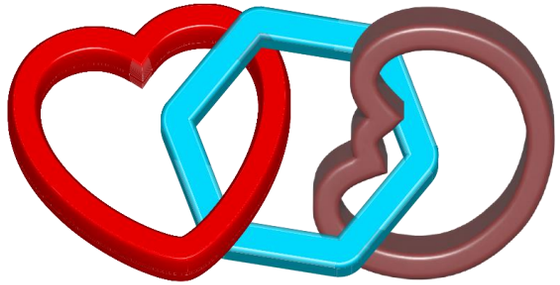


Inflammation in atherosclerosis: a translational journey

Prof. Peter Libby

Professor of Medicine

Harvard Medical School and Brigham & Women's Hospital

Boston, Verenigde Staten

Financial Disclosures:

Peter Libby, MD: *Grant/Research support*: Novartis, NovoNordisk, Genentech

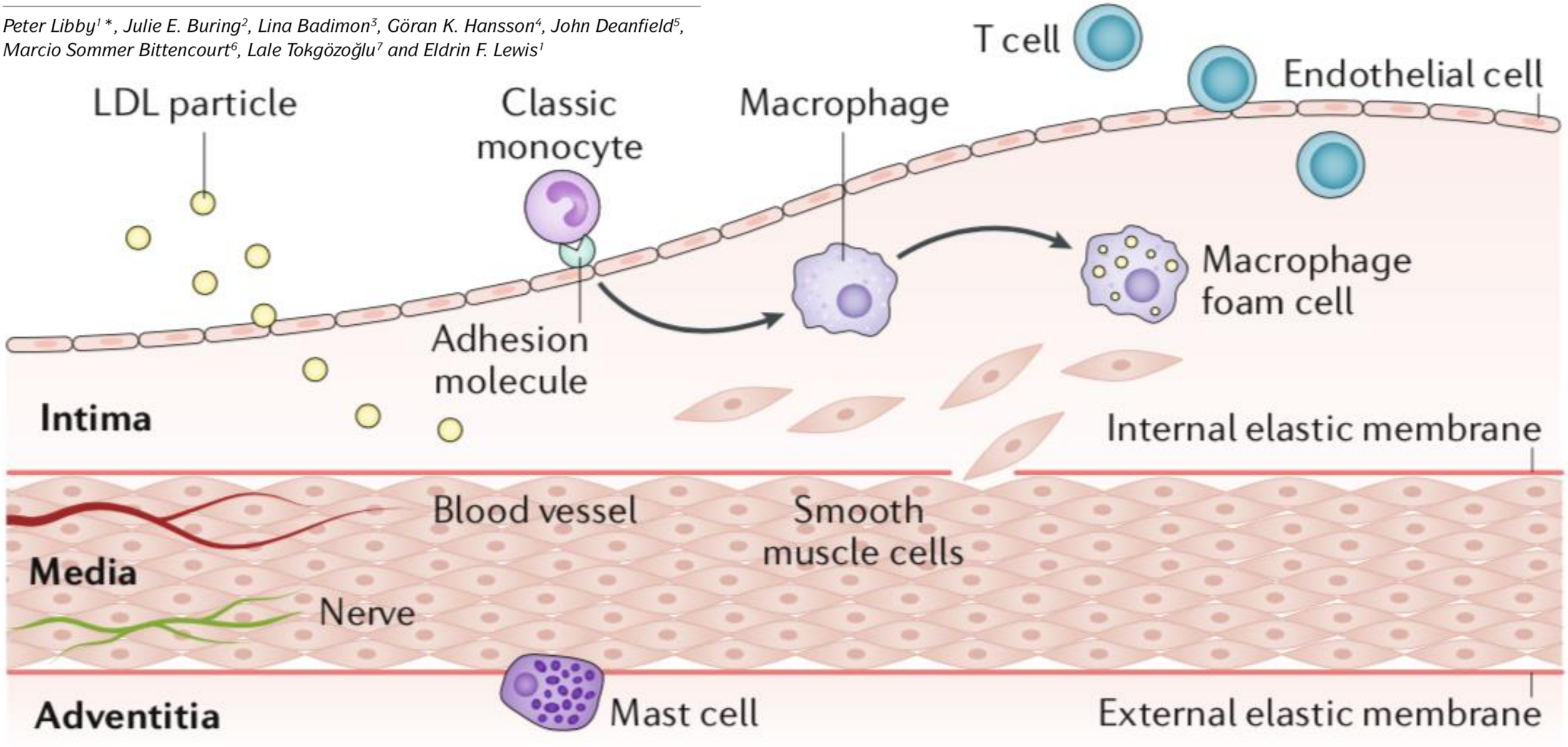
***Unpaid Consultant and/or unpaid steering or executive committee of clinical trials*: Amgen, Esperion, Kowa, Merck, Moderna, Novartis, Pfizer, Sanofi-Aventis-Regeneron. *Scientific Advisory Board:* Medimmune, DalCor, Amgen, Novartis, NovoNordisk, Olatec, Xbiotech. *Board*: Xbiotech. Dr. Libby declines all personal compensation from pharma or device companies. Dr. Libby has a financial interest in Xbiotech, a company developing therapeutic human antibodies. Dr. has a financial interest in TenSixteen Bio, a company targeting somatic mosaicism and clonal hematopoiesis of indeterminate potential (CHIP) to discover and develop novel therapeutics to treat age-related diseases. Dr. Libby's interests were reviewed and are managed by MassGeneralBrigham HealthCare in accordance with their conflict-of-interest policies.**

Inflammation in Lesion Initiation

Nature reviews | Disease Primers
https://doi.org/10.1038/ s41572-019-0106-z

Atherosclerosis

*Peter Libby[1] *, Julie E. Buring[2], Lina Badimon[3], Göran K. Hansson[4], John Deanfield[5], Marcio Sommer Bittencourt[6], Lale Tokgözoğlu[7] and Eldrin F. Lewis[1]*

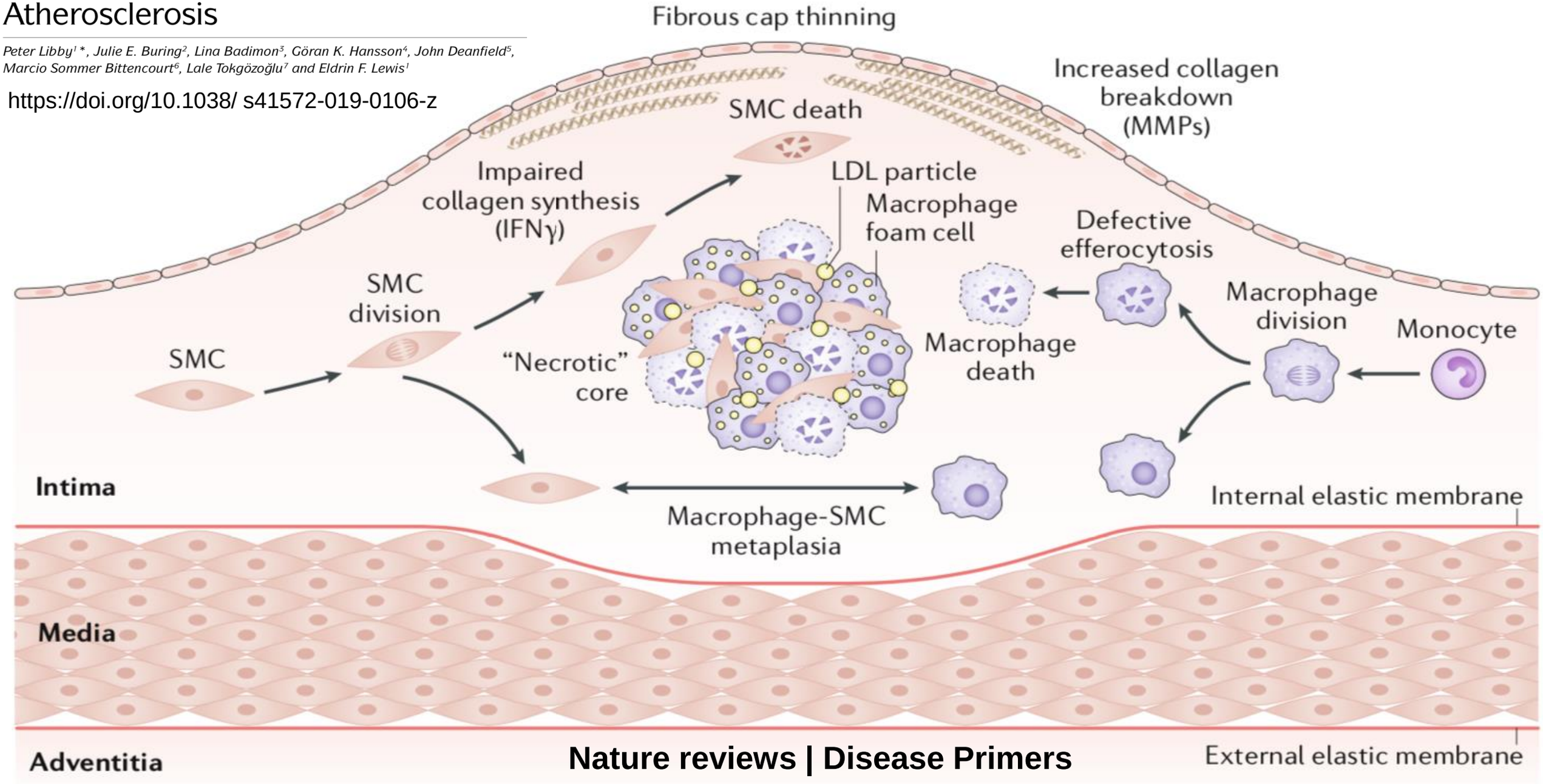


Life and Death in the Atheroma: Inflammation in Lesion

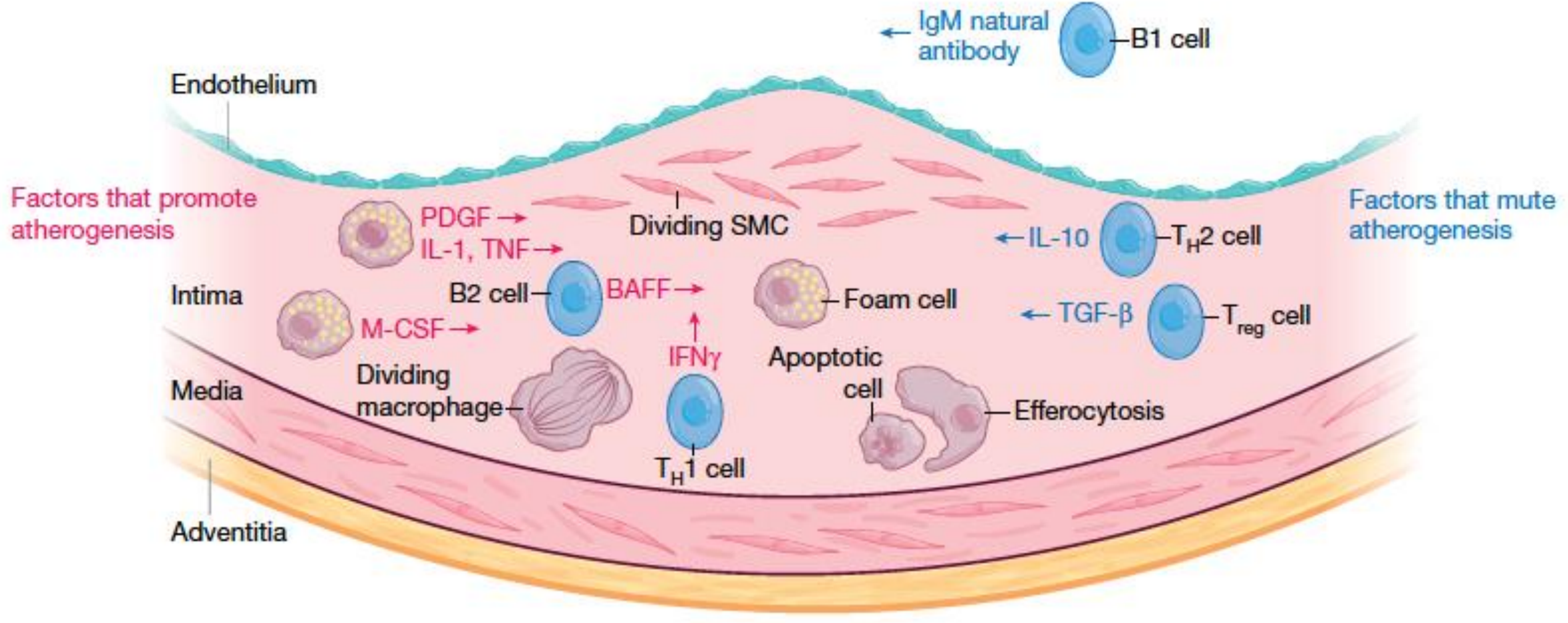
Atherosclerosis

*Peter Libby[1] *, Julie E. Buring[2], Lina Badimon[3], Göran K. Hansson[4], John Deanfield[5], Marcio Sommer Bittencourt[6], Lale Tokgözoğlu[7] and Eldrin F. Lewis[1]*

https://doi.org/10.1038/ s41572-019-0106-z



The progression of atherosclerosis: an interplay between factors that promote or mitigate atherogenesis



