



Trattamento della miocardite immunomediata

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26 giugno, 2026 SESSIONE: IL CUORE INFIAMMATO



**European
Reference
Network**

for rare or low prevalence
complex diseases

❖ **Network**
Heart Diseases
(ERN GUARD-HEART)

Sessione: il cuore infiammato

Trattamento della miocardite immuno-mediata

Prof. Alida LP Caforio, MD, PhD, FESC,

26 giugno, 2026



2025 ESC Guidelines for the management of myocarditis and pericarditis

Developed by the task force for the management of myocarditis and pericarditis of the European Society of Cardiology (ESC)

Endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC) and the European Association for Cardio-Thoracic Surgery (EACTS)

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Lights and shadows

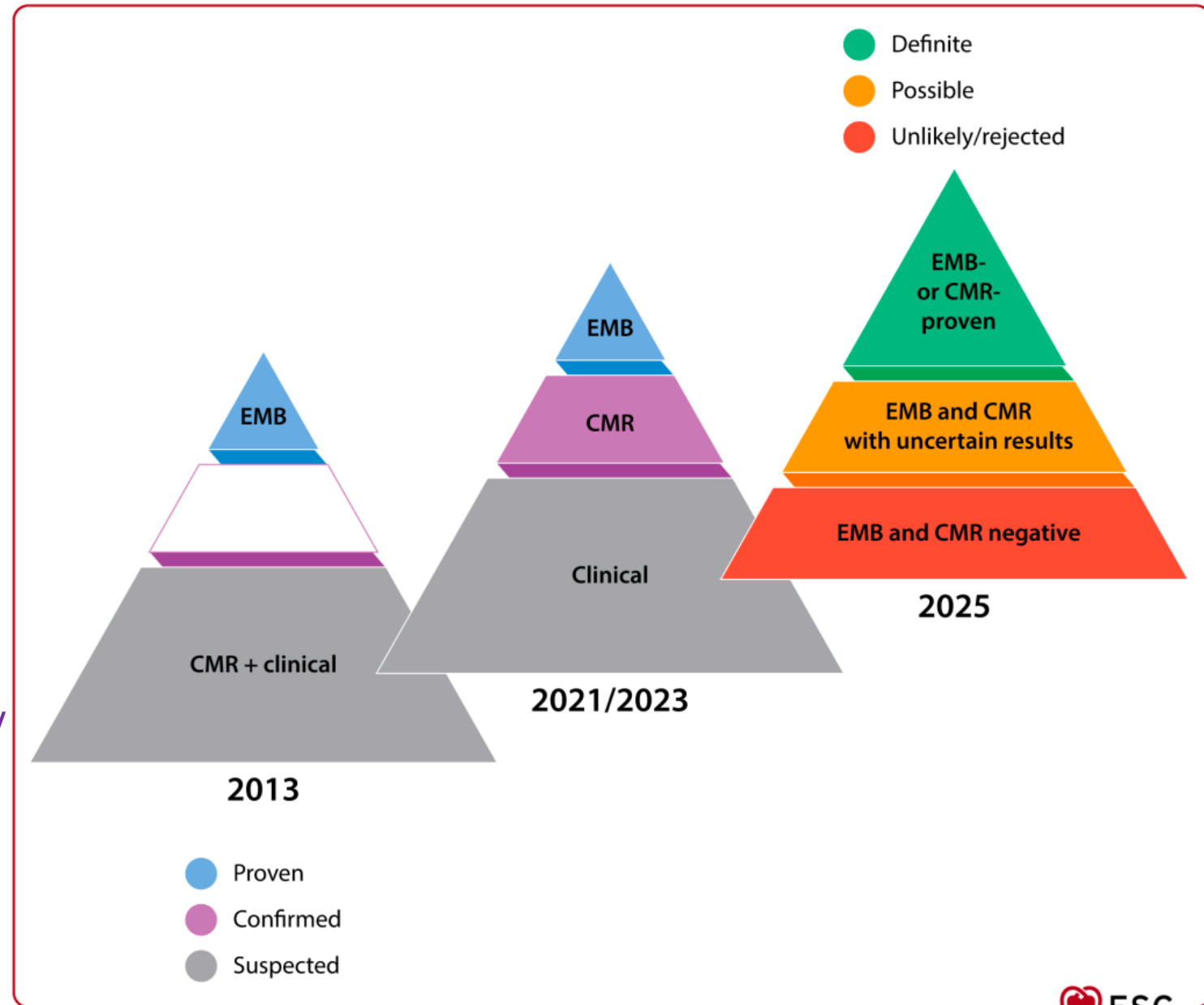
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Paradigm change in the clinical diagnosis of myocarditis

CMR is not equivalent of EMB

- CMR does not identify histopathological stage (acute/chronic/chronic active)
- CMR does not identify histotype (lymphocytic vs rare non lymphocytic histotypes)
- CMR may not differentiate myocarditis from non inflammatory phenocopies
- CMR does not identify myocarditis etiology and cannot direct etiology-specific therapies:
 - infectious or non infectious immunemediated/autoimmune
 - Specific infectious agents and load of myocardial infection



Terminology

Definition

Chronic myocarditis/pericarditis

Duration of symptoms >3 months

**What is Inflammatory cardiomyopathy
with or without DCM phenotype ?**

Inflammatory cardiomyopathy

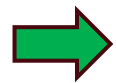
Chronic myocarditis in association with cardiac dysfunction and ventricular remodelling with clinical phenotype of hypokinetic, either dilated or non-dilated cardiomyopathy with/without arrhythmogenic substrate

- **Definition (Circulation, 1995 WHO/ISFC classification; Eur Heart J 2013)**
 - Myocarditis is an inflammatory disease of the myocardium and is diagnosed by **established histological, immunological and immunohistochemical criteria**
 - Inflammatory cardiomyopathy is **myocarditis in association di cardiac dysfunction.**
 - Inflammatory cardiomyopathy is **involved in the pathogenesis of DCM**, and includes
 - **Idiopathic, infectious and autoimmune subtypes**

Table 7 Clinical risk stratification to guide work-up in inflammatory myopericardial syndrome

Risk	High risk	Intermediate risk	Low risk
Myocarditis	• Acute HF/cardiogenic shock • Dyspnoea NYHA III–IV refractory to medical therapy • Cardiac arrest/syncope^a • Ventricular fibrillation/sustained ventricular tachycardia^a • High-level AV block^a	• New/progressive dyspnoea • Non-sustained ventricular arrhythmias • Persistent release or relapsing troponin	Stable symptoms or oligosymptomatic
	Imaging criteria:	Imaging criteria:	Imaging criteria:
	• Newly reduced LVEF (<40%)^a • Extensive LGE on CMR^a	• Newly mildly reduced LVEF (41%–49%) and/or WMA • Preserved LVEF (≥50%) and LGE ≥2 segments on CMR	• Preserved LVEF (≥50%) without LGE or limited LGE (<2 segments) on CMR

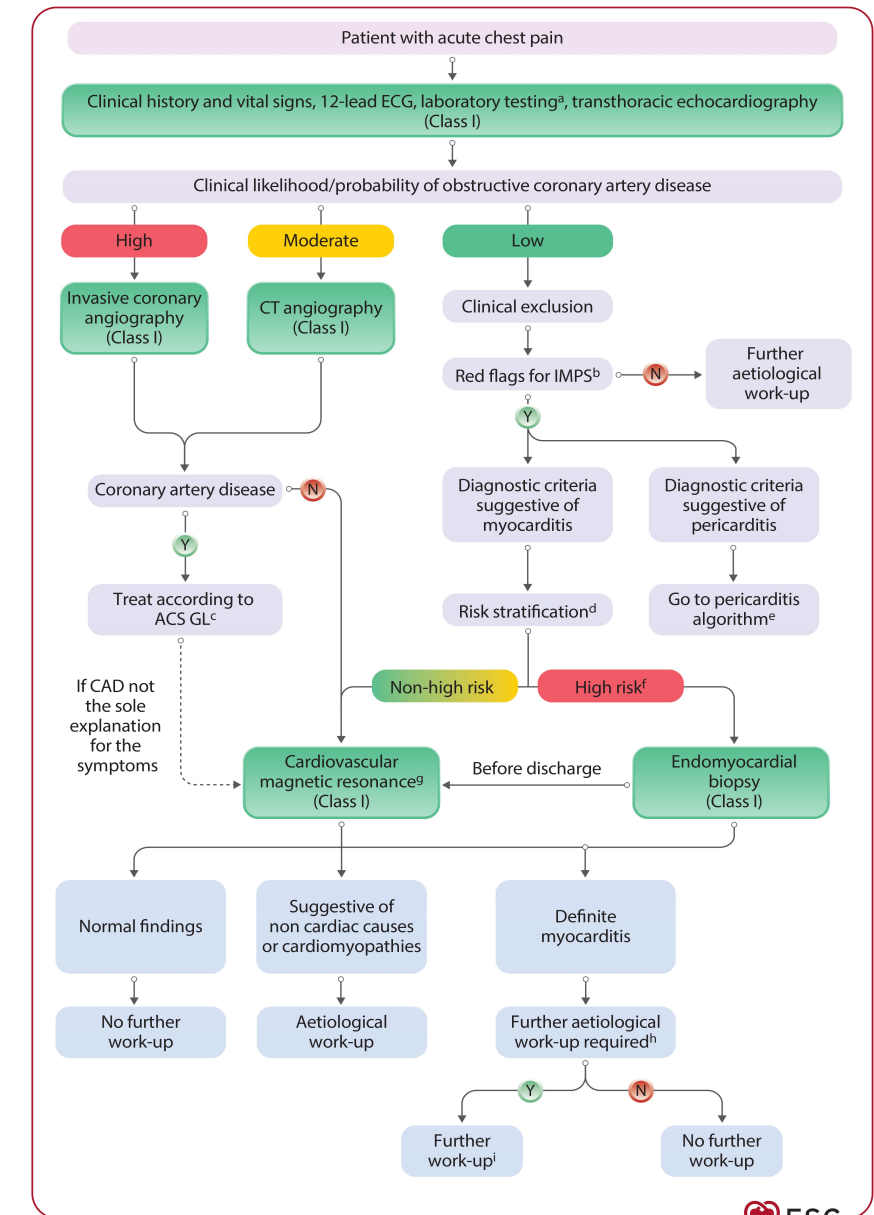
Lights....



CMR is recommended in patients with the clinical suspicion of myocarditis (using updated LL criteria) ³⁰ and/or pericarditis for the non-invasive diagnosis of inflammatory reaction. ^{110,115,129}	I	B
Hospital admission is recommended for patients with high-risk pericarditis ^d for monitoring and treatment. ^{105,130}	I	B
Hospital admission is recommended for patients with moderate- to high-risk myocarditis ^d for monitoring and treatment.	I	C
EMB ^e is recommended in patients with high-risk myocarditis ^d and/or haemodynamic instability, and/or in patients with intermediate-risk myocarditis not responding to conventional therapy in order to detect a specific histologic subtype and to assess the presence of viral genome for treatment. ^{34,63,73,131}	I	C
Invasive coronary angiography or coronary CT, depending on clinical likelihood, is recommended in patients with IMPS if an acute coronary syndrome is suspected to rule out obstructive coronary artery disease.	I	C
Hospital admission should be considered for patients with low-risk myocarditis ^d for monitoring and treatment.	IIa	C



Figure 9 Diagnostic algorithm for suspected myocarditis with acute chest pain presentation.



