



Goed Gebruik Geneesmiddelen

Casus Colchicine

Arend Mosterd

Cardioloog, Meander Medisch Centrum Amersfoort
Voorzitter, Werkgroep Cardiologische centra Nederland (WCN)

ZonMw congres Amsterdam 7 april 2016





Disclosure van belangen

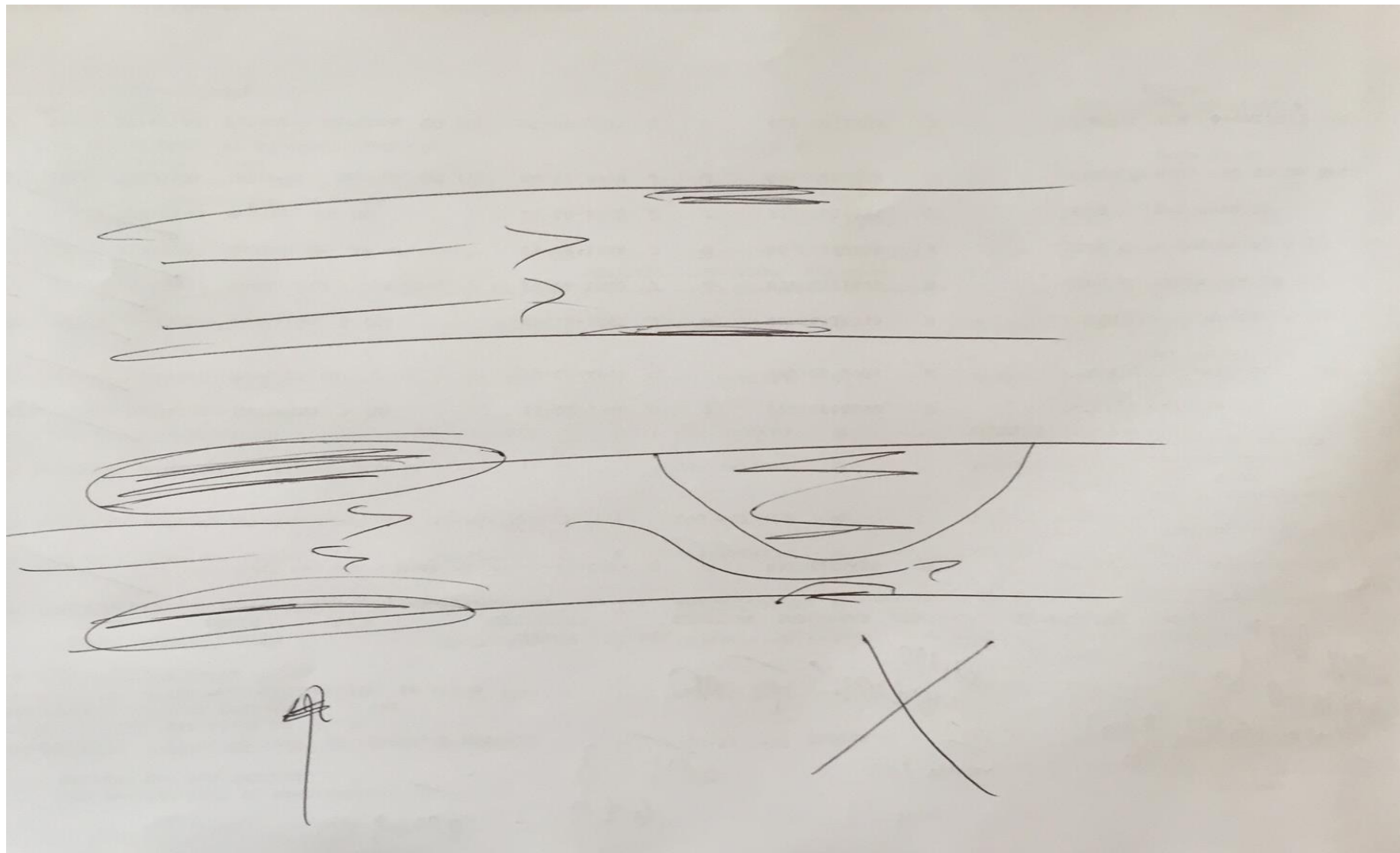
Arend Mosterd

(potentiële) belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
<ul style="list-style-type: none">• Onderzoeksgeld / Honorarium• Lopende subsidie aanvraag LoDoCo2• Aandelen: geen in individuele farma.	<ul style="list-style-type: none">• Pfizer (Spire - Lipiden)• Bayer / MSD (Victoria – HF)• Novartis (Paradigm & Relax AHF - HF)• ZON Mw 80-84800-98-15092.





