Reducing Inflammation to Reduce Cardiovascular Risk: The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

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

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

Is there evidence that reducing inflammation per se will reduce vascular events?
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

Evolocumab
Placebo

CV Death, MI, Stroke, Hosp for UA, or Cor Revasc
Residual Inflammatory Risk: Addressing the Obverse Side of the Atherosclerosis Prevention Coin

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

No Prior Proof of Concept
Low Grade Systemic Inflammation \textit{Precedes} By Many Years the Onset of Vascular Events

Ridker et al NEJM 1997; 336:973-9
Event-Free Survival According to Baseline Quintiles of hs-CRP and LDL Cholesterol

High Sensitivity C-Reactive Protein (hsCRP): A Test In Context

Ridker PM. JACC 2016;16:67:712-23
Inflammation is a Strong and Consistent Predictor of CV Risk

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

Emerging Risk Factor Collaborators, Lancet January 2010
Inflammation, Statin Therapy, and hsCRP: Initial Observations

**Relative Risk**

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

<table>
<thead>
<tr>
<th>Relative Risk</th>
<th>Pravastatin</th>
<th>Placebo</th>
<th>Pravastatin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation Absent</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Inflammation Present</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
</tr>
</tbody>
</table>

\[ -21.6\% \ (P=0.004!) \]

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

- Placebo: 0.25, 0.24, 0.23, 0.22, 0.21, 0.20, 0.19, 0.18
- Pravastatin: 0.25, 0.24, 0.23, 0.22, 0.21, 0.20, 0.19, 0.18


**Ridker et al Circulation. 1999;100:230-235.**
Clinical Relevance of Achieved LDL and Achieved CRP After ACS Treated with Statin Therapy

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

Ridker et al, Eur Heart J 2016;37:1729-22
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

4-week run-in

Ridker et al NEJM 2008;359:2195-2207

Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

Mean LDLC 104 mg/dL, Mean HDLC 50 mg/dL, hsCRP 4 mg/L
JUPITER
Fatal or Nonfatal Myocardial Infarction

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

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

Follow-up Years
Cumulative Incidence

- 55 %

Rosuvastatin

Placebo
JUPITER
Secondary Endpoint – All Cause Mortality

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

Placebo 247 / 8901
Rosuvastatin 198 / 8901

- 20 %

Cumulative Incidence

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

NEJM 2008;359:2195-2207
Can Inflammation Reduction, in the Absence of Lipid Lowering, Reduce Cardiovascular Event Rates?
From CRP to IL-6 to IL-1: Moving Upstream to Identify novel Targets for Atheroprotection

Libby P. Interleukin-1 Beta as a Target for Atherosclerosis: Biologic Basis for CANTOS and Beyond.
JACC 2017;70:2278-89
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

Stable CAD (post MI) Residual Inflammatory Risk (hsCRP ≥ 2 mg/L)

N = 10,061
39 Countries
April 2011 - June 2017
1490 Primary Events

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

Secondary Endpoint: MACE plus Unstable Angina Requiring Urgent Revascularization (MACE+)

Additional Adjudicated Endpoints: Cancer, Infection

Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

39 countries
> 1000 investigators

17482 Screened

10105 Entered Into Randomization Process

10061 Successfully Randomized

7377 Excluded Prior to Entering Randomization Process

- 146 refused consent
- 71 child-bearing potential
- 44 age out of range
- 251 no documented MI
- 3390 hsCRP < 2 mg/L
- 728 exclusionary concomitant disease
- 1873 tuberculosis risk factors
- 104 infectious disease
- 76 immunocompromised state
- 27 life threatening condition
- 574 withdrew consent
- 137 site closure
- 81 physician decision
- 49 unable to contact
- 7 adverse event
- 11 died
- 139 other reasons

44 Failed Randomization Process

- 41 Invalid randomization
- 3 major GCP violations

3344 placebo
18.1% discontinued study drug
3335 known final vital status
9 unknown final vital status

2170 canakinumab 50mg
16.7% discontinued study drug
2161 known final vital status
9 unknown final vital status

