New frontiers in cardiovascular research and residual risk

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New frontiers in cardiovascular research and residual risk



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High risk patients…

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

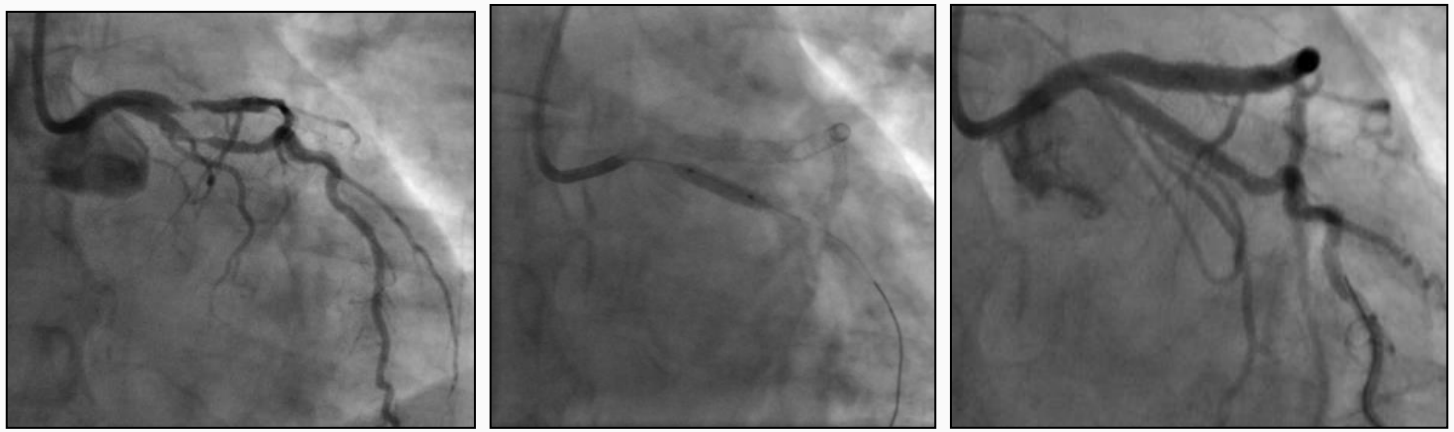
Invasive Treatment Strategy for Older Patients with Myocardial Infarction

V. Kunadian, H. Mossop, C. Shields, M. Bardgett, P. Watts, M.D. Teare, J. Pritchard, J. Adams-Hall, C. Runnett, D.P. Ripley, J. Carter, J. Quigley, J. Cooke, D. Austin, J. Murphy, D. Kelly, J. McGowan, M. Veerasamy, D. Felmeden, H. Contractor, S. Mutgi, J. Irving, S. Lindsay, G. Galasko, K. Lee, A. Sultan, A.G. Dastidar, S. Hussain, I.U. Haq, M. de Belder, M. Denvir, M. Flather, R.F. Storey, D.E Newby, S.J. Pocock, and K.A.A. Fox, for the British Heart Foundation SENIOR-RITA Trial Team and Investigators*

Kunadian V et al. N Engl J Med. 2024 Nov 7;391(18):1673-1684.

Background: Our population is rapidly ageing.....

88-year-old female with NSTEMI, multi-vessel stenting

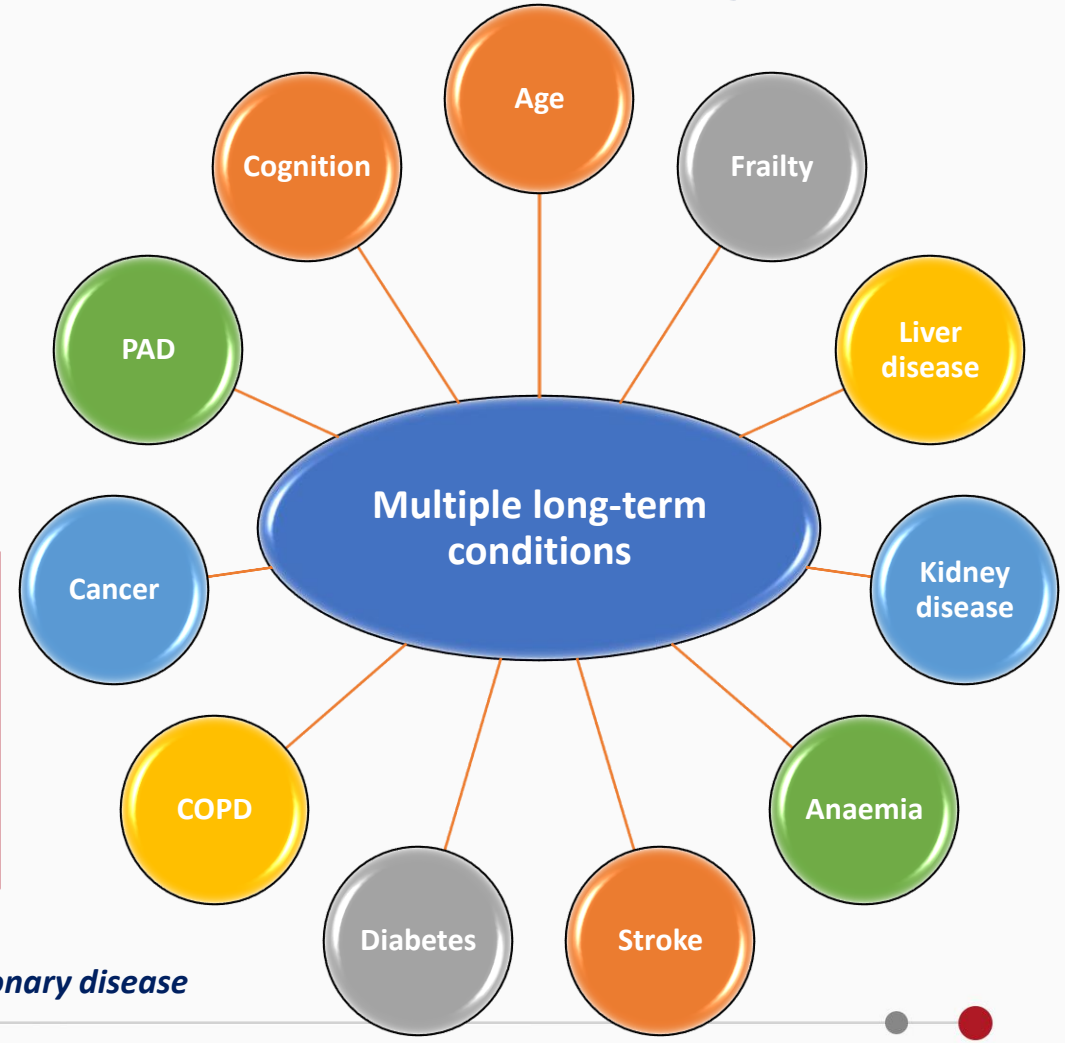


- Complex, ageing, calcified coronary arteries…
- Recurrent events, repeat hospitalisations, cost to service providers

- Frailty- high mortality
- Co-morbidity- high mortality
- Cognitive impairment- high mortality
- Frail patients-high risk plaque features

NIHR | Newcastle Biomedical Research Centre

Older adults are heterogeneous!



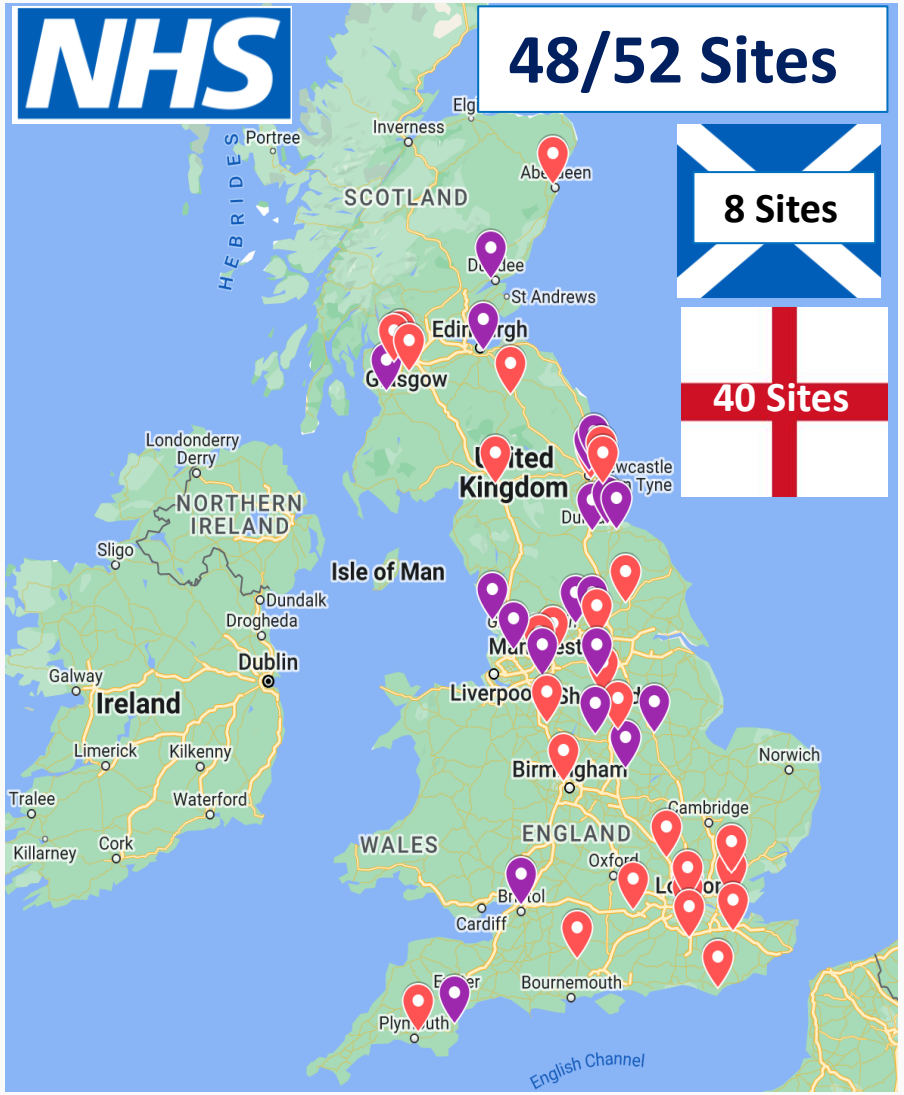
PAD-peripheral arterial disease, COPD-chronic obstructive pulmonary disease

Ratcovich et al. Eur Heart J Open. 2022 16;2(3):oeac035; Dirjayanto et al. Heart. 2024;110(6):416-424; Beska et al. BMJ Open. 2022;12(7):e061830

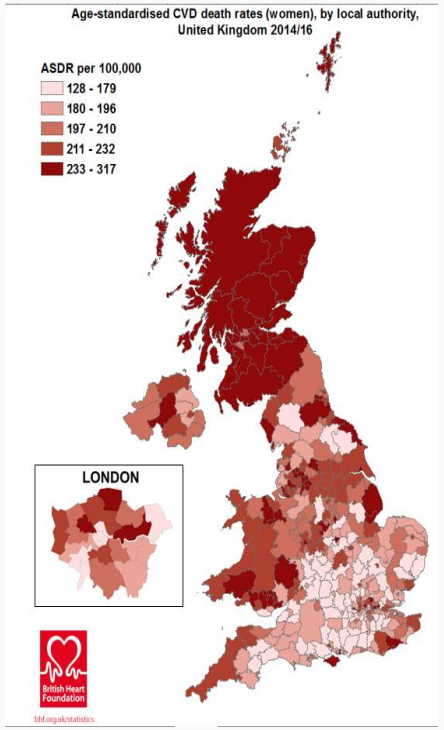
STUDY ORGANISATION

Site	No. of participants
Northumbria	171
Newcastle	167
North Tees	150
Chesterfield	94
South Tees	88
Darlington & Durham	68
Sheffield	57
Royal Derby	56
Ayrshire & Arran	53
Leeds	52
Torbay & South Devon	51
Edinburgh	45
South Manchester	32
Epsom & St Helier	31
Dundee	28
Bradford	28
Blackpool	28
Lincoln	27
Wrightington Wigan & Leigh	23
North Bristol	20
Leicester	20

Site	No. of participants
Plymouth	19
Basildon	17
Gateshead	16
Royal Free London	14
Pinderfields	13
Luton	13
York	13
West Middlesex	11
Sandwell Birmingham	11
Mid Essex	11
East Sussex	10
Glasgow-QEUH	10
Glasgow-Royal Alexandra	9
Surrey & Sussex	9
North Cumbria	8
Salford	6
South Tyneside	6
Sunderland	6
Maidstone	5
Aberdeen	5
Royal Oldham	5
Nottingham	3
Stoke	2
Lanarkshire	2
Royal Berkshire	2
Salisbury	1
Borders	1



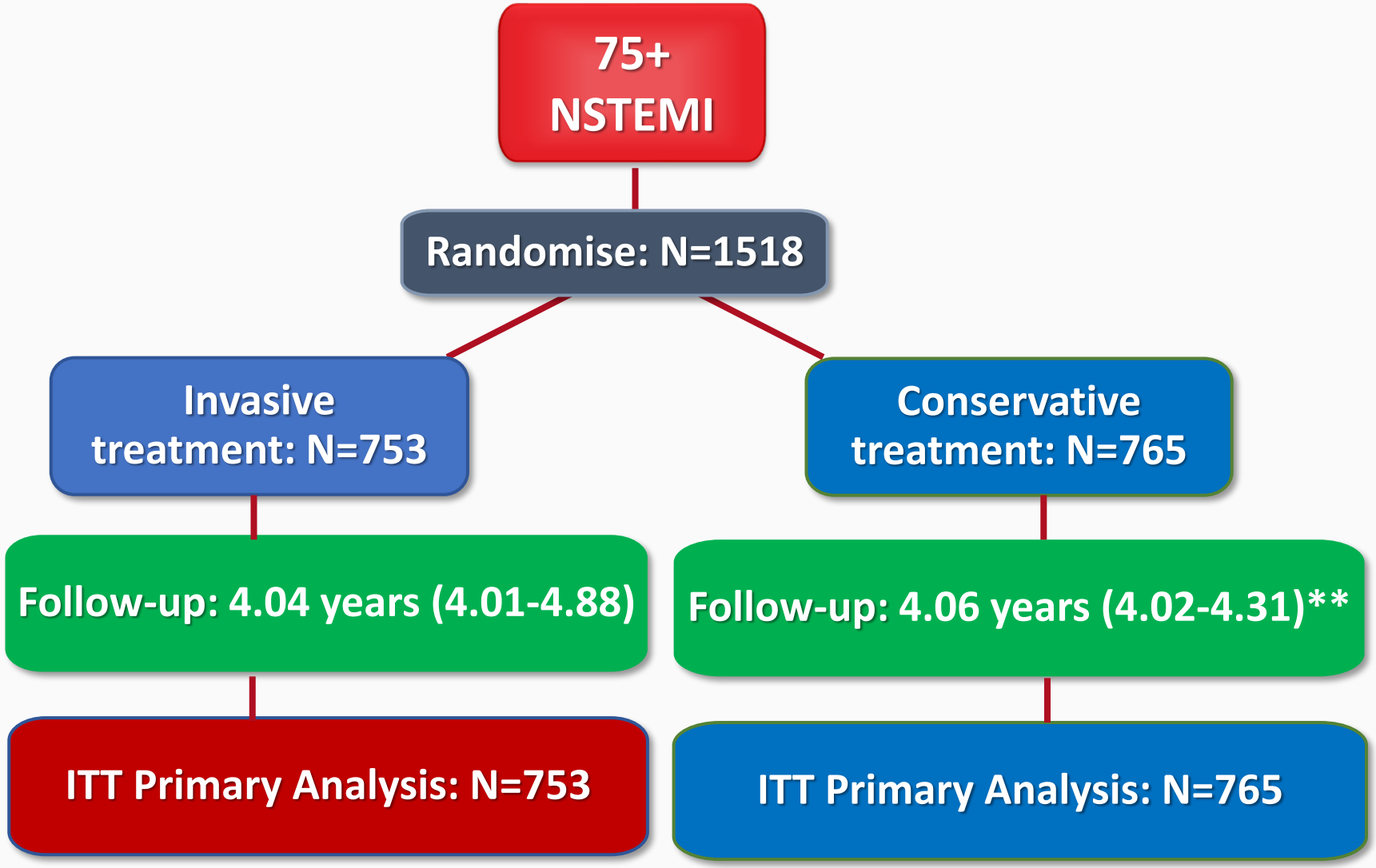
45% of patients recruited from Northeast of England



- Research to the patient!
- PCI and non-PCI centres

Kunadian V et al. N Engl J Med. 2024 Nov 7;391(18):1673-1684.

STUDY FLOW



- 1:5 screened patient was recruited*

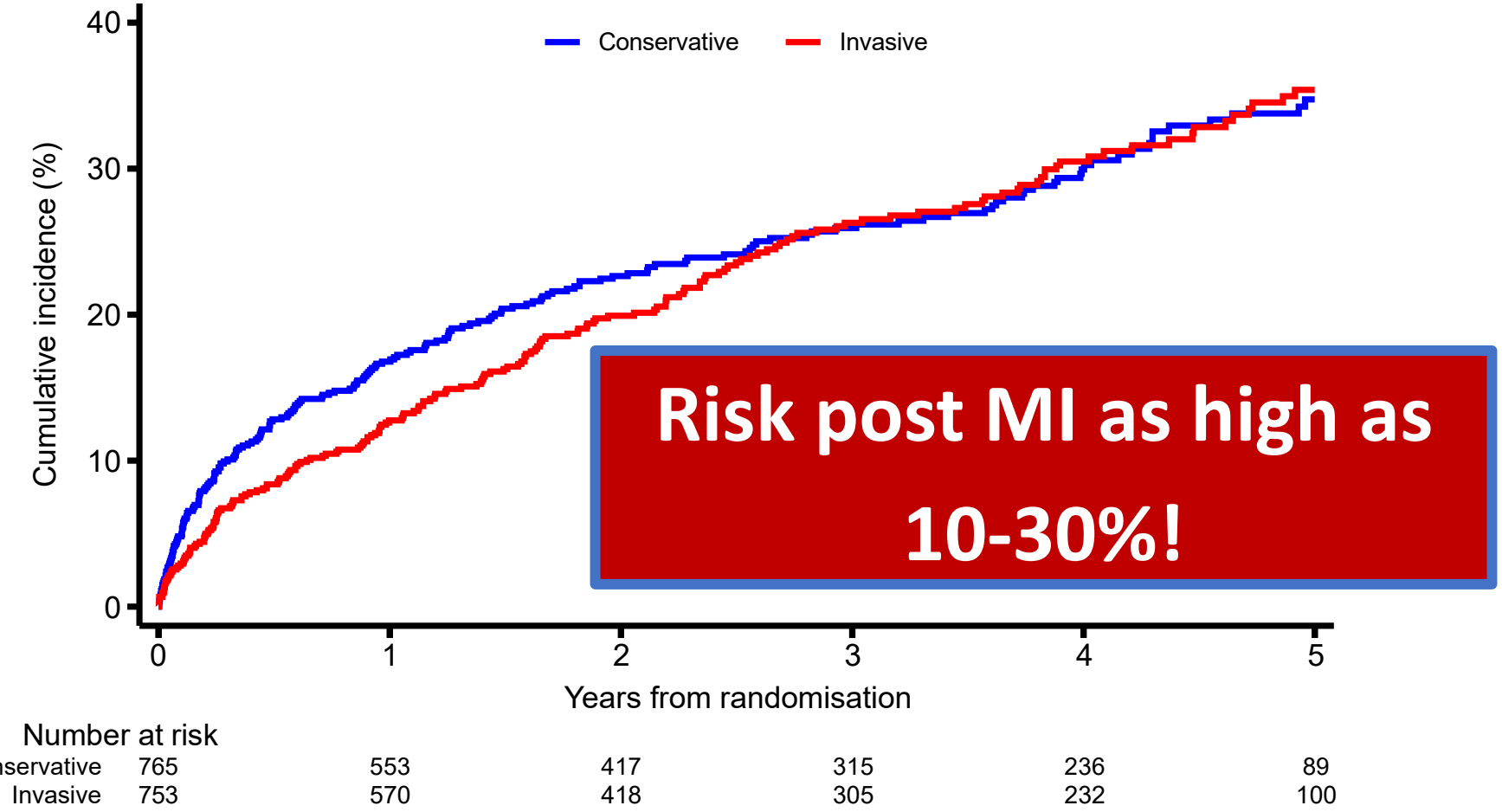
- 90% had angiography in the invasive group
- 5.6% in conservative group had angiography

- 98% events adjudicated by CEC
- Follow-up available for 98.9% of patients across all time points

**Given we are recruiting all comer patients who are heterogeneous-this was expected. As per screening log, the demographics of non-recruited patients were similar to recruited patients.*

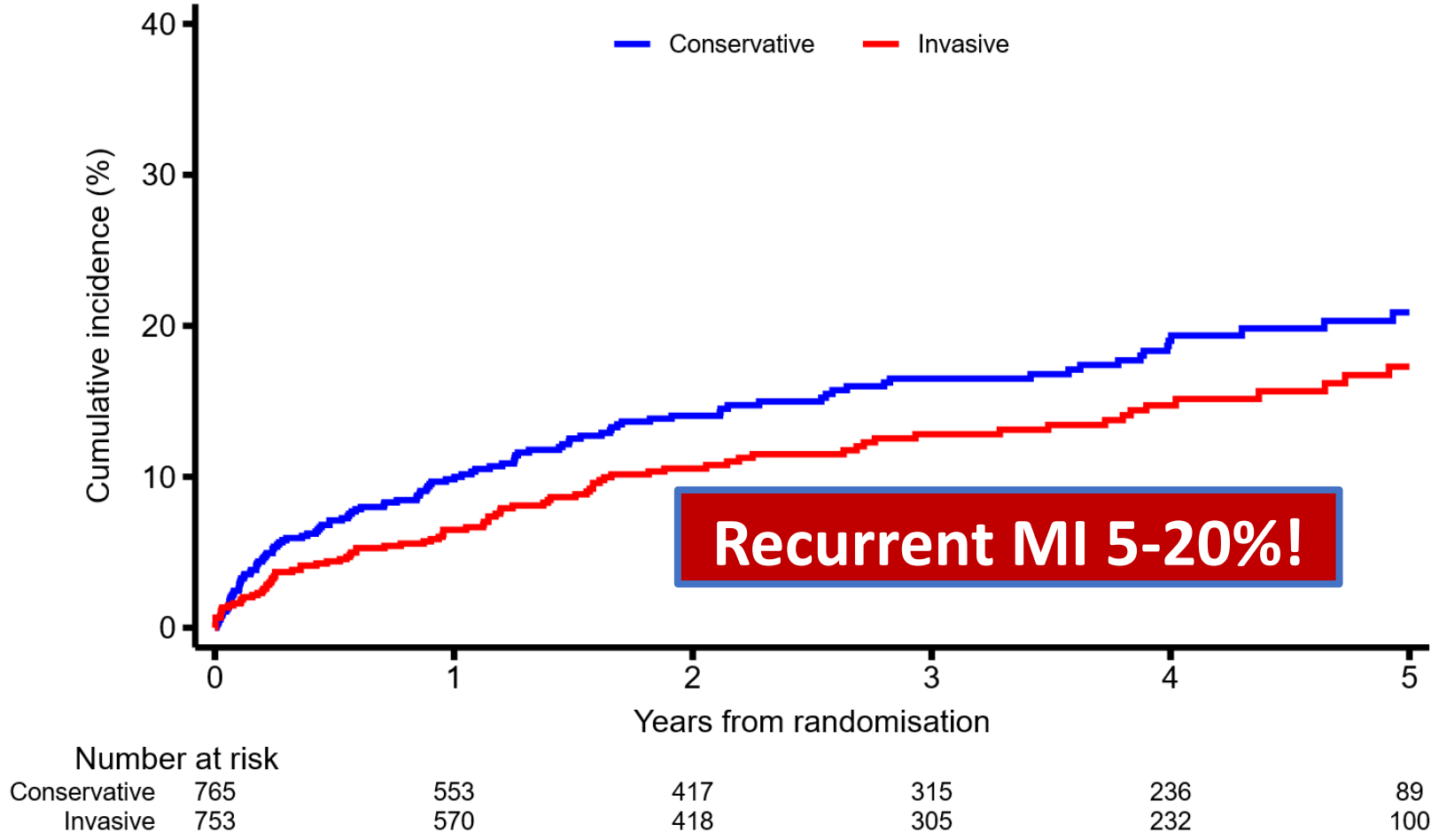
*** Median, 95% Confidence Interval. CEC-clinical events committee; ITT-intention to treat*

RESIDUAL RISK POST MI (NSTEMI): COMPOSITE OF CV DEATH OR NON-FATAL MI



Kunadian V et al. N Engl J Med. 2024 Nov 7;391(18):1673-1684.

