Anti-Inflammatory Therapy with Canakinumab for Atherosclerotic Disease

Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

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

Ridker ACC 2017
Declaration of interest

- Research contracts (Novartis)
- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Dr Ridker is listed as a coinventor on patents related to the use of inflammatory biomarker in cardiovascular disease.)
Low Grade Systemic Inflammation **Precedes** By Many Years the Onset of Vascular Events
Clinical Impact of Inflammation on Atherosclerosis

- Plasma levels of inflammatory biomarkers including hsCRP and IL-6 robustly predict first and recurrent cardiovascular events, independent of lipid levels.
- Statins are both lipid lowering and anti-inflammatory, and the greatest benefits of statin therapy accrue to those who not only lower LDLC, but who also lower hsCRP.
- In primary prevention, the JUPITER trial demonstrated that those with elevated hsCRP but low levels of LDLC markedly benefit from statin therapy.
- In secondary prevention, clinicians now distinguish between those with “residual cholesterol risk” and those with “residual inflammatory risk”

Ridker PM. JACC 2016;67:712-23
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 4.5mg/L

High Intensity Statin

“Residual Cholesterol Risk”
LDL 110 mg/dL (2.8 mmol/L)
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 70 mg/dL (1.8 mmol/L)
hsCRP 3.8 mg/L
Additional Inflammation Reduction

No Prior Proof of Concept

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Can Inflammation Reduction, in the Absence of Lipid Lowering, Reduce Cardiovascular Event Rates?

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From CRP to IL-6 to IL-1: Moving Upstream to Identify Novel Targets for Atheroprotection

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

Ridker PM, et al; Circulation 2012; 126:2739-2748

Ridker ESC 2017
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

CANTOS
N = 10,061
39 Countries
April 2011 - June 2017
1490 Primary Events
## Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

<table>
<thead>
<tr>
<th>Committee</th>
<th>Chair(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Adjudication Committee</td>
<td>Brenden Everett, Chair</td>
</tr>
<tr>
<td>Death Adjudication Committee</td>
<td>Brenden Everett, Chair</td>
</tr>
<tr>
<td>Cancer Adjudication Committee</td>
<td>Howard Burris, Chair</td>
</tr>
<tr>
<td>Infection Adjudication Committee</td>
<td>Vance Fowler, Ajit Limaye, Chairs</td>
</tr>
</tbody>
</table>
| Data and Safety Monitoring Board             | Rory Collins, Chair             
|                                             | Kent Bailey                    
|                                             | Bernard Gersh                  
|                                             | Helen Colhoun                  
|                                             | Roger Blumenthal               |
Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

39 countries
> 1000 investigators

17482 Screened

10105 Entered Into Randomization Process

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

10061 Successfully Randomized

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 - Baseline Clinical Characteristics

<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>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.1</td>
<td>61.1</td>
<td>61.2</td>
<td>61.1</td>
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<tr>
<td>Female (%)</td>
<td>25.9</td>
<td>24.9</td>
<td>25.2</td>
<td>26.8</td>
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<tr>
<td>Current smoker (%)</td>
<td>22.9</td>
<td>24.5</td>
<td>23.4</td>
<td>23.7</td>
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<tr>
<td>Diabetes (%)</td>
<td>39.9</td>
<td>39.4</td>
<td>41.8</td>
<td>39.2</td>
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<tr>
<td>Lipid lowering therapy (%)</td>
<td>93.7</td>
<td>94.0</td>
<td>92.7</td>
<td>93.5</td>
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<td>Renin-angiotensin inhibitors (%)</td>
<td>79.8</td>
<td>79.3</td>
<td>79.8</td>
<td>79.6</td>
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<td>Prior Revascularization (%)</td>
<td>79.6</td>
<td>80.9</td>
<td>82.2</td>
<td>80.7</td>
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<td>LDL cholesterol (mg/dL)</td>
<td>82.8</td>
<td>81.2</td>
<td>82.4</td>
<td>83.5</td>
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<td>HDL cholesterol (mg/dL)</td>
<td>44.5</td>
<td>43.7</td>
<td>43.7</td>
<td>44.0</td>
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<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>

Ridker ESC 2017
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

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<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>
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<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) HR 95%CI P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>4.5</td>
<td>1.0</td>
<td>(referent)</td>
<td>(referent)</td>
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<tr>
<td><strong>Secondary Endpoint</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR (per 100 person years) HR 95%CI P</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>5.1</td>
<td>1.00</td>
<td>(referent)</td>
<td>(referent)</td>
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</tbody>
</table>