2284 canakinumab 150mg
19.2% discontinued study drug
2279 known final vital status
5 unknown final vital status

2263 canakinumab 300mg
20.1% discontinued study drug
2259 known final vital status
4 unknown final vital status

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

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

HR 0.85
95%CI 0.76-0.96
P = 0.007

CANTOS: Primary Cardiovascular Endpoints

MACE

HR 0.83
95%CI 0.74-0.92
P = 0.0006

MACE - Plus

35 - 40% reductions in hsCRP and IL-6
No change in LDLC

CANTOS: Critical Unanswered Clinical Questions

Monoclonal Antibodies and the Era of Personalized Medicine
Can we predict who benefits the most from effective but expensive treatments?

Is there an easily identified clinical subgroup for whom benefits are large and might clearly outweigh hazards?

Is there an easily identifiable subgroup where there is evidence not only of reduced MACE, but also of reduced cardiovascular mortality and reduced all-cause mortality?

Is there an easily identified clinical subgroup for whom benefits are small and may not justify the hazards?

These biologically directed questions have broad implications for patient selection, for cost-effectiveness, for calculations of the number-needed-to-treat (NNT), and ultimately for personalized medicine, allowing us to get the right drug to the right patient, thus maximizing benefits while reducing costs as well as hazards.
CANTOS: Consistency of Effect Across All Patient Groups Defined by Baseline Clinical Characteristics

Can we use evidence of individual biologic drug response to define patient groups more or less likely to benefit from treatment with canakinumab?

Can we use the magnitude of reduction (or level achieved) of hsCRP or interleukin-6 following treatment with canakinumab to identify individual patients most likely to benefit?

Perform a series of sensitivity analyses to address the robustness of any informative findings.
CANTOS: Greater Risk Reduction Among Those With Greater hsCRP Reduction (MACE)

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>(95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.0</td>
<td>(ref)</td>
<td>(ref)</td>
</tr>
<tr>
<td>On-treatment hsCRP: ≥ 2.0 mg/L</td>
<td>0.95</td>
<td>(0.81, 1.09)</td>
<td>0.48</td>
</tr>
<tr>
<td>On-treatment hsCRP: &lt; 2.0 mg/L</td>
<td>0.75</td>
<td>(0.66, 0.85)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

25% reduction in risk for those achieving hsCRP < 2 mg/L
5% reduction in risk for those achieving hsCRP ≥ 2 mg/L
(No change in LDL cholesterol)

CANTOS Sensitivity Analysis I: Multivariate Adjustment* for Potential Confounding Factors Related to On-Treatment hsCRP Has Minimal Impact

<table>
<thead>
<tr>
<th>On-treatment hsCRP Threshold</th>
<th>Placebo</th>
<th>Canakinumab On-treatment hsCRP above threshold</th>
<th>Canakinumab On-treatment hsCRP below threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP &lt; or &gt; clinical cutpoint (2 mg/L)</td>
<td>HR (adjusted)</td>
<td>1.0 Referent</td>
<td>0.90 Referent</td>
</tr>
</tbody>
</table>

*HRs adjusted for age, gender, smoking, HTN, diabetes, BMI, baseline hsCRP, Baseline LDLC

<table>
<thead>
<tr>
<th>On-treatment hsCRP Threshold</th>
<th>Placebo</th>
<th>Canakinumab On-treatment hsCRP above threshold</th>
<th>Canakinumab On-treatment hsCRP below threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP &lt; or &gt; clinical cutpoint (2 mg/L)</td>
<td>HR (adjusted)</td>
<td>1.0, Referent</td>
<td>0.90, 0.79-1.02, 0.11</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsCRP &lt; or &gt; median (1.8 mg/L)</td>
<td>HR (adjusted)</td>
<td>1.0, Referent</td>
<td>0.90, 0.79-1.02, 0.10</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsCRP &gt; or &lt; 50 % reduction</td>
<td>HR (adjusted)</td>
<td>1.0, Referent</td>
<td>0.87, 0.76-1.00, 0.05</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsCRP &gt; or &lt; Median % reduction</td>
<td>HR (adjusted)</td>
<td>1.0, Referent</td>
<td>0.86, 0.75-0.98, 0.02</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HRs adjusted for age, gender, smoking, HTN, diabetes, BMI, baseline hsCRP, Baseline LDLC

