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Inflammatory cardiomyopathy: Position paper of the Italian Society of Cardiology Working Group on cardiomyopathies and pericardial diseases in collaboration with the Italian Society of Cardiology Working Group on cardiac magnetic resonance

Massimo Imazio [a,b,*], Valentina Jahnsen [c], Marco Merlo [c], Alberto Aimo [d,s], Camillo Autore [e], Andrea Barison [d,s], Barbara Bauce [f], Elena Biagini [g], Emanuele Bobbio [h,i], Francesco Cappelli [j], Silvia Castelletti [b], Valentino Collini [b], Flavio D'Ascenzi [k], Cesare De Gregorio [l], Santo Dellegrottaglie [m], Francesca Marzo [n], Beatrice Musumeci [o], Fabrizio Ricci [p], Francesco Venturelli [b], Roberto Pedrinelli [q], Stefania Paolillo [r], Pasquale Perrone-Filardi [r], Giuseppe Limongelli [i], Gianfranco Sinagra [c]

[a] Department of Medicine (DMED), University of Udine, Udine, Italy
[b] Cardiothoracic Department, University Hospital Santa Maria della Misericordia, Udine, Italy
[c] Cardiothoracovascular Department, Division of Cardiology, University of Trieste, Trieste, Italy
[d] Interdisciplinary Center for Health Sciences, Scuola Superiore Sant'Anna, Pisa, Italy
[e] Department of Cardiology and Respiratory Sciences, IRCCS San Raffaele Cassino, Cassino, FR, Italy
[f] Department of Cardiac-Thoracic-Vascular Sciences and Public Health, University of Padova, Padova, Italy
[g] Cardiology Unit, Cardiac Thoracic and Vascular Department, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy
[h] Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden
[i] Department of Translational Medical Sciences, Inherited and Rare Cardiovascular Diseases, University of Campania 'Luigi Vanvitelli', Monaldi Hospital, Naples, Italy
[j] Tuscan Regional Amyloid Center, Careggi University Hospital, Florence, Italy
[k] Department of Medical Biotechnologies, Sports Cardiology and Rehab Unit, University of Siena, Siena, Italy
[l] Department of Clinical and Experimental Medicine, Outpatient heart failure and cardiomyopathy office, University Hospital of Messina, Italy
[m] Division of Cardiology, Ospedale Medico-Chirurgico Accreditato Villa dei Fiori, Acerra, Naples, Italy
[n] Cardiology Unit, Infermi Hospital, Rimini, Italy
[o] Cardiology, Clinical and Molecular Medicine Department, Faculty of Medicine and Psychology, Sapienza University of Rome, Rome, Italy
[p] University Cardiology Division, SS Annunziata Hospital, Heart Department, ASL 02 Regione Abruzzo Lanciano-Vasto-Chieti, Chieti, Italy
[q] Cardiac, Thoracic and Vascular Department, University of Pisa, Pisa, Italy
[r] Department of Advanced Biomedical Sciences, Italian Society of Cardiology, Federico II University of Naples, Naples, Italy
[s] Cardiology and Cardiovascular Medicine Division, Fondazione Toscana Gabriele Monasterio, Pisa, Italy

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ABSTRACT

Inflammatory cardiomyopathy (iCMP) usually represents the chronic, hypokinetic phenotype within the myocarditis spectrum, characterized by persistent myocardial inflammation, systolic ventricular dysfunction, and adverse remodelling. It frequently evolves from prior acute or subacute myocarditis and is associated with significantly worse outcomes, including progression to dilated cardiomyopathy, heart failure, and arrhythmias. The condition arises from heterogeneous causes—infectious, autoimmune, or idiopathic—and may be influenced by genetic susceptibility, supporting a two-hit model in which environmental triggers interact with pathogenic variants.

Diagnosis requires a multimodal approach. While clinical presentation is variable and often non-specific, cardiac magnetic resonance (CMR) provides essential tissue characterization, enabling detection of inflammation and fibrosis. Endomyocardial biopsy (EMB) remains critical for defining histologic subtype, identifying viral genomes, and guiding targeted therapy, especially in intermediate- or high-risk cases. Genetic testing assists in

* Corresponding author at: Cardiothoracic Department, University Hospital Santa Maria della Misericordia, Piazzale Santa Maria della Misericordia 15, 33100 Udine, Italy.
E-mail address: massimo.imazio@uniud.it (M. Imazio).

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differentiating inherited CMPs and recognizing forms with distinctive inflammatory behavior, such as desmoplakin CMP.

