Anti-Inflammatory Therapy with Canakinumab for Atherosclerotic Disease and Lung Cancer

Paul M Ridker, MD, MPH
Eugene Braunwald Professor of Medicine
Brigham and Women’s Hospital,
Harvard Medical School, Boston MA, USA

on behalf of the worldwide investigators and participants in the
Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)
Declaration of interest

- Research contracts (Novartis)
- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Dr Ridker is listed as a co-inventor on patents related to the use of inflammatory biomarker in cardiovascular disease.)
Residual Inflammatory Risk: Addressing the Obverse Side of the Atherosclerosis Prevention Coin

Ridker PM. Eur Heart J 2016;37:1720-22

**Known Cardiovascular Disease**
- LDL 150 mg/dL (3.8 mmol/L)
- hsCRP 4.5 mg/L

**High Intensity Statin**

**“Residual Cholesterol Risk”**
- LDL 110 mg/dL (2.8 mmol/L)
- hsCRP 1.8 mg/L
  - Additional LDL Reduction

**“Residual Inflammatory Risk”**
- LDL 70 mg/dL (1.8 mmol/L)
- hsCRP 3.8 mg/L
  - Additional Inflammation Reduction

**IMPROVE-IT**: Ezetimibe 6% RRR

**FOURIER/SPIRE**: PCSK9 Inhibition q2 weeks 15% RRR

No Prior Proof of Concept
Primary Endpoint

Hazard ratio 0.85
(95% CI, 0.79-0.92)
P<0.0001

CV Death, MI, Stroke, Hosp for UA, or Cor Revasc

Months from Randomization

Placebo
Evolocumab

14.6%
12.6%
Percent Reduction in LDL Response to High Intensity Statin Therapy: Implications for PCSK9 Prescription

Ridker et al, Eur Heart J 2016;37:1373-9
The SPIRE Bococizumab Lipid Lowering Trials:
Wide Individual Variation in Percent Change in LDLC at **52 Weeks** with Bococizumab, Even Among Those Who Are Antidrug Antibody Negative*

* Analysis excludes non-compliant participants

Ridker ACC 2017
Residual Inflammatory Risk:
Addressing the Obverse Side of the Atherosclerosis Prevention Coin
Ridker PM. Eur Heart J 2016;37:1720-22

“Residual Cholesterol Risk”
LDL 110 mg/dL (2.8 mmol/L)
hsCRP 1.8 mg/L

“Residual Inflammatory Risk”
LDL 70 mg/dL (1.8 mmol/L)
hsCRP 3.8 mg/L

Known Cardiovascular Disease
LDL 150 mg/dL (3.8 mmol/L)
hsCRP 4.5 mg/L
High Intensity Statin

Additional
LDL Reduction

Additional
Inflammation Reduction

IMPROVE-IT: Ezetimibe 6% RRR
FOURIER/SPIRE: PCSK9 Inhibition q2 weeks 15% RRR

No Prior Proof of Concept

Ridker ESC 2017
ATHEROSCLEROSIS — AN INFLAMMATORY DISEASE

RUSSELL ROSS, Ph.D.

Inflammation, Atherosclerosis, and Coronary Artery Disease

Göran K. Hansson, M.D., Ph.D.
Inflammation in atherosclerosis: from pathophysiology to practice

Libby P et al JACC 2009;54:2129-38
Ridker et al NEJM 1997; 336:973-9
High Sensitivity C-Reactive Protein (hsCRP): A Test In Context

Possible Acute Phase Response
Repeat in 2 to 3 weeks

hsCRP

Lower Risk

Moderate Risk

Higher Risk

Relative Risk of Future CV Events

hsCRP (mg/L)

<0.5

0.5-1.0

1.0-2.0

2.0-3.0

3.0-4.0

4.0-5.0

5.0-10.0

10.0-20.0

>20

Inflammation, Statin Therapy, and hsCRP: Initial Observations

\[ P \text{ Trend} = 0.005 \]

**Relative Risk**

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Median hs-CRP (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pravastatin</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>Inflammation Absent</td>
<td>0.18</td>
</tr>
<tr>
<td>Inflammation Present</td>
<td>0.24</td>
</tr>
</tbody>
</table>

\(-21.6\% \quad (P=0.004)\)