RESIDUAL RISK POST MI (NSTEMI): NON-FATAL MYOCARDIAL INFARCTION

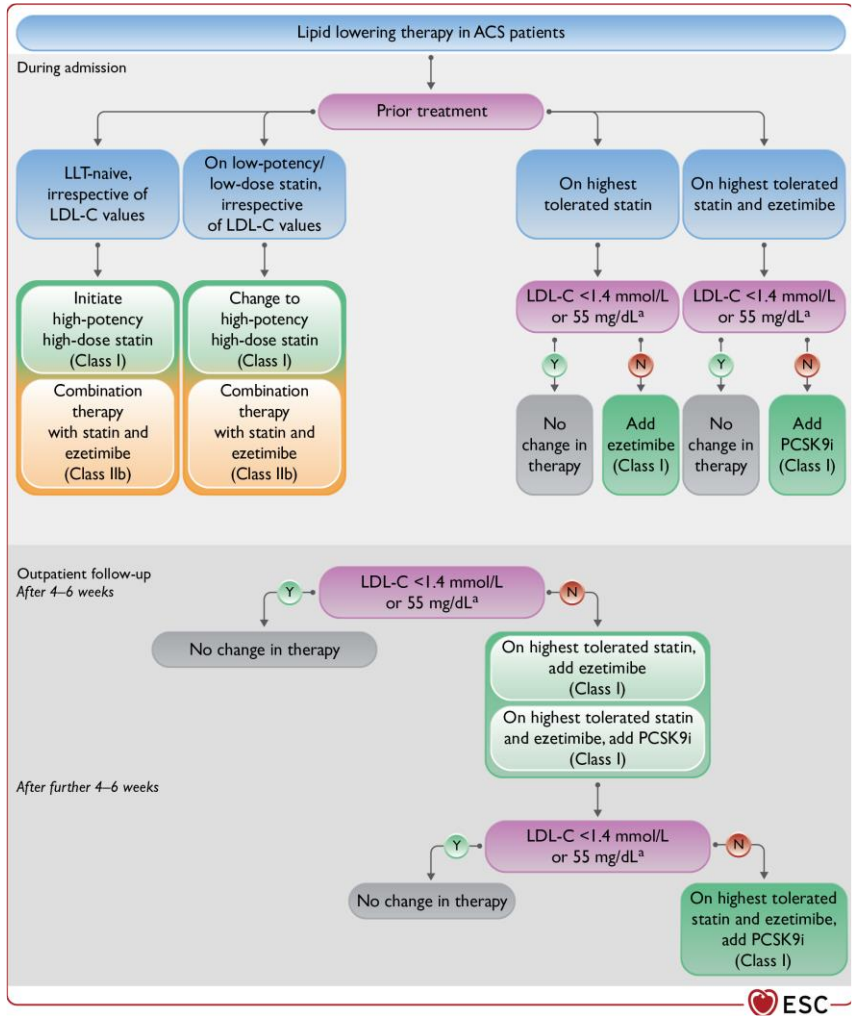


Kunadian V et al. N Engl J Med. 2024 Nov 7;391(18):1673-1684.

DESPITE GUIDELINE RECOMMENDED MEDICAL THERAPY…

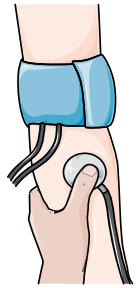
DISCHARGE MEDICAL THERAPY	Invasive Strategy N=752 (%)	Conservative Strategy N=762 (%)
Aspirin	682 (90.7%)	663 (87.0%)
$P2Y_{12}$ Receptor Antagonist	674 (89.6%)	719 (94.4%)
Clopidogrel	348 (46.3%)	405 (53.1%)
Ticagrelor	322 (42.8%)	313 (41.1%)
Prasugrel	4 (0.5%)	1 (0.1%)
None	20 (2.7%)	8 (1.0%)
Anticoagulant	170 (22.6%)	183 (24.0%)
Triple therapy	100 (13.3%)	91 (11.9%)
ACE inhibitor or ARB	536 (71.3%)	513 (67.3%)
Beta-blocker	596 (79.3%)	601 (78.9%)
Lipid lowering therapy	682 (90.7%)	688 (90.3%)

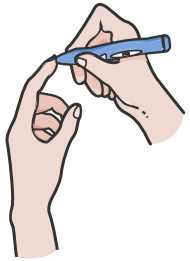
Kunadian V et al. N Engl J Med. 2024 Nov 7;391(18):1673-1684.

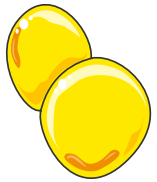


Byrne et al. EHJ 2023 12;44(38):3720-26

CONVENTIONAL RISK FACTORS







Characteristics	Invasive strategy N = 753 (%)	Conservative strategy N = 765 (%)
Hypertension	490 (65.1%)	500 (65.4%)
Diabetes	232 (30.8%)	234 (30.6%)
Smoking status		
Current smoker	35 (4.7%)	45 (6.0%)
Ex-smoker	358 (47.9%)	336 (44.4%)
Never smoked	355 (47.5%)	375 (49.6%)
Hypercholesterolemia	242 (32.2%)	231 (30.3%)
History of renal disease	156 (20.7%)	158 (20.7%)
Previous myocardial infarction	247 (32.8%)	227 (29.7%)
Previous PCI	163 (21.7%)	139 (18.2%)
Previous CABG	101 (13.4%)	80 (10.5%)
History of peripheral vascular disease	57 (7.6%)	61 (8.0%)
History of TIA/Stroke	128 (17.0%)	101 (13.2%)
History of COPD	115 (15.3%)	118 (15.4%)

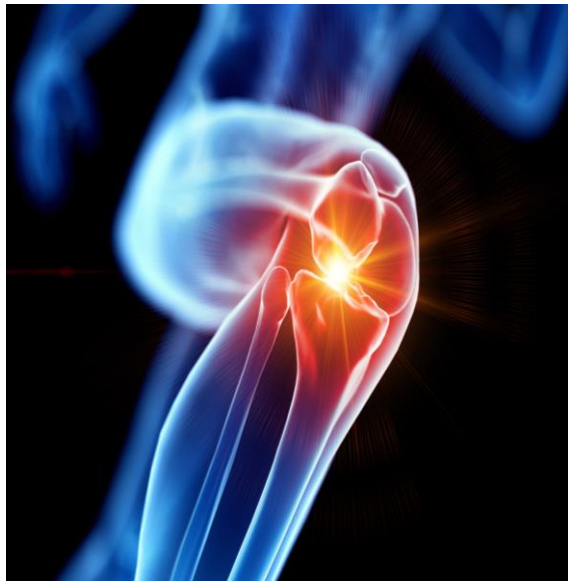
PCI-percutaneous coronary intervention; CABG-coronary artery byspass surgery; TIA-transient ischaemic attack; COPD-chronic obstructive pulmonary disease

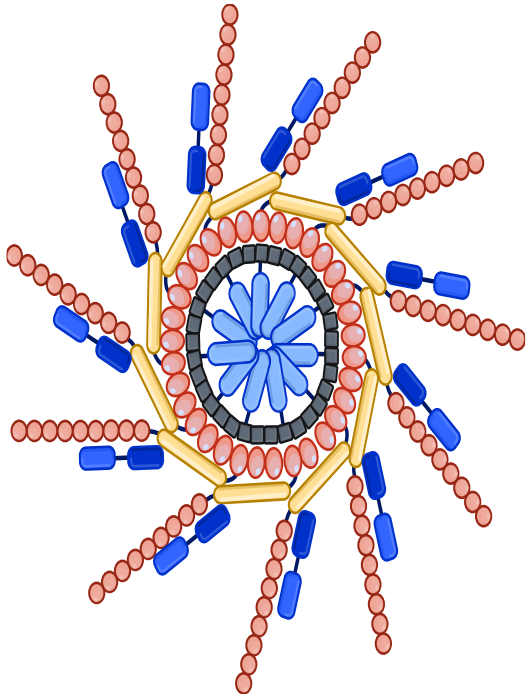
Kunadian V et al. N Engl J Med. 2024 Nov 7;391(18):1673-1684.

EMERGING RISK FACTOR: INFLAMMATION

Residual risk for developing a cardiovascular event may reflect aspects of atherogenesis, such as specific inflammatory pathways, which are not targeted by the current treatment strategies.

Inflammation





THE ASSOCIATION OF INFLAMMATORY BIOMARKERS AND LONG-TERM CLINICAL OUTCOMES IN OLDER ADULTS WITH NSTEACS

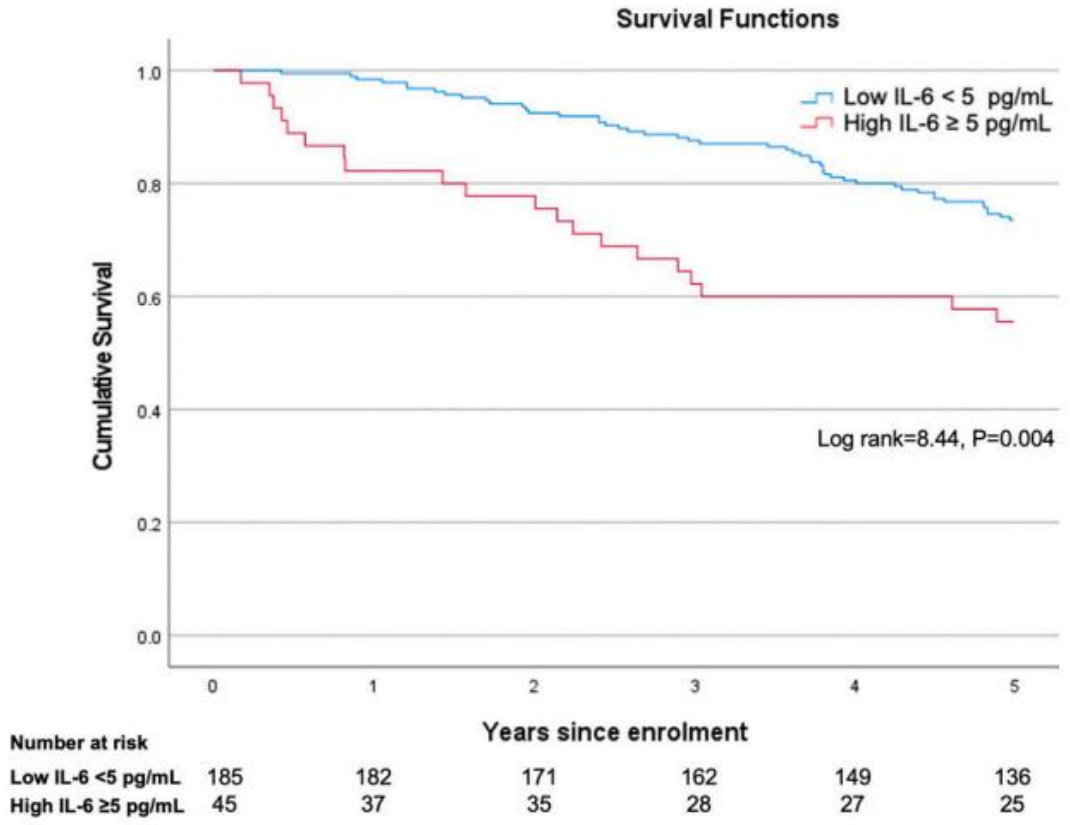


Fig. 2. Kaplan-Meier survival-analysis for all-cause mortality of patients according to IL-6.

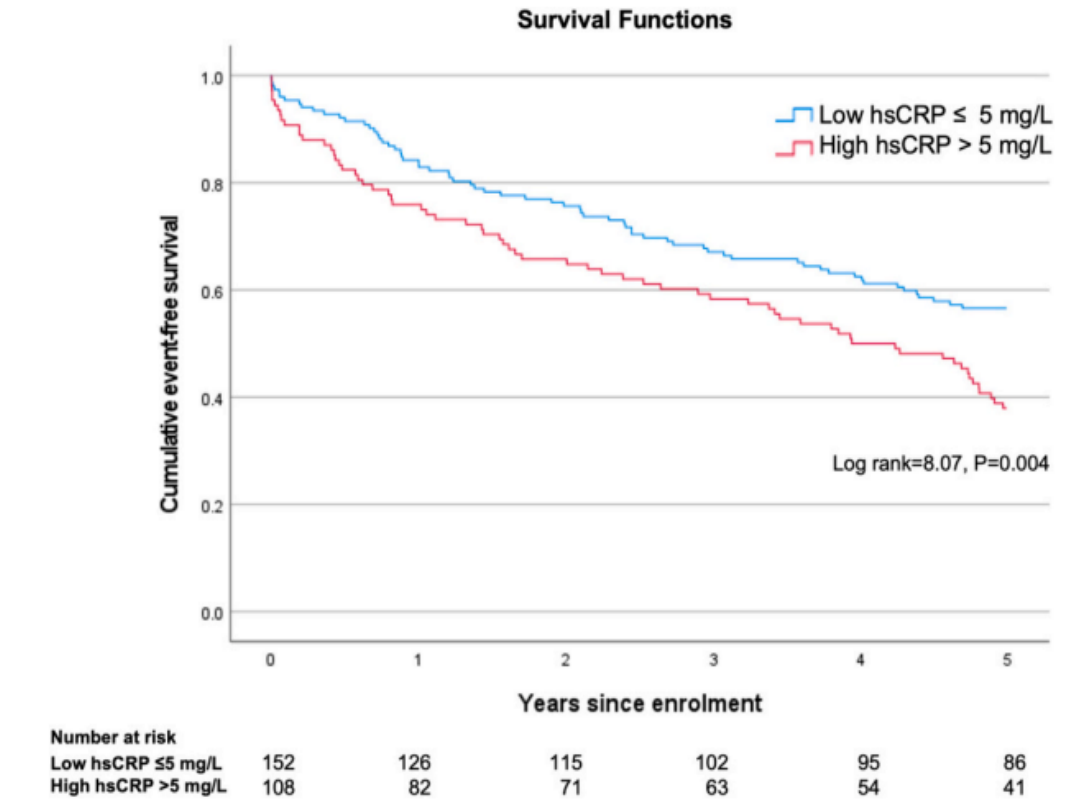
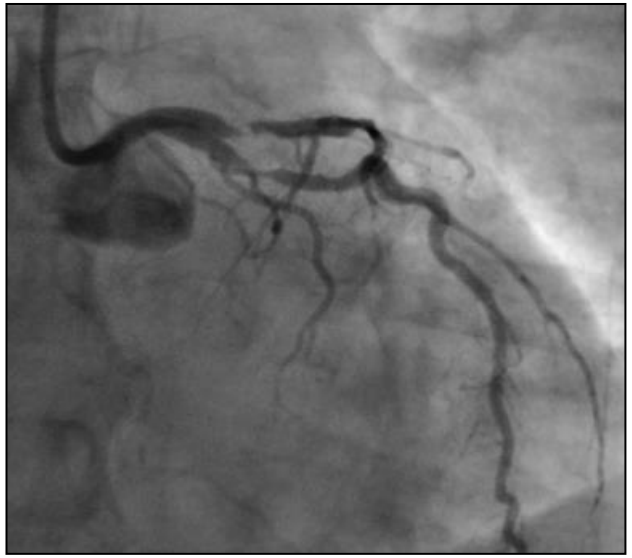
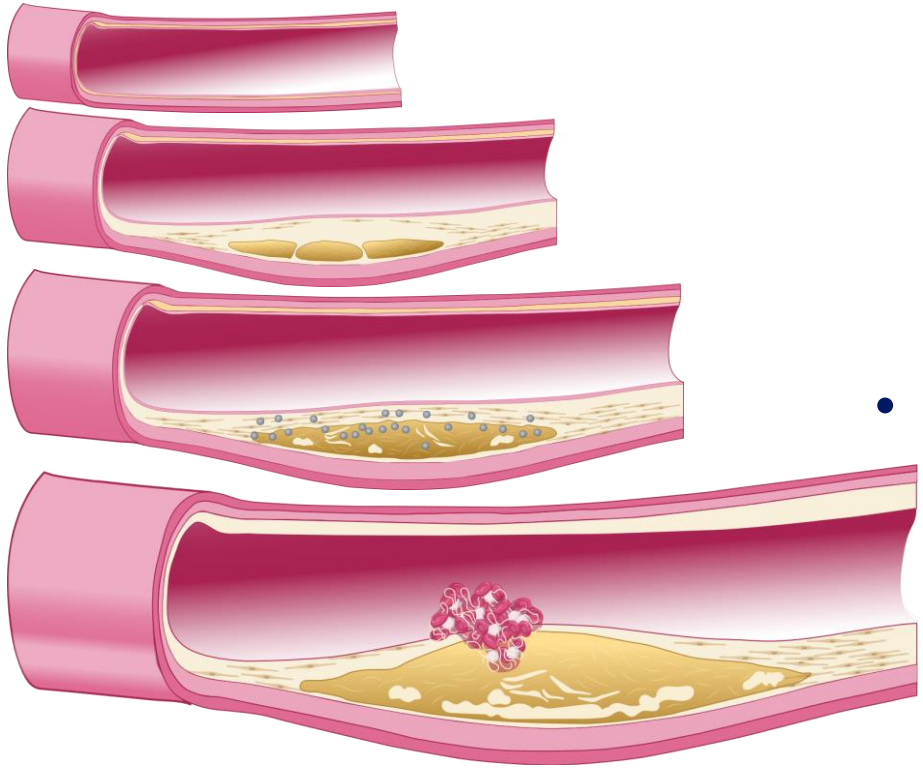


Fig. 4. Kaplan-Meier survival-analysis for MACCE of patients according to hsCRP.

Dirjayanto VJ, Kunadian V. Int J Cardiol. 2024 Aug 15;409:132177

FACTORS INVOLVED IN THE ACTIVATION OF THE NLRP3 INFLAMMASOME PATHWAY





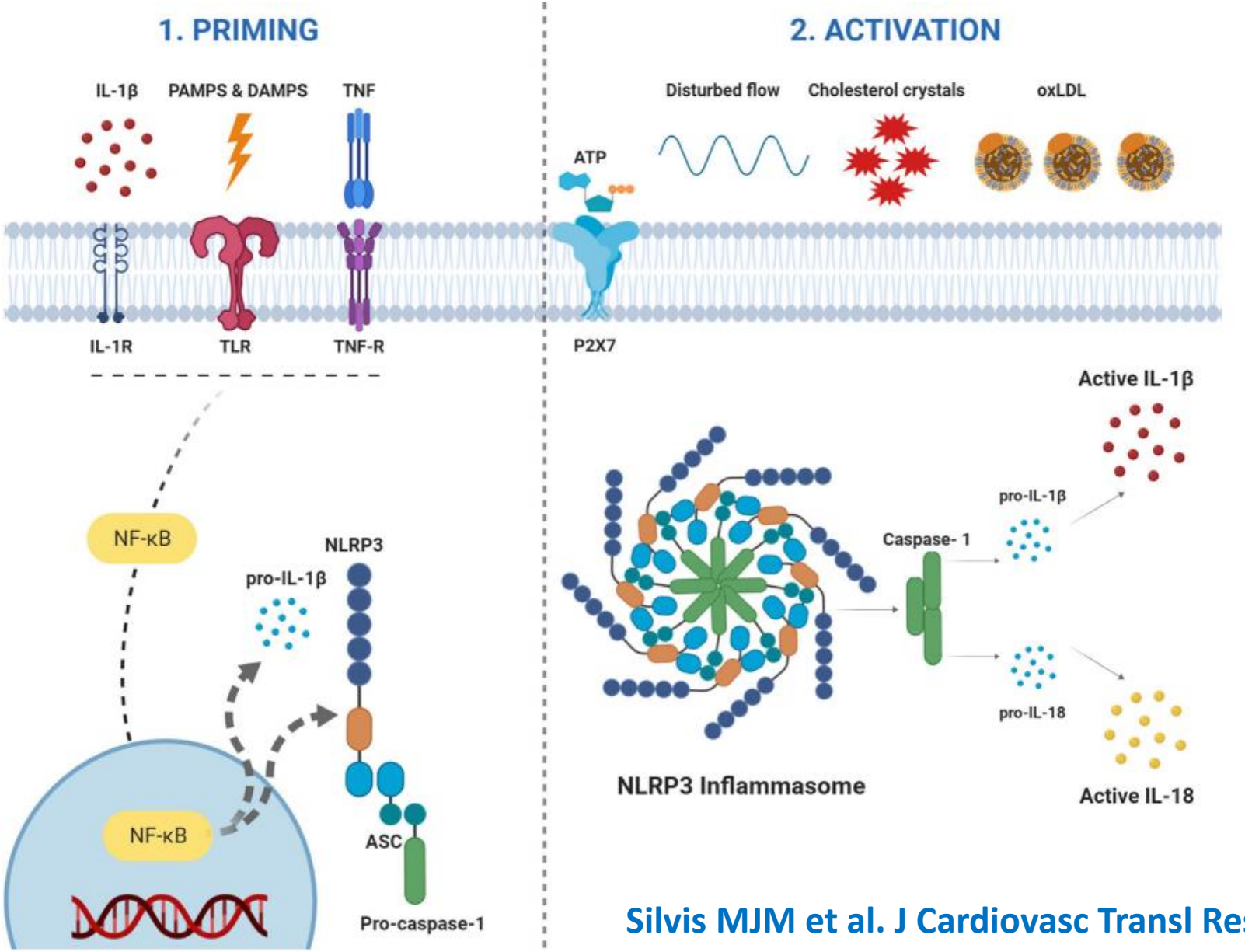
- Atherosclerosis, specifically the deposition of oxidised LDL and cholesterol in the vessel wall activate the NLRP3 inflammasome pathway
- Plaque rupture and hypoxia activate the NLRP3 inflammasome pathway

NLRP3: Nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3.

