Multivariable Hazard Ratio for CVD per 1-SD change (adjusted for Age, Gender, Smoking, DM, BP, and HDL)

hsCRP Total Cholesterol

1.20 (1.18-1.22)
1.17 (1.15-1.19)
Direct Comparison of Lipid Markers and hsCRP in 166,596 Individuals Followed For First-Onset Cardiovascular Disease (ERFC NEJM 2012;367:1310-1320)

- **Non-lipid risk factors**
  - plus TC
  - plus TC plus HDLC
  - plus TC plus HDLC plus hsCRP

- **Multivariable Hazard Ratio for CVD per 1-SD change**
  - (adjusted for Age, Gender, Smoking, DM, BP, and HDL)
  - hsCRP: 1.20 (1.18-1.22)
  - Total Cholesterol: 1.17 (1.15-1.19)

- **Change in C-statistic**
  - (as compared with non-lipid-based model)
  - 0.0043
  - 0.0050
  - 0.0039
C-Reactive Protein and Reclassification of Cardiovascular Risk in the Framingham Heart Study

Peter W.F. Wilson, MD; Michael Pencina, PhD; Paul Jacques, DS; Jacob Selhub, PhD; Ralph D’Agostino, Sr, PhD; Christopher J. O’Donnell, MD, MPH

**Background**—The relationship of circulating levels of high-sensitivity C-reactive protein (CRP) with cardiovascular disease (CVD) risk, particularly with consideration of effects at intermediate levels of risk, has not been fully assessed.

**Methods and Results**—Among 3006 offspring participants in the Framingham Heart Study free of CVD (mean age, 46 years at baseline), there were 129 hard coronary heart disease (CHD) events and 286 total CVD events during 12 years of follow-up. Cox regression, discrimination with area under the receiver operating characteristic curve, and net reclassification improvement were used to assess the role of CRP on vascular risk. In an age-adjusted model that included traditional risk factors, the net reclassification improvement when CRP was added was 11.8% for hard CHD (P=0.009), a value greater than that of LDL, HDL, or blood pressure in the Framingham Data.

The net reclassification improvement when CRP was added to traditional risk factors was 11.8% for hard CHD (P=0.009), a value greater than that of LDL, HDL, or blood pressure in the Framingham Data.

**Conclusions**—Circulating levels of CRP help to estimate risk for initial cardiovascular events and may be used most effectively in persons at intermediate risk for vascular events, offering moderate improvement in reclassification of risk. (Circ Cardiovasc Qual Outcomes. 2008;1:92-97.)

**Key Words:** epidemiology ■ inflammation ■ risk factors ■ statistics
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.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68</td>
<td>Years (Maximum age must be 80)</td>
</tr>
<tr>
<td>Do you currently smoke?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Systolic Blood Pressure (SBP)</td>
<td>125 mm/Hg</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>230 mg/dL</td>
<td></td>
</tr>
<tr>
<td>HDL or &quot;Good&quot; Cholesterol</td>
<td>45 mg/dL</td>
<td></td>
</tr>
<tr>
<td>High Sensitivity C-Reactive Protein (hsCRP)</td>
<td>4.5 mg/L</td>
<td></td>
</tr>
<tr>
<td>Did your Mother or Father have a heart attack before age 60?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>current Age</th>
<th>Age 78</th>
<th>Print</th>
<th>Age 68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Your 10-year risk (age 68)</td>
<td></td>
<td></td>
<td>29%</td>
</tr>
<tr>
<td>Your 10-year risk (age 68) if,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• your blood pressure was 120</td>
<td></td>
<td></td>
<td>23%</td>
</tr>
<tr>
<td>• your cholesterol was 160</td>
<td></td>
<td></td>
<td>18%</td>
</tr>
<tr>
<td>• your hsCRP was 0.5</td>
<td></td>
<td></td>
<td>24%</td>
</tr>
<tr>
<td>• all the above were optimal</td>
<td></td>
<td></td>
<td>11%</td>
</tr>
</tbody>
</table>

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 Man, 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 cohort of 1001 women without major CVD. We estimated risk using the Adult Treatment Panel III (ATP-III) and Reynolds Risk Score. Discrimination was compared using the concordance index (c-index). 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.)*

Cook NR et al, Circulation 2012;125:1748-1756
55 year old executive
Chief complaint
Stress and anxiety
No prior CV history
Non-smoker, no diabetes
Close associate recurrent MI
“elevated CRP”

TC 170
HDL 42
LDL 112
TG 80
hs-CRP 0.6
55 year old executive  
Chief complaint  
Stress and anxiety  
No prior CV history  
Non-smoker, no diabetes  
Close associate recurrent MI  
“elevated CRP”

TC 170  
HDL 42  
LDL 112  
TG 80  
hs-CRP 0.6
Checkup Finds Bush Fit and Healthy

By LAWRENCE K. ALTMAN

WASHINGTON, Aug. 4 — President Bush is in "outstanding health" and at very low risk for a heart attack, his doctors said today after performing Mr. Bush's first medical checkup since he took office.

