Pathophysiology of Cancer Therapy and Cardiotoxicity

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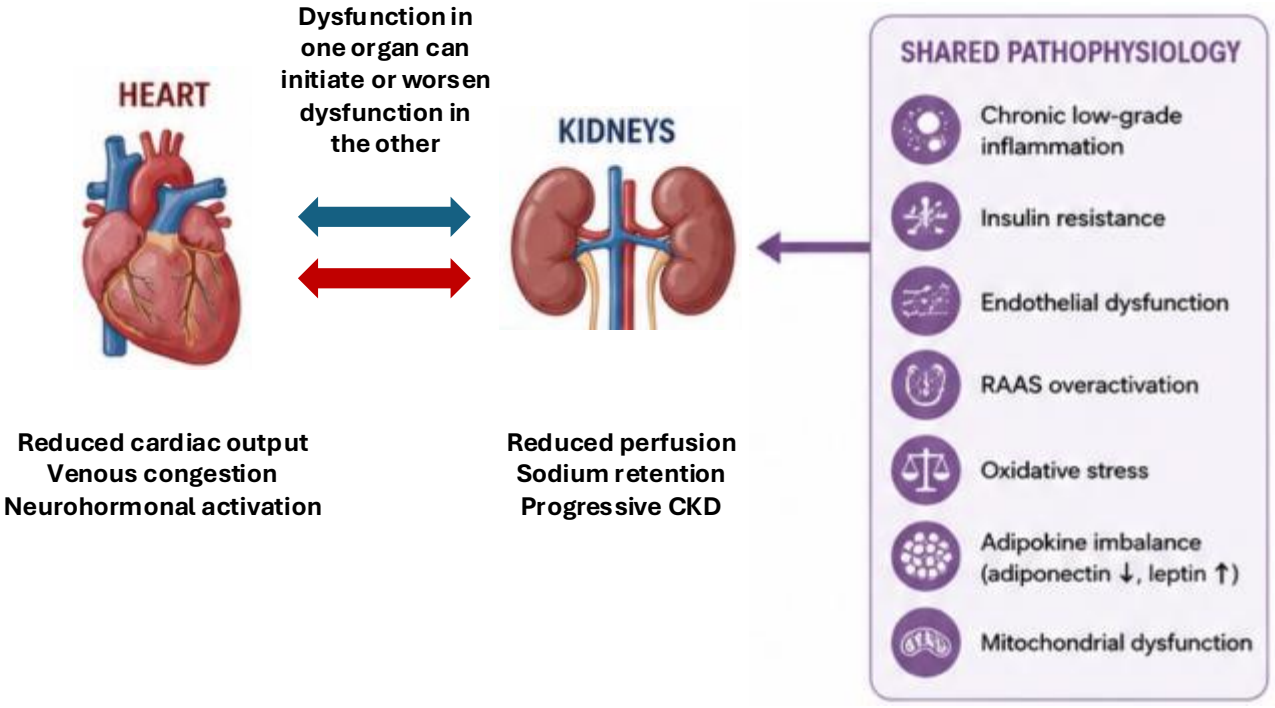
Learning Objectives

- To describe shared mechanisms of cardiac and renal toxicity from cancer therapy
- To describe the pathogenesis and clinical approach to ICI-related myocarditis
- To describe mechanisms for other selected cardiovascular toxicities and implications for prevention and management

Cardiac and Renal Toxicity: Different Triggers but Shared Biology

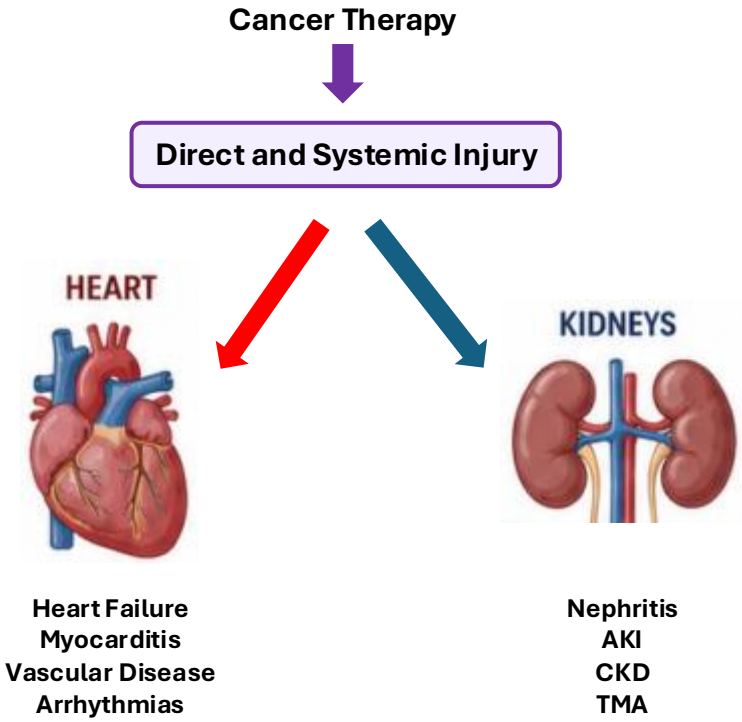
Traditional Cardio-Renal Syndrome



Reduced cardiac output
Venous congestion
Neurohormonal activation

Reduced perfusion
Sodium retention
Progressive CKD

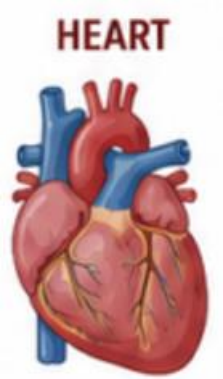
Cancer Therapy



Heart Failure
Myocarditis
Vascular Disease
Arrhythmias

Nephritis
AKI
CKD
TMA

Why are the Heart and Kidney Especially Vulnerable?



High Energy Demand
Mitochondria rich
High ATP use
ROS sensitive

High Vascular Dependance
Dense capillary beds
Endothelial dependence
Perfusion sensitive

