Anti-inflammatory therapy in cardiovascular disease

2019 ACP Oklahoma Chapter Scientific Meeting
October 4, 2019

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Relevant Disclosures and Resolution

*Under Accreditation Council for Continuing Medical Education guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.*

• No financial disclosures
Learning Objectives

Upon completion of this session, participants will improve their competence and performance by being able to:

• Describe the role of inflammation in the pathogenesis of atherosclerosis
• Describe the role of anti-inflammatory therapy in the prevention of cardiovascular events
The burden of atherosclerotic cardiovascular disease

Global deaths in 2016 (%)

- Ischaemic heart disease
- Stroke
- Hypertensive heart disease
- Cardiomyopathy
- Atrial fibrillation
- Aortic aneurysm
- Peripheral artery disease
- Other cardiovascular conditions
Pathogenesis of atherosclerotic lesions

Libby P et al. Nat Rev Dis Primers 2019
Complex interactions among components of the innate and adaptive immunity in atherogenesis

Shah PK et al. JACC 2014
Low Grade Systemic Inflammation *Precedes* By Many Years the Onset of Vascular Events

Ridker PM et al. Circulation 2000
Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein


Statins are both lipid lowering and anti-inflammatory, and the greatest benefits of statin therapy accrue to those who not only lower LDL-C, but who also lower hsCRP.
Residual Inflammatory Risk: Addressing the Obverse Side of the Atherosclerosis Prevention Coin

Ridker PM. Eur Heart J 2016;37:1720-22

![Diagram showing the relationship between residual cholesterol and inflammatory risk.

Known Cardiovascular Disease
LDL 150 mg/dL (3.8 mmol/L)
hsCRP 4.5 mg/L
High Intensity Statin

“Residual Cholesterol Risk”
LDL 110 mg/dL (2.8 mmol/L)
hsCRP 1.8 mg/L
Additional LDL Reduction

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

“Residual Inflammatory Risk”
LDL 70 mg/dL (1.8 mmol/L)
hsCRP 3.8 mg/L
Additional Inflammation Reduction

No Prior Proof of Concept

HRI
Heart Rhythm Institute
The University of Oklahoma Health Sciences Center
Can Inflammation Reduction, in the Absence of Lipid Lowering, Reduce Cardiovascular Event Rates?
From CRP to IL-6 to IL-1: Moving Upstream to Identify Novel Targets for Atheroprotection

Canakinumab (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
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

Stable CAD (post MI) Residual Inflammatory Risk (hsCRP ≥ 2 mg/L)

N = 10,061
39 Countries
April 2011 - June 2017
1490 Primary Events

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 (MACE)

Secondary Endpoint: MACE plus Unstable Angina Requiring Urgent Revascularization (MACE+)

“Residual Inflammatory Risk”
Baseline LDLc 82mg/dL (2.1mmol/L) but hsCRP 4.1 mg/L

CANTOS: Dose-Dependent Effects on Inflammatory Biomarkers and Lipids (48 Months)

Placebo SC q 3 mth
Canakinumab 50mg SC q 3 mth
Canakinumab 150mg SC q 3 mth
Canakinumab 300mg SC q 3 mth

Percent Change from Baseline (median)

hsCRP
LDLC
HDL C
TG

Months
0 3 6 9 12 24 36 48

Placebo  Canakinumab 60  Canakinumab 150  Canakinumab 300

CANTOS: Primary Cardiovascular Endpoints

MACE

- Placebo SC q 3 months
- Canakinumab 150/300 mg SC q 3 months

**MACE**

HR 0.85  
95% CI 0.76-0.96  
P = 0.007

**MACE - Plus**

HR 0.83  
95% CI 0.74-0.92  
P = 0.0006

35 - 40% reductions in hsCRP and IL-6
No change in LDLC

CANTOS: Consistency of Effect Across All Patient Groups Defined By Baseline Clinical Characteristics

- **Group**
  - Women
  - Men
  - Age < 60 yrs
  - Age ≥ 60 yrs
  - Diabetes
  - No diabetes
  - Non Smoker
  - Smoker
  - BMI < 30 kg/m²
  - BMI ≥ 30 kg/m²
  - LDL < 80 mg/dL
  - LDL ≥ 80 mg/dL
  - hsCRP < 4 mg/L
  - hsCRP ≥ 4 mg/L
  - HDLC > 45 mg/dL
  - HDLC ≤ 45 mg/dL
  - TG < 150 mg/dL
  - TG ≥ 150 mg/dL
  - Overall