Mr. Bush was monitored while he ran on a treadmill for 26 minutes with a maximum heart rate of 178 beats per minute. The findings placed him "in the top 2 percent of men his age in cardiovascular fitness," a White House statement signed by 14 doctors said.

Mr. Bush, 55, runs an average of three miles four times a week. He also swims, lifts weights and uses an elliptical trainer. His resting heart rate was reported as 43 beats a minute and his blood pressure as 118/74.

Mr. Bush, who is six feet tall, has lost nearly five pounds in the last year. His weight of 189.75 pounds is down from 194.5 pounds at his last checkup in June 2000, when he was governor of Texas. His body fat is normal at 14.5 percent, down from 19.94 percent.

"I'm in pretty good shape," Mr. Bush said after completing the 5-hour, 50-minute examination at Bethesda Naval Hospital.

The only new abnormality reported was the removal of three potentially cancerous lesions from Mr. Bush's face. Dr. Richard A. Keller, the chief dermatologist at Walter Reed Army Medical Center, used liquid nitrogen to remove the lesions, which are known as actinic keratoses. They are common and result from chronic sun exposure; if untreated, a small percentage of them can become skin cancers.

A White House spokesman described them as "small, dry patches" that had a red tint and felt "like sandpaper."

In 1998 and 1999, Mr. Bush had benign polyps removed from his colon after a routine examination. Another colonoscopy is not due until next year, the doctors said. Ultrasound tests of his abdomen performed today were normal.

Tests showed no change in Mr. Bush's mild high-frequency hearing loss, which does not affect his normal conversations.

A set of 70 blood and urine tests were all normal. They included tests for risk of heart disease: total cholesterol, 170; high density lipoprotein, 42; low density lipoprotein, 112; triglycerides 80; C-reactive protein, 0.4; and homocysteine, 8.6. A standard blood test for prostate cancer was a normal 0.78.

Mr. Bush suffers from seasonal allergies, wears reading glasses, smokes an occasional cigar and does not drink alcohol, according to the statement.

He takes vitamins but does not routinely use prescription medications and has not missed a day of work since his last checkup. The examination was performed by Dr. Kenneth H. Cooper of Dallas, who has given Mr. Bush annual checkups since 1989.

Dr. Cooper joined Dr. Richard J. Tubb, the White House physician, in supervising today's checkup.

The 14 doctors used a standard military phrase to describe Mr. Bush as "fit for duty." All but four of the doctors work at military hospitals. They also said, "All data suggest that he will remain so for the duration of his presidency."
Doctors Who Examine Bush Say He Is Exceptionally Fit

By LAWRENCE K. ALTMAN

WASHINGTON, Aug. 6 — President Bush’s second annual medical checkup since he took office found him in “extraordinary health,” his doctors said today, with his heart and lung function in the top 1 percent for men of his age, up from the top 2 percent a year ago.

The three-hour battery of tests that Mr. Bush, 56, underwent this morning show that he has no evidence of heart disease and a “very low” risk for a heart attack, the doctors said. They predicted that he would remain in excellent health for the rest of his term.

As Mr. Bush returned to the White House from the National Naval Medical Center in nearby Bethesda, Md., where the checkup was performed, he said he was “feeling good.” Later, Mr. Bush flew to his ranch in Texas for a monthlong working vacation.

In a five-page detailed statement released by the White House, the team of eight military and civilian doctors and health specialists who examined the president said that Mr. Bush had missed work due to illness in the White House and that he had not had a recurrence of the fainting episode he suffered in January when a pretzel stuck in his throat.

Mr. Bush fell off a sofa and cut his face in the fainting incident, which the White House said occurred while he was watching television.

Mr. Bush smokes an occasional cigar, abstains from alcohol and drinks diet sodas and coffee, the doctors said. Mr. Bush, who stands six feet tall, weighed 189 pounds, three-quarters of a pound less than at the checkup in August 2001. His body fat remained unchanged at 14.5 percent and down from 19.94 percent recorded in a checkup in June 2000.

He takes vitamins and an aspirin daily. Mr. Bush does not routinely use prescription medications except for a steroid nasal spray to prevent symptoms in allergy seasons.