CANTOS: Primary Clinical Outcome Effects on MACE and MACE +

Ridker ESC 2017
<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>Primary Endpoint</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 (0.93)</td>
<td>3.9 (0.85)</td>
<td>3.9 (0.86)</td>
<td>0.020</td>
</tr>
<tr>
<td>HR</td>
<td>1.0 (referent)</td>
<td>0.93 (0.80-1.07)</td>
<td>0.85 (0.74-0.98)</td>
<td>0.86 (0.75-0.99)</td>
<td></td>
</tr>
<tr>
<td>95%CI</td>
<td>(referent)</td>
<td>(0.80-1.07)</td>
<td>(0.74-0.98)</td>
<td>(0.75-0.99)</td>
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<tr>
<td>P</td>
<td></td>
<td>0.30</td>
<td>0.021*</td>
<td>0.031</td>
<td></td>
</tr>
<tr>
<td>Secondary Endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR (per 100 person years)</td>
<td>5.1 (referent)</td>
<td>4.6 (0.90)</td>
<td>4.3 (0.83)</td>
<td>4.3 (0.83)</td>
<td>0.003</td>
</tr>
<tr>
<td>HR</td>
<td>1.00 (referent)</td>
<td>0.90 (0.78-1.03)</td>
<td>0.83 (0.73-0.95)</td>
<td>0.83 (0.72-0.94)</td>
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<tr>
<td>95%CI</td>
<td>(referent)</td>
<td>(0.78-1.03)</td>
<td>(0.73-0.95)</td>
<td>(0.72-0.94)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.11</td>
<td>0.005*</td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant, adjusted for multiplicity, in accordance with the pre-specified closed-testing procedures

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CANTOS: Primary Cardiovascular Endpoint (MACE)

HR 0.85
95%CI 0.76-0.96
P = 0.007

39% reduction in hsCRP
No change in LDLC
15% reduction in MACE

The 150mg group met multiplicity adjusted thresholds for formal statistical significance for both the primary and secondary cardiovascular endpoints.
CANTOS: Key Secondary Cardiovascular Endpoint (MACE+)

The 150mg group met multiplicity adjusted thresholds for formal statistical significance for both the primary and secondary cardiovascular endpoints.

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

HR 0.83
95%CI 0.74-0.92
P = 0.0006

39% reduction in hsCRP
No change in LDLC
17% reduction in MACE+
<table>
<thead>
<tr>
<th>Endpoint</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>Primary</td>
<td>1.00</td>
<td>0.93</td>
<td>0.85</td>
<td>0.86</td>
<td>0.020</td>
</tr>
<tr>
<td>Secondary</td>
<td>1.00</td>
<td>0.90</td>
<td>0.83</td>
<td>0.83</td>
<td>0.002</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1.00</td>
<td>0.94</td>
<td>0.76</td>
<td>0.84</td>
<td>0.028</td>
</tr>
<tr>
<td>Urgent Revascularization</td>
<td>1.00</td>
<td>0.70</td>
<td>0.64</td>
<td>0.58</td>
<td>0.005</td>
</tr>
<tr>
<td>Any Coronary Revascularization</td>
<td>1.00</td>
<td>0.72</td>
<td>0.68</td>
<td>0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.00</td>
<td>1.01</td>
<td>0.98</td>
<td>0.80</td>
<td>0.17</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>1.00</td>
<td>0.72</td>
<td>0.63</td>
<td>0.46</td>
<td>0.035</td>
</tr>
<tr>
<td>CV Death</td>
<td>1.00</td>
<td>0.89</td>
<td>0.90</td>
<td>0.94</td>
<td>0.62</td>
</tr>
<tr>
<td>All Cause Mortality</td>
<td>1.00</td>
<td>0.94</td>
<td>0.92</td>
<td>0.94</td>
<td>0.39</td>
</tr>
</tbody>
</table>

CANTOS: Consistency of HRs Across All Cardiovascular Endpoints

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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

MACE
- Canakinumab Superior
- Canakinumab Inferior

MACE +
- Canakinumab Superior
- Canakinumab Inferior

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

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)
# 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>
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</thead>
<tbody>
<tr>
<td></td>
<td>50 mg (N=2170)</td>
<td>150 mg (N=2284)</td>
</tr>
<tr>
<td></td>
<td>300 mg (N=2263)</td>
<td>P-trend</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

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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 • Shahnur Dutta • Moshe Elkahets • Malka R. White • Eli Rech • Yaron Carmi • Xiaping Song • Tatyana Dvovkin • Yakov Krell • 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

Ron Apte, et al;
Cancer Metastasis Rev.
2006;25:387-408.

Anne Lewis, et al;
J Transl Med.