- **MACE**
- **MACE Plus**

Ridker et al Lancet 2018;391:319-328
CANTOS: Greater Risk Reduction With Greater Cytokine Inhibition (MACE)

**On-Treatment hsCRP**
- Placebo
- On-treatment hsCRP ≥ median
- On-treatment hsCRP < median

**On-Treatment IL-6**
- Placebo
- On-treatment IL-6 ≥ median
- On-treatment IL-6 < median

- MACE
  - 25% reduction in risk for those achieving hsCRP below median
  - 5% reduction in risk for those achieving hsCRP above median
  - (No change in LDL cholesterol)

- MACE
  - 36% reduction for those achieving IL-6 below median
  - No benefit for those achieving IL-6 above median
  - (No change in LDL cholesterol)

Lancet 2018;391:319-328
Eur Heart J 2018;39:3499-3507
CANTOS: 31% Reduction in Cardiovascular Mortality and All-Cause Mortality Among Participants with Robust Inhibition of the Inflammatory Response

35 - 40% reductions in hsCRP and IL-6
No change in LDLC

Circulation 2018;137:1763-1766
CIRT: low dose methotrexate for the prevention of atherosclerotic events

- 4786 patients with prior MI with DM or metabolic syndrome
- Methotrexate 15mg to 20mg weekly vs. placebo

Interleukin-1β Inhibition

- IL-1β
- IL-6
- hsCRP
- 15-17% reduction in MACE and MACE+
- 50-70% reduction in Lung Cancer

Low-Dose Methotrexate

- IL-1β
- IL-6
- hsCRP
- No reduction in MACE and MACE+
- No reduction in Lung Cancer
- Non-basal cell Skin Cancer
From CRP to IL-6 to IL-1: Moving Upstream to Identify Novel Targets for Atheroprotection

Prevented cardiovascular events

Colchicine

Reduced infarct size

Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease
Stefan M. Nideck, MD, MBBS, John W. Etelinder, MBBS, Charley A. Budgong, BSc (Hons), Petr L. Thompson, MD

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. Mortensen, Alexander M. K. Rothman, John P. Greenwood, Julian Gunn, Alex Chase, Bernard Clarke, Alastair S. Hall, Keith Poole, Claire Foley, Winaton Banya, Divian Wang, Marcus D. Fletcher, and David C. Crossman

Effect of a single dose of the interleukin-6 receptor antagonist tocilizumab on inflammation and troponin T release in patients with non-ST-elevation myocardial infarction: a double-blind, randomized, placebo-controlled phase 2 trial
Ola Kleveland, Gabor Kunst, Marie Bratlie, Thor Ulaland, Kasper Brinch, Espen Molle, Arndt E. Michel, Bjørn Berntsen, Brage H. Armundset, Terje Espevik, Sverre Aasthus, Jan Kristian Dams, Pål Andreassen, Rune Winther, and Lone Gulbrandsen

The selective NLRP3-inflammasome inhibitor MCC950 reduces infarct size and preserves cardiac function in a pig model of myocardial infarction
Prevented cardiovascular events

Colchicine

Decreased CRP

IL-1Ra

Decreased CRP and TnI

IL-6 Inhibitors

Reduced infarct size

NLRP3 Inhibitors
Residual Inflammatory Risk: Addressing the Obverse Side of the Atherosclerosis Prevention Coin

Ridker PM. Eur Heart J 2016;37:1720-22

[Diagram showing the relationship between known cardiovascular disease, high-intensity statin therapy, and residual cholesterol and inflammatory risk]

“Residual Cholesterol Risk”
- LDL 110 mg/dL (2.8 mmol/L)
- hsCRP 1.8 mg/L
- Additional LDL Reduction

FOURIER/SPIRE/ODYSSEY
PCSK9 Inhibition SC q 2 weeks 15% RRR

“Residual Inflammatory Risk”
- LDL 70 mg/dL (1.8 mmol/L)
- hsCRP 3.8 mg/L
- Additional Inflammation Reduction

CANTOS
Canakinumab 150-300mg SC q 3 months 15% RRR
How common is residual inflammatory risk?

