Toxicité cardiaque des Immunothérapies
30 Novembre 2024
Bruxelles
Myocardites et Immunothérapies

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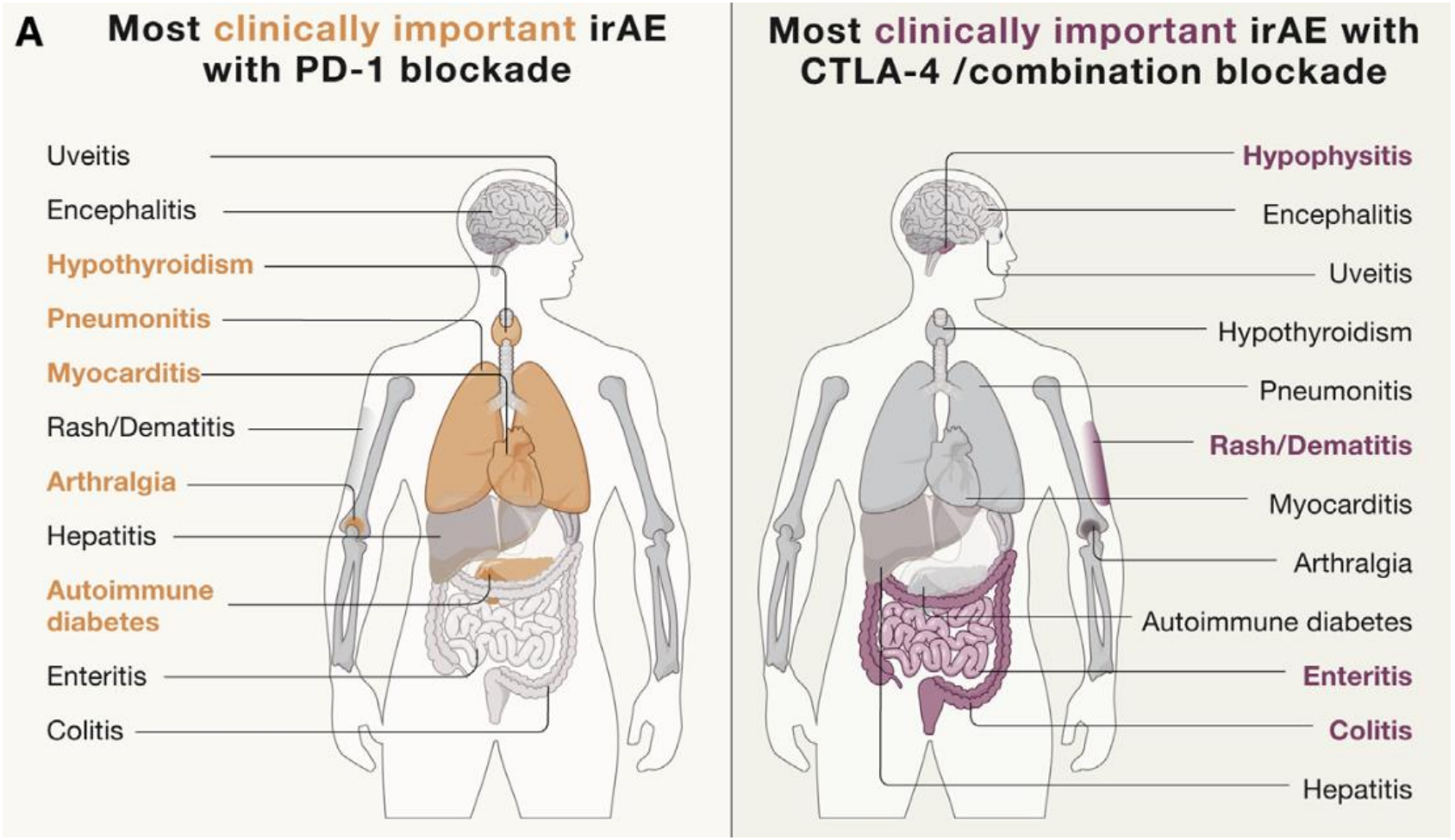
Hôpital Saint-Antoine AP-HP

Groupe de Cardio-Oncologie
Société Française de Cardiologie

Organs frequently affected by inflammatory toxicities of checkpoint blockade



Understanding and treating the inflammatory adverse events of cancer immunotherapy. Dougan et al. Cell (2021)

Heart Failure With Targeted Cancer Therapies: Mechanisms and Cardioprotection.

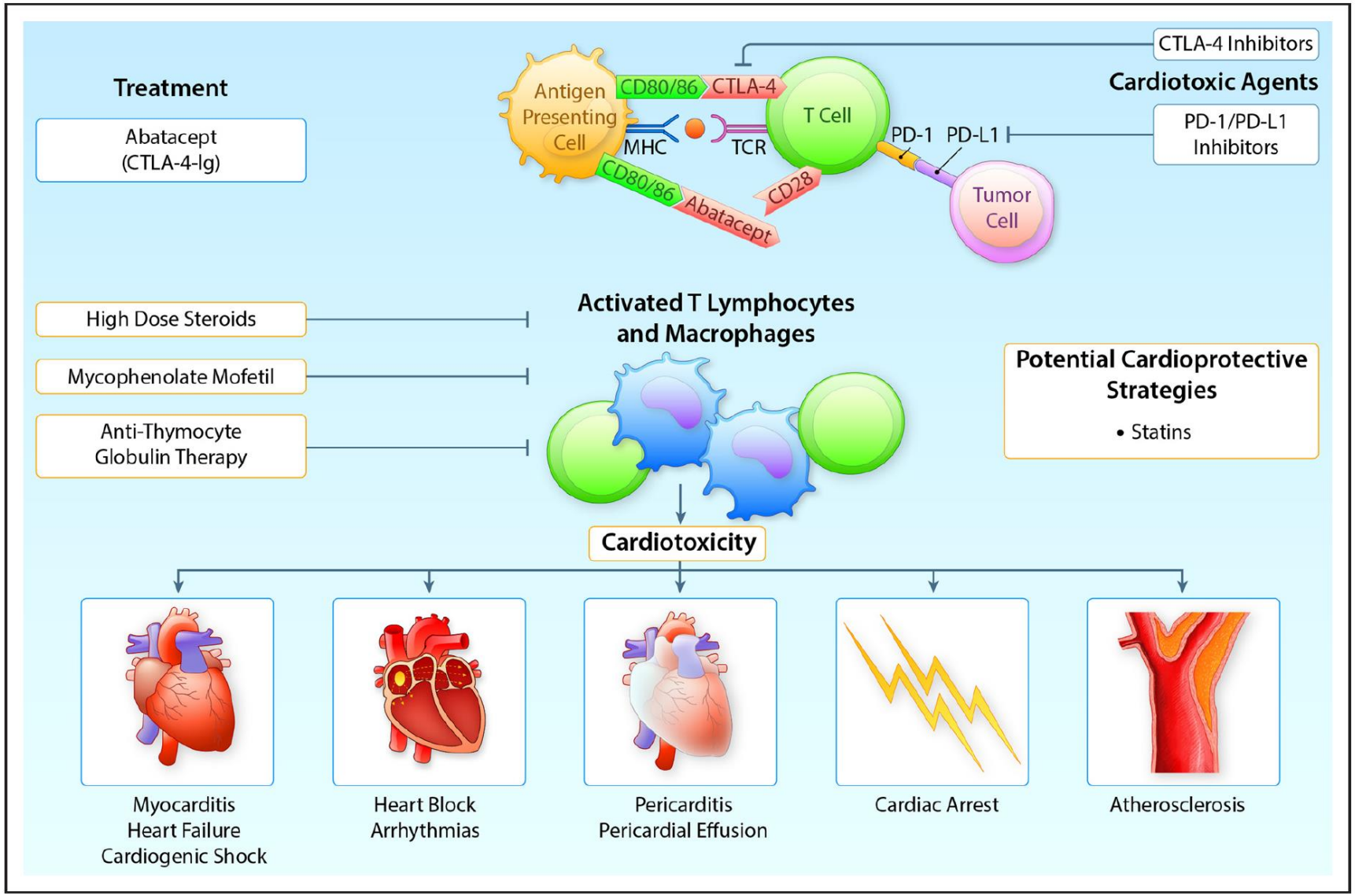
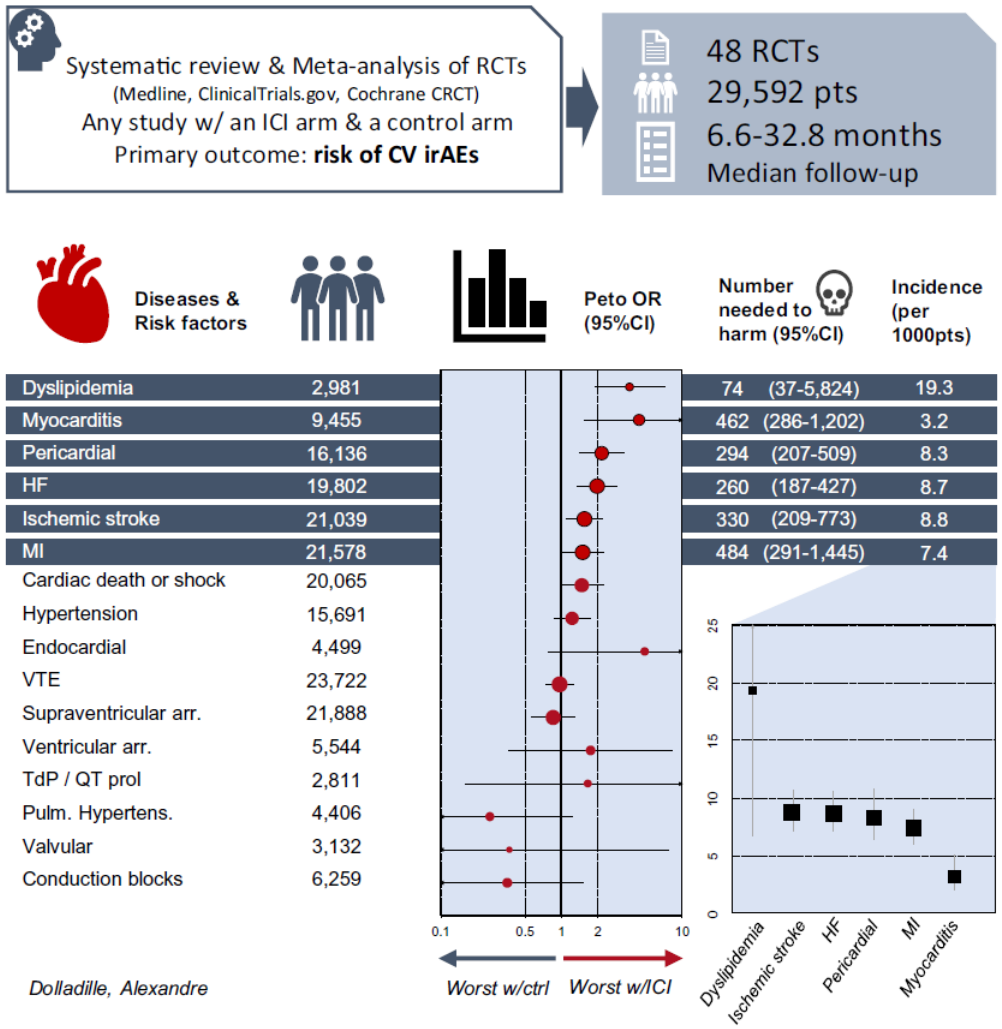


Figure 3. **Immune checkpoint inhibitors: mechanisms of cardiotoxicity and potential treatments.**

Hahn VS. *Circ Res*. 2021;128(10):1576-1593.

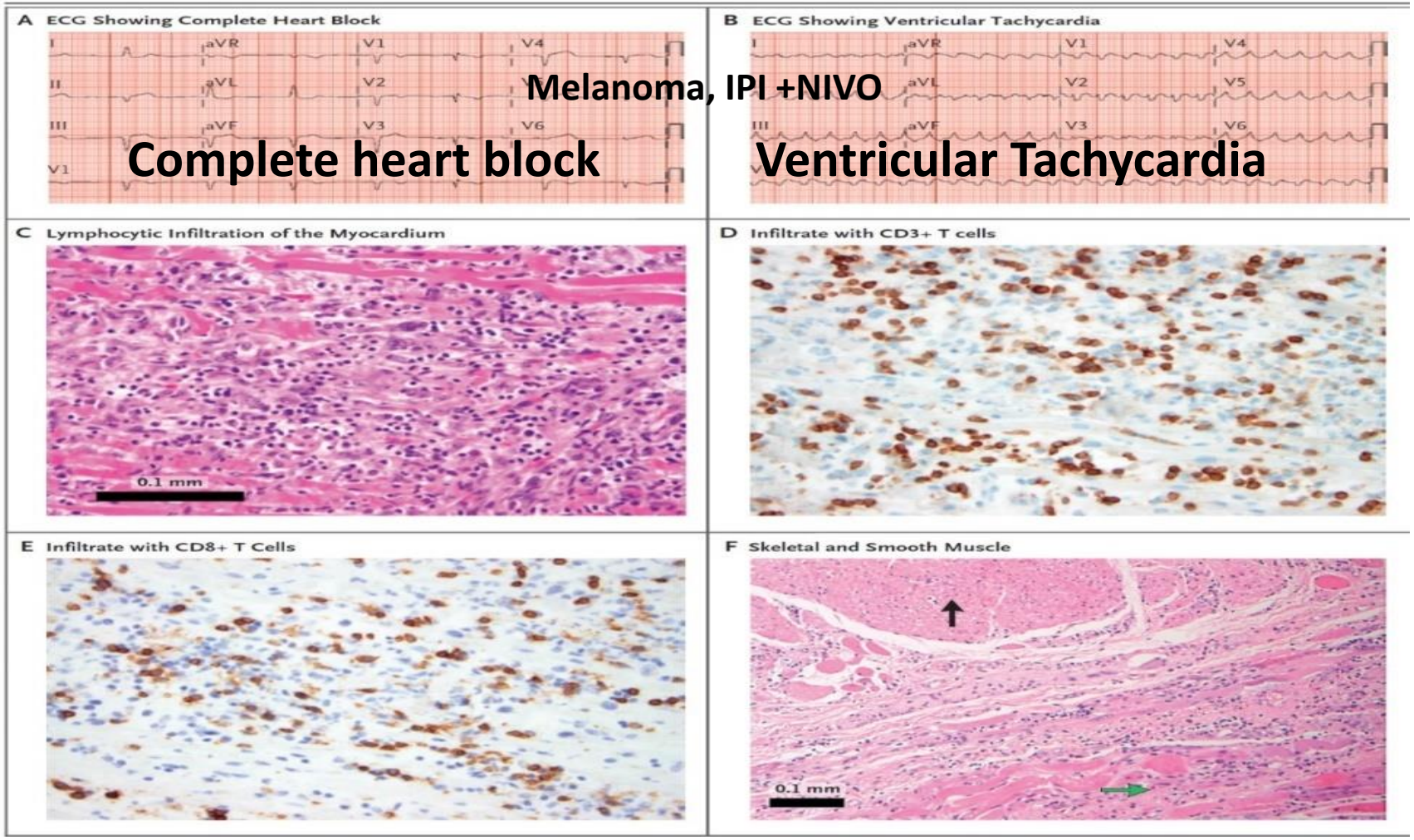
Cardiovascular immunotoxicities associated with immune checkpoint inhibitors: a safety meta-analysis



Incidence < 1%

Dolladille European Heart Journal 2021 : 42, 4964–4977

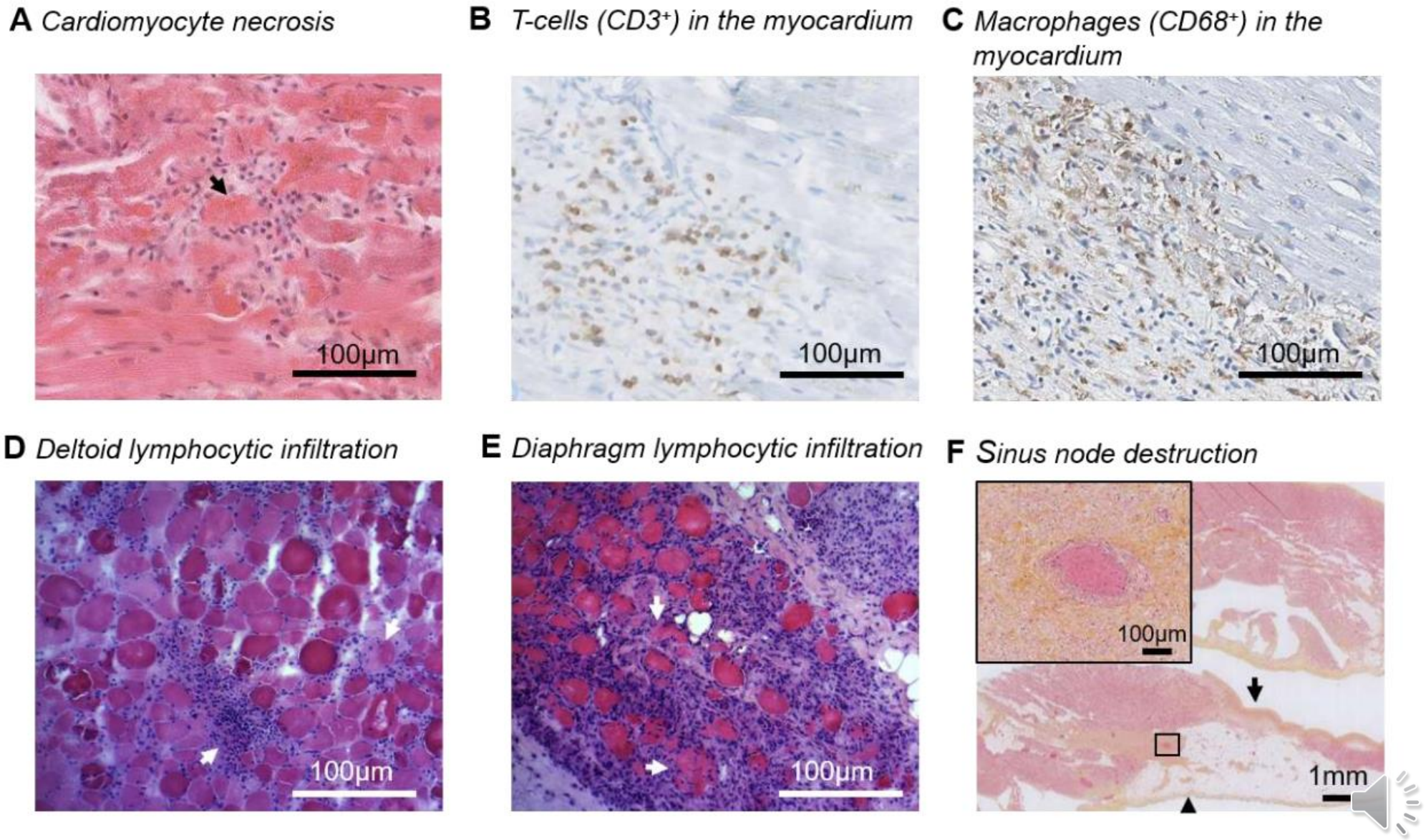
Fulminant Myocarditis with Combination Immune Checkpoint Blockade



Lymphocytic infiltration of the myocardium CD3+/CD4+/CD8+

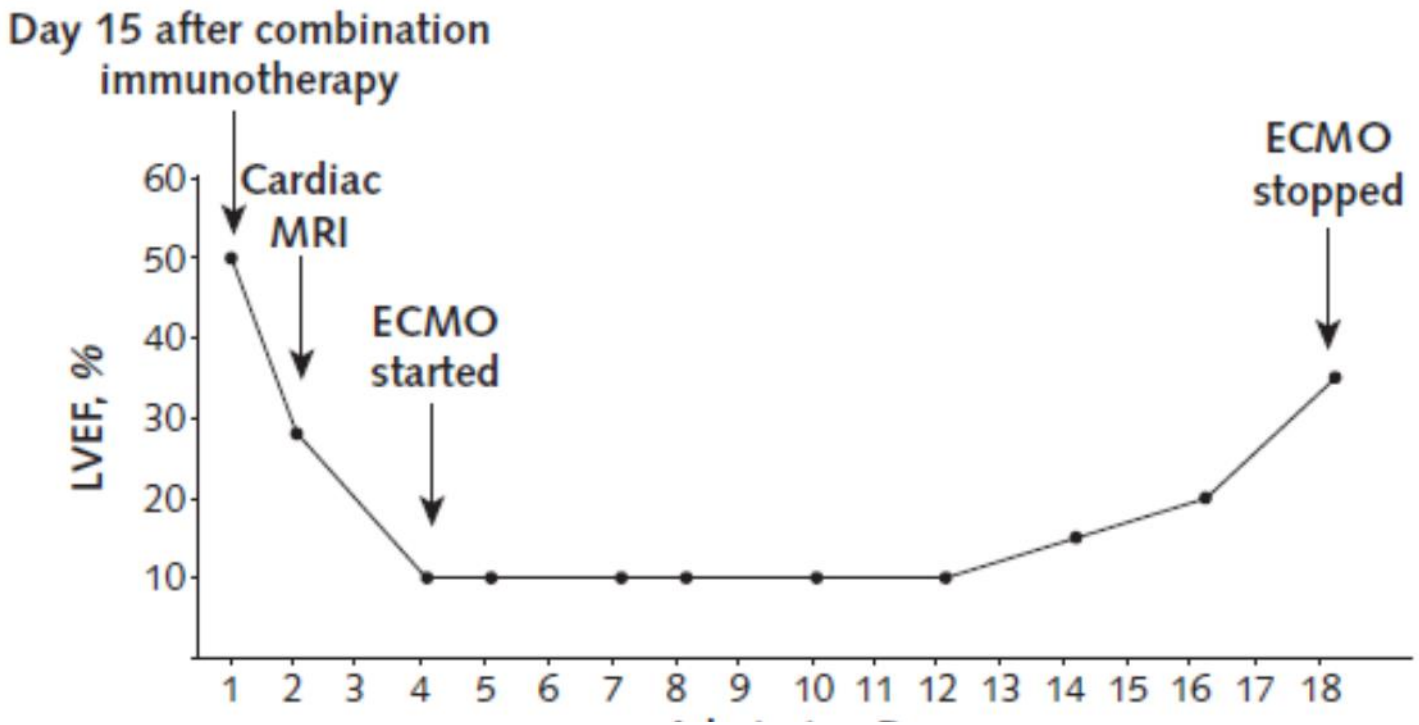
Johnson DB New Engl J Med 2016 ; 375 : 1749-1755

Abatacept/Ruxolitinib and Screening for Concomitant Respiratory Muscle Failure to Mitigate Fatality of Immune-Checkpoint Inhibitor Myocarditis.



Salem JE. Cancer Discov. 2023 May 4;13(5):1100-1115.

