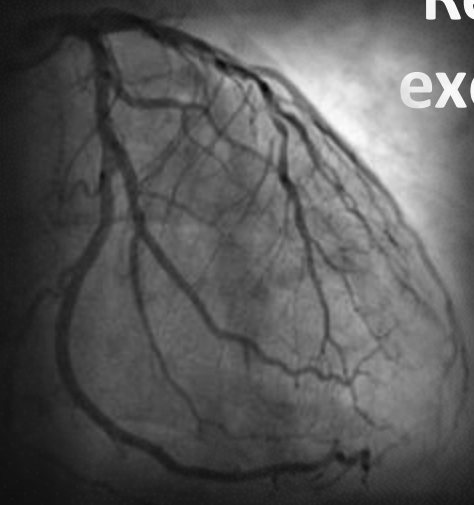


INVISIBLE LIFELINES: UNRAVELING THE CRITICAL ROLE OF CARDIAC MICROCIRCULATION

Complex network of vessels less than $\approx 500 \mu\text{m}$ ($1/2 \text{ mm}$) in diameter

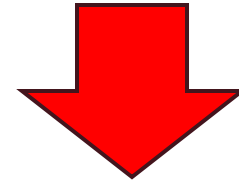
Responsible for regulating blood flow to and the exchange of oxygen, nutrients, and metabolites in the myocardium

Microvasculature handles over 90% of coronary resistance



Introduction-basics

Microcirculation is not visible on angiograms----*invisible lifeline*



Genetics
Environmental lifestyle choices
Metabolics
GDMT

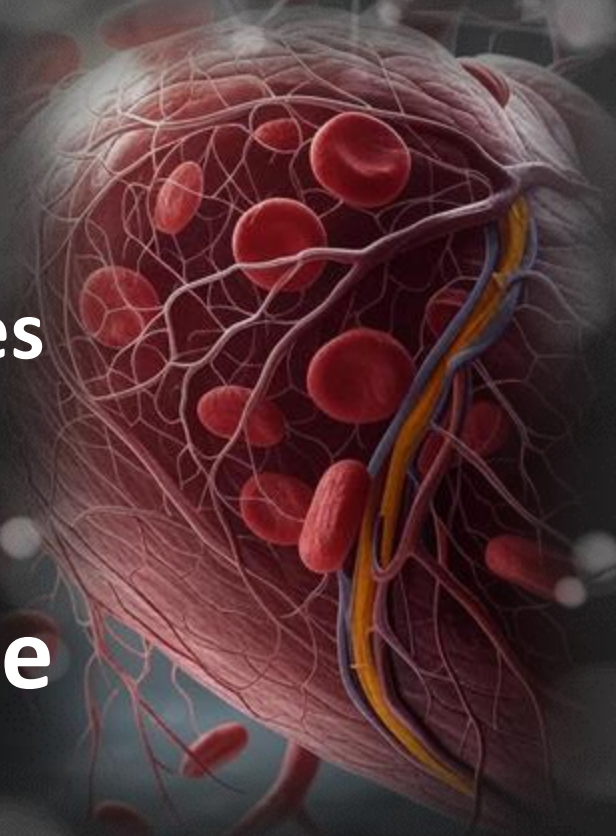
Stress-microcirculation increases

Hypertension

Insulin resistance

Metabolic diseases

Vascular disease

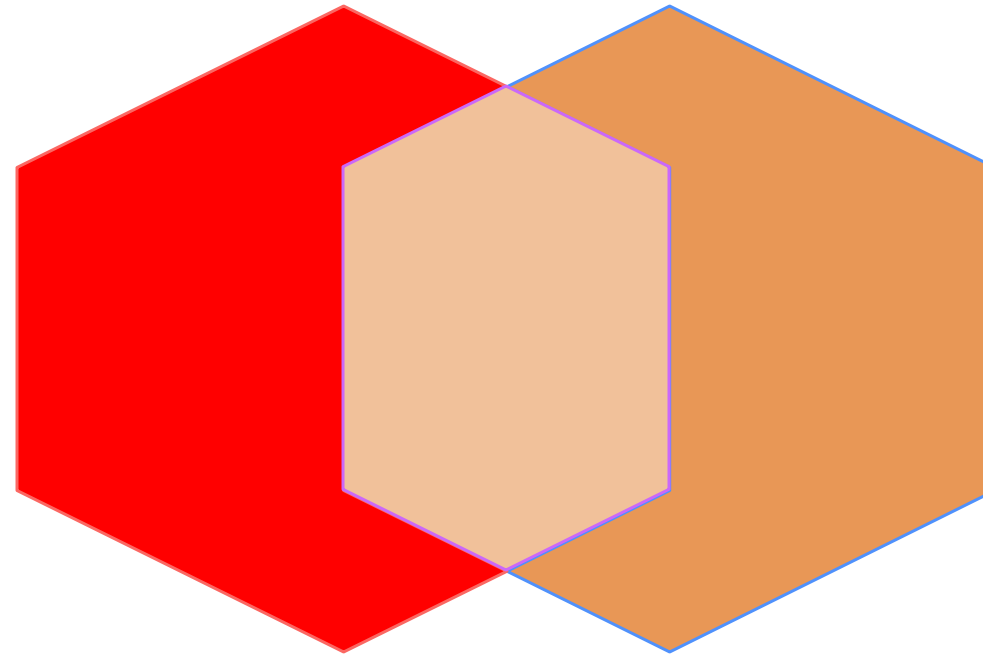


Where Coronary Blood Flow Meets Tissue Needs

Myocardial Perfusion Regulation

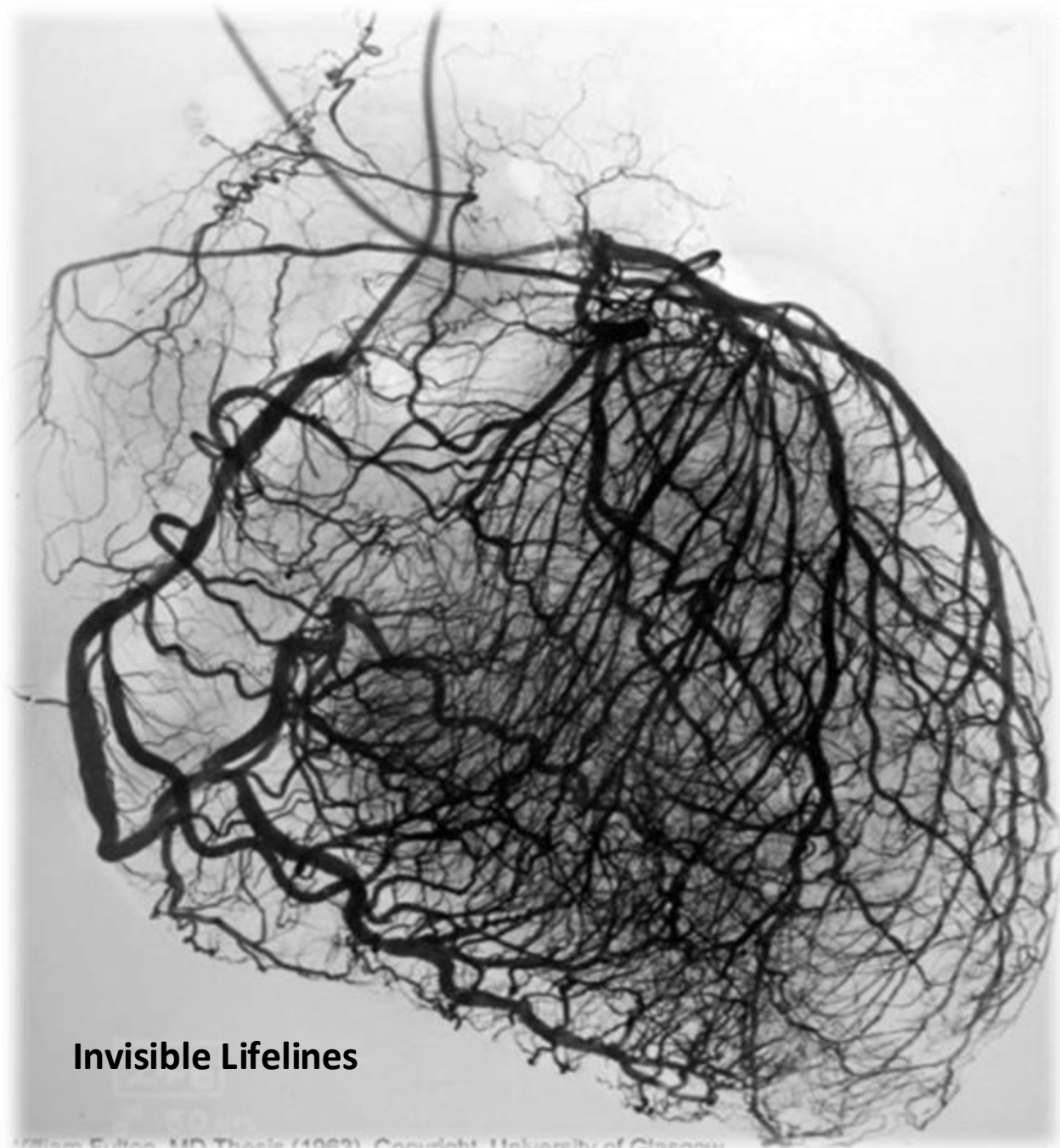
Integrated control of blood
flow and oxygenation

**Macrovascular
System**
Bulk blood delivery via
arteries



**Microvascular
Network**
Tissue-level perfusion and
exchange

Most disease in top 1/3 of coronaries



Invisible Lifelines

William Fulton, MD Thesis (1963). Copyright, University of Glasgow

Energy substrates Heart can pick

Free fatty acids are the primary energy source, providing 60–70% of the total ATP

Fatty acid translocase (CD36)
Helps move into cell

Glucose: In conditions of high workload or after a meal when insulin is elevated

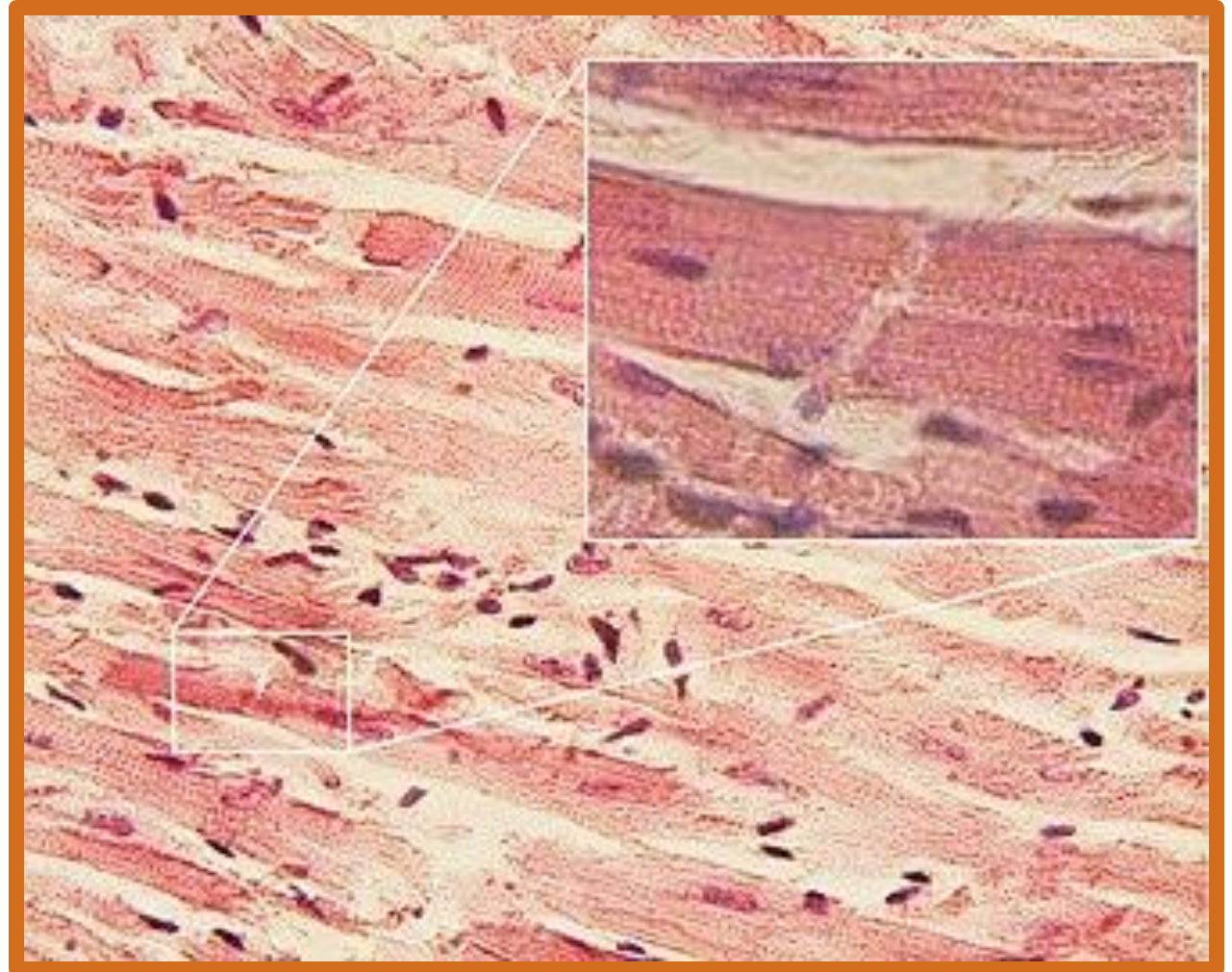
Contracting cardiomyocyte



Lactate: During exercise

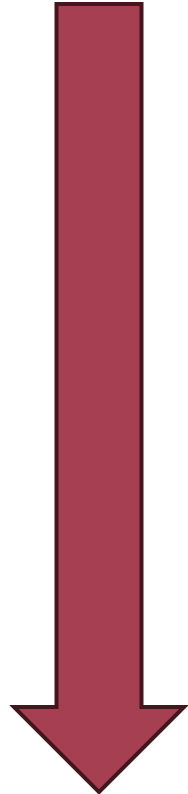
Ketone bodies: Most power per pound

Intricate network of capillaries surrounds each cardiomyocyte, ensuring a minimal diffusion distance



During reduced blood—**angina**—troponin leak

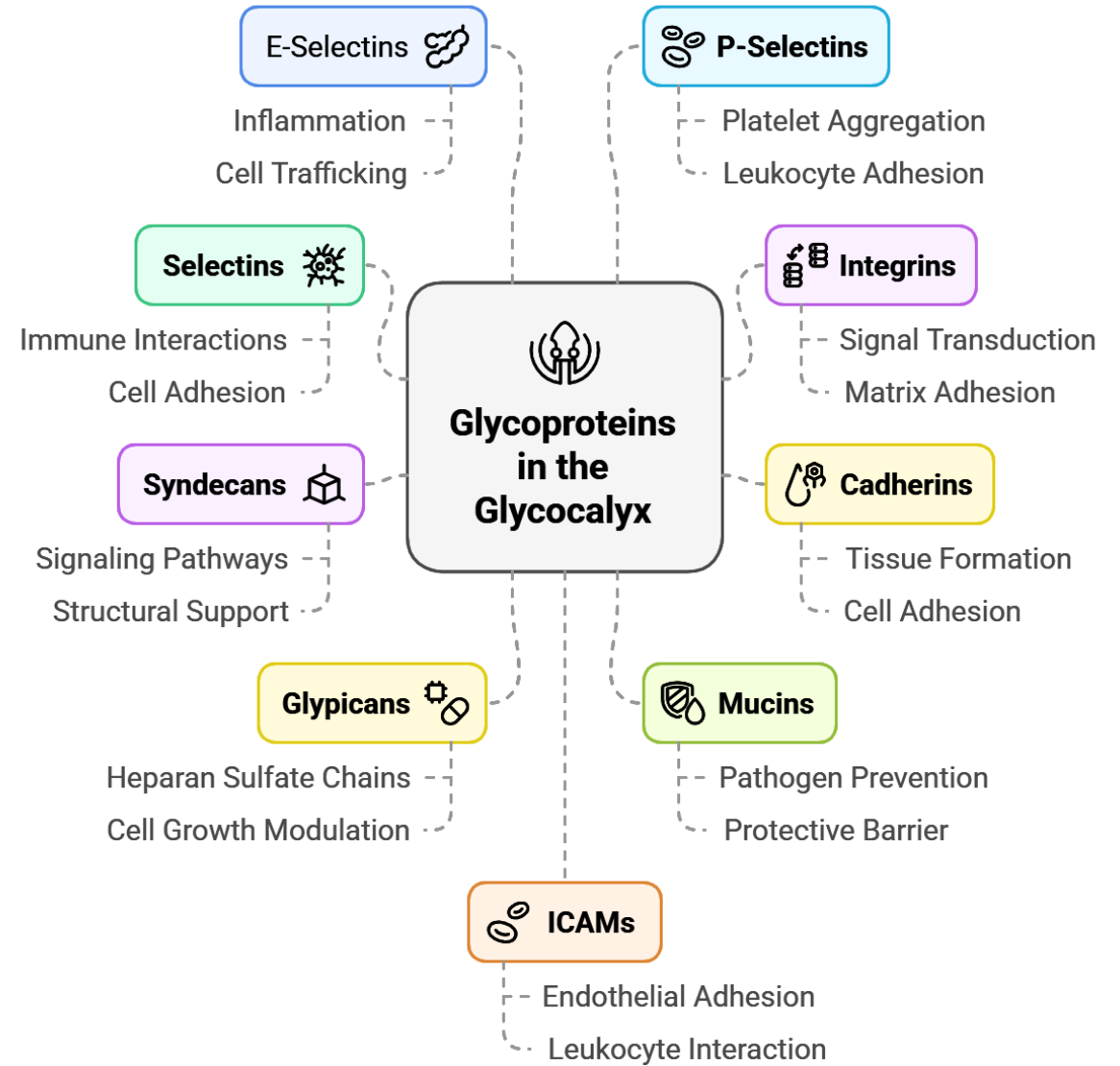
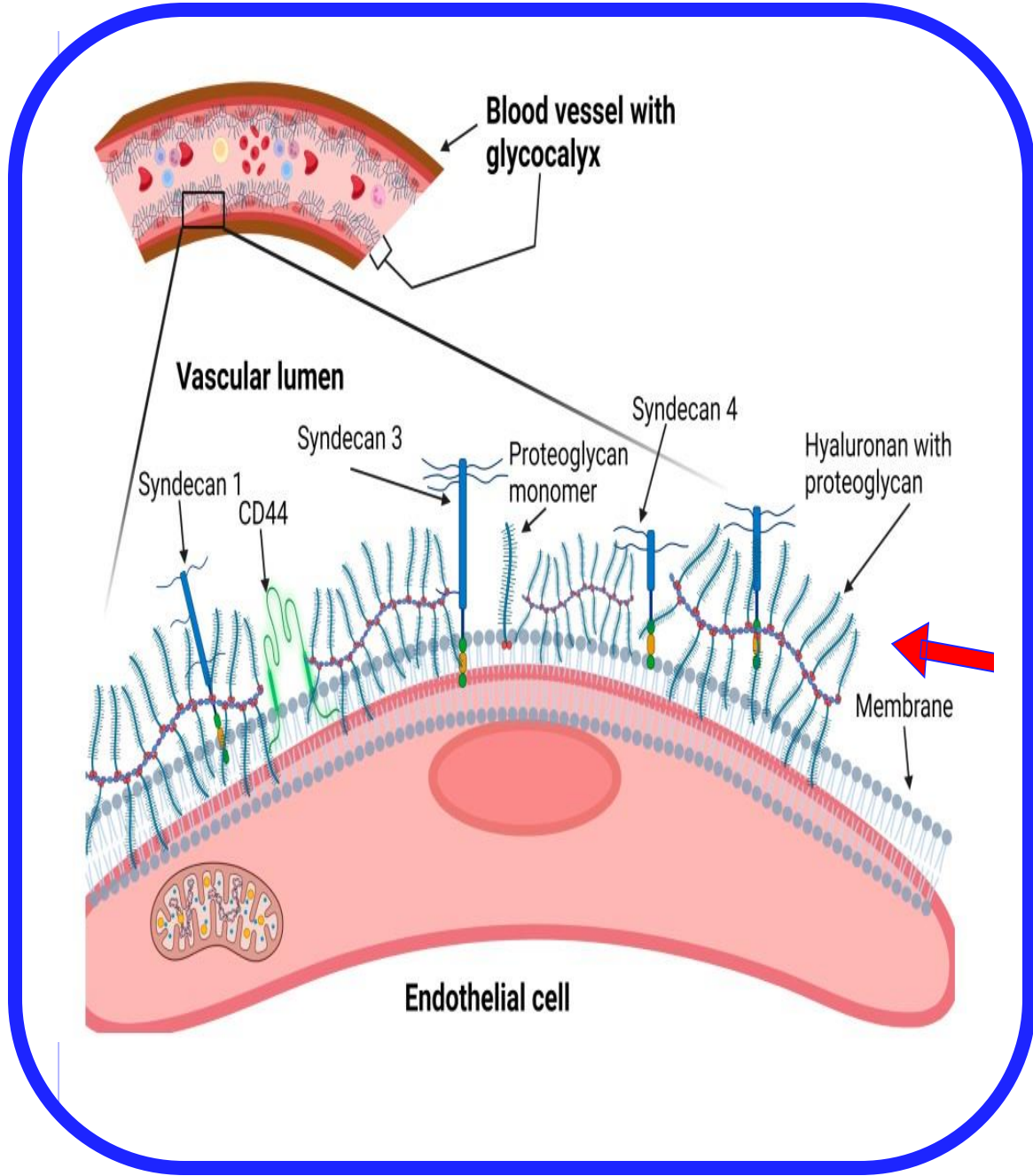
Anatomy and Physiology of Cardiac Microcirculation

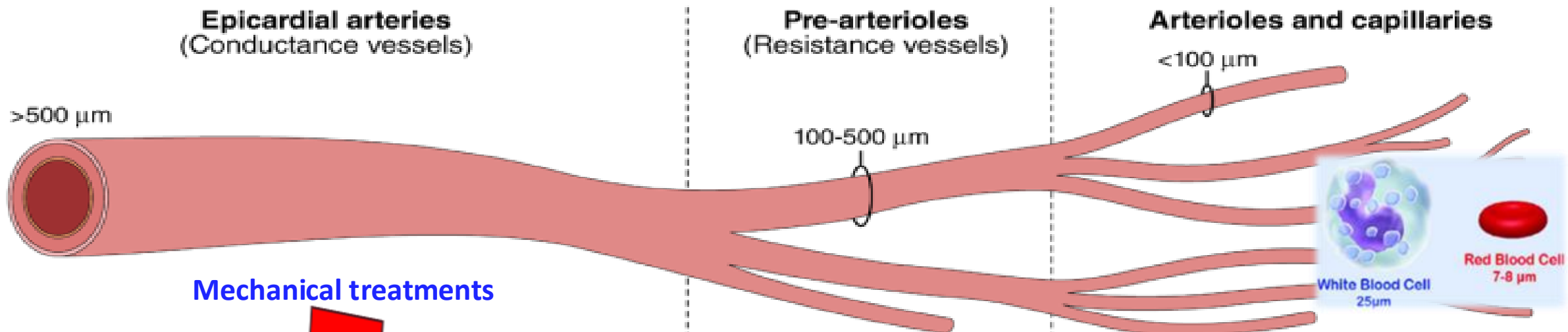


- Epicardial arteries (>500 μm) for low-resistance transport.
- Pre-arterioles (100-500 μm) to maintain pressure.
- Arterioles (<100 μm) for metabolic regulation via dilatation.
- Capillaries for **gas/nutrient exchange**. Oxygen
FFA/Glucose/Lactate/Ketones
- Role of **glycocalyx**, endothelial cells, smooth muscle, and pericytes in vascular tone.

