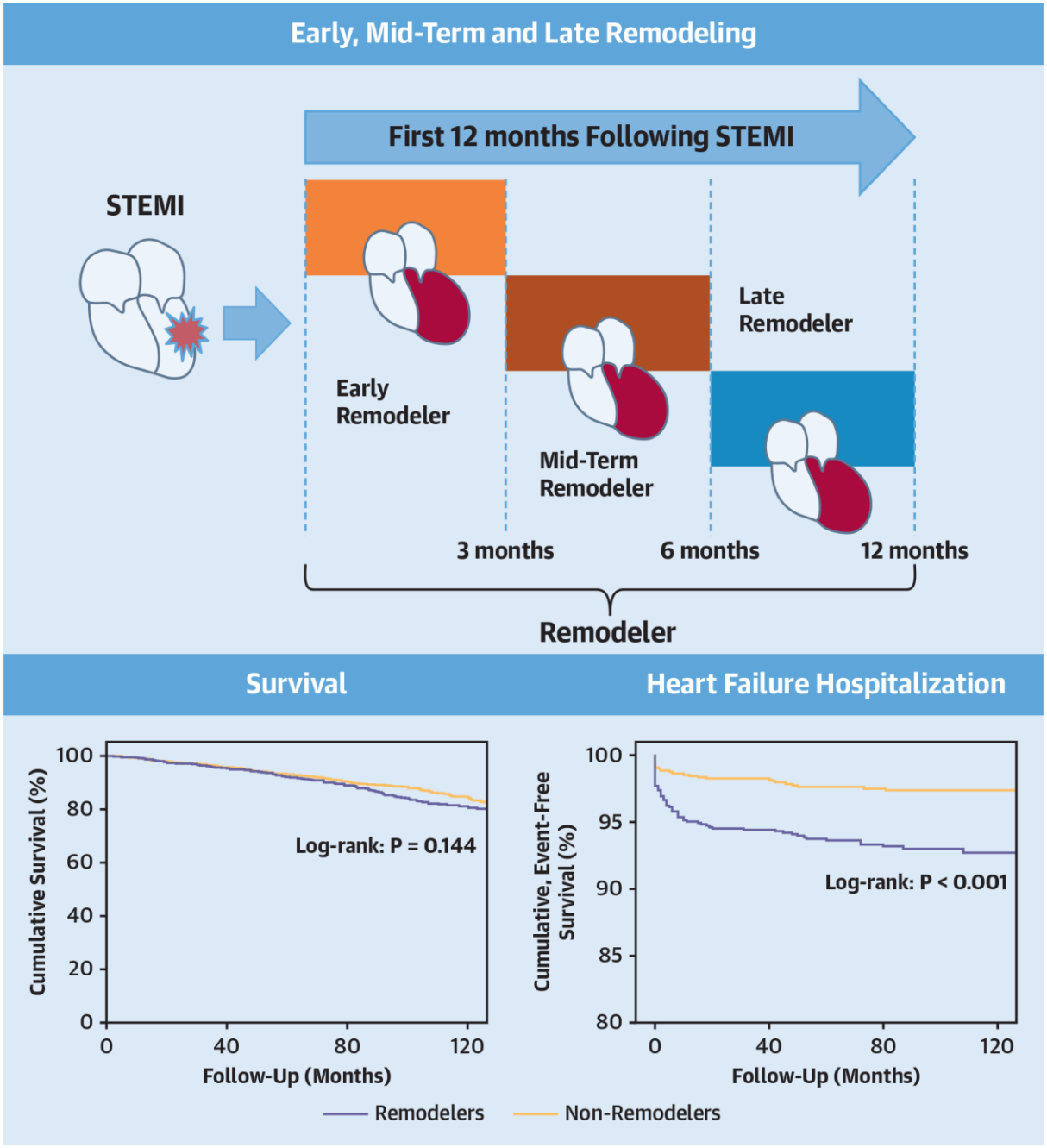
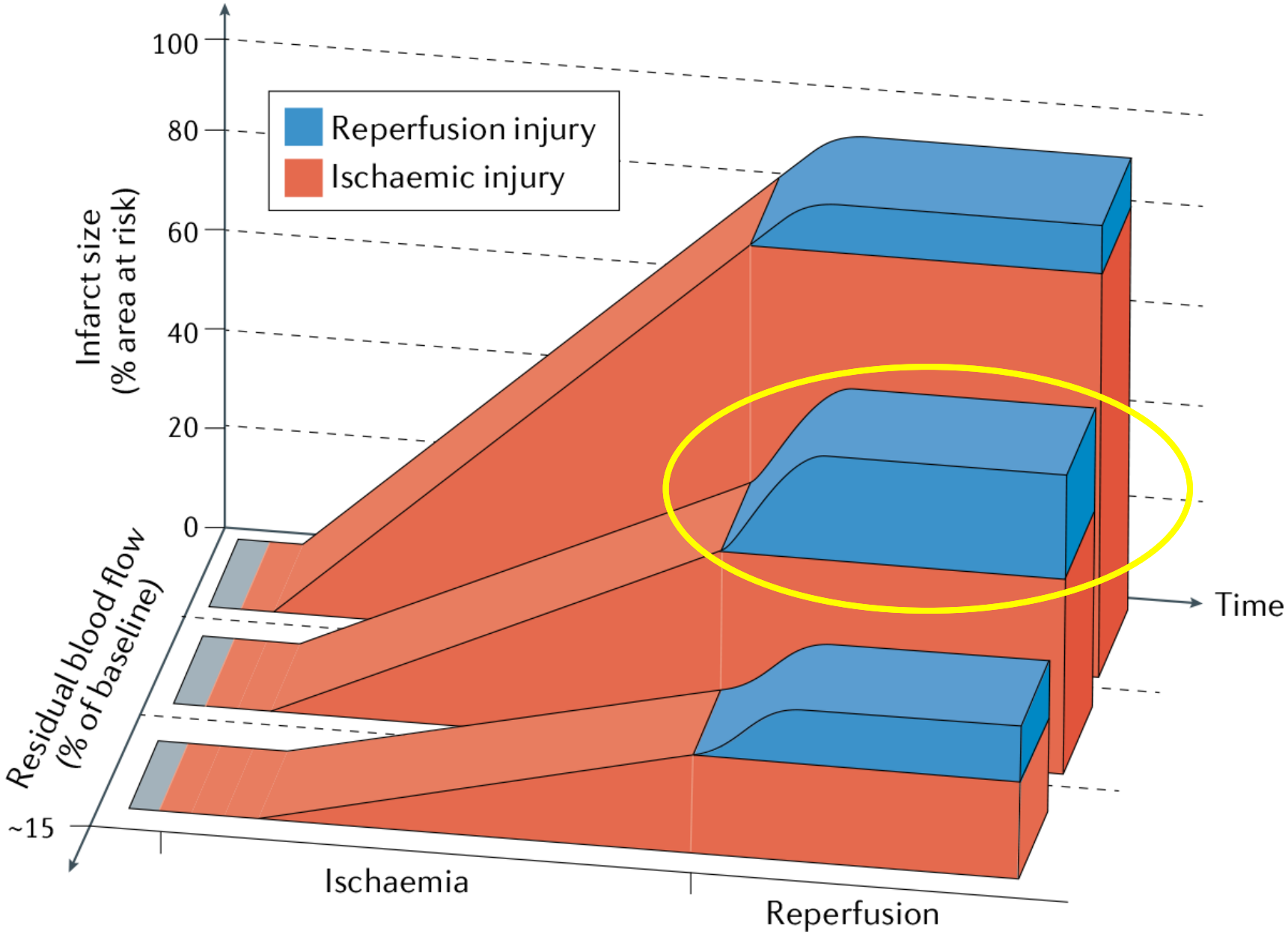
Strategie terapeutiche contro il danno da riperfusione: quali nuove prospettive?

Alessandro Bellis, MD PhD

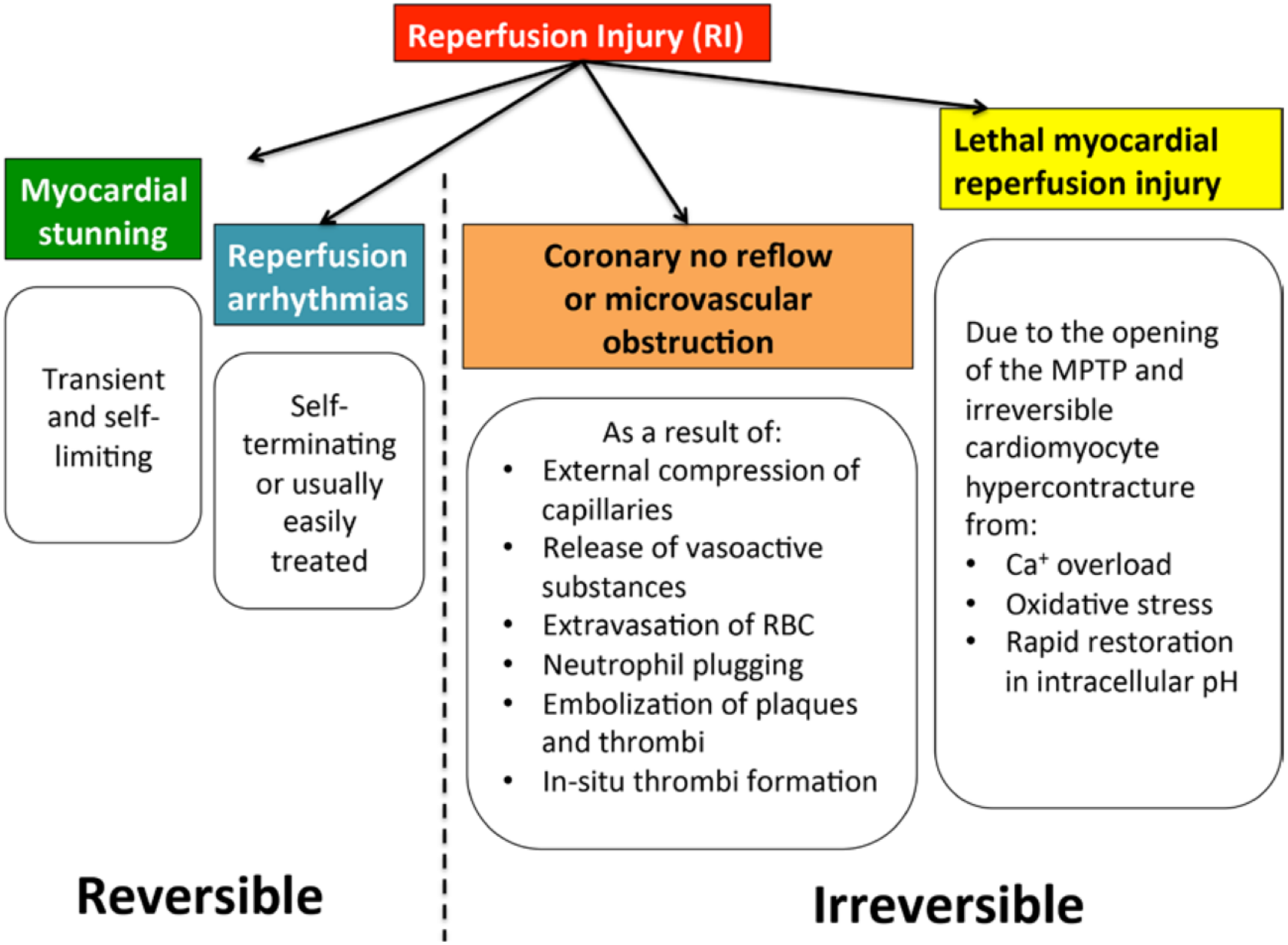
UTIC con Emodinamica
A.O.R.N. Antonio Cardarelli - Napoli



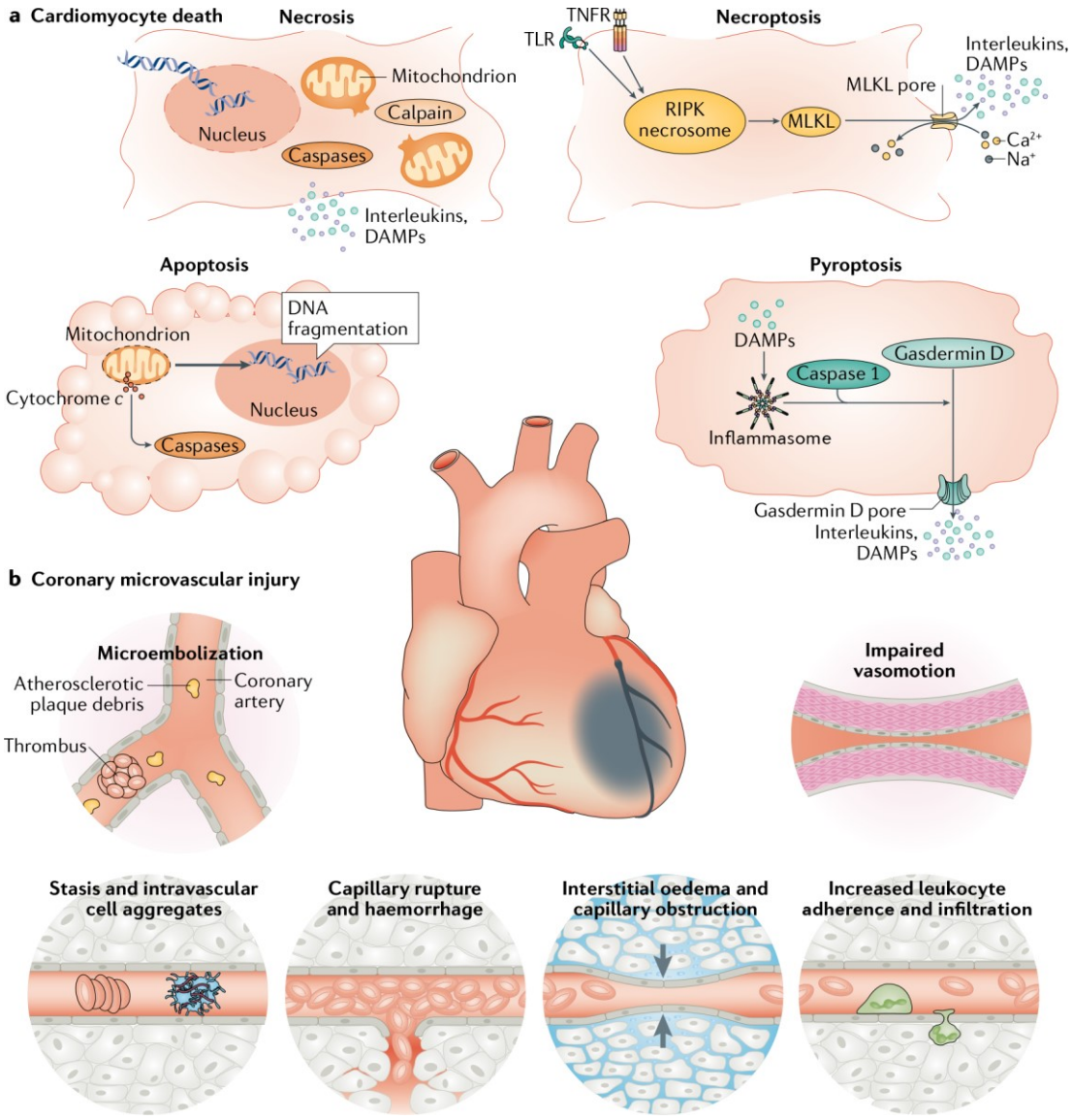
Van der Bijl P et al. JACC Heart Fail 8(2): 131-140.



Heusch G. Nat. Rev. Cardiol. 2020.



Bulluck H et al. Circ Cardiovasc Interv. 2017;10:e004373.



Heusch G. Nat. Rev. Cardiol. 2020.

ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–107
https://doi.org/10.1093/eurheartj/ehad191

2023 ESC Guidelines for the management of acute coronary syndromes

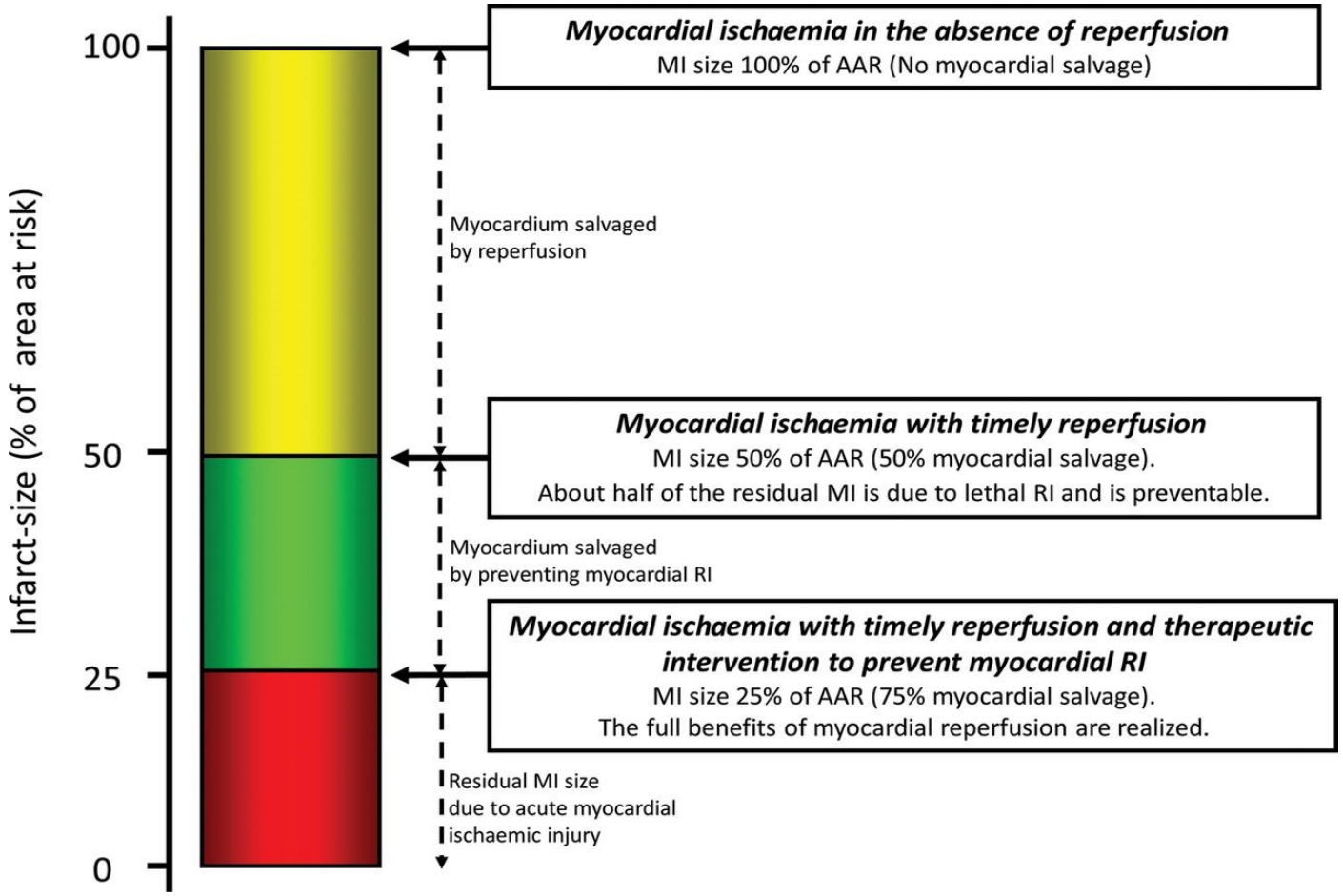
9.1.5.2. Interventions to protect the microcirculation

The damage inflicted on the myocardium during AMI is the result of ischaemia and subsequent reperfusion (ischaemia/reperfusion injury). In patient-level pooled analyses, infarct size and MVO are independent predictors of long-term mortality and HF in survivors of STEMI.[436,478] Strategies to reduce ischaemia/reperfusion injury in general (and MVO in particular) remain an unmet clinical need. Further information regarding interventions to protect the microcirculation that are under clinical or experimental investigation is presented in the Supplementary data online.

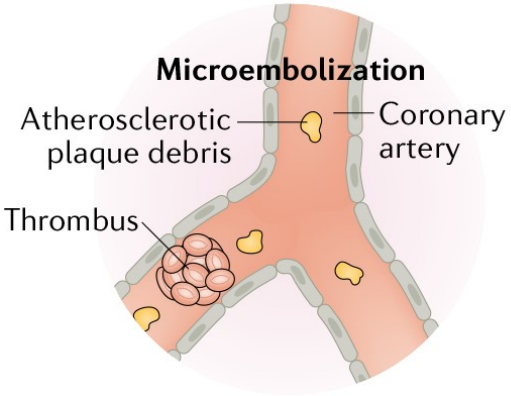
European Heart Journal (2013) **34**, 1714–1724
doi:10.1093/eurheartj/eht090

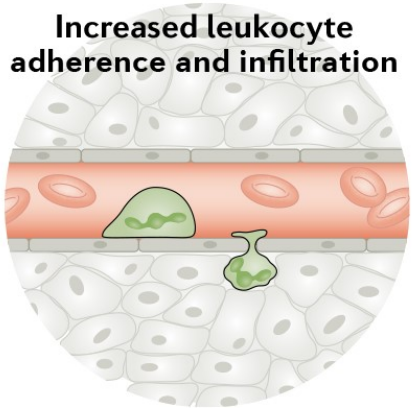
Novel therapeutic concepts

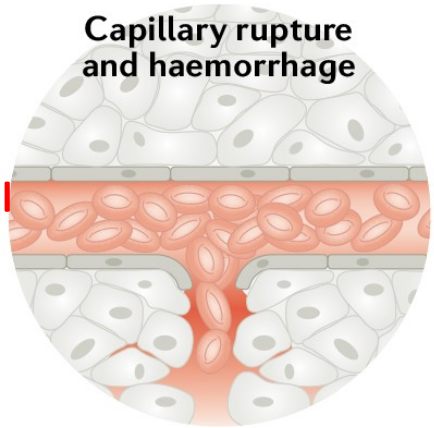
Myocardial reperfusion injury: looking beyond primary PCI

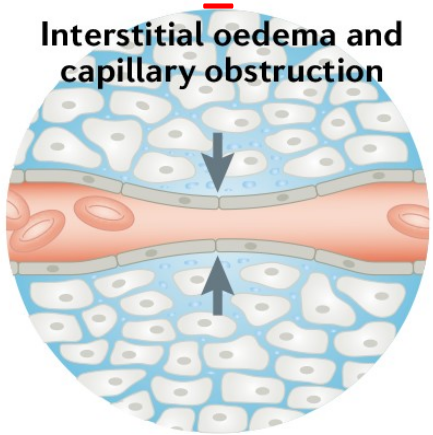


Frohlic GM et al. EHJ 2013, 34 (23): 1714–1722.



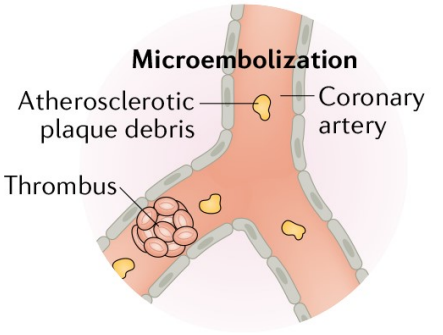






New Therapeutic Strategies against Myocardial-Reperfusion Injury

Circulation

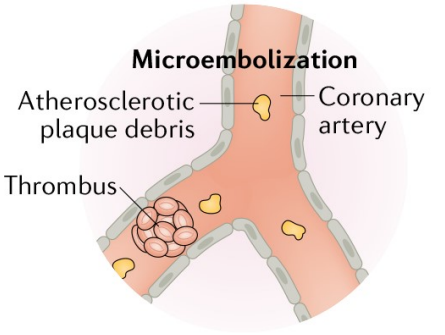


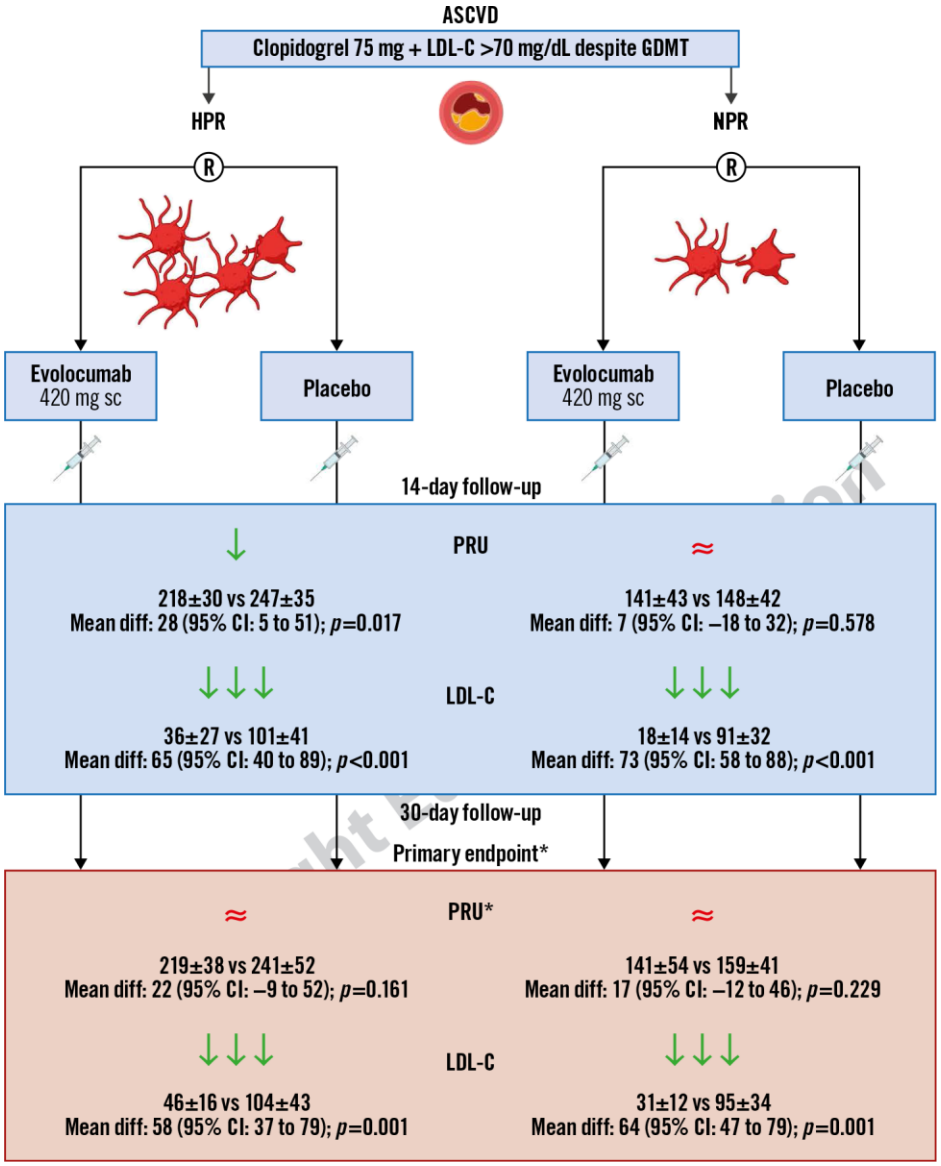
ORIGINAL RESEARCH ARTICLE

PCSK9 (Proprotein Convertase Subtilisin/Kexin 9) Enhances Platelet Activation, Thrombosis, and Myocardial Infarct Expansion by Binding to Platelet CD36

Qi Z et al. Circulation. 2021 Jan 5;143(1):45-61.

Impact of evolocumab on the pharmacodynamic profiles of clopidogrel in patients with atherosclerotic cardiovascular disease: a randomised, double-blind, placebo-controlled study

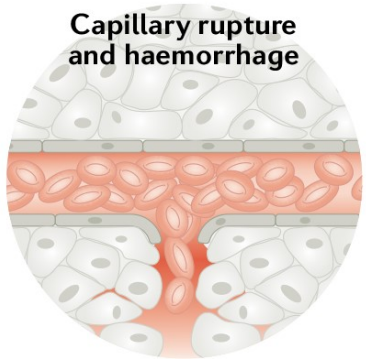




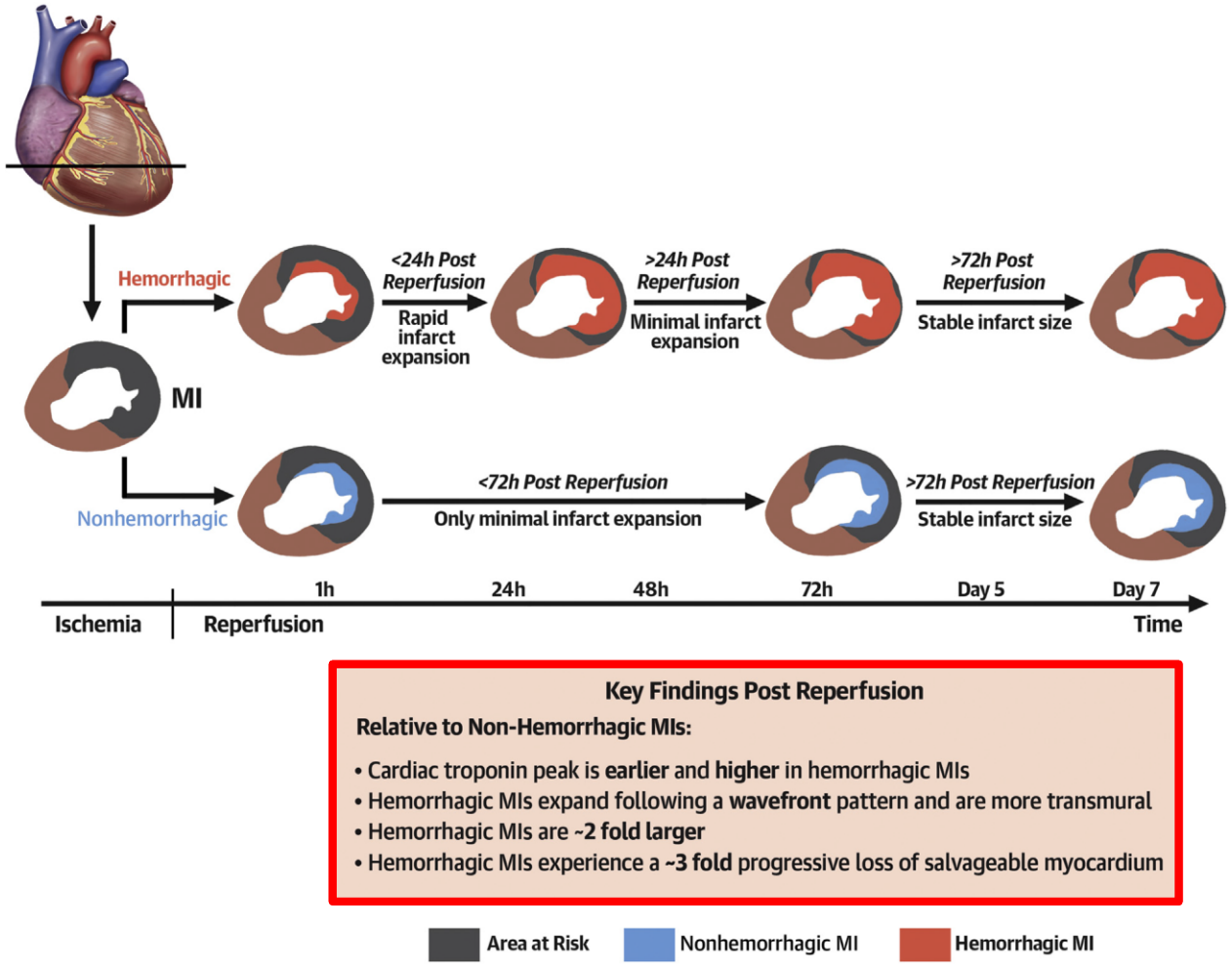
Franchi F et al. EuroIntervention. 2023;18:1254–1265.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 79, NO. 1, 2022

