Anti-platelet treatment in AMI and Inflammation

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Disclosures

Affiliation/Financial Relationship	Company
Consultant/Advisory/Speaking Engagements:	Affluent Medical, Boehringer Ingelheim, Chiesi USA, Cordis, Daiichi Sankyo, Esperion Science/Innovative Biopharma, Gaffney Events, Educational Trust, Global Clinical Trial Partners, Ltd., IQVIA, Medscape/WebMD Global, NovoNordisk, PeerView Institute for Medical Education, TERUMO Europe N.V., Radcliffe
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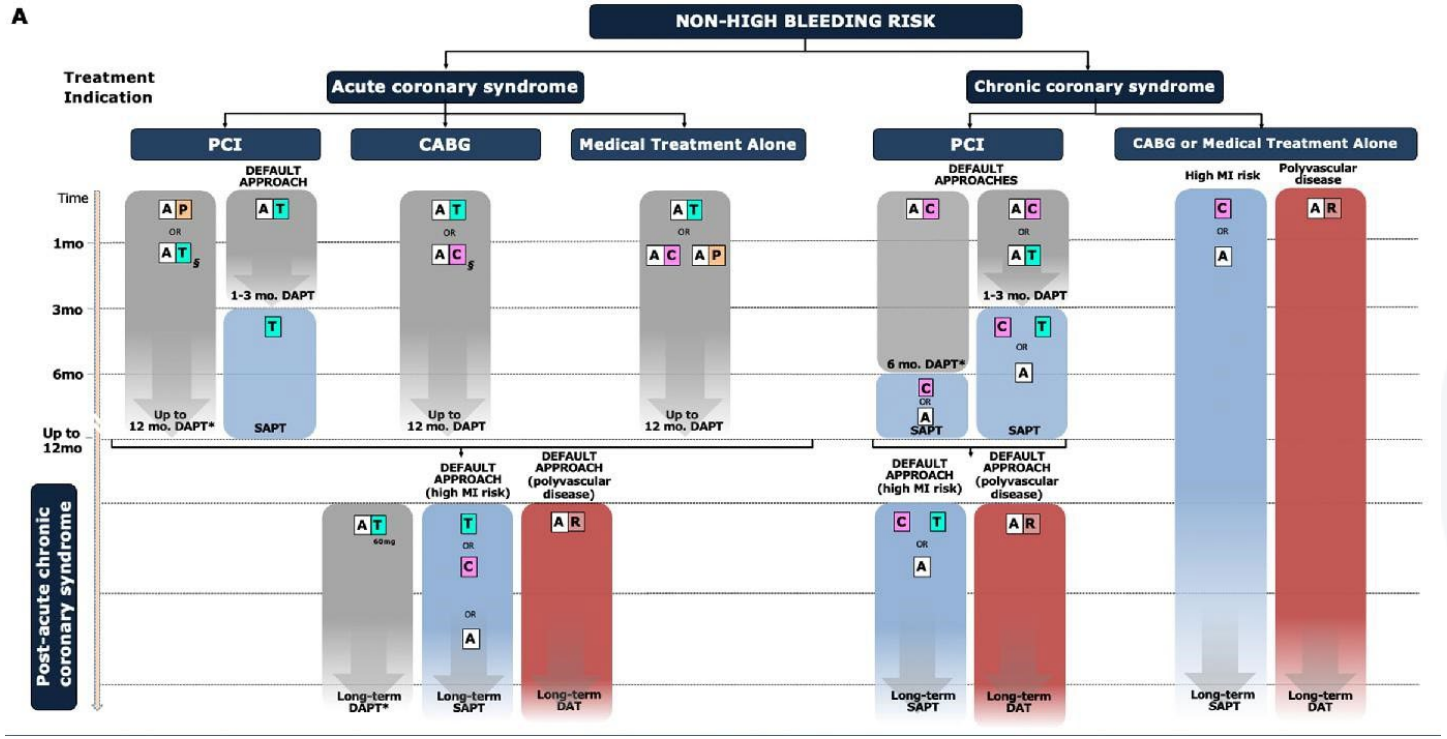
Equity <1% in:	Elixir Medical, Stel, ControlRad (spouse)
No Fees from:	SCAI (Women in Innovations Committee Member), Faculty CRF, Women as One
Honorarium:	AMA - JAMA Cardiology (Associate Editor), ACC (BOT Member, SC Member CTR Program)

Antithrombotic treatment strategies in patients with established coronary atherosclerotic disease

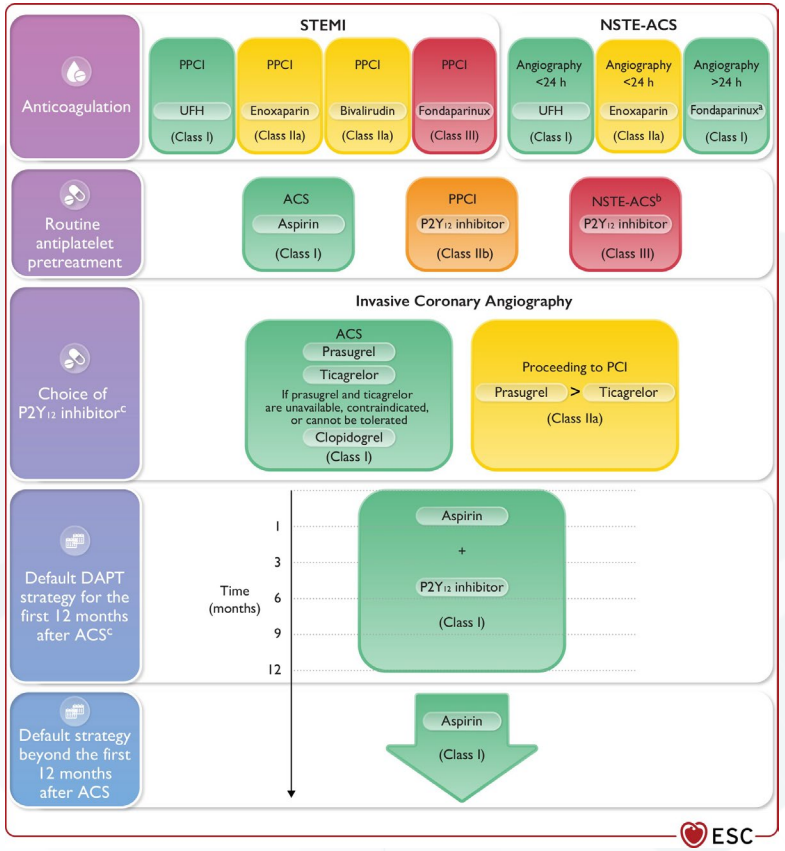
NON-HBR



Valgimigli M, et al. Eur Heart J Cardiovasc Pharmacother. 2023 Jul 29;9(5):462-496.

ESC European Society of Cardiology
European Heart Journal (2023) 44, 3720–3826
https://doi.org/10.1093/eurheartj/ehad191
ESC GUIDELINES

2023 ESC Guidelines for the management of acute coronary syndromes



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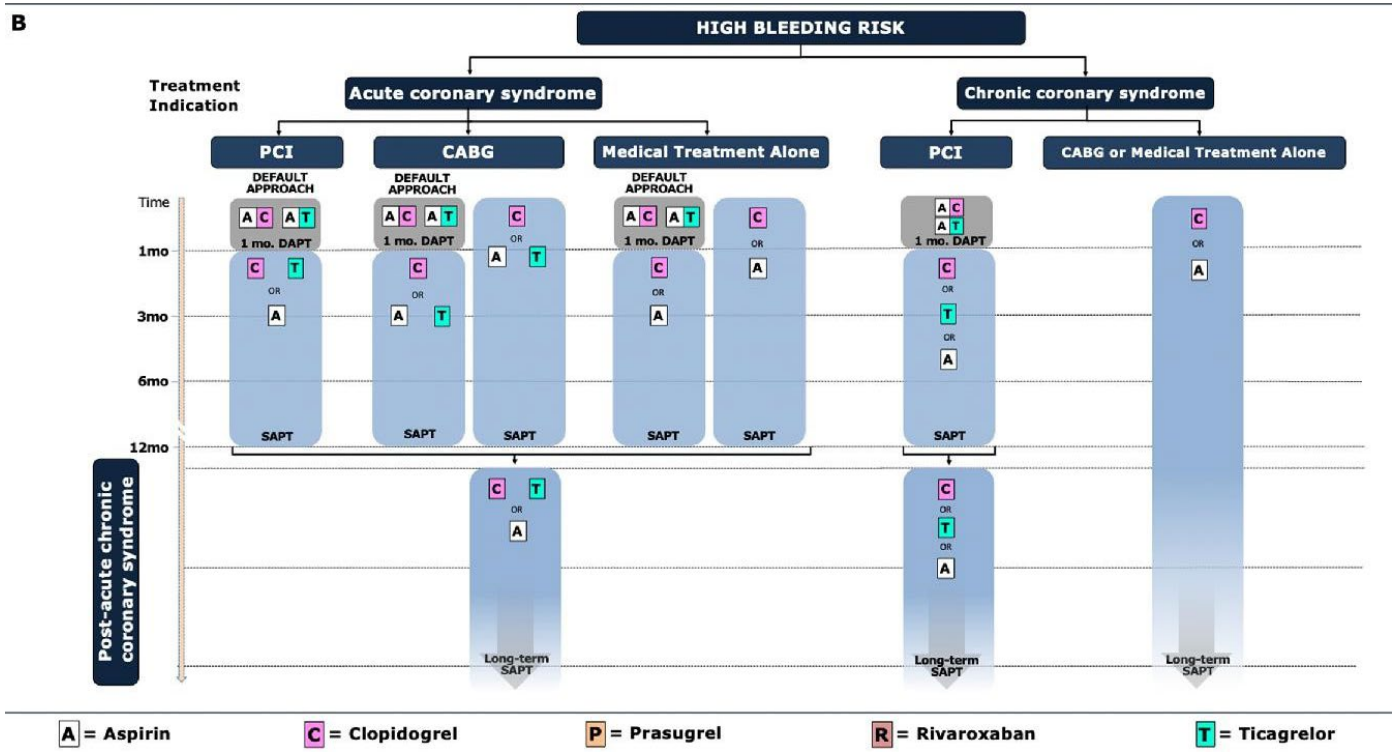
Antithrombotic treatment strategies in patients with established coronary atherosclerotic disease