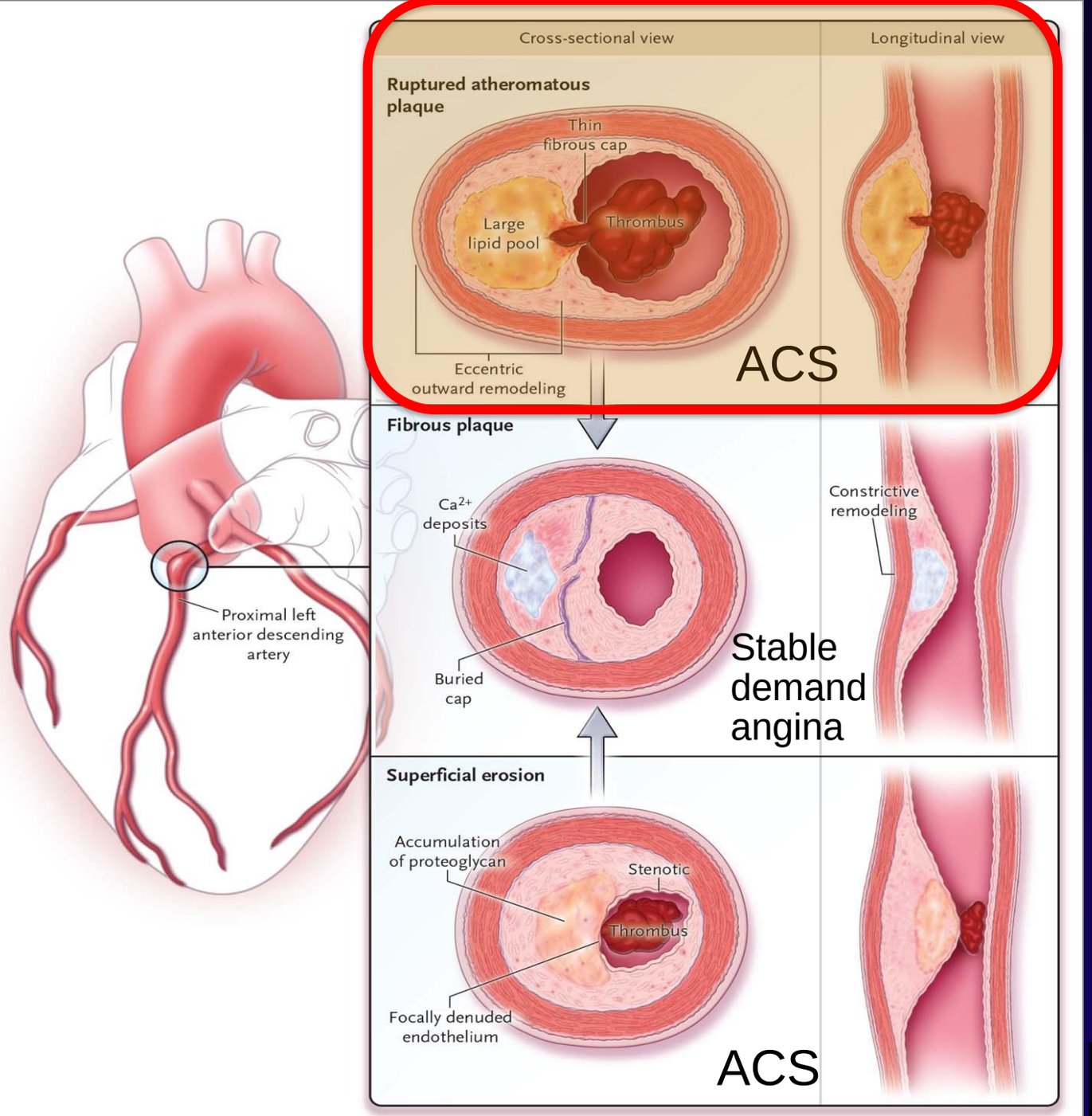
The changing landscape of atherosclerosis

Libby, Nature 2021 https://doi.org/10.1038/s41586-021-03392-8

Inflammation in Atherosclerosis

Peter Libby, *A Fire Within*

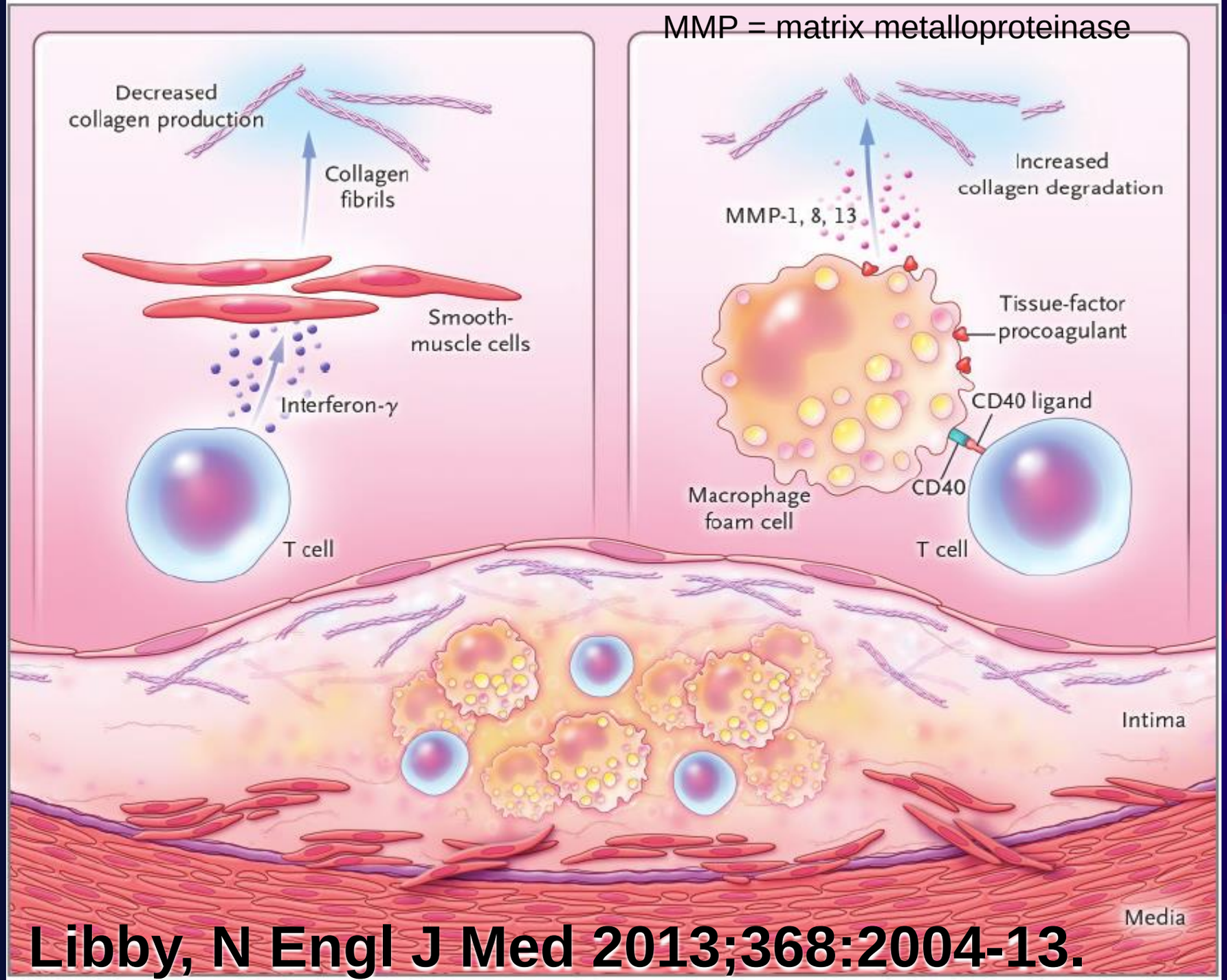
Scientific American 2002



Characteristics of Atherosclerotic Plaques Associated with Various Presentations of Coronary Artery Disease

Libby P. N Engl J Med 2013;368:2004-2013

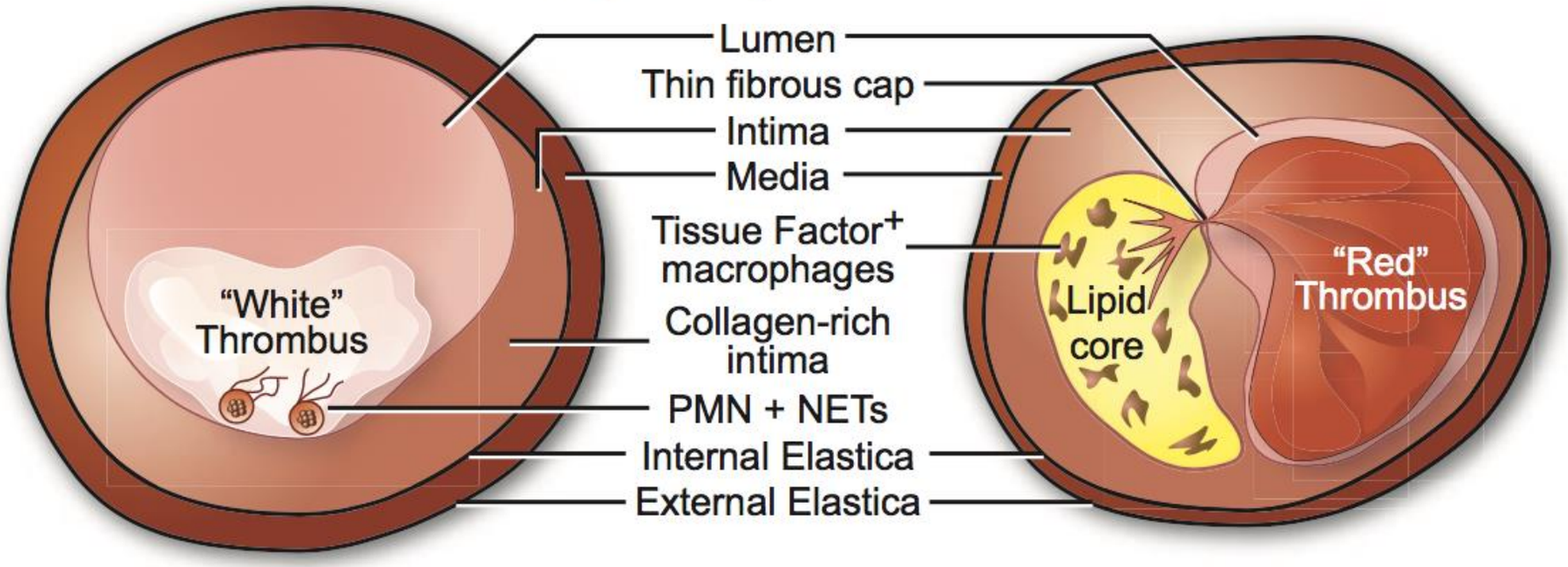
The NEW ENGLAND JOURNAL of MEDICINE



Inflammation contributes to plaque rupture and the pathogenesis of acute arterial thromboses

Libby, N Engl J Med 2013;368:2004-13.

Coronary Artery Cross Sections



Thrombosis due to Erosion

Fibrous cap thick & intact

"White" platelet-rich thrombus

Collagen trigger

Smooth muscle cells prominent

Often sessile, non-occlusive Thrombus

Usually less remodelled outward

Neutrophil extracellular traps (NETs) involved

More frequent in Non-STEMI?

Thrombosis due to Rupture

Thin fibrous cap with fissure

"Red" fibrin-rich thrombus

Tissue Factor trigger

Macrophages prominent

Often occlusive thrombus

Usually expansively remodelled

Less NET involvement?

More frequently cause STEMI?

Superficial erosion and the precision management of acute coronary syndromes: not one-size-fits-all.

