Discussant review:
- CANTOS -
The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study

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Declaration of interest

- I have nothing to declare
CANTOS: Canakinumab Anti-Inflammatory Thrombosis Outcomes Study

- Chronic inflammation in atherosclerosis
- Patient (and target) population
- Effect size, tailoring therapy
- Non-cardiovascular effects and safety
hsCRP reflects inflammation in humans

**Effect size**

![Effect size graph]

**Stability**

![Stability graph]
hsCRP reflects inflammation in humans

**effect size**

![Graph showing the effect size of hsCRP on myocardial infarction.](image)

**stability**

![Graph showing the stability of hsCRP levels over study follow-up years.](image)

**independent risk indication**

![Table showing risk ratios for hsCRP, Sysolic BP, Total cholesterol, and Non-HDL-C.](image)

**IL6 upstream signalling**

![Diagram illustrating IL6 upstream signalling.](image)
Activation of inflammasome - “clinical utility”

- NLRP3 inflammasome
- IL-1β
- TNF
- IL-6
- hsCRP

**Target**

**Converter**

**Distributor**

**Biomarker**

Cholesterol crystals induce local and systemic inflammation

**Experimental studies**

- monocytes & macrophages
- volume expansion
- intima perforation
Cholesterol crystals induce local and systemic inflammation

**Experimental studies**

- Monocytes & macrophages
- Volume expansion
- Intima perforation

**Human studies**

- Carotid artery
- Coronary artery
- Systemic effects

References:
- Circ. Res. 2017;120:1947-57
- Science. 2015;349:237-8
Residual risk in HR-patients with CAD: >50%

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

“Residual Inflammatory Risk”
LDL 80 mg/dL
hsCRP 3.8 mg/L
Additional Inflammation Reduction

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

CANTOS: Proof of Concept

Eur Heart J 2016;37:1720-22
PROSPECT - event rate post pPCI / AMI

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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<tr>
<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>
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Ridker ESC 2017
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 LDL-C
15% reduction in MACE

CANTOS: Key Secondary Cardiovascular Endpoint (MACE+)

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 LDL-C
17% reduction in MACE+

CANTOS: Consistency of HRs Across All Cardiovascular Endpoints

<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>
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<tr>
<td>Secondary</td>
<td>1.00</td>
<td>0.90</td>
<td>0.83</td>
<td>0.83</td>
<td>0.002</td>
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<tr>
<td>Myocardial Infarction</td>
<td>1.00</td>
<td>0.94</td>
<td>0.76</td>
<td>0.84</td>
<td>0.021</td>
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<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>
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<tr>
<td>Stroke</td>
<td>1.00</td>
<td>1.01</td>
<td>0.98</td>
<td>0.80</td>
<td>0.17</td>
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<tr>
<td>Cardiac Arrest</td>
<td>1.00</td>
<td>0.72</td>
<td>0.63</td>
<td>0.46</td>
<td>0.015</td>
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<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: Greater Risk Reduction Among Those With Greater hsCRP Reduction (MACE+)

Placebo
- Canakinumab (as treatment hsCRP > median)
- Canakinumab (as treatment hsCRP > median)

HR 0.73
95% CI 0.63-0.83
P = 0.0001

for those with reductions in hsCRP > median at 3-months (1.3 mg/L)
Tailored therapy in CAD

Known Cardiovascular Disease
- LDL 150 mg/dL
- hsCRP 4.5 mg/L
- High Intensity Statin

“Residual Cholesterol Risk”
- LDL high
- hsCRP low
- Additional LDL Reduction

“Residual Inflammatory Risk”
- LDL low
- hsCRP high
- Additional Inflammation Reduction

“Residual Thrombotic Risk”
- HTPR
- Additional antiplatelet & anticoagulant therapy
IL-1β in sterile inflammation and non-CVD

