Lipiden en inflammatie
Wat is de relatie?
Lessen van Lodoco

Dr Fabrice MAC Martens
Cardioloog Deventer Ziekenhuis
Voorzitter WCN

Disclosure belangen spreker – Dr. FMAC Martens, cardioloog

(potentiële) Belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Amarin, Amgen, Astra Zeneca, Bayer, BMS, Boehringer, Daiichi Sankyo, GSK, MSD, Novartis, NovoNordisk, Pfizer, Sanofi
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk:	• Vergoeding voor presentaties en adviesraden op het gebied van CVRM (lipiden, antitrombotica en antidiabetica) • Namens de NVVC, lid commissie nieuwe nationale richtlijn CVRM, de werkgroep implementatie ESC-richtlijnen, en de Landelijke Stuurgroep CVRM • NVVC adviseur CVRM en medicatie • Voorzitter WCN

Inhoud

- The lower LDL for longer, the better it is
- Inflammation and atherosclerotic disease
- Lodoco
- Wat zou een relatie tussen lipiden en inflammatie kunnen zijn?

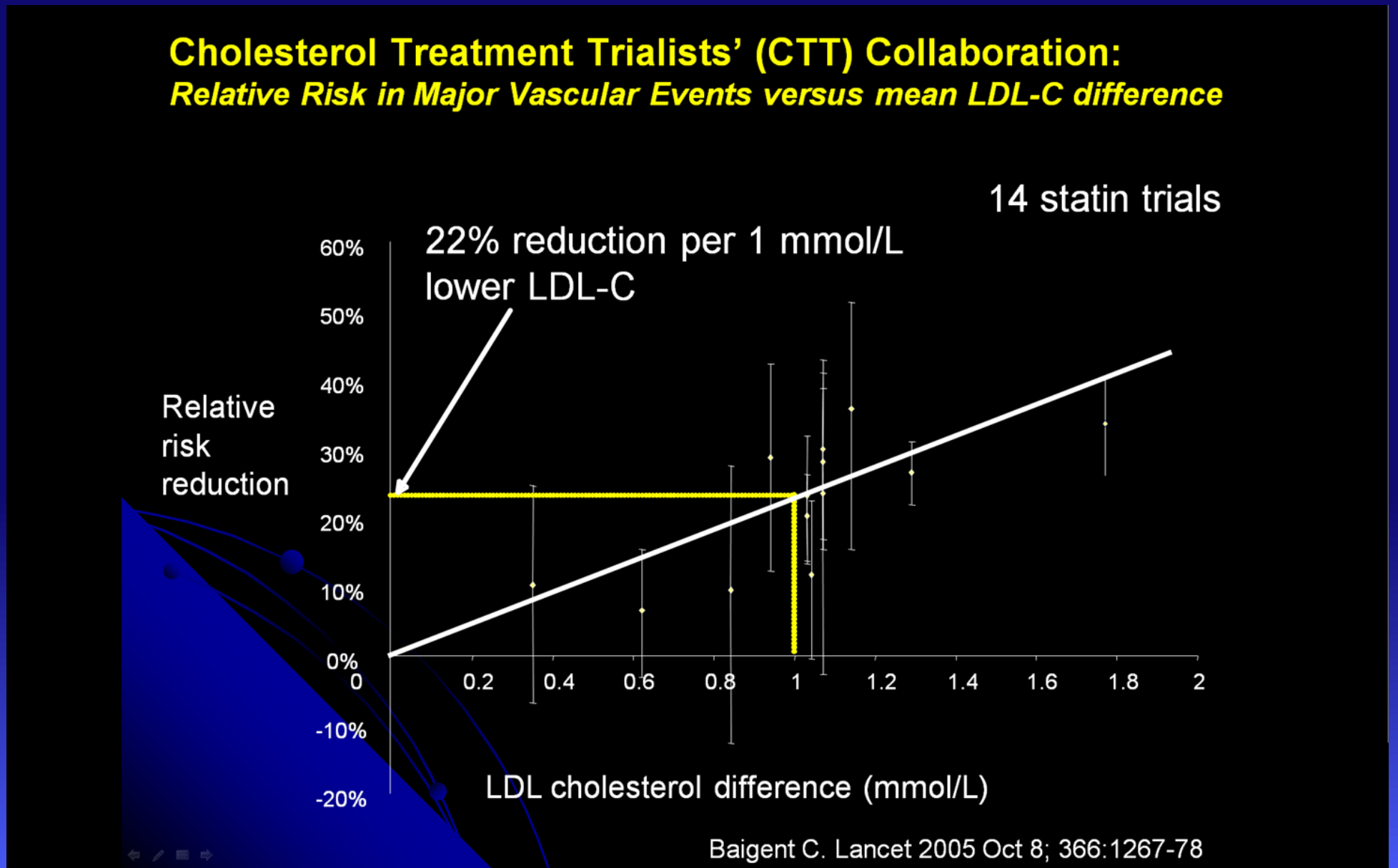
Is er een relatie tussen het cholesterol metabolism en inflammatoire processen?

a) Ja
b) Nee
c) Dat is ingewikkeld

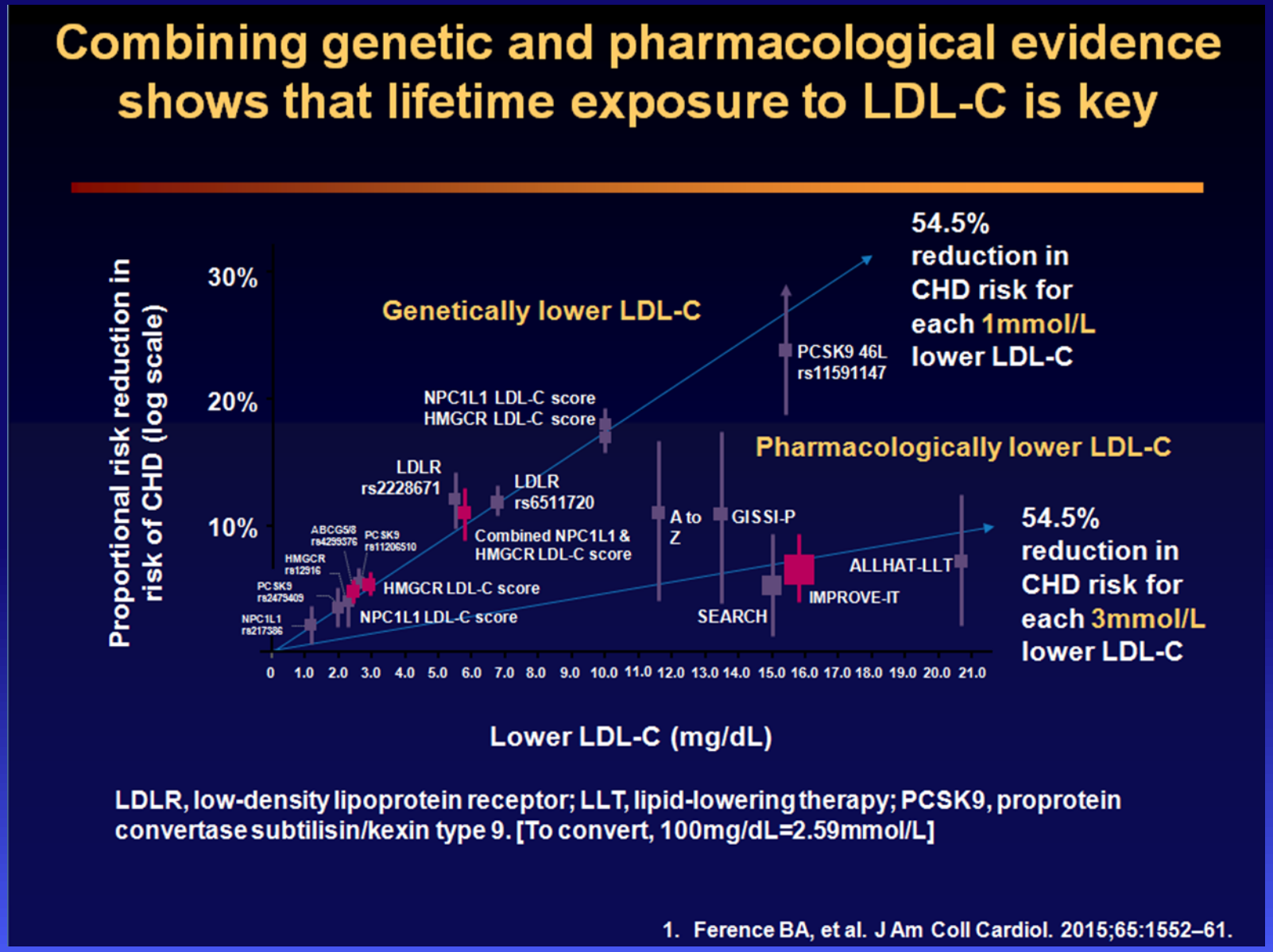
Inhoud

- The lower LDL for longer, the better it is

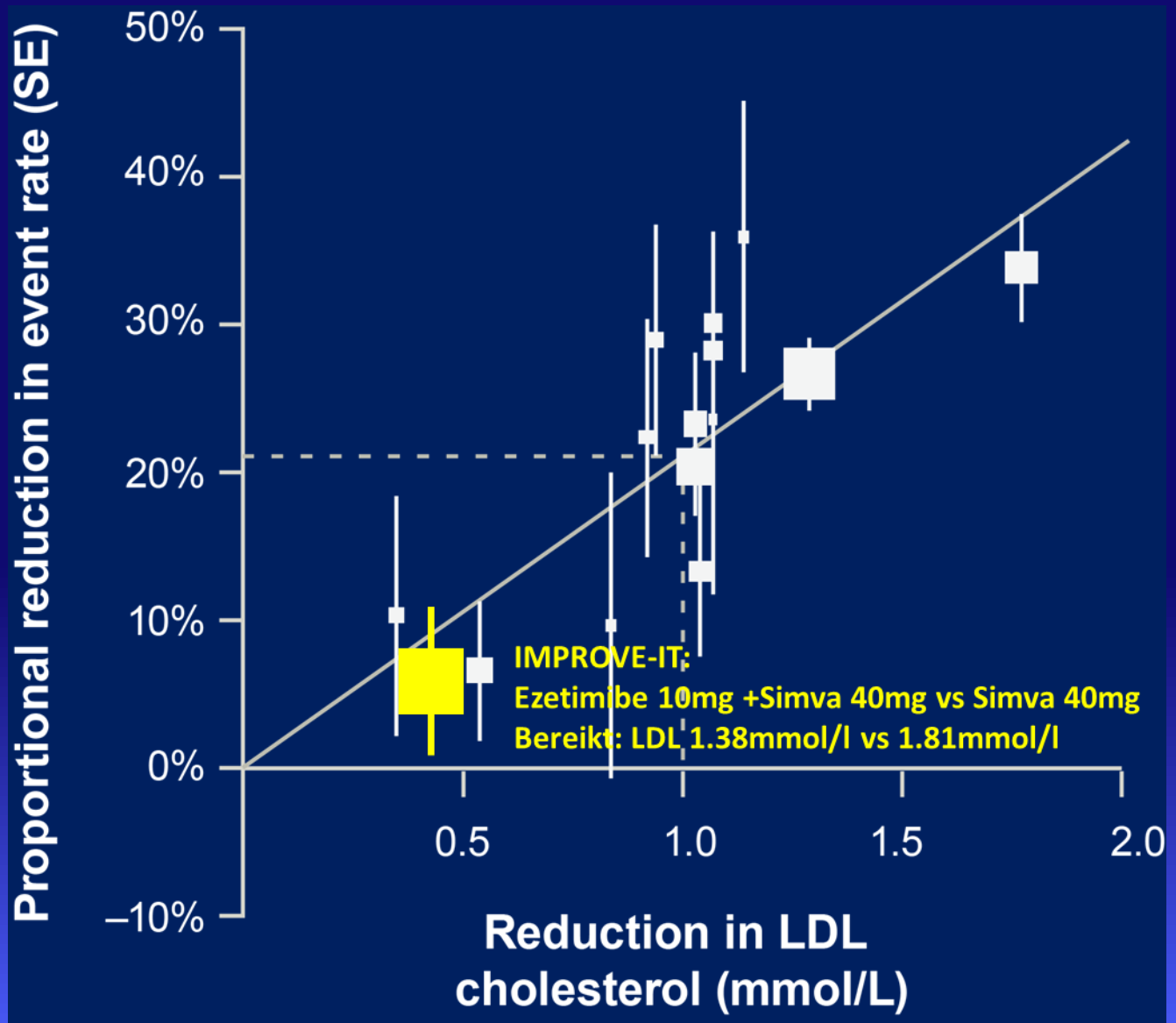
The lower LDL for longer, the better it is (statines)



The lower LDL for longer, the better it is (genetisch)

