- **<u>Cardiovascular management of patients treated with immune check point inhibitors</u>**
-
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- **-Section Head Cardio Oncology Cleveland Clinic Florida**
- **-Chair, Cardio-oncology Committee Florida ACC**
- **-Chair Elect, American College of Cardiology Leadership Council**
- **-American College of Cardiology Cross-Sectional Advocacy Committee**
- **-American Heart Association Cardio Oncology Committee**
- **-International Cardio-Oncology Society (ICOS) Education Committee**
- **-PI Global Cardio Oncology Registry**

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- I have no relevant financial disclosures
- **i3 Health and FLASCO have mitigated all relevant financial relationships**

Sean Tan et al. *J Am Coll Cardiol CardioOnc* 2022; 4:579-597.

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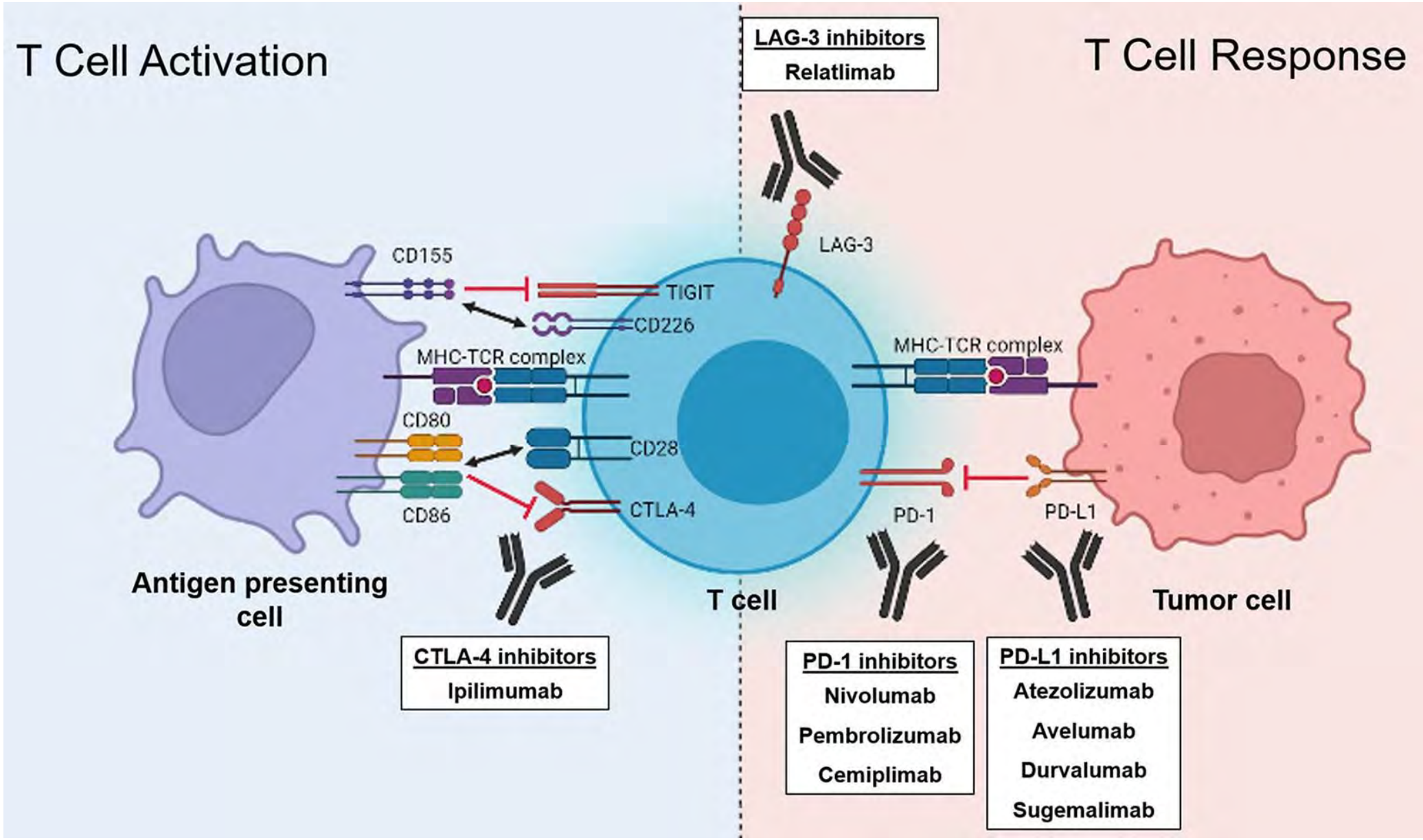
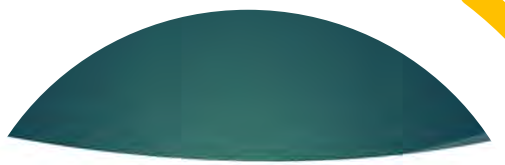


Immunotherapy has changed cancer treatment

- Monoclonal antibodies **that block negative regulators of the T cell immune response by turning off T cell inhibitor receptors** including CTLA4, PD1, PDL1 and GAL-3 receptors and “unleashing” the immune system.
- **Significant mortality benefit** in numerous cancer types.
- ICIs **regulate autoreactivity** that leads to disinhibited **cytotoxic T cells off-targeting healthy tissue in multiple organs**, known **as immune-related adverse events** (irAEs**) in up to 70% of patients** . **They are typically mild** and easy-to-manage events.
- However, **life-threatening high-grade events, such as ICI-associated cardiotoxicities, can also occur** and significantly **impact both cancer therapy and overall outcomes**

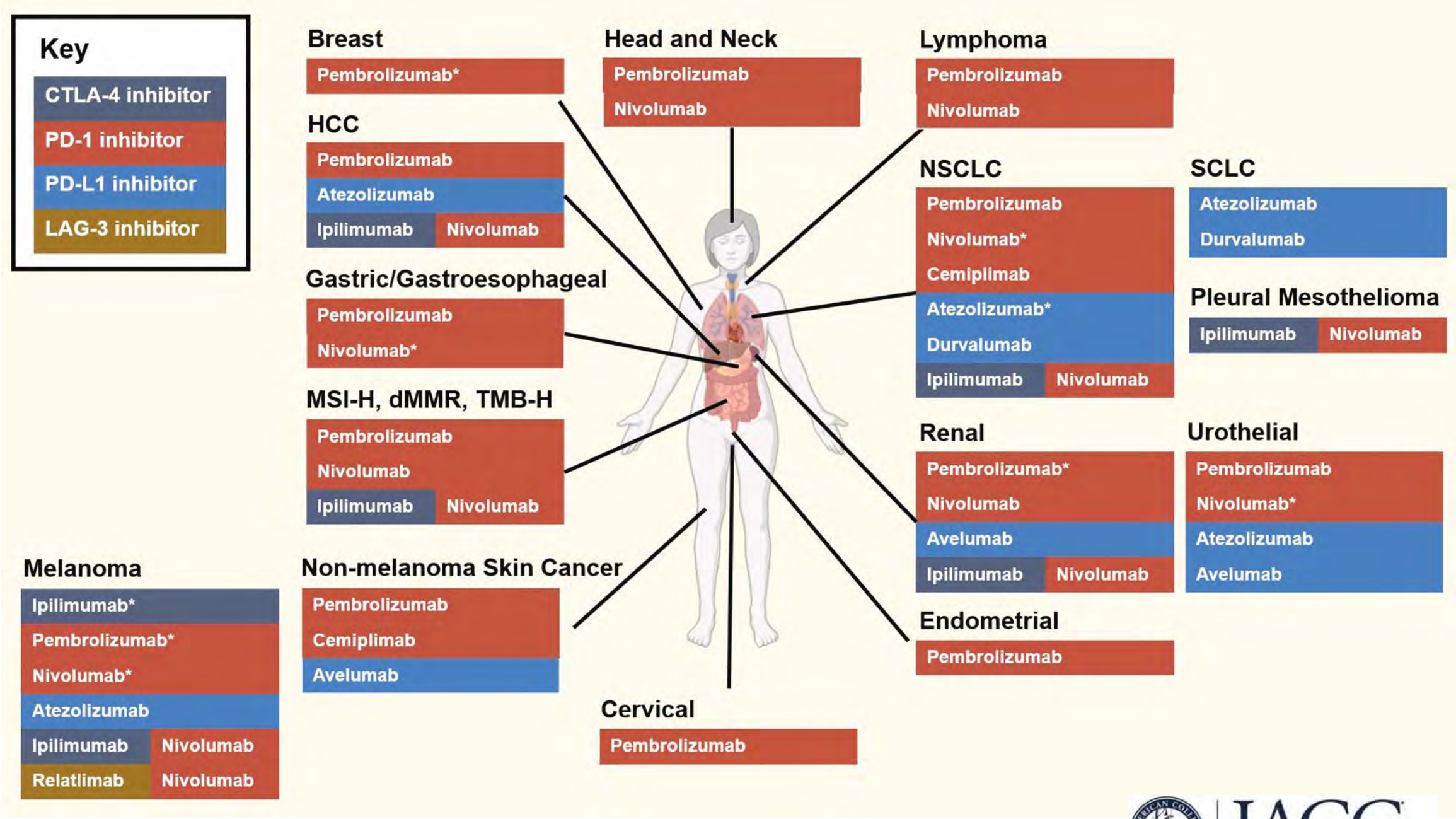


Immune check point inhibitors (ICIs).

Immunotherapy has changed cancer treatment

Antibodies that block negative regulators of the T cell immune response by turning off T cell inhibitor receptors including CTLA4, PD1 and PDL1 receptors and "unleashing" the immune system.

They have a significant mortality benefit in numerous cancer types but the augmented immune response leads to a range of auto immune disorders including cardiovascular toxicity.



Sean Tan et al. *J Am Coll Cardiol CardioOnc* 2022; 4:579-597.