Silvis MJM et al. J Cardiovasc Transl Res 2021;14:23–34

ROLE OF NLRP3 INFLAMMASOME AND IL-6 IN ATHEROSCLEROSIS

Priming of the NLRP3 inflammasome leads to the up-regulation of inflammasome components and pro-IL-1β

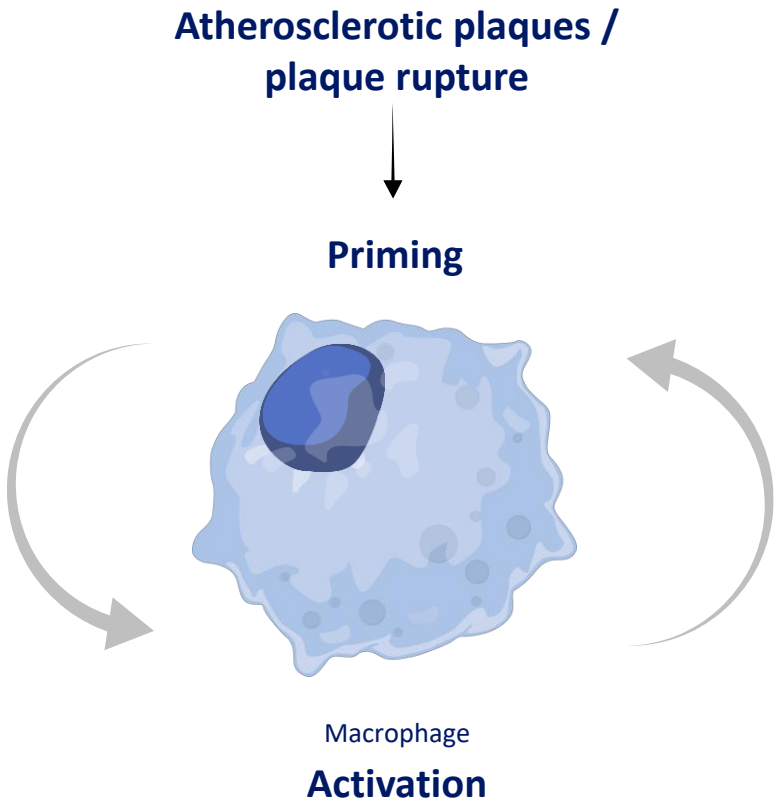


Activation of the NLRP3 inflammasome by uptake of CCs or oxLDL, extracellular ATP or disturbed blood flow

Silvis MJM et al. J Cardiovasc Transl Res 2021;14:23–34

NLRP3 INFLAMMASOME ACTIVATION LEADS TO IL-6 SECRETION

↑ **IL-6 production** ----------

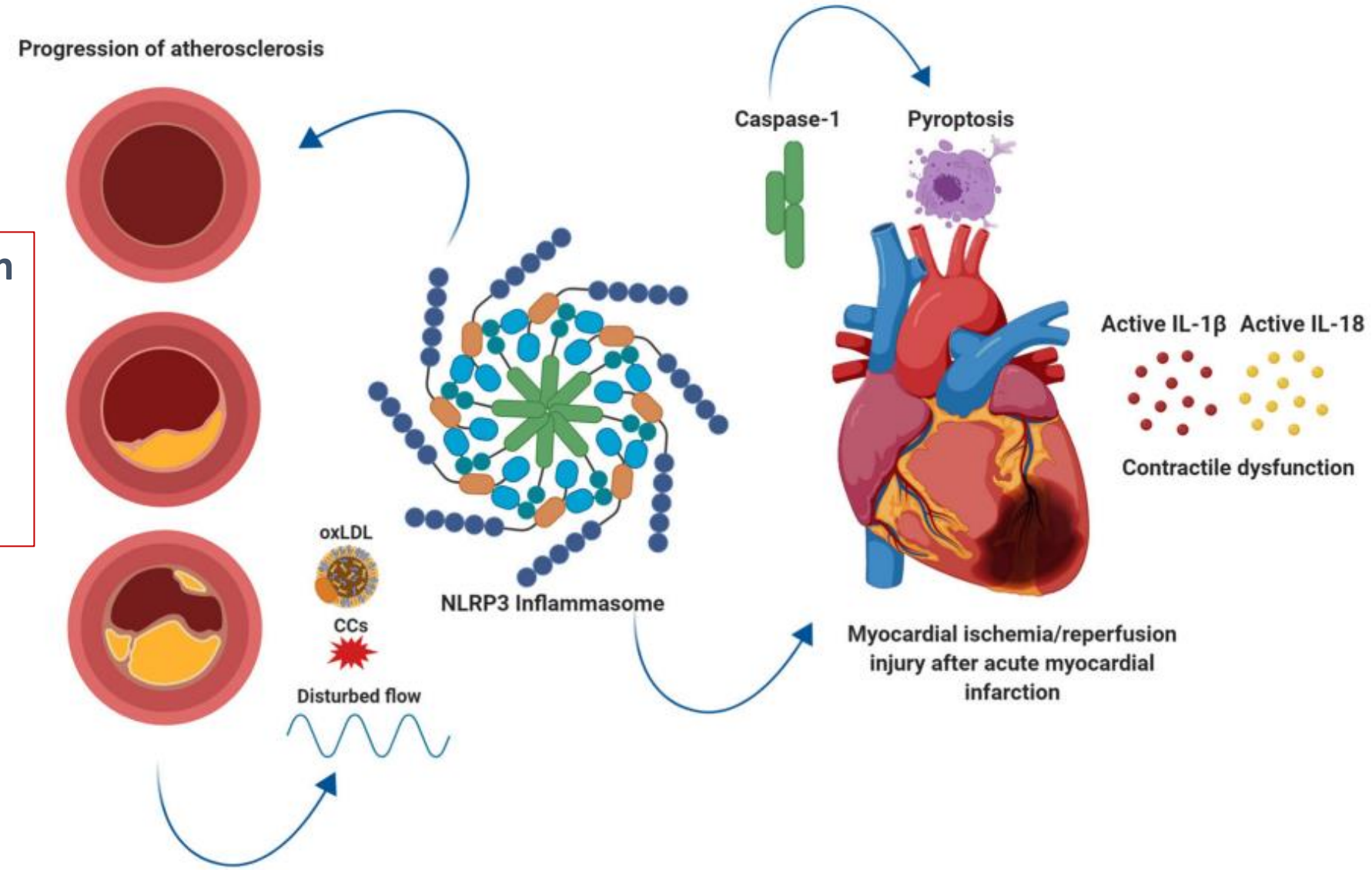


Inflammasome is a multiprotein complex leading to activation and release of interleukins

Silvis MJM et al. J Cardiovasc Transl Res 2021;14:23–34

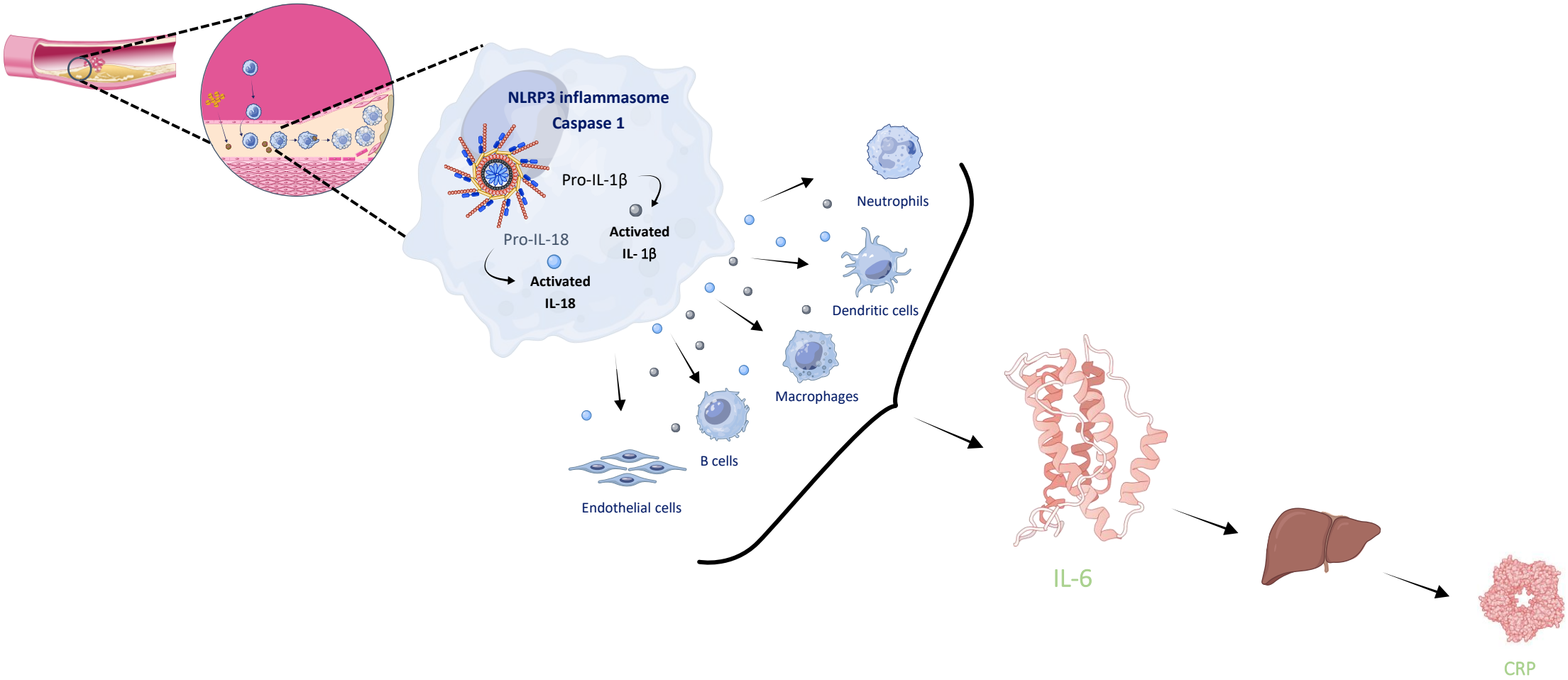
IL-6 IS CENTRAL ON THE PROGRESSION OF ATHEROSCLEROSIS

- Endothelial dysfunction
- Plaque rupture
- Cardiomyocyte injury
- Increased risk of CAD and MI



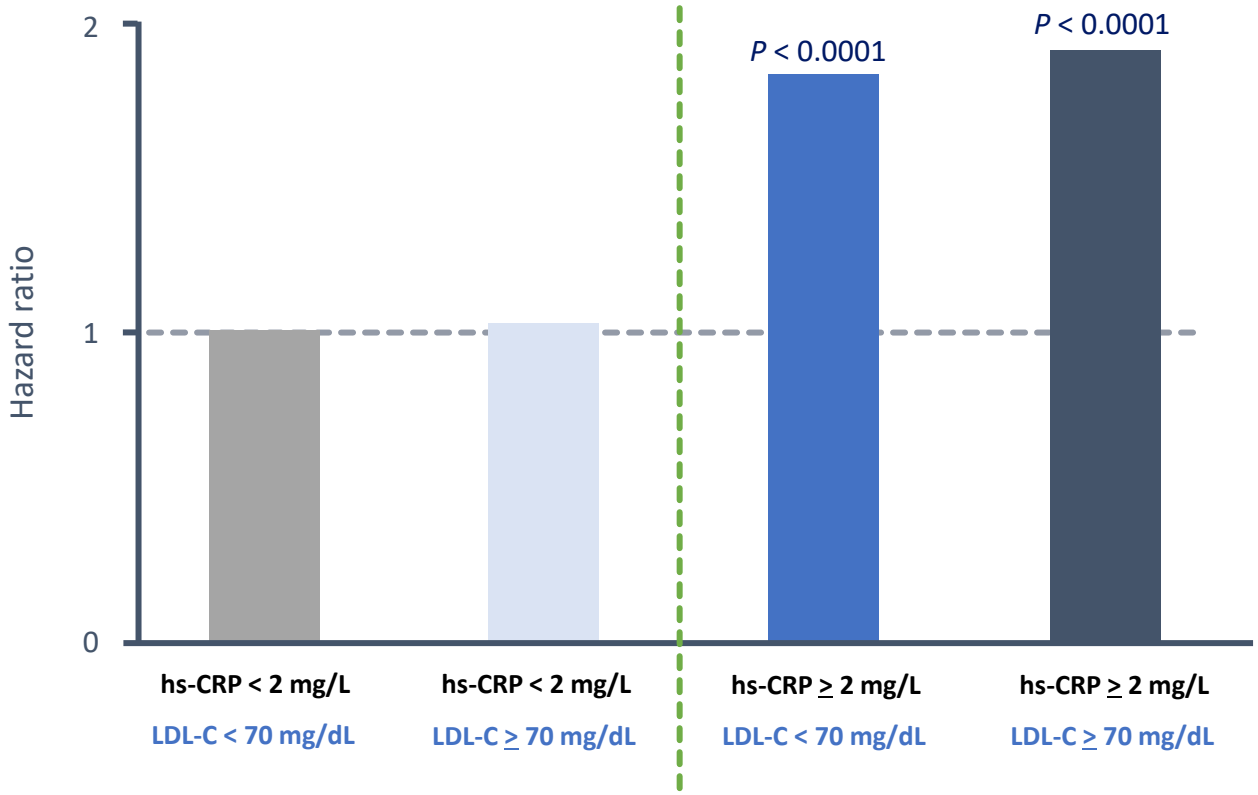
Silvis MJM et al. J Cardiovasc Transl Res 2021;14:23–34

ROLE OF NLRP3 INFLAMMASOME AND IL-6 IN ATHEROSCLEROSIS
IL-6 IS CENTRAL IN THE PROGRESSION OF ATHEROSCLEROSIS



Silvis MJM et al. J Cardiovasc Transl Res 2021;14:23–34

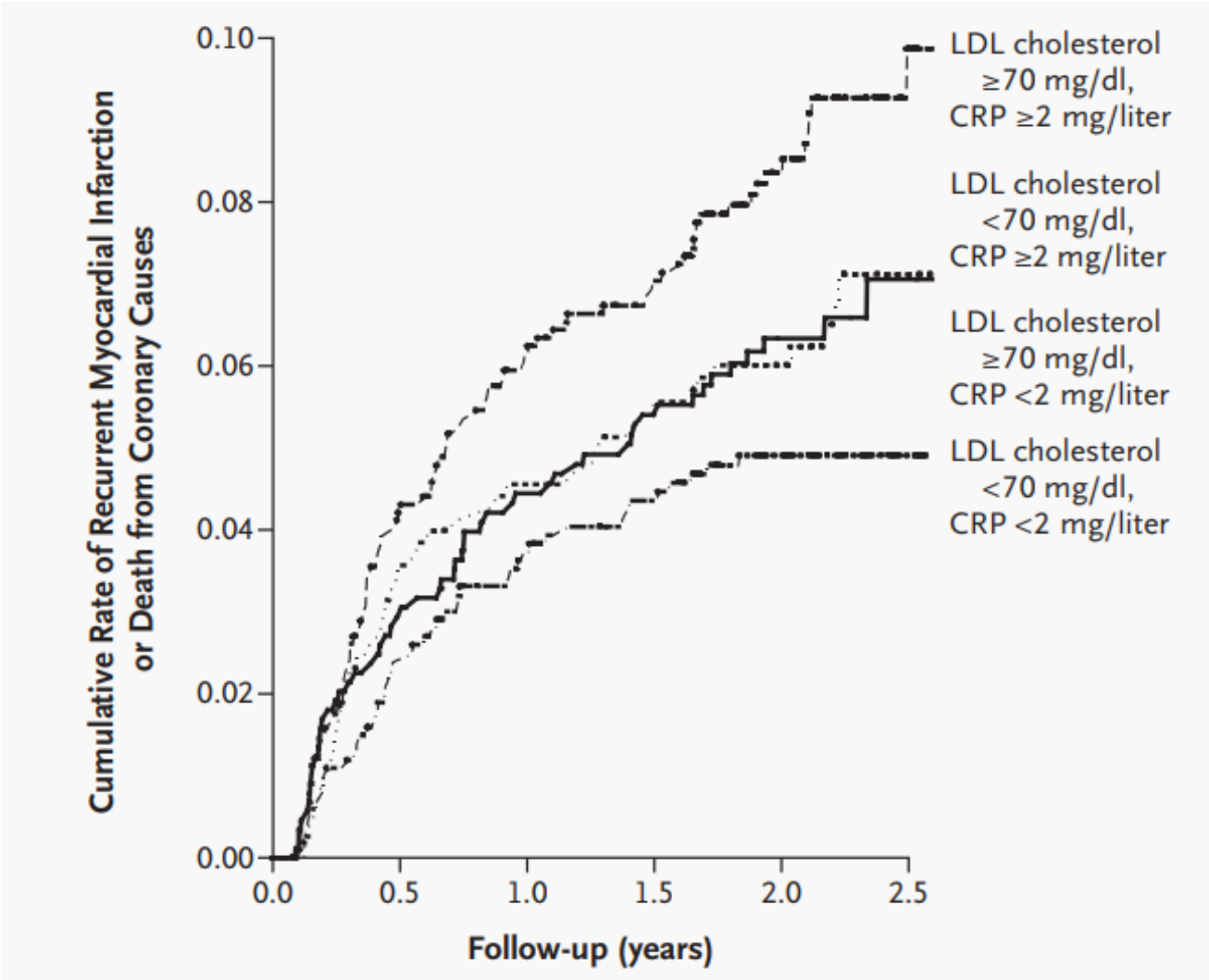
HS-CRP IS A POWERFUL DETERMINANT OF CARDIOVASCULAR DEATH IRRESPECTIVE OF LDL-C AMONG STATIN-TREATED PATIENTS



Cardiovascular death

Ridker PM, et al. Lancet. 2023;401(10384):1293-1301.

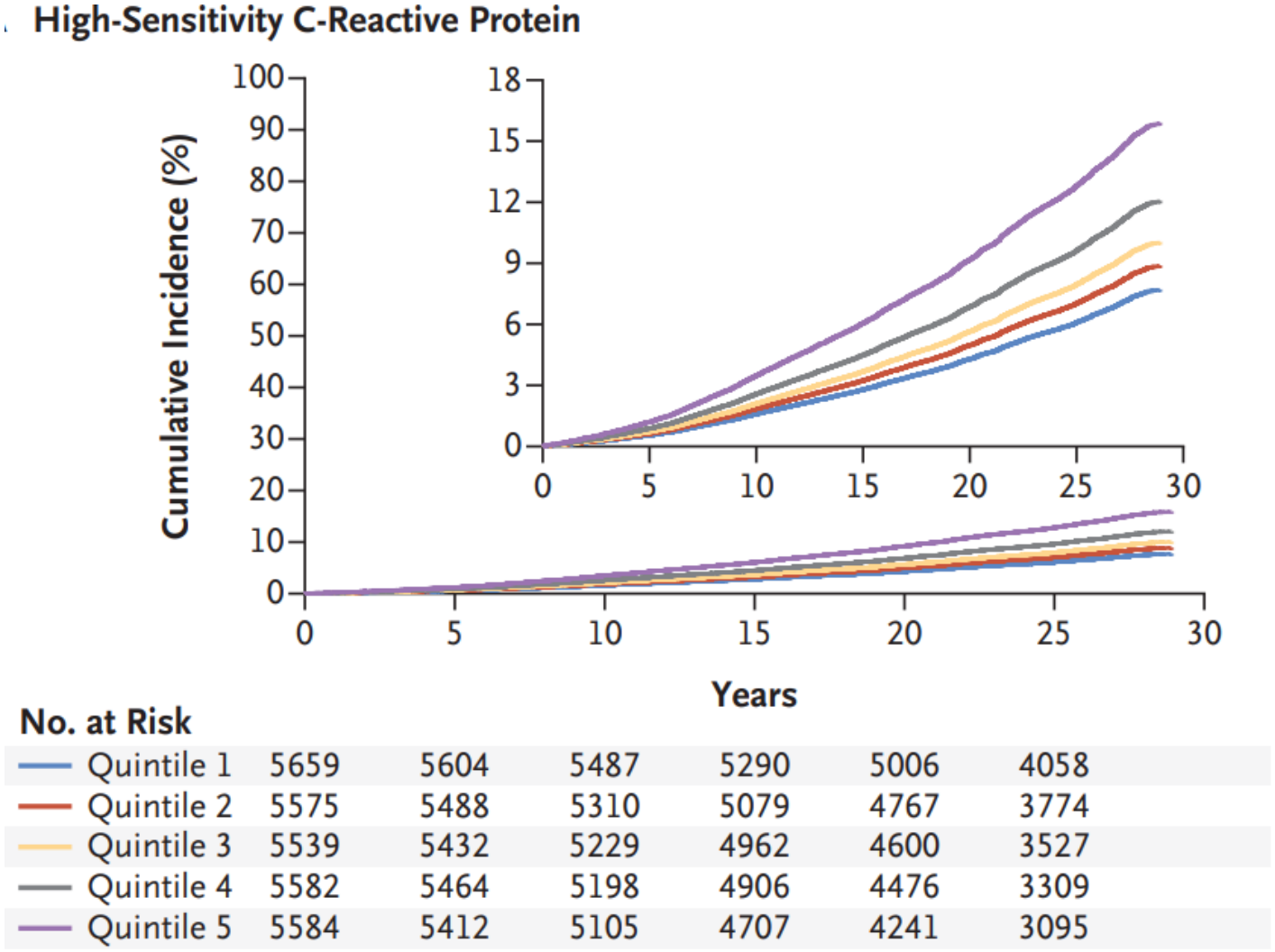
CRP LEVELS AND OUTCOMES AFTER STATIN THERAPY IN PATIENTS WITH AMI



Patients who have low CRP levels after statin therapy have better clinical outcomes than those with higher CRP levels, regardless of the resultant level of LDL cholesterol.