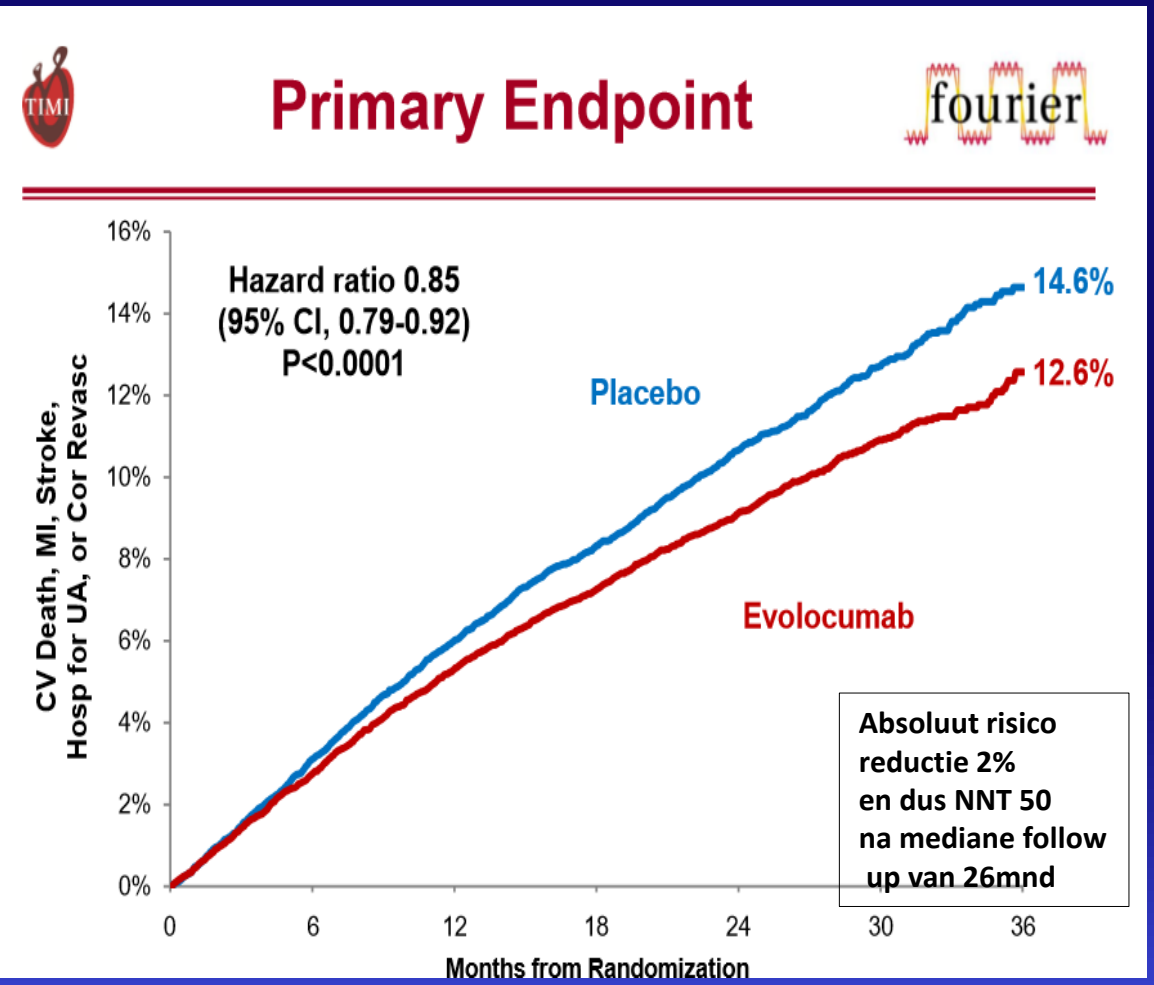


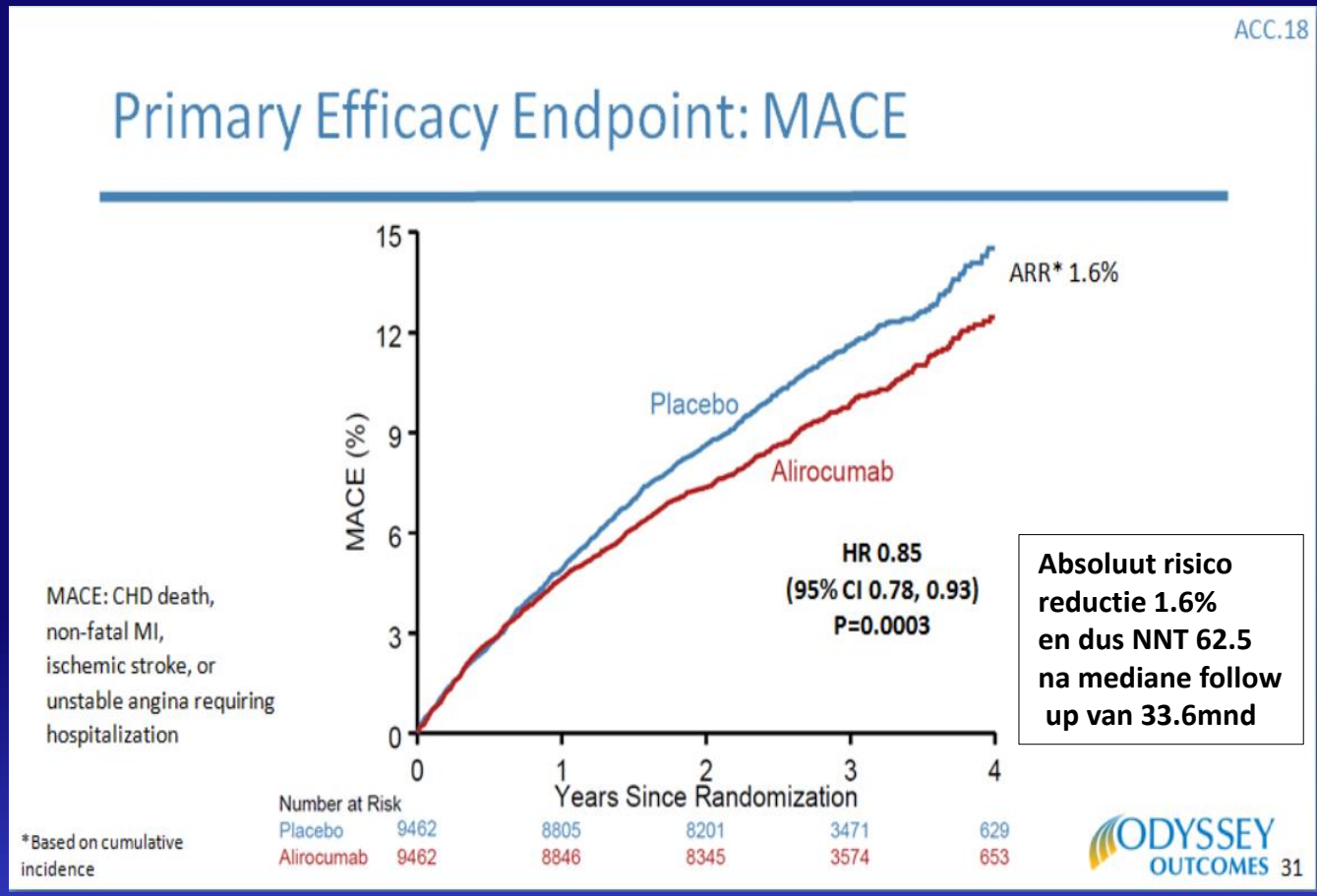
The lower LDL for longer, the better it is (icm Ezetimibe)



Improve-IT, NEJM 2015

The lower LDL for longer, the better it is (icm PCSK9i)





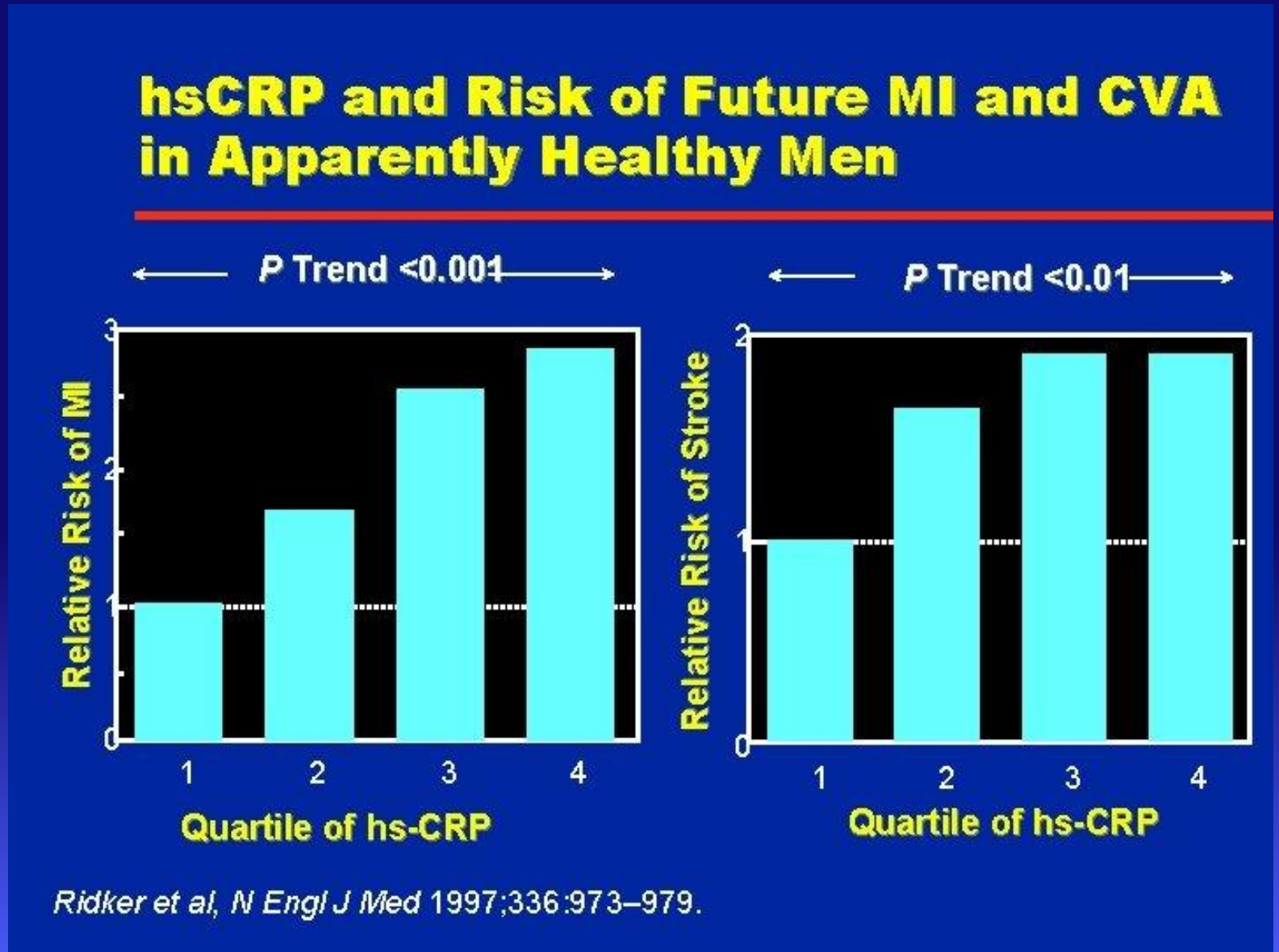
FOURIER, NEJM 2017

Odyssey Outcomes, NEJM 2018

Inhoud

- *The lower LDL for longer, the better it is*
- **Inflammation and atherosclerotic disease**

Inflammation and atherosclerotic disease (how it started)



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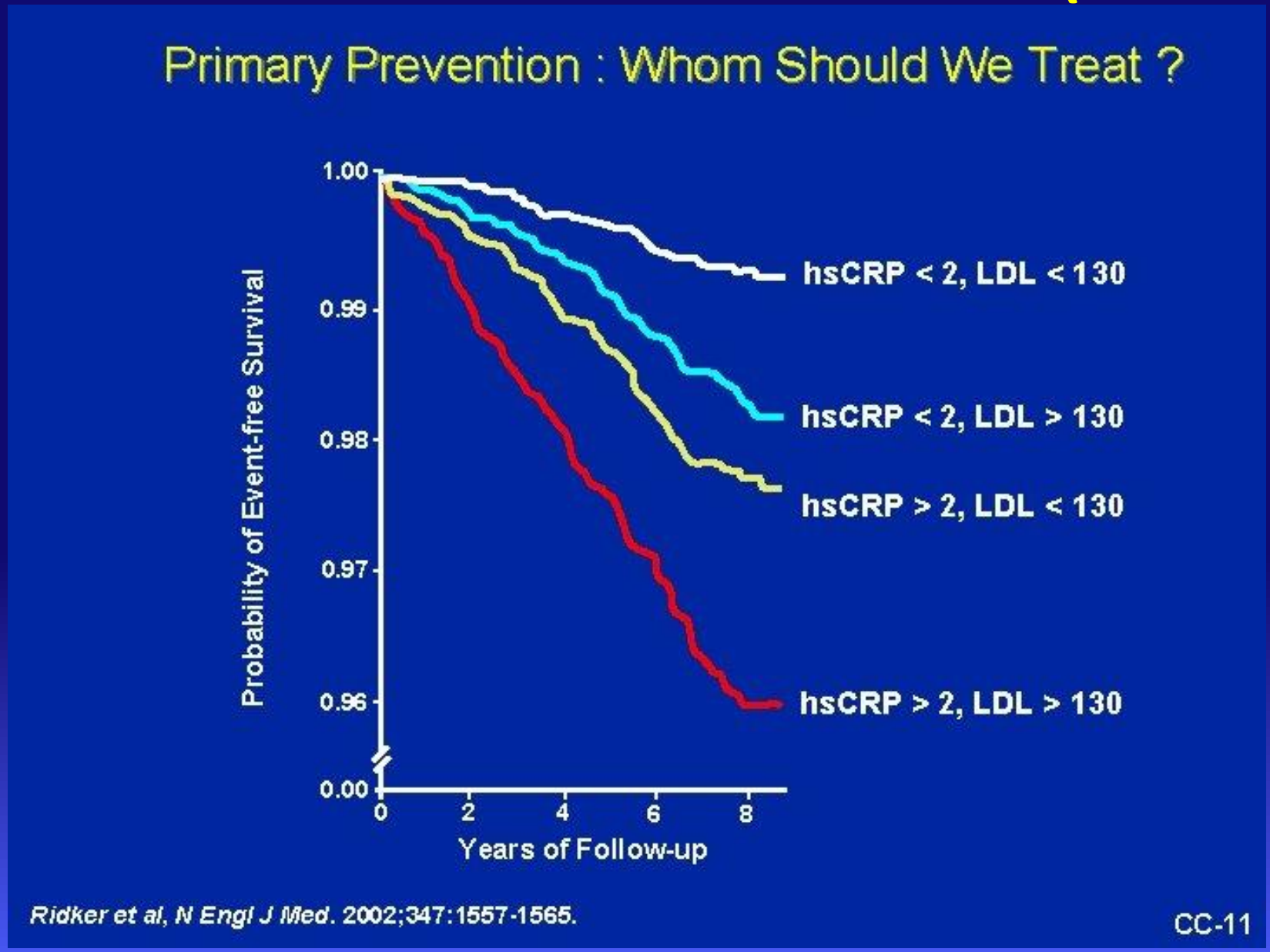

