How to Intervene in the Pro-Inflammatory State? Clinical Studies in Humans

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Harvard Medical School
Director, Center for Cardiovascular Disease Prevention
Brigham and Women’s Hospital, Boston MA
The magnitude of independent risk associated with inflammation is at least as large, if not larger, than that of BP and cholesterol.

<table>
<thead>
<tr>
<th></th>
<th>Risk Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP</td>
<td>1.37 (1.27-1.48)</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>1.35 (1.25-1.45)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>1.16 (1.06-1.28)</td>
</tr>
<tr>
<td>Non-HDLC</td>
<td>1.28 (1.16-1.40)</td>
</tr>
</tbody>
</table>

Risk Ratio (95%CI) per 1-SD higher usual values

Adjusted for age, gender, smoking, diabetes, BMI, triglycerides, alcohol, lipid levels, and hsCRP.

Emerging Risk Factor Collaborators, Lancet January 2010
JUPITER

Primary Trial Endpoint: MI, Stroke, UA/Revascularization, CV Death

HR 0.56, 95% CI 0.46-0.69
P < 0.00001

Number Needed to Treat (NNT) = 25

- 44 %

Ridker et al NEJM 2008;359:2195-2207
JUPITER
Achieved LDLC, Achieved hsCRP, or Both?

The Real Controversy:
Is the large benefit observed in the JUPITER trial due to lipid lowering, to inflammation inhibition, or to a combination of these two processes?
Intensification of Statin Therapy Results in a Rapid Reduction in Atherosclerotic Inflammation

Results of a Multicenter Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography Feasibility Study

Ahmed Tawakol, MD,*†‡ Zahi A. Fayad, PhD,§‖ Robin Mogg, PhD,‡ Achilles Alon, PhD,§‖ Michael T. Klimas, PhD,‡ Hayes Dansky, MD,§ Sharath S. Subramaniam, MD,‡ Amr Abdelbaky, MD,‡ James H. F. Rudd, MD, PhD,‡ Michael E. Farkouh, MD, MS,‡‖‖ Irene O. Nunes, PhD,‡‖ Chan R. Beals, MD,‡ Sahitha S. Shankar, MD§

Boston, Massachusetts; New York, New York; Whitehouse Station, New Jersey; Cambridge, United Kingdom; and Toronto, Ontario, Canada

Objectives
The study sought to test whether high-dose statin treatment would result in greater reductions in plaque inflammation than low-dose statins, using fluorodeoxyglucose-positron emission tomography/computed tomographic imaging (FDG-PET/CT).

Background
Intensification of statin therapy reduces major cardiovascular events.

Methods
Adults with risk factors or with established atherosclerosis, who were not taking high-dose statins (n = 83), were randomized to atorvastatin 10 versus 80 mg in a double-blind, multicenter trial. FDG-PET/CT imaging of the ascending thoracic aorta and carotid arteries was performed at baseline, 4, and 12 weeks after randomization and targeted to background ratio (TBR) of FDG uptake within the artery wall was assessed while blinded to time points and treatment.

Results
Sixty-seven subjects completed the study, providing imaging data for analysis. At 12 weeks, inflammation (TBR) in the index vessel was significantly reduced from baseline with atorvastatin 80 mg (% reduction [95% confidence interval]: 14.42% [8.1% to 19.9%]; p < 0.001), but not atorvastatin 10 mg (% reduction: 4.2% [2.3% to 10.4%]; p > 0.1). Atorvastatin 80 mg resulted in significant additional relative reductions in TBR versus atorvastatin 10 mg (10.6% [2.2% to 18.3%]; p = 0.01) at week 12. Reductions from baseline in TBR were seen as early as 4 weeks after randomization with atorvastatin 10 mg (6.4% reduction, p < 0.05) and 80 mg (12.5% reduction, p < 0.001). Changes in TBR did not correlate with lipid profile changes.