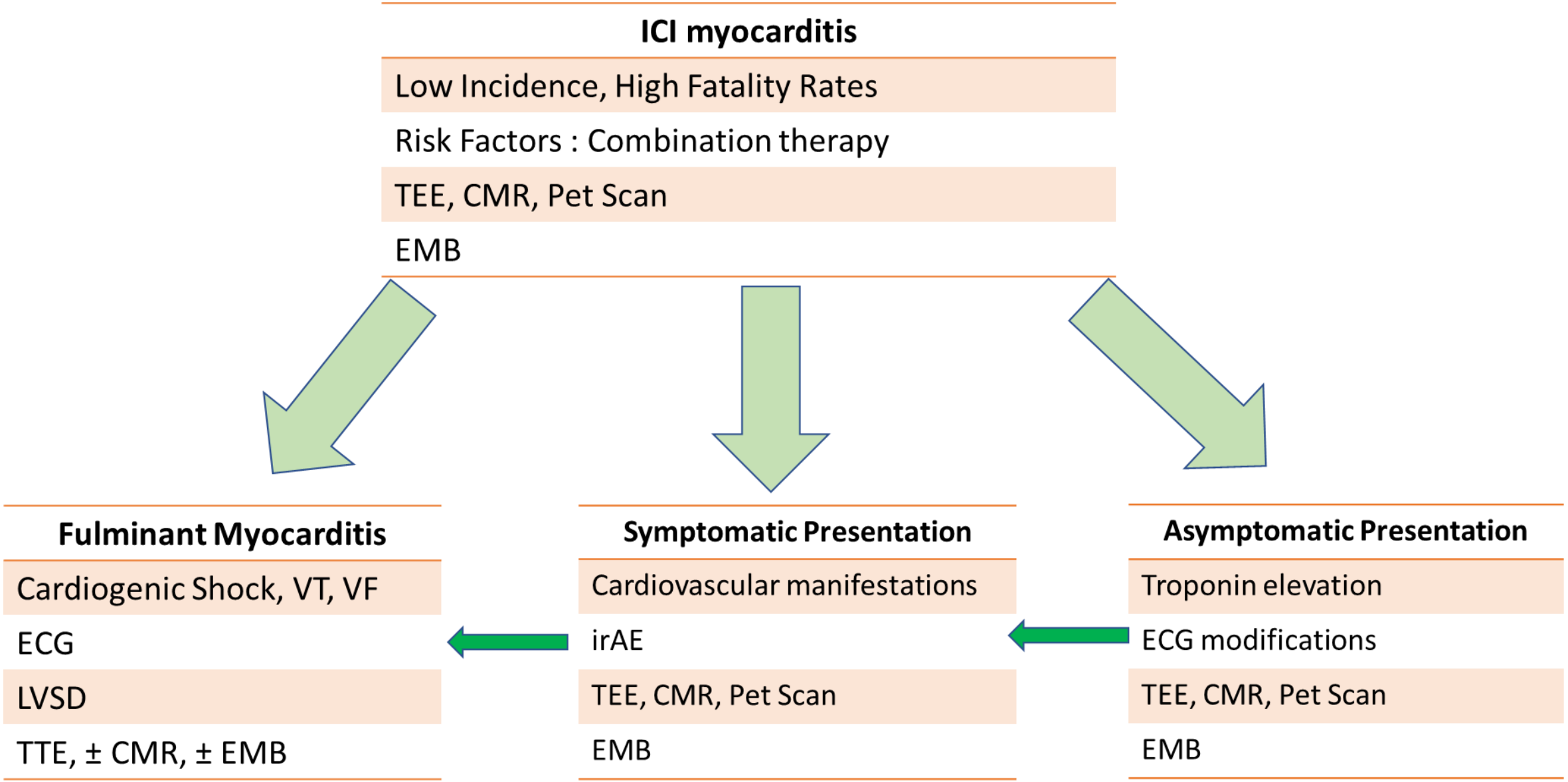
Survival After Fulminant Myocarditis induced by Immune-checkpoints inhibitors



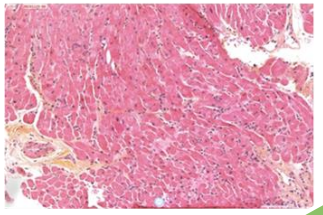
Early Onset **30 d** **First 3 Mo** **Combo therapy** **Previous auto imune disease**	**irAE** **Myasthenia like syndrom** **Myositis** **Hepatitis**	**Low incidence < 1 % but still** **High Fatality Rate** **40 to 50 %**

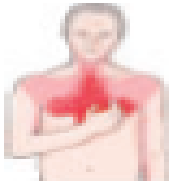
Arangalage D Ann Intern Med. 2017;167 :683-684.

ICI myocarditis – Clinical Presentation

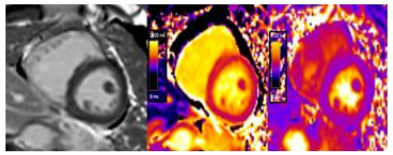


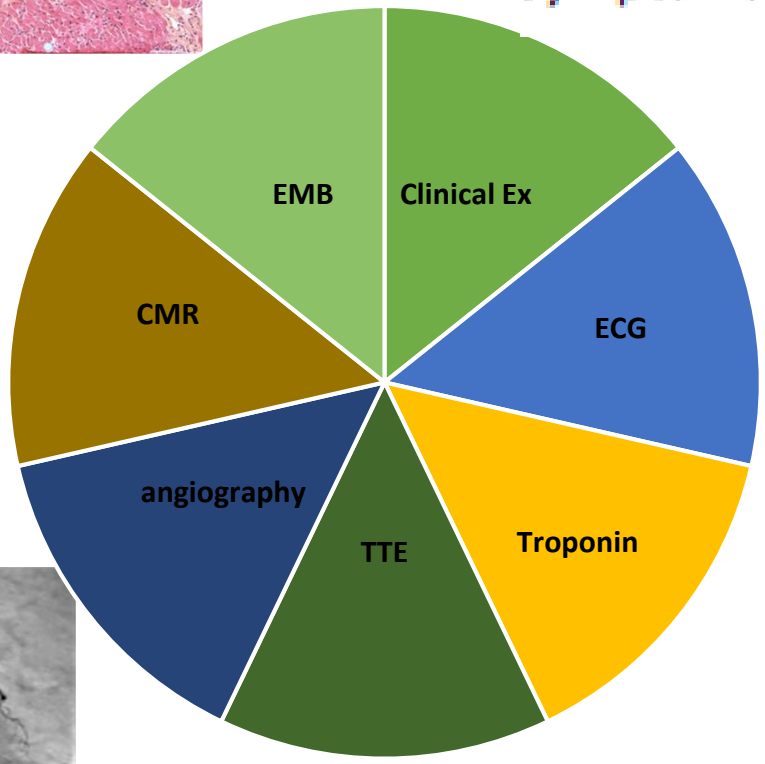
Diagnostic Work-Up in ICI myocarditis

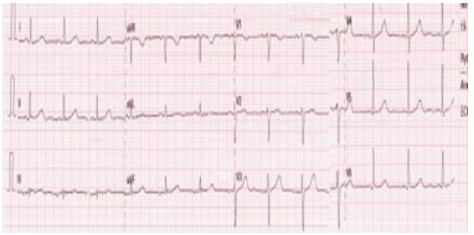


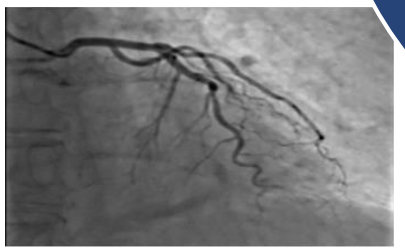


Symptoms†

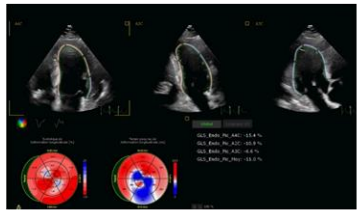




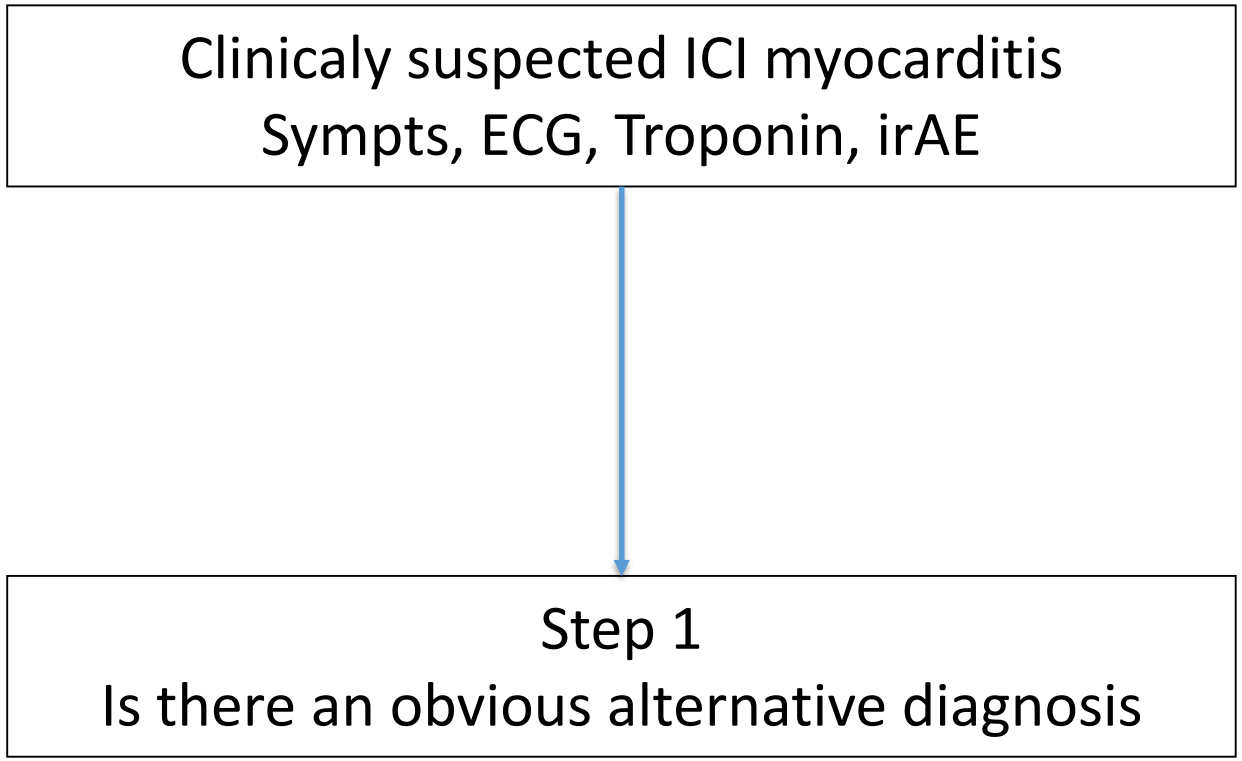




↑ Troponin

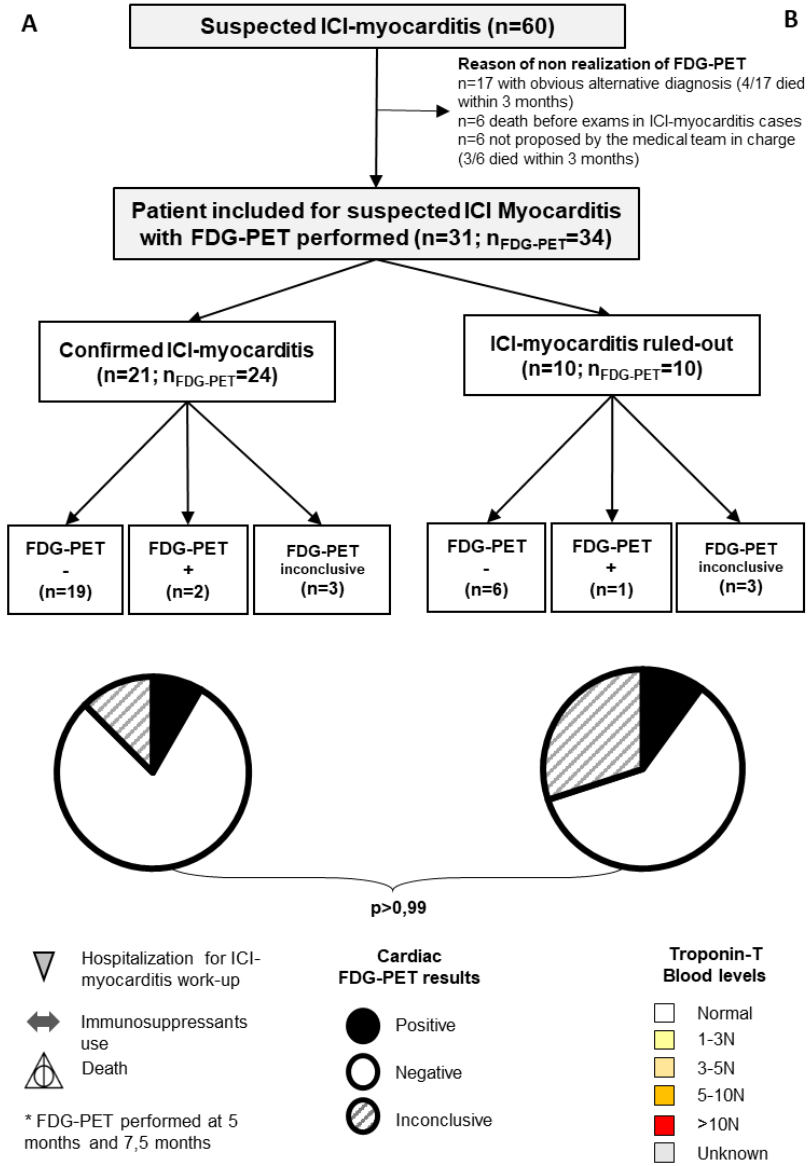


Caforio AL, Eur Heart J. 2013 ;34:2636-48, 2648-2648
Bonacca, Circulation 2019

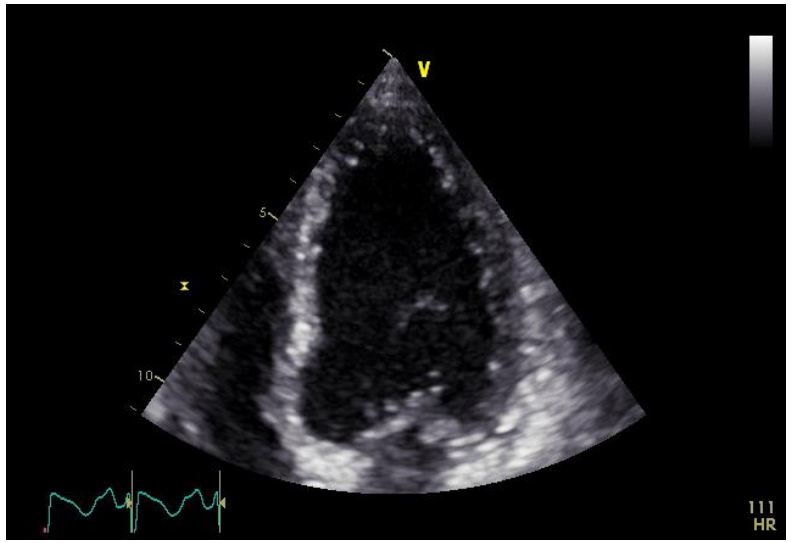

Clinicaly suspected ICI myocarditis
Sympts, ECG, Troponin, irAE
Step 1
Is there an obvious alternative diagnosis

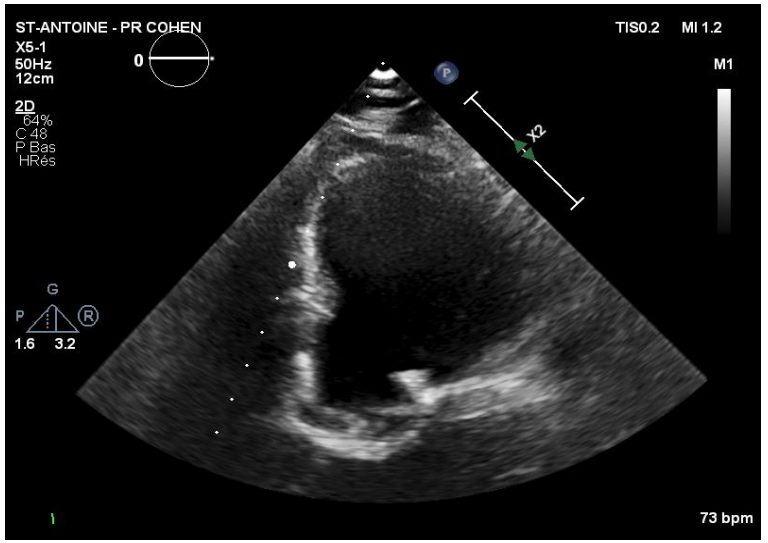
Suspected ICI-myocarditis – Experience of a two CO units

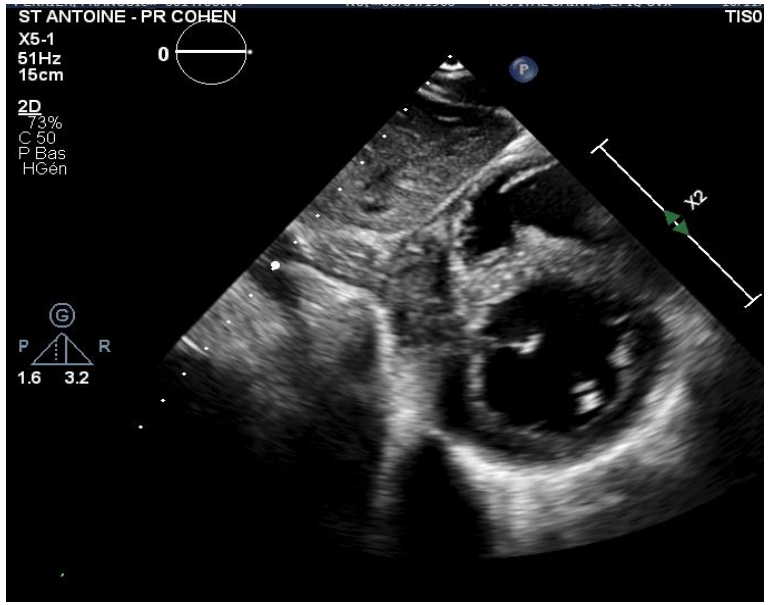
A

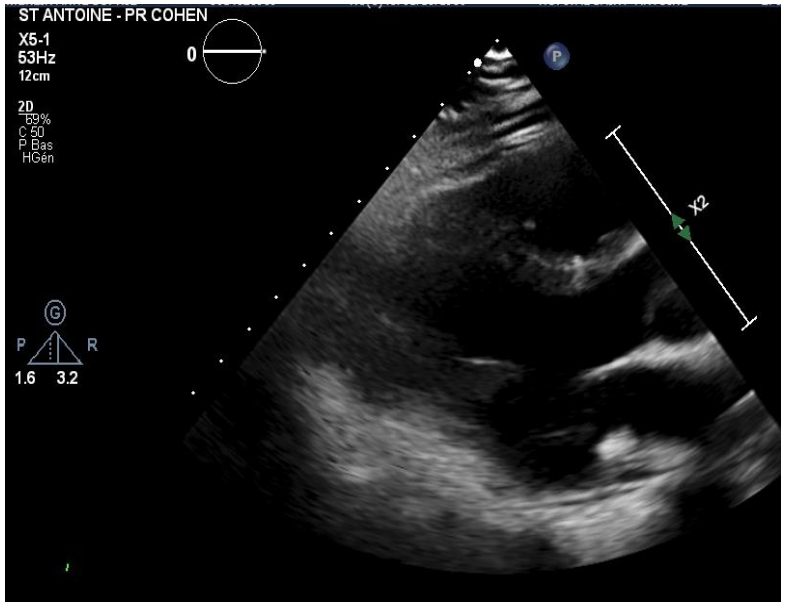


B



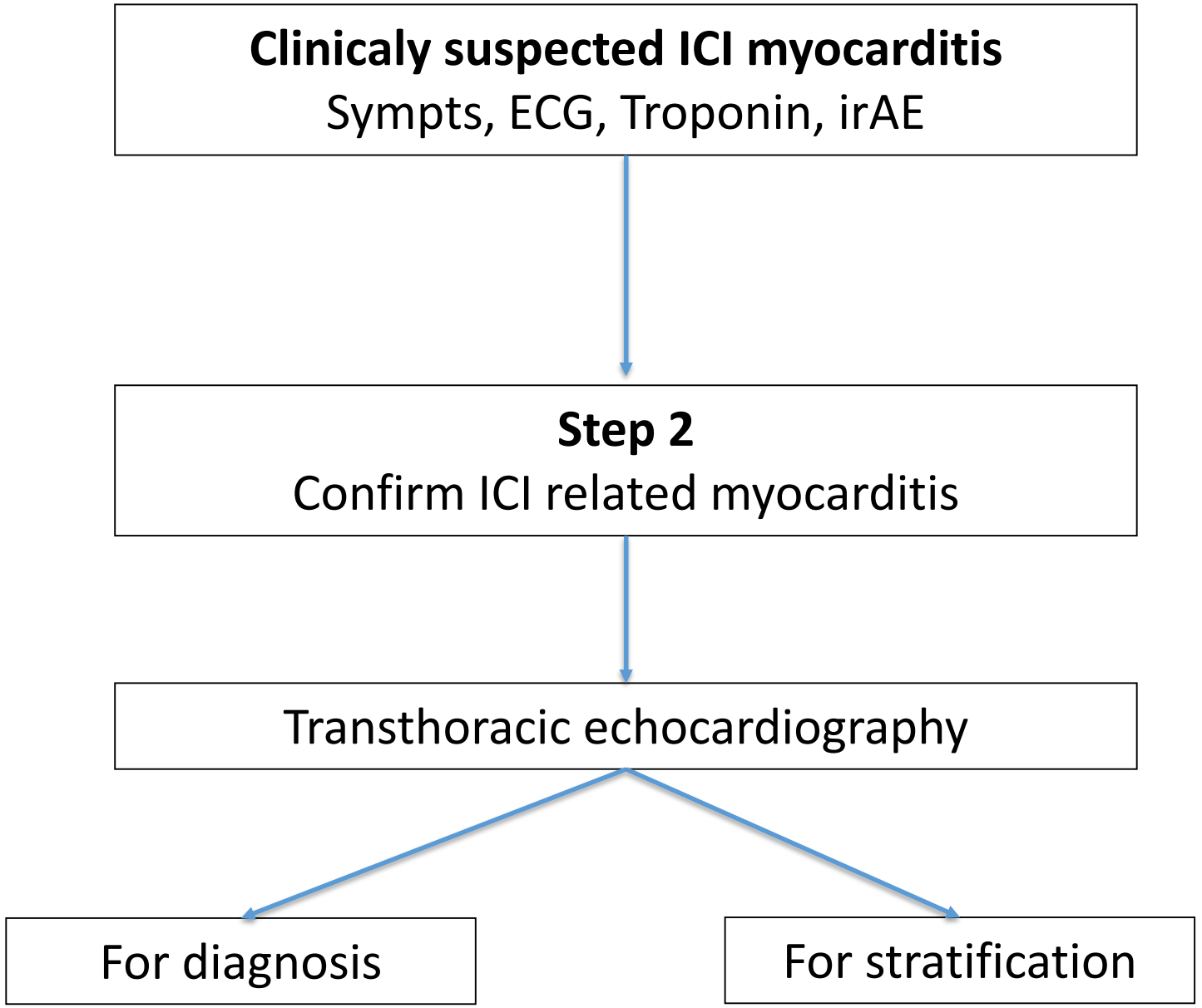




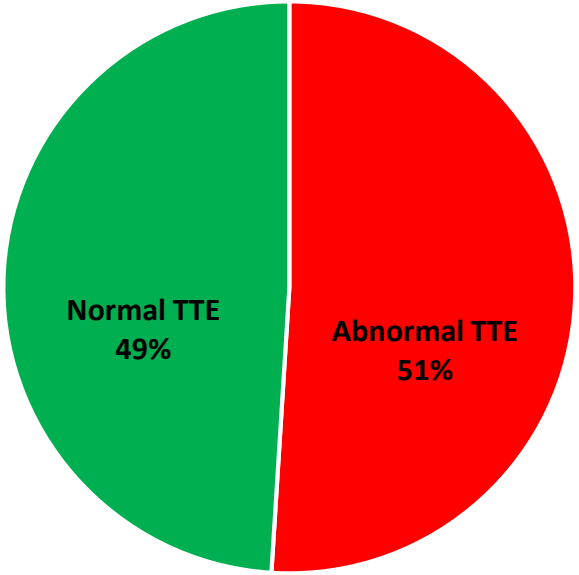


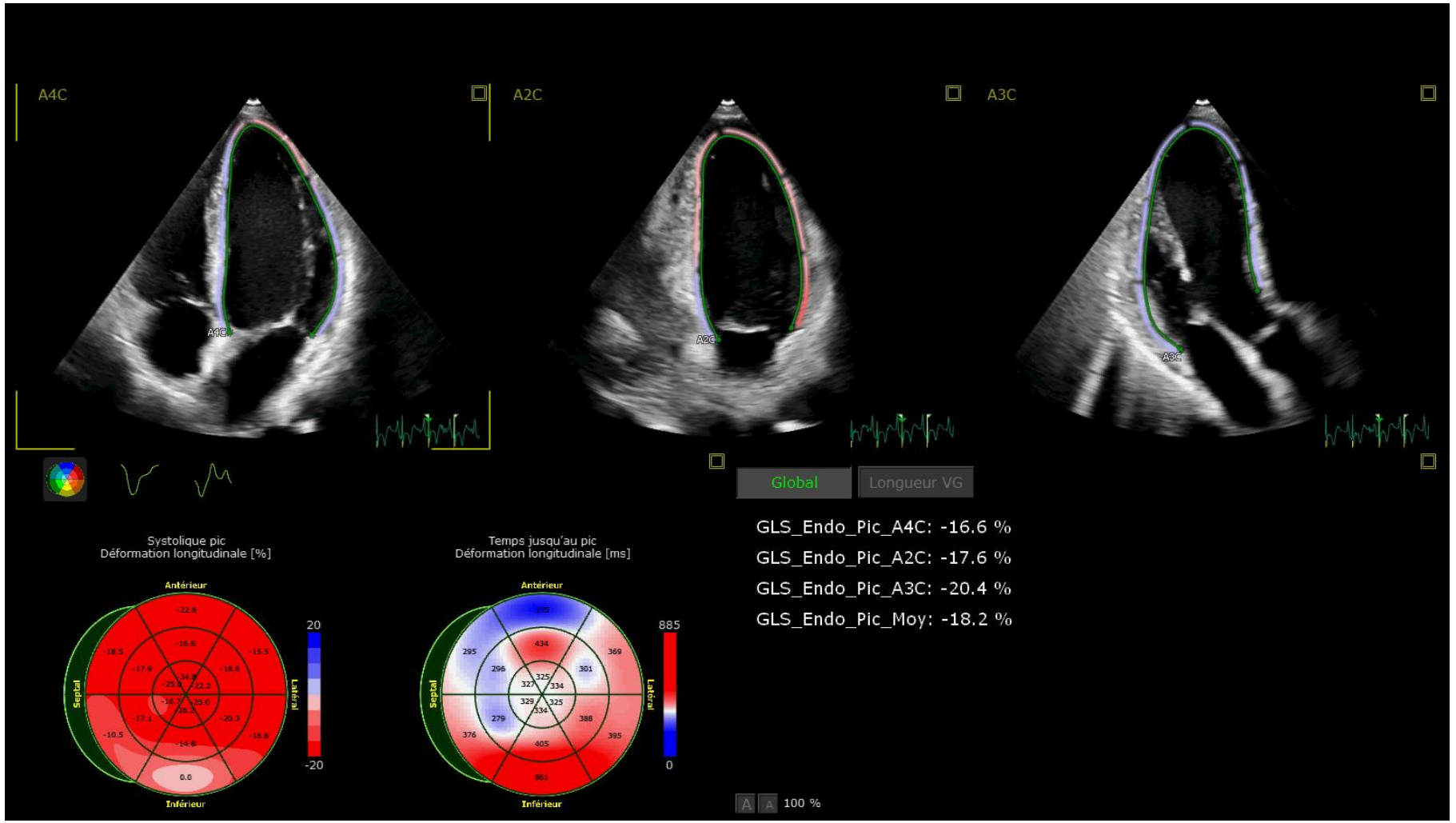
30 % of patients with a suspected ICI myocarditishad an obvious alternative diagnosis

Ederhy S *Arch Cardiovasc Dis*. 2022;115 : 114-116.


