



PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

ROMA

Centro Congressi
di Confindustria

Auditorium
della Tecnica

9^a Edizione

30 Settembre
1 Ottobre
2022

**ENDOCARDITI, MIOCARDITI, PERICARDITI ED INFIAMMAZIONE
CARDIACA: PERCORSI DIAGNOSTICI E TERAPEUTICI**

**DIAGNOSI, PROGNOSI E TERAPIA
PERSONALIZZATA DELLA MIOCARDITE**

Gentile Piero
Cardiologia 2 - Insufficienza Cardiaca e Trapianti
ASST Grande Ospedale Metropolitano Niguarda, Milano



Agenda

- APPROCCIO DIAGNOSTICO
- *Esordio con scompenso cardiaco*
- *Esordio aritmico maggiore*
- *Scenari particolari:*
 - *miocarditi eosinofile*
 - *miocarditi gigantocellulari*
 - *miocarditi di ICI*
 - *miocarditi e genetica*



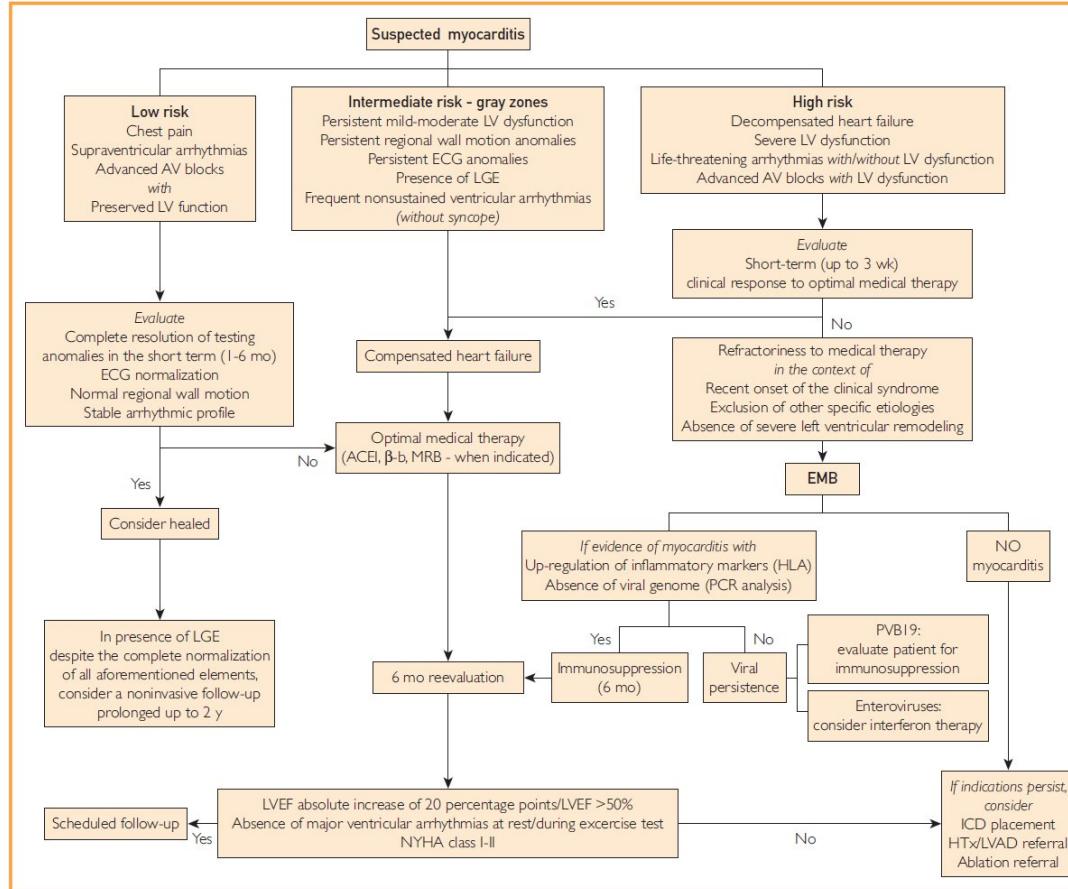
Agenda

- **APPROCCIO DIAGNOSTICO**
- *Esordio con scompenso cardiaco*
- *Esordio aritmico maggiore*
- *Scenari particolari:*
 - *miocarditi eosinofile*
 - *miocarditi gigantocellulari*
 - *miocarditi di ICI*
 - *miocarditi e genetica*



Myocarditis in Clinical Practice

Gianfranco Sinagra, MD, FESC; Marco Anzini, MD; Naveen L. Pereira, MD;
Rossana Bussani, MD; Gherardo Finocchiaro, MD; Jozef Bartunek, MD, PhD;
and Marco Merlo, MD



Agenda

- APPROCCIO DIAGNOSTICO
- ***Esordio con scompenso cardiaco***
- ***Esordio aritmico maggiore***
- ***Scenari particolari:***
 - ***miocarditi eosinofile***
 - ***miocarditi gigantocellulari***
 - ***miocarditi di ICI***
 - ***miocarditi e genetica***

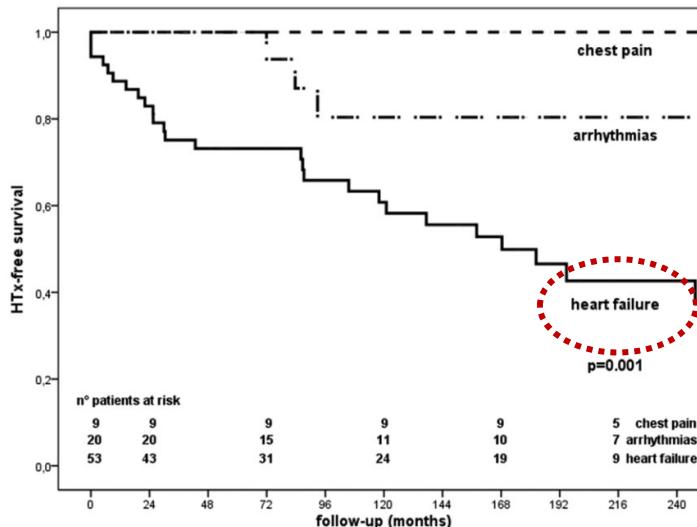


Long-Term Evolution and Prognostic Stratification of Biopsy-Proven Active Myocarditis

Marco Anzini, MD; Marco Merlo, MD; Gastone Sabbadini, MD; Giulia Barbati, PhD; Gherardo Finocchiaro, MD; Bruno Pinamonti, MD; Alessandro Salvi, MD; Andrea Perkan, MD; Andrea Di Lenarda, MD; Rossana Bussani, MD; Jozef Bartunek, MD, PhD; Gianfranco Sinagra, MD, FESC

Table 1. Baseline Characteristics of the Study Patients

Baseline Characteristics	n	Whole Population (n=82)	Heart Failure (n=53, 65%)	Arrhythmias (n=20, 24%)	Chest Pain (n=9, 11%)	P Value*
Histopathology						
Lymphocytic, n (%)	82	75 (91)	49 (92)	19 (95)	7 (78)	0.315
Eosinophilic, n (%)	82	5 (6)	3 (6)	1 (5)	1 (11)	0.616
Rheumatic, n (%)	82	1 (1)	0 (0)	0 (0)	1 (11)	0.106
Giant cell, n (%)	82	1 (1)	1 (2)	0 (0)	0 (0)	1



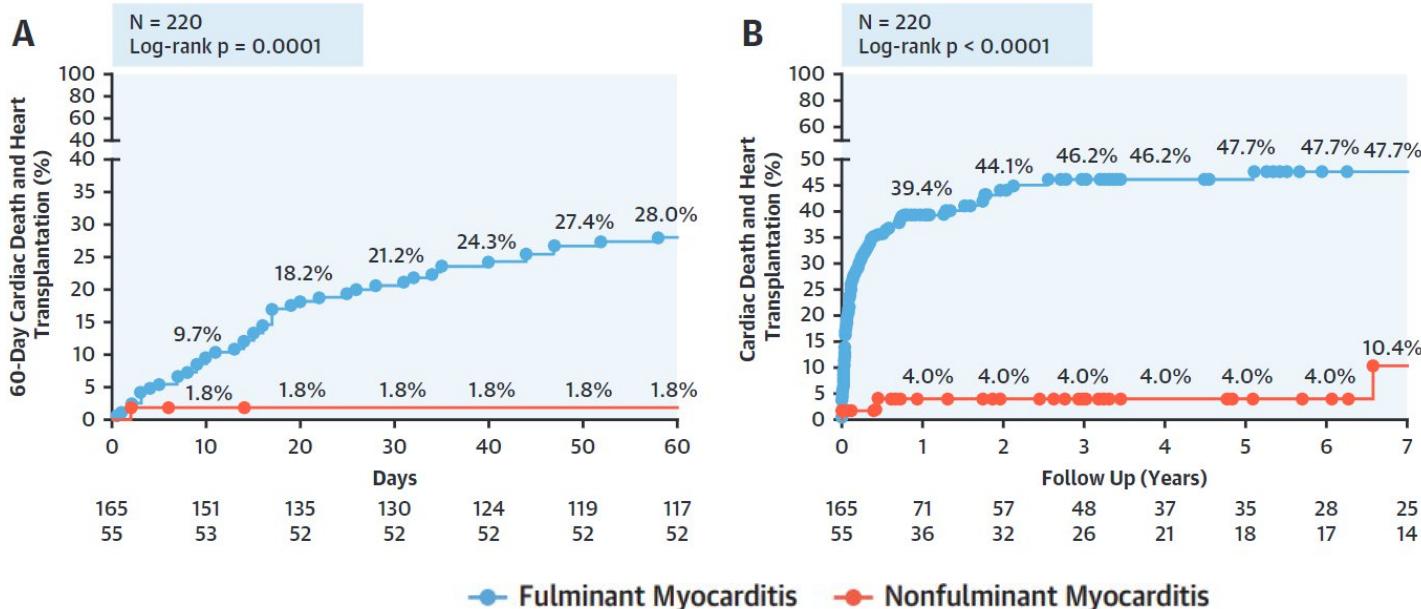
Fulminant Versus Acute Nonfulminant Myocarditis in Patients With Left Ventricular Systolic Dysfunction

- 220 patients (median age 42 years, 46.3% female)
 - histologically proven acute myocarditis
 - left ventricular systolic dysfunction at presentation

FULMINANT MYOCARDITIS:

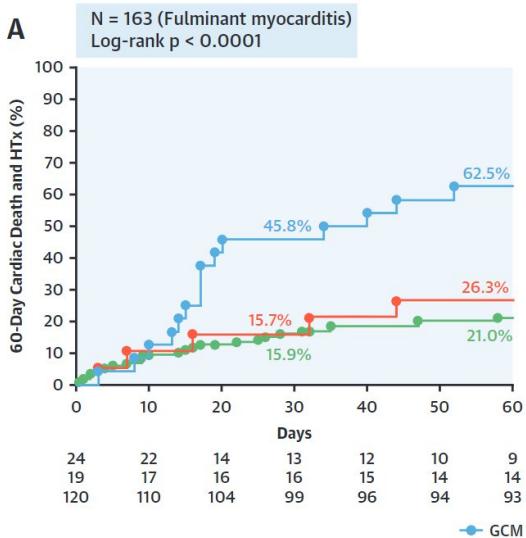
patients with hemodynamic compromise

requiring inotropes and/or mechanical circulatory support

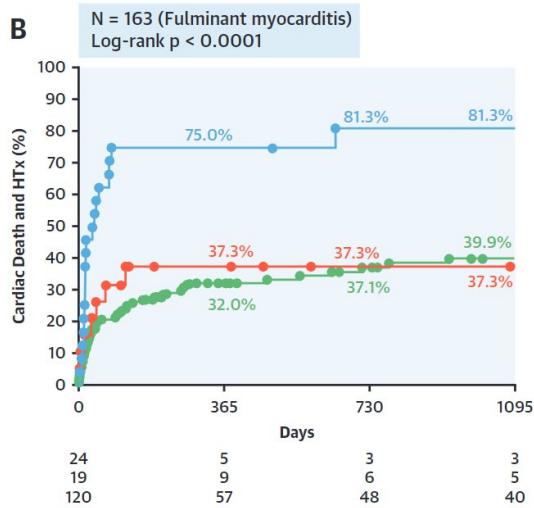


Fulminant Versus Acute Nonfulminant Myocarditis in Patients With Left Ventricular Systolic Dysfunction

A

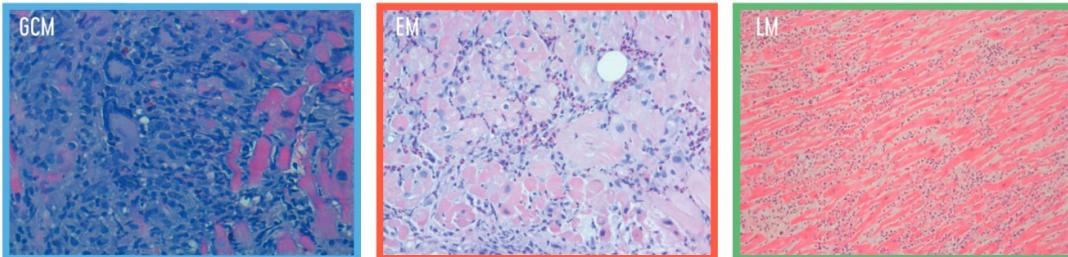


B



- Patients with FM have higher cardiac mortality and HTx
- Important role of EMB in FM patients: histologic sub-types are related to prognosis and may require specific treatment, with GCM portending the worst outcome

C



Agenda

- APPROCCIO DIAGNOSTICO
- *Esordio con scompenso cardiaco*
- ***Esordio aritmico maggiore***
- *Scenari particolari:*
 - *miocarditi eosinofile*
 - *miocarditi gigantocellulari*
 - *miocarditi di ICI*
 - *miocarditi e genetica*

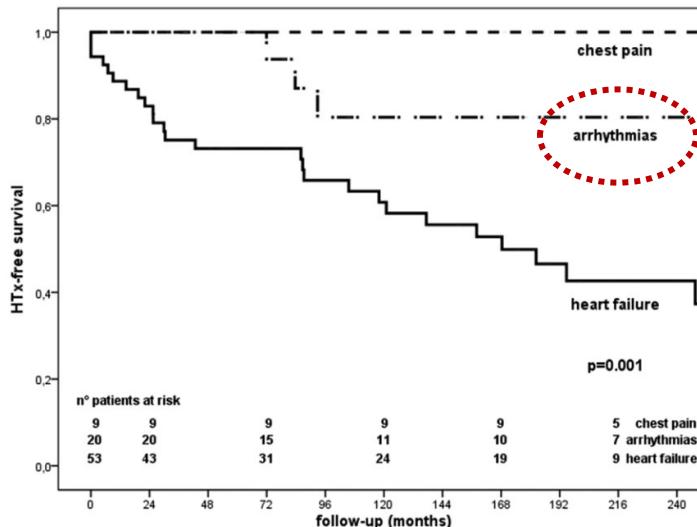


Long-Term Evolution and Prognostic Stratification of Biopsy-Proven Active Myocarditis

Marco Anzini, MD; Marco Merlo, MD; Gastone Sabbadini, MD; Giulia Barbati, PhD; Gherardo Finocchiaro, MD; Bruno Pinamonti, MD; Alessandro Salvi, MD; Andrea Perkan, MD; Andrea Di Lenarda, MD; Rossana Bussani, MD; Jozef Bartunek, MD, PhD; Gianfranco Sinagra, MD, FESC

Table 1. Baseline Characteristics of the Study Patients

Baseline Characteristics	n	Whole Population (n=82)	Heart Failure (n=53, 65%)	Arrhythmias (n=20, 24%)	Chest Pain (n=9, 11%)	P Value*
Histopathology						
Lymphocytic, n (%)	82	75 (91)	49 (92)	19 (95)	7 (78)	0.315
Eosinophilic, n (%)	82	5 (6)	3 (6)	1 (5)	1 (11)	0.616
Rheumatic, n (%)	82	1 (1)	0 (0)	0 (0)	1 (11)	0.106
Giant cell, n (%)	82	1 (1)	1 (2)	0 (0)	0 (0)	1



Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases

3. Arrhythmia

There are no specific recommendations for the management of arrhythmia in myocarditis, and so management should be in line with current ESC guidelines.^{157–162} Sinus bradycardia, prolonged QRS duration, increased left ventricular hypokinesis on echocardiography, persistent or fluctuating cardiac troponin levels may precede a life-threatening arrhythmia.¹⁰ Temporary pacing may be needed for complete atrio-ventricular block.¹⁰ Indication for cardioverter defibrillator implantation (ICD) is controversial, because myocarditis may heal completely. Bridging by a lifevest in patients with myocarditis and severe ventricular arrhythmia (ventricular tachycardia or fibrillation) could solve the transient problem.¹⁶³

Recommendations

18. ICD implantation should be deferred until resolution of the acute episode.
19. Arrhythmia management outside the acute phase should be in line with current ESC guidelines on arrhythmia and device implantation.

European Heart Journal (2013) 34, 2636–2648

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

During the acute phase of myocarditis, ICD implantation should be deferred until resolution of the acute episode. Because myocarditis may heal completely, the indication for ICD implantation and its timing remain controversial even beyond the acute stage. Bridging

Recommendations	Class ^a	Level ^b	Ref. ^c
Management of ventricular arrhythmias in inflammatory heart disease			
ICD implantation may be considered earlier in patients with giant cell myocarditis or sarcoidosis who had haemodynamically compromising sustained VA or aborted cardiac arrest, due to adverse prognosis of these conditions, if survival >1 year with good functional status can be expected.	IIb	C	600
A wearable defibrillator should be considered for bridging until full recovery or ICD implantation in patients after inflammatory heart diseases with residual severe LV dysfunction and/or ventricular electrical instability.	IIa	C	598, 599

AHA/ACC/HRS GUIDELINE

2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death

7.5. Myocarditis

Recommendations for Myocarditis

References that support the recommendations are summarized in Online Data Supplement 32.

COR	LOE	Recommendations
I	C-LD	<ol style="list-style-type: none"> In patients with life-threatening VT or VF associated with confirmed or clinically suspected myocarditis, referral to centers with mechanical hemodynamic support and advanced arrhythmia management is recommended.⁵⁷⁻⁵¹
IIb	C-LD	<ol style="list-style-type: none"> In patients with giant cell myocarditis with VF or hemodynamically unstable VT treated according to GDMT, an ICD and/or an antiarrhythmic medication may be considered if meaningful survival of greater than 1 year is expected.^{57.5-2-57.5-4}

Circulation. 2018;138:e272–e391.

2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

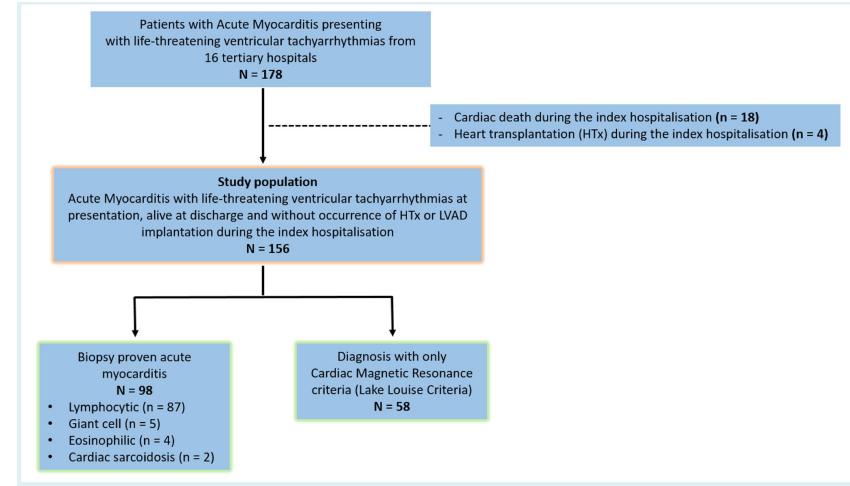
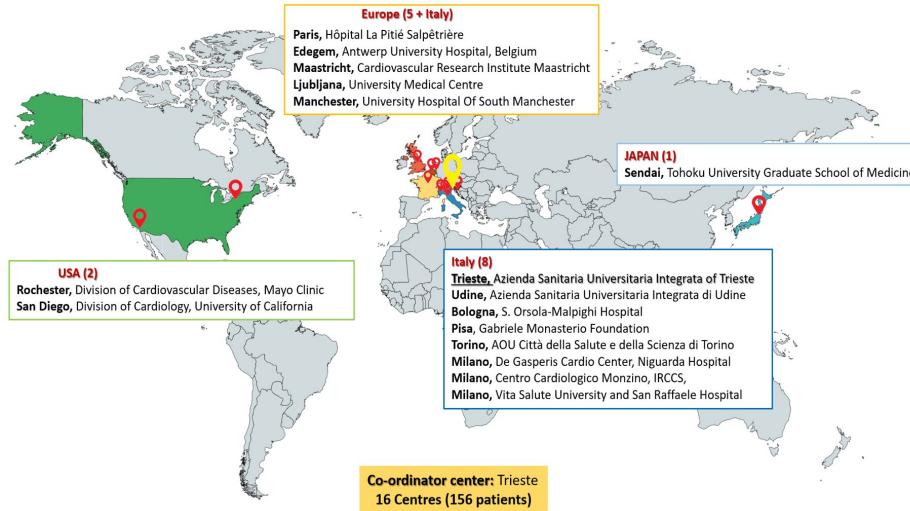
Recommendations	Class ^a	Level ^b
Secondary prevention of SCD and treatment of VA		
In patients with haemodynamically not-tolerated SMVT occurring in the chronic phase of myocarditis, an ICD implantation is recommended. ^{794,805}	I	C
In patients with haemodynamically not-tolerated sustained VT or VF during the acute phase of myocarditis, ICD implantation before hospital discharge should be considered. ^{788,794,806}	IIa	C