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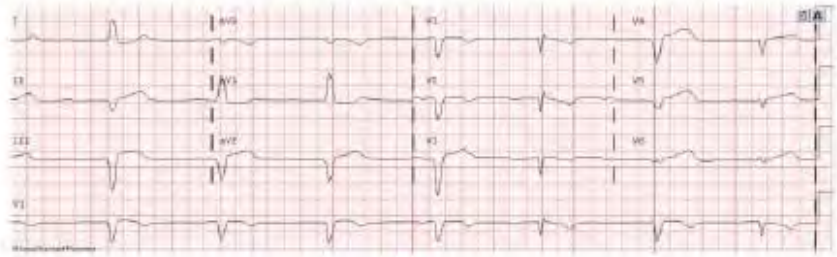
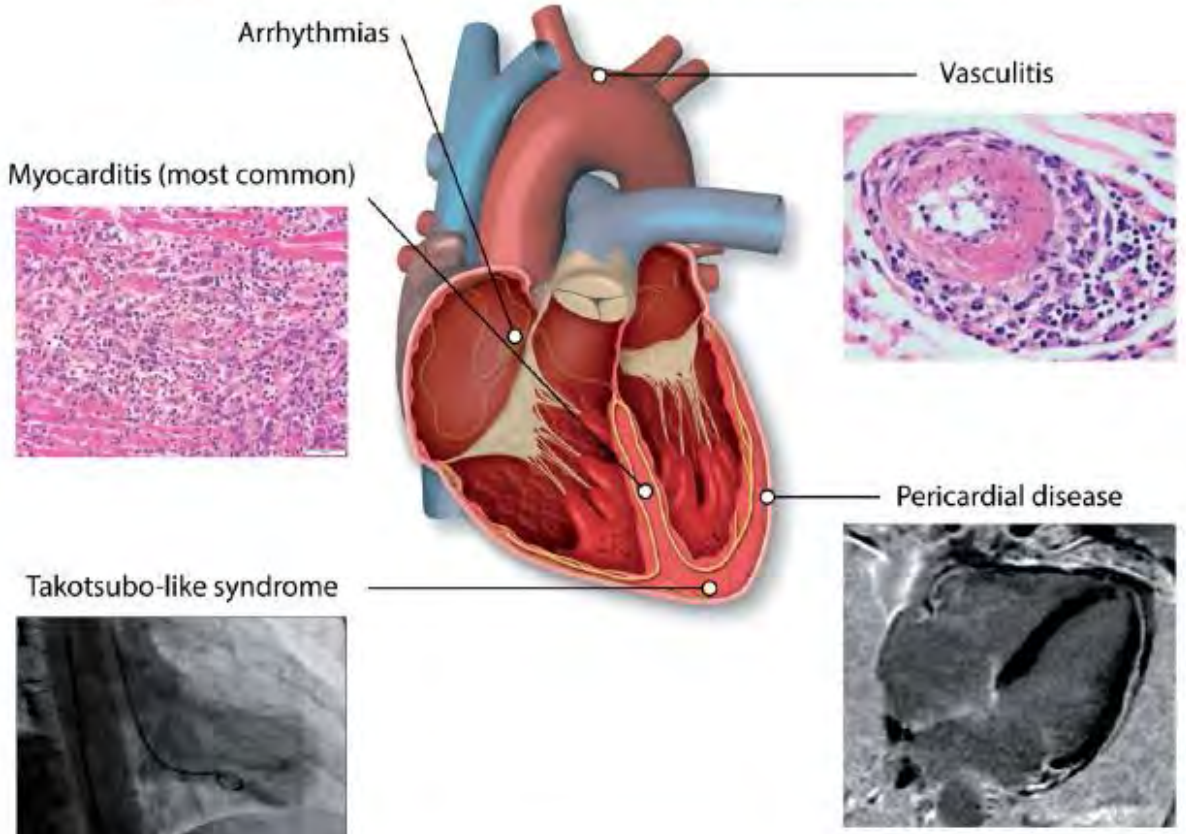
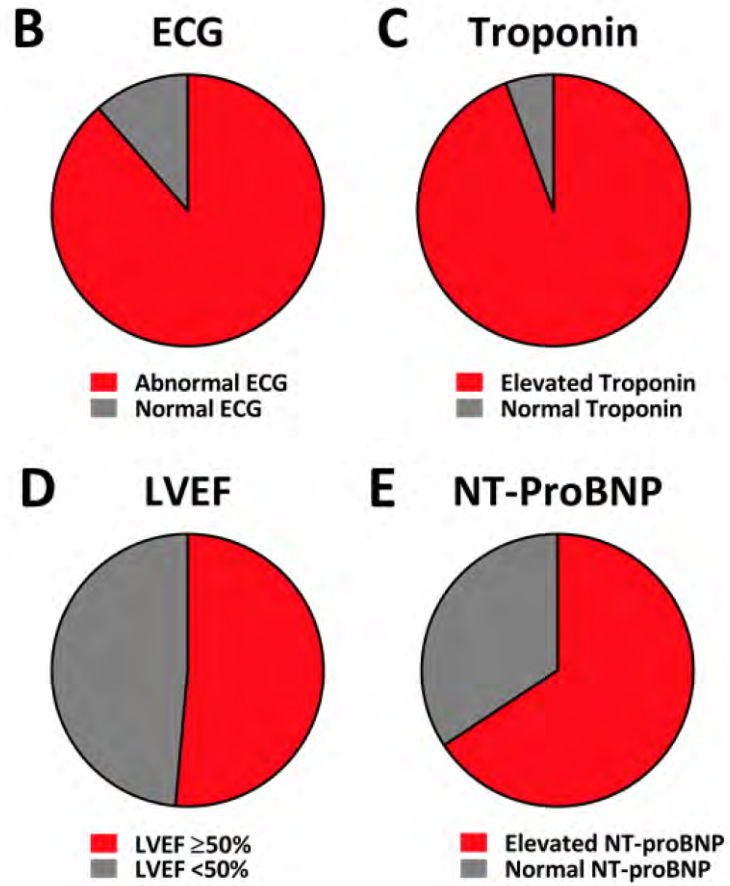
ICI-Associated Cardiovascular Toxicities





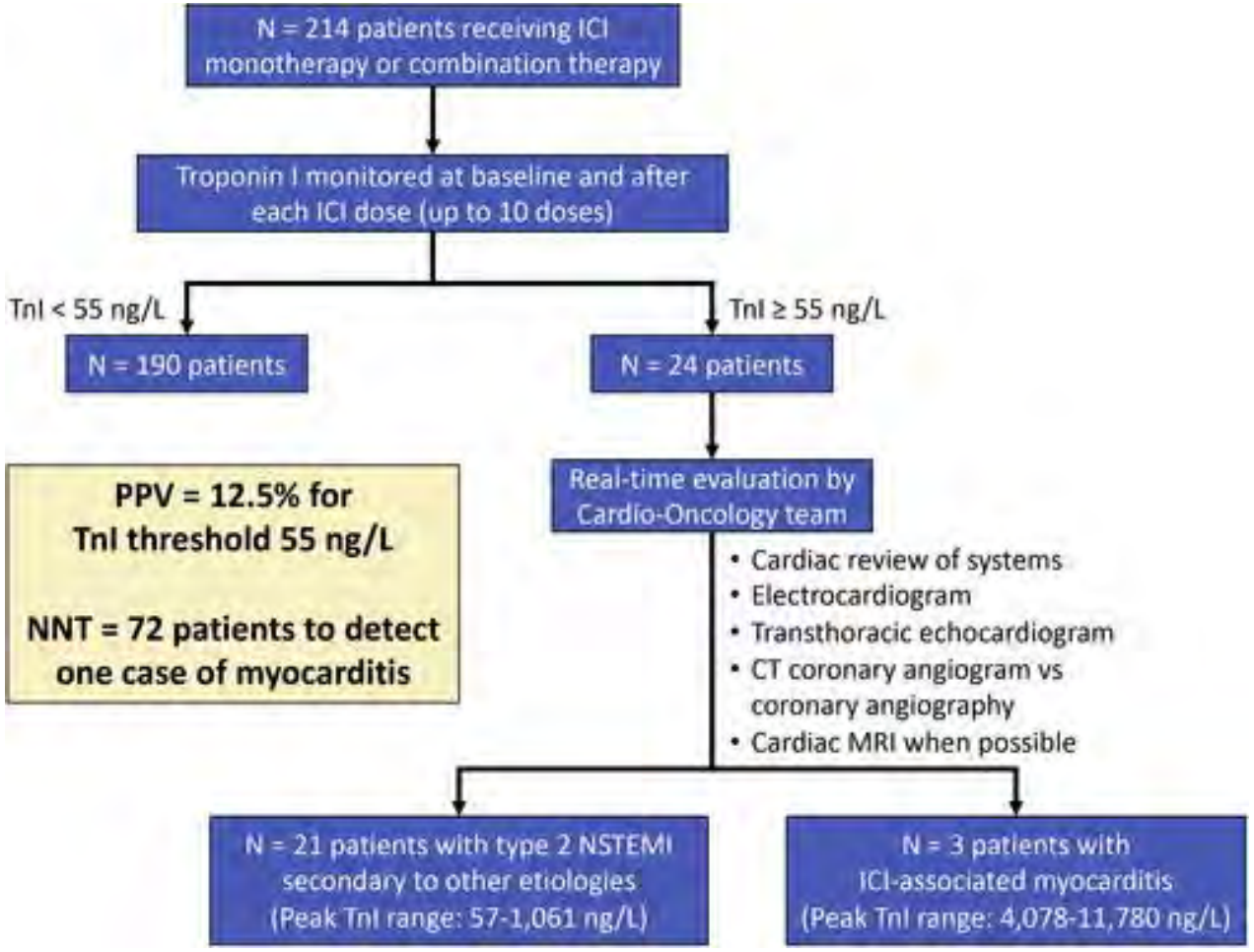
Hu, Florido…Moslehi. *CV Research*. 2019.

Summary of Presentations



- Nearly all myocarditis cases had a troponin elevation (94%)
- Most had a BNP or NT-proBNP elevation (66%).
- Abnormal EKG changes were noted in 83% of myocarditis cases.
- The LVEF was normal in 45% of cases and abnormal in 55%

Neiland et al JACC 2018



Myocarditis Surveillance Algorithm

HsTnI-based myocarditis surveillance with a multidisciplinary cardio-oncology team and outcomes, CT = computed tomography; HsTnI = high-sensitivity troponin I; ICI = immune checkpoint inhibitor; MRI = magnetic resonance image; NNT = number needed to test; PPV = positive predictive value; TnI = troponin I.

-Of 24 (11.2%) patients with a positive hsTnI, 3 had myocarditis (incidence: 1.4%) by consensus-based definitions

-HsTnI levels in the 3 cases of myocarditis were >20-times above ULN at diagnosis.

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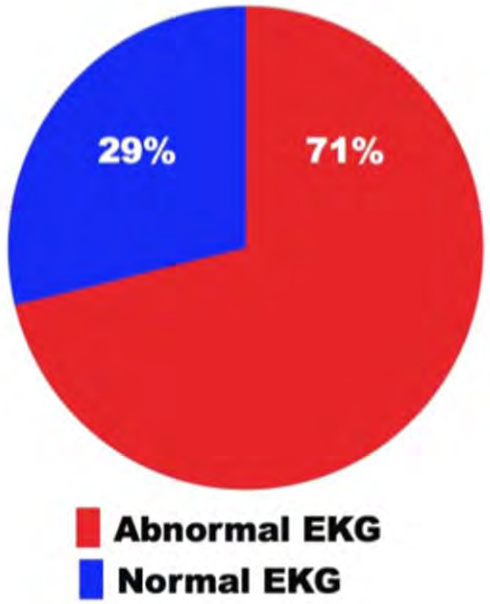
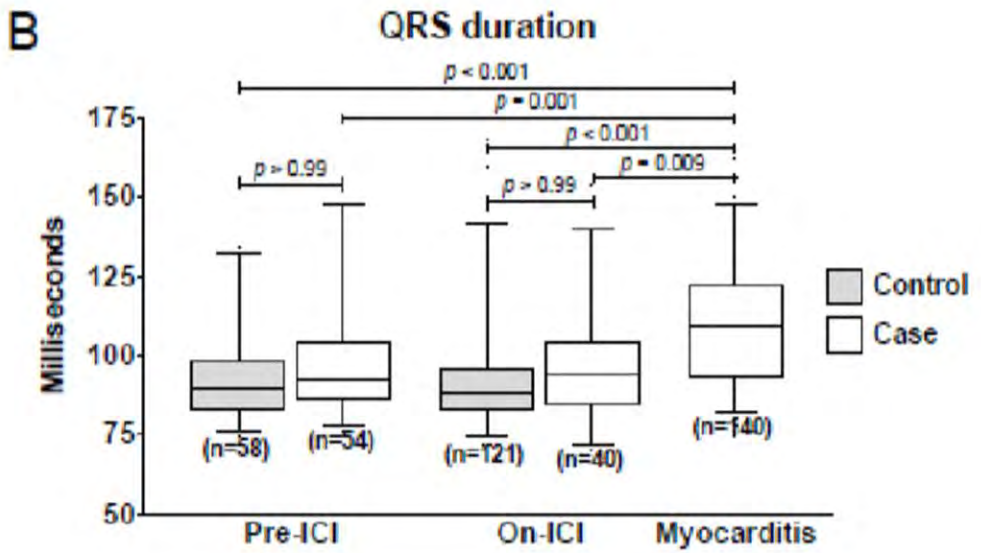
ECG abnormalities: QRS duration

