Interleukin-1 blockade in heart disease

Antonio Abbate, MD, PhD
‘James C. Roberts, Esq.’ Professor of Cardiology
Disclosures

Dr. Abbate has received research support from AB2Bio, Grifols, Janssen, Novartis, SERPIN, Swedish Orphan Biovitrum.

Dr. Abbate has served as an advisor to Novartis, Janssen, Gilead, Swedish Orphan Biovitrum, SERPIN, and XBiotech.
"This basically represents a new opportunity to treat the leading cause of death in the world and an opportunity that's outside of blood cholesterol and represents the culmination of probably 3 decades of work pursuing the hypothesis that inflammation is an important part of atherosclerosis," Dr Sekar Kathiresan (Massachusetts General Hospital, Boston, MA), who was not involved in the study, told theheart.org|Medscape Cardiology. Dr Benoit Arsenault (Université Laval, QC) echoed those sentiments on Twitter: "Amazing. This is a giant step forward for the inflammation hypothesis in atherosclerotic cardiovascular diseases."

There's a tremendous amount of animal model, work in cells, and observational epidemiology in humans that suggests inflammation plays a role, but Kathiresan said the last piece of the puzzle was whether a treatment could affect inflammation and reduce the risk of heart attack.
Topics

• Atherosclerosis is an inflammatory disease
• Interleukin-1-family cytokines as biomarkers in acute coronary syndromes
• Interleukin-1 blockade in experimental atherosclerosis models
• Interleukin-1 blockade in experimental MI
• The CANTOS pilot trial
• Pilot VCU-ART studies
• The CANTOS trial
Topics

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Paradigm Shift in the 1990s:
Atherosclerosis - an inflammatory disease

Mechanisms of Disease

FRANKLIN H. EPSTEIN, M.D., EDITOR

ATHEROSCLEROSIS — AN INFLAMMATORY DISEASE

RUSSELL ROSS, PH.D.

N Engl J Med 1999

Factors that Induce and Promote Inflammation or Atherogenesis

Numerous pathophysiologic observations in humans and animals led to the formulation of the response-to-injury hypothesis of atherosclerosis, which initially proposed that endothelial denudation was the first step in atherosclerosis. The most recent version of this hypothesis emphasizes endothelial dysfunction rather than denudation. Whichever process is at work, each characteristic lesion of atherosclerosis represents a different stage in a chronic inflammatory process in the artery; if unabated and excessive,

| TABLE 1. CHARACTERISTICS OF Atherosclerosis AND OTHER CHRONIC INFLAMMATORY DISEASES.* |
|---------------------------------|--------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **DISEASE**                     | **MONOcyTUES AND Macrophages** | **LYMPHocytes**                | **GRANUlocytes**                | **CONNECTive-Tissue Cells**     | **EXTRACellular Matrix**        | **Pathogenetic Mechanisms**     | **Studies**                     |
| Atherosclerosis                 | +                              | +                               | -                               | Smooth muscle cells             | Collagen types I, II, III, IV, elastin, fibronectin, proline, proteoglycan | Endothelial-cell injury and dysplasia; fibrosis; new matrix formation and degradation, necrosis core | Roye, Libby and Hanson, Ross and Fuster, Mather et al. |
| Cirrhosis                       | +                              | +                               | -                               | Fibroblasts, Ito cells           | Collagen types I and II, fibronectin, proteoglycan | Portal hypertensive injury; new matrix formation replacing necrotic parenchyma | Seward and Trembly, Seward et al. |
| Ehlers-Danlos syndrome          | +                              | +                               | +/-                             | Synovial fibroblasts             | Collagen types I and II, fibronectin, proteoglycan | Synovial-cell injury; erosion of cartilage; new matrix scarring (pannus) | Harr et al., Johnson et al. Magil and Cohen. |
| Glomerulonephritis              | +                              | +                               | -                               | Mesangial cells                  | Collagen types I and II, IV, fibronectin | Epithelial and endothelial cell injury and dysfunction; decrease in glomerular filtration; new matrix formation | Kahn et al., Landis, and Wexler, Brady et al. |
| Pulmonary fibrosis              | +                              | +                               | +/-                             | Smooth muscle cells, fibroblasts | Collagen types III and IV, fibronectin | Inflammatory exudate in alveoli and bronchi, organized by extracellular matrix deposition and scarring | Balfour et al., Balfour et al., Dillmann et al. |
| Chronic pancreatitis            | +                              | +                               | -                               | Fibroblasts                      | Collagen, fibronectin, proteoglycan | Epithelial (ductal) injury; periductal inflammation; acinar fat necrosis; new matrix formation | Balfour et al., Dillmann et al. |