The only abnormalities noted involved his hearing, skin and eyes.

Mr. Bush has a high frequency hearing loss in both ears from 4,000 to 8,000 kilohertz that is unchanged from last year’s examination. Mr. Bush’s hearing is excellent in the frequencies for speech, the doctors said. They also said that the degree and frequency involved do not affect normal conversation.

The doctors said that the small harmless red blotsches that appear on Mr. Bush’s nose are due to widened capillaries resulting from sun exposure. No treatment was given today, but they said that it may be needed in the future for the condition, known as telangiectasias. It is common.

In the last year, four small benign skin growths were removed from Mr. Bush’s face.

Mr. Bush occasionally uses reading glasses.

Mr. Bush is a fitness enthusiast, and his heart rate of 44 beats a minute and blood pressure of 106/70 reflected his training routine. He typically runs three miles four times a week, with average times from 8:45 minutes to 7:15 minutes a mile. He also routinely cross-trains with gym weights for 45 minutes twice a week and an elliptical trainer.

In an exercise treadmill test during the checkup, Mr. Bush ran for 27:02 minutes with a maximum heart rate of 169, or 97 percent of predicted heart rate, compared to 26 minutes last year.

An echocardiogram, or ultrasound test of the heart, was normal.

Blood tests showed that Mr. Bush’s total cholesterol was in the “desirable” level, at 177, His high density lipoprotein (HDL) was normal at 49. His low density lipoprotein (LDL) was in the “desirable/near optimal” level of 114, and the ratio of the total cholesterol to HDL was optimal at 3.6, the doctors said.

Additional tests for potential heart disease were also normal. They included triglycerides (69) and homocysteine (7.1). A test for C-reactive protein was 0.6, putting him in the lowest risk category.
Inflammation, Atherothrombosis, and Vascular Prevention: Three Translational Questions

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 -
Inflammation, Statin Therapy, and hsCRP: Initial Observations


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

"dual targets for statin therapy"

Primary Prevention: Whom Should We Treat?

Probability of Event-free Survival

- hsCRP < 2, LDL < 130
- hsCRP < 2, LDL > 130
- hsCRP > 2, LDL < 130
- hsCRP > 2, LDL > 130

Years of Follow-up

hsCRP as a Method to Target Statin Therapy in Primary Prevention: AFCAPS/TexCAPS

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Statin</th>
<th>Placebo</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>low LDLC / low CRP</td>
<td>0.025</td>
<td>0.022</td>
<td>----</td>
</tr>
<tr>
<td>low LDLC / high CRP</td>
<td>0.029</td>
<td>0.051</td>
<td>48</td>
</tr>
<tr>
<td>high LDLC / low CRP</td>
<td>0.020</td>
<td>0.050</td>
<td>33</td>
</tr>
<tr>
<td>high LDLC / high CRP</td>
<td>0.038</td>
<td>0.055</td>
<td>58</td>
</tr>
</tbody>
</table>

Median LDLC = 150 mg/dL
Median CRP = 2 mg/L

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

Ridker et al NEJM 2008;359:2195-2207

No Prior CVD or DM
Men > 50, Women > 60
LDL < 130 mg/dL
hsCRP > 2 mg/L

4-week run-in

Rosuvastatin 20 mg (N= 8901)

Placebo (N= 8901)

MI Stroke Unstable Angina 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 LDLC 104 mg/dL, Mean HDLC 50 mg/dL, hsCRP 4 mg/L
JUPITER
Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

Ridker et al NEJM 2008;359:2195-2207

HR 0.56, 95% CI 0.46-0.69
P < 0.00001

Number Needed to Treat (NNT\textsubscript{5}) = 25

Cumulative Incidence

Number at Risk

<table>
<thead>
<tr>
<th>Follow-up (years)</th>
<th>Rosuvastatin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8,901</td>
<td>8,901</td>
</tr>
<tr>
<td>1</td>
<td>8,901</td>
<td>8,621</td>
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<tr>
<td>2</td>
<td>8,412</td>
<td>8,353</td>
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<td>3</td>
<td>6,540</td>
<td>6,508</td>
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<tr>
<td>4</td>
<td>3,893</td>
<td>3,872</td>
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<tr>
<td>5</td>
<td>1,958</td>
<td>1,963</td>
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<tr>
<td>6</td>
<td>1,353</td>
<td>1,333</td>
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<tr>
<td>7</td>
<td>983</td>
<td>955</td>
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<tr>
<td>8</td>
<td>544</td>
<td>534</td>
</tr>
<tr>
<td>9</td>
<td>157</td>
<td>174</td>
</tr>
</tbody>
</table>

