مرکز آموزشی تحقیقاتی و درمانی قلب و عروق شهید رجایی

How to Monitor Cardiac Complications of Immune Checkpoint Inhibitor Therapy

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Landscape Of Immunotherapy

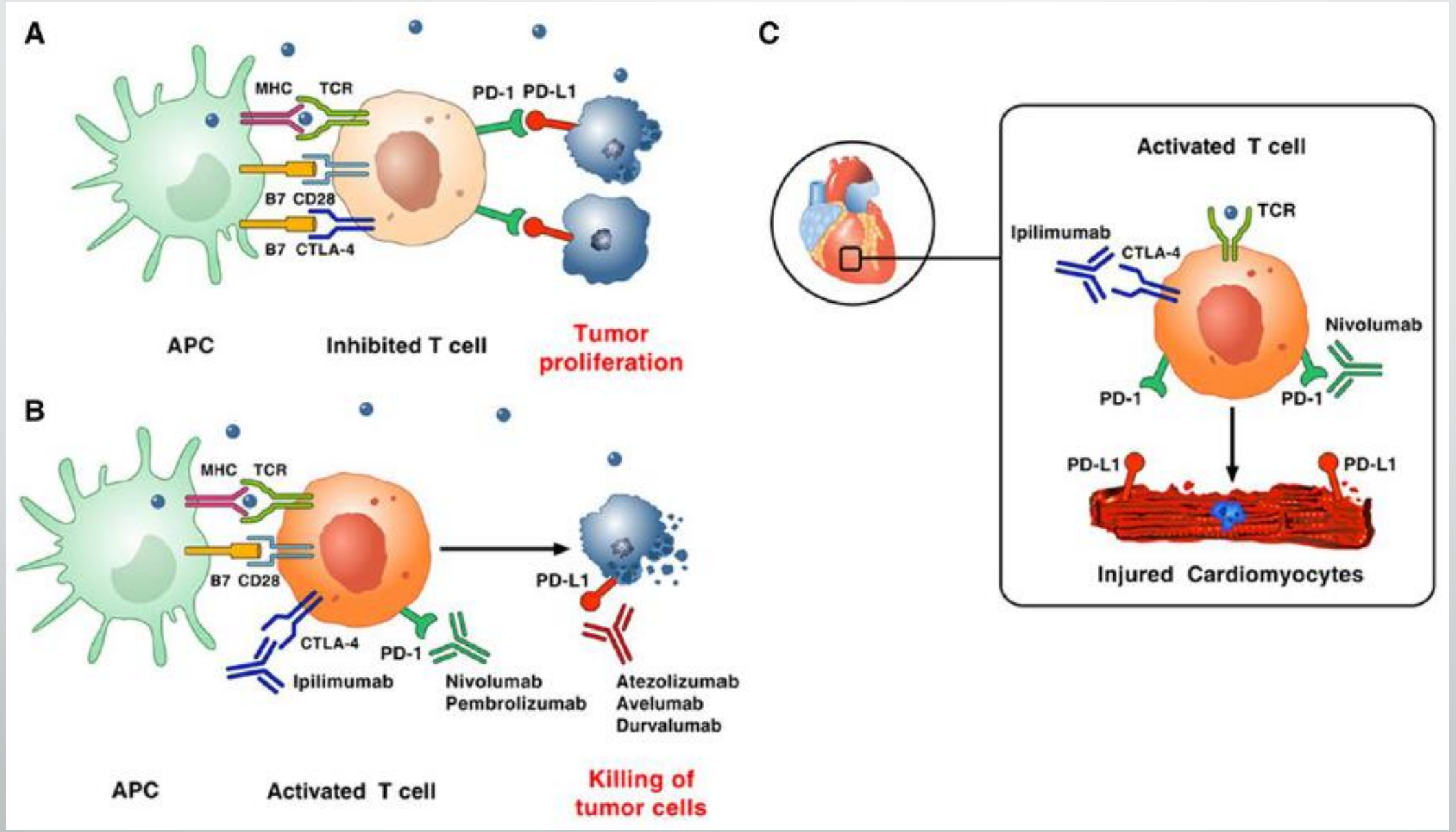
- The landscape of oncology has dramatically changed over the last decade with the advent of immunotherapy.
- Immunotherapy is any type of cancer treatment that leverages the immune system to fight cancer:
  - Cytokines to influence downstream immune cell activity (interferon, interleukin-2)
  - ***Immune checkpoint blockade with monoclonal antibodies to unleash T cell responses***
  - Adoptive cell therapies using components of the immune system to recognize cancer (chimeric antigen receptor–T cell therapy and natural killer cell therapy)
  - Vaccines to elicit immune responses
  - Oncolytic virus therapy (e.g., talimogene laherparepvec) engineered to directly kill the cell
  - Bispecific T cell engagers to link T cells to target antigens

Landscape Of Immunotherapy

- The concept of using the immune system in cancer treatment was first ***introduced by William Coley in the late 19th century*** but did not start to gain traction until more than a half-century later when the concept of immune surveillance of cancers was introduced by ***Thomas and Burnet***.
- The modern era of immune therapy began in 1985 with the first studies of interferon treatment in melanoma with eventual approval in 1995.
- However, after the approval of the ***first immune checkpoint inhibitor*** (ICI) targeting cytotoxic T-lymphocyte associated-antigen-4 (CTLA-4) in ***2011***, and subsequently 2 approvals for agents targeting another immune checkpoint, programmed death receptor-1 (PD-1), in 2014, there has been a ***dramatic change in both the care of patients with cancer (prolongation of progression-free and overall survival) and landscape of cancer clinical trials***.

