Wat is de rol van inflammatie bij (residueel) cardiovasculair risico?
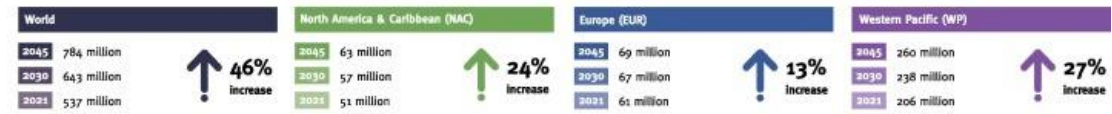
Dr. Nordin Hanssen

Endocrinoloog en vasculair geneeskundige, Amsterdam UMC
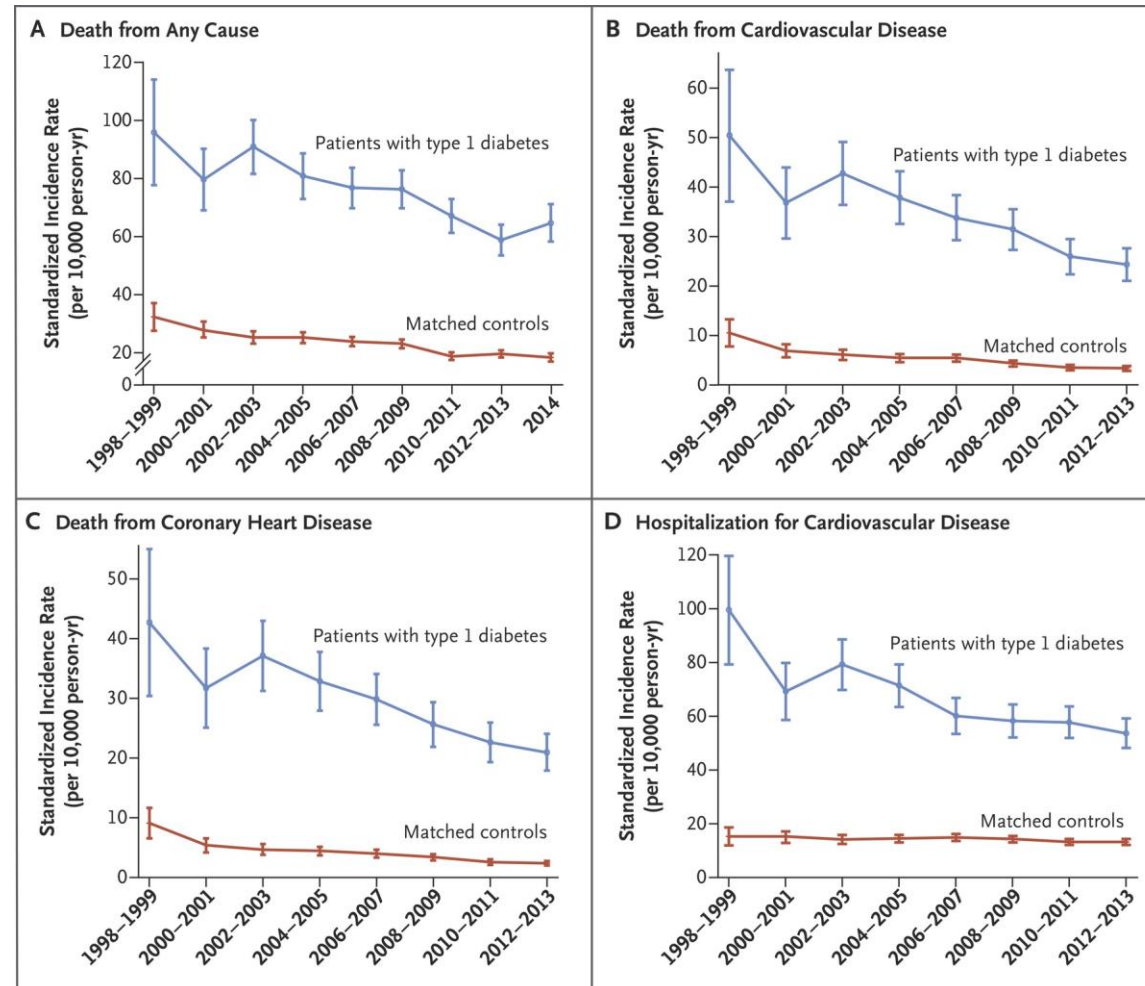
The elephant in the room

- 1 in 10 adults has diabetes
- Strongest increase Africa
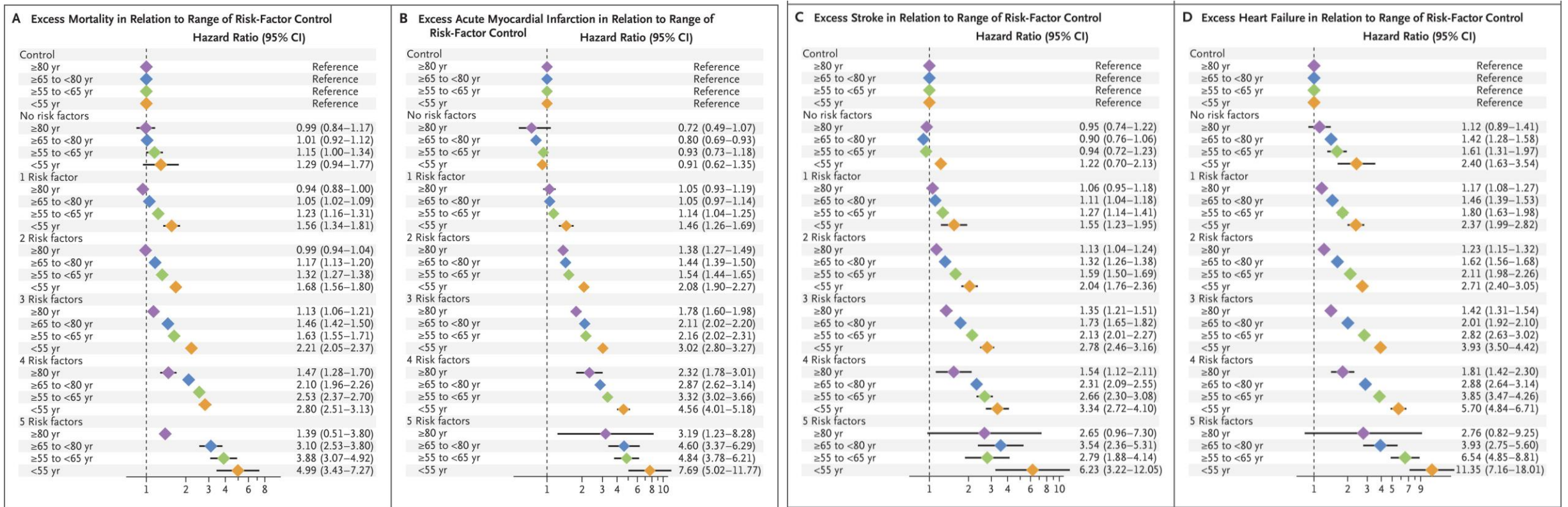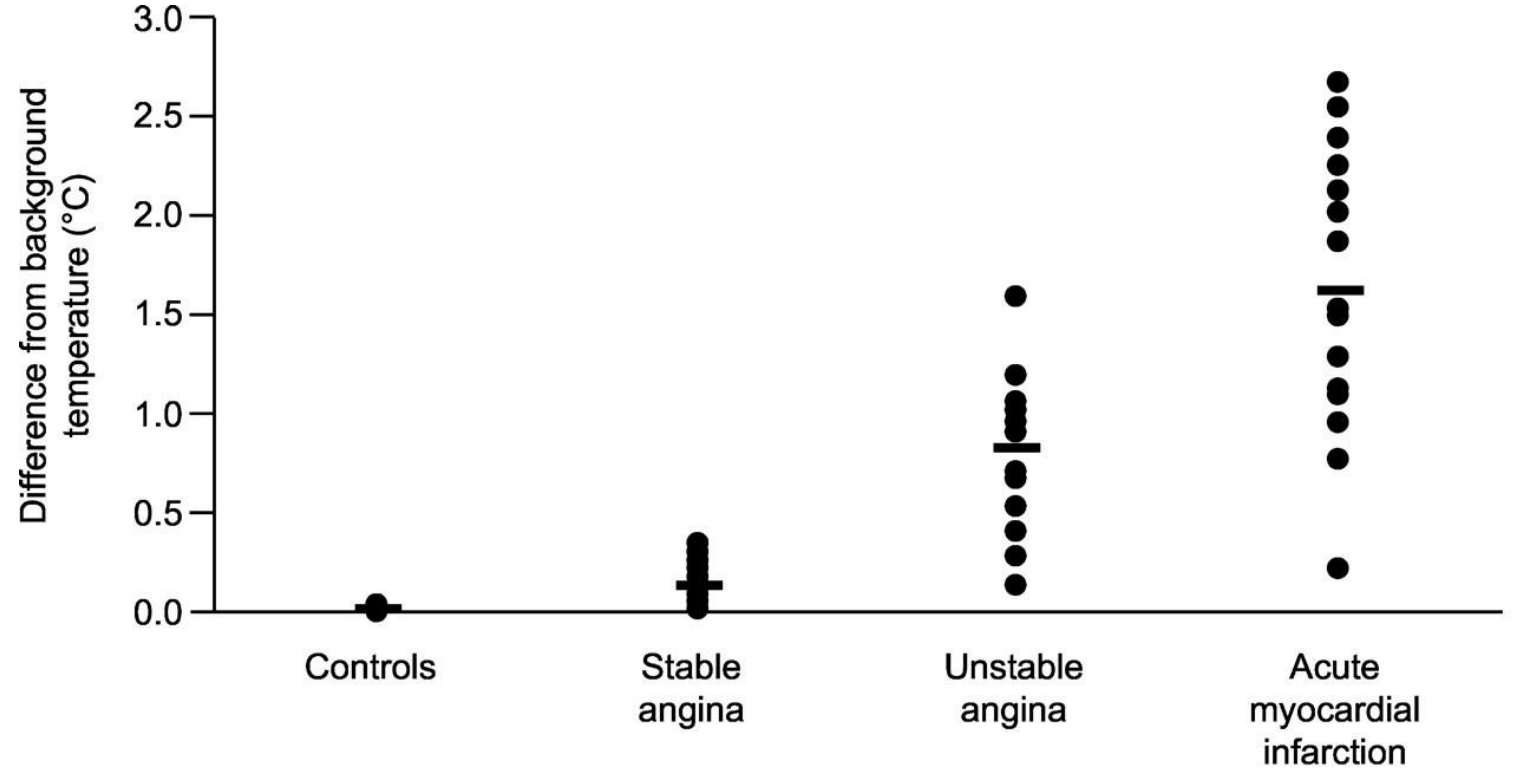- Almost half live in India and China