* This sign denotes the presence of a cell type, and minus sign its absence.

According to Google Scholar citations to date amount to 26,270 (7/1/17)
Paradigm Shift in the 1990s: Atherosclerosis - an inflammatory disease

Berk BC et al. Elevation of C-reactive protein in “active” coronary artery disease. *Am J Cardiol* 1990


The New England Journal of Medicine

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Volume 331 AUGUST 18, 1994 Number 7

THE PROGNOSTIC VALUE OF C-REACTIVE PROTEIN AND SERUM AMYLOID A PROTEIN IN SEVERE UNSTABLE ANGINA

Giovanna Liuzzo, M.D., Luigi M. Biasucci, M.D., J. Ruth Gallimore, B.Sc., Rita L. Grillo, B.Sc., Antonio G. Rebuzzi, M.D., Mark B. Pepys, M.D., Ph.D., and Attilio Maseri, M.D.

According to Google Scholar citations to date amount to 2,948 (7/1/17)
Topics

• Atherosclerosis is an inflammatory disease
• Interleukin-1-family cytokines as biomarkers in acute coronary syndromes
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• Pilot VCU-ART studies
• The CANTOS trial
IL-1 family

Table 2. The IL-1 family

<table>
<thead>
<tr>
<th>Family name</th>
<th>Name</th>
<th>Receptor</th>
<th>Coreceptor</th>
<th>Property</th>
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<tbody>
<tr>
<td>IL-1F1</td>
<td>IL-1α</td>
<td>IL-1RI</td>
<td>IL-1RacP</td>
<td>Proinflammatory</td>
</tr>
<tr>
<td>IL-1F2</td>
<td>IL-1β</td>
<td>IL-1RI</td>
<td>IL-1RacP</td>
<td>Proinflammatory</td>
</tr>
<tr>
<td>IL-1F3</td>
<td>IL-1Ra</td>
<td>IL-1RI</td>
<td>NA</td>
<td>Antagonist for IL-1α, IL-1β</td>
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<tr>
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<td>IL-18</td>
<td>IL-18Rα</td>
<td>NA</td>
<td>Receptor for IL-1β</td>
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<tr>
<td>IL-1F5</td>
<td>IL-36Ra</td>
<td>IL-1Rrp2</td>
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<td>IL-1F6</td>
<td>IL-36α</td>
<td>IL-1Rrp2</td>
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<tr>
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<td>IL-37</td>
<td>IL-18Rα</td>
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<td>IL-1F8</td>
<td>IL-36β</td>
<td>IL-18Rα</td>
<td>NA</td>
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<tr>
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<td>IL-18Rβ</td>
<td>IL-1Rrp2</td>
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<tr>
<td>IL-1F10</td>
<td>IL-36γ</td>
<td>IL-18Rα</td>
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<td></td>
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<tr>
<td>IL-1F11</td>
<td>IL-36α</td>
<td>IL-1Rrp2</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Dinarello CA. Blood 2011
Interleukin-1 blockers in experimental AMI

- Inflammatory cells ➔ IL-1β
- Necrotic cells ➔ (pro)IL-1α
- Endothelial Cells (healthy)
- IL-1Ra
- IL-1R1
- Inflammation
- Cell Death
Differential Effects of Human Interleukin-1 on Growth of Human Fibroblasts and Vascular Smooth Muscle Cells