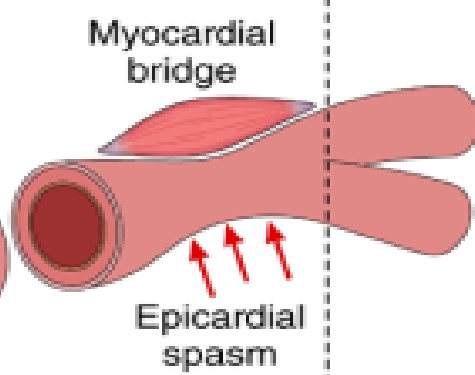
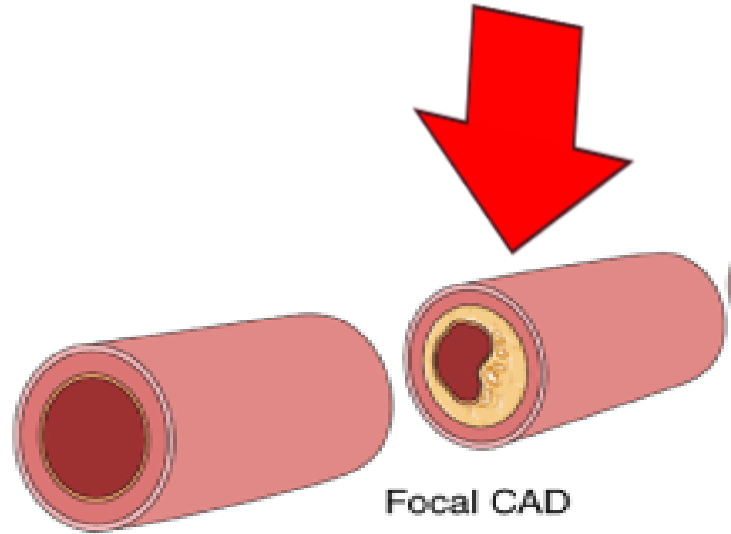
Microcirculation

Glycoproteins in the Glycocalyx: Roles and Functions

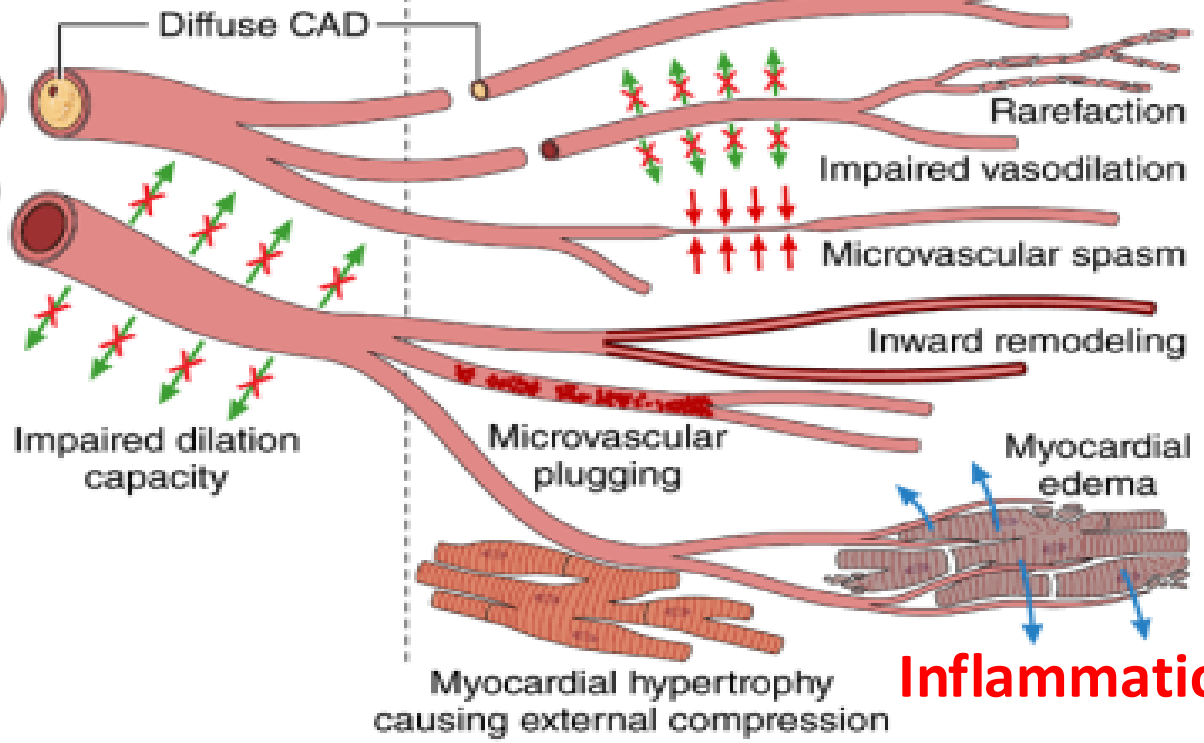




Mechanical treatments



Metabolic disease



smilowitz-et-al-2023
-coronary-microvascu

Macrocirculation

Microcirculation

Adapted from Smilowitz

Endothelial Cell Dynamics

1

Nitric oxide relaxes **smooth muscles**, causing vasodilation.

Nitric Oxide

2

Endothelin-1 promotes vasoconstriction, narrowing blood vessels.

Endothelin-1

3

Prostacyclin modulates vascular tone, preventing **platelet aggregation**.

Prostacyclin

4

Shear stress influences endothelial cell function and tone.

Shear Stress

5

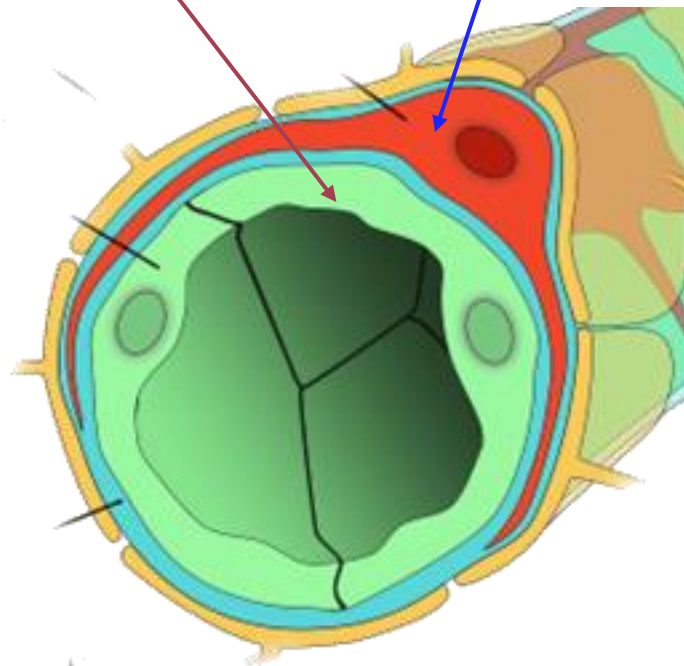
Chemical signals like acetylcholine affect vascular tone.

Chemical Signals

Vascular Tone Regulation 

Endothelial cell

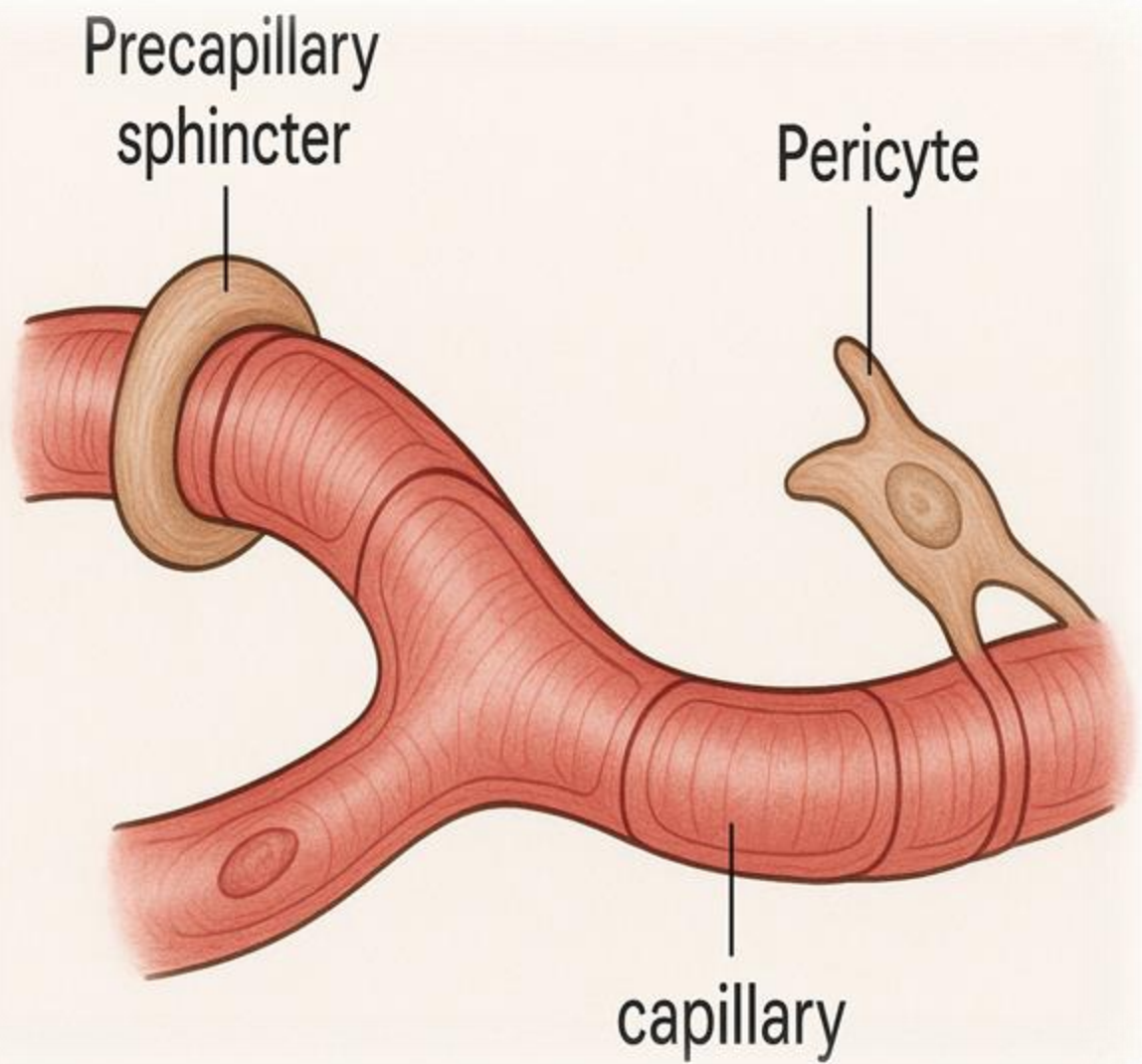
Pericyte



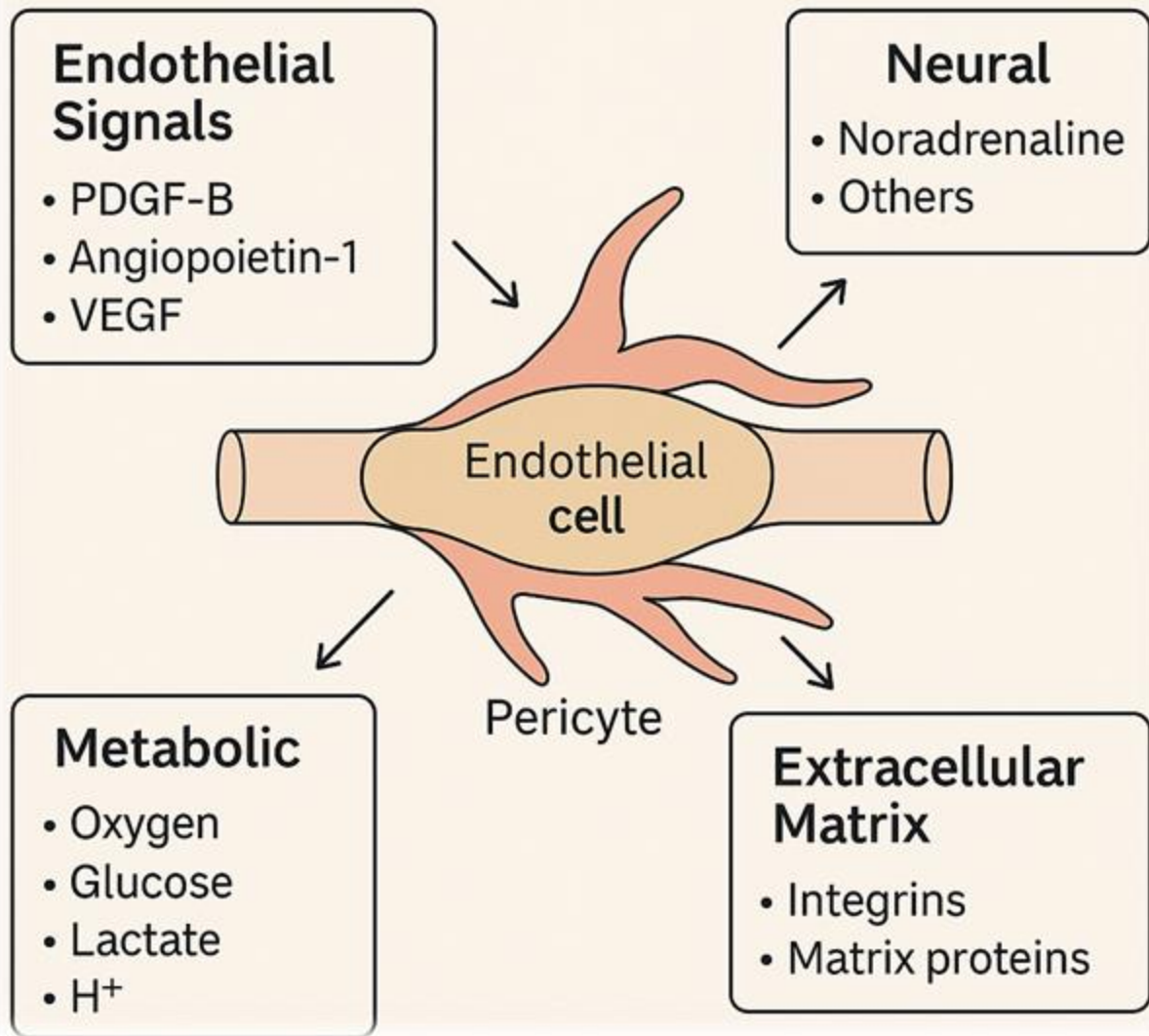
Hypoxia—increases oxidative stress

Alters glycolysis—**endothelial cell dysfunction**—increases lactate production

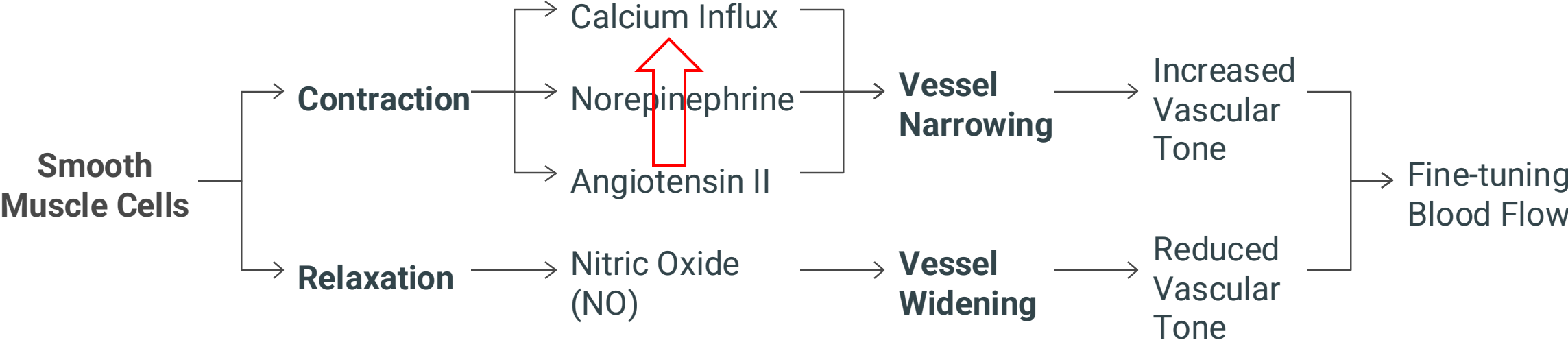




CONTROL OF PERICYTE



Smooth Muscle Cell Control of Vascular Tone



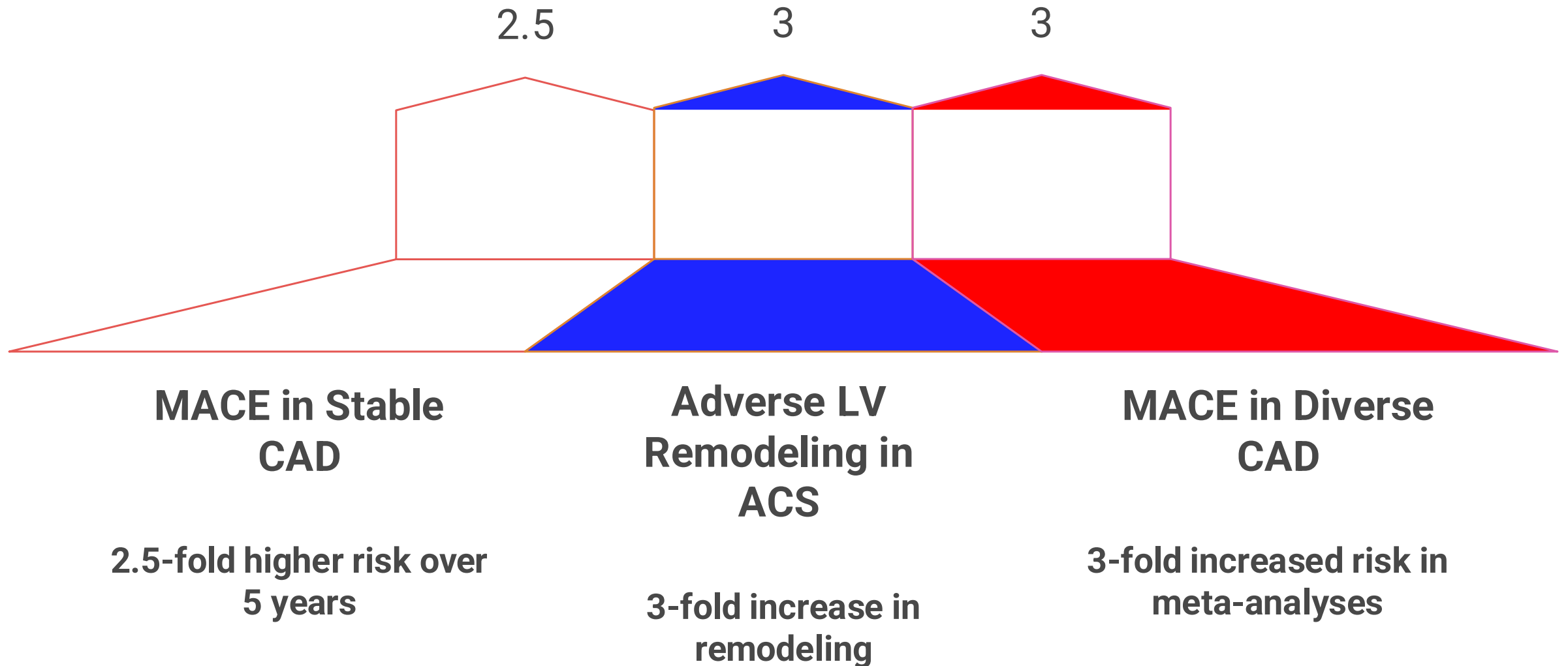


Physiology

- **Acute** adjustments: *Neurogenic*, **endothelial** (e.g., nitric oxide for vasodilation), and **metabolic factors**.
- **Chronic** adaptations: Structural remodeling influenced by **shear stress** and **inflammation**.

Coronary blood flow to oxygen demand:
healthy microvasculature can increase blood
flow 5-fold during stress

Impact of ↑↑ microcirculatory resistance on Cardiovascular Outcomes



The Endothelial Glycocalyx Cycle

Proatherogenic Course

The vasculature enters a proatherogenic state.

Decline in EC Health

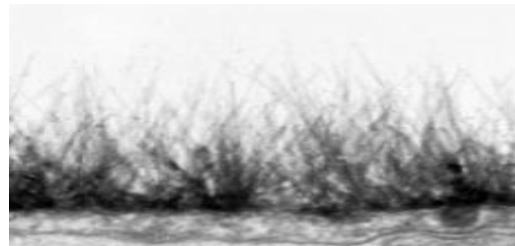
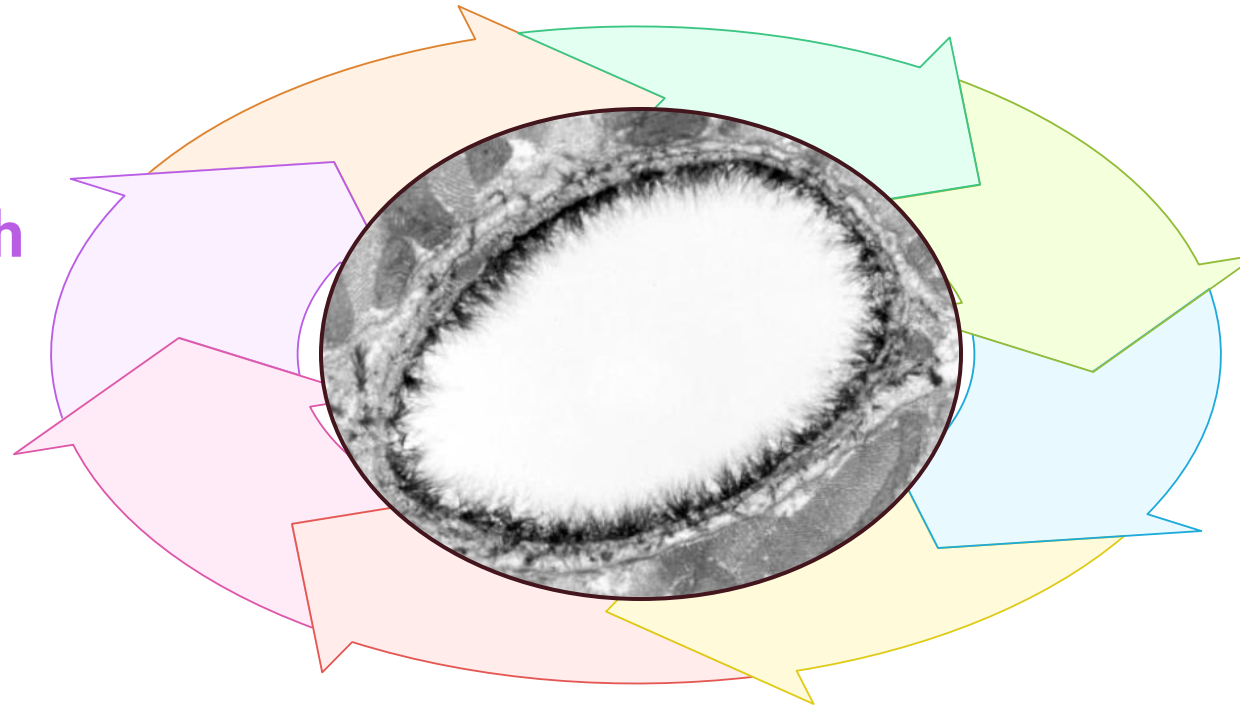
EC health declines due to GCX damage.

Compromised Integrity

Loss of GCX integrity affects EC architecture.

Deterioration

Exposure to glucose and ROS deteriorates the GCX.



Formation

The GCX is formed from proteoglycans, glycosaminoglycans, and glycolipids.