De spreekkamer





Inflammation & Coronairlijden

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THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Leukocytes Link Local and Systemic Inflammation in Ischemic Cardiovascular Disease

An Expanded “Cardiovascular Continuum”

Peter Libby, MD,^a Matthias Nahrendorf, MD,^b Filip K. Swirski, PhD^b

ABSTRACT

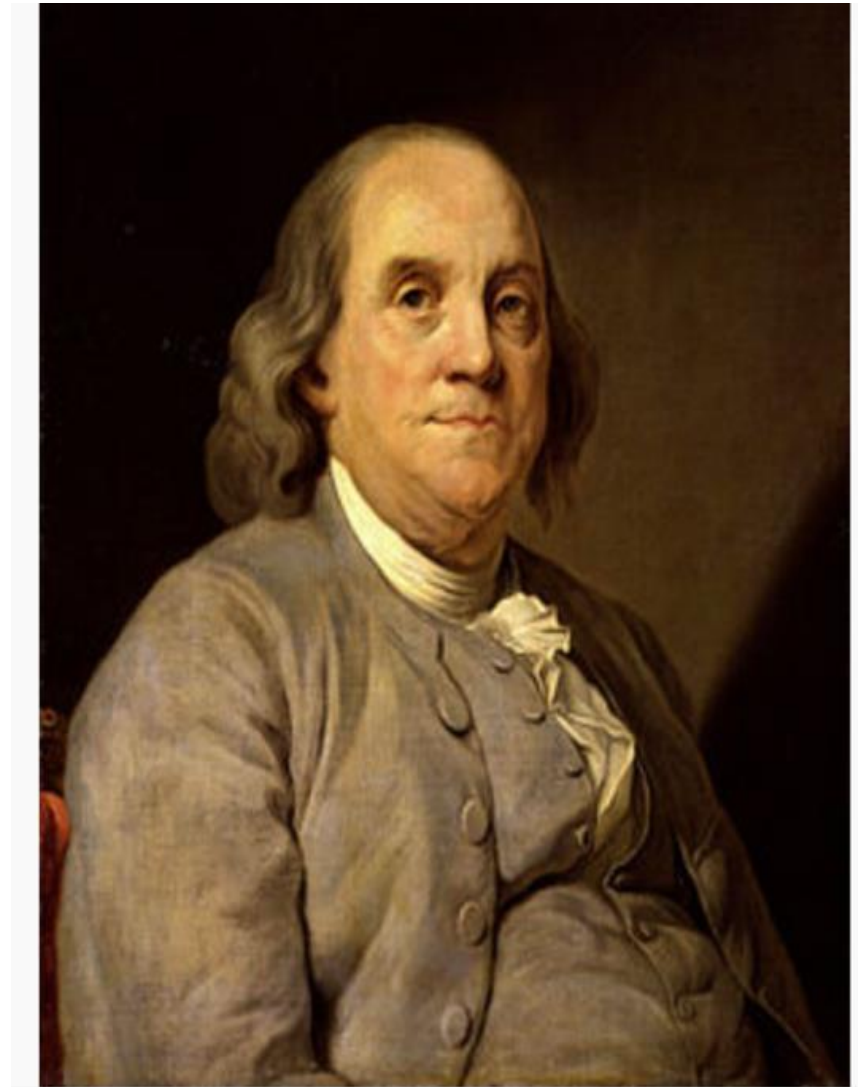
Physicians have traditionally viewed ischemic heart disease in a cardiocentric manner: plaques grow in arteries until they block blood flow, causing acute coronary and other ischemic syndromes. Recent research provides new insight