Mechanism Of Action

- Activation and proliferation of T lymphocytes secondary to antigen exposure usually require ***>1 stimulatory signal***. Interaction between T-cell receptors and the MHC on APCs causes T-cell activation.
- Co-stimulatory signal results from the interaction between B7 (CD80) (APCs) and CD28 (T cells). Inhibitory signals constitute interactions between CTLA-4 and B7 (CD80), and PD1 and PDL 1 or 2.
- ***Cancer exploits these pathways to escape from immune surveillance***. Many tumor cells overexpress the programmed death-ligand 1 (PD-L1), which binds to inhibitory receptors expressed on T lymphocytes, such as CTLA-4 and PD-1.
- The main effect of ICIs, is to break in the immune tolerance of the effector T lymphocytes, thereby potentiating their activity against tumor cells.


A
MHC
TCR
PD-1
PD-L1
B7
CD28
B7
CTLA-4
APC
Inhibited T cell
Tumor proliferation
B
MHC
TCR
B7
CD28
CTLA-4
PD-1
PD-L1
Ipilimumab
Nivolumab
Pembrolizumab
Atezolizumab
Avelumab
Durvalumab
APC
Activated T cell
Killing of tumor cells
C
Activated T cell
TCR
Ipilimumab
CTLA-4
Nivolumab
PD-1
PD-1
PD-L1
PD-L1
Injured Cardiomyocytes

Adverse Events Of ICIs

- Nonspecific activation of the immune system will lead to off-target immune-related adverse events (irAEs) to every organ system.
  - IrAEs are frequent, with clinically detectable ***irAEs in 70% to 90% of patients***.
  - The severity of irAEs is classified as low grade (grades 1 to 2), high grade (grades 3 to 4), and lethal (grade 5) according to the Common Terminology Criteria for Adverse Events, with more ***severe grades (grade 3 to 4) detected in 10% to 15%.***
  - ***These irAEs typically occur within the early phase of therapy (<12 weeks of therapy).***
  - Commonly encountered irAEs include endocrinopathy, hepatitis, colitis, and pneumonitis.

Adverse Events Of ICIs

- Briefly, there are ***several suggested potential mechanisms*** explaining the pathophysiology of irAEs:
  - Checkpoint blockade causes pre-existing tolerated self-reactive T cells to become deregulated in the periphery.
  - There is cross-reactivity between the target of an individual patient's antitumor immune response and normal tissues which share an epitope.
  - It is postulated that T cell receptors target a different but homologous muscle antigen as the tumor antigen such as troponin.

Cardiovascular Adverse Events Of ICIs

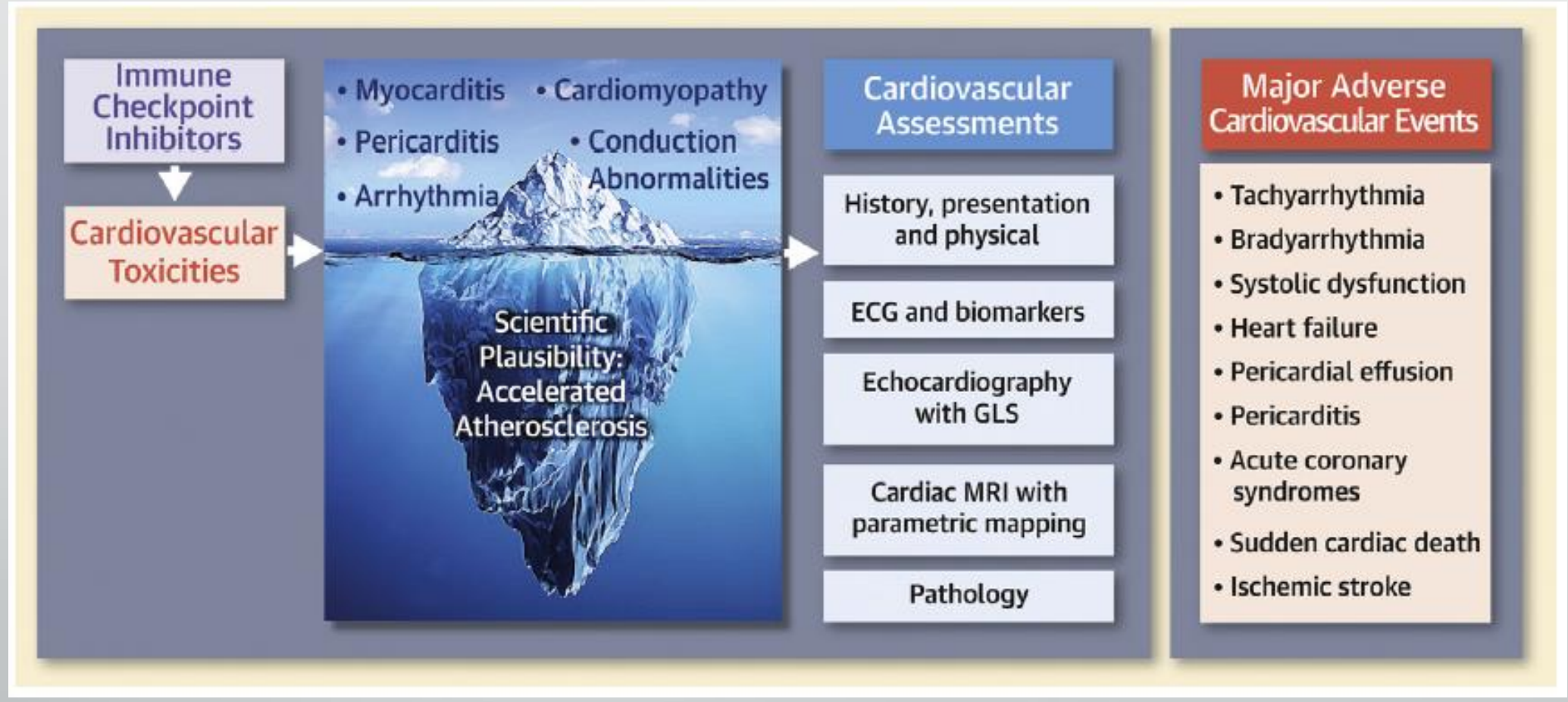
- ***CVAEs, are rare and range from myocarditis {the most commonly (45%)}*** and resultant heart failure to potentially serious arrhythmias, as well as ***pericarditis***, ***takotsubo syndrome, acute coronary syndrome (ACS), and vasculitis***.
- ***The overall incidence of left ventricular dysfunction with ICIs is lower compared with other chemotherapies.***
- ***Myocarditis*** has drawn most attention, for two reasons:
  - ICI-related myocarditis has an ***ominous prognosis***, since it may result in life-threatening heart failure or arrhythmias, sometimes with a fulminant course (approaching 50% mortality).
  - The risk of ICI-related myocarditis ***requires specific clinical surveillance***, unlike other CV irAEs.