Clinicaly suspected ICI myocarditis
Sympts, ECG, Troponin, irAE
Step 2
Confirm ICI related myocarditis
Transthoracic echocardiography
For diagnosis
For stratification

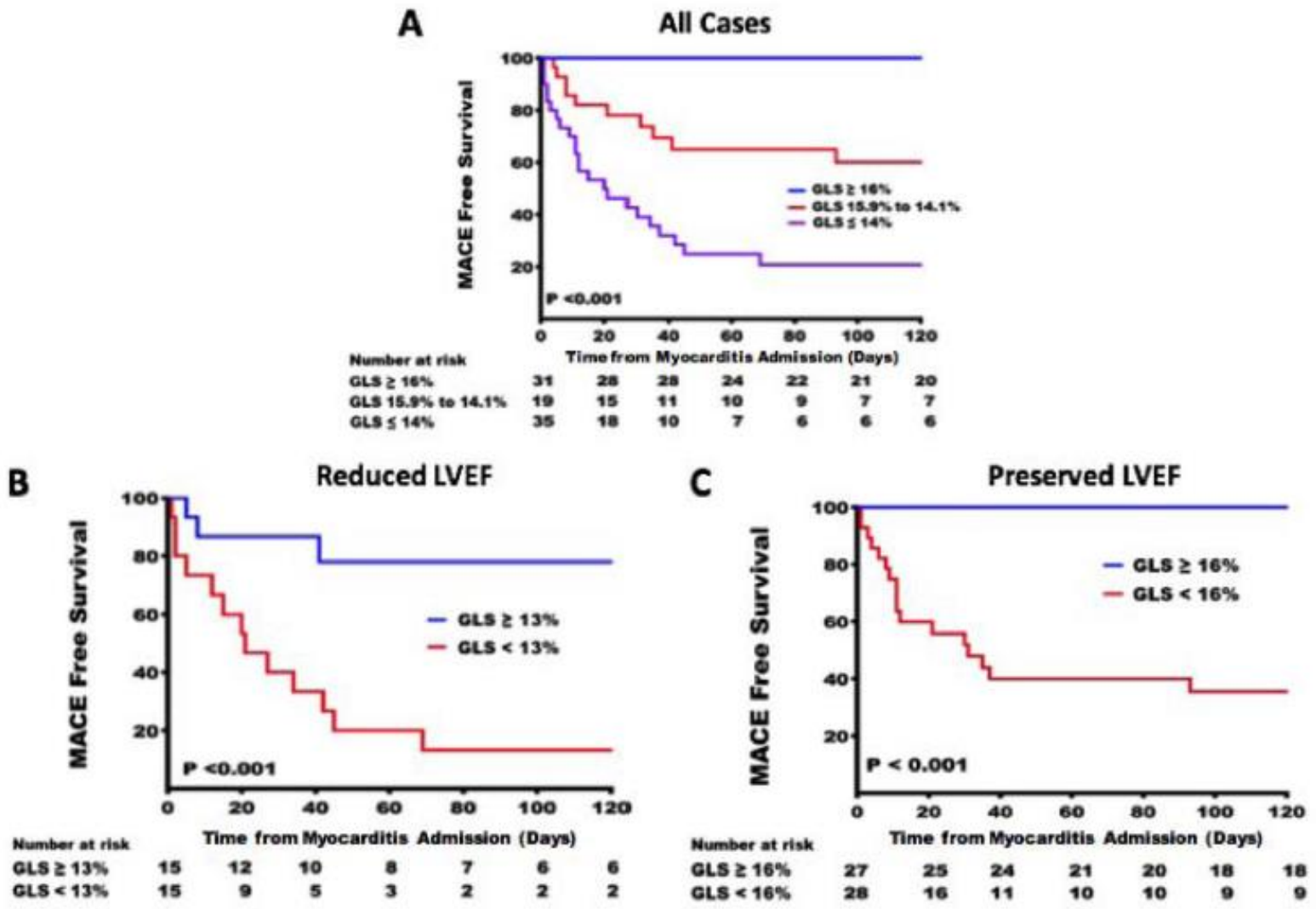
Transthoracic Echocardiography and ICI-associated Myocarditis



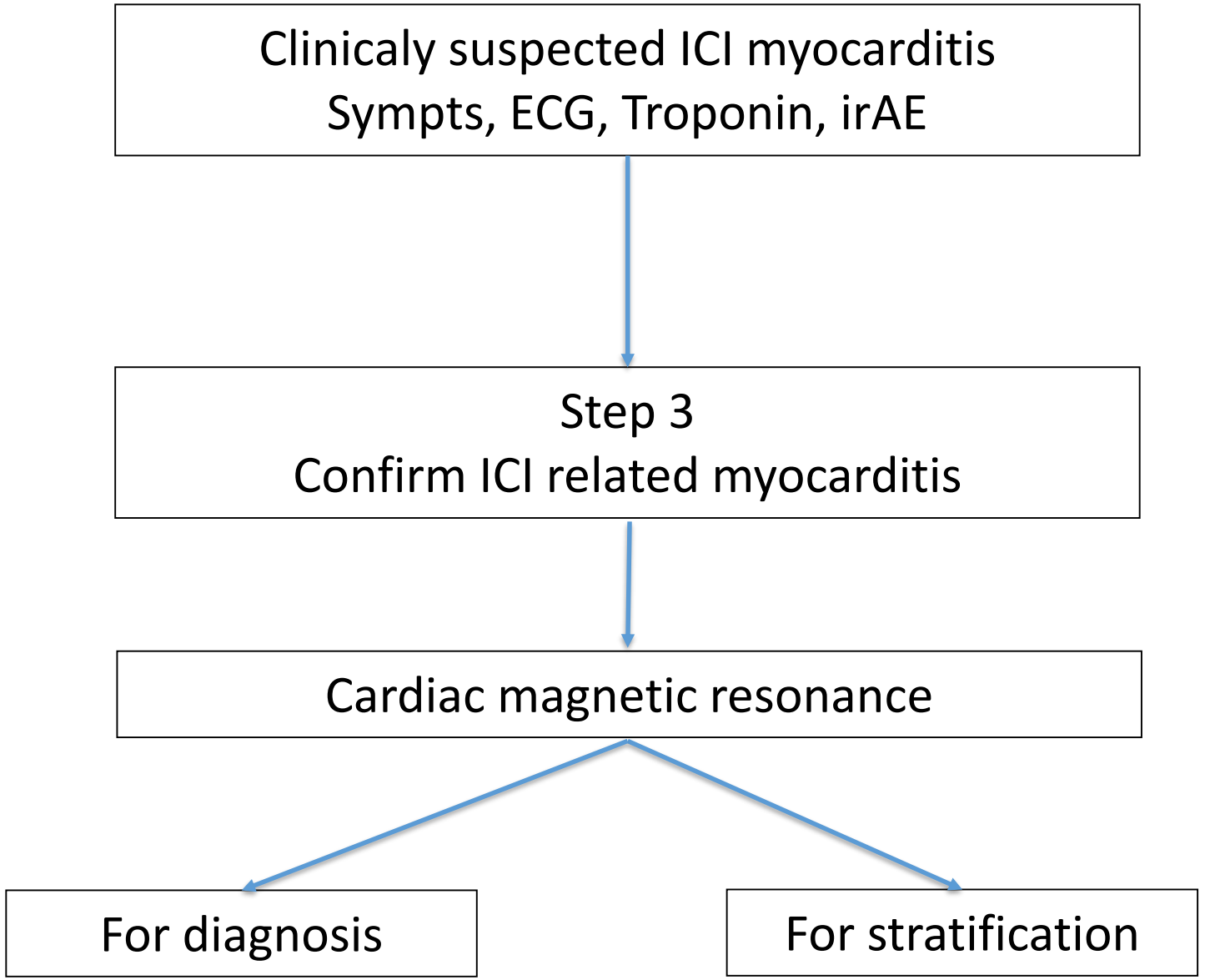


Mahmood J Am Coll Cardiol 2018 ; 71 : 1755 -64

Global Longitudinal Strain and Cardiac Events in Patients With Immune Checkpoint Inhibitor-Related Myocarditis



Awadalla M,. J Am Coll Cardiol. 2020 ;75(5):467-478.


Clinicaly suspected ICI myocarditis
Sympts, ECG, Troponin, irAE
Step 3
Confirm ICI related myocarditis
Cardiac magnetic resonance
For diagnosis
For stratification

Cardiac MRI Depicts Immune Checkpoint Inhibitor-induced Myocarditis: Cardiac MRI Results at baseline and FU examination

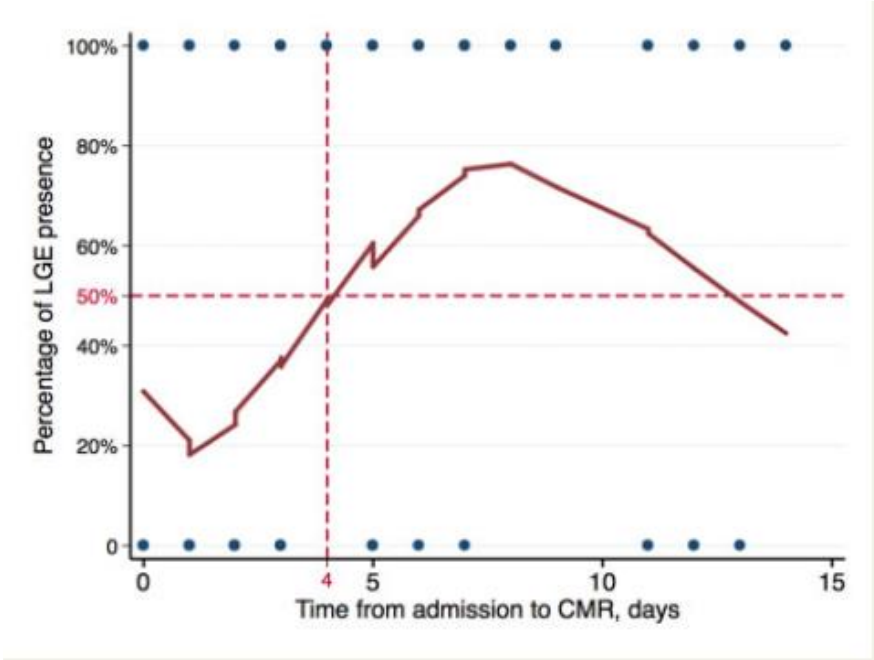
Variable	Baseline (n = 22)	Follow-up (n = 22)	P Value
Left ventricular ejection fraction (%)	62 ± 7	59 ± 7	.048*
Left ventricular end-diastolic volume index (mL/m^2)	73 ± 14	71 ± 13	.32
Left ventricular mass index (g/m^2)	47 ± 11	47 ± 15	.80
Visible myocardial edema†	0 (0)	2 (9)	.48
Visible myocardial LGE†	7 (32)	9 (41)	.48
Visible pericardial LGE†	0 (0)	1 (5)	>.99
Pericardial effusion†	1 (5)	10 (45)	.004*
Pleural effusion†	0 (0)	2 (9)	.48
T2 signal intensity ratio	1.5 ± 0.3	1.7 ± 0.3	.03*
LGE (%)	10.1 ± 5.5	12.0 ± 7.2	.21
Average systolic longitudinal strain (%)	−23.4 ± 4.8	−19.6 ± 5.1	.005*
Average systolic circumferential strain (%)	−23.8 ± 5.1	−23.2 ± 5.4	.56
Average systolic radial strain (%)	31.9 ± 8.0	29.3 ± 8.9	.13
T1 relaxation time, native (msec)	972 ± 26	1006 ± 36	<.001*
Extracellular volume fraction (%)	25.6 ± 4.5	26.0 ± 3.8	.86
T2 relaxation time (msec)	54 ± 3	58 ± 4	<.001*

Faron Radiology. 2021 Sep 28:210814.

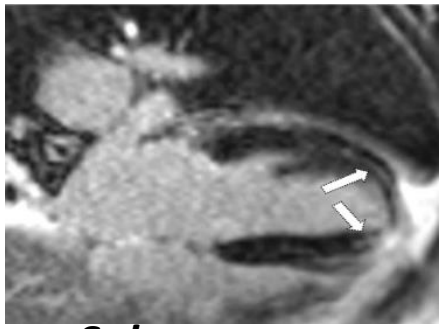
CMR and ICI myocarditis

LGE	%
None	23
Sub epicardial	17
Mild Myocardial	34
Diffuse	26

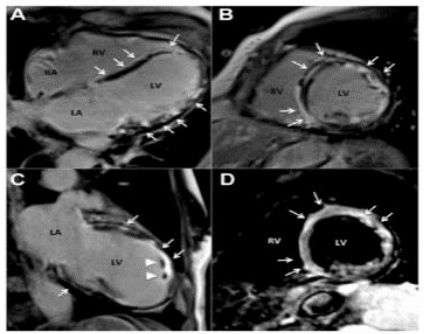
Mahmood J Am Coll Cardiol 2018 ; 71 : 1755 -64



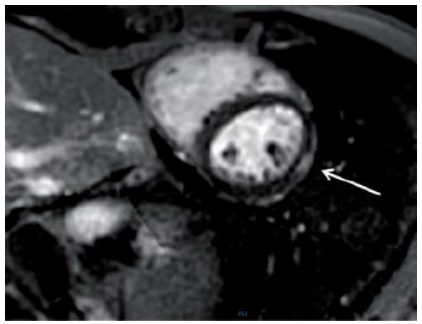
Zhang L, Eur Heart J. 2020 ;41:1733-1743.



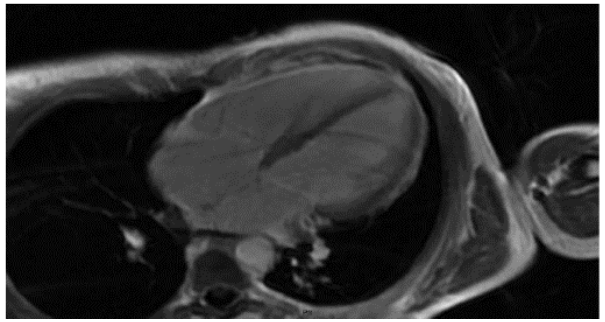
Salem
NEJM2019



Frigeri
Can J Cardiol 2018

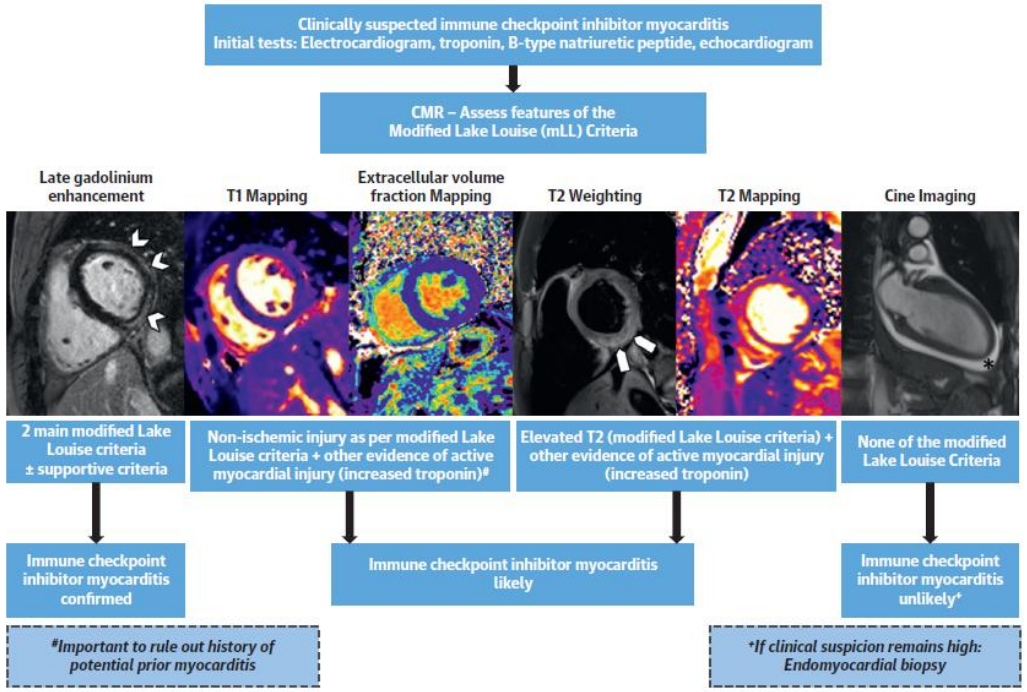


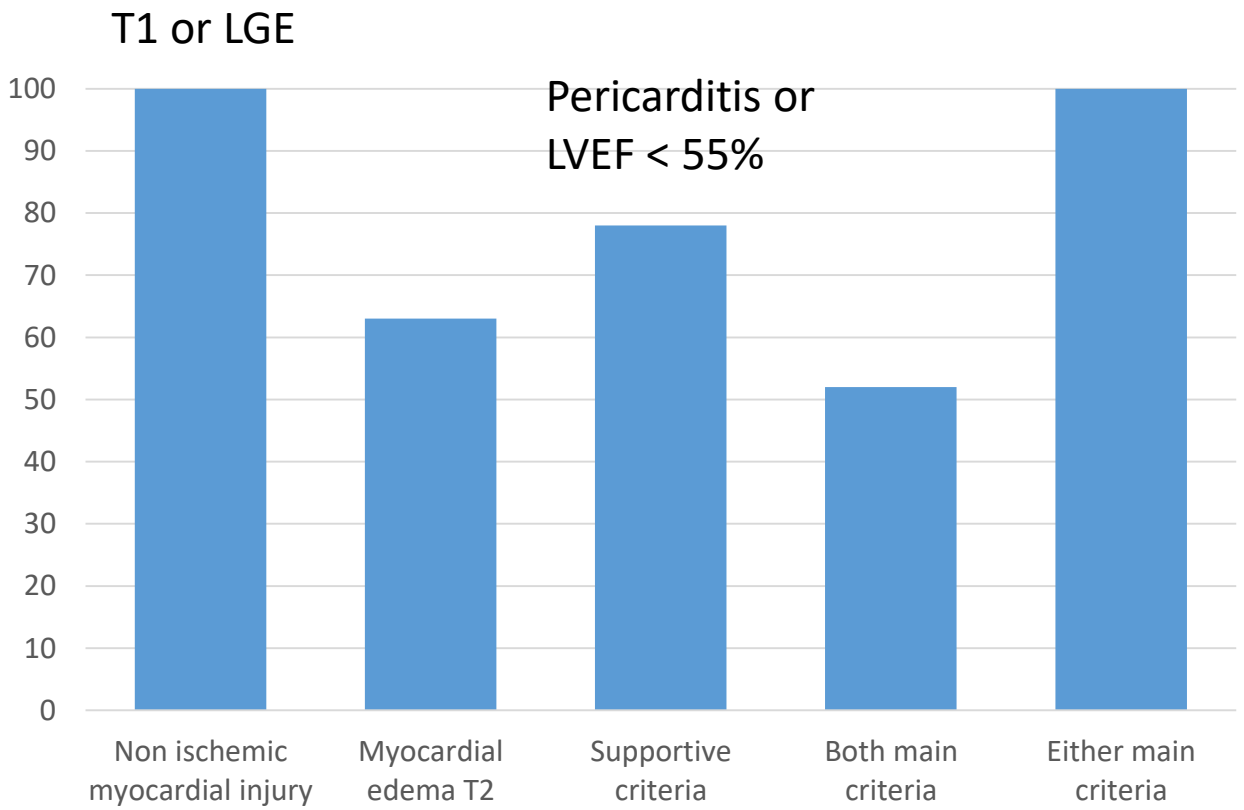
Mirabel
EHJ 2019



Arangalage
AIM 2017

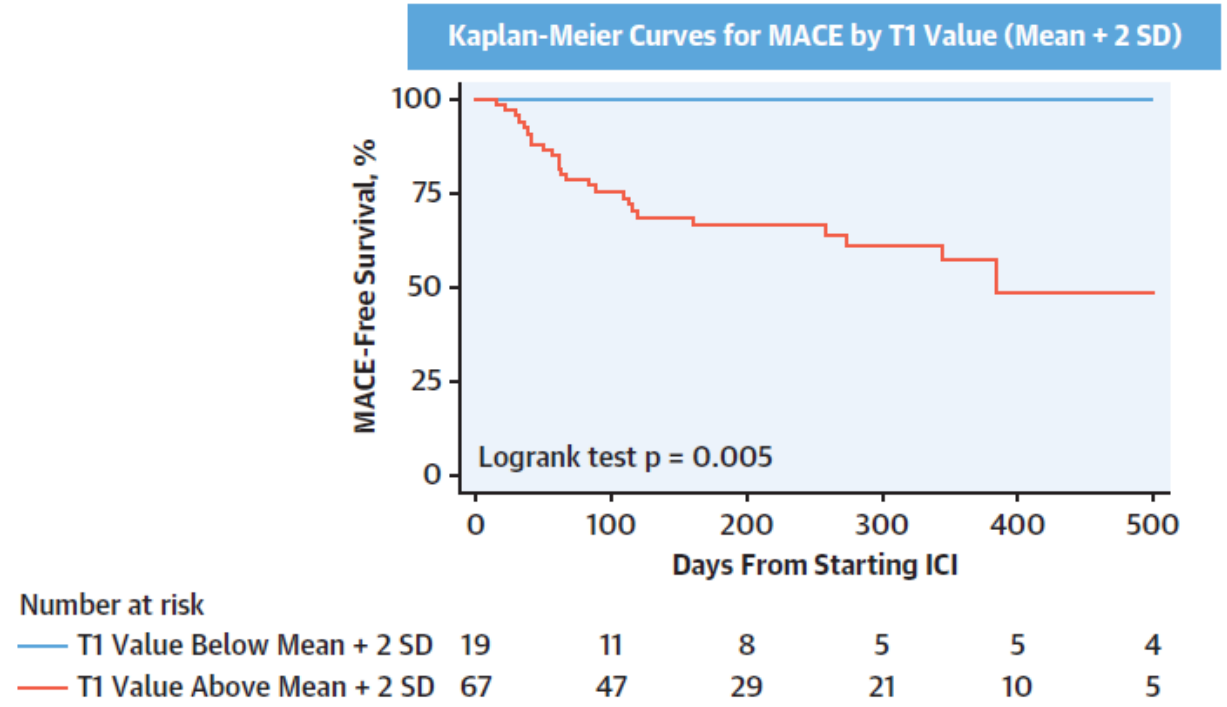
Myocardial T1 and T2 Mapping by Magnetic Resonance in Patients With Immune Checkpoint Inhibitor–Associated Myocarditis