HBR



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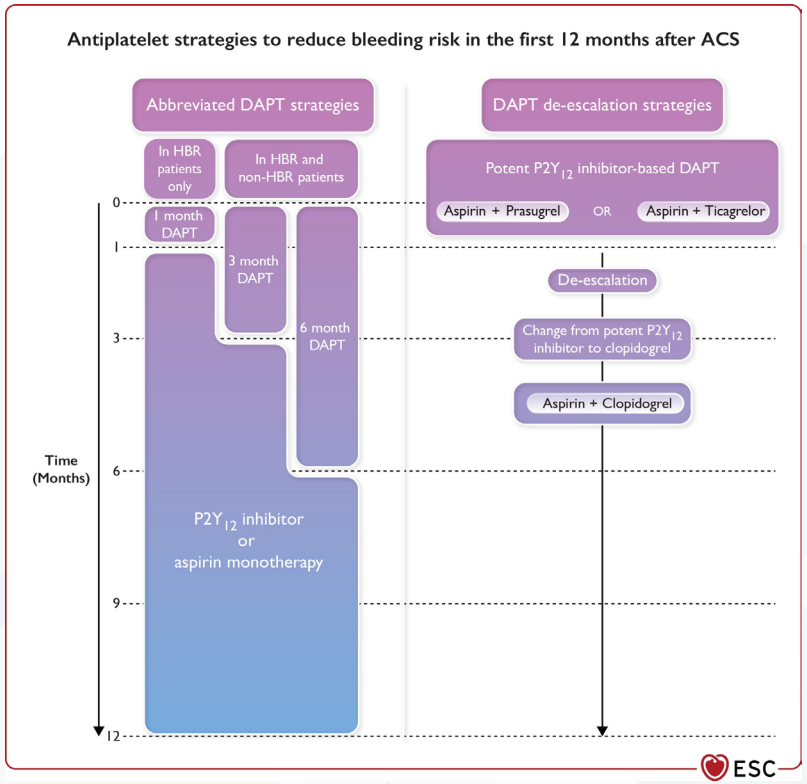
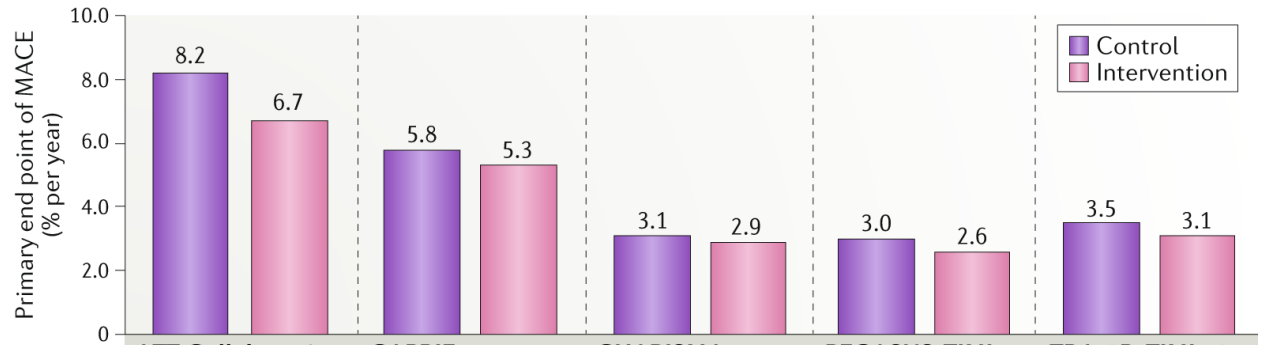


Byrne et al. Eur Heart J. 2023 Aug 25:ehad191.

Residual risk concept

Residual risk in patients with CAD treated with antiplatelet therapy

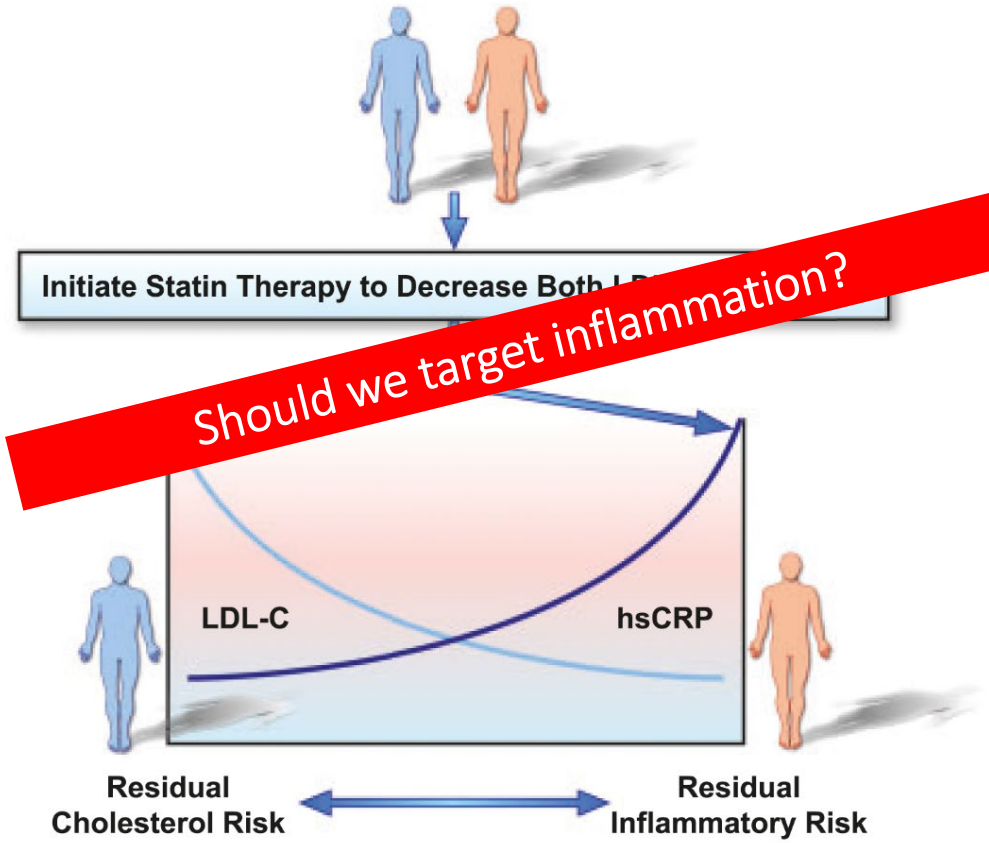


	ATT Collaboration[a]	CAPRIE	CHARISMA	PEGASUS-TIMI 54	TRA-2P–TIMI 50
Publication year	2009	1996	2006	2015	2012
Control	Control	Aspirin	Aspirin	Aspirin	Aspirin
Intervention	Aspirin	Clopidogrel	DAPT (clopidogrel + aspirin)	DAPT (ticagrelor + aspirin)	Vorapaxar + aspirin ± thienopyridine
HR (95% CI)	0.81 (0.75–0.87)	0.91 (0.84–1.00)	0.83 (0.72–0.96)	0.84 (0.74–0.95)	0.87 (0.80–0.94)
Therapy use in intervention group (%):					
ACEI or ARB	NA	NA	85.3	80.4	73.5
Lipid-lowering therapies	NA	NA	77.1–89.3	92.4	91.0

A mean residual risk of MACE of around 3%.

