Hart- en Vaatziekten

Geen kruid tegen gewassen?

Arend Mosterd

Cardioloog, Meander Medisch Centrum Amersfoort

Voorzitter, Werkgroep Cardiologische centra Nederland (WCN)

Goed Gebruik Geneesmiddelen

ZonMw congres Amsterdam 6 april 2017

Disclosure van belangen
Arend Mosterd

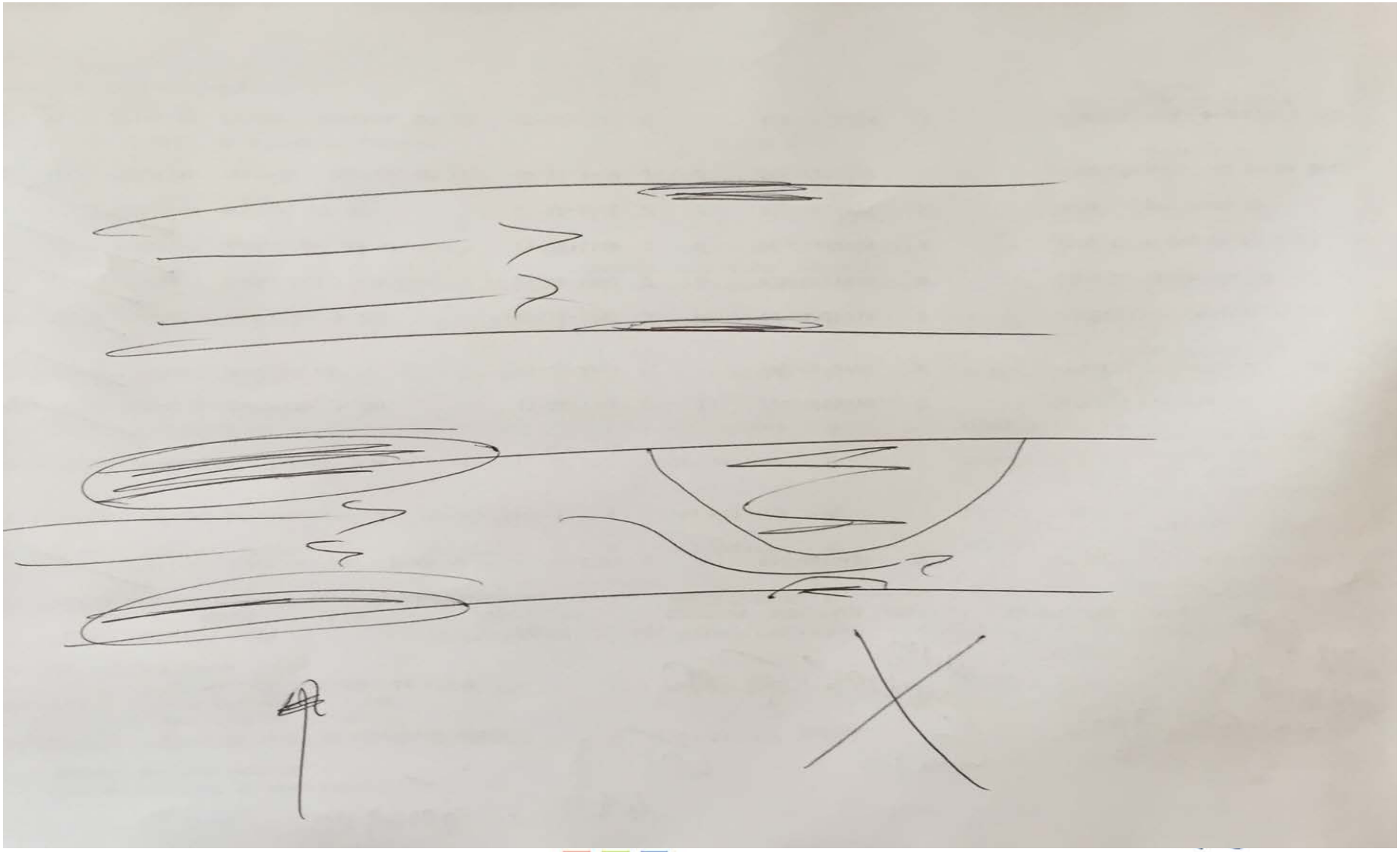
(potentiële) belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
• Onderzoeksgeld / Honorarium • Aandelen: geen in individuele farma.	• Pfizer (Spire - Lipiden) • Bayer / MSD (Victoria – HF) • Novartis (Paradigm & Relax AHF - HF) • ZON Mw 80-84800-98-15092 (LoDoCo2)

Nieuwe cholesterolremmer voorkomt hartziekte, maar wel tegen een hoge prijs

Twee jaar geleden kwam in Nederland een nieuw type cholesterolremmer op de markt. Nu blijkt: hij werkt. Maar het helpen van één patiënt kost een half miljoen euro.