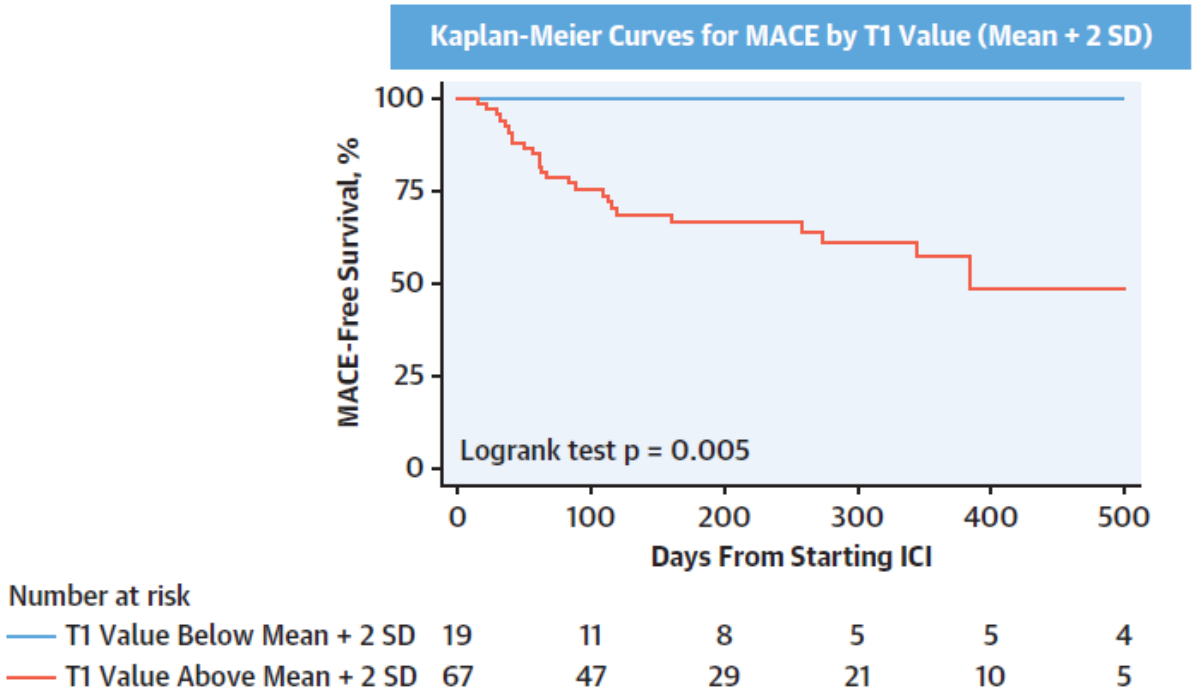




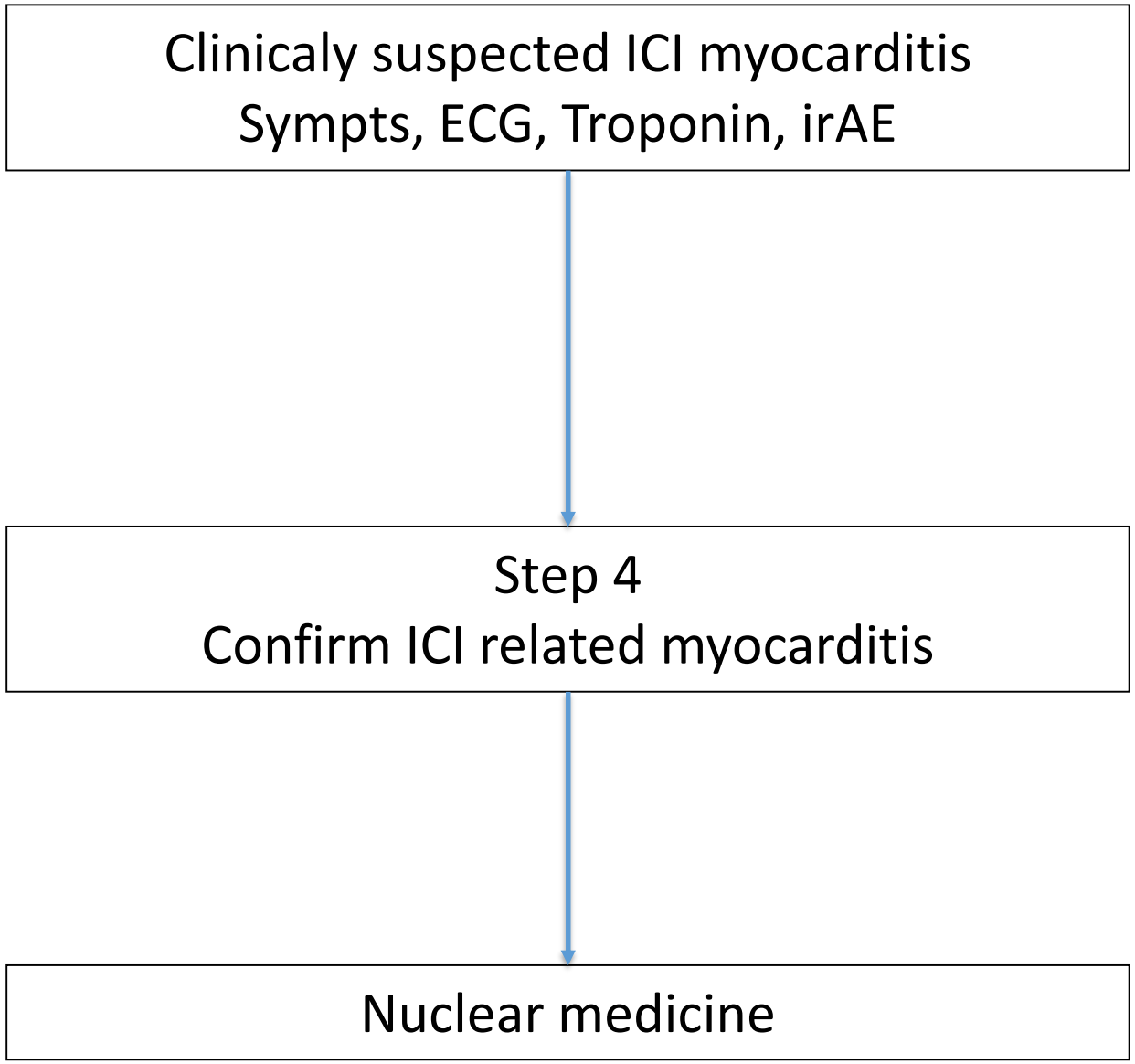
Thavendiranathan P J Am Coll Cardiol 2021 : 77 : 1503 - 16

Myocardial T1 and T2 Mapping by Magnetic Resonance in Patients With Immune Checkpoint Inhibitor–Associated Myocarditis



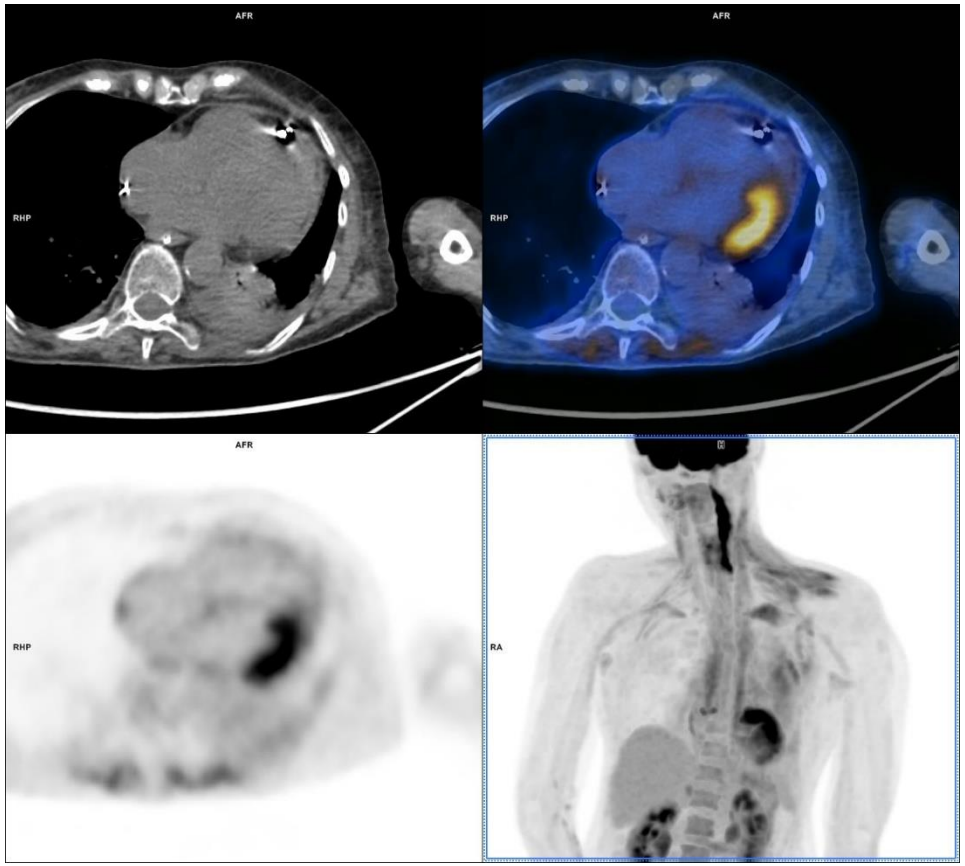


Thavendiranathan P J Am Coll Cardiol 2021 : 77 : 1503 - 16


Clinicaly suspected ICI myocarditis
Sympts, ECG, Troponin, irAE
Step 4
Confirm ICI related myocarditis
Nuclear medicine

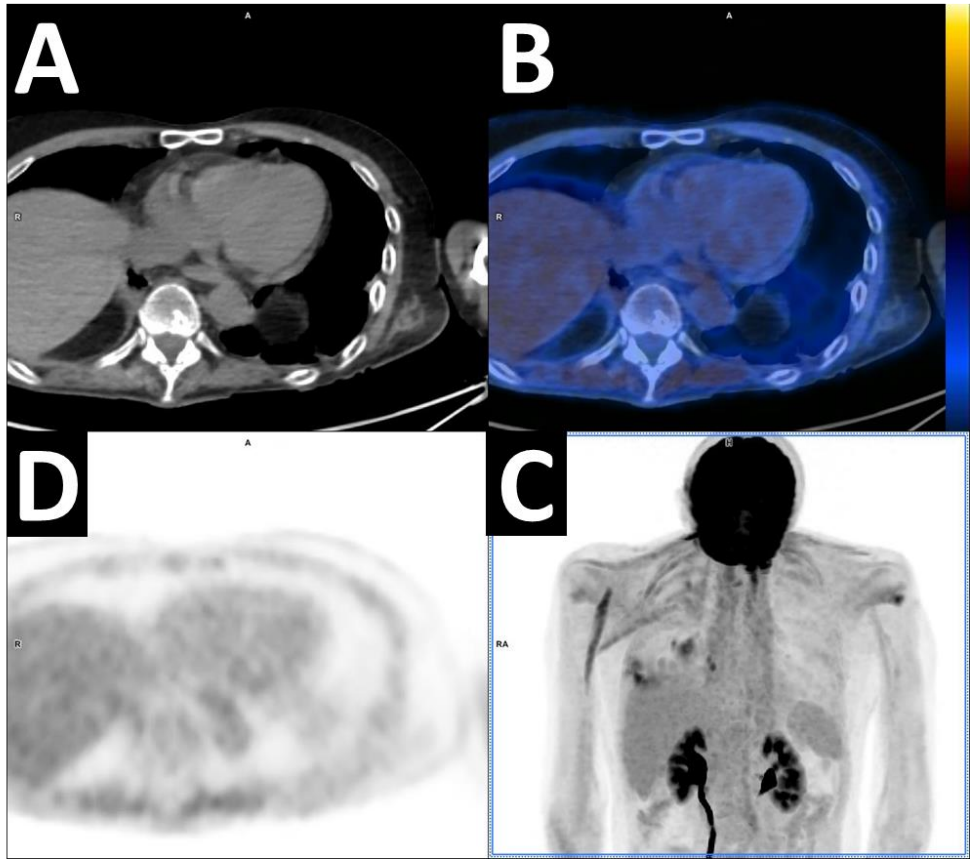
PET FDG and ICI myocarditis

EMB + / PET FDG +



69-year-old women with myocarditis under durvulumab proven on a histological sample. Focal myocardium lateral wall uptake of F-18-fluorodeoxyglucose on PET/CT scan

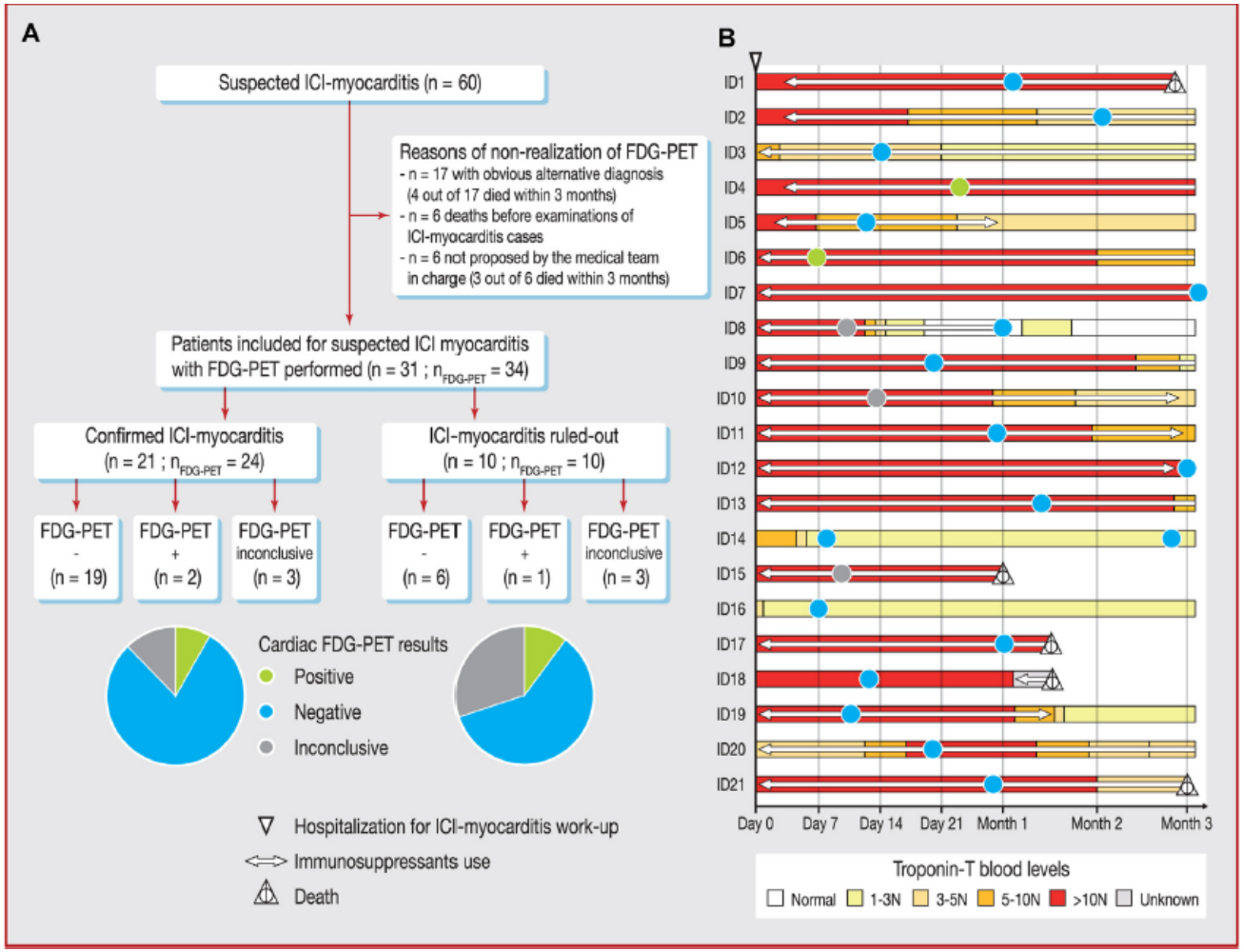
EMB + / PET FDG -



64-year-old woman with myocarditis under triple immunotherapy (nivolumab relatilimab and anti IDO1), proven on a histological sample. No myocardium uptake of F-18-fluorodeoxyglucose on PET/CT scan.

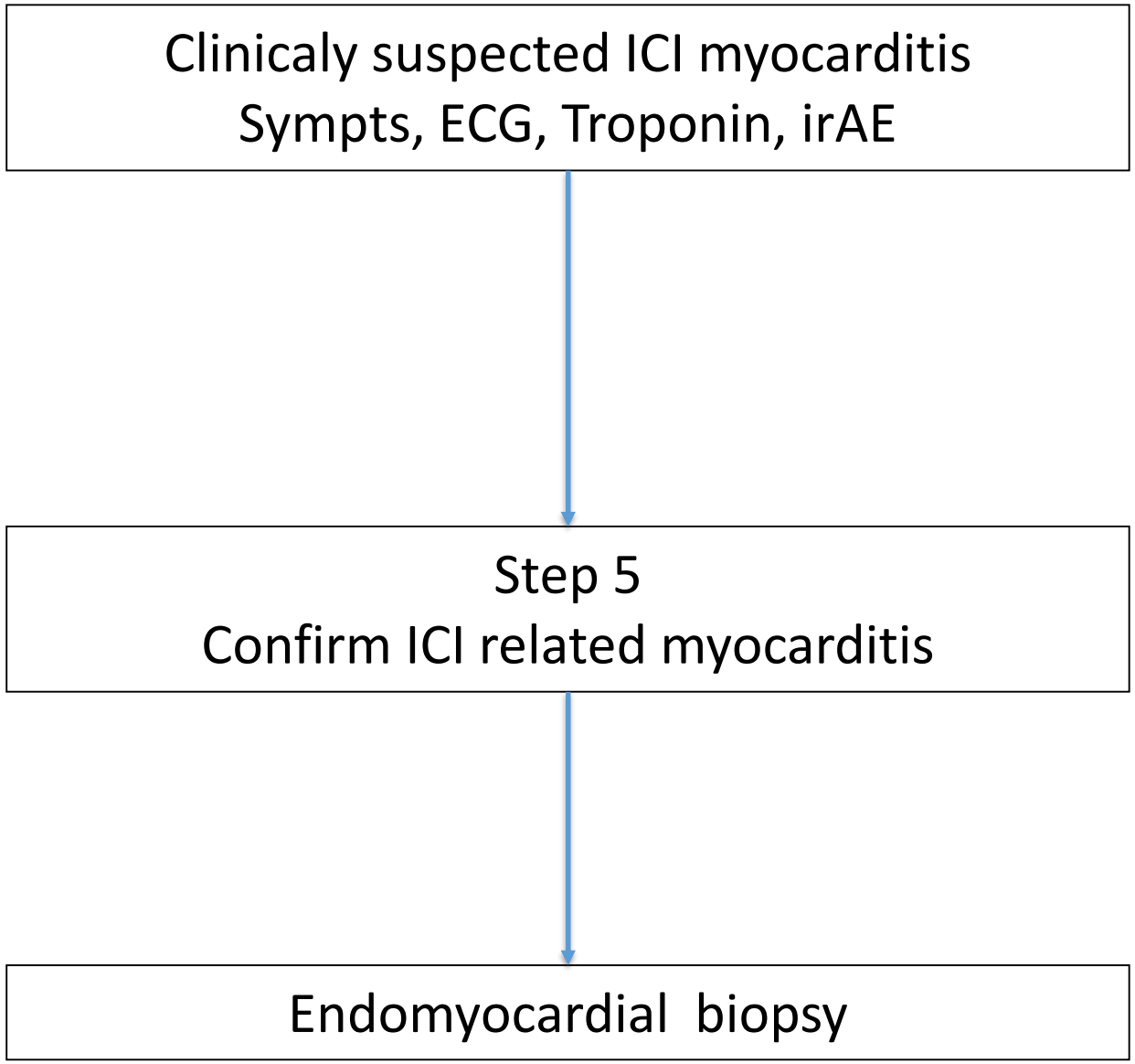
Ederhy S *Arch Cardiovasc Dis*. 2022;115 : 114-116.

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography imaging for the diagnosis of immune checkpoint inhibitor-associated myocarditis.

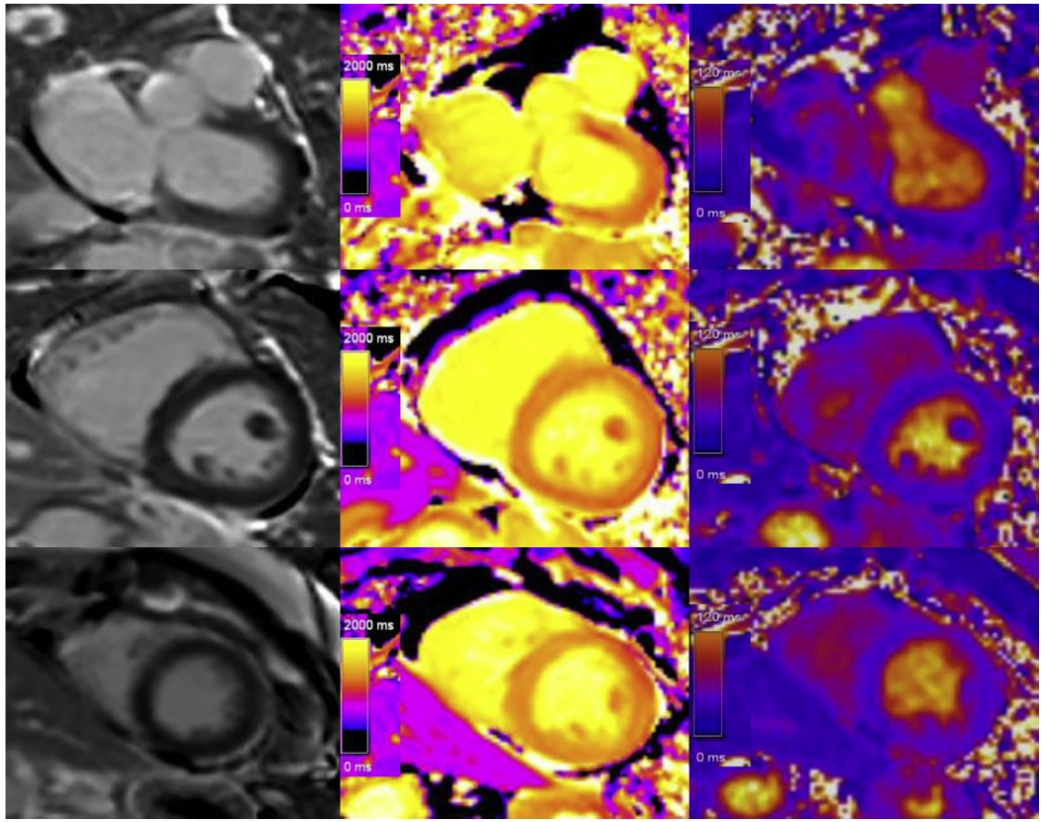


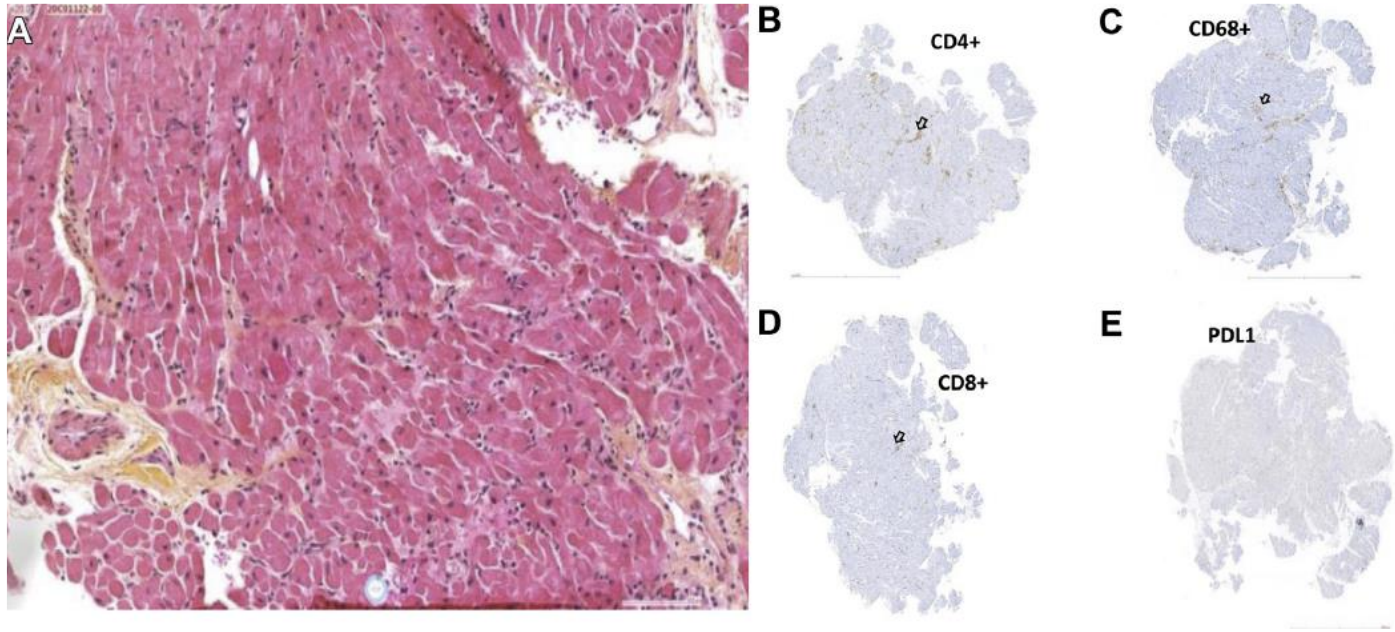
Sensibility : 9,5 % (1,2-30,4 %) ,**Specificity** : 87,5 % (42,1-99,6%), **PPV** : 66 (17,5-95%), **NPV** (24 (18,5- 30,6%)

Ederhy S *Arch Cardiovasc Dis*. 2022;115 : 114-116.