Ridker PM, et al., N Engl J Med. 2005;352(1):20-8.

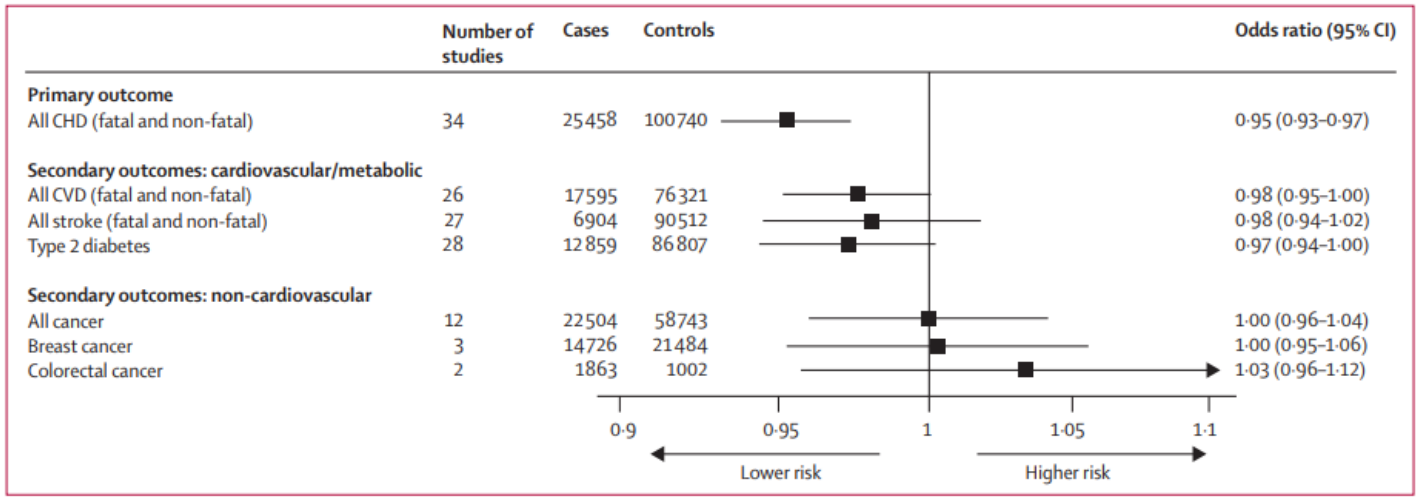
INFLAMMATION, CHOLESTEROL, LIPOPROTEIN(A), AND 30-YEAR CARDIOVASCULAR OUTCOMES IN WOMEN



A single combined measure of high-sensitivity CRP, LDL cholesterol, and lipoprotein(a) levels among initially healthy U.S. women was predictive of incident cardiovascular events during a 30-year period

Ridker et al NEJM 2024

IMPAIRMENT OF IL-6R SIGNALLING IS ASSOCIATED WITH A REDUCED RISK OF IHD EVENTS, INCLUDING AMI



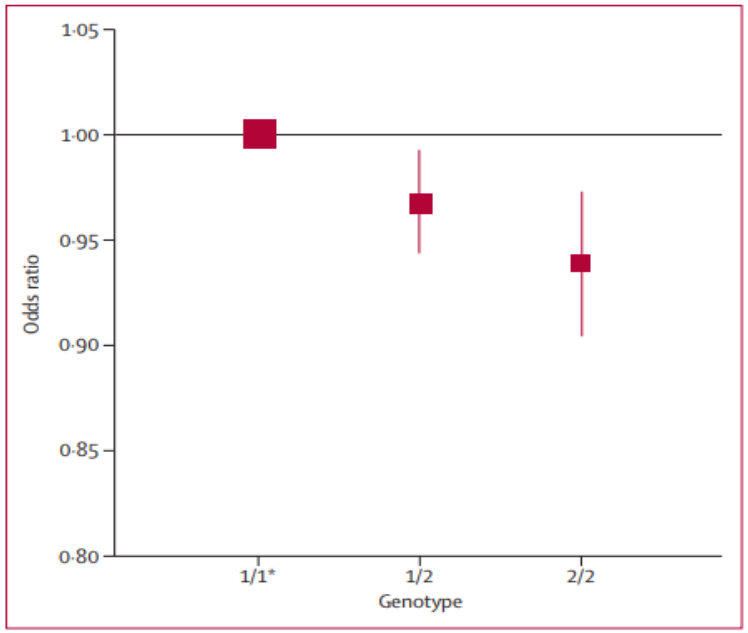


Figure 2: IL6R genotypes and risk of coronary heart disease

A Mendelian randomisation meta-analysis of 40 studies that included up to 133,449 individuals

Patients with IL-6R blockade (through the IL-6R rs7529229 SNP) had a lower risk of IHD events than those without this SNP.

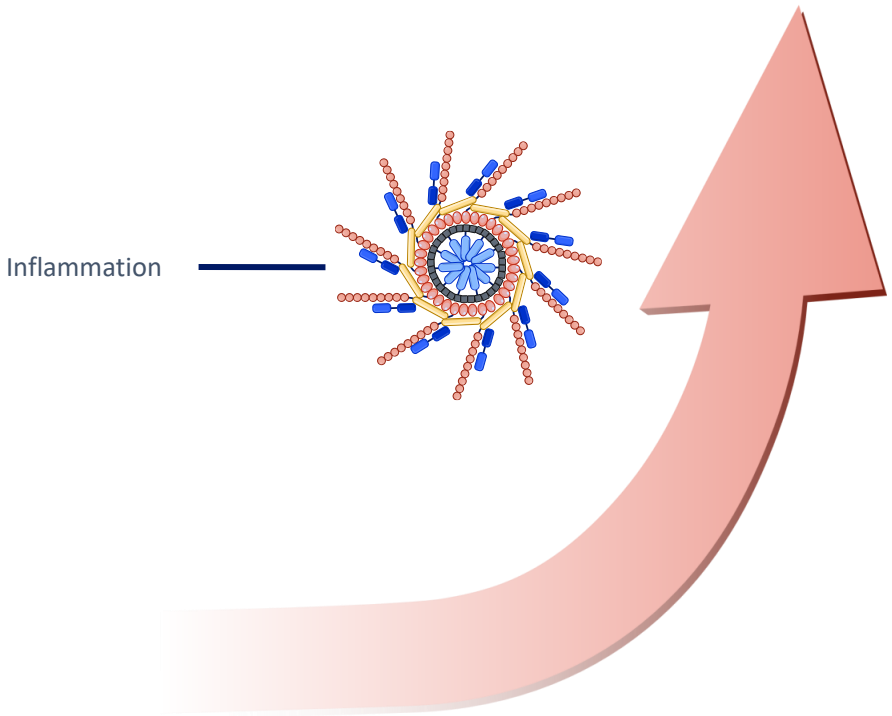
Swerdlow DI et al. Lancet 2012;379:1214–1224

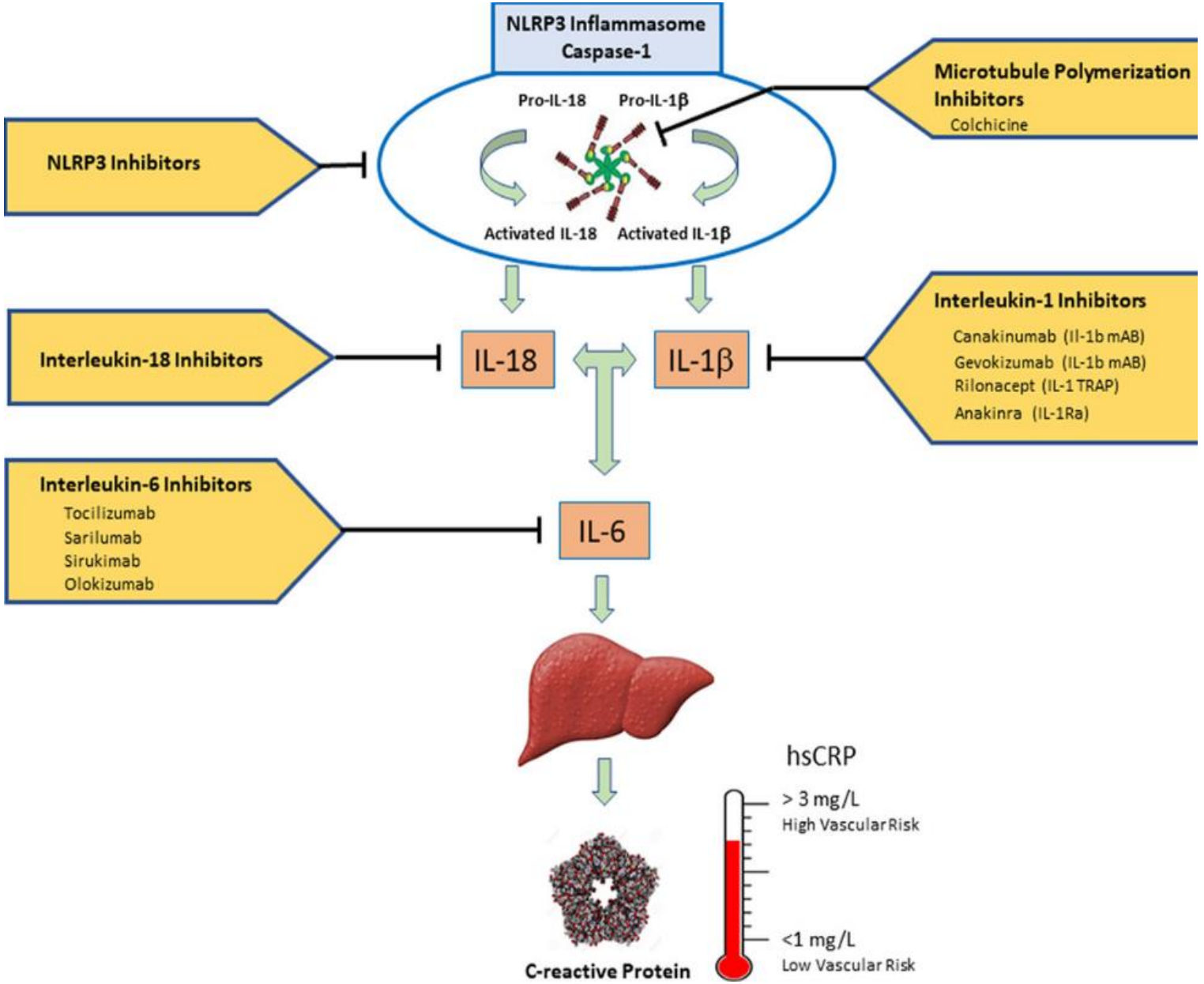
A genetic meta-analysis of 82 studies that included 51,441 patients with IHD and 136,226 controls

Patients with impaired IL-6R signalling (due to the Asp358Ala variant of IL-6R) had a lower risk of IHD† than those without this variant. For every copy of 385Ala inherited, the risk of IHD† decreased by 3.4% (95% CI: 1.8; 5.0)

Sarwar N et al. Lancet 2012;379:1205

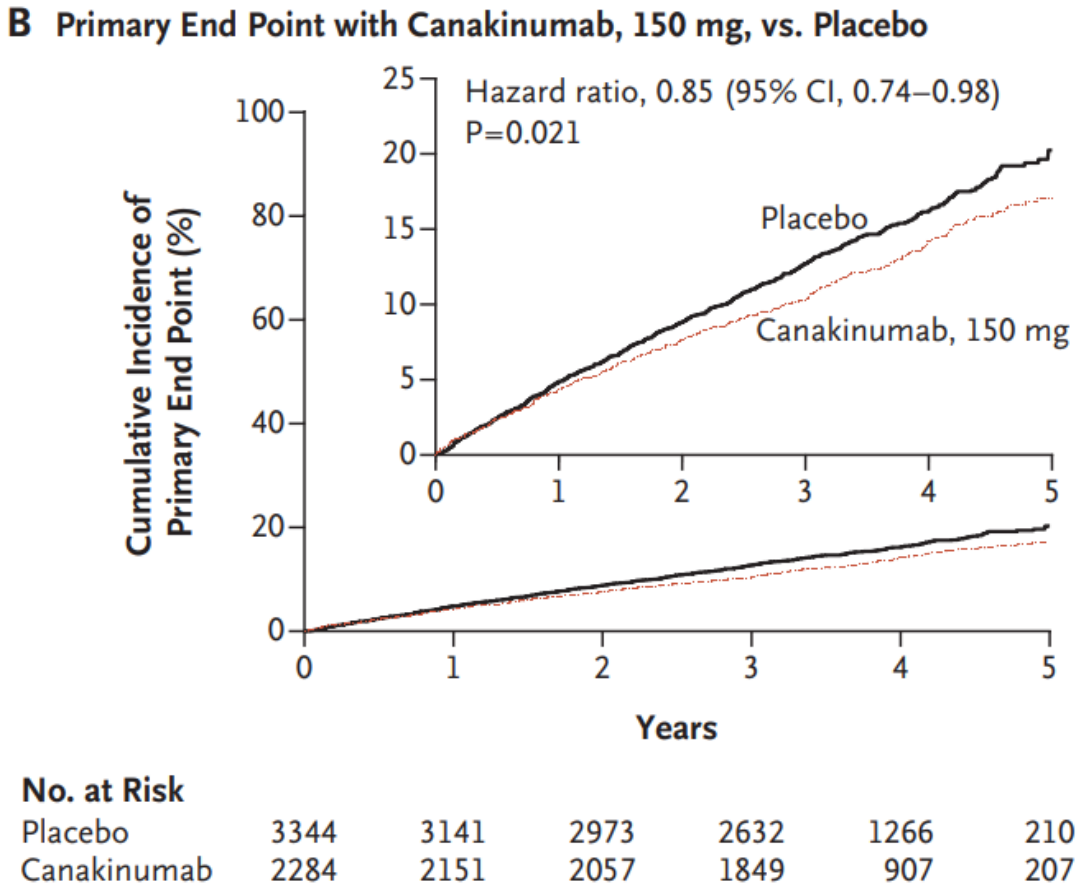
EMERGING RISK FACTOR
INFLAMMATION





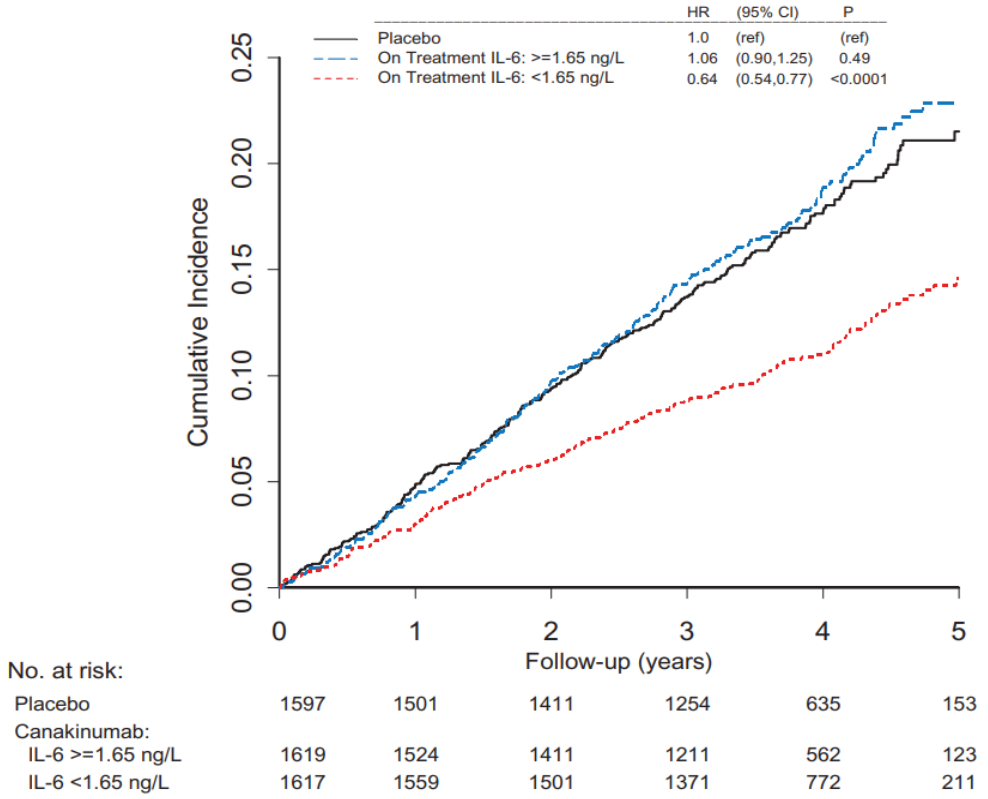
Ridker PM et al. Circulation 2020;141:787–789

CANTOS POST HOC ANALYSIS: LOWERING IL-6 LEVELS THROUGH IL-1B INHIBITION REDUCES THE RISK OF MACE POST AMI



The primary efficacy end point was nonfatal MI, nonfatal stroke, or cardiovascular death

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



MACE (composite of recurrent MI, stroke or CV death)

Canakinumab* was associated with a 36% reduction in MACE vs placebo in patients who achieved IL-6 levels below the study median of 1.65 ng/L (no significant difference for those with IL-6 levels ≥1.65 ng/L)

Ridker PM, et al., Eur Heart J. 2018;39(38):3499-3507

CANTOS: OVERVIEW OF ADVERSE EVENTS

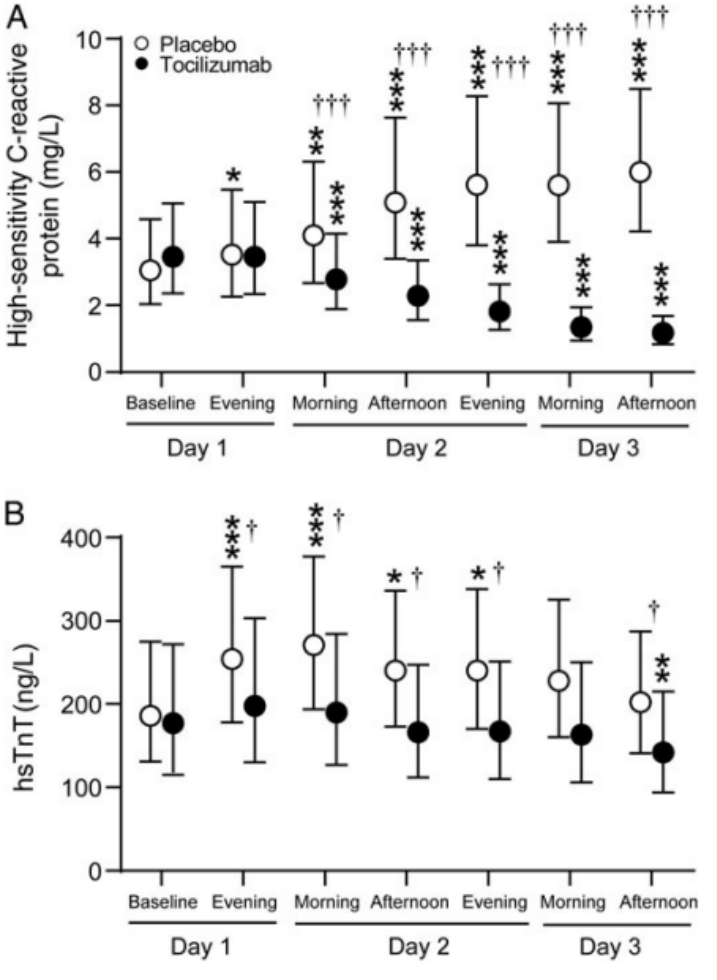
Adverse events (incident rate per 100 person-years)	Canakinumab (all doses) (N=6,717)	Placebo (N=3,344)	*P* Value For Combined Dose Groups vs. Placebo
Any serious adverse event	11.82	11.96	0.79
Any serious adverse event of infection			
Pneumonia	0.95	0.90	0.62
Urinary tract infection	0.21	0.22	0.87
Fatal infection or sepsis	0.31	0.18	0.02
Other adverse events			
Injection-site reactions	0.28	0.23	0.36
Arthritis	2.26	3.32	<0.001
Leukopenia	0.40	0.24	0.01
Any haemorrhage	3.78	4.01	0.31
Thrombocytopenia	0.60	0.43	0.03

Significantly higher incidence of fatal infection and sepsis with canakinumab than with placebo, as well as a reduction in platelet counts with no increase in bleeding risk

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

TOCILIZUMAB IN NSTEMI AND STEMI DEMONSTRATION OF SAFETY

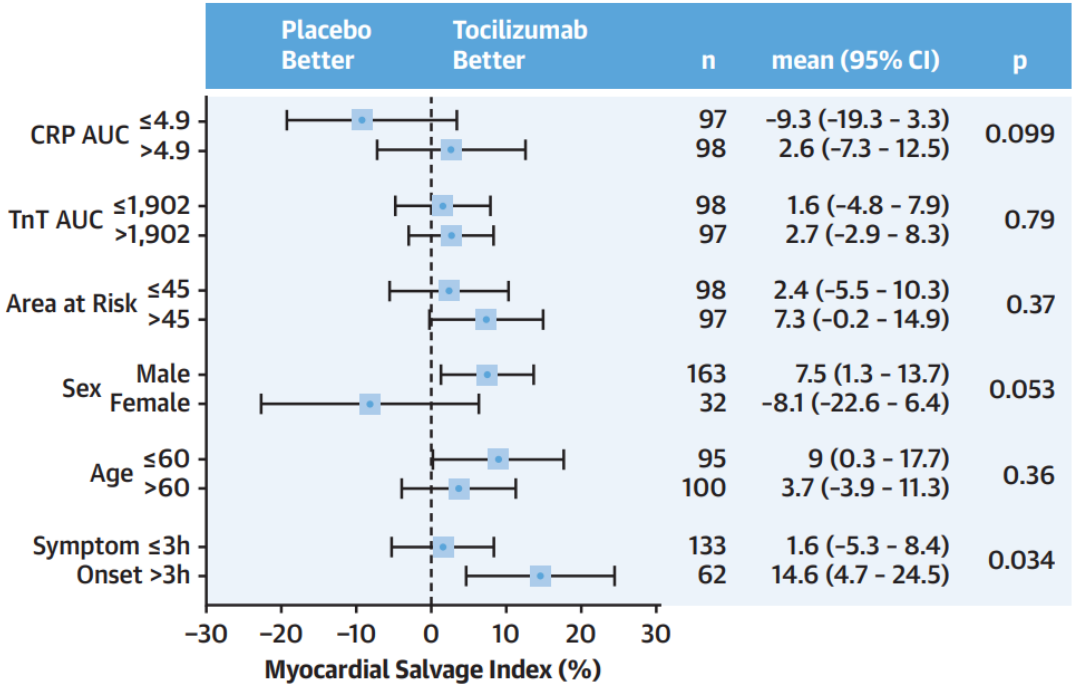
NSTEMI

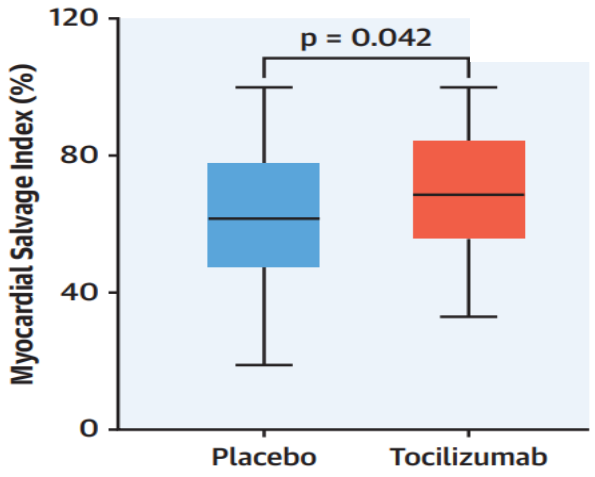


Tocilizumab (N=58), Placebo (N=59)