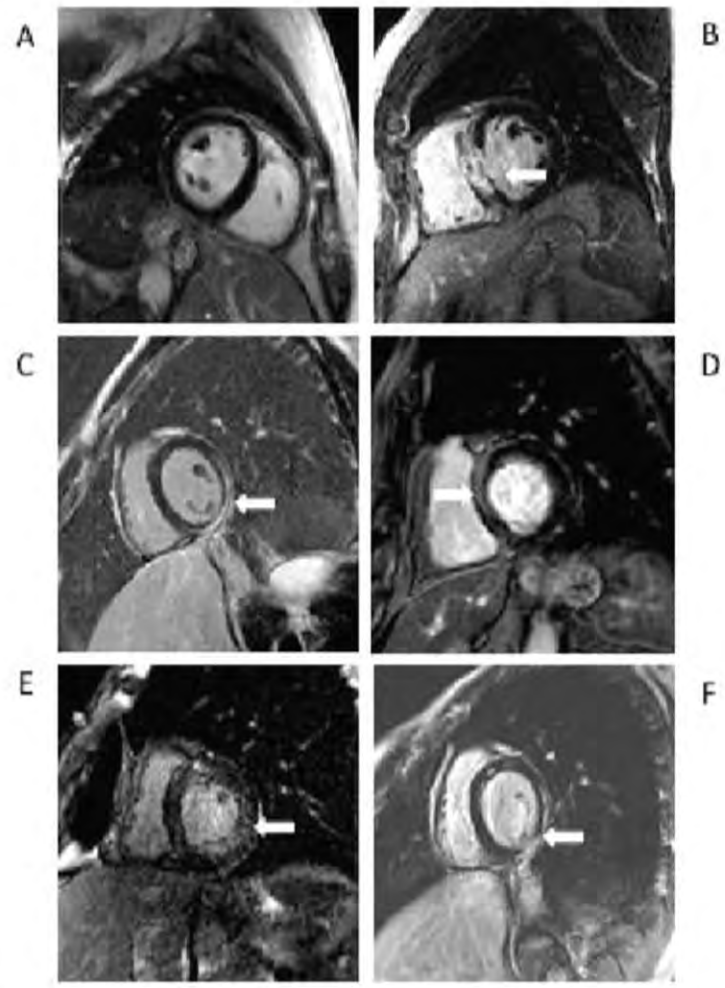
ECG/EKG





Mahmood, Fradley, JACC, 2018; Zlotoff, Gupta, Nohria et al, preliminary Data

MRI patterns in ICI myocarditis



Zhang, Gupta, Chen, Thavendiranathan, EHJ, 2020

- Representative LGE images from patients with ICI-associated myocarditis, showing a patient with no LGE (A); a patient with sub-endocardial/transmural LGE (B); a patient with sub-epicardial LGE (C); a patient with mid-myocardial LGE (D); a patient with diffuse LGE (E); a patient with mixed LGE (sub-epicardial, mid-myocardial and transmural) (F). Regions of LGE are highlighted using white arrows.
- When present, the patterns seen were:
  - Mid-myocardial: 18 (21.7%)
  - Sub-epicardial: 9 (10.8%)
  - Diffuse/patchy: 10 (12.1%)
  - Sub-endocardial/transmural: 3 (3.6%)

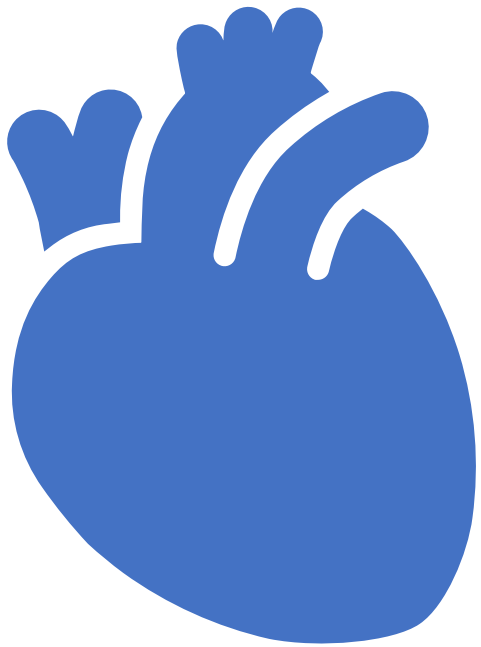
Role of MRI in Diagnosing ICI Myocarditis

LGE enhancement was present in **55 % of reduced LVEF** and **43 % of preserved LVEF**

Early MRI may have lower sensitivity. **Repeating in 72 hours improves detection rate.**

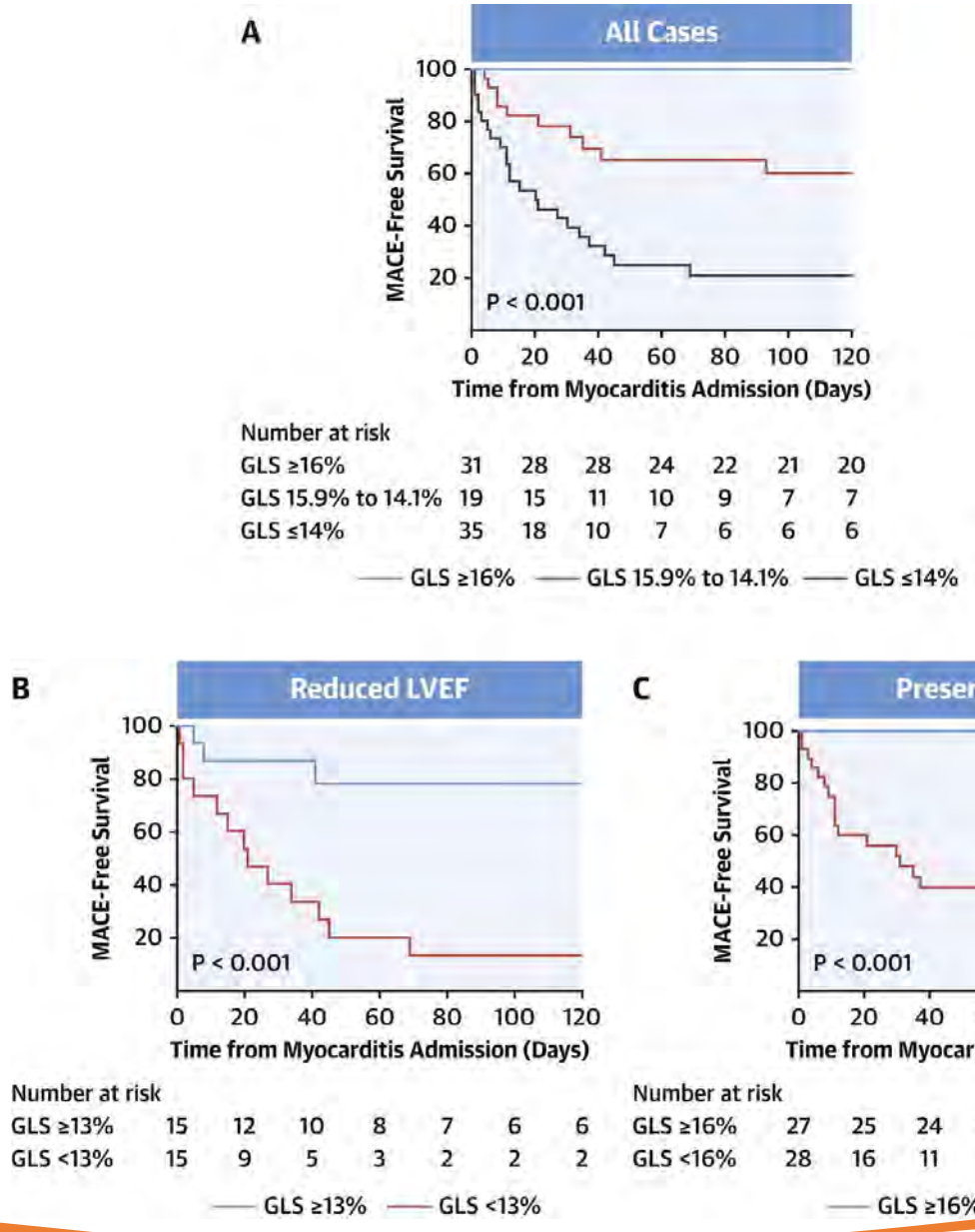
Caution in using CMR criteria alone to exclude ICI myocarditis. **Modified Lake Louis criteria**

- Zhang et al EHJ 2020

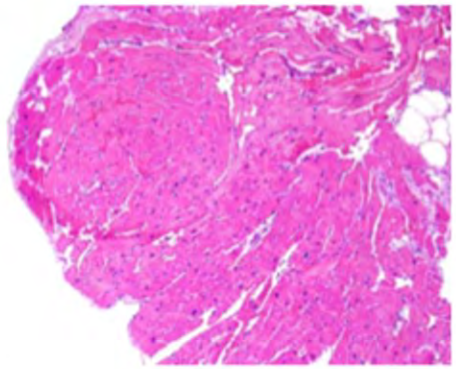


CMR criteria for ICI myocarditis

- **Cardiac MRI (CMR**) is the best noninvasive imaging modality for the diagnosis of myocarditis based on the **2018-Lake Louise (2018-LL) criteria**, **which identify major criteria, including edema and nonischemic myocardial injury.**
- Myocardial **edema** is evidenced by global or regional **T2 elevation** or hypersignal on T2-weighted sequences.
- Nonischemic **myocardial injury** is demonstrated by **late enhancement (LGE**), global or regional **native T1 elevation**, and/or extracellular volume fraction in a nonischemic distribution.
- **In the presence of 2 major criteria, the sensitivity and specificity of 2018-LL criteria are 88% and 96%, respectively**.

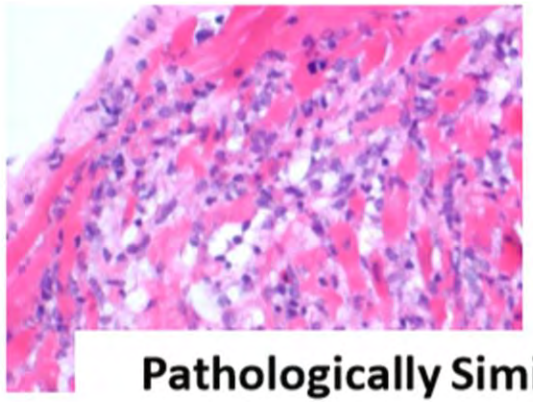

A
All Cases
MACE-Free Survival
100
80
60
40
20
P < 0.001
0 20 40 60 80 100 120
Time from Myocarditis Admission (Days)
Number at risk
GLS ≥16% 31 28 28 24 22 21 20
GLS 15.9% to 14.1% 19 15 11 10 9 7 7
GLS ≤14% 35 18 10 7 6 6 6
GLS ≥16%
GLS 15.9% to 14.1%
GLS ≤14%
B
Reduced LVEF
MACE-Free Survival
100
80
60
40
20
P < 0.001
0 20 40 60 80 100 120
Time from Myocarditis Admission (Days)
Number at risk
GLS ≥13% 15 12 10 8 7 6 6
GLS <13% 15 9 5 3 2 2 2
GLS ≥13%
GLS <13%
C
Preserved LVEF
MACE-Free Survival
100
80
60
40
20
P < 0.001
0 20 40 60 80 100 120
Time from Myocarditis Admission (Days)
Number at risk
GLS ≥16% 27 25 24 21 20 18 18
GLS <16% 28 16 11 10 10 9 9
GLS ≥16%
GLS <16%

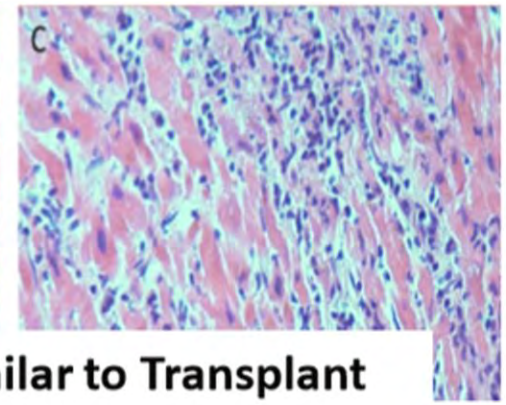
The gold standard is the endo-myocardial biopsy