Clinicaly suspected ICI myocarditis
Sympts, ECG, Troponin, irAE
Step 5
Confirm ICI related myocarditis
Endomyocardial biopsy

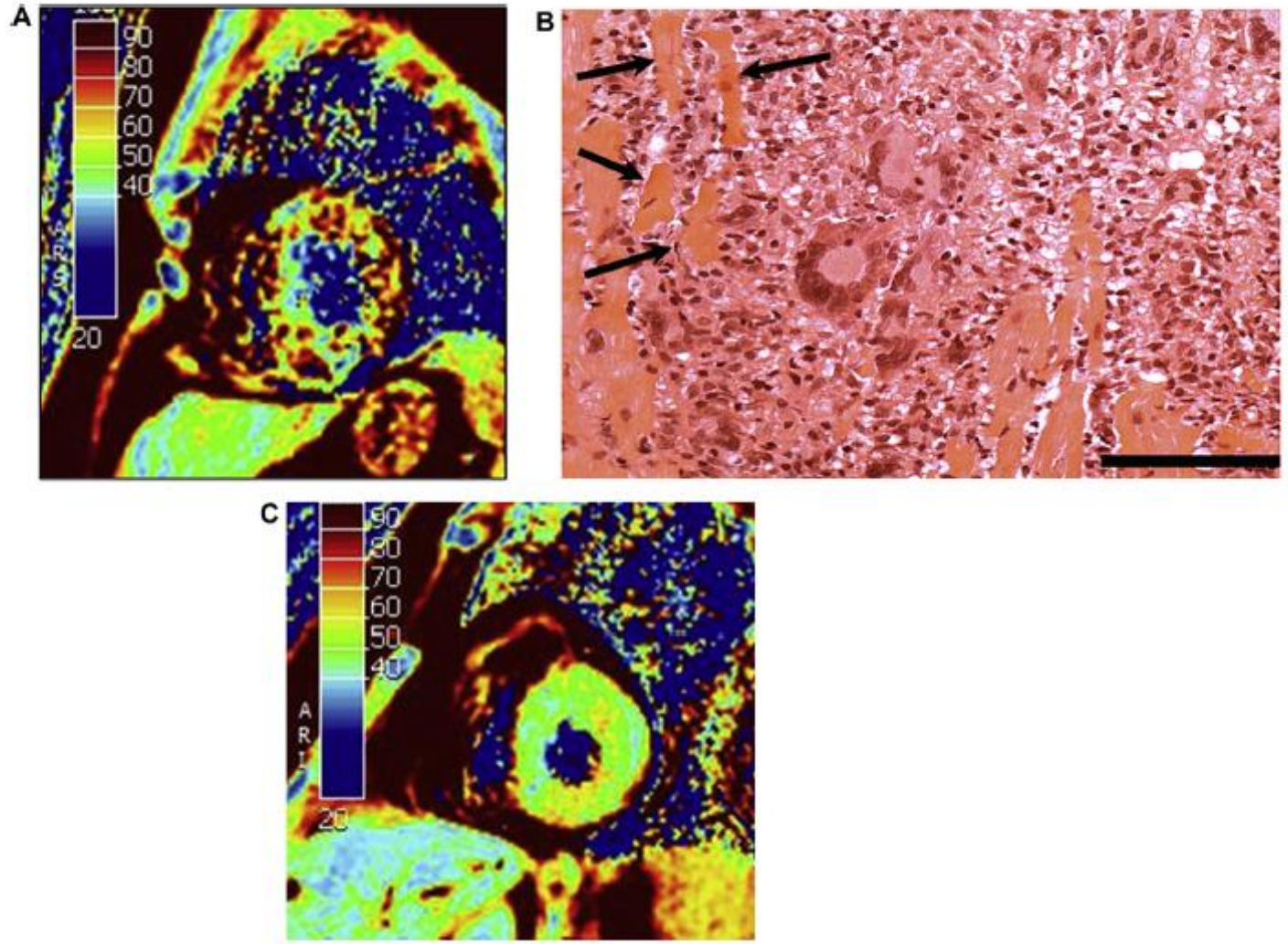
Immune Checkpoint Inhibitor Myocarditis With Normal Cardiac Magnetic Resonance Imaging: Importance of Cardiac Biopsy and Early Diagnosis.





Ederhy S. Can J Cardiol. 2021;37:1654-1656.

Late-Onset Giant Cell Myocarditis Due to Enterovirus During Treatment With Immune Checkpoint Inhibitors



57-year-old male, Symptoms , 27th course of Nivolumab for mRCC. ECG abnormalities. Troponin I 4,700 ng/l, BNP 466 ng/l. Normal coronary arteries. CMR : diffuse myocardial edema (T_2 = 74 ms, T_1 : 1,163 ms, ECV 35.5%, LVEF : 32%).

Mirabel M,. JACC CardioOncol. 2020 Sep 15;2(3):511-514..

Diagnostic Myocardite immunothérapie

Biopsie endomyocardique

Elévation de la troponine
Et IRM diagnostique (LLC- T1-T2- RT)

Elévation de la troponine
et 2 Critères mineurs

Clinique : CV et Immunomédié

ECG – TLM : TDR V ou TDC

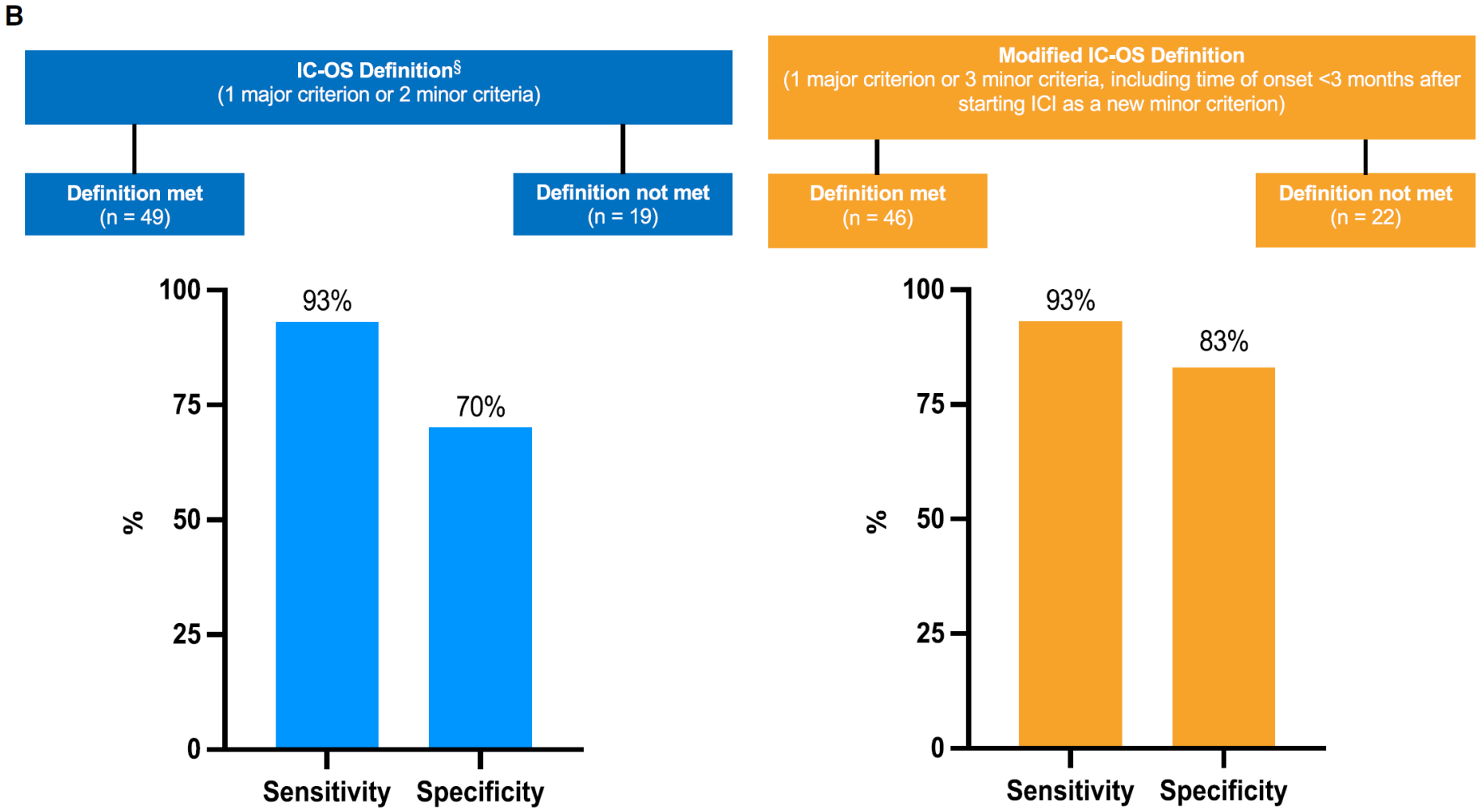
Imagerie : ↓FEVG, anomalie cinétique

IRM suggestive : T1 ou T2

Evènement immunomedié associé

Lyon AR [published online ahead of print, 2022 Aug 26]. *Eur Heart J*. 2022;ehac244. doi:10.1093/eurheartj/ehac244

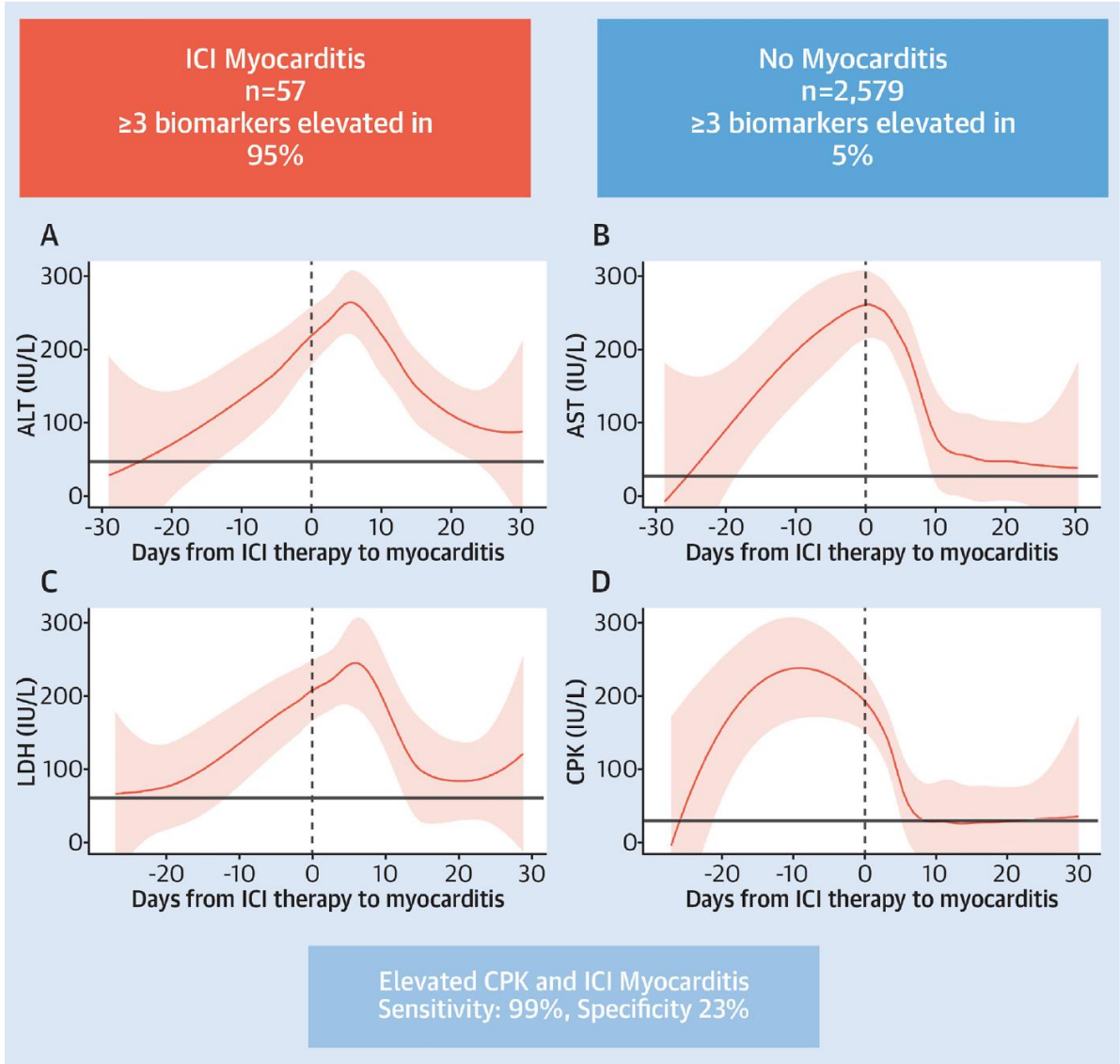
Diagnostic Value of the International Society of Cardio-Oncology Definition for Suspected Immune Checkpoint Inhibitor-Associated Myocarditis



Deharo F,. *J Am Heart Assoc*. 2023;12(8):e029211.

Biomarker Trends, Incidence, and Outcomes of Immune Checkpoint Inhibitor-Induced Myocarditis.

Longitudinal biomarker associations with ICI myocarditis



Vasbinder *JACC CardioOncol*. 2022;4(5):689-700.

Electrocardiographic Manifestations of Immune Checkpoint Inhibitor Myocarditis

Table. Presenting ECG of ICI-Myocarditis Compared With Baseline and as Predictors of All-Cause Mortality Using Survival Analyses Adjusting for Age and Sex*

	ICI-myocarditis, presenting ECG; median (IQR) N; n/N (%)	ICI-myocarditis, baseline ECG; median (IQR) N; n/N (%)	*P* value	Cox proportional hazards model for 30-day all-cause mortality; adjusted HR (95% CI), *P* value; N
Heart rate, bpm	93.9 (72.6–114.7) N=52	80.4 (68.1–94.8) N=52	0.009†	1.01 (0.99–1.02), *P*=0.40; N=125
PR length, ms‡	162.8 (136.0–186.0) N=42	154.1 (136.0–187.6) N=46	0.10†	1.00 (0.99–1.01), *P*=0.55; N=107
QTcF length, ms§	441.8 (414.9–462.6) N=49	421.0 (399.2–440.4) N=51	0.03†	1.00 (1.00–1.01), *P*=0.36; N=122
QRS length, ms	95.3 (85.7–118.2) N=52	93.2 (82.7–102.5) N=52	0.02†	1.00 (0.99–1.01), *P*=0.90; N=125
Sokolow-Lyon Index, mV‖	1.39 (0.85–2.03) N=52	1.69 (1.28–2.26) N=52	0.006†	0.57 (0.34–0.94), *P*=0.03; N=124
Conduction disorders¶	35/52 (67%)	23/52 (44%)	0.01#	1.56 (0.69–3.53), *P*=0.29; N=125
Bundle-branch block, left bundle	10/52 (19%)	3/52 (6%)	0.05#	1.00 (0.38–2.62), *P*=0.99; N=125
Bundle-branch block, right bundle	14/52 (27%)	9/52 (17%)	0.18#	1.48 (0.71–3.06), *P*=0.29; N=125
Fascicular block, left anterior	10/52 (19%)	5/52 (10%)	0.23#	0.85 (0.32–2.25), *P*=0.75; N=125
Fascicular block, left posterior	6/52 (12%)	2/52 (4%)	0.22#	1.34 (0.47–3.85), *P*=0.59; N=125
Heart block, first-degree	9/52 (17%)	7/52 (13%)	0.72#	0.83 (0.28–2.40), *P*=0.72; N=125
ECG findings of pericarditis	4/52 (8%)	1/52 (2%)	0.25#	0.75 (0.22–2.51), *P*=0.64; N=125
ST-segment–elevation, diffuse	3/52 (6%)	1/52 (2%)	0.62#	0.83 (0.25–2.81), *P*=0.76; N=125
Premature ventricular complex (all types)	9/52 (17%)	3/52 (6%)	0.08#	1.01 (0.37–2.75), *P*=0.99; N=125
Premature ventricular complex	9/52 (17%)	3/52 (6%)	0.08#	0.77 (0.26–2.30), *P*=0.64; N=125
Sinus mechanism	42/52 (81%)	46/52 (88%)	0.29#	0.76 (0.31–1.89), *P*=0.56; N=125
Normal sinus rhythm	17/52 (33%)	31/52 (60%)	0.002#	0.50 (0.23–1.09), *P*=0.08; N=125
Sinus tachycardia	25/52 (48%)	15/52 (29%)	0.02#	1.67 (0.80–3.49), *P*=0.17; N=125
Repolarization abnormalities	27/52 (52%)	13/52 (25%)	0.008#	1.52 (0.74–3.12), *P*=0.26; N=125
ST-segment depression, diffuse	5/52 (10%)	1/52 (2%)	0.22#	1.60 (0.48–5.30), *P*=0.44; N=125
ST-segment depression, regional	4/52 (8%)	0/52 (0%)	NA	0.53 (0.07–3.90), *P*=0.53; N=125
T wave inversions	21/52 (40%)	12/52 (23%)	0.07#	1.49 (0.71–3.12), *P*=0.29; N=125
Supraventricular arrhythmia	7/52 (13%)	6/52 (12%)	1.00#	2.21 (0.84–5.79), *P*=0.11; N=125
Atrial fibrillation	6/52 (12%)	5/52 (10%)	1.00#	1.83 (0.63–5.27), *P*=0.27; N=125
Uncategorized				
Premature atrial complex	5/52 (10%)	3/52 (6%)	0.68#	1.59 (0.47–5.38), *P*=0.46; N=125
Left ventricular hypertrophy	12/52 (23%)	16/52 (31%)	0.34#	0.49 (0.15–1.61), *P*=0.24; N=125
Low QRS voltage	4/52 (8%)	1/52 (2%)	0.37#	3.27 (0.95–11.23), *P*=0.06; N=125
P wave abnormality suggestive of left atrial enlargement	11/52 (21%)	9/52 (17%)	0.75#	1.10 (0.46–2.63), *P*=0.83; N=125
Q waves, pathological	8/52 (15%)	4/52 (8%)	0.22#	5.98 (2.8–12.79), *P*<0.001; N=125

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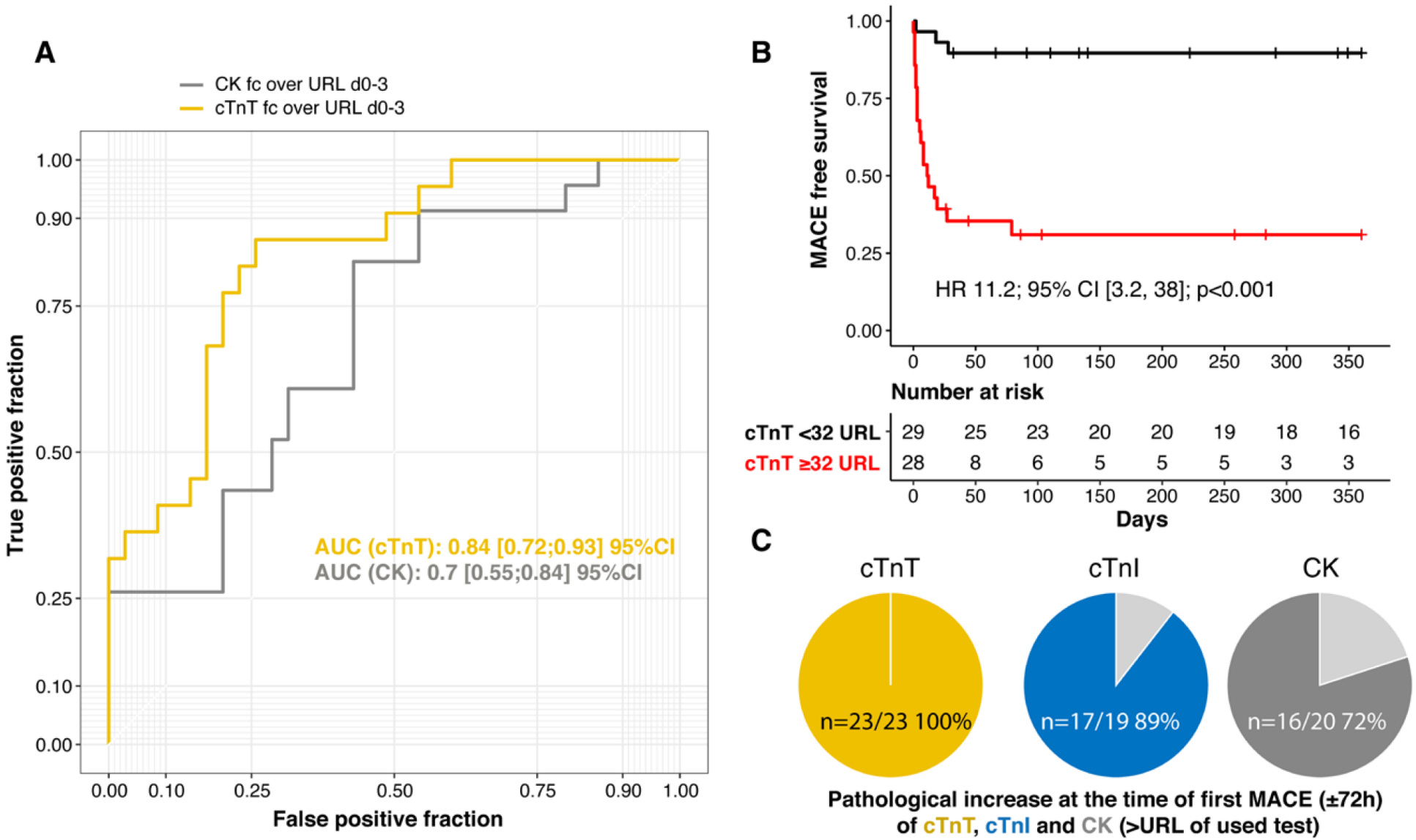
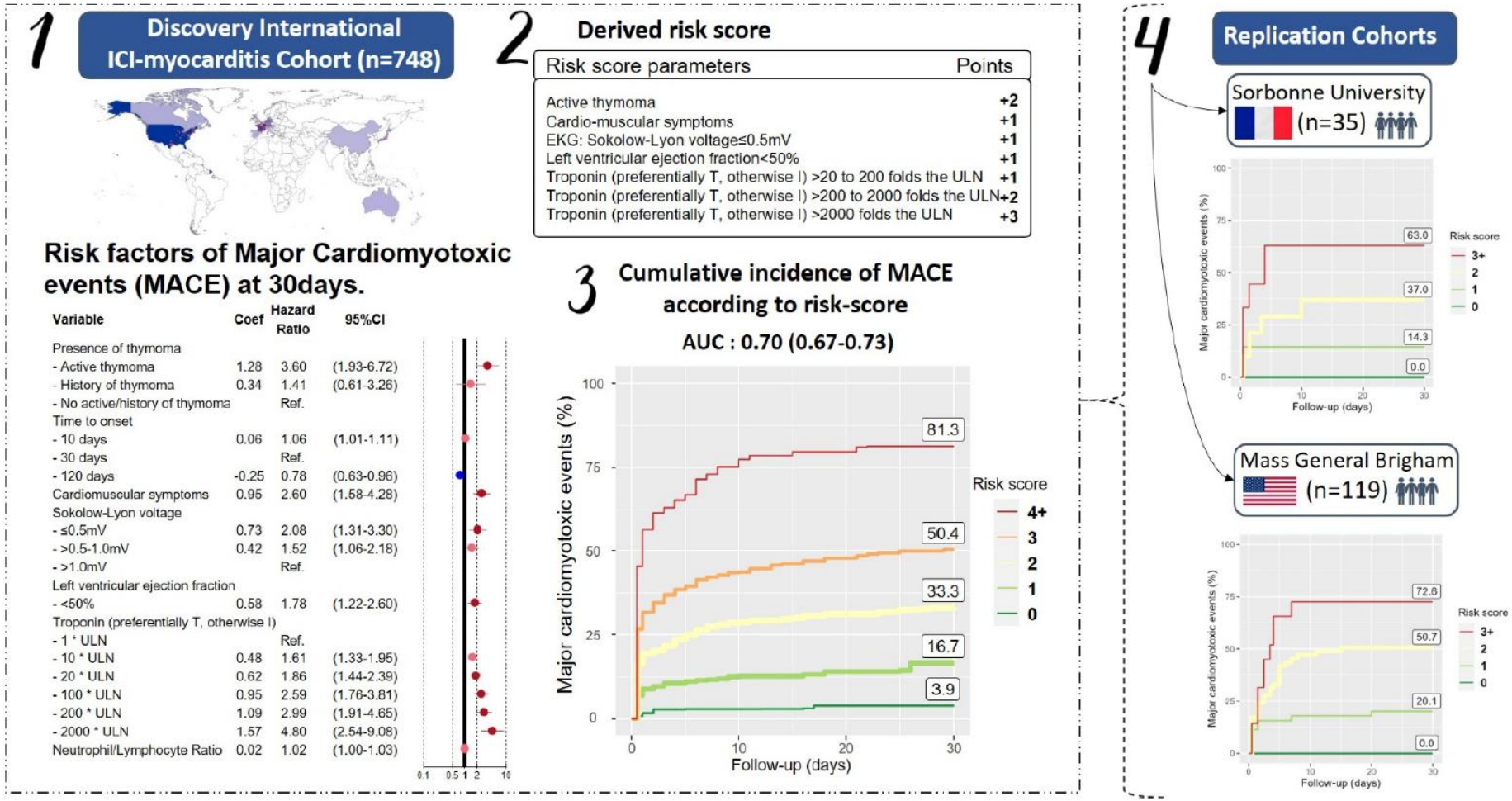
Cardiomuscular Biomarkers in the Diagnosis and Prognostication of Immune Checkpoint Inhibitor Myocarditis.



