Inflammation and Atherothrombosis: Where have we been? Where Are We Going?

Why Perform the CIRT and CANTOS Trials?

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Harvard Medical School
Director, Center for Cardiovascular Disease Prevention
Brigham and Women’s Hospital, Boston MA

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

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.

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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.

For More Information: (855) 437-9330

theCIRT.org theCANTOS.org
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? 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 -

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

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


P Trend <0.001

Relative Risk of MI

Quartile of hs-CRP

P Trend <0.01

Relative Risk of Stroke

Quartile of hs-CRP

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


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)</th>
<th>1.37 (1.27-1.48)</th>
</tr>
</thead>
<tbody>
<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-HDL-C</td>
<td>1.26 (1.16-1.40)</td>
</tr>
</tbody>
</table>

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

Emerging Risk Factor Collaborators, Lancet January 2010

CR-12
Direct Comparison of Lipid Markers and hsCRP in 166,596 Individuals Followed For First-Onset Cardiovascular Disease (ERFC NEJM 2012;367:1310-1320)

<table>
<thead>
<tr>
<th>Non-lipid risk factors plus TC</th>
<th>Change in C-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>plus TC plus HDLc</td>
<td>0.0043</td>
</tr>
<tr>
<td>plus TC plus HDLc plus hsCRP</td>
<td>0.0050</td>
</tr>
</tbody>
</table>

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

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)

www.reynoldsriskscore.org
"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."

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Inflammation, Statin Therapy, and hsCRP: Initial Observations

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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


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 ≥50, Women ≥60

LDL <130 mg/dL
hsCRP >2 mg/L

Rosuvastatin 20 mg (N=8901)
Placebo (N=8901)

4-week Run-in

MI
Serious 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 LDL 104 mg/dL, Mean HDL 50 mg/dL, hsCRP 4 mg/L

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
JUPITER: Fatal or Nonfatal Stroke

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

Placebo

ROSUVASTATIN

Follow-up (years)

0.000 0.005 0.010 0.015 0.020 0.025 0.030

Cumulative Incidence

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

JUPITER: Arterial Revascularization / Unstable Angina

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

Placebo (N = 143)

ROSUVASTATIN (N = 76)

Follow-up (years)

0.00 0.01 0.02 0.03 0.04 0.05 0.06

Cumulative Incidence

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

JUPITER: Secondary Endpoint – All Cause Mortality

NEJM 2008;359:2195-2207

Placebo

ROSUVASTATIN

Follow-up (years)

0.00 0.01 0.02 0.03 0.04 0.05 0.06

Cumulative Incidence

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

---
Primary Endpoint – Understudied or “Low Risk” Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Participants</td>
<td>17,882</td>
<td>0.54 (0.46-0.63)</td>
</tr>
<tr>
<td>Women</td>
<td>6,801</td>
<td>0.54 (0.37-0.80)</td>
</tr>
<tr>
<td>Age &gt; 70</td>
<td>2,085</td>
<td>0.41 (0.24-0.69)</td>
</tr>
<tr>
<td>Black, Hispanic, Other</td>
<td>5,117</td>
<td>0.43 (0.27-0.69)</td>
</tr>
</tbody>
</table>

"Low Risk" Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham Risk &lt; 10 %</td>
<td>8,822</td>
<td>0.56 (0.40-0.80)</td>
</tr>
<tr>
<td>BMI &lt; 25 mg/m2</td>
<td>4,073</td>
<td>0.59 (0.40-0.87)</td>
</tr>
<tr>
<td>No Hypertension</td>
<td>7,586</td>
<td>0.62 (0.44-0.87)</td>
</tr>
<tr>
<td>No metabolic Syndrome</td>
<td>10,206</td>
<td>0.60 (0.46-0.79)</td>
</tr>
</tbody>
</table>