So can we close this gap?

Rawshani et al NEJM 2017

How much (inflammatory) residual risk is there in diabetes?

A   Excess Mortality in Relation to Range of Risk-Factor Control
B   Excess Acute Myocardial Infarction in Relation to Range of Risk-Factor Control
C   Excess Stroke in Relation to Range of Risk-Factor Control
D   Excess Heart Failure in Relation to Range of Risk-Factor Control

Rawshani et al NEJM 2018

Textbook inflammation

Stefanadis et al Circulation 1999
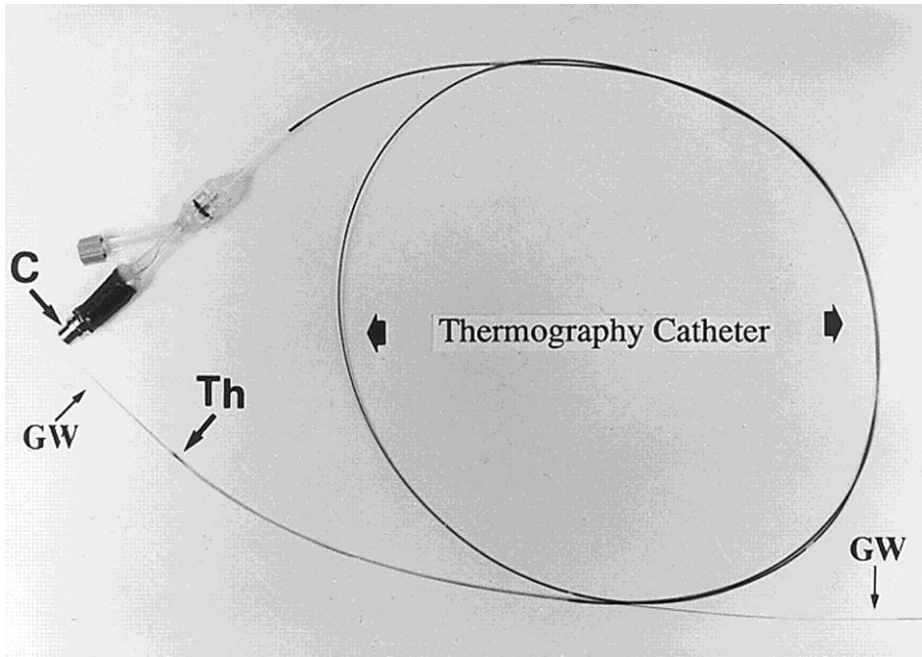
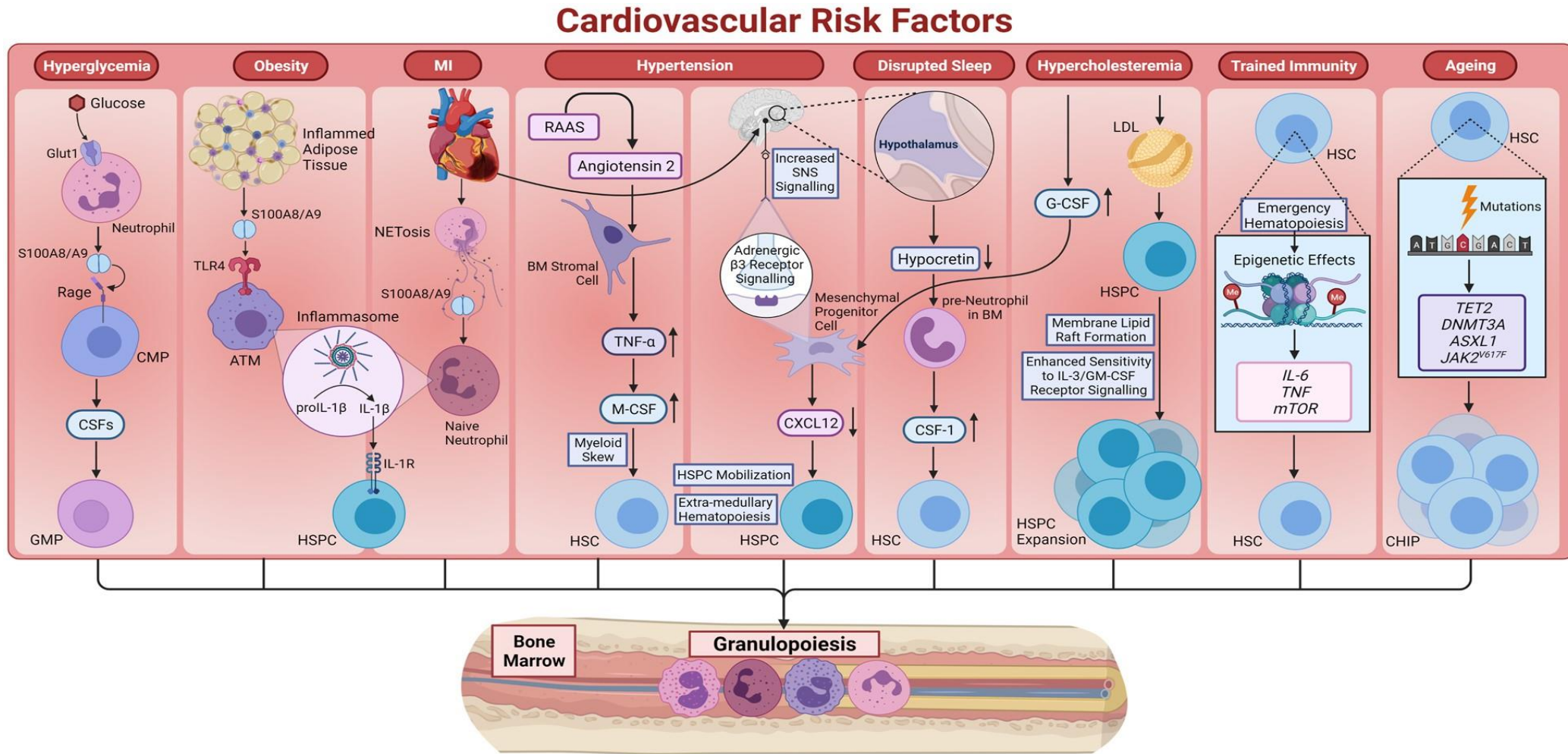# What we talk about when we talk about inflammation in diabetic cardiovascular disease