Lehmann LH, *Circulation*. 2023;148(6):473-486.

Predictors and Risk Score for Immune Checkpoint-Inhibitor-Associated Myocarditis Severity.



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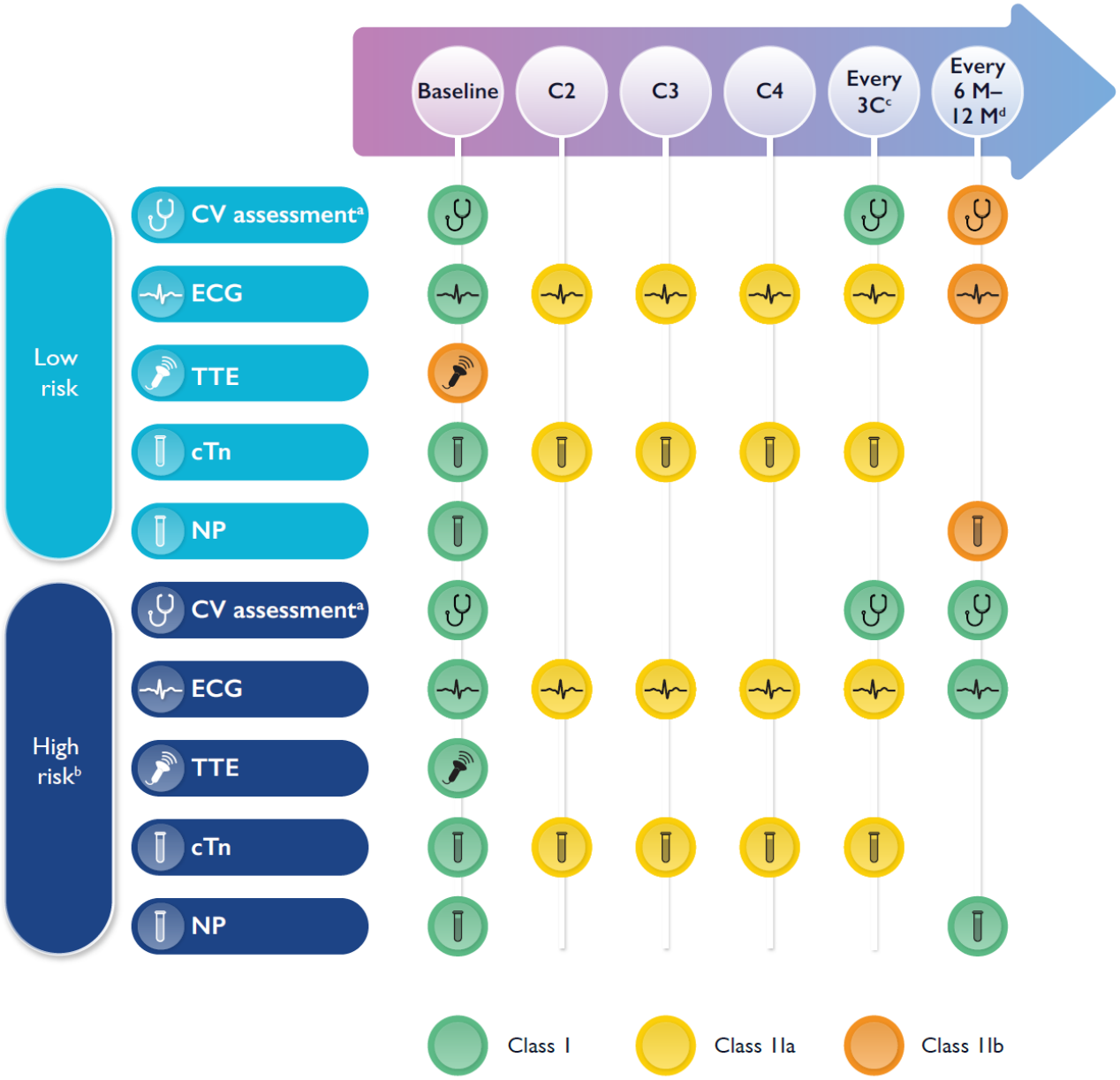
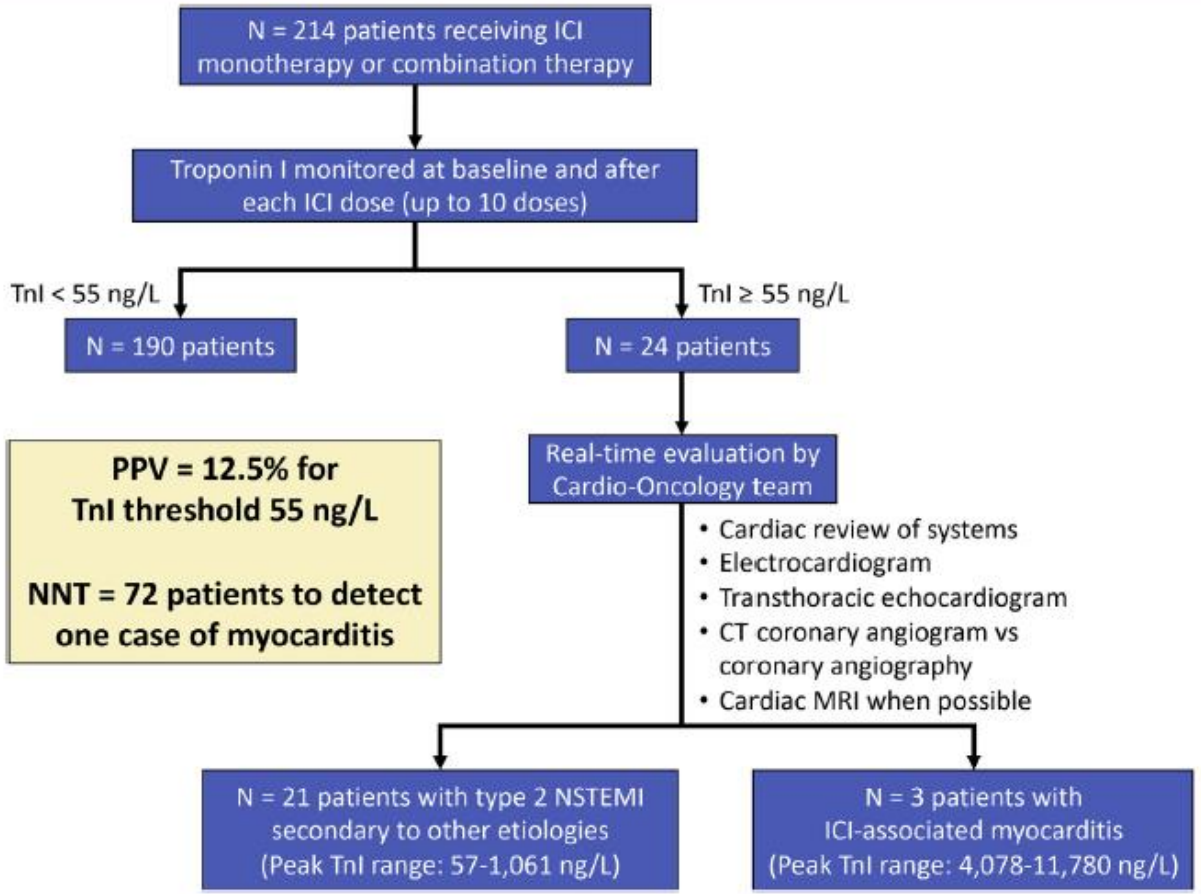
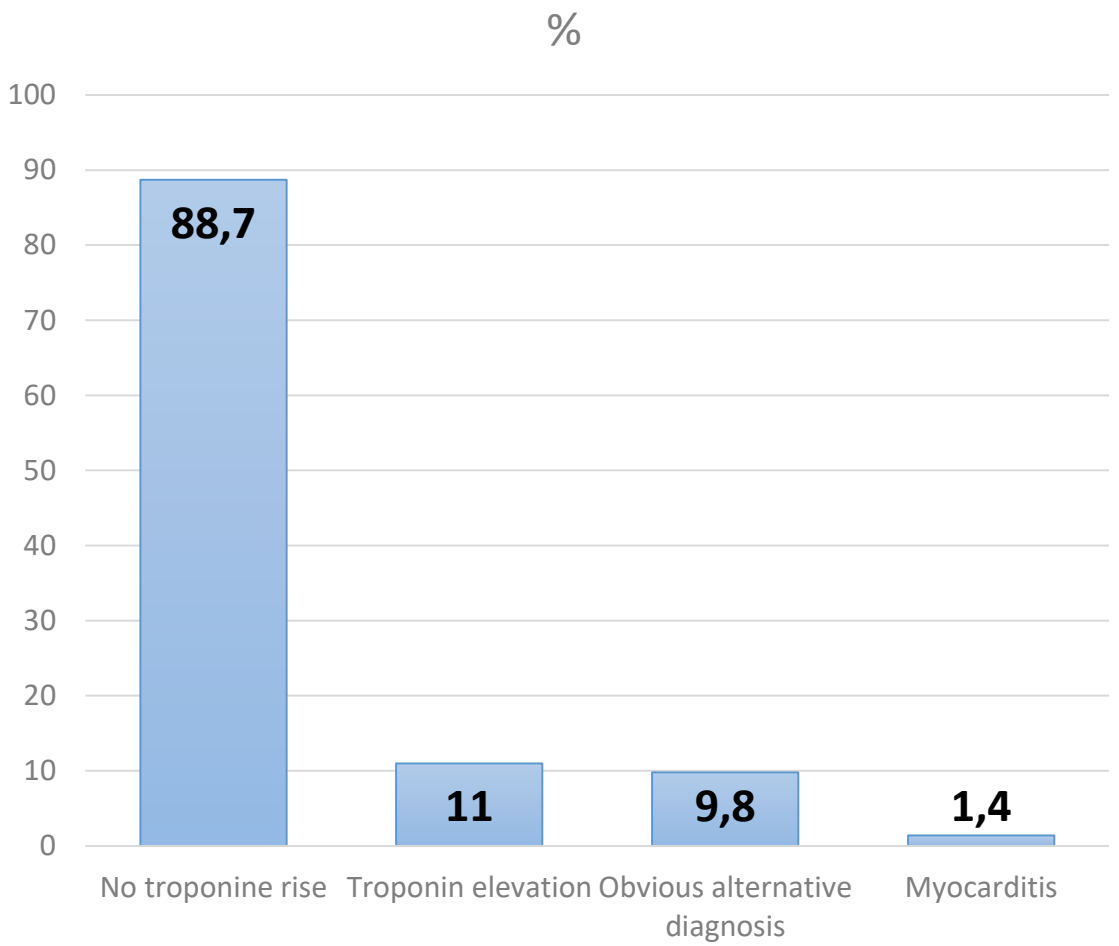
Immune checkpoint inhibitors surveillance protocol



Myocarditis Surveillance With High-Sensitivity Troponin I During Cancer Treatment With Immune Checkpoint Inhibitors





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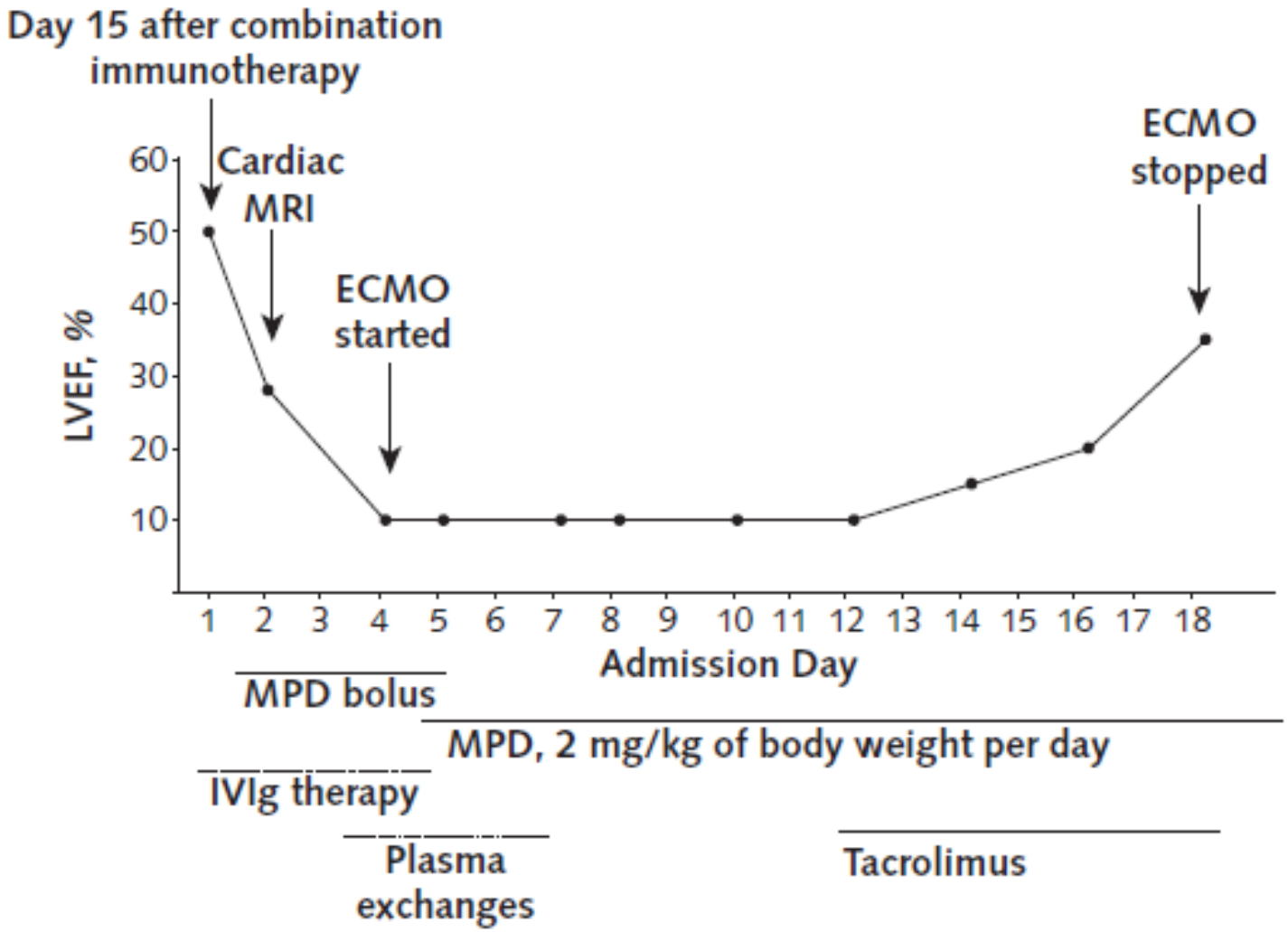
Survival After Fulminant Myocarditis Induced by Immune-Checkpoint Inhibitors



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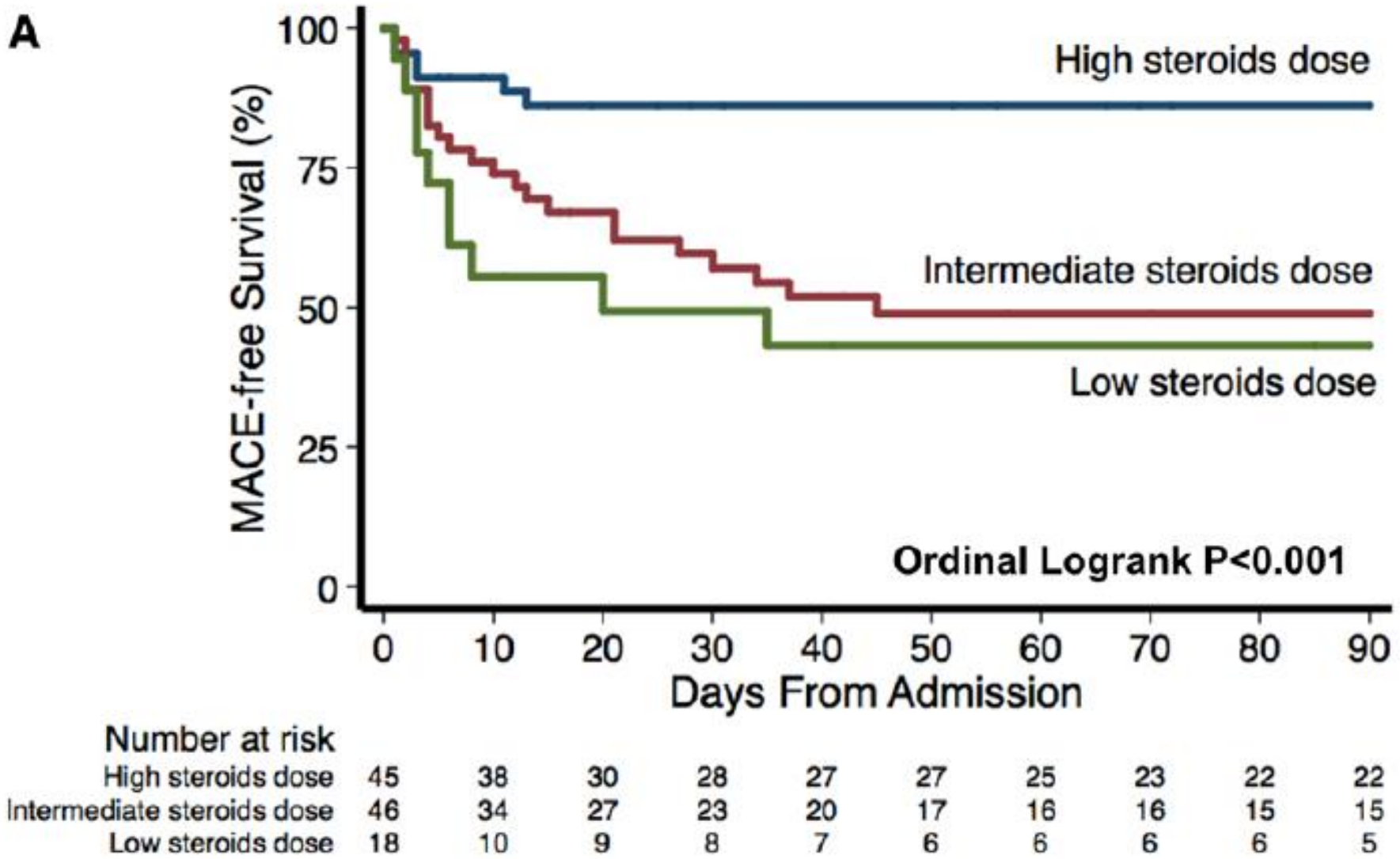
Major Adverse Cardiovascular Events and the Timing and Dose of Corticosteroids in Immune Checkpoint Inhibitor-Associated Myocarditis



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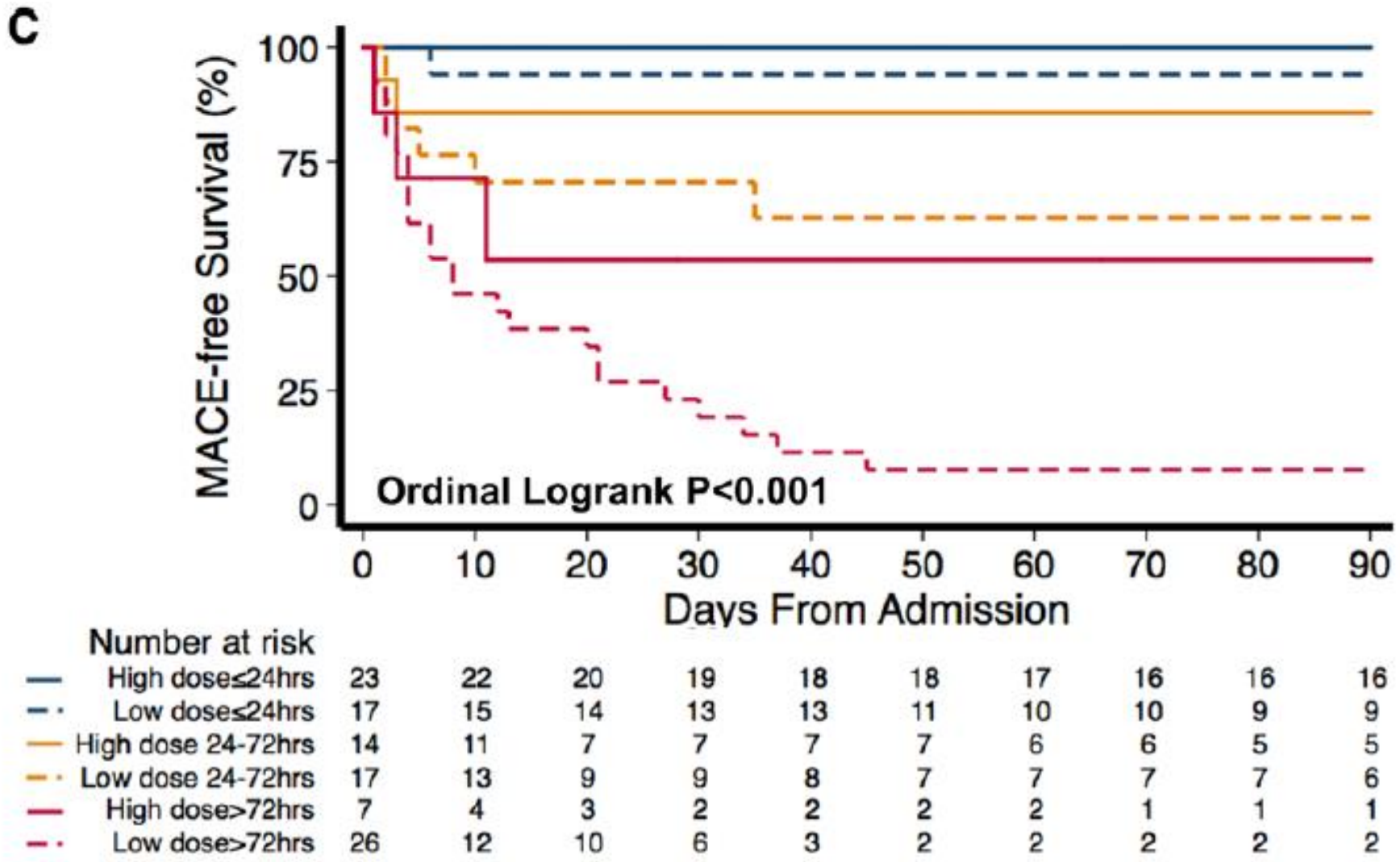
Major Adverse Cardiovascular Events and the Timing and Dose of Corticosteroids in Immune Checkpoint Inhibitor-Associated Myocarditis



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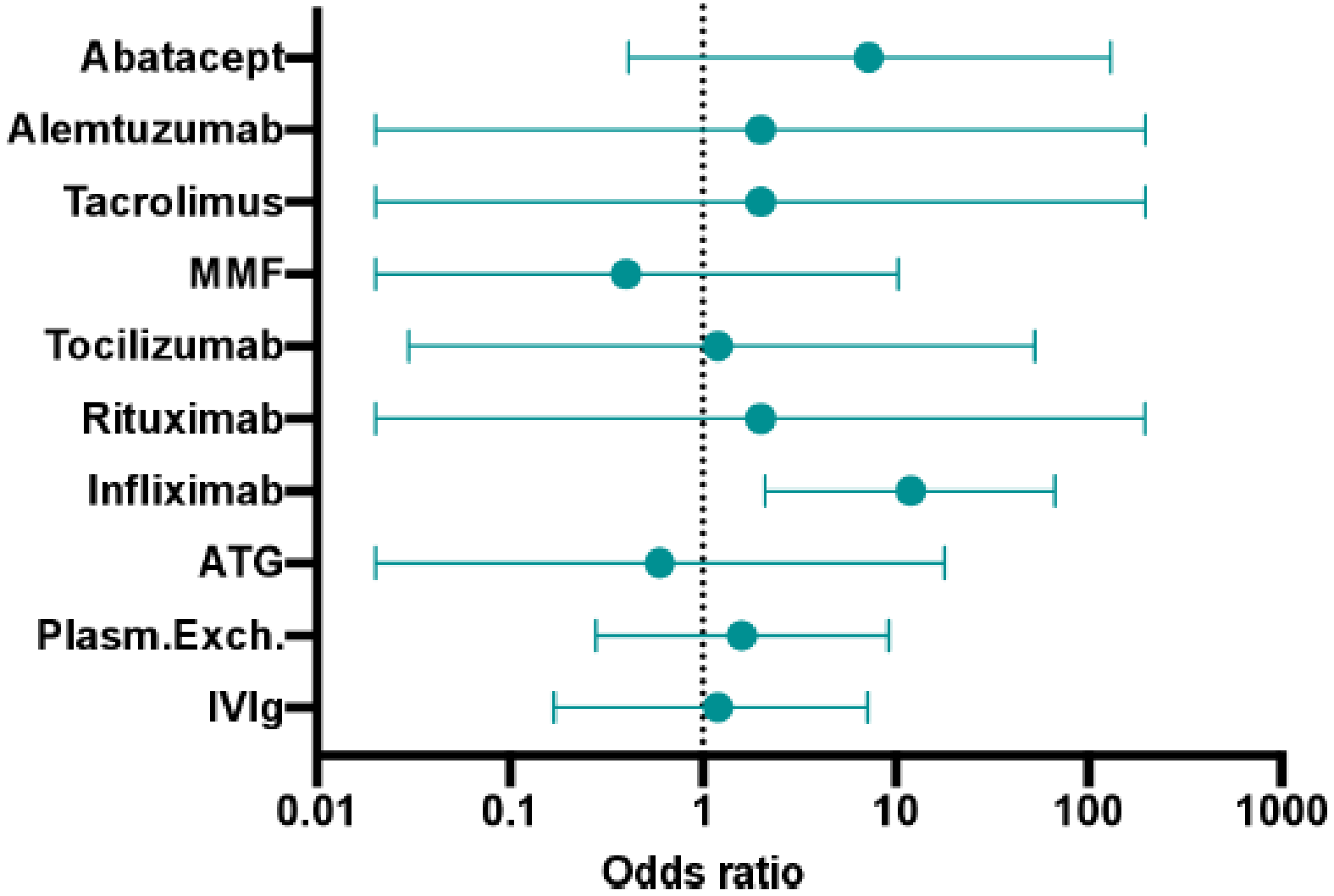
Intensified immunosuppressive therapy in patients with immune checkpoint inhibitor-induced myocarditis
Death from cardiovascular cause