Shedding

The GCX constantly sheds its components.

Regrowth

The GCX regrows to maintain its structure.

Mechanotransduction

The GCX mediates mechanotransduction

Twelve-months treatment with dapagliflozin improves endothelial glycocalyx and cardiovascular function in patients with type 1 diabetes mellitus

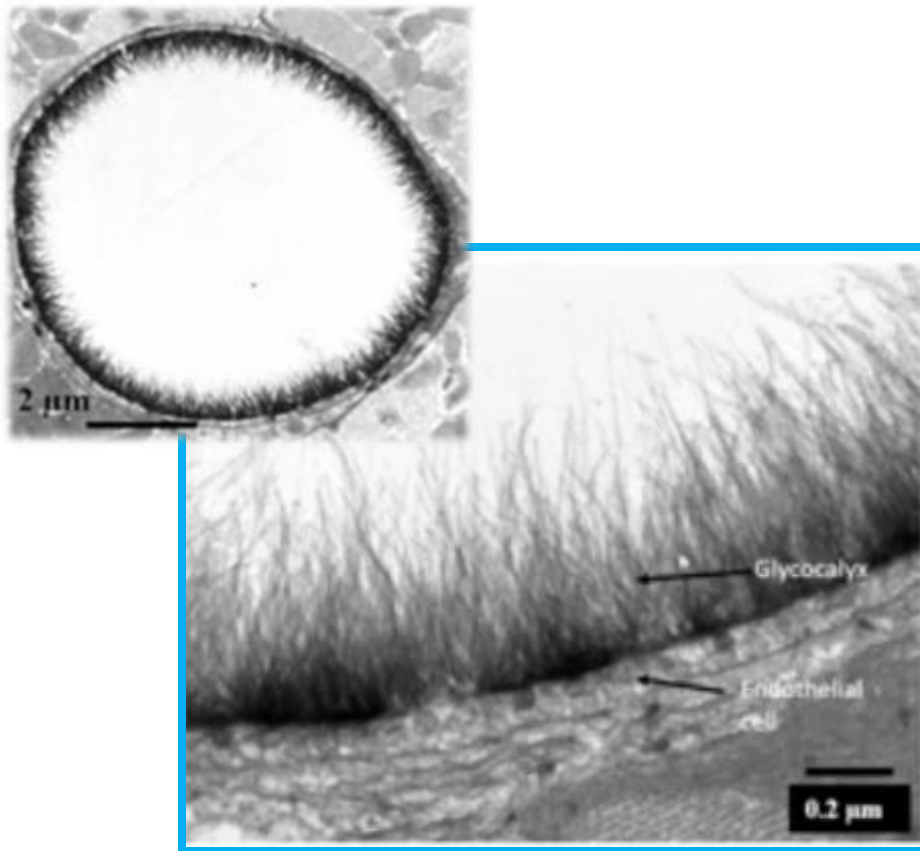
I. Ikonomidis¹, K. Katogiannis², A. Kountouri³, G. Pavlidis², J. Thymis², E. Korakas², G. Kostelli², E. Katsanaki², E. Michalopoulou², D. Vlachomitros², L. Pliouta³, K. Balampanis³, V. Lambadiari³

¹National & Kapodistrian University of Athens, Athens, Greece

²National & Kapodistrian University of Athens, Attikon University Hospital, 2nd Cardiology Department, Athens, Greece

³National & Kapodistrian University of Athens, 2nd Department of Internal Medicine, Research Unit and Diabetes Center, Attikon University Hospital, Athens, Greece

Funding Acknowledgements: None.



Background: Individuals diagnosed with type 1 diabetes mellitus (T1DM) exhibit indications of vascular and endothelial dysfunction earlier in comparison to healthy individuals. Evidence shows that SGLT-2 inhibitors (SGLT-2i) have a beneficial impact on cardiovascular health in individuals with type 2 diabetes mellitus (T2DM). We investigated the effects of dapagliflozin on endothelial and cardiovascular function in patients with T1DM.

Methods: We recruited in total 40 patients with T1DM and poor glycemic control who were treated with insulin and received dapagliflozin (n=20) or intensification of insulin treatment (n=20) (control group). We measured at baseline and at twelve months post-treatment the: a) Carotid-femoral pulse wave velocity (PWV-Complior; ALAM Medical) b) Central systolic blood pressure (cSBP) c) Perfused boundary region (PBR) of the sublingual arterial microvessels (marker of endothelial glycocalyx thickness) and d) Left ventricular global longitudinal strain (GLS) using speckle-tracking echocardiography.

Results: At baseline, patients among the two groups had similar age, sex, HbA1c and markers of endothelial and cardiovascular function ($p > 0.05$). After 12 months of treatment, patients who received dapagliflozin displayed an improvement in PBR5–25 (–16%, $p < 0.05$), in PWV (–9.3%, $p < 0.05$), in cSBP (–6%, $p < 0.05$) and in GLS (+4%, $P < 0.05$) compared to baseline. However, no statistically significant changes in PBR5–25, in PWV, in cSBP and in GLS were observed after intensification of insulin treatment (PBR5–25: +0.4%, PWV: -1%, cSBP: –2%, GLS: –1% at 4 months, $P > 0.05$), despite a similar HbA1c reduction (Table 1). Changes of PBR after one year treatment with dapagliflozin correlated with a concomitant reduction of PWV and cSBP ($P < 0.05$).

Conclusions: Twelve months treatment with dapagliflozin improves endothelial glycocalyx and cardiovascular function in patients with T1DM, independently of glycemic control.

	Dapagliflozin (n=20)				Controls (n=20)			
	baseline	12 months	p	Δ%	baseline	12 months	p	Δ%
PBR 5-25, μm	2.04±0.25	1.73±0.23	0.018	-16%	2.03±0.25	2.04±0.24	0.626	0.4
PWV, m/sec	10.62±2.78	9.63±2.31	0.015	-9.3	10.52±2.45	10.37±2.33	0.435	-1
cSBP, mmHg	126±15	118±13	0.035	-6	125±15	122±12	0.389	-2
GLS, %	-19.54±1.67	-20.32±1.47	0.032	4	-19.62±1.41	-19.55±1.72	0.543	-1



ehae666.2924 (2).pdf

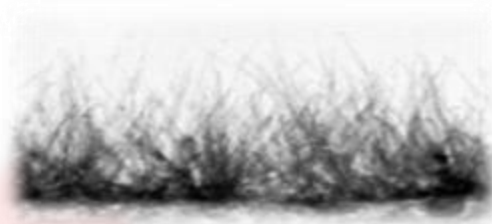


Atherosclerosis-natural history

Major diseases affecting human—**life expectancy**

Metabolic diseases

Obesity
Diabetes
Liver



Insulin resistance

Inflammation

Hypertension

New target

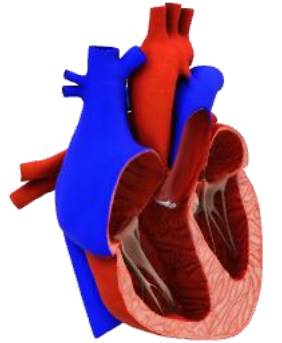
<130/80

Normal 117 systolic

ESC 2025

Surgery

Medicine

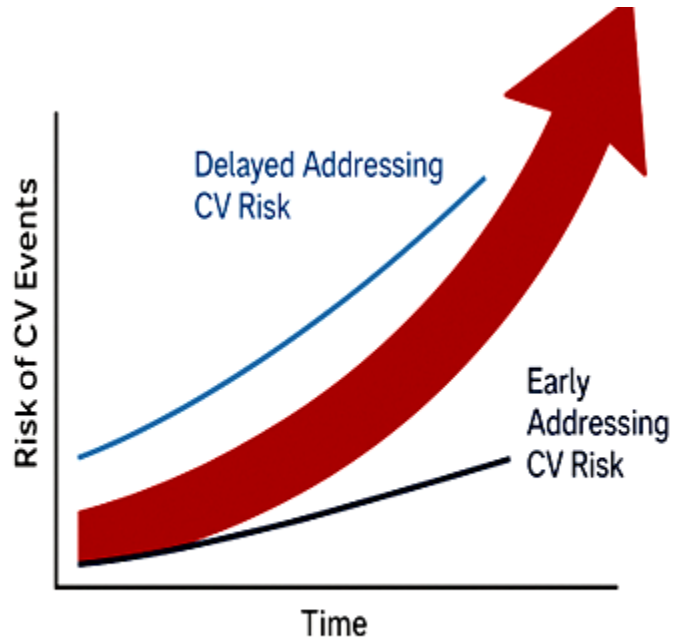


Can you reduce/eliminate excess risk of death/CV events in DM patients

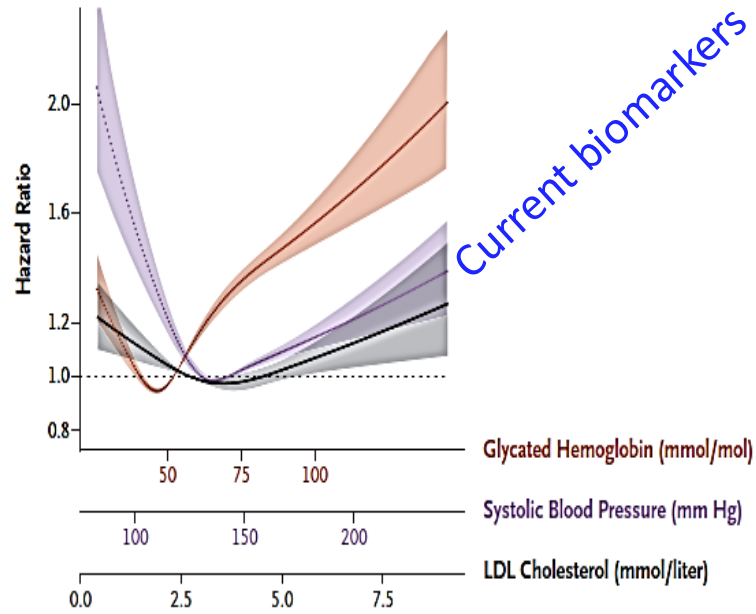
YES

271,174 patients with type 2 diabetes who were registered in the Swedish National Diabetes Register and matched them with 1,355,870 controls

N Engl J Med 2018;379:633-44

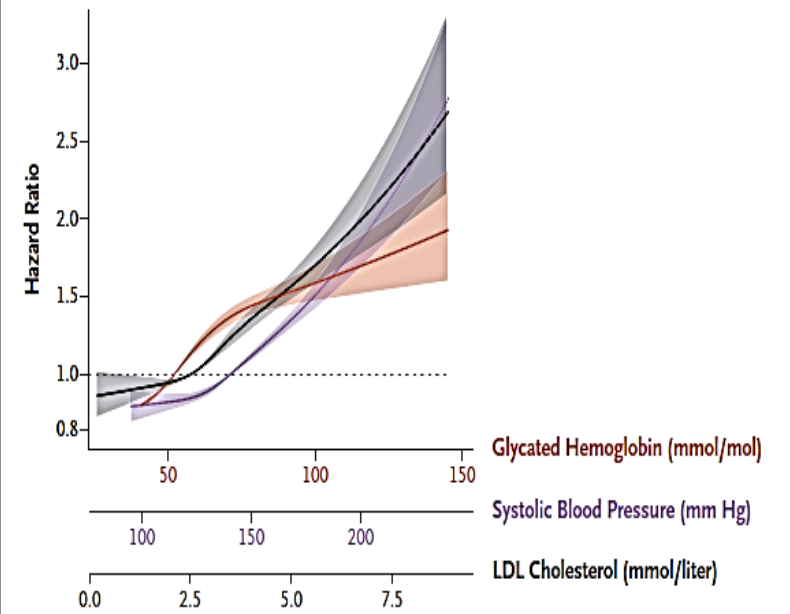


A Death from Any Cause

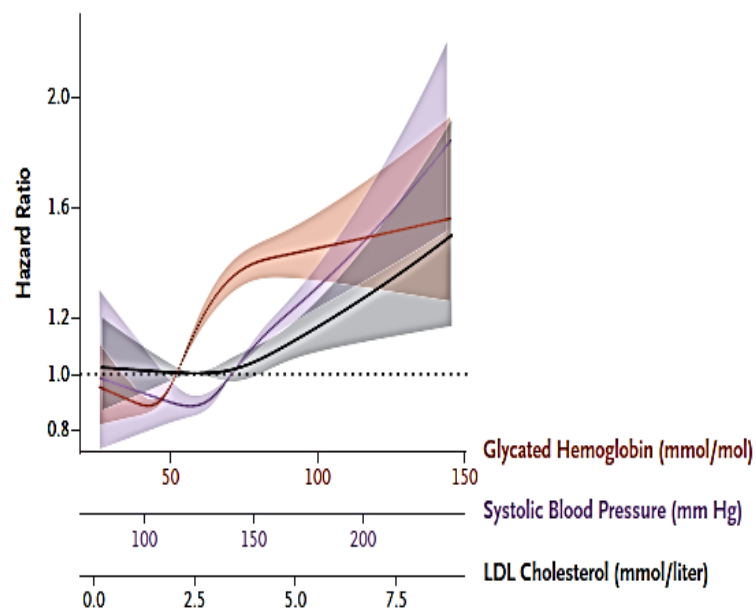


Current biomarkers

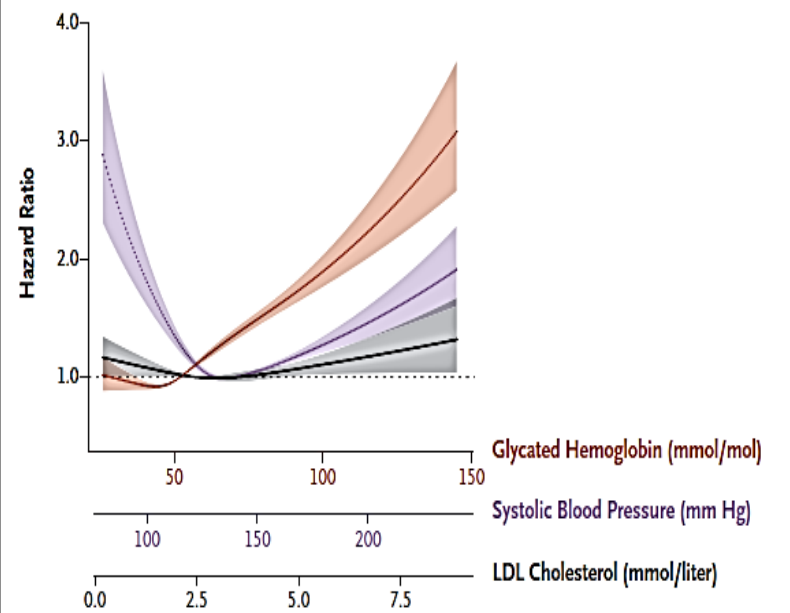
B Acute Myocardial Infarction

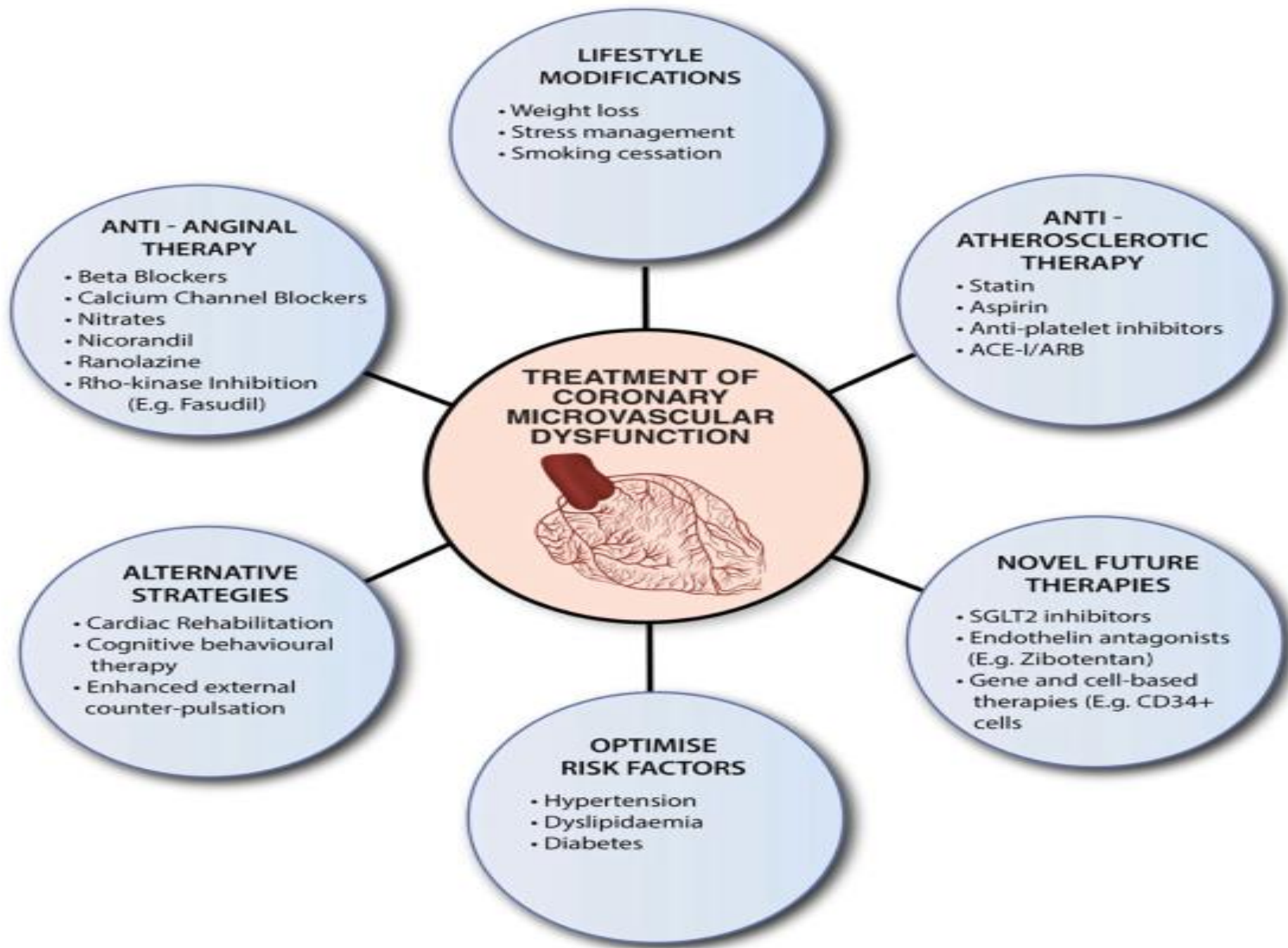


C Stroke



D Heart Failure





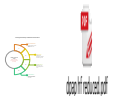
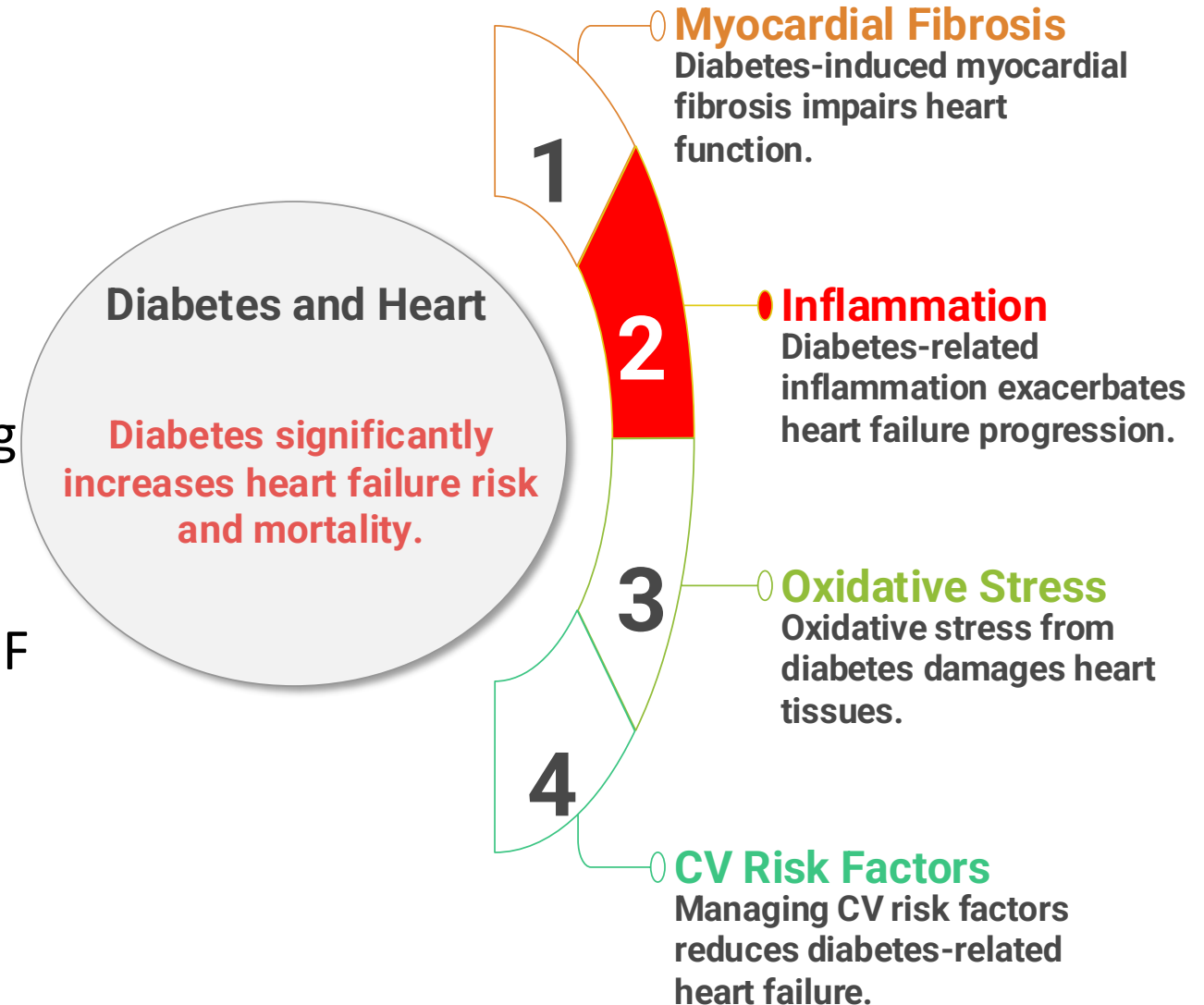
KEY POINTS: METABOLIC DISEASE

- Approximately 20–40% of HF patients have **type 2 diabetes**, increasing the risk of **CV events** and mortality.
- Diabetes contributes to HF through mechanisms like myocardial fibrosis, **inflammation**, and **oxidative stress**, forming a CV risk continuum.
- **Early management of CV risk factors** (e.g., glycemic control, blood pressure) reduces HF incidence and improves outcomes.