2010 ACC/AHA Guidelines for Assessment of Cardiovascular Risk in Asymptomatic Adults

"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

Primary Goal: LDLc

<table>
<thead>
<tr>
<th>Category</th>
<th>LDLc</th>
<th>HDLc</th>
<th>Triglycerides</th>
<th>hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&lt;2.5</td>
<td>&gt;1.0</td>
<td>&lt;150</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.5-3.5</td>
<td>&gt;1.0</td>
<td>&lt;150</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Low</td>
<td>&gt;3.5</td>
<td>&gt;1.0</td>
<td>&lt;150</td>
<td>&lt;2</td>
</tr>
</tbody>
</table>

Secondary Targets: TC/HDLc < 4, non-HDLc < 3.5 mmol/L, hsCRP < 2 mg/L, TG < 1.7 mmol/L, ApoB/A < 0.8
**JUPITER**

Achieved LDL-C, 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?

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**JUPITER**

Glynn et al NEJM 2010

Total Venous Thromboembolism

![Graph showing cumulative incidence of total venous thromboembolism over time with risk reductions and event rates for Placebo and Rosuvastatin.]

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**JUPITER**

Absolute Risk Reduction Increases With Increasing Levels of hsCRP

![Graph showing absolute risk reduction increases with increasing levels of hsCRP.]

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JUPITER
LDL reduction, hsCRP reduction, or both?

Ridker et al Lancet 2009;373:1175-82

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

The genetic determinants of rosvastatin-induced CRP reduction do not predict rosvastatin-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?
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>Statins</th>
<th>TNF Inhibition</th>
<th>IL-6 Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>LDL</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>HDL</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>TG</td>
<td>←</td>
<td>↑</td>
</tr>
<tr>
<td>Chylo</td>
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</tr>
<tr>
<td>CRP / IL-6</td>
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Issues in the Selection of Anti-inflammatory Agents for Trials of Cardiovascular Inflammation Inhibition

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<tr>
<th>Statins</th>
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<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>
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<td>↑</td>
<td>↑</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
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<td>↑</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
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</tr>
<tr>
<td>CRP / IL-6</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 RA</td>
<td>RA</td>
<td>0.4 (0.2 - 0.8)</td>
<td>Total Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.3 (0.2 - 0.7)</td>
<td>CV Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.4 (0.3 - 0.8)</td>
<td>CV Mortality</td>
<td>LDM &lt; 15 mg/wk</td>
</tr>
<tr>
<td>Netherlands RA</td>
<td>RA</td>
<td>0.3 (0.1 - 0.7)</td>
<td>CVD</td>
<td>LDM only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 (0.1 - 0.6)</td>
<td>CVD</td>
<td>LDM + SSZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 (0.1 - 0.6)</td>
<td>CVD</td>
<td>LDM + HCQ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 (0.1 - 0.6)</td>
<td>LDM + SSZ + HCQ</td>
<td></td>
</tr>
<tr>
<td>Miami VA</td>
<td>PsA</td>
<td>0.7 (0.6 – 0.9)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td></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>0.5 (0.3 – 0.8)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6 (0.3 – 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></td>
<td></td>
<td>0.4 (0.2 – 0.6)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td>QUEST-RA</td>
<td>RA</td>
<td>0.85 (0.6 – 0.9)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.82 (0.7 – 0.9)</td>
<td>MI</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.85 (0.3 – 1.3)</td>
<td>Stroke</td>
<td>LDM</td>
</tr>
<tr>
<td>UK Norfolk RA</td>
<td>RA, PsA</td>
<td>0.5 (0.3 – 1.2)</td>
<td>Total Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.3 (0.2 – 1.1)</td>
<td>CV Mortality</td>
<td>LDM</td>
</tr>
</tbody>
</table>

### Methotrexate Inhibits Atherogenesis in Cholesterol-fed Rabbits

- **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, diabetes or metabolic syndrome and either type 2 diabetes or metabolic syndrome.