Flynn et al Circ Res 2020
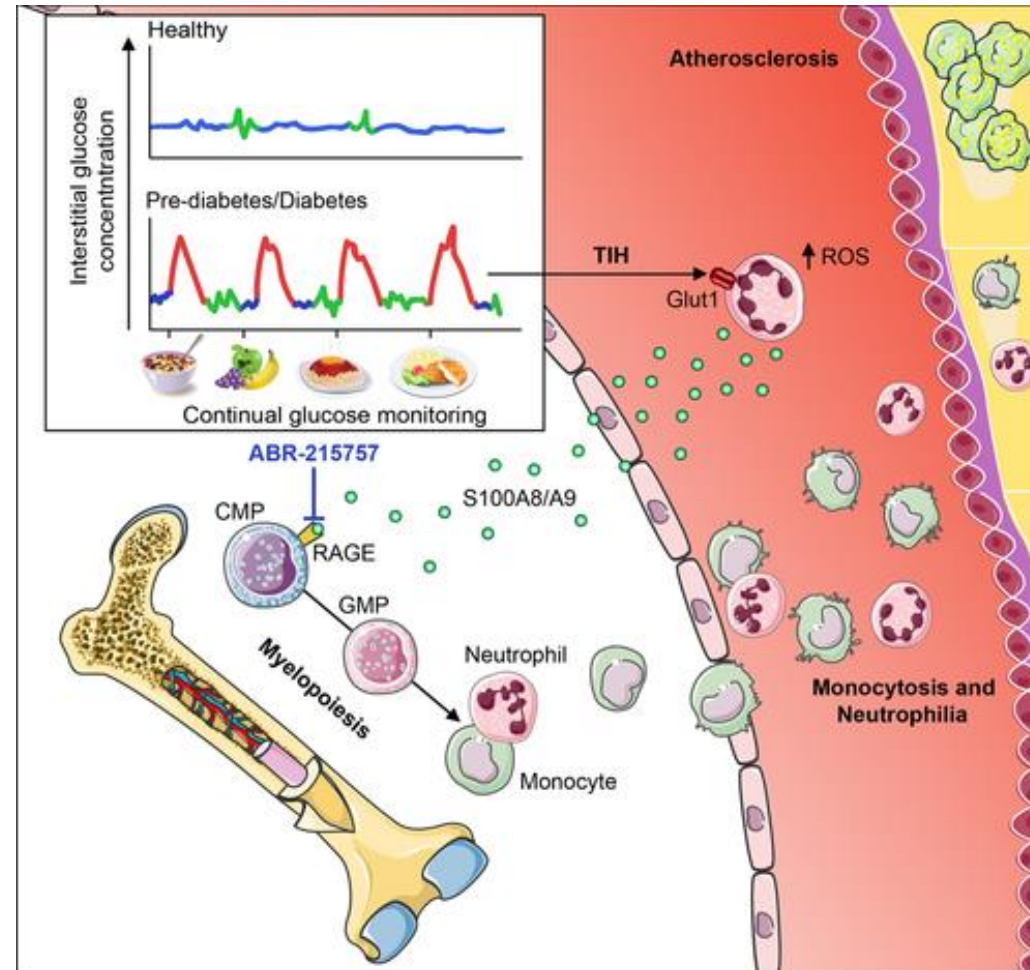
A multi-system challenge: how to tune this system?

Gopalkrishna et al. Cardiovasc Res 2022

Beyond cardiovascular risk

Hanssen et al. Circulation 2021
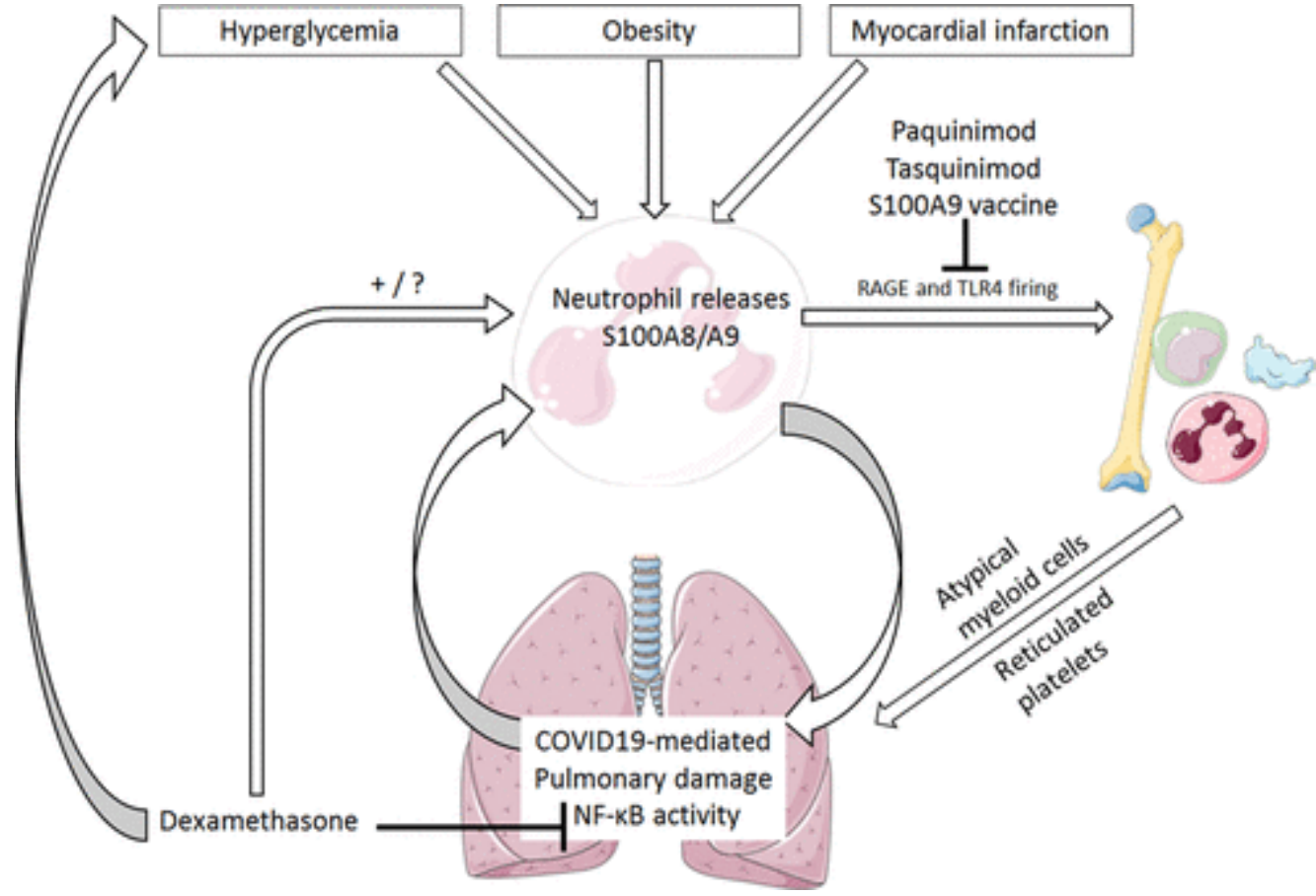
Adaptive immunity likely plays a role as well