Capodanno D et al., Nat Rev Cardiol . 2020 Apr;17(4):242-257

Residual cholesterol and inflammatory therapy

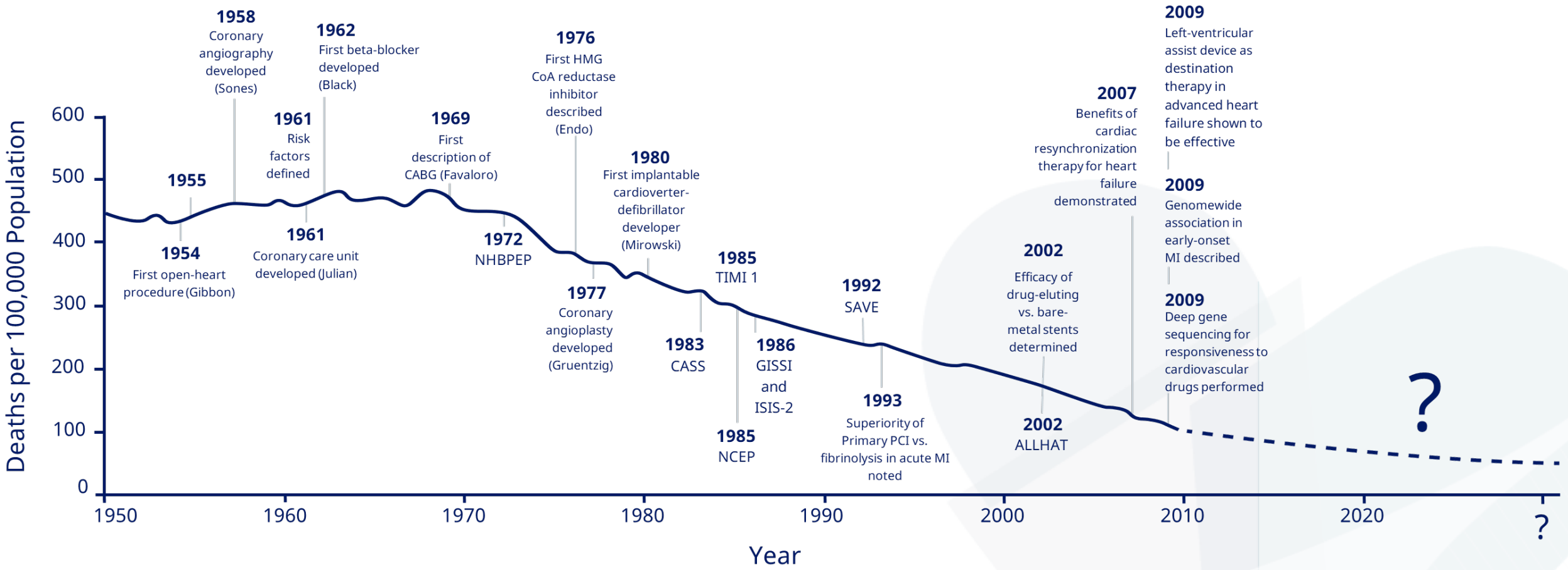


1 INFLAMMATORY HYPOTHESIS

2 EVIDENCE FROM ANTI-INFLAMMATORY STUDIES

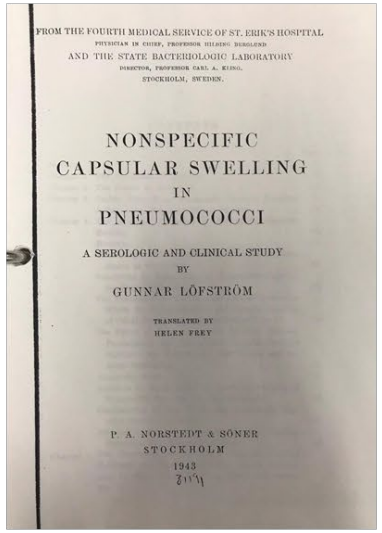
3 FUTURE PERSPECTIVES

A tale of coronary artery disease and myocardial infarction



First case reports of CRP elevation with acute ischemia

1943


FROM THE FOURTH MEDICAL SERVICE OF ST. ERIK'S HOSPITAL
PHYSICIAN IN CHIEF, PROFESSOR HILDING DIDRIKSEN
AND THE STATE BACTERIOLOGIC LABORATORY
DIRECTOR, PROFESSOR CARL A. KLING
STOCKHOLM, SWEDEN

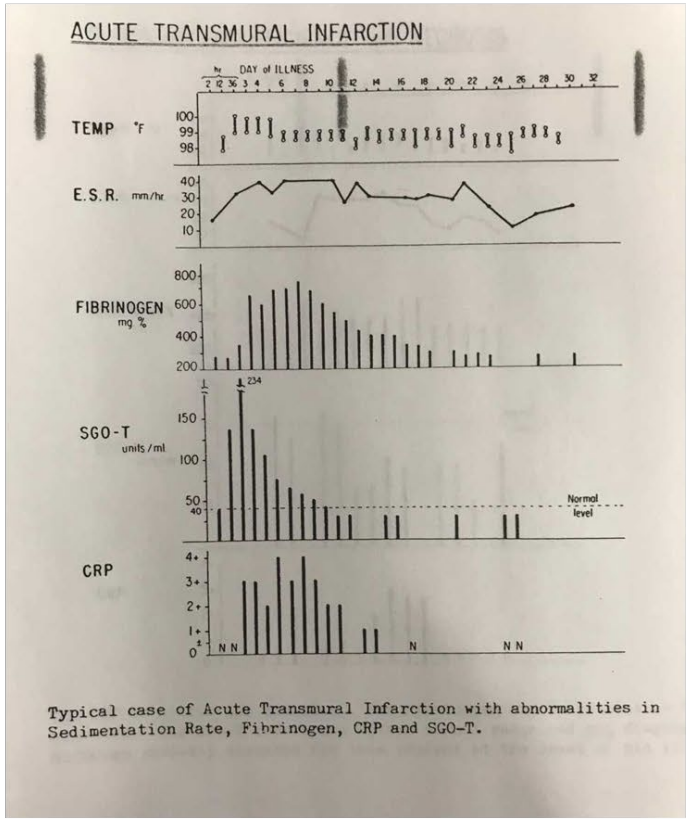
NONSPECIFIC
CAPSULAR SWELLING
IN
PNEUMOCOCCI

A SEROLOGIC AND CLINICAL STUDY
BY
GUNNAR LÖFSTRÖM

TRANSLATED BY
HELEN FREY

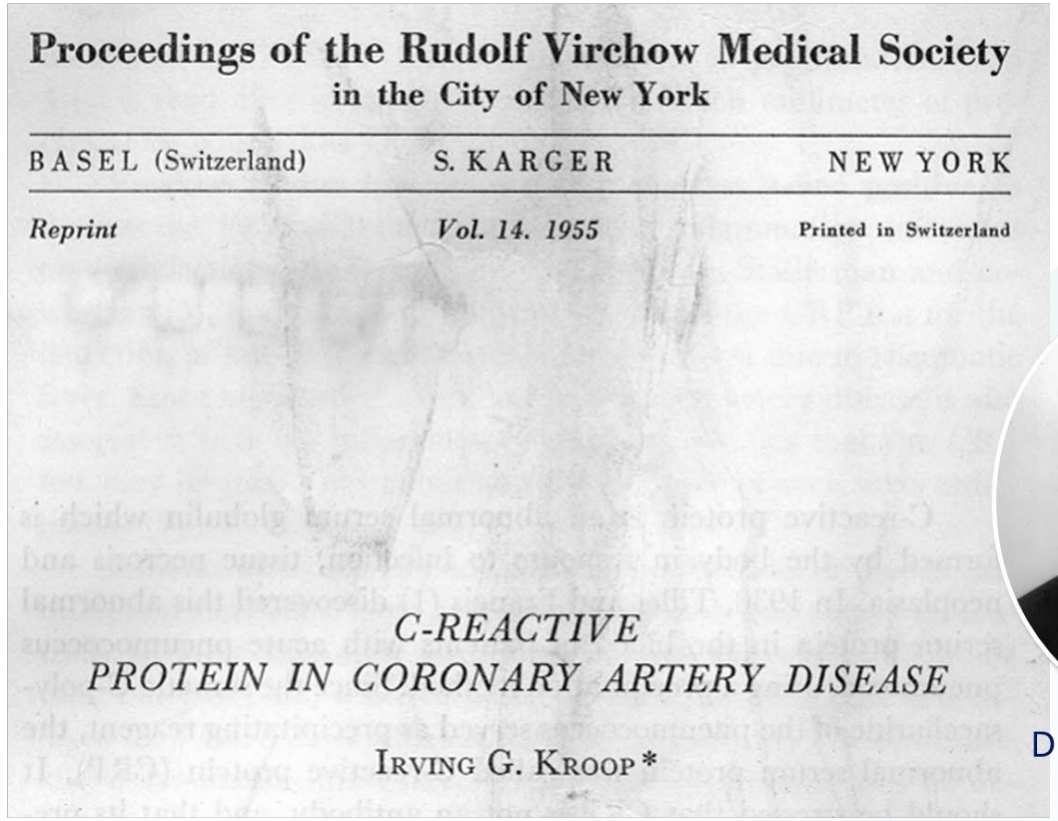
P. A. NORSTEDT & SÖNER
STOCKHOLM
1943

St. Erik´s Hospital, Stockholm



Typical case of Acute Transmural Infarction with abnormalities in Sedimentation Rate, Fibrinogen, CRP and SGO-T.