- 44%
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

Rosuvastatin

- 55 %
JUPITER
Fatal or Nonfatal Stroke

Ridker et al NEJM 2008;359:2195-2207

Cumulative Incidence

Follow-up Years

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

- 48 %

Placebo

Rosuvastatin
JUPITER
Arterial Revascularization / Unstable Angina

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

Placebo (N = 143)
- 47%

Rosuvastatin (N = 76)

Ridker et al NEJM 2008;359:2195-2207

Cumulative Incidence

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up (years)</td>
<td>8,901</td>
<td>8,901</td>
</tr>
<tr>
<td></td>
<td>8,640</td>
<td>8,641</td>
</tr>
<tr>
<td>1</td>
<td>8,426</td>
<td>8,390</td>
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<tr>
<td>2</td>
<td>6,550</td>
<td>6,542</td>
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<tr>
<td>3</td>
<td>3,905</td>
<td>3,895</td>
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<tr>
<td>4</td>
<td>1,966</td>
<td>1,977</td>
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<tr>
<td>5</td>
<td>1,359</td>
<td>1,346</td>
</tr>
<tr>
<td>6</td>
<td>989</td>
<td>963</td>
</tr>
<tr>
<td>7</td>
<td>547</td>
<td>538</td>
</tr>
<tr>
<td>8</td>
<td>158</td>
<td>176</td>
</tr>
</tbody>
</table>
Secondary Endpoint – All Cause Mortality

Placebo 247 / 8901
Rosuvastatin 198 / 8901

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

Cumulative Incidence

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

Follow-up (years)
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
### Adverse Events and Measured Safety Parameters

<table>
<thead>
<tr>
<th>Event</th>
<th>Rosuvastatin</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any SAE</strong></td>
<td>1,352 (15.2)</td>
<td>1,337 (15.5)</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>Muscle weakness</strong></td>
<td>1,421 (16.0)</td>
<td>1,375 (15.4)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Myopathy</strong></td>
<td>10 (0.1)</td>
<td>9 (0.1)</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Rhabdomyolysis</strong></td>
<td>1 (0.01)*</td>
<td>0 (0.0)</td>
<td>--</td>
</tr>
<tr>
<td><strong>Incident Cancer</strong></td>
<td>298 (3.4)</td>
<td>314 (3.5)</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Cancer Deaths</strong></td>
<td>35 (0.4)</td>
<td>58 (0.7)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Hemorrhagic stroke</strong></td>
<td>6 (0.1)</td>
<td>9 (0.1)</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>GFR (ml/min/1.73m² at 12 mth)</strong></td>
<td>66.8 (59.1-76.5)</td>
<td>66.6 (58.8-76.2)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>ALT &gt; 3xULN</strong></td>
<td>23 (0.3)</td>
<td>17 (0.2)</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Fasting glucose (24 mth)</strong></td>
<td>98 (91-107)</td>
<td>98 (90-106)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>HbA1c (% at 24 mth)</strong></td>
<td>5.9 (5.7-6.1)</td>
<td>5.8 (5.6-6.1)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Glucosuria (12 mth)</strong></td>
<td>36 (0.5)</td>
<td>32 (0.4)</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>Incident Diabetes</strong>**</td>
<td>270 (3.0)</td>
<td>216 (2.4)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Occurred after trial completion, trauma induced. All values are median (interquartile range) or N (%)

**Physician reported
JUPITER
Statins and the Development of Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Statin</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOSCOPS</td>
<td>Pravastatin</td>
<td>0.70 (0.50–0.98)</td>
</tr>
<tr>
<td>(Hypothesis Generating Trial)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROSPER</td>
<td>Pravastatin</td>
<td>1.34 (1.06–1.68)</td>
</tr>
<tr>
<td>LIPID</td>
<td>Pravastatin</td>
<td>0.91 (0.72–1.18)</td>
</tr>
<tr>
<td>HPS</td>
<td>Simvastatin</td>
<td>1.20 (0.98–1.35)</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>Atorvastatin</td>
<td>1.20 (0.91–1.44)</td>
</tr>
<tr>
<td>PROVE-IT</td>
<td>Atorvastatin</td>
<td>1.11 (0.67–1.83)</td>
</tr>
<tr>
<td></td>
<td>vs Pravastatin</td>
<td></td>
</tr>
<tr>
<td>CORONA</td>
<td>Rosuvastatin</td>
<td>1.13 (0.86–1.50)</td>
</tr>
<tr>
<td>JUPITER</td>
<td>Rosuvastatin</td>
<td>1.25 (1.05–1.54)</td>
</tr>
<tr>
<td>(Hypothesis Testing Trials)</td>
<td></td>
<td>1.12 (1.04–1.30)</td>
</tr>
</tbody>
</table>