Conclusions
Statin therapy produced significant rapid dose-dependent reductions in FDG uptake that may represent changes in atherosclerotic plaque inflammation. FDG-PET imaging may be useful in detecting early treatment effects in patients at risk or with established atherosclerosis. (Evaluate the utility of 18F-FDG-PET as a Tool to Quantify Atherosclerotic Plaque: NCT00703265) (J Am Coll Cardiol 2013;62:909–17) © 2013 by the American College of Cardiology Foundation.

Can Targeted Anti-Inflammatory Therapy Reduce Cardiovascular Event Rates and Prolong Life?
Targeting Inflammatory Pathways for the Treatment of Cardiovascular Disease

- Vessel Wall
  - 5-LO Inhibitors
  - FLAP Inhibitors
- Macrophage/Monocyte
  - Anti-CAMs
  - SIRT activators
  - CCR2 CCR5 Antagonists
- Adipose Tissue
  - Leukotriene Function
  - MMP-9
  - Adalimumab
  - Infliximab
  - Tocilizumab
  - Low Dose Methotrexate
  - Darapladib
  - Varespladib
  - Lp-PLA2
  - sPLA2
- NLRP3 Inflammasome
  - Canakinumab
  - Anakinra
  - Colchicine

Upstream Targets and Biomarkers
- Downstream Targets and Biomarkers

Vascular risk hsCRP (mg/L)
- High: > 3 mg/L
- Intermediate: 1-3 mg/L
- Low: < 1 mg/L

CRP RNA - Antisense Anti-CRP

PAI-1
Fibrinogen
SAA
IL-6 and Risk of Future MI in Apparently Healthy Men

$P = 0.01$

$P = 0.003$

$P = 0.3$

$P_{\text{Trend}} = 0.001$

Relative Risk of MI

Quartile of IL-6 (range, pg/dL)

1

2

3

4

$\leq 1.04$

1.04-1.46

1.47-2.28

$\geq 2.28$

0

1

2

3

4

Ridker et al, Circulation 2000;101:1767-1772
Relationship of IL-6 and Future Cardiovascular Events

Kaptoge et al, Eur Heart J 2013
Mendelian Randomization and the IL-6 Regulatory Pathway

Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies

IL6R Genetics Consortium and Emerging Risk Factors Collaboration*

Summary
Background Persistent inflammation has been proposed to contribute to various stages in the pathogenesis of cardiovascular disease. Interleukin-6 receptor (IL6R) signalling propagates downstream inflammation cascades. To assess whether this pathway is causally relevant to coronary heart disease, we studied a functional genetic variant known to affect IL6R signalling.

The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis

The Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium*

Summary
Background A high circulating concentration of interleukin 6 is associated with increased risk of coronary heart disease. Blockade of the interleukin-6 receptor (IL6R) with a monoclonal antibody (tocilizumab) licensed for treatment of rheumatoid arthritis reduces systemic and articular inflammation. However, whether IL6R blockade also reduces risk of coronary heart disease is unknown.
Effects of Polymorphism in the IL-6 Receptor Signaling Pathway On Downstream CRP Levels and Risks of Coronary Heart Disease

CRP Reduction (%) | Hazard Ratio CHD
---|---

- **rs2228145**
  - 1/1: CRP Reduction (%)
  - 1/2: CRP Reduction (%)
  - 2/2: CRP Reduction (%)

- **rs7529229**
  - C/C: Hazard Ratio for CHD
  - C/T: Hazard Ratio for CHD
  - T/T: Hazard Ratio for CHD

Sawar N et al, Lancet 2012;379;1205-13
Swerdlow et al, Lancet 2012;379;1214-24
Effects of Polymorphism in the IL-6 Receptor Signaling Pathway On Downstream CRP Levels and Risks of Coronary Heart Disease

Sawar N et al, Lancet 2012;379;1205-13
Swerdlow et al, Lancet 2012;379;1214-24
Testing the Inflammatory Hypothesis of Atherothrombosis: Do we attack the biomarker or attack the process?
Effect of Antisense Oligonucleotide Inhibitor of C-Reactive Protein Synthesis On the Endotoxin Challenge Response in Healthy Volunteers

Dose-dependent reductions in CRP (highly specific) without any impact on upstream cytokines (TNF-1 or IL-6), coagulation (D-dimer or F1+2), or clinical signs and symptoms (heart rate, temperature, blood pressure).