European Heart Journal (2022) 00, 1–130

Post-discharge arrhythmic risk stratification of patients with acute myocarditis and life-threatening ventricular tachyarrhythmias



European Journal of Heart Failure (2021)
doi:10.1002/ejhf.2288



Gentile P, Sinagra G., et al. EJHF 2021

Post-discharge arrhythmic risk stratification of patients with acute myocarditis and life-threatening ventricular tachyarrhythmias



European Journal of Heart Failure (2021)
doi:10.1002/ejhf.2288

	Major arrhythmic events (MAE) in the F-up N=58 (37%)
SCD, n (%)	1 (1)
Aborted SCD after VTs/VF, n (%)	10 (17)
Appropriate intervention of ICD, n (%)	47 (81)
Time to MAE, months	8 (2.5-24)*

LVEF at discharge:
51% (42-60)

Interventions on VF	30
Interventions on sVT	17
- ATP on sVT	6

*minimum time of 8 days

Median follow-up: 23 months (IQR 7–60)

Maximum follow-up: 284 months

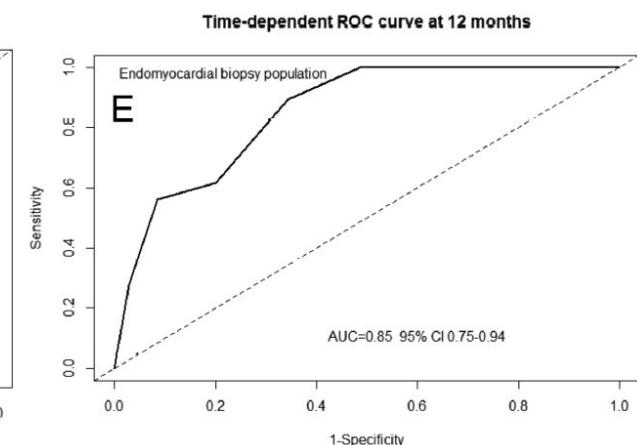
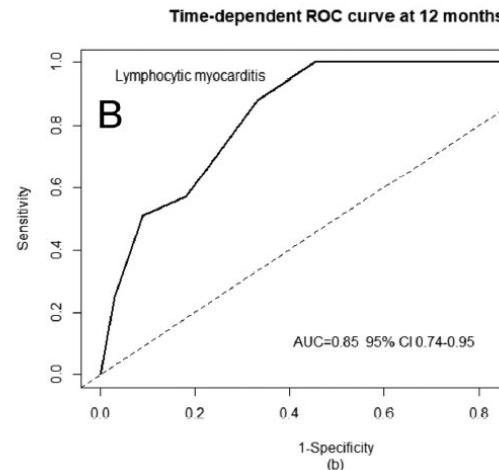
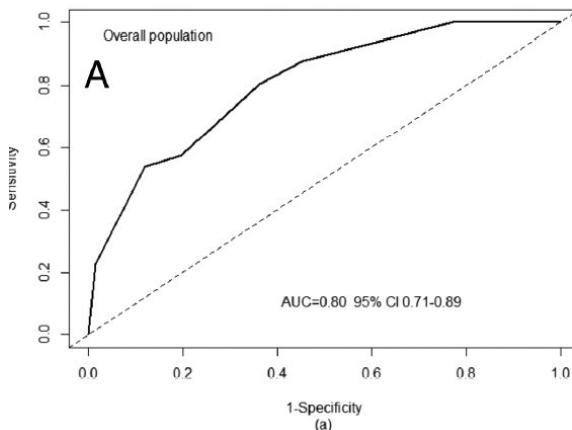
Gentile P, Sinagra G., et al. EJHF 2021

Post-discharge arrhythmic risk stratification of patients with acute myocarditis and life-threatening ventricular tachyarrhythmias

Table 2 Univariable and multivariable analysis for baseline prediction model of major arrhythmic events at follow-up

	HR (95% CI) for MAEs ^a			
	Unadjusted HR	P-value	Adjusted HR	P-value
Epoch of enrolment (1995–2004 vs. 2005–2019)	0.18 (0.03–1.32)	0.09		
Male sex	0.38 (0.18–0.81)	0.012		
Family history of cardiomyopathy	2.31 (1.04–5.15)	0.04		
Sustained ventricular tachycardia at presentation	2.24 (1.20–4.17)	0.011	2.90 (1.38–6.11)	0.005
LVEDV	1.01 (0.99–1.01)	0.07		
LGE involving ≥2 myocardial segments at CMR	3.56 (1.75–7.23)	<0.001	4.51 (2.39–8.53)	<0.001
Absence of positive STIR at CMR	1.90 (1.05–3.44)	0.033	2.59 (1.40–4.79)	0.002
Cardiac sarcoidosis	12.95 (2.69–62.34)	0.001		

Time-dependent ROC curve at 12 months



Gentile P, Sinagra G., et al. EJHF 2021

TABLE 2. Role and Typical Findings of Noninvasive Testing and Endomyocardial Biopsy in the Diagnostic Work-up of Myocarditis

Variable	Low risk	Intermediate risk	High risk
Personal history	Should always be thoroughly investigated ^{4,10,11} Flulike symptoms, insect bite (for <i>Borrelia</i> or <i>Rickettsia</i> suspicion), timing of symptoms onset, family history of cardiomyopathy, drugs or toxic substances assumption		
Electrocardiography	Diffuse and saddle-shaped ST-segment elevation Bradyarrhythmias or advanced AV conduction defects in the absence of LV dysfunction may be suggestive of infections by <i>Borrelia</i> or <i>Rickettsia</i>	Low voltages Discordance between the severity of the clinical scenario and the scarcity of electrocardiographic alterations (absence of left atrial dilation and left intraventricular conduction delay)	Bradyarrhythmias or advanced AV conduction defects in the presence of LV dysfunction may be suggestive of sarcoidosis or giant cell myocarditis

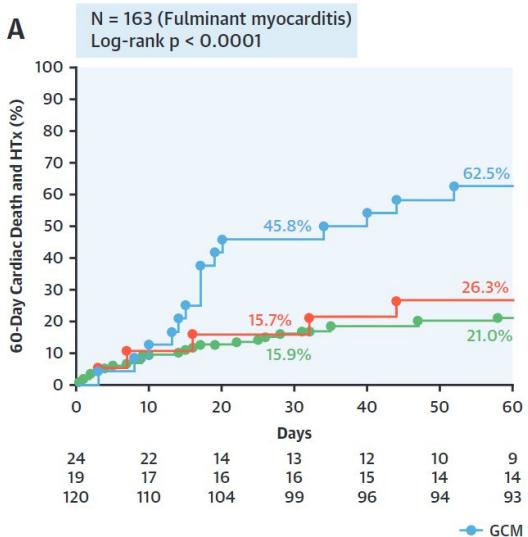
Agenda

- APPROCCIO DIAGNOSTICO
- *Esordio con scompenso cardiaco*
- *Esordio aritmico maggiore*
- *Scenari particolari:*
 - **miocarditi eosinofile**
 - **miocarditi gigantocellulari**
 - **miocarditi di ICI**
 - **miocarditi e genetica**

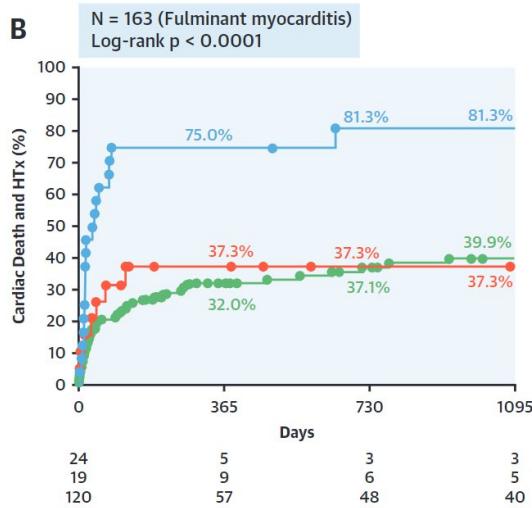


Fulminant Versus Acute Nonfulminant Myocarditis in Patients With Left Ventricular Systolic Dysfunction

A

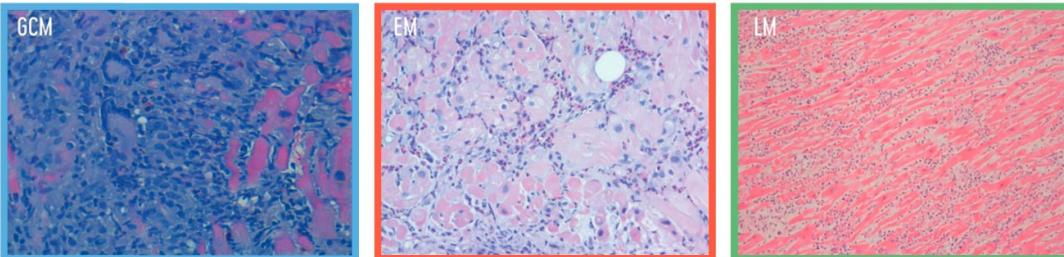


B



- Patients with FM have higher cardiac mortality and HTx
- Important role of EMB in FM patients: histologic sub-types are related to prognosis and may require specific treatment, with GCM portending the worst outcome