Immune Responsive
Resident immune cells
Rapid IFN responses
Autoimmunity

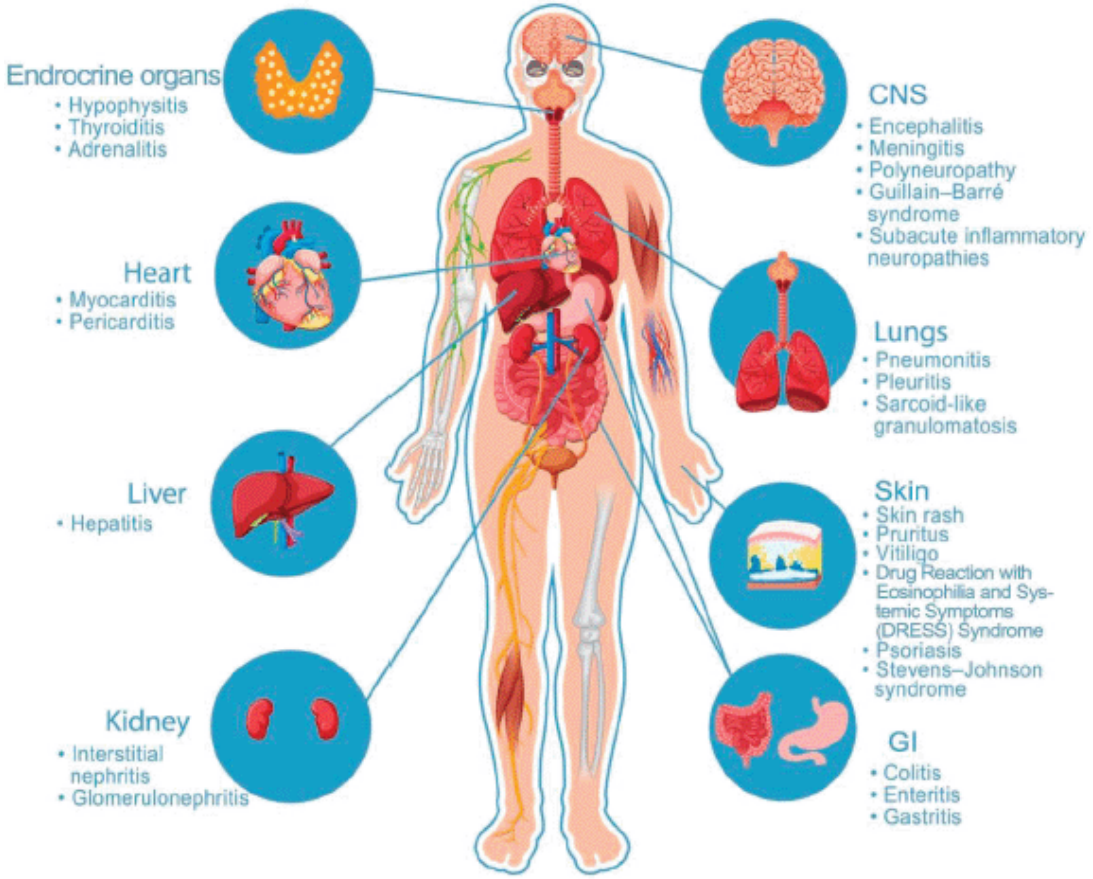
Limited Regeneration
Persistent injury

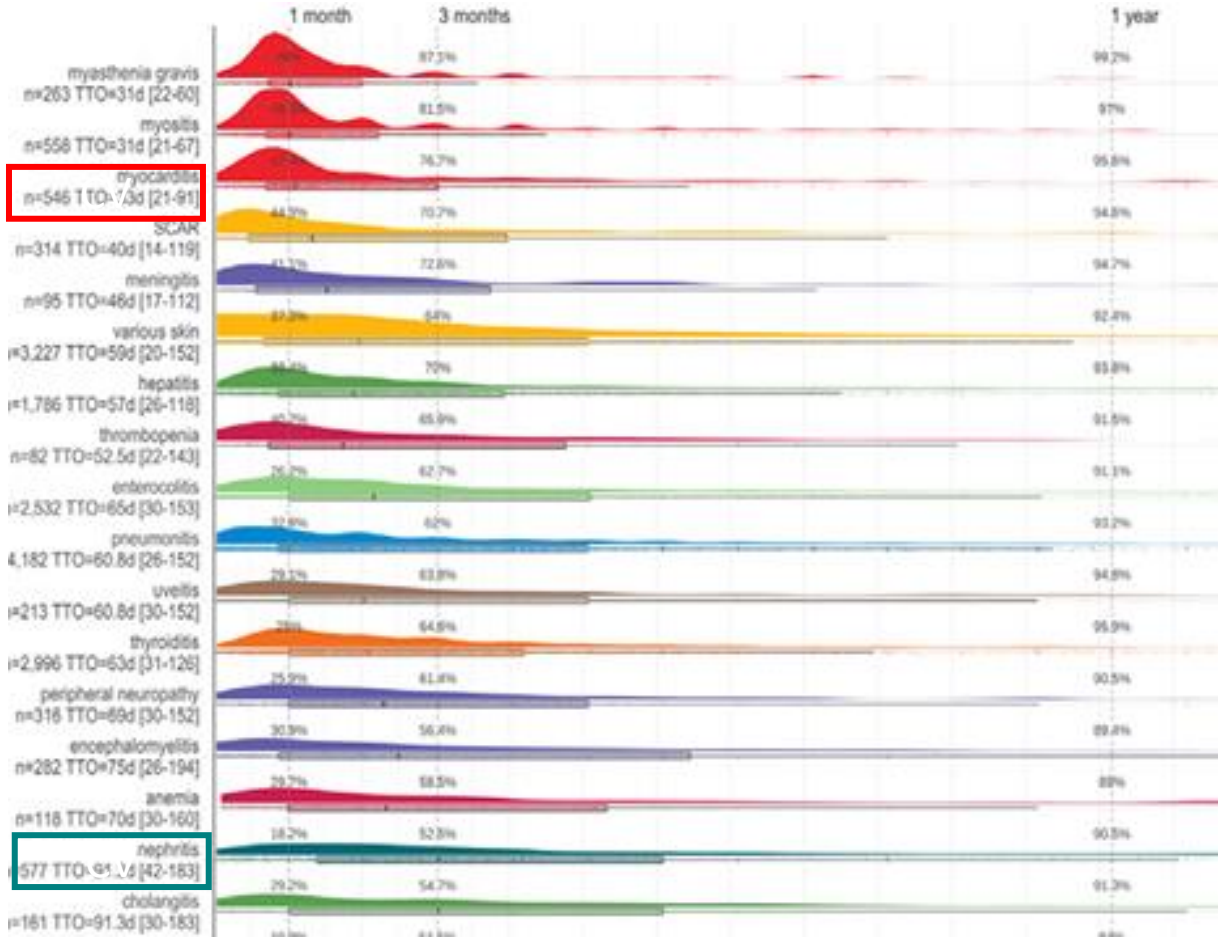
Shared Biology

Four major mechanisms underly most cardiac and renal cancer therapy related toxicity

IMMUNE	ENDOTHELIAL	MITOCHONDRIAL	FIBROTIC
• Loss of tolerance • T cell activation • Cytokine signaling	• ↓NO/prostacyclin • Capillary rarefaction • Microvascular ischemia	• ↑ROS • ATP failure • Cellular injury/dysfunction	• Inflammation • Fibroblast activation • ECM expansion

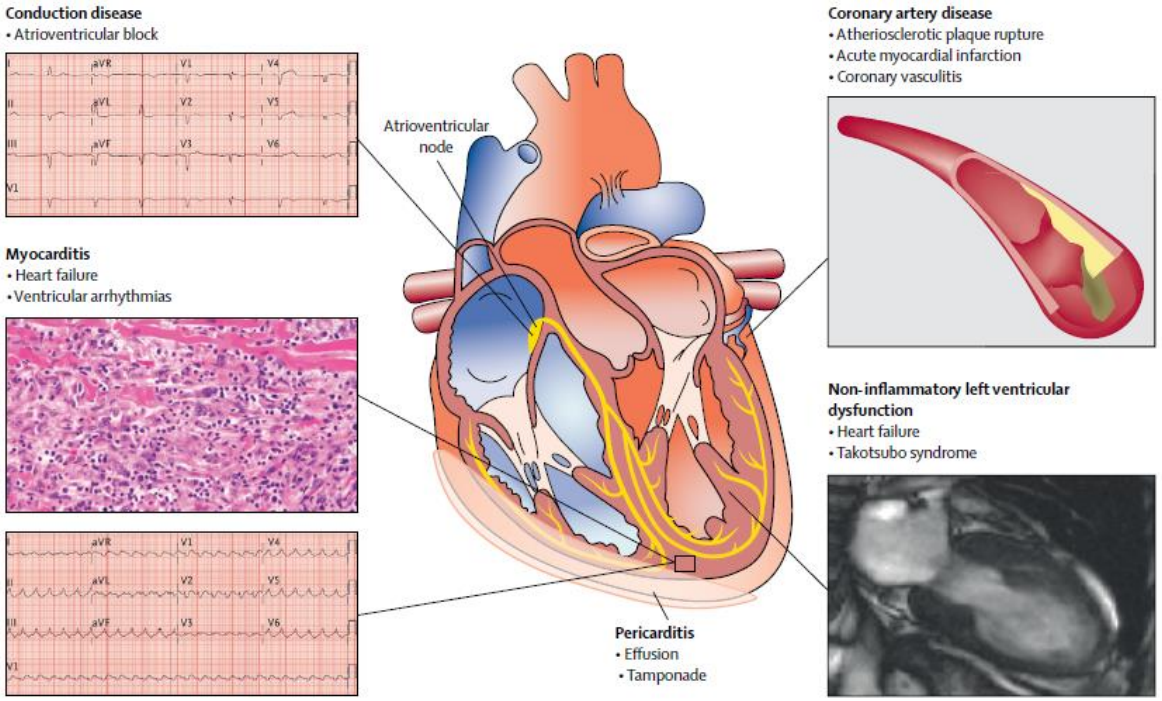
ICI Therapy: Immune Related Adverse Events





https://doi.org/10.3332/ecancer.2021.1314; Gougis et al. Lancet 2024;70:102536.

Cardiovascular Complications of ICI Therapy



31,321 ICI related complications in Vigibase

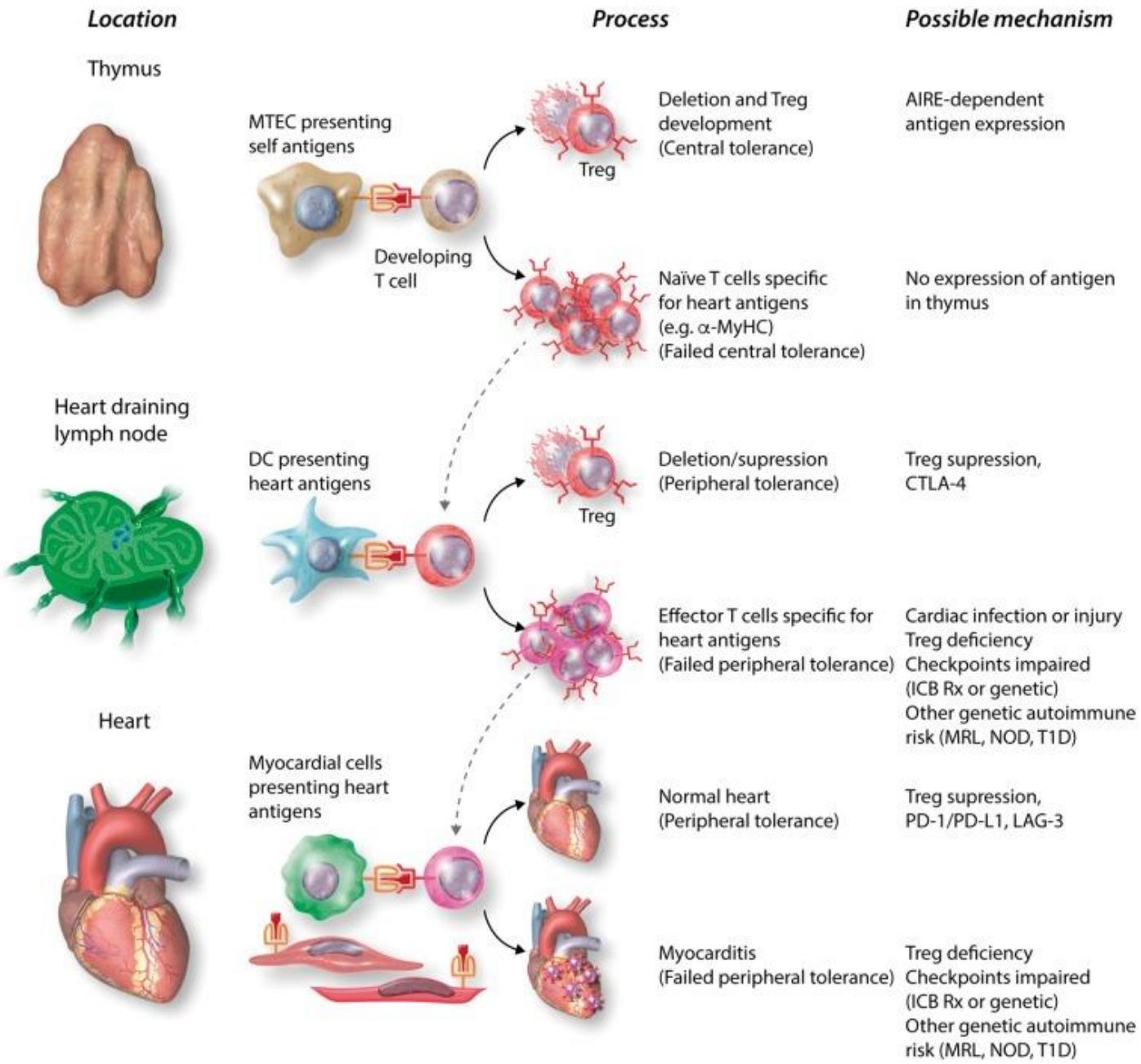
	Anti-PD-1 or anti-PD-L1 monotherapy (n=20,643)	Anti-CTLA-4 monotherapy (n=8,266)	Combination ICIs (n=2,412)	Death
Myocarditis	84 (0.41%)	6 (0.07%)	32 (1.33%)	50%
Pericardial disease	74 (0.36%)	13 (0.16%)	8 (0.33%)	21%
Vasculitis	56 (0.27%)	18 (0.22%)	8 (0.33%)	6%
Temporal arteritis	7 (0.03%)	10 (0.12%)	1 (0.04%)	
Polymyalgia rheumatica	14 (0.07%)	1 (0.01%)	1 (0.04%)	

- Characterized by elevation in Tn
- May or may not have LV dysfunction
- Often seen with myopathy (25%) and myasthenia gravis (11%)
- Risk Factors: Dual ICI therapy, thymoma, autoimmune disease, underlying CVD

Lyon et al. Lancet Oncol 2018;19:e447; Salem et al. Lancet Oncology 2018;19:1579; Munir et al. Nature Reviews Cancer 2024;24:540.