Management focuses on guideline-directed medical therapy for heart failure and treatment of underlying aetiologies. In biopsy-proven, virus-negative iCMP, immunosuppressive therapy may improve ventricular function and limit adverse remodelling, while antiviral strategies remain reserved for selected virus-positive cases. Arrhythmia management, including ICD implantation, is essential in patients with substantial fibrotic burden or arrhythmias. Prognosis depends on ventricular function, extent of fibrosis, viral persistence, arrhythmic burden, and recurrence of inflammatory "hot phases." Lifelong follow-up is warranted. This position paper provides a comprehensive framework for the diagnosis, risk stratification, and management of iCMP, highlighting current evidence, guideline alignment, and remaining gaps.

1. Introduction and background

The 2023 ESC Guidelines for the management of cardiomyopathies [1] proposed a phenotype classification of cardiomyopathies, including 5 main clinical conditions, hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), non-dilated left ventricular cardiomyopathy (NDLVC), arrhythmogenic right ventricular cardiomyopathy (ARVC), and restrictive cardiomyopathy (RCM).

The recent 2025 ESC Guidelines for the management of myocarditis and pericarditis introduce the definition of the umbrella term of inflammatory myopericardial syndromes (IMPS), as a starting point for the subsequent work-up of myocarditis and pericarditis, defining a spectrum of myocardial inflammation presentations of acute, subacute or chronic myocarditis, the last leading to inflammatory cardiomyopathy (iCMP) [2]. According to guidelines, iCMP is part of the spectrum of myocarditis, and precisely it is chronic myocarditis (> 3 months) with systolic ventricular dysfunction (EF <50%) and remodelling, manifesting as a hypokinetic phenotype, either dilated or non-dilated, with or without arrhythmogenic substrate [2]. iCMP represents the chronic phase of myocarditis in which persistent myocardial inflammation leads to ventricular dysfunction and structural remodelling, giving rise to dilated or non-dilated CMP phenotypes. Because iCMP overlaps clinically and morphologically with DCM, NDLVC and chronic myocarditis, a comparative framework is useful to clarify how these entities differ and intersect (Table 1).

Two main clinical pathways lead to iCMP: (i) patients with documented acute myocarditis who fail to achieve complete remission and evolve to chronic myocardial inflammation with LV dysfunction; and (ii) patients presenting de-novo with DCM/NDLVC or arrhythmias in whom active myocardial inflammation is detected ("occult" or "hot-phase" iCMP) [1,2].

This entity reflects persistent myocardial inflammation that could represent a therapeutic target to prevent progression and overlaps with NDLVC and DCM [2]. Outcomes are consistently worse compared with isolated myocarditis, underscoring its clinical significance [3–6].

The underlying pathophysiology involves myocardial inflammation, triggered by infection or non-infective causes, immune dysregulation, or toxic exposure, leading to myocyte injury, necrosis, apoptosis, and progressive fibrosis. The consequent adverse remodelling results in ventricular dysfunction, which may progress towards dilation, systolic impairment, and ultimately chronic heart failure.

Given its heterogeneous aetiology and variable presentation, early recognition is vital but challenging. Without intervention, approximately 30% of biopsy-proven myocarditis cases progress to DCM and symptomatic heart failure [1–6]. This highlights the importance of endomyocardial biopsy (EMB) in this condition in order to define the disease and have specific targets for treatment therapy. Timely, individualized management offers the best opportunity to halt progression, limit irreversible remodelling, and improve long-term patient outcomes.

This position statement synthesizes current evidence to guide clinicians in diagnosing and managing iCMP and provides standardized guidance to improve patient outcomes, since this condition has not been extensively treated in current guidelines [1,2]. Beyond summarizing existing guidelines, this position paper provides a disease-mechanism–driven framework for iCMP, introducing practical diagnostic and therapeutic algorithms (Figs. 1 and 2) that integrate cardiac magnetic resonance (CMR)-based detection of myocardial inflammation with EMB-guided aetiologic stratification to support personalized, targeted management of iCMP.

2. Epidemiology

The true incidence and prevalence of iCMP are difficult to ascertain, since non- specific data are available in literature and are especially related to myocarditis. According to data from the Global Burden of Disease Study, the worldwide prevalence of myocarditis increased from 320,623 cases in 1990 to 505,030 in 2021, with variations observed across different age groups and geographic regions [7,8]. The global annual incidence is estimated at approximately 16 cases per 100,000 individuals, although this figure may be underestimated due to the occurrence of subclinical cases [7,8].