(Hypothesis Testing Trials)
JUPITER
Incident Diabetes Limited to Those With Impaired Fasting Glucose

Ridker et al Lancet 2012;380:
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

Ridker et al Lancet 2012
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, 86 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, 134 vascular events or deaths were avoided by statin therapy for every 54 new cases of diabetes diagnosed.
- Statin therapy increased the time to diagnosis of diabetes by 5.4 weeks.
- **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
### Primary Goal: LDLC

<table>
<thead>
<tr>
<th>Level</th>
<th>Criteria</th>
<th>Goal</th>
<th>Class</th>
<th>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</td>
<td>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</td>
<td>Level A</td>
</tr>
<tr>
<td>Low</td>
<td>FRS &lt; 10 %</td>
<td>&lt;5mmol/L</td>
<td>Class IIA</td>
<td>Level A</td>
</tr>
</tbody>
</table>

### Secondary Targets

- TC/HDL-C < 4, non HDL-C < 3.5 mol/L
- hsCRP < 2 mg/L, TG < 1.7 mol/L, ApoB/A < 0.8
Guidelines: Statin Therapy in Primary Prevention
What works and in whom?

- Benefit Untested
- Low LDL Low hsCRP High HDL
- High LDL
- High hsCRP
- Low HDL

WOSCOPS
HR 0.70 (0.57-0.84)
MEGA
HR 0.67 (0.49-0.91) (pravastatin)

AFCAPS/TexCAPS
HR 0.63 (0.50-0.79) (lovastatin)

Circ Cardiovasc Qual Outcomes 2012;5:592-3
Eur Heart J 2013;34:1258-61
JUPITER
Consistent Effects in All Geographic Regions, All Pre-Specified Subgroups

<table>
<thead>
<tr>
<th>Region</th>
<th>N</th>
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<tbody>
<tr>
<td>USA</td>
<td>4021</td>
</tr>
<tr>
<td>Canada</td>
<td>2020</td>
</tr>
<tr>
<td>European Union</td>
<td>6023</td>
</tr>
<tr>
<td>Total</td>
<td>17802</td>
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</table>

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, No recognition by EMA
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 -
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
- Resting Platelet
- Activated Degranulating Platelet
- Activated Macrophage
- Reactive Oxygen Species
- Tissue Factor Procoagulant
- Pro-inflammatory Cytokines
- Lipid mediators Of inflammation

- Pro-inflammatory Mediators (e.g., CD40L, RANTES, IL-6)
Venous Endothelium - transmission electron micrograph
JUPITER
Total Venous Thromboembolism

Glynn et al NEJM 2010

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

Placebo 60 / 8901
- 43%

Rosuvastatin 34 / 8901

Cumulative Incidence

Follow-up (years)

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
Absolute Risk Reduction Increases With Increasing Levels of hsCRP

Baseline hsCRP

- >10 mg/L: 2,503
- >9 mg/L: 3,071
- >8 mg/L: 3,839
- >7 mg/L: 4,723
- >6 mg/L: 5,897
- >5 mg/L: 7,425
- >4 mg/L: 9,726
- >3 mg/L: 12,939
- >2 mg/L: 17,802

Ridker et al, Am J Card 2010;106:206-9
**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; 70 mg/dL, hsCRP &gt; 2 mg/L</td>
<td>1384</td>
<td>1.11</td>
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<tr>
<td>LDL &lt; 70 mg/dL, hsCRP &gt; 2 mg/L</td>
<td>2921</td>
<td>0.62</td>
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<tr>
<td>LDL &gt; 70 mg/dL, hsCRP &lt; 2 mg/L</td>
<td>726</td>
<td>0.54</td>
</tr>
<tr>
<td>LDL &lt; 70 mg/dL, hsCRP &lt; 2 mg/L</td>
<td>2685</td>
<td>0.38</td>
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</table>

<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; 70 mg/dL, hsCRP &gt; 1 mg/L</td>
<td>1874</td>
<td>0.95</td>
</tr>
<tr>
<td>LDL &lt; 70 mg/dL, hsCRP &gt; 1 mg/L</td>
<td>4662</td>
<td>0.56</td>
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<tr>
<td>LDL &gt; 70 mg/dL, hsCRP &lt; 1 mg/L</td>
<td>236</td>
<td>0.64</td>
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<tr>
<td>LDL &lt; 70 mg/dL, hsCRP &lt; 1 mg/L</td>
<td>944</td>
<td>0.24</td>
</tr>
</tbody>
</table>

*P < 0.001*

**Full Adjusted Hazard Ratio**
0.21, 95% CI 0.09-0.52, *P < 0.0001*
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
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.

