Inflammation and atherosclerosis: taming the fire

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Presenter Disclosures

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**Equity:** DalCor
Inflammation and immunity in atherosclerosis
Inflammation in atherosclerosis: The Future?

We need a series of studies to test the conjecture that a direct anti-inflammatory intervention will improve cardiovascular outcomes of patients with atherosclerosis beyond current standard care including high-dose statin.
5-LO as a potential therapeutic CV target

Cell Membrane Phospholipids

- Phospholipases
  - Steroids inhibit

Other lipoxygenases

- 5-Lipoxygenase

Arachidonic acid

- Cyclooxygenase
  - Aspirin, indomethacin inhibit

HETEs → HPETEs

5-HPETE

5-HETE (chemotaxis)

Leukotriene B4 (chemotaxis)

- Leukotriene A4 (LTA4)

- Leukotriene C4 (LTC4)

- Leukotriene D4 (LTD4)

- Leukotriene E4 (LTE4)

Vasoconstriction

Bronchospasm

Increased permeability

Prostaglandin G2 (PGG2)

Prostaglandin H2 (PGH2)

Prostacyclin (Causes vasoilation, inhibits platelet aggregation)

Thromboxane A2 (Causes vasoconstriction, promotes platelet aggregation)

PGD2

PGE2

PGF2α

Vasodilation

Potentiate edema
VIA-2291 Decreases ex Vivo Whole Blood LTB4 Production from Baseline through Week 12

** p < 0.0001 ANCOVA Change from Baseline

Error Bars represent 95% CI

Significant Decrease in hs-CRP in VIA-2291 100 mg Group versus Placebo at 24 Weeks
Change in non-calcified plaque volume and patients with new plaque lesions on serial coronary CT scans in the VIA-2291 groups versus placebo at 24 Weeks

Plaque volume (mm$^3$)

Pts with new plaques (%)

Dose-dependent reduction in biomarkers of cardiac damage observed in the first 24 hours

Effects of the P-Selectin Antagonist Inclacumab on Myocardial Damage After Percutaneous Coronary Intervention for Non–ST-Segment Elevation Myocardial Infarction

Results of the SELECT-ACS Trial

Jean-Claude Tardif, MD,* Jean-François Tanguay, MD,* Scott S. Wright, MD,† Valérie Duchatelle, MD,* Thibaut Petroni, MD,* Jean C. Grégoire, MD,* Reda Ibrahim, MD,* Therese M. Heinonen, DVM,‡ Stephen Robb, MD,§ Olivier F. Bertrand, MD, PhD,¶ Daniel Cournoyer, MSc,‡ Dominique Johnson, PhD,‡ Jessica Mann, MD, PhD,§ Marie-Claude Guertin, PhD,‡ Philippe L. L’Allier, MD*
The SELECT-ACS trial

**Percent change in troponin I over time**

Change at 24 hrs with inclacumab 20 mg/kg vs pbo:
diabetics -33.2%, non-diabetics -31.6% (p=0.03)

Tardif et al. J Am Coll Cardiol 2013;61:2048-2055
The inflammasome and secretion of interleukin-1
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA
Persistent Elevation of 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

Randomized
Canakinumab 50 mg
SC q 3 months

N = 10,000

Primary Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death

Secondary Endpoints: Total Mortality, New Onset Diabetes, Other Vascular Events

Exploratory Endpoints: DVT/PE; SVT; hospitalizations for CHF; PCI/CABG; biomarkers
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Group</th>
<th>HR* (95% CI)</th>
<th>Endpoint</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wichita</td>
<td>RA</td>
<td>0.4 (0.2 - 0.8)</td>
<td>Total Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.3 (0.2 - 0.7)</td>
<td>CV Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.4 (0.3 - 0.8)</td>
<td>CV Mortality</td>
<td>LDM &lt; 15 mg/wk</td>
</tr>
<tr>
<td>Netherlands</td>
<td>RA</td>
<td>0.3 (0.1 - 0.7)</td>
<td>CVD</td>
<td>LDM only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 (0.1 - 0.5)</td>
<td>CVD</td>
<td>LDM + SSZ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 (0.1 - 1.2)</td>
<td>CVD</td>
<td>LDM + HCQ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2 (0.1 - 0.5)</td>
<td>CVD</td>
<td>LDM + SSZ + HCQ</td>
</tr>
<tr>
<td>Miami VA PsA</td>
<td>RA</td>
<td>0.7 (0.6 - 0.9)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5 (0.3 - 0.8)</td>
<td>CVD</td>
<td>LDM &lt; 15 mg/wk</td>
</tr>
<tr>
<td></td>
<td>RA</td>
<td>0.8 (0.7 - 1.0)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6 (0.5 - 0.8)</td>
<td>CVD</td>
<td>LDM &lt; 15 mg/wk</td>
</tr>
<tr>
<td>CORRONA</td>
<td>RA</td>
<td>0.6 (0.3 - 1.2)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.4 (0.2 - 0.8)</td>
<td>CVD</td>
<td>TNF-inhibitor</td>
</tr>
<tr>
<td>QUEST-RA</td>
<td>RA</td>
<td>0.85 (0.8 - 0.9)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.82 (0.7 - 0.9)</td>
<td>MI</td>
<td>LDM</td>
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<tr>
<td></td>
<td></td>
<td>0.89 (0.8 - 1.0)</td>
<td>Stroke</td>
<td>LDM</td>
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<tr>
<td>UK Norfolk</td>
<td>RA, PsA</td>
<td>0.6 (0.4 - 1.0)</td>
<td>Total Mortality</td>
<td>LDM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5 (0.3 - 1.1)</td>
<td>CV Mortality</td>
<td>LDM</td>
</tr>
</tbody>
</table>
Cardiovascular Inflammation Reduction Trial (CIRT)
Primary Aims