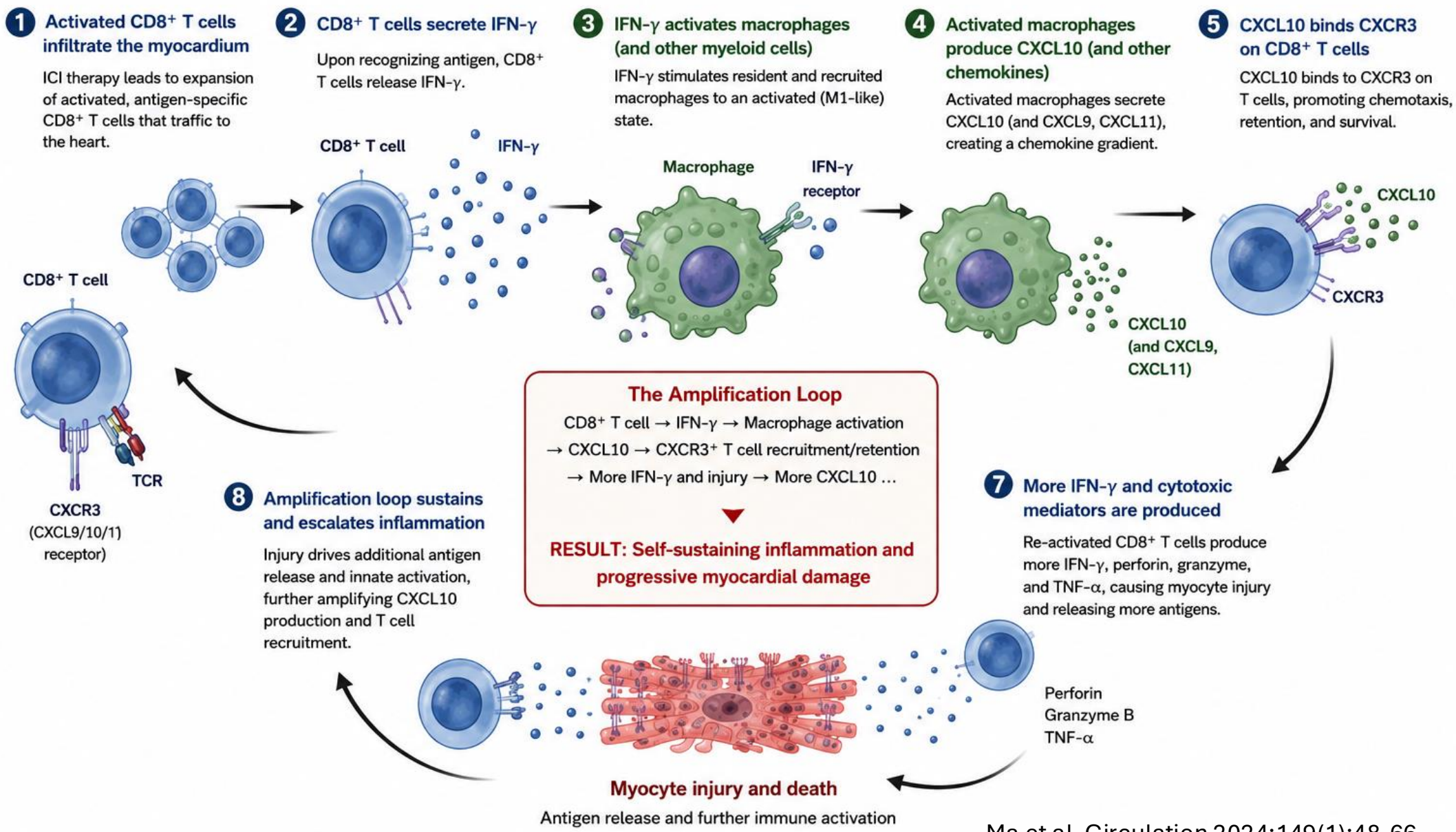
Pathogenesis of ICI Myocarditis

- Autoimmunity
- Animal models and pts with ICI myocarditis have increased levels of circulating α-MHC-specific CD8+ T cells



Axelrod et al. Nature 2022; 611:818–826.
Grabie et al. Cardiovasc Res. 2019;115(5):869–877.

The CD8⁺ T Cell – IFN-γ – Macrophage – CXCL10 Axis: A Feed-Forward Amplification Loop in ICI Myocarditis



Ma et al. Circulation 2024;149(1):48-66
Zhu et al. Circulation. 2022 Jul 26;146(4):316-335

Pathogenesis of ICI Myocarditis: Other Potential Triggers

- Shared tumor and heart antigens
- Molecular mimicry/ homologous epitopes
- Newly exposed antigens after cardiac injury
- HLA-dependent antigen presentation

Diagnostic Criteria for ICI Myocarditis

IC-OS 2021 Consensus

Either pathohistological diagnosis:

Multifocal inflammatory cell infiltrates with overt cardiomyocyte loss by light microscopy of cardiac tissue samples

Or clinical diagnosis [# §]:

A troponin elevation (new, or significant change from baseline) with 1 major criterion or a troponin elevation (new, or significant change from baseline) with 2 minor criteria after exclusion of acute coronary syndrome or acute infectious myocarditis based on clinical suspicion

Major Criterion

- CMR diagnostic for acute myocarditis (modified Lake Louise criteria)

Minor Criteria

- Clinical syndrome (including any one of the following: fatigue, muscle weakness, myalgias, chest pain, diplopia, ptosis, shortness of breath, orthopnea, lower extremity edema, palpitations, lightheadedness/dizziness, syncope, cardiogenic shock)
- Ventricular arrhythmia and/or new conduction system disease
- Decline in cardiac (systolic) function, with or without regional WMA in a non-Takotsubo pattern
- Other immune-related adverse events, particularly myositis, myopathy, myasthenia gravis
- Suggestive CMR (meeting some but not all of the modified Lake Louise citeria)

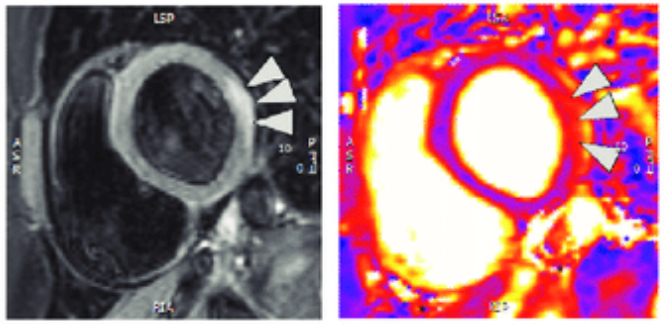
Both troponin I and troponin T can be used; however, troponin T may be falsely elevated in those with concomitant myositis.

Herrmann et al. Eur Heart J 2022;43:280-99.

Modified Lake Louise Criteria for Myocarditis

MAIN CRITERIA

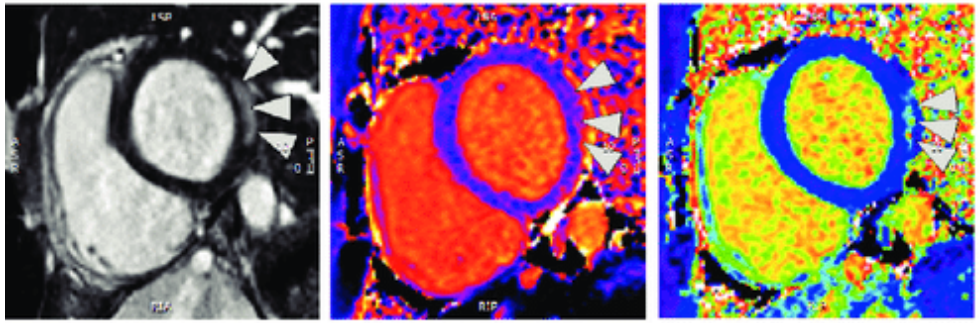
Myocardial Edema



Regional increase of T2 SI at T2w images

Regional native T2 increase at T2 mapping

Non-ischemic Myocardial Injury



Regional non-ischemic LGE

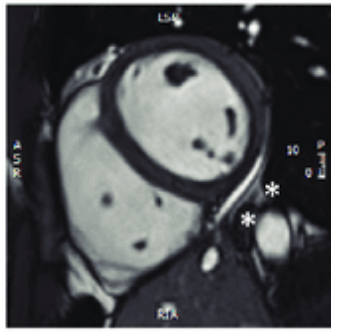
Regional native T1 increase at T1 mapping