Benjamin Franklin - Jicht



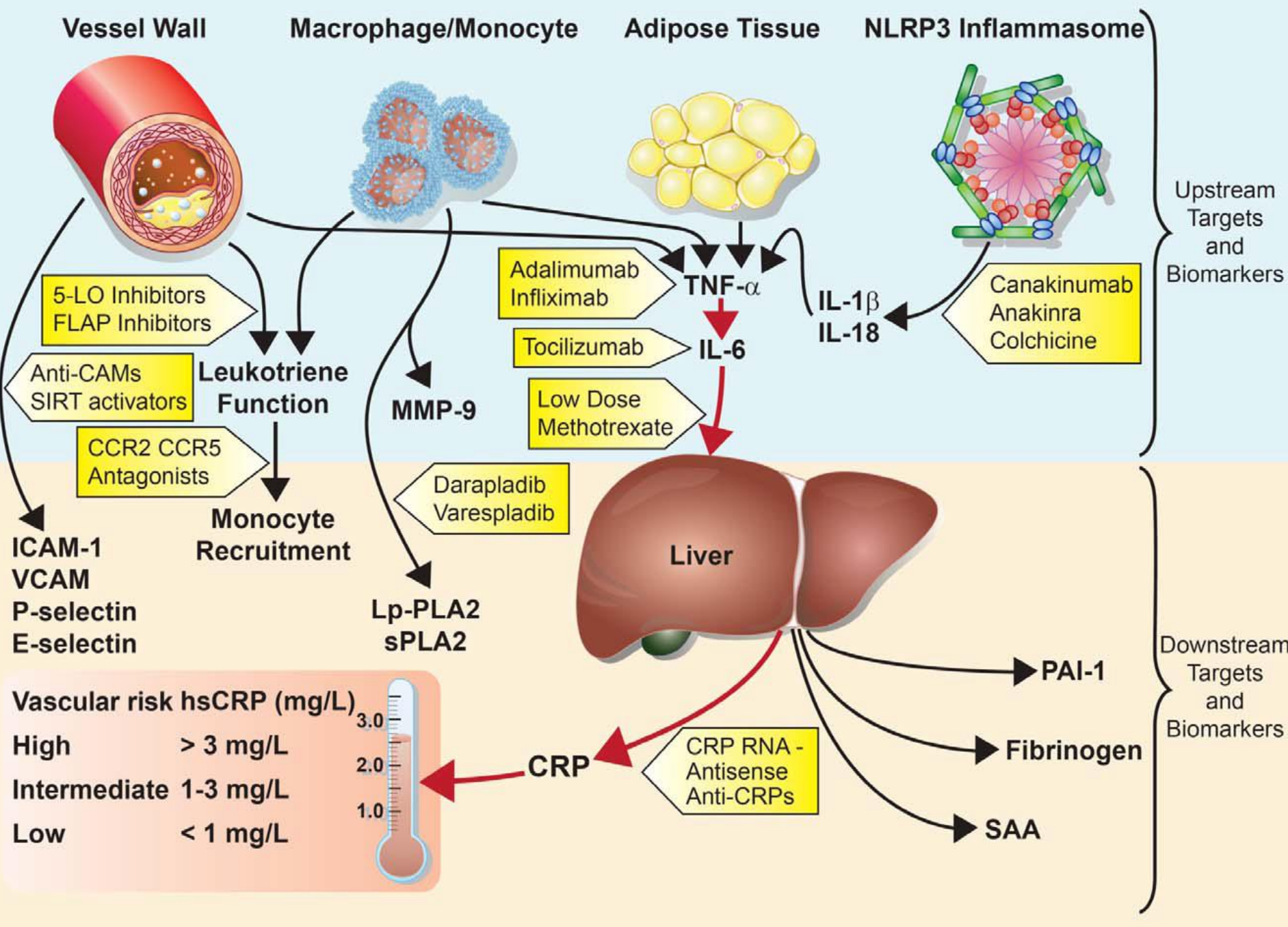


Benjamin Franklin - Jicht



- Herfsttijloos
- 4 mg colchicine

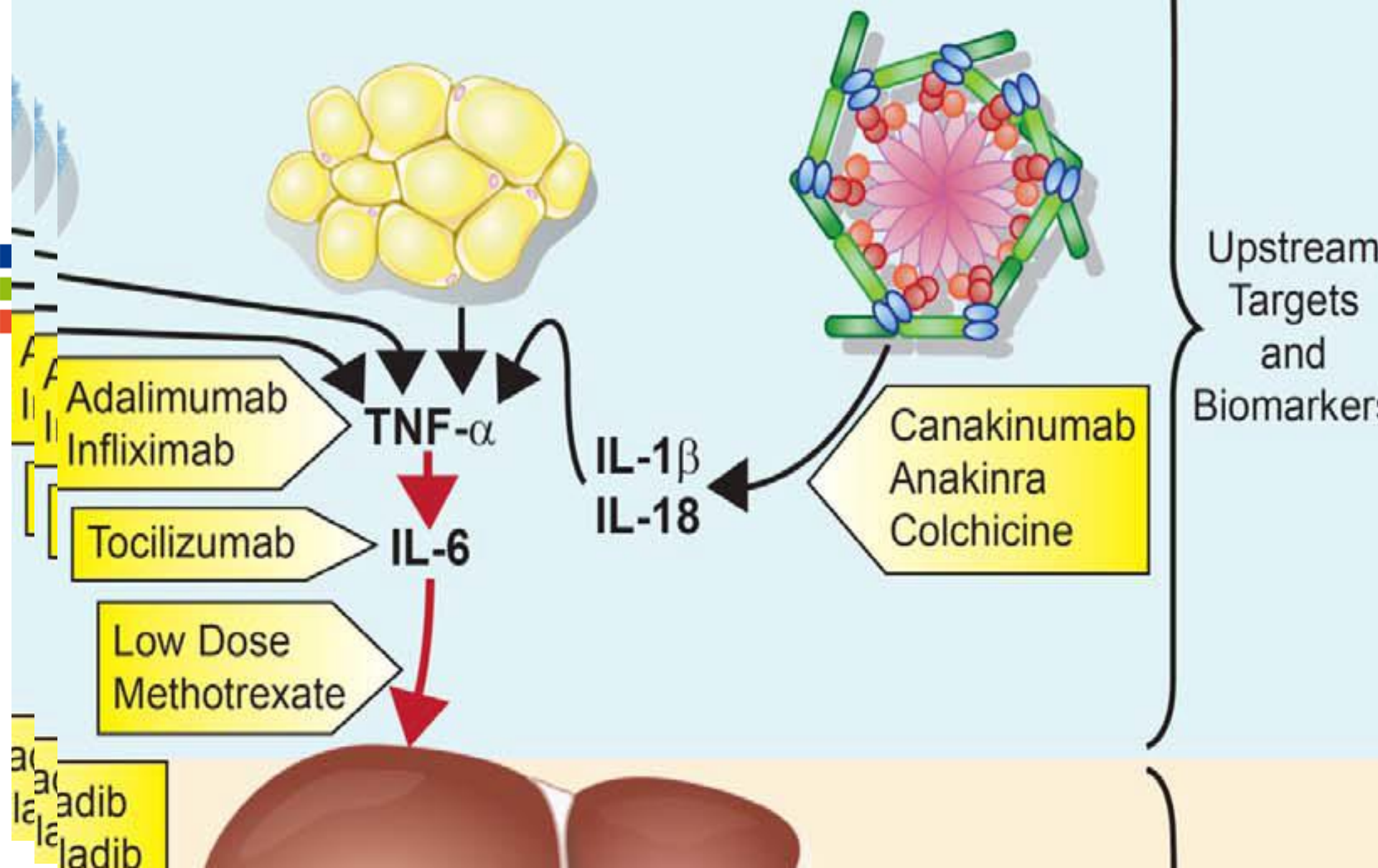




Leucocyte

Adipose Tissue

NLRP3 Inflammasome





Low Dose Colchicine (LoDoCo) to prevent CV events

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CLINICAL RESEARCH

Clinical Trial

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

Objectives

The objective of this study was to determine whether colchicine 0.5 mg/day can reduce the risk of cardiovascular events in patients with clinically stable coronary disease.

Background

The presence of activated neutrophils in culprit atherosclerotic plaques of patients with unstable coronary disease raises the possibility that inhibition of neutrophil function with colchicine may reduce the risk of plaque instability and thereby improve clinical outcomes in patients with stable coronary disease.

Methods

In a clinical trial with a prospective, randomized, observer-blinded endpoint design, 532 patients with stable coronary disease receiving aspirin and/or clopidogrel (93%) and statins (95%) were randomly assigned colchicine 0.5 mg/day or no colchicine and followed for a median of 3 years. The primary outcome was the composite incidence of acute coronary syndrome, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke. The primary analysis was by intention-to-treat.