Novek / Ridker, JAHA 2014
### Issues in the Selection of Anti-inflammatory Agents for Trials of Cardiovascular Inflammation Inhibition

<table>
<thead>
<tr>
<th></th>
<th>Statins</th>
<th>TNF inhibition</th>
<th>IL-6 Inhibition</th>
<th>LDM</th>
<th>IL-1β inhibition</th>
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<tbody>
<tr>
<td>TC</td>
<td>↓↓</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>LDL</td>
<td>↓↓</td>
<td>↑</td>
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<tr>
<td>HDL</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
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<tr>
<td>TG</td>
<td>⊃</td>
<td>↑</td>
<td>↑</td>
<td></td>
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<tr>
<td>Chylo</td>
<td>⊃</td>
<td>↑</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP / IL-6</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
For More Information:

theCIRT.org  theCANTOS.org
Cardiovascular Inflammation Reduction Trial (CIRT) (Ridker PI) 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 to Start June 2013
350 US and Canadian Sites
Methotrexate Inhibits Atherogenesis in Cholesterol-fed Rabbits

Bulgarelli et al, J Cardiovasc Pharmacol 2012;59:308-14
MTX Down Regulates 5 Pro-inflammatory Genes in TNF treated HUVECs

Bulgarelli et al, J Cardiovasc Pharmacol 2012;59:308-14
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Group</th>
<th>HR (95 % CI)</th>
<th>Endpoint</th>
<th>Exposure</th>
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<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>Choi 2002</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>
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<tr>
<td>Netherlands</td>
<td>RA</td>
<td>0.3 (0.1 – 0.7)</td>
<td>CVD</td>
<td>LDM only</td>
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<tr>
<td>van Helm 2006</td>
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<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</td>
<td>PsA</td>
<td>0.7 (0.6 – 0.9)</td>
<td>CVD</td>
<td>LDM</td>
</tr>
<tr>
<td>Pradanovich 2005</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>
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<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>
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<tr>
<td>Solomon 2008</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>
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<tr>
<td>Narango 2008</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>
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<tr>
<td>2008</td>
<td></td>
<td>0.5 (0.3 – 1.1)</td>
<td>CV Mortality</td>
<td>LDM</td>
</tr>
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</table>
Cardiovascular Inflammation Reduction Trial (CIRT) website

What is the Cardiovascular Inflammation Reduction Trial (CIRT)?

CIRT is a major new randomized trial sponsored by the US National Heart, Lung and Blood Institute. CIRT will directly test whether a common anti-inflammatory drug used for the treatment of rheumatoid arthritis (low dose methotrexate) can reduce the risk of heart attack, stroke, and cardiovascular death in patients who have suffered a prior heart attack.

Why worry about inflammation?

Inflammation plays a major role in heart attack and stroke. While inflammation is as important as cholesterol and high blood pressure, no clinical trial has tested whether reducing inflammation can reduce rates of these life-threatening disorders.

Who is eligible for CIRT?

Men and women who have suffered a prior heart attack and who have either type 2 diabetes or metabolic syndrome, two conditions associated with a pro-inflammatory state.
Cardiovascular Inflammation Reduction Trial (CIRT)
Simplified Flow Diagram – Five Phases to the Trial

1. 5 Week Open Label Run-In
2. 4 Month 15mg MTX Versus Placebo
3. 3 to 5 Years Variable Dose Methotrexate Versus Placebo Phase
4. 3 Month Washout Phase

MI / MVCAD
T2DM or Metabolic Syndrome

Office Visits
Safety Eval
Banked Plasma

Enrollment
Pre-randomization
Month 8
Month 24

MI Stroke CV Death Other Endpoints
Open Sites - 371
Total Randomized

May 15, 2015
Total randomized = 1,780
US = 1,571
Canada = 209
### Issues in the Selection of Anti-inflammatory Agents for Trials of Cardiovascular Inflammation Inhibition