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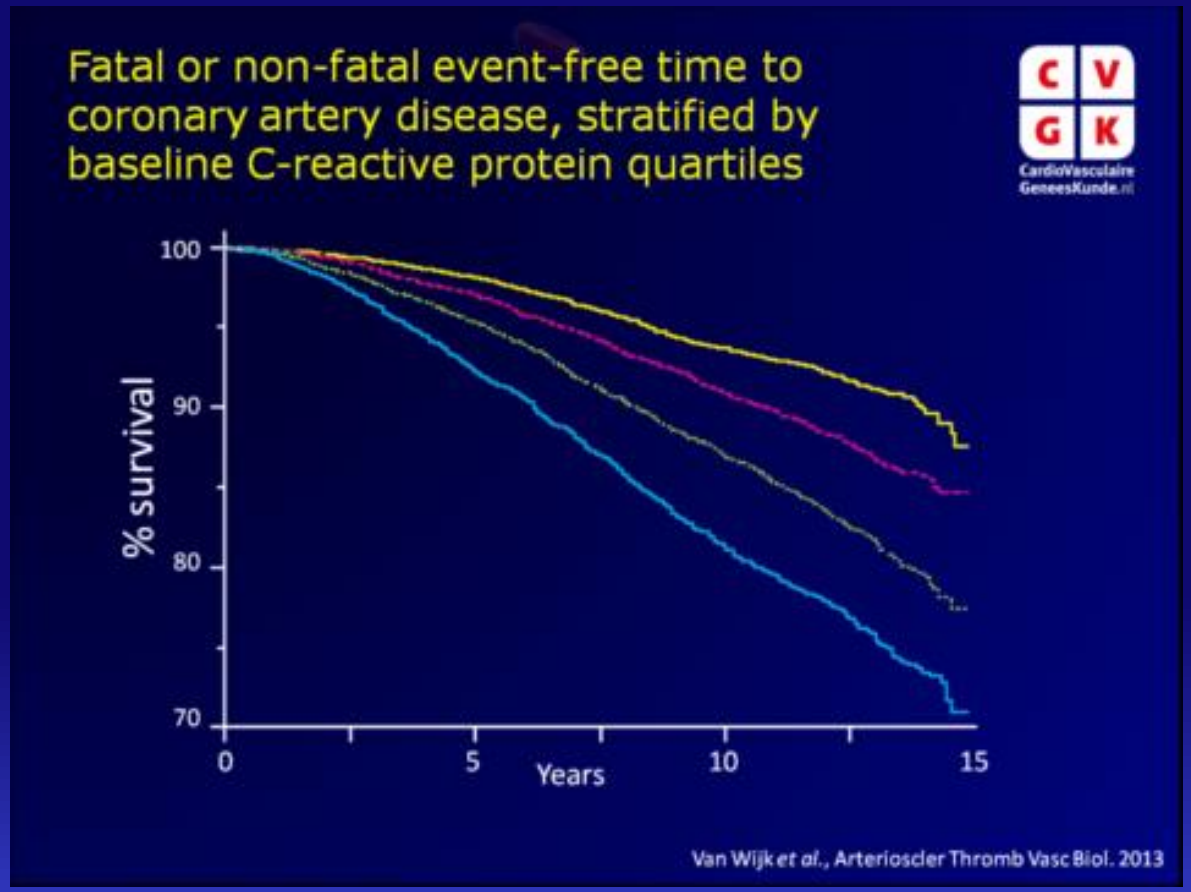
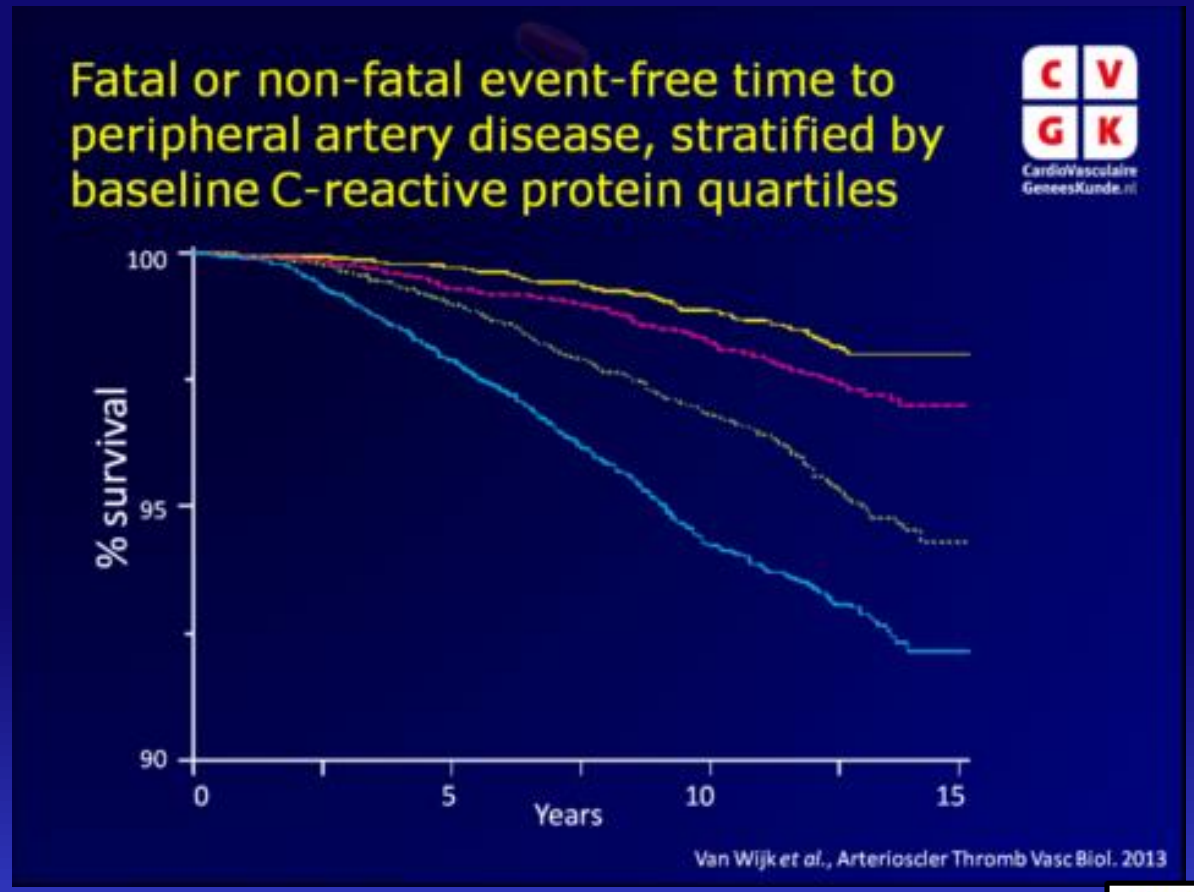
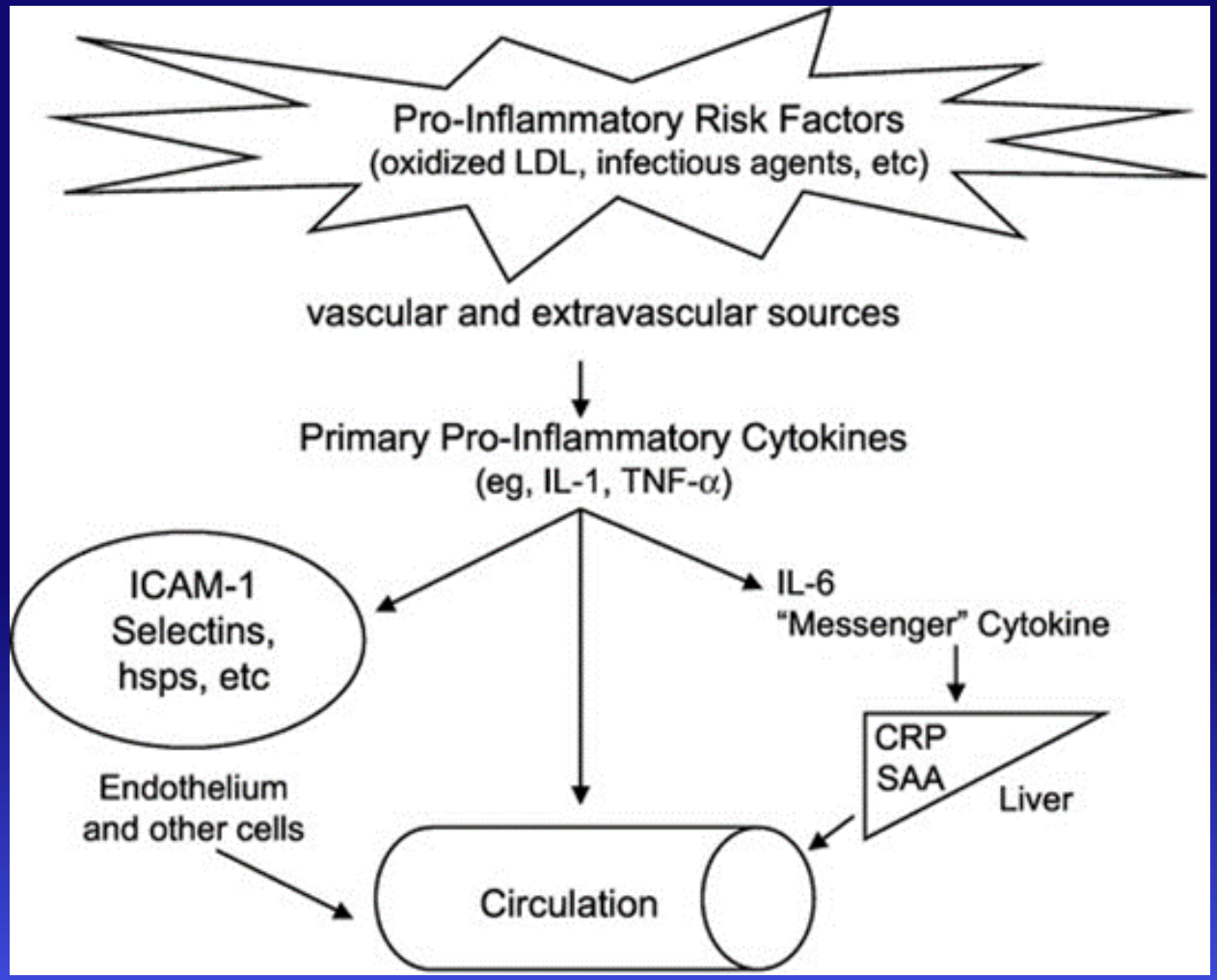




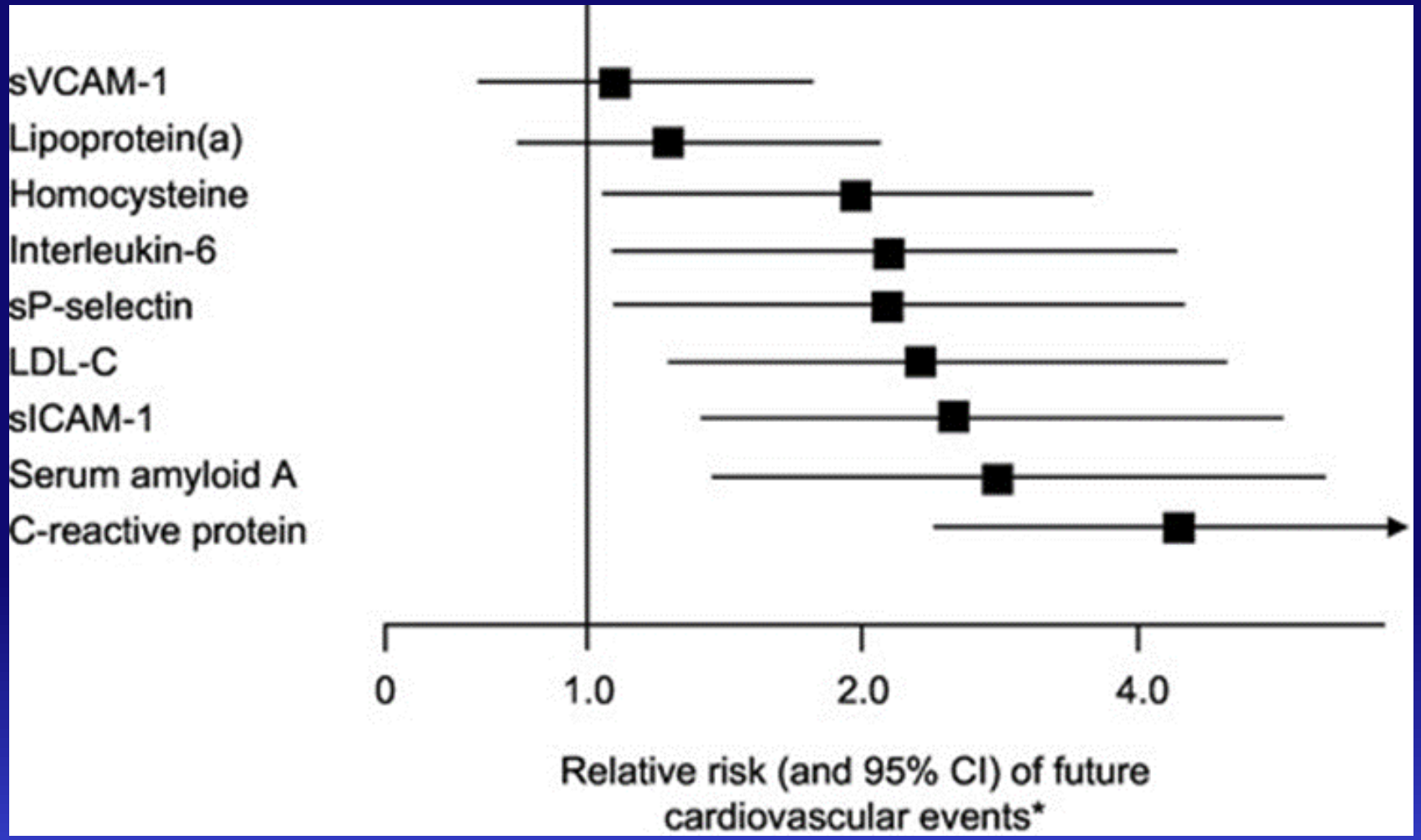
v Wijk, ATVB 2013

Inflammation and atherosclerotic disease (how it started)



James T Willerson and Paul M Ridker, Circulation. 2004;109:II-2–II-10

Inflammation and atherosclerotic disease (how it started)