### Cardiovascular Inflammation Reduction Trial (CIRT)

- **N = 7,000 NHLBI Sponsored**
- **Enrollment to Start March 2013**
- **300 U.S. and Canadian Sites**
Cardiovascular Inflammation Reduction Trial (CIRT)

Forms, Updates, and More Information – theCIRT.org website

TC
LDL
HDL
TG
Chylo
CRP / IL-6

Issues in the Selection of Anti-inflammatory Agents for Trials of Cardiovascular Inflammation Inhibition

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<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
IL-1R

Anti-Inflammatory

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

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
Cholesterol crystals activate the caspase-1-activating NLRP3 inflammasome to generate IL-1β and initiate atherosclerosis.
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
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) (Ridker P6)

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 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 = 17,750 Novartis (>4700 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? CIRT, CANTOS – Let’s find out
1:30pm

Biomarkers or Imaging:
Which is More Appropriate for Risk Stratification In the Asymptomatic Patient?

Paul M Ridker, MD, MPH
Eugene Braunwald Professor of Medicine
Director, Center for Cardiovascular Disease Prevention
Brigham and Women’s Hospital
Harvard Medical School, Boston, MA USA

Dr. Ridker is listed as a co-inventor on patents held by the Brigham and Women’s Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes.
Why debate biomarkers versus imaging at all?

After all, abundant evidence indicates that certain biomarkers (high LDLC, low HDLC, high hsCRP) as well as certain imaging tests (CAC) clearly predict risk in asymptomatic populations, and most studies suggest that imaging tests may well do a better job.

So why not simply image everyone and get rid of biomarkers altogether?

Two Conflicting World Views Regarding the Role of Screening in Primary Prevention

“If it predicts disease, it must be a good thing to measure”
Belief Driven Approach

“If I measure it, it will improve outcomes for my patient”
Evidence Driven Approach

Why do we need data?

“If a new test is more sensitive than an old test, it leads to the detection of extra cases. Results from trials that enrolled only patients detected by the old test may not apply. Clinicians need to wait for RCTs unless they [are] satisfied that the new test detects the same spectrum of disease or that the treatment response is similar across the spectrum.”

Why do we need data?

Isn’t it true that statins are effective in all patients?

Isn’t it true that the higher the absolute risk, the greater the benefit of statin therapy?

Absolutely NOT!

4-D, AURORA, CORONA, GISSI-HF, SEAS are all NULL statin trials in populations that are both at very high risk and known to have high CAC scores.

Statin Therapy in Primary Prevention
What works and in whom?

WOSCOPS
HR 0.70 (0.57-0.84)
MEGA
HR 0.67 (0.54-0.81)
(pravastatin)

AFCAPS/TexCAPS
HR 0.83 (0.50-0.75)
(lovastatin)
Why Are RCTs so Important? Why can’t we just rely on observational data?

The Role of Statins in CAC

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Type</th>
<th>SS</th>
<th>Change in CAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Callister</td>
<td>1998</td>
<td>Obs</td>
<td>149</td>
<td>45 % decrease</td>
</tr>
<tr>
<td>Raggi</td>
<td>2004</td>
<td>Obs</td>
<td>495</td>
<td>35 % decrease</td>
</tr>
<tr>
<td>Budoff</td>
<td>2000</td>
<td>Obs</td>
<td>131</td>
<td>61 % decrease</td>
</tr>
<tr>
<td>Budoff</td>
<td>2005</td>
<td>Obs</td>
<td>163</td>
<td>50 % decrease</td>
</tr>
<tr>
<td>Achenbach</td>
<td>2002</td>
<td>Obs</td>
<td>66</td>
<td>64 % decrease</td>
</tr>
<tr>
<td>Housley</td>
<td>2006</td>
<td>RCT</td>
<td>102</td>
<td>44 % increase</td>
</tr>
<tr>
<td>Terry</td>
<td>2007</td>
<td>RCT</td>
<td>80</td>
<td>No change</td>
</tr>
<tr>
<td>Schmermund</td>
<td>2006</td>
<td>RCT</td>
<td>366</td>
<td>No change</td>
</tr>
<tr>
<td>Raggi</td>
<td>2005</td>
<td>RCT</td>
<td>473</td>
<td>No change</td>
</tr>
<tr>
<td>Arad</td>
<td>2005</td>
<td>RCT</td>
<td>1005</td>
<td>No change</td>
</tr>
</tbody>
</table>

Why do we need data?