Circulation, 140(7), e294–e324

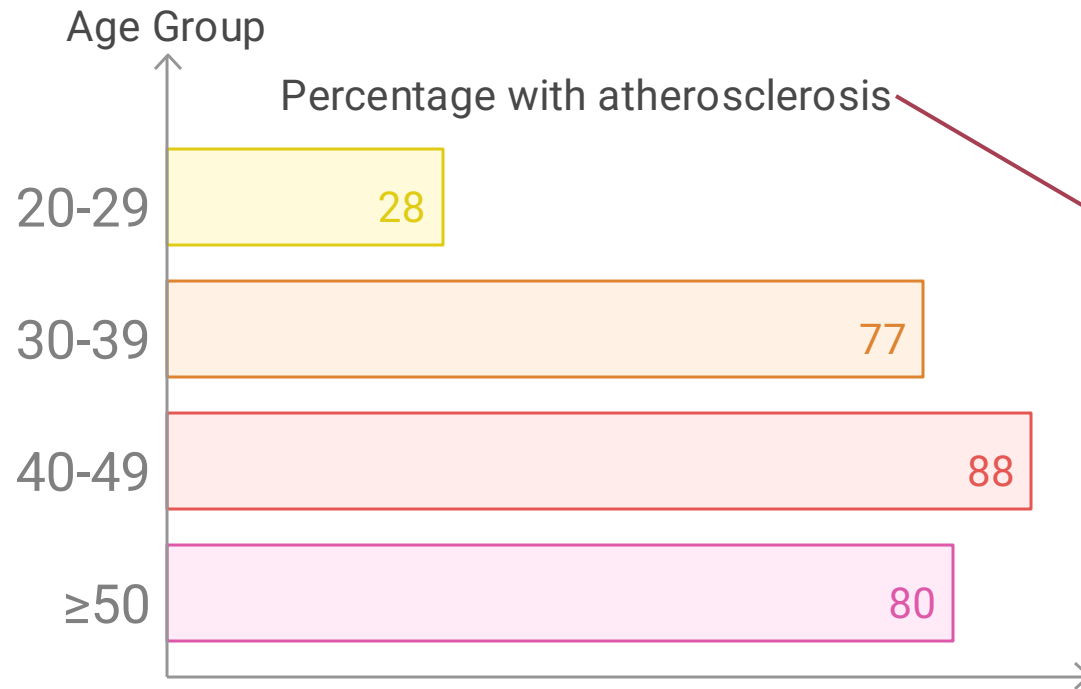
NEJM, 383(15), 1413–1424

Translational Pathways in CV disease

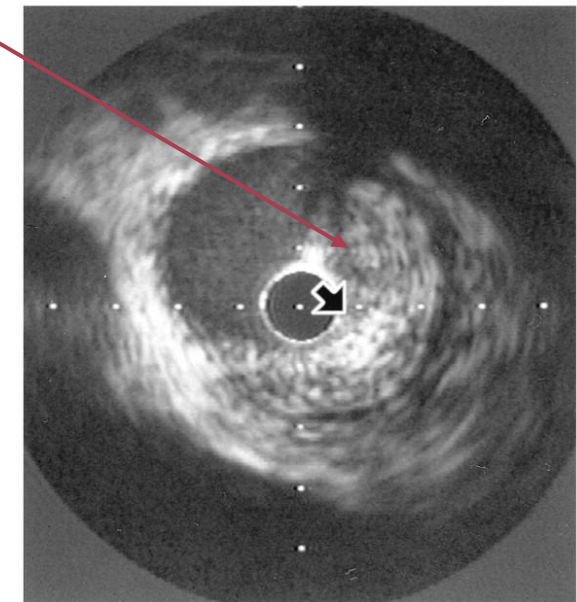
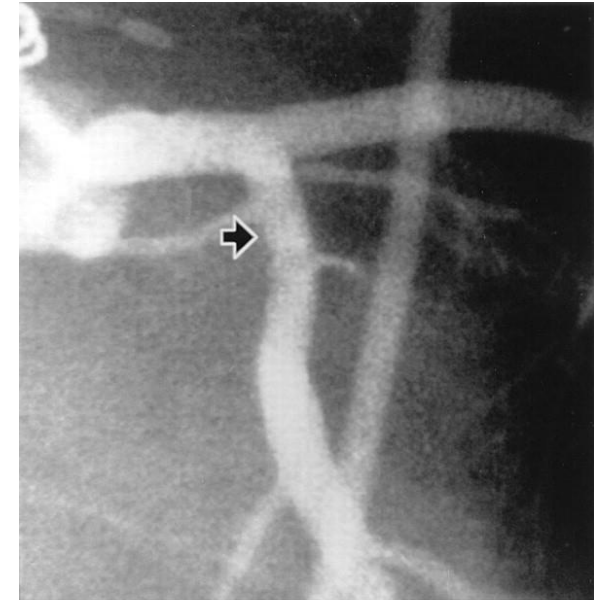


Translational biology-large vessels

57 patients-accidental deaths



Distribution by Age Group



Prospective study, 697 patients with acute coronary syndromes

3-year cumulative rate of major adverse cardiovascular events

After percutaneous coronary intervention.

Endpoint: major adverse cardiovascular events (death from cardiac causes, cardiac arrest, myocardial infarction, or rehospitalization due to unstable or progressive angina)

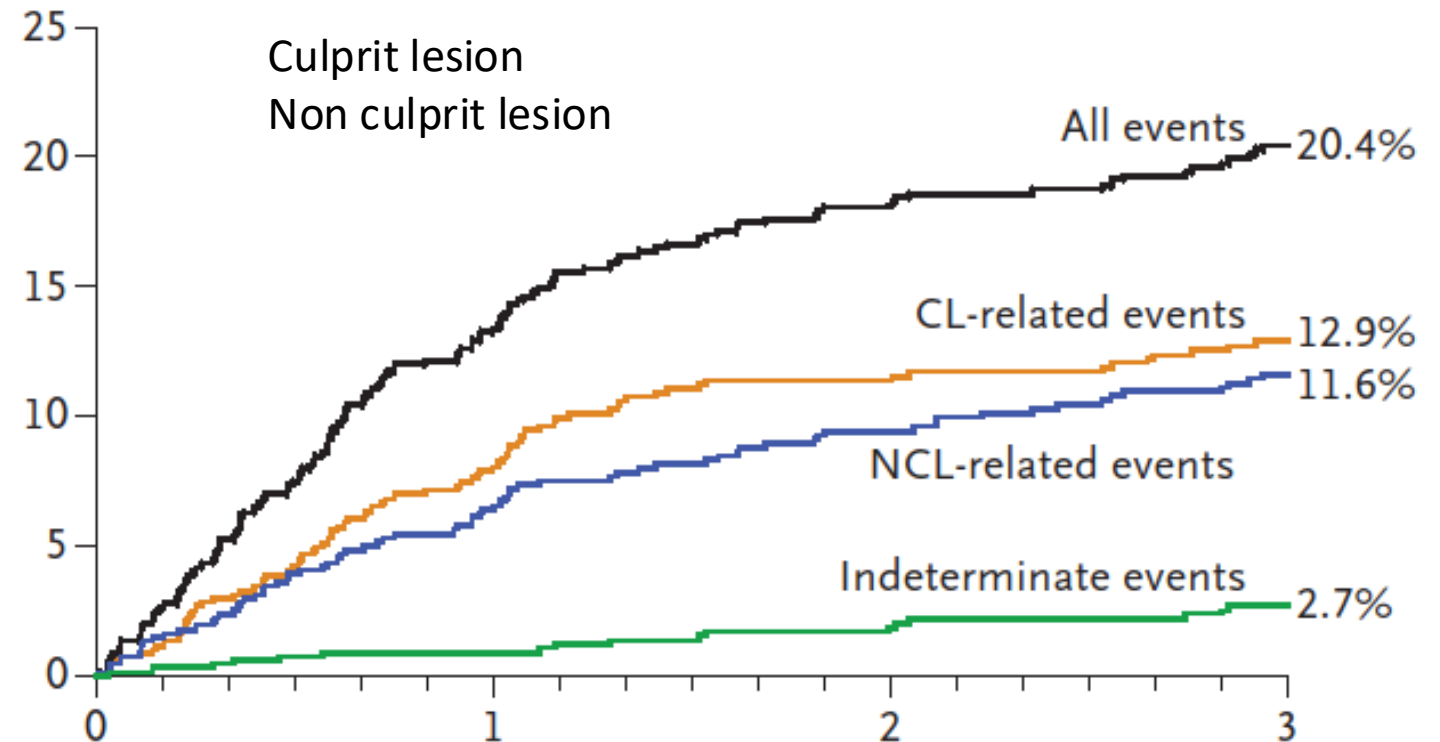


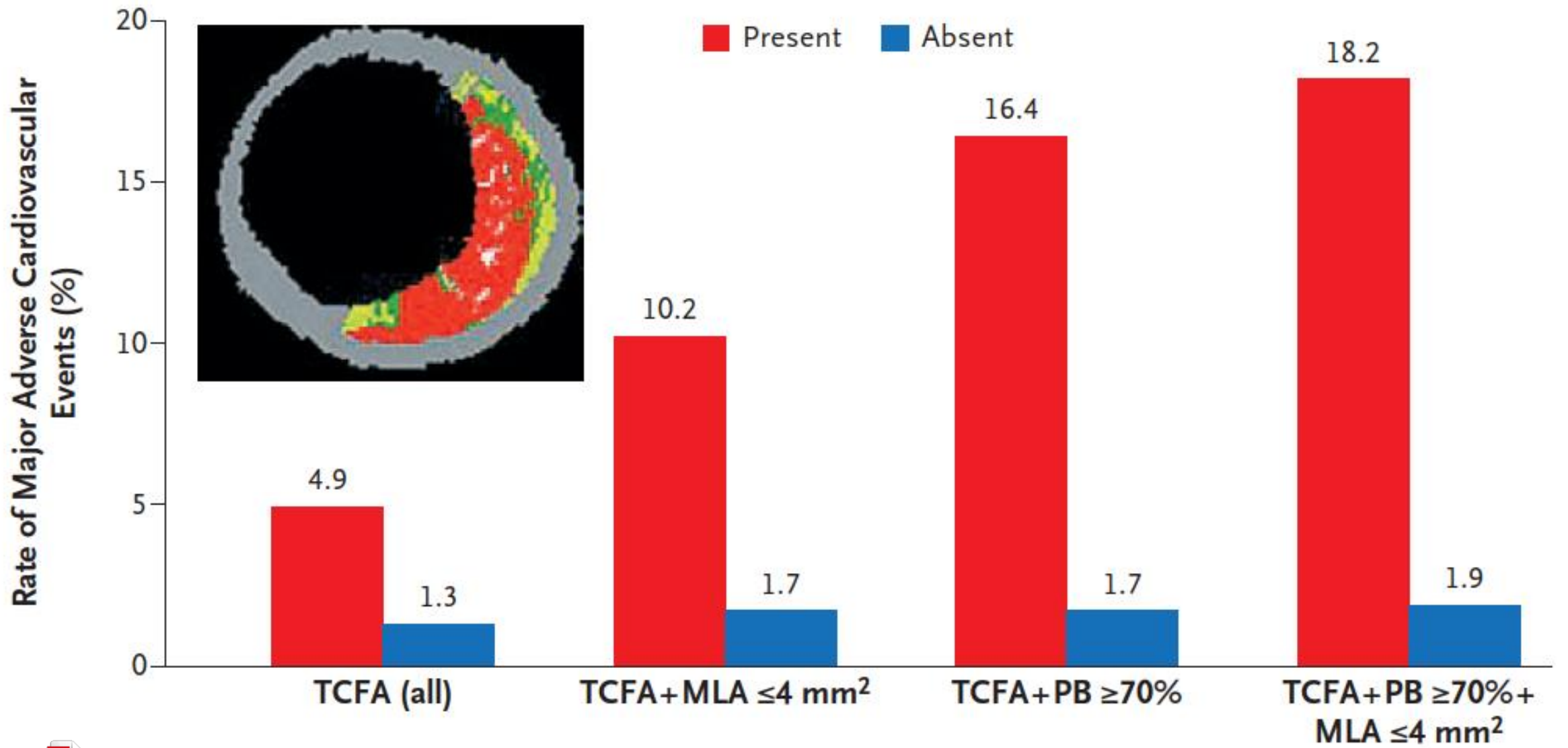
NEJMoa1002358 (2).pdf

N Engl J Med 2011;364:226-235

A Prospective Natural-History Study of Coronary Atherosclerosis

Gregg W. Stone, M.D., Akiko Maehara, M.D., Alexandra J. Lansky, M.D., Bernard de Bruyne, M.D., Ecaterina Cristea, M.D., Gary S. Mintz, M.D., Roxana Mehran, M.D., John McPherson, M.D., Naim Farhat, M.D., Steven P. Marso, M.D., Helen Parise, Sc.D., Barry Templin, M.B.A., Roseann White, M.A., Zhen Zhang, Ph.D., and Patrick W. Serruys, M.D., Ph.D., for the PROSPECT Investigators*





Clinical trials

Advancements in ACS Revascularization

Tailored DAPT duration

Adjusting DAPT based on patient-specific risks.



Individualized SCAD management

Tailored strategies for complex SCAD cases.



COMPLETE trial- PCI in high-risk patients

Complete procedure for high-risk individuals.

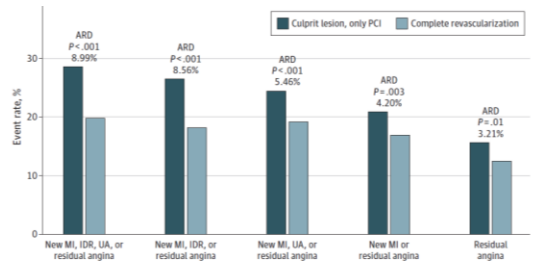


Early invasive strategy

Standard approach for NSTEMI/STEMI patients.



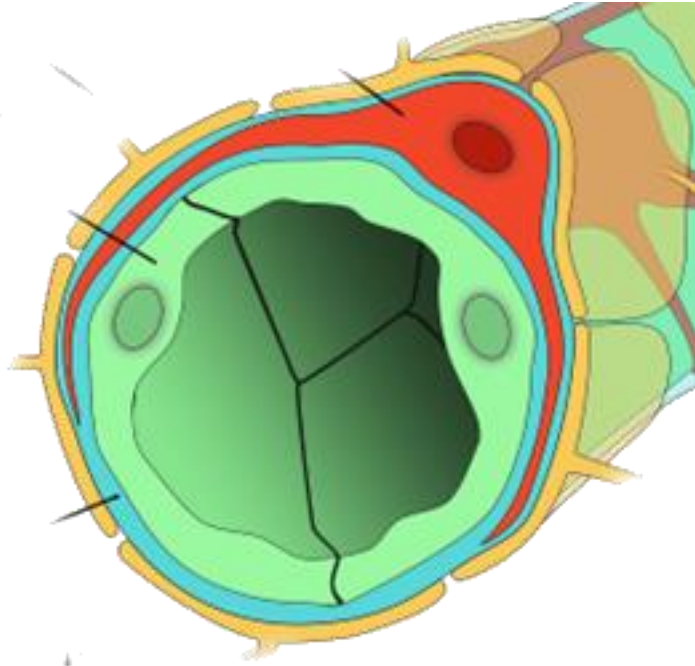
CV events



ARD indicates absolute risk difference; IDR, ischemia-driven revascularization; MI, myocardial infarction; PCI, percutaneous coronary intervention; UA, unstable angina.

OCT substudy revealed a large proportion of thin-cap fibroatheroma in nonculprit obstructive lesions

Can revascularization improve his prognosis? Even with EF<35



45 yo

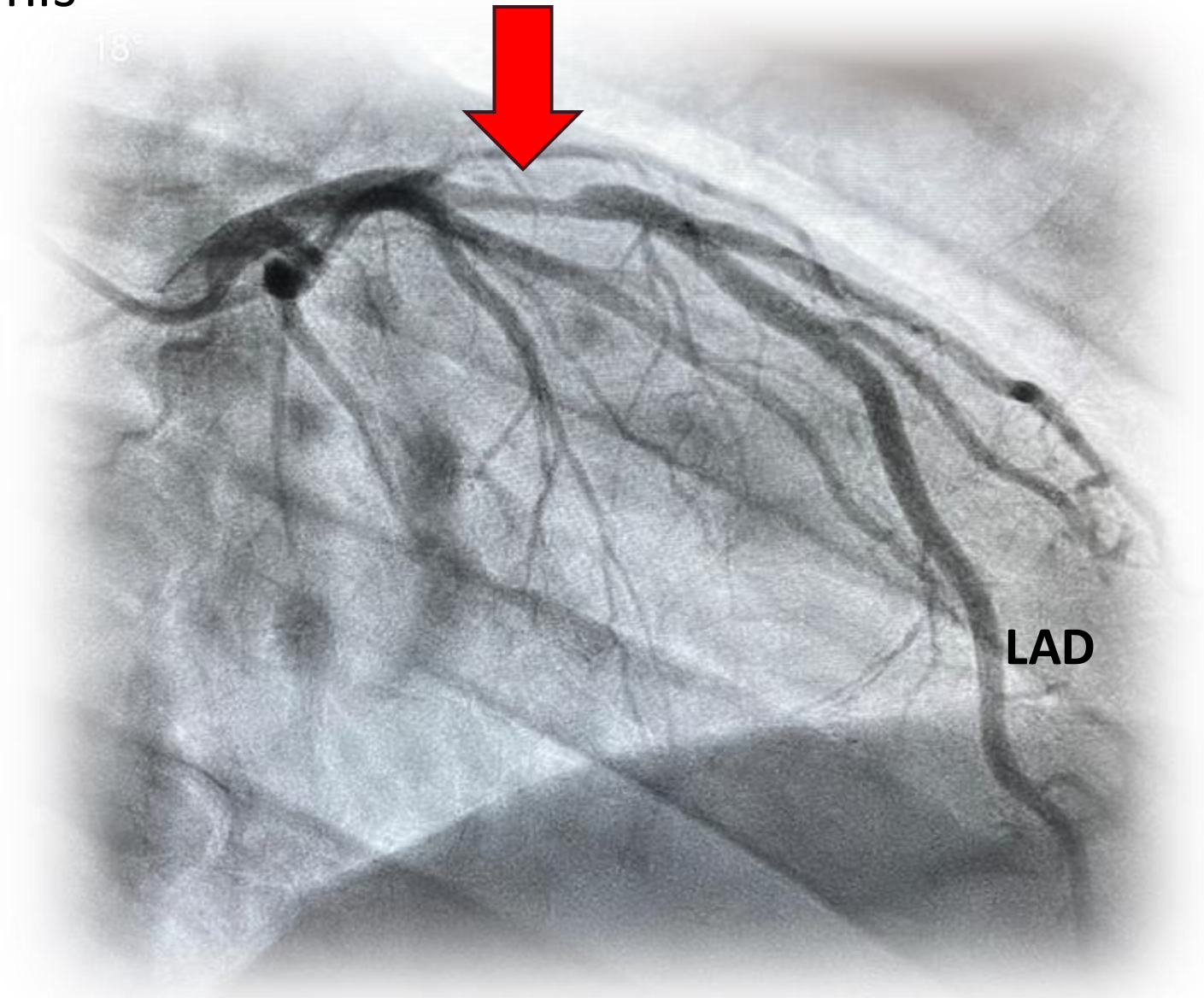
Exercises daily=no angina

BMI 22

BP 126/80

Low stress job

86 y/o Mom and dad actively living snow skiing



Stable ischemic heart disease

Should surgical revascularization be performed in patients with **stable multivessel** disease?

Perform Revascularization

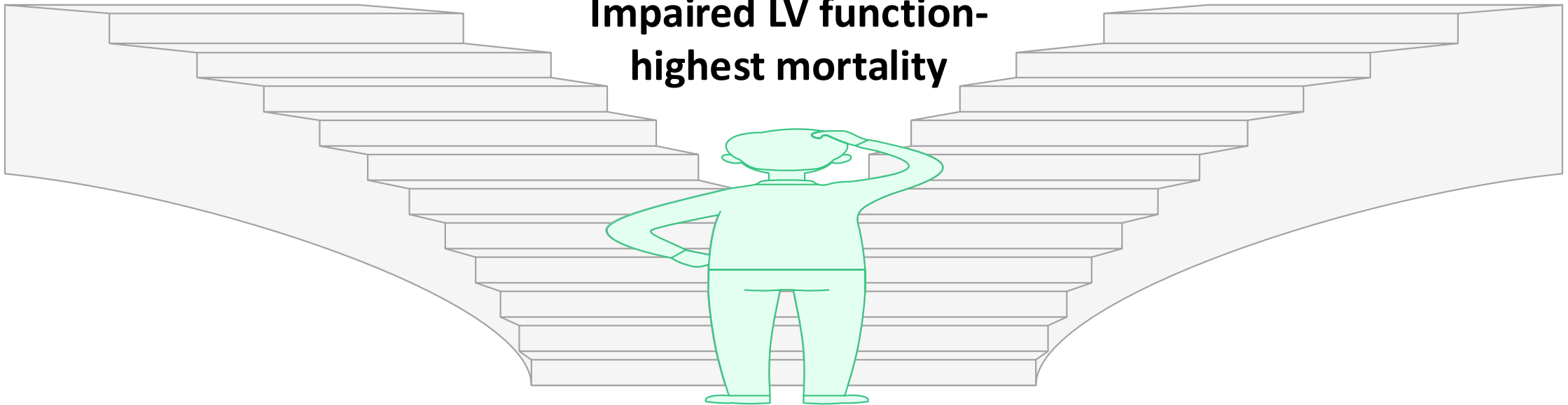
May improve **prognosis** and LV function if myocardial viability is present.

Evidence for Prognosis..
the likely course of a disease

Do Not Perform Revascularization

May lead to **higher mortality** rates without myocardial viability.

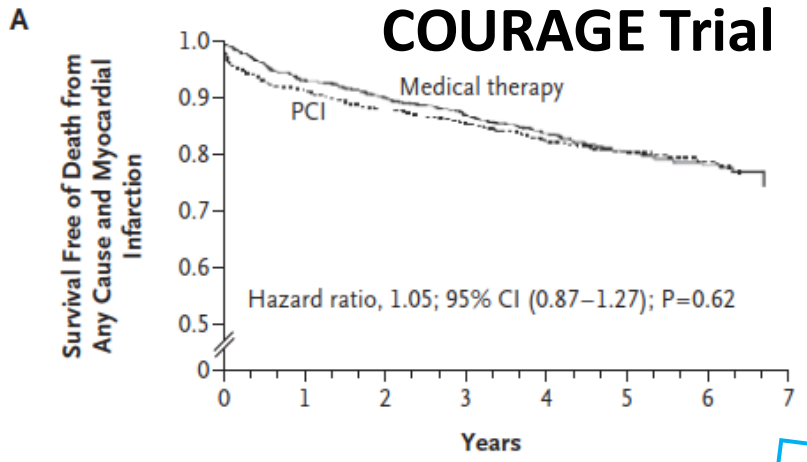
**Impaired LV function-
highest mortality**



Optimal Medical Therapy with or without PCI for Stable Coronary Disease

William E. Boden, M.D., Robert A. O'Rourke, M.D., Koon K. Teo, M.B., B.Ch., Ph.D., Pamela M. Hartigan, Ph.D., David J. Maron, M.D., William J. Kostuk, M.D., Merrill Knudtson, M.D., Marcia Dada, M.D., Paul Caspersen, Ph.D., Crystal L. Harris, Pharm.D., Bernard R. Chaitman, M.D., Leslie Shaw, Ph.D., Gilbert Gosselin, M.D., Shah Nawaz, M.D., Lawrence M. Tobe, M.D., Gerald Gau, M.D., Alex S. Blument, M.D., David C. Booth, M.D., Eric R. Bates, M.D., John A. Spertus, M.D., M.P.H., Daniel S. Berman, M.D., G.B. John Mancini, M.D., and William S. Weintraub, M.D., for the COURAGE Trial Research Group*

Randomized trial involving 2287 patients who had **objective evidence of myocardial ischemia** and significant coronary artery disease

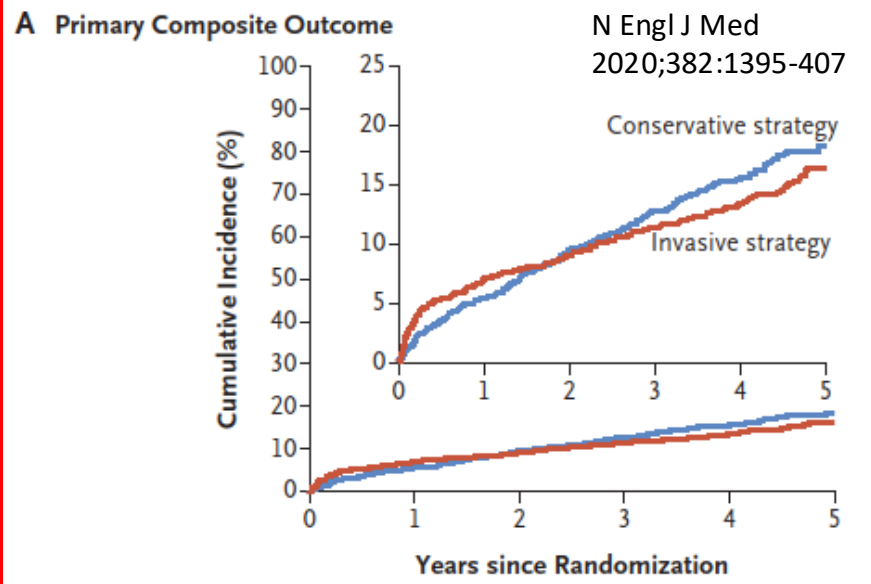


N Engl J Med 2007;356:1503-16.