Peter Libby, David J. Wyler, Maria W. Janicka, and Charles A. Dinarello

Endotoxin and Tumor Necrosis Factor Induce Interleukin-1 Gene Expression in Adult Human Vascular Endothelial Cells

Am J Pathol 1986

Inducible Interleukin-1 Gene Expression in Human Vascular Smooth Muscle Cells

Peter Libby, Jose M. Ordovas, Louis K. Birinyi, Kurt R. Auger, and Charles A. Dinarello

J Clin Invest 1986
Interleukin-1 Receptor Antagonist: A Sensitive Marker of Instability in Patients with Coronary Artery Disease

Giuseppe Patti MD,1 Andrea D’Ambrosio MD,1 Aldo Dobrina MD,3 Giordano Dicouzzo MD,1 Carlo Giansante MD,2 Nicola Fiotti MD,2 Antonio Abbate MD,1 Gianfranco Guarnieri MD,2 Germano Di Sciascio MD, FACC, FESC1

110 patients undergoing coronary angiography

- Stable Angina
- Unstable Angina
- Non-cardiac Chest pain

IL-1beta undetectable
IL-1Ra better discriminator than CRP
IL-1 as a biomarker in heart disease

73 patients with established CAD undergoing coronary artery stenting and had >1 year follow up.

IL-1beta undetectable
IL-1Ra better predictor than CRP

Am J Cardiol 2002

Prognostic Value of Interleukin-1 Receptor Antagonist in Patients Undergoing Percutaneous Coronary Intervention

Giuseppe Patti, MD, Germano Di Sciascio, MD, Andrea D’Ambrosio, MD, Giordano Dicuonzo, MD, Antonio Abbate, MD, and Aldo Dobrina, MD
IL-1 as a biomarker in heart disease

40 patients with established CAD undergoing coronary artery stenting and with serial blood testing at 3 and 6 months

IL-1beta not detectable
IL-1Ra better predictor than CRP

IL-1 as a biomarker in heart disease

Patti G et al. Interleukin-1 receptor antagonist levels correlate with extent of myocardial loss in patients with acute myocardial infarction. *Clin Cardiol* 2015
Topics

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IL-1 in heart disease: response to injury

Tissue injury

Sterile Inflammation

Additional Injury/Dysfunction

Atherogenesis
- Fatty streak → atheroma

Plaque Rupture
- Plaque complication → thrombosis

Acute Myocardial Infarction
- Ischemia → Necrosis

Heart Failure
- Cardiac enlargement/dysfunction
  - Exercise intolerance

Chronic (subclinical)

Acute

Chronic (low grade)

IL-1
Contemporary Reviews in Cardiovascular Medicine

Targeting Interleukin-1 in Heart Disease

Benjamin W. Van Tassell, PharmD; Stefano Toldo, PhD; Eleonora Mezzaroma, PhD; Antonio Abbate, MD, PhD

October 22, 2013

NORMAL ARTERY

PLAQUE FORMATION (Atheroma)

PLAQUE PROGRESSION (Occlusive Atheroma)

PLAQUE COMPLICATION (Atherothrombosis)

IL-1 activity

Endothelial dysfunction
Leukocyte activation
Protease activation
Platelet activation
Plaque Rupture
Thrombosis
The NLRP3 inflammasome

- **Cell injury** → release of PAMPs and DAMPs
- ATP → IL-1β → Autoinflammation
- P2X7 → IL-1β → Autoinflammation
- TLRs → IL-1RI → MyD88 → Cryopyrin activation
- Cryopyrin activation → Cryopyrin ASC Inflammasome
- NLRP3 Inflammasome → proIL-1β → IL-1β, proIL-18 → IL-18
- IL-1β, IL-18 → Autoinflammation
- PRIMING: NFκB
- TRIGGER: Cryopyrin activation
- Lysosome Destabilization