2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Table 32 Endomyocardial biopsy in patients with suspected myocarditis

Indication (see also Section 4.3). Progressive or persistent severe cardiac dysfunction and/or life-threatening ventricular arrhythmias and/or Mobitz type 2 second-degree or higher AV block with lack of short-term (<1-2 weeks) expected response to usual medical treatment. The aim is to identify aetiology and to indicate specific treatment (e.g. giant cell myocarditis, eosinophilic myocarditis, cardiac sarcoidosis, systemic inflammatory disorders). ^{97,98,917,918,958}
Number and sites of the samples A minimum of 5 but possibly at least 7 samples, 3 for pathology, 2 for infections (DNA, PCR) and 2 for RNA viruses/viral replication. Left and/or right ventricle. CMR or PET guided sampling may be considered. ⁹¹⁹
Aetiology Quantitative PCR viral genome analysis for common cardiotrophic viruses (parvovirus B19, HHV4, HHV6, enteroviruses, adenovirus and coxsackievirus) by rtPCR. Viral mRNA for active viral replication may be assessed although it has low sensitivity. On indication, search for CMV, HIV, <i>Borrelia</i> , <i>Coxiella burnetii</i> (Q-fever) and SARS-CoV-2.
Diagnosis of inflammation Immunohistochemistry with staining for anti-CD3-, CD4-, CD8- or CD45 antibodies for lymphocytes and anti-CD68 antibodies for macrophages and anti-HLA-DR antibodies. ^{907,917,918,959}
Therapeutic implications Immunosuppressive therapy may be indicated based on the results of EMB as in giant cell myocarditis or eosinophilic myocarditis and, possibly, also in sarcoidosis, vasculitis or selected patients with increased cardiac inflammation of unknown origin based upon multidisciplinary counselling. ^{98,917–919,954} Antibiotics: <i>Borrelia</i> (Lyme disease). Antiviral therapy: HIV, CMV, HHV6 pending on load and viral replication (mRNA).

- **Aim of EMB in suspected myocarditis in HF presentation: to identify etiology and specific treatment , i.e. antiviral or immunosuppression based upon multidisciplinary counselling**

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VOL. ■, NO. ■, 2024

EXPERT CONSENSUS DECISION PATHWAY

2024 ACC Expert Consensus Decision Pathway on Strategies and Criteria for the Diagnosis and Management of Myocarditis

A Report of the American College of Cardiology Solution Set Oversight Committee
Endorsed by the Heart Failure Society of America, International Society of Cardiomyopathies, Myocarditis and Heart Failure, and the Myocarditis Foundation

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TOP 10 KEY TAKEAWAY POINTS

3. Cardiac magnetic resonance (CMR) imaging and endomyocardial biopsy (EMB) are considered pivotal tests in the diagnosis of myocarditis.;... in patients with certain presentations—typically those with reduced ventricular function, deranged hemodynamics/ symptomatic HF, or electrical instability—an EMB is warranted to diagnose specific conditions that require etiology-directed therapies, including immunosuppressive agents.

Myocarditis diagnosis: – *molecular diagnosis of infectious myocarditis*

Viral myocarditis

Histological evidence for myocarditis associated with positive viral polymerase chain reaction (PCR) (Table 1).

Autoimmune myocarditis

Histological myocarditis with negative viral PCR, with or without serum cardiac autoantibodies (aabs) (Table 2).

N.B. There are autoimmune diseases (e.g. Hashimoto's thyroiditis) where aabs are mainly biomarkers, autoantibody-mediated forms (e.g. Graves' disease), in which aabs are pathogenic, and cell-mediated autoimmune diseases, which are negative for aabs. In all cases, autoimmune diseases are negative for infectious agents.

Viral and immune myocarditis

Histological myocarditis with positive viral PCR and positive cardiac aabs (Table 2).

N.B. A follow-up EMB may document persistent viral myocarditis, histological and virological resolution, or persistent virus-negative myocarditis, with or without serum cardiac aabs, e.g. post-infectious autoimmune disease.

- Antiviral therapy first, if available, to achieve viral clearance (off –label)
- Immunosuppression if clinically indicated (LV dysfunction, arrhythmia), viral clearance and persistent myocarditis at follow-up biopsy

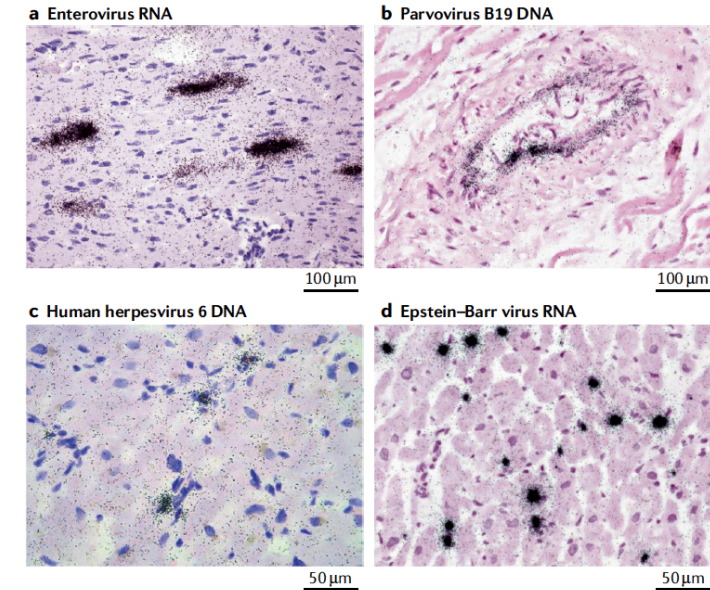


Fig. 4 | Visualization of viral nucleic acids in acute myocarditis. Viral nucleic acids in heart tissue samples from patients with acute myocarditis can be detected with radioactive in situ hybridization (black spots). Cell nuclei (purple) and cell cytoplasm and extracellular matrix (pink) are visualized with haematoxylin and eosin staining. Enteroviruses (panel a) infect and lyse cardiomyocytes, parvovirus B19 (panel b) infects endothelial cells, and human herpesviruses (panel c) and Epstein-Barr viruses (panel d) replicate in immune cells. Panels a and b x400, panels c and d x630.

NATURE REVIEWS | CARDIOLOGY



Caforio et al. Eur Heart J
2013; 34:2636-48

Calabrese et al., Diagn Mol Pathol 2002; 11(4):212-21

Myocarditis diagnosis: –immunological diagnosis of autoimmune/immune-mediated myocarditis

Viral myocarditis

Histological evidence for myocarditis associated with positive viral polymerase chain reaction (PCR) (Table 1).

Autoimmune myocarditis

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Viral and immune myocarditis

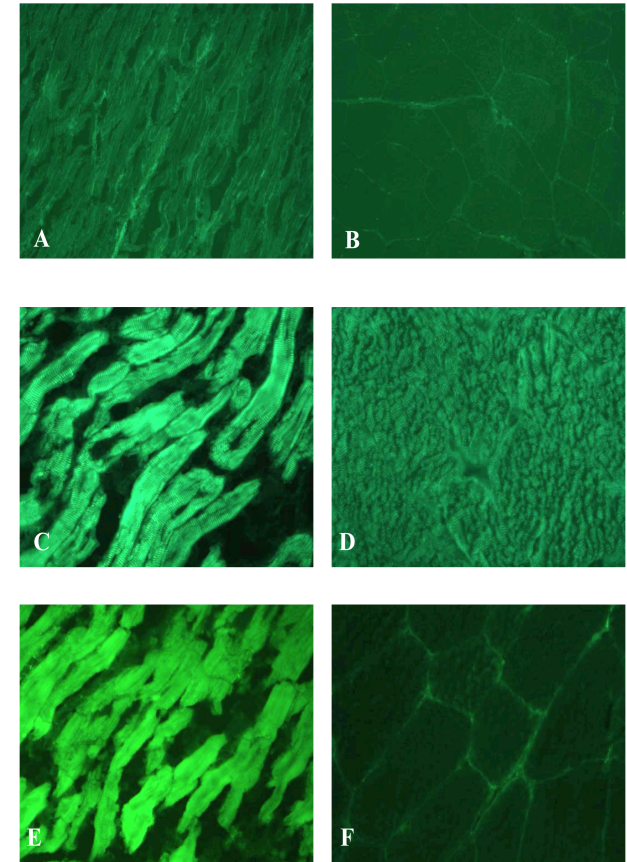
Histological myocarditis with positive viral PCR and positive cardiac aabs (Table 2).

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**Caforio et al. Eur Heart J
2013; 34:2636-48**

**Efficacy of
immunosuppression/
immunomodulation in
patients with proven
non infectious immune-
mediated/autoimmune
disease**

Do we have noninvasive biomarkers for
Autoimmune biopsy-proven myocarditis?
(60-81%): serum AHA pos virus PCR neg



Eur Heart J 2007; 28:1326-33

Recommendations for medical therapy in myocarditis (1)

Recommendations	Class	Level
<i>Management of symptoms</i>		
NSAIDs (together with proton pump inhibition) should be considered in patients with associated symptoms of pericarditis to reduce symptoms.	Ila	C
Colchicine should be considered in patients with myopericarditis to reduce recurrences	Ila	B
<i>Management of heart failure</i>		
Adherence to the ESC HF guidelines is recommended in cases of myocarditis with LV systolic dysfunction and/or HF to reduce symptoms and to improve LV function.	I	C
HF therapy should be considered in patients with myocarditis and LV systolic dysfunction for at least 6 months upon complete LV functional recovery to stabilize LV function.	Ila	C
<i>Management of arrhythmias</i>		
β-Blockers, with a continuation for at least 6 months, should be considered in patients with acute myocarditis, especially those with troponin elevation, to control symptoms and prevent arrhythmias.	Ila	C
Anti-arrhythmic treatment should be considered in post-myocarditis patients with recurrent, symptomatic VT to reduce arrhythmic burden.	Ila	C

Recommendations for management of arrhythmias and prevention of sudden cardiac death in myocarditis (1)

Recommendations	Class	Level
<i>Pacing in myocarditis</i>		
Temporary transvenous external pacing should be considered in patients with acute myocarditis and high-degree conduction disorders as a bridge to recovery.	Ila	C
<i>WCD in myocarditis</i>		
A WCD should be considered for 3–6 months in patients with sustained ventricular arrhythmia during the acute phase of myocarditis as a bridge to recovery.	Ila	C
<i>Ablation in myocarditis</i>		
Catheter ablation, performed in specialized centres, should be considered in post-myocarditis patients with recurrent symptomatic SMVT or ICD shocks in whom AAD are ineffective, not tolerated, or not desired.	Ila	C
<i>ICD in myocarditis</i>		
<i>Secondary prevention</i>		
ICD implantation is recommended in patients with non-active myocarditis and haemodynamically not-tolerated sustained VT to prevent SCD	I	C