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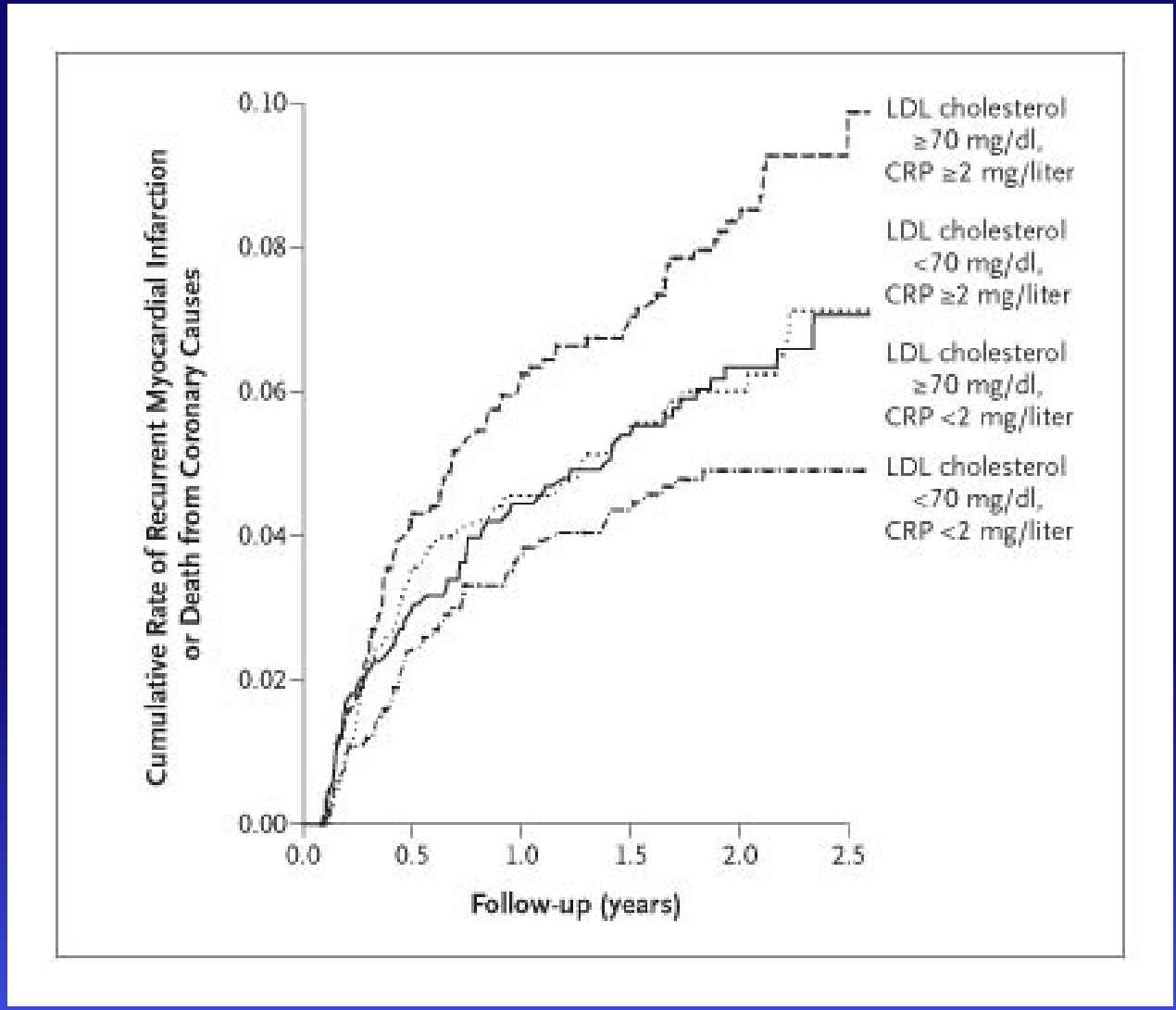
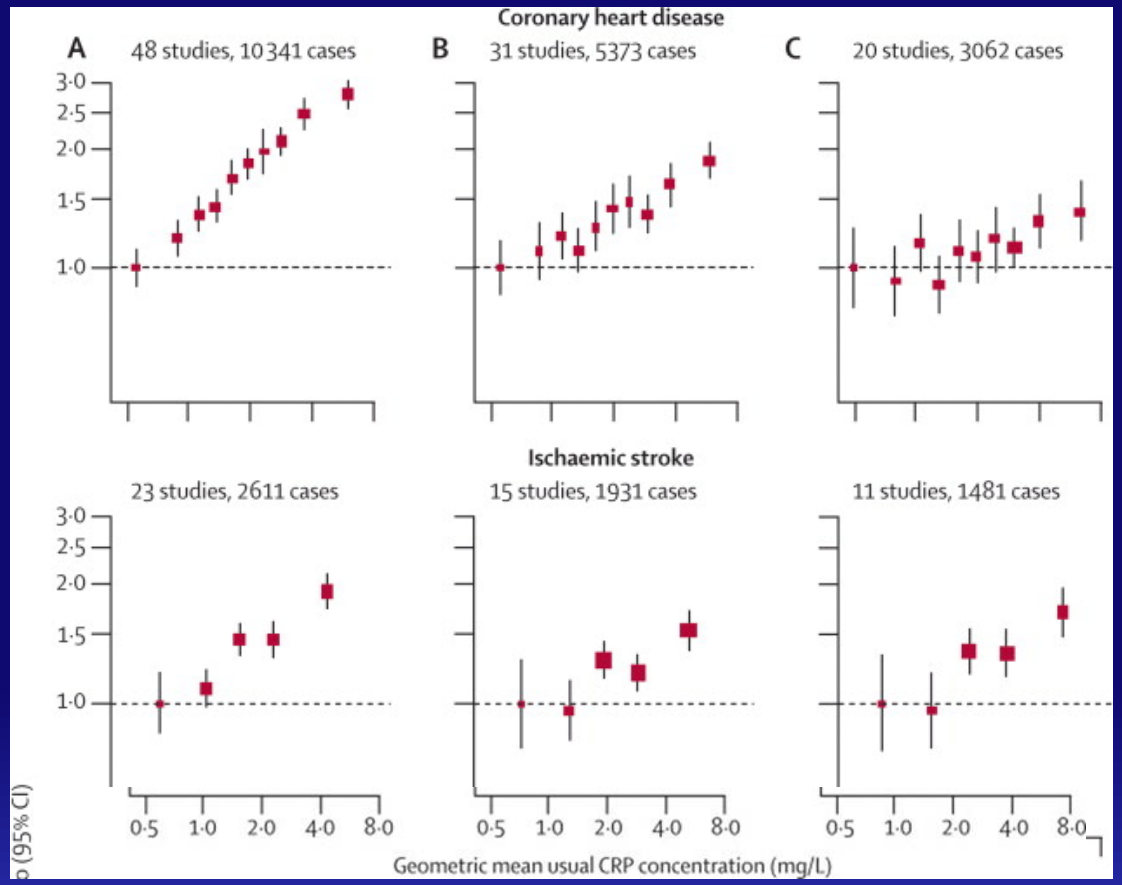
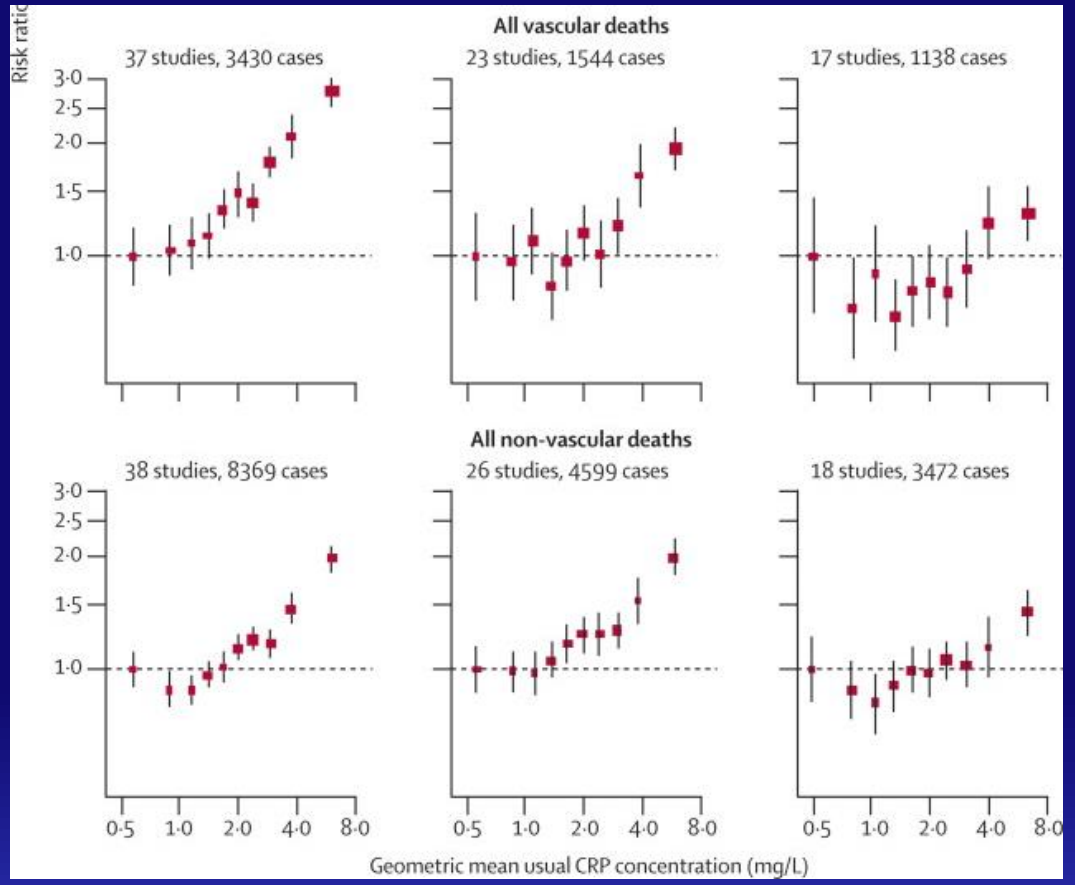
Inflammation and atherosclerotic disease (how it started)



Paul M Ridker, NEJM 2005

Inflammation and atherosclerotic disease (hs-CRP)



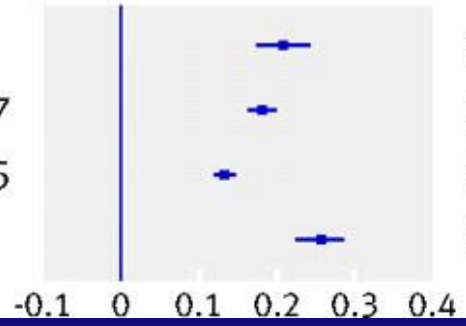


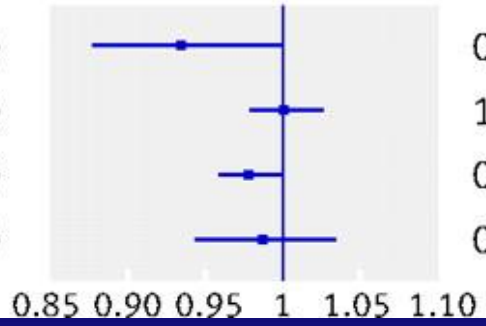
The adjustments were age, sex, and study only (A); age, sex, study, systolic blood pressure, smoking, history of diabetes, body-mass index, concentrations of $\log_e$ triglycerides, non-HDL cholesterol, and HDL cholesterol, and alcohol consumption (B); and (A) plus (B) plus fibrinogen (C). Studies with fewer than ten cases of any outcome were excluded from the analysis of that outcome.

Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010;375:132–40

Inflammation and atherosclerotic disease (genetisch)

Single nucleotide polymorphism	Allele frequency*	No of studies/cases /participants†	Per allele higher mean ln CRP (95% CI), mg/L	Per allele higher mean ln CRP (95% CI), mg/L	Per allele risk ratio for CHD (95% CI)	Per allele risk ratio for CHD (95% CI)
rs3093077	0.06	19/15 133/96 807		0.21 (0.17 to 0.24)		0.93 (0.87 to 1.00)
rs1205	0.67	43/40 527/172 567		0.18 (0.16 to 0.20)		1.00 (0.98 to 1.02)
rs1130864	0.30	41/37 145/157 905		0.13 (0.12 to 0.15)		0.98 (0.96 to 1.00)
rs1800947	0.94	31/31 636/93 507		0.26 (0.23 to 0.29)		0.99 (0.94 to 1.03)





Estimates of **association** of each single nucleotide polymorphism with ln concentrations of C reactive protein and risk of coronary heart disease (CHD). **No CAUSAL ROLE for hs-CRP.**

CCGC C-Reactive Protein Coronary Heart Disease Genetics Collaboration. Association between C reactive protein and coronary heart disease: mendelianrandomisationanalysis based on individual participant data. BMJ 2011;342:d548.

Inflammation and atherosclerotic disease

Despite such overwhelming evidence, a causal role for C-reactive protein in atherogenesis has remained highly controversial. First, C-reactive protein is significantly associated with various established cardiovascular risk factors including central obesity, hypertension, hypertriglyceridaemia, and low HDL cholesterol concentrations, making it difficult to discern whether C-reactive protein is a cause of coronary heart disease risk or merely a bystander to established risk factors. [4] The entanglement between C-reactive

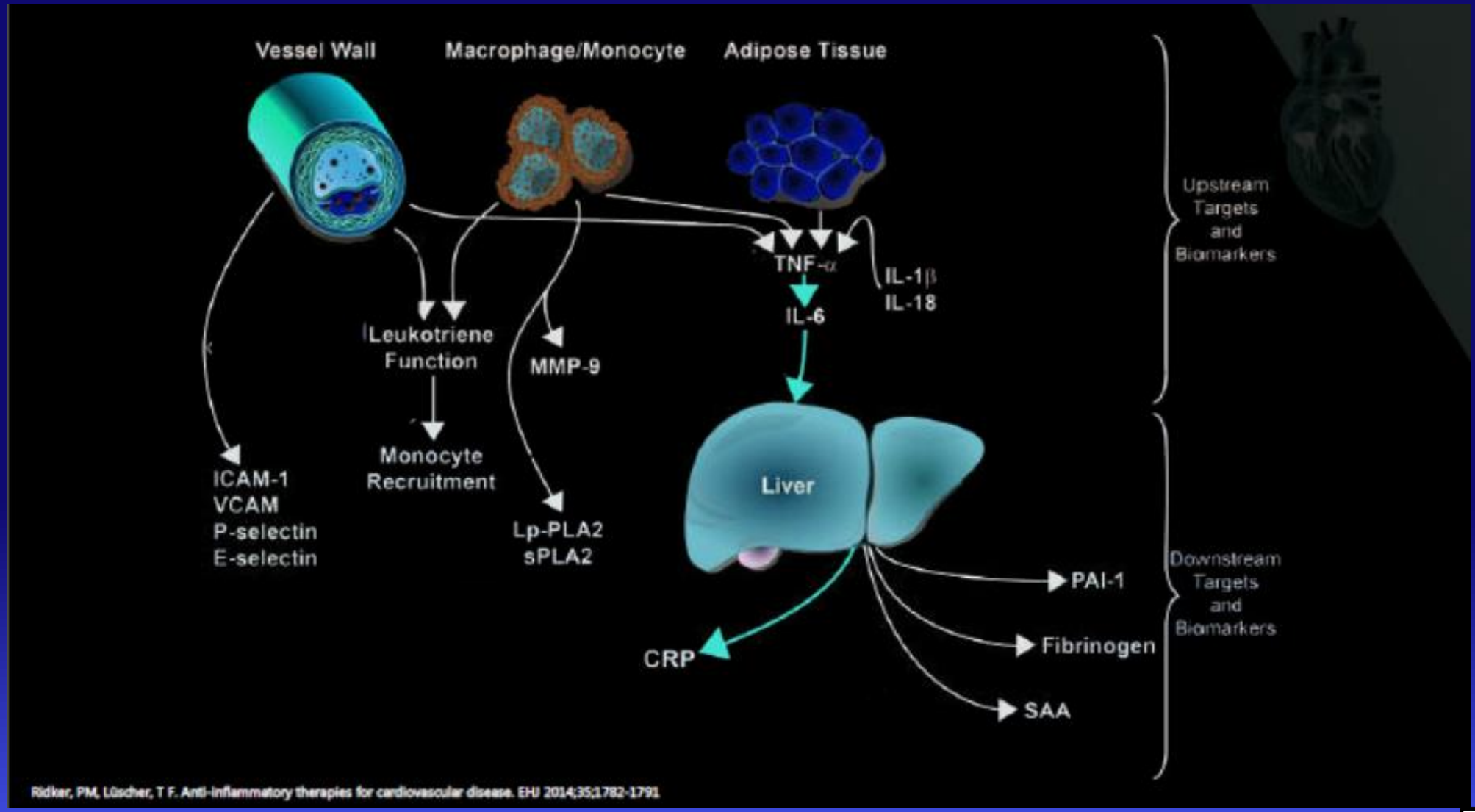
S Matthijs Boekholdt and Erik SG Stroes, Lancet, The, 2012-03-31, Volume 379, Issue 9822, Pages 1176-1178
Comment on “The interleukin-6 pathway and atherosclerosis”

Inflammation and atherosclerotic disease

causality of C-reactive protein in atherogenesis remains to be shown. Second, there is currently no evidence to show that selective targeting of inflammatory pathways modulates cardiovascular risk. The anti-inflammatory agents darapladib and varespladib, which target phospholipase activity, have shown encouraging results in early clinical trials using surrogate outcomes, but large-scale outcome trials with these agents as well as other anti-inflammatory compounds including methotrexate and canakinumab, an antibody targeting interleukin 1β, are ongoing. 6 7 8 9 However, the potential risks of these strategies consisting of systemic immunosuppression and adverse cardiometabolic effects have emphasised the need for further evidence that inflammation is causally involved in atherogenesis and concomitant cardiovascular risk.