Myocarditis, and its potential progression to iCMP, exhibits a marked sex disparity, with a higher incidence observed in males. In adolescents and young adults, the male-to-female ratio has been reported to reach 2.9:1 [9–11]. This male predominance is also associated with a less favourable prognosis compared to females. Emerging evidence suggests

Table 1
Conceptual distinction between chronic myocarditis, iCMP, NDLVC and DCM.

Feature	Chronic myocarditis	Inflammatory cardiomyopathy (iCMP)	NDLVC	DCM
Core definition	Persistent myocardial inflammation >3 months	Chronic myocarditis with ventricular dysfunction and remodelling	LV systolic dysfunction without dilation and possible presence of non-ischemic LGE	Dilated LV with systolic dysfunction
Pathophysiology	Ongoing immune or viral injury	Inflammation-driven remodelling and fibrosis	Heterogeneous	Heterogeneous end-stage phenotype
Ventricular function	Preserved or mildly reduced	Reduced	Preserved/reduced	Reduced
LV size	Normal or mildly enlarged	Normal or dilated	Non-dilated	Dilated
Inflammation	Present	Present and pathogenetic	May or may not be present	May or may not be present
CMR	Oedema ± LGE	Oedema + LGE with dysfunction	LGE variable	LGE common
EMB	Shows inflammation	Inflammation + remodelling	Variable	Variable
Immunosuppression	Selected virus-negative cases	Virus-negative active iCMP	Only if inflammatory	Only if inflammatory
Conceptual role	Disease state	Disease mechanism causing CMP	Phenotype	Phenotype

that sex hormones, particularly testosterone, may play a pivotal role in this disparity by promoting proinflammatory immune responses and enhancing fibrotic remodelling within the myocardium [10].

Progression to dilated cardiomyopathy occurs in up to 30% of cases with biopsy-proven myocarditis, particularly in patients presenting with significantly reduced LVEF at admission [2,3,11]. In a recent single centre small case series, iCMP (80% secondary to chronic myocarditis) represents 12% of the total cases of NDLVC [12].

3. Causes and classification

Inflammatory CMP encompasses a wide range of disorders characterized by myocardial inflammation with remodelling and some degree of left ventricular dysfunction. The condition may result from infectious agents, immune-mediated processes, or remain idiopathic when no definitive cause is found. Classification by aetiology is essential for guiding diagnostic evaluation and treatment strategies (Table 2).

3.1. Infectious causes

The most frequent causes of iCMP are presumed to be viral infections, particularly in developed countries. Commonly implicated viruses include *Coxsackie B virus*, *Adenovirus*, *Parvovirus B19*, *Human Herpesvirus 6 (HHV-6)*, and *Epstein–Barr virus (EBV)*. More recently, SARS-CoV-2 has emerged as a relevant viral trigger, with myocarditis reported in the context of both acute infection and post-viral syndromes such as MIS-C (Multisystem Inflammatory Syndrome in Children) [3,6,9,13]. Paediatric iCMP represents a distinct clinical entity within the spectrum of myocardial inflammatory disease. In children and adolescents, iCMP may follow viral myocarditis, multisystem inflammatory syndrome in children (MIS-C), or autoimmune and genetic conditions, often with different patterns of recovery, remodelling, and arrhythmic risk compared with adults. Although many paediatric patients show substantial functional recovery, a subset develops chronic ventricular dysfunction, myocardial fibrosis, or arrhythmias consistent with iCMP. The role of immunomodulatory therapy in this population remains largely empirical and extrapolated from adult experience, underscoring the need for paediatric-specific diagnostic, imaging, and therapeutic strategies.

In endemic areas, protozoal infections such as *Trypanosoma cruzi* (the agent of Chagas disease) remain a leading cause of iCMP and are associated with chronic myocarditis and progressive cardiac dysfunction. Other rare infectious triggers include bacterial pathogens (*Borrelia burgdorferi* in Lyme disease, *Mycoplasma pneumoniae*, and *Corynebacterium diphtheriae*) and fungal or parasitic infections, particularly in immunocompromised individuals [3,11].

3.2. Autoimmune causes

Immune-mediated myocarditis represents a distinct category and includes conditions such as giant cell myocarditis and cardiac sarcoidosis, where the myocardium is directly targeted by immune cells. These conditions often present with rapidly progressive heart failure or life-threatening arrhythmias and require immunosuppressive therapy [3,6].