Cardiovascular Adverse Events Of ICIs

Incidence of ADRs as reported within the VigiAccess/VigiBase from the World Health Organization global database for ADRs.

Drug	Total ADRs, *n*	Cardiac ADRs, *n* (%)	Proportion of cardiac ADRs			
			Myocarditis, *n* (%)	Pericardial disease, *n* (%)	Conduction abnormalities, *n* (%)	Stress cardiomyopathy, *n* (%)
Pembrolizumab	25,028	497 (1.99)	80 (16.10)	80 (16.10)	34 (6.84)	5 (1.00)
Nivolumab	49,506	1103 (2.23)	148 (13.40)	155 (14.10)	71 (6.44)	6 (0.54)
Atezolizumab	3627	94 (2.59)	10 (10.60)	16 (17.00)	6 (6.38)	1 (1.06)
Avelumab	505	16 (3.17)	4 (25.00)	2 (12.50)	2 (12.50)	0 (0.00)
Durvalumab	1329	34 (2.56)	4 (11.80)	7 (11.80)	0 (0.00)	0 (0.00)
Ipilimumab	26,030	471 (1.81)	69 (14.60)	42 (8.92)	39 (8.28)	4 (0.85)
Total	106,025	2215 (2.09)	312 (14.10)	302 (13.60)	152 (6.86)	16 (0.72)

ADR: adverse drug reactions.


Immune Checkpoint Inhibitors
Cardiovascular Toxicities
• Myocarditis
• Cardiomyopathy
• Pericarditis
• Conduction Abnormalities
• Arrhythmia
Scientific Plausibility: Accelerated Atherosclerosis
Cardiovascular Assessments
History, presentation and physical
ECG and biomarkers
Echocardiography with GLS
Cardiac MRI with parametric mapping
Pathology
Major Adverse Cardiovascular Events
• Tachyarrhythmia
• Bradyarrhythmia
• Systolic dysfunction
• Heart failure
• Pericardial effusion
• Pericarditis
• Acute coronary syndromes
• Sudden cardiac death
• Ischemic stroke

Why Monitoring Patients Treated With ICIs

- Though only a few cases of severe myocarditis were reported in clinical trials of ICIs, subsequent observations suggest a significantly higher incidence, from 0.04% up to 1.14%.
- It may be flawed by reporting bias (i.e., ***only the most severe cases were described***), whereas asymptomatic or mildly symptomatic forms may have gone unidentified or unreported.
- Hence, CV monitoring of patients receiving ICI therapy should not merely seek to diagnose overt cases of myocarditis; rather, its aim should be ***to recognize subclinical or asymptomatic cases, in order to avoid their progression.***

How to Manage ICIs-Related Myocarditis

- The median time to onset of myocarditis is 17 to 34 days, although it may develop soon after administration of the first dose of ICI.
- ***Patients are usually diagnosed by the finding of an elevated cardiac biomarker or a new onset arrhythmia on an ECG.***
- Clinical manifestations may vary; some patients remain asymptomatic, whereas others have dyspnea or severe hypotension due to cardiogenic shock.
- ***The management of ICI-related myocarditis represents a clinical challenge:***
  - ✓ Step 1: Baseline Cardio-Oncology Evaluation
  - ✓ Step 2: Screening Strategies
  - ✓ Step 3: Diagnosis of ICI-Related Myocarditis
  - ✓ Step 4: Management of ICI-Related Myocarditis

Step 1: Baseline Cardio-Oncology Evaluation

- There is no evidence that a pre-existing cardiac condition identifies patients at higher risk for ICI-related myocarditis. however, ***routine baseline cardiology evaluation of all patients scheduled to receive ICIs is both feasible and reasonable.***
- Presenting symptoms, signs, and laboratory data of ICI-related myocarditis can be mild and/or unspecific, and might be attributed to a broad spectrum of CV diseases, including acute and chronic coronary syndromes, left ventricular dysfunction, and arrhythmias.
- ***Collecting baseline clinical, ECG and echocardiography data would allow to recognize any change occurring during ICI therapy, facilitating early diagnosis of ICI-related myocarditis versus other cardiac Disorders.***

Step 2: Screening Strategies

- ***In asymptomatic patients, measurement of cardiac troponins is the strategy most often recommended to screen for ICI-related myocarditis.***
- ***ICI-related myocarditis usually occurs early during treatment and is more common with combination therapy, typically the anti-CTLA4 molecule ipilimumab with an inhibitor of PD-1/PD-L1 interaction (mostly pembrolizumab or nivolumab).***
- Screening is thus usually advised in the first 12 weeks of treatment.
- Since myocarditis may be associated with myositis, it may be reasonable to additionally assess CPK values.