Kondapalli et al. Circulation 2020

Vuong, J.T. et al. J Am Coll Cardiol. 2022;79(6):577–593.
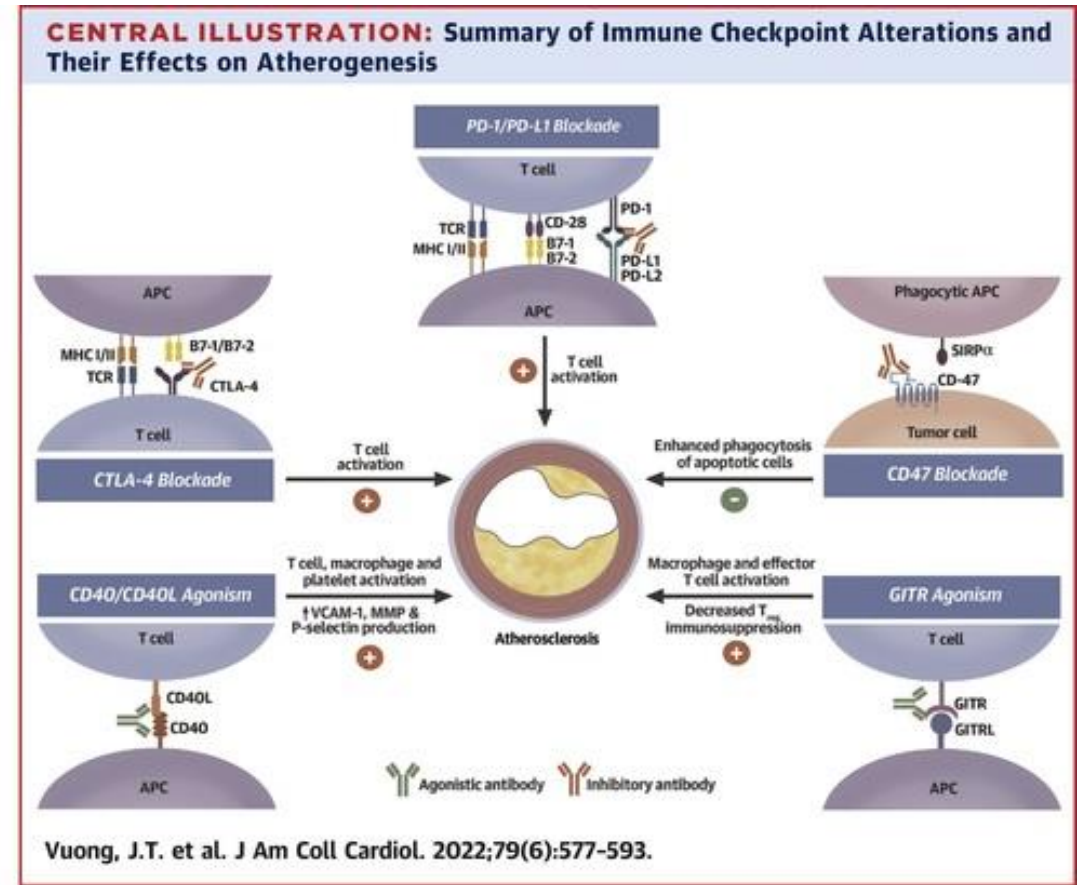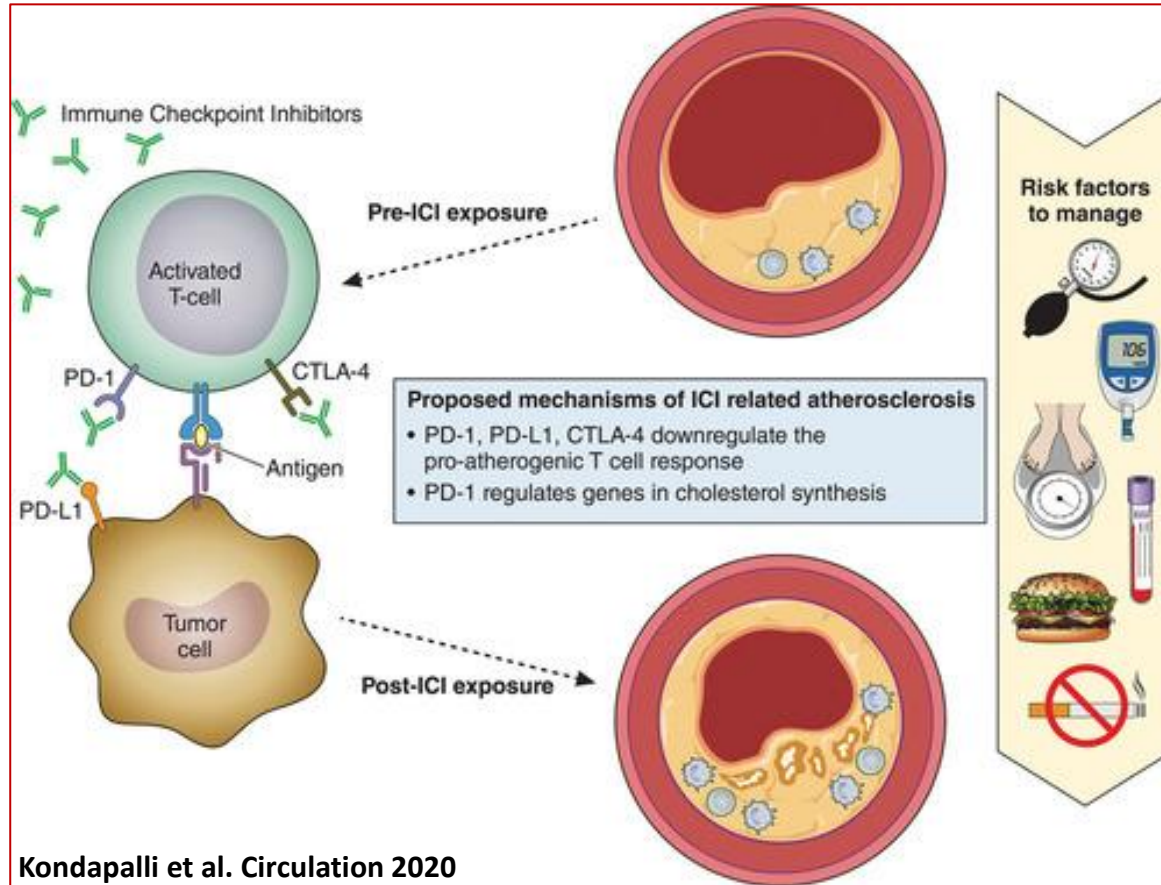
CRP, a reductionist view?
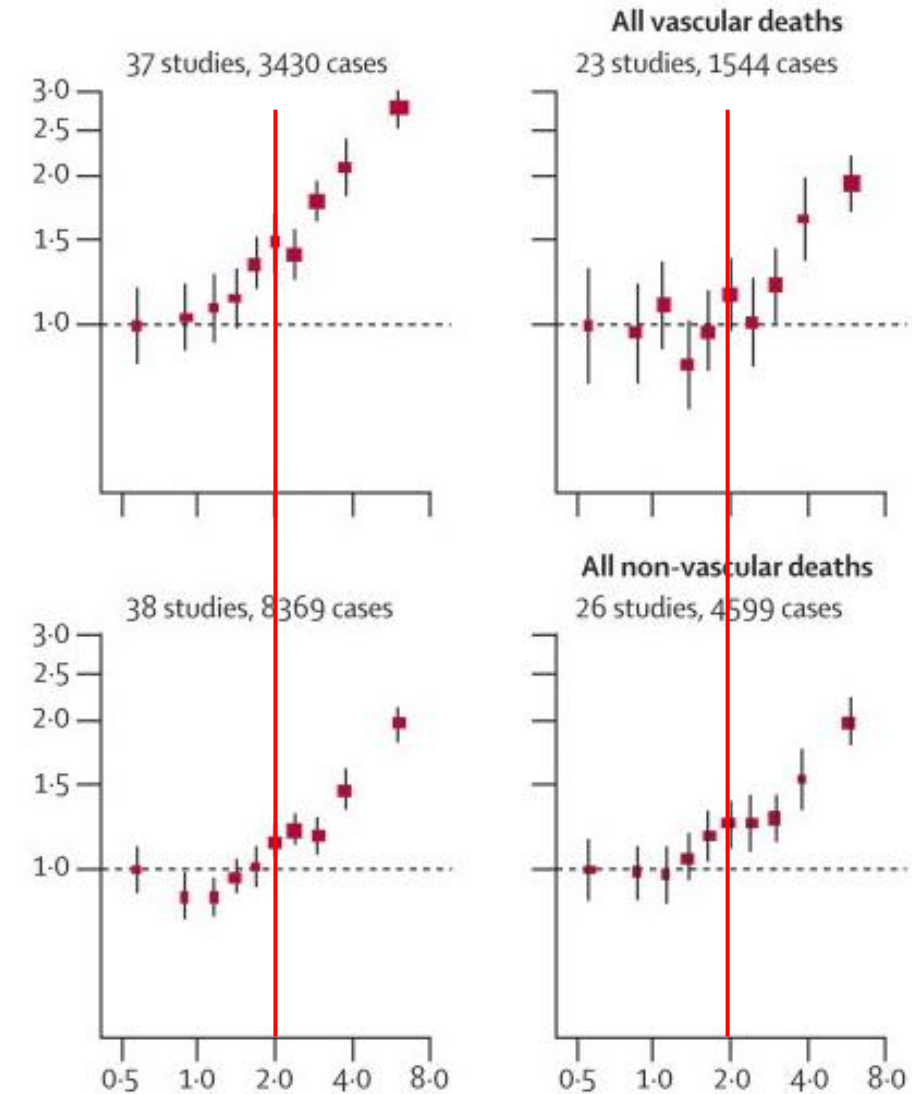
McFayden et al. Fronteers in immunology 2018