**Resident cell** (endothelial cells, fibroblasts, cardiomyocytes)

**Leukocytes recruited to the site of injury**

---

**The Inflammasome in Myocardial Injury and Cardiac Remodeling**

*Antioxid Redox Signal 2015;22:1146-1161.*

Stefano Toldo,1,2 Eleonora Mezzaroma,2,3 Adolfo Gabriele Mauro,1,2 Fadi Salloum,1 Benjamin Wallace Van Tassell,2,3 and Antonio Abbate1,2
The NLRP3 inflammasome

**LETTERS**

**NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals**

Cholesterol Crystals Activate the NLRP3 Inflammasome in Human Macrophages: A Novel Link between Cholesterol Metabolism and Inflammation

Kristiina Rajamäki, Jani Lappalainen, Katarina Öörni, Elina Välimäki, Sampsa Matikainen, Petri T. Kovanen, Kari K. Eklund

**Figure 5.** Cholesterol crystals (CHCs) cause destabilization of lysosomes and leakage of cathepsin B into the cytoplasm. CHC-treated or untreated live THP-1 macrophages were stained with cathepsin B substrate z-Arg-Arg-cresyl violet (panels i, iii) or with acidine orange (panels ii, iii). The fluorescent cresyl violet group of z-Arg-Arg-cresyl violet is dequenched upon cleavage of one or both of the arginines by cathepsin B. Acidine orange aggregates in the acidic pH of lysosomes, which changes the fluorescence emission of the dye from green to red. The images are representative of 3 experiments.

doi:10.1371/journal.pone.0011765.g005

**Figure 6.** Silencing of NLRP3 attenuates cholesterol crystal (CHC)-induced IL-1β secretion. (A) NLRP3 mRNA levels were...
Lack of Interleukin-1β Decreases the Severity of Atherosclerosis in ApoE-Deficient Mice

Hirokazu Kirii, Tamikazu Niwa, Yasuhiro Yamada, Hisayasu Wada, Kuniaki Saito, Yoichiro Iwakura, Masahide Asano, Hisataka Moriwaki, Mitsuru Seishima
Monoclonal antibodies targeting IL-1 beta reduce biomarkers of atherosclerosis in vitro and inhibit atherosclerotic plaque formation in Apolipoprotein E-deficient mice

Vinay Bhaskar*, Johnny Yin, Amer M. Mirza, Dan Phan, Sandra Vanegas, Hassan Issafras, Kristen Michelson, John J. Hunter, Seema S. Kantak

Preclinical Research, XOMA (US) LLC, 2910 Seventh Street, Berkeley, CA 94710, USA
Topics

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Interleukin-1 blockers

IL-1R1

(pro)IL-1α
IL-1β

rhIL-1Ra (Anakinra, Kineret, Swedish Orphan Biovitrum)

IL-1Trap (Arcalyst, Regeneron)

IL-1β MAb (Canakinumab, Novartis)
Interleukin-1 blockade in experimental AMI

Post-infarction cardiac remodeling

IL-1R1 KO in acute myocardial infarction

Myocardial Ischemia-reperfusion in the IL-1R1 KO mouse \textit{in vivo}

Myocardial Ischemia w/o reperfusion in the IL-1R1 KO (and IL-1Ra) mouse \textit{in vivo}


Interleukin-1 blockade in experimental AMI

Anakinra, a Recombinant Human Interleukin-1 Receptor Antagonist, Inhibits Apoptosis in Experimental Acute Myocardial Infarction

Antonio Abbate, MD*; Fadi N. Salloum, PhD*; Elena Vecile, PhD*; Anindita Das, PhD; Nicholas N. Hohe, BS; Stefania Straino, BS; Giuseppe G.L. Biondi-Zoccai, MD; Jon-Erik Houser, MD; Ian Z. Qureshi, PhD; Evan D. Ownby, MD; Edoardo Gustini, PhD; Luigi M. Biasucci, MD; Anna Severino, PhD; Maurizio C. Capogrossi, MD; George W. Vetrovec, MD; Filippo Crea, MD; Alfonso Baldi, MD; Rakesh C. Kukreja, PhD; Aldo Dobrina, MD