Step 2: Screening Strategies

- ***In case of troponin elevation in the screening setting, ICI therapy must be withhold*** .
- When a diagnosis of myocarditis is reached or the suspicion of myocarditis is strong, the patient should be admitted to a cardiology ward.
- Patients must be asked for symptoms such as chest pain, dizziness, palpitations, and dyspnea, and a ***12-lead ECG*** should be immediately performed.
- ***Troponins (and CPK) should be re-checked*** within 24 h, also measuring ***natriuretic peptides***.
- ***Transthoracic echocardiography*** should be performed within 24–48 h unless clinical instability requires urgent execution.

Step 2: Screening Strategies

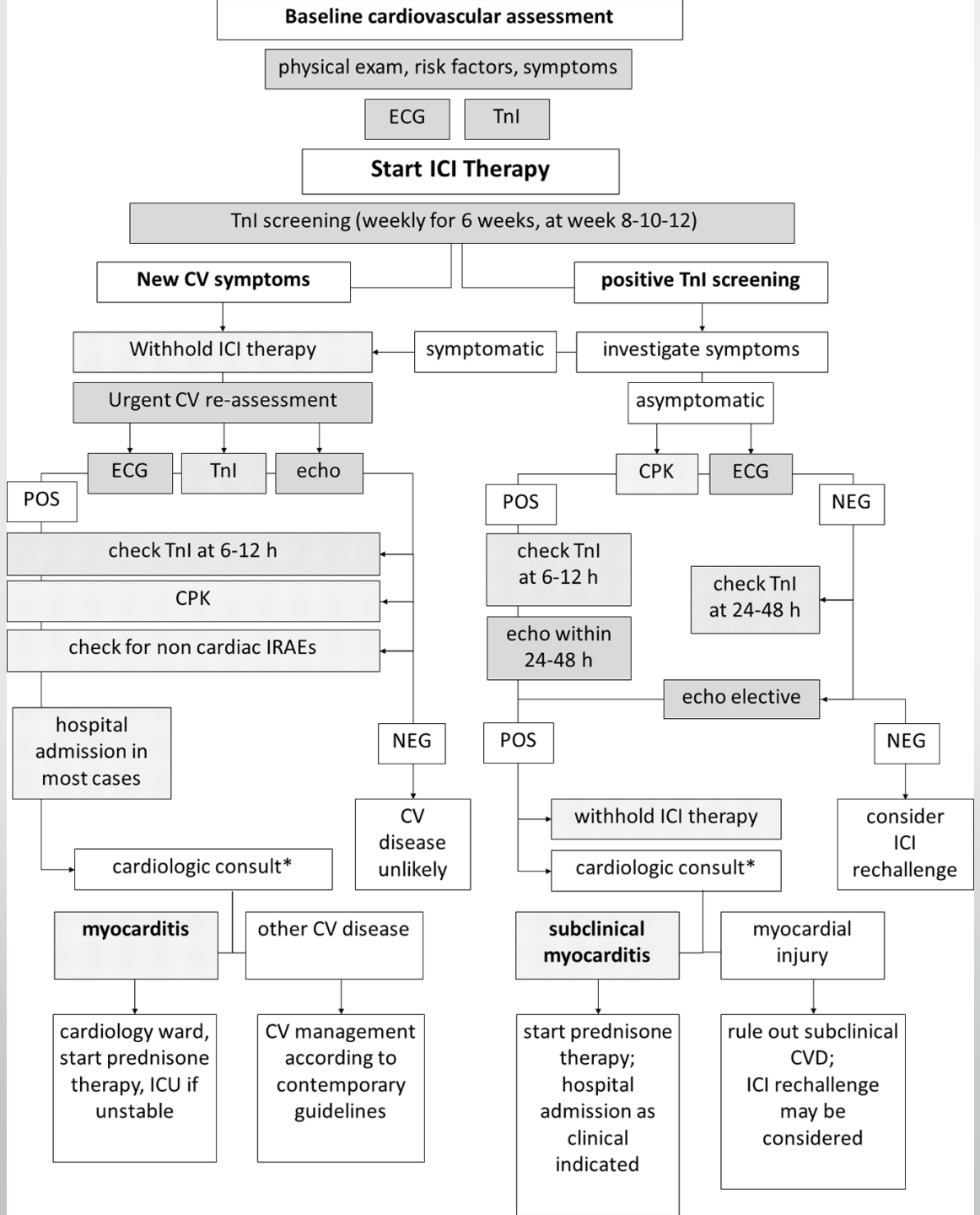
- Troponin leakage in itself is not specific and represents myocardial injury, which may be related to acute coronary syndromes (acute coronary artery plaque event), type 2 myocardial infarction (mismatch in oxygen demand/supply due to, among other causes, anemia or tachyarrhythmia with or without stable coronary lesions), myocarditis, cardiomyopathy, heart failure.
- ***Patients with known CV disease, CV risk factors, or severe clinical conditions are more likely to show troponin abnormalities that might not directly depend on ICIs therapy.***
- In contrast, patients with neither history of CV diseases nor experiencing stressors such as fever, anemia, oxygen desaturation, or tachycardia should raise suspicion, especially in case of persistent troponins elevation.