PROVE-IT
Ridker et al, NEJM 2005;352:20-8

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

- LDL >70 mg/dL
- hsCRP > 2mg/L
  - Neither Goal Achieved
- LDL <70 mg/dL
- hsCRP > 2mg/L
  - LDL Goal Achieved
- LDL > 70 mg/dL
- hsCRP < 2mg/L
  - hsCRP Goal Achieved
- LDL <70 mg/dL
- hsCRP < 2mg/L
  - Dual Goals Achieved

Eur Heart J 2016;37:1729-22
JUPITER

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

HR 0.56, 95% CI 0.46–0.69
P < 0.00001

Number Needed to Treat (NNT₅) = 25

Placebo 251 / 8901

Rosuvastatin 142 / 8901

Cumulative Incidence

Number at Risk

Follow-up (years)

Rosuvastatin 8,901 8,631 8,412 6,540 3,893 1,958 1,353 983 544 157
Placebo 8,901 8,621 8,353 6,508 3,872 1,963 1,333 955 534 174

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

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

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

<table>
<thead>
<tr>
<th>N</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>7832</td>
</tr>
<tr>
<td>LDL &gt; 70 mg/dL, hsCRP &gt; 1 mg/L</td>
<td>1874</td>
</tr>
<tr>
<td>LDL &lt; 70 mg/dL, hsCRP &gt; 1 mg/L</td>
<td>4662</td>
</tr>
<tr>
<td>LDL &gt; 70 mg/dL, hsCRP &lt; 1 mg/L</td>
<td>236</td>
</tr>
<tr>
<td>LDL &lt; 70 mg/dL, hsCRP &lt; 1 mg/L</td>
<td>944</td>
</tr>
</tbody>
</table>

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

Ridker et al. Lancet 2009;373:1175-82
From CRP to IL-6 to IL-1: Moving Upstream to Identify novel Targets for Atheroprotection

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

Circulation 2000;101:1767-1772
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 □

CRP Reduction (%)

Hazard Ratio for CHD

rs2228145

rs7529229

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

Swerdlow et al, Lancet 2012;379;1214-24
NLRP3 Cryopyrin Inflammasome, Caspase-1, and IL-1β Maturation
Endogenous Danger Signals in Vascular Biology?

Pyrophosphate crystals or pathogenic bacteria

Cleavage of pro-interleukin-1β

Secretion of mature interleukin-1β

Inflammation

Canakinumab (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

Canakinumab Dose (mg/month)

Fibrinogen

Interleukin-6

C-reactive Protein

Median Reduction

Ridker PM, et al; Circulation 2012; 126:2739-2748
Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

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

Randomized Canakinumab 50 mg SC q 3 months
Randomized Canakinumab 150 mg SC q 3 months
Randomized Canakinumab 300 mg SC q 3 months*
Randomized Placebo SC q 3 months

Primary CV Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death (MACE)

Key Secondary CV Endpoint: MACE + Unstable Angina Requiring Unplanned Revascularization (MACE+)

Critical Non-Cardiovascular Safety Endpoints: Cancer and Cancer Mortality, Infection and Infection Mortality

N = 10,061
39 Countries
April 2011 - June 2017
1490 Primary Events
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N=3347)</th>
<th>50 mg (N=2170)</th>
<th>150 mg (N=2284)</th>
<th>300 mg (N=2263)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.1</td>
<td>61.1</td>
<td>61.2</td>
<td>61.1</td>
</tr>
<tr>
<td>Female (%)</td>
<td>25.9</td>
<td>24.9</td>
<td>25.2</td>
<td>26.8</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>22.9</td>
<td>24.5</td>
<td>23.4</td>
<td>23.7</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>39.9</td>
<td>39.4</td>
<td>41.8</td>
<td>39.2</td>
</tr>
<tr>
<td>Lipid lowering therapy (%)</td>
<td>93.7</td>
<td>94.0</td>
<td>92.7</td>
<td>93.5</td>
</tr>
<tr>
<td>Renin-angiotensin inhibitors (%)</td>
<td>79.8</td>
<td>79.3</td>
<td>79.8</td>
<td>79.6</td>
</tr>
<tr>
<td>Prior Revascularization (%)</td>
<td>79.6</td>
<td>80.9</td>
<td>82.2</td>
<td>80.7</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>82.8</td>
<td>81.2</td>
<td>82.4</td>
<td>83.5</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>44.5</td>
<td>43.7</td>
<td>43.7</td>
<td>44.0</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>139</td>
<td>139</td>
<td>139</td>
<td>138</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>4.1</td>
<td>4.1</td>
<td>4.2</td>
<td>4.1</td>
</tr>
</tbody>
</table>
CANTOS: Dose-Dependent Effects on Inflammatory Biomarkers and Lipids (48 Months)