PUBLISHED BY ELSEVIER

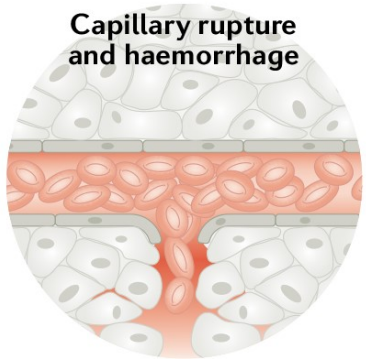


Intramyocardial Hemorrhage and the "Wave Front" of Reperfusion Injury Compromising Myocardial Salvage



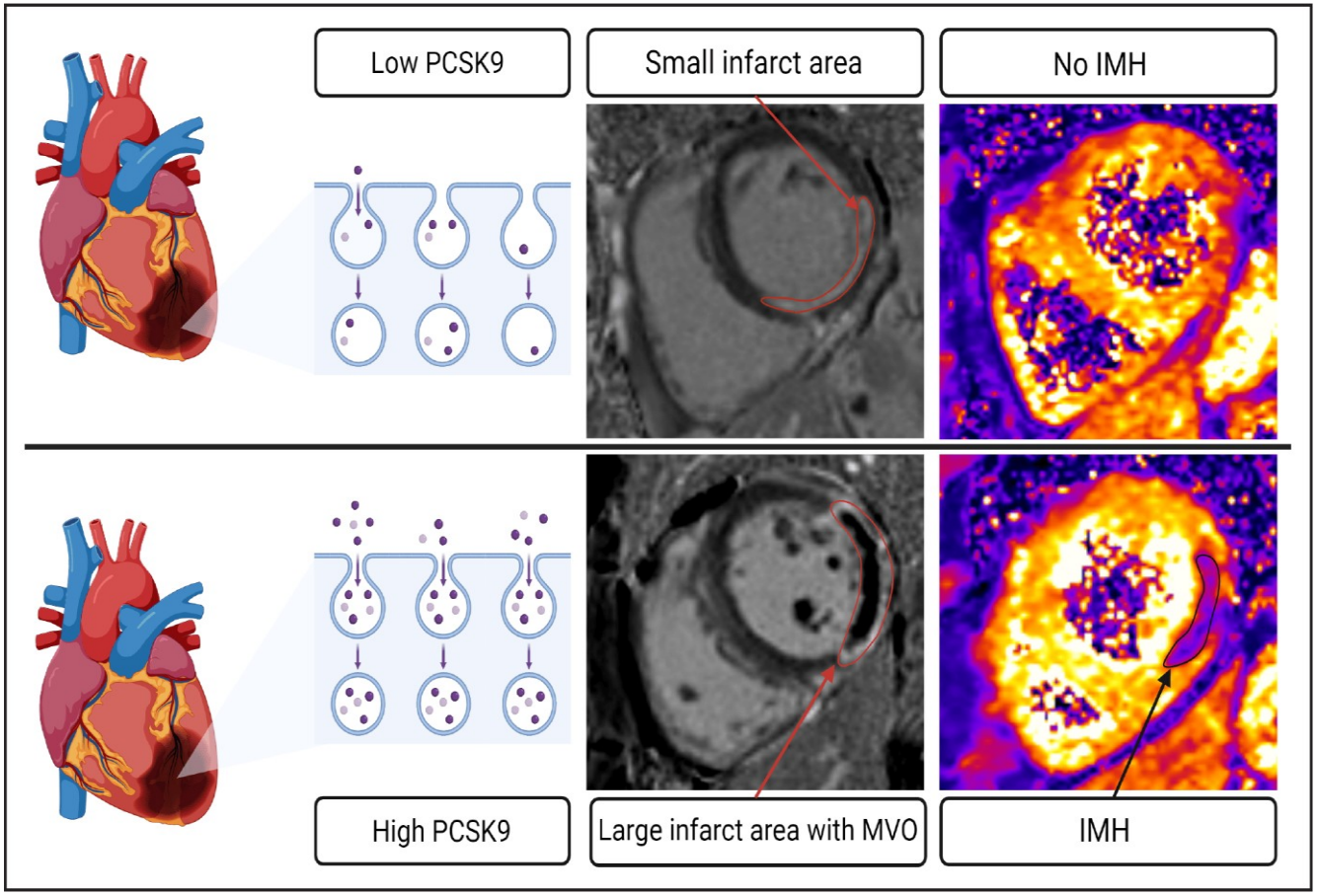
Liu T et al. J Am Coll Cardiol 2022;79:35–48.

Circulation: Cardiovascular Imaging



ORIGINAL ARTICLE

Association of Circulating PCSK9 With Ischemia-Reperfusion Injury in Acute ST-Elevation Myocardial Infarction

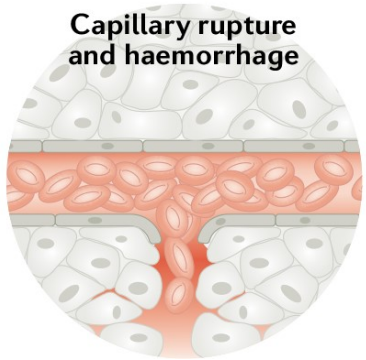


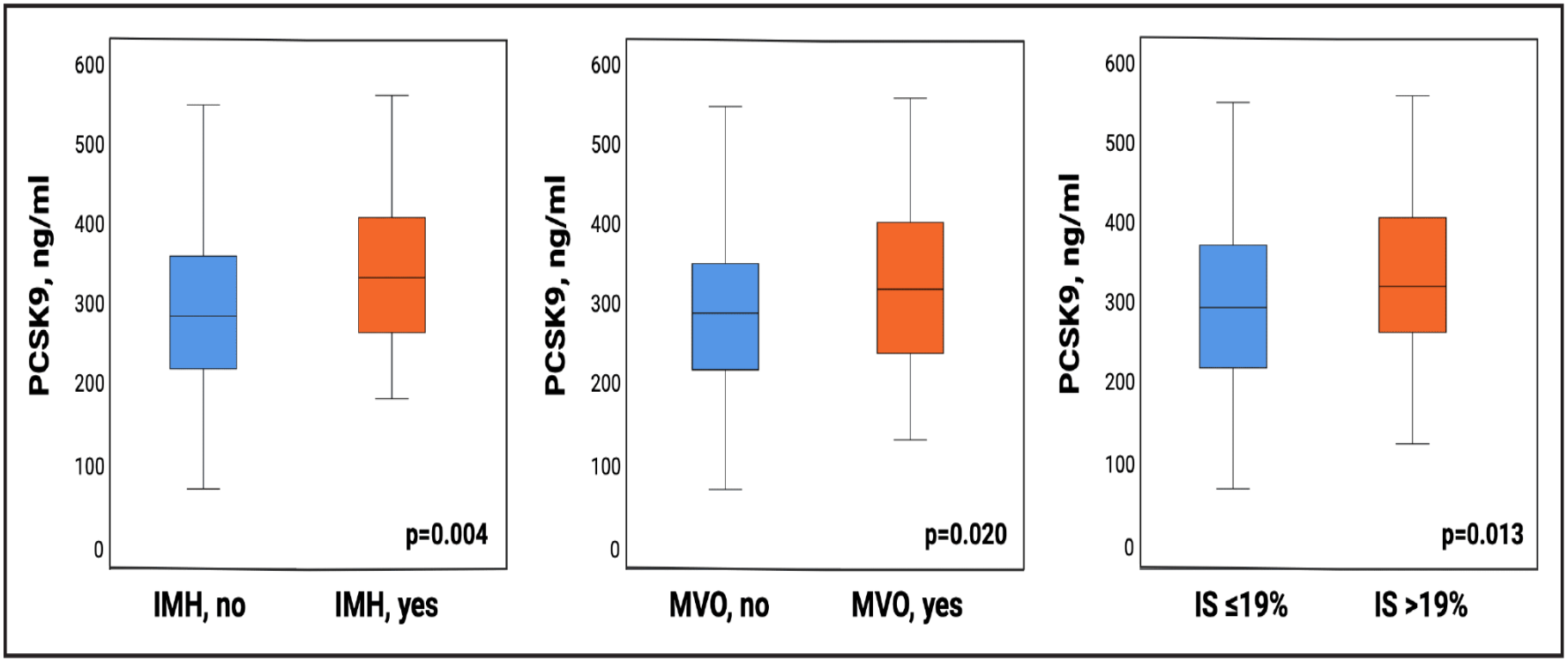
Tiller C. et al. Circ Cardiovasc Imaging. 2024;17:e016482.

Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

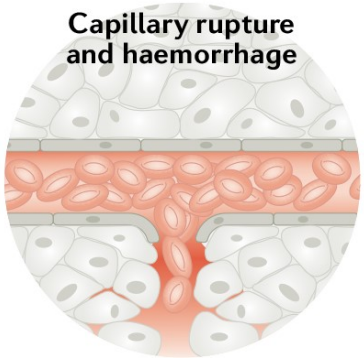
Association of Circulating PCSK9 With Ischemia-Reperfusion Injury in Acute ST-Elevation Myocardial Infarction





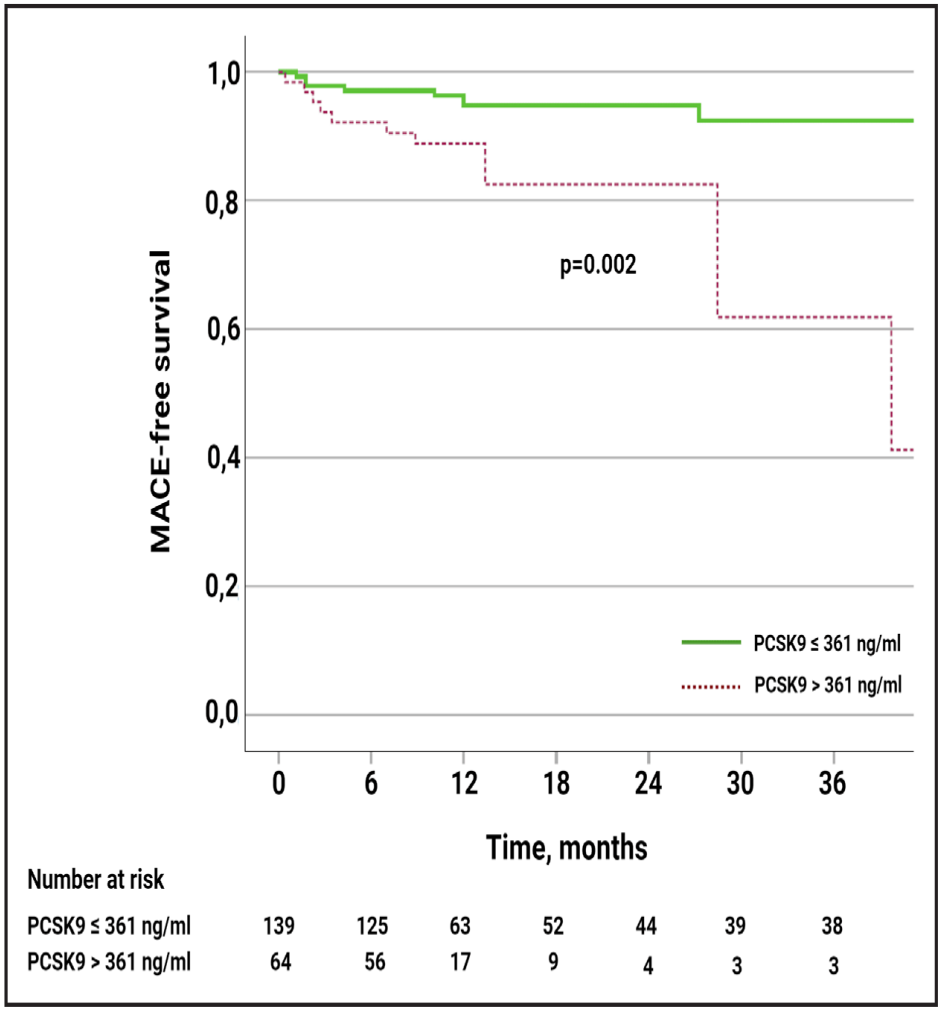
Tiller C. et al. Circ Cardiovasc Imaging. 2024;17:e016482.

Circulation: Cardiovascular Imaging

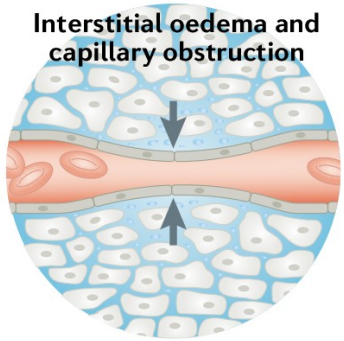


ORIGINAL ARTICLE

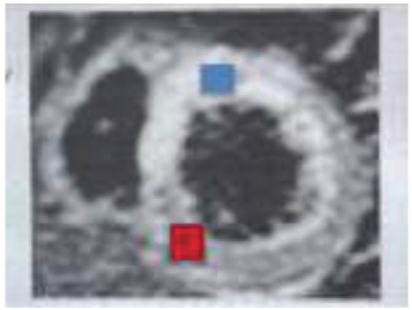
Association of Circulating PCSK9 With Ischemia-Reperfusion Injury in Acute ST-Elevation Myocardial Infarction



Tiller C. et al. Circ Cardiovasc Imaging. 2024;17:e016482.