C



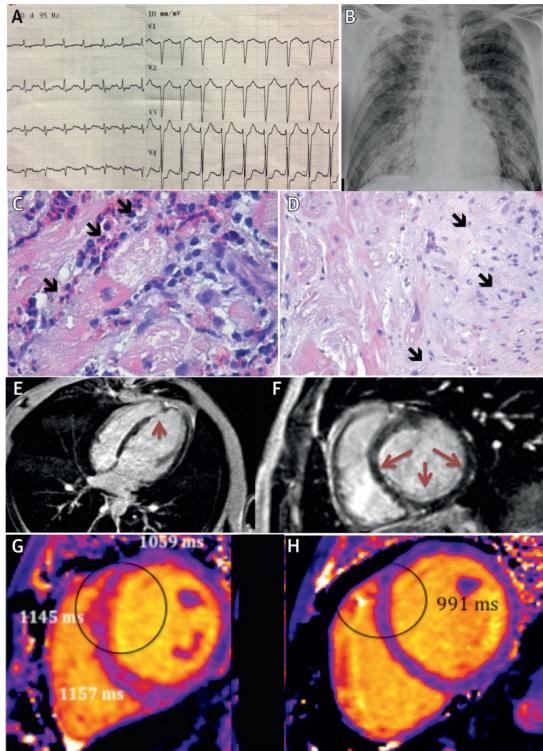
Eosinophilic Myocarditis

Journal of the American College of Cardiology

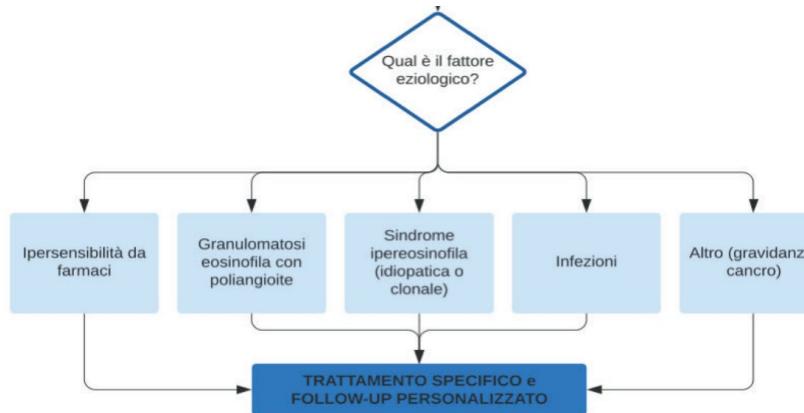
Volume 70, Issue 19, 7 November 2017, Pages 2363-2375

Characteristics, Treatment, and Outcomes

Michela Brambatti, MD,^a Maria Vittoria Matassini, MD,^b Eric D. Adler, MD,^a Karin Klingel, MD,^c
Paolo G. Camici, MD,^{d,e} Enrico Ammirati, MD, PhD^{e,f}



- 179 patients admitted to hospital with histologically proven EM.
- **Arrhythmia during the acute phase:** cardiac arrest: 27%
- **44.6% of cardiac arrest took place in hypersensitivity EM during hospitalization**



Prima linea

Metilprednisolone e.v. ad alte dosi per i primi 3 giorni (7-14 mg/kg), seguito da 1 mg/kg/die e successivo tapering*

In alternativa/in aggiunta

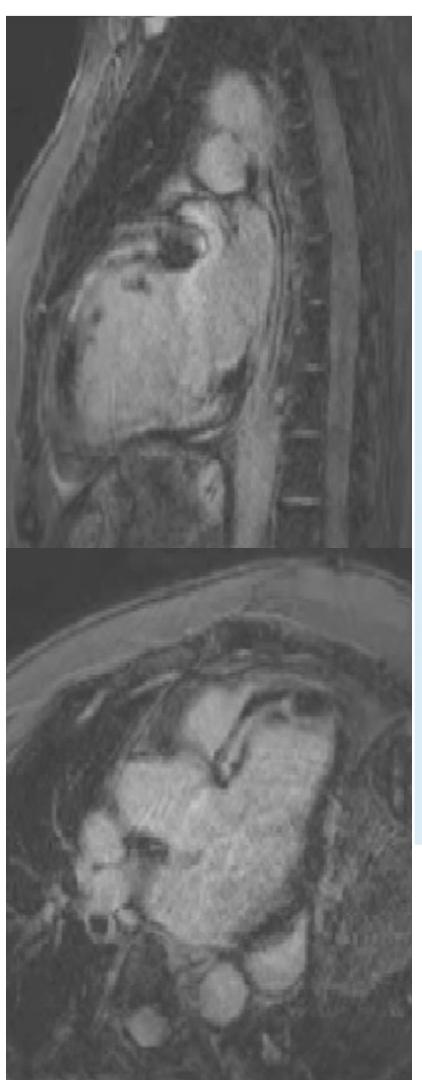
Nella forma da granulomatosi eosinofila con poliangioite: ciclofosfamide e.v. 600 mg/m² al giorno 1, 15 e 30

Nella forma da sindrome ipereosinofila variante mieloproliferativa: imatinib 100-400 mg/die per os per 4-28 giorni**

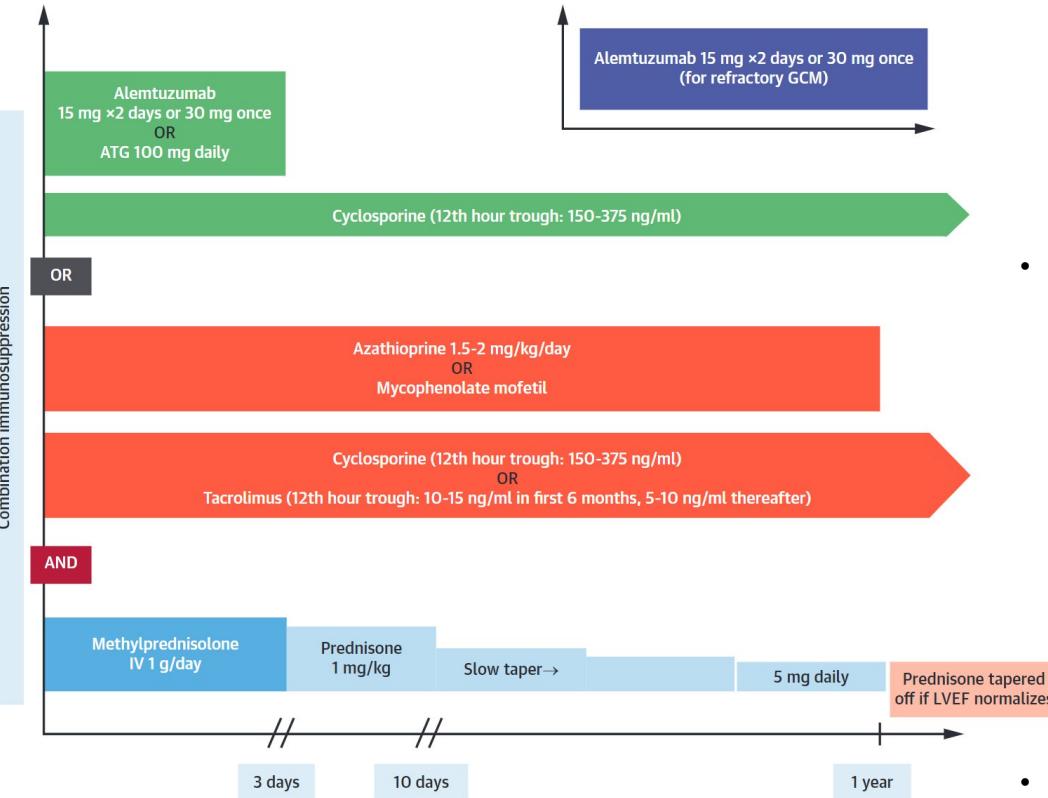
Nella forma da sindrome ipereosinofila idiopatica: mepolizumab e.v. 750 mg/4 settimane***

Nella forma associata a infezione elminica: albendazolo da 200 mg/die a 400 mg bid per os per 2-7 settimane

Nella forma da ipersensibilità: rimozione del farmaco che si sospetta essere causa della reazione allergica



Management of Patients With Giant Cell Myocarditis



- Immunosuppression together with GDMT for HF and arrhythmias, have improved the prognosis of patients with GCM (in patients with GCM, the rate of Death or cardiac transplantation at 1 year without immunosuppressive therapy was 100%).

- Immunosuppressive therapy typically involves 2 or 3drugs—most commonly corticosteroids and at least 1, and most often 2 additional immunosuppressiveagents—azathioprine +cyclosporine or mycophenolate + tacrolimus and/or antithymocyte globulin (ATG) or muromonab CD3 antibody or alemtuzuma+ cyclosporine

- **MCS and cardiac transplantation** have an evolving role in the management of patients with GCM

REVIEW ARTICLE

Immune-Related Adverse Events Associated with Immune Checkpoint Blockade

Michael A. Postow, M.D., Robert Sidlow, M.D., and Matthew D. Hellmann, M.D.

Table 1. Immune Checkpoint-Blocking Antibodies Approved by the Food and Drug Administration.*

Drug	Target	Indication
Ipilimumab	CTLA-4	Melanoma
Nivolumab	PD-1	Melanoma, non-small-cell lung cancer, renal-cell carcinoma, hepatocellular carcinoma, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, colorectal cancer with high microsatellite instability or mismatch-repair deficiency
Pembrolizumab	PD-1	Melanoma, non-small-cell lung cancer, classic Hodgkin's lymphoma, squamous-cell carcinoma of the head and neck, urothelial carcinoma, gastric cancer, solid tumors with high microsatellite instability or mismatch-repair deficiency
Atezolizumab	PD-L1	Non-small-cell lung cancer, urothelial carcinoma
Avelumab	PD-L1	Merkel-cell carcinoma, urothelial carcinoma
Durvalumab	PD-L1	Urothelial carcinoma

