Residual Inflammatory Risk and Residual Cholesterol Risk: Critical Analysis from CANTOS

Relationship of CRP Reduction to Cardiovascular Event Reduction Following Treatment with Canakinumab

Paul M Ridker MD, Jean MacFadyen BS, Brendan Everett MD, Peter Libby MD, Tom Thuren MD, and Robert Glynn, PhD
on behalf of the worldwide investigators and participants in the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)
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 (October 31, 2017)
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

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

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

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

CANTOS: Dose-Dependent Effects on Inflammatory Biomarkers and Lipids (48 Months)

CANTOS: Primary Cardiovascular Endpoints

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

**MACE**

HR 0.85
95%CI 0.76-0.96
P = 0.007

**MACE - Plus**

HR 0.83
95%CI 0.74-0.92
P = 0.0006

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

“Residual Cholesterol Risk”
- Known Cardiovascular Disease
  - LDL 150 mg/dL
  - hsCRP 4.5 mg/L
- High Intensity Statin
- Additional LDL Reduction
- FOURIER/SPIRE
  - PCSK9 Inhibition SC q 2 weeks 15% RRR

“Residual Inflammatory Risk”
- LDL 110 mg/dL
  - hsCRP 1.8 mg/L
- Additional LDL Reduction
- CANTOS
  - Canakinumab 150-300mg SC q 3 months 15%RRR
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: Critical Unanswered Clinical Questions

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

Two Analytic Approaches Applied to CANTOS:

1. Evaluate whether there are baseline clinical characteristics that can be used to define patient groups more or less likely to benefit from treatment with canakinumab.

2. If not, evaluate whether we can use evidence of biologic drug response to define patient groups more or less likely to benefit from treatment with canakinumab.
CANTOS: Consistency of Effect Across All patient Groups Defined By Baseline Clinical Characteristics

Group
- Women
- Men

Age
- < 60 yrs
- ≥ 60 yrs

Diabetes
- No diabetes
- Yes

Smoker
- Non Smoker
- Smoker

BMI
- < 30 kg/m2
- ≥ 30 kg/m2

LDLC
- < 80 mg/dL
- ≥ 80 mg/dL

hsCRP
- > 2 to < 4 mg/L
- ≥ 4 mg/L

HDLC
- > 45 mg/dL
- ≤ 45 mg/dL

TG
- < 150 mg/dL
- ≥ 150 mg/dL

Overall

MACE

MACE Plus
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)

Cumulative Incidence

<table>
<thead>
<tr>
<th>Treatment</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: &gt;=2.0 mg/L</td>
<td>0.95 (0.84, 1.09)</td>
<td>0.48</td>
</tr>
<tr>
<td>On Treatment hsCRP: &lt;2.0 mg/L</td>
<td>0.75 (0.66, 0.85)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Follow-up (years)
No. at risk:
Placebo
- 3182
- 3014
- 2853
- 2525
- 1215
- 200
Canakinumab:
- hsCRP >= 2.0 mg/L
  - 2868
  - 2724
  - 2574
  - 2258
  - 1087
  - 195
- hsCRP < 2.0 mg/L
  - 3484
  - 3353
  - 3214
  - 2890
  - 1411
  - 243

MACE
25% reduction in risk for those achieving hsCRP < 2 mg/L
5 % reduction in risk for those achieving hsCRP > 2mg/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) 95% CI</td>
<td>1.0 Referent</td>
<td>0.90 0.79-1.02 0.11</td>
</tr>
</tbody>
</table>

*HRs adjusted for age, gender, smoking, HTN, diabetes, BMI, baseline hsCRP, Baseline LDLC
### CANTOS Sensitivity Analysis II: Choice of Alternative Thresholds for 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) 95% CI P</td>
<td>1.0 Referent Referent</td>
<td>0.90 0.79-1.02 0.11</td>
</tr>
<tr>
<td>hsCRP &lt; or &gt; median (1.8 mg/L)</td>
<td>HR (adjusted) 95% CI P</td>
<td>1.0 Referent Referent</td>
<td>0.90 0.79-1.02 0.10</td>
</tr>
<tr>
<td>hsCRP &gt; or &lt; 50 % reduction</td>
<td>HR (adjusted) 95% CI P</td>
<td>1.0 Referent Referent</td>
<td>0.87 0.76-1.00 0.05</td>
</tr>
<tr>
<td>hsCRP &gt; or &lt; Median % reduction</td>
<td>HR (adjusted) 95% CI P</td>
<td>1.0 Referent Referent</td>
<td>0.86 0.75-0.98 0.02</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></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: Top Tertile</td>
<td>0.99</td>
<td>(0.86,1.14)</td>
<td>0.93</td>
</tr>
<tr>
<td>On Treatment hsCRP: Middle Tertile</td>
<td>0.83</td>
<td>(0.72,0.96)</td>
<td>0.014</td>
</tr>
<tr>
<td>On Treatment hsCRP: Lowest Tertile</td>
<td>0.71</td>
<td>(0.61,0.82)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Follow-up (years)