1955


Proceedings of the Rudolf Virchow Medical Society
in the City of New York

BASEL (Switzerland) S. KARGER NEW YORK

Reprint *Vol. 14. 1955* Printed in Switzerland

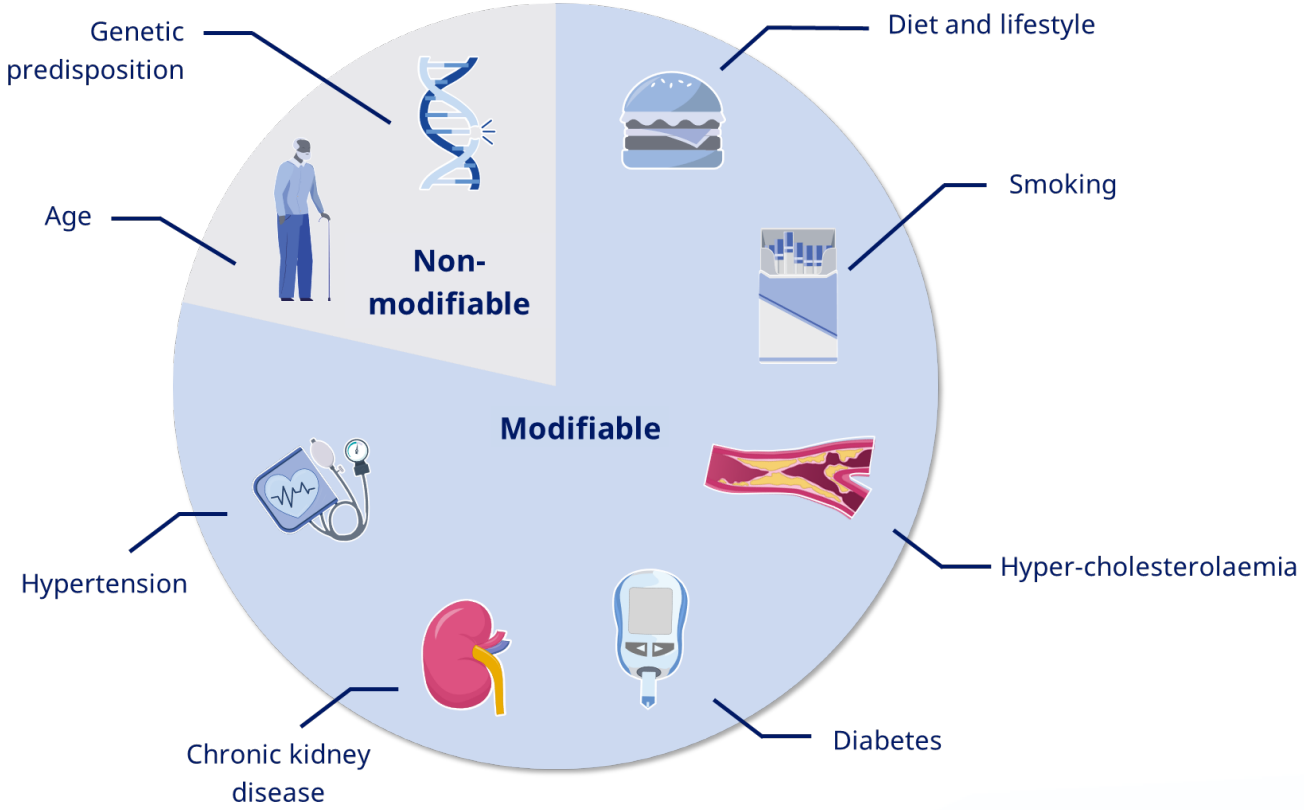
C-REACTIVE
PROTEIN IN CORONARY ARTERY DISEASE

IRVING G. KROOP*

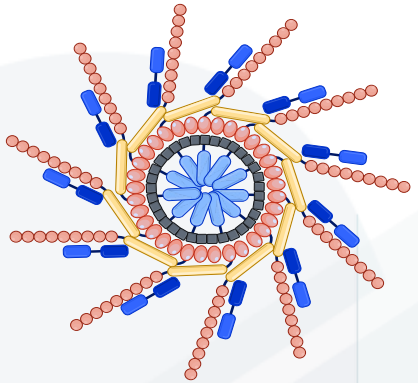

Dr Irving G. Kroop
1915 - 2013

Inflammation for CV risk stratification

Traditional risk factors

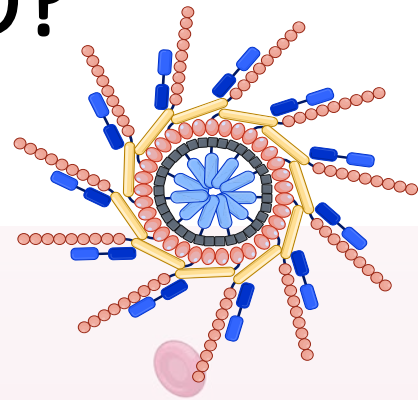


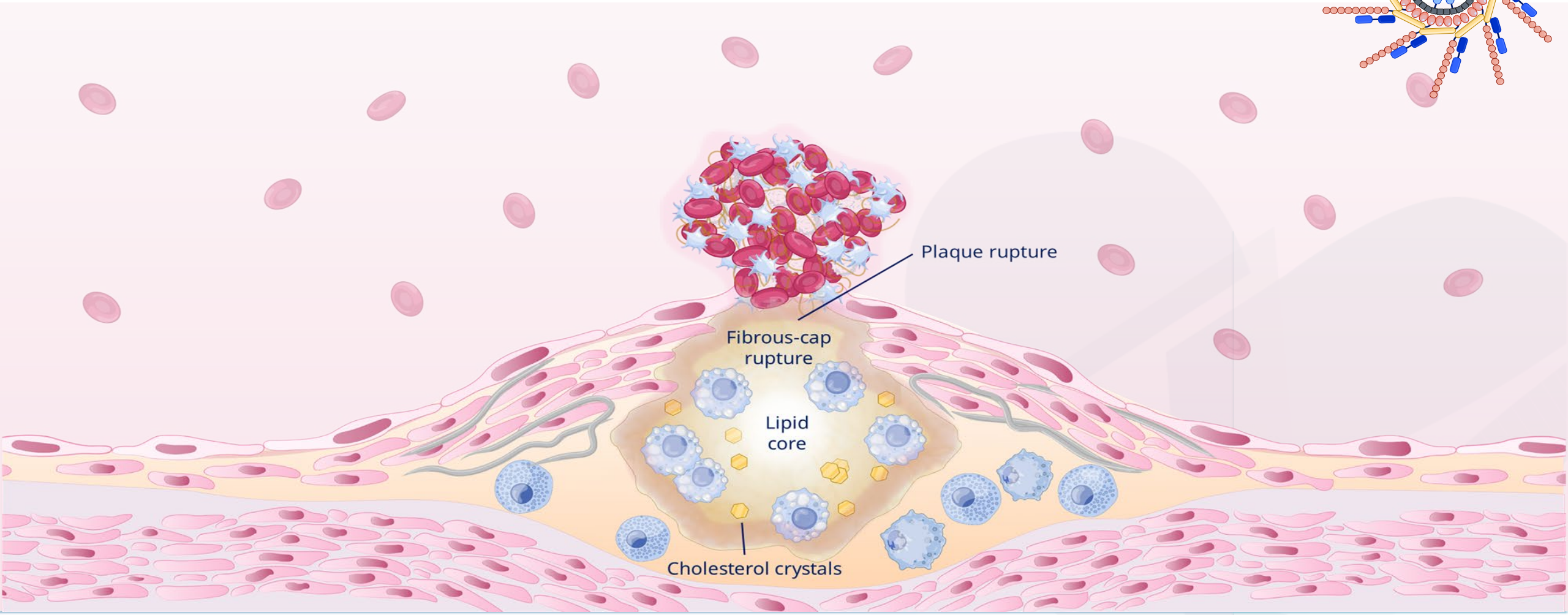
Emerging

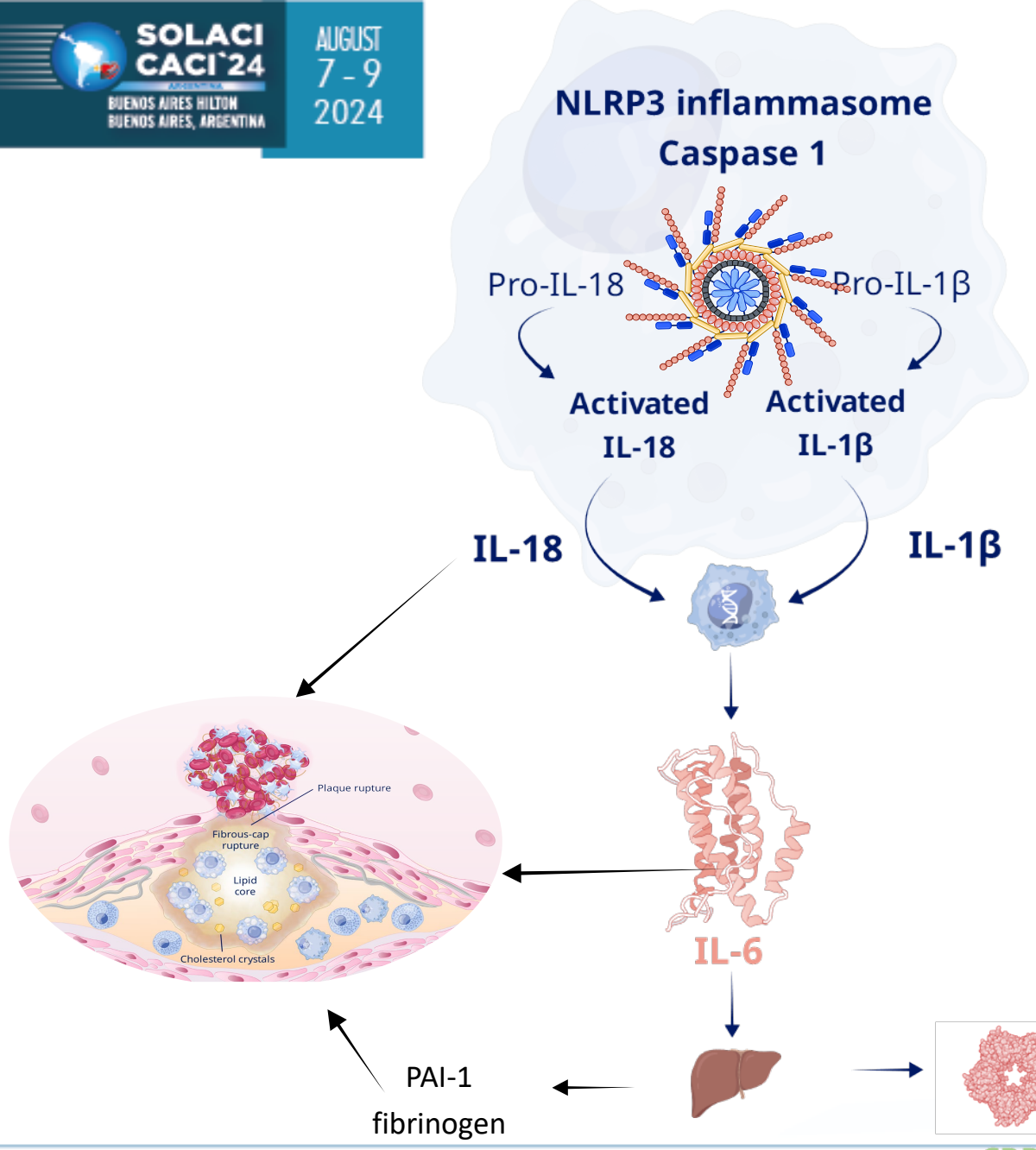


Inflammation

Why is inflammation relevant in CAD?