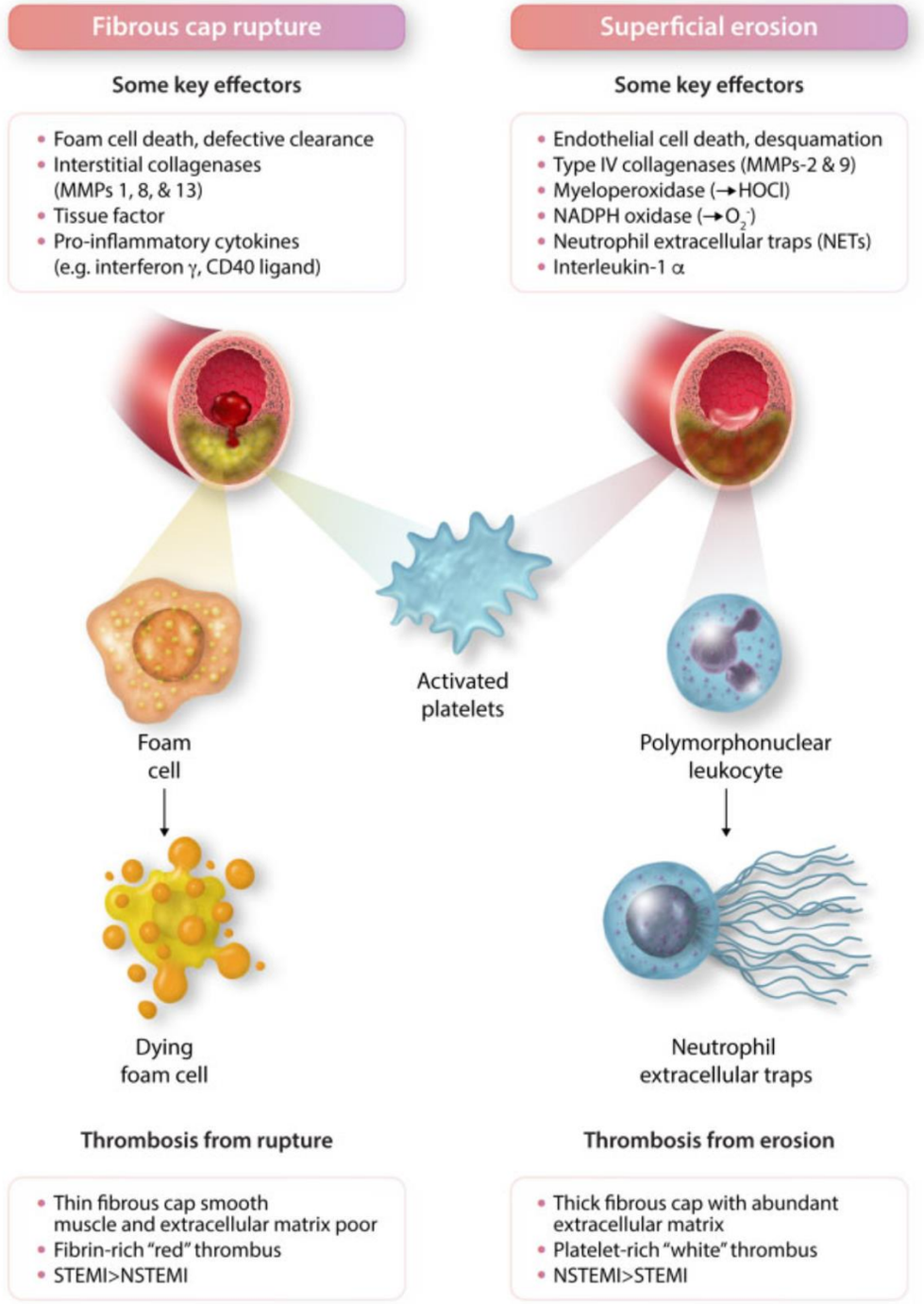
Peter Libby
European Heart Journal (2017) 0, 1–3
doi:10.1093/eurheartj/ehw599

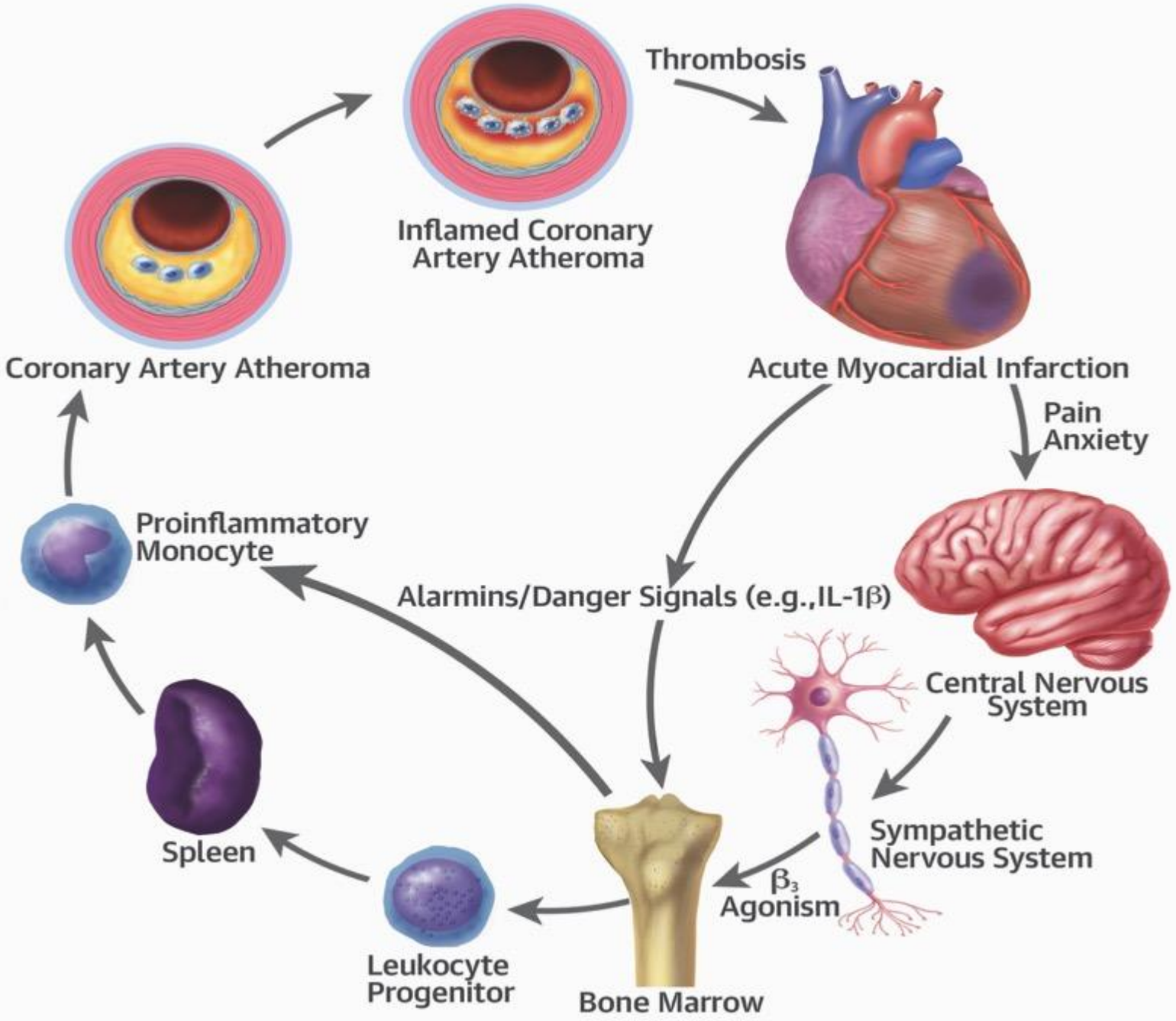
ESC European Society of Cardiology
Cardiovascular Research (2021) **00**, 1–12
doi:10.1093/cvr/cvab303

SPOTLIGHT REVIEW

Inflammation during the life cycle of the atherosclerotic plaque

❤Plaque rupture and erosion have distinct pathophysiologic mechanisms.





The Cardiovascular Continuum Revisited

Libby, Nahrendorf, Swirski

Leukocytes Link Local and Systemic Inflammation in Ischemic CVD

JACC. 67:1091, 2016

Google Scholar

Inflammation and atherosclerosis

Articles

About 1,930,000 results (**0.05** sec)

Google Scholar

Immunology and atherosclerosis

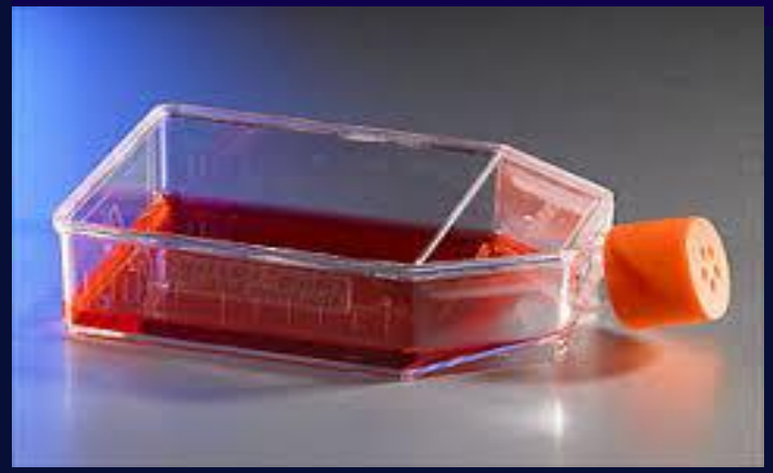
Articles

About 422,000 results (**0.06** sec)

Accessed 14 November 2023

Can Targeted Anti-Inflammatory Therapy Improve Cardiovascular Outcomes in Humans?

Can we translate inflammation biology in atherosclerosis to the clinic?



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https://doi.org/10.1016/j.jacc.2017.09.028

THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

Interleukin-1 Beta as a Target for Atherosclerosis Therapy

Biological Basis of CANTOS and Beyond

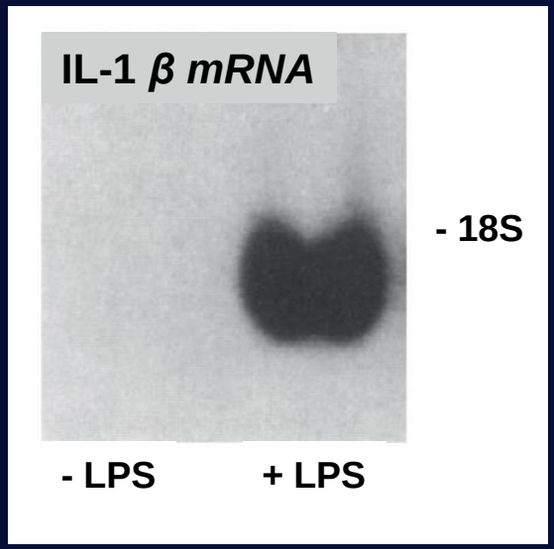
Peter Libby, MD

JACC VOL. 70, NO. 18, 2017 OCTOBER 31, 2017:2278–89

Interleukin-1β as a Target for Atherosclerosis Therapy: Biological Basis of CANTOS and Beyond