Regional ECV increase

SUPPORTIVE CRITERIA

1. Pericarditis
(Effusion at cine images or abnormal LGE, T2 or T1)

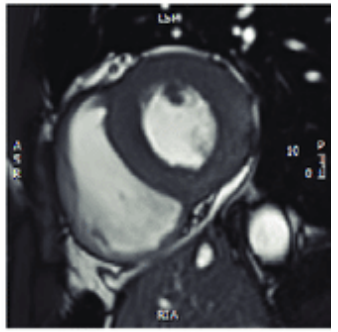
Mild pericardial effusion



Cine/diastole

2. Systolic LV Dysfunction
(Regional or global wall motion abnormality)

Normal LVEF



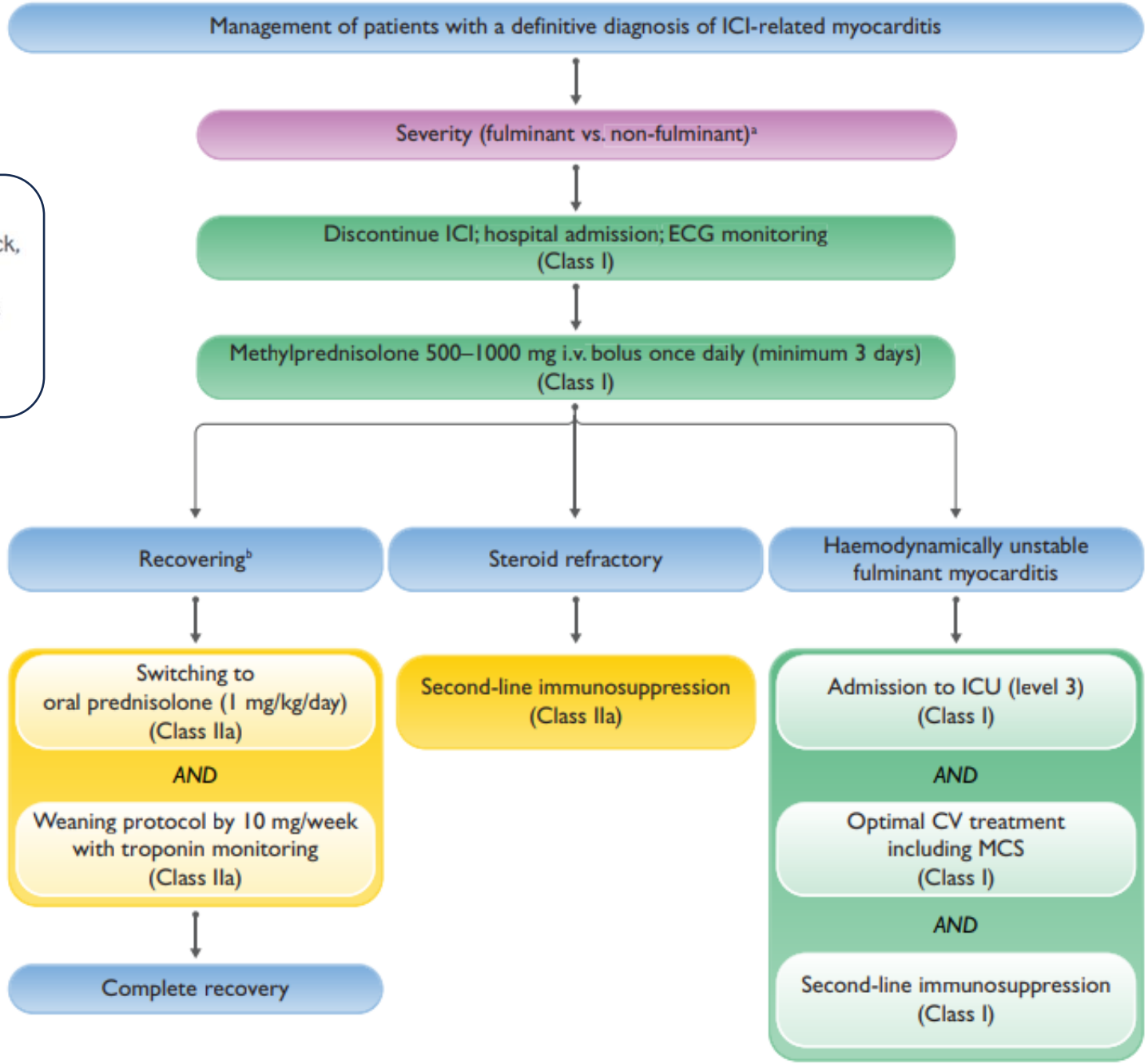
Cine/systole

Leiner et al. J Cardiovasc Magn Reason 2020;22:76

ICOS/ESC Grading and Treatment Algorithm

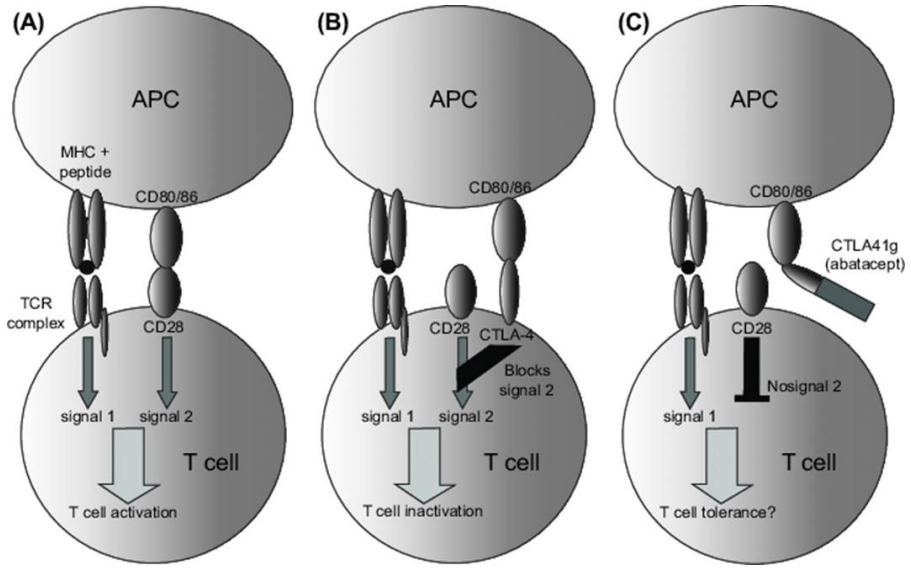
Severity

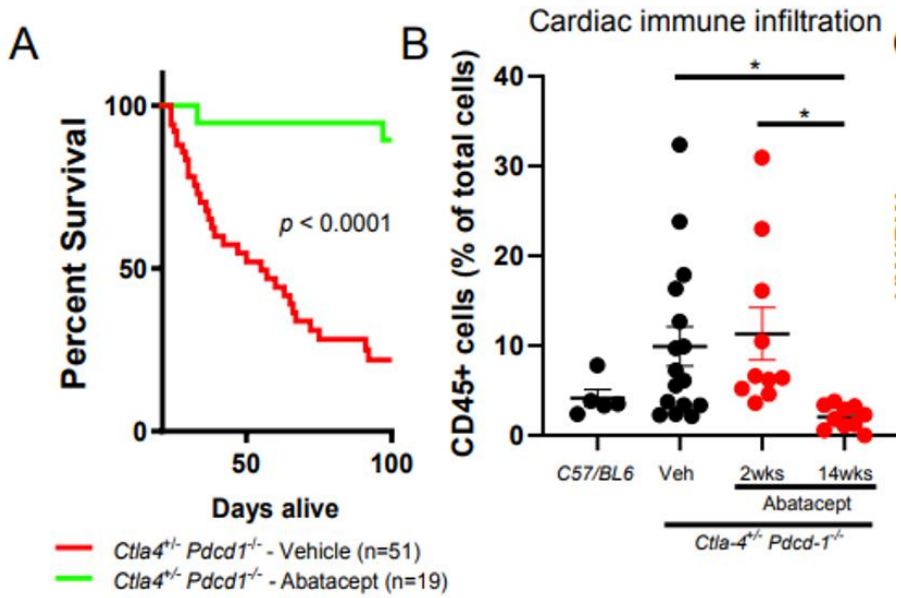
- Severe: hemodynamic instability, mechanical ventilation, high grade heart block, significant ventricular arrhythmia
- Non-severe (clinically significant): symptomatic but hemodynamic and electric stability; reduced ejection fraction may be present
- Smoldering: subclinical, no clinical signs or symptoms



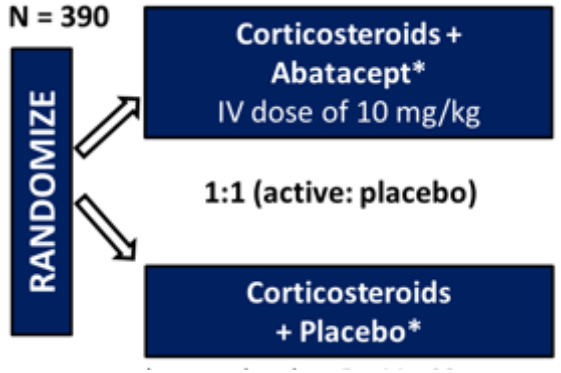
Lyons et al. Eur Heart J 2022;00:1–133

AbatacepT foR ImmUne checkpoint inhibitor associated Myocarditis (ATRIUM)





Pts with biopsy or clinical diagnosis of ICI myocarditis *and* no immunosuppressive therapy except steroids

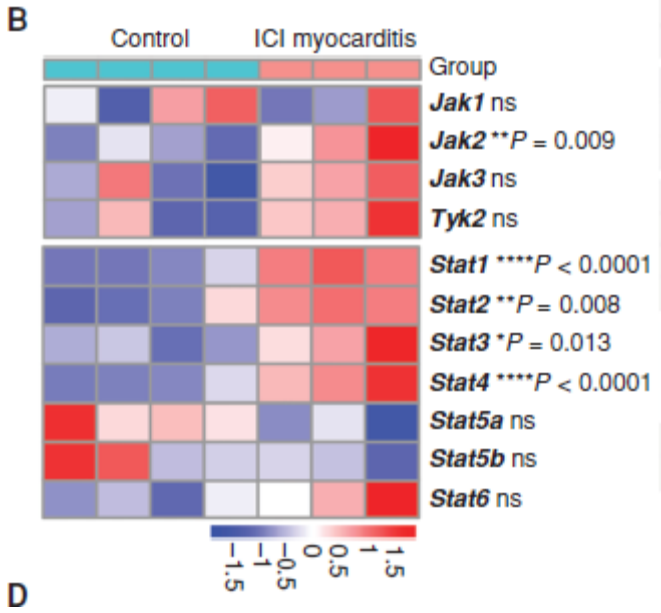


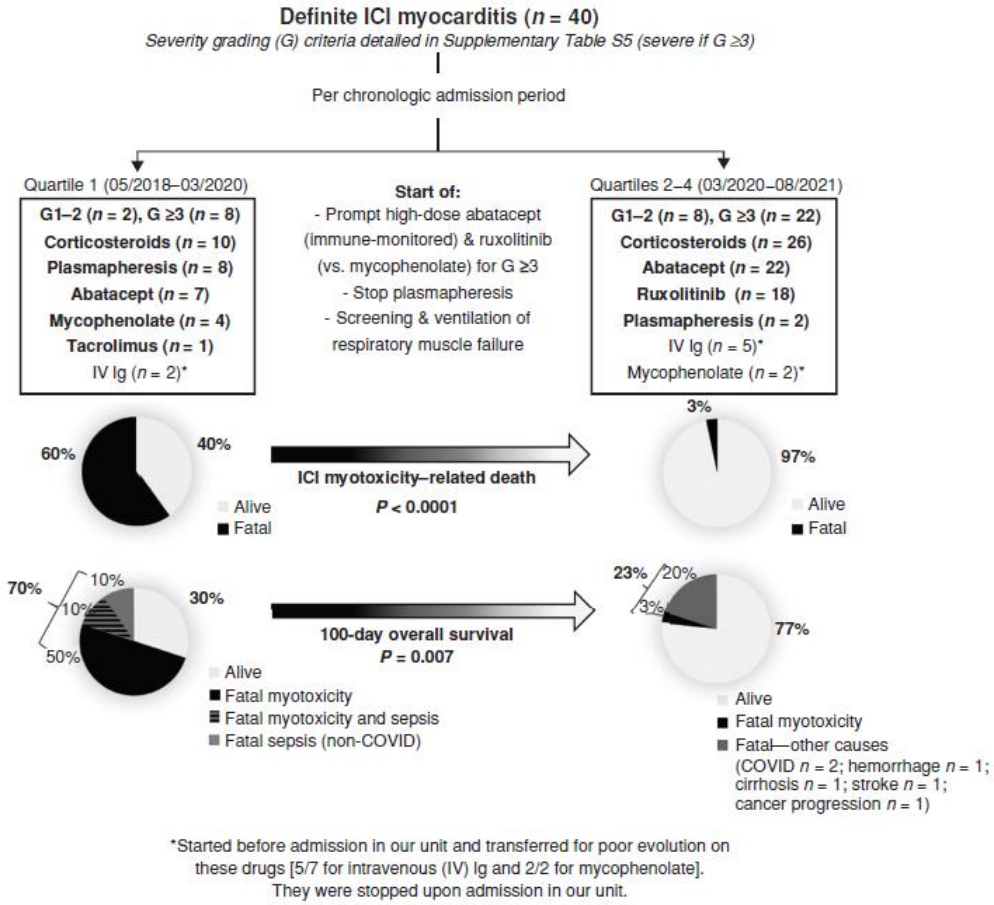
Primary Endpoint:
MACE = composite of CV death, cardiogenic shock, cardiac arrest, VT, bradyarrhythmia requiring PPM or new decompensated HF

Todd DJ et al. Int J Clin Prac. 2007;61:494-500.