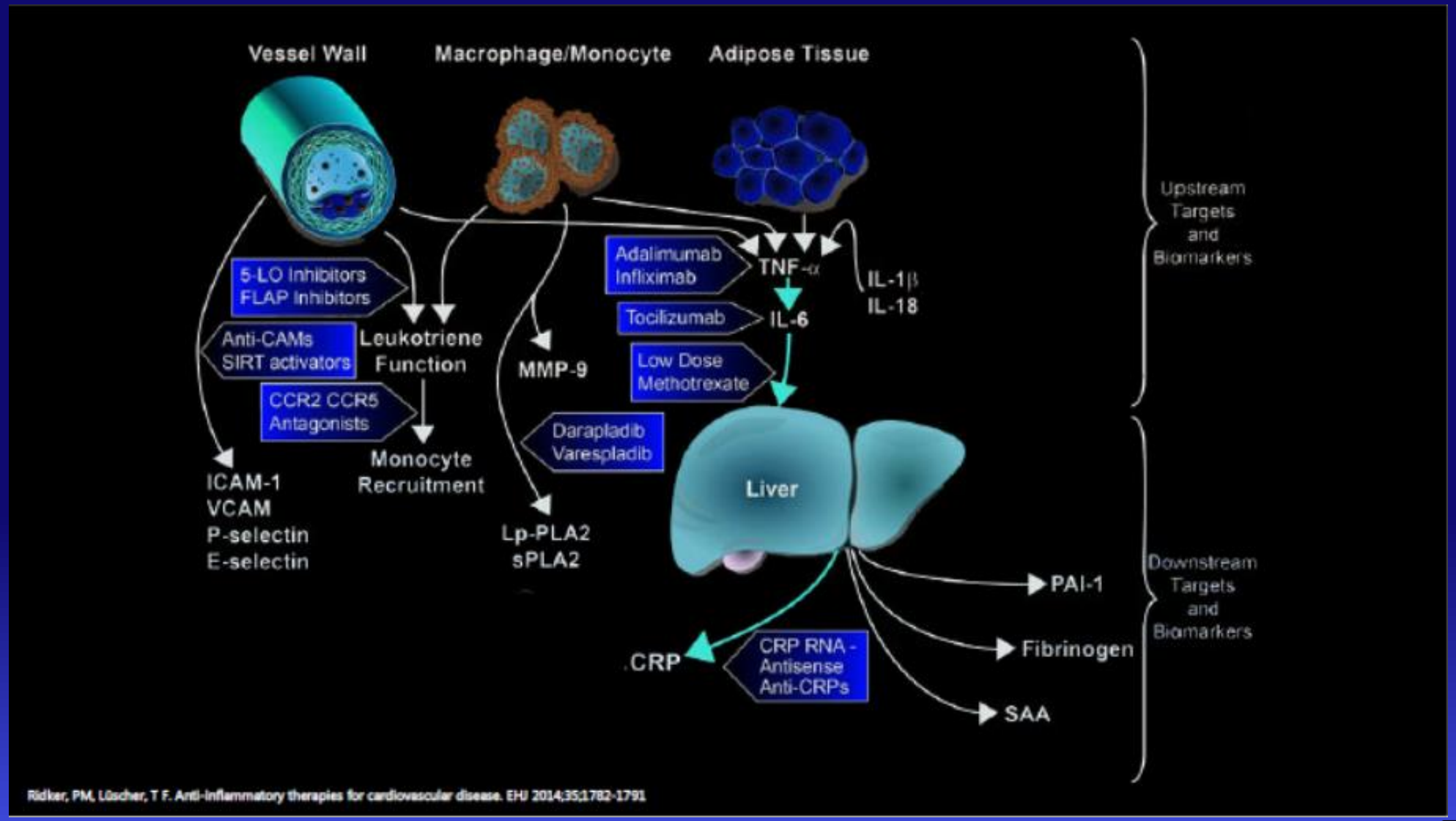
S Matthijs Boekholdt and Erik SG Stroes, Lancet, The, 2012-03-31, Volume 379, Issue 9822, Pages 1176-1178
Comment on “The interleukin-6 pathway and atherosclerosis”

Inflammation and atherosclerotic disease (mechanisms)



Ridker, PM, Lüscher, T F. Anti-inflammatory therapies for cardiovascular disease. EHJ 2014;35;1782-1791

Inflammation and atherosclerotic disease (targets)



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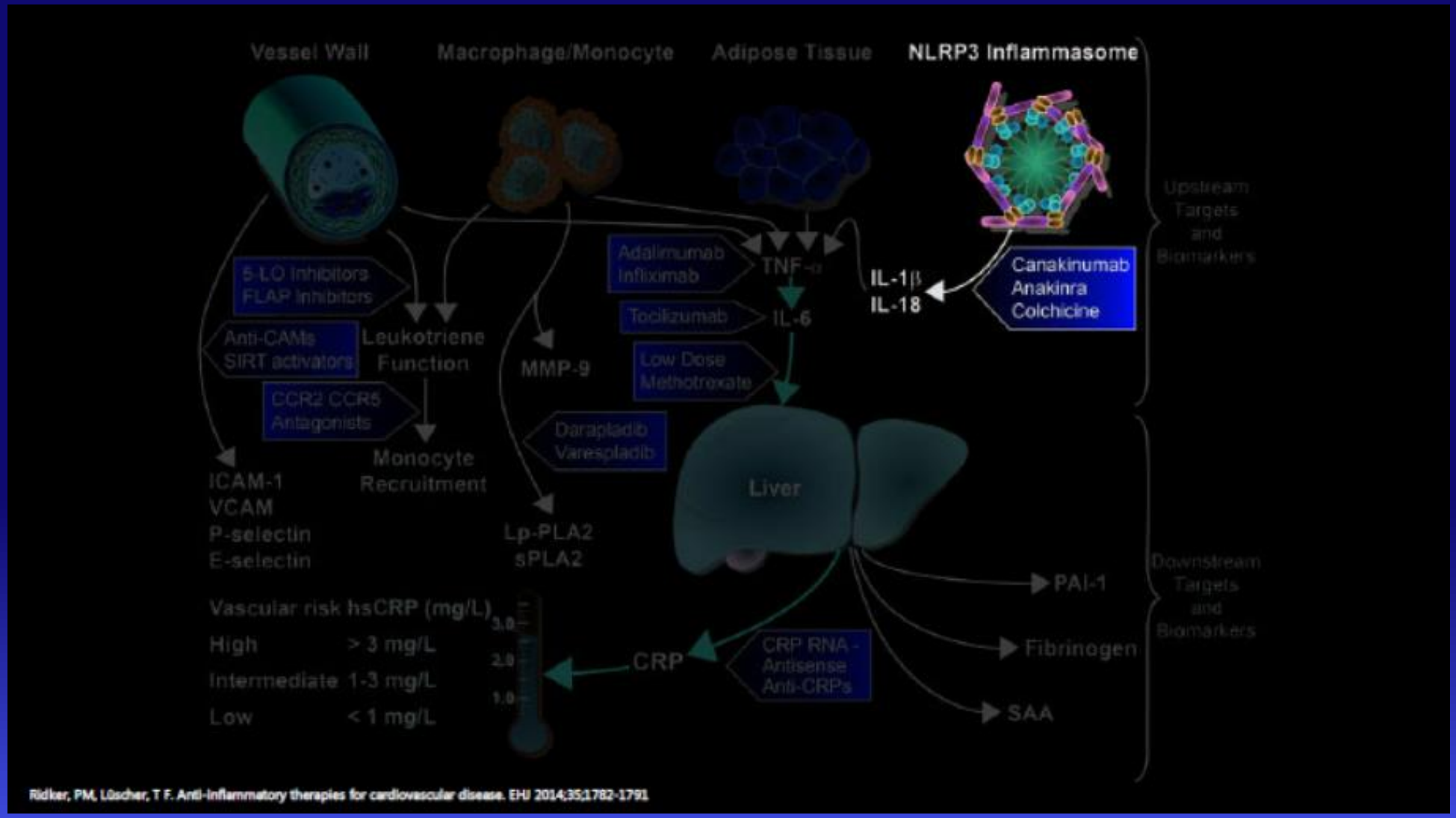

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Inhoud

- *The lower LDL for longer, the better it is*
- *Inflammation and atherosclerotic disease*
- **Lodoco**

Background

Inflammation is integral to the onset & progression of atherosclerosis.[1]

Colchicine is an ancient drug with broad anti-inflammatory effects:

- long-term treatment of gout and familial Mediterranean fever
- also effective in treatment of pericarditis
- use in gout associated with reduced CV risk.

Repurposing colchicine for coronary disease took a leap of faith "in the confident hope of a miracle".[2]

1. P Libby et al. 2018 JACC
2. M de Bertendona. 1583 Admiral of the Spanish Armada

Background

CANTOS proved that the specific anti-inflammatory effect of canakinumab reduced CV events in high-risk coronary patients.[1]

COLCOT proved that colchicine reduced CV events in patients following recent myocardial infarction.[2]

Evidence to support the routine use of colchicine for secondary prevention in patients with chronic coronary disease is limited.

Autumn Crocus
(*Colchicum autumnale*)

1. PM Ridker et al. 2017 NEJM
2. JC Tardif et al. 2019 NEJM

Objective: To determine whether colchicine 0.5mg once daily prevents CV events in chronic coronary disease

Design: Investigator-initiated, double-blind, placebo-controlled trial

Enrolment: Began in Australia (GenesisCare) in August 2014
Expanded to The Netherlands (Dutch Network for Cardiovascular Research - WCN) in October 2016

COLLEGE TER
BEOORDELING VAN
GENEESMIDDELEN

Protocol

Patients aged 35 – 82 years with proven coronary disease

No advanced renal disease, heart failure or severe valvular heart disease

↓

30-day open label run-in of colchicine 0.5mg daily

↓

Tolerant, clinically stable and willing

↓

Colchicine | **Placebo**

Planned to begin close-out 12 months after the last participant had been randomized

If 331 primary events had accrued – sufficient to detect a 30% effect of therapy with 90% power

6528

Enrolled

91.3% Tolerated open label therapy

5522

Randomized

Followed for a median of 29 months (12-64 months)

10.5% in each arm discontinued trial medication

5521

Close-out

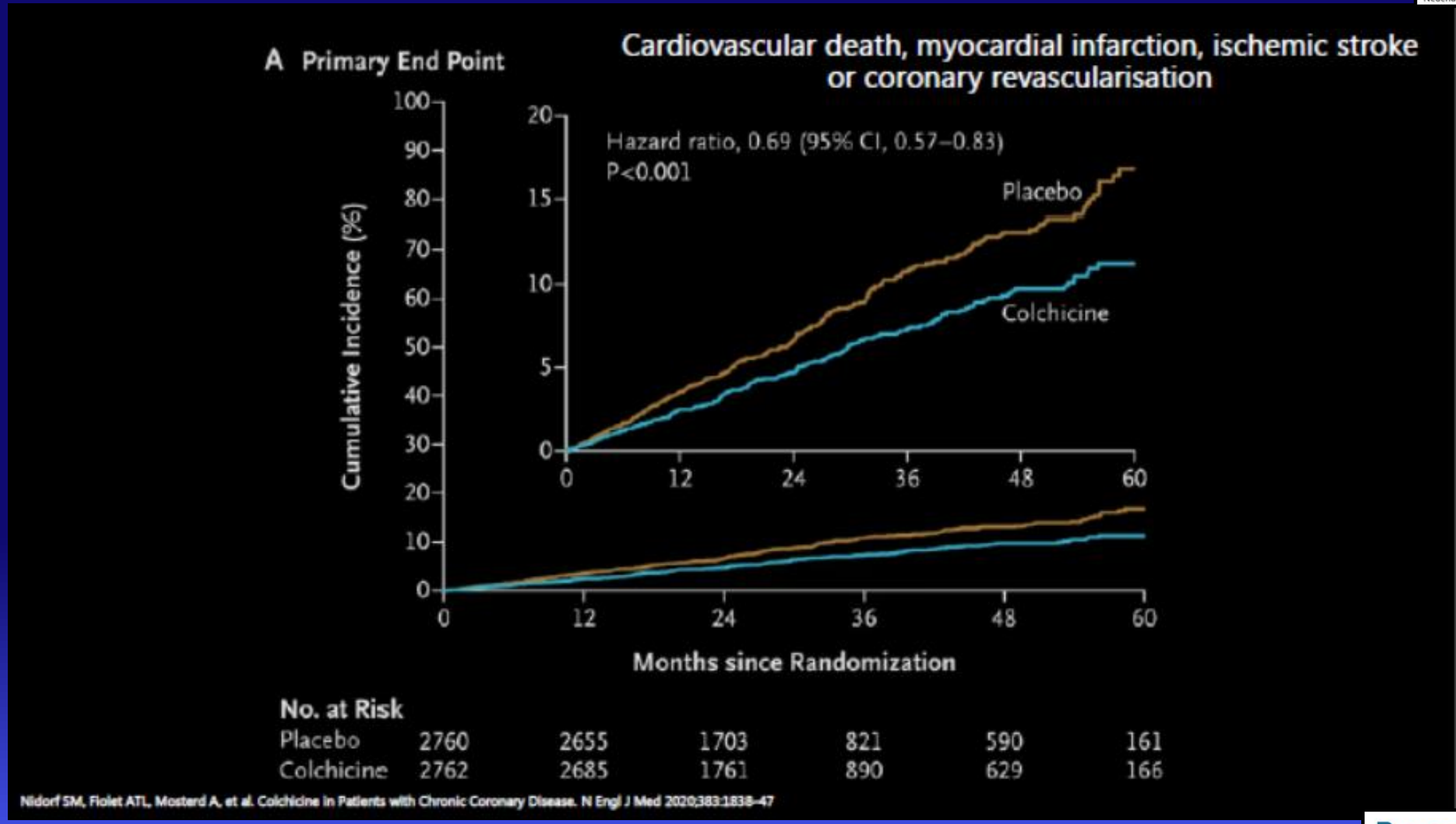
Began on December 4, 2019; Ended February 17, 2020