Additionally, myocarditis may occur as part of systemic autoimmune diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis, systemic sclerosis, and vasculitides (e.g. eosinophilic granulomatosis with polyangiitis). These patients often exhibit multisystem involvement, and myocardial inflammation may coexist with pericardial or valvular pathology.

3.3. Idiopathic cases

In a substantial proportion of cases, no infectious or autoimmune cause is identified. These are termed idiopathic or virus-negative iCMP. Despite the absence of detectable viral genomes or systemic autoimmunity, myocardial biopsy or imaging may still show persistent inflammation. These cases may reflect a post-infectious autoimmune response, cryptic infection, or a distinct primary immune dysregulation, and often respond to immunosuppressive therapies.

A genetic background may predispose patients to the development of LV dysfunction or arrhythmic presentations [14]. A paradigmatic example is desmoplakin cardiomyopathy (DSP-CMP), recently described as a distinct form of arrhythmogenic cardiomyopathy. DSP-CMP is characterized by episodes of acute myocardial injury with chest pain, troponin elevation, and normal coronary arteries, frequently mimicking

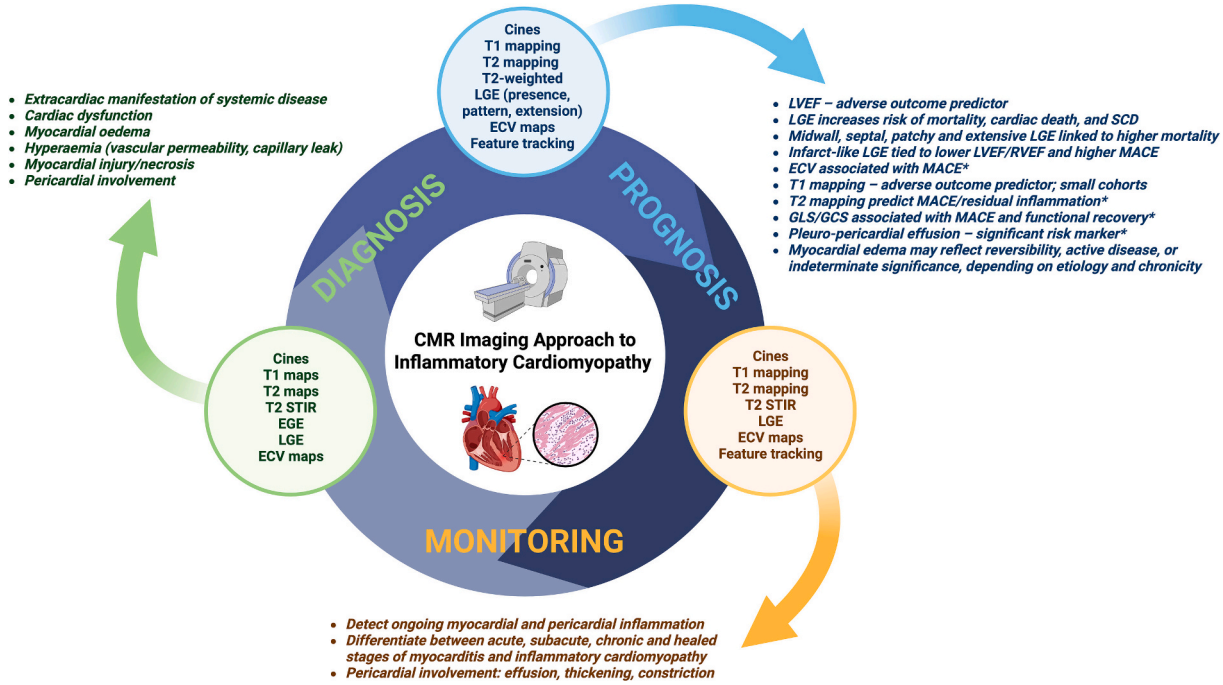

Fig. 1. The role of cardiac magnetic resonance (CMR) in the evaluation of inflammatory. CMP.

myocarditis or sarcoidosis. These inflammatory episodes lead to progressive LV fibrosis (often subepicardic), which may occur even in the absence of systolic dysfunction, and create a highly arrhythmogenic substrate with a substantial risk of ventricular arrhythmias [15].