Initial Invasive or Conservative Strategy for Stable Coronary Disease

D.J. Maron, J.S. Hochman, H.R. Reynolds, S. Bangalore, S.M. O'Brien, W.E. Boden, B.R. Chaitman, R. Senior, J. López-Sendón, K.P. Alexander, R.D. Lopes, L.J. Shaw, J.S. Berger, J.D. Newman, M.S. Sidhu, S.G. Goodman, W. Ruzyllo, G. Gosselin, A.P. Maggioni, H.D. White, B. Bhargava, J.K. Min, G.B.J. Mancini, D.S. Berman, M.H. Picard, R.Y. Kwong, Z.A. Ali, D.B. Mark, J.A. Spertus, M.N. Krishnan, A. Elghamazy, N. Moorthy, W.A. Hueb, M. Demkow, K. Mavromatis, O. Bockeria, J. Peteiro, T.D. Miller, H. Szwed, R. Doerr, M. Keltai, J.B. Selvanayagam, P.G. Steg, C. Held, S. Kohsaka, S. Mavromichalis, R. Kirby, N.O. Jeffries, F.E. Harrell, Jr., F.W. Rockhold, S. Broderick, T.B. Ferguson, Jr., D.O. Williams, R.A. Harrington, G.W. Stone, and Y. Rosenberg, for the ISCHEMIA Research Group*



ISCHEMIA



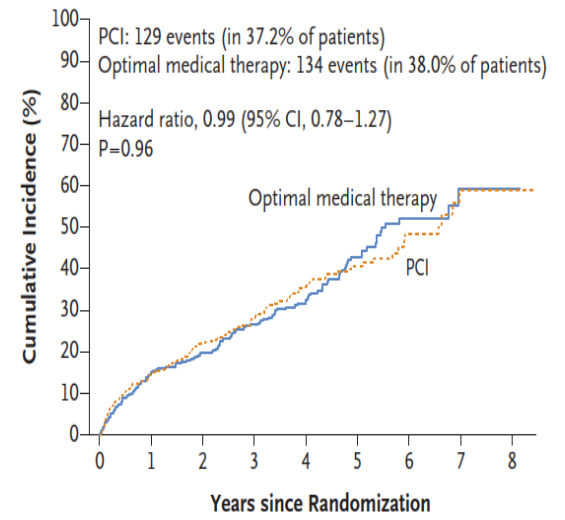
Excluded
Poor LV
LM or Prox LAD
Strongly +ETT

Excluded
Poor LV
LM

Randomly assigned 5179 patients with moderate or severe ischemia (>7%)

700 patients were randomized (347 to PCI, 353 to OMT alone)

REVIVED-BCIS2



No. at Risk

	0	1	2	3	4	5	6	7	8
PCI	347	295	262	179	130	80	32	14	3
Optimal medical therapy	353	299	276	191	142	82	33	10	1

LVEF <35%
14% Left Main Stented

N Engl J Med 2022;387:1351-60



Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction

Divaka Perera, M.D., Tim Clayton, M.Sc., Peter D. O’Kane, M.D., John P. Greenwood, Ph.D., Roshan Weerackody, Ph.D., Matthew Ryan, Ph.D., Holly P. Morgan, M.B., B.Ch., Matthew Dodd, M.Sc., Richard Evans, B.A., Ruth Canter, M.Sc., Sophie Arnold, M.Sc., Lana J. Dixon, Ph.D., Richard J. Edwards, Ph.D., Kalpa De Silva, Ph.D., James C. Spratt, M.D., Dwayne Conway, M.D., James Cotton, M.D., Margaret McEntegart, Ph.D., Amedeo Chiribiri, Ph.D., Pedro Saramago, Ph.D., Anthony Gershlick, M.D., Ajay M. Shah, M.D., Andrew L. Clark, M.D., and Mark C. Petrie, M.D., for the REVIVED-BCIS2 Investigators*

PCI vs. Medical Therapy for LV Dysfunction

Patients with a left ventricular ejection fraction of <35%

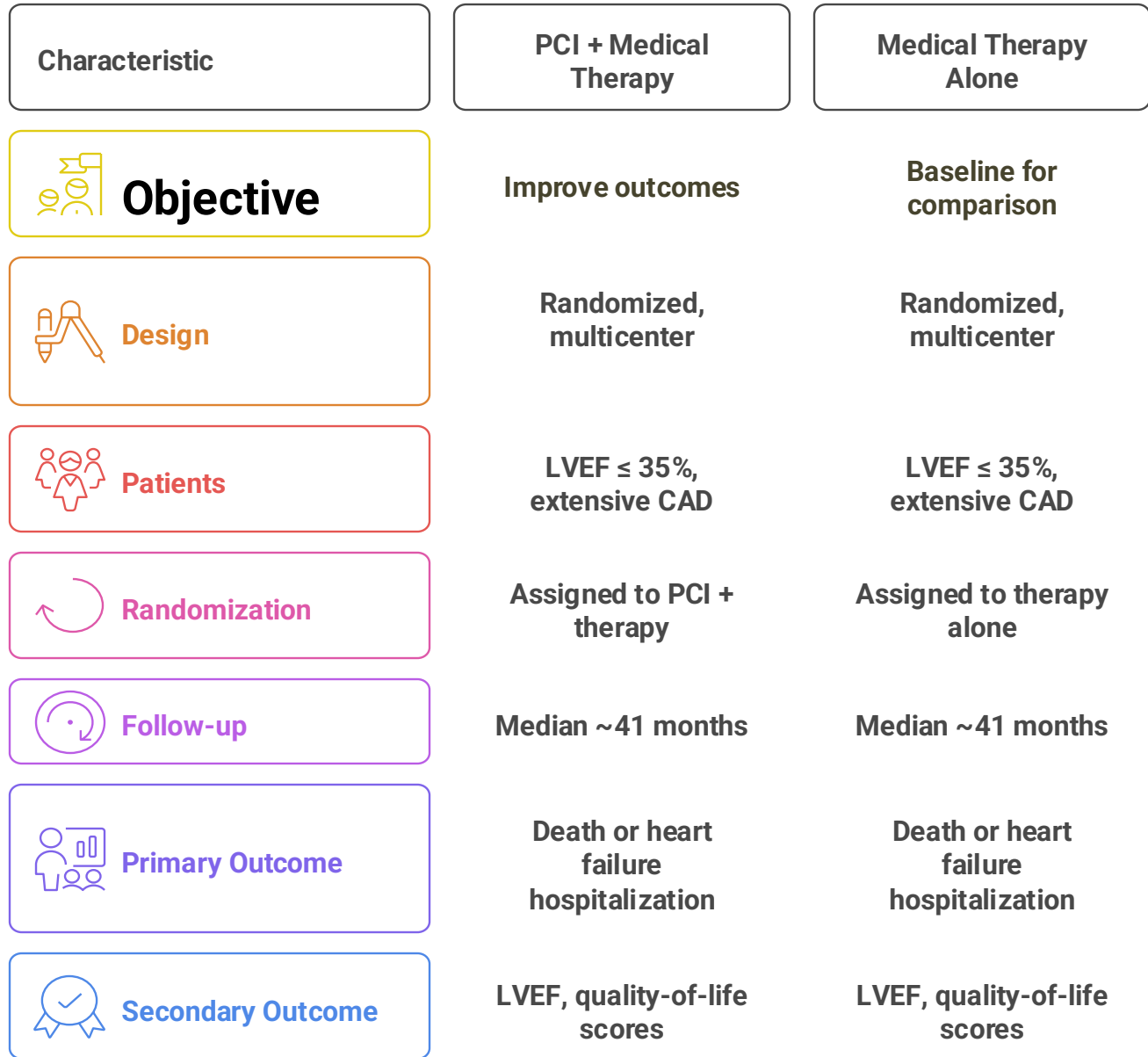
Extensive coronary artery disease amenable to PCI, and **demonstrable** myocardial viability to a strategy of either PCI plus optimal medical therapy or optimal medical therapy alone

Vessel size amenable to PCI >2.0 mm

Table 2. Primary and Secondary Outcomes.

Outcome	PCI (N=347)	Optimal Medical Therapy (N=353)	Treatment Effect (95% CI)*
Primary outcome			
Death from any cause or hospitalization for heart failure — no. (%)†	129 (37.2)	134 (38.0)	0.99 (0.78–1.27)

NS



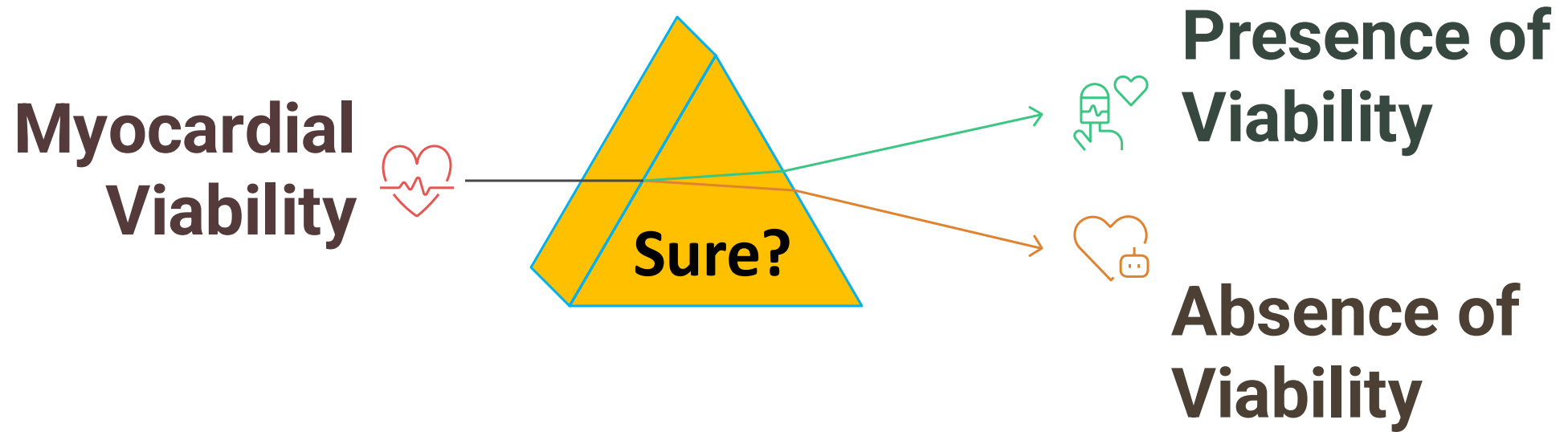
Patients with severe ischemic left ventricular systolic dysfunction who received optimal medical therapy, revascularization by **PCI did **not** result in a lower incidence of death from any cause or hospitalization for heart failure**

Table 2. Primary and Secondary Outcomes.

Outcome	PCI (N = 347)	Optimal Medical Therapy (N = 353)	Treatment Effect (95% CI)*
Primary outcome			
Death from any cause or hospitalization for heart failure — no. (%)†	129 (37.2)	134 (38.0)	0.99 (0.78–1.27)
Secondary outcomes‡			
Components of the primary outcome			
Death from any cause	110 (31.7)	115 (32.6)	0.98 (0.75–1.27)
Hospitalization for heart failure§	51 (14.7)	54 (15.3)	0.97 (0.66–1.43)
Death from cardiovascular causes — no. (%)¶	76 (21.9)	88 (24.9)	0.88 (0.65–1.20)
Acute myocardial infarction — no. (%)	37 (10.7)	38 (10.8)	1.01 (0.64–1.60)



Unveiling Myocardial Viability's Impact on Heart Prognosis



Revascularization to improve outcomes

In chronic coronary syndrome patients with left ventricular ejection fraction $\leq 35\%$

In CCS patients with LVEF $\leq 35\%$, it is recommended to choose between revascularization or medical therapy alone, after careful evaluation, preferably by the Heart Team, of coronary anatomy, correlation between coronary artery disease and LV dysfunction, comorbidities, life expectancy, individual risk-to-benefit ratio, and patient perspectives.

In surgically eligible CCS patients with LVEF $\leq 35\%$, revascularization may be preferred over medical therapy alone to improve outcomes.

In selected CCS patients with LVEF $\leq 35\%$, revascularization may be considered as a reasonable option.

	I	C
ed over	I	B
may be	IIb	B

after careful evaluation, preferably by the Heart Team, of coronary anatomy, correlation between coronary artery disease and LV dysfunction, comorbidities, life expectancy, individual risk-to-benefit ratio, and patient perspectives.

NO trial evidence required in level C

Revascularization to improve outcomes

In chronic coronary syndrome patients with left ventricular ejection fraction $\leq 35\%$

In CCS patients with LVEF $\leq 35\%$, it is recommended to choose between revascularization or medical therapy alone, after careful evaluation, preferably by the Heart Team, of coronary anatomy, correlation between coronary artery disease and LV dysfunction, comorbidities, life expectancy, individual risk-to-benefit ratio, and patient perspectives.

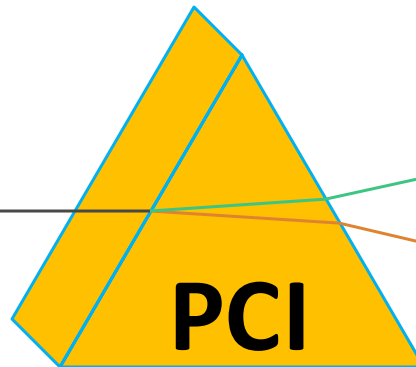
In surgically eligible CCS patients with multivessel CAD and LVEF $\leq 35\%$, myocardial revascularization with CABG is recommended over medical therapy alone to improve long-term survival.^{53,54,749,861}

In selected CCS patients with functionally significant MVD and LVEF $\leq 35\%$ who are at high surgical risk or not operable, PCI may be considered as an alternative to CABG.^{526,729}

I	C
I	B
IIb	B



Myocardial Viability



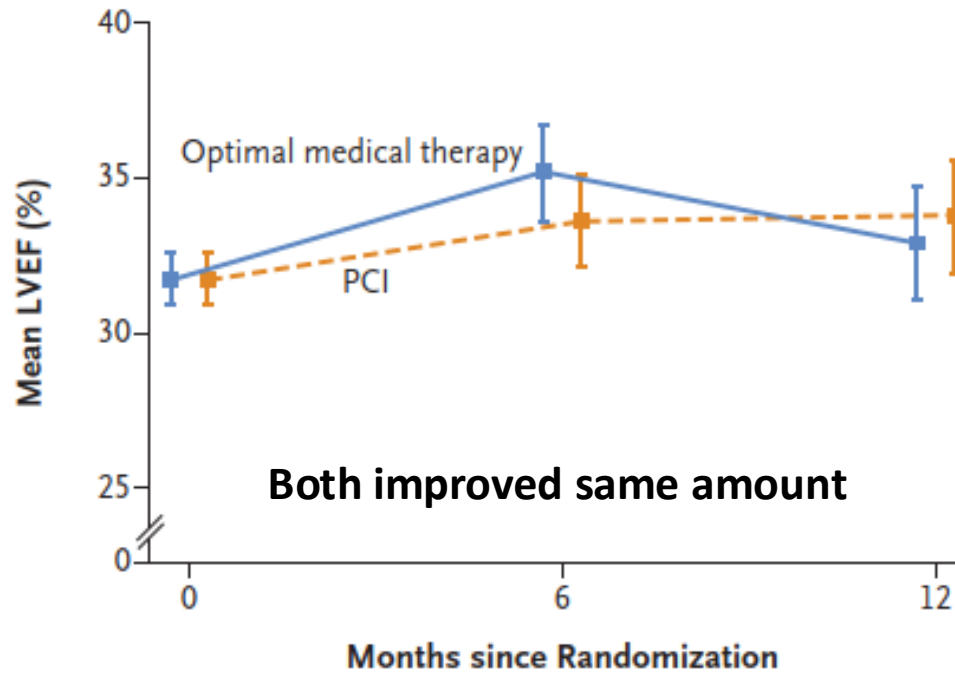
Improve LVEF?

..possibly stunning?



Reduce death / HHF?

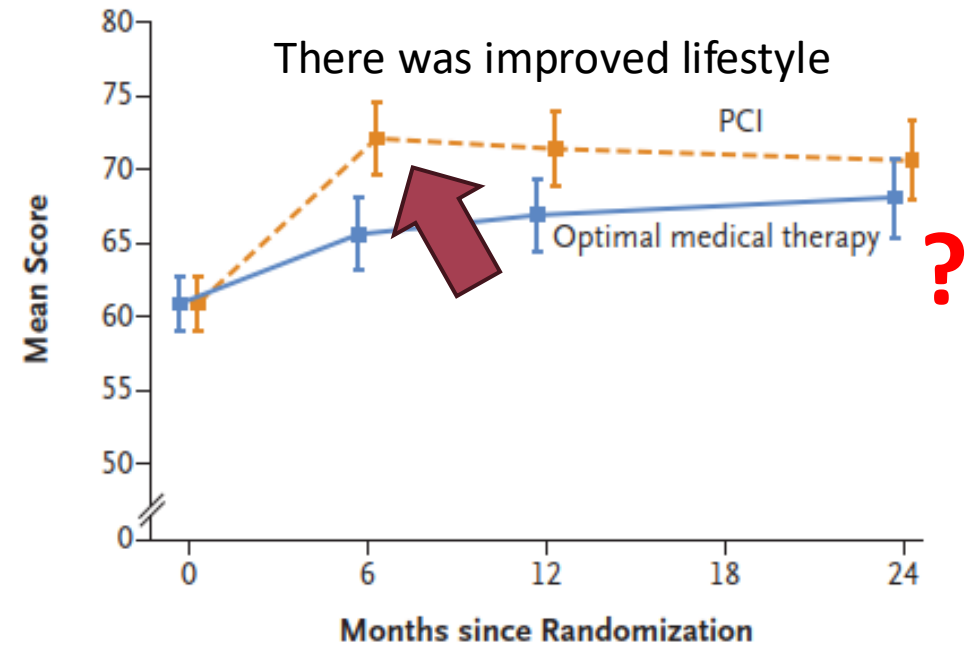
A Echocardiographic Estimates of LVEF



No. of Patients

PCI	264	276	262
Optimal medical therapy	276	264	267

B KCCQ Overall Summary Score



No. of Patients

PCI	319	270	268	228
Optimal medical therapy	318	285	268	228

Medical therapy drives EF improvement not PCI



Composite primary outcome was all-cause death or aborted sudden death (defined as an appropriate implantable cardioverter **defibrillator therapy or a resuscitated cardiac arrest) at a minimum of 24 months**

53.1% had an implantable defibrillator inserted before randomization or during follow-up

All-cause death or aborted sudden death occurred in 144 patients (41.6%) in the PCI group and 142 patients (40.2%) in the OMT group

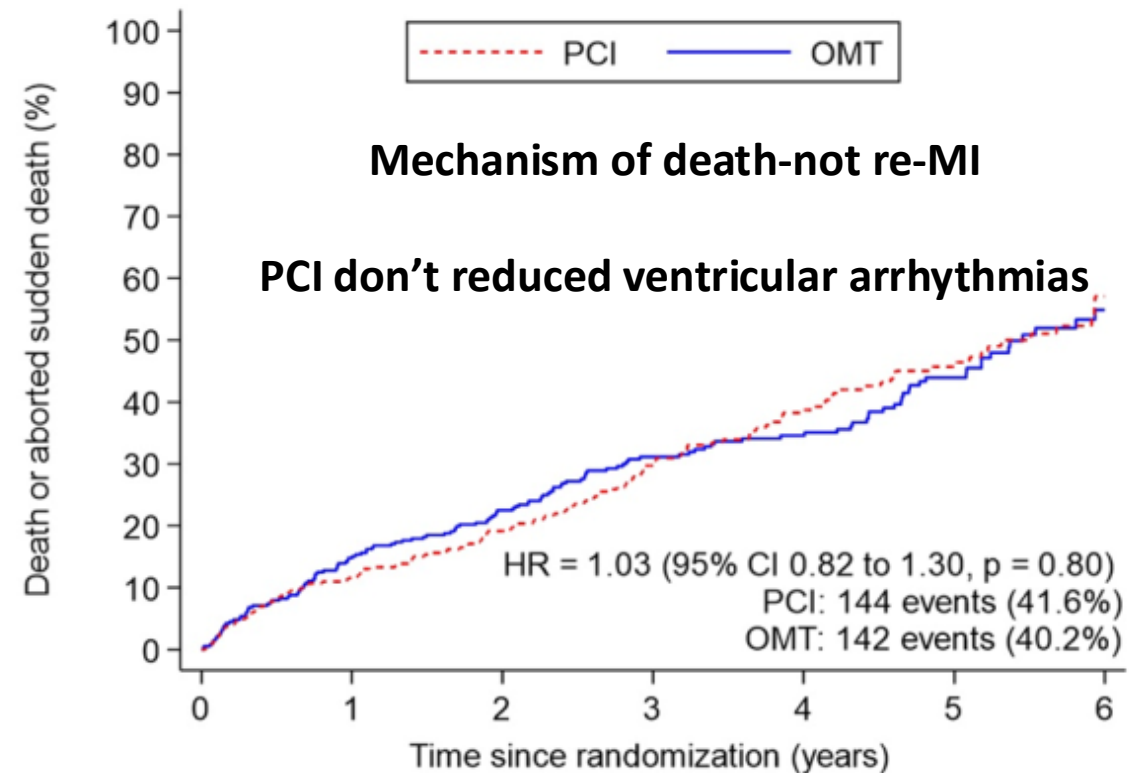
Circulation. 2023;148:862–871. DOI: 10.1161/CIRCULATIONAHA.123.065300



Arrhythmia and Death Following Percutaneous Revascularization in Ischemic Left Ventricular Dysfunction: Prespecified Analyses From the REVIVED-BCIS2 Trial

Divaka Perera¹, MD; Holly P. Morgan², MBBCh; Matthew Ryan, PhD; Matthew Dodd³, MSc; Tim Clayton⁴, MSc; Peter D. O’Kane⁵, MD; John P. Greenwood⁶, PhD; Simon J. Walsh, MD; Roshan Weerackody, PhD; Adam McDiarmid, PhD; George Amin-Youssef, MD; Julian Strange⁷, MD; Bhavik Modi, PhD; Timothy Lockie, PhD; Kai Hogrefe, MD; Fozia Z. Ahmed⁸, MD; Miles Behan, MD; Nicholas Jenkins, MD; Eltigani Abdelaal, MD; Michelle Anderson⁹, BA; Stuart Watkins¹⁰, MD; Richard Evans, BA; Christopher A. Rinaldi, MD; Mark C. Petrie¹¹, MD; for the REVIVED-BCIS2 Investigators*