Abatacept + Ruxolitinib for Refractory Overlap Syndrome

RNA-seq of mouse ICI-myocarditis model



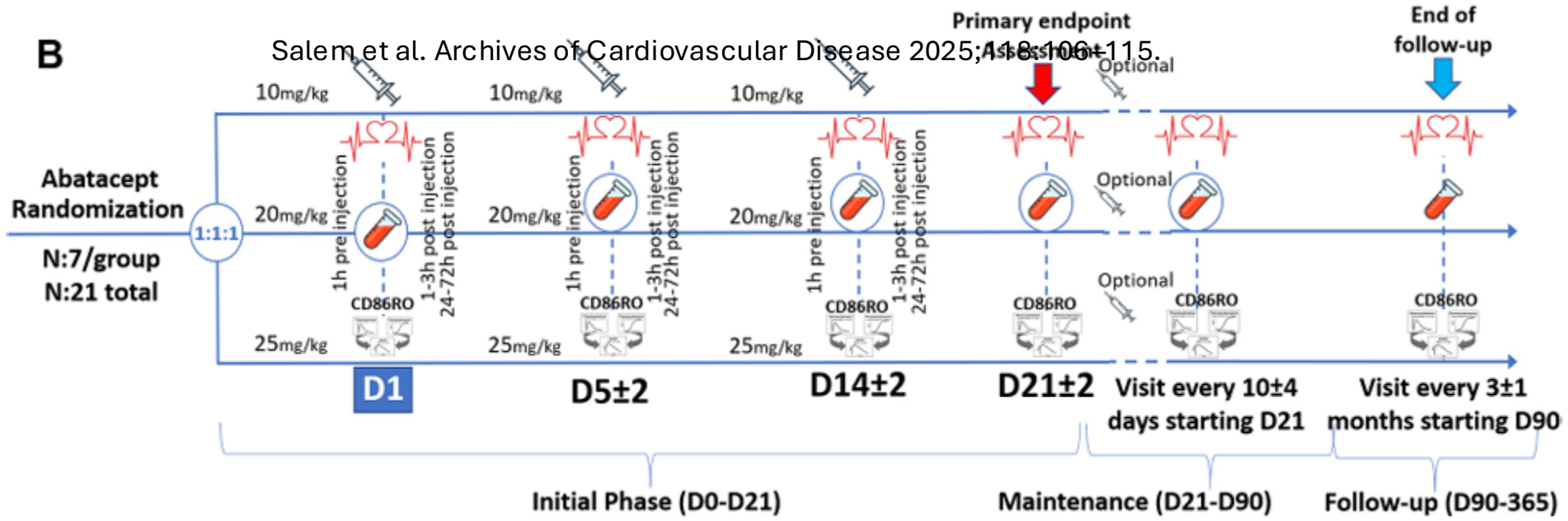


IFN-γ→JAK/STAT pathway→CXCL9 & CXCL10→CXCR3 T cell
Ruxolitinib inhibits JAK1/2

Salem et al. Cancer Discov 2023;13:1100–15.

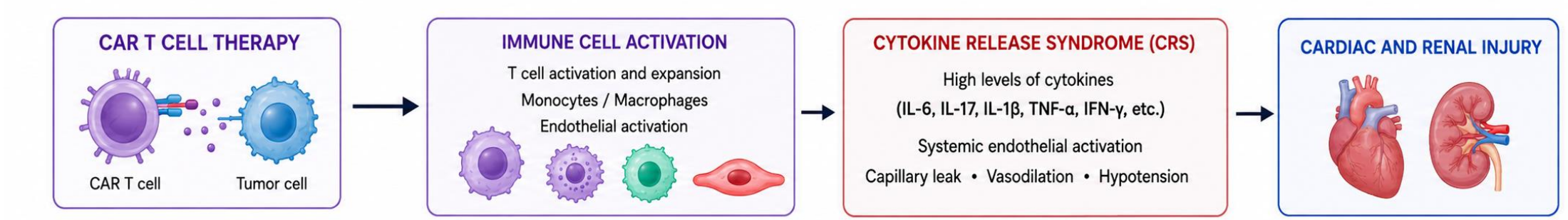
ACHLYS Trial: Dose Finding Study for Abatacept in ICI Myocarditis

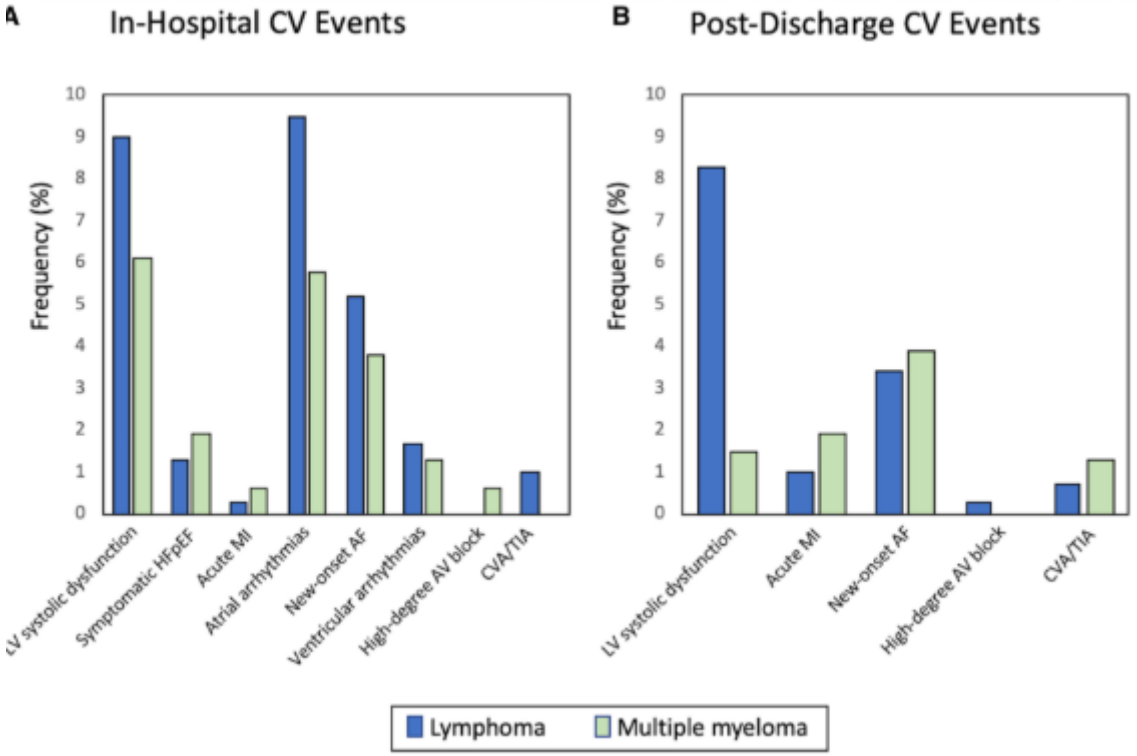
- Severe or steroid-resistant ICI myocarditis
- Intervention: Abatacept (10/20/25 mg/kg) + ruxolitinib 15 mg bid + corticosteroids
- Primary Endpoint: ≥ 80% CD86 receptor occupancy w/in 3 weeks



Salem et al. Archives of Cardiovascular Disease 2025;118:106–115.

CV Adverse Events of CAR T-cell Therapy





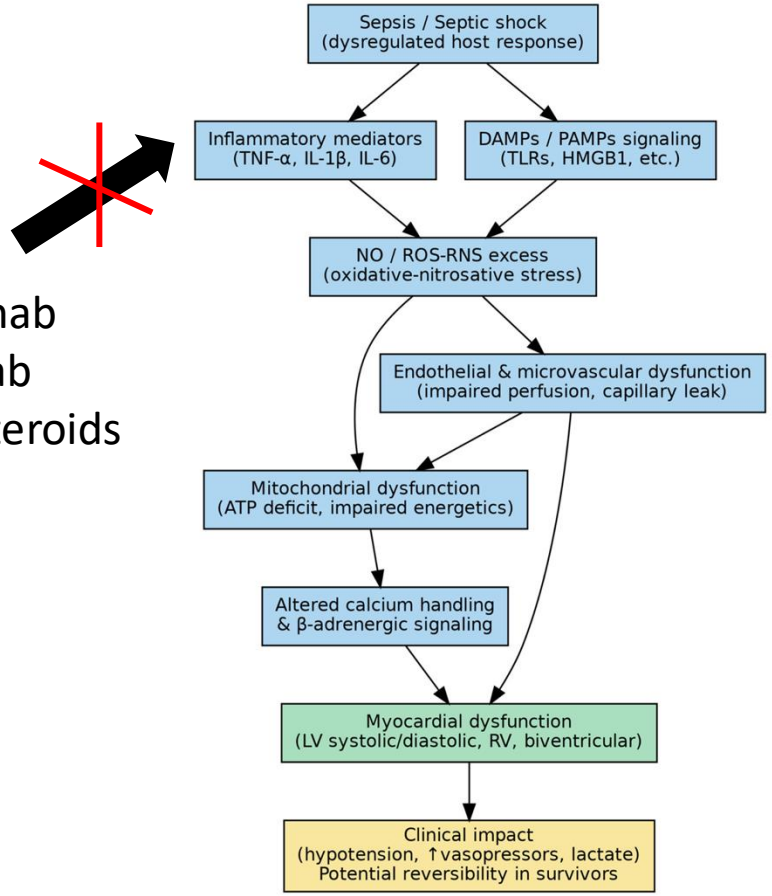
Predictors of CV Events

- CRS grade ≥ 2
- Underlying tumor burden
- Pre-existing CVD or CV RF
  - Cardiomyopathy or Afib

Itzhaki Ben Zadok et al. 2024;150 (22):1815-1817; Joseph et al. Curr Onc Rep. 2025;27:135–147.