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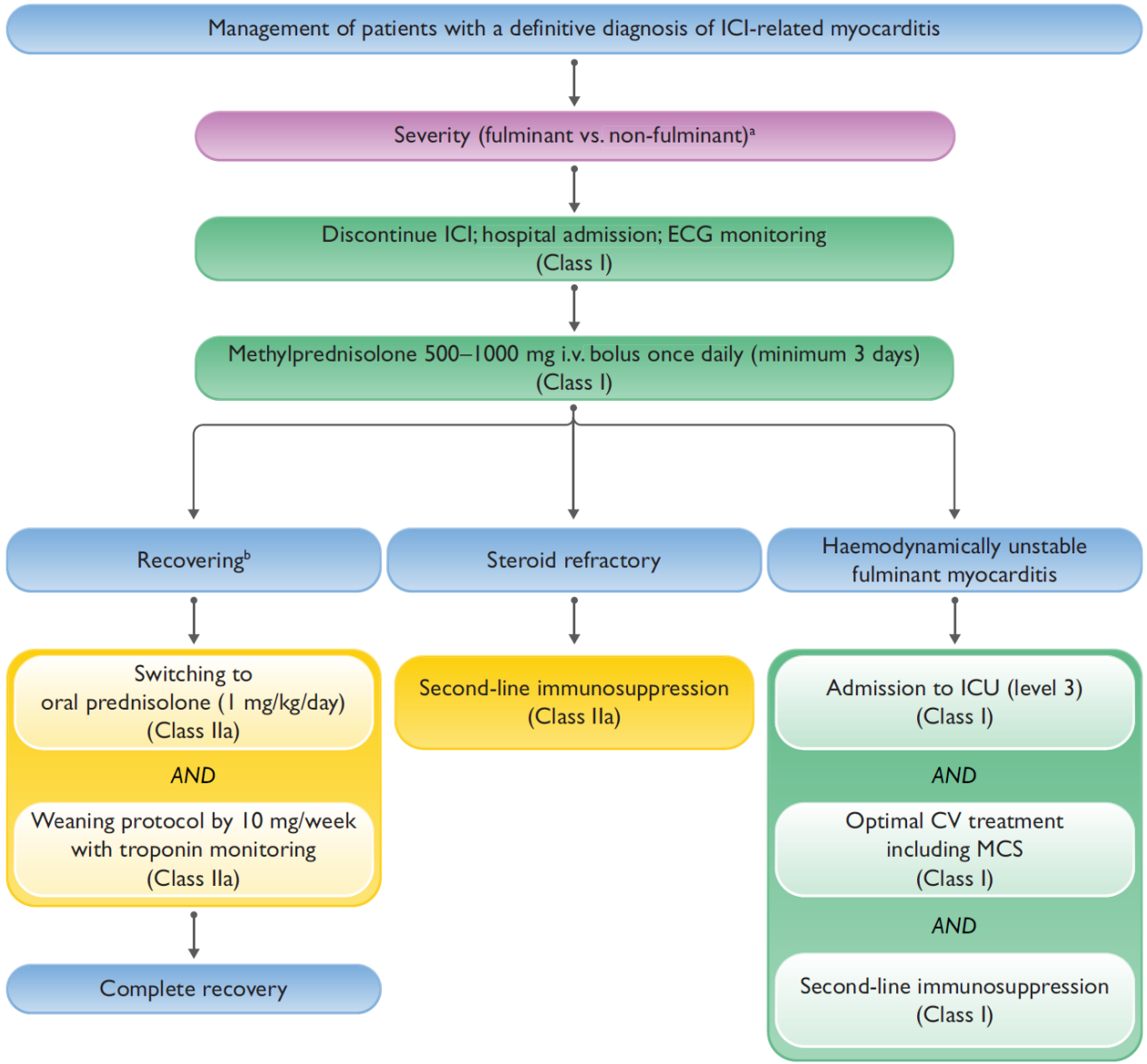
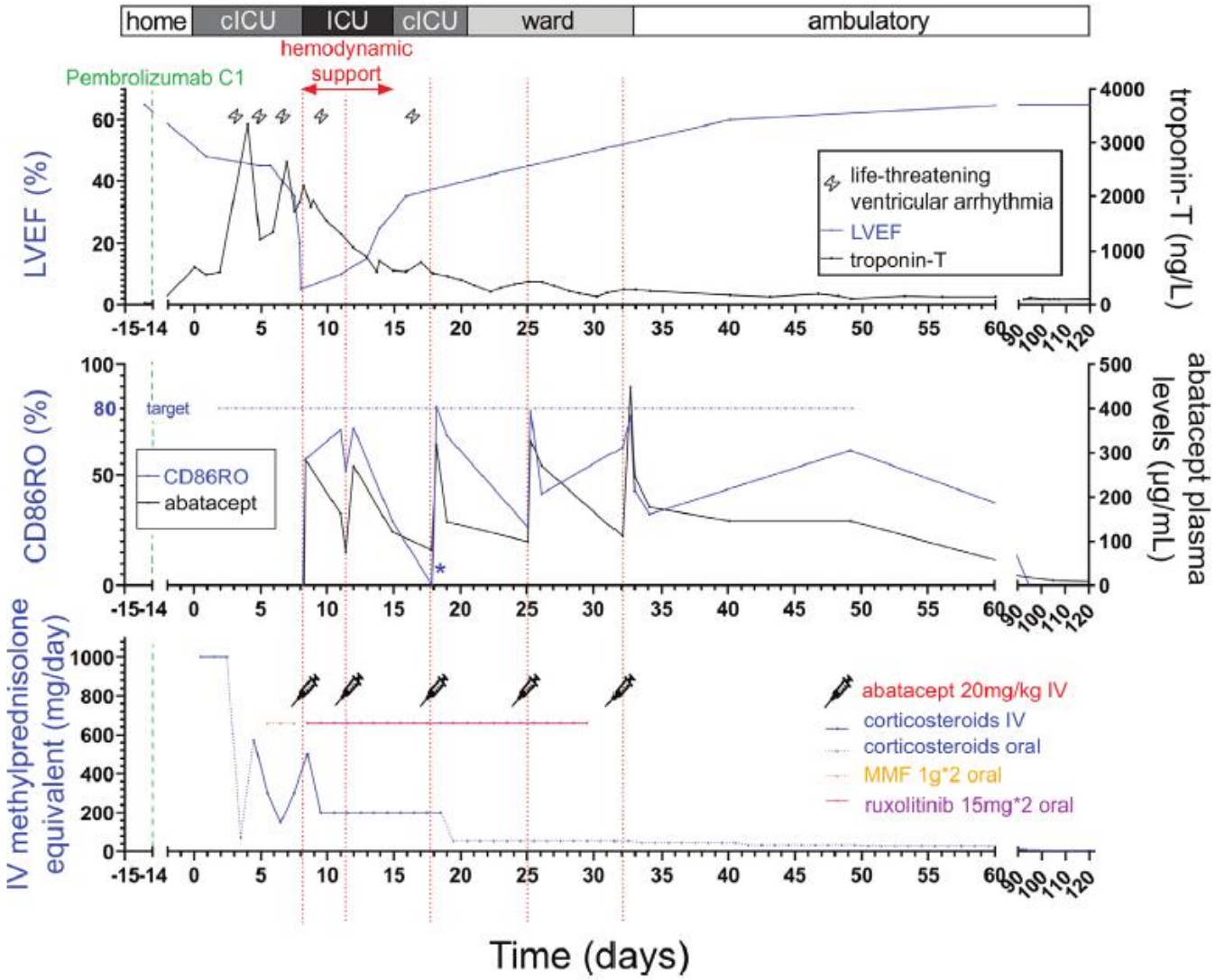
Management of patients with a definitive diagnosis of ICI-related myocarditis

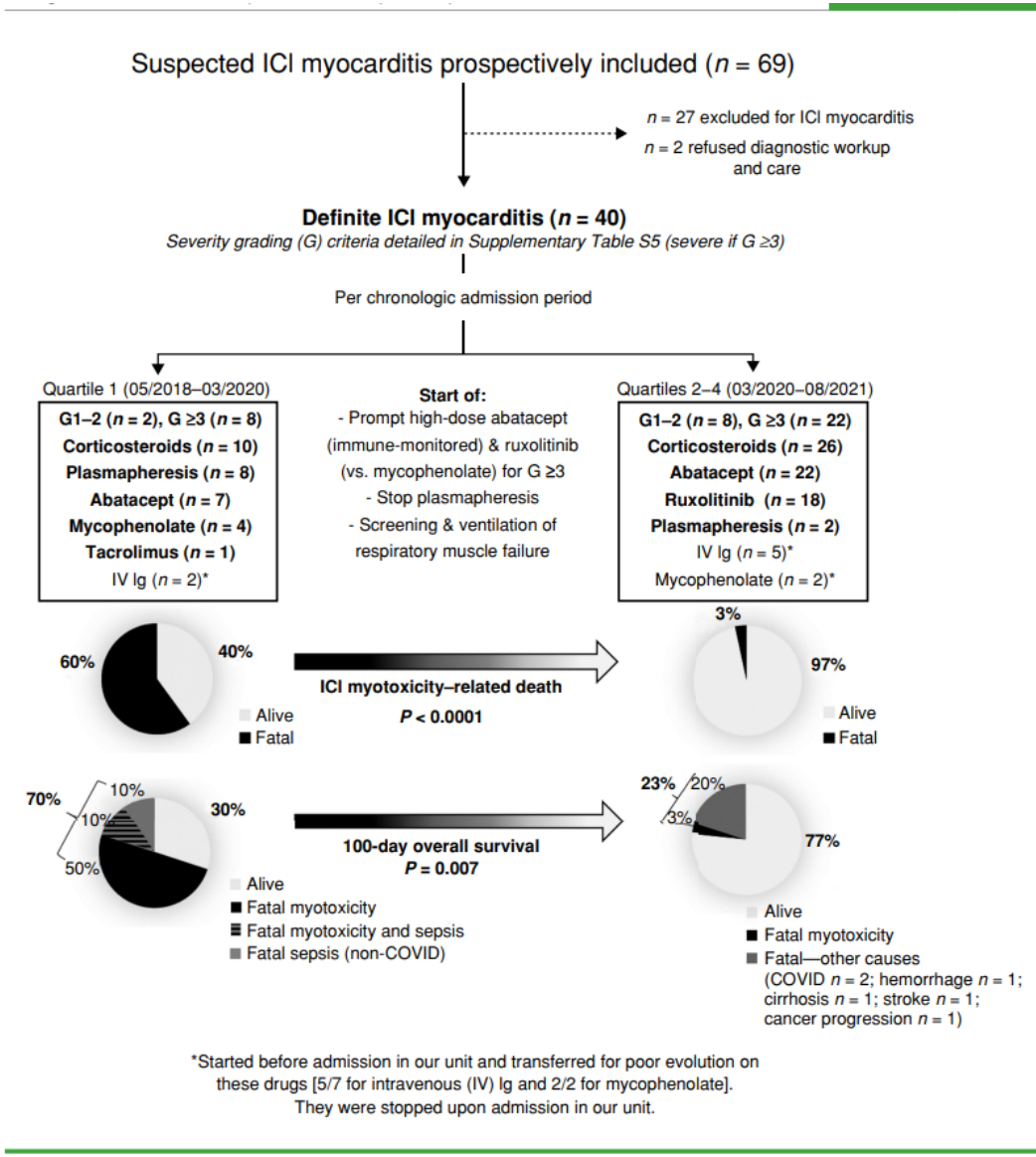


Reversal of immune-checkpoint inhibitor fulminant myocarditis using personalized-dose-adjusted abatacept and ruxolitinib: proof of concept



Nguyen LS,. *J Immunother Cancer*. 2022;10(4):e004699.

Abatacept/Ruxolitinib and Screening for Concomitant Respiratory Muscle Failure to Mitigate Fatality of Immune-Checkpoint Inhibitor Myocarditis.



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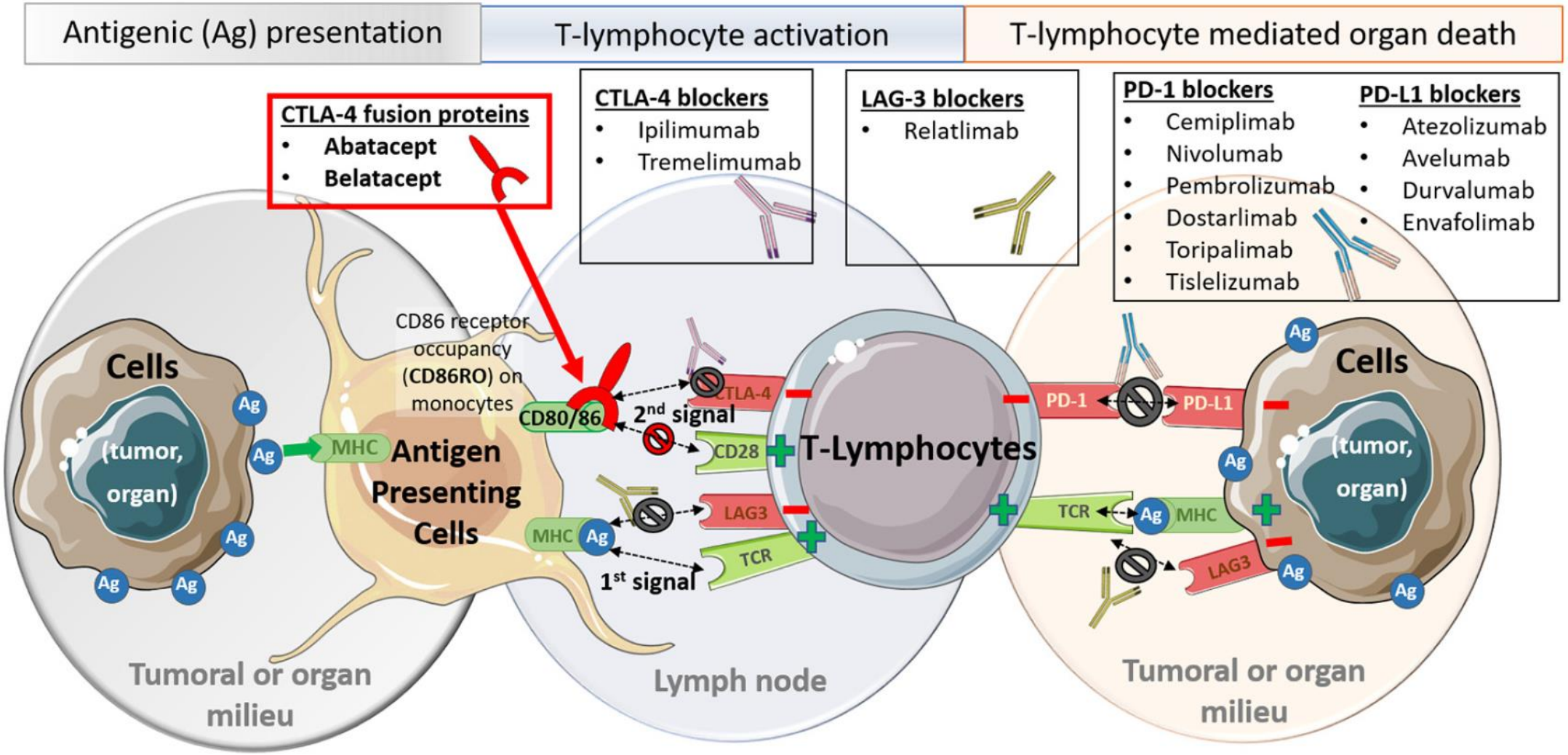
Immune Checkpoint Inhibitor Myocarditis Treatment Strategies and Future Directions.



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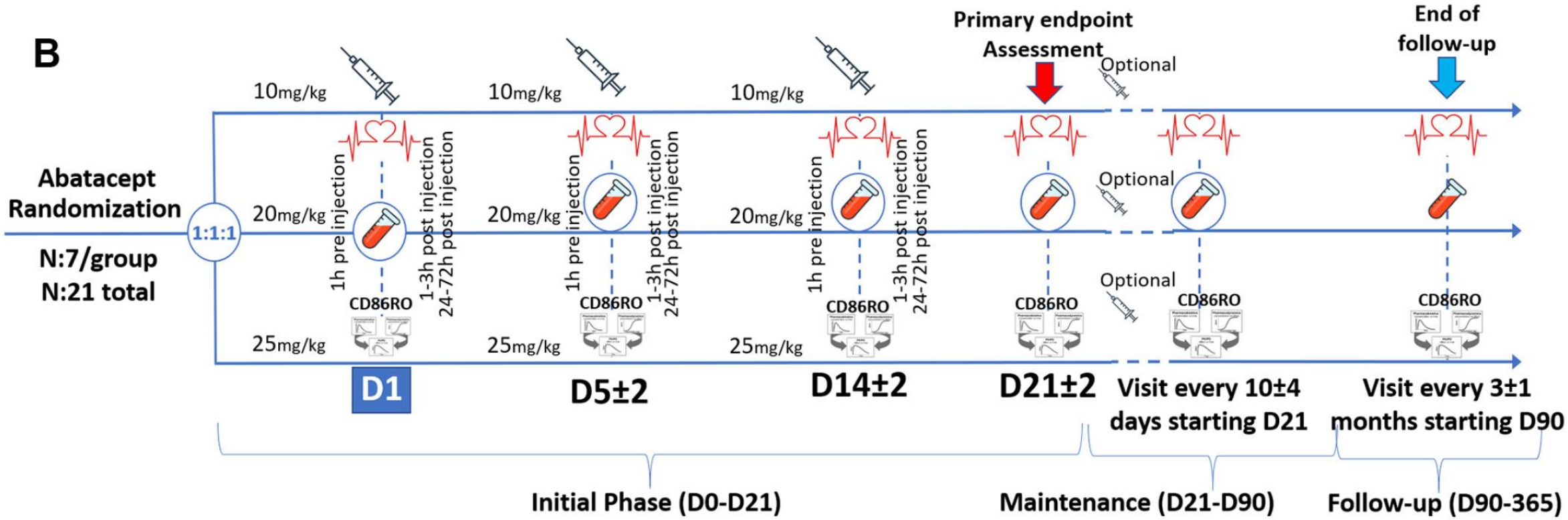
Immune Checkpoint Inhibitor Myocarditis Treatment Strategies and Future Directions.



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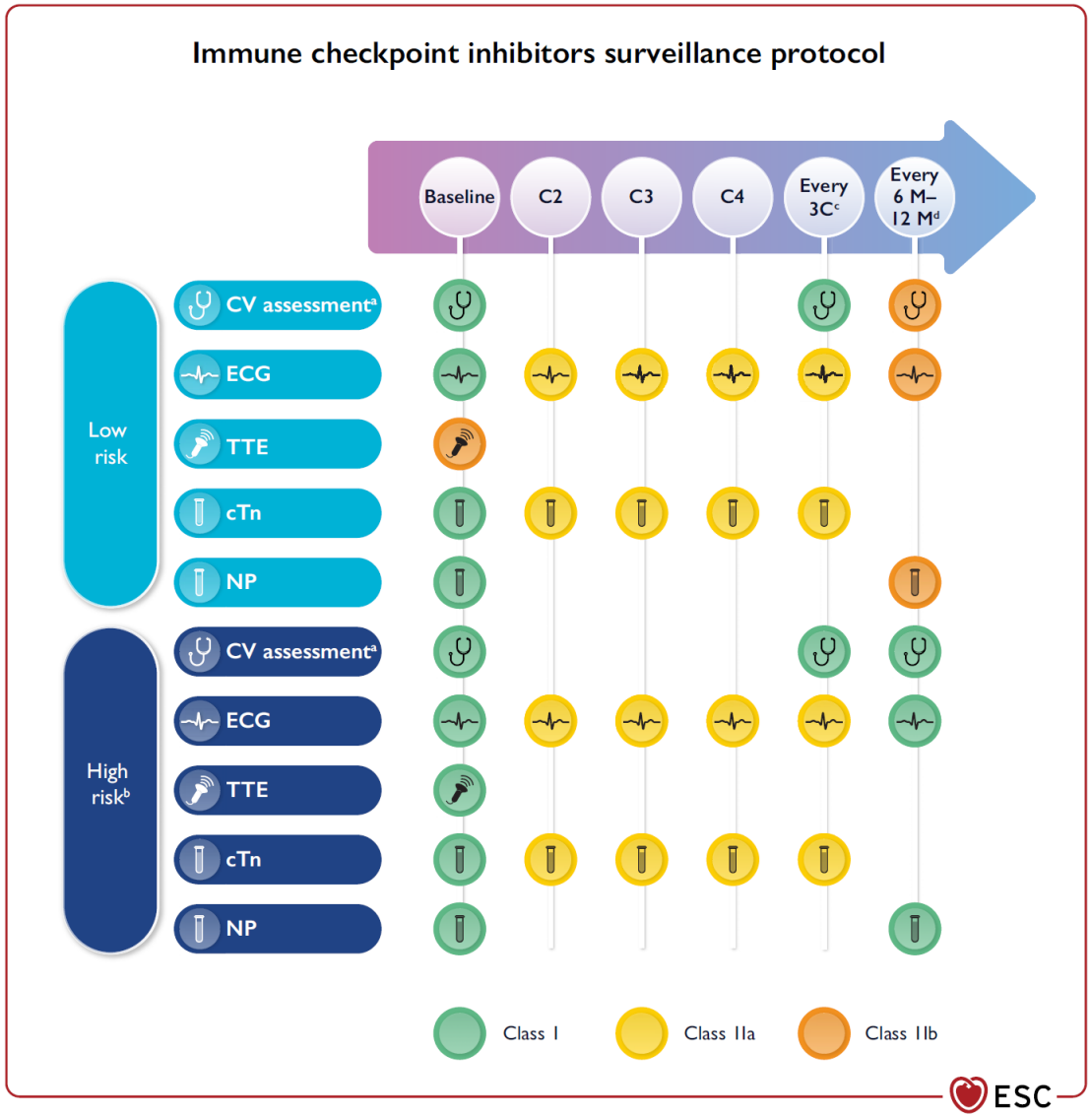
Immune checkpoint inhibitors surveillance protocol