Step 2: Screening Strategies

- These considerations, finally, ***highlight the potential benefit of a careful baseline cardiac evaluation.*** For instance, during the screening phase with troponins in lung cancer patients receiving ICIs, troponins may be elevated in a significant proportion of patients.
- The entity of this increase is minimal in most cases, just above the upper limit of normal, in a pattern resembling that of chronic heart failure, in particular in patients with known cardiac disorders or with a severely frail state and progression of cancer.

Step 2: Screening Strategies

- ***Importantly, is often necessary to repeat ECG, echocardiography, troponins, and physical examination, as a fundamental aspect is the dynamics of their changes.***
  - ***A slow and relatively small, but steady elevation of troponins is consistent with a diagnosis of myocarditis.***
  - In the case of minimal troponin abnormalities, ECG and echocardiography may be normal, and should be repeated after a few days if clinical suspicion and troponins elevation persists.
  - If troponins remain high, with no other identifiable causes, CMR may be useful.
  - If the patient is hemodynamically unstable, immediate admission to an ICU and an aggressive diagnostic and therapeutic workup are mandatory.

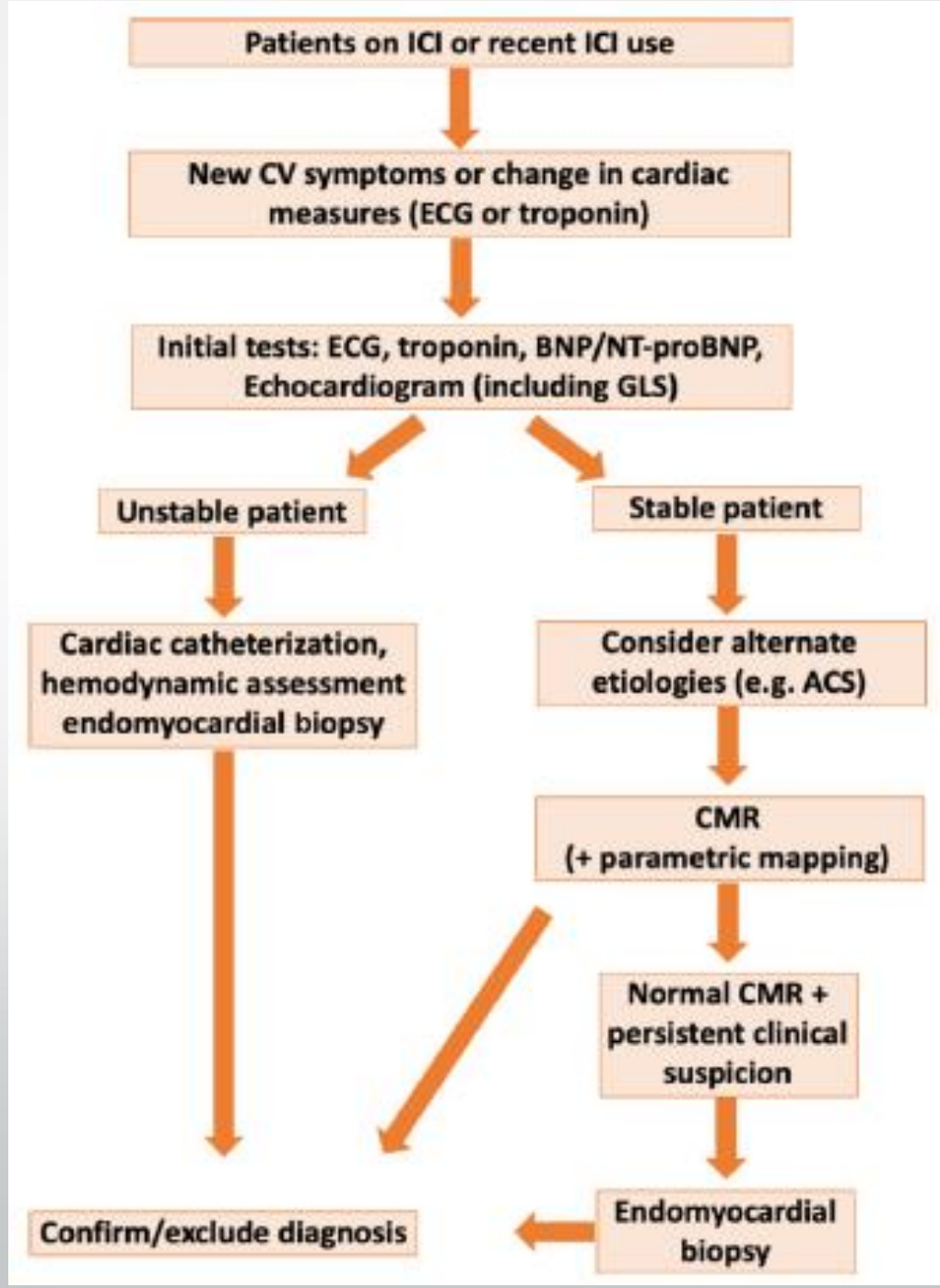

Baseline cardiovascular assessment
physical exam, risk factors, symptoms
ECG
TnI
Start ICI Therapy
TnI screening (weekly for 6 weeks, at week 8-10-12)
New CV symptoms
positive TnI screening
Withhold ICI therapy
symptomatic
investigate symptoms
Urgent CV re-assessment
asymptomatic
ECG
TnI
echo
CPK
ECG
POS
NEG
POS
check TnI at 6-12 h
CPK
check for non cardiac IRAEs
check TnI at 6-12 h
echo within 24-48 h
check TnI at 24-48 h
echo elective
hospital admission in most cases
NEG
POS
NEG
CV disease unlikely
withhold ICI therapy
consider ICI rechallenge
cardiologic consult*
cardiologic consult*
myocarditis
other CV disease
subclinical myocarditis
myocardial injury
cardiology ward, start prednisone therapy, ICU if unstable
CV management according to contemporary guidelines
start prednisone therapy; hospital admission as clinical indicated
rule out subclinical CVD; ICI rechallenge may be considered

