Cardiac Immune-Related Adverse Event Management Algorithm

Grading of myocarditis	Action	Follow up
Grade 1 Suspected myocarditis Minimal or no symptoms <u>Cardiac markers (approximate guide):</u> **Trop I 20-50ng/ml** **(or 2-5x baseline)** in the absence of other reason for elevated troponin	**<u>Investigations (compare to baseline)</u>** • ECG • Routine IO bloods including troponin, NT-pro-BNP, CK • CXR • Echocardiogram (urgent OP) **<u>Management</u>** • Strongly consider delaying I-O therapy • Repeat ECG and bloods in 2/52	**If returns to baseline:** • Resume routine monitoring **If worsens (in terms of symptoms or echocardiogram):** • Treat as G2
Grade 2 New cardiac symptoms e.g. dyspnoea, chest pain, palpitations, peripheral oedema, (pre-)syncope OR <u>Elevated cardiac markers:</u> **Trop I 50-100ng/ml** **(or 6-10x baseline)**	**<u>Investigations</u>** • Daily ECG / cardiac markers / CK (with other I-O bloods) • Echocardiogram + CMR • Infliximab screen + TPMT levels • Continuous ECG monitoring to assess for arrhythmias • Cardiac biopsy if diagnosis not clear **<u>Management</u>** • Admit and hold I-O therapy • IV Methylprednisolone 500-1000mg + PPI / bone protection ○ Consultant discretion • HF treatment • Cardiology to take over care with oncology input. • Transfer to a monitored cardiology bed ideally <24h • Monitor for high-risk features	**If improving:** • Use IV Methylprednisolone for minimum 3/7 • Then step down to PO Prednisolone 1mg/kg • Review response and continue oral steroid taper (5-10mg/week) • Consider ACE-I / beta-blocker • HF optimization • Weekly ECG / trop during steroid wean **If worsens / static (no clinical improvement and troponin reduction <50% from peak after 3 days):** • Treat as G3/4 **Initiation of steroid treatment may be delayed whilst waiting diagnostic confirmation if there is diagnostic uncertainty**
Grade 3 – 4 New onset of severe symptoms on minimal exertion or at rest OR haemodynamic instability OR <u>Elevated cardiac markers:</u> **Trop I >100ng/ml** **(or 10x baseline)** **NT-pro-BNP >2000** (however not always elevated, lower levels do not exclude myocarditis)	**<u>Investigations</u>** • As per G2 **<u>Management</u>** • These patients should be managed on CCU / Cardiology ward only • Discontinue I-O therapy • IV Methylprednisolone 1g + gastric/bone protection • Daily consultant review • Review ceilings of care • Anti-arrhythmic if required *(avoid amiodarone due to risk of pneumonitis)* • Close communication needed between cardiology and oncology teams.	**If improving:** • Use methylprednisolone for minimum 3/7 • Then PO Prednisolone 1mg/kg • Review ongoing response and continue taper (5-10mg/week) • Weekly ECG / trop during steroid wean • Optimise HF management **If worsens:** • Plasmapheresis indicated – need to involve appropriate teams. • Consider alternative immunosuppression with Mycophenolate, Tacrolimus or with biological agents e.g. Infliximab / Tocilizumab.

Please see following page for further information on I-O myocarditis, inpatient place of care, high risk features and steroid refractory disease.

Immunotherapy-related myocarditis

Introduction

Myocarditis is a rare complication of immunotherapy (I-O), affecting up to 1% of patients. Incidence rates are higher with combination immunotherapy (e.g. Ipilimumab / Nivolumab). Despite its relatively low occurrence, I-O myocarditis has one of the highest mortality rates of all the immunotherapy toxicities – mortality is estimated between 25 – 50%. (Palaskas, 2020). This group of patients are at extremely high risk of rapid deterioration, and the updated guideline aims to reflect this with a focus on timely patient transfer to Cardiology-led units.