Wim Köhler
17 maart 2017

De spreekkamer van de cardioloog



Coronairlijden

Coronairlijden

Coronairlijden

Onrust in de vaatwand

Stolsel leidt tot afsluiting…

… & afsluiting leidt tot infarct

Voorkomen

1) Vaatwandkalk → Cholesterolverlaging

2) Stolselvorming

3) Openscheuren

Voorkomen

1) Vaatwandkalk → Cholesterolverlaging

2) Stolselvorming →Bloedverdunners

3) Openscheuren

Voorkomen

1) Vaatwandkalk → Cholesterolverlaging

2) Stolselvorming →Bloedverdunners

3) Openscheuren → Ontstekingsremmers?

Inflammatie & Coronairlijden

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 67, NO. 9, 2016

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacc.2015.12.048

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

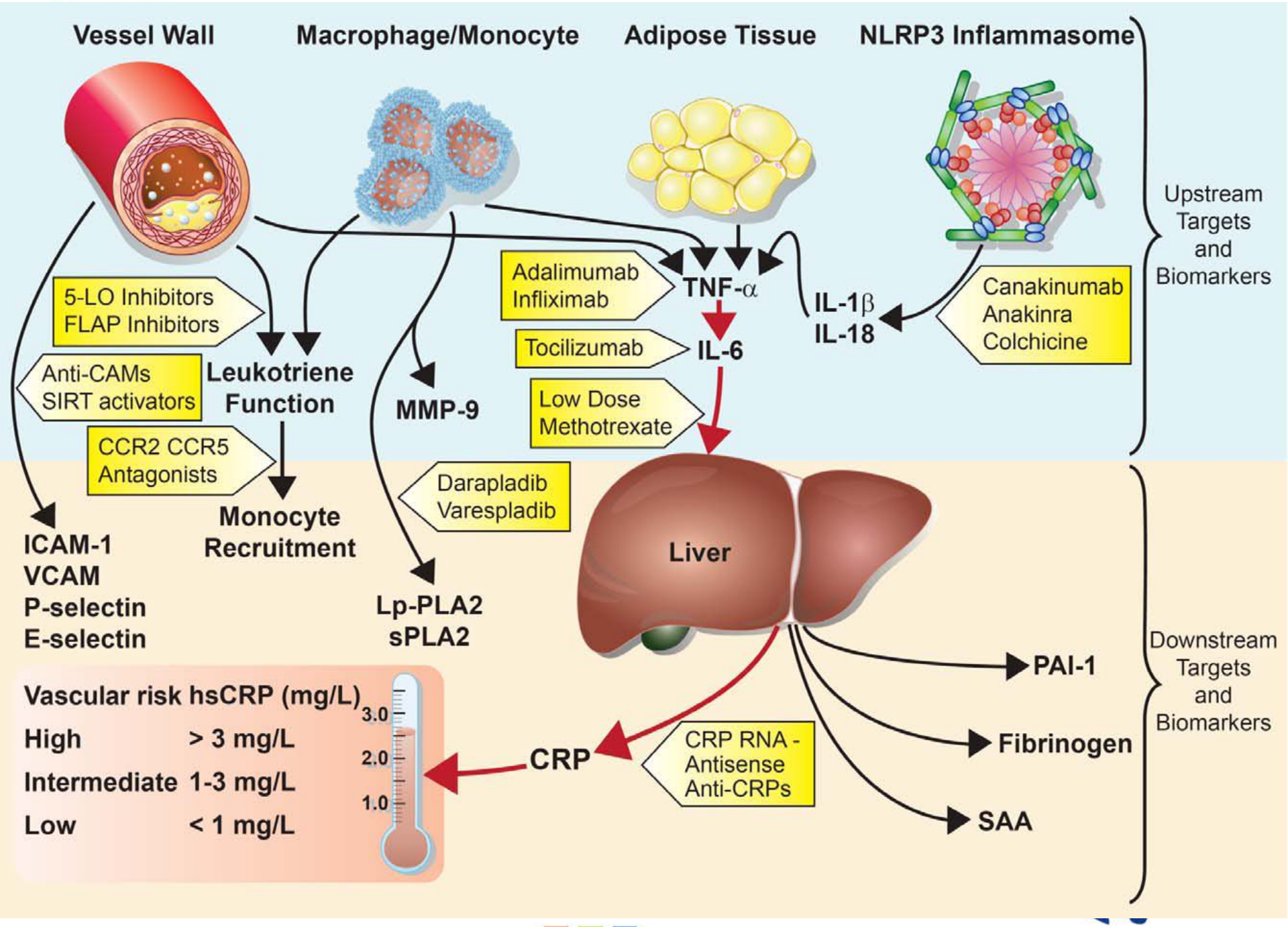
Leukocytes Link Local and Systemic Inflammation in Ischemic Cardiovascular Disease