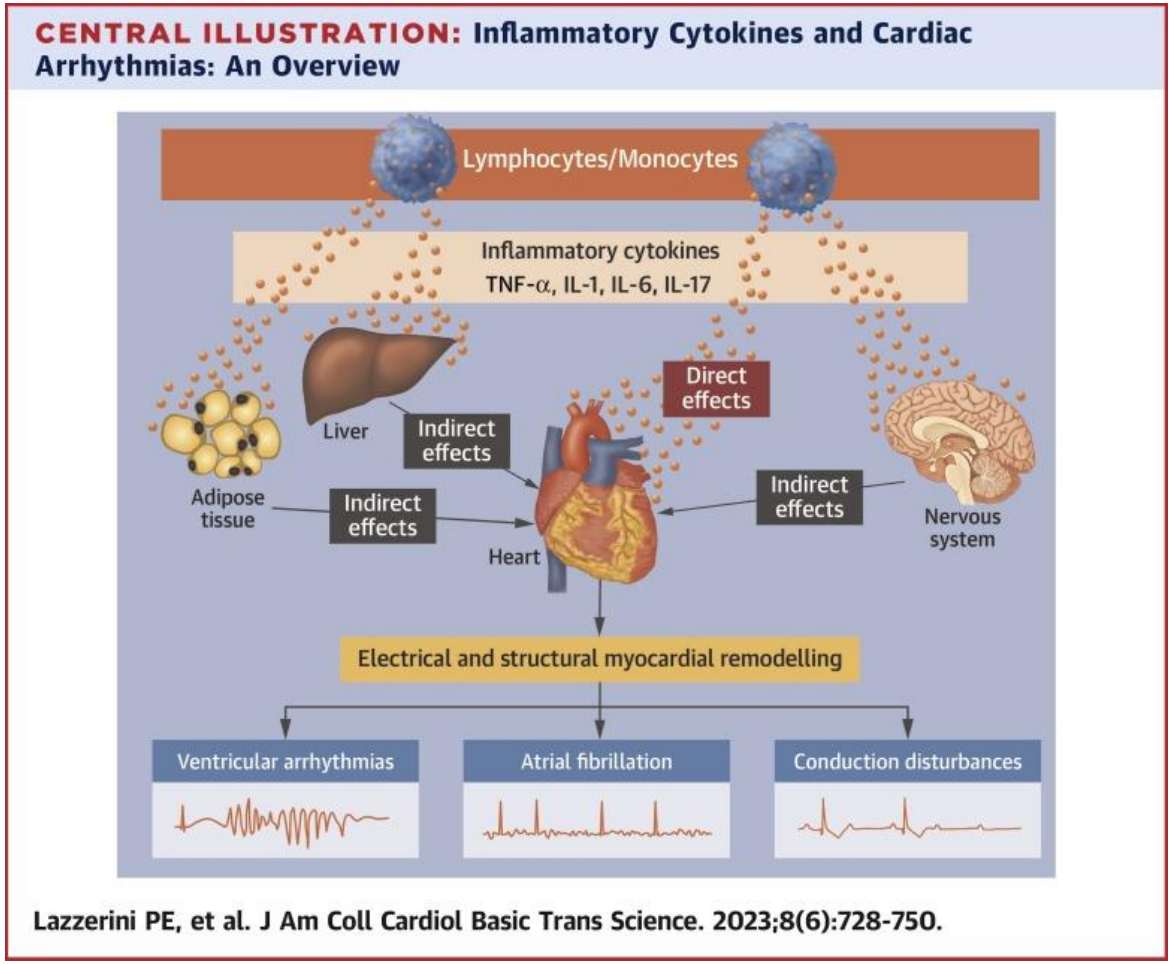
Cardiotoxicity from Cytokine Release Syndrome

Myocardial Dysfunction



Tocilizumab
Siltuximab
Corticosteroids
Anakinra

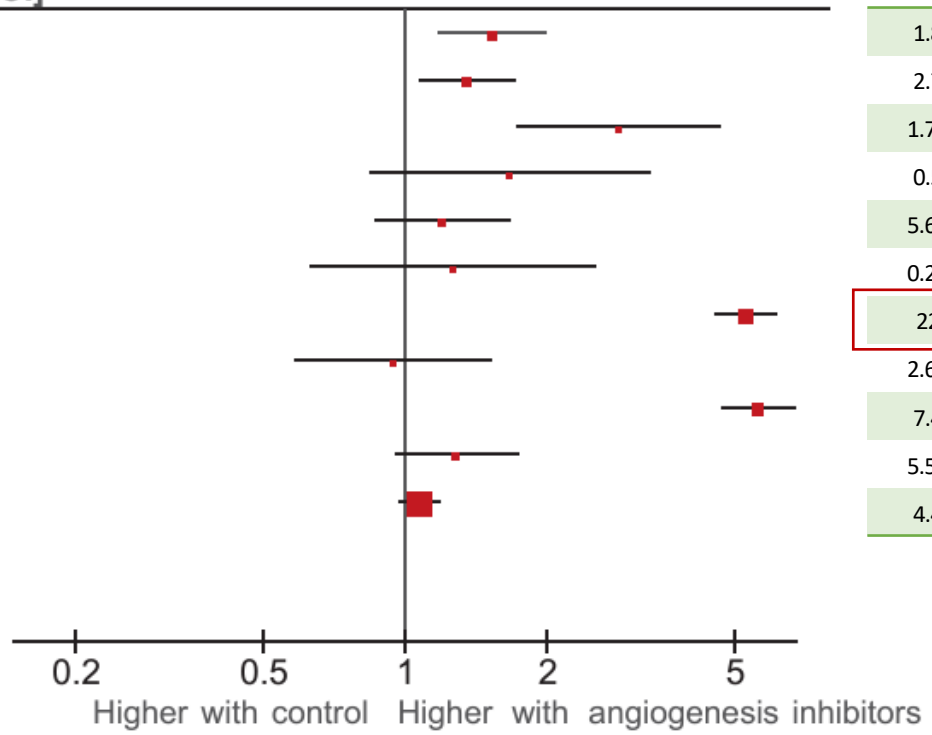
Arrhythmias



Padureanu et al. *Int. J. Mol. Sci.* **2026**, *27*(6), 2552

CV Toxicities of TKIs

Toxicity	Odds Ratio [95% CI]	TKI	No TKI
Arterial thromboembolism	1.52 [1.17, 1.98]	1.8%	1.1%
Cardiac dysfunction	1.35 [1.06, 1.70]	2.7%	1.95%
Cardiac ischemia	2.83 [1.72, 4.65]	1.75%	0.56%
Congestive Heart Failure	1.66 [0.84, 3.30]	0.5%	0.28%
Deep vein thrombosis	1.20 [0.86, 1.66]	5.66%	4.73%
Fatal cardiovascular events	1.26 [0.63, 2.53]	0.25%	0.17%
Hypertension	5.28 [4.53, 6.15]	22%	5.2%
Pulmonary embolism	0.94 [0.58, 1.52]	2.65%	2.77%
Severe hypertension	5.59 [4.67, 6.69]	7.4%	1.32%
Unspecified thromboembolism	1.28 [0.95, 1.73]	5.58%	5.53%
Unspecified venous thromboembolism	1.07 [0.97, 1.19]	4.4%	3.95%



Abdel Qadir et al. Cancer Rx Reviews 2017;53:120.

NORMAL VEGF SIGNALING: MAINTAINS CARDIOVASCULAR AND RENAL HOMEOSTASIS

HEART

VEGF → VEGFR2

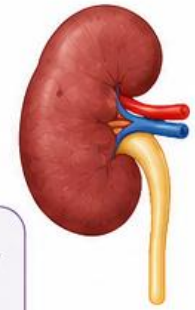
Endothelial Cell

- PLCγ → IP_3/DAG → ↑ Ca^{2+}
  - eNOS activation
  - NO production
  - Vasodilation
- PI3K → AKT → eNOS
  - NO production
  - Endothelial survival
  - Barrier integrity
- MAPK/ERK → Gene expression
  - Cell survival
  - Proliferation
  - Angiogenesis
- Other pathways (e.g., Src) → Cytoskeletal stability
  - Junction integrity
  - Vascular stability
  - Anti-inflammatory

Normal coronary microvasculature

- Adequate perfusion
- Normal hemodynamics
- Healthy myocardium

KIDNEY



Endothelial Cell

Normal glomerular & peritubular microvasculature

- Intact filtration barrier
- Normal GFR
- Tubular homeostasis

VEGF INHIBITORS (e.g., bevacizumab, sunitinib, pazopanib)

- PLCγ ↓ → IP_3/DAG ↓ → ↓ Ca^{2+}
- PI3K ↓ → AKT ↓ → ↓ eNOS
- MAPK/ERK ↓ → ↓ Gene expression
- Other pathways (e.g., Src) ↓ → ↓ Cytoskeletal stability ↓

COMMON ENDOTHELIAL CONSEQUENCES

- ↓ Prostacyclin (PGI_2)
- ↑ Endothelin-1 (ET-1)
- ↓ Nitric Oxide (NO)
- ↑ Reactive Oxygen Species (ROS)

Endothelial dysfunction
- Inflammation
- Increased permeability
- Capillary rarefaction

CARDIAC CONSEQUENCES

- ↑ Vasoconstriction & microvascular dysfunction
- LV hypertrophy / remodeling
- ↑ Afterload & wall stress
- Myocardial fibrosis
- Myocardial ischemia
- LV dysfunction / cardiomyopathy → Heart failure & arrhythmias