Troponin

Not all troponin release is myocarditis. Consider cardiac and non-cardiac troponin releasing conditions. See table S3 from ESC acute chest pain guideline (also attached in this document).

Points to note regarding inpatient care

- Patients with a diagnosis of G2 I-O myocarditis should be transferred to a cardiology bed within 24h of a G2 diagnosis, assuming not for palliative care.
- AGM beds on JR site should be avoided (if patient coming from another hospital / Churchill), transfer must be directly to Cardiology.
- Whether on the Cardiology ward / CCU / Oncology, any patient with a diagnosis of G3 I-O myocarditis should have a daily consultant review.

High risk features

Whilst awaiting transfer to Cardiology, clinicians should be aware of the following high-risk features:

- Widening QRS (on daily ECG); AV block
- New unexplained hypotension
- CXR changes
- Increasing O2 requirement
- Increase in ectopic beat frequency
- Worsening renal function
- Features of cardiogenic shock – hypotension with organ malperfusion (eg cerebral/ renal)

Development of any of the above signifies **myocardial irritability** and should prompt consultant to consultant discussion to expedite transfer. If transfer is delayed, a review on-site by the on-call cardiology consultant may be appropriate.

Steroid refractory disease

There is a limited evidence-base available to guide the management of steroid-refractory I-O myocarditis, owing to the rarity of this disease. Options include escalation of immunosuppression or plasmapheresis to directly remove the circulating immune complexes. We suggest planning for plasmapheresis as the next line of treatment once steroid-refractory disease is confirmed, with the subsequent addition of further immune-modulators. Care should be taken with using Infliximab in this setting, as it can potentially worsen heart failure.

Additional information:

- Clinicians should be aware of concurrent I-O toxicities. Myocarditis occurs commonly with I-O myositis and I-O myasthenia gravis (Triple M' syndrome). In view of this, patients being treated for I-O myocarditis should regularly have their swallow checked, and clinicians should be vigilant for signs of fatigability.
- Biomarkers can sometimes provide false reassurance. Down-trending biomarkers e.g. Trop / BNP should be taken into account alongside the clinical picture, in the context of a patient being treated for I-O myocarditis.

ESC definitions of Cancer therapy-related cardiovascular toxicity definitions
(European Heart Journal (2022) 43, 4229–4361 https://doi.org/10.1093/eurheartj/ehac244)

CTRCD		
Symptomatic CTRCD (HF)[a,b]	Very severe	HF requiring inotropic support, mechanical circulatory support, or consideration of transplantation
	Severe	HF hospitalization
	Moderate	Need for outpatient intensification of diuretic and HF therapy
	Mild	Mild HF symptoms, no intensification of therapy required
Asymptomatic CTRCD	Severe	New LVEF reduction to <40%
	Moderate	New LVEF reduction by ≥10 percentage points to an LVEF of 40–49% *OR* New LVEF reduction by <10 percentage points to an LVEF of 40–49% AND either new relative decline in GLS by >15% from baseline OR new rise in cardiac biomarkers[c]
	Mild	LVEF ≥ ***50%*** AND new relative decline in GLS by >15% from baseline AND/OR new rise in cardiac biomarkers[c]
ICI myocarditis (either pathohistological diagnosis or clinical diagnosis)		
Pathohistological diagnosis (EMB)	Multifocal inflammatory cell infiltrates with overt cardiomyocyte loss by light microscopy	
Clinical diagnosis[d]	**cTn elevation** (new or significant change from baseline)[e] **with 1 major criterion or 2 minor criteria,** after exclusion of ACS and acute infectious myocarditis based on clinical suspicion[f]	
	Major criterion: • CMR diagnostic for acute myocarditis (modified Lake Louise criteria)[g]	
	Minor criteria: • Clinical syndrome (including any one of the following: fatigue, myalgias, chest pain, diplopia, ptosis, shortness of breath, orthopnoea, lower-extremity oedema, palpitations, light-headedness/dizziness, syncope, muscle weakness, cardiogenic shock) • Ventricular arrhythmia (including cardiac arrest) and/or new conduction system disease • Decline in LV systolic function, with or without regional wall motion abnormalities in a non-Takotsubo pattern • Other immune-related adverse events, particularly myositis, myopathy, myasthenia gravis • Suggestive CMR[h]	
Severity of myocarditis	• **Fulminant:** Haemodynamic instability, HF requiring non-invasive or invasive ventilation, complete or high-grade heart block, and/or significant ventricular arrhythmia • **Non-fulminant:** including symptomatic but haemodynamically and electrically stable patients and incidental cases diagnosed at the same time as other immuno-related adverse events. Patients may have reduced LVEF but no features of severe disease • **Steroid refractory**: non-resolving or worsening myocarditis (clinical worsening or persistent troponin elevation after exclusion of other aetiologies) despite high-dose methylprednisolone	
Recovery from myocarditis	• **Complete recovery**: Patients with complete resolution of acute symptoms, normalization of biomarkers, and recovery of LVEF after discontinuation of immunosuppression. CMR may still show LGE or elevated T1 due to fibrosis, but any suggestion of acute oedema should be absent • **Recovering**: Ongoing improvement in patient clinical symptoms, signs, biomarkers, and imaging parameters, but not yet normalized, while on tapering doses of immunosuppression	