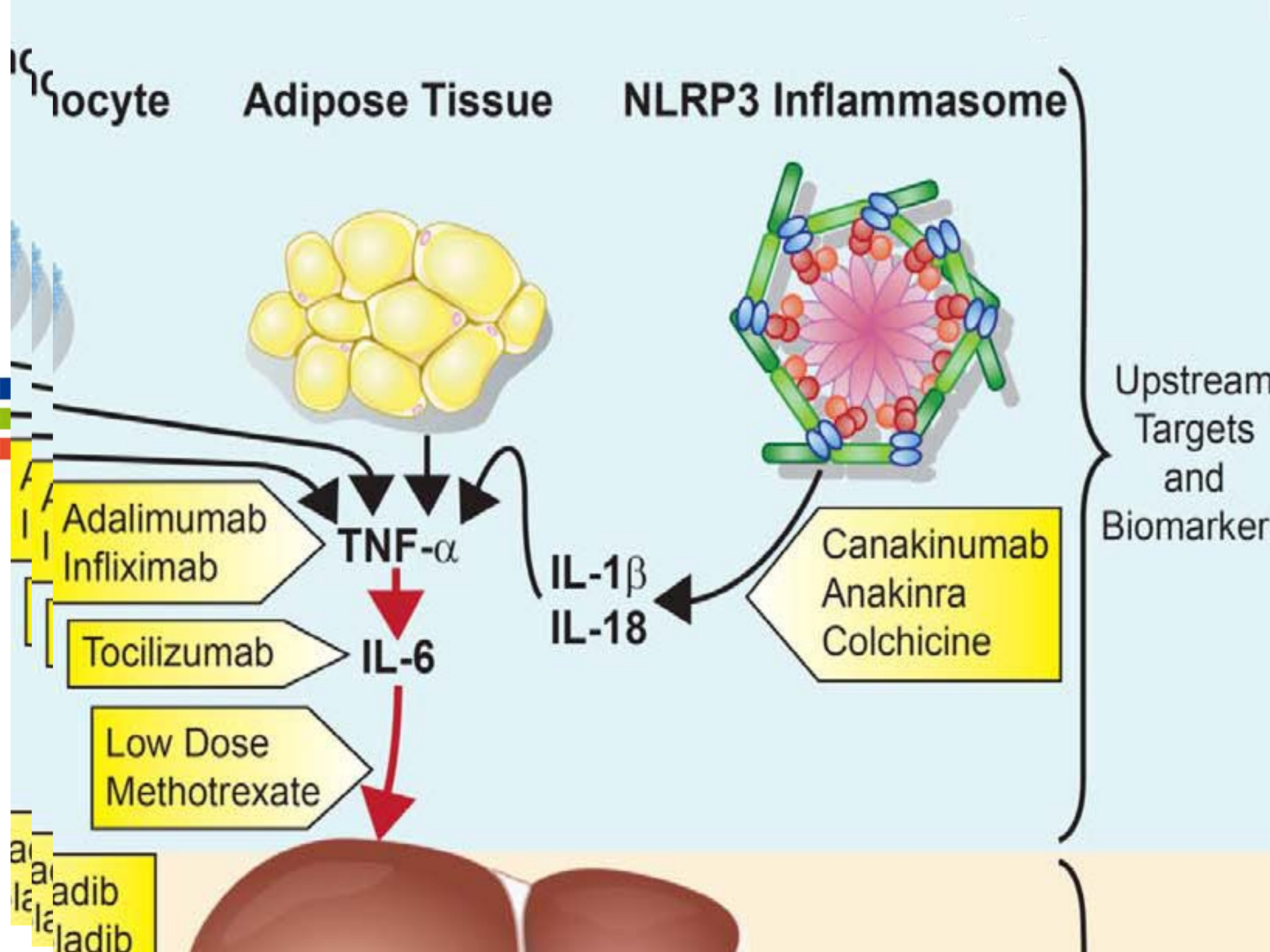
An Expanded "Cardiovascular Continuum"