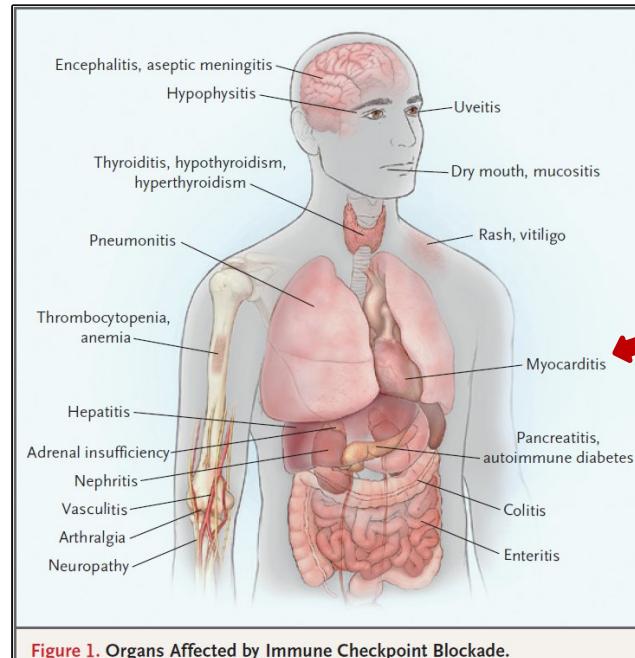


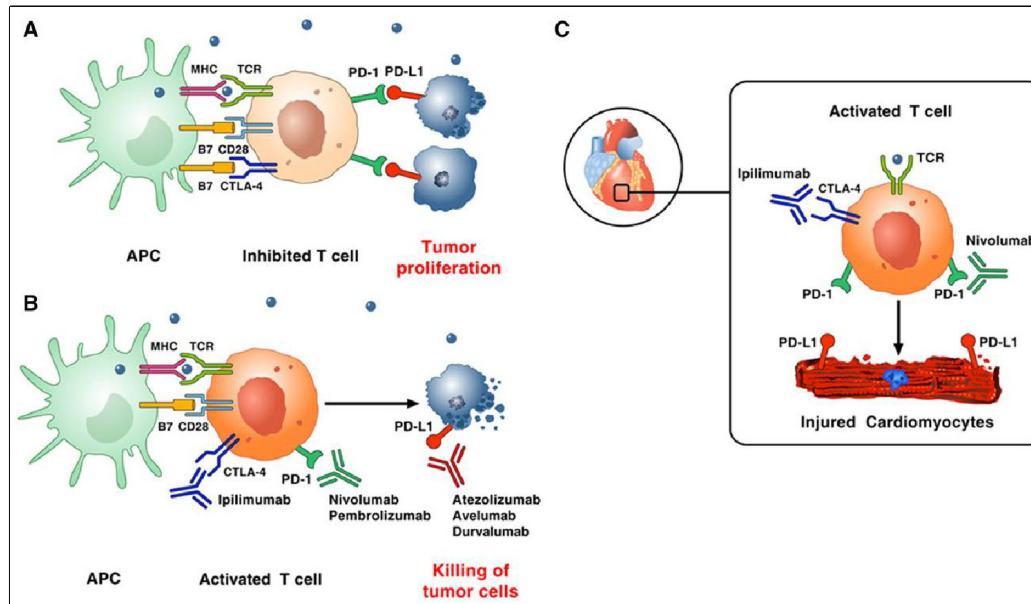
Figure 1. Organs Affected by Immune Checkpoint Blockade.

Cardiac Toxicity of Immune Checkpoint Inhibitors

Cardio-Oncology Meets Immunology

Circulation

Gilda Varricchi, MD, PhD
Maria Rosaria Galdiero,
MD, PhD
Carlo G. Tocchetti, MD, PhD



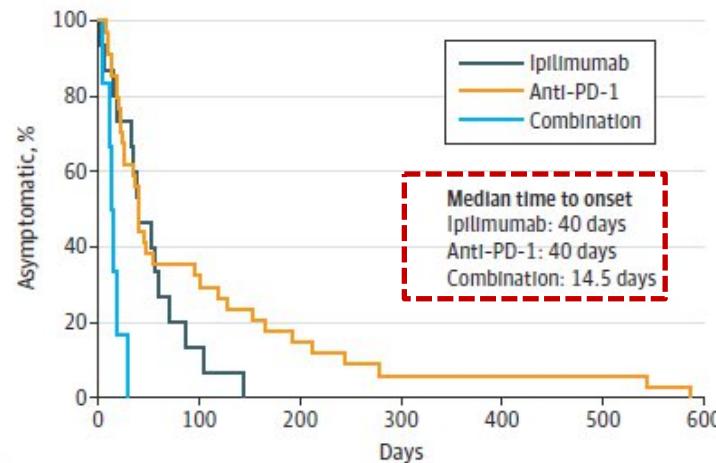
Circulation. 2017;

L'Incidenza di miocarditi da immune checkpoint inhibitor (ICI) è stata riportato
dello 0.06-1.33% tra i pz in terapia con tali farmaci.

Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors

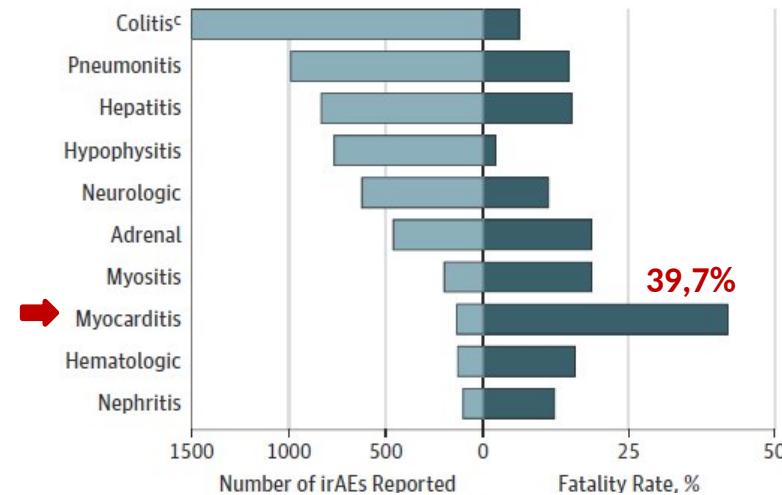
A Systematic Review and Meta-analysis

Figure 2. Time to Symptom Onset of Fatal Toxic Effects by ICI Regimen



No. at risk	0	30	60	90	120	150	180	210	240	270	300	330	360	390	420	450	480	510	540	570	600
Ipilimumab	15	13	11	9	7	5	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Anti-PD-1	34	32	29	26	23	20	17	14	11	8	5	2	0	0	0	0	0	0	0	0	0
Combination	6	5	4	3	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Cases and fatality rates



To determine the risk of fatality associated with particular toxic effects, we assessed fatality rates for different classes of toxic effects (Figure 1C). Myocarditis appeared to present the highest risk of death, with 52 (39.7%) deaths among 131 cases.

Pneumonitis, hepatitis, myositis, nephritis, neurologic, and hematologic toxic effects all had fatalities in 10% to 17% of reported cases. Hypophysitis, adrenal insufficiency, and colitis had the lowest reported fatality rates (2%, 3.7%, and 5%, respectively).

Myocarditis in Patients Treated With Immune Checkpoint Inhibitors

TABLE 3 Comparison of Myocarditis Cases With and Without MACE

	No MACE (n = 19)	MACE (n = 16)	p Value
Age at start of ICI, yrs	66.0 ± 13.2	63.0 ± 13.6	0.44
Female	6 (32.0)	4 (25.0)	0.72
ICI to onset of myocarditis	57 (6–235)	31 (4–151)	0.135
Number of ICI doses	5.2 ± 8	3 ± 3	0.40
CV risk factors			
Current or prior smoking	7 (37.0)	8 (50.0)	0.51
Hypertension	14 (74.0)	11 (69.0)	1.00
Diabetes mellitus	7 (37.0)	5 (31.0)	1.00
Single agent vs. combined			
Combination (current regimen)	9 (47.0)	3 (19.0)	0.08
Monotherapy (current regimen)	10 (53.0)	13 (81.0)	
Type of combined ICI			
Ipilimumab + Nivolumab	6 (32.0)	3 (19.0)	0.46
Ipilimumab + Pembrolizumab	1 (5.3)	0 (0.0)	1.00
Tremelimumab + Avelumab	1 (5.3)	0 (0.0)	1.00
Tremelimumab + Durvalumab	1 (5.3)	0 (0.0)	1.00
Type of monotherapy ICI*			
Pembrolizumab	9 (47.0)	2 (13.0)	0.035
Nivolumab	0 (0.0)	7 (44.0)	0.002
Ipilimumab	1 (5.3)	1 (6.3)	1.00
Tremelimumab	0 (0.0)	1 (6.3)	0.46
Atezolizumab	0 (0.0)	2 (13.0)	0.20
Avelumab	0 (0.0)	0 (0.0)	—
Durvalumab	0 (0.0)	0 (0.0)	—

Nearly one-half of all myocarditis cases (46%) experienced a MACE:

Causes of death included

- 2 sudden deaths;
- 2 documented ventricular arrhythmias;
- 2 of progressive cardiogenic shock.

Of the 16 MACE, 6 (38%) occurred in patients with a normal LVEF

As compared with non-MACE myocarditis cases, those who experienced a MACE had a **higher admission, peak, and discharge/final troponin T value**.

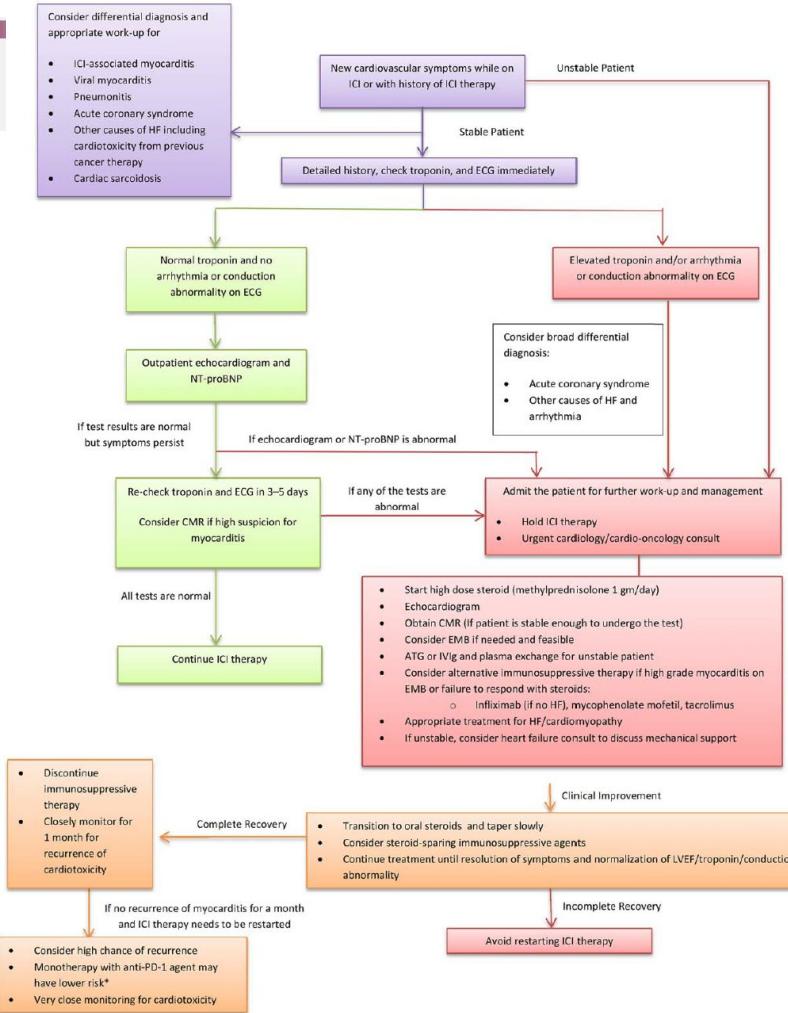
Steroids were initial treatment of myocarditis in 31 (89%) cases. A **higher initial steroid dose** was associated with lower rate of MACE