Myocardial Ischemia w/o reperfusion in the mouse with recombinant IL-1 receptor antagonist (anakinra)

![Graph showing survival rates and LV EDD over time with and without anakinra treatment.](image-url)

Anakinra treatment shows significantly higher survival rates compared to saline control, with a P-value of 0.013.
Inhibiting IL-1 in acute myocardial infarction

Myocardial Ischemia w/o reperfusion in the mouse with IL-1Trap blocking IL-1β and IL-1α, as well as IL-1Ra

Myocardial Ischemia w/o reperfusion in the mouse with a genetically engineered murine anti-IL-1β antibody (XOMA)


Delayed **IL-1β blockade in AMI**

Myocardial Ischemia w/o reperfusion with a *murine anti-IL-1β antibody* (Novartis)

- **Baseline**
- **Coronary artery ligation**
- **7 days**
- **28 days**
- **70 days**

### Echocardiogram
- **Contractile Reserve**
- **Screening Echocardiogram:**
  - Infarct >4 seg.
  - LVEF<40%
  - LVEDD >4.4 mm

### LV catheterization
- **Echocardiogram**
- **Contractile Reserve**
- **Pathology samples**

### Pathology samples

---

**LVEDD (mm)**

- **7 days**
- **28 days**
- **70 days**

- **Control-AB**
- **IL-1β-AB**

P=0.26

---

Toldo et al. *J Cardiovasc Pharmacol* 2014;64:1-6
Delayed **IL-1β blockade** in AMI

![Graphs showing LVEF and MPI changes over time with IL-1β blockade and control groups.](image)

- **LVEF (%)**:
  - IL-1β-AB (from day 7)
  - Control-AB
  - Baseline: 30, 25, 20
  - P-values: 0.022, 0.028

- **MPI**:
  - IL-1β-AB (from day 17)
  - Control-AB
  - Baseline: 0.8, 0.6

- **LVEDP**
  - Sham, Control-AB, IL-1β-AB
  - P-values: <0.01, 0.030

- **LVEF change (%) after isoproterenol**
  - Baseline, 7 days, 70 days
  - IL-1β-AB (from day 67)

*Toldo et al. J Cardiovasc Pharmacol 2014;64:1-6*
The inflammasome is an intracellular macromolecular structure responsible for sensing "danger" or "injury" and amplifying the inflammatory response.
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CANTOS Pilot trial

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

Circulation 2012

556 patients treated monthly for 3 months

![Graph showing the effects of Canakinumab dose on various parameters such as Fibrinogen, Interleukin-6, and C-reactive Protein. The graph illustrates the median reduction (%) for different doses.]

Table 6. Number (and Percentage) of Treatment-Emergent Adverse Events During the Trial Period

<table>
<thead>
<tr>
<th>Variable</th>
<th>Canakinumab Dose (per mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 mg (N=93)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>33 (35.5%)</td>
</tr>
<tr>
<td>Infection</td>
<td>10 (10.8%)</td>
</tr>
</tbody>
</table>
Canakinumab phase II IIS study in pre-diabetes/diabetes

Arterial Effects of Canakinumab in Patients With Atherosclerosis and Type 2 Diabetes or Glucose Intolerance

J Am Coll Cardiol 2016

P=0.06
(1 year)

Effect on glycemic control
- Fasting blood glucose levels
- Insulin resistance and β-cell function
- Hemoglobin A1c levels (HbA1c)
- Glucose tolerance

Effect on arterial structure and function
- Atherosclerosis burden
- Aortic distensibility

All P>0.05
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VCU-ART Pilot studies

VCU-ART: 10 patients with STEMI
VCU-ART2: 30 patients with STEMI

Cardiac MR, Doppler Echocardiography, CRP and BNP determination

1:1 randomization

24-96 h

Complete history and physical

10-14 weeks

Anakinra 100 mg SQ or placebo every 24 hours for 14 days

* * * blood sampling (CBC with diff.)