- Reduced AUC for hs-CRP
- Reduced AUC for hs-TnT
- **No safety concerns**

STEMI



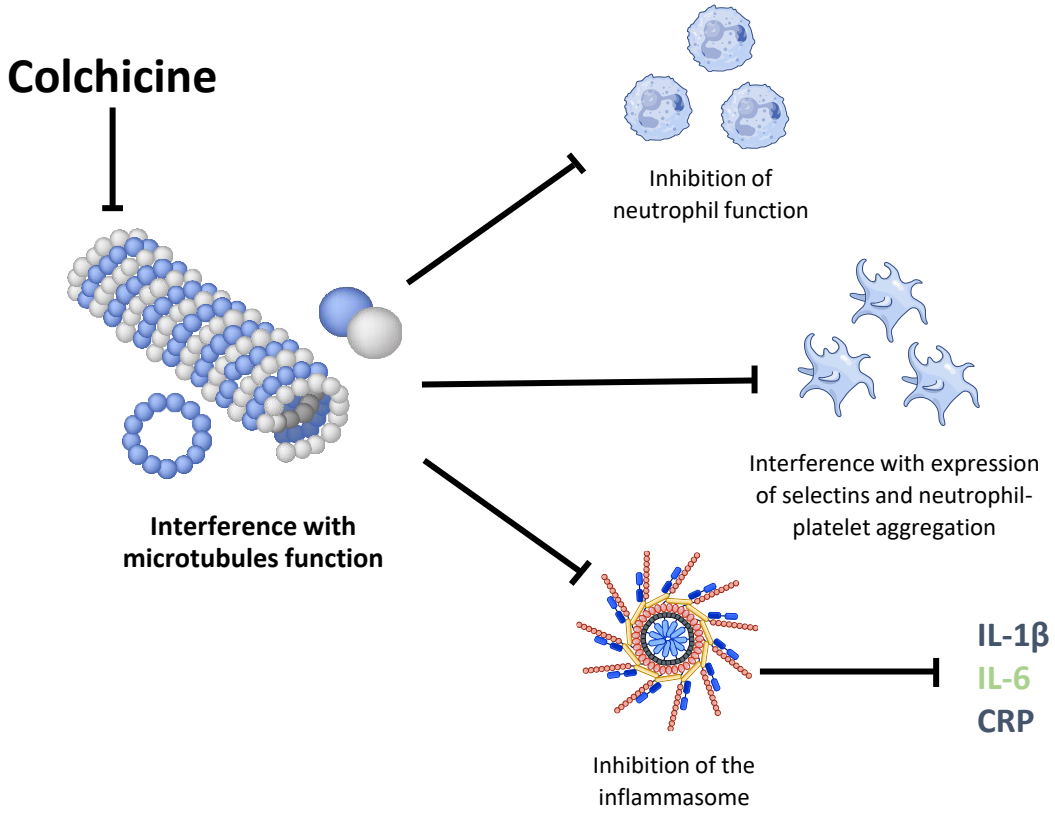


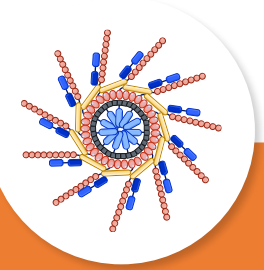
Tocilizumab (N=101), Placebo (N=98)

- Improved myocardial salvage, symptom onset > 3 hours
- Reduced microvascular obstruction but no difference in infarct size
- **No safety concerns**

Kleveland O et al., Eur Heart J. 2016;37(30):2406-13;
Broch K et al., J Am Coll Cardiol. 2021;77(15):1845-

ANTI-INFLAMMATORY ACTION OF COLCHICINE RESULTS IN INHIBITION OF THE NLRP3 INFLAMMASOME





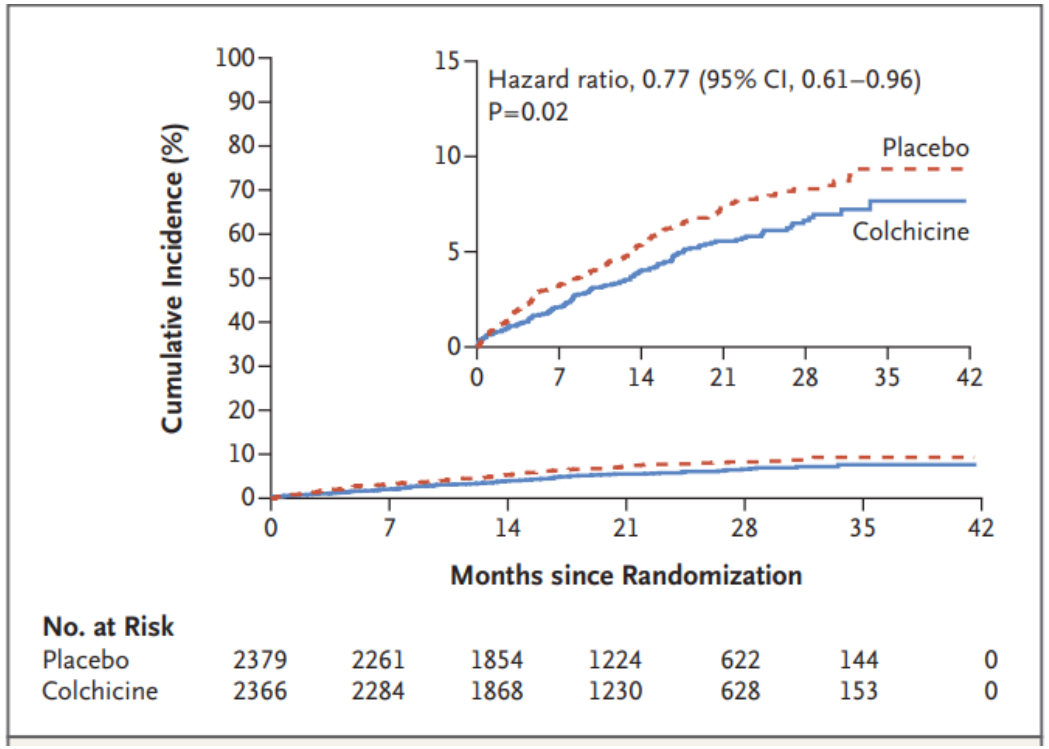
Mechanism of action

Colchicine is a microtubule polymerisation inhibitor that **impedes assembly** of the NLRP3 inflammasome, thereby blocking a downstream inflammatory signalling cascade that includes IL-1β, **IL-6** and CRP

Imazio M & Nidorf M. Eur Heart J 2021;42:2745–2760; Ridker PM et al. Circulation 2020;141:787–789

COLCHICINE TRIALS

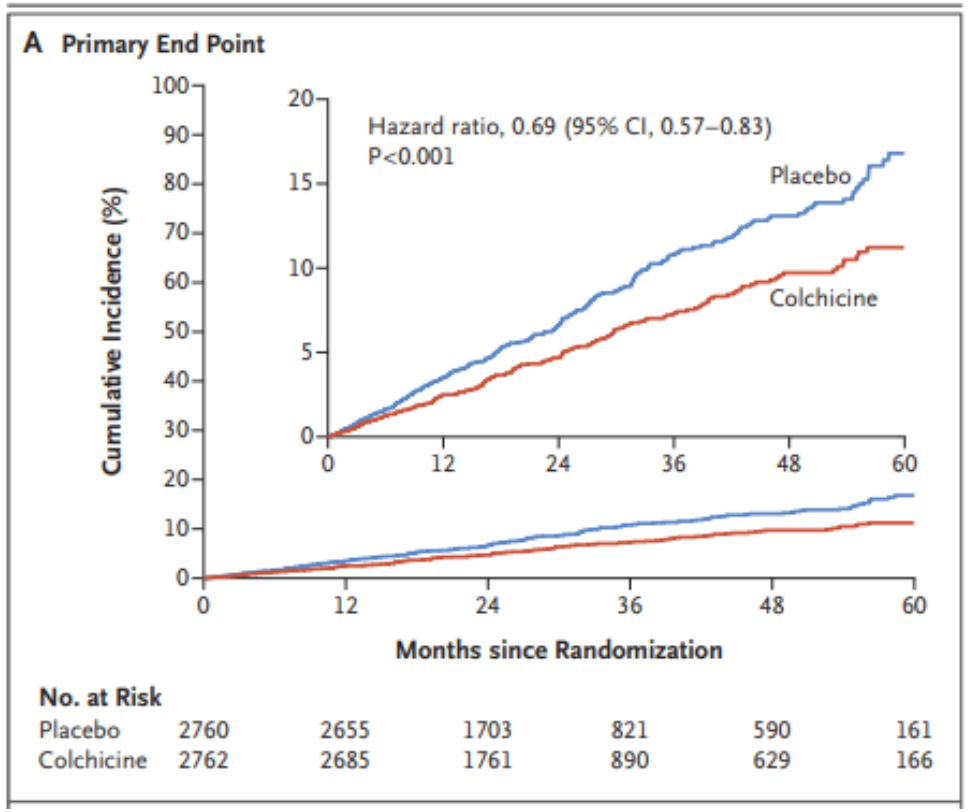
COLCOT: N=4,745 recent MI



Composite endpoint of CV death, resuscitated cardiac arrest, MI, stroke or urgent hospitalisation for angina leading to coronary revascularisation

Tardif JC et al. N Engl J Med 2019;381:2497–2505;

LoDoCo2: N=5,522 stable CAD



Composite endpoint of CV death, MI, ischaemic stroke or ischaemia driven coronary revascularisation

Nidorf SM et al. N Engl J Med 2020;383:1838–1847

ESC GUIDELINES

ESC European Society of Cardiology
European Heart Journal (2024) **45**, 3415–3537
https://doi.org/10.1093/eurheartj/ehae177

2024 ESC Guidelines for the management of chronic coronary syndromes

Developed by the task force for the management of chronic coronary syndromes of the European Society of Cardiology (ESC)

Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS)

Authors/Task Force Members: Christiaan Vrints *†, (Chairperson) (Belgium), Felicita Andreotti *†, (Chairperson) (Italy), Konstantinos C. Koskinas‡, (Task Force Co-ordinator) (Switzerland), Xavier Rossello ‡, (Task Force Co-ordinator) (Spain), Marianna Adamo (Italy), James Ainslie (United Kingdom), Adrian Paul Banning (United Kingdom), Andrzej Budaj (Poland), Ronny R. Buechel (Switzerland), Giovanni Alfonso Chiariello (Italy), Alaide Chieffo (Italy), Ruxandra Maria Christodorescu (Romania), Christi Deaton (United Kingdom), Torsten Doenst [1] (Germany), Hywel W. Jones (United Kingdom), Vijay Kunadian (United Kingdom), Julinda Mehilli (Germany), Milan Milojevic [1] (Serbia), Jan J. Piek (Netherlands), Francesca Pugliese (United Kingdom), Andrea Rubboli (Italy), Anne Grete Semb (Norway), Roxy Senior (United Kingdom), Jurrien M. ten Berg (Netherlands), Eric Van Belle (France), Emeline M. Van Craenenbroeck (Belgium), Rafael Vidal-Perez (Spain), Simon Winther (Denmark), and ESC Scientific Document Group

Recommendation	Class[a]	Level[b]
In CCS patients with atherosclerotic CAD, low-dose colchicine (0.5 mg daily) should be considered to reduce myocardial infarction, stroke, and need for revascularization.[714–716]	IIa	A

CLEAR Trial

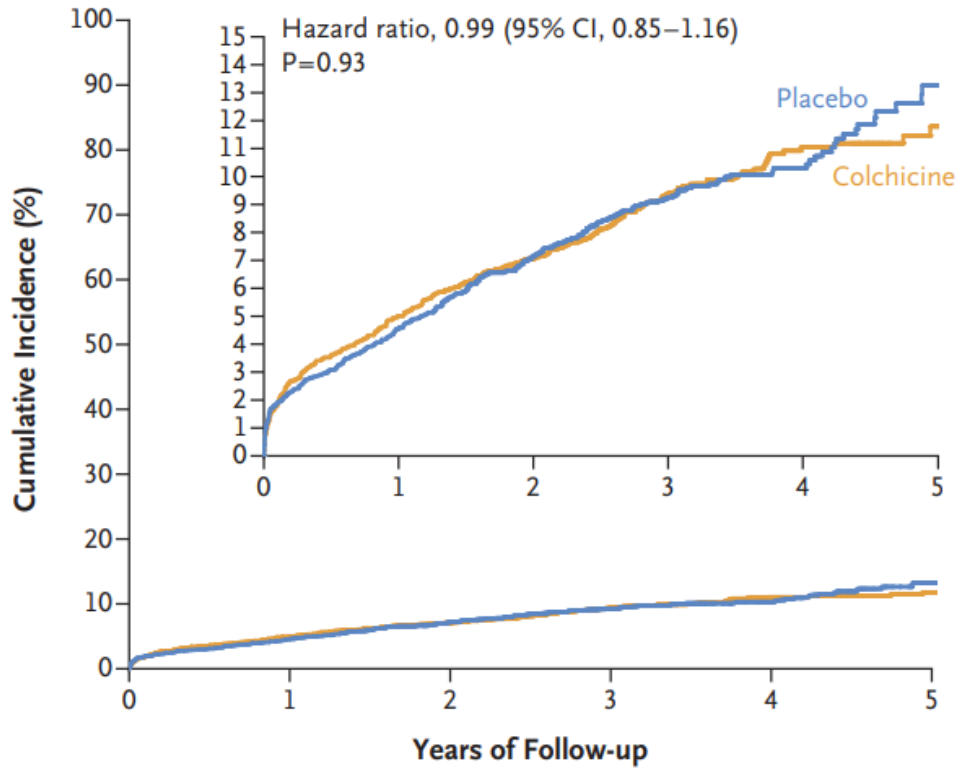


Figure 1. Kaplan–Meier Event Curves for Death from Cardiovascular Causes, Recurrent Myocardial Infarction, Stroke, or Ischemia-Driven Revascularization.

The inset shows a magnified version of the graph.

Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristic	Colchicine (N=3528)	Placebo (N=3534)
Demographic characteristics		
Mean age — yr	60.6±10.3	60.7±10.3
Age >75 yr — no. (%)	301 (8.5)	270 (7.6)
Female sex — no. (%)	725 (20.5)	713 (20.2)
Race or ethnic group — no. (%)†		
American Indian or Alaskan Native	7 (0.2)	3 (0.1)
Asian	95 (2.7)	89 (2.5)
Black	24 (0.7)	23 (0.7)
Native Hawaiian or other Pacific Islander	9 (0.3)	9 (0.3)
White	3233 (91.6)	3249 (91.9)
Other	153 (4.3)	159 (4.5)
Geographic region — no. (%)		
North America	1010 (28.6)	1012 (28.6)
Europe	2356 (66.8)	2359 (66.8)
Other	162 (4.6)	163 (4.6)
Clinical characteristics		
Killip class ≥II — no. (%)‡	25 (0.7)	24 (0.7)
NSTEMI at presentation — no. (%)	165 (4.7)	184 (5.2)
STEMI at presentation — no. (%)	3363 (95.3)	3350 (94.8)

Jolly SS et al. NEJM 2024

ANAKINRA (IL-1 RECEPTOR ANTAGONIST) IN NSTEMI AND STEMI: THE MRC-ILA HEART STUDY

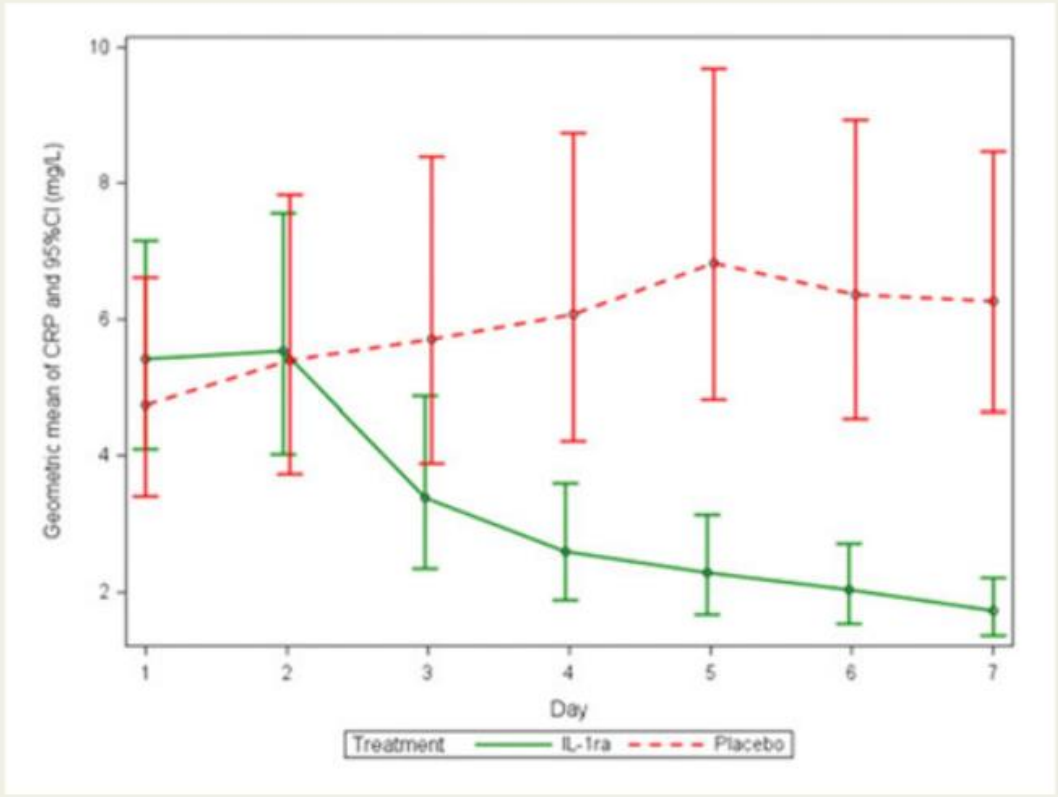


Figure 2 Geometric mean of high sensitivity C-reactive protein over the first 7 days of treatment with IL-1ra or placebo (95% CI) calculated for primary outcome analysis.

Following 14 days IL-1ra treatment inflammatory markers were reduced

Anakinra IL-1Ra

NSTEMI

Anakinra (N=93)
Placebo (N=89)

✓Demonstrated safety

✓Reduced area under hs-CRP curve

Morton AC et al., Eur Heart J. 2015;36(6):377-84.

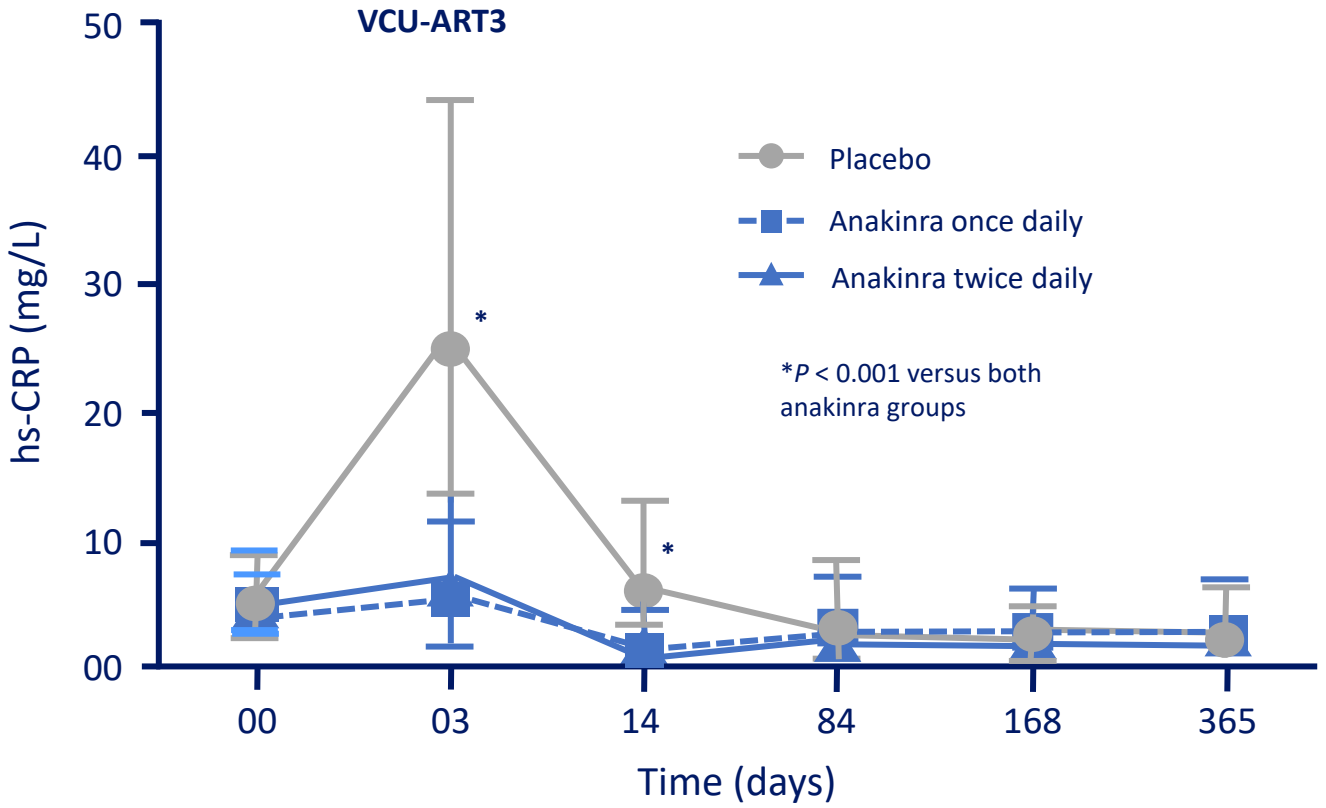
ANAKINRA (IL-1 RECEPTOR ANTAGONIST) IN NSTEMI AND STEMI THE VCU-ART3 STUDY

VCU-ART3

- 99 STEMI patients treated for 2 weeks

Anakinra one daily (N=33)
Anakinra twice daily (N=31)
Placebo (N=35)

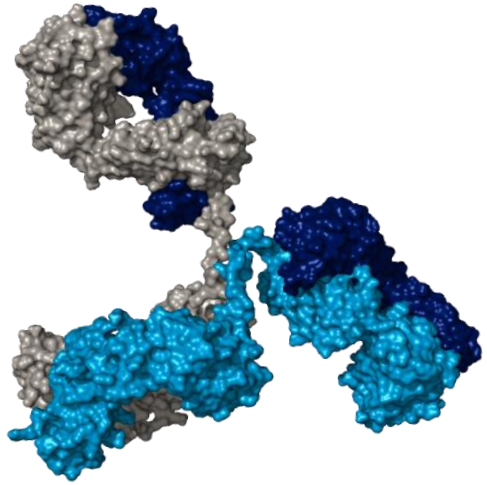
- Area under hs-CRP curve significantly lower
- Reduced rate of death or new-onset heart failure
- Safe, no myocardial rupture
- No increase in infections



Abbate A et al., J Am Heart Assoc. 2020;9(5):e014941.