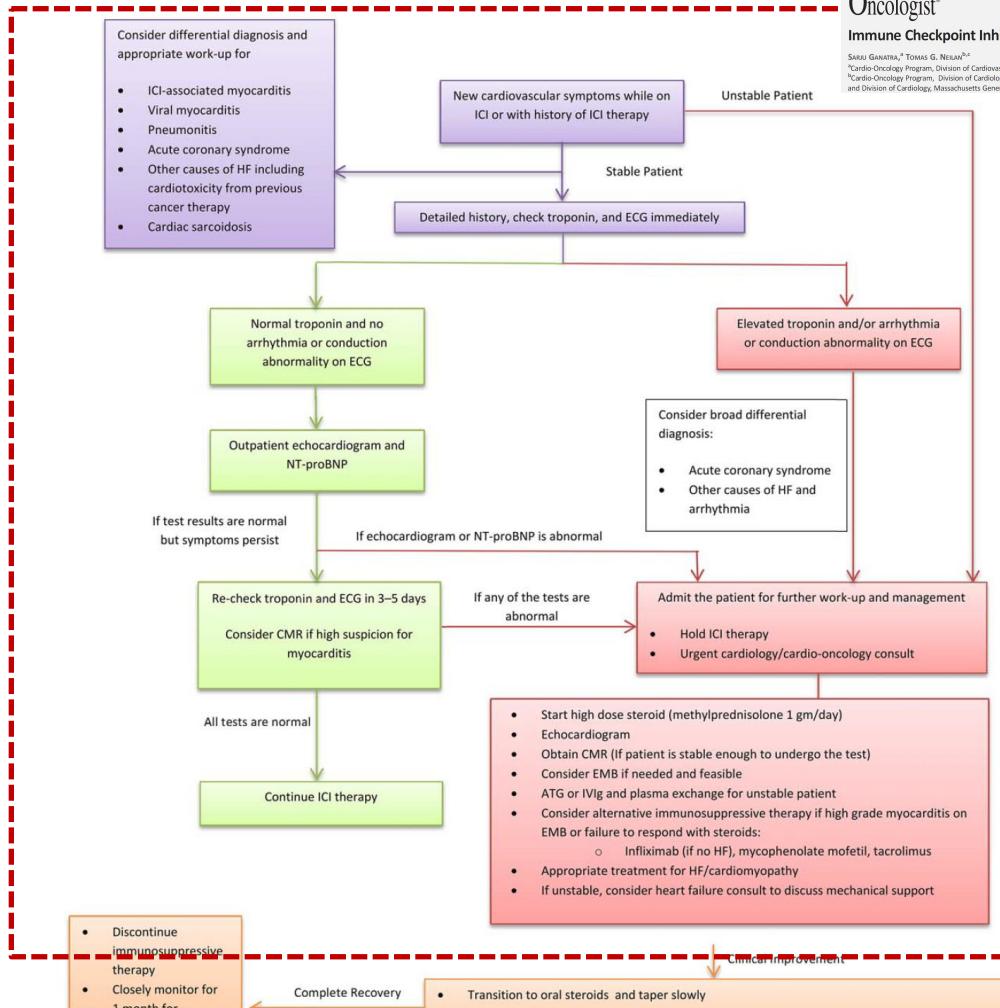


Immune Checkpoint Inhibitor-Associated Myocarditis

Sara Gherardi,¹ Tomas G. Neumann²

¹Cardio-Oncology Program, Division of Cardiovascular Medicine, Lahey Hospital and Medical Center, Burlington, Massachusetts, USA;
²Cardio-Oncology Program, Division of Cardiology, Department of Medicine and ³Cardiac MR PET CT Program, Department of Radiology and Division of Cardiology, Massachusetts General Hospital, Boston, Massachusetts, USA



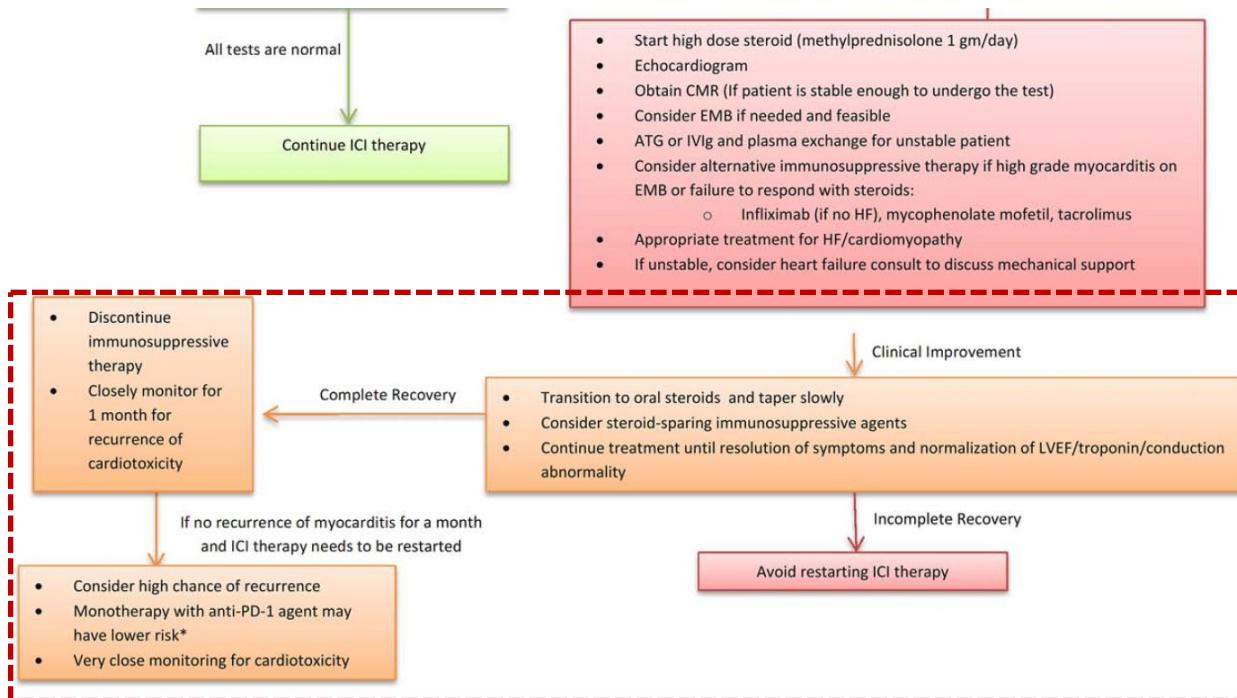


Immune Checkpoint Inhibitor-Associated Myocarditis

SARJU GANATRA,^a TOMAS G. NEILAN^{b,c}

^aCardio-Oncology Program, Division of Cardiovascular Medicine, Lahey Hospital and Medical Center, Burlington, Massachusetts, USA;

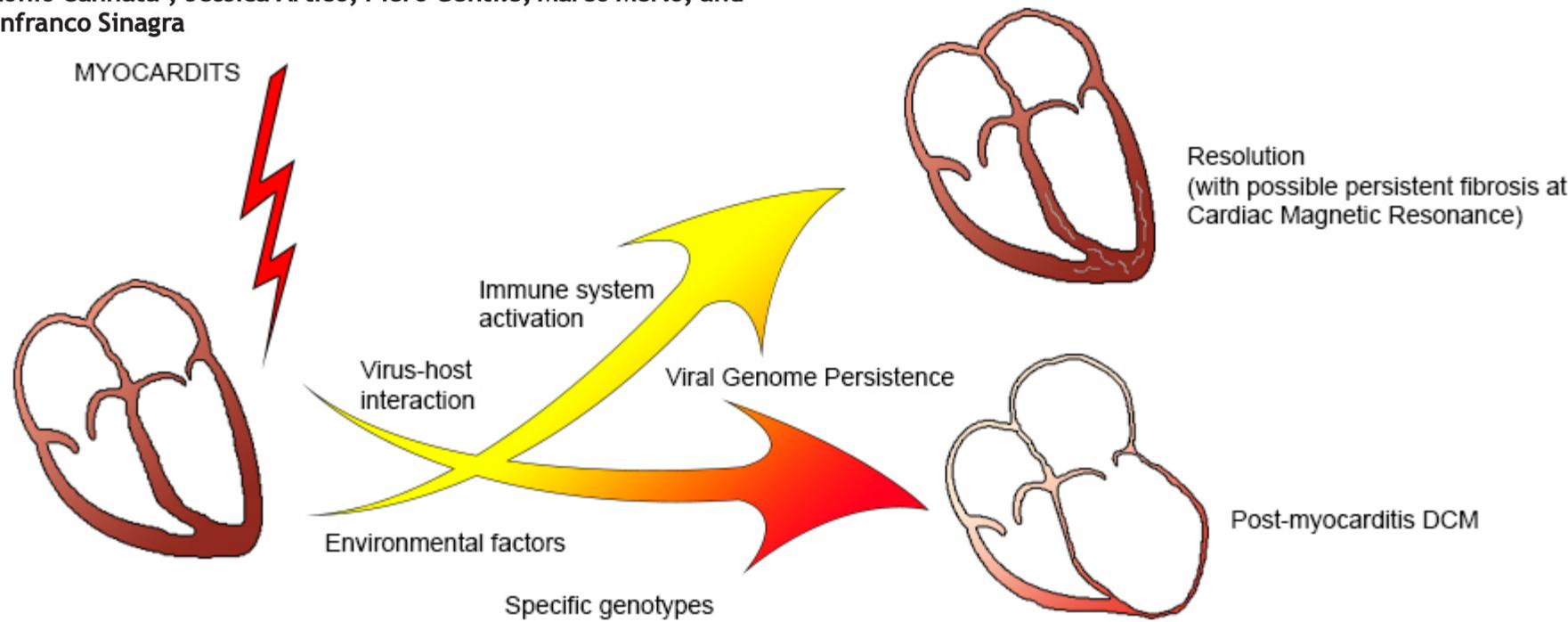
^bCardio-Oncology Program, Division of Cardiology, Department of Medicine and ^cCardiac MR PET CT Program, Department of Radiology and Division of Cardiology, Massachusetts General Hospital, Boston, Massachusetts, USA



Myocarditis evolving in cardiomyopathy: when genetics and offending causes work together

European Heart Journal Supplements 2019;21:B90-B95

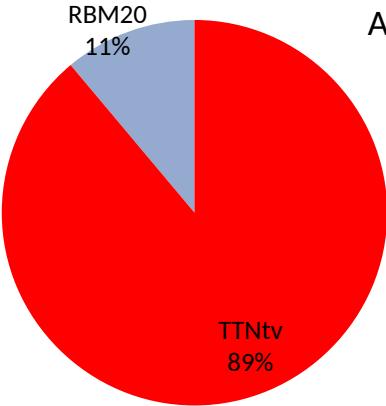
Antonio Cannata¹, Jessica Artico, Piero Gentile, Marco Merlo, and Gianfranco Sinagra



Lymphocytic Myocarditis

A Genetically Predisposed Disease?

