Hot Stuff: How Can Measurement of Inflammation Guide Precision in Today’s Prevention Practice

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Relevant Disclosures

• Research grants to my institution
  – Amgen, Merck, Eisai, Astra Zeneca, Novartis, The Medicines Company

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  – Medscape, Merck, Servier, Amgen

• Consultant
  – Daiichi Sankyo, Servier, Lexicon, Kowa, Merck, Novartis, Novo Nordisk, NIH
A Quarter of a Century of Treating LDL-C

For LDL-C, 1 mmol/L = 38.67 mg/dL.

Courtesy of M. Sabatine and R. Giugliano
Are we done?

Despite improvements in CV outcomes with aggressive lipid lowering, there remains significant residual risk for recurrent CV events.
Residual Risk in PCSK9i Trials

Annualized Event Rates of 3-4% per year despite ↓↓LDL-C

Consider the Following Case

- Mr LP is a 65yo M with prior MI, T2DM, obesity (BMI 30).
- Meds: On ASA, atorvastatin 80, metformin
- Labs: LDL 80mg/dL, Cr 1.5, hsCRP 3.5, HbA1c 7.5%, Lp(a) 50

What are Mr. LP’s drivers of residual CV risk?
What are the determinants of residual risk?

Adapted from Ridker, P. JACC 2018;72(25).

**Known ASCVD**

High Intensity Statin

**Residual Risk**
- Conventional (HTN, smoking, DM, obesity)

**Biomarker**
- Many
- LDL-C>70
- hsCRP>2
- TG>150
- Lp(a)>50

**RCT Evidence**
- DM – SGLT2i, GLP-1RA
  - Obesity – SELECT*
- IMPROVE-IT, FOURIER, SPIRE, ODYSSEY, ORION-4*
- CANTOS
- COMPASS, DAPT, PEGASUS
- REDUCE-IT, STRENGTH*, PROMINENT*
- Pending

*Results pending*
Inflammation: In the Causal Pathway of ASCVD

ASCVD, atherosclerotic cardiovascular disease.
Lower LDL and lower CRP Associated with Lower Rates of CV Events in PROVE IT

Lower LDL and lower CRP Associated with Lower Rates of CV Events in PROVE IT

LDL > 70 mg/dL, CRP > 2 mg/L
LDL > 70 mg/dL, CRP < 2 mg/L
LDL < 70 mg/dL, CRP > 2 mg/L
LDL < 70 mg/dL, CRP < 2 mg/L
LDL < 70 mg/dL, CRP < 1 mg/L


For LDL-C, 1 mmol/L = 38.67 mg/dL.
Lower LDL and lower CRP Associated with Lower Rates of CV Events in IMPROVE IT

<table>
<thead>
<tr>
<th>1 Yr Mean</th>
<th>LDL-C</th>
<th>hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simva</td>
<td>69.9</td>
<td>3.8</td>
</tr>
<tr>
<td>EZ/Simva</td>
<td>53.2</td>
<td>3.3</td>
</tr>
<tr>
<td>Absolute Δ</td>
<td>-16.7</td>
<td>-0.5</td>
</tr>
<tr>
<td>% Δ</td>
<td>-24%†</td>
<td>-19%†</td>
</tr>
</tbody>
</table>

CV death, MI, stroke, coronary revasc or UA

- Neither Target: 38.9%
- Only LDL<70mg/dL: 33.4%
- Only hs-CRP<2mg/L: 33.7%
- Both Targets: 28.0%

†p<0.05


For LDL-C, 1 mmol/L = 38.67 mg/dL.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial</th>
<th>CV Event Reduction</th>
<th>LDL-C Lowering</th>
<th>hs-CRP Lowering</th>
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<tbody>
<tr>
<td>Statins</td>
<td>Many</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Statin + Ezetimibe</td>
<td>IMPROVE-IT</td>
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<td>Yes</td>
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<td>PCSK9 inhibitors</td>
<td>FOURIER, SPIRE 1 &amp; 2, ODYSSEY OUTCOMES</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Canakinumab</td>
<td>CANTOS</td>
<td>?</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Low dose MTX</td>
<td>CIRT</td>
<td>?</td>
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*Is the CV benefit due solely to LDL-C lowering or can targeted anti-inflammatory therapy improve outcomes?*
Low Dose MTX Does Not Alter CRP or MACE

IL-1β inhibition reduces MACE without LDL-C change

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<th>LDL-C</th>
<th>hsCRP</th>
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<tr>
<td>Baseline</td>
<td>82.8</td>
</tr>
<tr>
<td>Placebo at 3M</td>
<td>82.0</td>
</tr>
<tr>
<td>Canakinumab at 3M</td>
<td>84.0</td>
</tr>
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</table>

Absolute Δ | 2.0  | -1.7 |
% Δ | 1.1%  | -59%† |

†p<0.05

BMI, body mass index; For LDL-C, 1 mmol/L = 38.67 mg/dL.

CANTOS Trial: Proof of Principle for Role of Residual Inflammatory Risk

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But…Is inflammation still an important, modifiable risk factor in the face of very low LDL-C?