ZILTIVEKIMAB: TARGETING IL-6 IN CVD

Ziltivekimab is a **human monoclonal antibody** directed against the IL-6 ligand

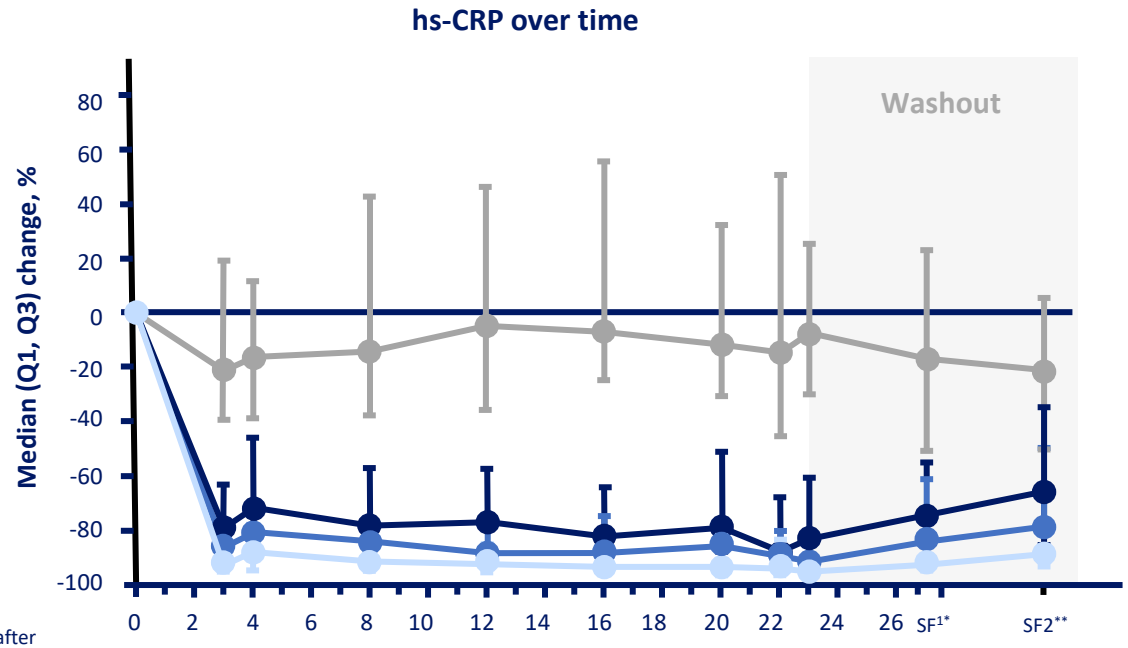


ZILTIVEKIMAB

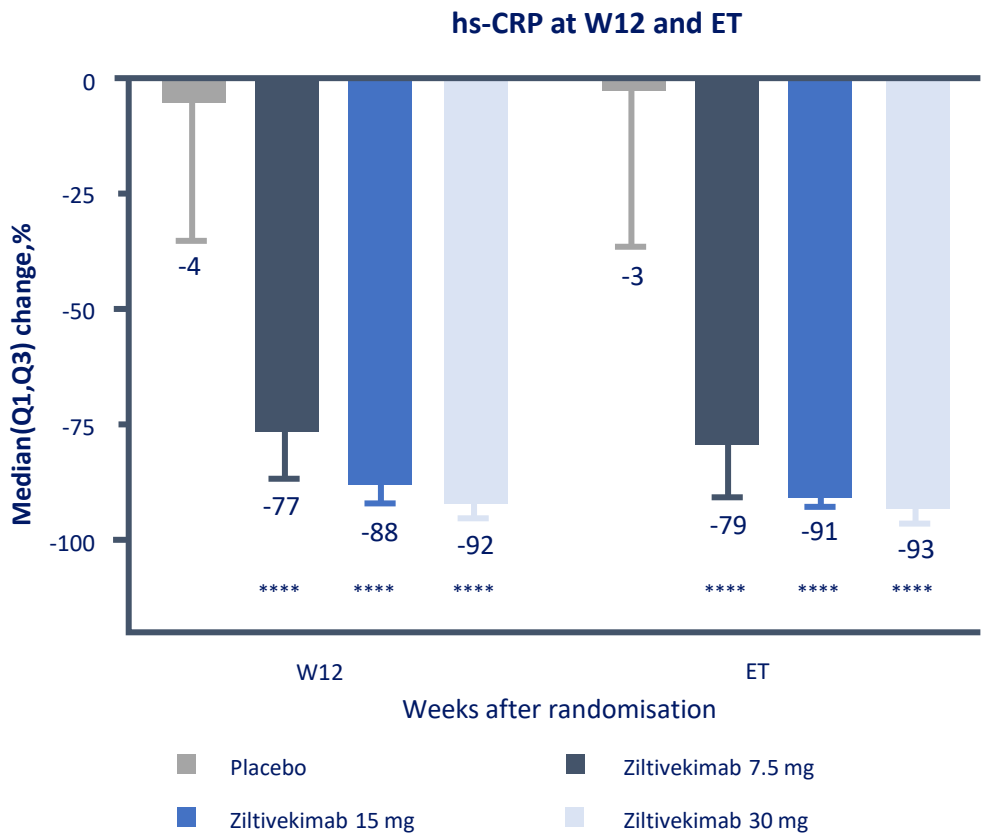
Anti-inflammatory agent administered **once monthly** as a **subcutaneous injection**

Ridker PM et al. Lancet 2021;397:2060–2069.

RESCUE PHASE 2: PRIMARY ENDPOINT
MEDIAN PERCENT CHANGE FROM BASELINE IN HS-CRP



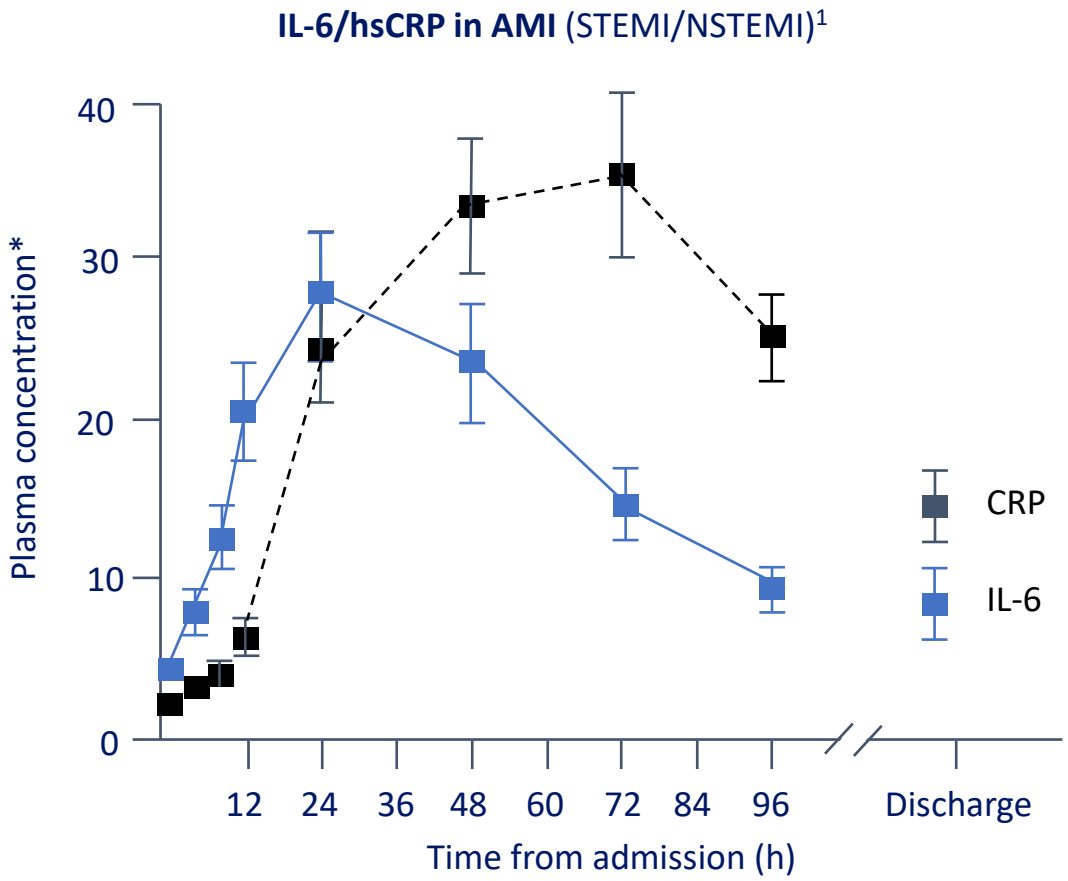
Weeks after randomisation				
Placebo (N)	66	57	31	52
7.5 mg (N)	66	58	32	53
15 mg (N)	66	61	34	55
30 mg (N)	66	57	30	53



At 12 weeks all ziltivekimab groups significantly reduced hs-CRP levels compared to placebo. No difference in rate of infections between ziltivekimab and placebo arm

*Ridker PM, et al. Lancet 2021; 397:2060–9.

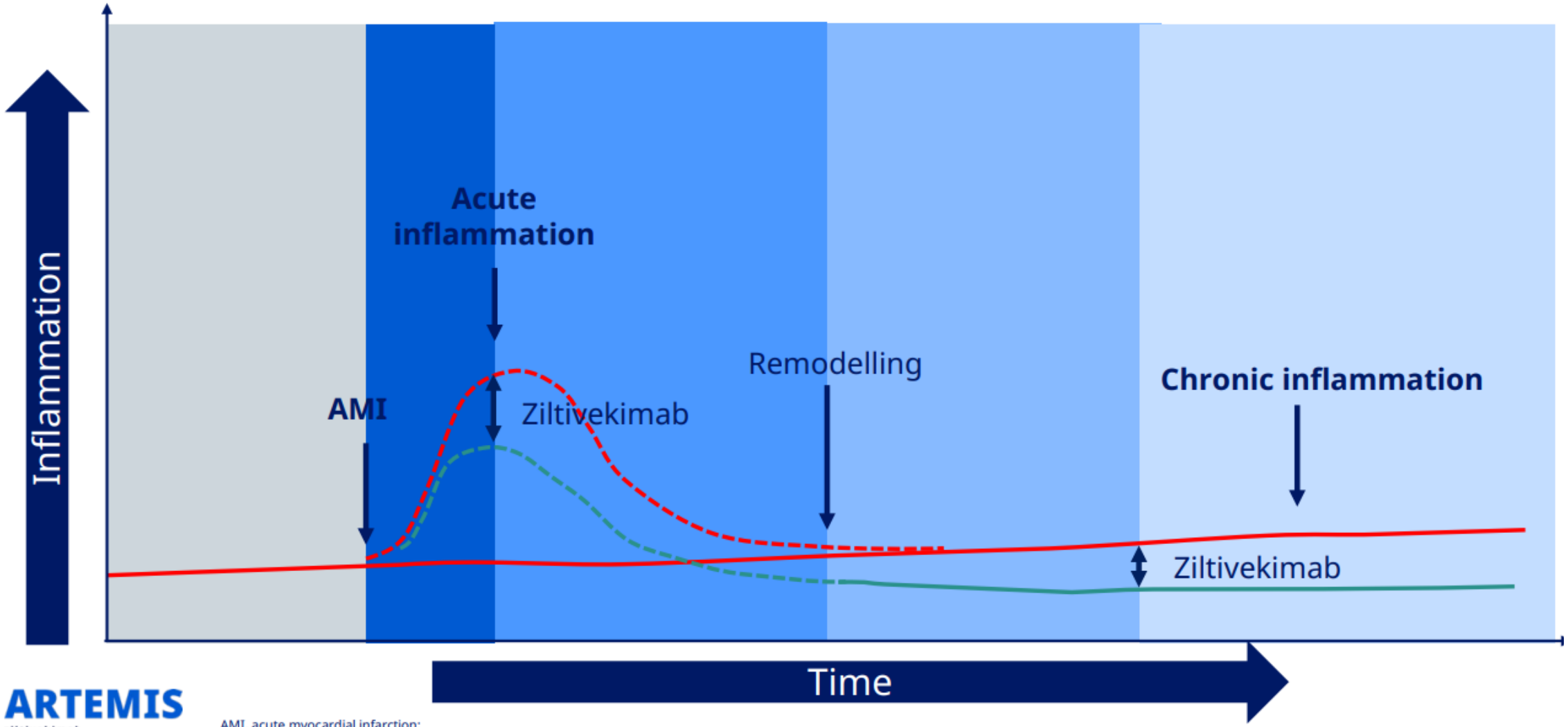
IL-6/HS-CRP IN THE ACUTE SETTING OF AMI/ACS



45 patients with blood drawn at various time intervals from admission to discharge

Gomaraschi M et al. Atherosclerosis. 2009;202(1):304-11.

Concept of ziltivekimab effect in AMI



ARTEMIS
ziltivekimab in patients with acute myocardial infarction

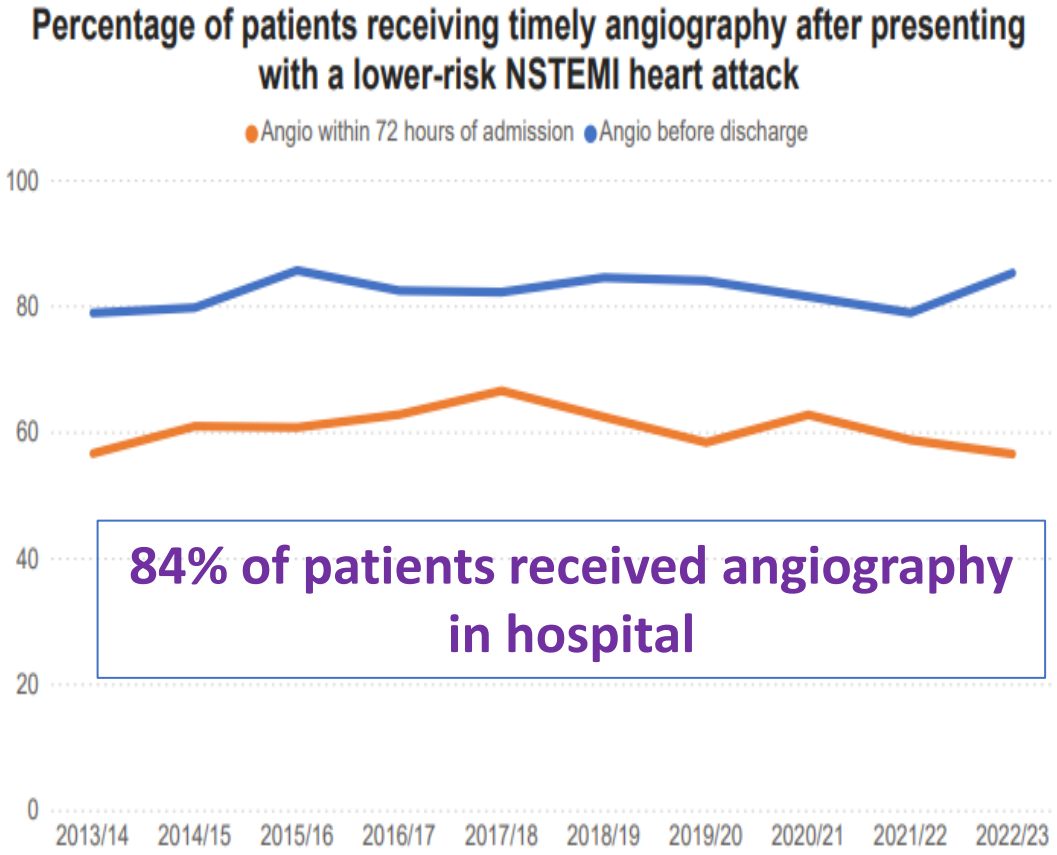
AMI, acute myocardial infarction;

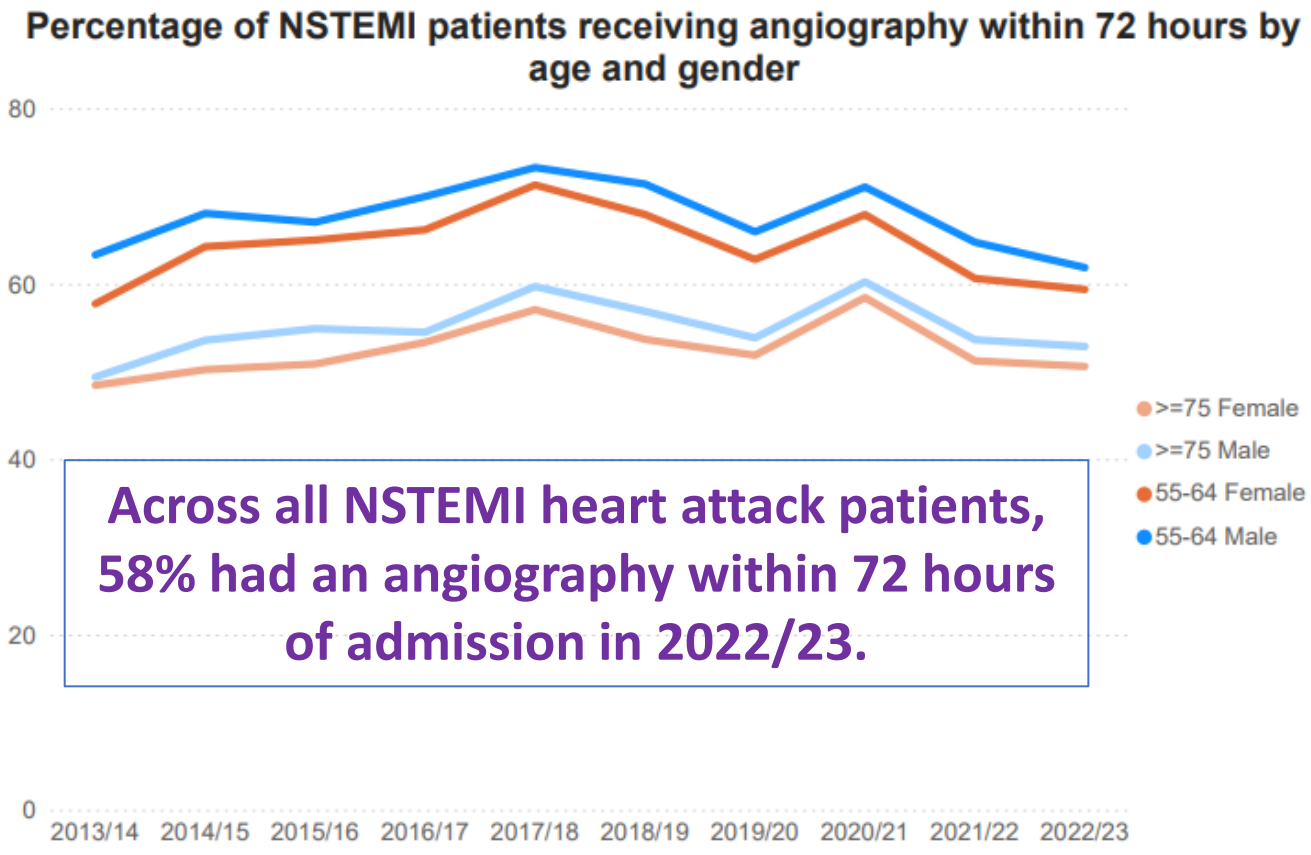
PROCEDURAL CHARACTERISTICS NSTEMI PATIENTS

Angiography performed – no. (%)#	680 (90.3%)
Radial access – no. (%)	607 (89.3%)
Multivessel disease – no. (%)	380 (55.9)
Median days from admission to angiography (IQR)	5 (3, 7)
Median days from randomization to angiography (IQR)	3 (1, 5)
Reason not performed	
Clinical decision – no. (%)	35 (4.6%)
Participant decision – no. (%)	21 (2.8%)
Participant too unwell – no. (%)	13 (1.7%)
Participant died – no. (%)	3 (0.4%)
Not known – no. (%)	1 (0.1%)
Revascularization performed – no. (%)	376 (49.9%)
PCI – no. (%)	351 (46.6%)*
CABG – no. (%)	25 (3.3%)
Median days from admission to PCI (IQR)	5 (3, 7)**
Median days from randomization to PCI (IQR)	2 (1, 4)
Median days from admission to CABG (IQR)	18 (13, 27)

Kunadian V et al. N Engl J Med. 2024 Nov 7;391(18):1673-1684.