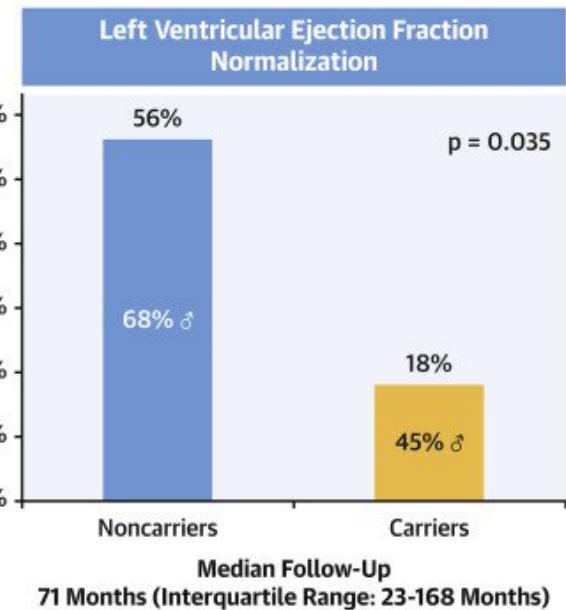
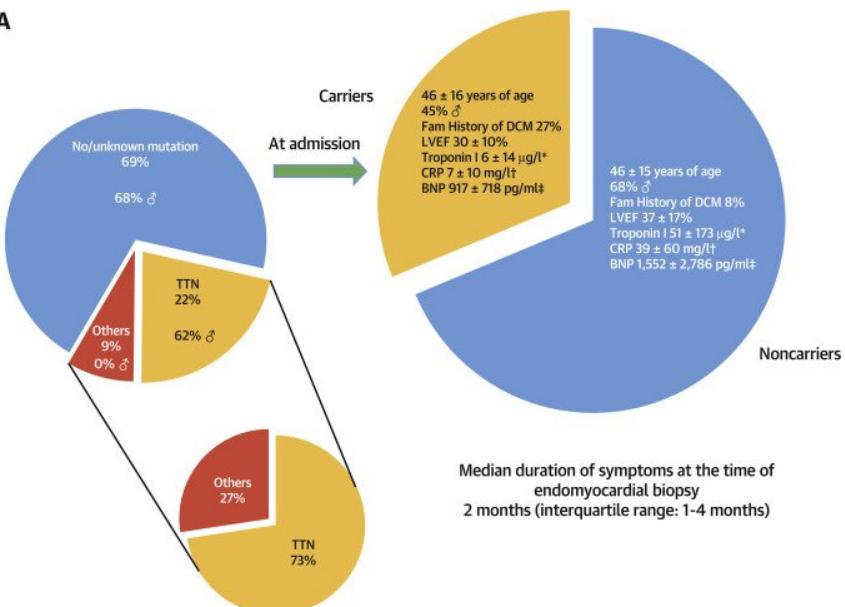
36 patients with biopsy proven myocarditis



Artico, Merlo, Cannata', Gentile et al. JACC 2020;75:3098-3099

Patients with biopsy-proven myocarditis, heart failure at admission and positive genetic testing

A



Acute Myocarditis Associated With Desmosomal Gene Variants

Ammirati E, Gentile et al. JACC HF. 2022

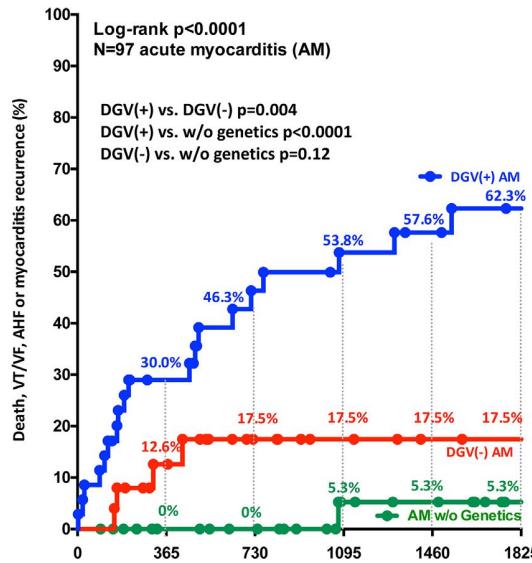
97 patients with Acute Myocarditis (*Tn*⁺ and CMR/EMB)

36 with AM and DGV+

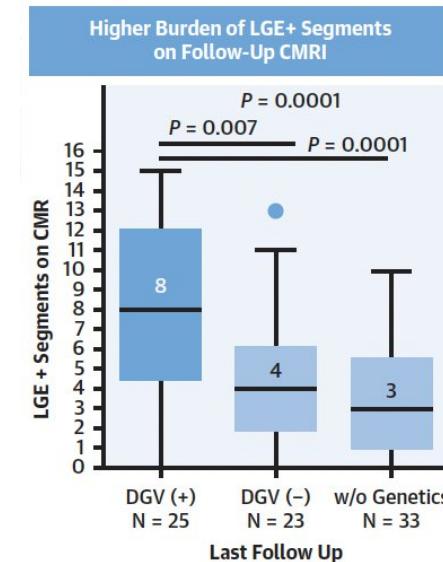
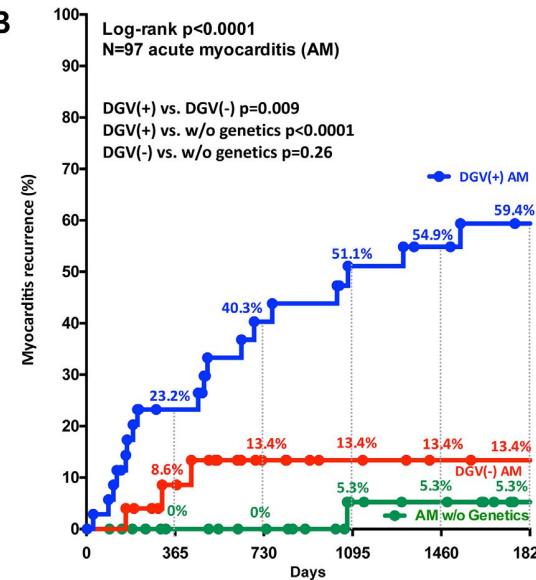
25 with AM and DGV-

36 with AM without genetics testing

A



B



Take home messages

- Esistenza di diversi scenari clinici con associate prognosi differenti
- Importanza del dato istologico in specifici sottogruppi di pazienti con sospetta miocardite (es miocardite eosinofila e gigantocellulare)
- Non affidarsi alla FEVS nella definizione del rischio aritmico alla dimissione di paziente con miocardite ed esordio aritmico maggiore
- L'Incidenza di miocarditi da immune checkpoint inhibitor (ICI) è stata riportato dello 0.06-1.33% tra i pz in terapia con tali farmaci. Prevalenza maggiore in pz con terapia combinata. Esordiscono in genere dopo 34 gg - 3 mesi dall'inizio della terapia con un 46% di MACE (maggior rischio chi ha alti valori di Tn). Trattamento con interruzione di terapia e cortisone.
- Pensare alla genetica nei pazienti con particolare presentazione clinica
- Testare e confermare le nostre ipotesi...

MYTHS TRIAL

MYocarditis TTherapy with Steroids

Study duration: 3 years Study Start: Oct. 2021 Follow up: 6 months

Single blind, randomized controlled, multicenter, international, phase III trial – **Coordinating center: Niguarda hospital, Milan, ITALY**
PI: Dr. Enrico Ammirati



Suspected AM complicated by acute HF cardiogenic shock (LVEF<41% & LVEDD <56 mm on echo)



Control arm (n=144)
(placebo)

Intervention arm (n=144)
(i.v. methylprednisolone 1g x 3d)

Primary endpoint:

To demonstrate a reduction in the rate of all-cause death, HTx, LVAD implant, need for upgrading t-MCS, VA treated with DC shock, hospitalization due to HF, VA, AVB



Clinicaltrials.gov: NCT05150704

Funded by the Italian Ministry of Health (GR-2019-12368506)

USJPEU MYTHS TRIAL – INVESTIGATOR DRIVEN PRAGMATIC INTERNATIONAL TRIAL 3 continents, 10 nations



US
CALIFORNIA - UCSD (1)
TEXAS (2)
VIRGINIA (2)
COLORADO (1)
NY (2)

EU
ITALY (18)
SPAIN (8)
BELGIUM (3)
SWEDEN (3)
DENMARK (1)
CZECH REP (1)
FRANCE (1)
FINLAND (1)

JP
JAPAN (2)

CENTERS
that are active
15
+
CENTERS
with IRB approval
4
CENTERS
sent protocol to IRB
10
CENTERS
expressed interest
17
TOTAL
46

Grazie

Myocarditis in Patients Treated With Immune Checkpoint Inhibitors

TABLE 2 Baseline Cancer Demographics

	Myocarditis (n = 35)	Control (n = 105)	p Value
Single agent vs. combined			
Combination (ever received)	12 (34.3)	10 (9.5)	<0.001
Combination (current regimen)	12 (34.3)	2 (1.9)	<0.001
Monotherapy (current regimen)	23 (65.7)	103 (96.0)	
Combined ICI			
Ipilimumab (anti-CTLA4) + nivolumab (anti-PD1)	9 (26.0)	9 (8.6)	0.02
Ipilimumab (anti-CTLA4) + pembrolizumab (anti-PD1)	1 (2.9)	0 (0.0)	0.25
Tremelimumab (anti-CTLA4) + avelumab (anti-PDL1)	1 (2.9)	0 (0.0)	0.25
Tremelimumab (anti-CTLA4) + durvalumab (anti-PDL1)	1 (2.9)	1 (1.0)	0.44
Current monotherapy ICI†			
Pembrolizumab (anti-PD1)	11 (31.0)	41 (39.0)	0.54
Nivolumab (anti-PD1)	7 (20.0)	53 (51.0)	0.002
Ipilimumab (anti-CTLA4)	2 (5.7)	9 (8.6)	0.73
Tremelimumab (anti-CTLA4)	1 (2.9)	0 (0.0)	0.25
Atezolizumab (anti-PDL1)	2 (5.7)	0 (0.0)	0.06
Avelumab (anti-PDL1)	0 (0.0)	0 (0.0)	—
Durvalumab (anti-PDL1)	0 (0.0)	0 (0.0)	—
Overall types of ICI			
Any anti-PD1	28 (80.0)	102 (97.0)	0.002
Any anti-CTLA4	18 (51.0)	29 (27.0)	0.01
Any anti-PDL1	4 (11.0)	2 (2.0)	0.03
Pembrolizumab	16 (46.0)	49 (47.0)	1.00
Nivolumab	16 (46.0)	60 (57.0)	0.25
Ipilimumab	15 (43.0)	28 (27.0)	0.09
Atezolizumab	2 (5.7)	1 (1.0)	0.15
Avelumab	1 (2.9)	0 (0.0)	0.25
Durvalumab	1 (2.9)	1 (1.0)	0.44
Tremelimumab	3 (8.6)	1 (1.0)	0.048
Days of follow-up	209 ± 300	281 ± 286	0.69



Compared with controls, myocarditis cases were more likely to have received combination ICI.