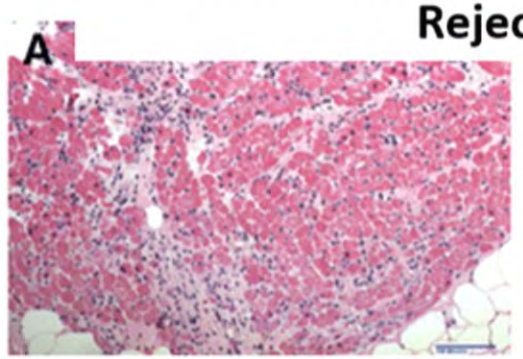
Normal Cardiac Biopsy

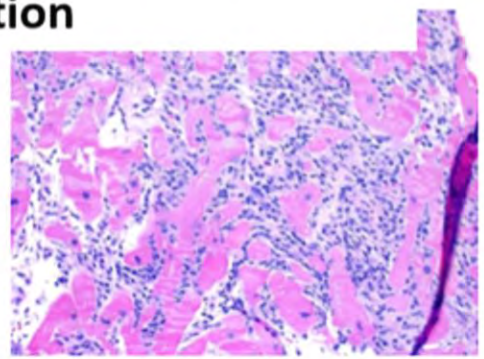
Cases





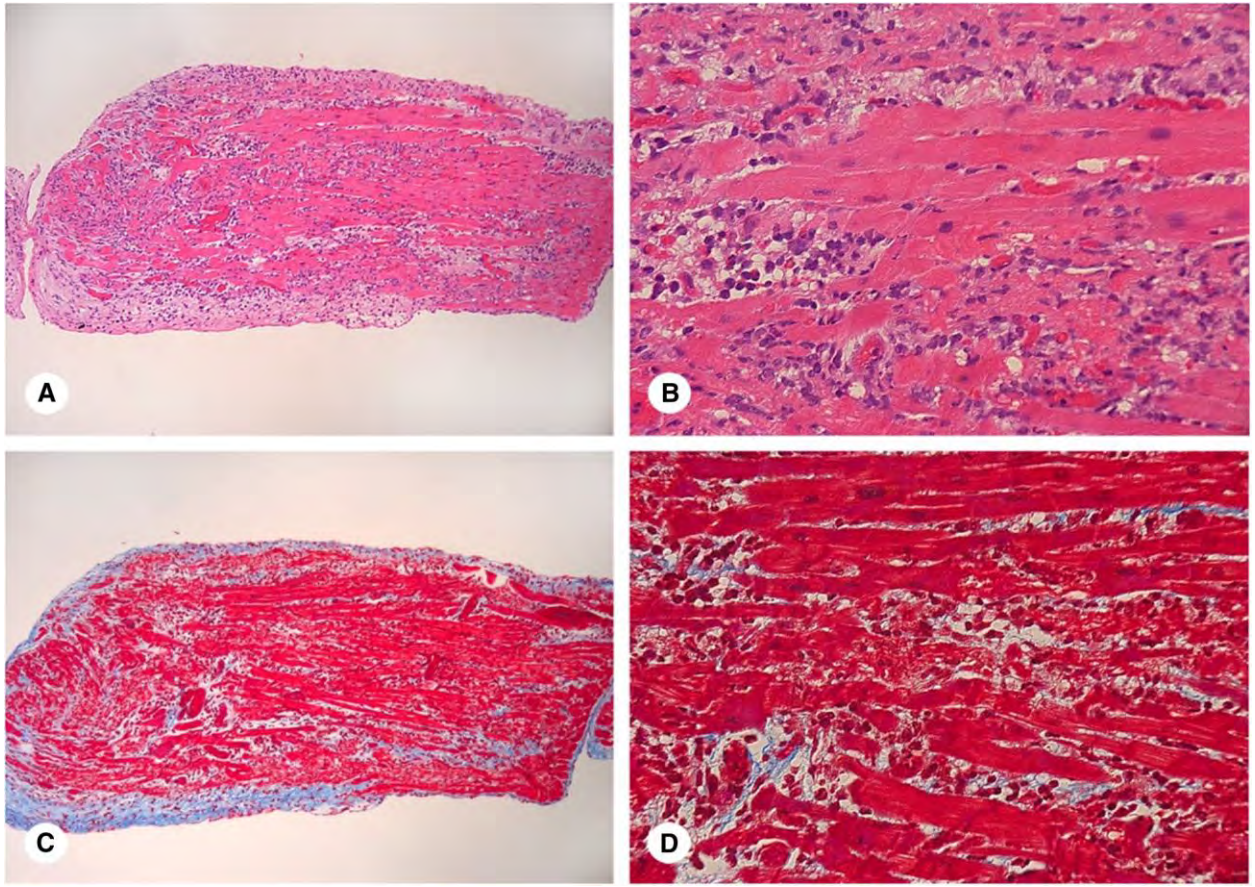
Pathologically Similar to Transplant Rejection





Norwood, JITC, 2017; Ganatra, The Oncologist, 2017

Figure 4 Endomyocardial biopsy: A and C. Light micrograph of a biopsy sample of myocardium.



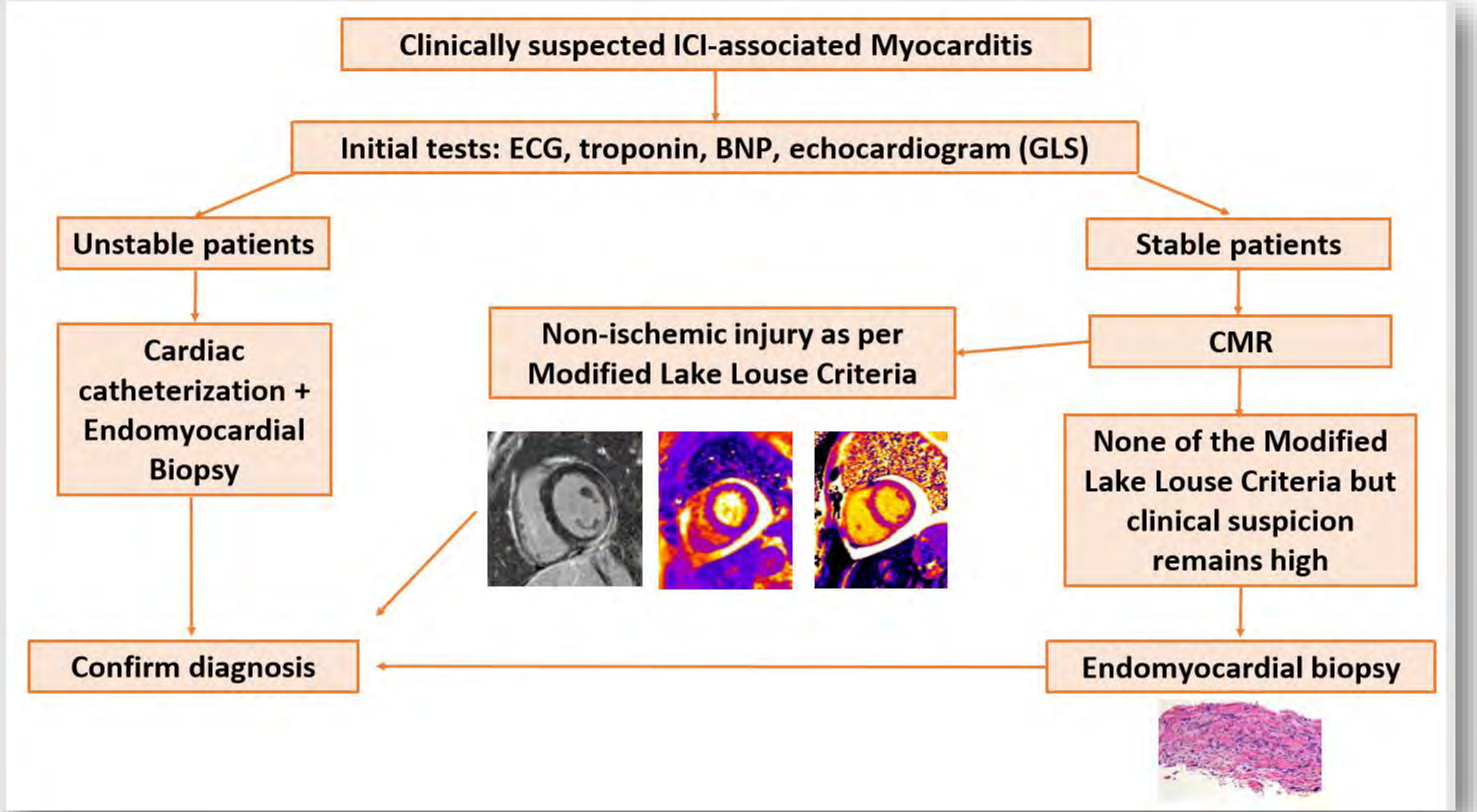
Eur Heart J - Case Rep, Volume 4, Issue 3, June 2020, Pages 1–8, https://doi.org/10.1093/ehjcr/ytaa051

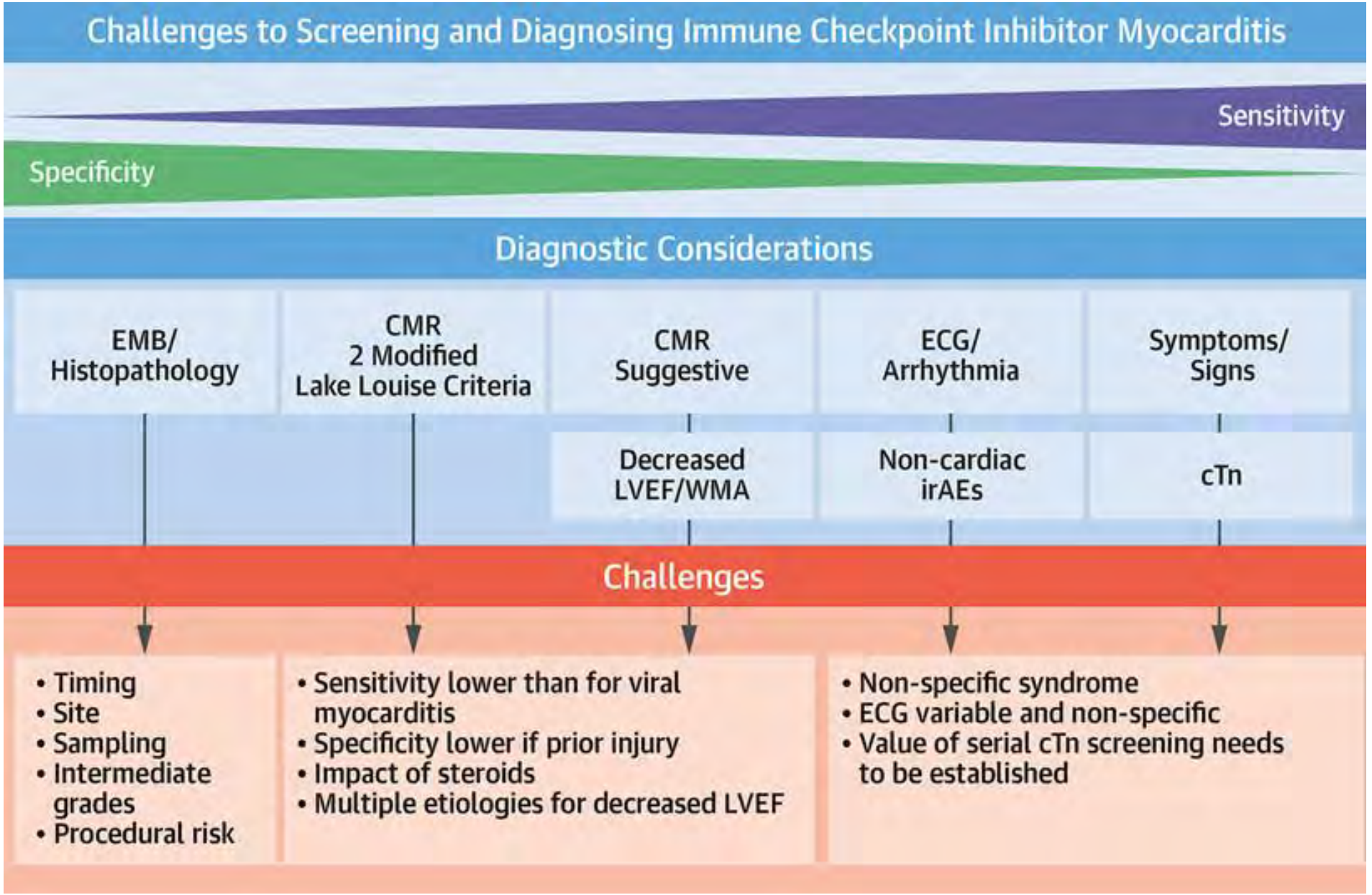
Endomyocardial biopsy Limitations

- True sensitivity and specificity are not known.
- Concern for sampling error.
- Positive predictive value considered to be 100 % (Hawk et al, Mayo Clinic Proceedings)
- EMB safety. Complications 4.3 % (major 0.8 %, minor 3.3 %) Bermpeis et al JACC HF 2022
- Complications rate much lower at high volume centers.

Need for simple decisive pathways

ESC European Society of Cardiology





Franck Thuny et al. *J Am Coll Cardiol CardioOnc* 2022; 4:624-628.