Following High-Intensity Statins

PROVE-IT

44% Residual Inflammatory Risk
14% Residual Cholesterol Risk
13% Both
29% Neither

Following High-Intensity Statins Plus Ezetimibe

IMPROVE-IT

39% Residual Inflammatory Risk
14% Residual Cholesterol Risk
14% Both
33% Neither

Following High-Intensity Statins Plus PCSK9 Inhibition

SPIRE-1 / SPIRE-2

46% Residual Inflammatory Risk
10% Residual Cholesterol Risk
7% Both
37% Neither

hsCRP ≥ 2 mg/L
LDLC < 70 mg/dL

hsCRP < 2 mg/L
LDLC ≥ 70 mg/dL
Strategies to improve inflammatory risk

Ridker PM et al. Front Cardiovasc Med 2019
LDL Reduction Alone Does Not Address Residual Inflammatory Risk

Relationships of hsCRP Levels With Future Cardiovascular Events Among High-Risk Patients Treated with Both Statins and PCSK9 Inhibitors

**FOURIER**

<table>
<thead>
<tr>
<th>hsCRP</th>
<th>Incidence rate / 3 years</th>
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<tbody>
<tr>
<td>&lt;1mg/L</td>
<td>10</td>
</tr>
<tr>
<td>1-3mg/L</td>
<td>12</td>
</tr>
<tr>
<td>&gt;3mg/L</td>
<td>16</td>
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</tbody>
</table>

**SPIRE 1/2**

<table>
<thead>
<tr>
<th>hsCRP</th>
<th>Incidence rate / 100 person years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1mg/L</td>
<td>2</td>
</tr>
<tr>
<td>1-3mg/L</td>
<td>3.5</td>
</tr>
<tr>
<td>&gt;3mg/L</td>
<td>4</td>
</tr>
</tbody>
</table>

Bohula et al, Circulation 2018;138:131-140
Pradhan et al, Circulation 2018;138:141-149
Strategies to improve residual risk for secondary prevention

Known Cardiovascular Disease
- LDL 150 mg/dL
- hsCRP 4.5 mg/L
- TG 240 mg/dL

High Intensity Statin

Residual Cholesterol Risk
- LDL 110 mg/dL
- hsCRP 1.8 mg/L
- TG 180 mg/dL
  Additional LDL Reduction

Residual Inflammatory Risk
- LDL 60 mg/dL
- hsCRP 3.8 mg/L
- TG 180 mg/dL
  Additional Inflammation Reduction

Residual Triglyceride Risk
- LDL 60 mg/dL
- hsCRP 1.8 mg/L
- TG 220 mg/dL
  Additional TG Reduction

J Am Coll Cardiol 2018;72:3320-3331
REDUCE-IT: EPA vs. placebo

Residual Inflammatory Risk: Addressing the Obverse Side of the Atherosclerosis Prevention Coin

Residual cholesterol risk: PCSK9 inhibitor

Residual inflammatory risk: Canakinumab, colchicine

Residual triglyceride risk: EPA

Ridker PM et al. Front Cardiovasc Med 2019
Directions for the Development of Future Anti-Cytokine Therapies for Atherothrombosis

NLRP3 Inflammasome

Inflammasome Inhibitors

Pro-IL-18

Pro-IL-1β

Active-IL-1β

Active-IL-18

Many cell types

Anti-IL-18 antibodies
IL-18 binding protein

Anti-IL-1β antibodies
IL-1 receptor antagonist

Anti-IL-6, IL-6R antibodies

Hepatocyte

CRP

Ridker ESC 2019
Coronary artery plaque characteristics and treatment with biologic therapy in severe psoriasis: results from a prospective observational study


Potential New Targets: Chemokine CCL21 in ACS

CENTRAL ILLUSTRATION: Admission Levels of CCL21 and Prognosis in Acute Coronary Syndrome