The Emerging Risk Factors Collaboration. Lancet 2010

CRP is a risk marker, not a risk factor

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)

-0.1 0 0.1 0.2 0.3 0.4

0.85 0.90 0.95 1 1.05 1.10

BUT WHAT DOES IT MEAN???

C Reactive Protein Coronary Heart Disease Genetics Collaboration, BMJ 2011

Blood or imaging?

Oikonomou et al. Cardiovascular Research 2021
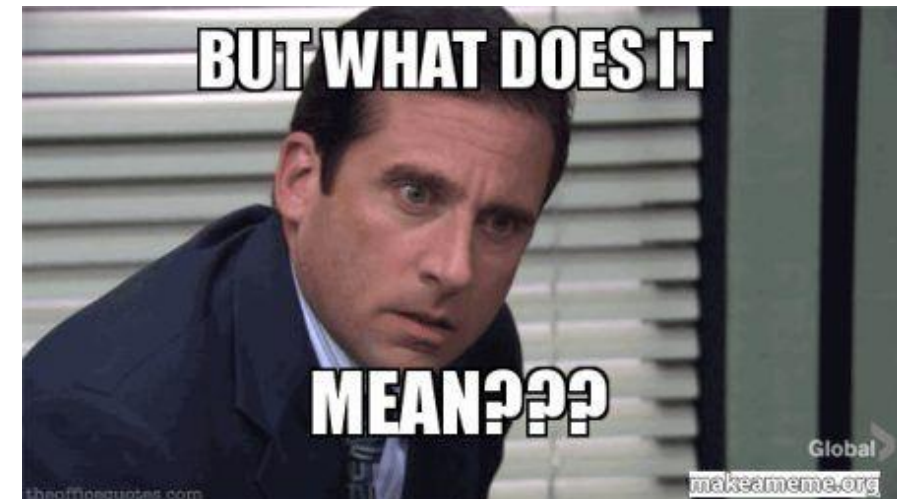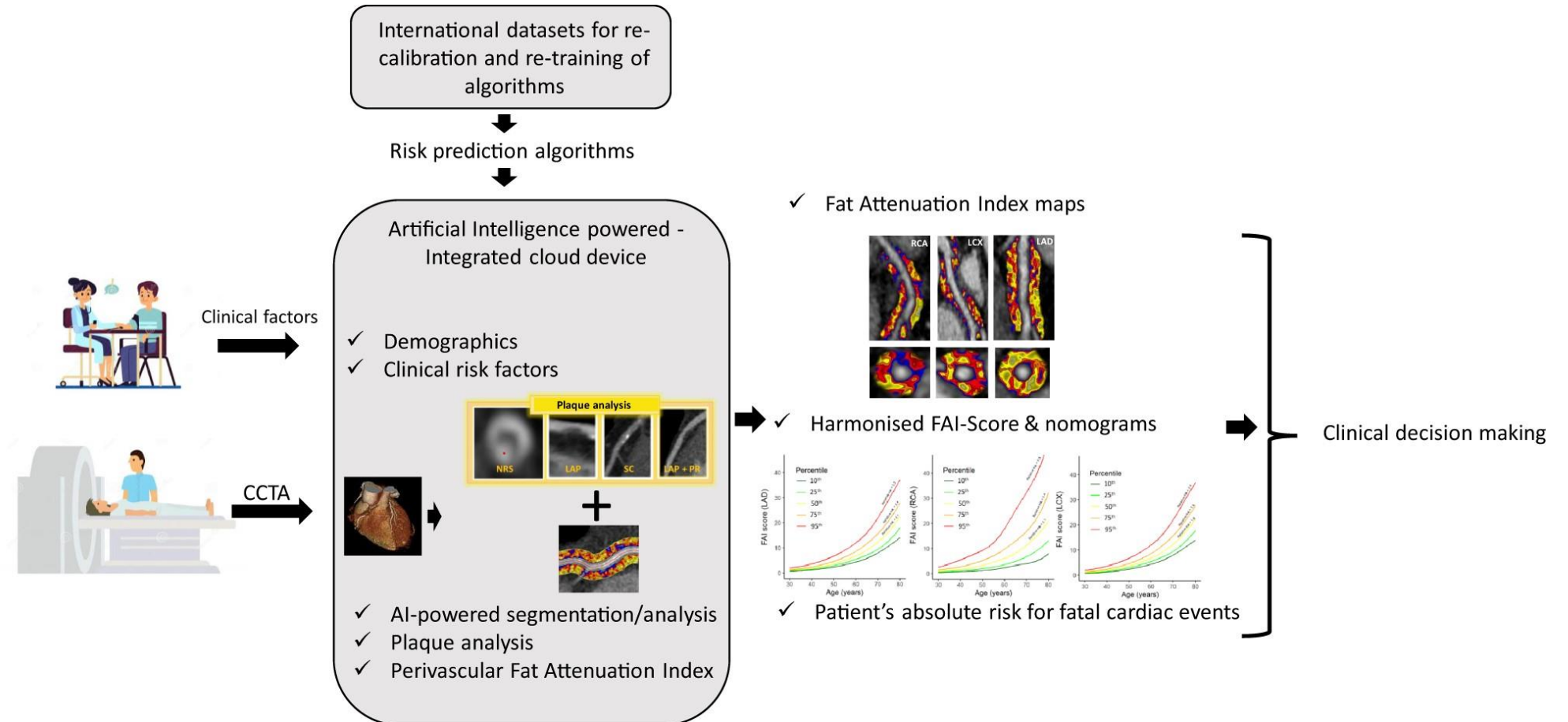
Reducing inflammation by targeting conventional risk

- Type 2 diabetes mellitus (n=22)