CANTOS Sensitivity Analysis III: Cardiovascular Outcomes According to **On-treatment Tertiles of hsCRP** Measured After the Initial dose of Canakinumab (MACE)

<table>
<thead>
<tr>
<th>Tertile</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.0 (ref)</td>
<td>(ref)</td>
</tr>
<tr>
<td>On-treatment hsCRP: Top tertile</td>
<td>0.99 (0.86, 1.14)</td>
<td>0.93</td>
</tr>
<tr>
<td>On-treatment hsCRP: Middle tertile</td>
<td>0.83 (0.72, 0.96)</td>
<td>0.014</td>
</tr>
<tr>
<td>On-treatment hsCRP: Lowest tertile</td>
<td>0.71 (0.61, 0.82)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

29% reduction for those achieving lowest hsCRP tertile
17% reduction for those achieving middle hsCRP tertile
1% reduction for those achieving highest hsCRP tertile
(No change in LDL cholesterol)

CANTOS Sensitivity Analysis IV. Cardiovascular Outcomes According to On-Treatment Levels of Interleukin-6 Above or Below the Study Median After the Initial Dose of Canakinumab (MACE)

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.0 (ref)</td>
<td>(ref)</td>
</tr>
<tr>
<td>Canakinumab: &gt;=1.64 ng/L</td>
<td>1.06 (0.90,1.25)</td>
<td>0.64</td>
</tr>
<tr>
<td>Canakinumab: &lt;1.64 ng/L</td>
<td>0.64 (0.53,0.77)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Follow-up (years) No. at risk:
- Placebo: 1597 1501 1411 1254 635 153
- Canakinumab: Interleukin-6 >=1.64 ng/L: 1638 1542 1427 1227 569 124
- Canakinumab: Interleukin-6 <1.64 ng/L: 1598 1541 1485 1355 765 210

36% reduction for those achieving IL-6 below median
No benefit for those achieving IL-6 above median
(No change in LDL cholesterol)

Ridker AHA 2017
<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Placebo (N = 3182)</th>
<th>Canakinumab On-treatment hsCRP &gt; 2mg/L (N = 2868)</th>
<th>Canakinumab On-treatment hsCRP &lt; 2 mg/L (N = 3484)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (adjusted)</td>
<td>1.0</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>95% CI P</td>
<td>Referent</td>
<td>0.79-1.02</td>
</tr>
<tr>
<td>MACE</td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>HR (adjusted)</td>
<td>1.0</td>
<td>0.91</td>
</tr>
<tr>
<td>MACE - Plus</td>
<td>95% CI P</td>
<td>Referent</td>
<td>0.81-1.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>CV Death</td>
<td>HR (adjusted)</td>
<td>1.0</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>95% CI P</td>
<td>Referent</td>
<td>0.82-1.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td>All-Cause</td>
<td>HR (adjusted)</td>
<td>1.0</td>
<td>1.05</td>
</tr>
<tr>
<td>Mortality</td>
<td>95% CI P</td>
<td>Referent</td>
<td>0.90-1.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.56</td>
</tr>
</tbody>
</table>

HRs adjusted for age, gender, smoking, HTN, diabetes, BMI, baseline hsCRP, Baseline LDLC

CANTOS: 31% Reduction in Cardiovascular Mortality and All-Cause Mortality Among Participants with Robust Inhibition of the Inflammatory Response

35 - 40% reductions in hsCRP and IL-6
No change in LDLC
## CANTOS Sensitivity Analysis VI: Consistent Effects at All Doses of Canakinumab (MACE)