Short-Term

Long-Term

Non-Pharmacologic Approaches to Inflammation Inhibition

Vagal Regulation of Innate Immunity: The Neuro-Inflammatory Reflex

Koopman FA et al. PNAS 2016;113:8284-9

Non-Pharmacologic Approaches to Inflammation Inhibition

Vagal Regulation of Innate Immunity: The Neuro-Inflammatory Reflex

Auricular Branch of Vagus Nerve

Fallgatter AJ et al. J Neural Transm 2003

Brain Stim 2015;8:624-36
Non-Pharmacologic Approaches to Inflammation Inhibition

Vagal Regulation of Innate Immunity: The Neuro-Inflammatory Reflex

Low-Level Transcutaneous Electrical Vagus Nerve Stimulation Suppresses Atrial Fibrillation

Stavros Stavrakis, MD, PhD,* Mary Beth Humphrey, MD, PhD,* Benjamin J. Scherlag, PhD,* Yanqing Hu, PhD,* Warren M. Jackman, MD,* Hiroshi Nakagawa, MD, PhD,* Deborah Lockwood, MD,* Ralph Lazzara, MD,* Sunny S. Pu, MD, PhD*

TRanscutaneous Electrical vAgus nerve sTimulation to suppress Atrial Fibrillation (TREAT-AF): A Randomized Clinical Trial

Low-Level Tragus Stimulation for the Treatment of Ischemia and Reperfusion Injury in Patients With ST-Segment Elevation Myocardial Infarction

A Proof-of-Concept Study

Lilei Yu, MD, PhD, Bing Huang, MD, PhD, Sunny S. Po, MD, PhD, Tuantuan Tan, MD, PhD, Menglong Wang, MD, Liping Zhou, MD, Guannan Meng, MD, Shexiu Yuan, MD, Xiaoya Zhou, MD, Phd, Xuefei Li, MD, Zhuo Wang, MD, Songyun Wang, MD, Hong Jiang, MD
Low level vagal stimulation in STEMI decreases inflammation

**A**

**IL-6**

- **BS:** Control: 100 ng/L, LL-TS: 120 ng/L
- **24h:** Control: 150 ng/L, LL-TS: 160 ng/L

**B**

**IL-1β**

- **BS:** Control: 1500 pg/L, LL-TS: 1800 pg/L
- **24h:** Control: 2000 pg/L, LL-TS: 2400 pg/L

**C**

**HMGB1**

- **BS:** Control: 10 ng/ml, LL-TS: 15 ng/ml
- **24h:** Control: 20 ng/ml, LL-TS: 25 ng/ml

**D**

**TNF-α**

- **BS:** Control: 100 ng/L, LL-TS: 150 ng/L
- **24h:** Control: 200 ng/L, LL-TS: 250 ng/L
Low level vagal stimulation in STEMI decreases ventricular arrhythmias

A

Total-VPB

Control    LL-TS

B

I-VPB

Control    LL-TS

C

C-VPB

Control    LL-TS

D

VT

Control    LL-TS
Non-Pharmacologic Approaches to Inflammation Inhibition

STATE-OF-THE-ART PAPER

The Effects of Diet on Inflammation
Emphasis on the Metabolic Syndrome
Dario Giugliano, MD, PhD,* Antonio Ceriello, MD,† Katherine Esposito, MD, PhD*
Naples, Italy; and Coventry, United Kingdom

- omega-3, fish
- saturated and trans fats
- fruits, vegetables, nuts
- whole grains
- sugar
- exercise
- alcohol
- smoking

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 María Lamuela-Raventos, D.Pharm., Ph.D., Lluis 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 Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators
The therapeutic focus in atherosclerosis has shifted from lipid lowering to treating inflammation

Novel nanoimmunotherapies, aimed at modulating innate immune responses in cardiovascular diseases

Conclusions

- Atherosclerosis is driven by lipid accumulation and inflammation
- hsCRP is a strong risk factor for cardiovascular disease
- In primary prevention, targeting patients with high hsCRP with a statin reduces cardiovascular outcomes even in the presence of normal LDL
- In secondary prevention, inflammation inhibition, without lipid lowering reduces cardiovascular outcomes
- Patients with residual inflammatory risk and residual cholesterol risk have distinct etiology of recurrent events
- Neuroimmunomodulation (vagus nerve stimulation) may be a novel way to improve cardiovascular outcomes
Thank you

“Science begets knowledge; opinion, ignorance”

Hippocrates