Results

The primary outcome occurred in 15 of 282 patients (5.3%) who received colchicine and 40 of 250 patients (16.0%) assigned no colchicine (hazard ratio: 0.33; 95% confidence interval [CI] 0.18 to 0.59; $p < 0.001$; number needed to treat: 11). In a pre-specified secondary on-treatment analysis that excluded 32 patients (11%) assigned to colchicine who withdrew within 30 days due to intestinal intolerance and a further 7 patients



Low Dose Colchicine (LoDoCo) to prevent CV events

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Number Needed to Treat = 11
Too good to be true?

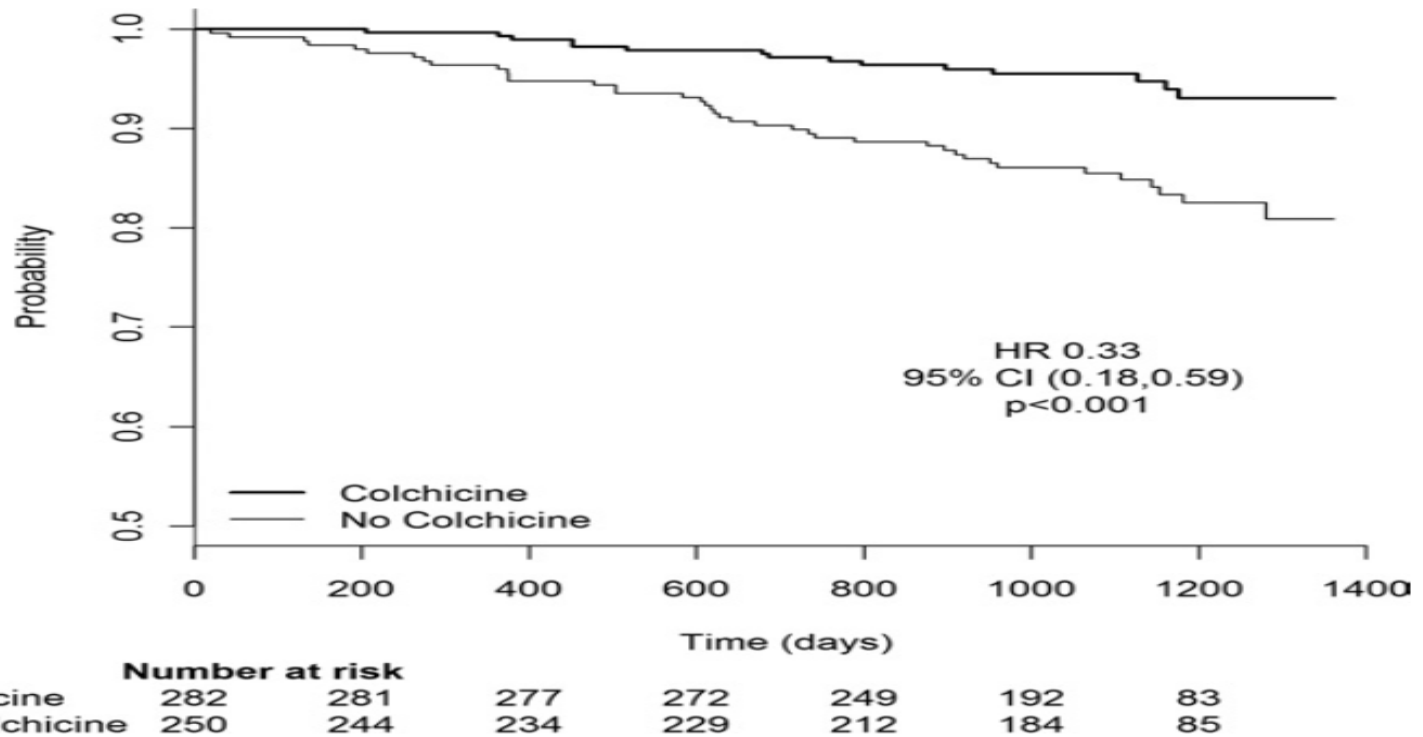


Figure 2

Freedom From the Primary Outcome

Freedom from the primary outcome (acute coronary syndrome, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke) by treatment. CI = confidence interval; HR = hazard ratio.



Editorial to LoDoCo paper

"Need for a large randomized outcome trial"

prior event, elevated CRP levels, and type 2 diabetes (15).