<table>
<thead>
<tr>
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<tr>
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<td>↓↓</td>
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<td>↔</td>
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</tr>
<tr>
<td>LDL</td>
<td>↓↓</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>HDL</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
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<tr>
<td>TG</td>
<td>↔</td>
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<td>↔</td>
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<tr>
<td>Chylo</td>
<td>↔</td>
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</tr>
<tr>
<td>CRP / IL-6</td>
<td>↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓</td>
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</tr>
</tbody>
</table>
The Balance of IL-1 and IL-1Ra: Key Regulatory Proteins for Innate Immunity

Pro-Inflammatory

IL-1α
IL-1β

Anti-Inflammatory

IL-1Ra

IL-1R
Application of IL-1β promotes arterial intimal thickening in porcine coronary artery

Shimokawa et al. (1996) J Clin Invest 97:769

Lack of IL-1β decreases severity of atherosclerosis in ApoE-deficient mice

NLRP3 Cryopyrin Inflammasome, Caspase-1, and IL-1β Maturation
Endogenous Danger Signals in Vascular Biology?

Crystals activate the NLRP3 inflammasome

exogenous particles

Alum  Silica  Asbestos

endogenous material

Cholesterol  Uric acid

Courtesy Eicke Latz  Phase transition from soluble to crystalline as a “danger signal”
Vascular Medicine

Sterol Regulatory Element Binding Protein 2 Activation of NLRP3 Inflammasome in Endothelium Mediates Hemodynamic-Induced Atherosclerosis Susceptibility

Han Xiao, MD, PhD; Min Lu, MD, PhD; Ting Yang Lin, MS; Zhen Chen, PhD; Gang Chen, MD; Wei-Chi Wang, PhD; Traci Marin, MS; Tzu-pin Shentu, PhD; Liang Wen, PhD; Brendan Gongol, MS; Wei Sun, MD; Xiao Liang, MD, PhD; Ju Chen, PhD; Hsien-Da Huang, PhD; Joao H.F. Pedra, PhD; David A. Johnson, PhD; John Y-J. Shyy, PhD


Editorial

Atheroprone Flow Activation of the Sterol Regulatory Element Binding Protein 2 and Nod-Like Receptor Protein 3 Inflammasome Mediates Focal Atherosclerosis

Jun-ichi Abe, MD, PhD; Bradford C. Berk, MD, PhD

Canakinumab (Ilaris, Novartis)

- high-affinity human monoclonal anti-human interleukin-1β (IL-1β) antibody currently indicated for the treatment of IL-1β driven inflammatory diseases (Cryopyrin-Associated Period Syndrome [CAPS], Muckle-Wells Syndrome)
- designed to bind to human IL-1β and functionally neutralize the bioactivity of this pro-inflammatory cytokine
- long half-life (4-8 weeks) with CRP and IL-6 reduction for up to 3 months
Effects of Interleukin-1β Inhibition With Canakinumab on Hemoglobin A1c, Lipids, C-Reactive Protein, Interleukin-6, and Fibrinogen

A Phase IIb Randomized, Placebo-Controlled Trial

Paul M Ridker, MD, MPH; Campbell P. Howard, MD; Verena Walter, Dipl Math (FH); Brendan Everett, MD; Peter Libby, MD; Johannes Hensen, MD; Tom Thuren, MD, PhD, on behalf of the CANTOS Pilot Investigative Group

Canakinumab Dose (mg/month)

Median Reduction (%)

Fibrinogen

Interleukin-6

C-reactive Protein

Ridker PM, et al; Circulation 2012; 126:2739-2748
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) (Ridker PI)

Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA
Persistent Elevation of hsCRP ($> 2$ mg/L)

Randomized
Canakinumab 50 mg SC q 3 months

Randomized
Canakinumab 150 mg SC q 3 months

Randomized
Canakinumab 300 mg SC q 3 months

Randomized
Placebo SC q 3 months

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

N = 10,000
Novartis

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) (Ridker PI)
CANTOS Trial Update