No. at risk:
- Placebo: 3182, 3014, 2853, 2525, 1215, 200
- Canakinumab:
  - Top Tertile: 2090, 1983, 1866, 1632, 789, 139
  - Middle Tertile: 2044, 1947, 1866, 1660, 821, 146
  - Lowest Tertile: 2218, 2147, 2056, 1856, 888, 153

MACE
- 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 V: Multivariable Adjusted Hazard Ratios for Additional Pre-Specified Cardiovascular Outcomes According to On-treatment hsCRP Levels Above or Below 2 mg/L After Drug Initiation

<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></td>
<td></td>
</tr>
<tr>
<td></td>
<td>95% CI P</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Referent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Referent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>1.0</td>
<td>0.90</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>Referent</td>
<td>0.79-1.02</td>
<td>0.66-0.85</td>
</tr>
<tr>
<td></td>
<td>0.11</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MACE - Plus</td>
<td>1.0</td>
<td>0.91</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>Referent</td>
<td>0.81-1.03</td>
<td>0.66-0.83</td>
</tr>
<tr>
<td></td>
<td>0.14</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CV Death</td>
<td>1.0</td>
<td>0.99</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>Referent</td>
<td>0.82-1.21</td>
<td>0.56-0.85</td>
</tr>
<tr>
<td></td>
<td>0.95</td>
<td></td>
<td>0.0004</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>1.0</td>
<td>1.05</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>Referent</td>
<td>0.90-1.22</td>
<td>0.56-0.81</td>
</tr>
<tr>
<td></td>
<td>0.56</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

HRs adjusted for age, gender, smoking, HTN, diabetes, BMI, baseline hsCRP, Baseline 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>1.0</td>
<td>0.96</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>Referent</td>
<td>0.80-1.14</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>Referent</td>
<td>0.63</td>
<td>0.02</td>
</tr>
<tr>
<td>150 mg SC q 3 months</td>
<td>1.0</td>
<td>0.86</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>Referent</td>
<td>0.71-1.04</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>Referent</td>
<td>0.11</td>
<td>0.003</td>
</tr>
<tr>
<td>300 mg SC q 3 months</td>
<td>1.0</td>
<td>0.87</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>Referent</td>
<td>0.71-1.07</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>Referent</td>
<td>0.18</td>
<td>0.0009</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)</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>0.75-1.07</td>
</tr>
<tr>
<td>300 mg SC q 3 months</td>
<td>HR (counterfactually modelled)</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>0.74-1.04</td>
</tr>
</tbody>
</table>
CANTOS: Additional Non-Cardiovascular Clinical Benefits

Incident Lung Cancer

<table>
<thead>
<tr>
<th>Treatment</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>0.77</td>
<td>(0.49-1.20)</td>
<td>0.25</td>
</tr>
<tr>
<td>Canakinumab 150 mg</td>
<td>0.61</td>
<td>(0.39-0.97)</td>
<td>0.034</td>
</tr>
<tr>
<td>Canakinumab 300 mg</td>
<td>0.33</td>
<td>(0.18-0.59)</td>
<td>0.00008</td>
</tr>
</tbody>
</table>

P-trend across groups = 0.0003

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

No. at risk:
<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Canakinumab:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>hsCRP &gt;= 1.8 mg/L</td>
</tr>
<tr>
<td>0</td>
<td>3182</td>
<td>3193</td>
</tr>
<tr>
<td>1</td>
<td>3110</td>
<td>3111</td>
</tr>
<tr>
<td>2</td>
<td>3017</td>
<td>2998</td>
</tr>
<tr>
<td>3</td>
<td>2721</td>
<td>2683</td>
</tr>
<tr>
<td>4</td>
<td>1343</td>
<td>1325</td>
</tr>
<tr>
<td>5</td>
<td>240</td>
<td>241</td>
</tr>
</tbody>
</table>
### CANTOS: Adverse Effects

Incidences Rates of Fatal Infection are Not Related to On-Treatment Levels of hsCRP

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Placebo (N = 3182)</th>
<th>Canakinumab On-treatment hsCRP ≥ 2mg/L (N = 2868)</th>
<th>Canakinumab On-treatment hsCRP &lt; 2 mg/L (N = 3484)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal Infection</td>
<td>0.18</td>
<td>0.35</td>
<td>0.27</td>
</tr>
<tr>
<td>Incidence rate (per 100 person years)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusions:
The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

1. Overall, 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. It has been uncertain, however, if there are patient groups where the benefits of treatment clearly outweigh potential hazards.

3. The current analysis suggests that 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.
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. We believe these observations 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. For example, 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.

9. Details of the CANTOS hsCRP reduction data are available on-line today at The Lancet.org.