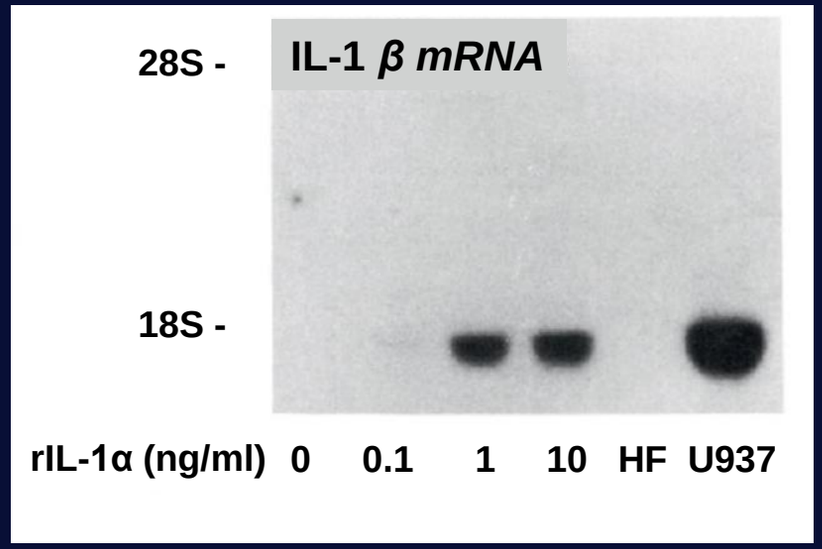
1986

Inducible IL-1 β expression in human endothelial cells



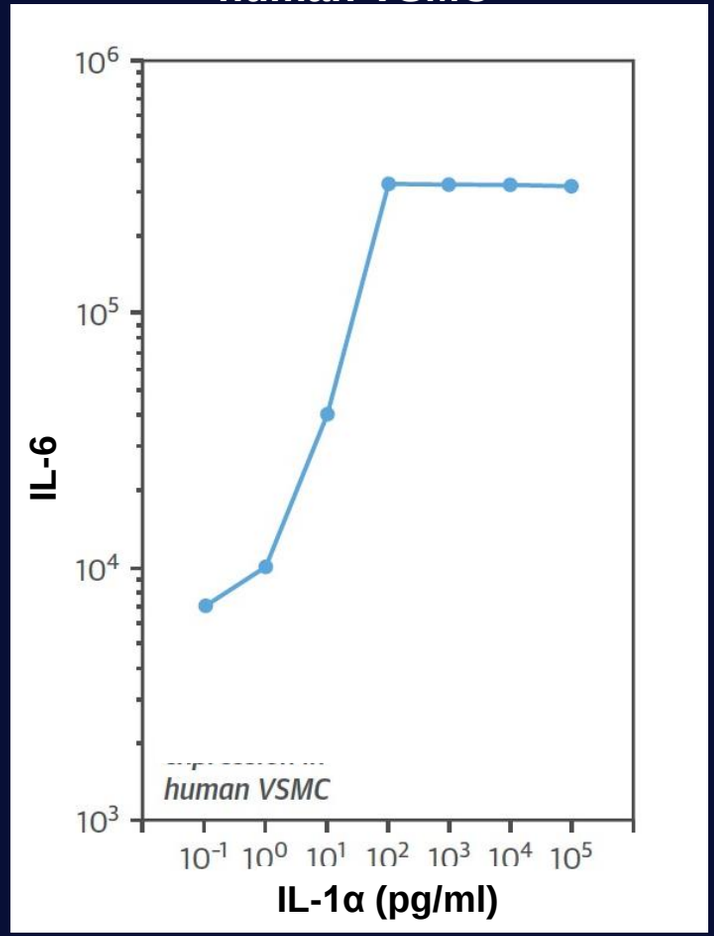
1987

IL-1 induces IL-1 in human endothelial cells



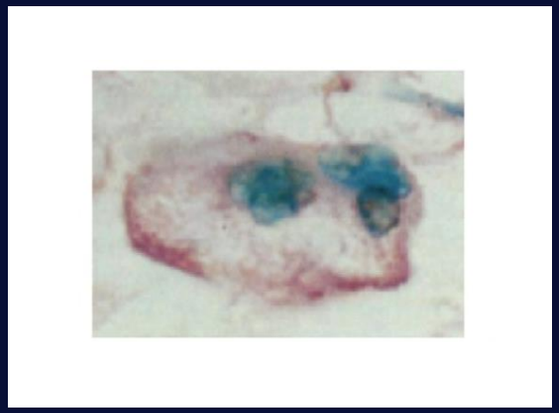
1990

IL-1 induces IL-6 expression in human VSMC



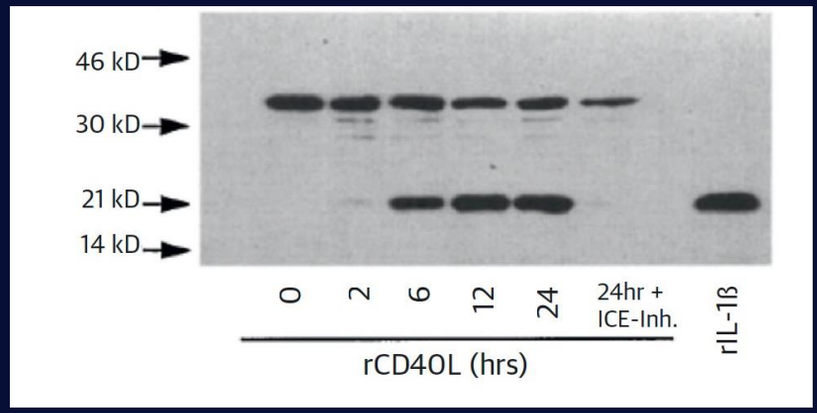
1995

Caspase-1 expression in a foam cell in human atheroma



1997

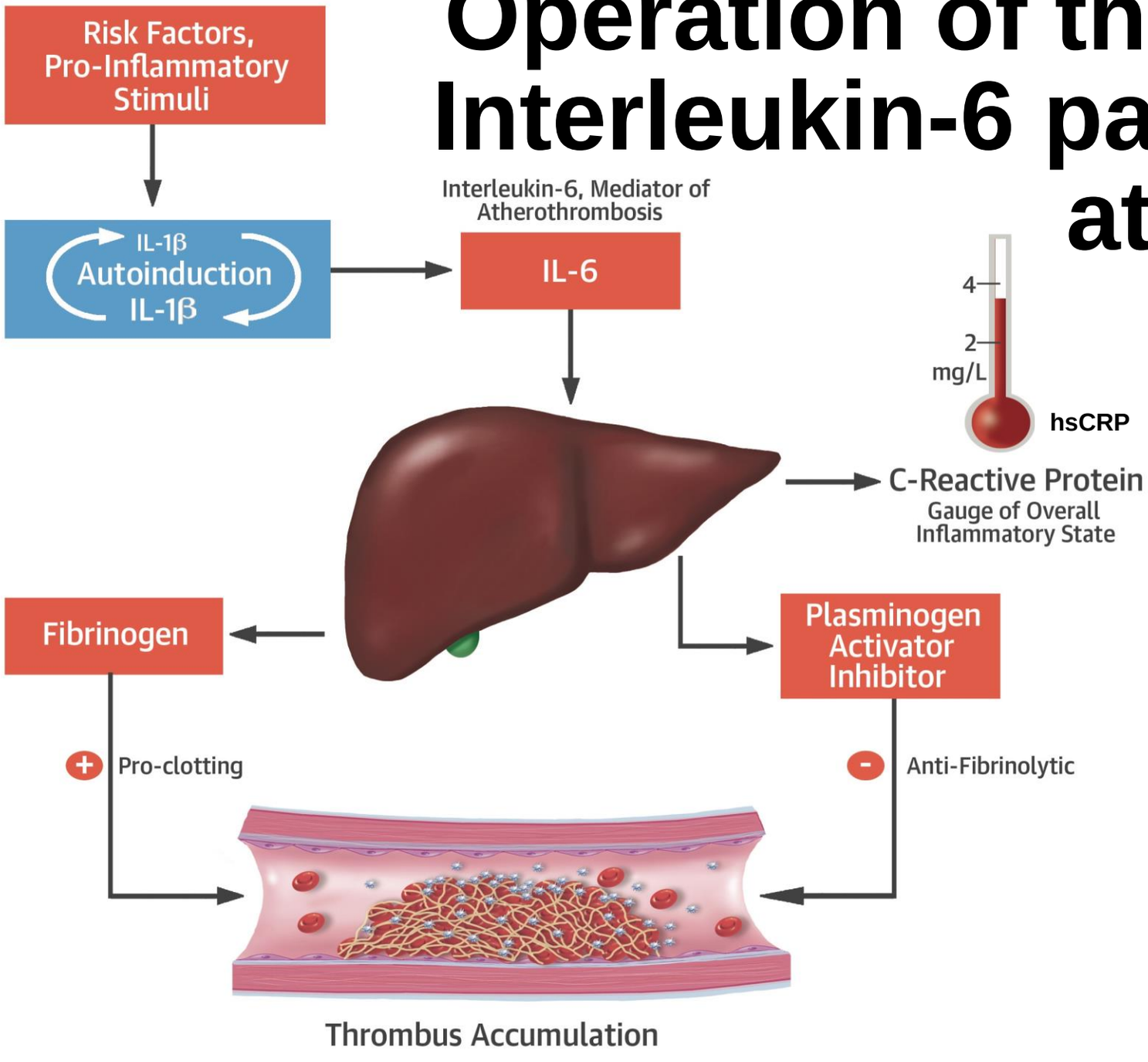
Caspase-1 activates IL-1 β in human VSMC



IL: Interleukin
VSMC: Vascular Smooth Muscle Cells

Libby JACC 70, 2017:2278–89

Operation of the Interleukin-1β-Interleukin-6 pathway in human atherothrombosis



Libby
IL-1β as a Target for Therapy JACC 2017;70:2278

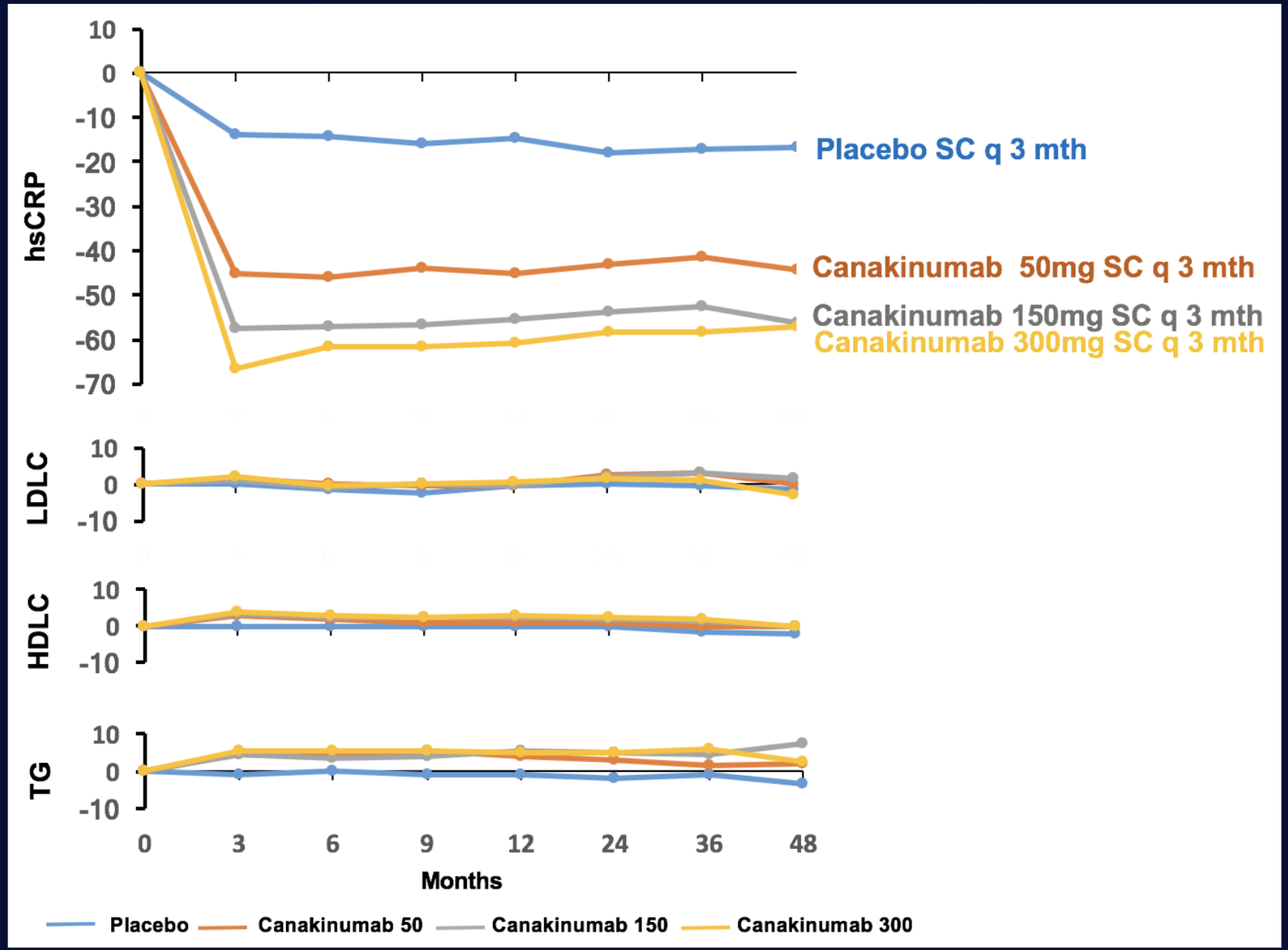
Interleukin-1β inhibition and the prevention of recurrent cardiovascular events: Rationale and Design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

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*

CANTOS: a 10,061 person phase III Trial

Am Heart J 2011;162:597-605

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



Robust lowering of CRP - a gauge of inflammation

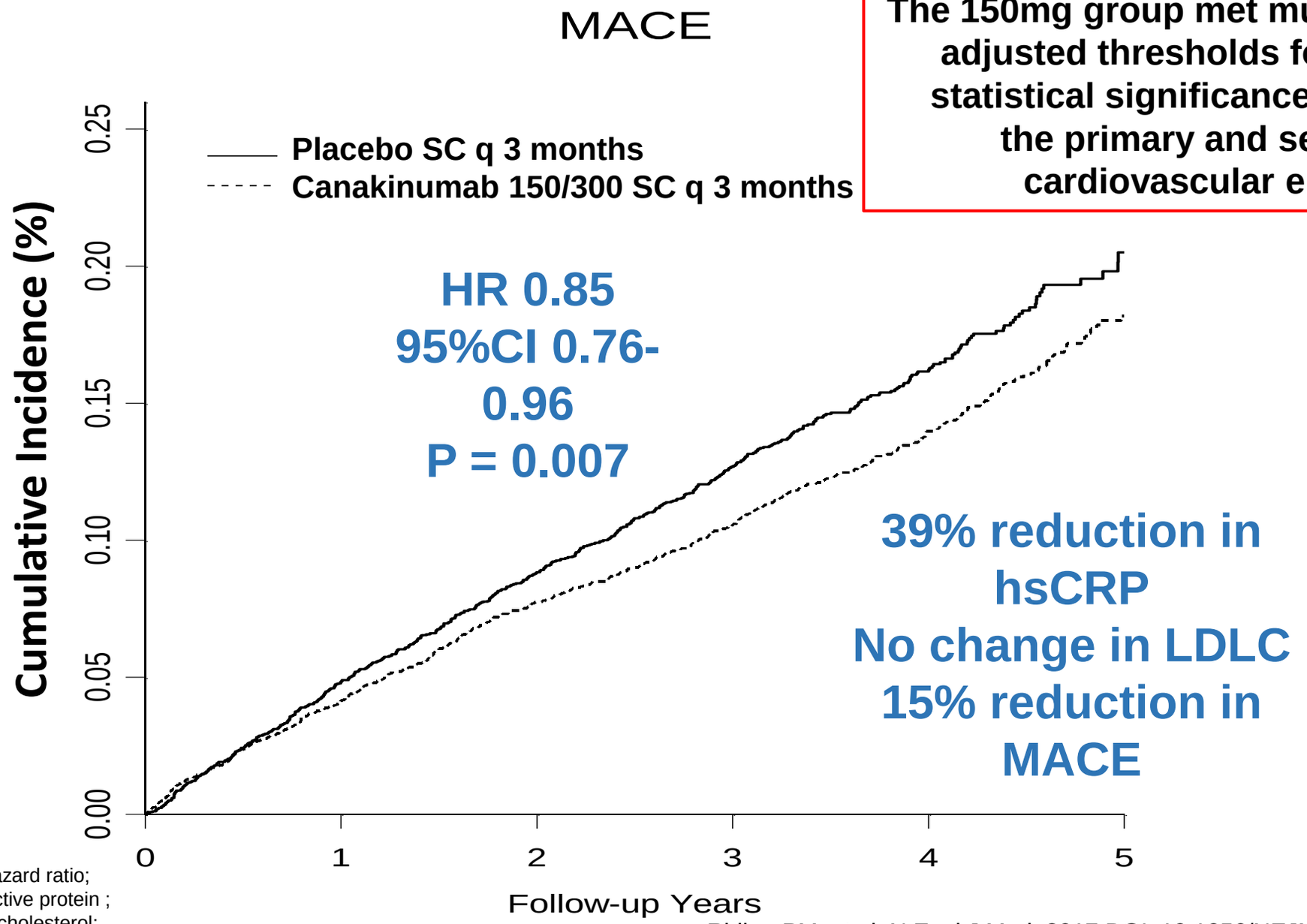
No change in atherogenic lipids

HDLC, high-density lipoprotein; cholesterol hsCRP, high-sensitivity C-reactive protein; LDLC, low-density lipoprotein cholesterol; SC, subcutaneous; TG, triglyceride