99.9% Final end point status known

Population

- 43 hospitals
- 5520 patients (3618 Netherlands, 1904 Australia)
- Mean age 66 years
- ~ 85% with prior acute coronary syndrome
- ~ 95% with eGFR > 60 ml/min/1.73m^2
- ~ 99% antiplatelet agents or anticoagulants
- ~ 97% lipid lowering agents (93% statins)
- ~ 72% renin–angiotensin inhibitors

SM Nidorf et al. 2020 NEJM



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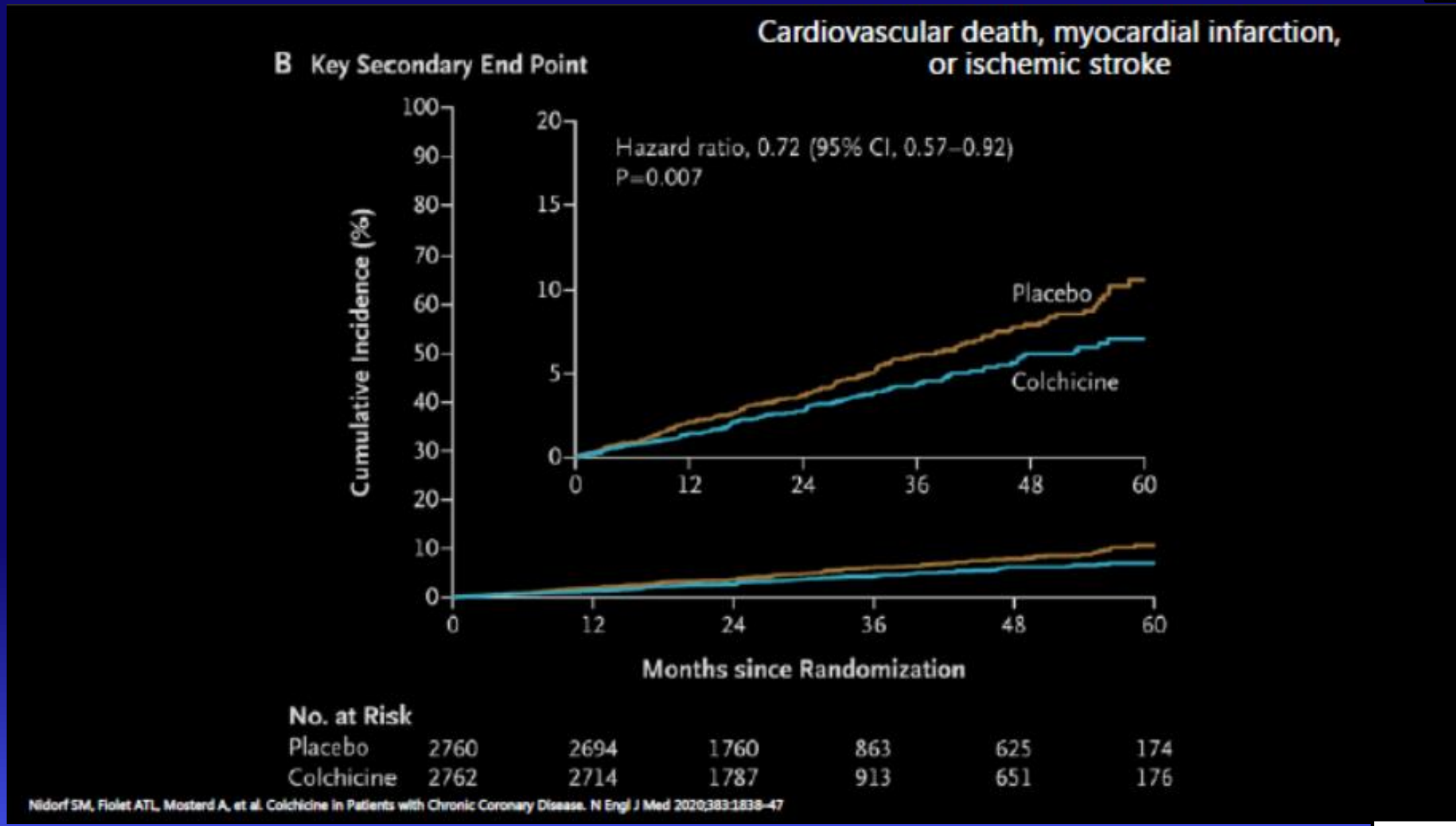

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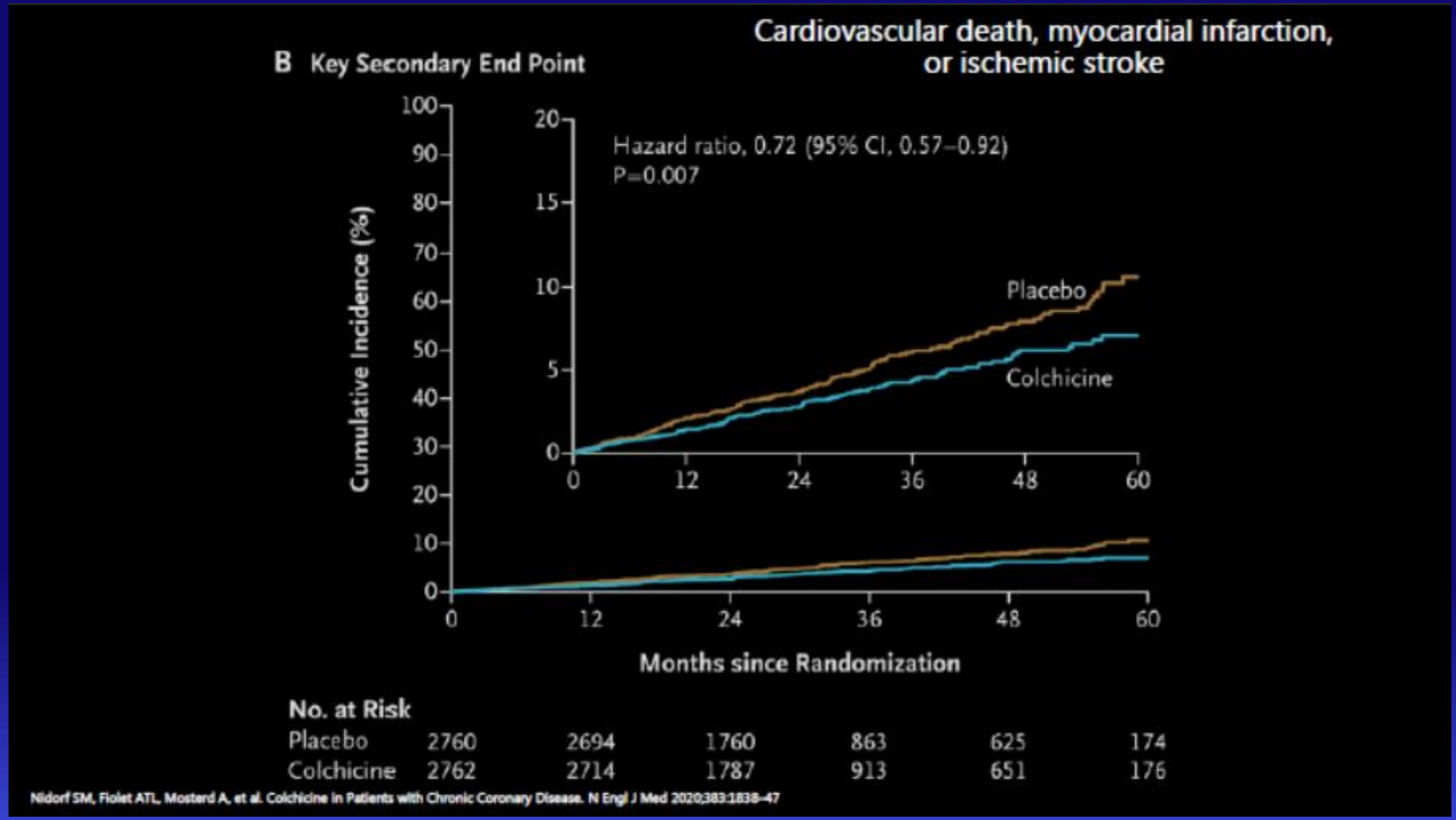


SM Nidorf et al. 2020 NEJM

Efficacy

End Point	Colchicine (N=2762) no. of patients (%)	Colchicine (N=2762) no. of events/100 person-yr	Placebo (N=2760) no. of patients (%)	Placebo (N=2760) no. of events/100 person-yr	Hazard Ratio (95% CI)	P Value
Ischemia-driven coronary revascularization	135 (4.9)	1.8	177 (6.4)	2.4	0.75 (0.60–0.94)	0.01
Myocardial infarction	83 (3.0)	1.1	116 (4.2)	1.5	0.70 (0.53–0.93)	0.01
Ischemic stroke	16 (0.6)	0.2	24 (0.9)	0.3	0.66 (0.35–1.25)	0.20
Death from any cause	73 (2.6)	0.9	60 (2.2)	0.8	1.21 (0.86–1.71)	
Cardiovascular death	20 (0.7)	0.3	25 (0.9)	0.3	0.80 (0.44–1.44)	

Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. N Engl J Med 2020;383:1838–47

SM Nidorf et al. 2020 NEJM

Safety

Event	Colchicine (N=2762)		Placebo (N=2760)		Hazard Ratio or Cumulative Incidence Ratio (95% CI)
	no. of patients/ total no. (%)	*no. of events/100 person-yrs*	*no. of patients/ total no. (%)*	*no. of events/100 person-yrs*	
Noncardiovascular death	53/2762 (1.9)	0.7	35/2760 (1.3)	0.5	1.51 (0.99–2.31)
Diagnosis of cancer	120/2762 (4.3)	1.6	122/2760 (4.4)	1.6	0.98 (0.76–1.26)
Hospitalization for infection	137/2762 (5.0)	1.8	144/2760 (5.2)	1.9	0.95 (0.75–1.20)
Hospitalization for pneumonia	46/2762 (1.7)	0.6	55/2760 (2.0)	0.7	0.84 (0.56–1.24)
Hospitalization for gastrointestinal reason	53/2762 (1.9)	0.7	50/2760 (1.8)	0.7	1.06 (0.72–1.56)
Gout	38/2762 (1.4)	—	95/2760 (3.4)	—	0.40 (0.28–0.58)
Neutropenia	4/2762 (0.1)	—	3/2760 (0.1)	—	NR
Myotoxic effects†	3/2762 (0.1)	—	3/2760 (0.1)	—	NR
Myalgia‡	384/1811 (21.2)	—	334/1807 (18.5)	—	1.15 (1.01–1.31)
Dysesthesia: numbness or tingling‡	143/1811 (7.9)	—	150/1807 (8.3)	—	0.95 (0.76–1.18)

Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. N Engl J Med 2020;383:1838–47

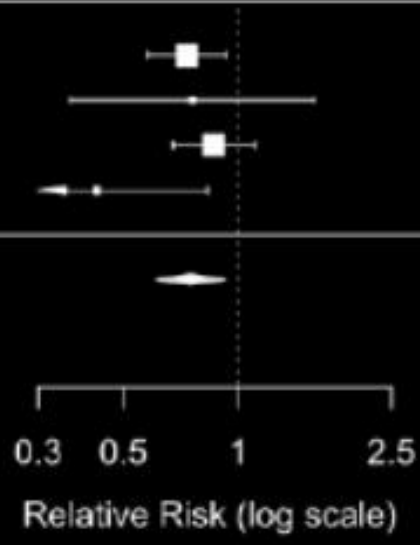
SM Nidorf et al. 2020 NEJM

Efficacy, pooled

Composite of myocardial infarction, stroke, or cardiovascular death (major adverse cardiovascular events)

Acronym or author	Colchicine Events/total (%)	Comparator Events/total (%)	Weight (GIV)	Relative Risk (95% CI)
LoDoCo2, 2020	115/2762 (4.2%)	157/2760 (5.7%)	43.4 %	0.73 (0.58 to 0.93)
COPS, 2020	12/396 (3.0%)	16/399 (4.0%)	7.2 %	0.76 (0.36 to 1.58)
COLCOT, 2019	111/2366 (4.7%)	130/2379 (5.5%)	40.9 %	0.86 (0.67 to 1.10)
LoDoCo, 2013	12/282 (4.3%)	25/250 (10.0%)	8.6 %	0.43 (0.22 to 0.83)
Totals:	250/5806	328/5788	100 %	0.75 (0.61 to 0.92)

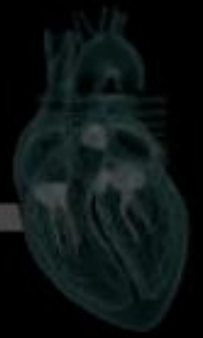
I^2 = 23.9%. Random effects model for overall effect, p = 0.005



Fiolet ATL, Opstal, TSJ, Mosterd A, et al. The efficacy and safety of low-dose colchicine in patients with coronary disease: a systematic review and meta-analysis of randomised trials. EHJ 2021 (Online ahead of print)

Fiolet ATL et al. A systematic review and meta-analysis of randomized trials with low-dose colchicine in patients with coronary disease EHJ 2021

Efficacy, pooled



Myocardial infarction

Significant relative risk reduction

↓ 22%

RR 0.78 (95% CI 0.64 to 0.94)

Stroke

Significant relative risk reduction

↓ 46%

RR 0.54 (95% CI 0.34 to 0.86)

Coronary revascularisation

Significant relative risk reduction

↓ 23%

RR 0.77 (95% CI 0.66 to 0.90)

Cardiovascular death

No significant relative risk reduction

RR 0.82 (95% CI 0.55 to 1.23)

Fiolet ATL, Opstal, TS., Mosterd A, et al. The efficacy and safety of low-dose colchicine in patients with coronary disease: a systematic review and meta-analysis of randomised trials. EHJ 2021 (Online ahead of print)

Fiolet ATL et al. A systematic review and meta-analysis of randomized trials with low-dose colchicine in patients with coronary disease EHJ 2021