UK MINAP: MANAGEMENT OF NSTEMI





ARTEMIS: Study design (Phase 3)

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

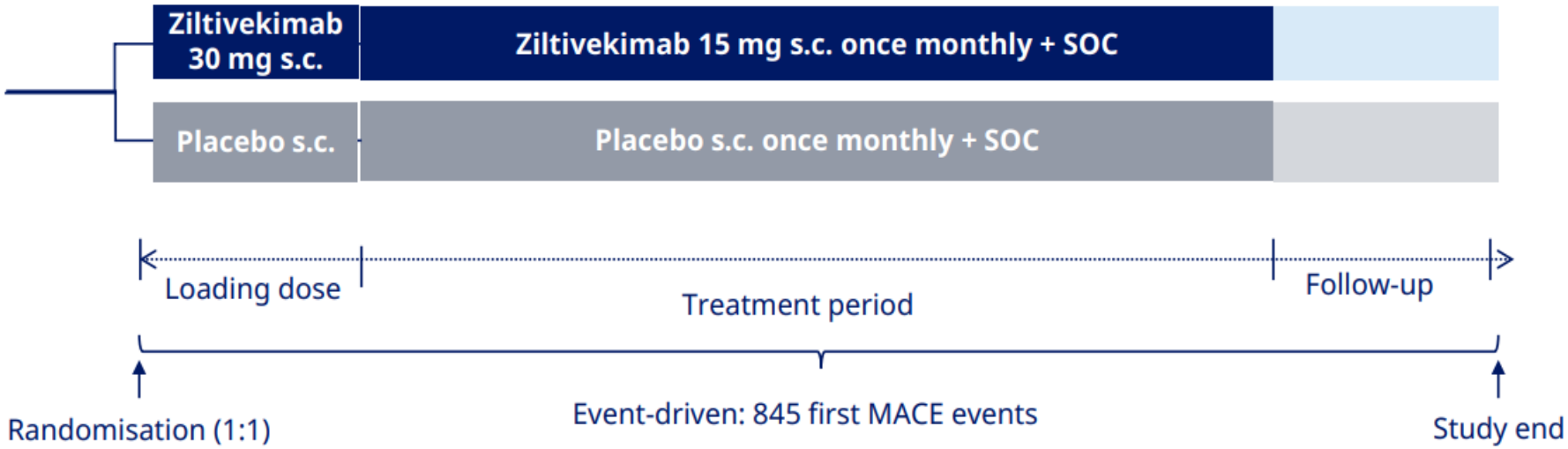
10,000 patients

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



Study 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 (nf) 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

Advancing the access to cardiovascular diagnosis and treatment among women with cardiovascular disease

A joint British Cardiovascular Societies' consensus document

Professor Vijay Kunadian

Consensus Document Chair and Lead

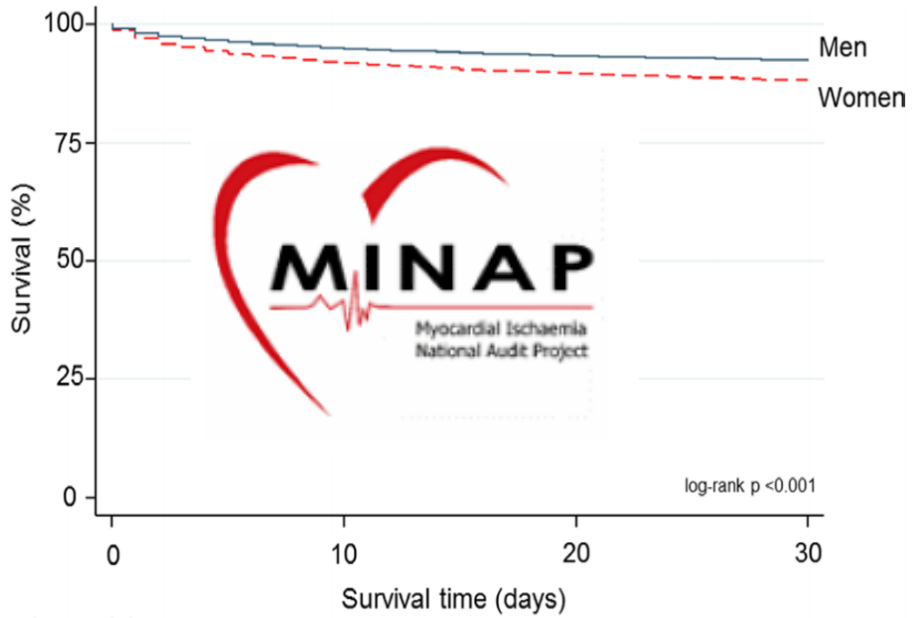
Personal Chair and Clinical Professor of Interventional Cardiology
Honorary Academic Consultant Interventional Cardiologist
Newcastle upon Tyne, United Kingdom

British Cardiovascular Society

Tayal U…..Kunadian V. Heart. 2024 Oct 28;110(22):e4

Higher mortality among women after MI and PCI

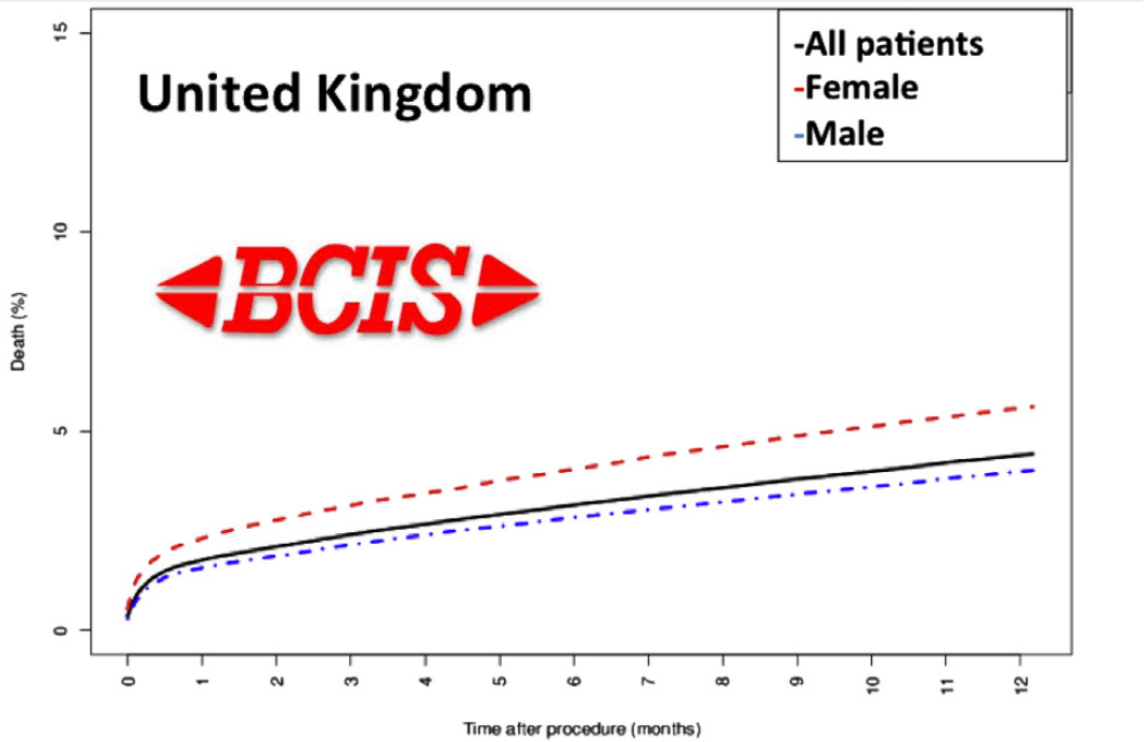
MINAP



Total number at risk

Women	238,489	219,810	213,910	210,335
Men	452,801	430,472	422,909	418,527

Thirty-day GRACE risk score adjusted mortality was higher among women than men (mean 9.9% vs 6.3%, p <0.001)
Wilkinson et al. Heart 2019;105:516–523

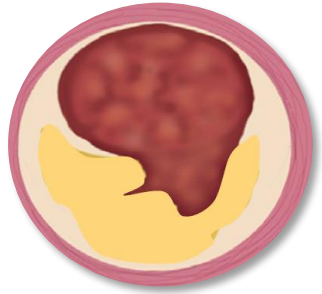


No. at risk	0 months	1 month	6 months	12 months
Female	85546	83586	82095	80744
Male	245913	242070	238954	236035

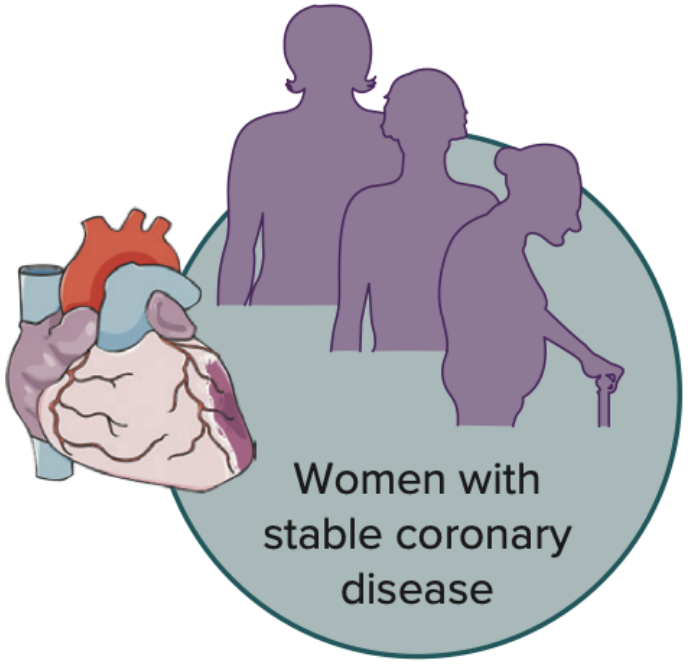
Women compared with men continue to experience higher all-cause mortality after PCI for coronary artery disease
Kunadian et al. Am J Cardiology 2017 Jan 15;119(2):210-216

CORONARY ARTERY DISEASE IN WOMEN

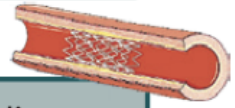
- Women presenting with obstructive CAD are older and have more comorbidities than men
- Women less likely to be referred for diagnostic assessment
- Sex differences in the plaque extent and composition detected in patients <65 years
- More complications and bleeding risk following NSTEMI in women
- ANOCA/INOCA more frequent among women compared to men
- MINOCA disproportionately affects women



Worse outcomes in women with ACS compared to men persist after adjustment for age and comorbidities



Women, more frequently than men, have:
- PCI via femoral access
- Procedure-related bleeding complications
- Treatment with bare metal stents

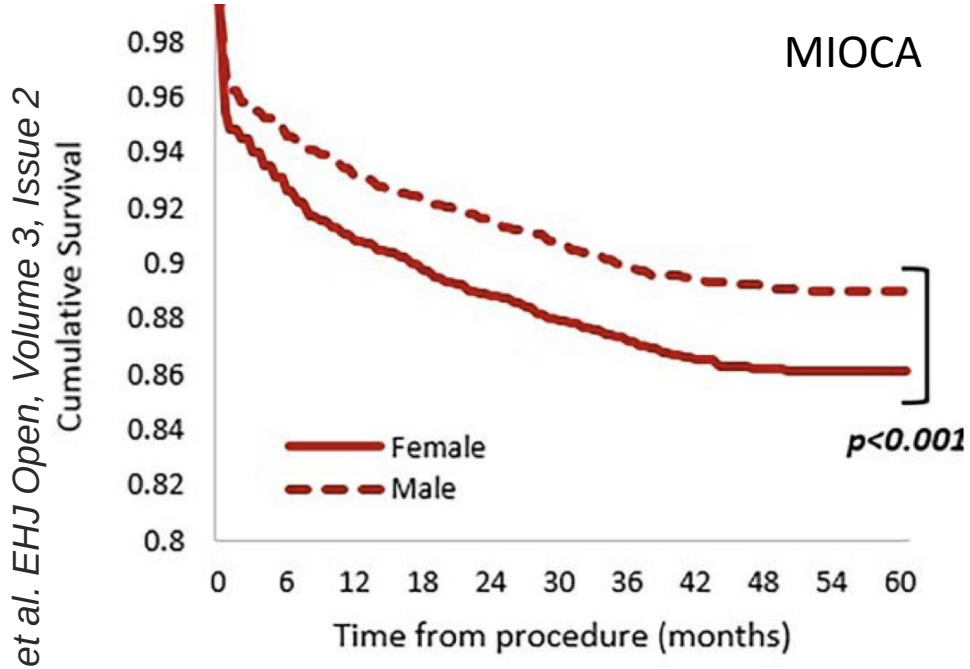


Women less often receive guideline-recommended treatment for angina

Women have a higher risk than men of short- and long-term adverse events

Sambola A., et al. Eur Cardiol. 2023 Mar 2;18:e06.

MIOCA



Lawless M, et al. EHJ Open, Volume 3, Issue 2

Number at risk, MIOCA

Months	6	12	18	24	30	36	42	48	54	60
Females	3296	3231	3193	3159	3102	2698	2249	1962	1657	685
Males	7760	7639	7571	7502	7345	6312	5309	4617	3861	1609

Sex differences in treatment and outcomes among myocardial infarction patients presenting with and without obstructive coronary arteries

Table 4 Discharge medications and sex differences stratified by diagnosis

	MIOCA				*P*-value	MINOCA				*P*-value
	Male		Female			Male		Female		
	n = 7826		*n* = 3383			*n* = 678		*n* = 543		
Discharge medication										
ACEi/ARB, *n* (%)	7171	(91.2)	2939	(86.9)	<0.001	377	(55.6)	313	(57.6)	0.475
Aldosterone antagonist, *n* (%)	586	(7.5)	196	(5.8)	0.002	44	(6.5)	22	(4.1)	0.061
Aspirin, *n* (%)	7548	(96.0)	3176	(93.9)	<0.001	316	(46.6)	212	(39.0)	0.008
Beta-blocker, *n* (%)	7016	(89.2)	2956	(87.4)	0.004	381	(56.2)	290	(53.4)	0.331
Clopidogrel/prasugrel, *n* (%)	4217	(53.6)	1655	(48.9)	<0.001	120	(17.7)	81	(14.9)	0.193
Ticagrelor, *n* (%)	3246	(41.3)	1477	(43.7)	0.019	42	(6.2)	31	(5.7)	0.722
Statin, *n* (%)	7448	(94.7)	3114	(92.0)	<0.001	411	(60.6)	315	(58.0)	0.356

MIOCA, myocardial infarction with obstructive coronary arteries; MINOCA, myocardial infarction with non-obstructive coronary arteries; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Lawless, Kunadian et al. Eur Heart J Open. 2023 Mar 27;3(2):oead033

Sex differences in treatment and outcomes among myocardial infarction patients presenting with and without obstructive coronary arteries

Table 5 Follow-up and outcomes and sex differences stratified by diagnosis

	MIOCA				*P*-value	MINOCA				*P*-value
	Male		Female			Male		Female		
	n = 8203		*n* = 3558			*n* = 795		*n* = 644		
Follow-up										
Mean, *years (SEM)*	4.79	(0.02)	4.82	(0.02)	0.303	4.64	(0.05)	4.62	(0.06)	0.779
Median, *years (SD)*	4.71	(1.48)	4.8	(1.48)	0.190	4.48	(1.39)	4.52	(1.40)	0.773
Emergency first readmission[a]										
One-year, *n* (%)	465	(5.7)	207	(5.8)	0.749	40	(5.0)	27	(4.2)	0.453
Long-term, *n* (%)	1020	(12.4)	450	(12.6)	0.748	80	(10.1)	51	(7.9)	0.160
Mortality rate										
One-year, *n* (%)	564	(6.9)	327	(9.2)	<0.001	60	(7.5)	42	(6.5)	0.451
Long-term, *n* (%)	915	(11.2)	505	(14.2)	<0.001	81	(10.2)	70	(10.9)	0.970

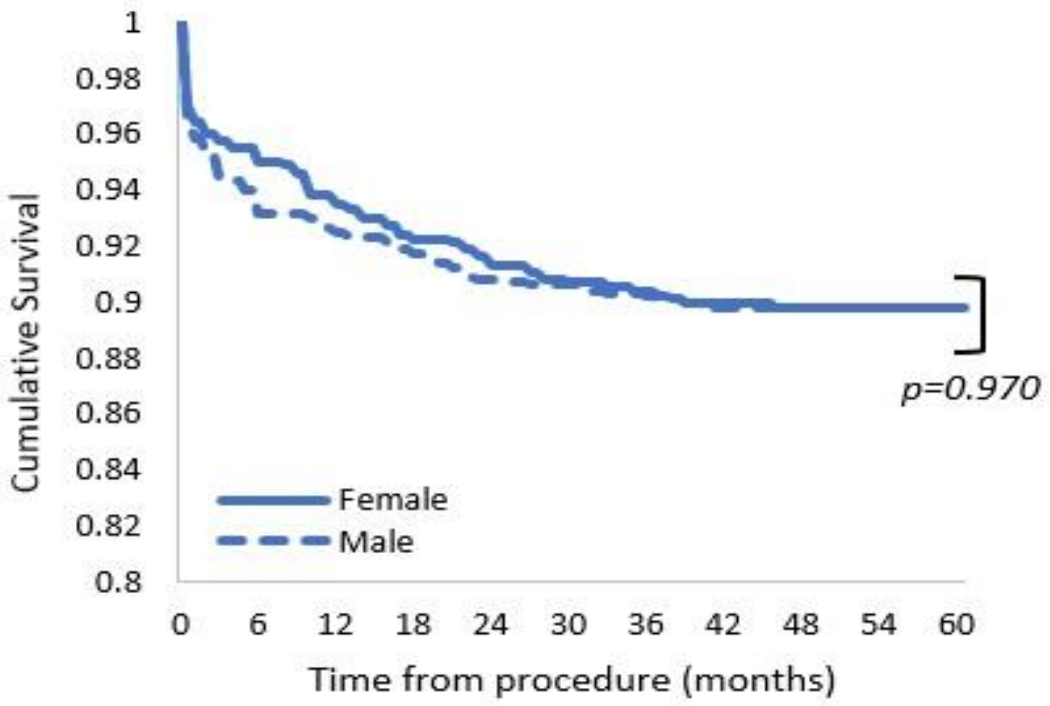
MIOCA, myocardial infarction with obstructive coronary arteries; MINOCA, myocardial infarction with non-obstructive coronary arteries; SEM, standard error of the mean; SD, standard deviation.

[a]For heart failure and myocardial infarction.

Lawless, Kunadian et al. Eur Heart J Open. 2023 Mar 27;3(2):oead033

Sex differences in treatment and outcomes among myocardial infarction patients presenting with and without obstructive coronary arteries

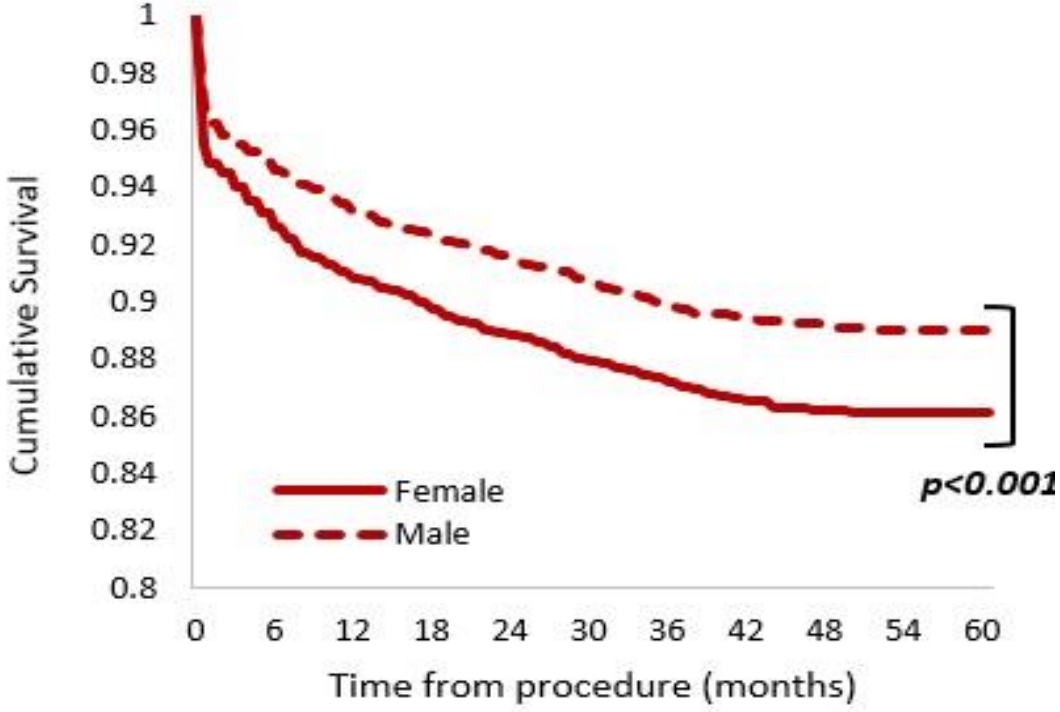
A.1) MINOCA



Number at risk, MINOCA

Months	6	12	18	24	30	36	42	48	54	60
Females	612	602	594	588	576.5	501	419.5	333	273	98
Males	740	735	729	722	714	621	533	447	351	139

A.2) MIOCA



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Lawless, Kunadian et al. Eur Heart J Open. 2023 Mar 27;3(2):oead033

DISEASE CONDITION	ACTIONABLE POINTS
Traditional CV risk factors	⇒Raise awareness of the suboptimal control of some of the traditional CV risk factors in women to proactively identify any untreated risk factor in the early stage ⇒Promote awareness campaigns among premenopausal women to proactively seek support to address modifiable CV risk factors
Women specific risk factors	⇒Raise awareness among public and clinicians about the link between female specific risk factors and CVD ⇒Determine how to integrate reproductive life course events into personalised CV care to improve risk prediction for women ⇒Investigation of specific subsets such as pregnant, pre- or post-menopausal women through dedicated study protocols in collaboration with other specialties such as obstetrics and/or gynaecologists
Coronary artery disease	⇒Increase awareness among public and clinicians that CAD is the leading cause of mortality for women. ⇒Avoid delays in access to care in the setting of ACS. ⇒Provide a complete diagnostic work-up in case of non-obstructive coronary arteries (MINOCA, ANOCA, INOCA which occur more frequently in women) to investigate the underlying mechanism and direct medical therapy. ⇒Proactively enrol female patients with CAD in research studies and undertake women-only studies.