Median left ventricular ejection fraction was 28%

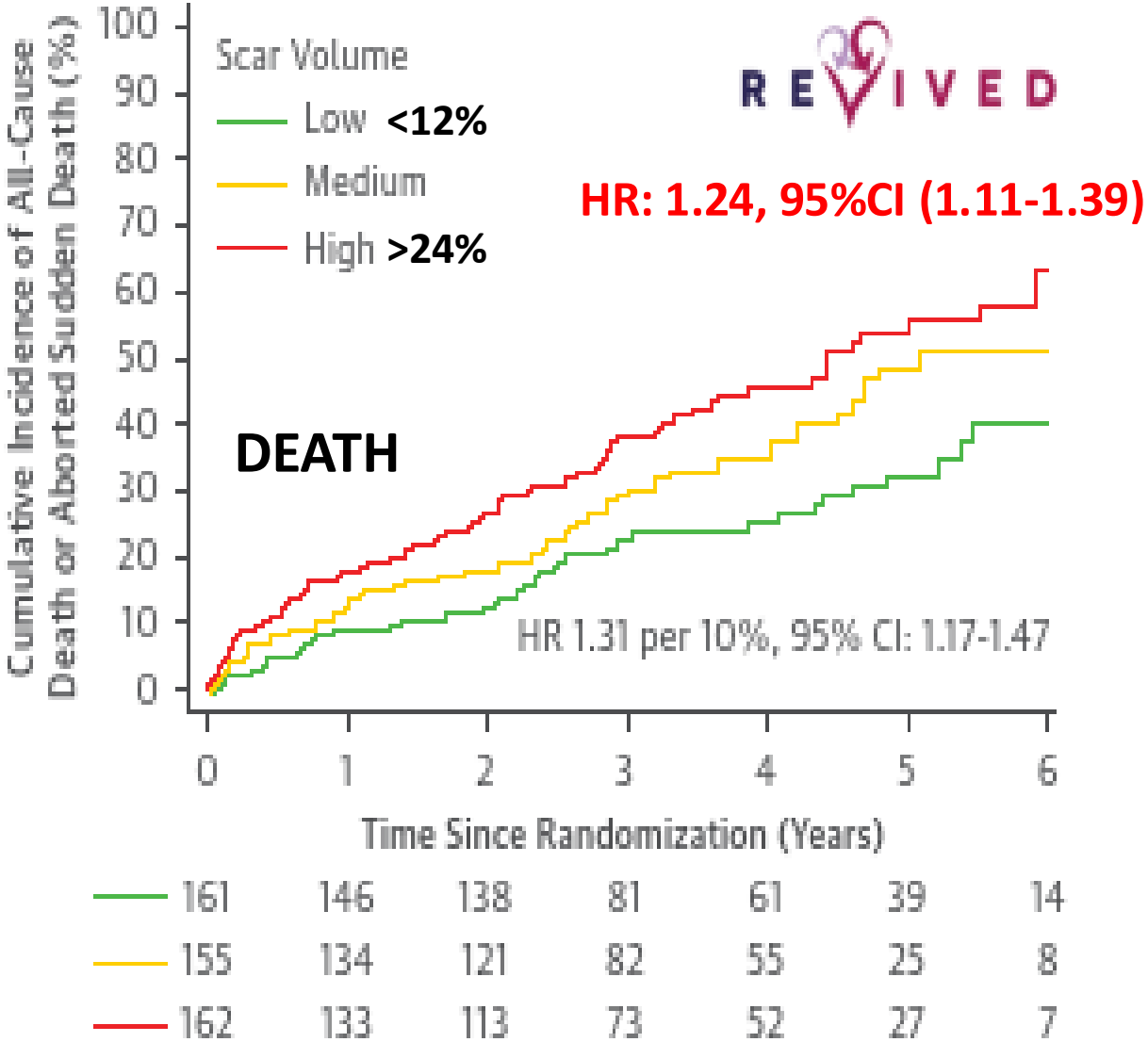
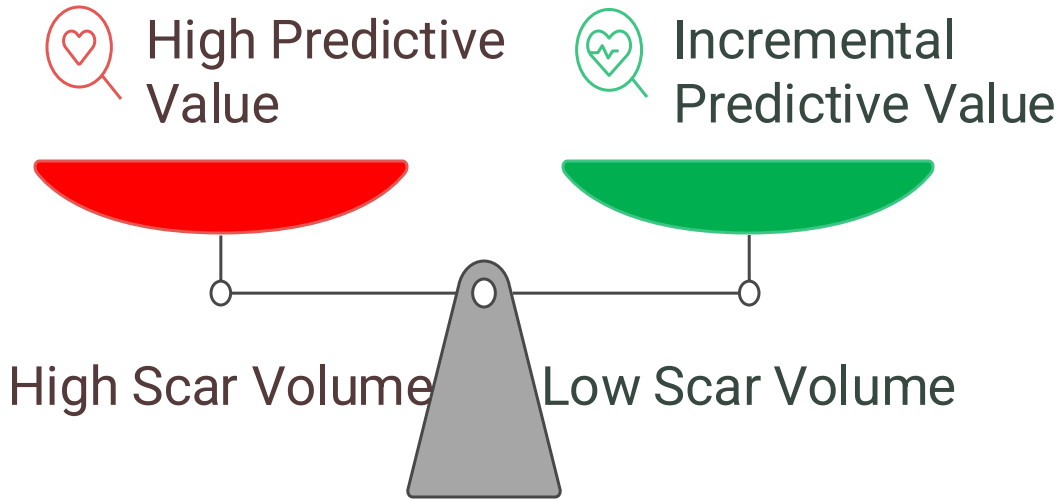


**No evidence to support delaying
implantation merely to assess the effect of
percutaneous
coronary intervention because the latter
was **not**
found to improve left ventricular function**

Circulation. 2023;148:862–871

Scar: <18% (IQR: 5%-14%), >18% (IQR: 21%-32%)

Scar Volume and Arrhythmic Risk

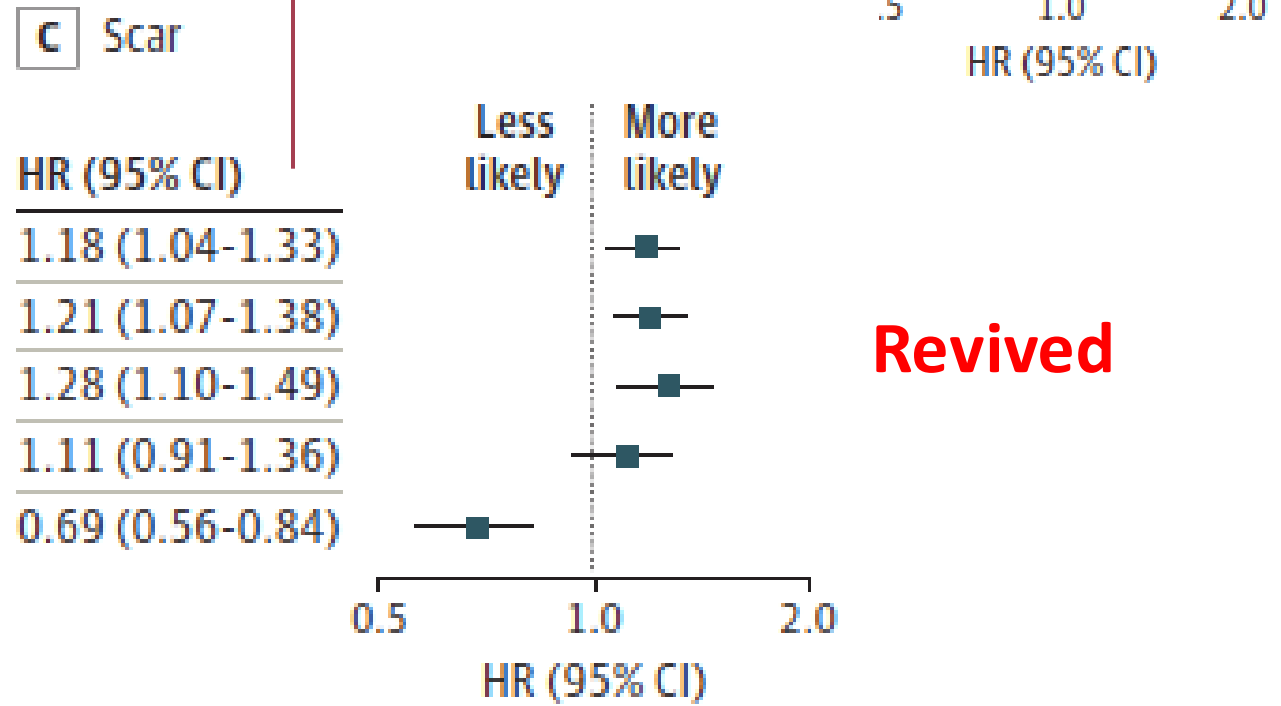
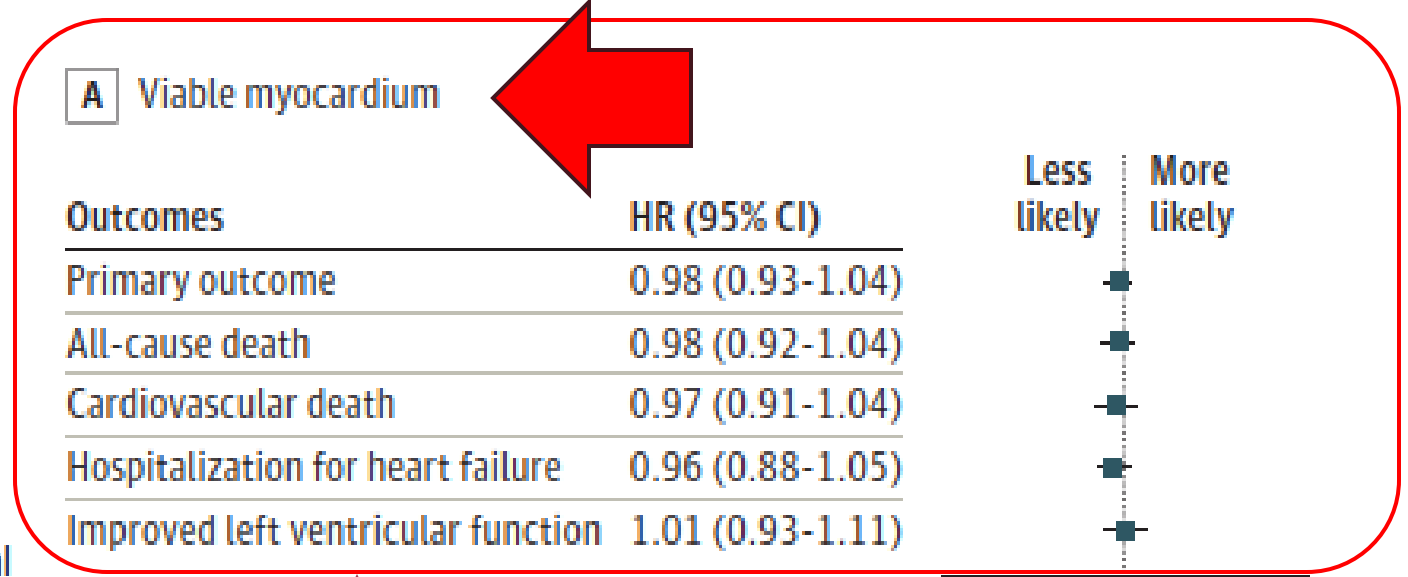


STICH trial investigators did not find that improvement in left ventricular function affected survival

JAMA Cardiology | Original Investigation

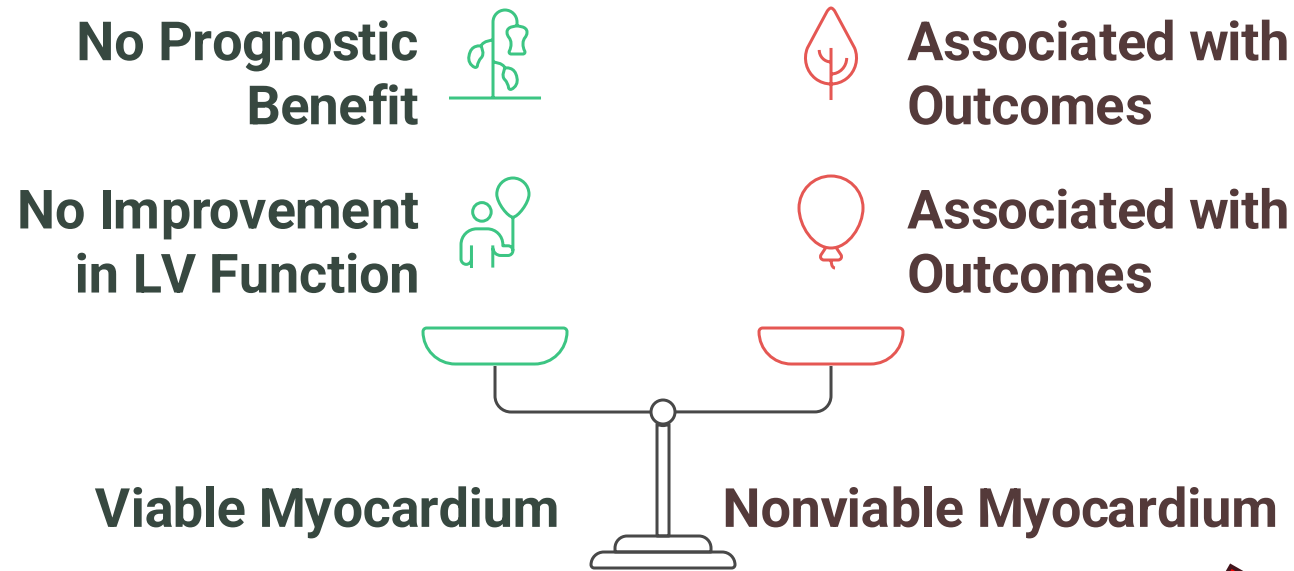
Viability and Outcomes With Revascularization or Medical Therapy in Ischemic Ventricular Dysfunction
A Prespecified Secondary Analysis of the REVIVED-BCIS2 Trial

A greater scar burden was associated with an increased incidence of the primary outcome (HR per 10% absolute increase in scar burden, 1.18; 95% CI, 1.04-1.33; P= .009), all-cause death, and cardiovascular death

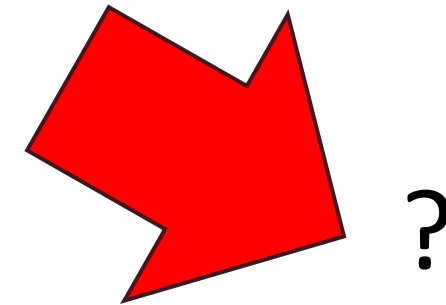


Revived

Myocardial Viability and Prognostic Outcomes



Patients who experience improvement in left ventricular function by 6 months have markedly better event-free survival than those who do not



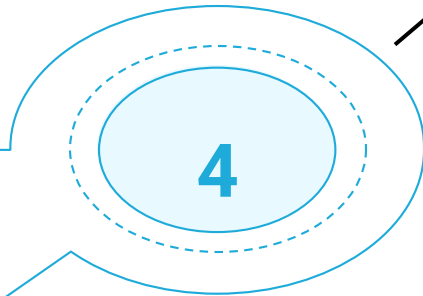
4 pillars heart failure drugs were not used

Clinical trial summary

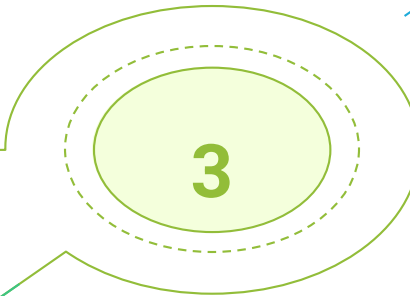
Evolution of Heart Disease Treatment

New ones coming

Current Meds Impact
Introduction of SGLT2i and ARNI significantly reducing mortality and CV events

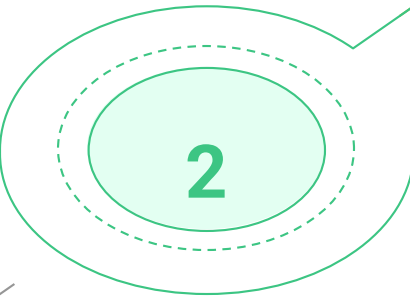


LVEF <35%
14% Left Main Stented **Revive Trial**
Revive trial with low EF and left main patients finding no difference




Viability-no difference

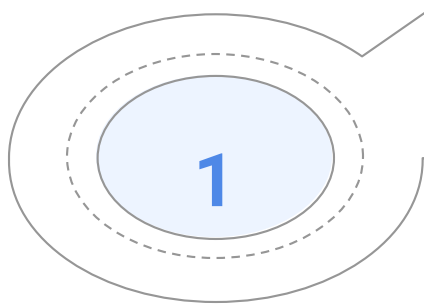
Excluded
Poor LV
LM



Ischemia Trial
Ischemia trial with increased risk patients showing no difference



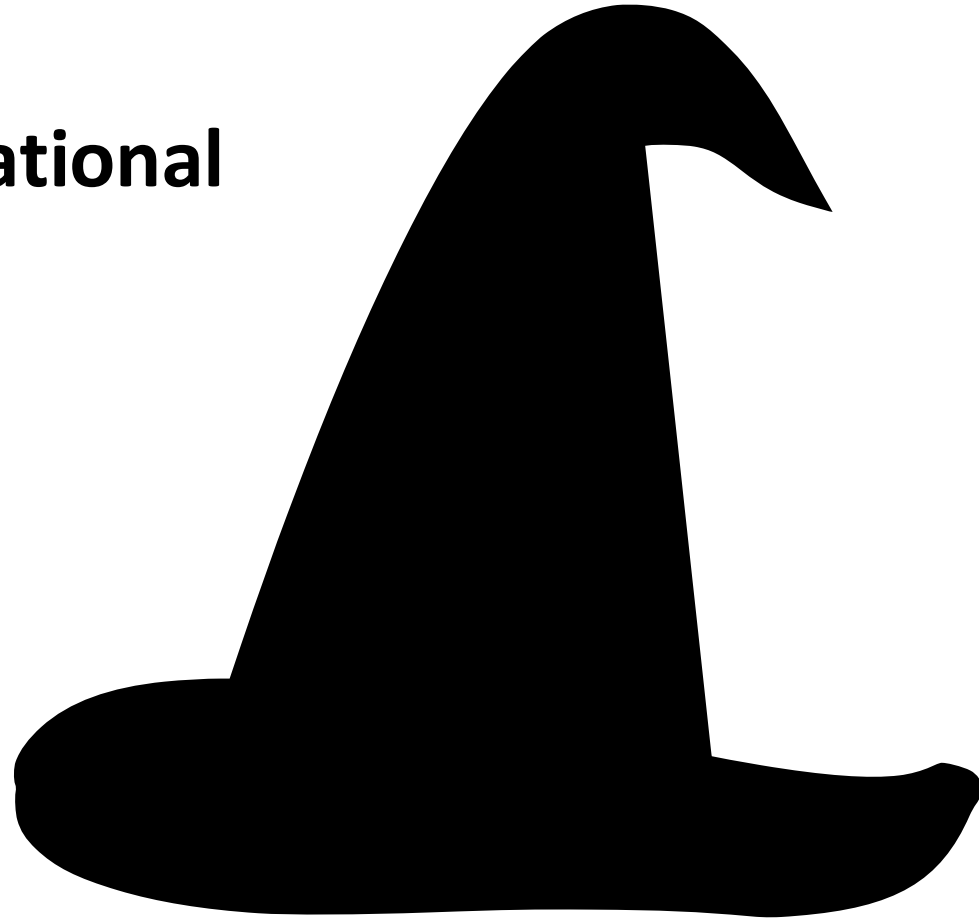
Excluded
Poor LV
LM or Prox LAD
Strongly +ETT



Initial Trial-no difference
Courage trial comparing PCI and medical treatment in low-risk patients



Research-translational



Metabolic Changes During Ischemia and Reperfusion

Switch to Anaerobic Metabolism

The body shifts to anaerobic metabolism due to oxygen deprivation.

Amino Acid Release

Glutamic acid, aspartic acid, and alanine are released early.

Succinate Accumulation

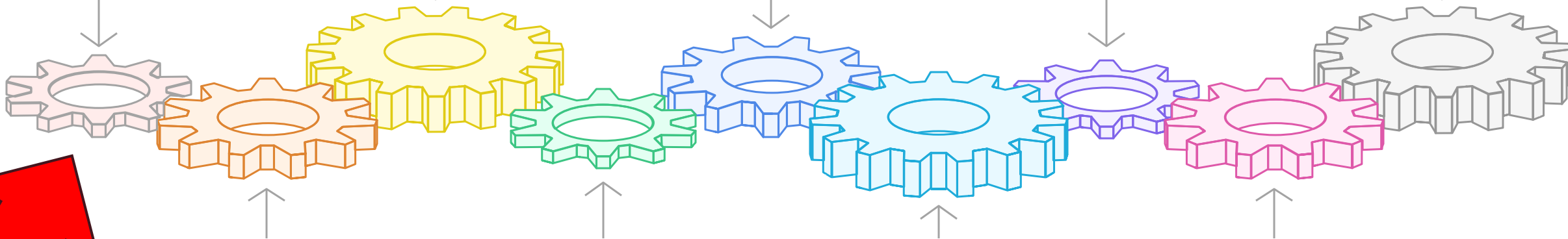
Succinate accumulates during ischemia.

Succinate Oxidation

Succinate is rapidly oxidized upon reperfusion.

Tissue Damage

Tissue damage results from the ROS burst.



Lactic Acid Detection

Lactic acid is the first metabolite detected due to anaerobic metabolism.

Mitochondrial Changes

Changes in mitochondrial shuttling and amino acid transamination occur.

Reperfusion

Blood flow is restored to the tissue.

ROS Burst

A burst of reactive oxygen species occurs.



Metabolomic Markers in Heart Disease

L-glutamic acid, L-aspartic acid, and L-alanine

1

High AUC indicates strong diagnostic accuracy for AMI.

Diagnostic Performance

These amino acids reflect metabolic dysregulation in ischemia, rising rapidly due to disrupted energy metabolism in damaged myocytes

2

Elevated metabolites predict adverse outcomes in AMI patients.