Step 3: Diagnosis of ICI-Related Myocarditis

- A diagnostic workup for ICI-related myocarditis starts either in asymptomatic subjects with positive results of troponins screening, as previously discussed, or in symptomatic patients.
- ICI-related myocarditis (and myocarditis in general) may have a various degree of presentation, from indolent and subclinical to life-threatening.
- Symptoms include dyspnea, chest pain, fatigue, palpitations, dizziness, and syncope, resulting from left and/or right ventricular dysfunction, pericardial involvement with or without pericardial effusion, and atrial and/or ventricular brady- or tachyarrhythmias.
- ***The golden rule is to never underestimate these symptoms in the context of therapies with ICIs, considering myocarditis as a real possibility, as it may rapidly escalate to cardiogenic shock.***

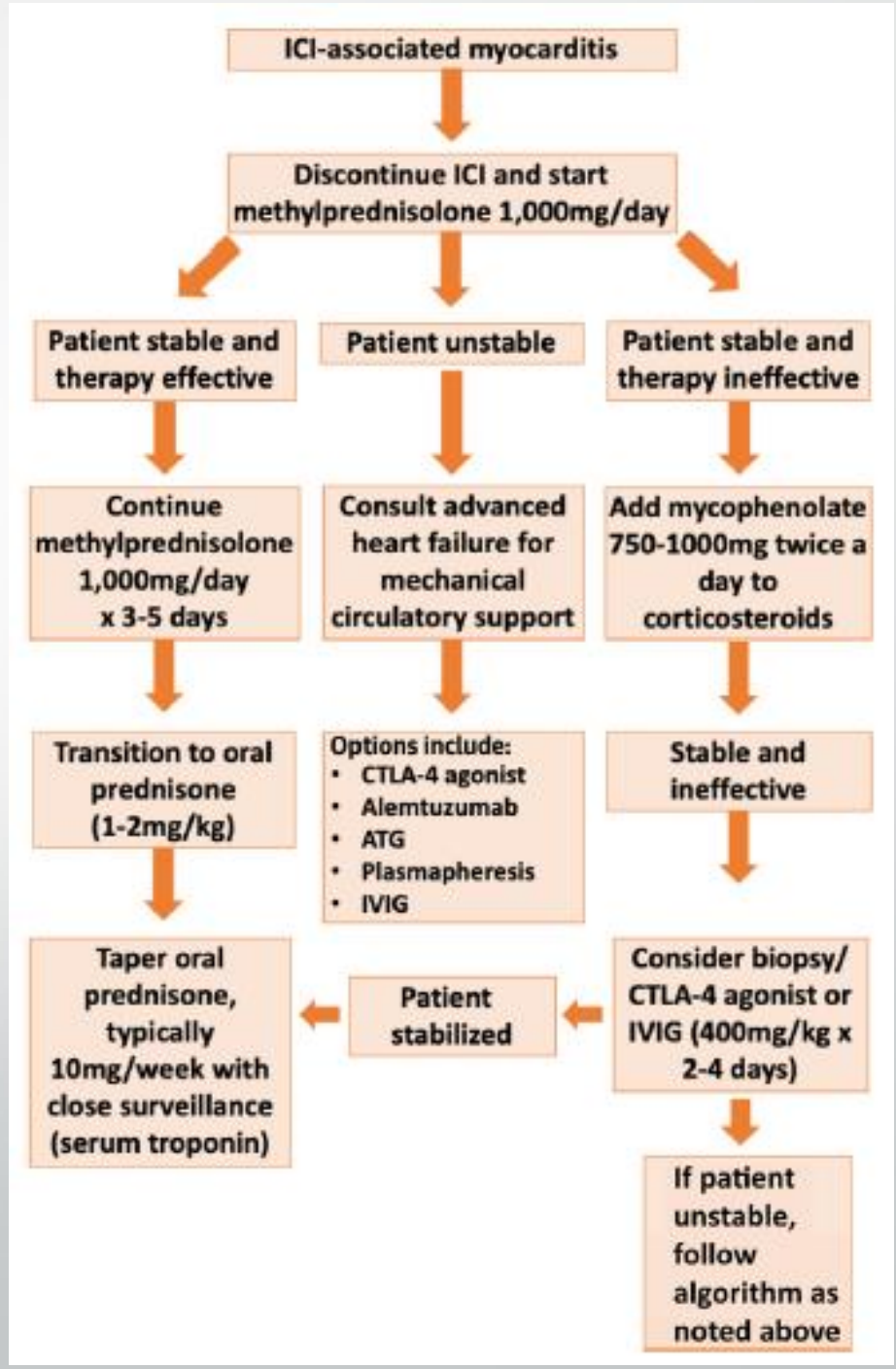
Step 3: Diagnosis of ICI-Related Myocarditis

- When the patient life is deemed safe by appropriate monitoring or hospital admission, CMR and endo-myocardial biopsy is to be considered as per myocarditis clinical guidelines.
- ***EMB is the gold standard for diagnosis of ICI-induced myocarditis***. However, due to its invasive nature and potential for serious complications, ***it should be reserved for patients who do not respond to initial therapy or in cases where the diagnosis is in doubt.***