- 40mg atorvastatin 3 months

- DOTATATE PET-CT to image M1 macrophages

- No correlation crp and DOTATATE uptake

Oostveen & Kaiser et al, submitted

CENTRAL ILLUSTRATION: Atorvastatin treatment in adults with type 2 diabetes reduces uptake of 68Ga-Dotatate across the cardio-hematopoietic axis.
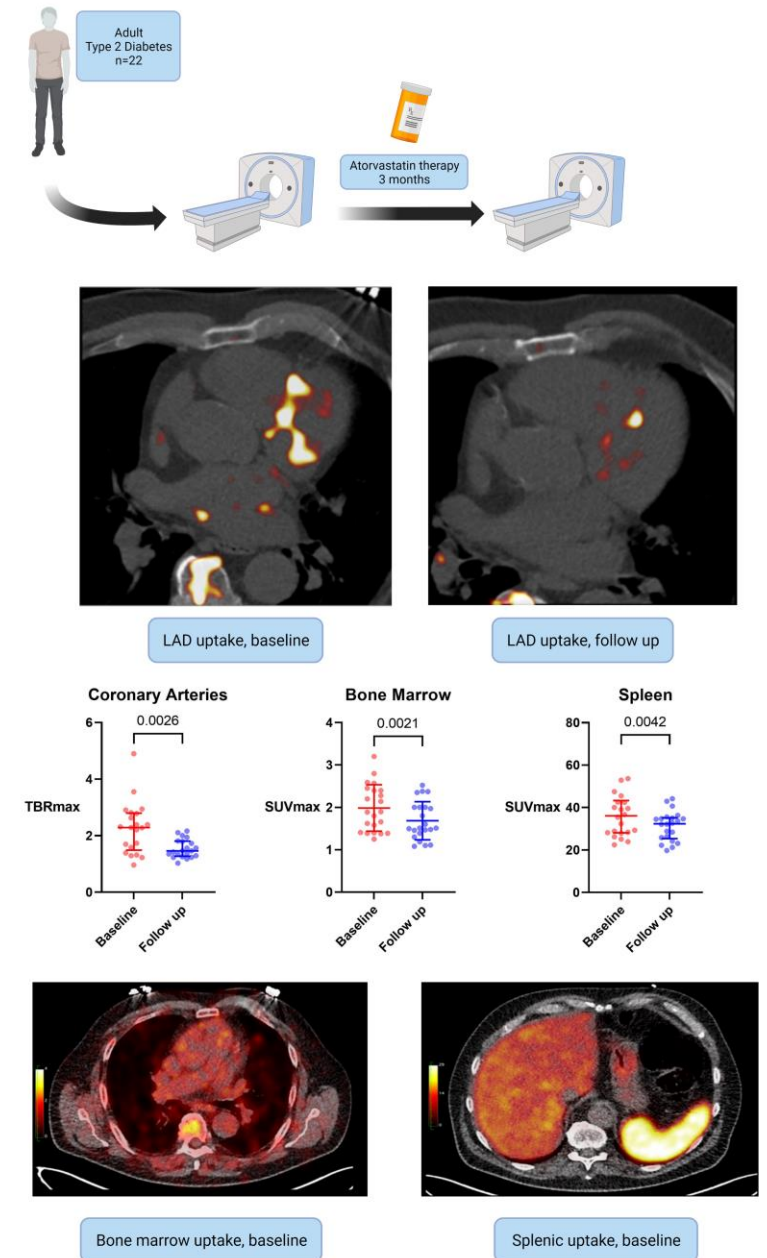
Inflammatory diseases, cardiovascular risk

Hansildaar et al. Lancet Rheumatology 2021
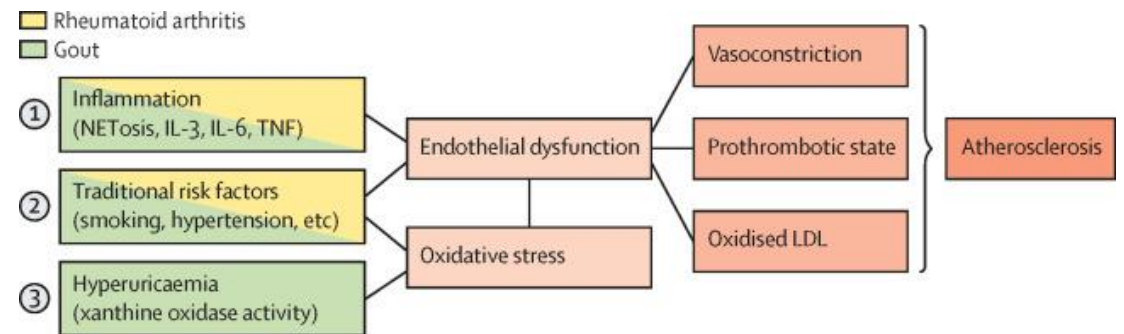
Can we reduce risk further by targeting inflammation?

- Colchicine 0.5mg

- <30 days myocardial infarction

Tardif et al. NEJM 2019

Colchicine

The NEW ENGLAND JOURNAL of MEDICINE

Colchicine in Patients with Chronic Coronary Disease

MULTICENTER, DOUBLE-BLIND, RANDOMIZED, CONTROLLED TRIAL

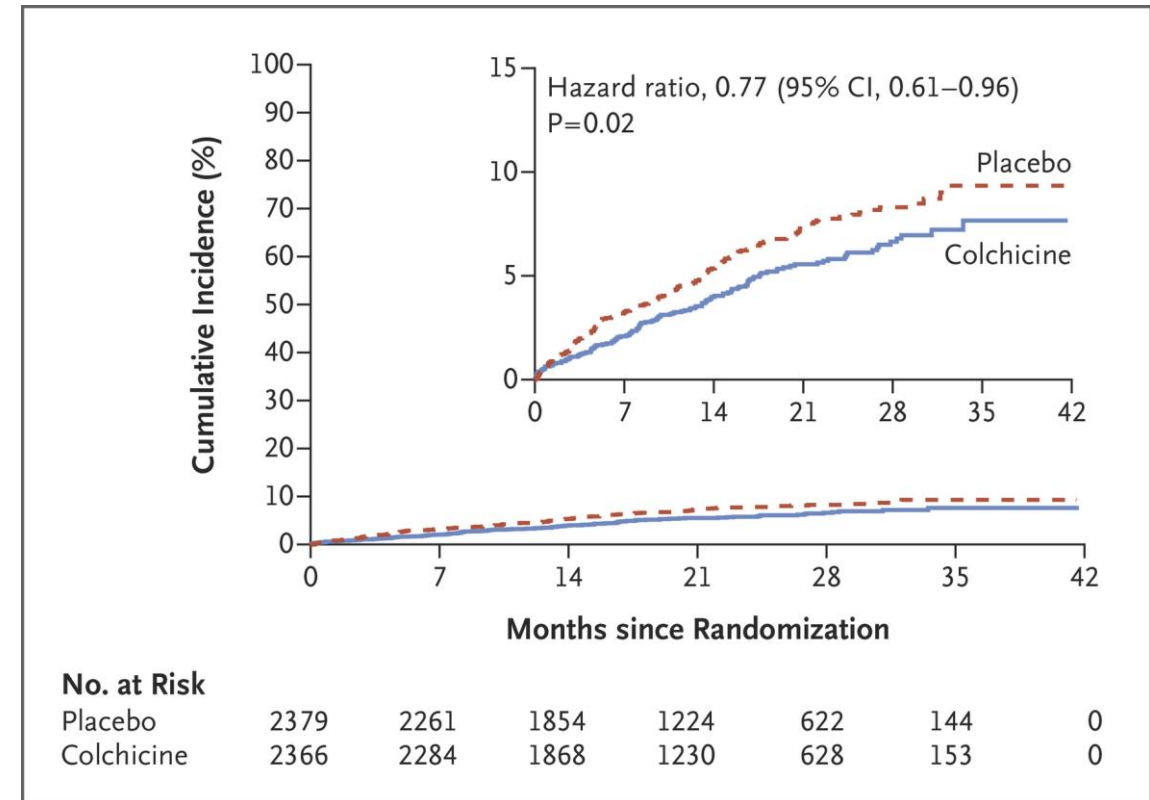|	Colchicine (0.5 mg/day)	Placebo
5522 Patients with chronic coronary disease	N=2762	N=2760
Cardiovascular death, spontaneous MI, ischemic stroke, or coronary revascularization	6.8%	9.6%
	HR, 0.69; 95% CI, 0.57 to 0.83; P<0.001	
Death from noncardiovascular causes	0.7 events per 100 person-yr	0.5 events per 100 person-yr

Lower risk of cardiovascular events for patients receiving colchicine

S.M. Nidorf et al. 10.1056/NEJMoa2021372

CANTOS

- Canakinumab (anti-il1beta)