Is there randomized trial evidence demonstrating that asymptomatic patients who do not already have an indication for a statin benefit from statin therapy if they are identified by an imaging test? NO

Are there patients with a current indication for a statin who you would stop treatment based on data from an imaging test? NO
Why do we need data?

When there is no evidence to support doing a test, then toxicity or adverse consequences of the test become major problems.

What about radiation exposure?

**Original Investigation**

Coronary Artery Calcification Screening

*Estimated Radiation Dose and Cancer Risk*

Kwang Pyo Kim, MD, Andrew J. Enzinger, MD, PhD, Amy Bavrygore & Gonzalez, DNP

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Radiation Dose (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBCT</td>
<td>0.6 – 1.0</td>
</tr>
<tr>
<td>MDCT</td>
<td>0.9 – 2.0</td>
</tr>
<tr>
<td>CXR</td>
<td>0.01 – 0.02</td>
</tr>
</tbody>
</table>

Increased Cancer Risk > 2.3 mSv

"The estimated lifetime cancer risk is 42 cases per 100,000 men and 62 per 100,000 women... These radiation risks can be compared with potential benefits from screening when such estimates are available".

Arch Int Med 2009;169:1188-1194

What about incidentalomas?

**Non-Invasive Angiography**

Core Curriculum

Incidental Findings with Cardiac CT Evaluation—Should We Read Beyond the Heart?

Matthew J. Budesat, MD, Hans Fischer, MD, and Ambaram Gopal, MD

" > 50% of participants may have at least one non-calcified nodule"

"Current limitations thus include the cost and morbidity of follow-up and further testing, the small but difficult to quantify potential risk of cancer associated with multiple follow-up CT scans, and the potential for increased anxiety of both the patient and the physician about non-significant pathology"
The Role of Expert Opinion

“I know there is no outcome data, but when I tell my patient their CAC score, they improve their risk factor profiles and have better medication compliance”

Imaging Advocate, ACC 2011

What About Surrogate Endpoints? Doesn’t CAC at least improve those?

Hacker DG, et al; Arch Intern Med 2011; epublished

What About EISNER? Wasn’t that a positive study?”

“Compared with no scanning, randomization to CAC was associated with superior coronary artery disease risk factor control”
EISNER Trial Results - Rozanski et al, JACC March 28, 2010

<table>
<thead>
<tr>
<th></th>
<th>No-Scan</th>
<th>Scan</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quit smoking, %</td>
<td>44</td>
<td>49</td>
<td>NS</td>
</tr>
<tr>
<td>Regular exercise, %</td>
<td>36</td>
<td>37</td>
<td>NS</td>
</tr>
<tr>
<td>Change in DBP, mm Hg</td>
<td>-4</td>
<td>-5</td>
<td>NS</td>
</tr>
<tr>
<td>Change in SBP, mm Hg</td>
<td>-5</td>
<td>-7</td>
<td>0.02</td>
</tr>
<tr>
<td>Change in TC, mg/dL</td>
<td>-16</td>
<td>-21</td>
<td>NS</td>
</tr>
<tr>
<td>Change in HDL, mg/dL</td>
<td>-1</td>
<td>-1</td>
<td>NS</td>
</tr>
<tr>
<td>Change in TG, mg/dL</td>
<td>-9</td>
<td>-10</td>
<td>NS</td>
</tr>
<tr>
<td>Change in LDL, mg/dL</td>
<td>-11</td>
<td>-17</td>
<td>0.04</td>
</tr>
<tr>
<td>Change in glucose, mg/dL</td>
<td>-2</td>
<td>-0</td>
<td>NS</td>
</tr>
<tr>
<td>Change in weight, lbs</td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>New lipid meds, %</td>
<td>25</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>New BP meds, %</td>
<td>18</td>
<td>24</td>
<td>0.02</td>
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<tr>
<td>New DM meds, %</td>
<td>3</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>New ASA use, %</td>
<td>7</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>Adherence to lipid meds, %</td>
<td>86</td>
<td>86</td>
<td>NS</td>
</tr>
<tr>
<td>Adherence to BP meds, %</td>
<td>90</td>
<td>94</td>
<td>NS</td>
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<tr>
<td>Adherence to DM meds, %</td>
<td>93</td>
<td>88</td>
<td>NS</td>
</tr>
<tr>
<td>Adherence to ASA, %</td>
<td>31</td>
<td>27</td>
<td>NS</td>
</tr>
</tbody>
</table>