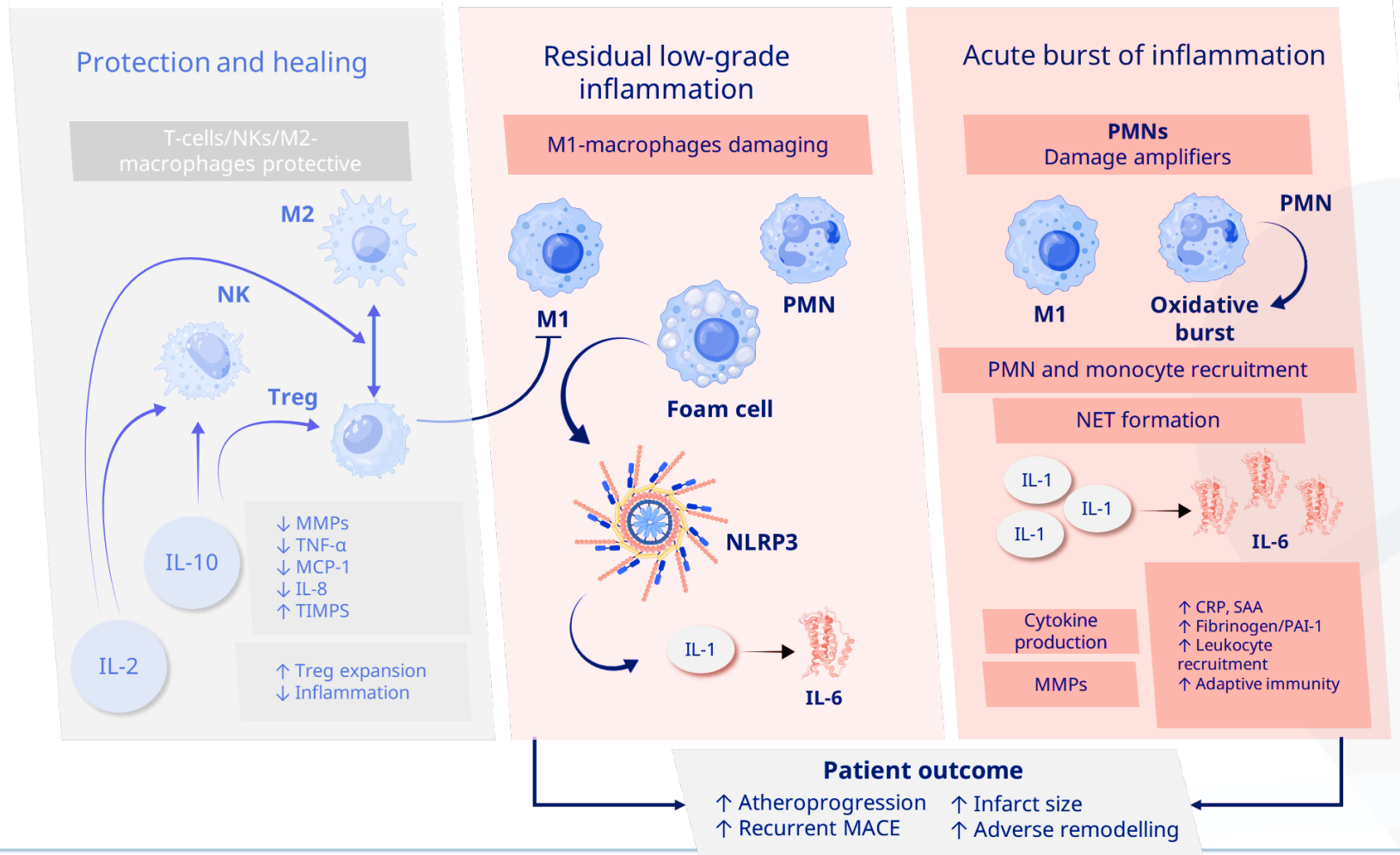


- **Inflammation** plays a relevant role in **atherosclerosis** development and progression
- **Inflammasome** chronic activation is pivotal for induction of inflammatory cytokine cascade
- **Cytokines (IL-1, IL-6)** are upstream signal regulators that can be **pharmacologically targeted**
- **CRP** and other acute-phase proteins serve as **downstream biomarkers** of the inflammatory response

Vascular risk	hs-CRP (mg/L)
High	> 3
Intermediate	1-3
Low	< 1

hsCRP, highly sensitive C-reactive protein; IL, interleukin; RIR, residual inflammatory risk
Ridker PM. *Circulation* 2020;141:78–7789

Concept of inflammation in MI



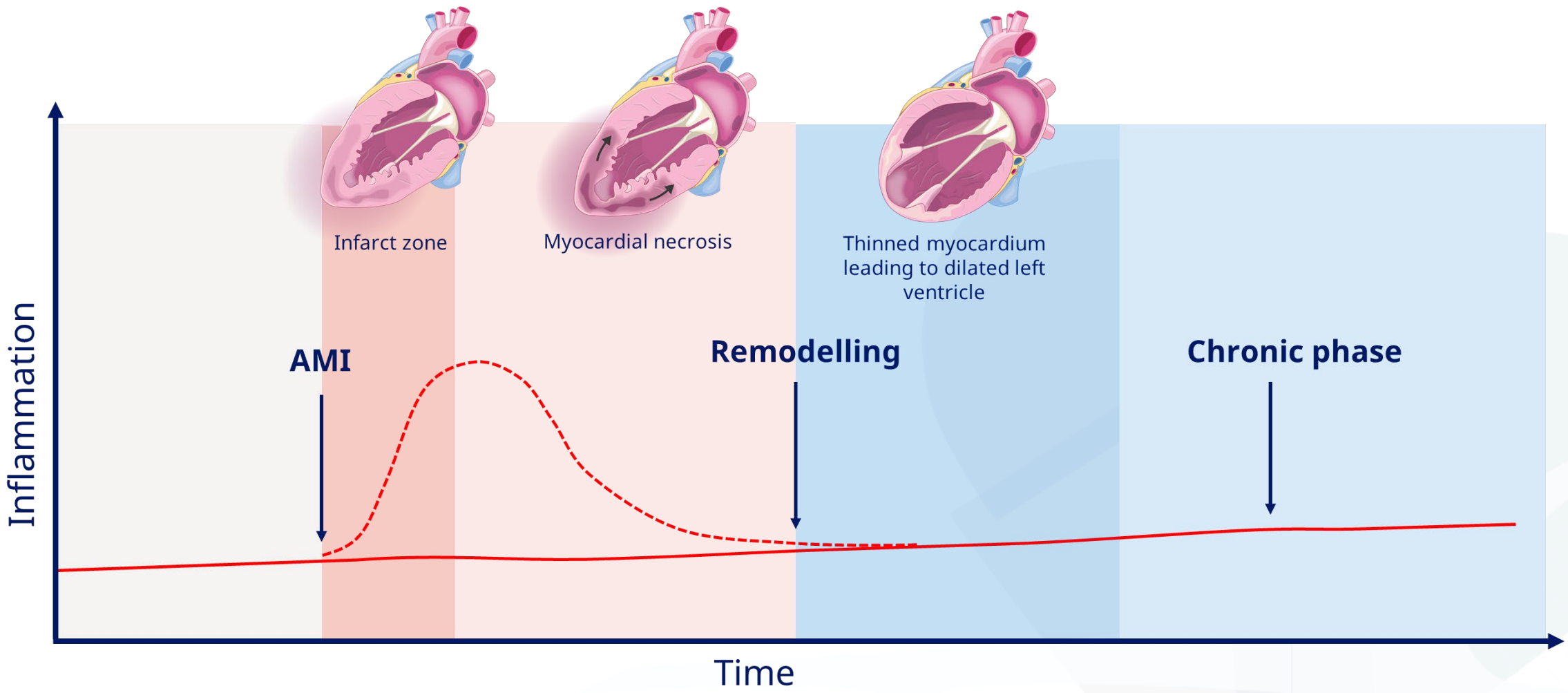
Early phase: acute burst of inflammation and oxidative stress triggered by plaque rupture, thrombosis and myocardial necrosis
→ **PMNs, IL-1, IL-6**

Late phase: smouldering **low-grade persistent inflammatory state**, entailing **residual inflammatory risk**
→ **inflammasome, IL-1, IL-6**