- Prior MI + CRP>2mg/L

- Trade-off: more (fatal) infections

- Effect dependent on CRP after 3 months
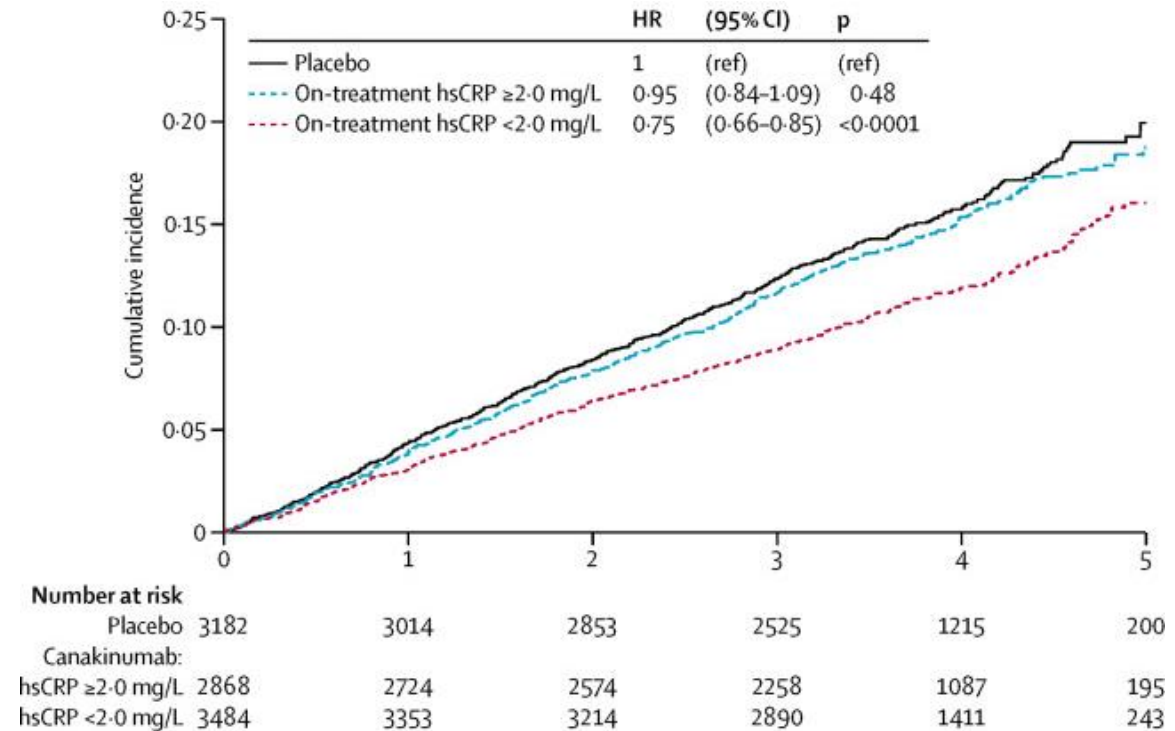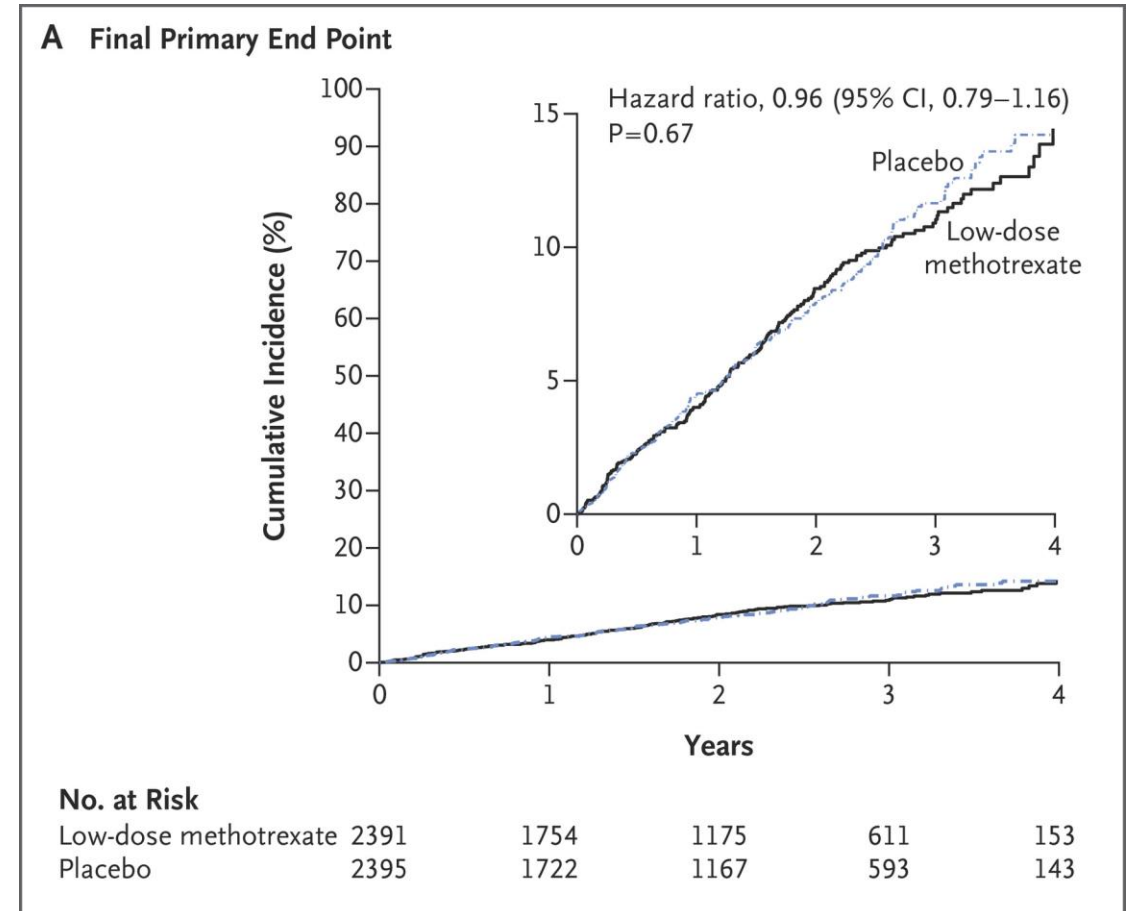 - All   NNT 24
  - CRP <2mg/L   NNT 16
  - CRP ≥2mg/L   NNT 57

	HR	(95% CI)	p
Placebo	1	(ref)	(ref)
On-treatment hsCRP ≥2·0 mg/L	0·95	(0·84–1·09)	0·48
On-treatment hsCRP <2·0 mg/L	0·75	(0·66–0·85)	<0·0001