Ridker PM, et al. N Engl J Med. 2017;DOI: 10.1056/NEJMoa1707914

CANTOS: Primary Cardiovascular Endpoint (MACE)

The 150mg group met multiplicity adjusted thresholds for formal statistical significance for both the primary and secondary cardiovascular endpoints



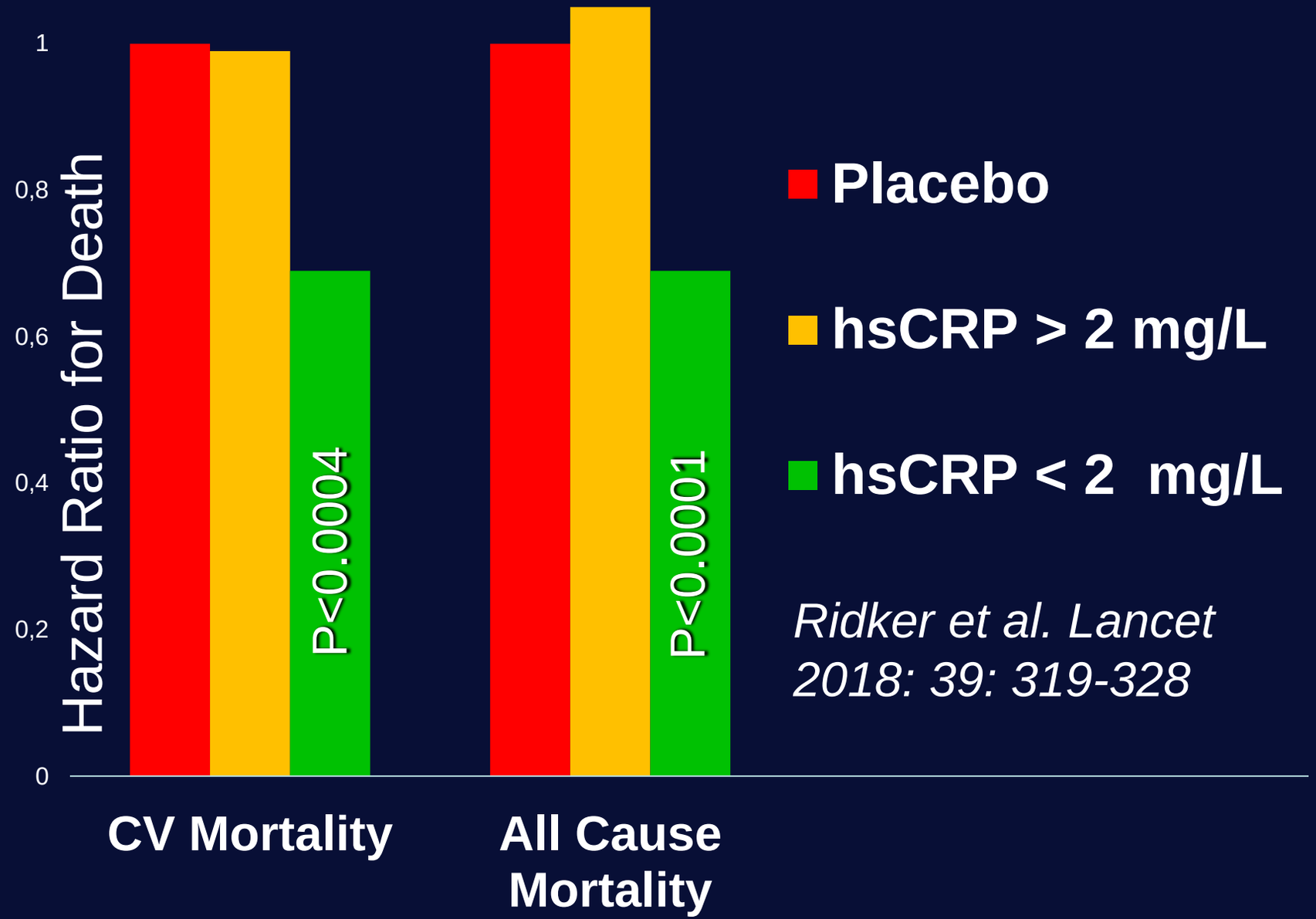
HR 0.85
95%CI 0.76-0.96
P = 0.007

39% reduction in hsCRP
No change in LDLC
15% reduction in MACE

CI, confidence interval; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein ; LDLC, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; SC, subcutaneous

Ridker PM, et al. N Engl J Med. 2017;DOI: 10.1056/NEJMoa1707914

IL-1β blockade reduces cardiovascular and total mortality by 31 % in canakinumab responders



- Placebo
- hsCRP > 2 mg/L
- hsCRP < 2 mg/L

Ridker et al. Lancet 2018: 39: 319-328

Multivariable Adjusted Hazard Ratios (HR) for Pre-Specified Cardiovascular Outcomes According to On-treatment hsCRP Levels Above or Below 2 mg/L After Drug Initiation

HRs adjusted for age, gender, smoking, HTN, diabetes, BMI, baseline hsCRP, Baseline LDLC

CANTOS: Additional Outcomes (per 100 person years of exposure)

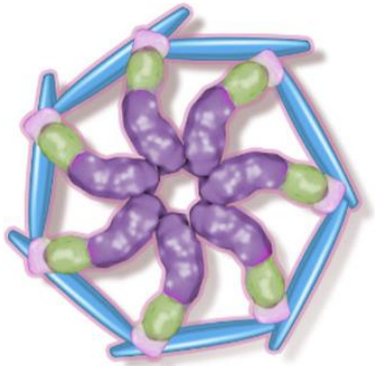
		Canakinumab SC q 3 months			
Adverse Event	**Placebo (N=3347)**	**50 mg (N=2170)**	**150 mg (N=2284)**	**300 mg (N=2263)**	**P-trend**
Any SAE	12.0	11.4	11.7	12.3	0.43
Leukopenia	0.24	0.30	0.37	0.52	0.002
Any infection	2.86	3.03	3.13	3.25	0.12
Fatal infection	0.18	0.31	0.28	0.34	0.09/0.02*
Injection site reaction	0.23	0.27	0.28	0.30	0.49
Any Malignancy	1.88	1.85	1.69	1.72	0.31
Fatal Malignancy	0.64	0.55	0.50	0.31	0.0007
Arthritis	3.32	2.15	2.17	2.47	0.002
Osteoarthritis	1.67	1.21	1.12	1.30	0.04
Gout	0.80	0.43	0.35	0.37	0.0001
ALT > 3x normal	1.4	1.9	1.9	2.0	0.19
Bilirubin > 2x normal	0.8	1.0	0.7	0.7	0.34

* P-value for combined canakinumab doses vs placebo

ALT, alanine aminotransferase;
SAE, serious adverse event; SC, subcutaneous

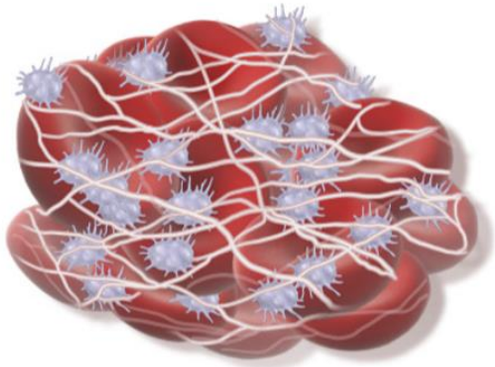
Ridker PM, et al. N Engl J Med. 2017;DOI: 10.1056/NEJMoa1707914

Interleukin-6 is downstream of IL-1 in Innate Immune Signaling

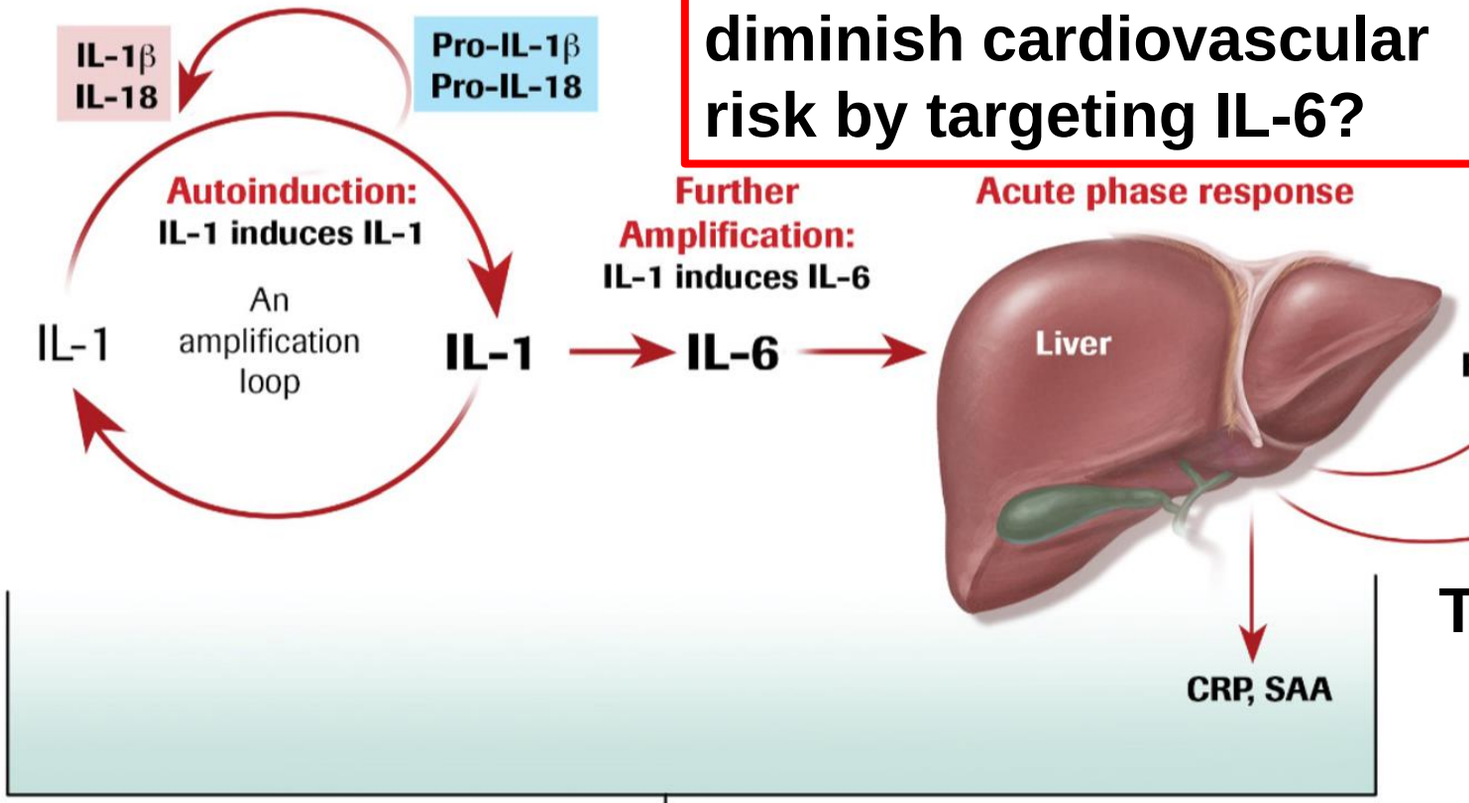


Inflammasome

Can we preserve IL-1β's role in host defenses but diminish cardiovascular risk by targeting IL-6?