Adjusted for age, gender, smoking, diabetes, BMI, triglycerides, alcohol, lipid levels, and hsCRP
Can Targeted Anti-Inflammatory Therapy Reduce Cardiovascular Event Rates and Prolong Life?
Testing the Inflammatory Hypothesis of Atherothrombosis:
Do we attack the biomarker or attack the process?
Cardiovascular Inflammation Reduction Trial (CIRT)

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

Persistent Evidence of Inflammation

Anti-Inflammatory Intervention  
Placebo

Nonfatal MI, Nonfatal Stroke, Cardiovascular Death, Incident T2DM

How to define?  
What agent to study?

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>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>↓↓</td>
<td>↑</td>
<td>↑</td>
<td>⇔</td>
<td>⇔</td>
</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>
### LDM and CVD: Observational Evidence

<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</td>
<td>RA</td>
<td>0.4 (0.2 - 0.8)</td>
<td>Total Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td>Choi 2002</td>
<td>RA</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>
</tr>
<tr>
<td>van Helm 2006</td>
<td>RA</td>
<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>Pradanovich 2005</td>
<td>RA</td>
<td>0.5 (0.3 – 0.8)</td>
<td>CVD</td>
<td>LDM &lt; 15 mg/wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.8 (0.7 – 1.0)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6 (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 (0.3 – 1.2)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td>Solomon 2008</td>
<td></td>
<td>0.4 (0.2 – 0.8)</td>
<td>CVD</td>
<td>TNF-inhibitor</td>
</tr>
<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>
<td></td>
<td>0.82 (0.7 – 0.9)</td>
<td>MI</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.89 (0.8 – 1.0)</td>
<td>Stroke</td>
<td>LDM</td>
</tr>
<tr>
<td>UK Norfolk 2008</td>
<td>RA, PsA</td>
<td>0.6 (0.4 – 1.0)</td>
<td>Total Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<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
Cardiovascular Inflammation Reduction Trial (CIRT)

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.

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

Persistent Evidence of Inflammation
Diabetes or Metabolic Syndrome

MTX 15-20 mg
Weekly

Placebo

Nonfatal MI, Nonfatal Stroke,
Cardiovascular Death

N = 7,000  NHLBI-Sponsored
Enrollment to Start March 2013
350 US and Canadian Sites
What is the Cardiovascular Inflammation Reduction Trial (CIRT)?

CIRT is a major new randomized trial sponsored by the US National Heart, Lung, and Blood Institute. CIRT will directly test whether a common anti-inflammatory drug used for the treatment of rheumatoid arthritis (low dose methotrexate) can reduce the risk of heart attack, stroke, and cardiovascular death in patients who have suffered a prior heart attack.

Why worry about inflammation?

Inflammation plays a major role in heart attack and stroke. While inflammation is as important as cholesterol and high blood pressure, no clinical trial has tested whether reducing inflammation can reduce rates of these life-threatening disorders.

Who is eligible for CIRT?

Men and women who have suffered a prior heart attack and who have either type 2 diabetes or metabolic syndrome, two conditions associated with a pro-inflammatory
## 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>
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<td>↑</td>
<td>↑</td>
<td>←→</td>
<td>←→</td>
</tr>
<tr>
<td>LDL</td>
<td>↓↓</td>
<td>↑</td>
<td>↑</td>
<td>←→</td>
<td>←→</td>
</tr>
<tr>
<td>HDL</td>
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<td>↑</td>
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<td>←→</td>
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</tr>
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<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>
The Balance of IL-1 and IL-1Ra: Key Regulatory Proteins for Innate Immunity

IL-1α
IL-1β
IL-1Ra

Pro-Inflammatory

Anti-Inflammatory

IL-1R
IL-1: Potential Roles in Atherogenesis and Methods of Inhibition

- IL-1 type II Decoy Receptor
- IL-1r/IL-1r accessory protein
- IL-1 type 1 Receptor
- IL-1α,β
- Anti IL-1β antibody Canakinumab
- IL-1 Receptor Antagonist
- Endogenous Exogenous Anakinra
- iNOS
- Endothelin-1
- Chemokines/cytokines
- Adhesion molecules
- Endothelial & Smooth Muscle Proliferation
- Macrophage Activation
- Endothelial Dysfunction
- Athero-progression