ICOS definition of Myocarditis. EHJ Dec 2021

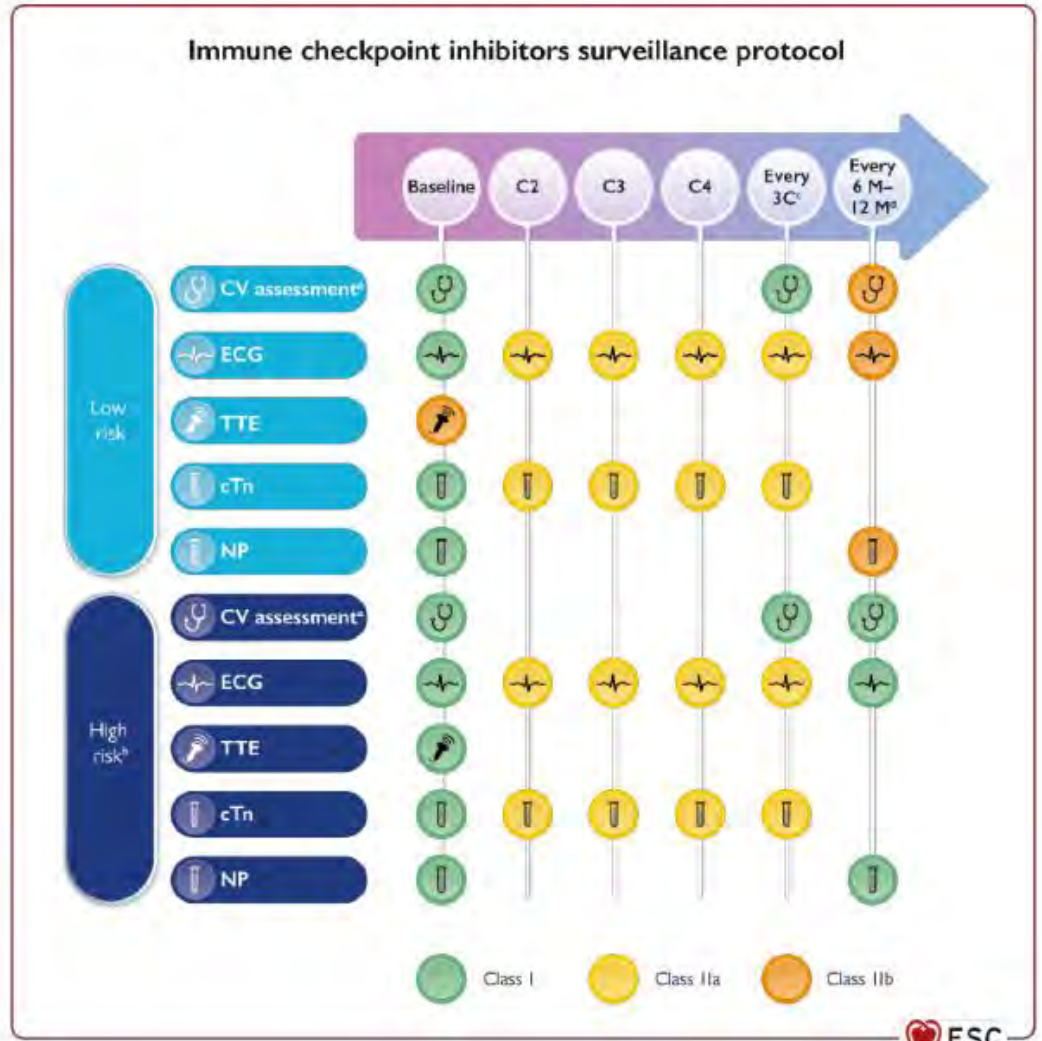
Pathway 1: Pathology: Definitive myocarditis based on Dallas Criteria

Pathway 2: Troponin elevation (significant change) + 1 major or 2 minor criteria

- **Major criteria: Diagnostic Cardiac MRI (Lake Louis criteria) with T1 and T2 abnormalities criteria**
- **Minor Criteria (2 minor criteria)**
- **A. New symptoms: chest pain, SOB, weakness, Myalgia, orthopnea, edema, palpitations, syncope**
- **B. New ventricular arrhythmia and/or new intraventricular conduction delay/QRS prolongation**
- **C. Decline in LVEF with/without WMA, without Takotsubo pattern**
- **D. Other immune related adverse effects (myositis, myopathy, myasthenia)**
- **E. MRI: Suggestive but non diagnostic MRI**
- **F. Biopsy: Suggestive but non diagnostic pathology (inflammation but no necrosis/myocyte destruction)**

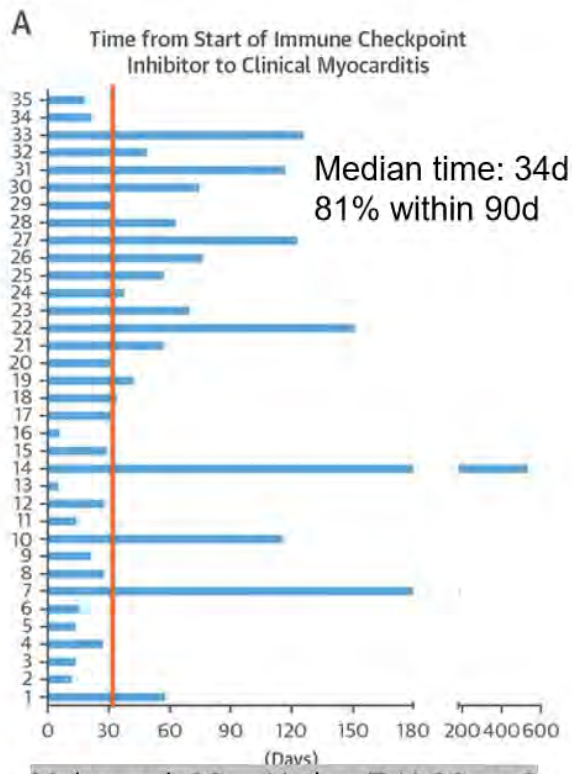
Figure 20

Cardiovascular surveillance in patients treated with immune checkpoint inhibitors



2022 ESC Guidelines on cardio-oncology
(*European Heart Journal*; 2022 – doi: 10.1093/eurheartj/ehac244)

When do ICI myocarditis occur?



Mahmood, SS.... Neilan, T JACC 2018

- WHO's Vigibase: 101 cases.
  - 64% occurred after 1st or 2nd dose.
  - 76% within first 6 weeks.

Moslehi, J, Lancet 2018

Memorial Sloan Kettering Cancer Center

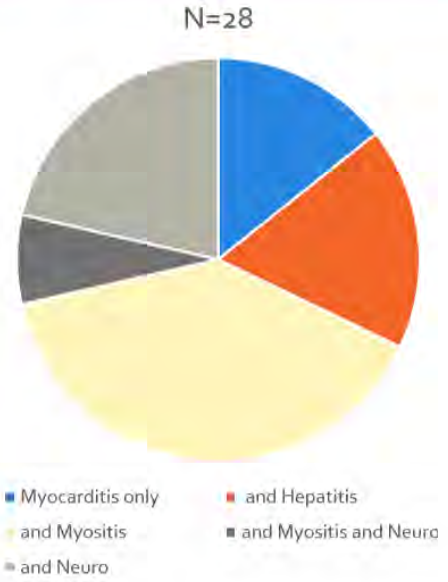
Co-occurring IRAEs with Myocarditis (MSK)

ICI Myocarditis rarely presents as single Immune Adverse Effect

Co-occurring IRAEs with Myocarditis (MSK)

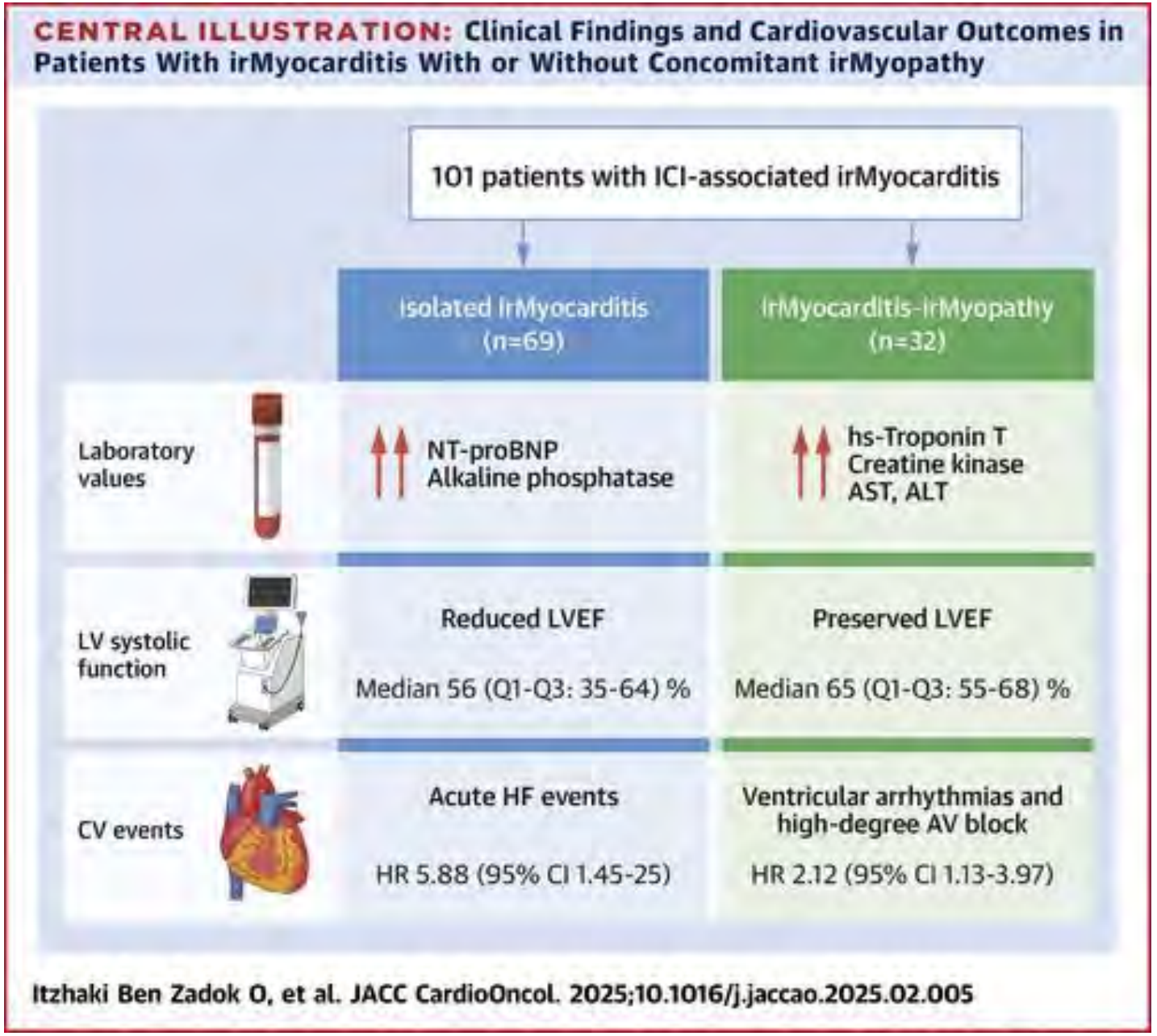
Myocarditis alone=4
+1 IRAE=11
+2 IRAE= 7
+3 IRAE= 5
+4 IRAE= 4

Myositis, myasthenia, hepatitis, thyroiditis, dermatitis, pneumonitis, colitis, hypophysitis



If other IRAE, look for signs of myocarditis, esp if myositis.
If hospitalized for IRAE, serial troponin/ECG.