N = 10,065
## CANTOS Trial Update

### Enrollment laboratory values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Range</th>
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<tbody>
<tr>
<td>hsCRP</td>
<td>4.3 (2.9-7.3) mg/L</td>
<td></td>
</tr>
<tr>
<td>LDLC</td>
<td>2.2 (1.7-2.8) mmol/L</td>
<td>84 (66-109)  mg/dL</td>
</tr>
<tr>
<td>HDLC</td>
<td>1.1 (1.0-1.4) mmol/L</td>
<td>44 (37-52)   mg/dL</td>
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<tr>
<td>TC</td>
<td>4.2 (3.6-4.9) mmol/L</td>
<td>161 (139-191) mg/dL</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>1.6 (1.2-2.2) mmol/L</td>
<td>140 (101-195) mg/dL</td>
</tr>
<tr>
<td>SBP</td>
<td>130 (120-140) mmHg</td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>79 (72-84) mmHg</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>29.8 (26.6-33.8) kg/m²</td>
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<tr>
<td>HbA1c</td>
<td>6.0 (5.6-6.7) %</td>
<td></td>
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<tr>
<td>Diabetic type II</td>
<td>38 %</td>
<td></td>
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<tr>
<td>eGFR MDRD</td>
<td>79 (64-93) mL/min/1.73m²</td>
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<tr>
<td>Hypertension</td>
<td>79 %</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>76 %</td>
<td></td>
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<tr>
<td>Revascularized</td>
<td>55 %</td>
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What About p38 MAP Kinase Inhibition?
Losmapimod
BID

Randomize 1:1
Double blind

PLACEBO

Study drug prior to any coronary revascularization or fibrinolysis for qualifying event

Losmapimod: A potent p38 MAPK Inhibitor

Hypothesis: losmapimod will attenuate inflammatory processes in the vascular wall, stabilizing plaques and reducing risk of subsequent plaque rupture

Study Treatment for 12 weeks

End of Treatment Visit
(Primary Efficacy Evaluation)

Post-treatment F/U at 24 weeks

1° EP: CV Death, MI, Severe Recurrent Ischemia → Urgent Revasc
Principal 2° EP: CV Death, MI
“The challenges in targeting inflammation in any chronic inflammatory disease lie in three properties that are critical for evolutionary survival: redundancy, compensation, and necessity.”

Monitor for infection, TB, cancer

Balance potential vascular benefits with probable risks
The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study

The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study

Allison C. Morton\textsuperscript{1†}, Alexander M. K. Rothman\textsuperscript{4,2†}, John P. Greenwood\textsuperscript{3}, Julian Gunn\textsuperscript{1,2}, Alex Chase\textsuperscript{4}, Bernard Clarke\textsuperscript{5}, Alistair S. Hall\textsuperscript{3}, Keith Fox\textsuperscript{6}, Claire Foley\textsuperscript{7}, Winston Banya\textsuperscript{7}, Duolao Wang\textsuperscript{8}, Marcus D. Flather\textsuperscript{7,9}, and David C. Crossman\textsuperscript{10*}

hsCRP, Aspirin, and Risks of Future Myocardial Infarction

Relative Risk
Myocardial Infarction

Quartile of C-Reactive Protein

Placebo
Aspirin
Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease

Stefan M. Nidorf, MD, MBBS,* John W. Eikelboom, MBBS,† Charley A. Budgeon, BSc (Hons),‡ Peter L. Thompson, MD§
Perth, Australia; and Hamilton, Ontario, Canada

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Angel Martinez-González, M.D., Ph.D., for the PREDIMED Study Investigators*
Are the anti-inflammatory effects of lipid-lowering relevant for clinical practice?

<table>
<thead>
<tr>
<th>Agent</th>
<th>Event Reduction</th>
<th>LDL-Lowering</th>
<th>CRP-Lowering</th>
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<tbody>
<tr>
<td>Statins</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ezetimibe + Statin</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>PPAR/Fibrates</td>
<td>??</td>
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