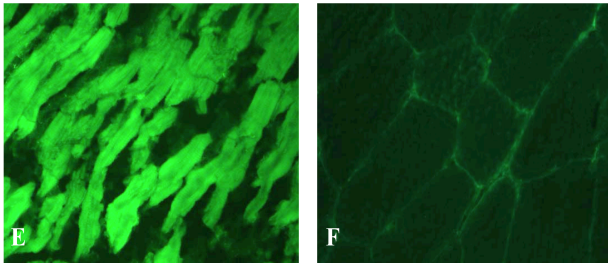
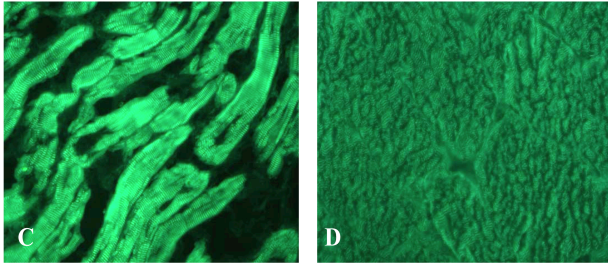
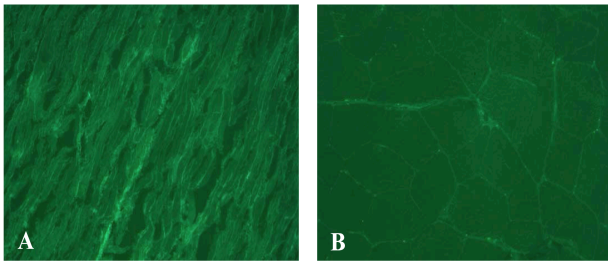
Recommendations for management of arrhythmias and prevention of sudden cardiac death in myocarditis (2)

Recommendations (Continued)	Class	Level
<i>Secondary prevention (Continued)</i>		
ICD implantation should be considered in patients with non-active myocarditis and haemodynamically tolerated sustained VT to prevent SCD.	Ila	C
ICD implantation may be considered in patients with acute myocarditis and sustained VA (VT/VF) in the acute phase to prevent SCD.	Ilb	C
<i>Primary prevention</i>		
ICD implantation may be considered in patients with myocarditis after the acute phase (3–6 months) and persistent risk factors for VA to prevent SCD	Ilb	C

Major Criteria of Autoimmune Disease

Witebsky E, Rose NR

- Mononuclear cell infiltrate and abnormal HLA expression in the target organ (organ-specific disease) or in various organs (nonorgan-specific disease) **in the absence of infectious agents**
- **Circulating autoantibodies (Abs) and/or autoreactive lymphocytes in patients (pts) and family members**
- Abs and/or autoreactive lymphocytes within the affected organ
- Identification and isolation of autoantigen(s) (Ags) involved
- Disease induction in animals after immunization with Ags and/or passive transfer of serum, Abs and/or lymphocytes
- **Efficacy of immunosuppression/immunomodulation in pts**
- ***Autoimmune disease= fulfillment of 2 or more major criteria***



International Journal of Cardiology 179 (2015) 166–177

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



Frequency of the cardiac antibodies detected by IFL in heart disease

Caforio et al, Eur J Heart Fail, 2002; Caforio et al, Lupus 2005

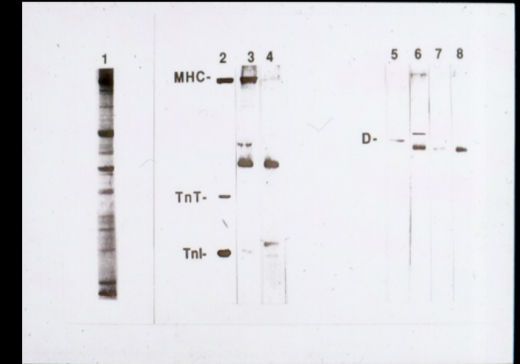
	Organ-specific n (%)	Cross-reactive-1 n (%)	Cross-reactive-2 n (%)	Neg n (%)
DCM (n=327)	83 (25)*^	35 (11)*^^	3 (1)	206 (63)
Myocarditis (n=161)	54 (33) *^	22 (14)**^	3 (6)	82 (51)
Relatives of DCM (n=567)	176 (31)*^	7 (1)	12 (2)	372 (66)
Other heart disease (OCD) (n=160)	1 (1)	7 (4)	5 (3)	147 (92)
Ischemic heart failure (IHF) (n=141)	1 (1)	1 (1)	8 (6)	131 (92)
Normals (n=270)	7 (2.5)	8 (3)	9 (3)	246 (91)

* p=0.0001 vs OCD or IHF; **p=0.0002 vs OCD
^ p=0.0001 and ^^p=0.0003 vs normals

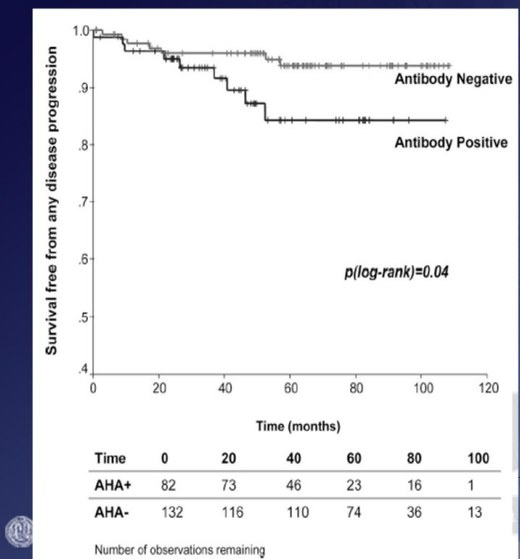
University of Padua

MHC as antigens in DCM-immunoblotting

Caforio et al, Circulation 1992



Survival free from any progression (DCM, LVE, DFS) by cardiac antibody status at diagnosis in relatives classified as normal at baseline



Caforio et al, Circulation 2007; 115, January 2/9

Passive transfer of affinity-purified anti-heart autoantibodies (AHA) from sera of patients with myocarditis induces experimental myocarditis in mice

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^c The Zabudowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel

^d Schwartz-Kip, Chair of Autoimmunity, Sackler Faculty of Medicine, Tel-Aviv University, Israel

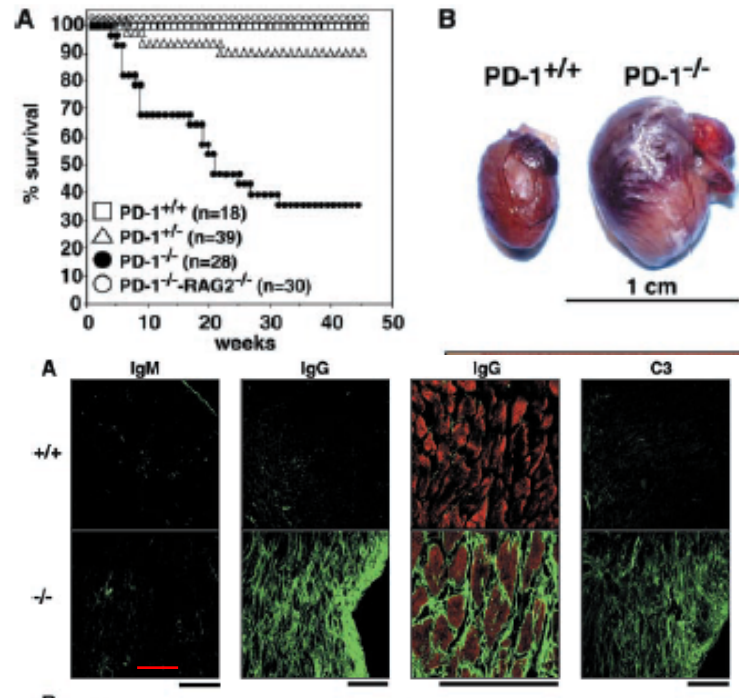
^e Wolfson Medical Center, Holon, Sackler Faculty of Medicine Tel Aviv University, Israel

^f Division of Rheumatology, Dept of Experimental and Clinical Sciences University of Padua, Padua, Italy

^g Clinical Pharmacology, Dept of Experimental and Clinical Sciences University of Padua, Padua, Italy

^h Clinical Immunology, Dept of Medicine University of Padua, Padua, Italy

Autoimmune Dilated Cardiomyopathy in PD-1 Receptor-Deficient Mice

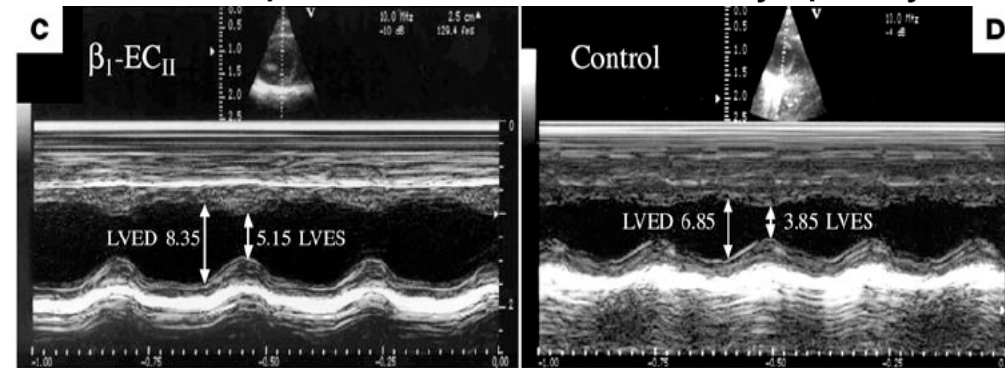


Autoaabs against TnI responsible for DCM in PD-1 receptor-deficient mice

Nishimura et al. Science 2001; 291:319-22

Okazaki et al. Nature Med

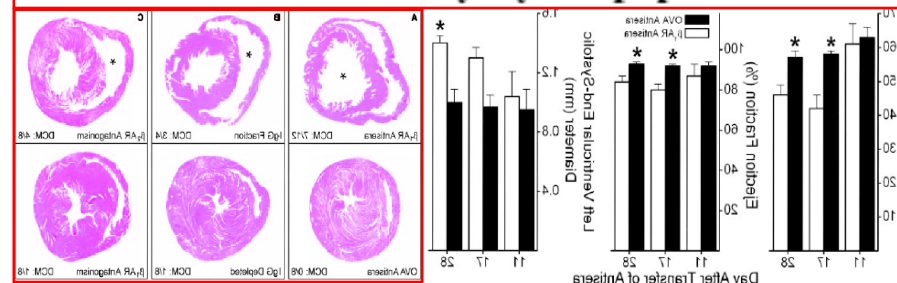
Direct evidence for a β_1 -adrenergic receptor-directed autoimmune attack as a cause of idiopathic dilated cardiomyopathy



Autoaabs against beta-1 adrenergic receptor responsible for DCM in rats

Jahns R, et al JCI 2004:1419-29

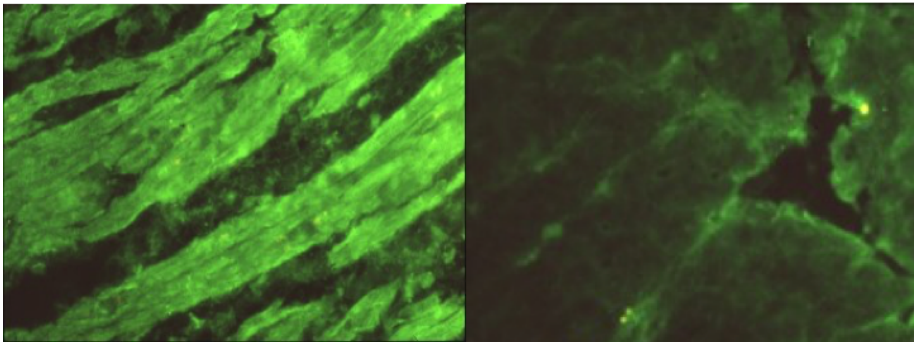
β_1 -Adrenergic Receptor Autoantibodies Mediate Dilated Cardiomyopathy by Agonistically Inducing Cardiomyocyte Apoptosis