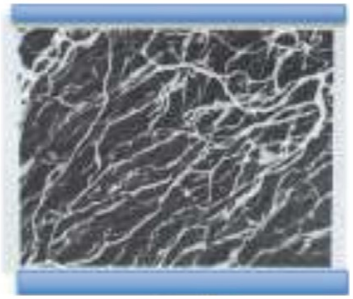


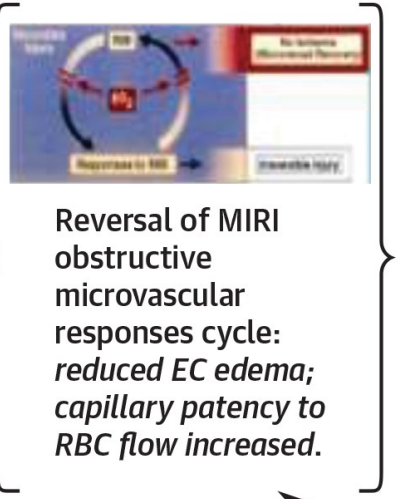
Normal Capillaries



CMR <3 h Reperfusion
Post Anterior STEMI

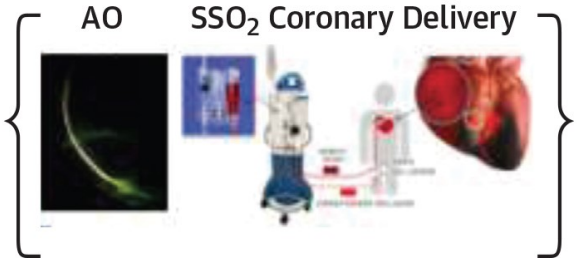
30′ Reperfusion
After 90′ Ischemia





Anaerobic reverts to aerobic metabolism: *reduced cell edema.*

Increased contraction: *edema removal via lymphatics.*

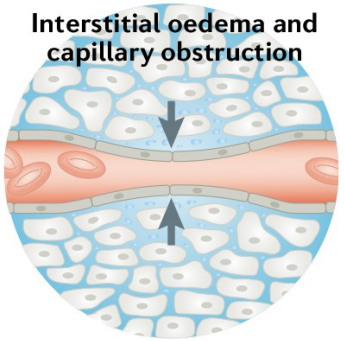


Starling's Principle:
Edema Removal

1) Reduced capillary hydrostatic pressure: *autoregulatory vasoconstriction via HBO Tissue O_2.*
2) Increased capillary osmotic Pressure: *High [O_2] in plasma; extravascular O_2 consumption creates osmotic gradient.*

Welt FGP et al. J Am Coll Cardiol 2024;83:2196–2213.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 83, NO. 22, 2024

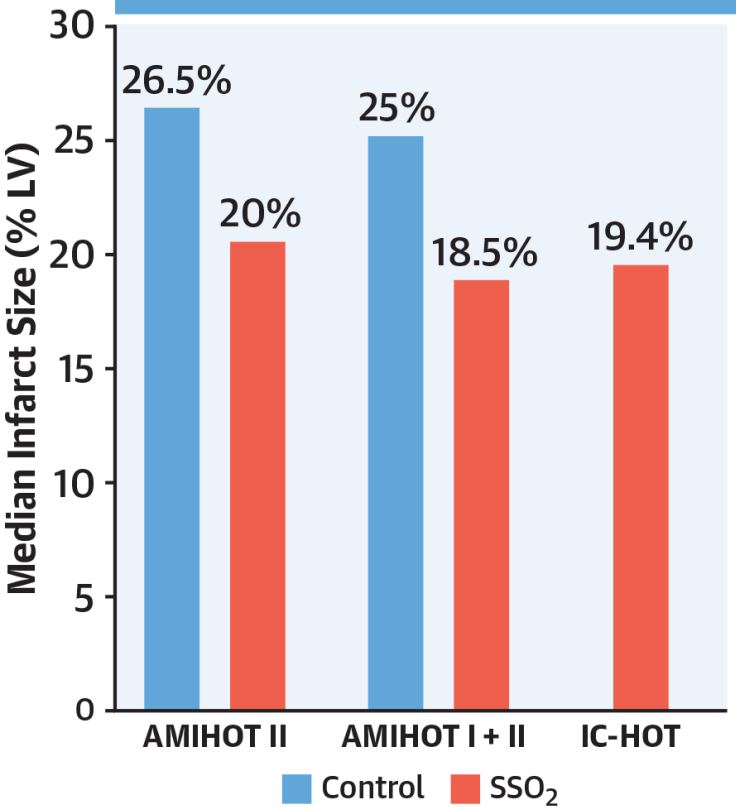


JACC SCIENTIFIC STATEMENT

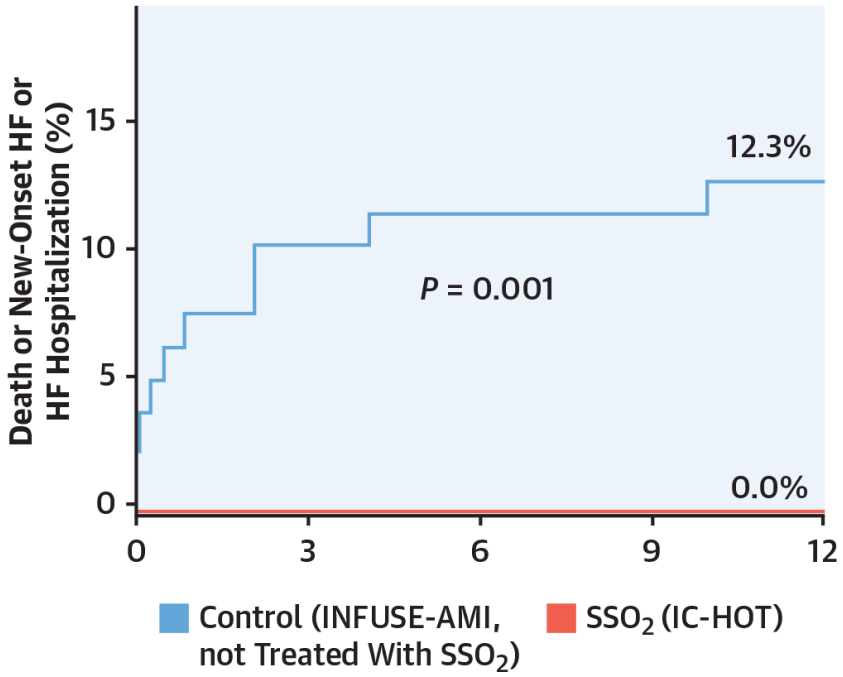
Reperfusion Injury in Patients With Acute Myocardial Infarction

JACC Scientific Statement

CLINICAL STUDIES

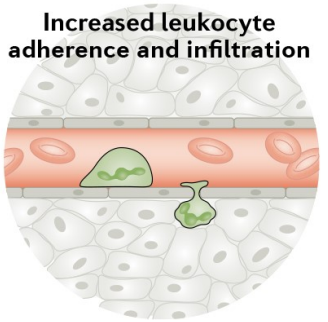


IC-HOT vs INFUSE-AMI Outcomes at 1 Year in Propensity-Score Matched Patients (N = 166 [83 Pairs])

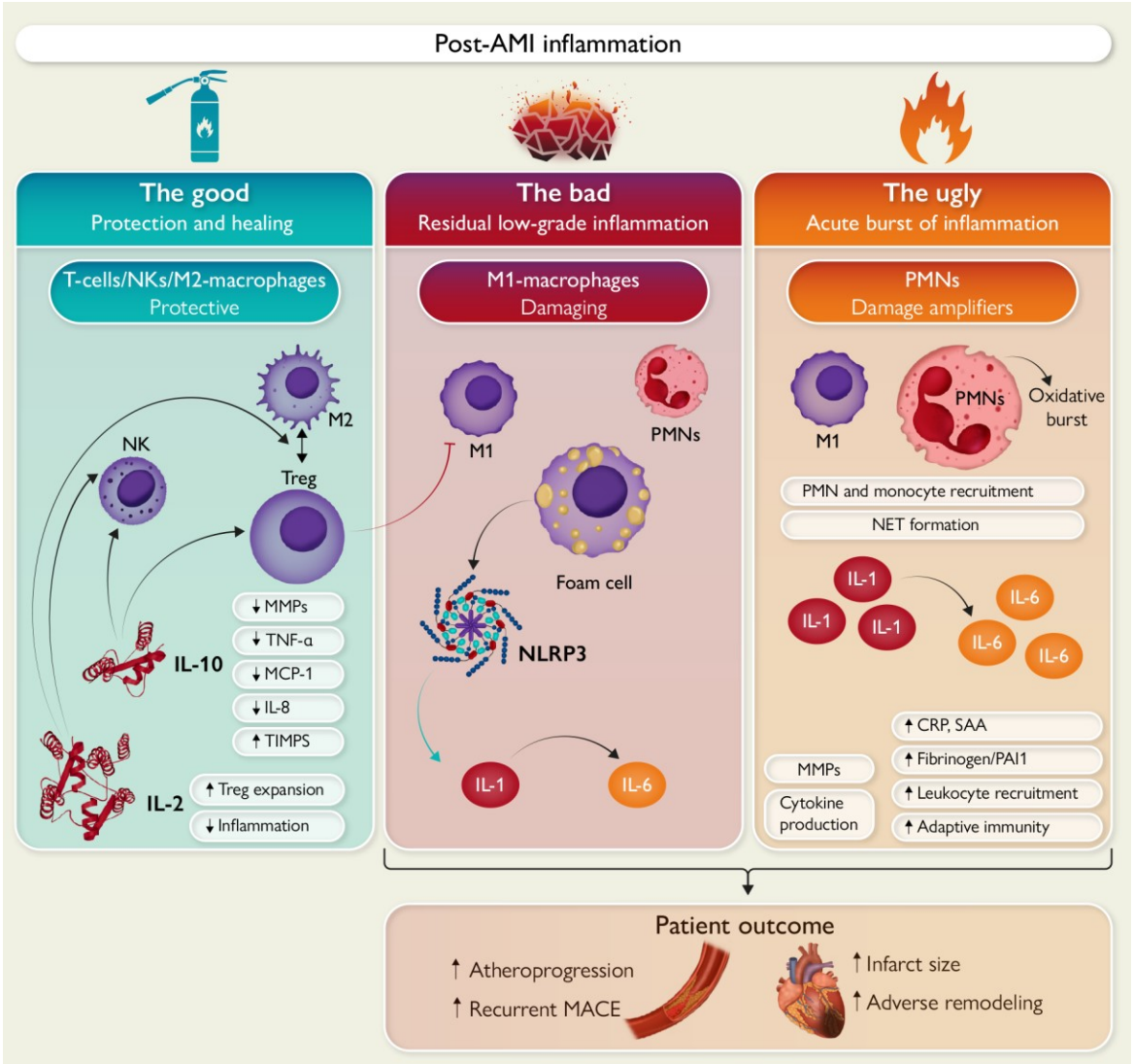


Welt FGP et al. J Am Coll Cardiol 2024;83:2196–2213.

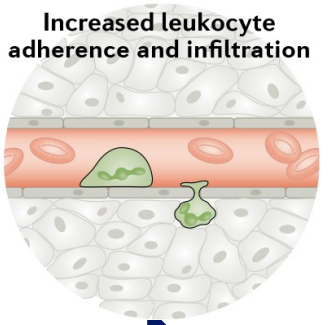
ESC European Society of Cardiology
European Heart Journal (2024) **45**, 89–103
https://doi.org/10.1093/eurheartj/ehad486



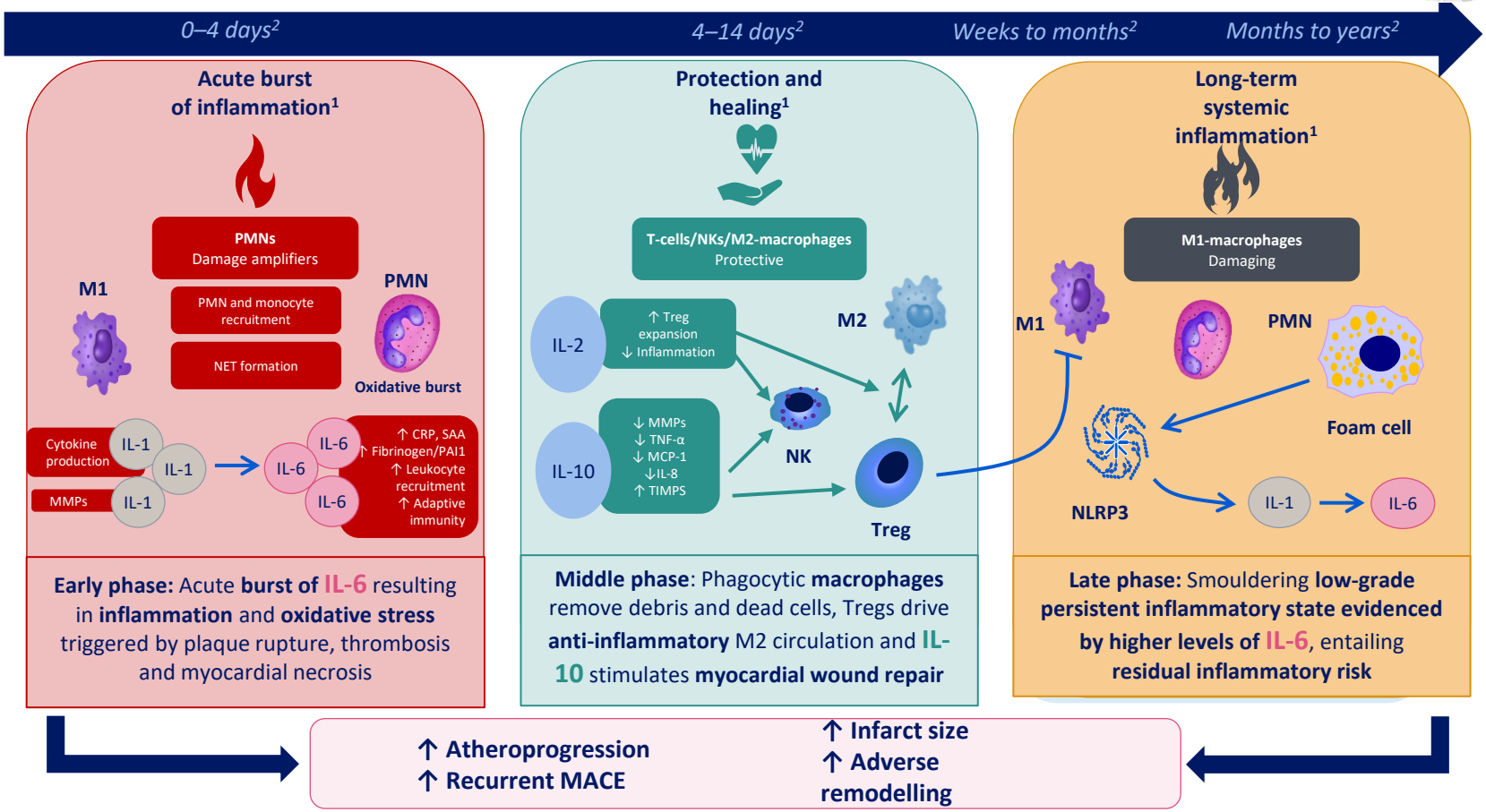
Inflammation in acute myocardial infarction: the good, the bad and the ugly



Matter MA al. European Heart Journal (2024) 45, 89–



Post-AMI inflammation[1]

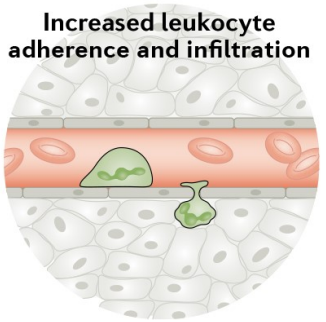


AMI, acute myocardial infarction; CRP, C-reactive protein; IL-1, interleukin-1; IL-10, interleukin-10; IL-2, interleukin-2; IL-6, interleukin-6; IL-8, interleukin-8; M1, macrophage type 1; M2, macrophage type 2; MACE, major adverse cardiovascular event; MCP, monocyte chemoattractant protein; MMP, matrix metalloproteinase; NET, neutrophil extracellular trap; NK, natural killer cell; NLRP3, NOD [nucleotide oligomerisation domain]-, LRR [leucine-rich repeat]- and PYD [pyrin domain]-containing protein 3; PAI1, plasminogen activator inhibitor 1; PMN, polymorphonuclear neutrophil; SAA, serum amyloid A; TIMPS, tissue inhibitors of metalloproteinases; TNF-α, tumour necrosis factor alpha; Treg, regulatory T cell