MTX, methotrexate; PCSK9, proprotein convertase subtilisin/kexin type 9.
hsCRP Levels Risk Stratify for CV Events Even When Achieved LDL-C <20 mg/dL

Adjusted* 3 Year Rate of PEP

N=2707

LDL-C (per doubling):
- Adj* HR 1.09 (1.05-1.14)
- p<0.0001

hsCRP (per doubling):
- Adj* HR 1.09 (1.07-1.12)
- p<0.0001

Conclusions:
- LDL-C & hsCRP are independent predictors of CV events
- hsCRP is an important prognostic marker even at very low LDL-C

*Adjusted for age, BMI, sex, race, region, prior MI, prior stroke, PAD, HTN, DM, CHF, smoking, eGFR<60, high-intensity statin, ezetimibe, baseline LDL-C, HDL-C and log(TG)

Fewer CV Events with Low Dose Colchicine after ACS

**COLCOT Trial**

![Graph showing cumulative incidence over months since randomization for placebo and colchicine groups.](image)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Placebo (N=2379)</th>
<th>Colchicine (N=2366)</th>
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</thead>
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<tr>
<td>2379</td>
<td>2261</td>
<td>1854</td>
</tr>
<tr>
<td>2284</td>
<td>1868</td>
<td>1224</td>
</tr>
<tr>
<td>1224</td>
<td>622</td>
<td>628</td>
</tr>
<tr>
<td>622</td>
<td>144</td>
<td>153</td>
</tr>
<tr>
<td>153</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**End Points**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Colchicine (N=2366)</th>
<th>Placebo (N=2379)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
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<tr>
<td>Primary composite end point</td>
<td>131 (5.5)</td>
<td>170 (7.1)</td>
<td>0.77 (0.61–0.96)</td>
<td>0.02†</td>
</tr>
<tr>
<td>Components of primary end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>20 (0.8)</td>
<td>24 (1.0)</td>
<td>0.84 (0.46–1.52)</td>
<td></td>
</tr>
<tr>
<td>Resuscitated cardiac arrest</td>
<td>5 (0.2)</td>
<td>6 (0.3)</td>
<td>0.83 (0.25–2.73)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>89 (3.8)</td>
<td>98 (4.1)</td>
<td>0.91 (0.68–1.21)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>5 (0.2)</td>
<td>19 (0.8)</td>
<td>0.26 (0.10–0.70)</td>
<td></td>
</tr>
<tr>
<td>Urgent hospitalization for angina leading to revascularization</td>
<td>25 (1.1)</td>
<td>50 (2.1)</td>
<td>0.50 (0.31–0.81)</td>
<td></td>
</tr>
<tr>
<td>Secondary composite end point‡</td>
<td>111 (4.7)</td>
<td>130 (5.5)</td>
<td>0.85 (0.66–1.10)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>43 (1.8)</td>
<td>44 (1.8)</td>
<td>0.98 (0.64–1.49)</td>
<td></td>
</tr>
<tr>
<td>Deep venous thrombosis or pulmonary embolus</td>
<td>10 (0.4)</td>
<td>7 (0.3)</td>
<td>1.43 (0.54–3.75)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>36 (1.5)</td>
<td>40 (1.7)</td>
<td>0.93 (0.59–1.46)</td>
<td></td>
</tr>
</tbody>
</table>

Note that predominantly driven by Angina/Revasc

Await Results of LoDoCo2 as Validation of Benefit of Low-Dose Colchicine

LoDoCo2 Trial

*N=5522*

- Proven Clinically Stable CAD on Optimal Medical Therapy

30 day open label colchicine 0.5mg/day

- Colchicine 0.5mg
- Placebo

Primary Endpoint: AC Syndrome, Stroke, Fatal or Nonfatal OoHCA

Secondary Endpoints: Atrial Fibrillation, New Onset Diabetes, CV Death

What can we do right now?

- Elevation of hsCRP is a marker of residual (inflammatory) risk

- Use this information to target modifiable risk factors that impact inflammatory risk (e.g. obesity, sedentary lifestyle, smoking, diabetes)

- Otherwise, continue to optimize other modifiable risk factors (e.g. lipids, blood pressure)
What does that mean for Mr LP?

- Mr LP is a 65yo M with prior MI, T2DM, obesity (BMI 30).
  - Meds: On ASA, atorva 80, metformin
  - Labs: LDL 80mg/dL, Cr 1.5, hsCRP 3.5, HbA1c 7.5%, Lp(a) 50

- Treatment plan:
  - Diet and exercise (beneficial effects on inflammation, weight, diabetes, renal)
  - Add additional lipid lowering therapy (ezetimibe +/- PCSK9i)
  - Add GLP-1RA and/or SGLT2i for diabetes and obesity
  - Consider ticagrelor or rivaroxaban for residual thrombotic risk
Summary

- Inflammation is an independent risk factor for worse CV outcomes
- Pharmacologic interventions limited at this time. Await additional results for benefit of colchicine.
- Carefully consider multiple axes of residual risk and optimize as able, including classic risk factors which contribute to inflammatory risk