Early and late phase inflammation affect cardiovascular patients' outcomes

Matter MA, et al. Eur Heart J. 2024;45:89-103

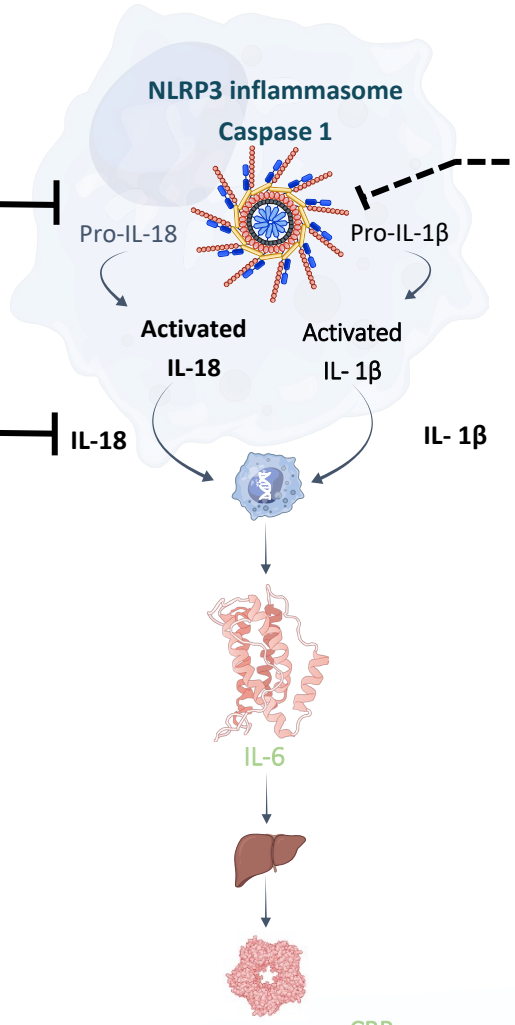
Concept of inflammation in MI



Road Map for Anti-Cytokine Therapies Development

NLRP3 Inhibitors

Interleukin-18 Inhibitors



Microtubule Polymerization Inhibitors **Colchicine**

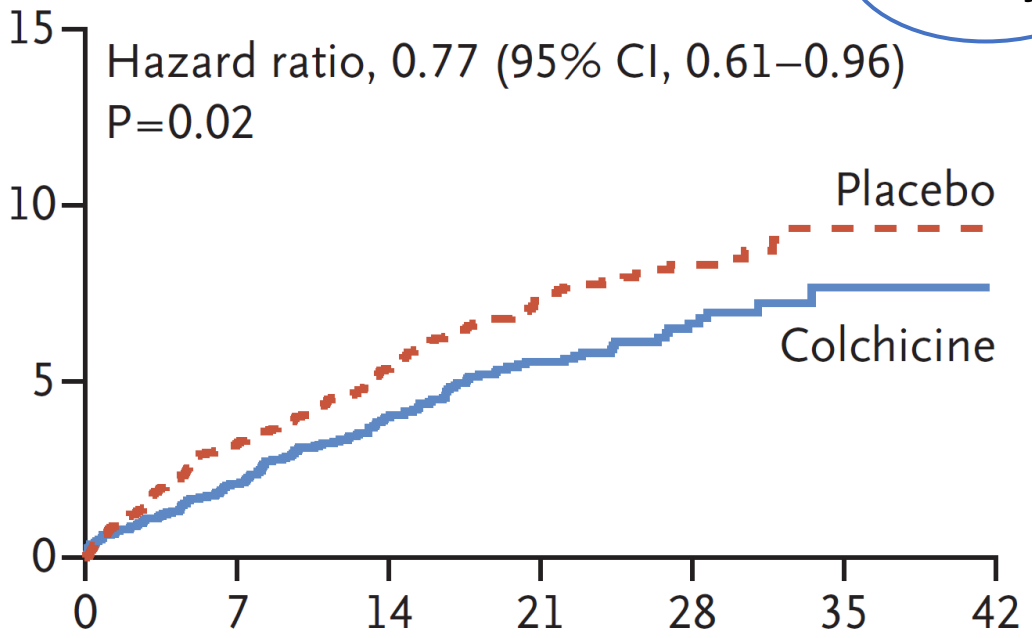
Proven Efficacy
COLCOT, LoDoCo2
2019, 2020

hsCRP, highly sensitive C-reactive protein; IL, interleukin; RIR, residual inflammatory risk
Ridker PM. *Circulation* 2020;141:78–7789

Colchicine for CV risk reduction

COLCOT (N=4,745 recent MI)[1]

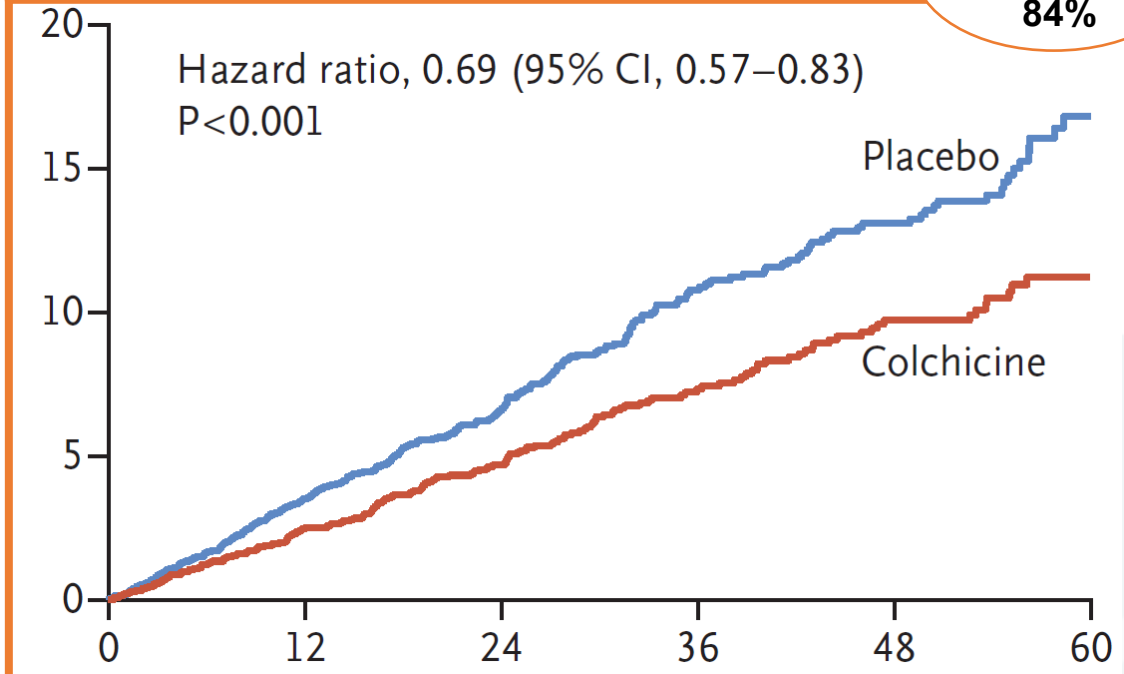
Post MI <30 days



MACE+ HR 0.68 (0.54–0.81), 32% RRR[2]

LoDoCo2 (N=5,522 stable CAD)[3]

Post ACS 84%



MACE HR 0.69 (0.57-0.83); P<0.001 for superiority

eGFR > 60 HR 0.67 (95% CI 0.55–0.81)
eGFR < 60 HR 1.18 (95% CI 0.53–2.63)

1. Tardif JC et al. *NEJM* 2019;381:2497–2505; 2. Samuel M et al. *Can J Cardiol* 2021;37:776–785; 3. Nidorf SM et al. *NEJM* 2020;383:1838–1847

Colchicine

European Society of Cardiology

2023 Guidelines on Acute Coronary Syndromes

Patients with ACS

Low-dose colchicine (0.5 mg once daily) may be considered

Particularly if other risk factors are insufficiently controlled or if recurrent cardiovascular disease events occur under optimal therapy

IIb A

FDA APPROVED

June 20, 2023

"to reduce the risk of myocardial infarction, stroke, coronary revascularization, and cardiovascular death in adult patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease"

- **Contraindicated** in patients with severe renal or liver dysfunction
- **Should be temporarily discontinued** when taking medications that inhibit the CYP3A4 and P-glycoprotein

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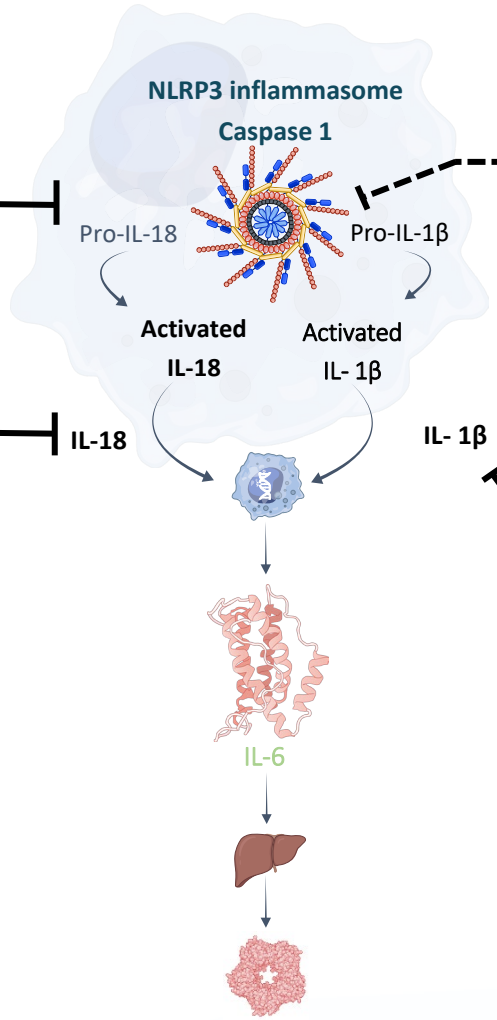
Interleukin-18 Inhibitors