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


Vessel Wall
Macrophage/Monocyte
Adipose Tissue
NLRP3 Inflammasome
Upstream Targets and Biomarkers
5-LO Inhibitors
FLAP Inhibitors
Anti-CAMs
SIRT activators
Leukotriene Function
CCR2 CCR5 Antagonists
Monocyte Recruitment
ICAM-1
VCAM
P-selectin
E-selectin
MMP-9
Lp-PLA2
sPLA2
Adalimumab
Infliximab
TNF-α
Tocilizumab
IL-6
IL-1β
IL-18
Canakinumab
Anakinra
Colchicine
Low Dose Methotrexate
Darapladib
Varespladib
Liver
PAI-1
Fibrinogen
SAA
CRP
CRP RNA - Antisense Anti-CRPs
Downstream Targets and Biomarkers
Vascular risk hsCRP (mg/L)
High > 3 mg/L
Intermediate 1-3 mg/L
Low < 1 mg/L
3.0
2.0
1.0

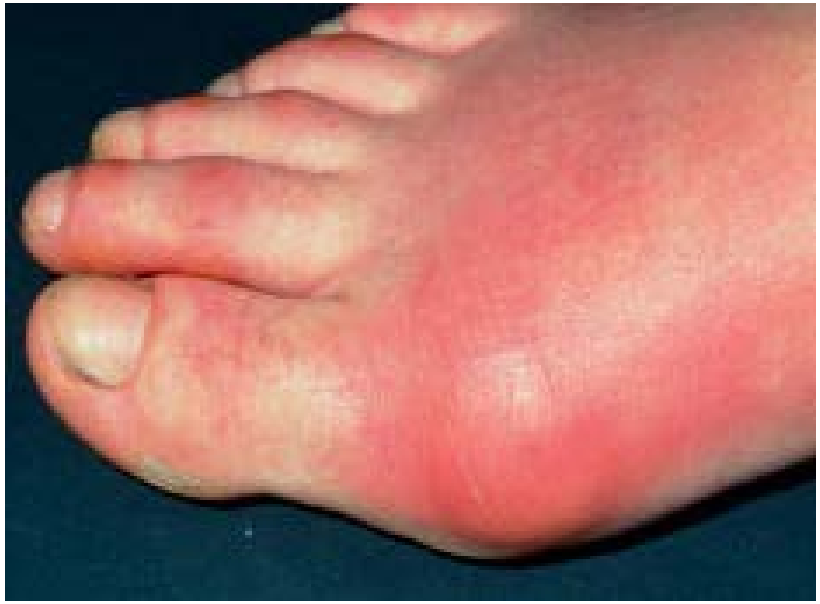

ocyte
Adipose Tissue
NLRP3 Inflammasome
Upstream
Targets
and
Biomarker
Adalimumab
Infliximab
TNF-α
IL-1β
IL-18
Canakinumab
Anakinra
Colchicine
Tocilizumab
IL-6
Low Dose
Methotrexate

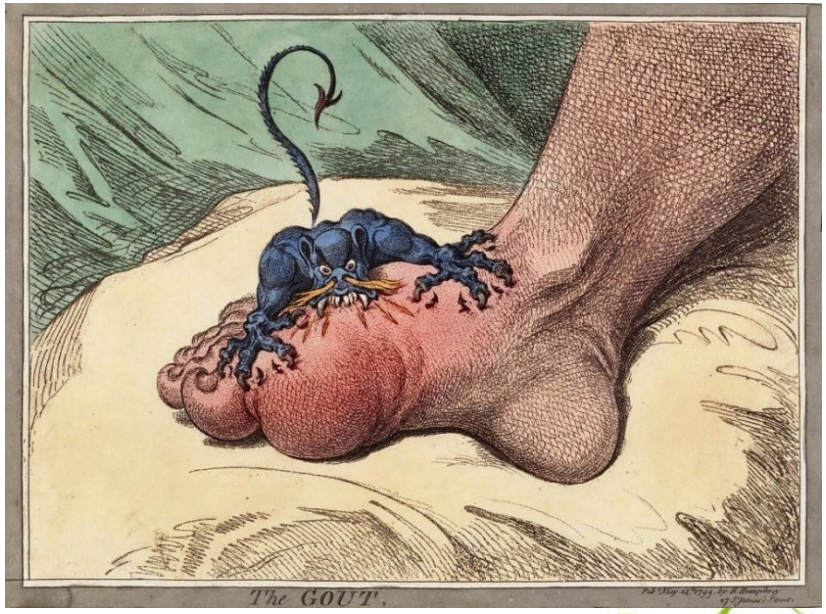
Herfsttijloos

(Colchicum autumnale)