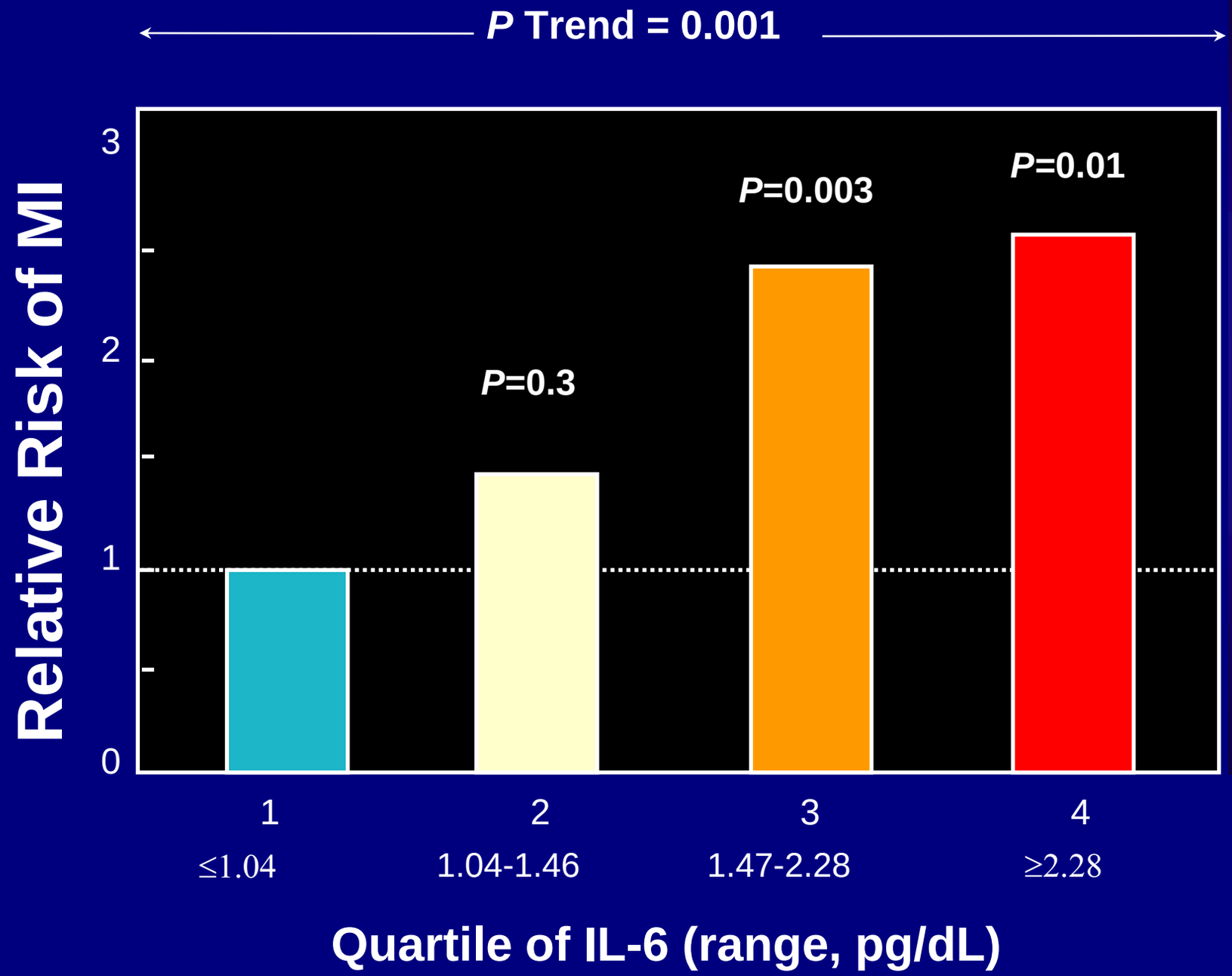
Thrombus formation and stability



Targeting Inflammatory Pathways in Cardiovascular Disease: The Inflammasome, Interleukin-1, Interleukin-6 and Beyond

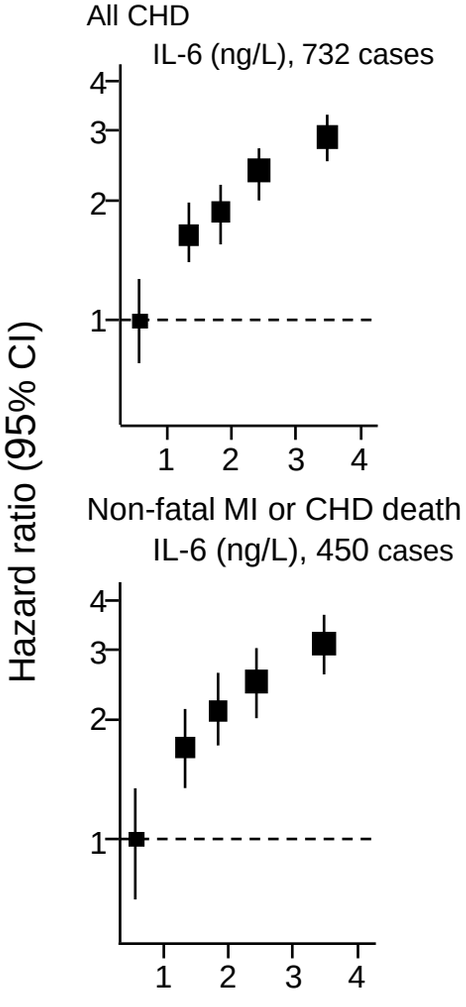
Cells **2021**, *10*, 951

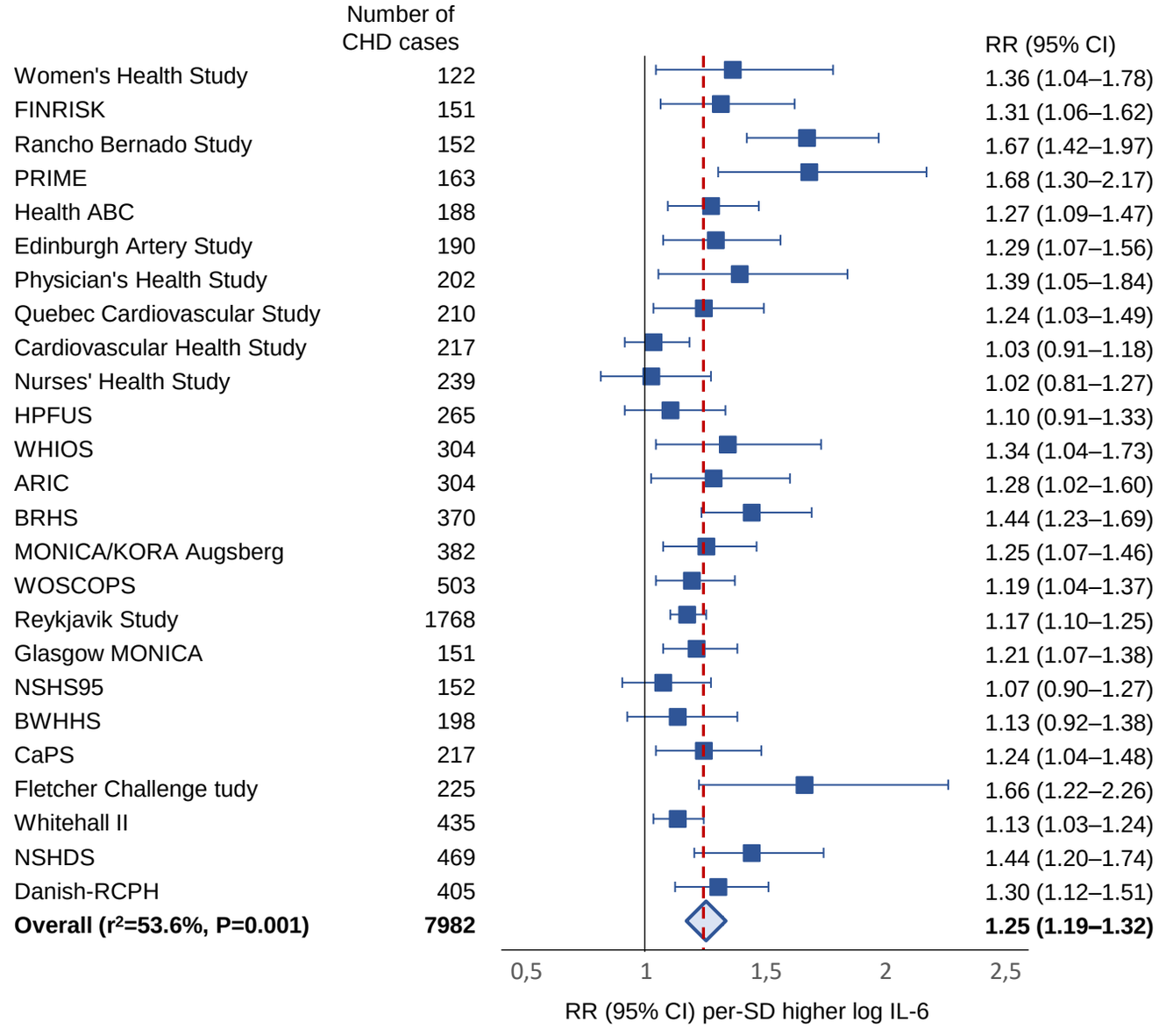
Interleukin 6 (IL-6) Independently Predicts Cardiovascular Risk



Ridker PM et al. Circulation. 2000;101(15):1767-1772.

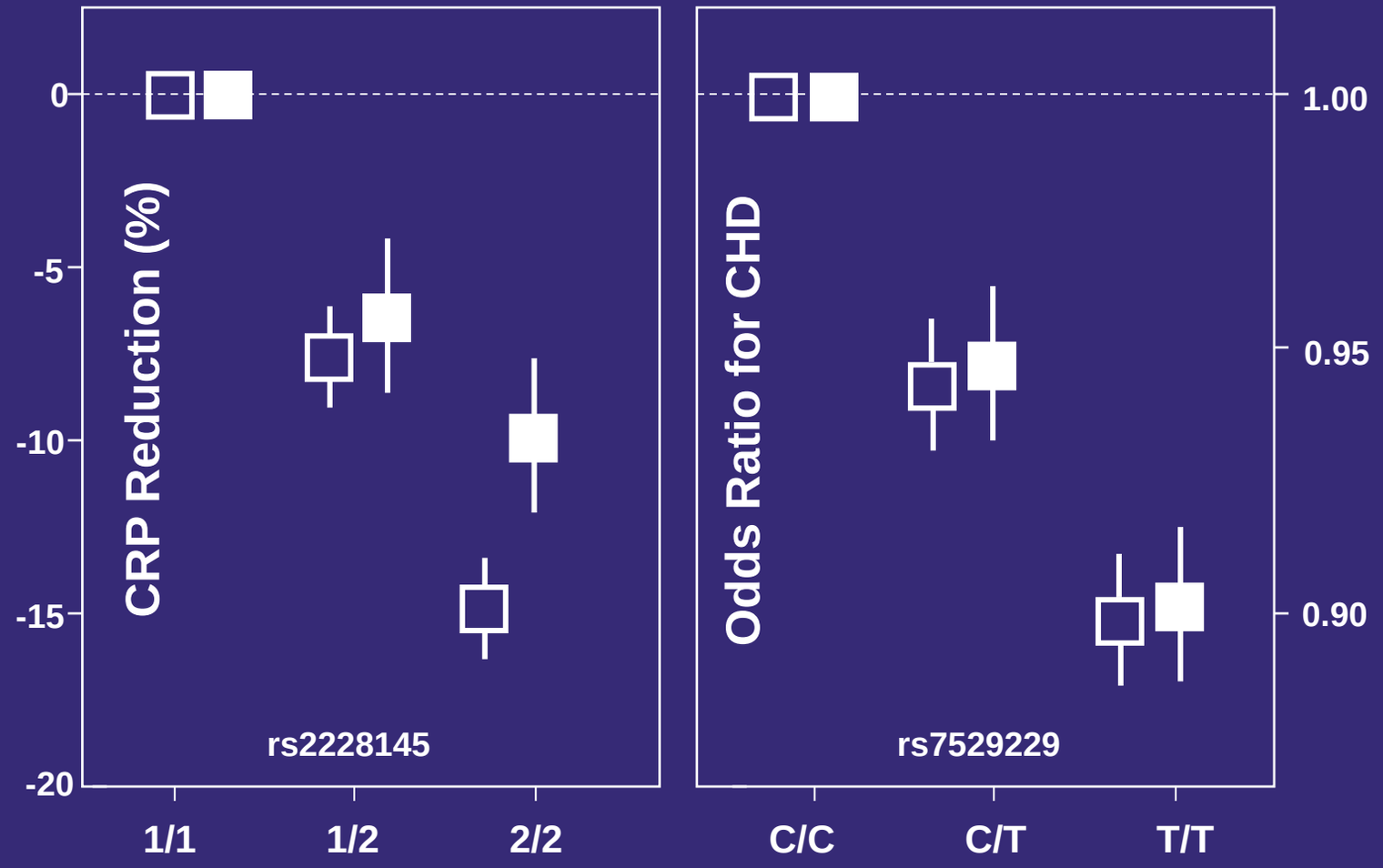
IL-6 Concentrations Powerfully Predict Future Cardiovascular Events





Kaptoge et al, Eur Heart J 2014;35:578-589

Human Genetic Evidence Supports *Causality* of Interleukin 6 in Cardiovascular Risk



Polymorphisms in the IL-6 Receptor Signaling Pathway Influence CRP Levels and Risk of Coronary Heart Disease

CRP Reduction (%) □

Odds Ratio CHD ■

Figure adapted from Sarwar N et al. *Lancet.* 2012;379(9822):1205-1213 and Swerdlow DI et al. *Lancet.* 2012;379(9822):1214-1224.