Microtubule Polymerization Inhibitors **Colchicine**

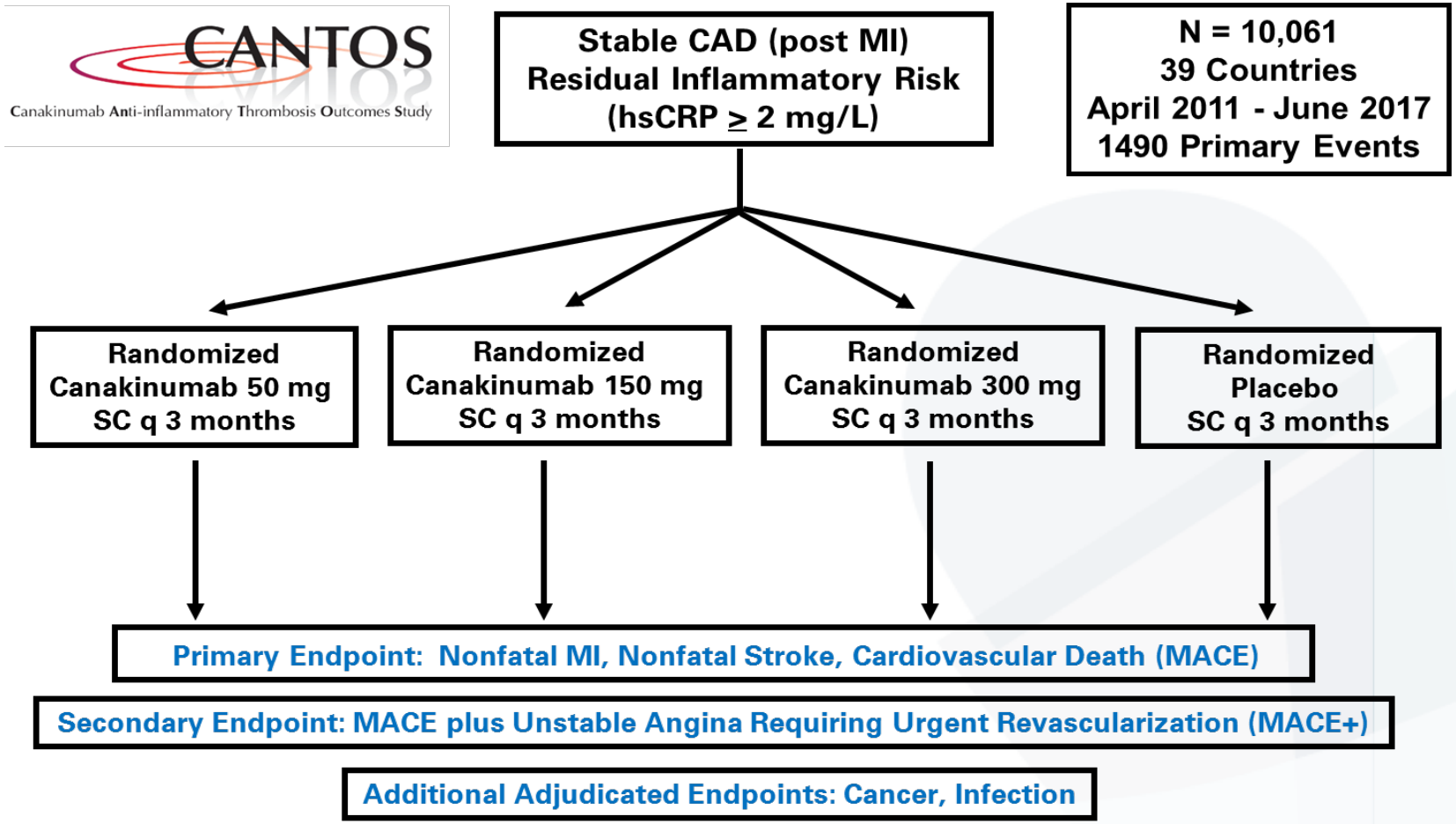
Proven Efficacy
COLCOT, LoDoCo2
2019, 2020

Interleukin-1 Inhibitors **Canakinumab**

Proven Efficacy
CANTOS
2017

hsCRP, highly sensitive C-reactive protein; IL, interleukin; RIR, residual inflammatory risk
Ridker PM. *Circulation* 2020;141:78–7789

Canakinumab: A human monoclonal antibody neutralizing IL-1β



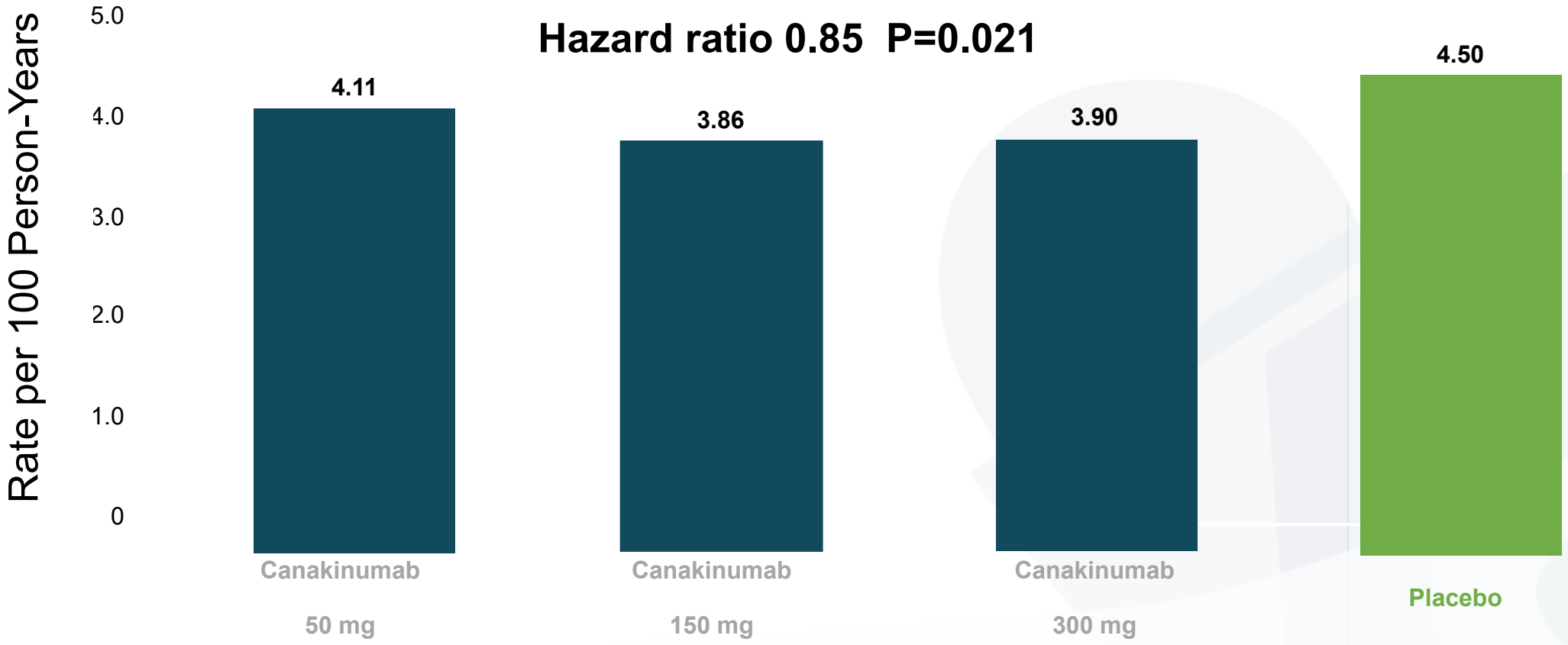
Ridker PM et al. *N Engl J Med* 2017;377:1119–1131

CANTOS Study

Major Adverse Cardiac Events at ~3.7 Years

Cardiovascular death, stroke, myocardial infarction

Hazard ratio 0.85 P=0.021



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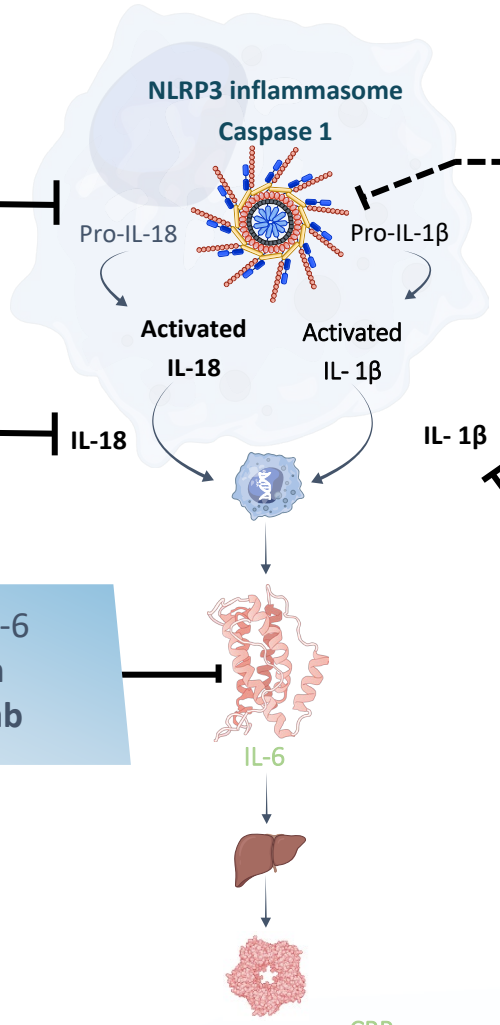