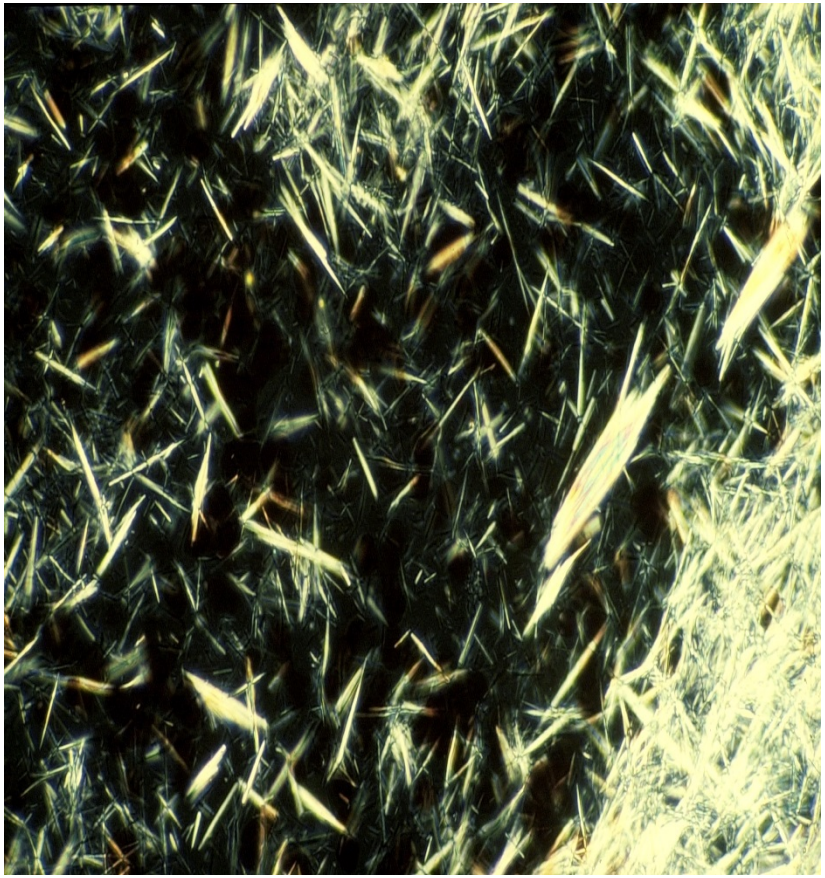
- Krokus – achtige plant
- Meer dan 2000 jaar geleden al gebruikt
- Sterke ontstekingsremming
- Niet duur