Tayal U…..Kunadian V. Heart. 2024 Oct 28;110(22):e4

2024 ESC CCS Guidelines

ANOCA/INOCA

Diagnosis and Management

Professor Vijay Kunadian

MBBS, MD, MRCP, FRCP, FACC, FESC, PG Dip (Clinical Trials)

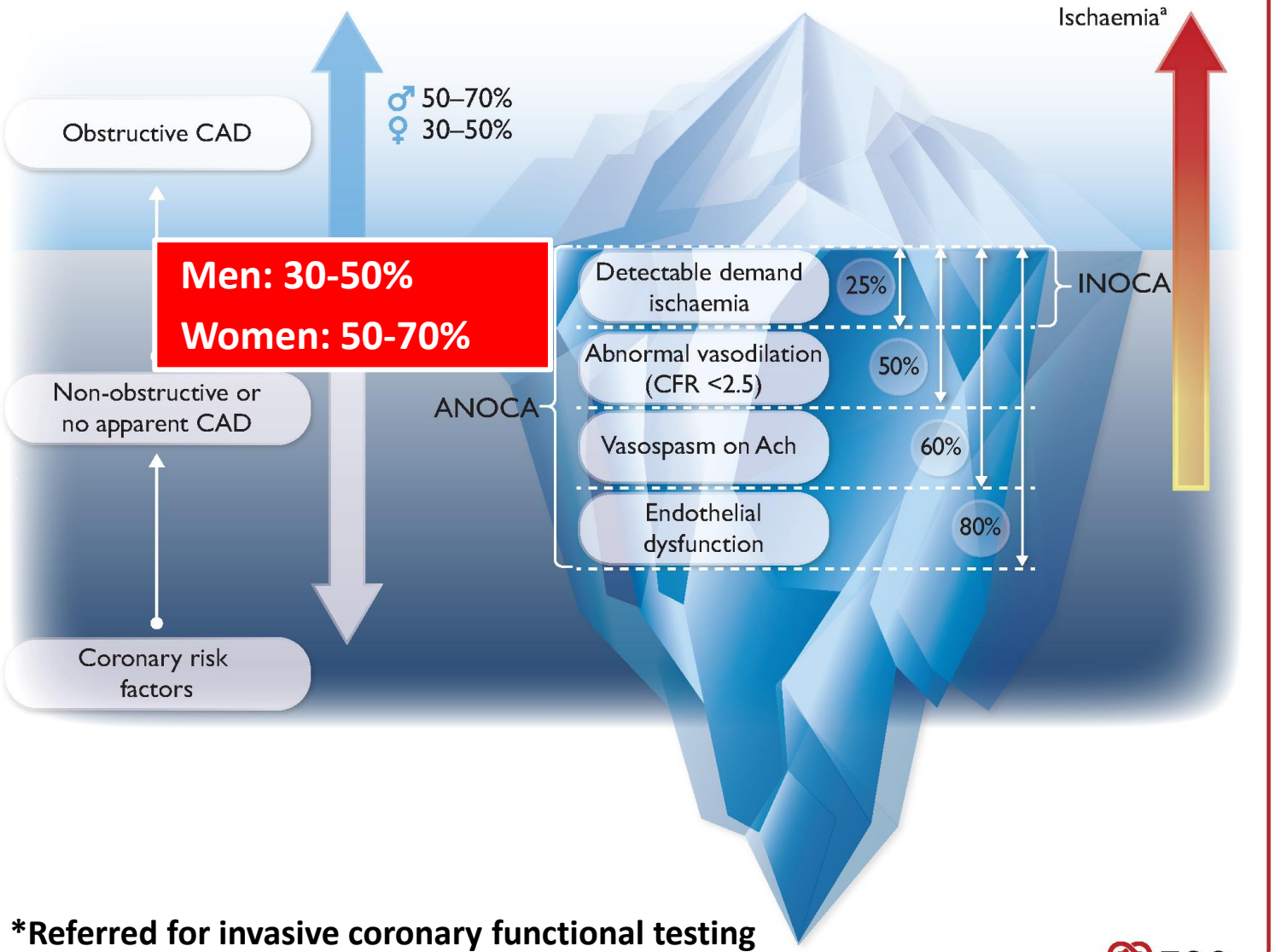
Personal Chair and Clinical Professor of Interventional Cardiology
Honorary Academic Consultant Interventional Cardiologist
Newcastle upon Tyne, United Kingdom

ANOCA/INOCA

- ANOCA: Angina with non-obstructive coronary arteries

- INOCA: Ischaemia with non-obstructive coronary arteries

Figure 12: PREVALENCE OF ANOCA/INOCA*

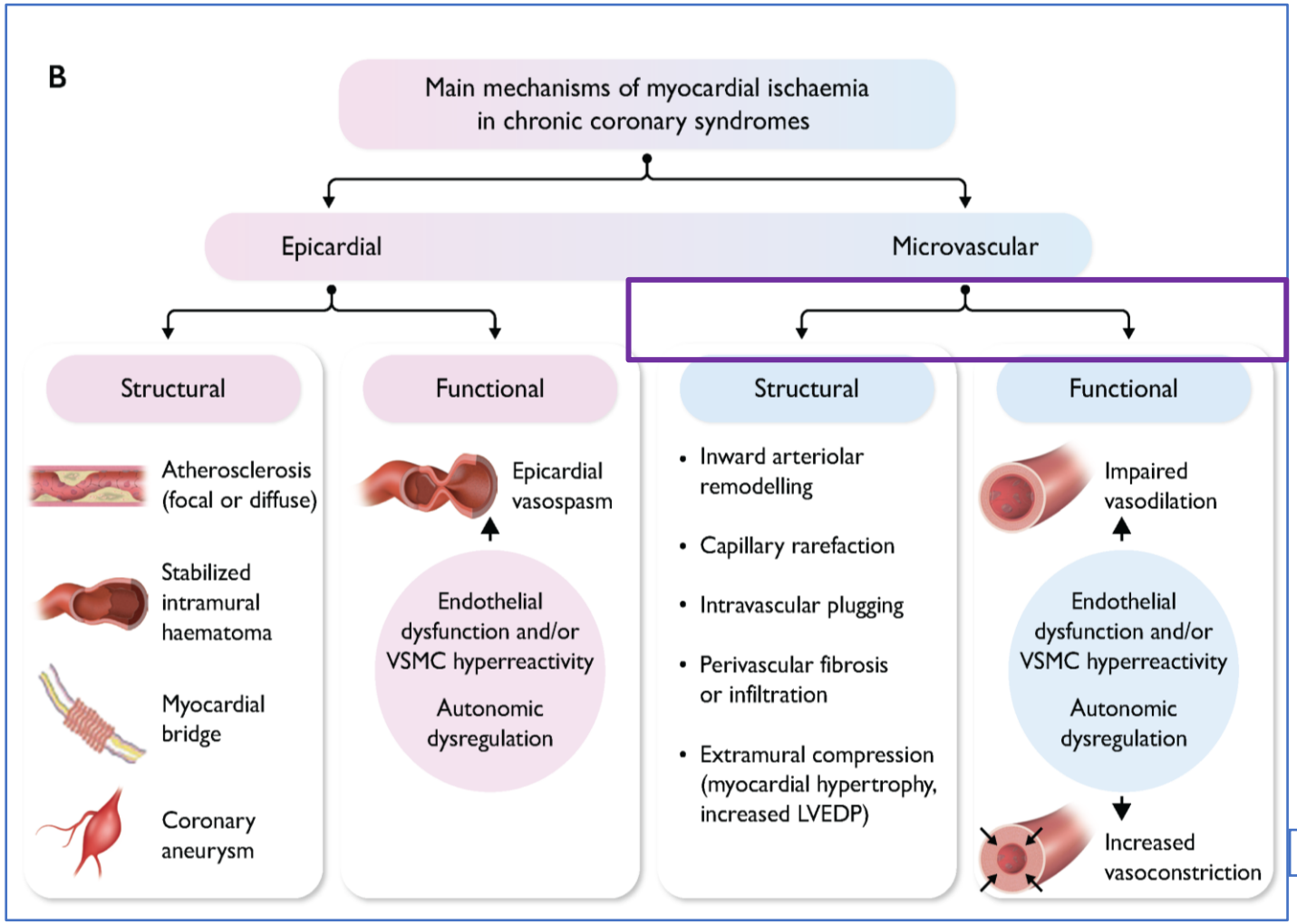


*Referred for invasive coronary functional testing

Among ANOCA patients:

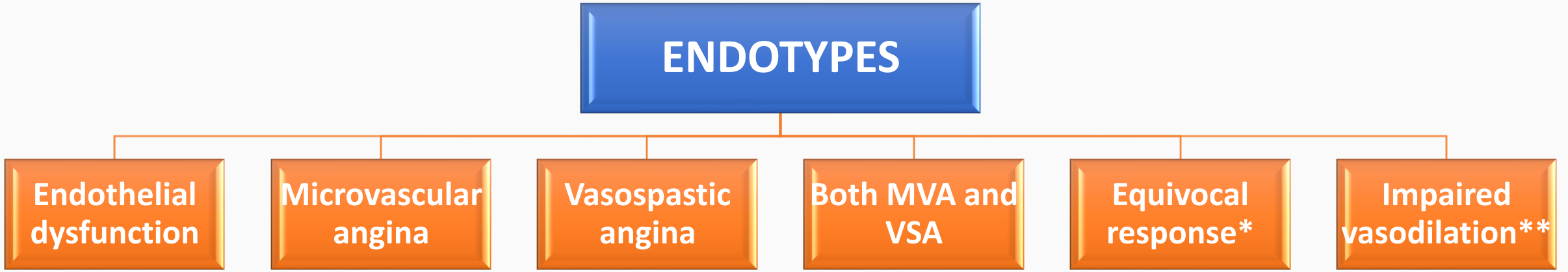
✓ Endothelial dysfunction	80%
✓ Vasospasm	60%
✓ Abnormal vasodilation	50%
✓ Ischaemia, INOCA	25%

FIGURE 1: MECHANISMS OF MYOCARDIAL ISCHAEMIA



Coronary microvascular dysfunction (CMD) is functional part of microvacular disease, that is impaired vasodilation and/or increased vasoconstriction.

ANOCA/INOCA ENDOTYPES



***Equivocal response- Angina without fulfilling criteria for MVA/VSA**

****Impaired vasodilation (low coronary flow reserve and/or high microvascular resistance)**

MVA-microvascular angina; VSA-vasospastic angina

ANOCA/INOCA: THE CONSEQUENCES…

- ANOCA/INOCA are rarely correctly diagnosed
- No tailored therapy is prescribed for these patients
- Patients continue to experience recurrent angina with impaired quality of life
- Repeated hospitalizations, coronary angiographies, adverse CV outcomes in the short and long term
- Paradoxical reassurance by the treating physician
- Physician may even refute the underlying symptoms

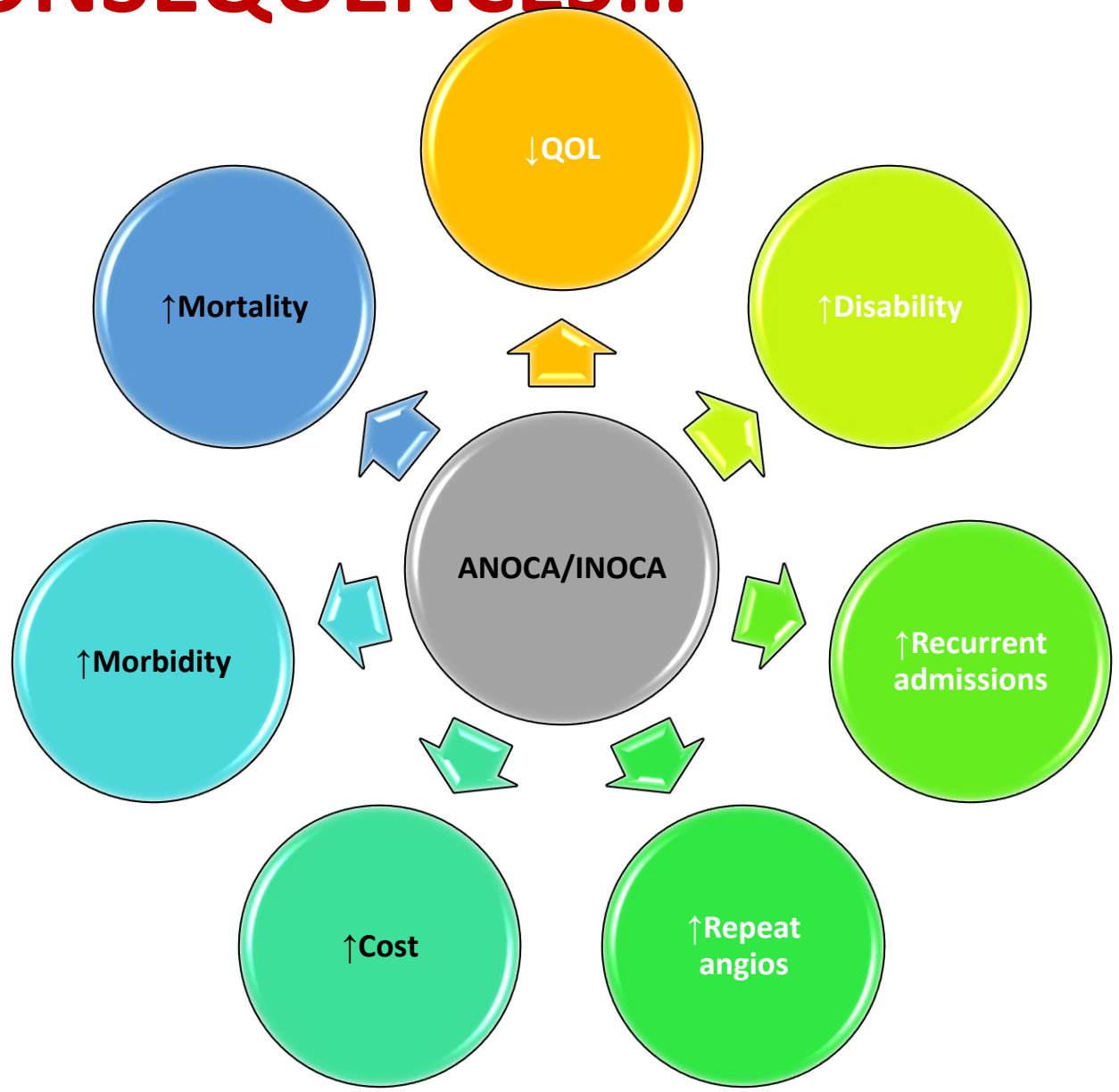


Figure 3: SYMPTOMS

Patients present with a wide spectrum of symptoms and signs

Patients may present with symptoms like angina occurring with obstructive CAD

Patients can also present with other symptoms such as breathlessness, pain between the shoulder blades, indigestion, nausea, extreme fatigue, weakness, vomiting and/or sleep disturbances.

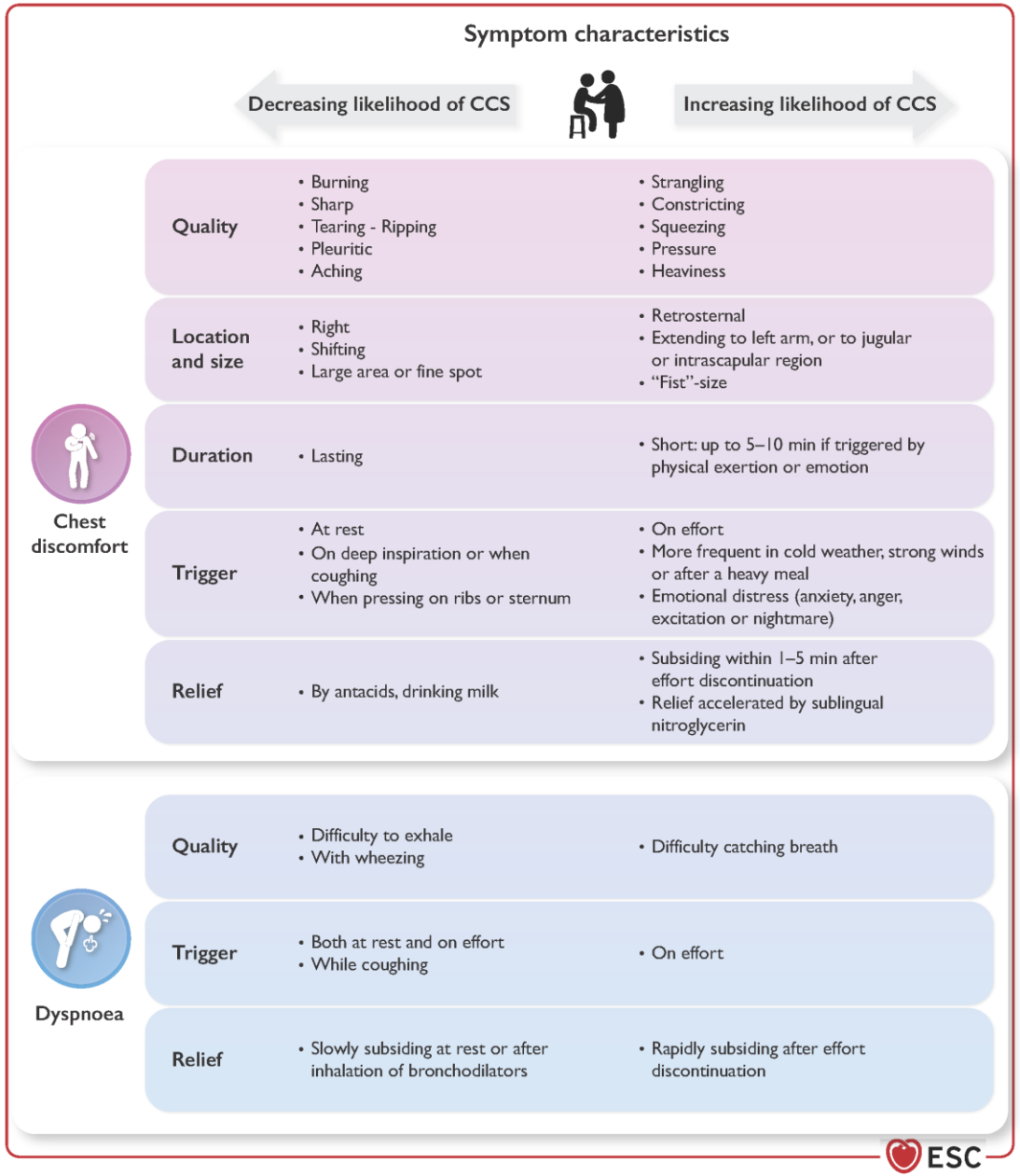
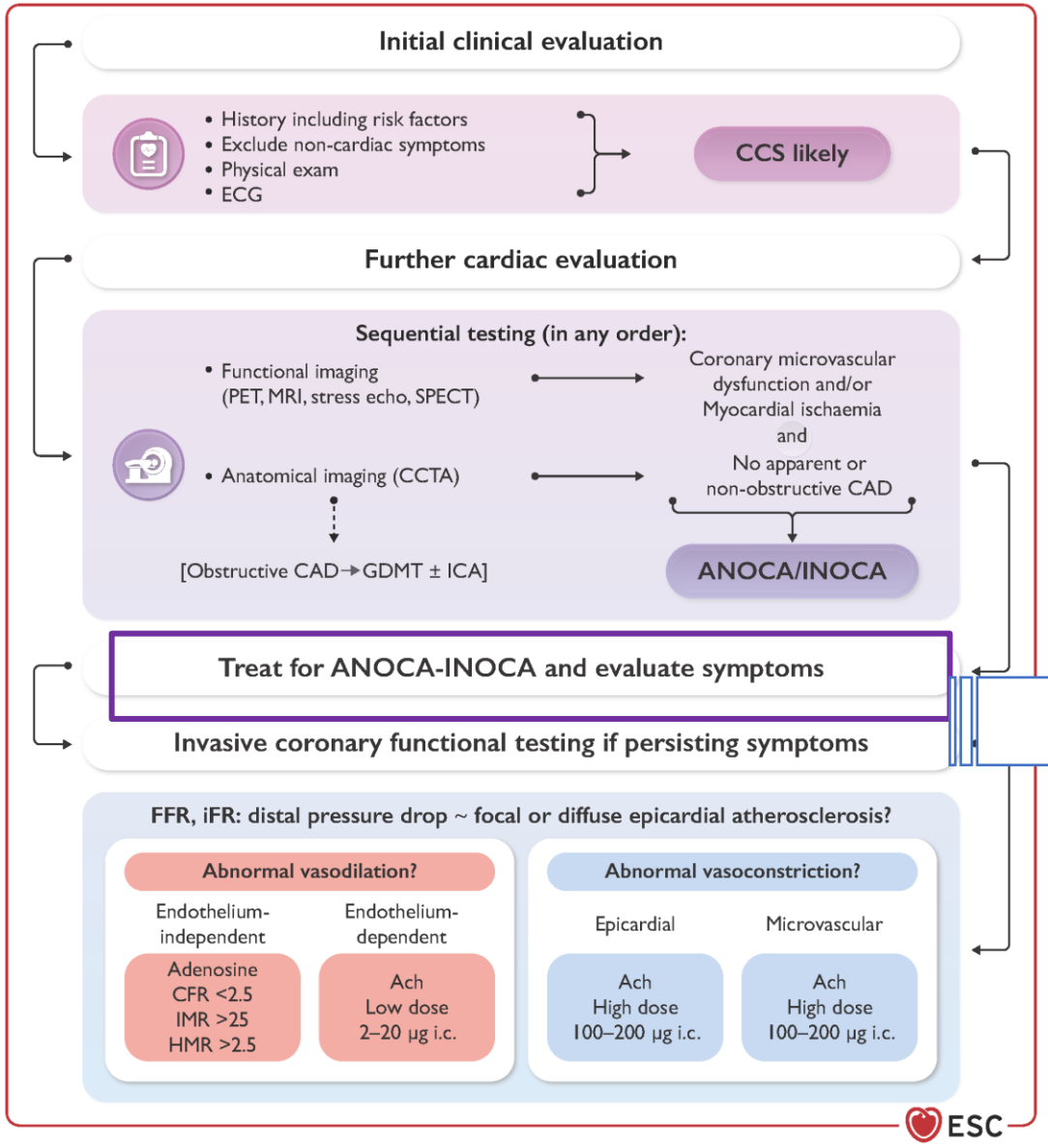


Figure 13: Diagnostic algorithm



Initial Clinical Evaluation

Non-invasive evaluation

Persisting symptoms

Invasive coronary functional testing (ICFT)

CONCLUSION

- There is still **high residual risk post MI** despite guideline recommended therapy
- **Inflammation** plays a key role in initiation, progression and destabilization of atherosclerotic plaque
- **Persistent inflammation post AMI** is associated with an increased risk of future CV events independent of traditional risk factors
- Clinical trial evidence of canakinumab and tocilizumab support investigation of **NLRP3 inflammasome pathway inhibition** in AMI
- The cytokine **IL-6 modulates inflammation** in AMI
- We await ongoing phase 3 trials of IL-6 inhibition

Thank you for your attention…..