Memorial Sloan Kettering Cancer Center



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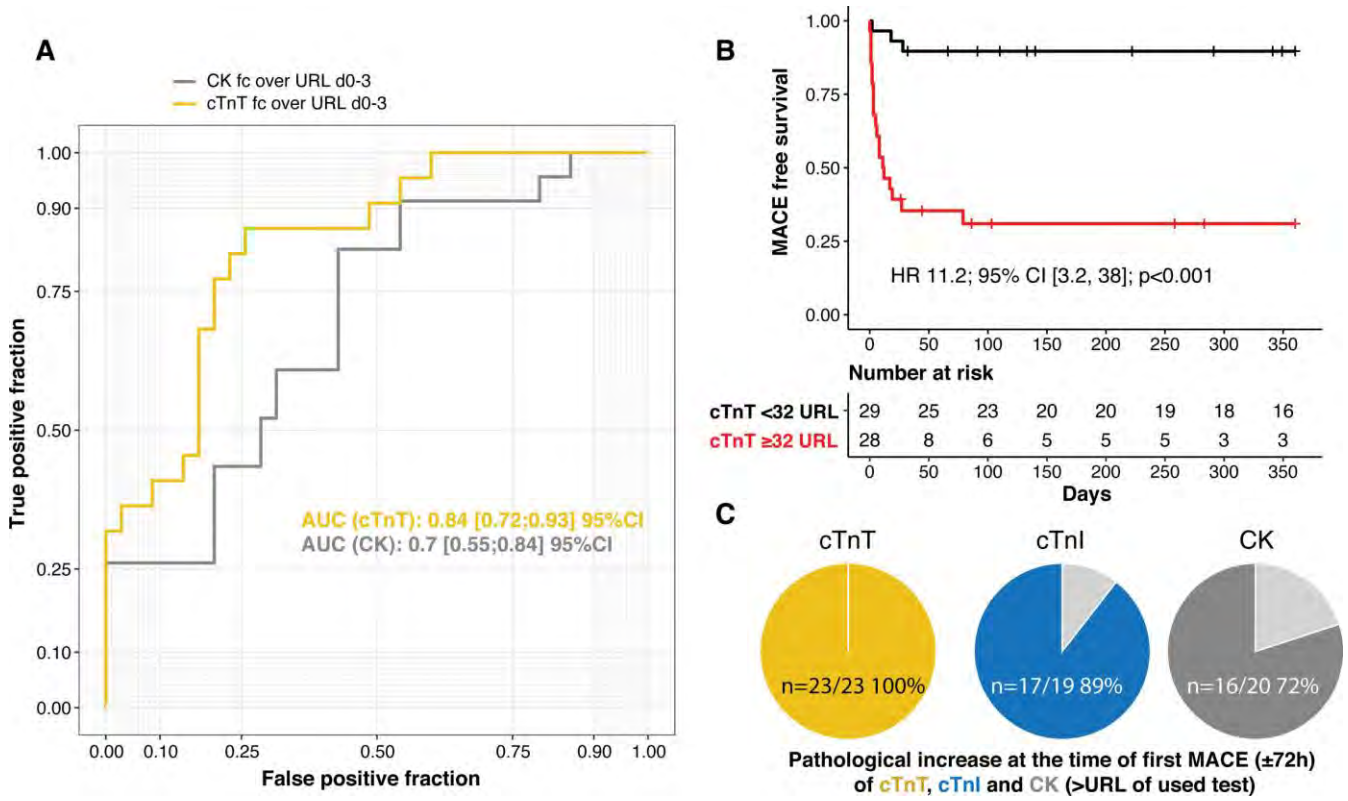
Clinical Perspective

What Is New?

- Circulating levels of cardiac troponin-I (cTnI) and creatine kinase (CK) normalized earlier in the course of immune checkpoint inhibitor myocarditis, whereas cardiac troponin-T (cTnT) levels continued to stay elevated. cTnT was increased in all patients at the time of the first major adverse cardiavascular events (MACE), wheras cTnI and CK were within normal ranges in up to one-quarter of patients with MACE.
- A cTnT level <32× the upper reference limit within 3 days of an ICI myocarditis diagnosis was associated with a minimal risk of MACE.
- When diagnosing or surveilling ICI myocarditis, a normal cTnI value may justify a confirmatory cTnT evaluation to avoid missing active cardiomuscular pathologic involvement.

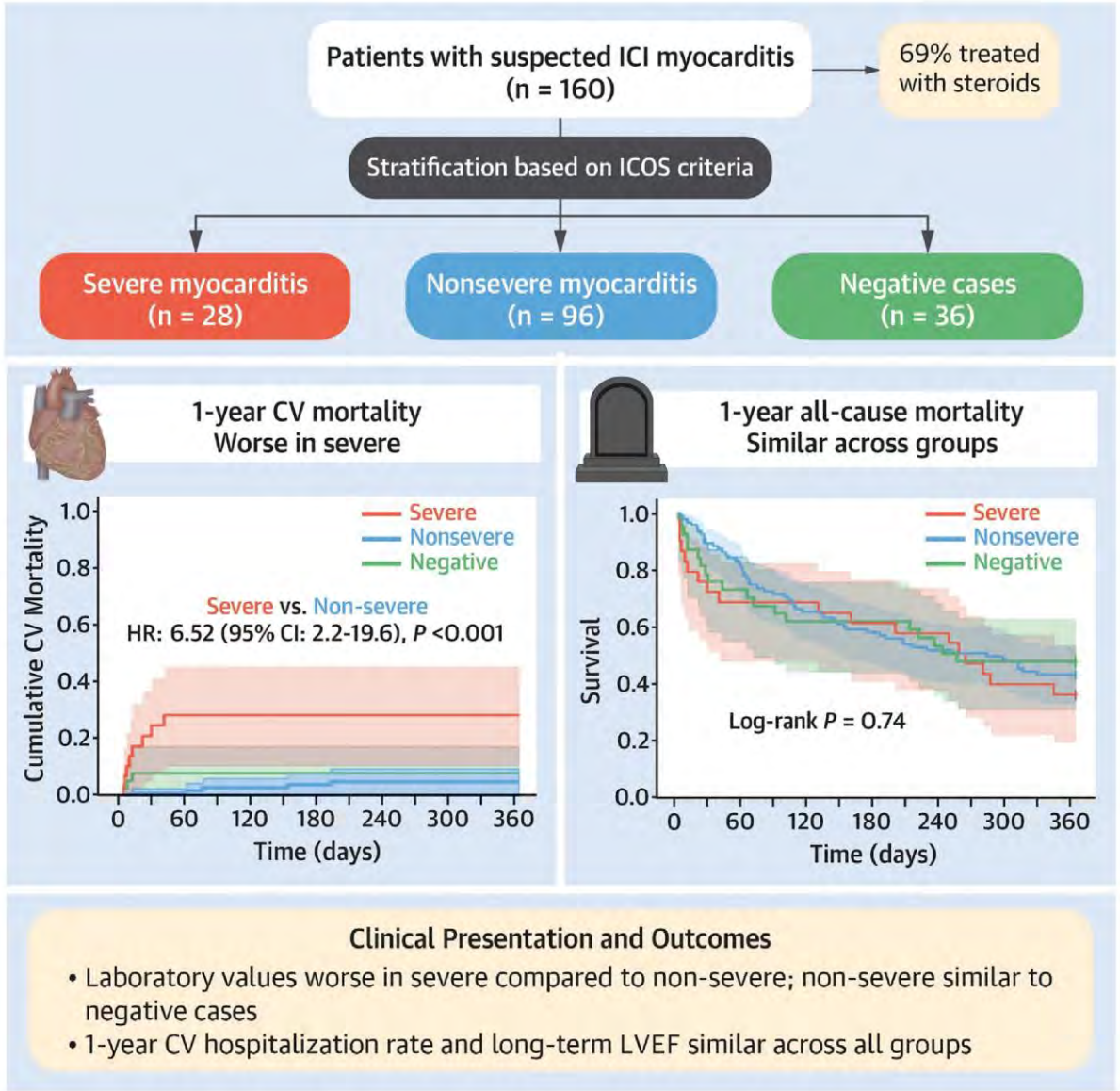
What Are the Clinical Implications?

- Circulating levels of cTnT are associated with MACE and are more often elevated at the time of MACE in patients with ICI myocarditis patients compared with CK and cTnI.
- Kinetic changes of circulating levels of cTnT within the first 72 hours of admission in ICI myocarditis are associated with risk of MACE.



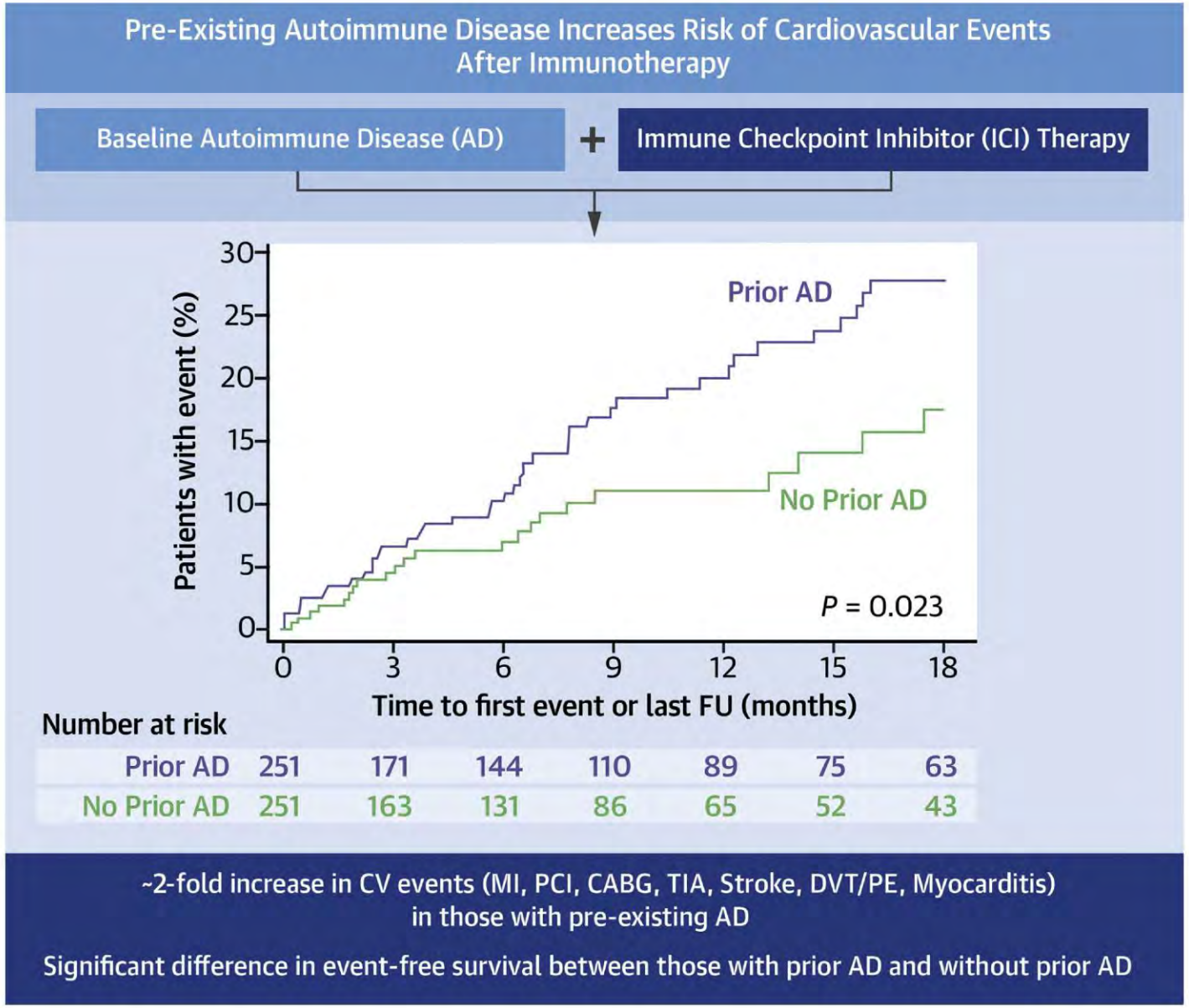
Lorenz H. Lehmann. Circulation. Cardiomuscular Biomarkers in the Diagnosis and Prognostication of Immune Checkpoint Inhibitor Myocarditis, Volume: 148, Issue: 6, Pages: 473-486, DOI: (10.1161/CIRCULATIONAHA.123.062405)

CENTRAL ILLUSTRATION: 1-Year Outcomes in Patients With Severe vs Nonsevere Immune Checkpoint Inhibitor Myocarditis



Itzhaki Ben Zadok O, et al. J Am Coll Cardiol CardioOnc. 2023;5(6):732-744.