Prognostic Value

AMI vs UA Discrimination



3

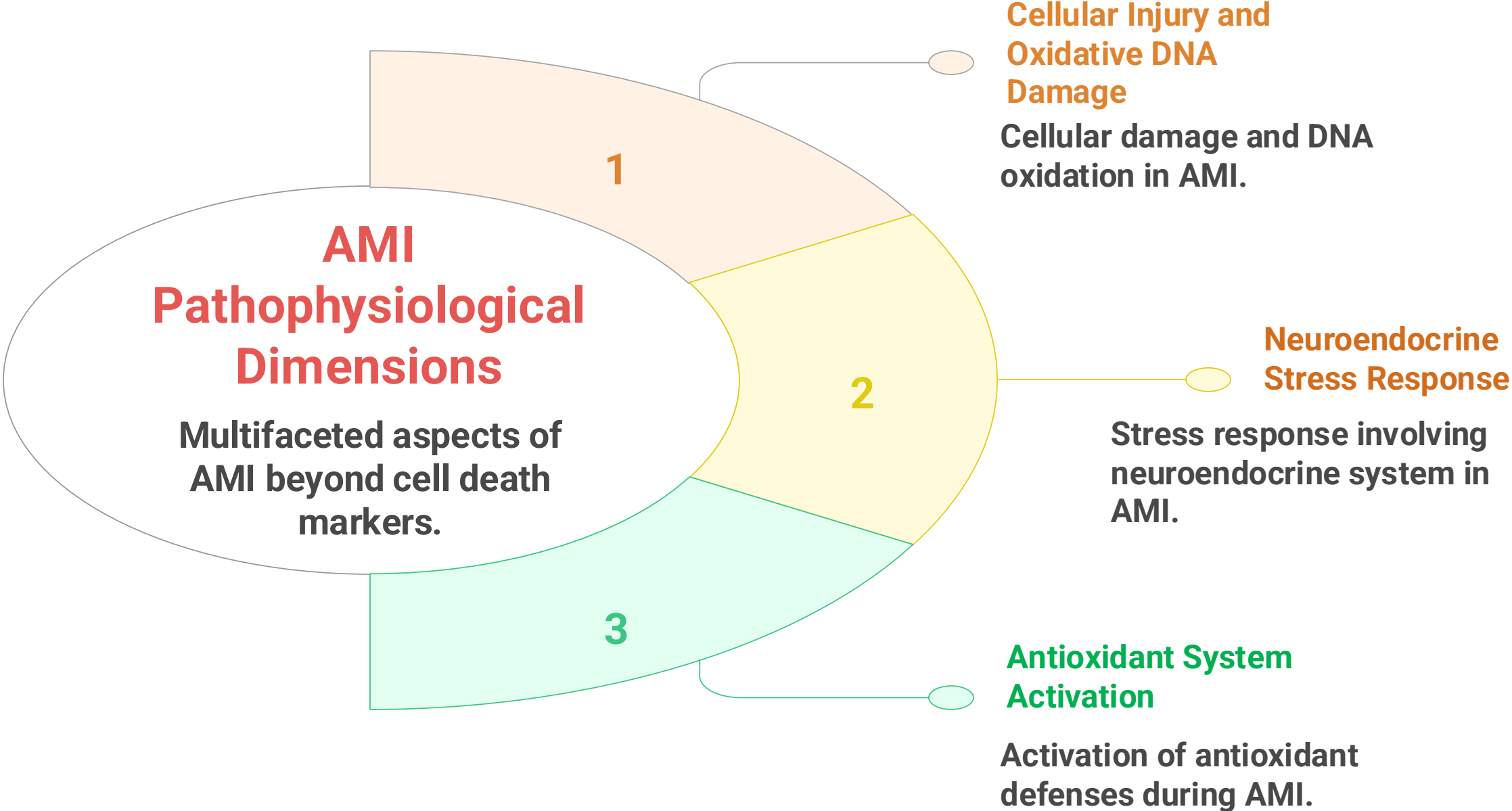
Metabolites reflect disrupted energy metabolism in ischemia.

Mechanism

Mitochondrial DNA-released - inflammation



Unveiling AMI's Pathophysiological Dimensions



Pathway	Metabolite	SGLT2i Action	Clinical Benefit
Oxidative Stress	S-(methyl) glutathione	↑ Antioxidant defense (Nrf2, GPx, CAT)	↓ Myocyte ROS, protects myocardium
Purine Metabolism	2-Hydroxy-6-Aminopurine	↓ Purine degradation, ↓ uric acid	↓ Inflammatory oxidative DNA damage
Steroid Hormones	17α-Hydroxyprogesterone	↓ Cortisol/aldosterone signaling	↓ Endothelial dysfunction & cardiac stress



SGLT2 Inhibitors' Protective Mechanisms

1

SGLT2 inhibitors reduce DNA oxidative damage effectively.

**Oxidative
Damage
Reduction**

2

SGLT2 inhibitors regulate metabolic imbalances in AMI.

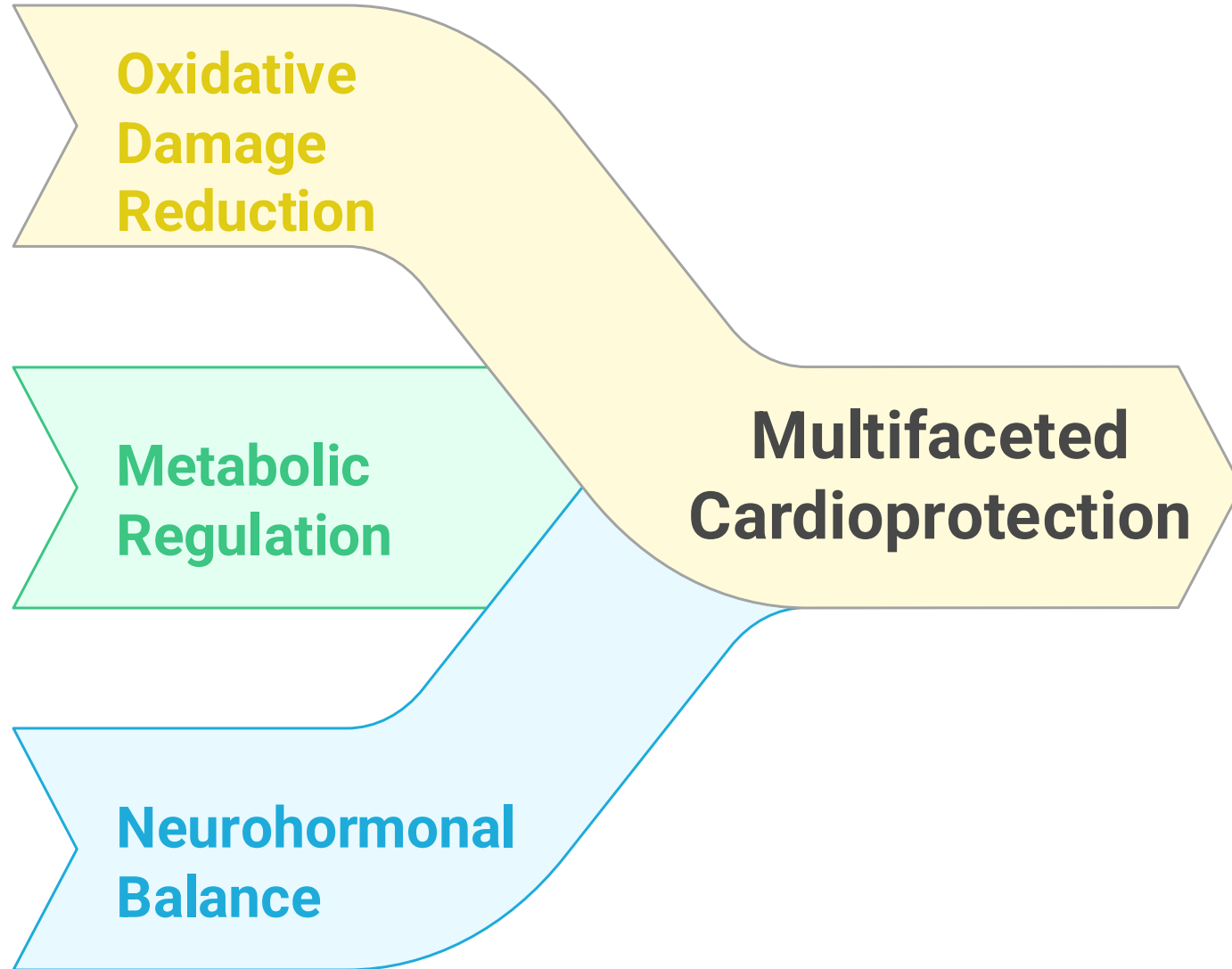
**Metabolic
Regulation**

3

SGLT2 inhibitors balance neurohormonal levels in AMI.

**Neurohormonal
Balance**

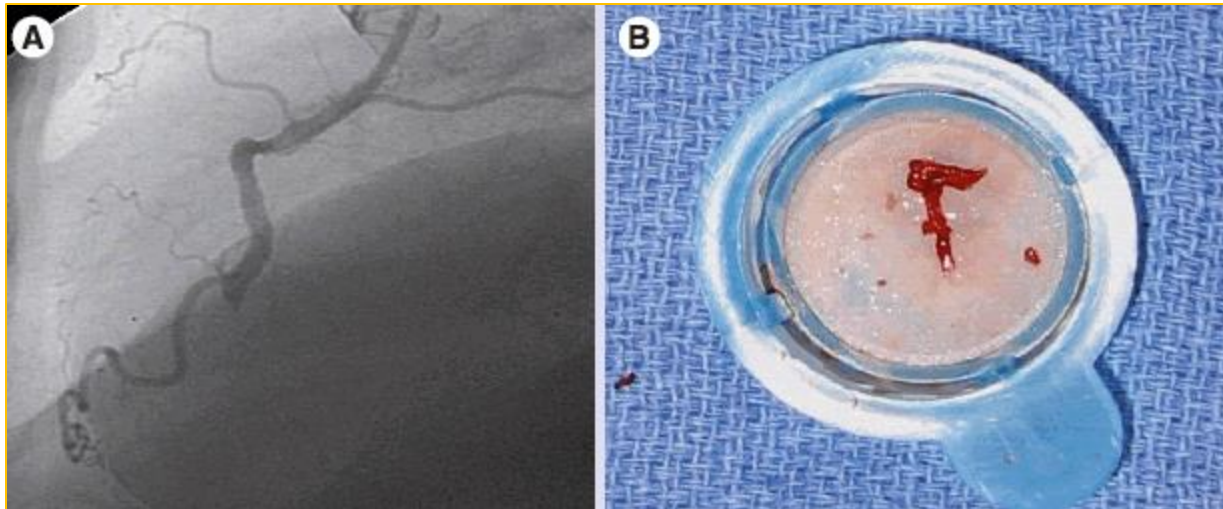
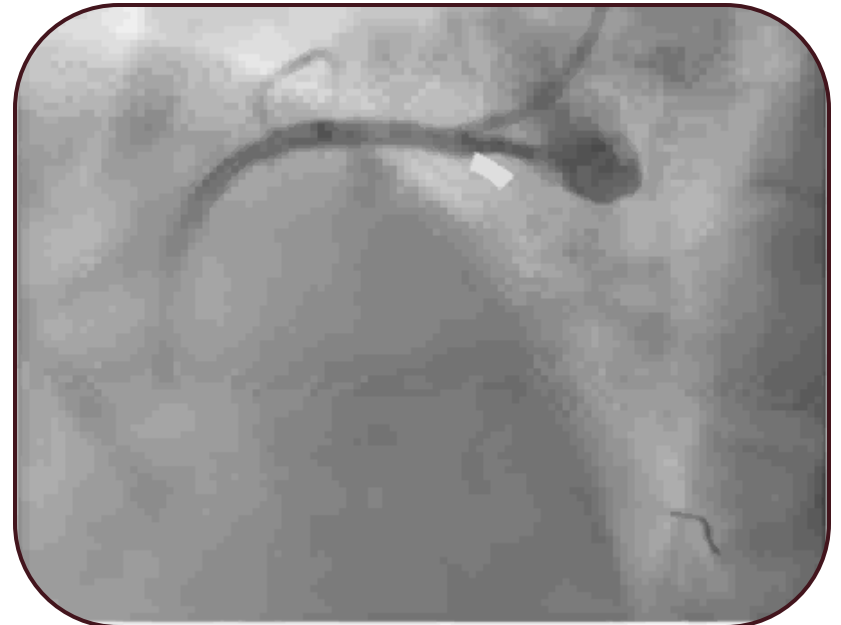
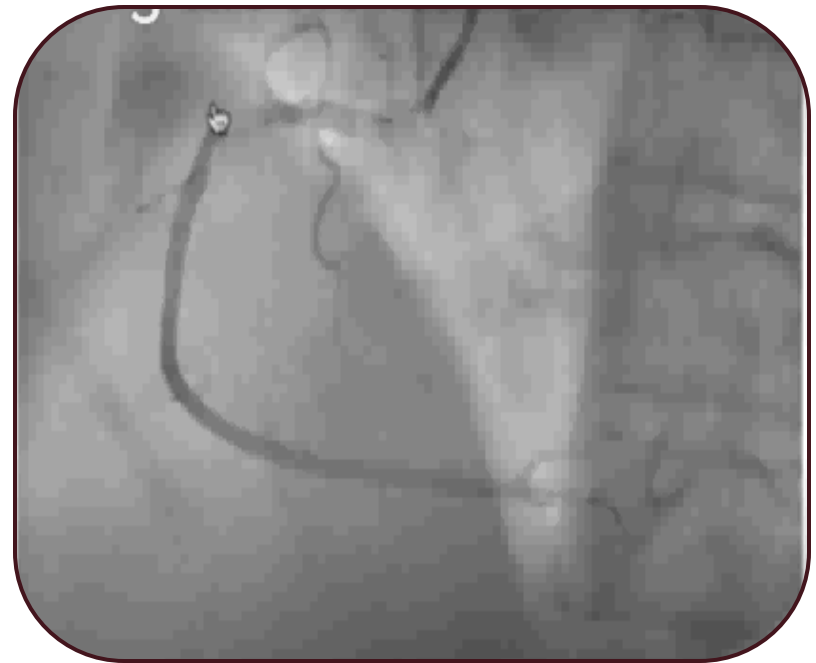
**Multifaceted
Cardioprotection**



Empagliflozin in Acute Myocardial Infarction Reduces No-Reflow and Preserves Cardiac Function by Preventing Endothelial Damage

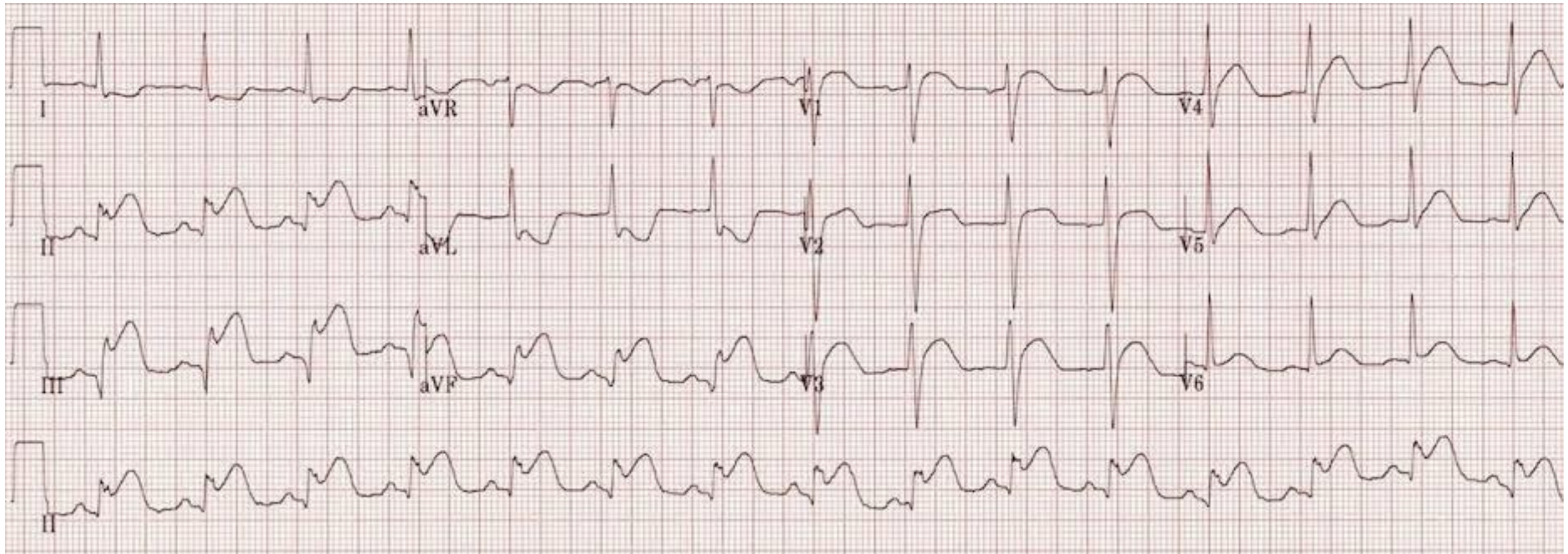


Panagiota Efstathia Nikolaou, PhD,^{a,b} Lara S.F. Konijnenberg, MD, PhD,^b Ioannis V. Kostopoulos, PhD,^c Marios Miliotis, PhD,^d Nikolaos Mylonas, MSc,^a Anastasios Georgoulis, PhD,^a George Pavlidis, MD, PhD,^e Carolien T.A. Kuster, MSc,^b Vince P.A. van Reijmersdal, MSc,^b Tom T.J. Luiken, MSc,^f Anna Agapaki, PhD,^g Rona Roverts, PhD,^h Nikolaos Orogas, PhD,^c Dimitris Grigoriadis, PhD,^d Gaëtan Pallot, PhD,ⁱ Pierre Boucher, MSc,ⁱ Nikolaos Kostomitsopoulos, PhD,^j Michael Paul Pieper, PhD,^k Stéphane Germain, PhD,ⁱ Yannis Loukas, PhD,^l Yannis Dotsikas, PhD,^l Ignatios Ikonomidis, MD, PhD,^e Artemis G. Hatzigeorgiou, PhD,^d Ourania Tsitsilonis, MD, PhD,^c



JACC: BASICTOTRANSLATIONALSCIENCEVOL. 10, NO. 1, 2025 Empagliflozin and Microvascular Injury JANUARY 2025: 43–61





Crushing chest pain intermittent in last 45 minutes

Healthy nondiabetic mice (C57BL6)



Empagliflozin (EMPA) pre-treatment (6 weeks) 10mg/kg/day



Ischemia (30 min)/ Reperfusion (2 hours)

Acute myocardial infarction (AMI)

FACS of heart tissue



CHANGES IN TRANSCRIPTOME

Endothelial cells

Cardiomyocytes

Fibroblasts



AMI Altered
EMPA Altered/Restored

AMI No change
EMPA Altered

AMI Altered
EMPA No change

EMPA Pre-Treatment Ischemia (30 min)/ Reperfusion (48 hours) 10mg/kg/day

Thioflavin S
↓ No reflow

Cardiac MRI
↓ Infarct size

Cardiac MRI
%Global longitudinal strain (GLS) improvement

EMPA given during Reperfusion Ischemia (30 min)/ Reperfusion (48 hours) 10mg/kg/day

Electron microscopy
↓ Microvascular injury

Flow cytometry
↓ Inflammatory cell infiltration

Protein analysis
↓ MMP-2
↓ ICAM-1

JACC Basic Transl Sci. 2025;10:43–61

Evans blue

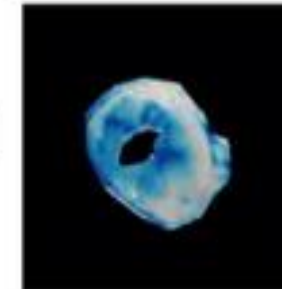
Sham



Control-AMI



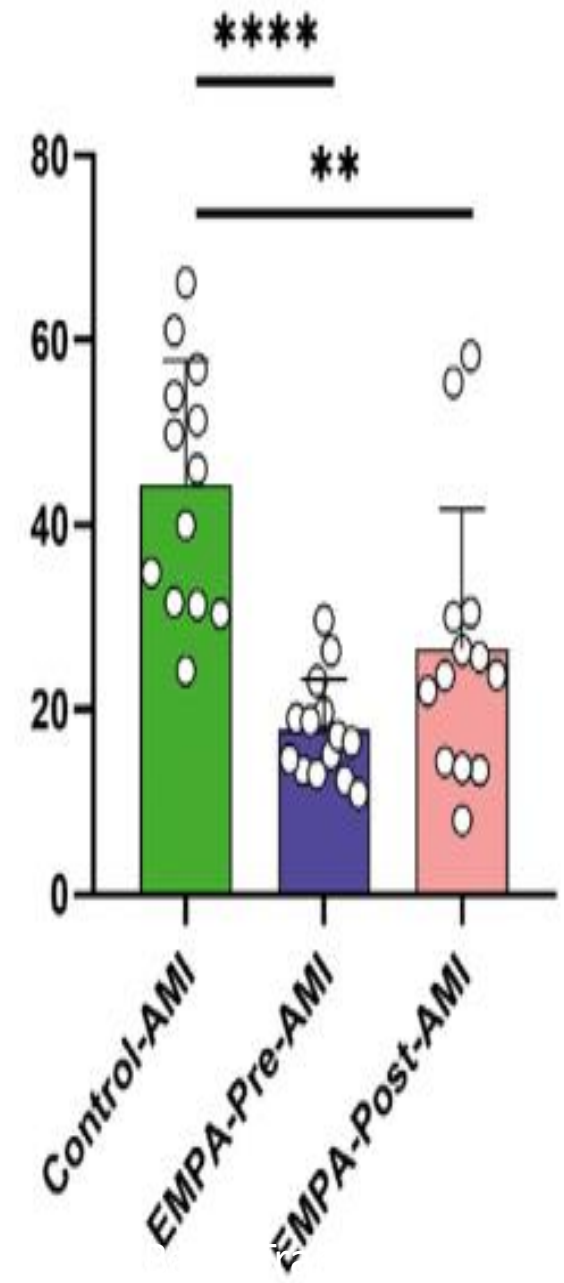
EMPA-Pre-AMI



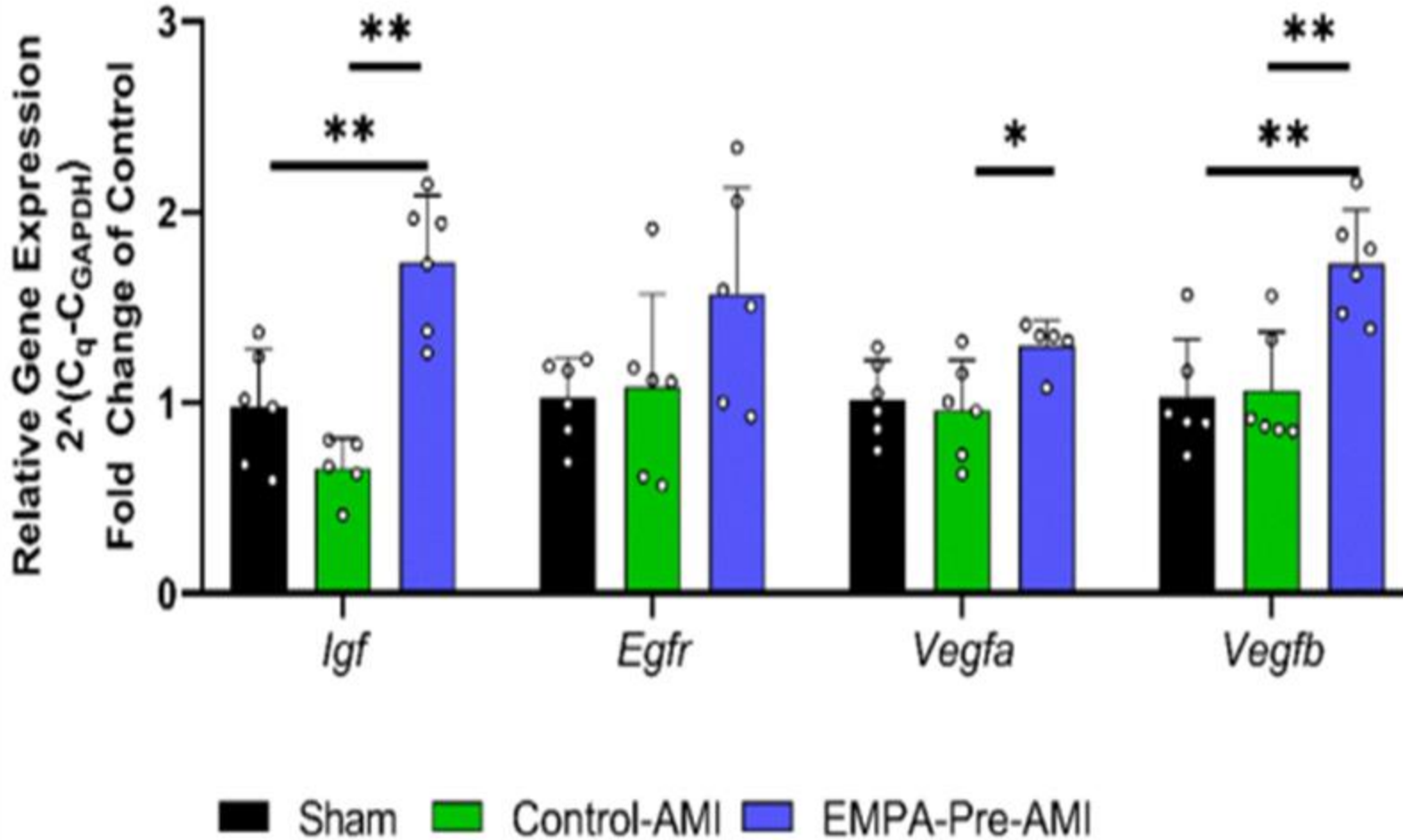
EMPA-Post-AMI



%Infarct/Area at Risk

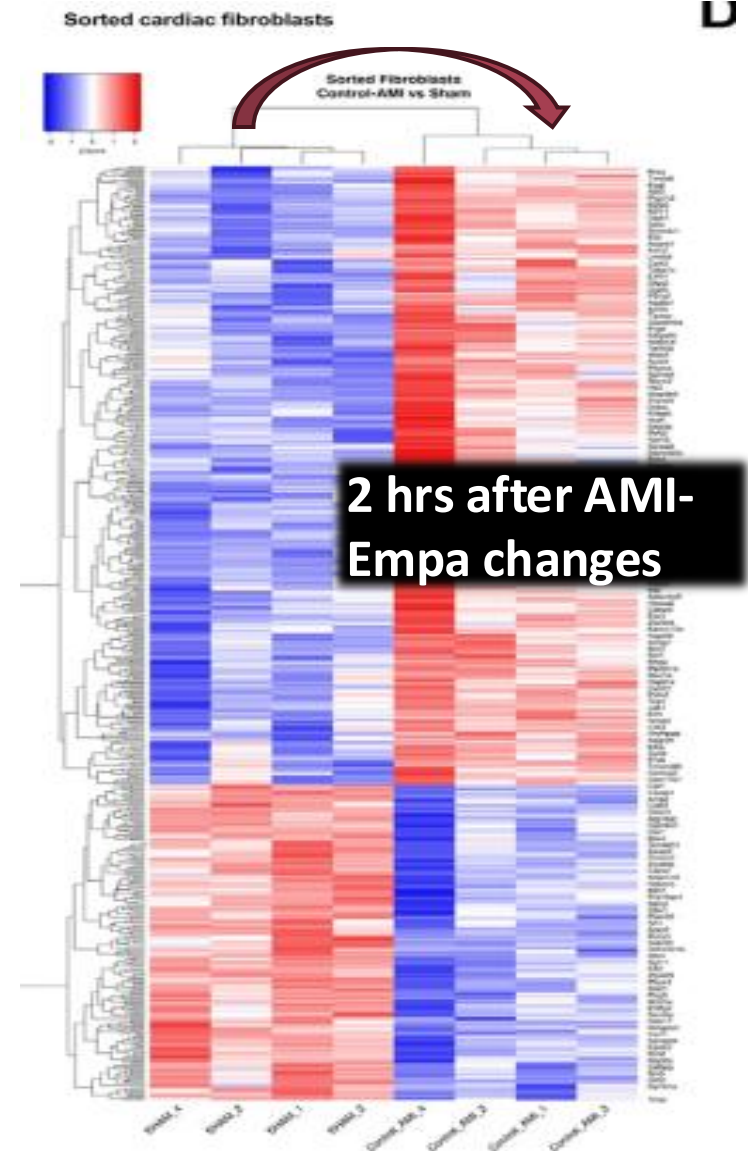


Significant Reactome pathways between the Control-AMI and EMPA-Pre-AMI group 2 hours after reperfusion