4. Diagnostic evaluation and criteria

The clinical presentation of iCMP is heterogeneous and may range from asymptomatic cases incidentally detected by echocardiography or CMR to symptomatic patients presenting with heart failure or arrhythmic manifestations. Arrhythmias are a frequent mode of presentation and commonly include ventricular arrhythmias and conduction disturbances, reflecting active myocardial inflammation and fibrotic or infiltrative involvement [16]. Sustained or non-sustained ventricular tachycardia and high-grade atrioventricular block may therefore be early or predominant manifestations of the disease. Supraventricular arrhythmias, such as atrial fibrillation, may also occur, particularly in the presence of atrial remodelling and heart failure. In specific forms of iCMP, including cardiac sarcoidosis, the first clinical manifestation may be life-threatening ventricular arrhythmias or sudden cardiac death [17,18].

Nevertheless, patients with iCMP are often hemodynamically stable, experiencing a gradual decline in left ventricular (LV) systolic function that may go undiagnosed.

In most cases ECG abnormalities are non-specific, including ST-segment and T-wave changes. PR prolongation, atrioventricular block, and bundle branch blocks are more characteristic of sarcoidosis, Lyme carditis, and systemic sclerosis [17,19]. Fragmented QRS complexes and an infero-lateral infarct pattern may be observed in sarcoidosis [20], while pseudo-infarct Q waves are more typical of systemic sclerosis. PR depression may be present in cases of systemic lupus erythematosus [21].

Table 2
Aetiological classification of inflammatory cardiomyopathy (iCMP).

Category	Aetiology	Examples
Infectious	Viral, bacterial, protozoal, fungal	Coxsackie B, parvovirus B19, SARS-CoV-2, Trypanosoma cruzi, *Borrelia burgdorferi*
Autoimmune	Primary immune-mediated or systemic disease	Giant cell myocarditis, cardiac sarcoidosis, SLE, rheumatoid arthritis
Idiopathic	No identified cause	Virus-negative myocarditis with persistent inflammation

Inflammatory CMP usually reflects a subacute/chronic phase and biomarkers may be not necessarily elevated (e.g. myocardial lesion and systemic inflammation). Troponin elevation reflects ongoing myocardial injury and more than half of biopsy-proven inflammatory CMP cases show elevated troponin levels [2,5]. However, there is no direct correlation between these levels and the severity of cardiac dysfunction [24]. Eosinophilia is often associated with eosinophilic myocarditis [25]. Natriuretic peptides levels reflect the degree of heart failure and ventricular dysfunction and have been identified as prognostic markers in the setting of acute myocarditis [26].

Echocardiography is crucial to assess wall motion abnormalities, biventricular function, and the extent of remodelling. CMR is crucial for tissue characterization as it can evaluate the presence and extent of inflammation and fibrosis [2,22,23]. Non-ischaemic myocardial inflammation can be diagnosed by CMR according to the updated Lake Louise Criteria (LLC) (see Fig. 1). This is based on at least one T2-based criterion plus ideally one T1-based criterion. Having both a positive T2-based criterion and a T1-based criterion will increase specificity for diagnosing AM, but a diagnosis of possible myocarditis can still be made by having only one (i.e. T2-based or T1-based) criterion in an