Adapted from Fearon W, Fearon D. Circulation 2008;117:2577-9
Application of IL-1β promotes arterial intimal thickening in porcine coronary artery

Shimokawa et al. (1996) J Clin Invest 97:769

ApoE KO ApoE KO, IL-1β KO

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
Phase transition from soluble to crystalline as an endogenous “danger signal”

Molecular identification of a danger signal that alerts the immune system to dying cells

Yan Shi¹, James E. Evans² & Kenneth L. Rock¹

Phase transition from soluble to crystalline is a “danger” signal

Homeostasis
Uric Acid
40 - 60 µg/ml

Cell death, tissue injury
Uric Acid
> 70 µg/ml
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”
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 Nuñez⁹, Max Schnurr⁹, 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.

Courtesy, George S. Abela, MD.
IL-6 and Risk of Future MI in Apparently Healthy Men

\[ P = 0.01 \]

\[ P = 0.003 \]

\[ P = 0.3 \]

Quartile of IL-6 (range, pg/dL)

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

Relative Risk of MI

0
1
2
3
4

1
2
3
4

\[ \leq 1.04 \]

1.04-1.46

1.47-2.28

\[ \geq 2.28 \]

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
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) (Ridker PI)

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

Randomized
Canakinumab 50 mg
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
(>6000 currently)
Trying a New Line of Attack in Heart Disease

Two Major Clinical Trials Test If Treating Inflammation Can Cut the Risk of a Heart Attack or Stroke

BY RON WINSLOW

Two major clinical trials are testing for the first time whether treating inflammation can reduce the risk of a heart attack or stroke, potentially opening up a new line of attack in the battle against cardiovascular disease.

Until now, strategies to fight these killers have focused largely on well-known risk factors such as high blood process with anti-inflammatory drugs isn't known.

"This goes beyond simply asking, is inflammation a marker of risk (for cardiovascular disease) to asking if it's a target for therapy," said Paul M. Ridker, director of the center for cardiovascular-disease prevention at Harvard-affiliated Brigham and Women's Hospital in Boston, who is leading both trials.

These are especially high-risk patients for whom current optimal treatment often fails. "We've kind of run out of our tool kit for these individuals and yet they're still having events," said Gary Gibbons, director of the NIH's National Heart, Lung and Blood Institute, which officially funded the study.

The Novartis trial, which is testing the company's anti-inflammatory
Two Major Trials Test Hypothesis That Inflammation Causes Heart Disease

By Alex Kuchler

Two major cardiovascular trials under way for the first time will test for the first time whether inflammation is a cause of heart disease, and thus a cause of heart attacks or strokes, that can be treated with drugs designed to directly fight inflammation. 

Until now, inflammation has been largely ignored as a risk factor for heart attacks, with drugs that block inflammation only useful when inflammation is already severe enough to cause symptoms, such as rheumatoid arthritis. But receptor activator of nuclear factor kappa B ligand (RANKL) inhibitors, is a new class of drugs developed by Novartis, are designed to treat inflammation before it causes damage.

In addition, the trials will test whether inflammation contributes to atherosclerosis, a condition that can lead to heart attacks.

Massive Trials to Test Inflammation Hypothesis

It's not often that eminent scientists enlist 24,000 volunteers and tens of millions of dollars to put their credibility on the line, but that's exactly what cardiologist Paul Ridker is doing. More than 20 years ago, early in his career at Harvard Medical School's Brigham and Women's Hospital in Boston, he began nurturing the idea that inflammation is deeply intertwined with cardiovascular disease. Ridker has never been able to prove that the body's inflammatory response causes heart attacks—or that blocking it can save lives. But he has built his case bit by bit. Now, his theory is being put to the test in a pair of massive clinical trials, both of which he's heading. One was launched last year by Novartis, and the other was announced last month by the U.S. National Heart, Lung, and Blood Institute (NHLBI).

Ridker is well known among cardiologists for his research on the role of inflammation in heart disease. His finding that a specific protein, called C-reactive protein (CRP), is a strong predictor of heart attacks and strokes has helped shape treatment guidelines for people at high risk of these events. But until now, he has been unable to show that reducing CRP levels with drugs can prevent heart attacks.
"We await with great interest the outcome of an ongoing trial of the ability of canakinumab, a human monoclonal antibody that neutralizes IL-1β, to reduce CVD in high-risk patients with existing CVD. This placebo controlled study will be a key test of the hypothesis that inhibition of inflammation will be an important new strategy to reduce the burden of CVD"
We await with great interest the outcome of an ongoing trial of the ability of canakinumab, a human monoclonal antibody that neutralizes IL-1β, to reduce CVD in high-risk patients with existing CVD. This placebo controlled study will be a key test of the hypothesis that inhibition of inflammation will be an important new strategy to reduce the burden of CVD.