Jicht



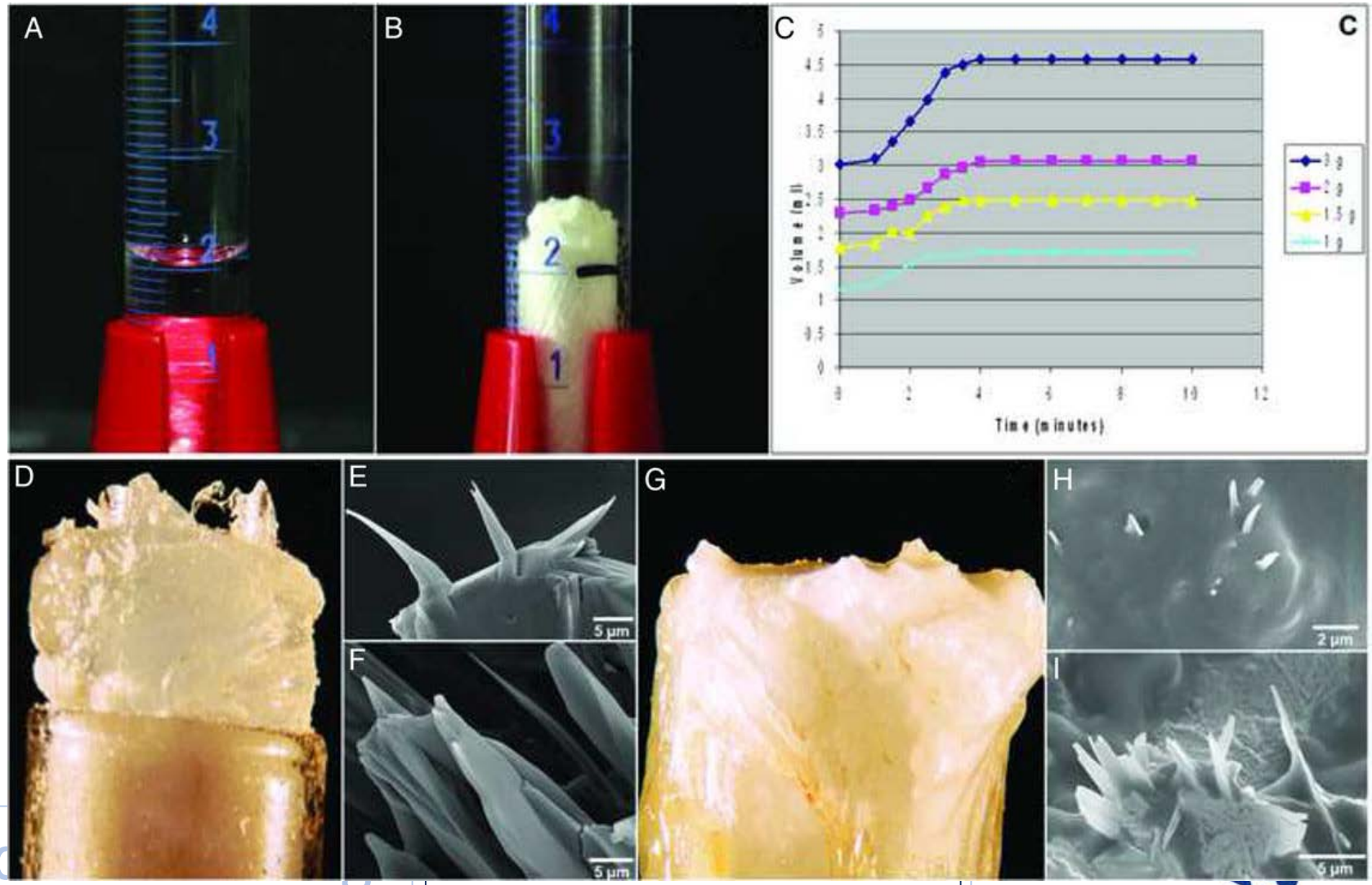


Jicht in de vaatwand?



Cholesterol crystal induced arterial inflammation

Janoudi A. et al. Eur Heart J 2016;37:1959-67



Low Dose Colchicine (LoDoCo) to prevent CV events

Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 4, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.10.027

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

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.