Jane-wit et al, Circulation 2007: 116:399-410

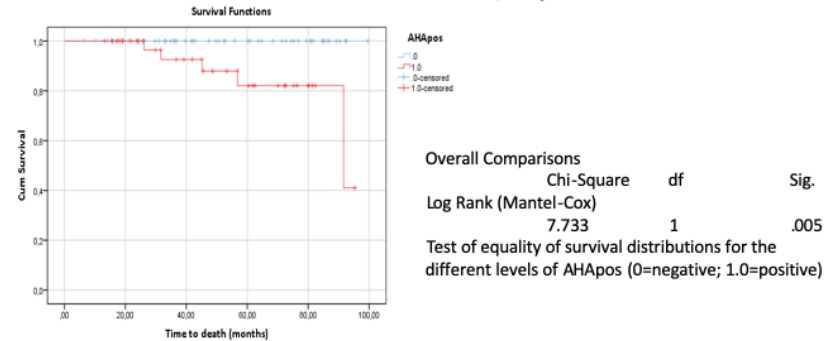
Serum Organ-Specific Anti-Heart and Anti-Intercalated Disk Autoantibodies as New Autoimmune Markers of Cardiac Involvement in Systemic Sclerosis: Frequency, Clinical and Prognostic Correlates

Diagnostics
2021, 11,
2165. <https://doi.org/10.3390/diagnostics1112165>



Organ-specific AHA positive serum on human heart (x400)

Same serum on human skeletal muscle: negative (x400)



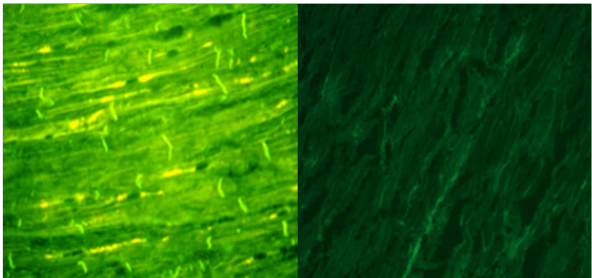
Kaplan-Meier curve comparing survival in SSc patients as a function of AHA status.

Take-home message: The high frequencies of AHA and AIDA suggest a high burden of underdiagnosed autoimmune cardiac involvement (HInv) in SSc. In keeping with the negative prognostic impact of HInv in SSc, AHA were associated with dismal prognosis.

STUDY POPULATION: 29 pts with a biopsy-proven diagnosis of extracardiac sarcoidosis and

EMB-proven or clinically suspected CS.

CONTROLS: 30 age-matched pts with a biopsy-confirmed diagnosis of extracardiac sarcoidosis without cardiac involvement.



25 pts (86%) tested POSITIVE for **AHAs** and 18 (62%) for **AIDA**.

SENSITIVITY was 86% and SPECIFICITY 95% for **AHAs** and 62% and 98% for **AIDA**, respectively.

CONCLUSION: AHAs and AIDAs may play a role as biomarkers in risk stratifying in silent, subclinical, early cardiac involvement

(Caforio, A.L.P.; Baritussio, A.; Marcolongo, R.; et al. Serum Anti-Heart and Anti-Intercalated Disk Autoantibodies: Novel Autoimmune Markers in Cardiac Sarcoidosis. J. Clin. Med. 2021, 10, 2476)

Padua myocarditis cohort (n=1188): Biopsy-proven (n=413); Clinically and CMR suspected=755)

Biopsy-proven:

- Lymphocytic myocarditis in 92% of cases
- 79.5% autoimmune etiology
- 20.5% viral etiology

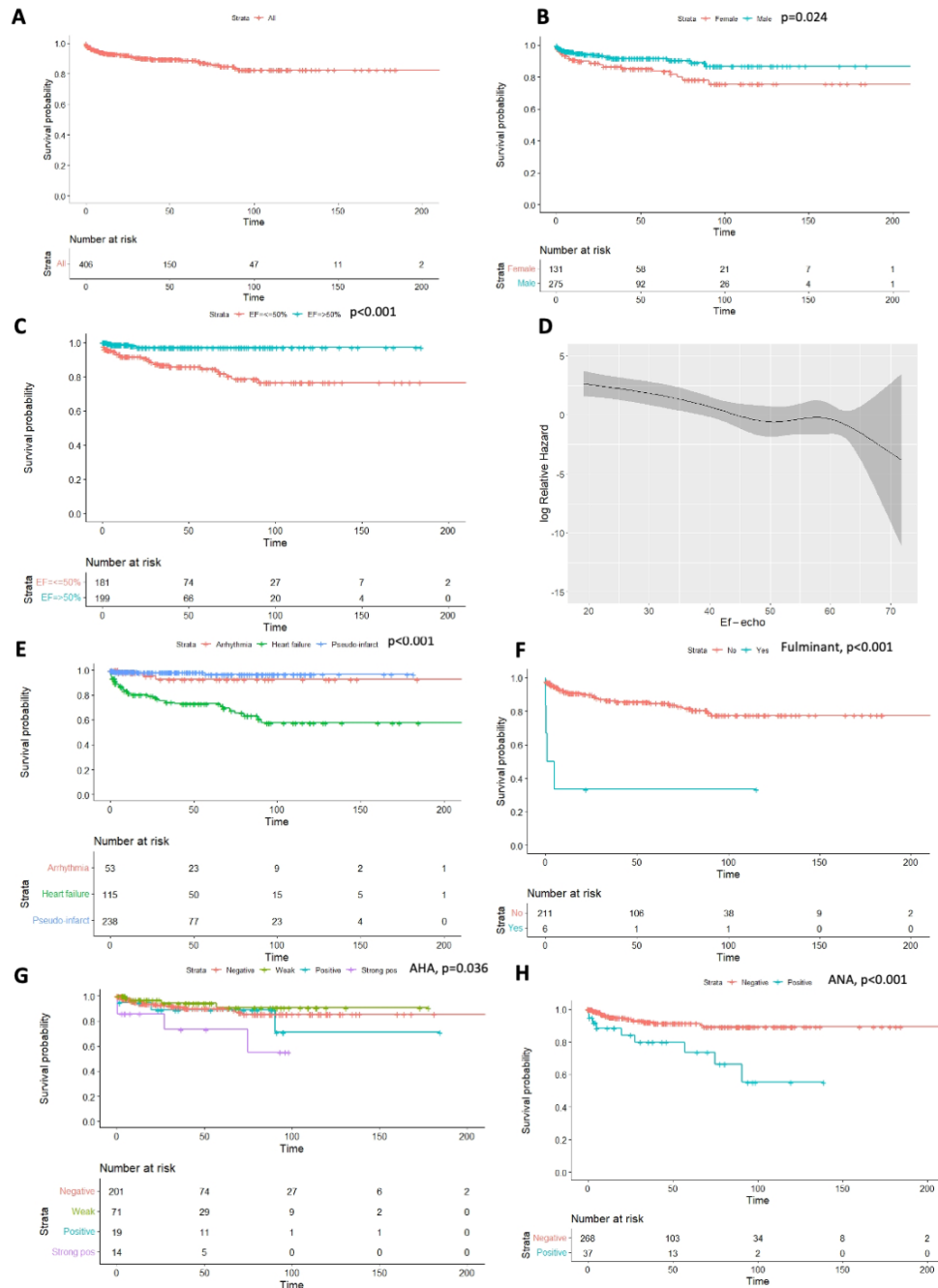
Independent predictors of death/transplant before immunosuppression:

- Female gender
- Fulminant presentation
- Low LVEF (echo or CMR) at diagnosis
- High titre serum AHA
- High titre serum ANA
- Biopsy confirmed diagnosis

Independent predictors of myocarditis relapse before immunosuppression:

- Young age and Previous history of myocarditis

Independent predictors of poor response to relapse after immunosuppression.



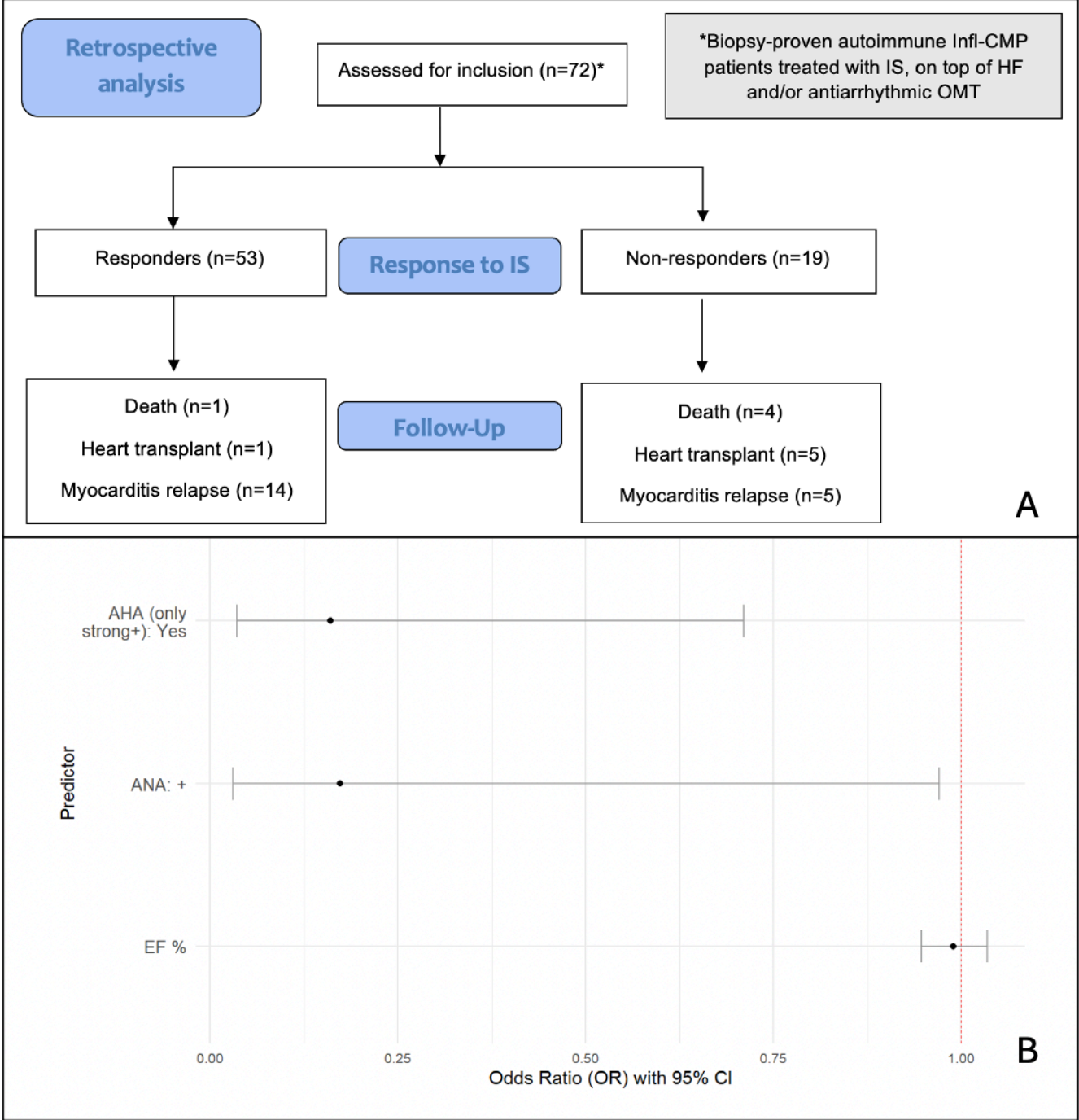
Baritussie et al, Eur J Heart Fail 2022
Giordani, JACC Basic Transl Sci 2025