The median change in FRS in BOTH groups was ZERO

Death or MI was HIGHER in the scan group than in the no-scan group (2.1 vs 1.0 %, P=0.08)

EISNER Trial Results - Rozanski et al, JACC March 28, 2010

What about managed care?

In a world heading toward accountable care Organizations (ACOs), the core questions in primary prevention screening are no longer about C-statistics or reclassification, but rather focus directly on how the activity of screening will impact on the lives of our patients and on improvements in their outcomes

Is there evidence that the test leads to a proven intervention that the patient otherwise would not have received? Biomarkers –Yes, Imaging - No
Two World Views Regarding Screening in Primary Prevention

If you want to practice evidence-free medicine, increase expenses to our health care system, irradiate your patients, and take the medical-legal risk of performing un-indicated downstream procedures, order imaging tests in the asymptomatic patient.

If you want to practice evidence-based medicine, improve outcomes, and use medical resources wisely, order a simple panel of inexpensive biomarkers in the asymptomatic patient.
Taming Inflammation to Reduce Cardiovascular Risk
A BWH / BRI Story

CIRT CANTOS
Brendan Everett
Aruna Pradhan
Elaine Zahrarv
Eric Curniff
Joji Grossbard
Jean MacFadyen
Nina Paynter
Bohdan Polonsky
Ellie Danielson
Maria Sanchez
Paul Ridker
Rheumatology
Dan Solomon
Mike Weinfall

Inflammation Biology
Peter Libby
Michael Gimbrone
Nader Rifai

Computational Biology
Dan Chasman
Audrey Chu
Franco Giulanini
Linda Rode

Preventive Medicine
Nancy Cook
Samia Mora
Julie Buring
Jacqueline Suk Danik
JoAnn Marson
Harriet Samuelson

BWH DOM
Eugene Braunwald
Victor Dzau
Marc Pfeffer
Joe Loscalzo

AstraZeneca (JUPITER)
Novartis (CANTOS)
JUPITER
Statins and the Development of Diabetes

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pravastatin</th>
<th>HR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>WOSCOPS</td>
<td>0.70</td>
<td>(0.56–0.98)</td>
</tr>
<tr>
<td>PROSPER</td>
<td>1.34</td>
<td>(1.06–1.66)</td>
</tr>
<tr>
<td>LIPID</td>
<td>0.91</td>
<td>(0.72–1.18)</td>
</tr>
<tr>
<td>HPS</td>
<td>1.20</td>
<td>(0.98–1.53)</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>1.20</td>
<td>(0.91–1.44)</td>
</tr>
<tr>
<td>PROVE-IT</td>
<td>1.11</td>
<td>(0.83–1.50)</td>
</tr>
<tr>
<td>CORONA</td>
<td>1.13</td>
<td>(0.84–1.50)</td>
</tr>
<tr>
<td>JUPITER</td>
<td>1.25</td>
<td>(1.05–1.54)</td>
</tr>
</tbody>
</table>

JUPITER
Incident Diabetes Limited to Those With Impaired Fasting Glucose

Ridker et al Lancet 2012;380:
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 deaths 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 benefit of statin therapy exceed the diabetes hazard, including among individuals at high risk for developing diabetes. Long-term microvascular effects unknown.