Anti-Inflammatory Therapy with Canakinumab for the Prevention and Management of Diabetes

A Pre-Specified Secondary Endpoint from the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

Brendan M. Everett MD, Marc Y. Donath MD, Aruna D. Pradhan MD, Tom Thuren MD, Prem Pais MD, Jose C. Nicolau MD, Robert J Glynn PhD, Peter Libby MD, and Paul M Ridker MD

on behalf of the worldwide investigators and participants in the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)
IL-1β Inhibition and Type 2 Diabetes

• Observational and experimental data support a pathologic role for subclinical inflammation in both insulin resistance and impaired insulin production and the development of type 2 diabetes

• Cellular and animal experiments suggest prolonged hyperglycemia and amyloid deposition in pancreatic islet cells lead to induction of the NLRP3 inflammasome and activation of IL-1β in pancreatic islet cells

• A randomized trial of anakinra, an IL-1 receptor antagonist, showed improvements in beta cell function and peripheral glucose sensitivity, as well as reductions in HbA1c, in a randomized trial in 70 patients with established type 2 diabetes (Larsen NEJM 2007)
Aims

• We tested the effects of canakinumab on major cardiovascular events in patients with and without diabetes at baseline

• We tested whether baseline concentrations of hsCRP and IL-6 associate with new onset diabetes in patients without diabetes at baseline

• We evaluated the effect of canakinumab on HbA1c in patients with and without established diabetes.

• In a protocol pre-specified secondary analysis, we tested whether canakinumab would reduce the risk of adjudicated cases of new onset type 2 diabetes among those with protocol-defined pre-diabetes at trial entry.
Definitions Pre-Diabetes and New Onset Diabetes

• Baseline pre-diabetes
  • HbA1c of 5.7 to <6.5% at screening or randomization OR
  • Fasting plasma glucose of 100 to 125 mg/dL (5.6-6.9 mmol/L) at screening or randomization

• New onset diabetes
  • HbA1c ≥ 6.5% on two occasions within 6 weeks of one another OR
  • Fasting plasma glucose ≥126 mg/dL on two occasions within 6 weeks of one another OR
  • A combination of an elevated HbA1c or fasting plasma glucose within 6 weeks OR
  • A new prescription of an anti-diabetic medication

• Centrally adjudicated by endocrinologists who were blinded to study drug allocation.
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
Canakinumab 300 mg SC q 3 months
Randomized
Placebo SC q 3 months

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

Primary Cardiovascular Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death (MACE)
Secondary Cardiovascular Endpoint: MACE plus Unstable Angina Requiring Urgent Revascularization (MACE+)

Pre-Specified Secondary Endpoint: New Onset Diabetes among Patients with Protocol-Defined Pre-Diabetes at Trial Entry

New Onset Diabetes in CANTOS

Stable CAD (post MI)  
Residual Inflammatory Risk  
(hsCRP ≥ 2 mg/L)  
N=10,061

Baseline Diabetes  
N=4,057 (40%)  
1. MACE and MACE Plus

Baseline Pre-Diabetes  
N=4,960 (49%)  
2. Baseline hsCRP and IL-6 and New Onset Diabetes

Baseline Normal Glucose  
N=1,044 (11%)  
3. Effects of Canakinumab on HbA1c

4. Effects of Canakinumab on New Onset Diabetes in Patients with Pre-Diabetes at Trial Entry
Effects of Canakinumab on MACE and MACE Plus Among Those With and Without Diabetes at Study Entry

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Canakinumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>5.53</td>
<td>4.98</td>
</tr>
<tr>
<td>Pre-Diabetes</td>
<td>3.93</td>
<td>3.38</td>
</tr>
<tr>
<td>Normoglycemia</td>
<td>3.43</td>
<td>2.79</td>
</tr>
<tr>
<td>Overall</td>
<td>4.50</td>
<td>3.95</td>
</tr>
</tbody>
</table>

MACE

P-heterogeneity=0.86

MACE Plus

Canakinumab Superior

P-heterogeneity=0.56
Baseline hsCRP and IL-6 and Incident Diabetes in CANTOS

Both hsCRP and IL-6 remained statistically significant after multivariable adjustment. IL-6 remained significant after further adjustment for baseline HbA1c.
Change in hsCRP and IL-6 after canakinumab in patients with pre-diabetes at baseline

<table>
<thead>
<tr>
<th>Dose</th>
<th>Median Percent (IQR) Reduction Compared to Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hsCRP</td>
</tr>
<tr>
<td>50 mg</td>
<td>-49.2 (-20.0, -67.2)</td>
</tr>
<tr>
<td>150 mg</td>
<td>-61.5 (-33.3, -75.8)</td>
</tr>
<tr>
<td>300 mg</td>
<td>-67.1 (-43.2, -80.6)</td>
</tr>
</tbody>
</table>