ESC European Society of Cardiology

European Heart Journal (2022) **00**, 1–13
https://doi.org/10.1093/eurheartj/ehac444

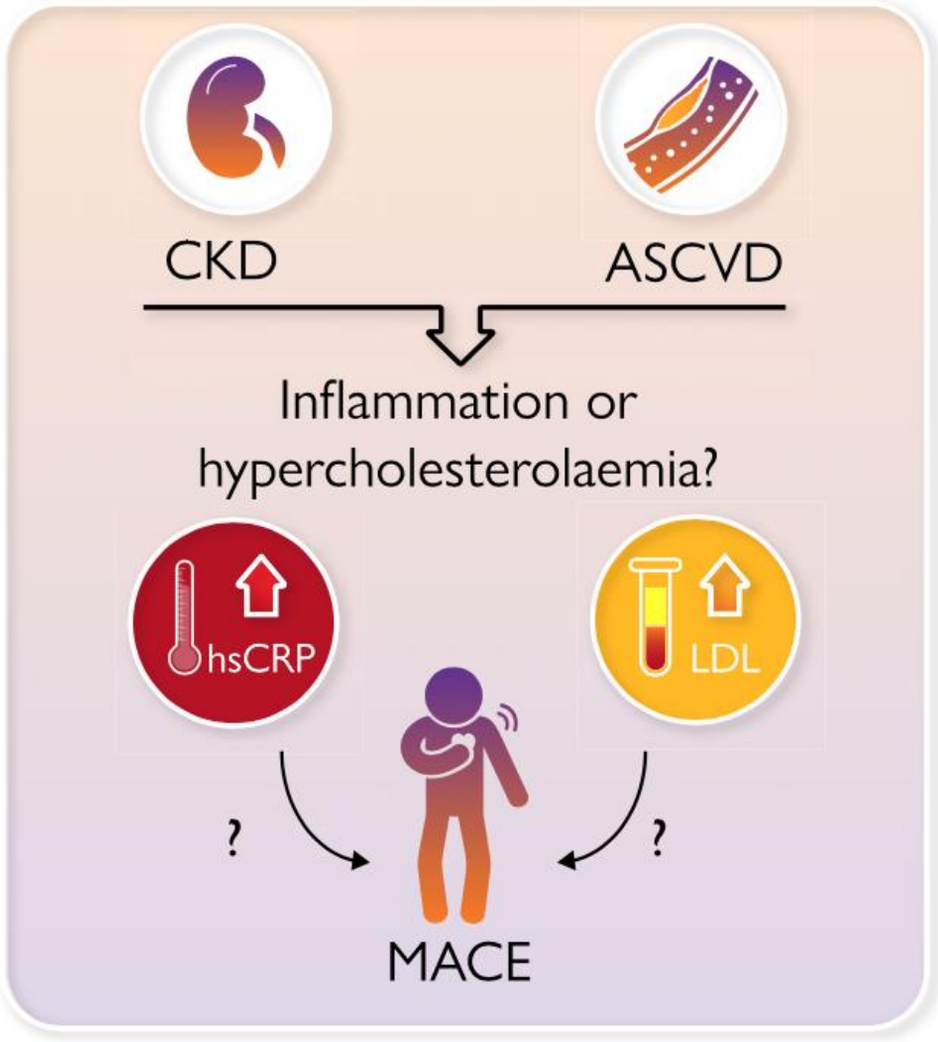
CLINICAL RESEARCH
Epidemiology and prevention

Inflammation drives residual risk in chronic kidney disease: a CANTOS substudy

Paul M Ridker [1,2]*, Katherine R. Tuttle[3], Vlado Perkovic[4], Peter Libby[2], and Jean G. MacFadyen[1]

Online August 10 2022

Inflammation drives residual risk in chronic kidney disease: a CANTOS substudy



9051 CANTOS participants	Comparing top to bottom quartile: hsCRP	Comparing top to bottom quartile: LDL-C
7959 without CKD	HR 1.45 (P < 0.0001)	HR 1.64 (P < 0.0001)
1092 with CKD	HR 1.50 (P = 0.021)	HR 1.04 (P = 0.80)

HR = Hazard Ratio

Paul M Ridker, Katherine R. Tuttle, Vlado Perkovic, Peter Libby, and Jean G. MacFadyen
European Heart Journal (2022) 00, 1–13 https://doi.org/10.1093/eurheartj/ehac444

THE LANCET

IL-6 inhibition with ziltivekimab in patients at high atherosclerotic risk: a double-blind, randomised, placebo-controlled, phase 2 trial

*Paul M Ridker, Matt Devalaraja, Florian M M Baeres, Mads D M Engelmann, G Kees Hovingh, Milana Ivkovic, Larry Lo, Douglas Kling, Pablo Pergola, Dominic Raj, Peter Libby, Michael Davidson, on behalf of the RESCUE Investigators**

Lancet 2021; 397:2060-2069.

RESCUE Design

Trial Conduct

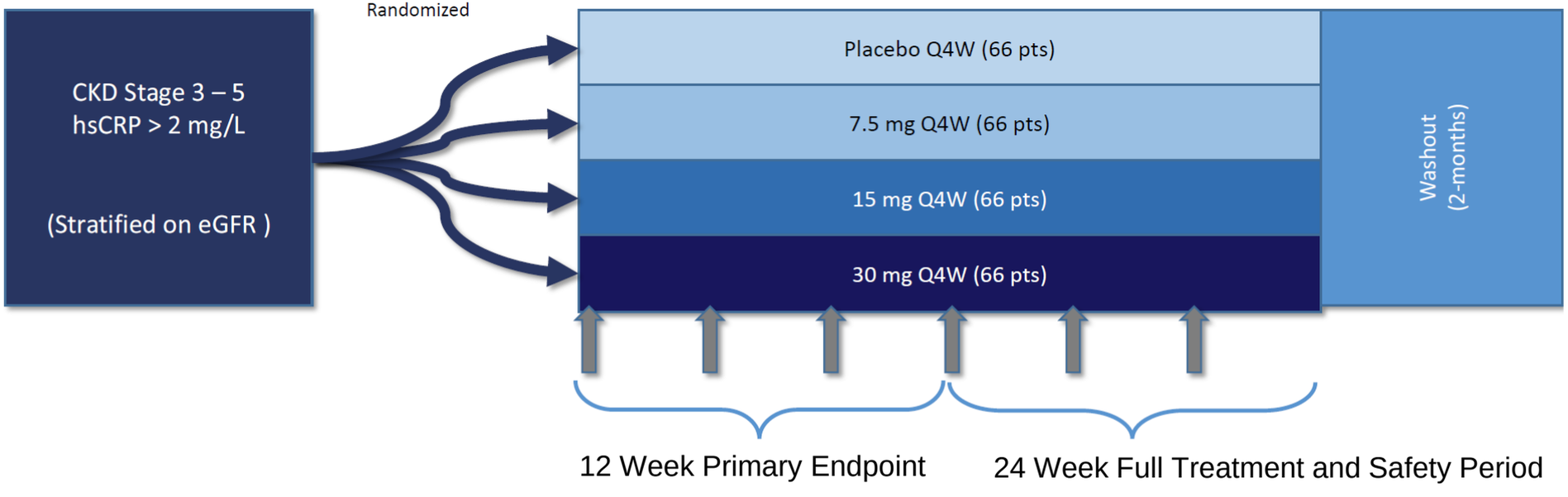
June 17, 2019 - January 14, 2020
40 US clinical sites
264 participants randomized
SC placebo or
SC ziltivekimab 7.5, 15, 30 q 4 weeks

Major Inclusion Criteria

Age ≥ 18 years
Stage 3 – 5 CKD
hsCRP ≥ 2 mg/L

Major Exclusion Criteria

ANC < 2 x 10^9 Platelet Count < 120 x 10^9
Spot urine to creatinine ratio > 4
Active TB or
History of HIV, hepatitis B, hepatitis C

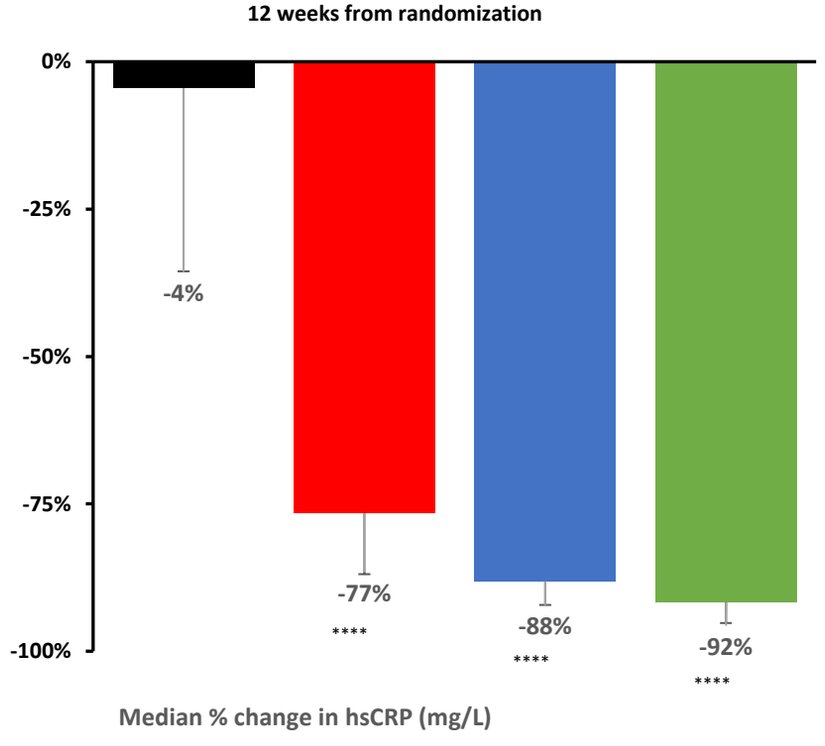


Primary Endpoint: Percent change in hsCRP from baseline to 12 weeks
Secondary Endpoints: Percent change in fibrinogen, haptoglobin, SAA, sPLA2, Lp(a), and lipid levels

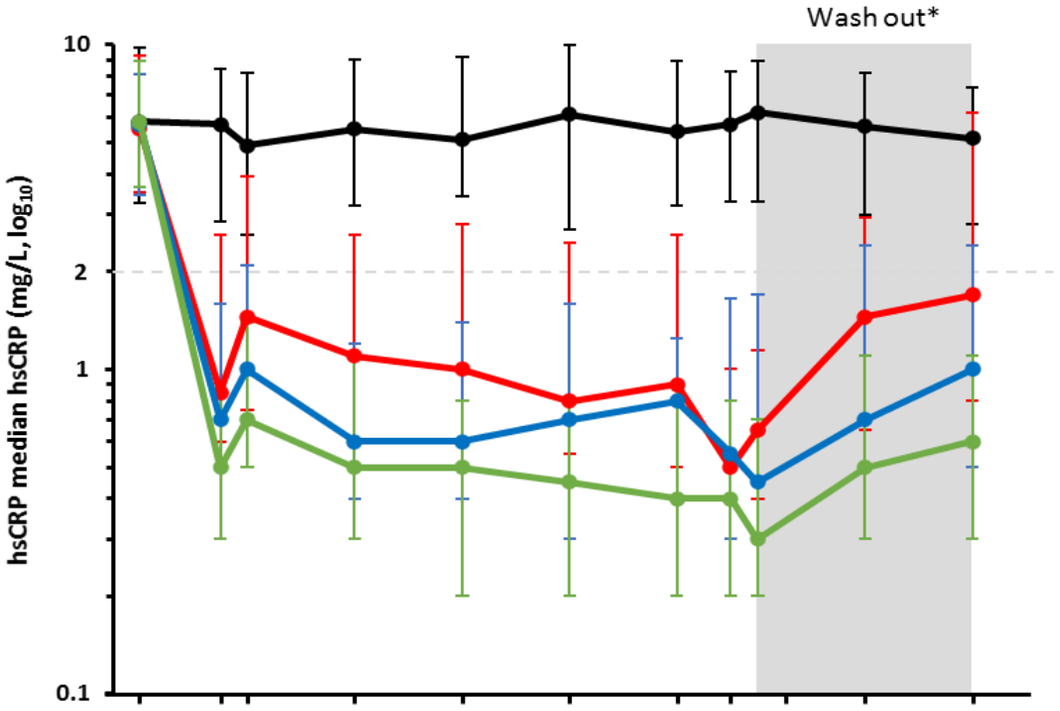
Ridker et al., Lancet 2021; 397:2060-2069.

RESCUE: Primary Result – Change in hsCRP at 12 weeks

A



B



Weeks from randomization	0	3	4	8	12	16	20	22	24	SF1	SF2
Placebo (n)	66	64	65	63	57	46	35	27	31	49	52
Zilti 7.5 mg (n)	66	64	64	62	58	52	39	28	32	52	53
Zilti 15 mg (n)	66	66	64	61	61	49	40	28	34	51	55
Zilti 30 mg (n)	66	62	62	61	57	50	39	29	30	49	53

Placebo Zilti 7.5 mg Zilti 15 mg Zilti 30 mg

**** P< 0.001

Ridker et al, Lancet 2021;397:2060-2069

Ziltivekimab Cardiovascular Outcomes Study (ZEUS)

ZEUS: Phase 3a trial design

CVOT in ASCVD patients with CKD treated with ziltivekimab

6200 patients
- ASCVD
- CKD stage 3–4
- hsCRP ≥2 mg/L

Randomisation (1:1)

- **Ziltivekimab once-monthly 15 mg + standard of care**
- **Placebo once-monthly + standard of care**

Trial information
- Double-blinded
- Trial start in 2021
- Event-driven

Primary endpoint
- Time to the first occurrence of MACE (*CV death, non-fatal MI or non-fatal stroke*)

Secondary endpoints
- Time to first occurrence of expanded MACE (*CV death, non-fatal MI, non-fatal stroke or urgent coronary revascularisation*)
- Number of hospitalisations for HF or urgent HF visits
- Time to all cause death
- Time to first occurrence of composite CKD endpoint (*≥ 40% GFR reduction, kidney death, CKD stage 5, dialysis treatment or kidney transplant*)

Why CKD with elevated hsCRP?