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

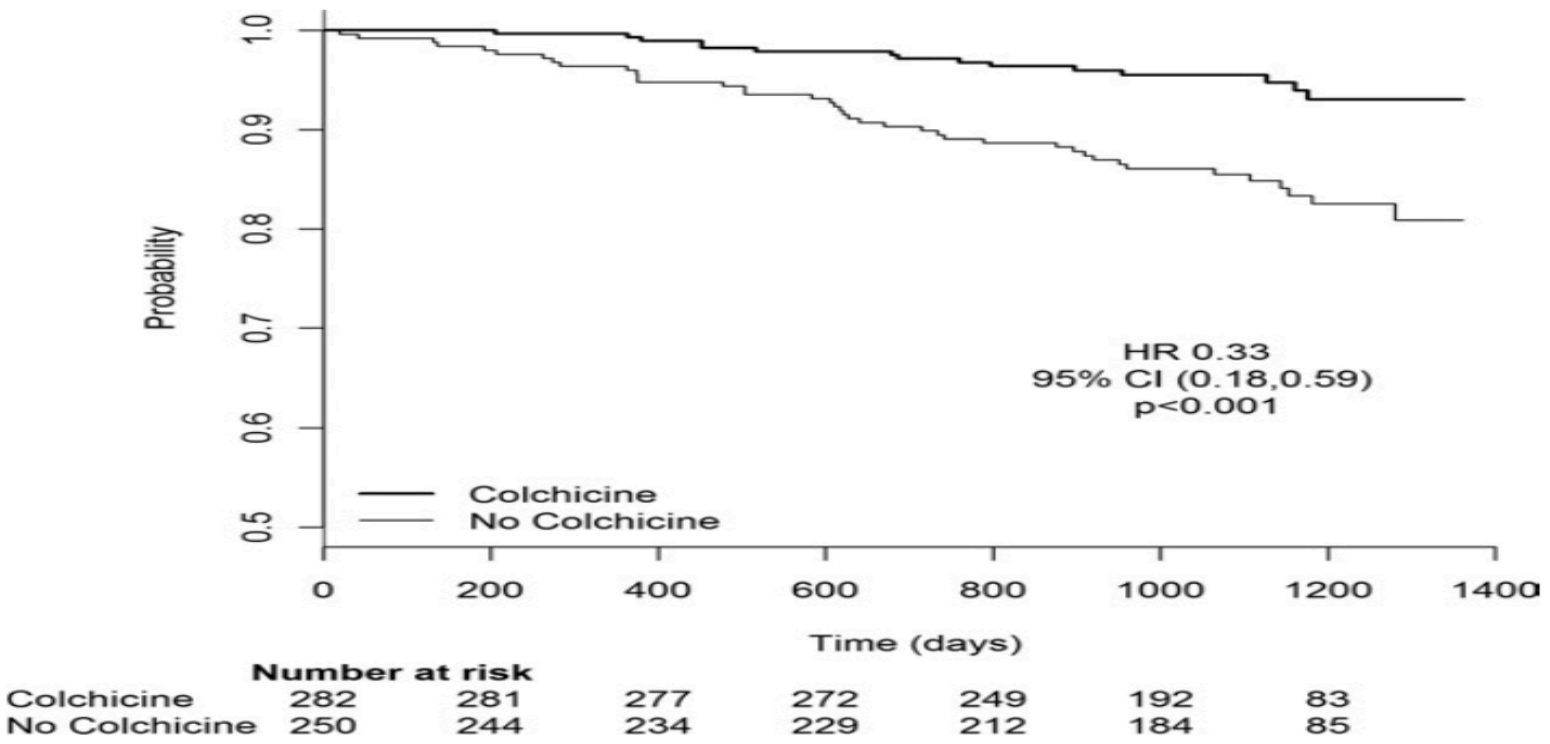


Figure 2 **Freedom From the Primary Outcome**

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 AMI, 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.

WCN

Werkgroep Cardiologische centra Nederland

Holland Heart House

WCN
Werkgroep Cardiologische centra Nederland

- 1000-3000 pts/yr randomized in clinical trials
  - Innovative pharma
  - Investigator initiated

- Strong independent network of >55 cardiology sites
- Investigators in international study positions
- Authors of scientific publications

- *Change guidelines to improve patient care*

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:
  - Cardiovascular death
  - Non fatal acute coronary syndrome
  - Non fatal ischemic stroke
- N = 4.115 (to detect 30% risk reduction over 3 yrs)

April 2016

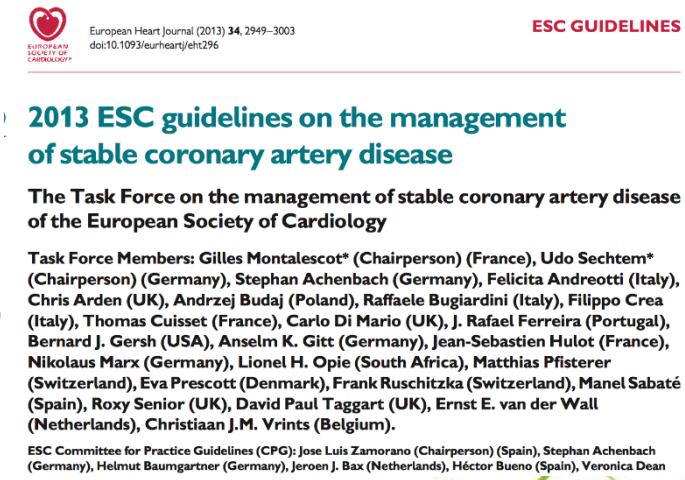
- De Amerikaanse voorverkiezingen in New York worden gewonnen door Hillary Clinton (Democraten) en Donald Trump (Republikeinen).
- Ecuador wordt in korte tijd twee maal getroffen door een aardbeving. De eerste heeft een kracht van 7,8 op de schaal van Richter en de twee een kracht van 6,1 op de schaal van Richter.
- Popster Prince overlijdt op 21 april 2016. Hij werd 57 jaar oud.
- Venezuela kampt met extreme droogte. Hierdoor ontstaat er een tekort aan energie.
- De omvang van het schandaal rondom Panama Papers wordt steeds groter.

LoDoCo2
Potential & Hurdles as of April 2016

- 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/eht296

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), Felicita 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

LoDoCo2
April 2017

- Potential outcomes
  - An affordable drug for many
  - Potential savings > 25 million Euro / yr (RIVM)
  - Change of the guidelines
  - Prime example of drug rediscovery

- Hurdles taken
  - Financing LoDoCo2
    - 20% WCN, in addition to pro bono collaboration of cardiologists
    - 40% TEVA / Disphar / Tio farma
    - 40% Zon MW GGG
  - Scientific Advice – joint session with CBG and ZIN (sept 2017)
    - Changes to protocol (endpoints / interim analyses)
    - Supporting innovation / drug rediscovery

LoDoCo2
Enrollment in the Netherlands

site #	plaats	run in	rand
1001	Alkmaar	173	110
1002	Amersfoort	125	68
1003	Apeldoorn	45	25
1004	Breda	47	28
1006	Den Bosch	10	-
1013	Zuyderland	47	33
1015	Haarlem/ Hoofddorp	2	-
1016	Meppel	77	55
1019	Sneek	59	41
1020	Veldhoven	16	4
totaal		601	364

March 29 2017

(CV) Drug Rediscovery - Challenges

- Penny wise, pound foolish
  - LoDoCo (and 6GT) – dogged enthusiasm of idealists
  - Need for a sustainable “business” model