- Placebo SC q 3 mth
- Canakinumab 50mg SC q 3 mth
- Canakinumab 150mg SC q 3 mth
- Canakinumab 300mg SC q 3 mth

**Percent Change from Baseline (median)**

**hsCRP**

**LDLC**

**HDLC**

**TG**

**Months**

Ridker ESC 2017
# CANTOS: Primary Clinical Outcome Effects on MACE and MACE +

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=3347)</th>
<th>50 mg (N=2170)</th>
<th>150 mg (N=2284)</th>
<th>300 mg (N=2263)</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR (per 100 person years)</td>
<td>4.5 (referent)</td>
<td>4.1 (referent)</td>
<td>3.9 (referent)</td>
<td>3.9 (referent)</td>
<td>0.020</td>
</tr>
<tr>
<td>HR</td>
<td>1.0 (referent)</td>
<td>0.93 (referent)</td>
<td>0.85</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>95%CI</td>
<td>0.80-1.07</td>
<td>0.74-0.98</td>
<td>0.75-0.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.30</td>
<td>0.021*</td>
<td>0.031</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Secondary Endpoint** | 5.1 (referent) | 4.6 (referent) | 4.3 (referent) | 4.3 (referent) | 0.003   |
| IR (per 100 person years) | 1.00 (referent) | 0.90 (referent) | 0.83           | 0.83           |         |
| HR                  | 1.00 (referent) | 0.78-1.03      | 0.73-0.95      |               |         |
| 95%CI               | 0.72-0.94       | 0.005*         | 0.004          |               |         |
| P                   | 0.11             | 0.005*         | 0.004          |               |         |

*Statistically significant, adjusted for multiplicity, in accordance with the pre-specified closed-testing procedures*
CANTOS: Primary Cardiovascular Endpoint (MACE)

Placebo SC q 3 months
Canakinumab 150/300 SC q 3 months

HR 0.85
95%CI 0.76-0.96
P = 0.007

39% reduction in hsCRP
No change in LDLC
15% reduction in MACE (P=0.007)
17% reduction in MACE+ (P=0.0006)
30% reduction in need for revascularization procedures (P<0.0001)

The 150mg group met multiplicity adjusted thresholds for formal statistical significance for both the primary and secondary cardiovascular endpoints
CANTOS: Consistency of Effect Across All Patient Groups

Group

- Women
- Men
- Age < 60 yrs
- Age ≥ 60 yrs
- Diabetes
- No diabetes
- Non Smoker
- Smoker
- BMI < 30 kg/m2
- BMI ≥ 30 kg/m2
- LDLC < 80 mg/dL
- LDLC ≥ 80 mg/dL
- hsCRP < 4 mg/L
- hsCRP ≥ 4 mg/L
- HDLC > 45 mg/dL
- HDLC ≤ 45 mg/dL
- TG < 150 mg/dL
- TG ≥ 150 mg/dL

Overall
CANTOS: Greater Risk Reduction Among Those With Greater hsCRP Reduction (MACE+)

HR (95%CI)       P
1.0 (referent)    (referent)
0.95 (0.84-1.08)  0.47
0.73 (0.63-0.83)  0.0001

HR 0.73
95%CI 0.63-0.83
P=0.0001

for those with reductions in hsCRP ≥ median at 3-months (1.8 mg/L)
Sub-clinical chronic inflammation increases cancer risk (hsCRP is also a risk factor for certain cancers, in particular lung cancer)

Inflammation in the tumor micro-environment impacts upon tumor initiation, progression, invasiveness, and metastatic progression

Chronic Inflammation, Tumor Progression, and IL-1 Inhibition

The involvement of IL-1 in tumorigenesis, tumor invasiveness, metastasis and tumor-host interactions


Why not treat human cancer with interleukin-1 blockade?