- **Large unmet need**
- **Very high cardiovascular risk**
- **particular biologic state**
  - **LDL-C less relevant for outcomes**
  - **Inflammation more relevant for outcomes**
- **Colchicine is relatively contraindicated in CKD**

Where is IL-6 inhibition going ?

Will interleukin-6 inhibition with ziltivekimab improve cardiovascular outcomes:

- ♡ **In individuals with a history of atherosclerotic disease, chronic kidney disease, and residual inflammatory risk? (ZEUS ~ 70% enrolled)?**
- ♡ **In patients with heart failure and preserved ejection fraction? (HERMES - initiating)?**
- ♡ **In patients with acute myocardial infarction and acute coronary ischemia? (ARTEMIS - in planning)?**

Libby P, Rocha VZ. All roads lead to IL-6: A central hub of cardiometabolic signaling. Int J Cardiol 2018; 259: 213–215.

Ridker PM, Rane M. Interleukin-6 Signaling and Anti-Interleukin-6 Therapeutics in Cardiovascular Disease Circulation Research 2021;128:1728-46.

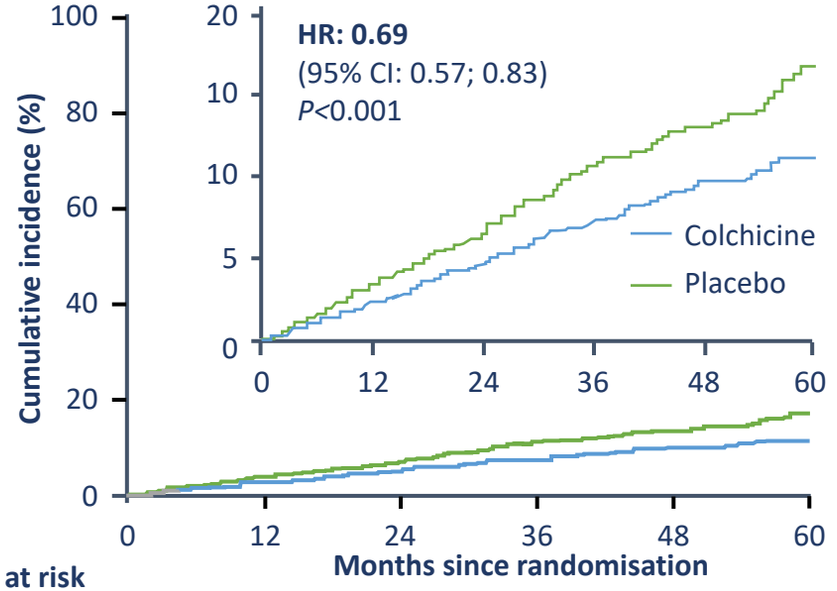
Libby P. Targeting Inflammatory Pathways in Cardiovascular Disease: The Inflammasome, Interleukin-1, Interleukin-6 and Beyond. Cells 2021;10(4):951.

Inflammation – Beyond Cytokines

- Inflammasome inhibitors
- Incretin mimetics
- Colchicine

Colchicine Reduces Cardiovascular Risk

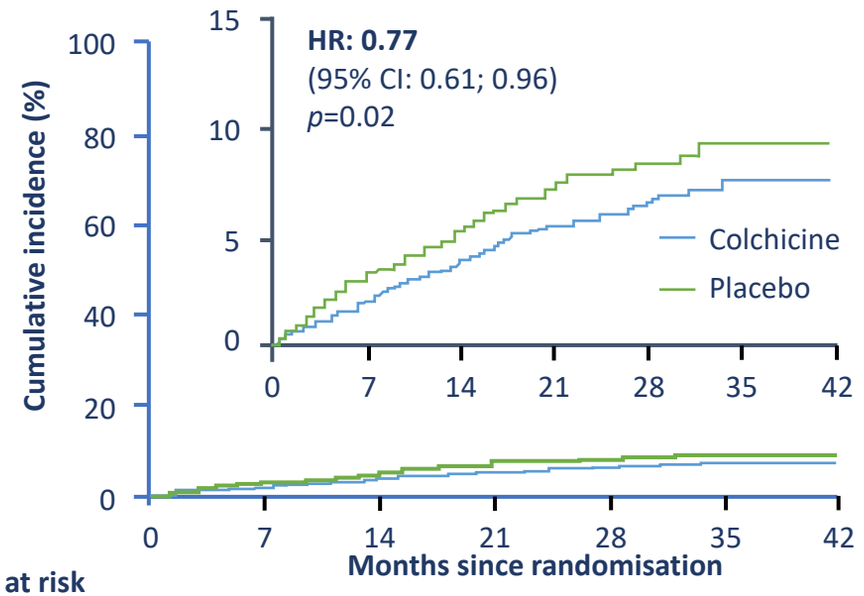
LoDoCo2: N=5,522 stable CAD[1]



No. at risk						
Placebo	2760	2655	1703	821	590	161
Colchicine	2762	2685	1761	890	629	166

eGFR >60 ml/min/1.73 m^2 **– HR 0.66 (95% CI: 0.54–0.80)**
eGFR <60 ml/min/1.73 m^2 **– HR 1.19 (95% CI: 0.53–2.65)**

COLCOT: N=4,745 recent MI[2]



No. at risk							
Placebo	2379	2261	1854	1224	622	144	0
Colchicine	2366	2284	1868	1230	628	153	0

MACE+: HR: 0.68 (95% CI: 0.54; 0.81)
All-cause mortality: HR: 1.04 (95% CI: 0.61; 1.78)

CAD, coronary artery disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MACE, major adverse cardiovascular event; MACE+, MACE plus heart failure and thromboembolic events; MI, myocardial infraction

1. Nidorf SM et al. N Engl J Med 2020;383:1838–1847; 2. Tardif JC et al. N Engl J Med 2019;381:2497–2505; 3. Samuel M et al. Can J Cardiol 2021;37:776–785; 4. Ridker PM and Rane M. Circulation Research 2021;128:1728–1746

FDA Approves Colchicine Tablets for Reducing Cardiovascular Risk

Jun 20, 2023

Patrick Campbell

Announced by AGEPHA Pharma US on June 20, 2023, the US FDA approval of colchicine 0.5 mg tablets (Lodoco) for reducing cardiovascular event risk marks the first approval in agency history for an anti-inflammatory atheroprotective cardiovascular treatment.

The US Food and Drug Administration had awarded approval to colchicine 0.5 mg tablets (Lodoco) for reducing the risk of myocardial infarction (MI), stroke, coronary revascularization, and cardiovascular death in adult patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease.

Announced by parent company AGEPHA Pharma USA on June 20, 2023, the approval, which is supported by data from a 5522-person trial purporting a 31% relative reduction in risk of cardiovascular events, marks the first indication in FDA history for an anti-inflammatory atheroprotective cardiovascular treatment, according to a statement from AGEPHA.[1]

The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

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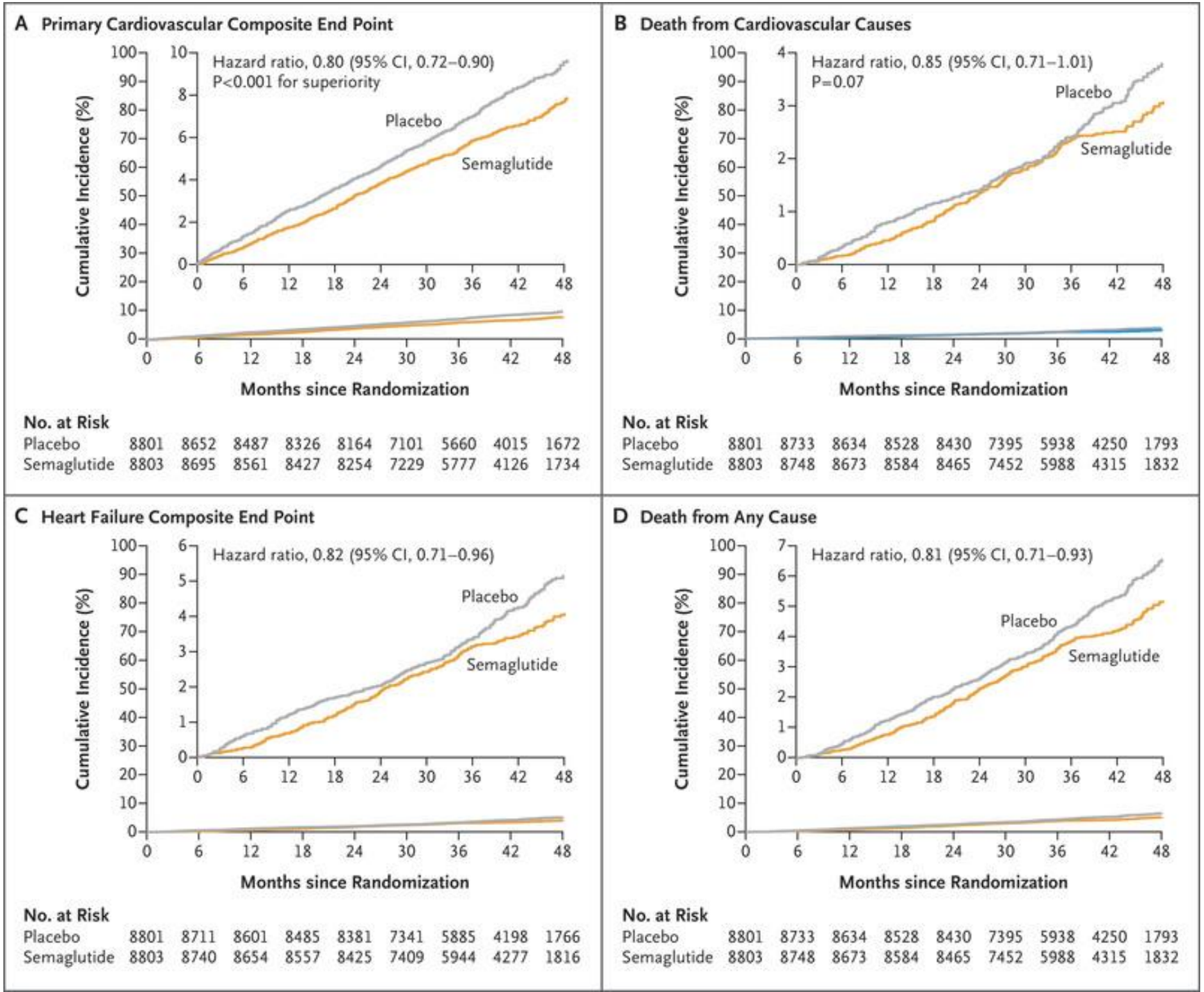

SELECT: Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

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Table 3. Supportive Binary and Continuous Secondary End Points.*

End Point	Semaglutide (N=8803)	Placebo (N=8801)	Difference (95% CI)†
Glycated hemoglobin level of <5.7% among patients with baseline glycated hemoglobin level of ≥5.7% — no./total no. (%)‡			
At week 52	3848/5831 (66.0)	1136/5748 (19.8)	10.15 (9.18 to 11.23)
At week 104	3775/5750 (65.7)	1211/5663 (21.4)	8.74 (7.91 to 9.65)
Mean change from randomization to week 104			
Body weight — %	−9.39±0.09	−0.88±0.08	−8.51 (−8.75 to −8.27)
Waist circumference — cm	−7.56±0.09	−1.03±0.09	−6.53 (−6.79 to −6.27)
Glycated hemoglobin level — percentage points	−0.31±0.00	0.01±0.00	−0.32 (−0.33 to −0.31)
Systolic blood pressure — mm Hg	−3.82±0.16	−0.51±0.16	−3.31 (−3.75 to −2.88)
Diastolic blood pressure — mm Hg	−1.02±0.10	−0.47±0.10	−0.55 (−0.83 to −0.27)
Heart rate — beats/min	3.79±0.11	0.69±0.11	3.10 (2.80 to 3.39)
EQ-5D-5L index score§	0.01±0.00	−0.01±0.00	0.01 (0.01 to 0.02)
EQ-5D-VAS score§	2.52±0.16	0.92±0.16	1.60 (1.16 to 2.04)
High-sensitivity CRP level — %	−39.12	−2.08	−37.82 (−39.70 to −35.90)
Total cholesterol level — %	−4.63	−1.92	−2.77 (−3.37 to −2.16)
HDL cholesterol level — %	4.86	0.59	4.24 (3.70 to 4.79)
LDL cholesterol level — %	−5.25	−3.14	−2.18 (−3.22 to −1.12)
Triglyceride level — %	−18.34	−3.20	−15.64 (−16.68 to −14.58)

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes
DOI: 10.1056/NEJMoa2307563

Inflammation in atherothrombosis

Inflammation is a common contributor to atherothrombosis and is becoming clinically actionable.

Anti-inflammatory therapy of atherothrombosis

"Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning."

Winston Churchill

https://www.brainyquote.com/quotes/winston_churchill_163144

Thanks!

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