RESEARCH LETTER

Serum Anti-Heart
and Antinuclear
Autoantibodies Are
Independent Predictors
of Response to
Immunosuppressive
Therapy in Autoimmune
Biopsy-Proven
Inflammatory
Cardiomyopathy

J A C C : B A S I C T O T R A N S L A T I O N A L S C I E N C E

V O L . 10 , N O . 7 , 2025



Immunoglobulin adsorption in patients with idiopathic dilated cardiomyopathy

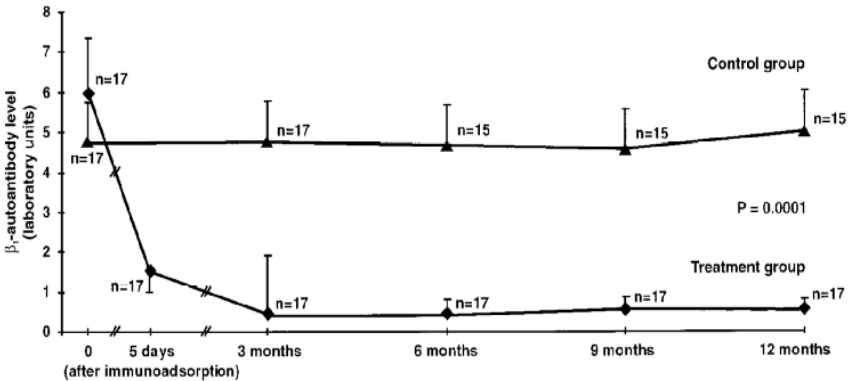


Figure 1. One-year repeated measures (mean±SD) of β_1 -AAB level with treatment and control groups.

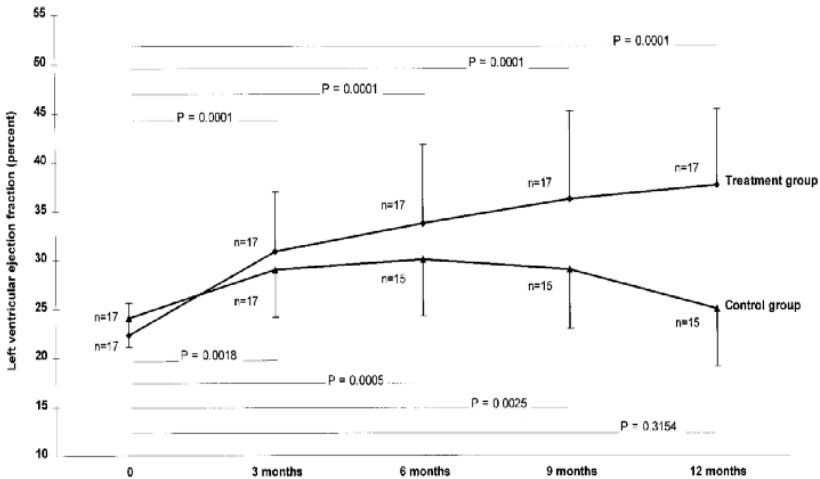


Figure 2. One-year repeated measures (mean±SD) of LVEF within 2 groups. P values were derived through 1-way ANOVA (contrast transformation).

Muller et al,
Circulation
2000;101:385-91



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of Cardiology

European Journal of Heart Failure (2024)
doi:10.1002/ehf.3476

STUDY DESIGN

Multicentre, randomized, double-blind, prospective study on the effects of ImmunoAdSorptiOn on cardiac function in patients with Dilated CardioMyopathy (IASO-DCM): Rationale and design

Marcus Dörr^{1,2}, Michael Böhm^{3†}, Erland Erdmann⁴, Stefan Groß^{1,2}, Amir-Abbas Mahabadi⁵, Matthias Nauck^{2,6}, Georg Nickening⁷, Heinz-Peter Schultheiss^{8†}, Alexander Staudt^{9†}, Karl Werdan¹⁰, Finn Waagstein^{11†}, Åke Hjalmarson^{11†}, and Stephan B. Felix^{1,2*†}

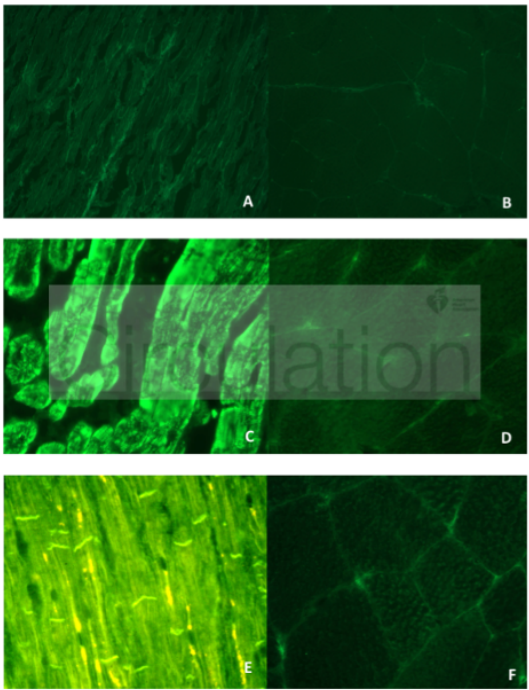
Pilot studies indicate that immunoabsorption with subsequent IgG substitution (IA/IgG) induces beneficial effects in patients with dilated cardiomyopathy (DCM) and heart failure. This placebo-controlled study investigates whether IA/IgG treatment enhances left ventricular (LV) systolic function as compared to a control group receiving pseudo-treatment.

This multicentre, randomized, double-blind, parallel-group trial aims to include 200 patients with heart failure due to DCM (LV ejection fraction [LVEF] <40%) on optimized guideline-directed heart failure medication. Participants are randomly assigned in a 1:1 ratio to IA/IgG using protein-A columns, or to pseudo-immunoabsorption followed by an intravenous infusion without IgG. Follow-up visits take place by telephone after 1 and 3 months and at the study centres after 6, 12 and 24 months. The primary efficacy endpoint is the change in LVEF from baseline to 6 months determined by contrast echocardiography, analysed at a core lab. In addition, LV end-diastolic and end-systolic volumes will be analysed as secondary endpoints over the entire study period to assess whether IA/IgG affects LV remodelling. As main secondary outcome, a composite of all-cause death, cardiac resuscitation, hospitalization for heart failure, and need for cardiac surgery to improve myocardial pump function will be evaluated after 24 months. In addition, exploratory outcomes as well as safety endpoints related to the treatment will be assessed throughout the whole study period.

Evidence from Family Studies for Autoimmunity in Arrhythmogenic Right Ventricular Cardiomyopathy: Associations of Circulating Anti-Heart and Anti-Intercalated Disk Autoantibodies with Disease Severity and Family History

Alida L.P. Caforio, Federica Re, Andrea Avella, Renzo Marcolongo, Pasquale Baratta, Mara Seguso, Nicoletta Gallo, Mario Plebani, Alvaro Izquierdo-Bajo, Chun-Yan Cheng, Petros Syrris, Perry M. Elliott, Giulia d'Amati, Gaetano Thiene, Cristina Basso, Dario Gregori, Sabino Iliceto, and Elisabetta Zachara

Ahead of Print • Publication Date (Web): 02 Mar 2020



Clinical Perspective

What is new?

- This is the first family study reporting an increased frequency of serum organ-specific anti-heart autoantibodies (AHA) and anti-intercalated disk autoantibodies (AIDA) in a sizable arrhythmogenic right ventricular cardiomyopathy (ARVC) cohort of patients and relatives as compared to controls, in keeping with autoimmune involvement.
- Positive AHA status was associated with lower left ventricular ejection fraction (LVEF), higher frequency of cardiac symptoms and implantable cardioverter defibrillator implantation, positive AIDA with lower biventricular ejection fraction (EF).
- Another unique finding is that AHA and/or AIDA positive status was more common in familial than in sporadic pedigrees.

What are the clinical implications?

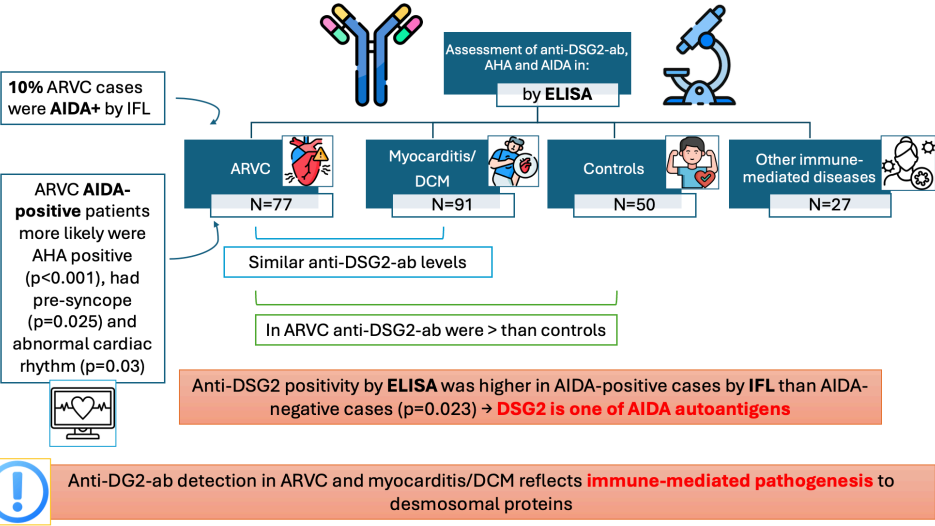
- Presence of organ-specific AHA and AIDA provides evidence of autoimmunity in the majority (85%) of familial and in almost half (45%) of sporadic ARVC. In probands and in affected relatives these antibodies were associated with disease severity features.