Insulin-like growth factor (IGF) and epidermal growth factor (EGF)

Vascular endothelial growth factor A



Fibroblast changes



EMPACT-MI

Double-blind, randomized, placebo-controlled, event-driven trial

Randomized 6522 patients hospitalized for **acute myocardial infarction** at risk for HF on the basis of newly developed left ventricular ejection fraction of <45%



Effect of Empagliflozin on Heart Failure Outcomes After Acute Myocardial Infarction: Insights From the EMPACT-MI Trial

Adrian F. Hernandez, MD, MHS; Jacob A. Udell, MD; W. Schuyler Jones, MD; Stefan D. Anker, MD, PhD; Mark C. Petrie, MD; Josephine Harrington, MD; Michaela Mattheus, Dipl Biomath; Svenja Seide, Dr sc hum; Isabella Zwiener, PhD; Offer Amir, MD; M. Cecilia Bahit, MD; Johann Bauersachs, MD; Antoni Bayes-Genis, MD; Yundai Chen, MD; Vijay K. Chopra, MD; Gemma A. Figtree, MD; Junbo Ge, MD; Shaun G. Goodman, MD;

Circulation. 2024;149:1627–1638.

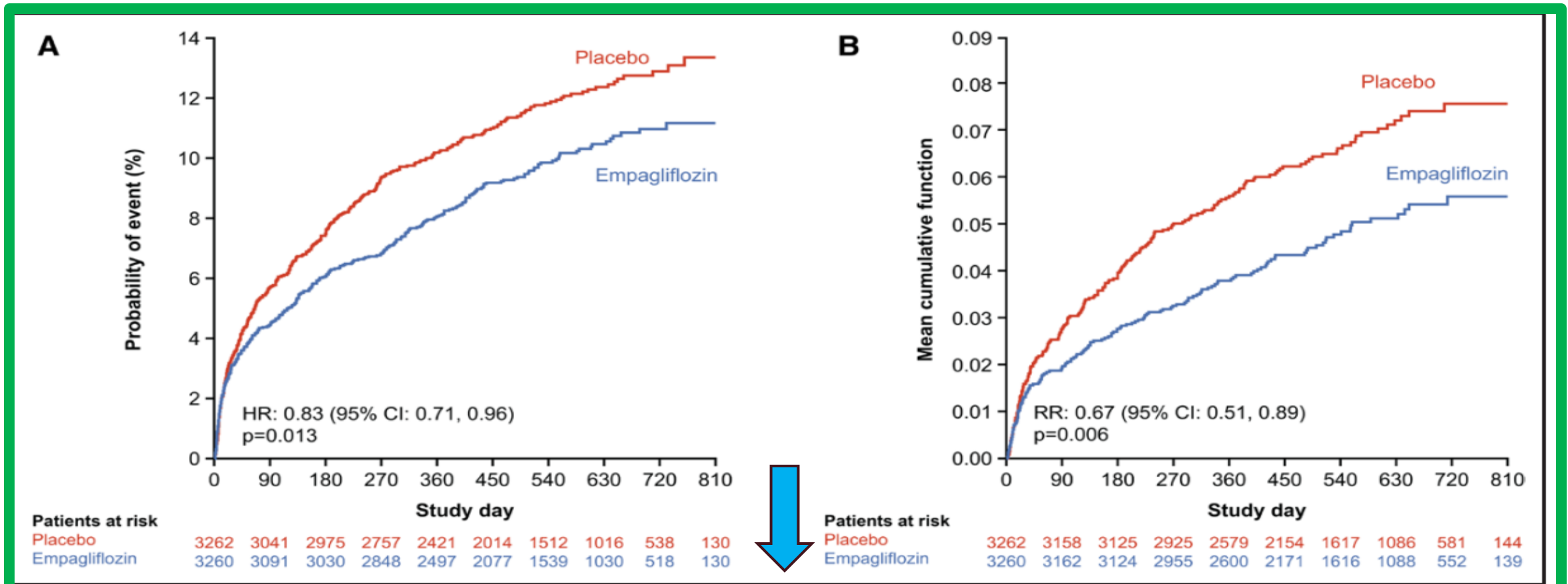
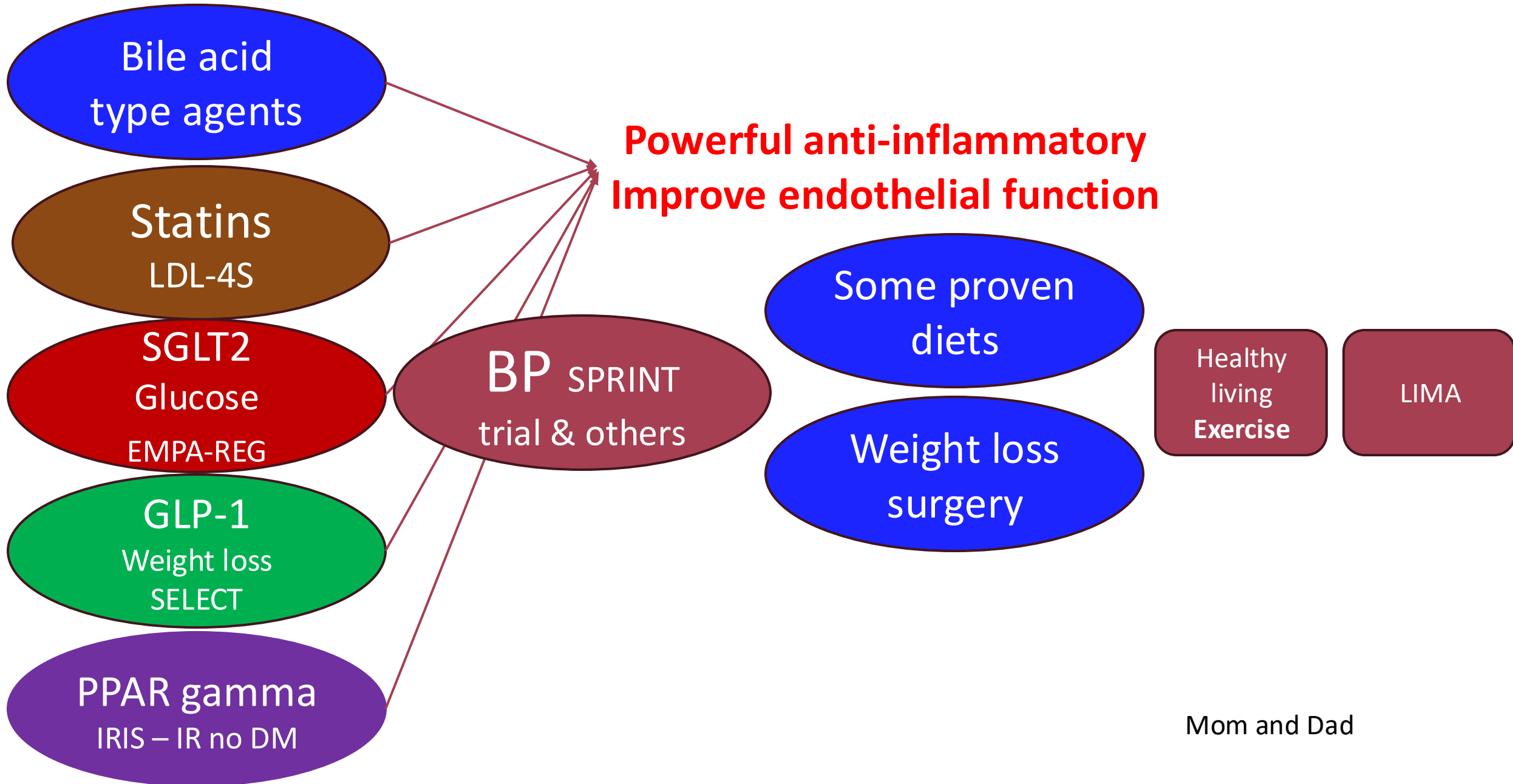


Figure 1. Time to first adverse event of heart failure or all-cause death and total number of heart failure hospitalizations.

Proven to reduce CV events and mortality



SGLT2i Cellular Repair Mechanism

Nrf2

Blood Glucose Reduction

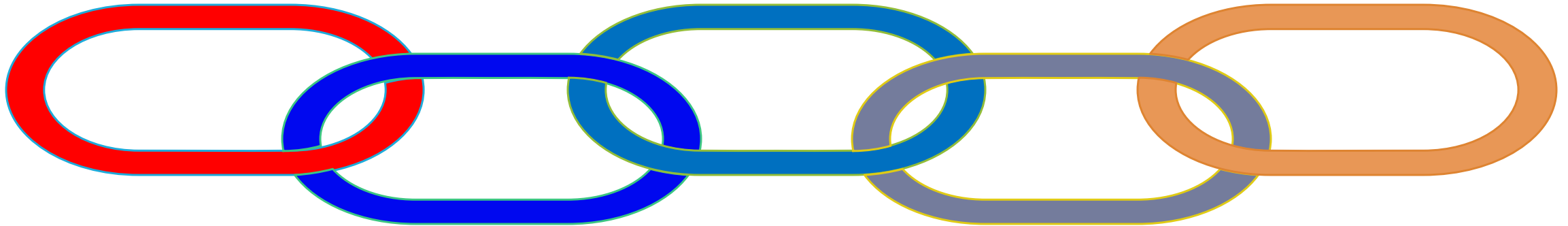
Gliflozin lowers blood glucose levels, reducing oxidative stress in diabetic conditions.

Upregulation

Phosphorylated STAT3 and activated Akt up-regulate Nrf2, a key **antioxidant transcription factor**.

Inflammation Reduction

Lower oxidative stress reduces pro-inflammatory cytokines, aiding wound healing.



STAT3/Akt Activation

SGLT2i **activates** STAT3 and Akt pathways, crucial for **cellular repair**.

Antioxidant Boost

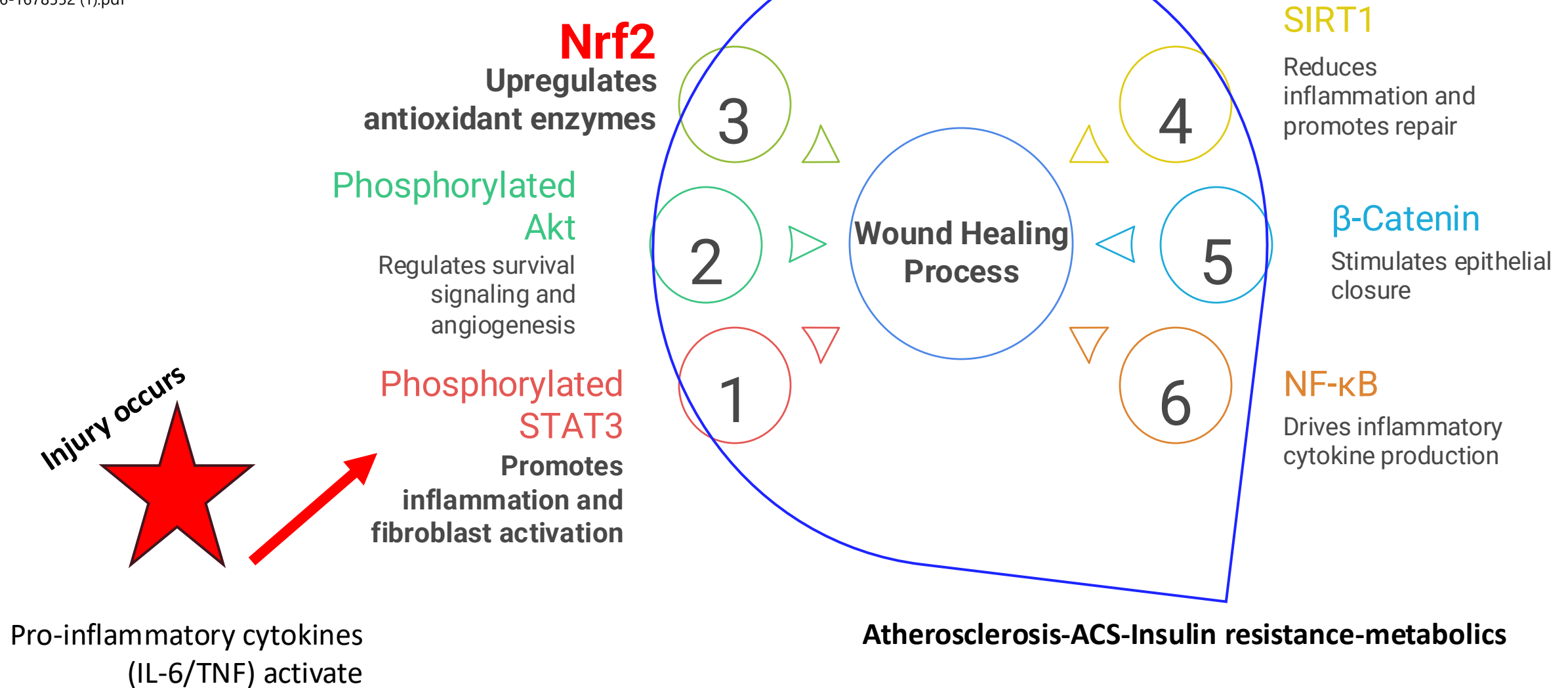
Increased Nrf2 boosts antioxidants like glutathione and superoxide dismutase.



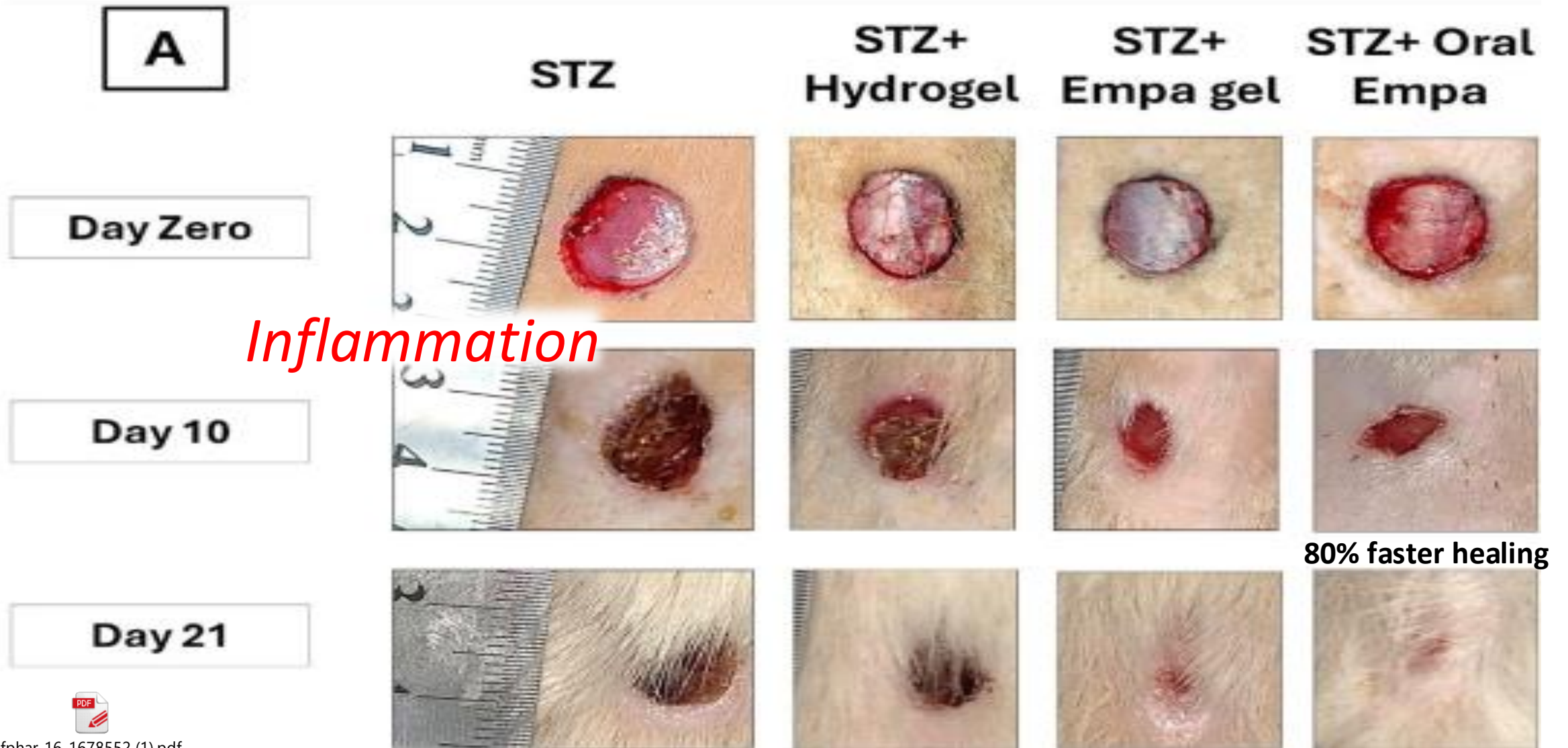
Molecular Pathways in Wound Healing (inflammation)



fphar-16-1678552 (1).pdf



Effect of SGLT2 inhibitor on the wound healing



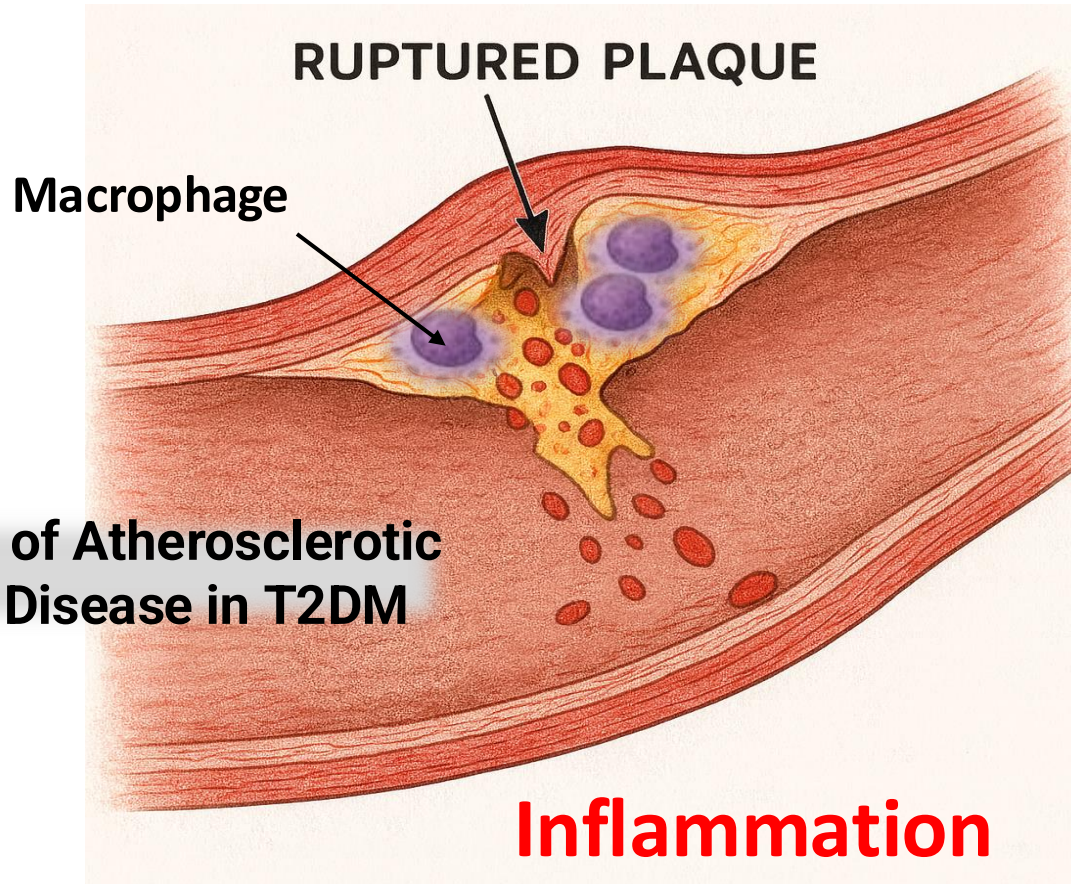
fphar-16-1678552 (1).pdf

Gliflozin targeting STAT3 Akt/Nrf2 axis promoting diabetic wound healing in rat model

Front. Pharmacol., 07 September 2025

Important cardiovascular considerations 2025

Pathophysiology of Atherosclerotic Cardiovascular Disease in T2DM



Atherosclerotic Cardiovascular Disease
The ultimate outcome of the disease



Endothelial Dysfunction and Plaque Instability
Direct consequences of inflammation and oxidative stress



Inflammatory and Oxidative Pathways
Key processes driving disease progression



Metabolic Disturbances
Initial triggers of the disease cascade

Insulin Resistance
Core cause disrupting metabolic balance



THANK YOU

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