VCU-ART and VCU-ART2 studies:

VCU-ART and VCU-ART2 studies:

VCU-ART studies: Extended F/U
Abbate et al. Am J Cardiol 2015
### Table 3
Adverse cardiovascular events

<table>
<thead>
<tr>
<th>Patients with events</th>
<th>Placebo</th>
<th>Anakinra</th>
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<tbody>
<tr>
<td></td>
<td>1  2  3</td>
<td>4  5  6  7</td>
</tr>
<tr>
<td>Death (cardiac death)</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Acute coronary syndromes</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>- STEMI</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>- NSTEMI</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>- Unstable Angina</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>- Revascularization</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Heart failure</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>- LVEF &lt;40%</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>- NYHA III/IV</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>- BNP &gt;100 pg/ml</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>- LVEDP &gt;16 mm Hg</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>- Hospitalization</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Stroke (ischemic)</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

The Table shows 22 events occurring in 16 patients, 9 in the placebo group and 7 in the anakinra group. LVEF, NYHA class, BNP and LVEDP values refer to the time when the diagnosis of heart failure was diagnosed, which varies between patients.

BNP = Brain natriuretic peptide; LVEDP = Left ventricular end-diastolic pressure; LVEF = Left ventricular ejection fraction; NSTEMI = non-STEMI; NYHA = New York Heart Association; STEMI = ST-segment elevation myocardial infarction.
IL-1 blockade in STEMI

- VCU-ART3– NIH funded - ongoing

Aim 1.1
- CRP

Aim 1.2
- Echo

Aim 2
- Clinical End-points

80 patients enrolled to date
Anakinra in acute decompensated HF

C

Normalized CRP vs Days

D

% change in CRP (72 hours)

Anakinra in acute decompensated HF

Congestion markers (peripheral edema, pulmonary congestion, JVD, S3 gallop) were assessed by investigators blinded to treatment allocation.
Anakinra in chronic stable systolic HF

IL-1beta

Cytokines plasma (pg/mL)

P=0.011

IL-1beta

IL-6

P=0.015

hsCRP (mg/L)

P=0.016

Anakinra in chronic stable systolic HF

P=0.016

P=0.031

Recently Decompensated Heart failure Anakinra Response Trial (REDHART)

Heart Failure Admission → Discharge

LVEF <50%
CRP >2 mg/l
Impaired exercise capacity

within 2 weeks

Van Tassell BW et al. Eur J Heart Fail 2017 (abstract)
Recently Decompensated Heart failure
Anakinra Response Trial (REDHART)

Hospitalization for Decompensated Systolic (LVEF<50%) Heart Failure (n=60)

Anakinra (n=20) - Follow-up
Placebo (n=20) - Follow-up

CPX Labs Echo CPX Labs Echo
Discharge (within 2 weeks) 2 weeks 4 weeks 12 weeks 24 weeks
REDHART clinical trial

Effect on peak VO\textsubscript{2}  
(primary endpoint: interval change at 2 weeks)

<table>
<thead>
<tr>
<th>Weeks</th>
<th>N=</th>
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<tr>
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<tr>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>24</td>
<td>12</td>
</tr>
</tbody>
</table>

Treatment
- Placebo
- Anakinra (2 weeks)
- Anakinra (12 weeks)

* P<0.05 vs baseline

Van Tassell BW et al. Eur J Heart Fail 2017 (abstract)
**REDHART clinical trial**

**Survival free of Readmission of HF**

- **Anakinra (12 weeks)**
- **Anakinra (2 weeks)**
- **Placebo (12 weeks)**
- **Registry (untreated)**