<table>
<thead>
<tr>
<th>Canakinumab Dose</th>
<th>Placebo</th>
<th>Canakinumab On-treatment hsCRP &gt; 2mg/L</th>
<th>Canakinumab On-treatment hsCRP &lt; 2 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mg SC q 3 months</td>
<td>HR (adjusted) 95% CI P</td>
<td>1.0 Referent</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Referent</td>
<td>0.63</td>
</tr>
<tr>
<td>150 mg SC q 3 months</td>
<td>HR (adjusted) 95% CI P</td>
<td>1.0 Referent</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Referent</td>
<td>0.11</td>
</tr>
<tr>
<td>300 mg SC q 3 months</td>
<td>HR (adjusted) 95% CI P</td>
<td>1.0 Referent</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Referent</td>
<td>0.18</td>
</tr>
</tbody>
</table>

HRs adjusted for age, gender, smoking, HTN, diabetes, BMI, baseline hsCRP, Baseline LDLC

The proportions of those treated who achieved hsCRP levels < 2 mg/L were 44%, 55%, and 65% in the 50mg, 150mg, and 300mg canakinumab groups, respectively.

CANTOS Sensitivity Analysis VII:

Similar Results Observed in a Causal Inference Analysis Which Modelled Potential Outcomes Using Baseline Covariates for Individual Patients Treated With Canakinumab Had They Counterfactually Been Allocated to Placebo (and then Comparing the Modelled Effects to the Observed Effects)

<table>
<thead>
<tr>
<th>Canakinumab Dose</th>
<th>Canakinumab On-treatment hsCRP &gt; 2mg/L</th>
<th>Canakinumab On-treatment hsCRP &lt; 2 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg SC q 3 months</td>
<td>HR (counterfactually modelled) 95% CI</td>
<td>0.90 0.75-1.07</td>
</tr>
<tr>
<td>300 mg SC q 3 months</td>
<td>HR (counterfactually modelled) 95% CI</td>
<td>0.93 0.74-1.04</td>
</tr>
</tbody>
</table>

## CANTOS: Additional Outcomes (per 100 person years of exposure)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (N=3347)</th>
<th>Canakinumab SC q 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>50 mg (N=2170)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>12.0</td>
<td>11.4</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0.24</td>
<td>0.30</td>
</tr>
<tr>
<td>Any infection</td>
<td>2.86</td>
<td>3.03</td>
</tr>
<tr>
<td>Fatal infection</td>
<td>0.18</td>
<td>0.31</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>0.23</td>
<td>0.27</td>
</tr>
<tr>
<td>Any Malignancy</td>
<td>1.88</td>
<td>1.85</td>
</tr>
<tr>
<td>Fatal Malignancy</td>
<td>0.64</td>
<td>0.55</td>
</tr>
<tr>
<td>Arthritis</td>
<td>3.32</td>
<td>2.15</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>1.67</td>
<td>1.21</td>
</tr>
<tr>
<td>Gout</td>
<td>0.80</td>
<td>0.43</td>
</tr>
<tr>
<td>ALT &gt; 3x normal</td>
<td>1.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Bilirubin &gt; 2x normal</td>
<td>0.8</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* P-value for combined canakinumab doses vs placebo

ALT, alanine aminotransferase; SAE, serious adverse event; SC, subcutaneous

Immunity, Inflammation, and Cancer

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

Ron N. Apte · Shahar Dotan · Moshe Elkabets · Malka R. White · Eli Reich · Yaron Carmi · Xiaping Song · Tatyana Dvozkin · Yakov Krelin · Elena Voronov

Journal of Translational Medicine

Review

Interleukin-1 and cancer progression: the emerging role of interleukin-1 receptor antagonist as a novel therapeutic agent in cancer treatment

Anne M Lewis1,2, Sheelu Varghese1,3, Hui Xu1 and H Richard Alexander*1,3

Why not treat human cancer with interleukin-1 blockade?