Of the combination therapies at the time of presentation, anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA4) with anti-programmed cell death protein 1 (anti-PD1) was the most frequent in cases.

Myocarditis in Patients Treated With Immune Checkpoint Inhibitors

TABLE 3 Comparison of Myocarditis Cases With and Without MACE

	No MACE (n = 19)	MACE (n = 16)	p Value
Myocarditis presentation			
Chest pain	7 (37.0)	5 (31.0)	1.00
Shortness of breath	11 (58.0)	14 (88.0)	0.07
Orthopnea	3 (16.0)	7 (44.0)	0.13
Paroxysmal nocturnal dyspnea	3 (16.0)	3 (19.0)	1.00
Fatigue	4 (21.0)	6 (38.0)	0.45
ECG, myocarditis admission			
Sinus rhythm	17 (90.0)	10 (63.0)	0.10
QRS interval, ms	102 ± 19	103 ± 20	0.83
QTc interval, ms	457 ± 28	457 ± 44	0.98
Echocardiography, myocarditis admission			
New LVEF, %	49 ± 17	41 ± 18	0.25
Change in LVEF from baseline	16 ± 16	19 ± 11	0.66
Left ventricular internal dimensions in diastole, mm	49 ± 6	47 ± 14	0.41
Pericardial effusion	5 (26.0)	1 (7.7)	0.19
Late gadolinium enhancement on a cardiac magnetic resonance study†			
None	6 (33.0)	2 (15.0)	0.41
Subepicardial	3 (16.0)	3 (23.0)	1.00
Mid-myocardial	4 (21.0)	8 (62.0)	0.06
Diffuse	5 (26.0)	4 (31.0)	1.00
Elevated troponin	17 (90.0)	16 (100.0)	0.48
Troponin T, ng/ml‡			
Admission	0.54 (0.01-1.55)	1.18 (0.19-5.90)	0.01
Peak	1.33 (0.01-3.5)	2.68 (0.24-7.63)	0.01
Final/discharge	0.14 (0.01-1.55)	1.45 (0.03-6.41)	0.002

TABLE 3 Comparison of Myocarditis Cases With and Without MACE

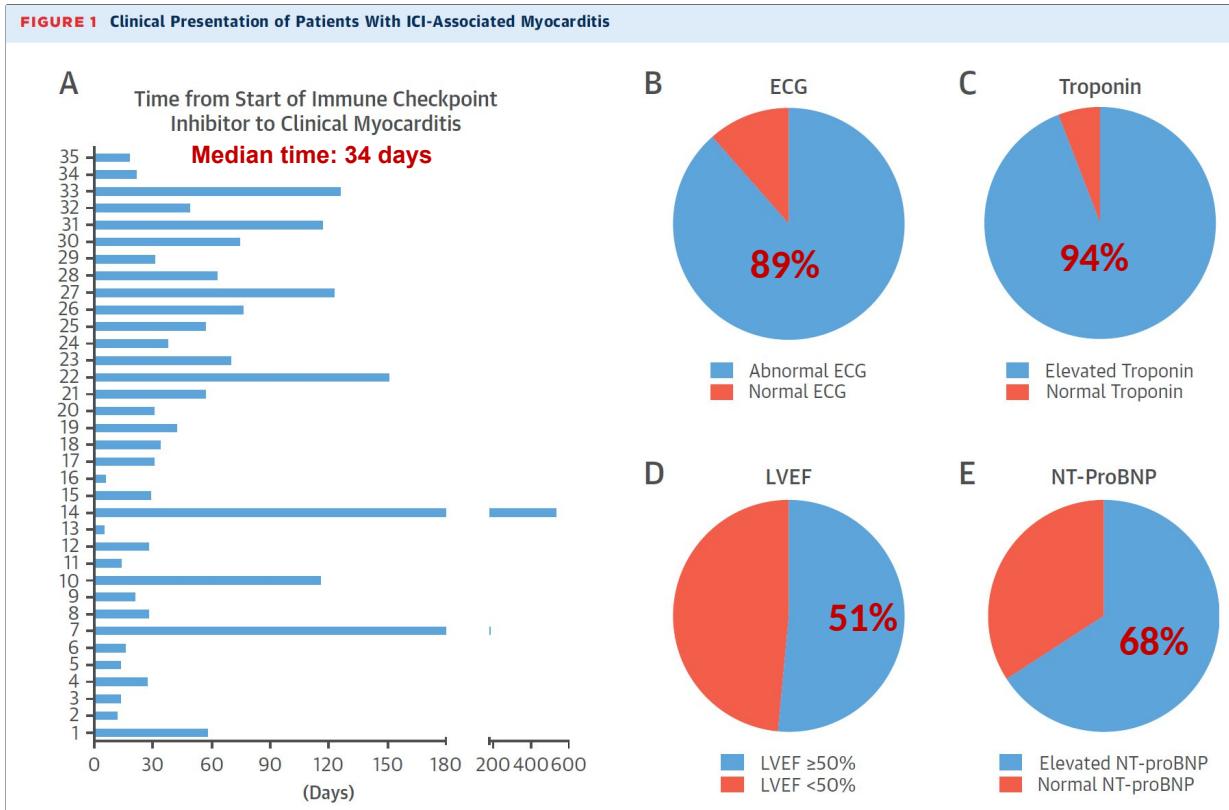
	No MACE (n = 19)	MACE (n = 16)	p Value
BNP or NT-proBNP	12 (63.0)	11 (69.0)	1.00
Serum sodium (admission), meq/l	137.0 ± 3.9	135.0 ± 4.1	0.144
Serum creatinine (admission), mg/dl	1.1 (0.5-2.6)	1.1 (0.5-3.9)	0.84
White cell count (admission), cells/ml³	8.4 (4.4-14.5)	11.6 (3.1-35.7)	0.133
Hemoglobin (admission), g/dl	12.0 ± 1.9	12.8 ± 2.9	0.31
Number of patient on steroids before myocarditis	4 (21.0)	3 (19.0)	1.00
Initial steroid dose, mg	160.0 (0.0-1,000.0)	72.5 (0.0-1,000.0)	0.055
Initial steroid dose/body weight, (mg/kg)	2.06 (0.00-20.20)	0.84 (0.00-14.40)	0.041
Time from admission to steroid administration, h	18.3 ± 12.8	27.2 ± 17.5	0.12

Of the 16 MACE, 6 (38%) occurred in patients with a normal LVEF

As compared with non-MACE myocarditis cases, those who experienced a MACE had a **higher admission, peak, and discharge/final troponin T value**.

Steroids were initial treatment of myocarditis in 31 (89%) cases. A **higher initial steroid dose** was associated with lower rate of MACE

Myocarditis in Patients Treated With Immune Checkpoint Inhibitors



SARIU GANAPATHY,^a TOMAS G. NEILAN^{b,c}

^aCardio-Oncology Program, Division of Cardiovascular Medicine, Lahey Hospital and Medical Center, Burlington, Massachusetts, USA;
^bCardio-Oncology Program, Division of Cardiology, Department of Medicine and ^cCardiac MR PET CT Program, Department of Radiology and Division of Cardiology, Massachusetts General Hospital, Boston, Massachusetts, USA

What are the predictors of outcome?

Pre-ICI LVEF

Elevated cTn and presence of conduction abnormalities are predictors of worse outcomes/MACE.

Cardiac troponin

Retrospective data from the registry does not show any correlation between baseline LVEF and MACE.

Electrical conduction abnormality

Higher level of cTn is shown to be associated with MACE, heart failure, and arrhythmia.

Electrical conduction abnormalities may suggest underlying severe myocarditis and has been reportedly associated with fulminant outcomes.

How to treat?

Corticosteroids

There are no prospective studies evaluating various treatment regimens but several clinical experience-based algorithms provide detailed practical guidance for management. Cessation of ICI therapy and immunosuppression are the cornerstones of treatment.

High-dose corticosteroids (1,000 mg methylprednisolone/day for first 3 days followed by oral prednisone 1 mg/kg) is usually the first line of therapy in the acute phase.

Immunosuppressive therapy

For unstable patients: ATG or IVIg and plasma exchange need to be considered. For stable patients: Tacrolimus or mycophenolate mofetil or infliximab may be considered for patients with evidence of high-grade myocarditis on biopsy or for those who fail to respond to corticosteroid therapy or as a steroid-sparing agent. Note: Infliximab is contraindicated in presence of moderate to severe HF.

Is it safe to restart ICI after myocarditis?

There may be a risk of recurrence. There are no prospective data to guide this complex decision, which needs to be individualized with multidisciplinary discussion considering the cancer status, response to immunotherapy, availability of alternative effective therapy, severity of cardiotoxicity, regression of toxicity with immunosuppressive therapy, and patient preference after weighing risks and benefits.

Which agent to use if there is a need to restart immunotherapy?

Retrospective study has observed lower incidence of cardiotoxicity with anti-PD-1 monotherapy. Another retrospective study also shows the safety of anti-PD-1 therapy in patients who needed to restart ICI therapy after discontinuation of anti-CTLA-4 agent secondary to irAE requiring immunosuppression. It is unclear what to do if original cardiotoxicity was noted with anti-PD-1 agent.