Time (weeks):
- 2
- 12
- 24

Survival rates:
- 100%
- 80%
- 60%
- 40%
- 20%

Statistical analysis:
- P=0.136 Log-Rank Test
- Placebo vs Anakinra (12 weeks): P=0.027

*Van Tassell BW et al. Eur J Heart Fail 2017 (abstract)*
Effect of Anakinra on Recurrent Pericarditis Among Patients With Colchicine Resistance and Corticosteroid Dependence

The AIRTRIP Randomized Clinical Trial

Antonio Brucato, MD; Massimo Imazio, MD, FESC; Marco Gattorno, MD; George Lazaros, MD; Silvia Maestrini, MD; Mara Carraro, RN; Martina Finetti, MD; Davide Cumetti, MD; Alessandra Carobbio, MSc; Nicolino Ruperto, M"; Gian Luca Erre, MD

Figure 2. Kaplan-Meier Analysis of Patients With Recurrent Pericarditis Free of Relapse in the Double-Blind Withdrawal Phase, From Day 0 to Day 180 After Randomization (Intention-to-Treat Analysis)
Topics

• Atherosclerosis is an inflammatory disease
• Interleukin-1-family cytokines as biomarkers in acute coronary syndromes
• Interleukin-1 blockade in experimental atherosclerosis models
• Interleukin-1 blockade in experimental MI
• The CANTOS pilot trial
• Pilot VCU-ART studies
• The CANTOS trial
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

Interleukin-1β inhibition and the prevention of recurrent cardiovascular events: Rationale and Design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

Paul M Ridker, MD, a,b,d Tom Thuren, MD, c,d Andrew Zalewski, MD, c,d and Peter Libby, MD b,d Boston, MA; and East Hanover, NJ

Figure 1

Double-blinded, placebo-controlled, randomized

Three active treatment arms (50, 150 and 300 mg quarterly)

Event-driven

Original plan on clinicaltrials.gov:
• 7,320 patients (4/2011, 2 doses)
• 17,200 patients (9/2011, 3 doses, 4 yrs)
• 10,000 patients (2/2014, 5 yrs)
• Final 10,060
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA
Persistent Elevation of hsCRP ($\geq$ 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
ExploratoryEndpoints: DVT/PE; SVT; hospitalizations for CFH; PCI/CABG; biomarkers
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

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CANTOS is designed as an event-driven trial with all primary analyses conducted on an intention-to-treat basis. Power estimates are based on the assumption of a sample size of 17,200 randomized participants assigned in a 1:1:1:1:1.5 allocation ratio between canakinumab 50 mg quarterly, canakinumab 150 mg quarterly, canakinumab 300 mg quarterly, and placebo. Trial completion is anticipated to occur after the accrual of at least 1,400 primary end points. This number of primary end points should provide approximately 90% power to detect the superiority of at least 1 dose of canakinumab compared with placebo, assuming a hazard reduction of 20%. The protocol also prespecifies analyses to detect the superiority of the combined canakinumab arms compared with placebo.

No efficacy stopping rules pre-specified in the study design but futility rules were specified for all 3 doses.

In the protocol, efficacy analysis is hierarchical with highest dose considered first.

Estimated result is a >20% reduction in a combined end-point of CV death or MI or stroke with 1 or more of canakinumab doses (with an estimated ARR of >2%)
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

Unanswered questions as of today:

1. Which component of the combined endpoint is driving efficacy? MI? stroke? CV death? All?
2. What is the side-effect profile?
3. What is the cost? And the cost-effectiveness of this expensive biodrug?
4. Are there additional benefits in the secondary endpoint?
5. Can subgroups be identified who are predicted to benefit more or less?
Conclusions

I. Atherosclerosis is an inflammatory disease

II. IL-1/IL-6/CRP biomarkers can inform prognosis in patients with, or at risk, for heart disease

III. IL-1 blockade is the first targeted anti-inflammatory strategy that improves cardiovascular outcomes in patients with heart disease

The CANTOS trial
Thank you for your attention

VCU-ART