Step 4: Management of ICI-Related Myocarditis

- Published guidelines for myocarditis suggest ***immunosuppressive therapy only once a viral etiology has been ruled out with endomyocardial biopsy, or when myocarditis is associated with known (non-cardiac) autoimmune disorders***. This latter consideration holds true for ICI-related myocarditis, in which treatment is mostly based on the use of glucocorticoids.
- ***The American Society of Clinical Oncology and the Society for Immunotherapy of Cancer guidelines recommend starting with 1–2 mg/kg of oral or intravenous steroids, to be tapered in the following 4 to 6 weeks.***

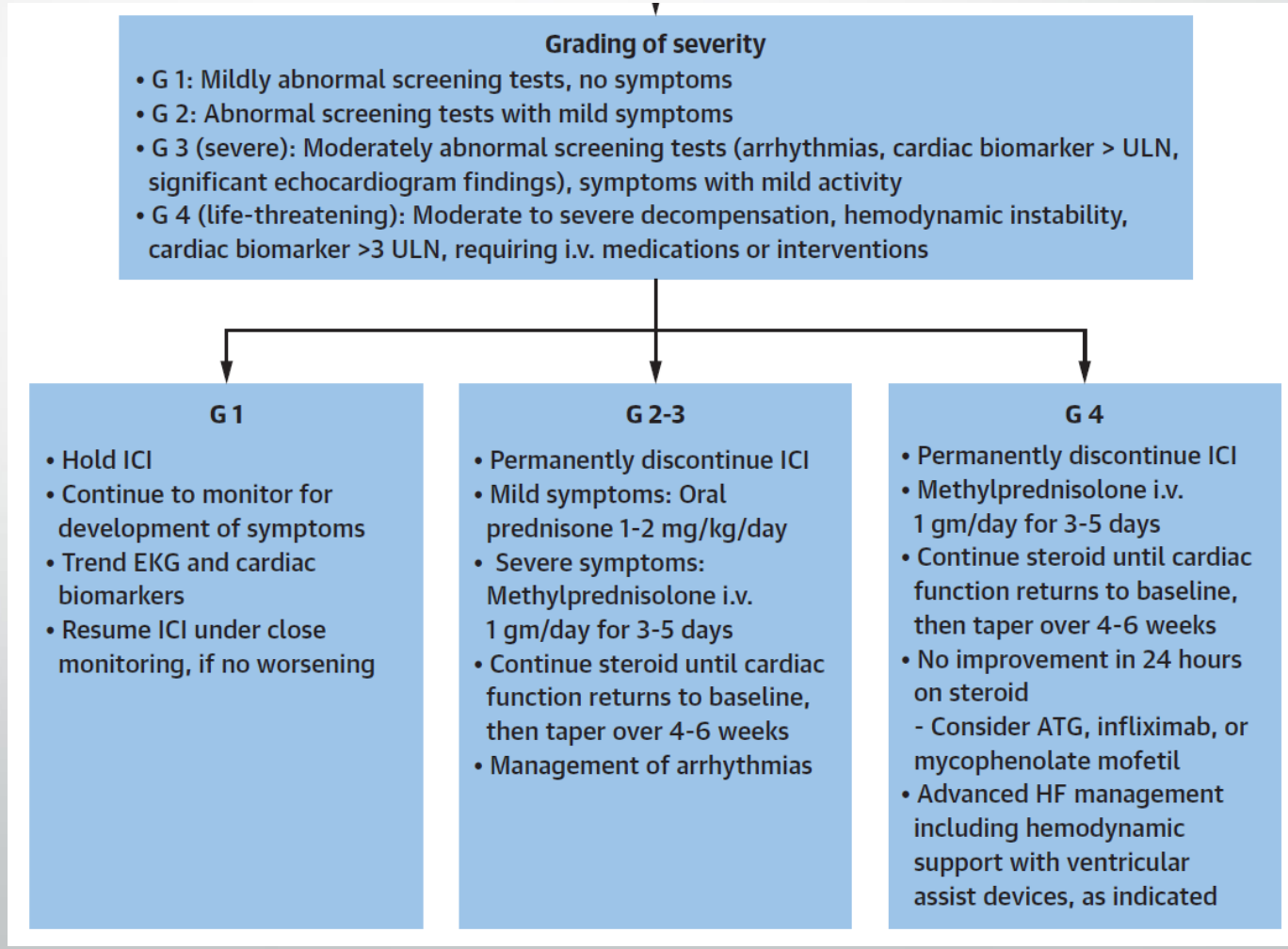


Step 4: Management of ICI-Related Myocarditis

- ***Response is usually evaluated clinically and by measuring troponins levels.***
  - If troponins rise again during tapering, corticosteroids dosage should be increased again and attempts at tapering should be postponed.
  - Guidelines recommend other immune-modulatory therapies only in cases without immediate response (within 24hr) to steroids. These may include ***mycophenolate, infliximab, anti-thymocyte globulins, alemtuzumab, and abatacept.***
    - Alemtuzumab, and abatacept, should be used with caution since few cases have been reported. Moreover, ***high dose infliximab is contraindicated in left ventricular dysfunction***
- These vulnerable patients with underlying cancer who have also been treated with immunosuppressive therapies for irAEs should be vigilantly monitored for potential risk of opportunistic infections