Inhoud

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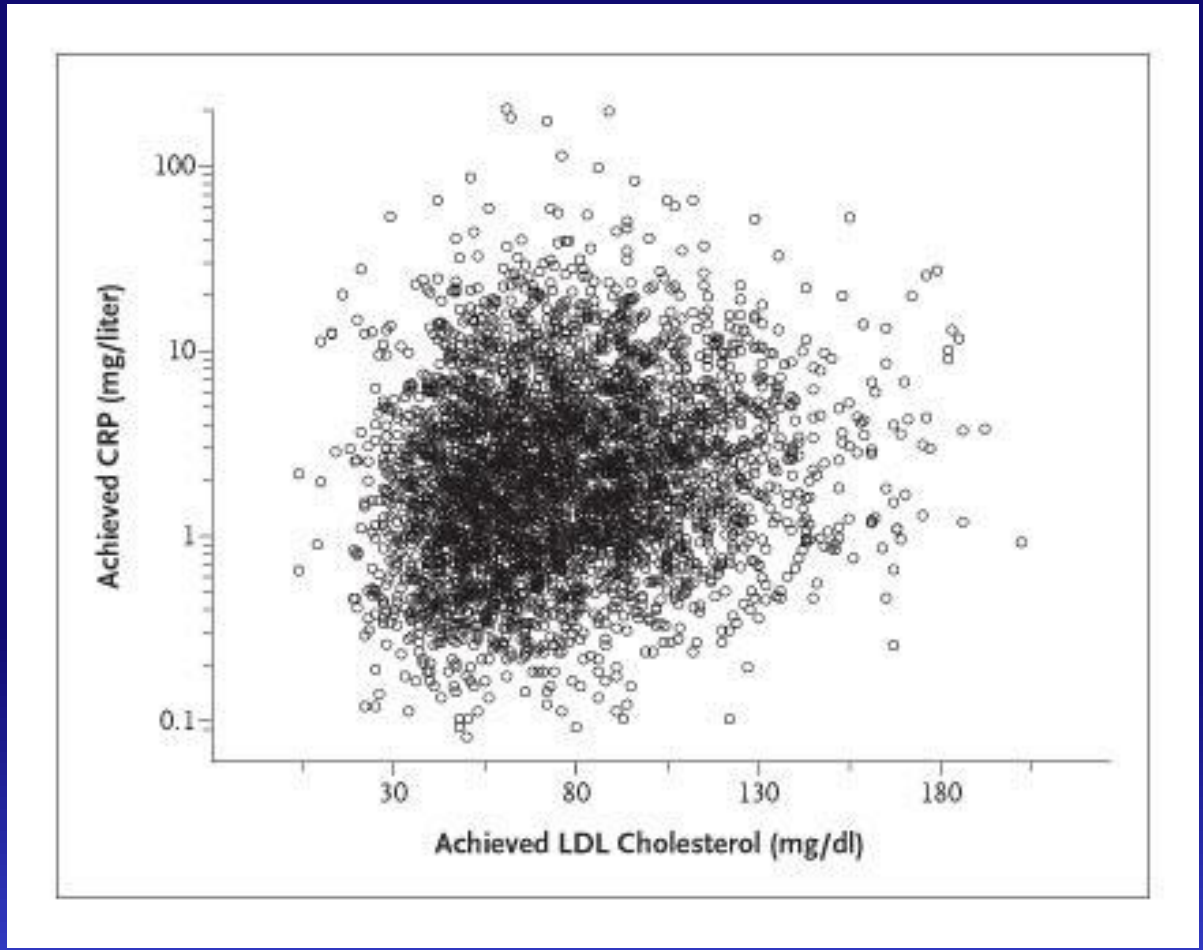
- *Inflammation and atherosclerotic disease*
- *Lodoco*
- **Wat zou een relatie tussen lipiden en inflammatie kunnen zijn?**

Wat zou een relatie tussen lipiden en inflammatie kunnen zijn?



Paul M Ridker, NEJM 2005

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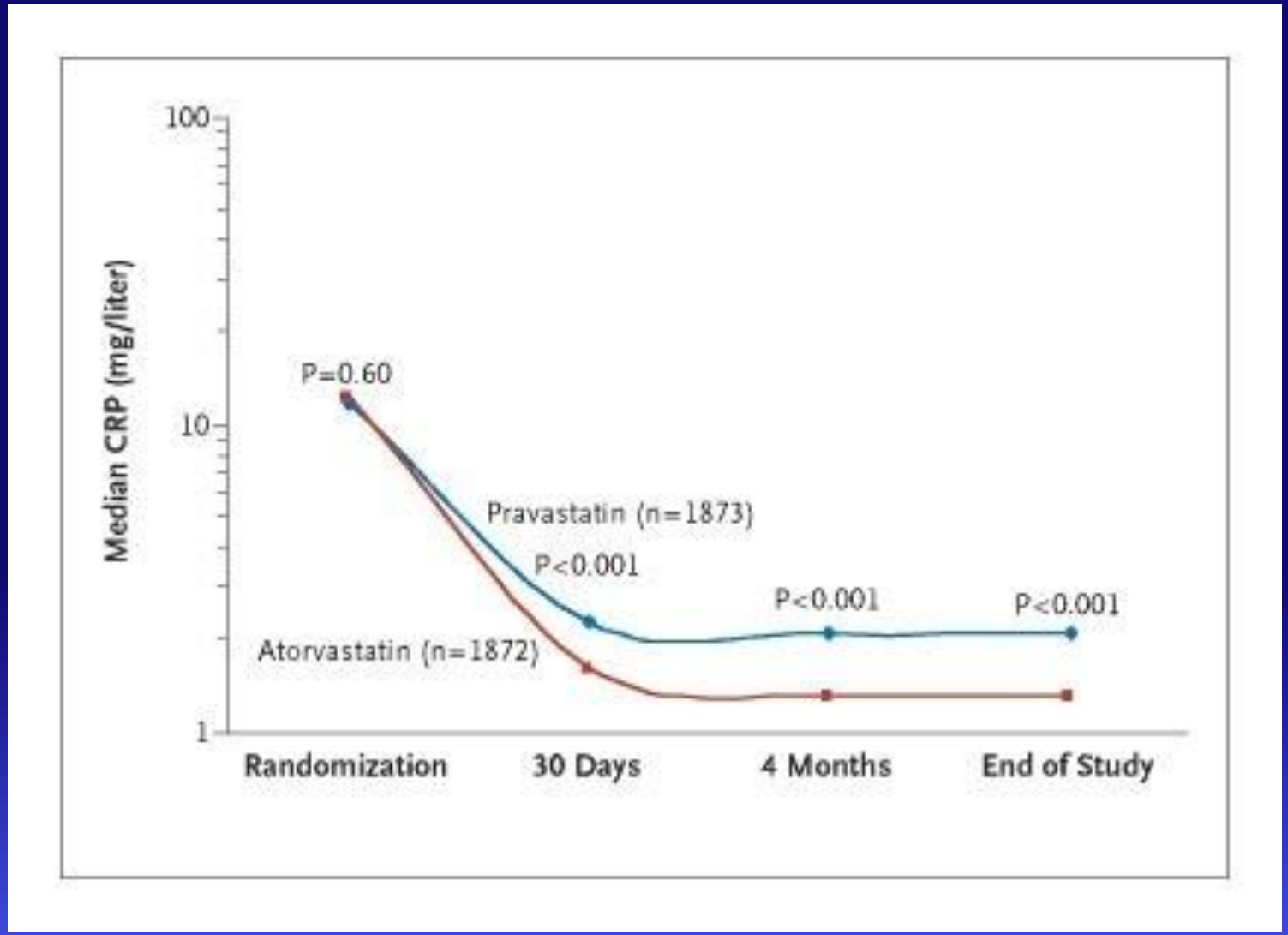
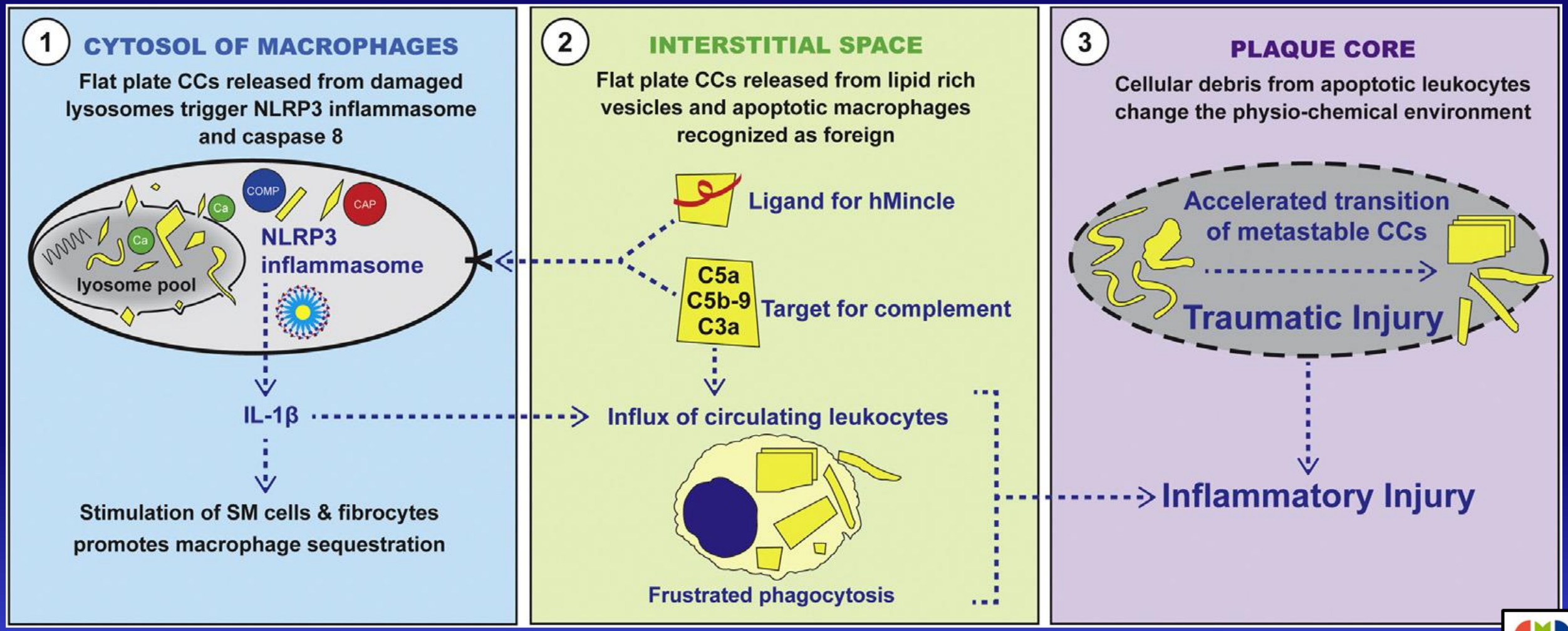