CLINICAL OUTCOMES

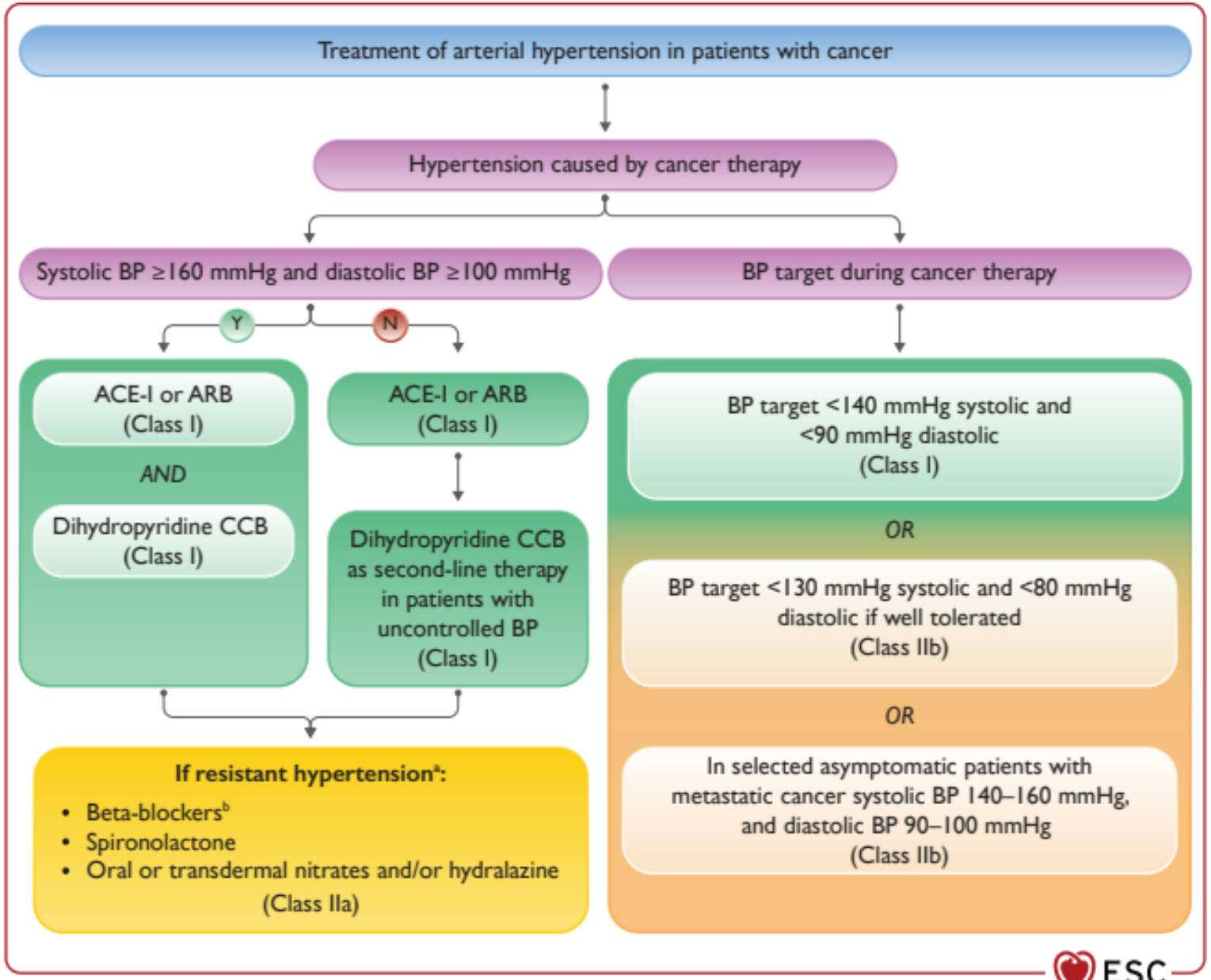
- Hypertension
- Fluid retention
- Increased CV events
- Worsening kidney function
- Heart failure

RENAL CONSEQUENCES

- Glomerular endothelial injury → Proteinuria
- Tubular injury & apoptosis
- ↑ Sodium retention & volume expansion
- ↓ GFR → CKD progression
- Thrombotic microangiopathy (TMA) → AKI

Surveillance and Management of TKI Associated Hypertension

- Daily home BP monitoring for the first cycle, each dose increase and Q2-3 weeks thereafter
- *Hold therapy for:*
  - *SBP ≥ 180/110*
  - *End-organ damage*



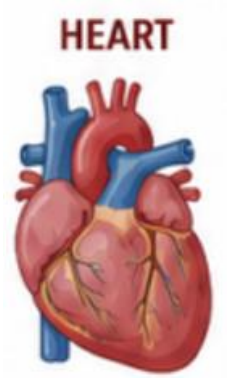
Lyons et al. Eur Heart J 2022;00:1-133.

Anthracyclines

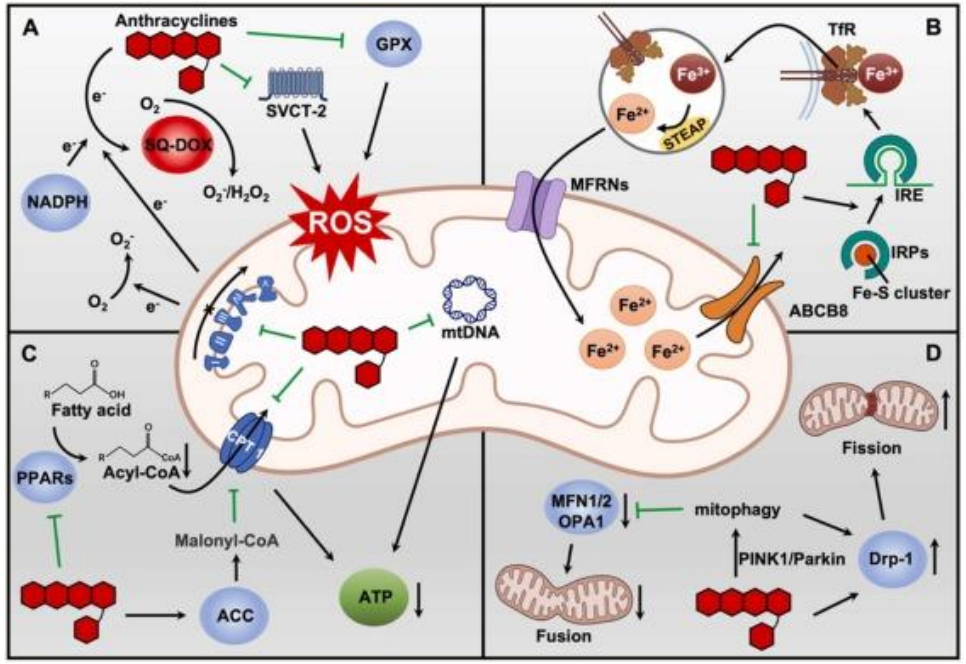
Anthracyclines

↓

Mitochondrial Dysfunction



Cardiomyocyte Injury
Progressive LV dysfunction
(26% @ 550 mg/m^2
Can present late)

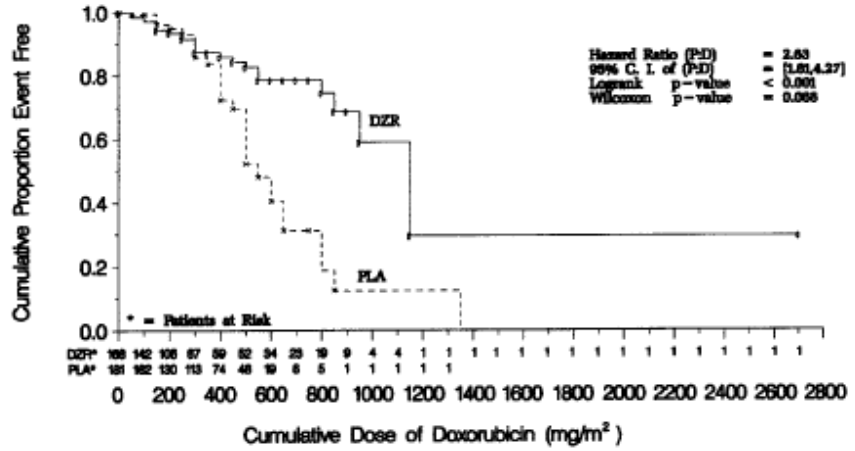


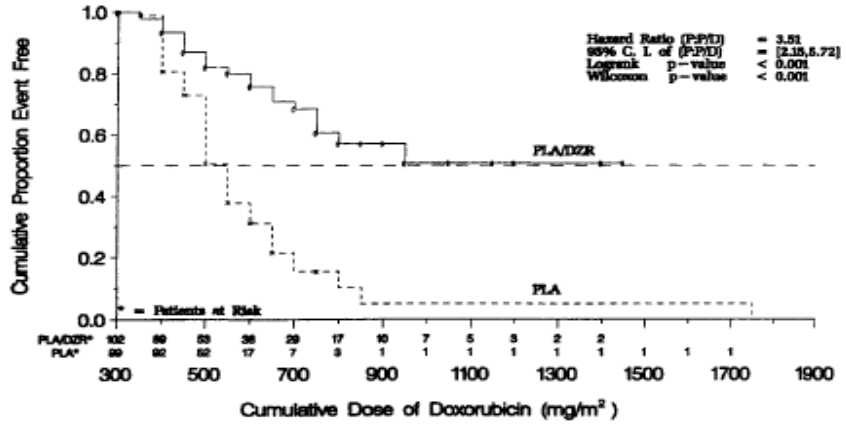
Tubular cells are
mitochondria-rich
Potential susceptibility to
oxidative injury