Number at risk
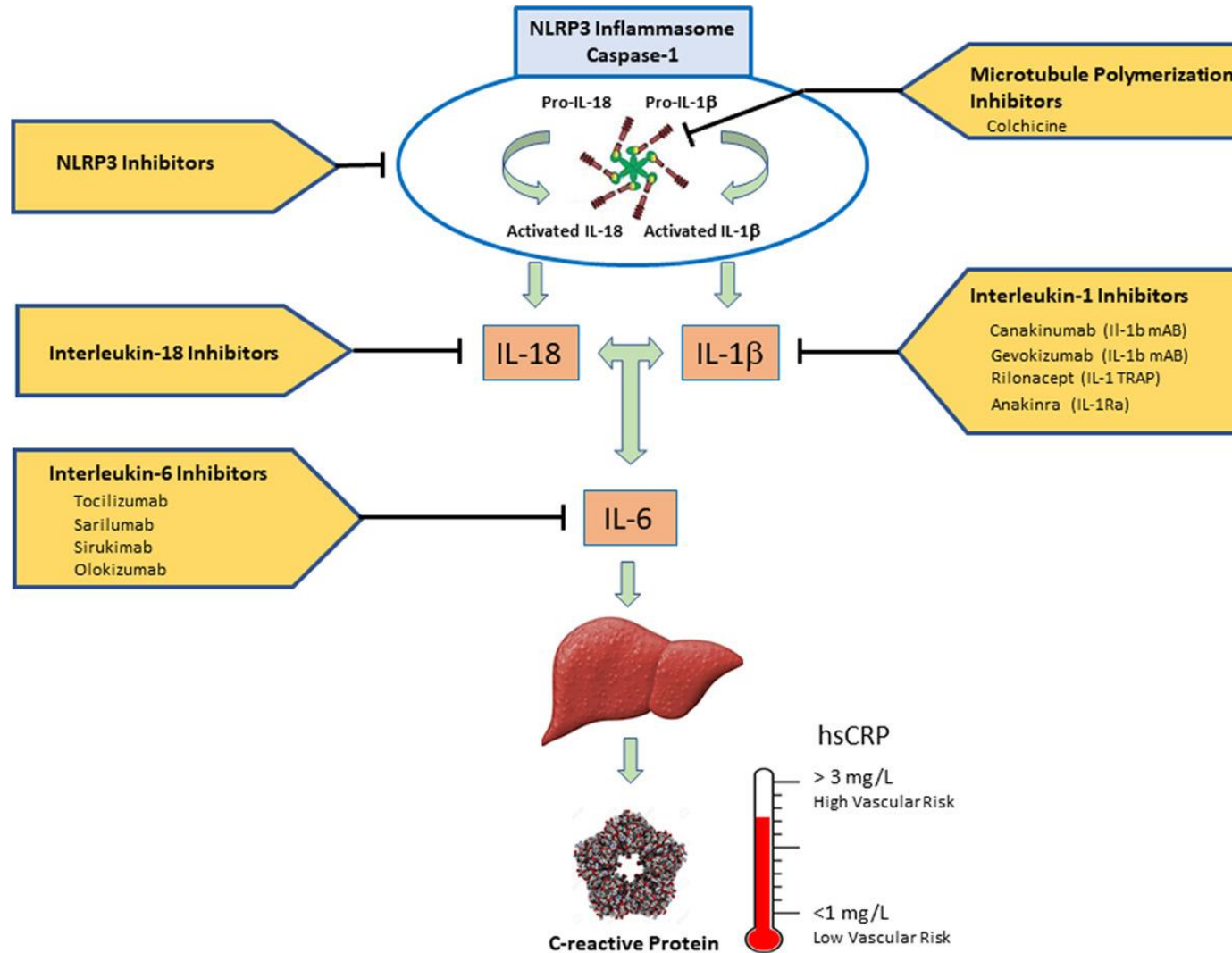|	0	1	2	3	4	5
Placebo	3182	3014	2853	2525	1215	200
Canakinumab: hsCRP ≥2·0 mg/L	2868	2724	2574	2258	1087	195
hsCRP <2·0 mg/L	3484	3353	3214	2890	1411	243

The way inflammation is lowered matters

- Low-dose methotrexate did not reduce cardiovascular disease in individuals with prior CVD + type 2 diabetes or metabolic syndrome

- Median CRP 1.5mg/L

- No effects IL1, IL6 or CRP

A **Final Primary End Point**

Hazard ratio, 0.96 (95% CI, 0.79–1.16)
P=0.67

No. at Risk
Low-dose methotrexate 2391 / 1754 / 1175 / 611 / 153
Placebo 2395 / 1722 / 1167 / 593 / 143

Ridker et al NEJM 2019

Trials inform mechanism

Ridker Circulation 2020

New kid on the block

- Ziltivekimab (anti IL6)

- N=264, CKD + CRP≥2
- Once weekly 24 weeks
- Placebo, 7.5, 15 or 30mg

- CRP up to -87.8% lower

Ridker et al Lancet 2021
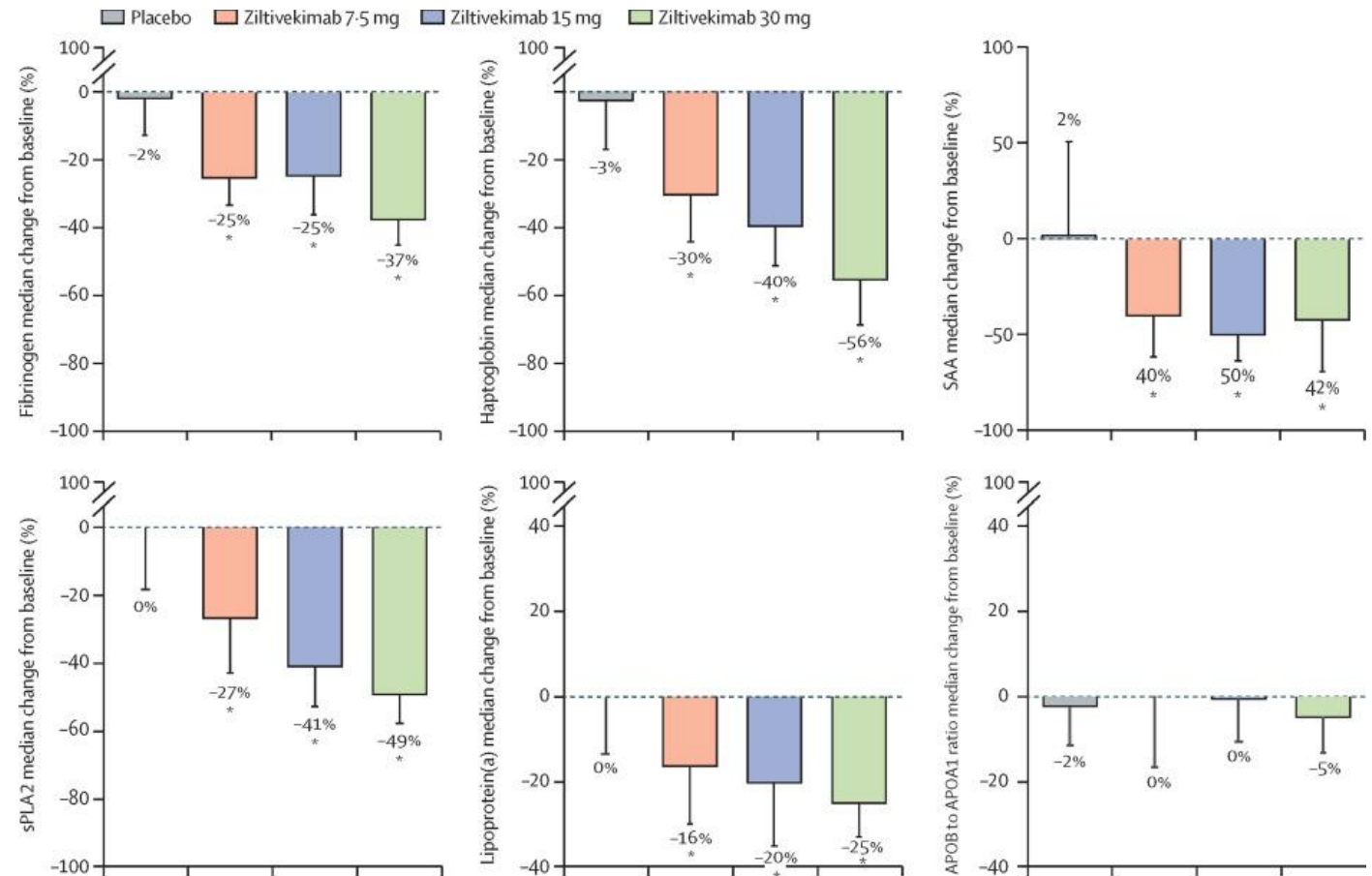
Ready for the guidelines?

Colchicine in Acute Coronary Syndrome: When to Commence?

Sep 15, 2021 | aernoud fiolet; Tjerk Simon Jacob Opstal, MD; Peter Thompson, MD; Jan Hein Cornel

Expert Analysis

Share via: f t in ✉ +   🖶 Print   Font Size A A A

Quick Takes

- The insights emanating from recent large clinical trials studying the role of colchicine as anti-inflammatory treatment in patients with coronary disease come with new questions for regular clinical practice, such as when to commence treatment.

- Current data suggest initiating treatment early after myocardial infarction (MI) or in patients without cardio-renal failure treated in the outpatient clinic.

- The effect of colchicine persists throughout prolonged treatment, irrespective of timing of a prior acute coronary syndrome (ACS).

Take home message

- Inflammation in diabetes and cardiovascular risk is a complex mechanism, CRP does not fully capture this process
  - Is there a role for imaging?

- Optimising conventional risk factors also reduces inflammation

- Colchicine and canicunimab reduce cardiovacular risk
  - There will be new kids on the block

- Major challenges remain
  - Who benefits?
  - Adverse events?