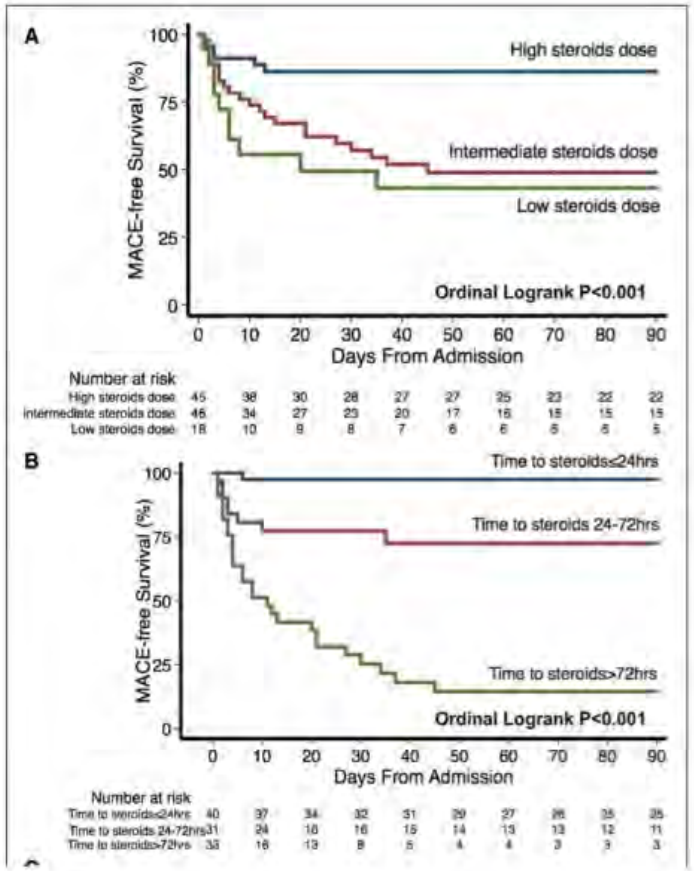
CENTRAL ILLUSTRATION: Baseline Autoimmune Disease Increases Risk for CV Events After Immunotherapy



Lee C, et al. J Am Coll Cardiol CardioOnc. 2022;4(5):660-669.

- Retrospective analysis from 6,884 patients treated with ICIS at a multicenter academic network.
- Case controlled matched 251 patients with AD vs 251 matched controlled without baseline AD.

High dose steroids ASAP



- N=126, multicenter retrospective
- ASCO/SITC/NCCN recommendations: 1-2mg/kg/day or 1 gram methylprednisolone daily as soon as high suspicion.

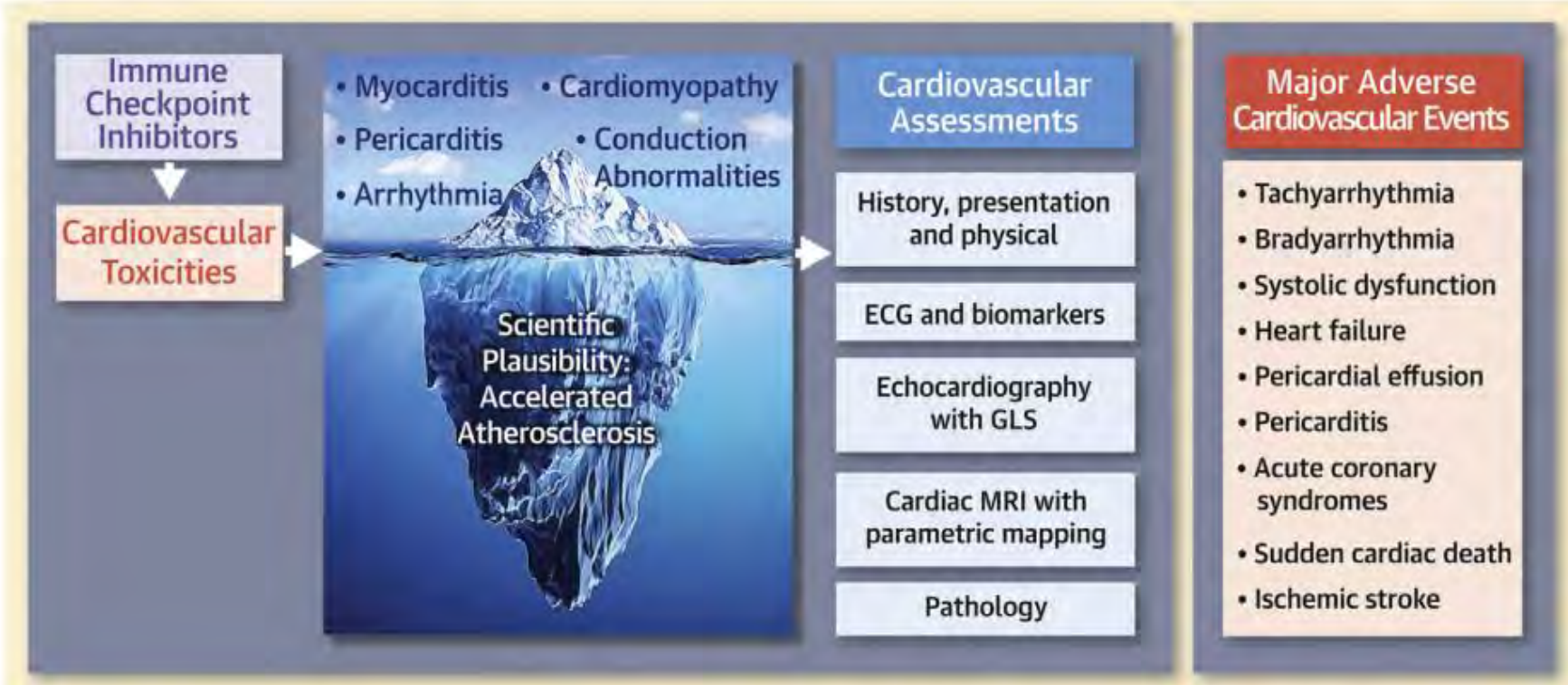
Zhang, et al. Circulation 2020:141:2031-2034.

Memorial Sloan Kettering Cancer Center

ICI myocarditis treatment beyond corticosteroids

- Infliximab, associated to worsening outcomes. Worsens heart failure
- **IVIG** and plasmapheresis with some results.
- **Mycophenolate** orally now more commonly used.
- **Abatacept**, CTLA 4 agonist, has shown promising results. ATRIUM trial, RCT, under way (50 US centers) T Neilan, MGH.
- Abatacept maybe suboptimal for fulminant myocarditis, slow onset. Ideally to combine with JAK inhibitors-Ruxolitinib for rapid onset and synergy for CD86 blockade
- **Anti-thymocyte Globulin (ATG)** has had reported success for refractory cases Stringer et al JACC 2020.
- **Common mechanism** for these drugs: **inactivation of T cells** that play a role in this **exacerbated immune responses**

CENTRAL ILLUSTRATION Immune Checkpoint Inhibitors Leading to Cardiotoxicities and Major Adverse Cardiovascular Events



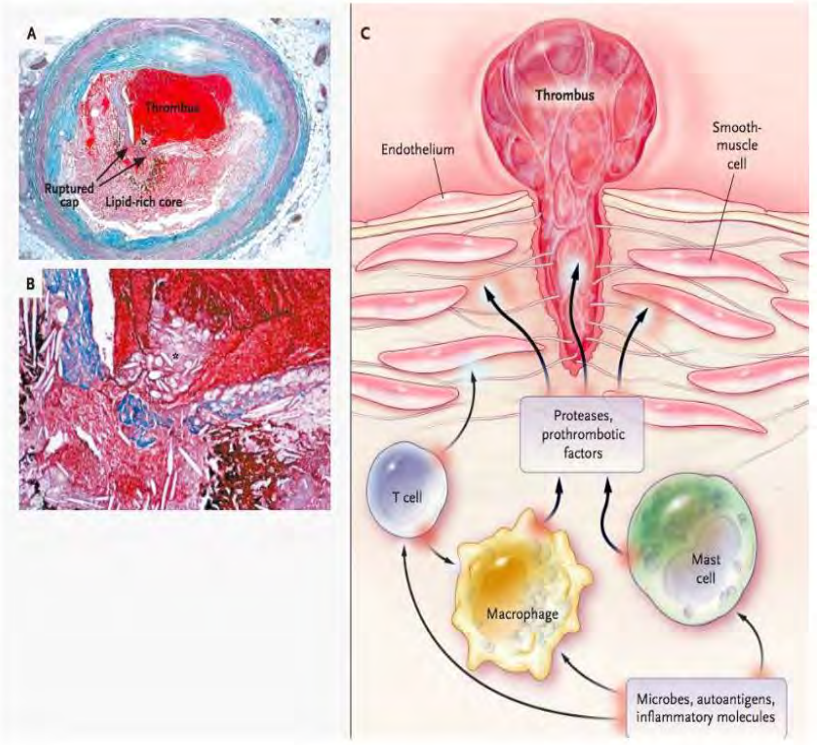
Zhang, L. et al. J Am Coll Cardiol CardioOnc. 2021;3(1):35-47.

Immune checkpoint inhibitors can lead to cardiovascular toxicities, which include myocarditis and pericarditis. Although there are no robust clinical data to support whether immune checkpoint inhibitors (ICIs) accelerate atherosclerosis, there is significant scientific plausibility to support the hypothesis that ICI use increases atherosclerosis. The public health impact of defining the association between ICI and atherosclerosis is significant. Patients with new cardiac signs or symptoms should undergo thorough cardiovascular assessments to evaluate the occurrence of cardiovascular outcomes. ECG = electrocardiogram; GLS = global longitudinal strain.

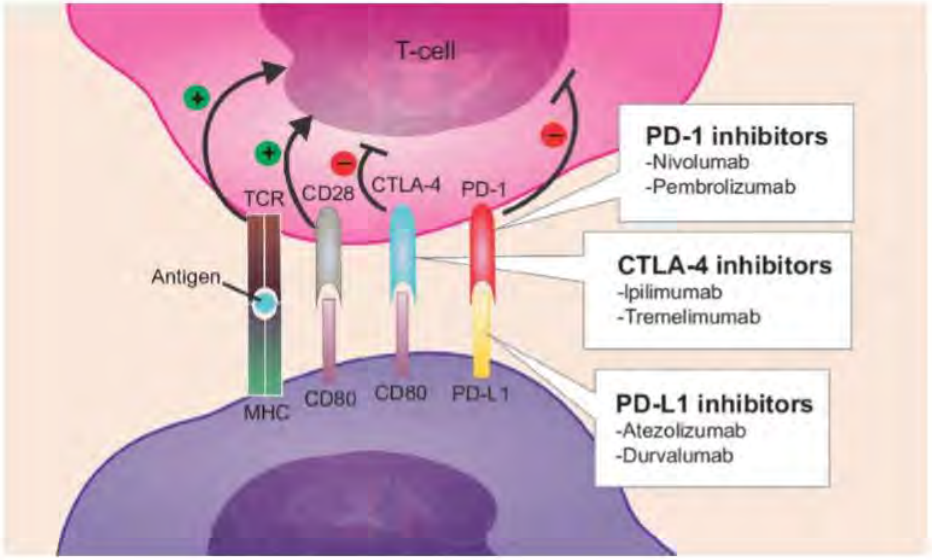
Beyond myocarditis: ICI and atherosclerosis. MGH working group