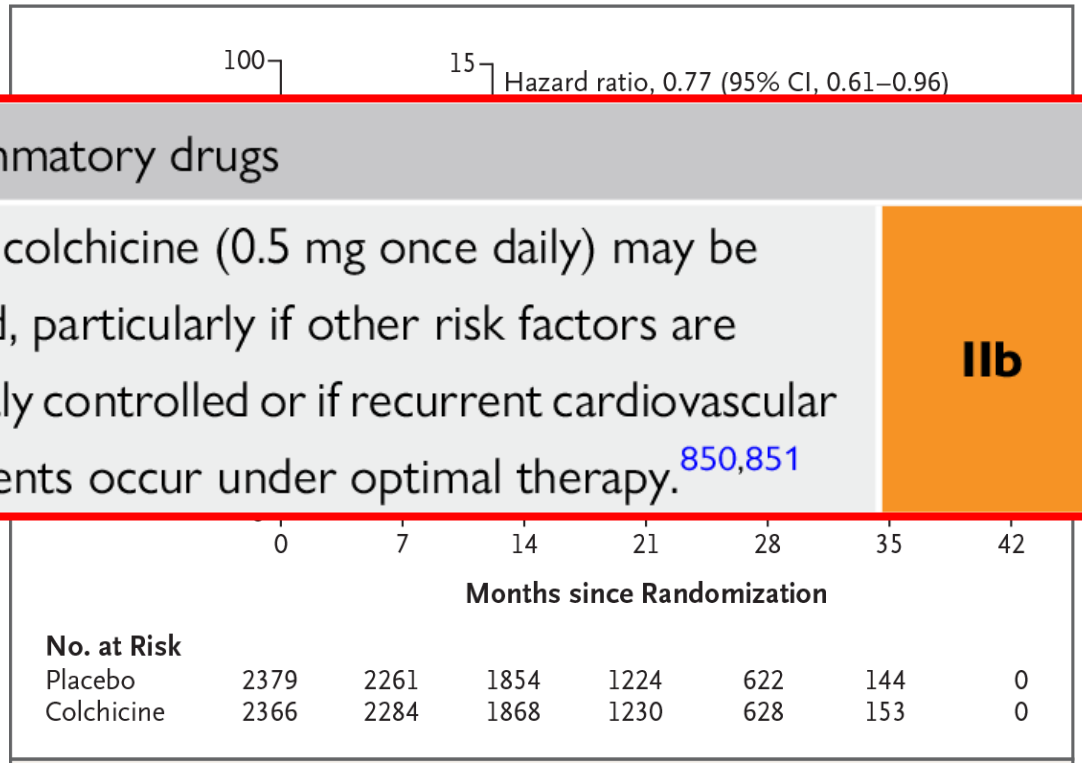
[1]Matter MA al. European Heart Journal (2024) 45, 89–103.
[2]Prabhu SD, Frangogiannis NG. Circ Res 2016;119:91–

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 26, 2019 VOL. 381 NO. 26



Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction



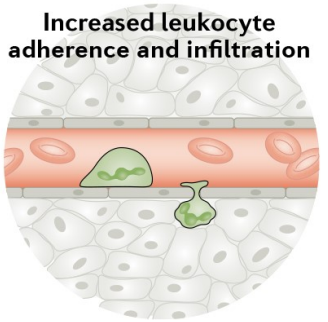
Anti-inflammatory drugs

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.[850,851]

IIb **A**

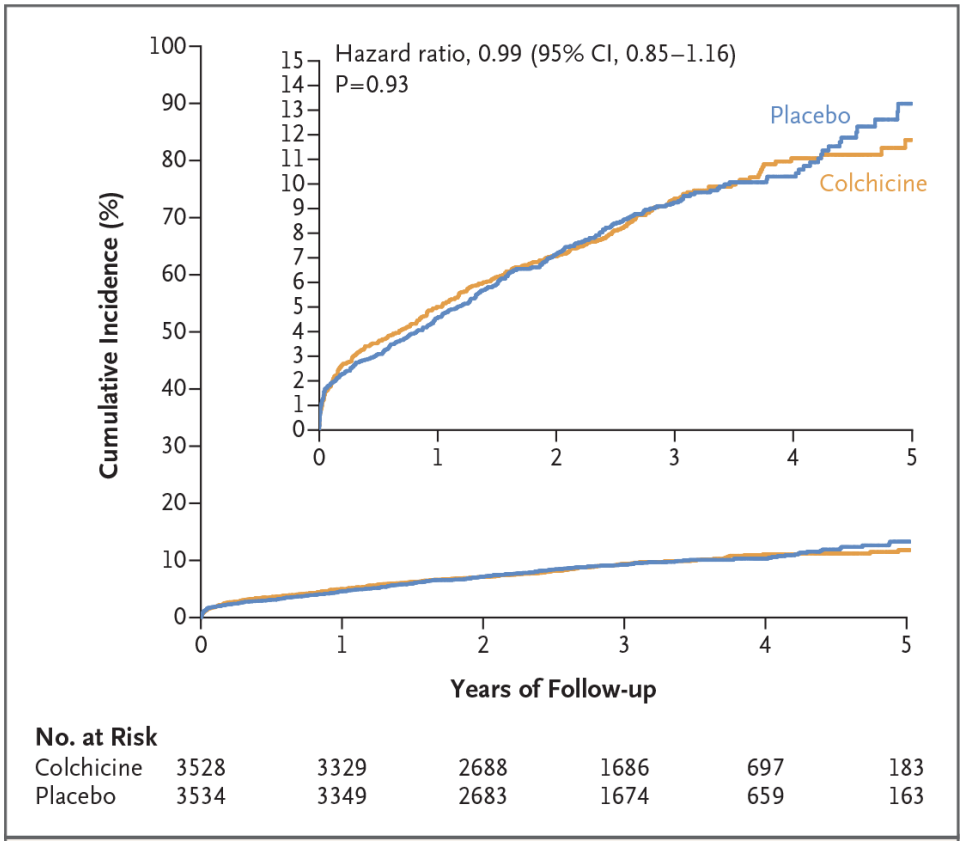
Tardif JC et al. N Engl J Med 2019;381:2497-505.

ORIGINAL ARTICLE



Colchicine in Acute Myocardial Infarction

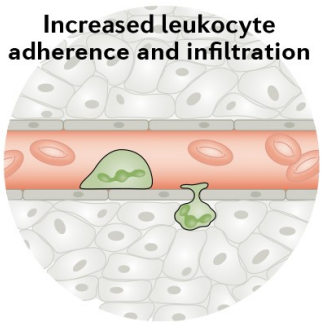
S.S. Jolly, M.-A. d'Entremont, S.F. Lee, R. Mian, J. Tyrwhitt, S. Kedev, G. Montalescot, J.H. Cornel, G. Stanković, R. Moreno, R.F. Storey, T.D. Henry, S.R. Mehta, M. Bossard, P. Kala, J. Layland, B. Zafirovska, P.J. Devereaux, J. Eikelboom, J.A. Cairns, B. Shah, T. Sheth, S.K. Sharma, W. Tarhuni, D. Conen, S. Tawadros, S. Lavi, and S. Yusuf, for the CLEAR Investigators*



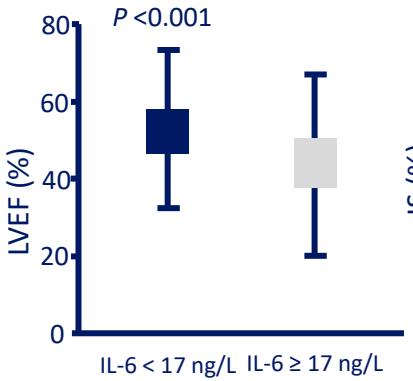
Jolly JJ et al. N Engl J Med. 2024 Nov 17. doi: 10.1056/NEJMoa2405922.

ESC European Society of Cardiology
European Heart Journal: Acute Cardiovascular Care (2022) **11**, 113–123
https://doi.org/10.1093/ehjacc/zuab110
ORIGINAL SCIENTIFIC PAPER
Biomarkers

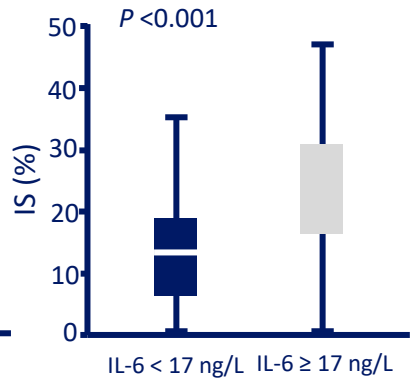
Association of plasma interleukin-6 with infarct size, reperfusion injury, and adverse remodelling after ST-elevation myocardial infarction



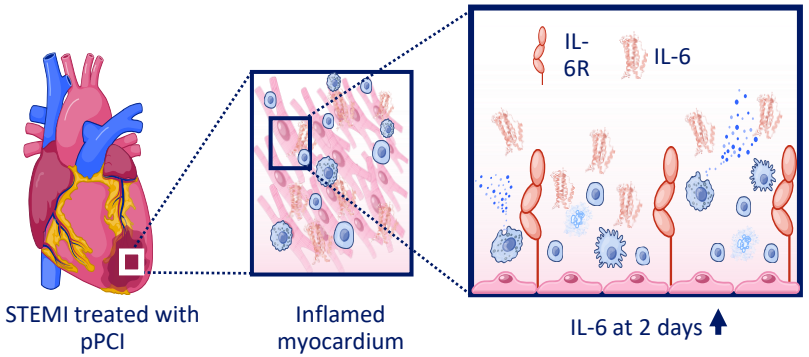
Myocardial function



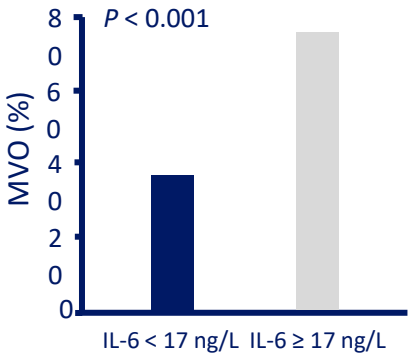
Myocardial scar

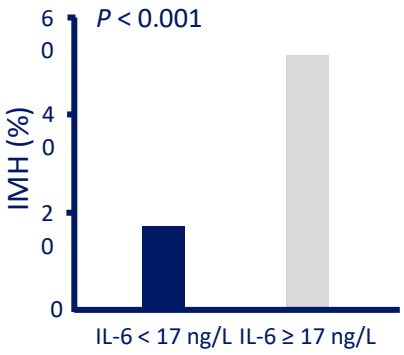


IL-6 and myocardial injury



Reperfusion injury





170 consecutive STEMI patients treated with PCI

- Blood sampling on Day 2
- CMR on Day 4

High concentrations of IL-6 48 h after STEMI were associated with:

- Worse myocardial function
- Larger infarct extent
- Greater reperfusion injury
- Adverse LV remodeling

CMR, cardiac magnetic resonance; IL, interleukin; IMH, intramyocardial haemorrhage; IS, infarct size; LV, left ventricular; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; MVO, microvascular obstruction; STEMI, ST-segment elevation myocardial infarction.

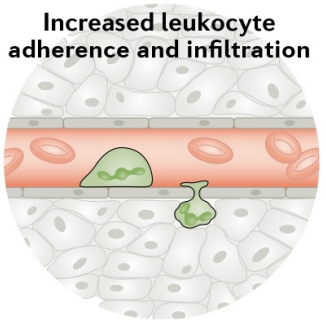
Tiller C et al. European Heart Journal: Acute Cardiovascular Care (2022) 11, 113–123.

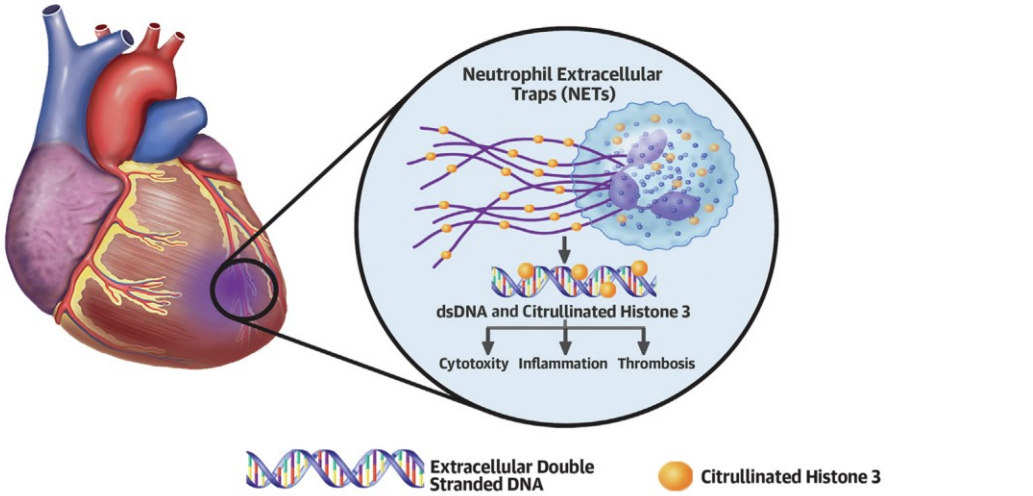
ORIGINAL RESEARCH

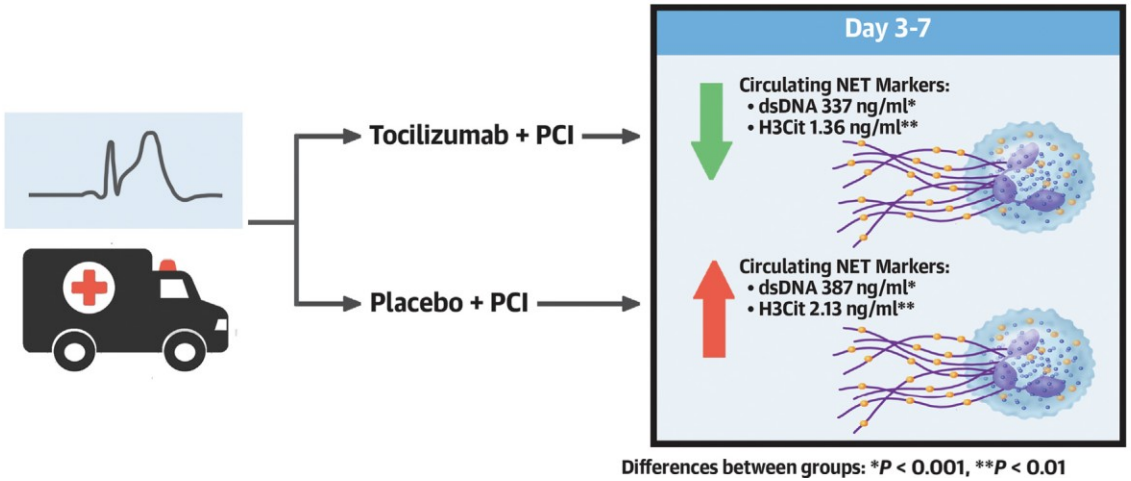
ISCHEMIC HEART DISEASE

Neutrophil Extracellular Traps in ST-Segment Elevation Myocardial Infarction

Reduced by Tocilizumab and Associated With Infarct Size







Differences between groups: *$P < 0.001$, **$P < 0.01$

Kindberg KM et al. JACC Adv. 2024;3:101193.