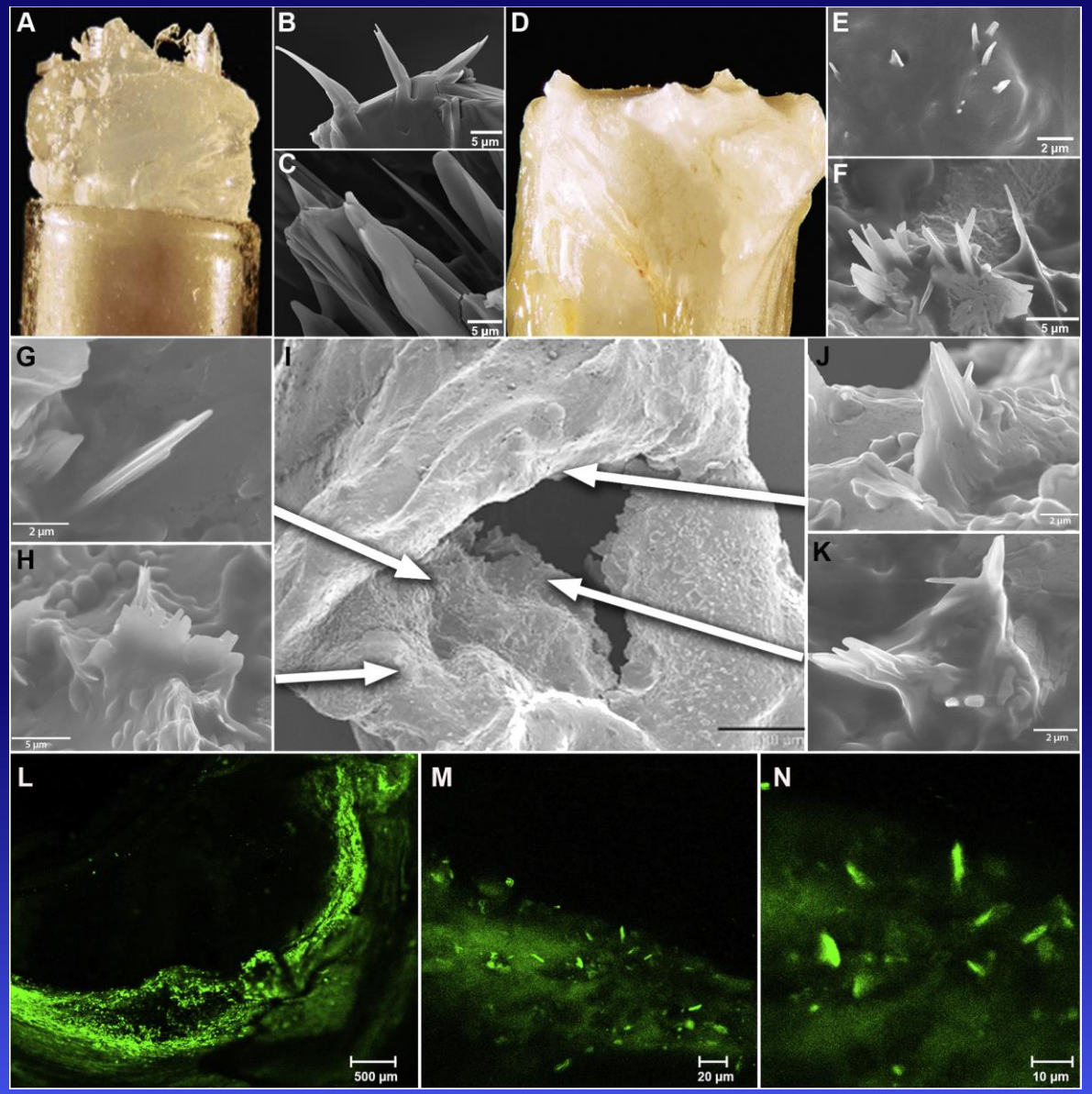
Paul M Ridker, NEJM 2005

Inflammatoir process in de plaque core



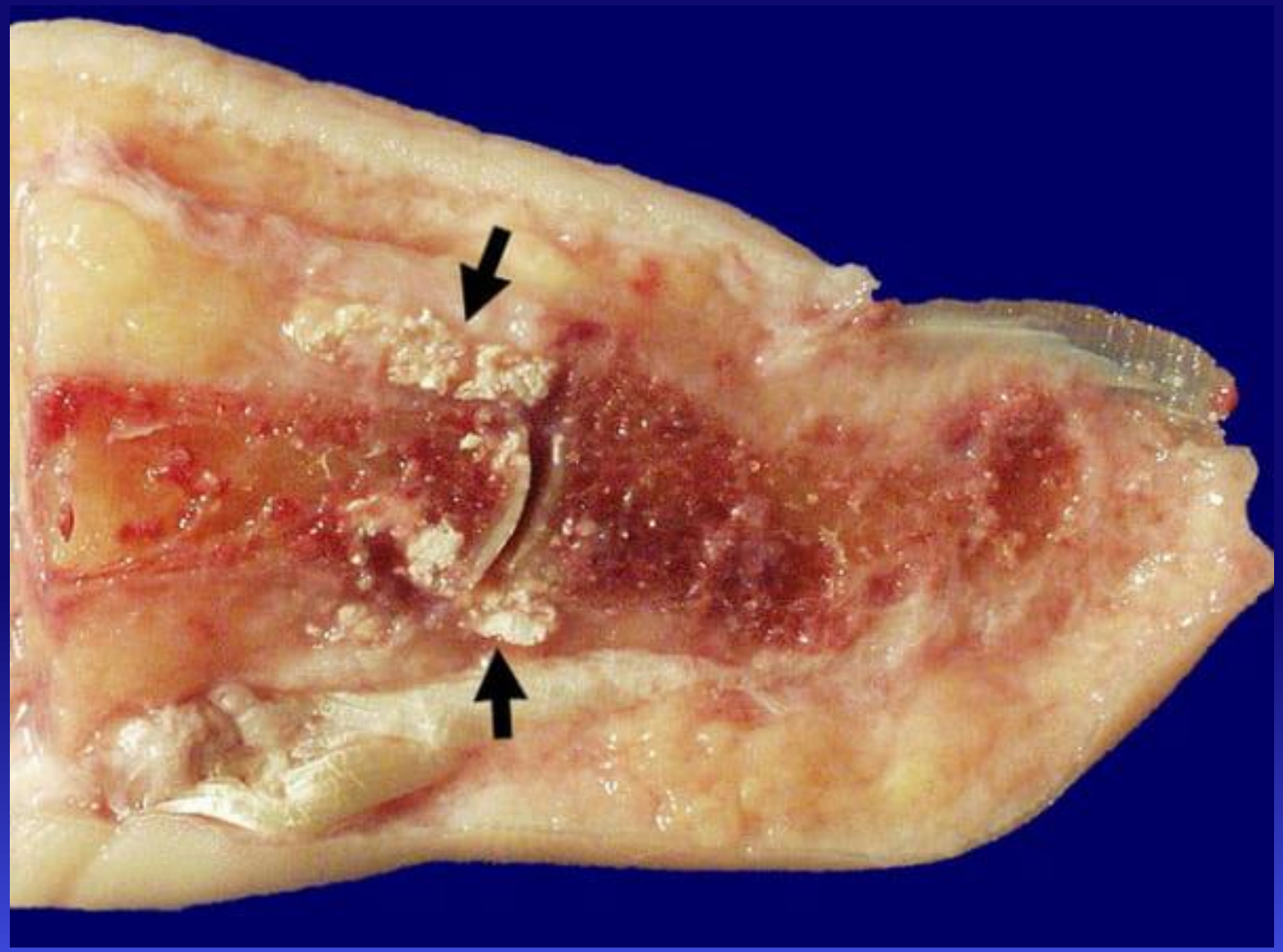
Nidorf et al, Journal of Clinical Lipidology, Vol 14, No 5, October 2020
V Oostrom et al, Atherosclerosis 2007 Jan; 190(1):167-73

Crystal-induced inflammation in the plaque core



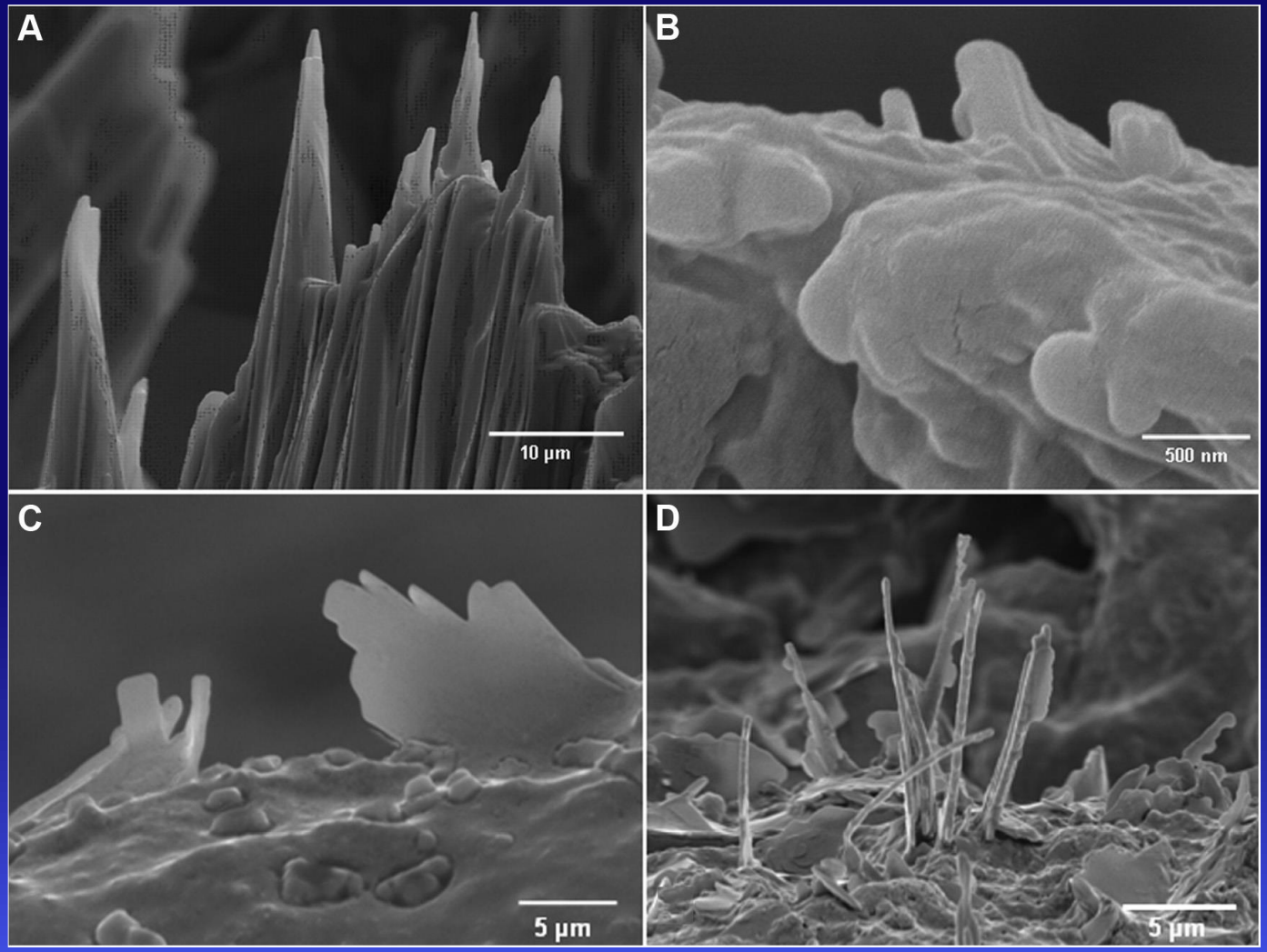
Nidorf et al, Journal of Clinical Lipidology, Vol 14, No 5, October 2020

Crystal-induced inflammation in the plaque core and toes



Nidorf et al, Journal of Clinical Lipidology, Vol 14, No 5, October 2020

Aspirates from culprit coronary arteries during acute myocardial infarction



Nidorf et al, Journal of Clinical Lipidology, Vol 14, No 5, October 2020

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- Werkt het tegengaan van insulin-resistentie ook anti-inflammatoir
  (remming FFA, TGs, glucose, zowel middels anti-diabetica, als EPA)
- **Anti-inflammatoire werking lijkt echter geen gunstig effect te hebben op het lipidmetabolisme**

Wat zou een relatie tussen lipiden en inflammatie kunnen zijn in Lodoco?

- Binnenkort publicatie over effect op lipiden na 30dg Colchicine…
  maar de anti-inflammatoire werking lijkt lipidonafhankelijk…
- Er volgt een CT-coronairen substudie
- Er volgt een cross-sectioneel sample van 1800 pat na 60mnd Colchicine

P

Is anti inflammatoire behandeling met bijvoorbeeld Colchicine een optie naast optimale cholesterolverlagende behandeling?

a) Ja
b) Nee

Is anti inflammatoire behandeling met bijvoorbeeld Colchicine een optie naast optimale cholesterolverlagende behandeling?

Caveats when prescribing colchicine

- At this stage: off-label prescription and no guideline endorsement (yet)
- Do not use in case of impaired renal function, known hematologic conditions (neutropenia)
- Do not use concomitantly with selected drugs:

  e.g. clarithromycin, verapamil (maintenance tx), anti-fungal & anti-rejection therapy

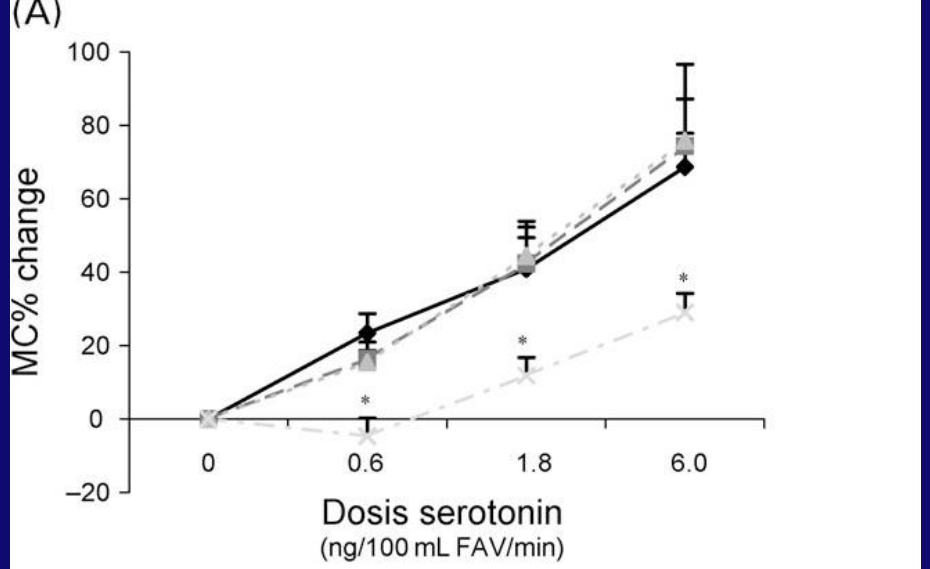
Controversie

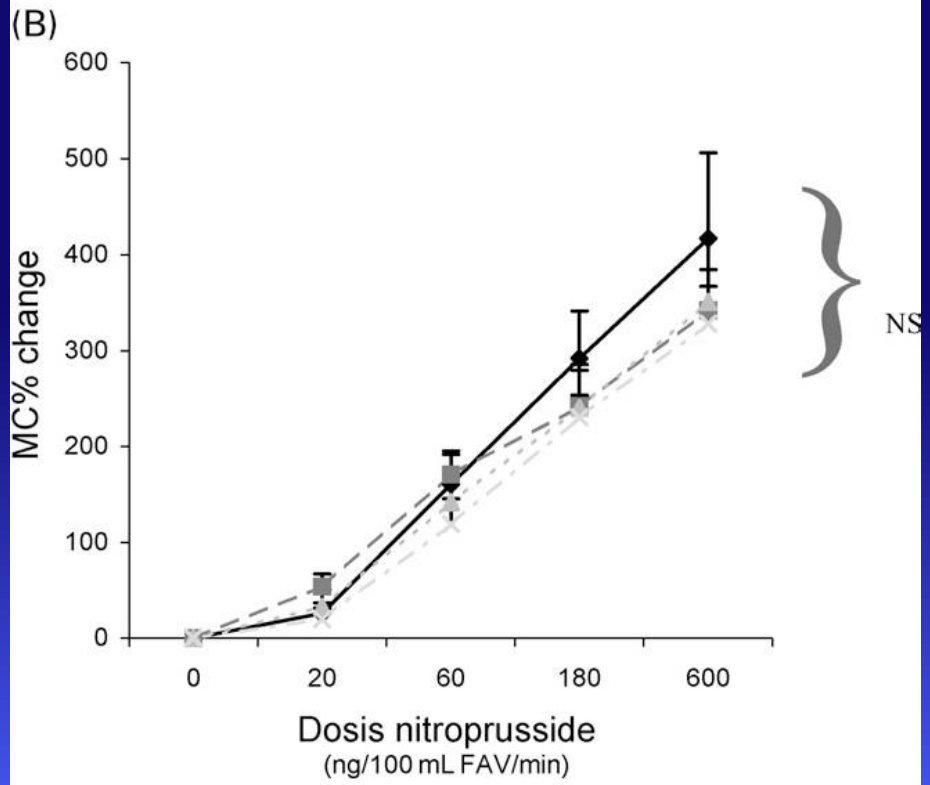
metabool syndroom. Ontsteking verandert ons metabolisme, waaronder de samenstelling van het LDL en HDL. De serum triglyceride concentratie stijgt, het HDL-cholesterol daalt en er ontstaat "small dense" LDL en "dysfunctioneel" HDL. Deze combinatie vormt karakteristieke dyslipidemie van het metabool syndroom. Het sterk verhoogde LDL-cholesterol van patiënten met familiaire hypercholesterolemie staat niet op zichzelf, maar gaat samen met lage graad ontsteking en "small dense" LDL en HDL. Een LDL-cholesterol reductie blijkt geen synoniem van een CRP reductie. Een daling van het LDL-cholesterol correleert vaak met een CRP daling bij statinegebruik, correleert niet met een CRP verandering bij de behandeling met PCSK9 inhibitors of bij de consumptie van plantensterolen, en correleert met een

Muskiet (Prof Klinisch Chemicus), Ned Tijdschr Klin Chem Labgeneesk 2016; 41: 253-265

“Twee halve waarheden maken nog geen hele waarheid”

Multatuli





NS

European Heart Journal (2006) 27, 1605–1609
doi:10.1093/eurheartj/ehl079

Clinical research
Vascular medicine

TNF-α induces endothelial dysfunction in diabetic adults, an effect reversible by the PPAR-γ agonist pioglitazone

Fabrice M.A.C. Martens[1], Ton J. Rabelink[2], Jos op 't Roodt[2], Eelco J.P. de Koning[2], and Frank L.J. Visseren[1*]