- To directly test the inflammatory hypothesis of atherothrombosis
- To evaluate in a randomized, double-blind, placebo-controlled trial whether MTX given at a target dose of 20 mg po weekly over a three-year period will reduce rates of recurrent myocardial infarction, stroke, or cardiovascular death among patients with a prior history of myocardial infarction and either type 2 diabetes or metabolic syndrome.

N = 7,000  NHLBI-Sponsored
Enrollment Started June 2013
350 US and Canadian Sites
In patients with acute pericarditis, colchicine, when added to conventional anti-inflammatory therapy, significantly reduced the rate of incessant or recurrent pericarditis.
The effect of adding colchicine became evident early, continued to accrue over time, and was largely driven by a reduction in ACS unrelated to stent disease.

Colchicine Cardiovascular Outcomes Trial (COLCOT)

Post-MI ≤30 days (n=4500 patients)
On statin, anti-platelet agents, ±RAASi, ±BB

Treated according to natl guidelines
PCI completed if applicable

Colchicine 0.5 mg daily
Placebo

Primary endpoint: CV death, cardiac arrest, MI, stroke, urgent hospitalization for angina requiring coronary revasc.

Secondary endpoints: Components of primary, total mortality; CV death, cardiac arrest, MI, stroke

Sponsored by Quebec Gov. and CIHR
Primary Endpoint:

Time from randomization to the first cardiovascular event

Cardiovascular Event includes:

- Cardiovascular death
- Resuscitated cardiac arrest
- Acute MI
- Stroke
- Urgent hospitalization for angina requiring coronary revascularization
Secondary Endpoints: Time from randomization to:

- Total mortality
- Components of the primary endpoint
- Composite of:
  - CV death
  - Resuscitated Cardiac Arrest
  - Acute MI
  - Stroke

Exploratory Endpoints: Time from randomization to:

- Deep venous thrombosis, pulmonary embolus
- Atrial fibrillation
- Heart failure hospitalization
- Coronary revascularization
**Percent change in hs-CRP (dal-OUTCOMES)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo-adjusted GM % change in hs-CRP</th>
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<tbody>
<tr>
<td></td>
<td>GG</td>
</tr>
<tr>
<td>3 months (n= 5211)</td>
<td>**</td>
</tr>
<tr>
<td></td>
<td>AG</td>
</tr>
<tr>
<td>24 months (n= 1701)</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>AA</td>
</tr>
<tr>
<td>36 months (n= 2424)</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>End of trial (n= 5243)</td>
<td>**</td>
</tr>
</tbody>
</table>

**Significance Levels**
- **P < 0.001**
- *P < 0.05*
- NS P > 0.05

Treatment Effect by Genotypes

Tested for main study primary outcome or unanticipated coronary revascularization (Primary PGx endpoint)

**Treatment Effect by Genotypes**

**ADCY9 rs1967309**

**GG**

Cumulative incidence curve genotype GG

<table>
<thead>
<tr>
<th>Time to event (days)</th>
<th>Dalcetrapib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>933</td>
<td>956</td>
</tr>
<tr>
<td>200</td>
<td>870</td>
<td>898</td>
</tr>
<tr>
<td>400</td>
<td>820</td>
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<td>778</td>
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<tr>
<td>1000</td>
<td>329</td>
<td>339</td>
</tr>
<tr>
<td>1200</td>
<td>74</td>
<td>75</td>
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</tbody>
</table>

**AG**

Cumulative incidence curve genotype AG

<table>
<thead>
<tr>
<th>Time to event (days)</th>
<th>Dalcetrapib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1313</td>
<td>1342</td>
</tr>
<tr>
<td>200</td>
<td>1242</td>
<td>1253</td>
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<tr>
<td>400</td>
<td>1189</td>
<td>1211</td>
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<tr>
<td>600</td>
<td>1159</td>
<td>1170</td>
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<tr>
<td>800</td>
<td>937</td>
<td>946</td>
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<tr>
<td>1000</td>
<td>504</td>
<td>504</td>
</tr>
<tr>
<td>1200</td>
<td>120</td>
<td>119</td>
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</table>

**AA**

Cumulative incidence curve genotype AA

<table>
<thead>
<tr>
<th>Time to event (days)</th>
<th>Dalcetrapib</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>462</td>
<td>452</td>
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<tr>
<td>200</td>
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<td>200</td>
<td>186</td>
</tr>
<tr>
<td>1200</td>
<td>51</td>
<td>33</td>
</tr>
</tbody>
</table>

**Events:**

main study primary outcome or unanticipated coronary revascularization
Personalized therapy for inflammation in atherosclerosis?

Subsets of patients with atherosclerosis might particularly benefit from a direct anti-inflammatory intervention to improve CV outcomes, and better characterization including with pharmacogenomics should be considered.