Atherosclerosis and immune activation

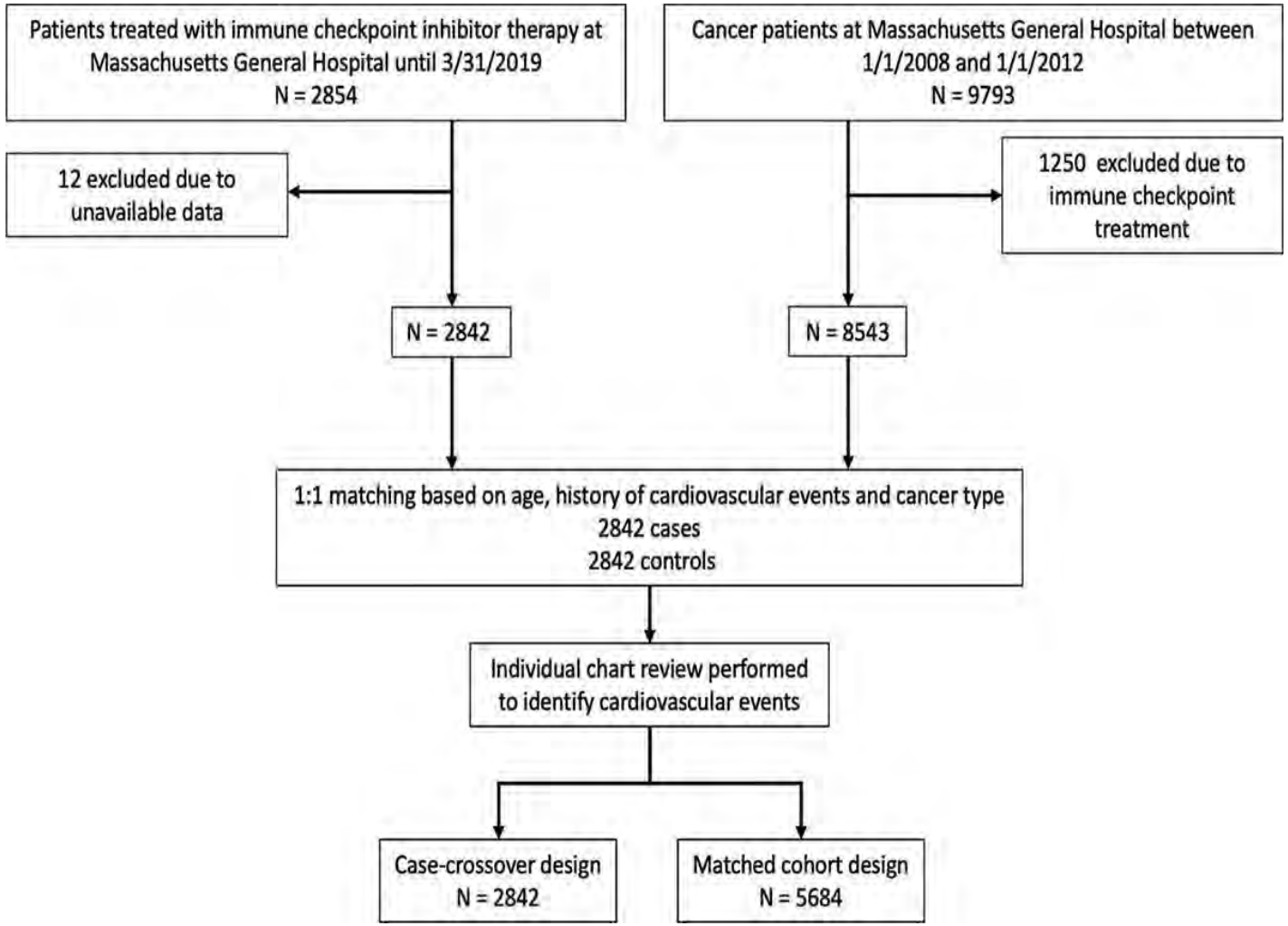
- Atherosclerosis is a model of immune activation.
- Role of inflammation and immune modulation in CVD is well established.
- Immune cells (macrophages, T cells and mast cells) constitute an important part of an atheroma.
- Anti-inflammatory therapy targeting the interleukin-1β in reducing CV events.



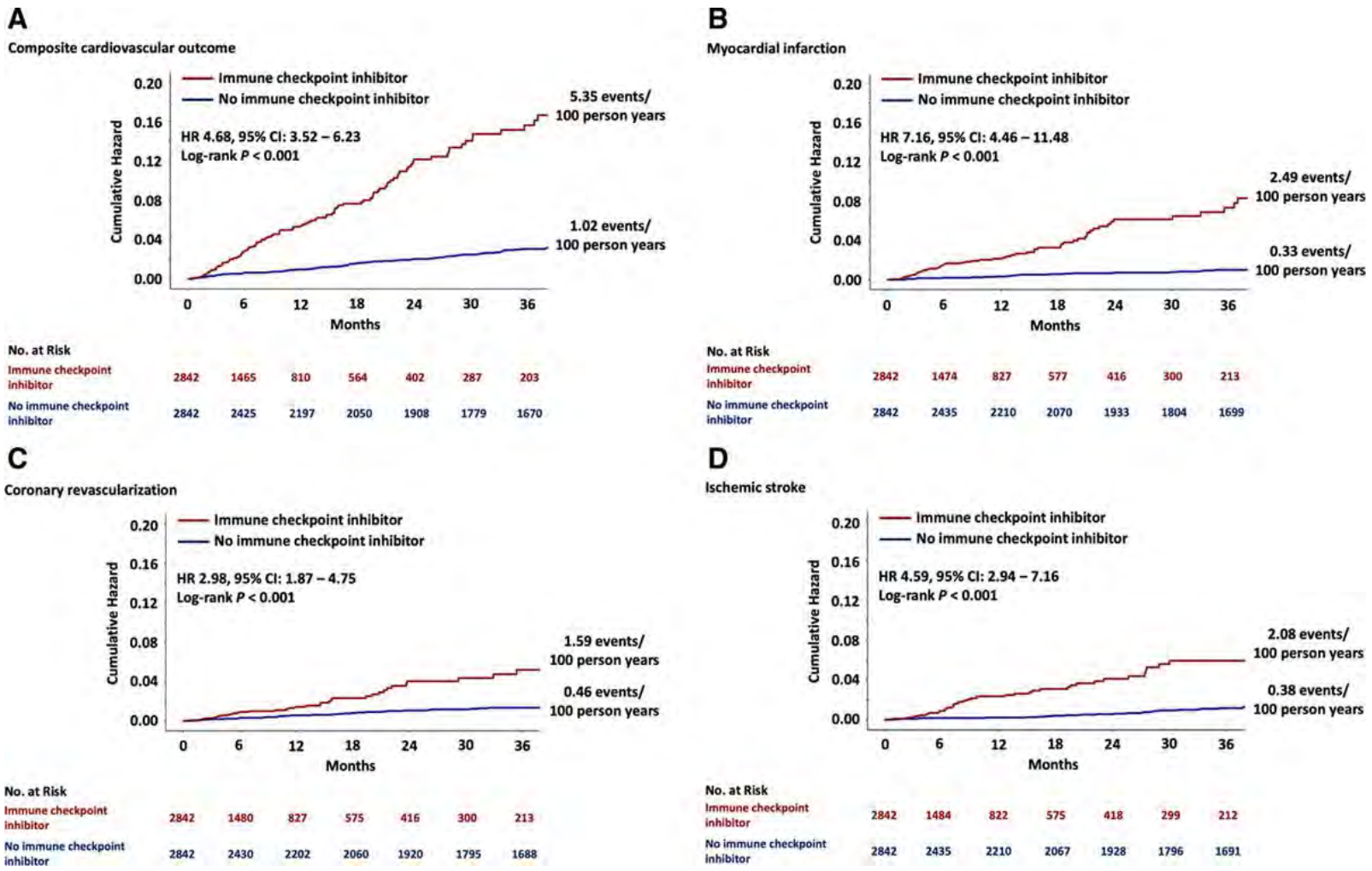
Mechanisms facilitating accelerated atherosclerosis



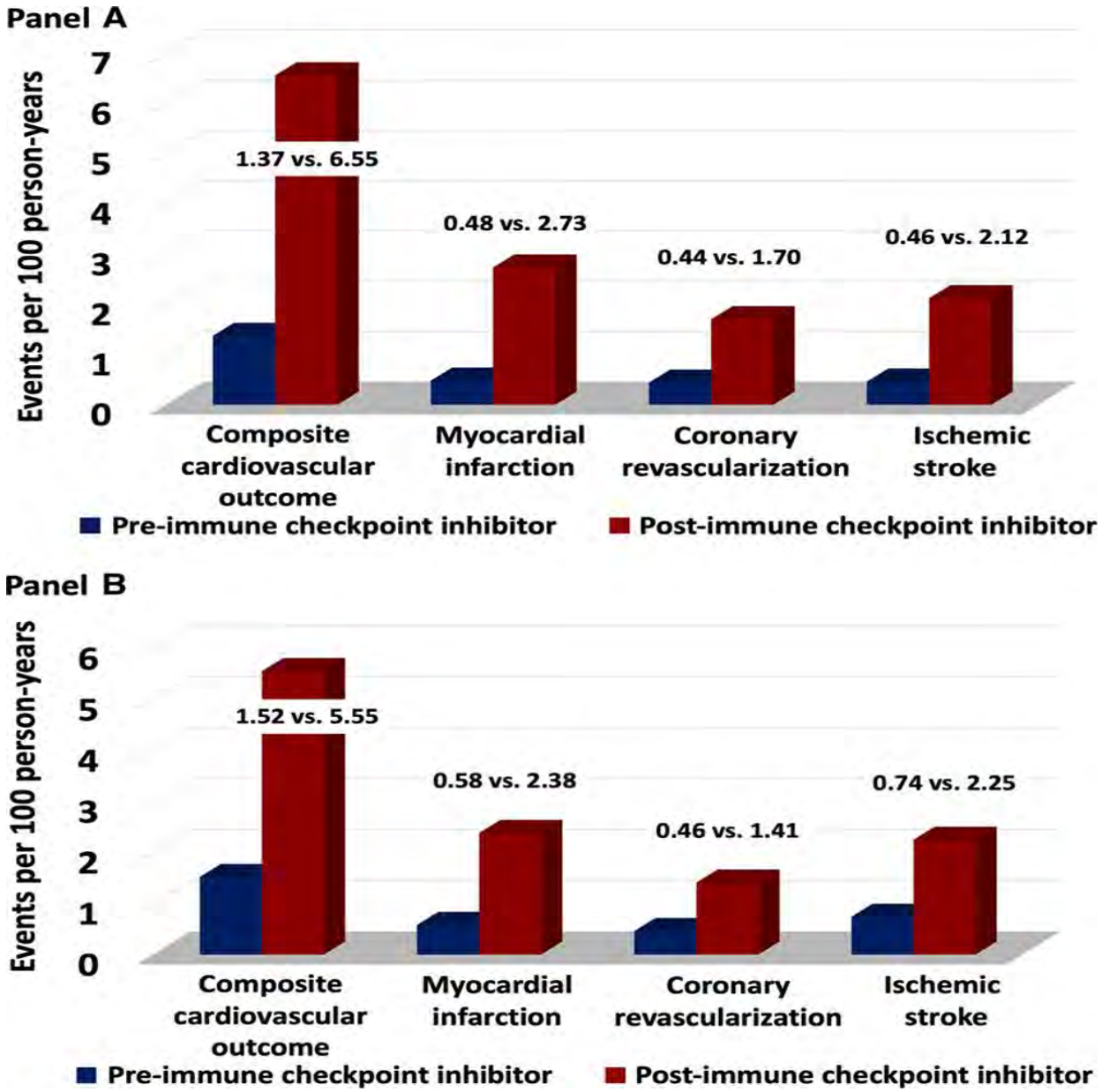
- Animal data show that:
  - Blockade of PD-L1 increases inflammation and accelerates atherosclerosis.
  - Blockade of PD-1 increases inflammation and accelerates atherosclerosis.
  - CTLA4 agonists lead to decreased inflammation and reduced atherosclerotic burden.



Zsofia D. Drobni. Circulation. Association Between Immune Checkpoint Inhibitors With Cardiovascular Events and Atherosclerotic Plaque, Volume: 142, Issue: 24, Pages: 2299-2311, DOI: (10.1161/CIRCULATIONAHA.120.049981)



Zsofia D. Drobni. Circulation. Association Between Immune Checkpoint Inhibitors With Cardiovascular Events and Atherosclerotic Plaque, Volume: 142, Issue: 24, Pages: 2299-2311, DOI: (10.1161/CIRCULATIONAHA.120.049981)



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Atherosclerosis and plaque volume before and after ICI

ICIs and Atherosclerosis – Preliminary Data

Table. Absolute and relative change in thoracic atherosclerotic plaque volume before and after ICI showing a >3-fold increase in total and NCP plaque progression with starting an ICI.

			Scan 0 - Scan 1	Scan 1 – Scan 2	P Value
Absolute change	Indexed change/year, mm^3/year	Total plaque volume	13.8 (-240, 122)	103 (0, 511)	0.02
		Non-calcified plaque volume	-18.2 (-274, 57)	53 (0, 382)	0.02
Relative change	Indexed change/year, %/year	Total plaque volume	2.1% (-13.0%, 18.6%)	6.7% (2.2%, 28.1%)	0.17
		Non-calcified plaque volume	-2.3% (-14.0%, 12.7%)	5.3% (1.4%, 40.1%)	0.14

Zsofia Drobni, Prelim Data