Discussion of CANTOS
"Relationship of CRP Reduction to Cardiovascular Event Reduction Following Treatment with Canakinumab"

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Atherosclerotic Cardiovascular Disease (CVD)

circulating apoB-lipoproteins (LDL, remnant lipoproteins)

Subendothelial apoB-lipoproteins
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Subendothelial apoB-lipoproteins

Disturbed blood flow
Systemic risk factors (smoking, diabetes, etc.)

Genetic factors
Age/clonal hematopoiesis

Inflammation
Defective resolution of inflammation
Atherosclerotic Cardiovascular Disease (CVD)

- Circulating apoB-lipoproteins (LDL, remnant lipoproteins)
- Subendothelial apoB-lipoproteins
  - Disturbed blood flow
  - Systemic risk factors (smoking, diabetes, etc.)
- Inflammation
- Defective resolution of inflammation
- Atherosclerosis
- CVD
Proven Therapeutic Approach

- Circulating apoB-lipoproteins (LDL, remnant lipoproteins)

↓ Subendothelial apoB-lipoproteins

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Highly Intensive LDL Lowering in Highest Risk Patients

- Circulating apoB-lipoproteins (LDL, remnant lipoproteins)

↓↓ Subendothelial apoB-lipoproteins

- Disturbed blood flow
- Systemic risk factors (smoking, diabetes, etc.)

↓↓ Inflammation

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Unproven Therapeutic Hypothesis

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↓ Inflammation

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Key Issues About Targeting Inflammation

• Is there a *dominant* inflammatory factor?

• Will *compensatory* responses to anti-inflammatory therapy prevent efficacy?

• Will compromise of *host defense* cause unacceptable adverse events?
The Premise of CANTOS

Subendothelial apoB-LPs
Cholesterol

Disturbed blood flow
Genetic factors
Systemic risk factors
Age/clonal hematopoiesis

IL-1β

Atherosclerosis

CVD
(Major Adverse Cardiac Events-MACE)

IL-6

liver
thrombotic factors
CRP

Libby and others
CANTOS
Anti-IL-1β Therapy of High-Risk Subjects

Ridker et al. (2017) *NEJM* 377:119-1131
CANTOS
A Landmark Study

- Conceptual advance: inflammation, importance of IL-1β in atherosclerotic CVD
- Future promise of targeting inflammation to combat CVD

Ridker et al. (2017) *NEJM* 377:119-1131
CANTOS

Issues Arising From the Original Analysis

• Dose effect
• Host defense
• ? Similar benefit by lowering LDL further ?
• Cardiovascular mortality
• Is benefit related to level of inflammation suppression
Host Defense
Fatal Infections or Sepsis

Incidence rates of fatal infections or sepsis per 100 person-years

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.00</td>
</tr>
<tr>
<td>50-mg</td>
<td>0.12</td>
</tr>
<tr>
<td>150-mg</td>
<td>0.24</td>
</tr>
<tr>
<td>300-mg</td>
<td>0.36</td>
</tr>
<tr>
<td>All doses</td>
<td>0.36</td>
</tr>
</tbody>
</table>

$P = 0.02$
CANTOS

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Room to Move in Lowering LDL?

FOURIER

Statin + Placebo

Statin + Evolocumab

HR = 0.85 for MACE (P<0.001)

Sabatine et al. (2017) NEJM 376:1713-1722
? Room to Move in Lowering LDL ?

FOURIER

CANTOS mean LDL = 82.8 mg/dl

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CANTOS
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CANTOS: CRP-Response Subgroup Analysis

Implications

• Strengthens biological premise

• Addresses issues of concern from original analysis
  • Greater MACE effect in responders with all 3 doses
  • Reduced CV and all-cause mortality in responders

• Fatal infections were similar among responders and non-responders
  • Potential for higher benefit:risk ratio in responders
  • ? Mechanism ?

• Hypothesis-generating for future prospective studies using a targeted approach
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Where do we go from here?

• Further prospective testing of anti-inflammatory Rx
  • Optimize efficacy and minimize adverse effects via targeted approach and infectious disease monitoring
    • Optimize route of delivery and lower cost, *e.g.*, oral inflammasome inhibitors
    • ? Use in primary prevention in select subjects
    • Integration with intense LDL lowering
  • Integration with drugs for diabetes that show a CV-protective effect (*SGLT2* inhibitors, liraglutide)
  • Drugs that enhance resolution of inflammation
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Treatment of High-Risk Patients

- Untreated
- Maximum statin effect
- Intense LDL lowering or targeted Inflamm Rx
- Intense LDL lowering and targeted Inflamm Rx

Relative CV risk
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Nature's Way of Resolving Inflammation May Spare Host Defense

Inflammatory response

Cytokines (e.g., IL-1β, TNFα)

Kill pathogens

... but at the expense of collateral tissue damage
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Inflammatory response

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Lipid and protein resolution mediators (e.g., resolvins, IL-10)
- Dampen inflammation
- Repair tissue damage
- Clear residual pathogens
Advanced human atheroma have impaired resolution and are deficient in resolution mediators
Therapeutic Potential of Resolving Mediator Therapy in the Post-CANTOS Era

• Advanced human atheroma have impaired resolution and are deficient in resolution mediators

• Resolution mediator therapy blocks plaque progression in animal models of advanced atherosclerosis
The Outlook for Testing Inflammation-
Targeting Strategies

Pre-CANTOS
The Outlook for Testing Inflammation-Targeting Strategies

Pre-CANTOS

Post-CANTOS