Charles A. Dinarello.
CANTOS: Additional Non-Cardiovascular Clinical Benefits

Cancer Mortality

<table>
<thead>
<tr>
<th>Group</th>
<th>HR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.0 (referent)</td>
<td>(referent)</td>
</tr>
<tr>
<td>Canakinumab 50 mg</td>
<td>0.86 (0.59-1.24)</td>
<td>0.42</td>
</tr>
<tr>
<td>Canakinumab 150 mg</td>
<td>0.78 (0.54-1.13)</td>
<td>0.19</td>
</tr>
<tr>
<td>Canakinumab 300 mg</td>
<td>0.49 (0.31-0.75)</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

P-trend across groups = 0.0007

Canakinumab 300 mg
51% reduction in death from any cancer
P = 0.0009

Ridker ESC 2017
**CANTOS: Additional Non-Cardiovascular Clinical Benefits**

**Incident Lung Cancer**

<table>
<thead>
<tr>
<th></th>
<th>HR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.0 (referent)</td>
<td>(referent)</td>
</tr>
<tr>
<td>Canakinumab 50 mg</td>
<td>0.77 (0.49-1.20)</td>
<td>0.25</td>
</tr>
<tr>
<td>Canakinumab 150 mg</td>
<td>0.61 (0.39-0.97)</td>
<td>0.034</td>
</tr>
<tr>
<td>Canakinumab 300 mg</td>
<td>0.33 (0.18-0.59)</td>
<td>0.00008</td>
</tr>
</tbody>
</table>

P-trend across groups = 0.0003

Canakinumab 300 mg
67% reduction in incident lung cancer
P =0.00008

Ridker ESC 2017
# CANTOS: Additional Non-Cardiovascular Clinical Benefits

## Fatal Lung Cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>HR</th>
<th>(95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.0</td>
<td>(referent)</td>
<td>(referent)</td>
</tr>
<tr>
<td>Canakinumab 50 mg</td>
<td>0.71</td>
<td>(0.40-1.26)</td>
<td>0.24</td>
</tr>
<tr>
<td>Canakinumab 150 mg</td>
<td>0.64</td>
<td>(0.36-1.14)</td>
<td>0.13</td>
</tr>
<tr>
<td>Canakinumab 300 mg</td>
<td>0.23</td>
<td>(0.10-0.54)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

P-trend across groups = 0.0002

![Cumulative Incidence Graph](image)

Canakinumab 300 mg 77% reduction in fatal lung cancer

P = 0.0002

Ridker ESC 2017
Residual Inflammatory Risk:
Addressing the Obverse Side of the Atherosclerosis Prevention Coin

*Ridker PM. Eur Heart J 2016;37:1720-22*

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

- **High Intensity Statin**

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

- **Additional LDL Reduction**

- **IMPROVE-IT:** Ezetimibe 6% RRR
- **FOURIER/SPIRE:** PCSK9 Inhibition q2 weeks 15% RRR

**“Residual Inflammatory Risk”**
- LDL 80 mg/dL
- hsCRP 3.8 mg/L

- **Additional Inflammation Reduction**

- **No Prior Proof of Concept**
- **Canakinumab:** 150mg SC q 3 months 15% RRR

Ridker ESC 2017
How Common is Residual Inflammatory Risk?

PROVE-IT

- Residual Inflammatory Risk: 44%
- Residual Cholesterol Risk: 29%
- Both: 14%
- Neither: 14%

IMPROVE-IT

- Residual Inflammatory Risk: 39%
- Residual Cholesterol Risk: 33%
- Both: 14%
- Neither: 14%

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? Yes (hsCRP, 1997)

Is there evidence that individuals identified at increased risk due to inflammation benefit from a therapy they otherwise would not have received? Yes (statins, JUPITER 2008)

Is there evidence that reducing inflammation per se will reduce vascular events? Yes (CANTOS, ESC 2017)

“Lower is better” appears to be true for both LDLC and hsCRP in both primary and secondary prevention.
CANTOS: Adding a New Axis to the Oxford LDL Lowering Line

Relative Risk Reduction (%) vs % Reduction in LDL-C

Ridker ESC 2017