The National Heart, Lung, and Blood Institute, a part of the National Institutes of Health, has launched an international multi-site trial to determine whether a common anti-inflammatory drug can reduce heart attacks, strokes, and deaths due to cardiovascular disease in people at high risk for them.
Probiotics, Inflammation, Weight Loss, and Vascular Risk
FDA Food Pyramid

HSPH Food Pyramid
Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., María-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Angel Martinez-González, M.D., Ph.D., for the PREDIMED Study Investigators
Advertisement Campaigns
• $635 million (McDonald’s)
• $298 million (Burger King)
• $224 million (Coca Cola)

Photo courtesy of Randal Thomas
What is translational research? How does an integrated health care system support it?

- Bench
- Bedside
- Population
- Affiliated Network
- Hospitals Clinics

T1, T2, T3
SEROLOGICAL REACTIONS IN PNEUMONIA WITH A NON-PROTEIN SOMATIC FRACTION OF PNEUMOCOCCUS*

By WILLIAM S. TILLETT, M.D., AND THOMAS FRANCIS, Jr., M.D.
(From the Hospital of The Rockefeller Institute for Medical Research)
(Received for publication, June 26, 1930)

It has been shown (1) that pneumococci contain two constituents which are chemically and antigenically distinct. One of these, the type-specific component, is a complex polysaccharide, predominantly present in the capsule of the organism; the other, a substance common to the pneumococcus species, is the so-called nucleoprotein, contained for the most part in the body of the cell. That these two chemically distinct fractions are responsible for the production of two qualitatively different antibodies has been demonstrated (1, 2).

The present report is based upon observations made with a third fraction derived from pneumococci and chemically distinct from both type-specific capsular polysaccharide and non-type-specific somatic nucleoprotein. For purposes of reference this substance is designated Fraction C. The chemical nature of Fraction C and the method of purification together with certain experimental observations are presented in a separate communication (3). In this report it is sufficient to state that Fraction C is a non-protein material of somatic origin and appears to be a carbohydrate common to the pneumococcus species. Although final proof of its exact nature rests upon chemical analysis, nevertheless convincing evidence of the separate identity of Fraction C is brought out by the serological reactions to be described.

Material and Methods

Preparation of Fraction C.—The material employed in the serological tests was derived from a degraded, non-type-specific R strain of Pneumococcus. A strain of this character was employed in order to minimize the presence of type-specific carbohydrate. Fraction C was obtained in the following manner: The organisms

* Presented before the American Society for Clinical Investigation at a meeting held in Atlantic City, May 5, 1930.
Crystallization of CRP

Maclyn McCarty

Oswald Avery, Colin MacLeod

“The Transforming Principle”

Genes are made of DNA

suspended in 35 cc. of physiological saline and brought into solution by the dropwise addition of saturated sodium citrate. A small amount of insoluble material was removed by centrifugation and discarded.

Crystallization.—The citrated solution (36 cc.) was mixed with an equal volume of saturated sodium sulfate solution (prepared at 37°C) and held at 37°C. This step was included for its possible effect in causing further dissociation of the polysaccharide-protein complex by the action of the high salt concentration. The half-saturated solution remained entirely clear. After 2 hours an additional 72 cc. of saturated sodium sulfate was added, bringing the final concentration to 0.75 saturation. A light amorphous precipitate formed which
Osmond A
Shelton E*
PNAS 1977;
74:739-43

Pentraxin Structure
(NCI*)
C-REACTIVE PROTEIN IN CORONARY ARTERY DISEASE

Irving G. Kroop*
A STUDY OF C-REACTIVE PROTEIN IN THE SERUM OF PATIENTS WITH CONGESTIVE HEART FAILURE

SAMUEL K. ELSTER, M.D.
EUGENE BRAUNWALD, M.D.
and
HARRISON F. WOOD, M.D.
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From the Departments of Medicine and Microbiology, The Mount Sinai Hospital, New York, Irvington House, Irvington-on-Hudson-New York, and the Department of Pediatrics, New York University College of Medicine.
Received for publication July 27, 1955.
*Rosenstock Foundation Fellow in Medicine.
**Postdoctoral Research Fellow of the National Heart Institute, U. S. P. H. S.

To Paul -
Best wishes

[Signature]

Eugene Braunwald
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? CIRT, CANTOS – Let’s find out