CRP & (non) cardiovascular mortality

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Risk ratio (95% CI)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>All vascular deaths</td>
<td>37</td>
<td>136,912</td>
<td>3430</td>
<td>1.82 (1.66–2.00)</td>
<td>&lt;0.0001</td>
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<tr>
<td>All non-vascular deaths</td>
<td>38</td>
<td>138,063</td>
<td>8369</td>
<td>1.55 (1.46–1.66)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Cancer deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory/intrathoracic cancer</td>
<td>24</td>
<td>51,356</td>
<td>666</td>
<td>2.32 (1.96–2.74)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>8</td>
<td>18,276</td>
<td>130</td>
<td>1.88 (1.39–2.55)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blood-related cancer</td>
<td>14</td>
<td>45,806</td>
<td>220</td>
<td>1.57 (1.24–1.99)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Digestive cancer</td>
<td>25</td>
<td>64,058</td>
<td>906</td>
<td>1.44 (1.23–1.70)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Genitourinary-related cancer</td>
<td>17</td>
<td>48,646</td>
<td>502</td>
<td>1.45 (1.18–1.87)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Non-cancer non-vascular deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Respiratory disease</td>
<td>22</td>
<td>73,342</td>
<td>915</td>
<td>1.67 (1.44–1.92)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Digestive system (except liver) disease</td>
<td>13</td>
<td>32,943</td>
<td>173</td>
<td>1.72 (1.24–2.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endocrine, nutritional, and metabolic disease</td>
<td>8</td>
<td>24,505</td>
<td>180</td>
<td>1.64 (0.97–2.77)</td>
<td>0.063</td>
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<tr>
<td>Nervous system disorder</td>
<td>11</td>
<td>37/3/7</td>
<td>280</td>
<td>0.90 (0.64–1.28)</td>
<td>0.559</td>
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<tr>
<td>External causes (violence/suicide/trauma)</td>
<td>19</td>
<td>74,631</td>
<td>356</td>
<td>1.26 (1.05–1.52)</td>
<td>0.014</td>
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<tr>
<td>Unclassified deaths</td>
<td>9</td>
<td>30,455</td>
<td>786</td>
<td>1.57 (1.37–1.81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>Placebo (N=2347)</td>
<td>50 mg (N=2170)</td>
<td>150 mg (N=2284)</td>
<td>300 mg (N=2233)</td>
<td>P-trend</td>
</tr>
<tr>
<td>--------------------</td>
<td>------------------</td>
<td>----------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>--------</td>
</tr>
<tr>
<td>Any SAE</td>
<td>12.0</td>
<td>11.4</td>
<td>11.7</td>
<td>12.3</td>
<td>0.43</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0.24</td>
<td>0.30</td>
<td>0.37</td>
<td>0.52</td>
<td>0.002</td>
</tr>
<tr>
<td>Any infection</td>
<td>2.86</td>
<td>3.03</td>
<td>3.13</td>
<td>3.25</td>
<td>0.12</td>
</tr>
<tr>
<td>Fatal infection</td>
<td>0.18</td>
<td>0.31</td>
<td>0.28</td>
<td>0.34</td>
<td>0.09/0.02*</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>0.23</td>
<td>0.27</td>
<td>0.28</td>
<td>0.30</td>
<td>0.49</td>
</tr>
<tr>
<td>Any Malignancy</td>
<td>1.88</td>
<td>1.85</td>
<td>1.69</td>
<td>1.72</td>
<td>0.31</td>
</tr>
<tr>
<td>Fatal Malignancy</td>
<td>0.64</td>
<td>0.55</td>
<td>0.50</td>
<td>0.31</td>
<td>0.0007</td>
</tr>
<tr>
<td>Arthritis</td>
<td>3.32</td>
<td>2.15</td>
<td>2.17</td>
<td>2.47</td>
<td>0.002</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>1.67</td>
<td>1.21</td>
<td>1.12</td>
<td>1.30</td>
<td>0.04</td>
</tr>
<tr>
<td>Gout</td>
<td>0.80</td>
<td>0.43</td>
<td>0.35</td>
<td>0.37</td>
<td>0.0001</td>
</tr>
<tr>
<td>ALT &gt; 3x normal</td>
<td>1.4</td>
<td>1.9</td>
<td>1.9</td>
<td>2.0</td>
<td>0.19</td>
</tr>
<tr>
<td>Bilirubin &gt; 2x normal</td>
<td>0.8</td>
<td>1.0</td>
<td>0.7</td>
<td>0.7</td>
<td>0.34</td>
</tr>
</tbody>
</table>

* P-value for combined canakinumab doses vs placebo

**CANTOS: Additional Non-Cardiovascular Clinical Benefits**

**CANCER MORTALITY**

- Placebo: 1.0 (95% CI: 0.86-1.14)
- Canakinumab 50 mg: 0.86* (0.61-1.24)
- Canakinumab 150 mg: 0.78 (0.54-1.13)
- Canakinumab 300 mg: 0.45 (0.23-0.75)

P-trend across groups = 0.0007

**CANTOS: Additional Non-Cardiovascular Clinical Benefits**

**INCIDENT LUNG CANCER**

- Placebo: 1.0 (95% CI: 1.00-1.00)
- Canakinumab 50 mg: 0.77 (0.57-1.03)
- Canakinumab 150 mg: 0.69 (0.49-1.00)
- Canakinumab 300 mg: 0.53 (0.33-0.81)

P-trend across groups = 0.0003

**CANTOS: Additional Non-Cardiovascular Clinical Benefits**

**FATAL LUNG CANCER**

- Placebo: 1.0 (95% CI: 1.00-1.00)
- Canakinumab 50 mg: 0.71 (0.50-1.00)
- Canakinumab 150 mg: 0.64 (0.43-1.00)
- Canakinumab 300 mg: 0.56 (0.35-0.88)

P-trend across groups = 0.0002

**Canakinumab 300 mg**

51% reduction in death from any cancer
P = 0.0009

**Canakinumab 300 mg**

67% reduction in incident lung cancer
P = 0.0009

**Canakinumab 300 mg**

17% reduction in fatal lung cancer
P = 0.0002
CANTOS: Canakinumab Anti-Inflammatory Thrombosis Outcomes Study

• supports the concept of causal anti-inflammatory therapy in atherosclerosis
• offers the perspective of tailored indication, treatment & monitoring of anti-inflammatory therapy in secondary prevention in high risk patients
• need to proof the transition of this concept to patients with AMI
• safety has to be further evaluated in post-trial registries in cardiology and oncology, as with other anti-inflammatory agents tested in ongoing trials