Charles A. Dinarello.
Cancer Metastasis Rev
CANTOS and Incident Cancer
The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study

1. The atherosclerosis patients enrolled in CANTOS were at unusually high risk for certain inflammatory cancers, in particular lung cancer.

2. This is due to several issues including older age, a high prevalence of current and past smoking, and the enrollment only of those with elevated hsCRP (elevated hsCRP levels are an independent risk marker for lung cancer).

3. The randomized design of CANTOS ensures that prevalent cancers undiagnosed at trial entry as well as measured and unmeasured cancer risk factors are equally distributed among treatment groups.

4. A Cancer Adjudication Committee of oncologists was established at trial initiation.
CANTOS: Additional Non-Cardiovascular Clinical Benefits

Cancer Mortality

- Placebo: HR 1.0 (referent) P (referent)
- Canakinumab 50 mg: HR 0.86 (0.59-1.24) P = 0.42
- Canakinumab 150 mg: HR 0.78 (0.54-1.13) P = 0.19
- Canakinumab 300 mg: HR 0.49 (0.31-0.75) P = 0.0009

P-trend across groups = 0.0007

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

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CANTOS: Additional Non-Cardiovascular Clinical Benefits

Incident Lung Cancer

<table>
<thead>
<tr>
<th>Group</th>
<th>HR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (referent)</td>
<td>1.0 (referent)</td>
<td></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

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CANTOS: Additional Non-Cardiovascular Clinical Benefits

Fatal Lung Cancer

<table>
<thead>
<tr>
<th>Treatment</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>0.71 (0.40-1.26)</td>
<td>0.24</td>
</tr>
<tr>
<td>Canakinumab 150 mg</td>
<td>0.64 (0.36-1.14)</td>
<td>0.13</td>
</tr>
<tr>
<td>Canakinumab 300 mg</td>
<td>0.23 (0.10-0.54)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

P-trend across groups = 0.0002

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

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Conclusions:
The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

1. CANTOS was designed to directly test the inflammatory hypothesis of atherothrombosis.

2. As shown in these data, inhibition of IL-1β with SC canakinumab given once every three months among patients with a prior myocardial infarction substantially lowered the inflammatory biomarkers hsCRP and IL-6 while having no beneficial impact on atherogenic lipids.

3. Concordantly, while the 50 mg dose of canakinumab did not have cardiovascular efficacy compared to placebo during an average follow-up period of 3.7 years, hazard reductions of 15% for the primary endpoint of MACE (P=0.007) and 17% for the secondary endpoint of MACE+ (P=0.006) were observed for the combined 150mg and 300mg doses groups. The 150mg group met all pre-specified multiplicity adjusted thresholds for statistical significance for both the primary and secondary cardiovascular outcomes.
Conclusions: The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

4. In exploratory analyses, relative hazard reductions of 27% (P<0.001) were observed among those with the lowest levels of on-treatment hsCRP measured at 3 months. Thus, “lower is better” appears to be true for inflammation as well as LDLC.

5. Given mild neutropenia and an increase in risk of fatal infection, patients being considered for treatment with canakinumab will require monitoring for early signs and symptoms of infection in a manner similar to that currently done for individuals taking other biologic anti-inflammatory agents.

6. Placebo event rates in CANTOS were high, approaching 25% at five years. These data thus affirm that statin-treated patients with “residual inflammatory risk” as assessed by baseline hsCRP ≥2 mg/L have future event rates as high, if not higher, than statin-treated patients with “residual cholesterol risk”. These two patient groups differ substantially and require different personalized approaches to treatment.
Conclusions:
The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

7. Inflammation is also a determinant of invasiveness, progression, and metastasis for certain cancers. In exploratory analyses within CANTOS, those allocated to canakinumab had large dose-dependent relative risk reductions in deaths due to cancer (P=0.0007), incident lung cancers (P<0.0001), and fatal lung cancer (P=0.0002) such that those in the canakinumab 300mg group had a 50 percent reduction in cancer fatality (P=0.0009). Replication of these data is required.

8. In conclusion, these randomized placebo-controlled trial data demonstrate that targeting the IL-1β 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. These data provide proof that inflammation inhibition, in the absence of lipid lowering, can improve atherothrombotic outcomes and potentially alter the progression of some fatal cancers.
Conclusions: 
The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) 

9. In addition to thanking our dedicated investigators and coordinators in 39 countries worldwide, the CANTOS Executive Committee and Steering Committee wish to thank the sponsor, Novartis, for their foresight and willingness to work with us in pursuit of entirely novel methods for atheroprotection and cancer prevention.

10. Details of the CANTOS Cardiovascular Outcomes manuscript are available at NEJM.org while details of the CANTOS Oncology Outcomes manuscript are available at the Lancet.org.