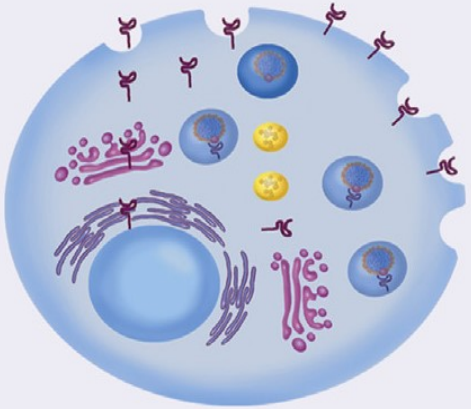
Cellular Resistance to Reperfusion Injury

Intracellular Target

1. Inhibition of Cell Death Pathways (Necrosis, Apoptosis, Pyroptosis, Necroptosis)

Intracellular Target

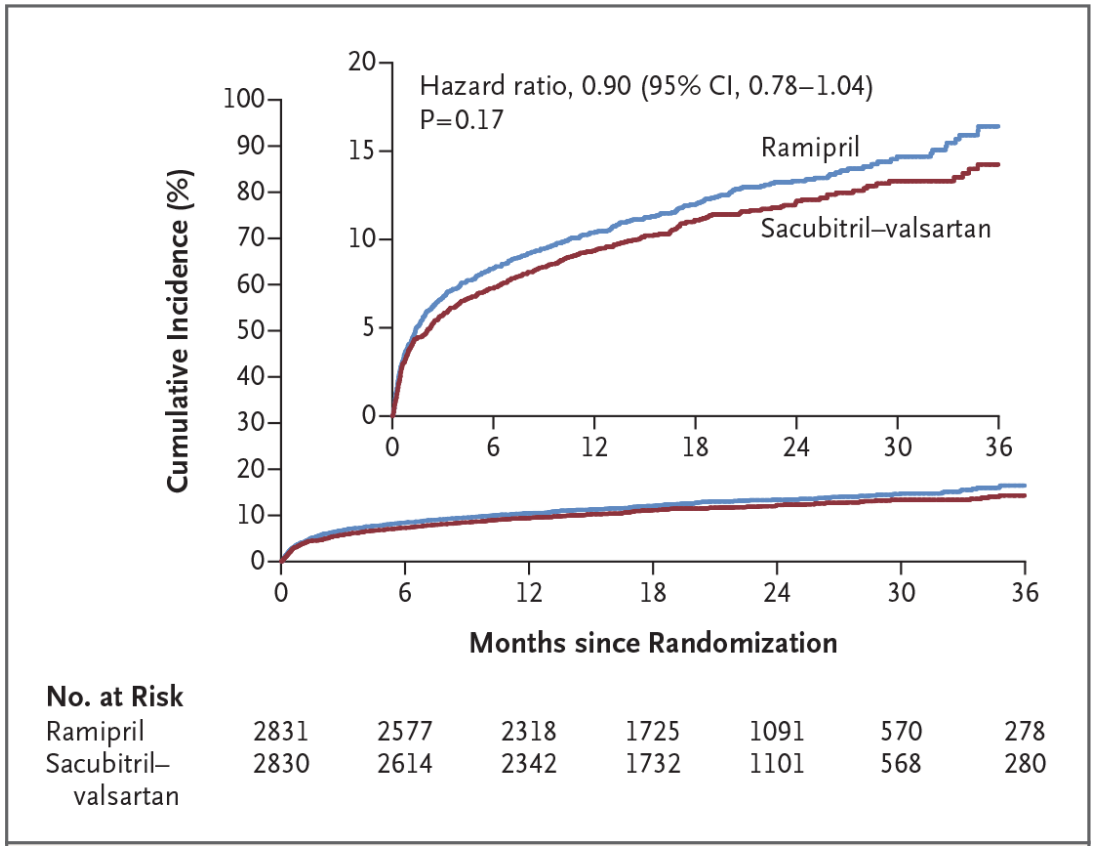
2. Activation of Endogenous Pro-Survival Pathways (RISK, SAFE, PKG)



Modified by Davidson SM et al. J Am Coll Cardiol 2019;73:89–99.

ORIGINAL ARTICLE

Angiotensin Receptor–Neprilysin Inhibition in Acute Myocardial Infarction

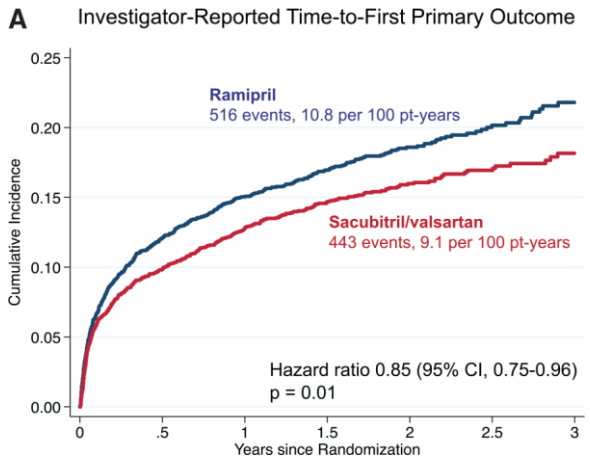


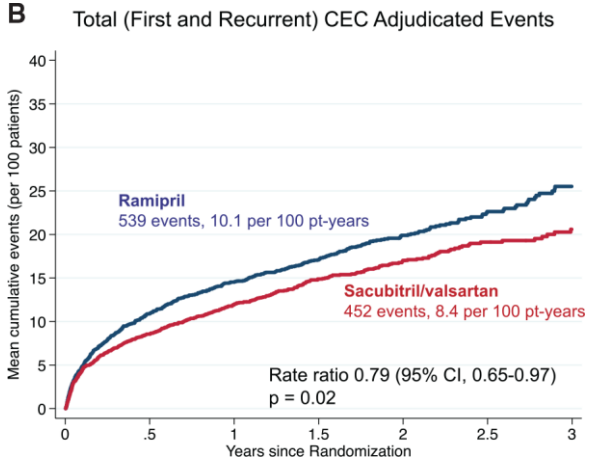
No. at Risk							
Ramipril	2831	2577	2318	1725	1091	570	278
Sacubitril–valsartan	2830	2614	2342	1732	1101	568	280

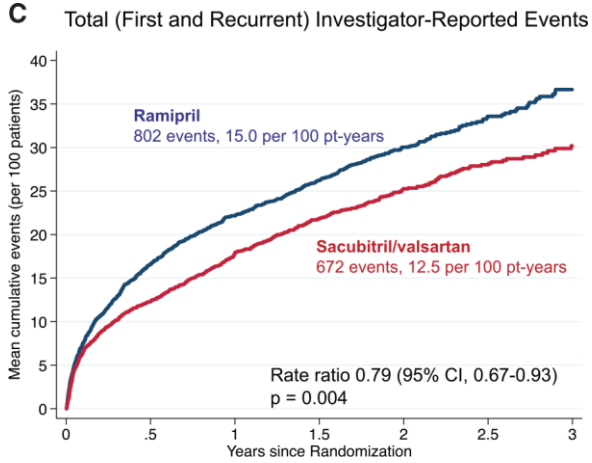
Circulation

RESEARCH LETTER

Impact of Sacubitril/Valsartan Versus Ramipril on Total Heart Failure Events in the PARADISE-MI Trial





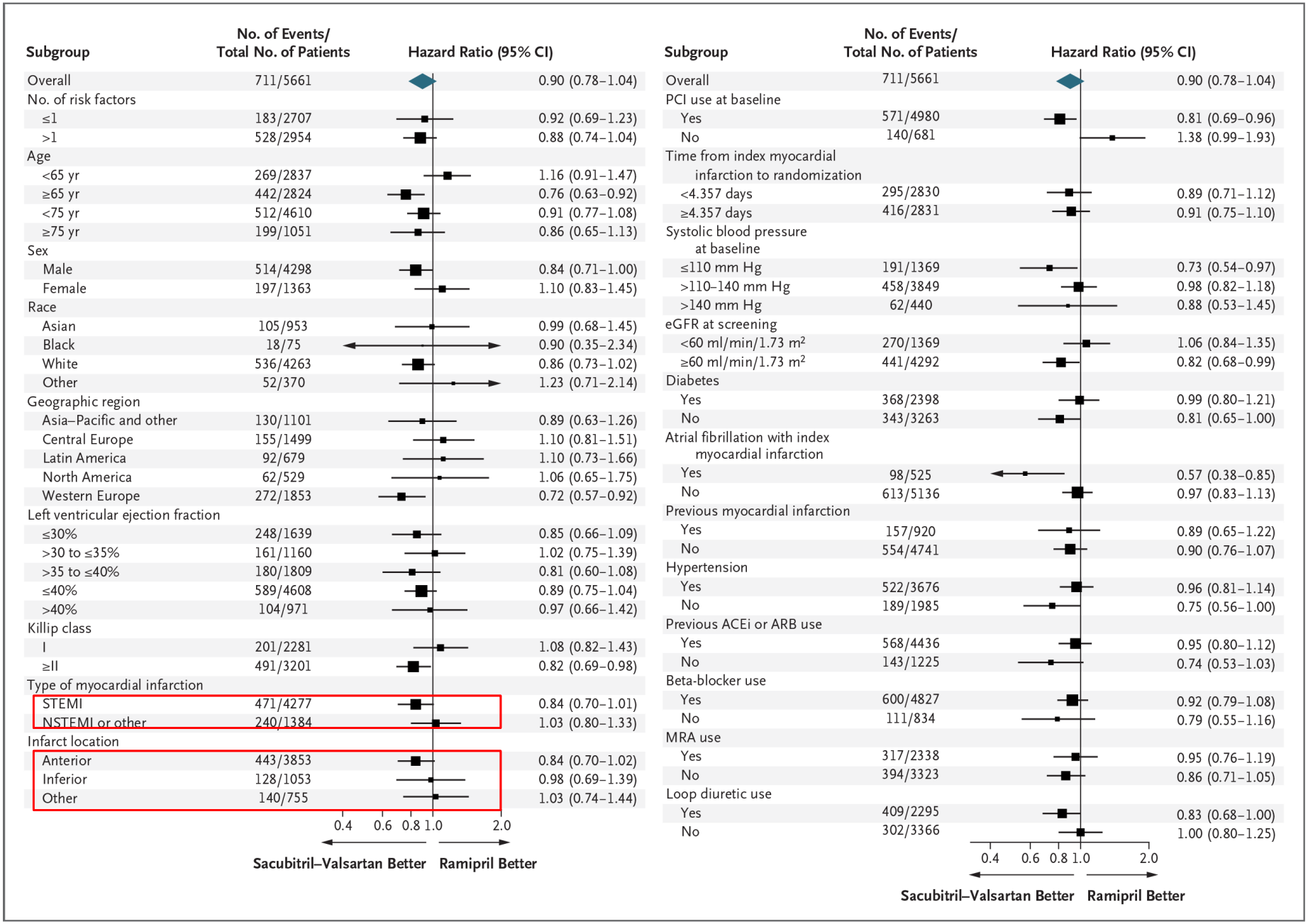


Pfeffer MA et al. Circulation. 2022;145:87–89.

ESC HEART FAILURE
ESC Heart Failure (2022)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14159

EDITORIAL

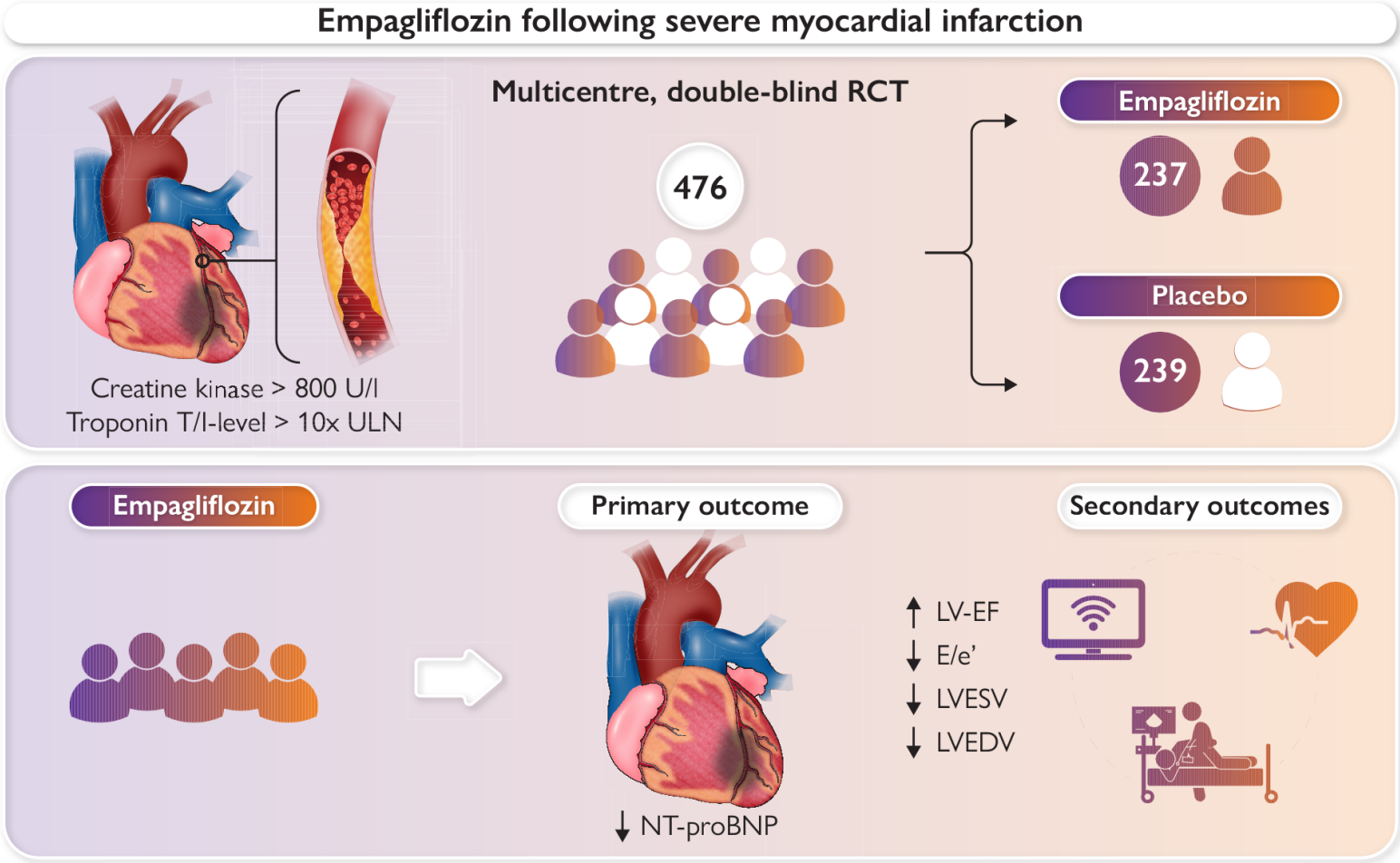
The PARADISE-MI trial: a new opportunity to improve the left ventricular remodelling in reperfused STEMI



Pfeffer MA et al. N Engl J Med 2021;385:1845-55.

ESC European Society of Cardiology
European Heart Journal (2022) **43**, 4421–4432
https://doi.org/10.1093/eurheartj/ehac494

Empagliflozin in acute myocardial infarction: the EMMY trial

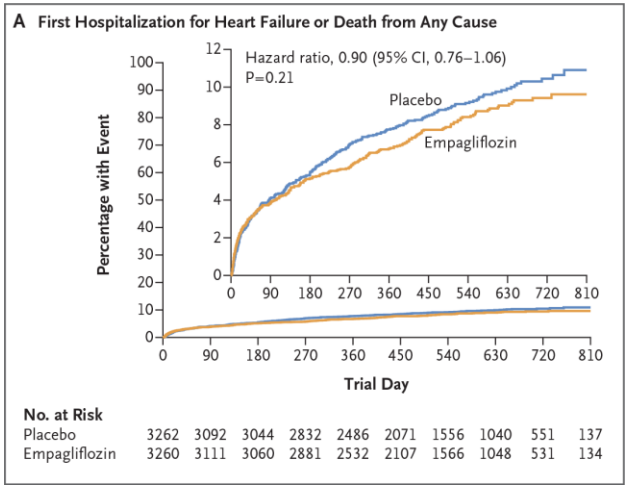


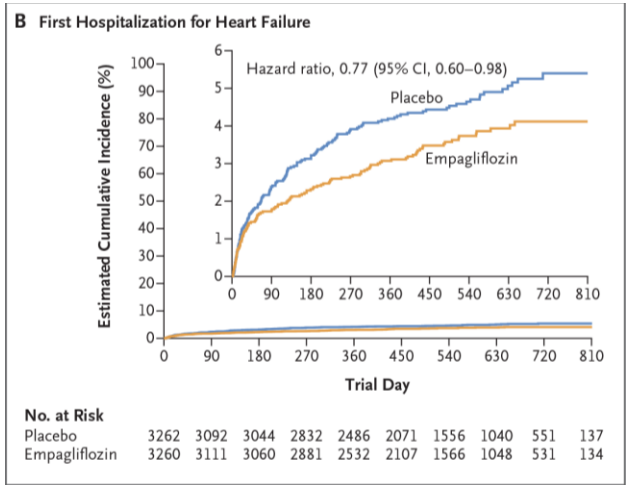
von Lewinski D et al. European Heart Journal (2022) 43, 4421–4432.