Article

Prevalence and Correlates of Anti-DSG2 Antibodies in Arrhythmogenic Right Ventricular Cardiomyopathy and Myocarditis: Immunological Insights from a Multicenter Study

Andrea Silvio Giordani ^{1,†}, Elena Pontara ^{1,†}, Cristina Vicenzetto ¹, Anna Baritussio ¹, Maria Grazia Peloso Cattini ¹, Elisa Bison ¹, Federica Re ², Renzo Marcolongo ¹, Shaylyn Joseph ³, Diptendu Chatterjee ³, Meena Fatah ³, Robert M. Hamilton ³ and Alida Linda Patrizia Caforio ^{1,*}



ORIGINAL RESEARCH ARTICLE

Prognostic Role of Myocarditis-Like Episodes and Their Treatment in Patients With Pathogenic Desmoplakin Variants

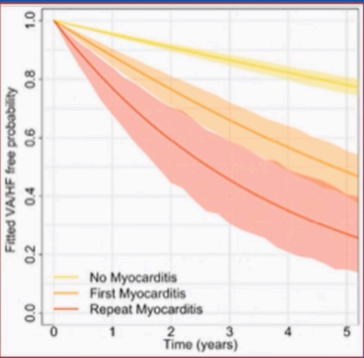


Table 3. Long-Term Follow-Up Outcomes of the DSPMyo+ Cohort Stratified by Use of Immunosuppressive Treatment at the Time of a Myocarditis-Like Episode

	Outcomes	DSP Myo+ (n=177)	DSP-Myo+ treated (n=63)	DSP-Myo+ not treated (n=114)	P Value
Follow-up time, median (IQR), y		6.4 (4.0–10.5)	6.5 (3.6–10.6)	6.4 (4.0–10.5)	0.919
VA events, n (%)		69 (39.0)	9 (14.3)	60 (52.6)	<0.001
Rapid arrhythmia		34 (19.2)	6 (9.5)	28 (24.6)	0.015
HF hospitalizations, n (%)		43 (24.3)	6 (9.5)	37 (32.5)	0.001
Myocarditis episodes at follow-up, median (IQR), n		1 (0–1)	1 (0–1)	1 (0–1)	0.080
LVAD/HT/death, n (%)		15 (8.44)	3 (4.8)	12 (10.5)	0.187
LVAD		1 (0.6)	0	1 (0.9)	1.000
HT		13 (7.3)	2 (3.1)	11 (9.6)	0.141
Death		2 (1.1)	1 (1.6)	1 (0.9)	1.000

DSP indicates desmoplakin; HF, heart failure; HT, heart transplantation; IQR, interquartile range; LVAD, left ventricular assist device; and VA, ventricular arrhythmia.

IMMUNOSUPPRESSION



Who should be treated (Indications)?

- diagnostic certainty: **biopsy-proven, autoimmune** myocarditis
- poor/bad prognosis if not treated: **left or biventricular dysfunction (with/without hemodynamic stability, life-threatening arrhythmia).**
- poor response to or failure of other treatments: **refractory, not improving on standard therapy**
- ominous histology phenotype (**giant cell, sarcoidosis, eosinophilic**)

Exclusion criteria?

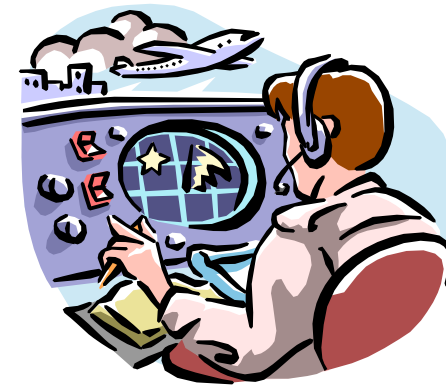
- hidden infection or malignancy
- critical impairment of liver/kidney function
- severe immunodeficiency
- major psychiatric disorders, alcohol and/or drug abuse
- pregnancy, lactation



DOCTOR-PATIENT PARTNERSHIP FOR CLINICAL RISK MANAGEMENT



PATIENT



DOCTOR

Marcolongo R et al. "Clinical Management and Follow-up of Myocarditis Patients on Immunosuppressive Therapy", in MYOCARDITIS, Pathogenesis, Diagnosis and Treatment, Editor A.L.P. Caforio, Springer, 2020.

Marcolongo R et al. Gérer le risque clinique avec le patient: une contribution possible de l'éducation thérapeutique du patient. Gestion Hospitalière, 2008, 477 Juin/Juliet : 417-422

Main mechanisms of action

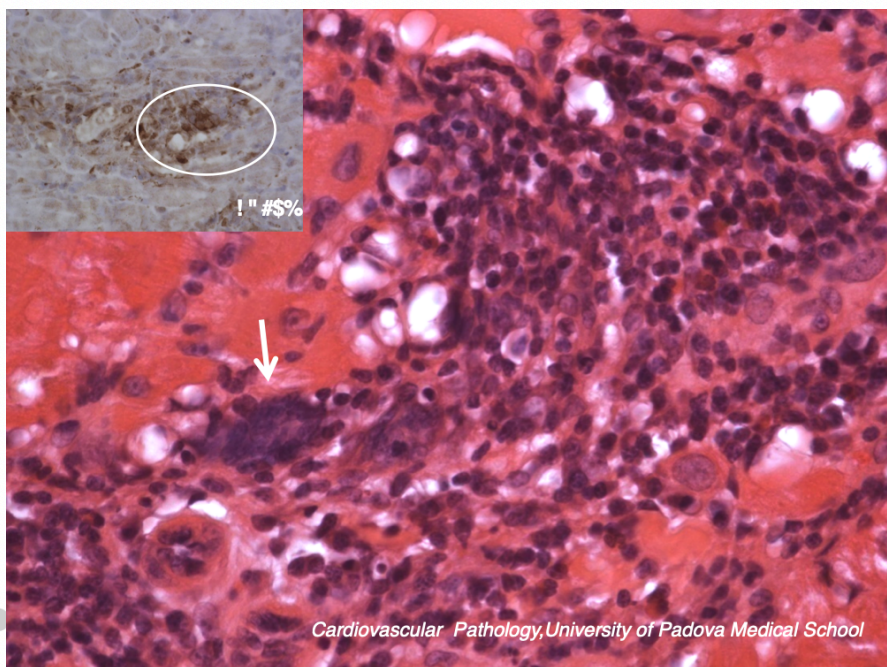
- T-cell suppression (e.g., corticosteroids, cyclosporine, abatacept)
- B-cell depletion (rituximab)
- Cytokine inhibition (TNF- α blockers like infliximab, adalimumab)
- DNA synthesis inhibition (azathioprine, mycophenolate, methotrexate)
- Immunoglobulin replacement/modulation (IVIG)
- Plasma filtration (plasmapheresis)

Recommendations for medical therapy in myocarditis (2)

Recommendations	Class	Level
<i>Immunosuppressive therapy</i>		
Corticosteroids should be considered in patients with fulminant, non-infectious forms of myocarditis to stabilize the patients.	IIa	C
Corticosteroids may be considered in patients with acute myocarditis with impaired LVEF if refractory to standard HF therapy to stabilize patients.	IIb	C
Routine use of immunosuppressive therapy is not recommended in acute myocarditis with preserved LV function because no outcome benefit has been shown.	III	C

Recommendations for giant-cell myocarditis

Recommendations	Class	Level
EMB is recommended in patients with suspected GCM due to unexplained new-onset HF of up to 2 weeks associated with a normal or dilated left ventricle and new ventricular arrhythmias, second- or third-degree AVB, or failure to respond to usual care within 1 to 2 weeks to initiate specific treatment.	I	C
Combined immunosuppressive therapy is recommended in patients with a diagnosed GCM.	I	C

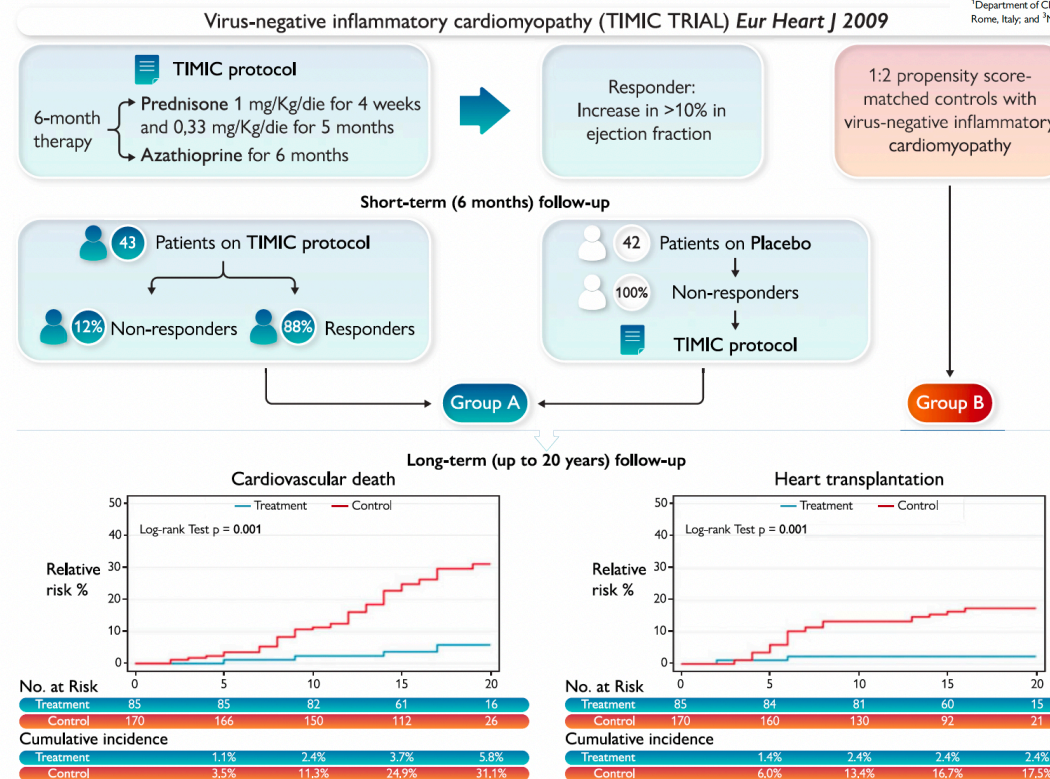


Hematoxylin eosin stain, original magnification 60X. Note the inflammatory cell infiltrate characterized by lymphomonocytes, eosinophils, and giant cell (arrow) associated to myocardial damage. In the insert immunohistochemical staining with giant cell positivity for the macrophage marker CD68.

Immunosuppressive therapy in virus-negative inflammatory cardiomyopathy: 20-year follow-up of the TIMIC trial

Cristina Chimenti^{1,2}, Matteo Antonio Russo³, and Andrea Frustaci^{1,2*}

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EMB: active virus-negative lymphocytic myocarditis relapse after IS interruption

- double IS (steroid+azathioprine)
- Effective and safe on symptomatic relapses

Box plots of the distribution of left ventricular ejection fraction and left ventricular end-diastolic volume at baseline, short-term (6 months), and long-term follow-up in patients on TIMIC protocol (blue) and control patients (green) are presented in the left upper panel. The composite endpoint of cardiovascular death and heart transplantation (primary outcome) during follow-up in patients on TIMIC protocol (blue line) and control patients (red line) is shown in the left lower panel. The incidence of cardiovascular death (right upper panel) and heart transplantation (right lower panel) during follow-up in patients on TIMIC protocol (blue line) and controls (red line) is also presented.

Immunosuppressive Therapy and Risk Stratification of Patients With Myocarditis Presenting With Ventricular Arrhythmias

Giovanni Peretto, MD,^{a,b} Simone Sala, MD,^a Giacomo De Luca, MD,^{b,c} Renzo Marcolongo, MD,^d Corrado Campochiaro, MD,^c Silvia Sartorelli, MD,^c Moreno Tresoldi, MD,^e Luca Foppoli, ME,^f Anna Palmisano, MD,^b Antonio Esposito, MD,^{b,g} Francesco De Cobelli, MD,^{b,g} Stefania Rizzo, MD,^h Gaetano Thiene, MD,^h Cristina Basso, MD,^b Lorenzo Dagna, MD,^{b,c} Alida Linda Patrizia Caforio, MD, PhD,ⁱ Paolo Della Bella, MD^{a,b}

ABSTRACT

OBJECTIVES This study sought to investigate the effects of immunosuppression on arrhythmic myocarditis.