While we await new trials, the striking additional reduction in events in statin-treated patients on anti-inflammatory therapy already suggests a new concept: the lipid effects of statins may predominantly inhibit atherogenesis, whereas specific anti-inflammatory agents, such as colchicine, may work synergistically with statins to inhibit plaque rupture. If the results can be confirmed, this study may one day stand as the seminal trial in the use of anti-inflammatory therapy to cool off hot hearts.

Reprint requests and correspondence: Dr. James Forrester, Department of Cardiology, Cedars-Sinai Medical Center, Suite 121 East, Los Angeles, California 90048. E-mail: forrester@cshs.org.



Large CV outcome trials

Pegasus TIMI 54 (n = 21.162)

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Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction

Marc P. Bonaca, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Marc Cohen, M.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., Eva C. Jensen, M.D., Ph.D., Giulia Magnani, M.D., Sameer Bansilal, M.D., M. Polly Fish, B.A., Kyungah Im, Ph.D., Olof Bengtsson, Ph.Lic., Ton Oude Ophuis, M.D., Ph.D., Andrzej Budaj, M.D., Ph.D., Pierre Theroux, M.D., Mikhail Ruda, M.D., Christian Hamm, M.D., Shinya Goto, M.D., Jindrich Spinar, M.D., José Carlos Nicolau, M.D., Ph.D., Robert G. Kiss, M.D., Ph.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Peter Held, M.D., Ph.D., Eugene Braunwald, M.D., and Marc S. Sabatine, M.D., M.P.H.,
for the PEGASUS-TIMI 54 Steering Committee and Investigators*

ABSTRACT

BACKGROUND

The potential benefit of dual antiplatelet therapy beyond 1 year after a myocardial infarction has not been established. We investigated the efficacy and safety of ticagrelor, a P2Y₁₂ receptor antagonist with established efficacy after an acute coro-

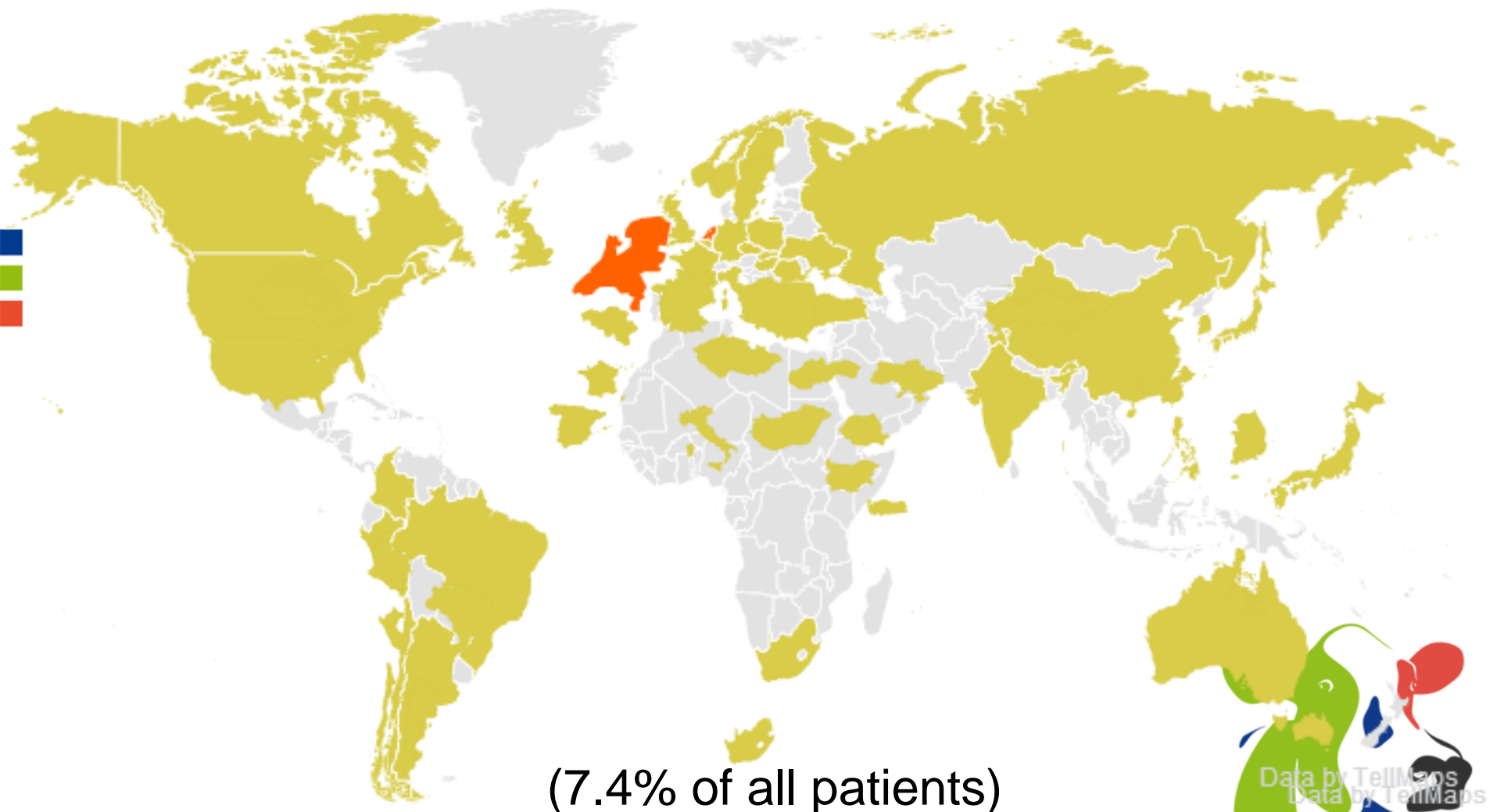
The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Bonaca at the TIMI Study Group, Cardiovascular Division, Brigham and Wom-