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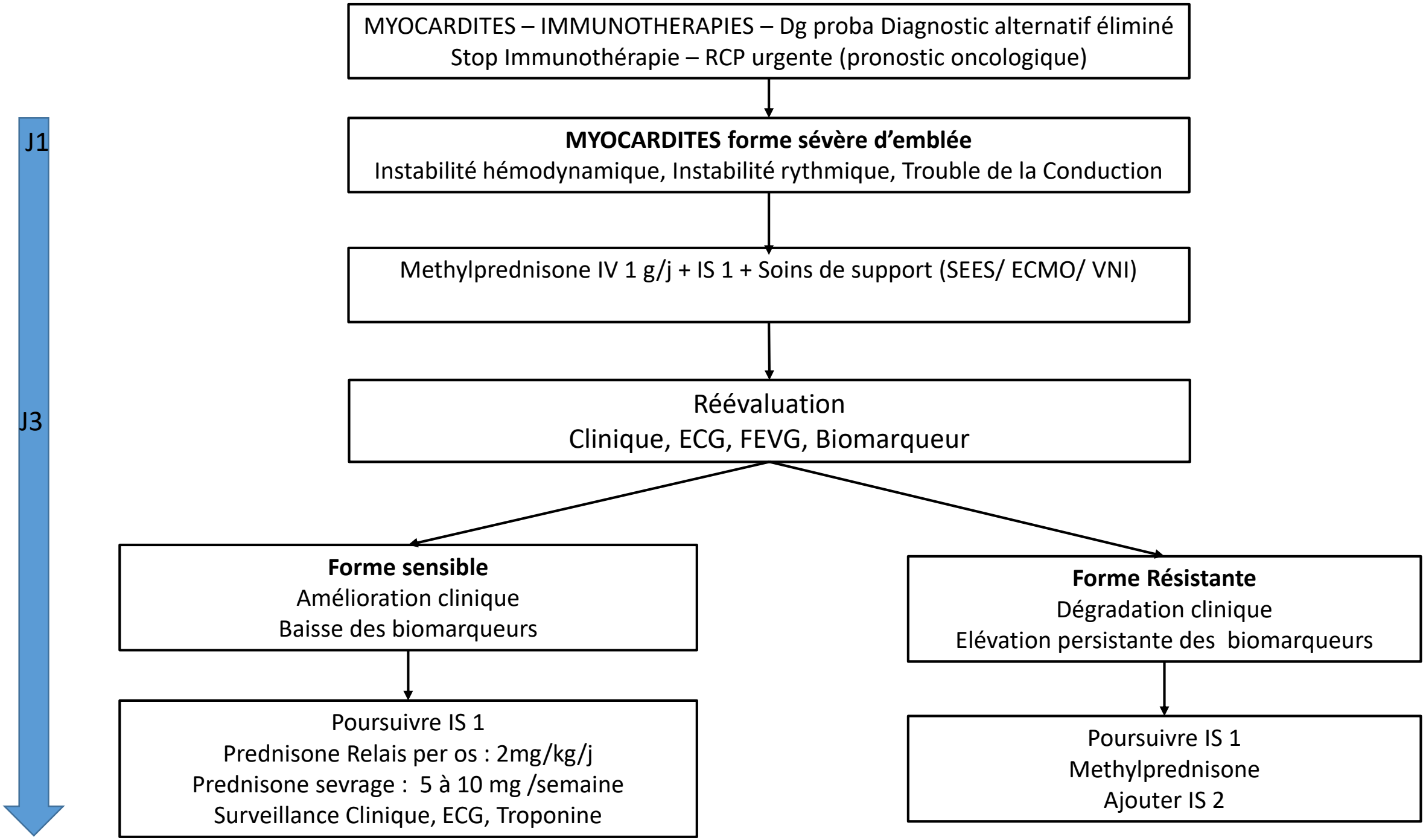
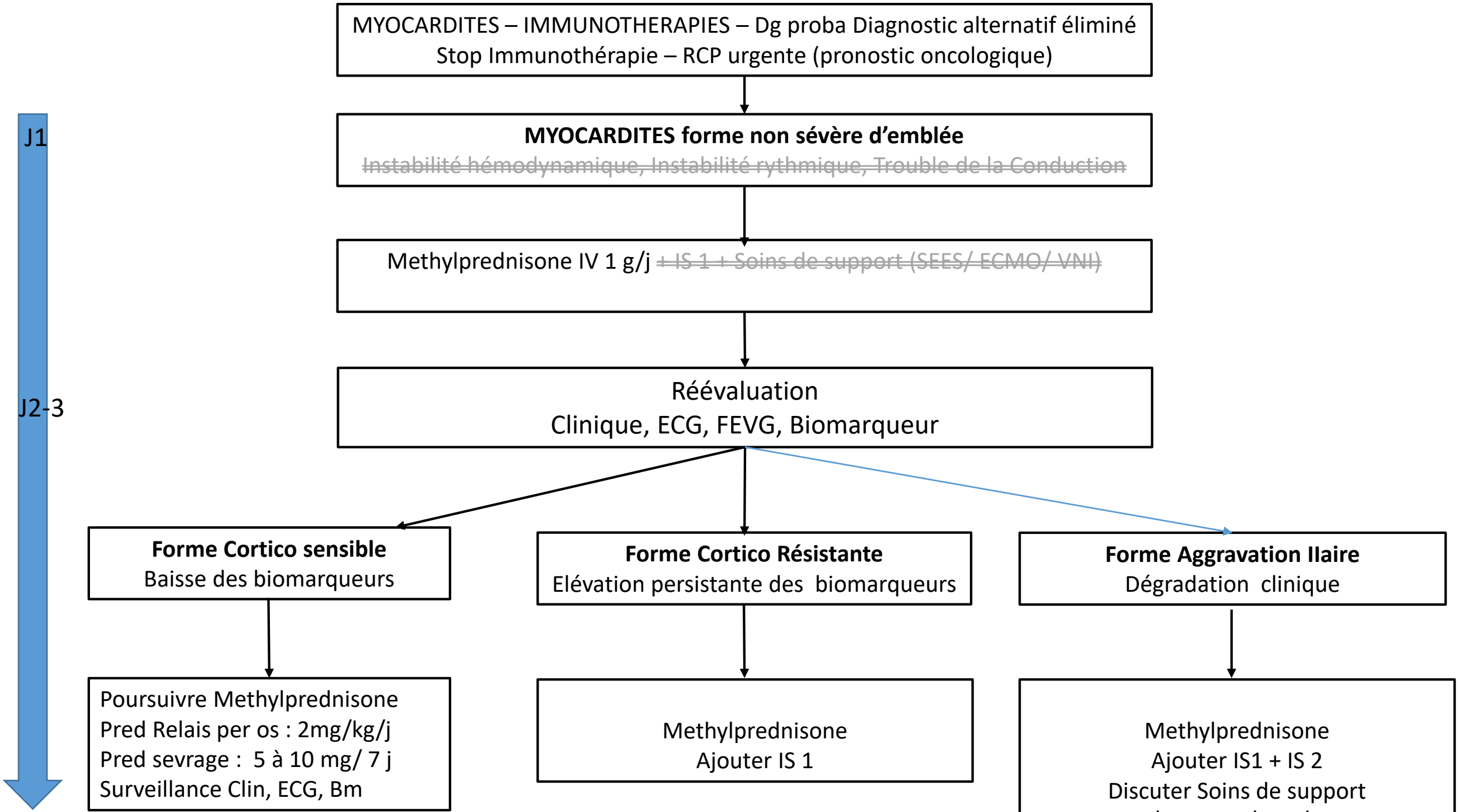
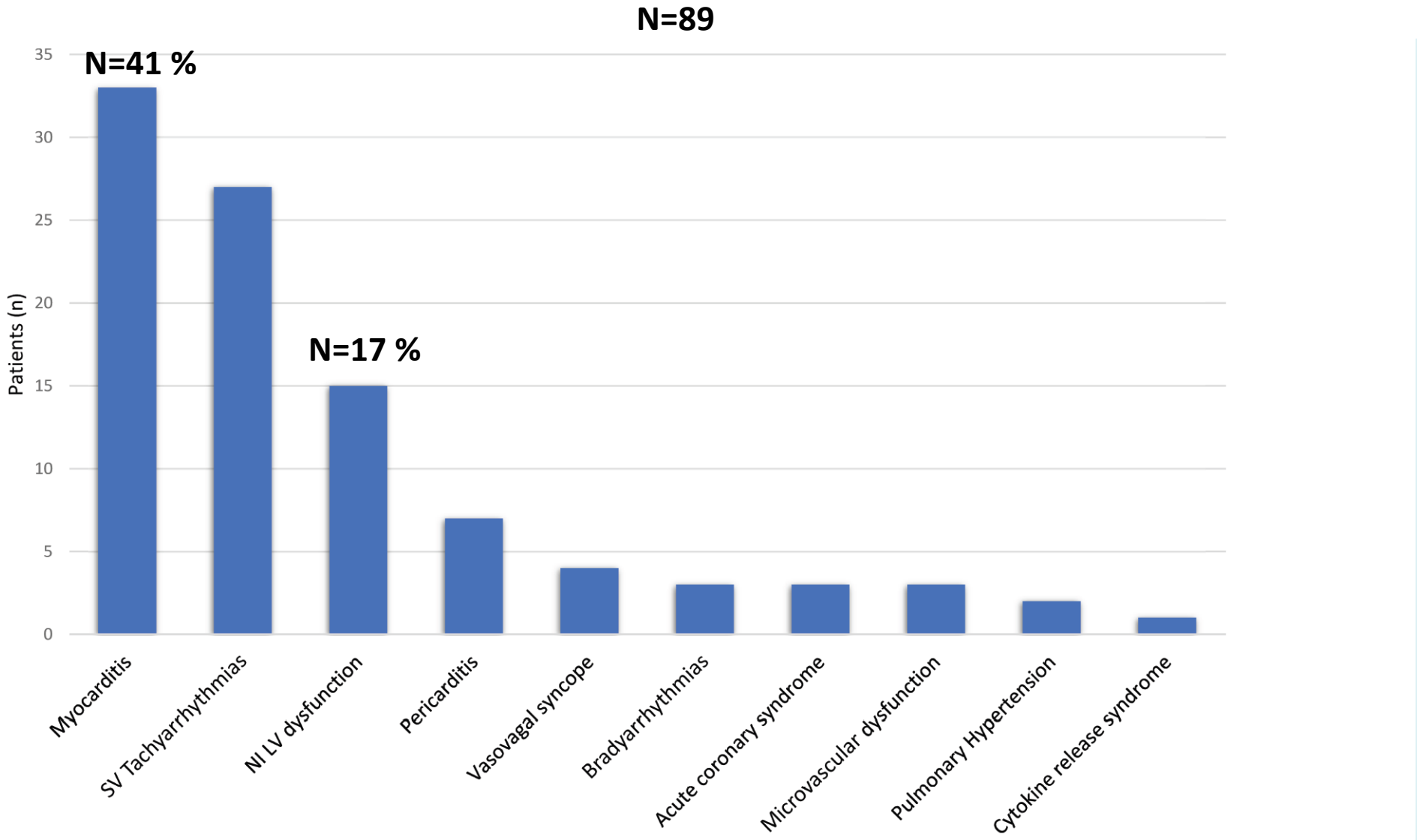

MYOCARDITES – IMMUNOTHERAPIES – Dg proba Diagnostic alternatif éliminé
Stop Immunothérapie – RCP urgente (pronostic oncologique)
J1
MYOCARDITES forme sévère d'emblée
Instabilité hémodynamique, Instabilité rythmique, Trouble de la Conduction
Methylprednisone IV 1 g/j + IS 1 + Soins de support (SEES/ ECMO/ VNI)
J3
Réévaluation
Clinique, ECG, FEVG, Biomarqueur
Forme sensible
Amélioration clinique
Baisse des biomarqueurs
Forme Résistante
Dégradation clinique
Elévation persistante des biomarqueurs
Poursuivre IS 1
Prednisone Relais per os : 2mg/kg/j
Prednisone sevrage : 5 à 10 mg /semaine
Surveillance Clinique, ECG, Troponine
Poursuivre IS 1
Methylprednisone
Ajouter IS 2


MYOCARDITES – IMMUNOTHERAPIES – Dg proba Diagnostic alternatif éliminé
Stop Immunothérapie – RCP urgente (pronostic oncologique)
J1
MYOCARDITES forme non sévère d'emblée
Instabilité hémodynamique, Instabilité rythmique, Trouble de la Conduction
Methylprednisone IV 1 g/j + IS 1 + Soins de support (SEES/ ECMO/ VNI)
J2-3
Réévaluation
Clinique, ECG, FEVG, Biomarqueur
Forme Cortico sensible
Baisse des biomarqueurs
Forme Cortico Résistante
Elévation persistante des biomarqueurs
Forme Aggravation Ilaire
Dégradation clinique
Poursuivre Methylprednisone
Pred Relais per os : 2mg/kg/j
Pred sevrage : 5 à 10 mg/ 7 j
Surveillance Clin, ECG, Bm
Methylprednisone
Ajouter IS 1
Methylprednisone
Ajouter IS1 + IS 2
Discuter Soins de support
SEES/Inotrope/ VNI/ECMO

Incidence of cardiovascular adverse events in patients with immune checkpoint inhibitors



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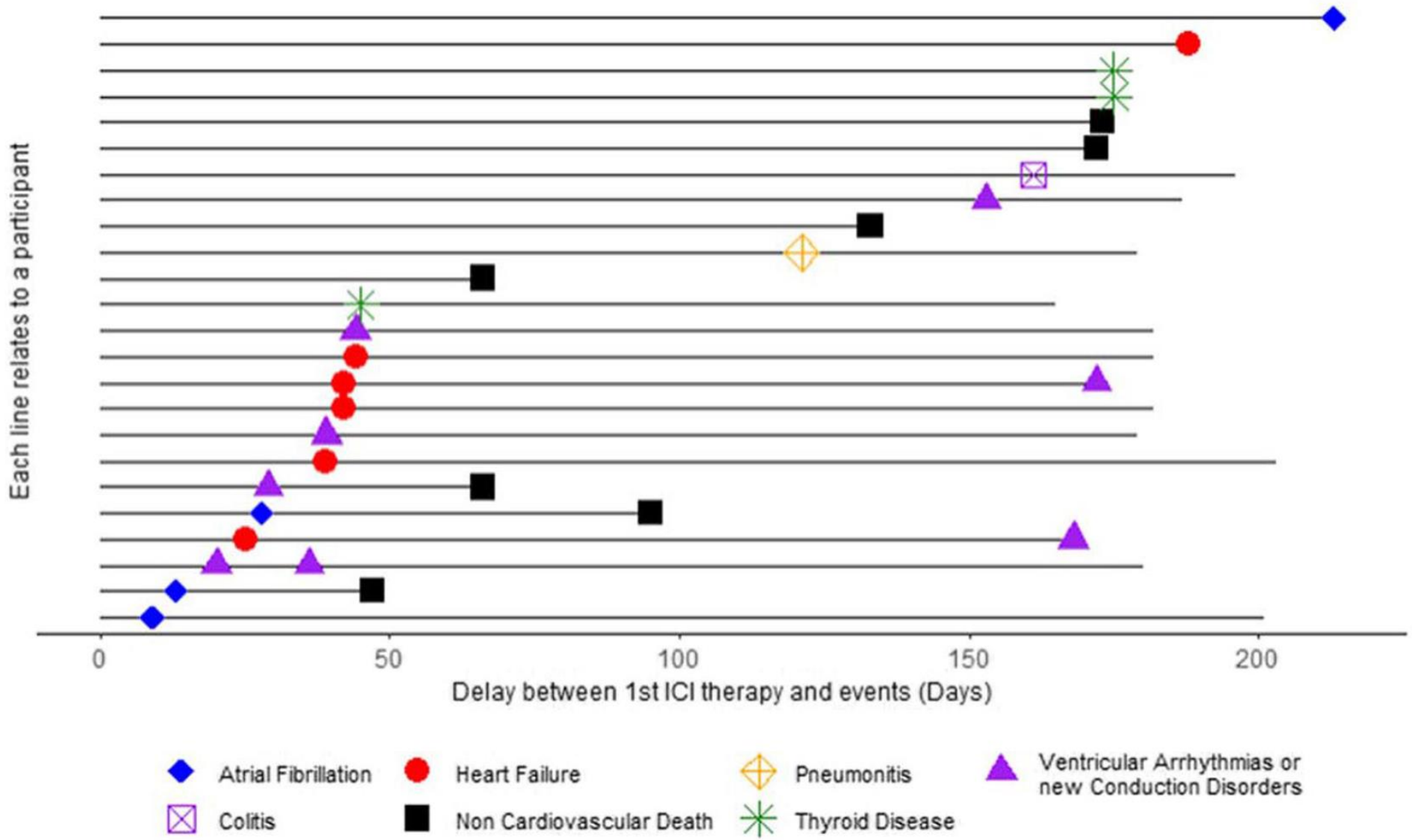
Adverse myocardial and vascular side effects of immune checkpoint inhibitors : A prospective multimodal cardiovascular assessment.



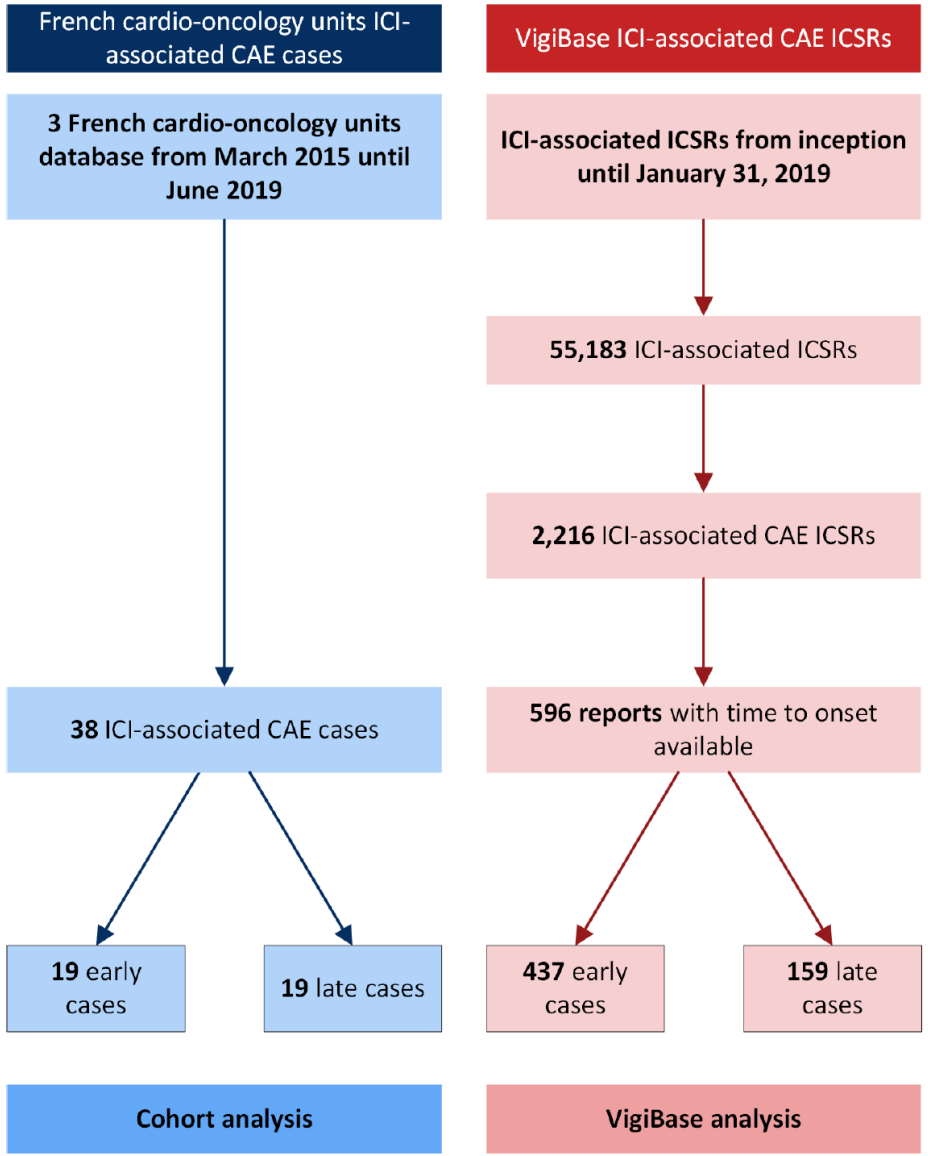
Mirabel M. Clin Res Cardiol. 2024 Aug;113(8):1263-1273.

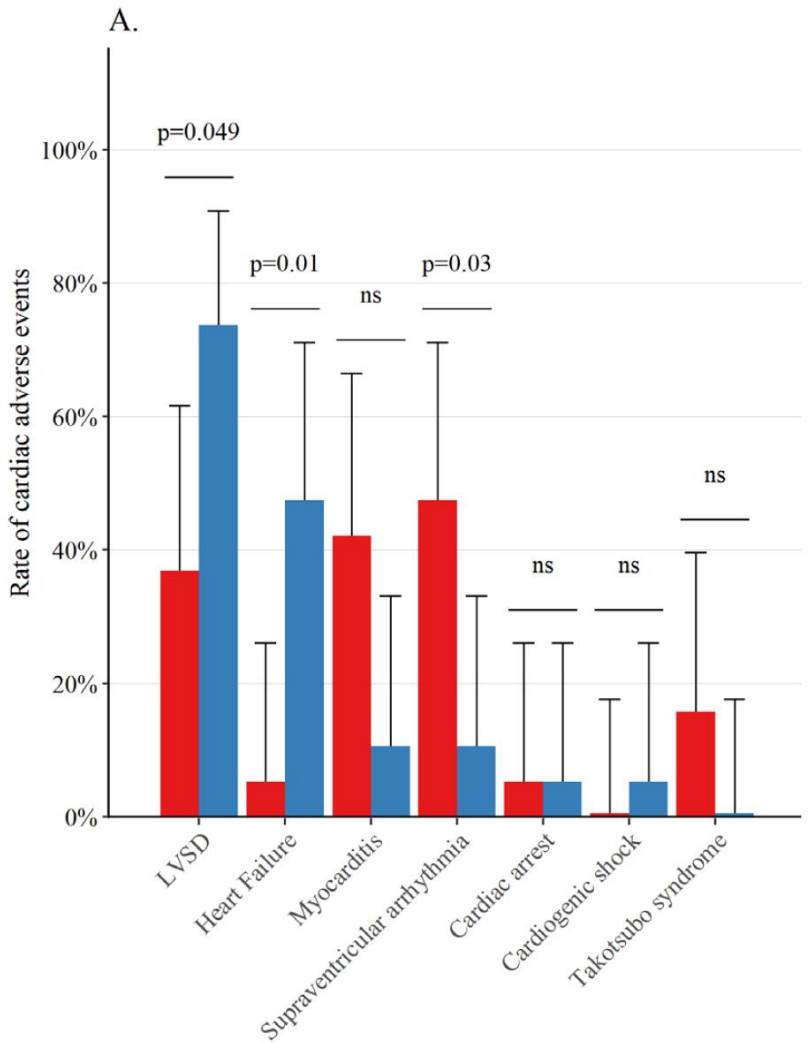
Adverse myocardial and vascular side effects of immune checkpoint inhibitors: a prospective multimodal cardiovascular assessment.
Multivariate competitive risk analysis of predictors of HF at 6 weeks of initiation of ICIs

Variable	Heart failure $N=5$	No Heart failure $N=40$	Other CV event $N=4$	SHR (CI)	P value
Male, N (%)	5 (13.16)	30 (78.95)	3 (7.89)	1.49 [0.86–2.59]	0.153
Age, mean (SD)	63.8 (10.23)	64.33 (11.36)	65.25 (11.32)	1.00 [0.98–1.02]	0.882
Body mass index, mean (SD)	26.08 (4.94)	24.25 (5.22)	30.23 (7.74)	0.96 [0.92–1.01]	0.116
Right ventricular ejection fraction on cMRI, mean (SD)	47.8 (5.07)	54.18 (7.06)	50.75 (6.7)	1.03 [0.99–1.07]	0.098
Serum creatinine micromol/L, mean (SD)	**105.8 (48.81)**	**83.4 (24.05)**	**95.25 (18.15)**	**0.99 [0.98–1.00]**	**0.006**
Brain natriuretic peptide ng/L, mean (SD)	195.2 (168.86)	69.95 (63.79)	30.75 (23.63)	1.00 [0.99–1.01]	0.720
Ultrasensitive Tropinin Ic ng/L, mean (SD)	11.4 (9.74)	6.72 (8.99)	5.33 (2.52)	0.98 [0.94–1.02]	0.297

Mirabel M. Clin Res Cardiol. 2024 Aug;113(8):1263-1273.

Late cardiac adverse events in patients with cancer treated with immune checkpoint inhibitors





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Conclusion

- **Low Incidence** ≈1 %, **High Fatality Rate** ≈ 50 %
- Need for a **robust and early diagnosis**
- **Diagnosis** based on a combination of :

Clinical presentation, ECG, Tp, CMR and EMB

- **Limitations** of Clinical presentation, ECG, Tp, TTE CMR should be known
- **Central role for EMB** but need for expertise
- **Treatment** : corticosteroid, early intervention , high dose

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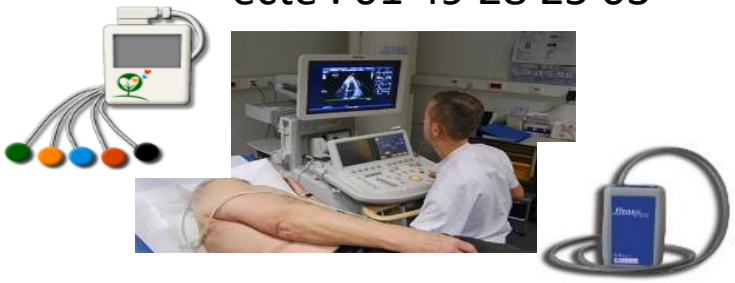
Sur PSL

Sur SAT

Hôpitaux Universitaires Est Parisien

Saint-Antoine • Rothschild

Trousseau La Roche-Guyon • Tenon



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