BACKGROUND The effects of immunosuppressive therapy (IST) on ventricular arrhythmia (VA) have not been reported in patients with immune-mediated biopsy-proven myocarditis. Furthermore, myocarditis arrhythmic risk is still unpredictable.

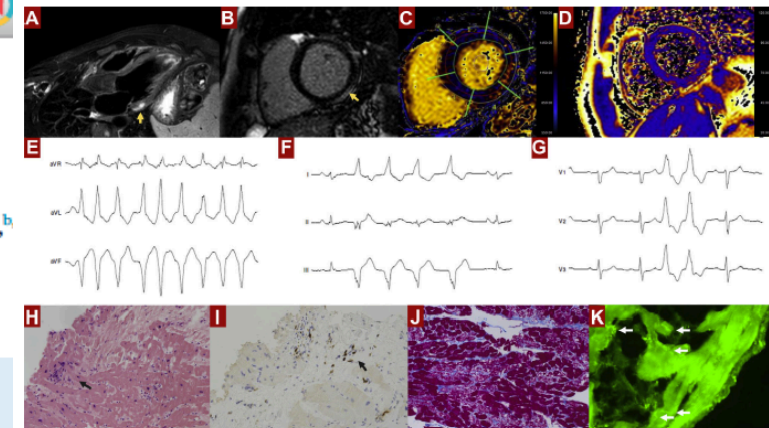
METHODS We enrolled 255 patients with biopsy-proven virus-negative myocarditis and VA (major: ventricular fibrillation, ventricular tachycardia; minor: nonsustained ventricular tachycardia, Lown grade ≥ 2 premature ventricular complexes) at presentation. Serum cardiac autoantibodies (antiheart antibodies, anti-intercalated disk autoantibodies [AIDA]) were detected by a standardized indirect immunofluorescence technique. Whenever accepted and noncontraindicated, IST was started. Control individuals (IST⁻) were chosen after 1:1 matching to IST⁺ patients by age, sex, ethnicity, left ventricular ejection fraction, VA type, and treatment.

RESULTS A total of 58 matched patient couples (age 42 ± 13 years; 67% male) were analyzed in the main study cohort. IST duration was 12 ± 1 months. By the 24-month prospective follow-up, major VA occurred in 6 IST⁺ versus 10 IST⁻ patients ($p = 0.42$), with no episodes following IST termination. As compared to IST⁻ patients, IST⁺ patients showed a significant reduction in minor VA burden, as well as improvement in clinical, laboratory, and imaging findings (all $p < 0.05$). Major VA onset and positive AIDA status were independently associated with major VA at follow-up (hazard ratio [HR]: 14.2; 95% confidence interval [CI]: 2.9 to 68.7 and HR: 8.0; 95% CI: 2.6 to 25.2, respectively; both $p < 0.001$). Furthermore, in the whole study population ($N = 255$), IST was independently associated with protection from major VA (HR: 0.3; 95% CI: 0.2 to 0.7; $p = 0.01$) at 38 ± 21 months of follow-up.

CONCLUSIONS In patients with immune-mediated virus-negative myocarditis presenting with VA, IST is associated with positive effects on minor VA and nonarrhythmic endpoints. Short-term effects are limited on major VA, which were independently associated with major VA onset and positive AIDA. (J Am Coll Cardiol EP 2020;6:1221-34)

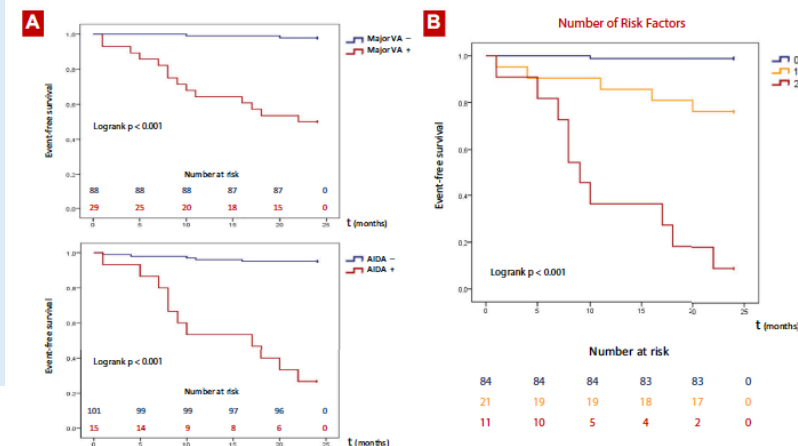


FIGURE 1 Diagnostic Techniques



Representative examples of the main diagnostic techniques used in this study, including CMR and EMB, are shown. (A) CMR STIR sequence showing myocardial edema in the basal segment of the lateral LV wall (arrow). (B) CMR LGE sequence showing abnormal signal in the subepicardium of the posterior LV wall (arrow) in a nonischemic pattern distribution consistent with myocarditis. (C) CMR T1 mapping sequence showing LV short-axis segmentation for analysis. (D) CMR T2 mapping sequence. (E) Sustained ventricular tachycardia during acute myocarditis. (F) Nonsustained ventricular tachycardia during acute myocarditis. (G) Couple of premature ventricular complexes during acute myocarditis. (H) EMB hematoxylin and eosin stain showing myocardial lymphocytic inflammatory infiltrates (arrow) consistent with active myocarditis. (I) EMB immunohistochemistry assay showing CD3⁺ $>7/\text{mm}^2$ lymphocytic inflammatory infiltrates (arrow). (J) EMB trichrome stain showing the absence of significant areas of myocardial replacement fibrosis (blue). (K) Standard indirect immunofluorescence of a patient's serum on human heart (original magnification: $\times 400$), giving an organ-specific AHA and AIDA autoantibody patterns: strong positive cytoplasmic and fine striational staining of cardiac myocytes (AHA) and strong linear staining of the intercalated disks (AIDA) (arrows). AHA = antiheart antibodies; AIDA = anti-intercalated disk autoantibodies; CD = cluster of differentiation; CMR = cardiac magnetic resonance; EMB = endomyocardial biopsy; LGE = late gadolinium enhancement; LV = left ventricular; STIR = T2-weighted short tau inversion recovery.

FIGURE 3 Kaplan-Meier Curves About Predictors of Major VA in Follow-Up



(A) Kaplan-Meier curves in the population ($n = 116$) regarding each independent risk factor for major VA during follow-up, as assessed by multivariable analysis (Supplemental Table 5). (B) Combined Kaplan-Meier curve showing the differential outcome, based on the cumulative number of risk factors (range 0 to 2). In each graph, the x-axis shows time (in months), and the y-axis shows event-free survival rate (event = major VA during follow-up). The number at risk and log rank p value are shown in each graph. Overall, major VA during follow-up was significantly more common in patients presenting with baseline major VA and AIDA positivity, alone or in association. Abbreviations as in Figure 1.

Infectious-negative myocarditis associated with systemic autoimmune and immune-mediated diseases (SIDs)

Systemic lupus erythematosus

Recommendation

- (1) EMB, applying histology, immunohistology and (RT-)PCR for detection of infectious agents, may be useful for diagnosis of SLE myocarditis, since SLE patients are at high risk of infection due to the disease itself and to immunosuppressive treatment.^{22,82}

Systemic sclerosis

- (2) EMB may be considered in patients with clinically suspected myocarditis; immunosuppressive treatment is indicated in EMB-proven infection-negative myocarditis.^{22,63,66,85}

Sarcoidosis

- (2) Corticosteroids are the first line treatment.^{16,48} Other immunosuppressive drugs may be valid alternatives (see Supplementary material online, Table S9).^{16,48}

Eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome)

- (2) The diagnosis of EGPA myocarditis may reinforce the indication to immunosuppression.^{67,68}

Granulomatosis with polyangiitis (formerly Wegener's granulomatosis)

Recommendation

- (1) Since cardiovascular GPA involvement may predict poor prognosis and/or higher risk of relapse,^{103,104} an upgraded immunosuppressive regimen may be considered.¹⁰⁵

Inflammatory myopathies

- (1) Myocarditis may be found in IMs patients with or without myositis-specific Abs and it may be an indication to a more intensive immunosuppressive regimen.^{70,107,109–111}

Myasthenia gravis

- (2) Myasthenia gravis patients with GCM myocarditis should be promptly treated with adequate immunosuppression according to the patient's age and the clinical condition.^{22,72,73}

Autoinflammatory diseases

- (1) Myocarditis, although uncommon, should be suspected in some non-hereditary AD, such as Still's disease and Behçet's disease if cardiac red flags similar to other SIDs are present.^{136,137}

Etiology and immunodulation/
immunosuppression (IS):

- Potentiate background IS
- Personalised therapy



ESC

European Society
of Cardiology

European Heart Journal (2017) **38**, 2649–2662
doi:10.1093/eurheartj/ehx321

Therapy for specific forms of myocarditis (1)

Lymphocytic myocarditis (virus-negative)

1st line therapy	<u>Non-severe</u> : prednisone 1 mg/kg/day p.o. then tapered <u>Severe</u> : i.v. methylprednisolone 7–14 mg/kg/day for 3 days, then 1 mg/kg/day p.o.
2nd line therapy	Oral corticosteroids + azathioprine ^a or mycophenolate mofetil ^b , cyclosporine ^c , methotrexate ^d
3rd line therapy	IVIG ^e or plasmapheresis ^f

Eosinophilic myocarditis

1st line therapy	Same as lymphocytic myocarditis + Treat EM-associated condition if identified
2nd line therapy	Same as lymphocytic myocarditis + Treat EM-associated condition if identified
3rd line therapy	-

^aAzathioprine (immunosuppressant purine analog): 1–2 mg/kg per day p.o. (typically 100–150 mg daily, in 1–2 divided doses, main target: lymphocytes).

^bMycophenolate mofetil (immunosuppressant that inhibits inosine monophosphate dehydrogenase, main target: lymphocytes): 500–1000 mg p.o. b.i.d. (total 1–2 g/day).

^cCyclosporine (calcineurin inhibitor that prevents IL-2 transcription in activated T-cells): ~3–5 mg/kg/day p.o. (divided b.i.d.) adjusted to target trough levels ~150–250 ng/mL

^dMethotrexate (antimetabolite that inhibits dihydrofolate reductase and other folate-dependent steps, reducing proliferation of active lymphocytes): 15–20 mg/week p.o. or s.c. (low-dose weekly, with folic acid supplementation).

^eIVIG (immunomodulatory therapy providing pooled IgG antibodies) =standard dose off-label 2 g/kg total dose, typically administered over 1 to 2 days; alternative dosing: 0.4 g/kg/day for 5 consecutive days (less commonly used in myocarditis but sometimes used in autoimmune settings).

^fPlasmapheresis (therapeutic plasma exchange that filters out and removes circulating autoantibodies, immune complexes, and inflammatory mediators) 3–5 sessions in 5–10 days.

Therapy for specific forms of myocarditis (3)

Cardiac sarcoidosis

1st line therapy	<u>Non-severe</u> : prednisone 1 mg/kg/day p.o., tapering from 40–60 mg daily <u>Severe</u> : i.v. methylprednisolone 7–14 mg/kg/day for 3 days, then 1 mg/kg/day p.o.
2nd line therapy	Methotrexate ^d (1st choice), or azathioprine ^a mycophenolate mofetil ^b , cyclophosphamide ^h
3rd line therapy	Infliximab ^j or adalimumab ^k , rituximab ⁱ

^aAzathioprine (immunosuppressant purine analog): 1–2 mg/kg per day p.o. (typically 100–150 mg daily, in 1–2 divided doses, main target: lymphocytes).