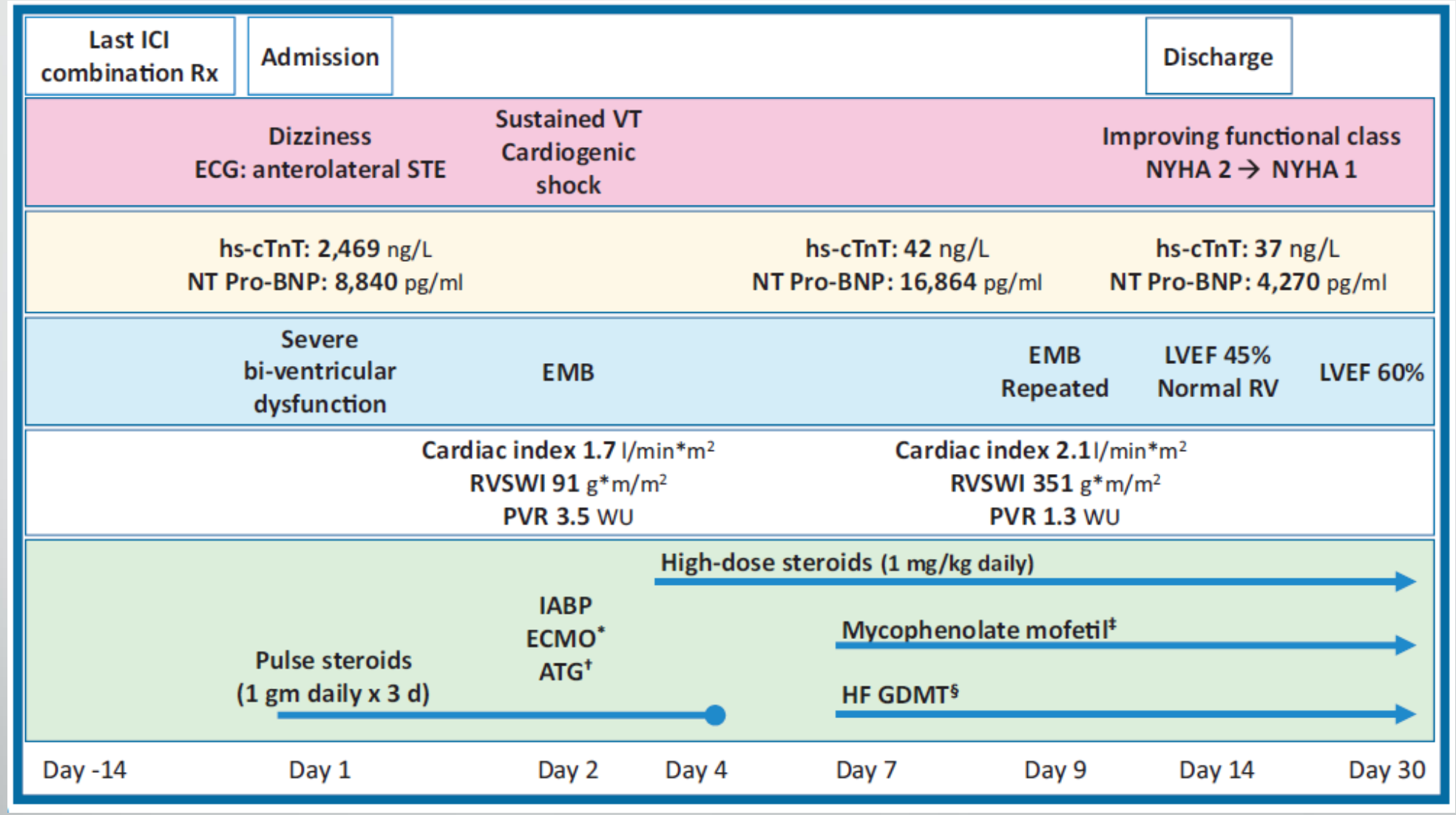
Re-challenge of ICIs

- ***If troponin testing shows normalization of values, and CPK values had always remained normal, without clinical, ECG, or echocardiographic alterations, ICIs may be restarted since a definite diagnosis of myocardial irAE cannot be achieved.***
- Similarly, if troponin positivity is deemed to be related to cardiac disorders different from myocarditis, it may be reasonable to consider, a re-challenge of ICIs.
- ***When a definite diagnosis of myocarditis is reached or cannot be excluded, ICIs are not to be re-started, even if clinical, ECG and echocardiographic findings are within normal range***



Case Study

- 53-year-old female patient, an active smoker, received a diagnosis in early 2019 of poor-risk, ***metastatic renal cell carcinoma with invasion of the inferior vena cava and hepatic veins***.
- Pre-treatment TTE revealed ***thrombotic involvement of the RA*** with normal biventricular function (LVEF: 60%).
- The patient underwent unilateral total nephrectomy, tumor extraction from the inferior vena cava, and right atrial thrombectomy.
- Post-surgical computed tomography revealed a ***mass extending from the stomach to the liver and further invasion of the tumor to the liver and lungs.***
- ***Adjuvant combination immunotherapy with the ipilimumab and nivolumab was administered every 3 weeks for 3 cycles.***


Last ICI combination Rx
Admission
Discharge
Dizziness
ECG: anterolateral STE
Sustained VT
Cardiogenic shock
Improving functional class
NYHA 2 → NYHA 1
hs-cTnT: 2,469 ng/L
NT Pro-BNP: 8,840 pg/ml
hs-cTnT: 42 ng/L
NT Pro-BNP: 16,864 pg/ml
hs-cTnT: 37 ng/L
NT Pro-BNP: 4,270 pg/ml
Severe bi-ventricular dysfunction
EMB
EMB Repeated
LVEF 45% Normal RV
LVEF 60%
Cardiac index 1.7 l/min*m²
RVSWI 91 g*m/m²
PVR 3.5 WU
Cardiac index 2.1 l/min*m²
RVSWI 351 g*m/m²
PVR 1.3 WU
High-dose steroids (1 mg/kg daily)
IABP
ECMO*
ATG†
Mycophenolate mofetil‡
Pulse steroids
(1 gm daily x 3 d)
HF GDMT§
Day -14
Day 1
Day 2
Day 4
Day 7
Day 9
Day 14
Day 30

Thank you for your attention