These reductions are similar to those observed in the CANTOS trial population as a whole.
HbA1c (%) and Percent Change in HbA1c from Baseline: Pre-diabetes

<table>
<thead>
<tr>
<th>Month of Study</th>
<th>Placebo</th>
<th>50mg</th>
<th>150mg</th>
<th>300mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.6</td>
<td>5.7</td>
<td>5.8</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>5.7</td>
<td>5.8</td>
<td>5.9</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>5.8</td>
<td>5.9</td>
<td>6.0</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>5.9</td>
<td>6.0</td>
<td>6.1</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>6.0</td>
<td>6.1</td>
<td>6.2</td>
<td>6.3</td>
</tr>
</tbody>
</table>

P-value vs. placebo <0.0001 <0.0001 <0.0001
HbA1c (%) and Percent Change in HbA1c from Baseline: Diabetes

HbA1c (%) and Percent Change in HbA1c from Baseline

Month of Study

Placebo  50mg  150mg  300mg

P-value vs. placebo  0.95  0.92  0.30
Canakinumab and Incident Diabetes in Patients with Pre-Diabetes: CANTOS

Canakinumab and Incident Type 2 Diabetes

Cumulative Incidence (%)

- Placebo
- Canakinumab 50mg
- Canakinumab 150mg
- Canakinumab 300mg

Log-rank P=0.84

Canakinumab and Incident Type 2 Diabetes

Cumulative Incidence (%)

- Placebo
- Canakinumab

Log-rank P=0.85
CANTOS: Incidence Rates and Effects of Canakinumab on New Onset Diabetes Among Those With Pre-Diabetes at Study Entry

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>50 mg</th>
<th>150 mg</th>
<th>300 mg</th>
<th>All Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjudicated Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N Events/N at risk</td>
<td>246/1645</td>
<td>161/1089</td>
<td>171/1094</td>
<td>169/1132</td>
<td>501/3315</td>
</tr>
<tr>
<td>IR (per 100 person years)</td>
<td>4.20</td>
<td>4.24</td>
<td>4.35</td>
<td>4.12</td>
<td>4.23</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.0</td>
<td>1.04 (0.85-1.27)</td>
<td>1.03 (0.85-1.26)</td>
<td>0.98 (0.80-1.19)</td>
<td>1.01 (0.87-1.18)</td>
</tr>
<tr>
<td>P</td>
<td>(referent)</td>
<td>0.70</td>
<td>0.75</td>
<td>0.80</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Physician Reported Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N Events/N at risk</td>
<td>279/1645</td>
<td>186/1089</td>
<td>191/1094</td>
<td>190/1132</td>
<td>567/3315</td>
</tr>
<tr>
<td>IR (per 100 person years)</td>
<td>4.84</td>
<td>4.97</td>
<td>4.92</td>
<td>4.68</td>
<td>4.85</td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td>1.0</td>
<td>1.06 (0.88-1.27)</td>
<td>1.02 (0.84-1.22)</td>
<td>0.97 (0.80-1.16)</td>
<td>1.01 (0.88-1.17)</td>
</tr>
<tr>
<td>P</td>
<td>(referent)</td>
<td>0.56</td>
<td>0.88</td>
<td>0.70</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Everett ACC 2018
Conclusions: CANTOS Diabetes
The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study

• Interleukin-1β inhibition with canakinumab reduces major adverse cardiovascular event rates among high-risk atherosclerosis patients with diabetes and pre-diabetes, as well as among those with normoglycemia.

• Our data confirm that baseline concentrations of the inflammatory biomarkers hsCRP and IL-6 predict the onset of type 2 diabetes in CANTOS.
Conclusions: CANTOS Diabetes
The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study

• Interleukin-1β inhibition with canakinumab reduces HbA1c in patients with pre-diabetes for approximately 9-12 months, but effects were attenuated over time

• Canakinumab does not prevent the progression from pre-diabetes to diabetes among patients with prior myocardial infarction and hsCRP \( \geq 2 \text{ mg/L} \)
Accepted Manuscript

Anti-Inflammatory Therapy with Canakinumab for the Prevention and Management of Diabetes

Brendan M. Everett, MD, MPH, Marc Y. Donath, MD, Aruna D. Pradhan, MD, MPH, Tom Thuren, MD, Prem Pais, MD, Jose C. Nicolau, MD, Robert J. Glynn, ScD, Peter Libby, MD, Paul M. Ridker, MD, MPH

PII: S0735-1097(18)33483-1
DOI: 10.1016/j.jacc.2018.03.002
Reference: JAC 24732

To appear in: Journal of the American College of Cardiology

Received Date: 14 February 2018
Revised Date: 28 February 2018
Accepted Date: 1 March 2018

Thank you!

Brendan M. Everett, MD, MPH
beverett@bwh.harvard.edu

Director, General Cardiology Inpatient Service
Assistant Professor of Medicine, Harvard Medical School

www.brighamandwomens.org/heart