Microtubule Polymerization Inhibitors **Colchicine**

Proven Efficacy
COLCOT, LoDoCo2
2019, 2020

Interleukin-1 Inhibitors **Canakinumab**

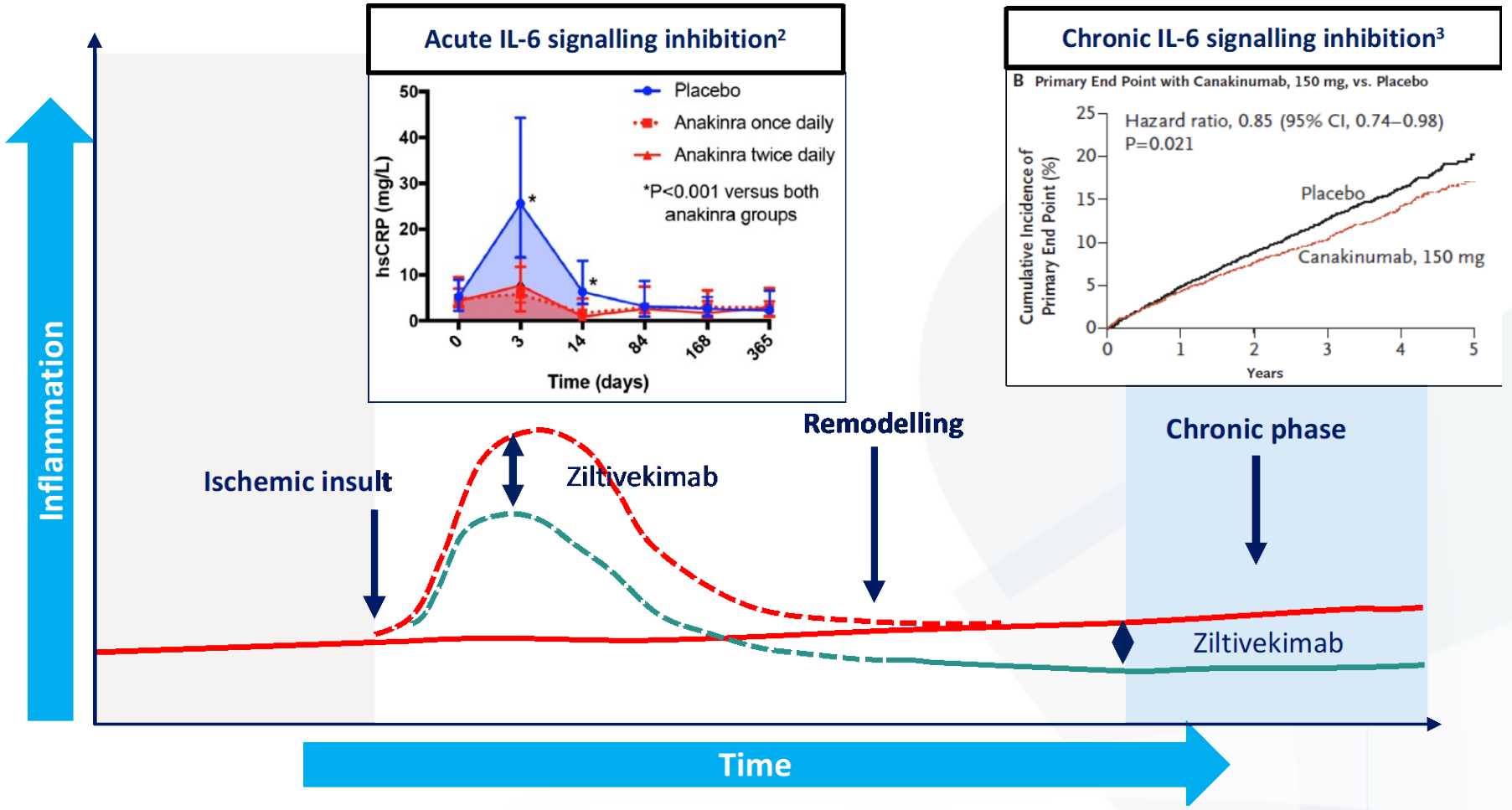
Proven Efficacy
CANTOS
2017

Interleukin-6 Inhibition **Ziltivekimab**

Under Investigation
ZEUS
HERMES

hsCRP, highly sensitive C-reactive protein; IL, interleukin; RIR, residual inflammatory risk
Ridker PM. *Circulation* 2020;141:78–7789

Concept of ziltivekimab effect in AMI



Abbate A et al. JAHA. 2020. Ridker P et al. NEJM 2017.

ARTEMIS: Study Design

A randomised, parallel-group, double-blind, placebo-controlled, cardiovascular outcome trial

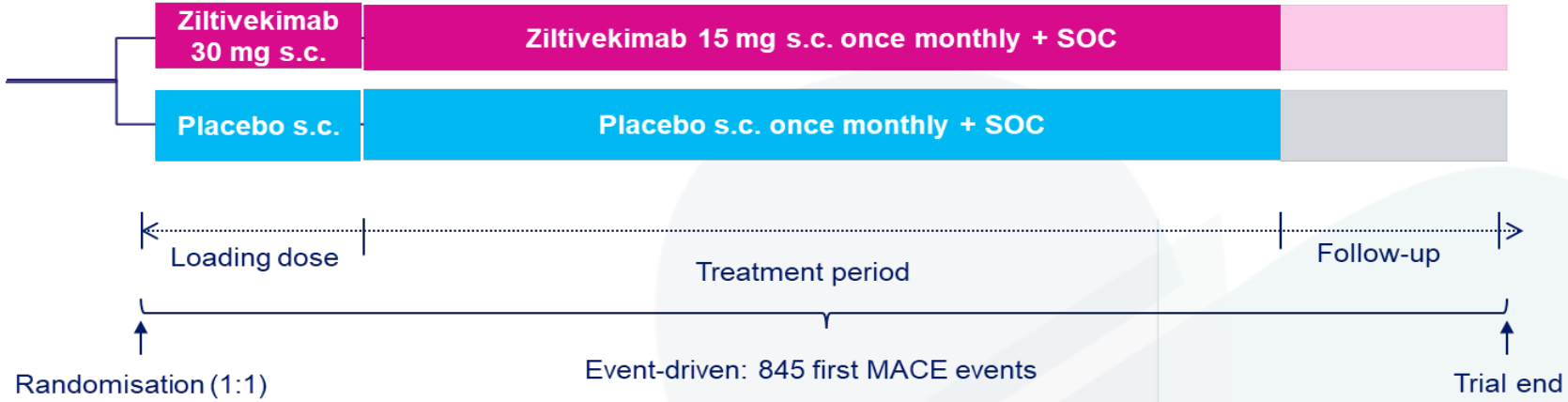
10,000 participants

AMI (STEMI or NSTEMI)

Angiographic evidence of type 1 MI

≥ 1 enrichment criteria

Randomisation as early as possible & latest within 36 h STEMI / 48 h NSTEMI



Trial objective	Primary endpoint	Confirmatory secondary endpoints (hierarchy)
To demonstrate the superiority of a loading dose of ziltivekimab 30 mg s.c. versus placebo s.c. followed by 15 mg s.c. once monthly vs placebo s.c. both added to standard of care, in reducing the risk of MACE in participants with angiographic evidence type 1 MI.	Time to the first occurrence of 3-component MACE • CV death • Non-fatal MI • Non-fatal stroke	Time to the first occurrence of • Coronary MACE (CV-death, non-fatal MI, Ischaemia-Driven Coronary Revascularization (ID-CR)) • Expanded MACE (CV death, nf MI, nf Stroke, ID-CR, HHF, Urgent HF • CV death • Expanded HF (CV death, HHF, Urgent HF, or Outpatient HF visit) • All-cause death

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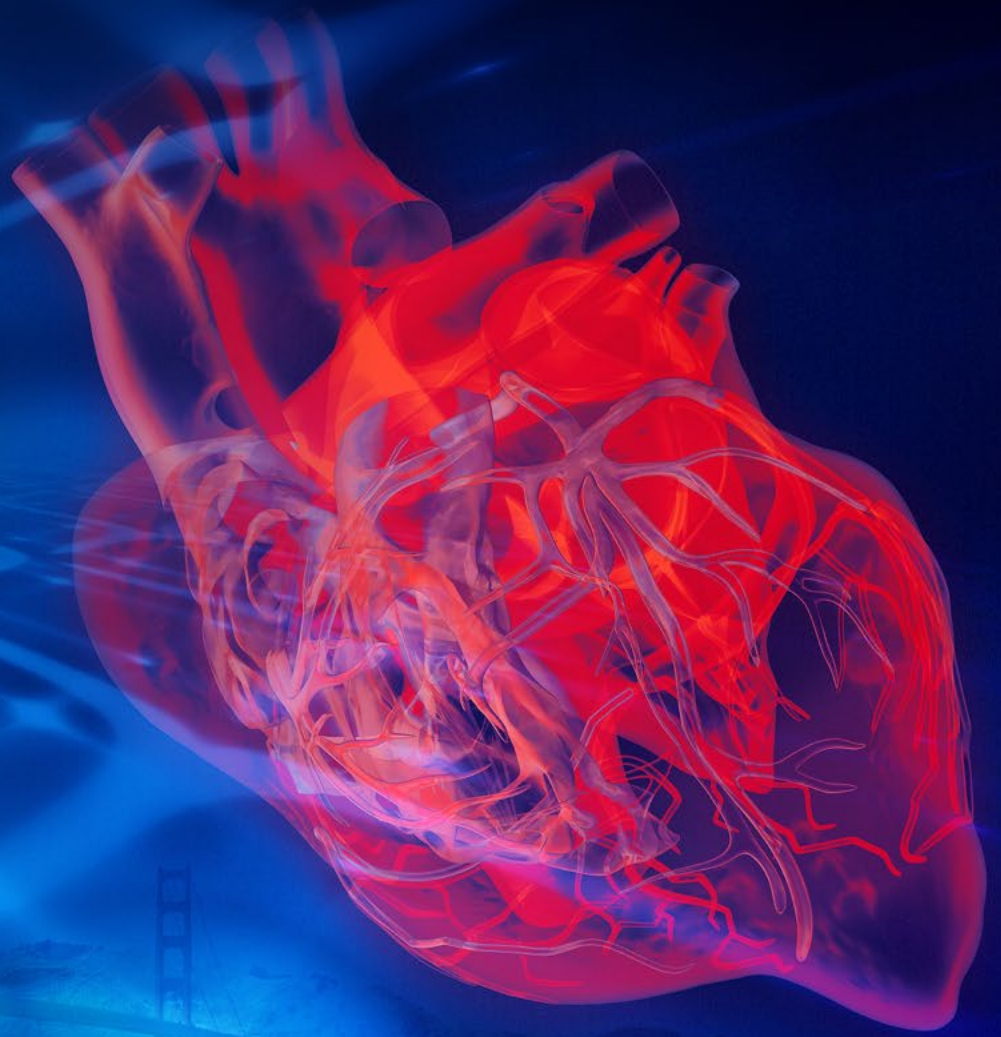

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TCT

OCTOBER 23–26, 2023
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Thank you!

@DrRoxMehran

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