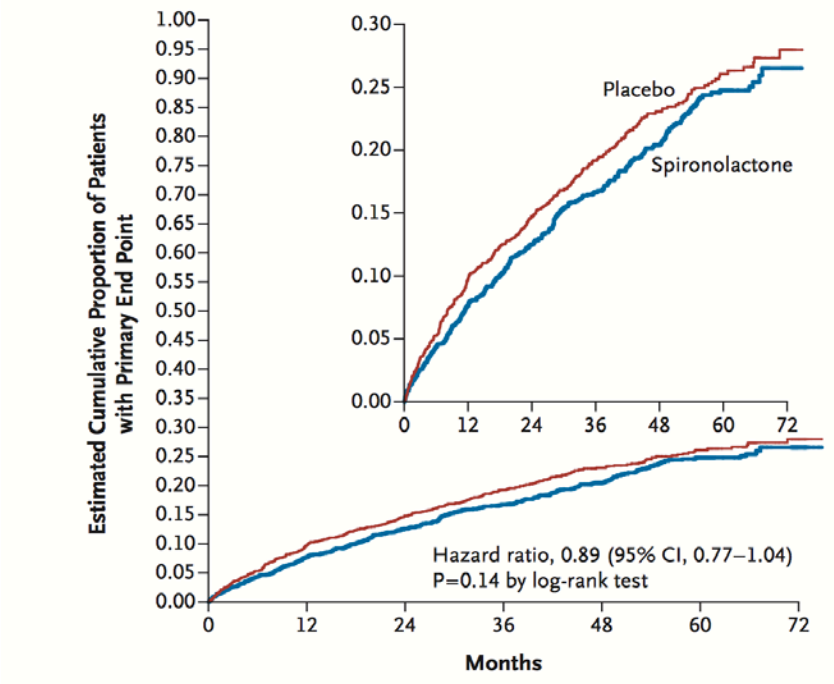
- “local” distraction: hospital pharmacies

(CV) Drug Rediscovery - Opportunities

- LoDoCo as blueprint for future projects
  - Fruitful collaboration with (generic) pharma
  - Strong cardiology network
    - Academic (NHLI – “from bedside to bench”) – PhD programs
    - Non academic (WCN)
  - Implementation of new drugs (indications) guaranteed
  - Netherlands Heart Foundation / Hart- en Vaatgroep
  - Ministry, Zon Mw, CBG, ZIN

(CV) Drug Rediscovery - Opportunities

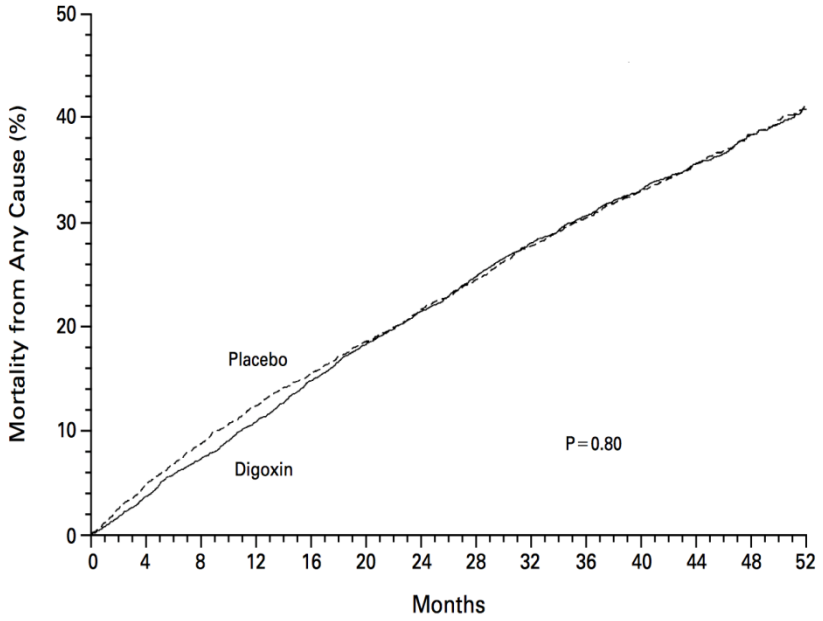
(CV) Drug Rediscovery - Opportunities



No. at Risk							
Spironolactone	1722	1502	1168	870	614	330	53
Placebo	1723	1462	1145	834	581	331	53

Figure 1. Kaplan–Meier Plot of Time to the First Confirmed Primary-Outcome Event.

The primary outcome was a composite of death from cardiovascular causes,



No. of Patients at Risk														
Placebo	3403	3239	3105	2976	2868	2758	2652	2551	2205	1881	1506	1168	734	339
Digoxin	3397	3269	3144	3019	2882	2759	2644	2531	2184	1840	1475	1156	737	335

Figure 1. Mortality in the Digoxin and Placebo Groups.

The number of patients at risk at each four-month interval is shown below the figure.

TOPCAT – Spironolacton vs placebo

Digoxine vs placebo