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

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

Ridker PM et al. Lancet. 2017;390:1833-1842
CANTOS: Additional Non-Cardiovascular Clinical Benefits
Incident Lung Cancer

Ridker PM et al. Lancet. 2017;390:1833-1842
CANTOS: Additional Non-Cardiovascular Clinical Benefits
Fatal Lung Cancer

Canakinumab 300 mg
77% reduction in fatal lung cancer
P=0.0002

Placebo
Canakinumab 50 mg
Canakinumab 150 mg
Canakinumab 300 mg

HR (95%CI)      P
1.0   (referent) (referent)
0.71  (0.40-1.26)  0.24
0.64  (0.36-1.14)  0.13
0.23  (0.10-0.54)  0.0002

P-trend across groups = 0.0002

Ridker PM et al. Lancet. 2017;390:1833-1842
CANTOS: Greater Risk Reduction for Incident Lung Cancer With Greater hsCRP Reduction

Lung Cancer
71% reduction for those achieving hsCRP below median
No significant benefit for those achieving hsCRP above median

Ridker AHA 2017
CANTOS : Adverse Effects
Incidence Rates of Fatal Infection are Not Related to On-Treatment Levels of hsCRP

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Fatal Infection Incidence rate (per 100 person years)</td>
<td>0.18</td>
<td>0.35</td>
<td>0.27</td>
</tr>
</tbody>
</table>
Conclusions:
The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

1. CANTOS demonstrates that targeting the IL-1b to IL-6 pathway of innate immunity with canakinumab reduces cardiovascular event rates and potentially reduces rates of incident lung cancer and lung cancer mortality.

2. CANTOS thus provides critical proof-of-concept that inflammation inhibition, in the absence of lipid lowering, can improve atherothrombotic outcomes.

3. The magnitude of hsCRP reduction following a single dose of canakinumab may provide a simple clinical method to identify individuals most likely to accrue the largest cardiovascular and cancer benefits from continued treatment.
Conclusions: The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

4. For example, among those who achieved levels of hsCRP <2mg/L after a single dose of canakinumab, continued long-term treatment was associated with a 25% reduction in MACE (P<0.0001), a 31% reduction in cardiovascular mortality (P=0.0004) and a 31% reduction in all-cause mortality (P<0.0001). By contrast, effects were smaller in magnitude and non-significant for all of these endpoints among those with a less profound inflammatory response.

5. The differential outcomes observed in CANTOS on the basis of achieved hsCRP concentration were robust to the choice of on-treatment measures, were minimally affected by adjustment for baseline clinical characteristics, were observed at all individual canakinumab doses, and were consistent in causal inference analyses.
Conclusions:
The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

6. The CANTOS data have clinical importance not only for the pathophysiology of inflammation and future drug development, but also for patient selection, cost-effectiveness, and personalized medicine.

7. The 5-year number-needed-to-treat (NNT) for the endpoint of myocardial infarction, stroke, coronary revascularization, or death from any cause was 16 among those with on-treatment concentrations of hsCRP <2mg/L. By contrast, the 5-year NNT was 57 for those treated with canakinumab who did not achieve this inflammation threshold.

8. The main hazard of canakinumab – a small but statistically significant increase in fatal infection – was not related to on-treatment hsCRP levels. As such, the use of biologic response to canakinumab may also provide a simple selection tool to maximize benefit without increasing clinical hazard.
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

CANTOS
Canakinumab 150mg SC q 3 months 15% RRR
How Common is Residual Inflammatory Risk?

PROVE-IT

- Residual Inflammatory Risk: 44%
- Residual Cholesterol Risk: 13%
- Both: 14%
- Neither: 29%

IMPROVE-IT

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

hsCRP > 2 mg/L
LDLC < 70 mg/dL

hsCRP < 2 mg/L
LDLC > 70 mg/dL

hsCRP > 2 mg/L
LDLC > 70 mg/dL

hsCRP < 2 mg/L
LDLC < 70 mg/dL

CANTOS: Adding a New Axis to the Oxford LDL Lowering Line

% Reduction in LDL-C

Relative Risk Reduction (%)

CANTOS

AF/TEX
ASCOT
CARDS
HPS
LIPID
LIPS
PROSPER
4S
ALERT
ASPEN
SPARCL
WOSCOPS
JUPITER

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Cardiovascular Inflammation Reduction Trial (CIRT)
Primary Aims (NHLBI - Ridker PI)

- 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 atherosclerosis and either type 2 diabetes or metabolic syndrome.

N = 7,000  NHLBI-Sponsored  350 US and Canadian Sites
Arthur Eisner  1907-1956
Frances Eisner 1909-1974