Li, et al. Biomedicine and Pharmacotherapy. 2024;179:117312

Dexrazoxane: iron chelator

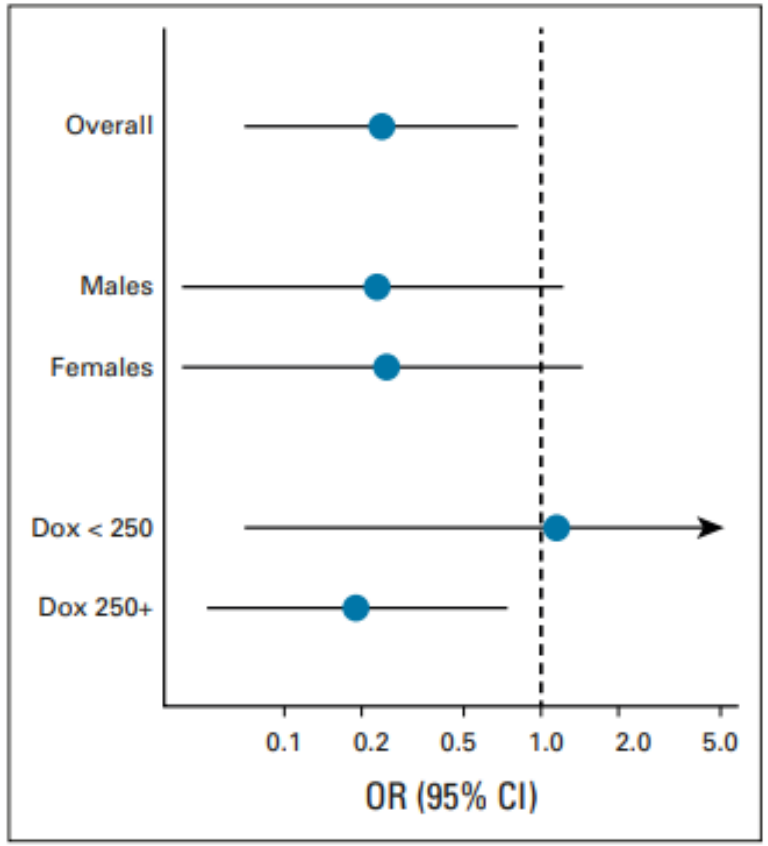
534 pts with advanced breast CA





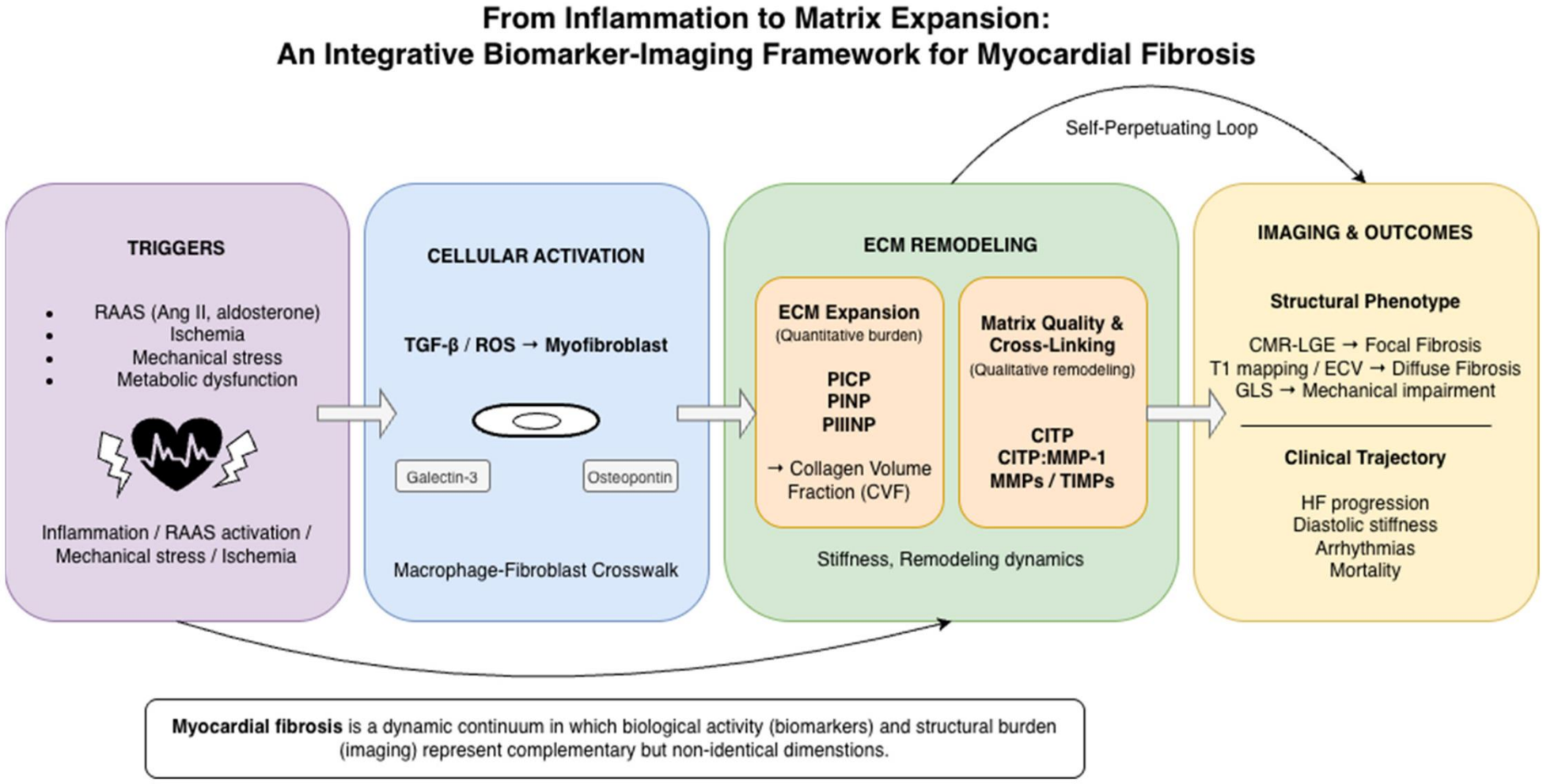
Lyu et al. Cancer Res. 2007;67(18):8839; Swain J Clin Onc 1997;15:1318; Swain J Clin Onc 1997;15:1333

N=195 pediatric pts, ALL, NHL, or osteosarcoma
Mean F/U 18.1 ± 2.7 yrs

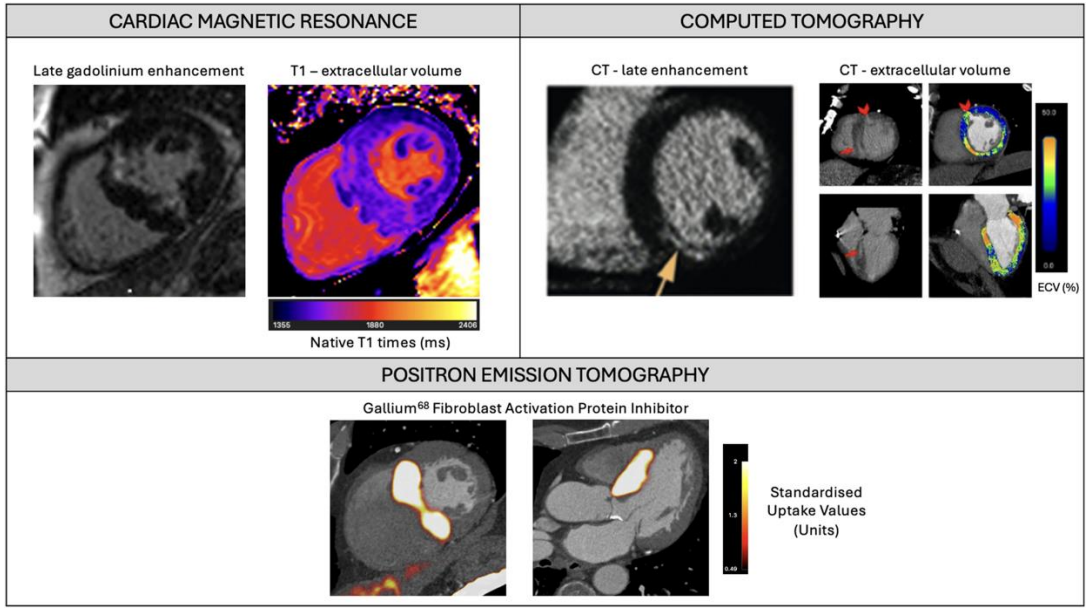


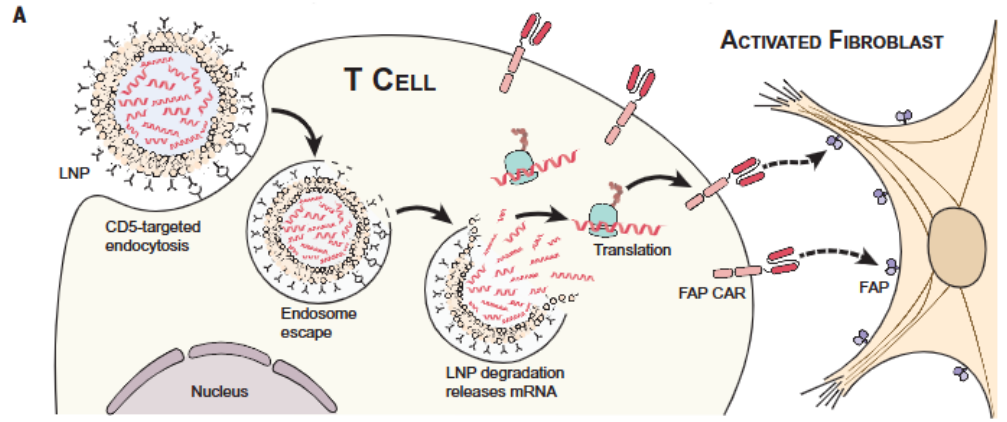
Chow et al. JCO 2023;41(12):2248-57

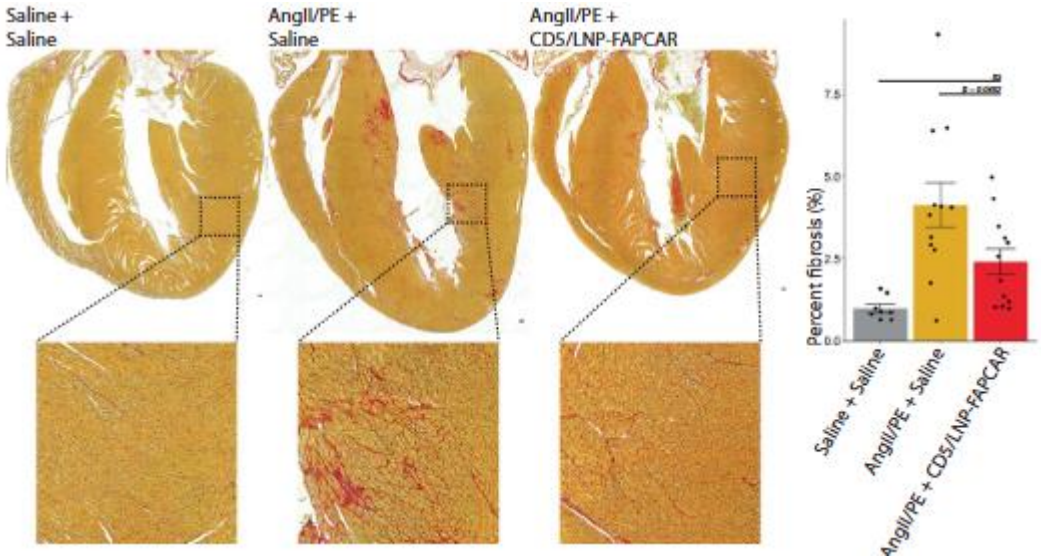
Cardiotoxicity and Fibrosis



Fibroblast Activating Protein (FAP) as an Imaging and Therapeutic Target







Ezeani et al. Int J Cardiovasc Imag; 2026;42:1431–1448;
Rurik et al. Science 2022;375(6576):9196.

Take Home Points

Lesson

1. Shared pathways of toxicity could lead to common protective and treatment pathways
2. Understanding mechanisms may allow detection before phenotypic disease
3. Organ cross-talk matters

Future Implications

Immune modulation, endothelial protection, mitochondrial protection, anti-fibrotic strategies

Early markers of injury e.g. urinary/serum CXCL10, VCAM-1, ICAM-1, etc.

Disease in one amplifies the other

Think beyond the organ – even though the phenotype is organ-specific – the biology is not!

Thank you!