^bMycophenolate mofetil (immunosuppressant that inhibits inosine monophosphate dehydrogenase, main target: lymphocytes): 500–1000 mg p.o. b.i.d. (total 1–2 g/day).

^dMethotrexate (antimetabolite that inhibits dihydrofolate reductase and other folate-dependent steps, reducing proliferation of active lymphocytes): 15–20 mg/week p.o. or s.c. (low-dose weekly, with folic acid supplementation).

^hCyclophosphamide (cytotoxic alkylating agent that crosslinks DNA in rapidly dividing cells, main target: lymphocytes): 600 mg/m² i.v. bolus on days 1, 15, and 30 (pulse therapy).

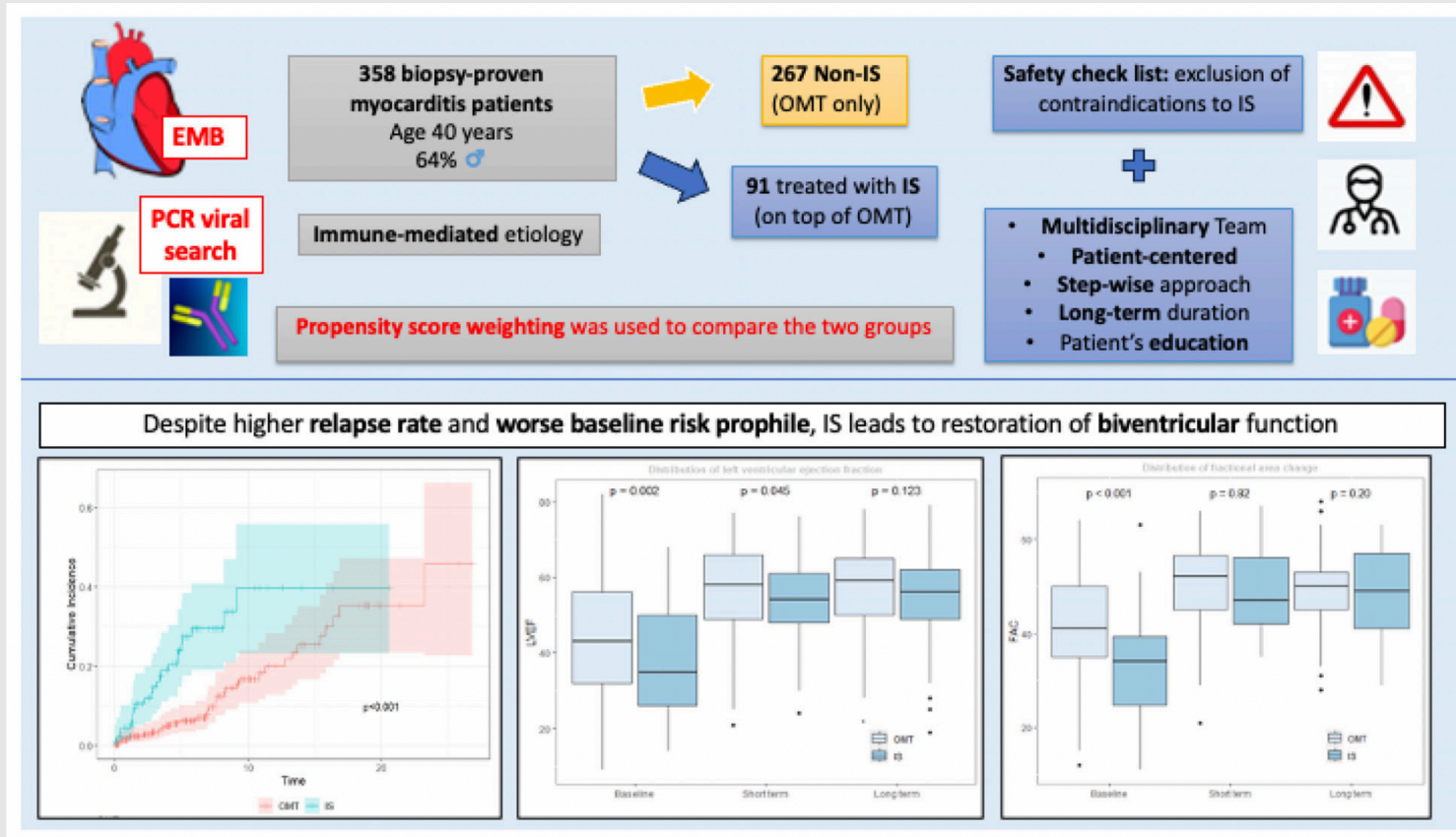
ⁱRituximab (monoclonal antibody against CD20 on B cells): 375 mg/m² i.v. weekly ×4 doses (one month).

^jInfliximab (monoclonal antibody against TNF-α): 5 mg/kg i.v. at weeks 0, 2, 6, then every ~8 weeks (maintenance).

^kAdalimumab (anti-TNF-α fully human monoclonal antibody) 40 mg SC every week (or every 2 weeks, per clinical response).

Do EMB data change clinical management? YES

Graphical Abstract



Long-term efficacy and safety of tailored immunosuppressive therapy in immune-mediated biopsy-proven myocarditis: A propensity-weighted study

Alida Linda Patrizia Caforio^{1*}, Andrea Silvio Giordani¹, Anna Baritussio¹, Davide Marcolongo¹, Cristina Vicenzetto¹, Giuseppe Tarantini¹, Massimo Napodano¹, Giuseppe Toscano², Dario Gregori³, Gloria Brigiari³, Patrizia Bartolotta³, Elisa Carturan⁴, Monica De Gaspari⁴, Stefania Rizzo⁴, Cristina Basso⁴, Sabino Iliceto¹, and Renzo Marcolongo¹

Prolonged tailored immunosuppressive therapy (IS) is effective and safe in biopsy-proven immune-mediated myocarditis, either lymphocytic or non-lymphocytic, with or without heart failure at diagnosis; immunosuppressive therapy type and duration should be tailored and supervised by a multidisciplinary Cardioimmunology Team. EMB, endomyocardial biopsy; FAC, fractional area change; LVEF, left ventricular ejection fraction; OMT, optimal medical therapy; PCR, polymerase chain reaction.

Recommendations for inflammatory cardiomyopathy



Recommendations	Class	Level
Guideline-directed heart failure treatments are recommended in patients with inflammatory cardiomyopathy to improve and/or stabilize left ventricular function.	I	C
Specific medical therapy for the potentially underlying systemic disease is recommended in inflammatory cardiomyopathy.	I	C
Immunosuppressive therapy, guided by endomyocardial biopsy, should be considered in virus-negative inflammatory cardiomyopathies to suppress the autoimmune response. * 34,131,551-555	IIa	B

ESC Levels of evidence



Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

*34 Caforio ALP, et al. *Eur J Heart Fail* 2024;26:1175–85.
131 Chimenti C, et al.. *Eur Heart J* 2022; 43:3463–73
551 Frustaci A,. *Eur Heart J* 2009;30:30:1995–2002.
552. Escher F, et al. *Clin Res Cardiol* 2016;105:1011–20.
553. Merken J, et al.. *Circ Heart Fail* 2018;11:e004228.
554. De Luca G, et al.. *J Autoimmun* 2020;106:10[?]330.
555 Peretto G, et al. *JACC Clin Electrophysiol* 2020;6:1221–34.

Therapy in myocarditis: *Take-home messages*

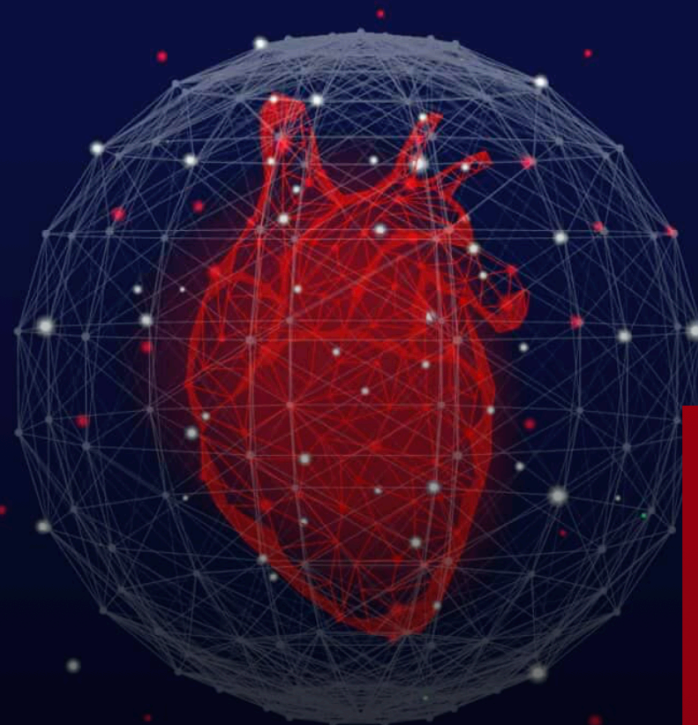
- Diagnosis and etiology-directed therapy in myocarditis/ inflammatory cardiomyopathy is based upon EMB (histology, immunohistology, viral PCR).
- EMB identifies etiology that has prognostic implications:
 - Biopsy-proven autoimmune myocarditis has dismal prognosis if untreated with IS
 - Long-term tailored immunosuppression guided by EMB is associated with improved biventricular function and is safe in non-infectious autoimmune myocarditis/ inflammatory cardiomyopathy with or without concomitant systemic immune-mediated disease.
- High titre serum AHA and AIDA are non invasive autoimmune markers of dismal prognosis and of poor response to immunosuppression in autoimmune myocarditis
- **EMB :should be offered to all high and intermediate risk patients ..and to selected low risk patients (i.e. recurrent, non resolving symptoms), when clinically indicated, to provide tailored etiology-directed therapy**



MASTER II LIVELLO

CARDIM

Cardioimmunologia



Inizio attività: 09/12/2025

Durata: Annuale

Sede: Padova

Lingua di erogazione: Italiano

CFU: 60



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- Prof. C Basso, Prof S Rizzo, Prof. K Pillichou, Dr M Bueno-Marin

• Laboratory Medicine

- Prof. D Basso, Dr. N Gallo

• Medical Statistics

- Prof. D Gregori

Non cardiac specialties: Rheumatology, Pneumology, Dermatology, Hematology, Internal Medicine

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Univ of Turin (Prof V Poli), Bambin Gesù, Rome (Prof. Drago), Univ of Bari (prof. T. Bottio)

International Network: Prof M Cunningham, Prof L Cooper (USA), ESC working on myocardial and pericardial disease (prof. M Imazio, Prof. T Schope), ERN Guard-Heart (Prof. A Wilde)

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the European Union
NextGenerationEU

Biopsy-proven pediatric and adult giant cell and other rare immune-mediated forms of myocarditis: creation

of a prospective multicenter Italian registry and a biobank network to identify clinical, immune and genetic predictors of dismal prognosis, relapse and response to immunosuppressive therapy

Patients, relatives and care-givers: AMICAV (Associazione Malattie Infiammatorie Cardio-vascolari)



A.M.I.Cav

Associazione Malattie Infiammatorie Cardiovascolari



***“There are three phAses to
treatment: diagnosis, diagnosis
and diagnosis.”***

***William Osler. Principles and
Practice of Medicine, 1892***