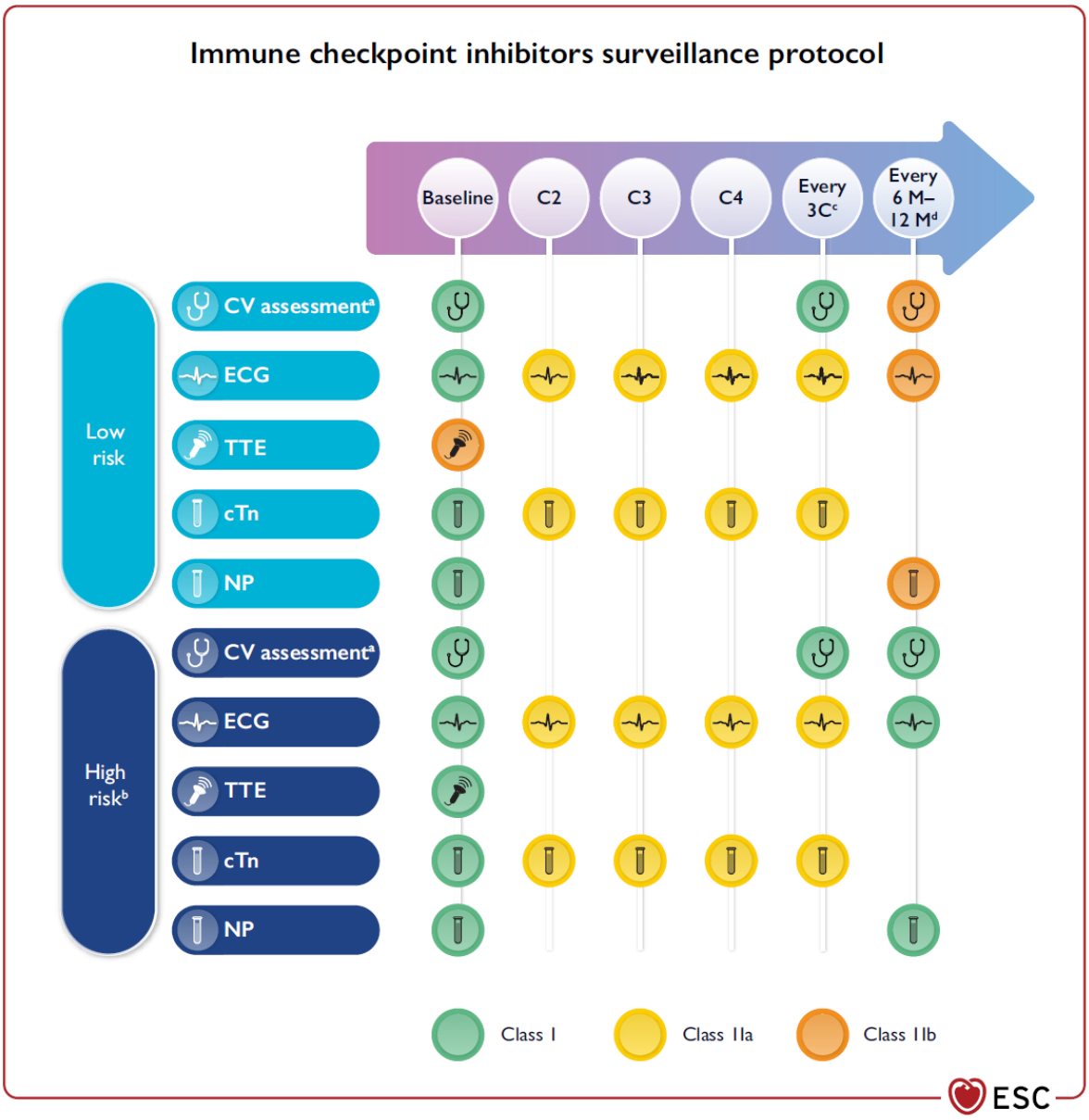

Figure 20 Cardiovascular surveillance in patients treated with immune checkpoint inhibitors. BNP, B-type natriuretic peptide; BP, blood pressure; C, chemotherapy cycle; cTn, cardiac troponin; CV, cardiovascular; CVD, cardiovascular disease; CTRCD, cancer therapy-related cardiac dysfunction; ECG, electrocardiogram; HbA1c, glycated haemoglobin; ICI, immune checkpoint inhibitors; M, months; NP, natriuretic peptides (including BNP and NT-proBNP); NT-proBNP, N-terminal pro-B-type natriuretic peptide; TTE, transthoracic echocardiography. [a]Including physical examination, BP, lipid profile, and HbA1c. [b]Dual ICI, combination ICI-cardiotoxic therapy, ICI-related non-CV events, prior CTRCD or CVD. [c]Every three cycles until completion of therapy to detect subclinical ICI-related CV toxicity. [d]In patients who require long-term (>12 months) ICI treatment.