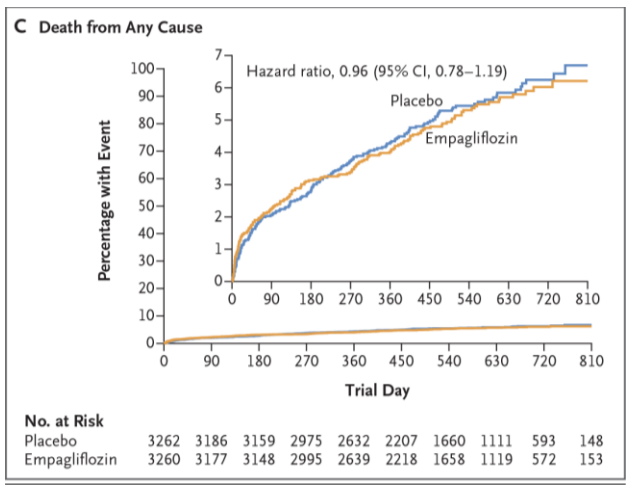
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 25, 2024 VOL. 390 NO. 16

Empagliflozin after Acute Myocardial Infarction







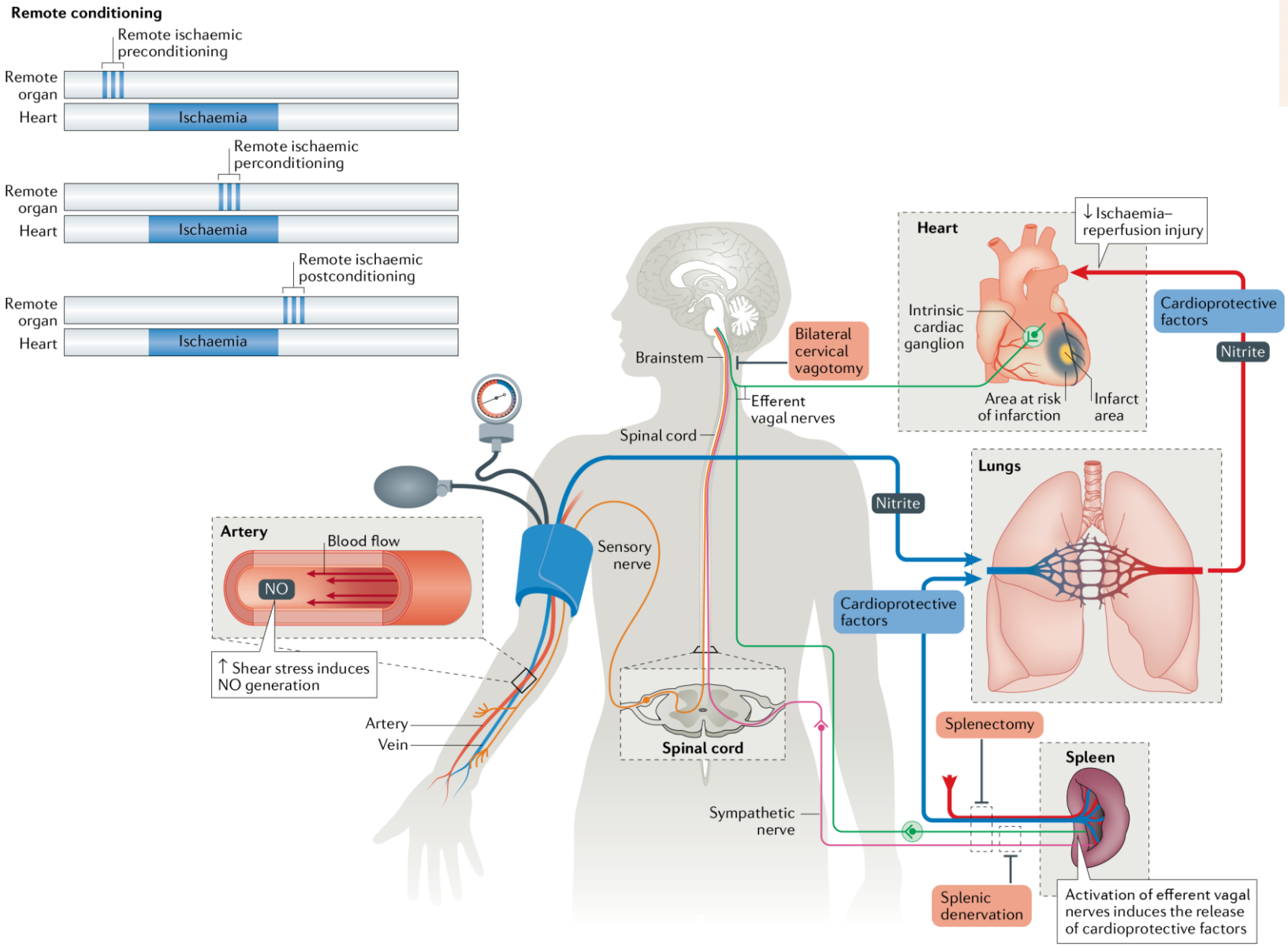
Butler J et al. N Engl J Med. 2024;390:1455-66.

EDITORIALS

Decreasing the Risk of Heart Failure in a Changing Post–Myocardial Infarction Environment

eling. However, with time, the risk of cardiovascular events decreases markedly as these processes subside, and prompt revascularization, as occurs in the majority of patients (including those in the EMPACT-MI trial), leads to substantial reversal of myocardial stunning.[1] Thus, some of the patients in this trial probably recovered, with a resulting lower risk of subsequent heart failure.

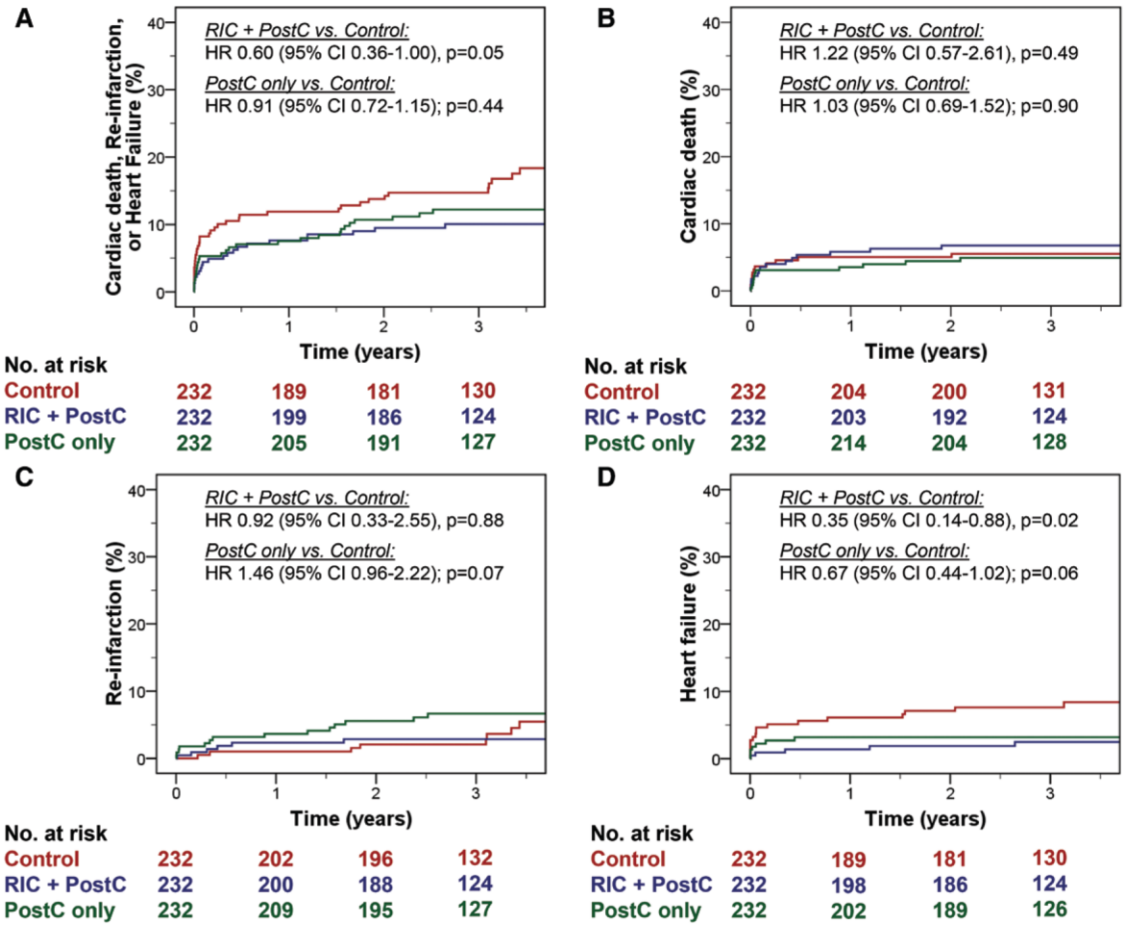
cardiovascular trials. This raises the question of whether alternative, yet appropriate[10] outcome measures (e.g., the total number of events rather than the first event, investigator-reported events rather than centrally adjudicated events, or heart-failure events that did not lead to hospitalization) to increase rates of the primary end-point event should be used. Whether the use of such measures



Heusch G. Nat. Rev. Cardiol. 2020.

Combined Intrahospital Remote Ischemic Perconditioning and Postconditioning Improves Clinical Outcome in ST-Elevation Myocardial Infarction

Long-Term Results of the LIPSIA CONDITIONING Trial



Stiermaier T et al. Circ Res. 2019;124:1482-1491.

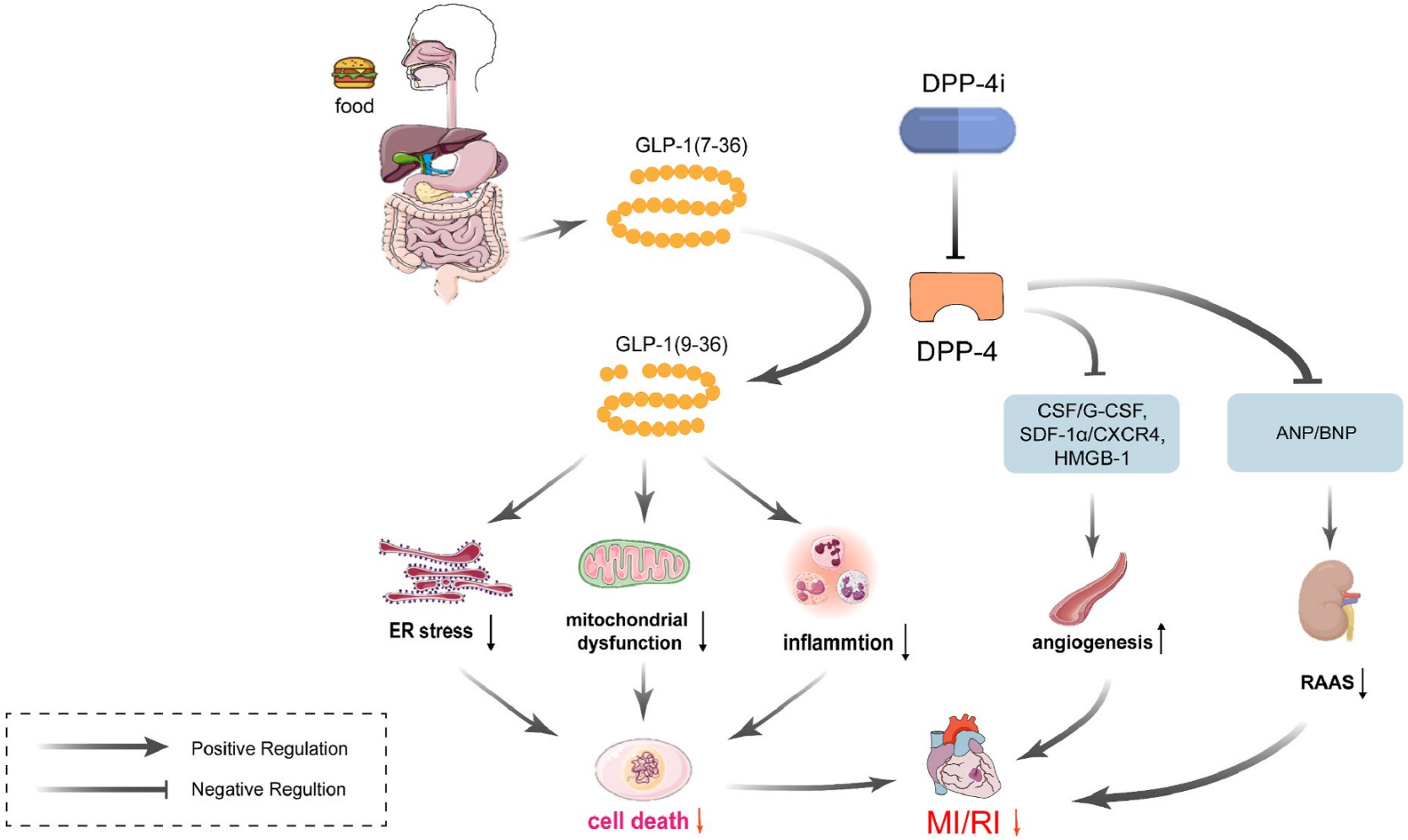
European Journal of Pharmacology 976 (2024) 176698

Contents lists available at ScienceDirect

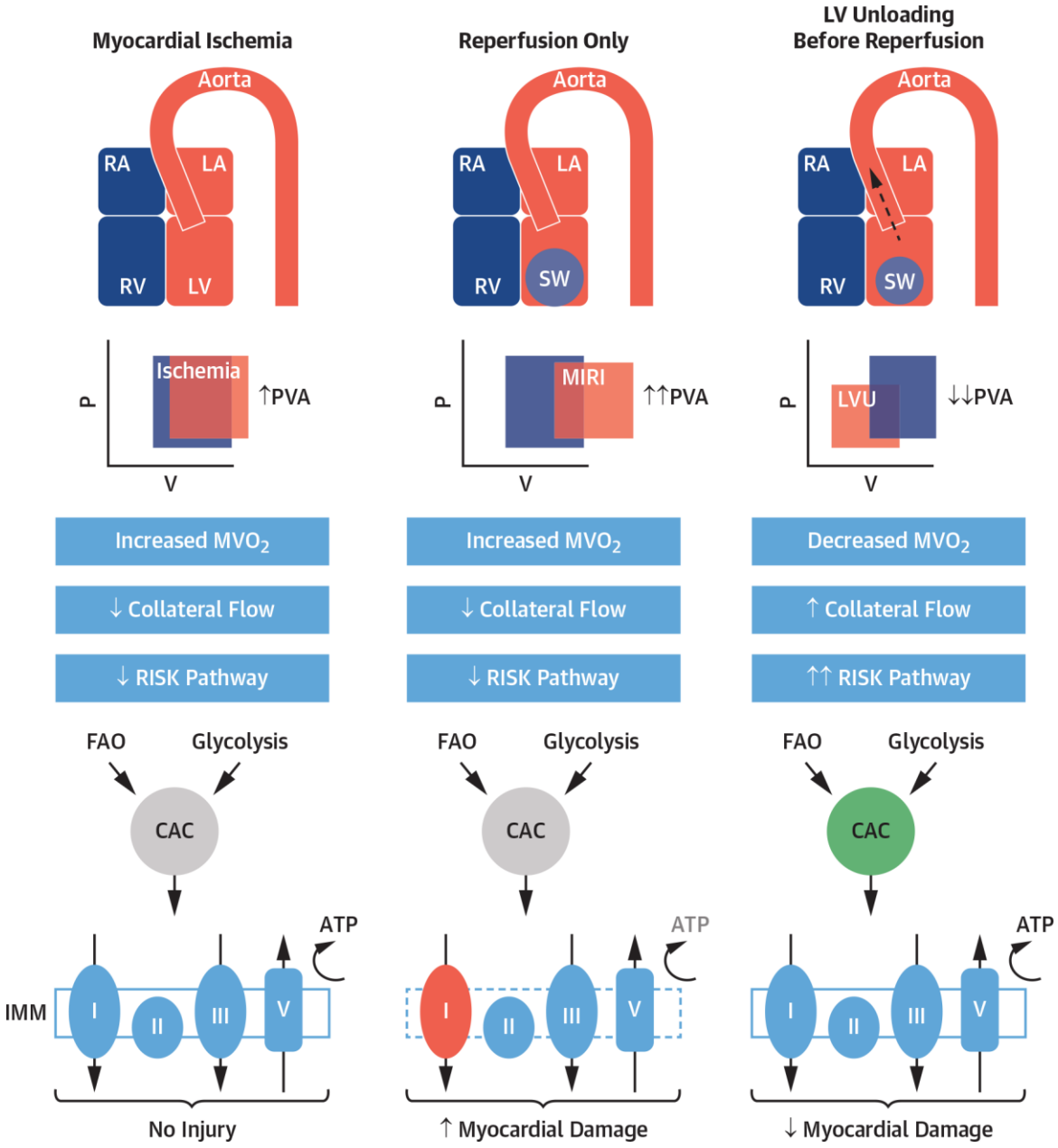
European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

The benefits of oral glucose-lowering agents: GLP-1 receptor agonists, DPP-4 and SGLT-2 inhibitors on myocardial ischaemia/reperfusion injury



Huang XD et al. Eur J Pharmacol. 2024 Aug 5:976:176698.