Netherlands outperforms Rest of World



21162 patients, 1143 sites, 31 countries, 6 continents





WCN

Werkgroep Cardiologische centra Nederland



Holland
Heart
House





Aims of the WCN

Change guidelines to improve patient care

Initiate and execute scientific drug research

Support member sites

GCP guidelines & Standard Operating Procedures

Education & conferences





WCN

Werkgroep Cardiologische centra Nederland

- 2000-3000 pts/ yr randomized in clinical trials
- Strong independent network of >55 cardiology sites
- Investigators in international study positions
- Authors of scientific publications





Low dose colchine in stable CAD

LoDoCo2

Hypothesis

Low dose colchicine will significantly reduce cardiovascular events in a stable CAD population

Australia & WCN The Netherlands





LoDoCo2

Key characteristics

- Double blind, randomised clinical trial
- 0.5 mg colchicine daily vs placebo
- Stable coronary artery disease
- Primary outcome:
 - Acute coronary syndrome
 - Out-of-hospital cardiac arrest
 - Ischemic stroke
- N = 4.115 (to detect 30% risk reduction over 3 yrs)





LoDoCo2

Potential & Hurdles

- Potential outcomes
 - An affordable drug for many
 - Potential savings > 25 million Euro / yr (RIVM)
 - Change of the guidelines
 - Prime example of drug rediscovery
- Hurdles
 - Financing LoDoCo2
 - Implementation (off-label prescription?)
- Parties involved:
 - Prescribers & Patients
 - Generic Pharma Industry
 - Ministry, Zon Mw, CBG, ZIN



European Heart Journal (2013) 34, 2949–3003
doi:10.1093/eurheartj/ehz296

ESC GUIDELINES

2013 ESC guidelines on the management of stable coronary artery disease

The Task Force on the management of stable coronary artery disease of the European Society of Cardiology

Task Force Members: Gilles Montalescot* (Chairperson) (France), Udo Sechtem* (Chairperson) (Germany), Stephan Achenbach (Germany), Felicità Andreotti (Italy), Chris Arden (UK), Andrzej Budaj (Poland), Raffaele Bugiardini (Italy), Filippo Crea (Italy), Thomas Cuisset (France), Carlo Di Mario (UK), J. Rafael Ferreira (Portugal), Bernard J. Gersh (USA), Anselm K. Gitt (Germany), Jean-Sebastien Hulot (France), Nikolaus Marx (Germany), Lionel H. Opie (South Africa), Matthias Pfisterer (Switzerland), Eva Prescott (Denmark), Frank Ruschitzka (Switzerland), Manel Sabaté (Spain), Roxy Senior (UK), David Paul Taggart (UK), Ernst E. van der Wall (Netherlands), Christiaan J.M. Vrints (Belgium).

ESC Committee for Practice Guidelines (CPG): Jose Luis Zamorano (Chairperson) (Spain), Stephan Achenbach (Germany), Helmut Baumgartner (Germany), Jeroen J. Bax (Netherlands), Héctor Bueno (Spain), Veronica Dean