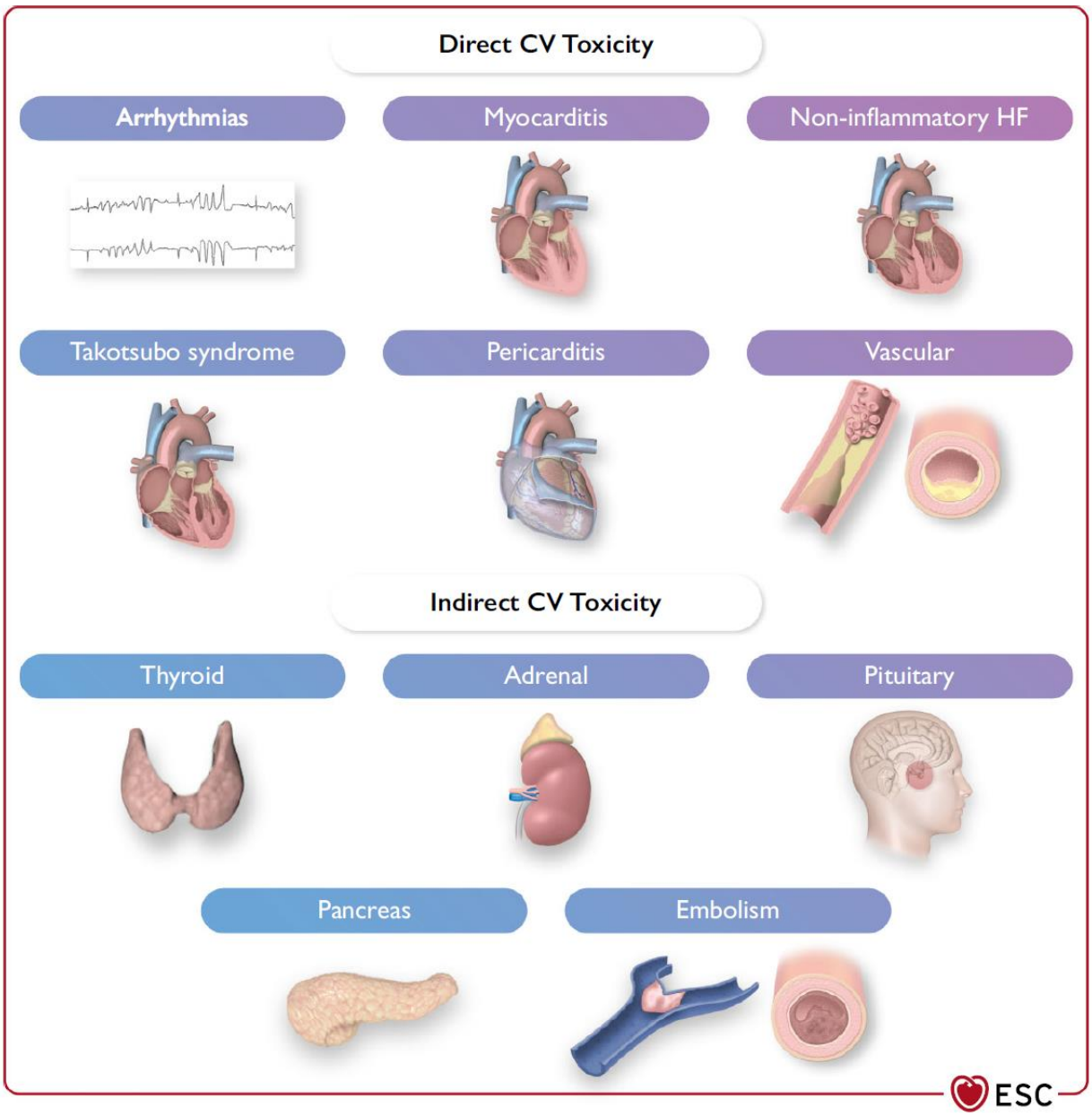

Figure 27 Direct and indirect immune checkpoint inhibitor-related cardiovascular toxicity. CV, cardiovascular; HF, heart failure.

Table S3 Conditions other than acute Type 1 myocardial infarction associated with cardiomyocyte injury (i.e. cardiac troponin elevation)

Myocardial injury related to acute myocardial ischaemia because of oxygen supply/demand imbalance (Type 2 MI)
Reduced myocardial perfusion, e.g.:
• Coronary artery spasm, microvascular dysfunction
• Coronary embolism
• Non-atherosclerotic coronary artery dissection
• Sustained bradyarrhythmia
• Hypotension or shock
• Respiratory failure
• Severe anaemia
Increased myocardial oxygen demand, e.g.:
• Sustained tachyarrhythmia
• Severe hypertension with or without left ventricular hypertrophy
Other causes of myocardial injury
Cardiac conditions:
• Heart failure
• Myocarditis[a]
• Cardiomyopathy (any type)
• Takotsubo syndrome
• Cardiac contusion or cardiac procedures (CABG, PCI, valvular interventions, ablation, pacing, cardioversion, or endomyocardial biopsy)
Systemic conditions:
• Sepsis, infectious disease
• Chronic kidney disease
• Stroke, subarachnoid haemorrhage
• Pulmonary embolism, pulmonary hypertension
• Infiltrative diseases (e.g. amyloidosis, sarcoidosis, haemochromatosis, scleroderma)
• Myocardial drug toxicity or poisoning (e.g. doxorubicin, 5-fluorouracil, trastuzumab, snake venoms)
• Critically ill patients
• Hypo- and hyper-thyroidism
• Strenuous exercise
• Rhabdomyolysis

CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention.
[a]Includes myocardial extension of endocarditis or pericarditis.

Issue date:	18.6.2025
Version No:	2.1
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