Welt FGP et al. J Am Coll Cardiol 2024;83:2196–2213.

Combination Strategies For Multi-Target Cardioprotection

Protective Modality

1. Ischemic Conditioning

2. Pharmacological Protection

3. Physical Intervention

Time of Application

1. During Ischemia

Pre-pPCI Phase

2. At Reperfusion

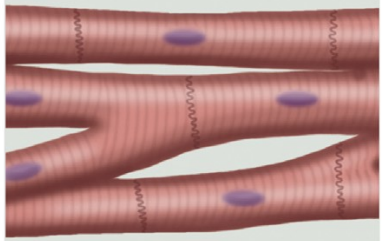
During-pPCI Phase

3. Late Into Reperfusion

Post-pPCI Phase

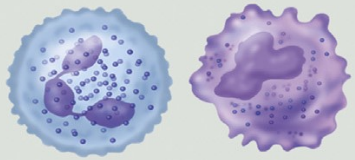
Cellular Target

1. Cardiomyocytes



2. Non-Cardiomyocytes, Microvascular Obstruction

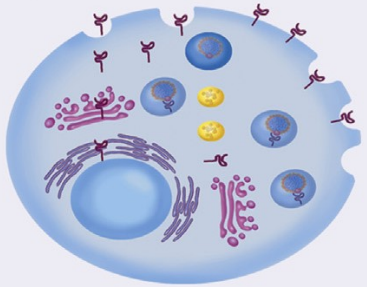
3. Circulating Cells



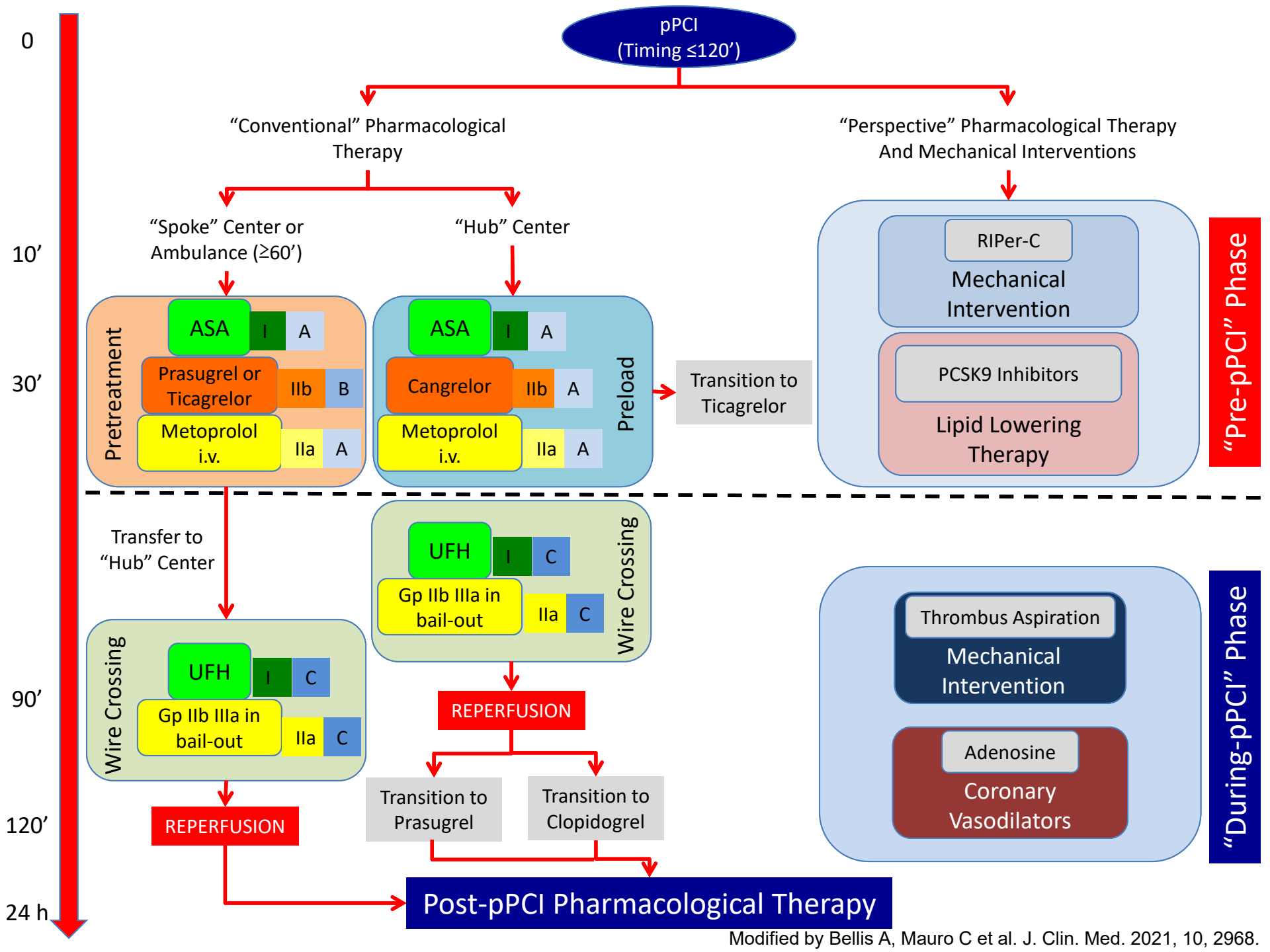
Intracellular Target

1. Inhibition of Cell Death Pathways (Necrosis, Apoptosis, Pyroptosis, Necroptosis)

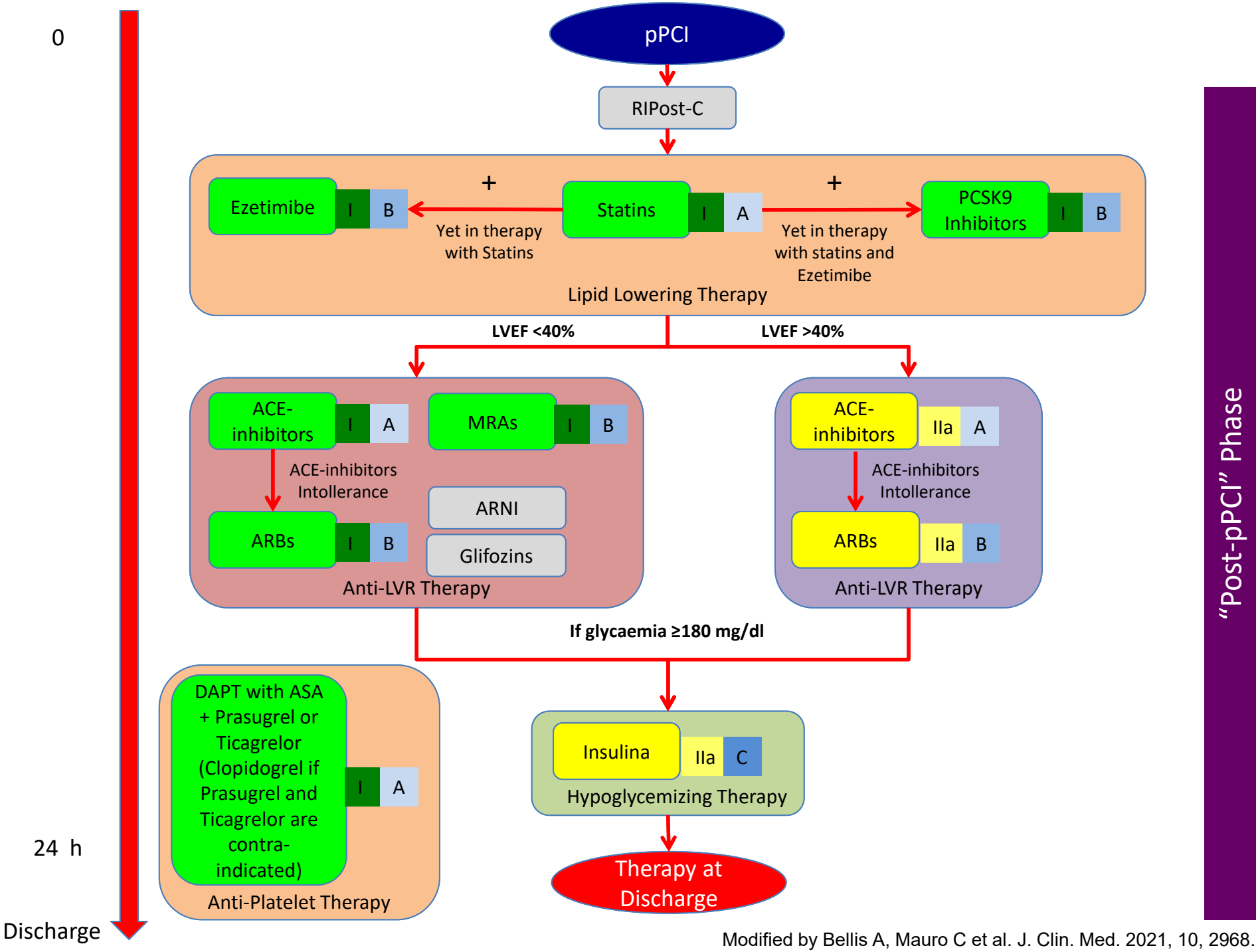
2. Activation of Endogenous Pro-Survival Pathways (RISK, SAFE, PKG)



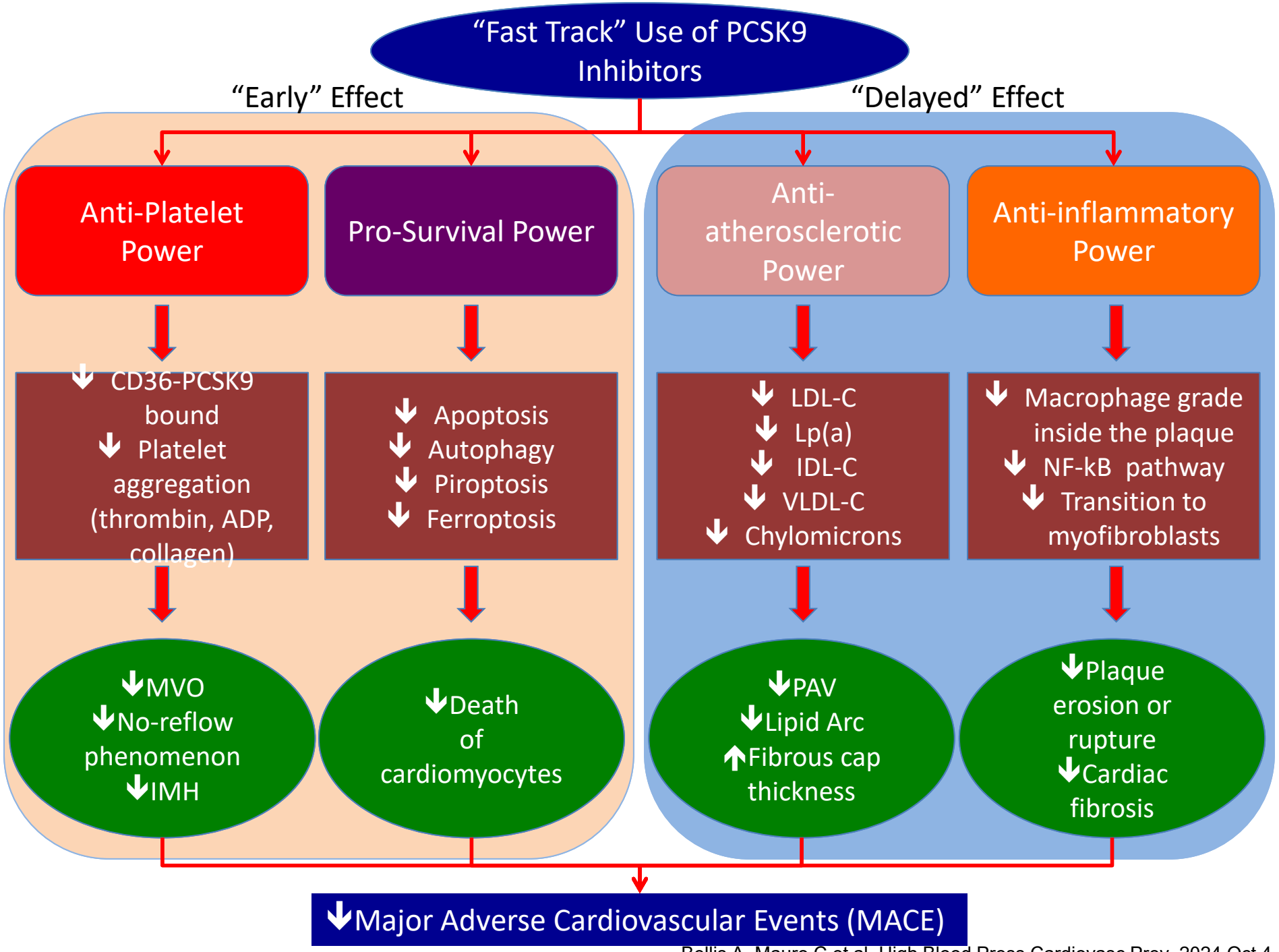
Davidson SM et al. J Am Coll Cardiol 2019;73:89–99.



Modified by Bellis A, Mauro C et al. J. Clin. Med. 2021, 10, 2968.



Modified by Bellis A, Mauro C et al. J. Clin. Med. 2021, 10, 2968.



Bellis A, Mauro C et al. High Blood Press Cardiovasc Prev. 2024 Oct 4.