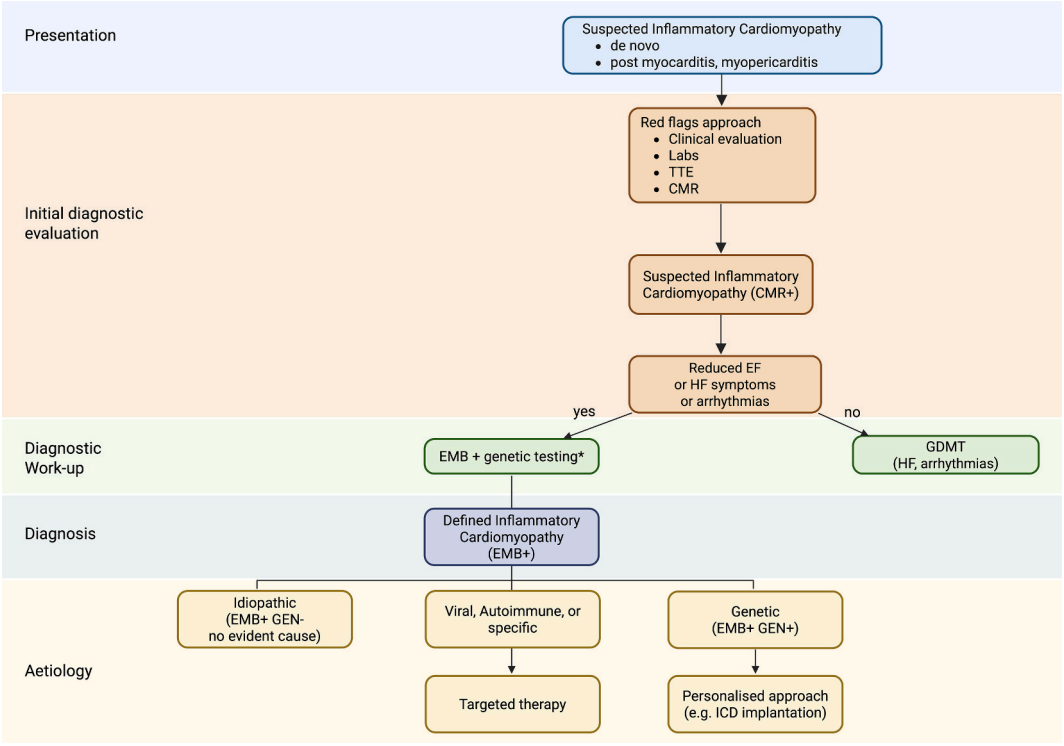

Fig. 2. Practical management algorithm for the diagnosis and treatment of inflammatory cardiomyopathy (iCMP). EMB is required for a definite diagnosis and to allow targeted therapy.
*performed concurrently with or after EMB, not mandatory in all cases; GDMT = Guidelines Directed Medical Therapy. CMR, cardiac magnetic resonance; EMB, endomyocardial biopsy; EF, ejection fraction; GEN, genetic; HF, heart failure; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association class; TTE, transthoracic echocardiogram.

appropriate clinical scenario, although with less specificity. Supportive criteria include pericardial abnormalities (which, however, suggest concomitant pericarditis), and global or regional left ventricular (LV) systolic dysfunction on cine imaging [2,22]. A multimodality imaging approach including CT and FDG-PET should be considered not only when specific inflammatory diseases such as sarcoidosis are suspected, but also in patients with chronic cardiomyopathies and arrhythmic phenotypes to identify active myocardial inflammation, particularly when CMR is inconclusive or contraindicated (e.g. in ICD carriers) [27]. FDG-PET may help differentiate active inflammatory activity from irreversible scar and guide further diagnostic or therapeutic decisions. However, its specificity is limited by physiological myocardial glucose uptake and by non-specific inflammatory signals, requiring standardized patient preparation and careful integration with clinical, CMR and histological findings [2,11,17]. On this basis, adequate dietary preparation prior to FDG PET-CT is essential for the assessment of myocardial inflammation. Suppression of physiological myocardial glucose uptake—typically achieved through a high-fat, low-carbohydrate diet followed by a prolonged fasting period—is critical to enhance the contrast between inflammatory FDG uptake and background myocardial activity. Inadequate dietary preparation may result in diffuse physiological myocardial uptake, substantially reducing diagnostic accuracy and potentially leading to false-negative or non-interpretable studies.

Although myocardial oedema on CMR (typically assessed by T2-weighted imaging or T2 mapping) is a hallmark feature of acute myocardial inflammation, its absence does not exclude iCMP. Even in EMB–proven iCMP, CMR-based oedema may be falsely negative in a substantial proportion of patients. This is particularly evident in EMB-confirmed acute myocarditis, where oedema is not uniformly present. The prevalence of detectable oedema is influenced by several factors, including the timing of CMR acquisition relative to symptom onset, with sensitivity declining as inflammation evolves or becomes more focal or chronic. Furthermore, oedema detection is known to be reduced in specific clinical scenarios, such as patients presenting with heart failure, advanced myocardial remodelling, or diffuse low-grade inflammation, where T2-based techniques may lack sufficient contrast. Technical factors, scanner variability, and the use of qualitative versus quantitative T2 assessment also contribute to limited sensitivity. Therefore, the absence of myocardial oedema on CMR should be interpreted with caution and does not preclude active myocardial inflammation, particularly when EMB demonstrates inflammatory infiltrates. On this basis, EMB is needed in suspected iCMP to detect the histologic type, possible presence of viral genomes and to allow targeted treatment (e.g. immunosuppression, see dedicated chapter) [2].

Genetic testing also plays a crucial role in evaluating iCMP, particularly in distinguishing inherited forms of CMP from myocarditis and in identifying underlying genetic predispositions [28]. Gene panels are indicated in patients with a family history of CMP or SCD, and in those with phenotypes suggestive of an inherited disorder [2]. In the two-hit hypothesis of iCMP pathogenesis, an underlying genetic variant (first hit) predisposes the myocardium to adverse responses when exposed to an environmental trigger (second hit), most commonly a viral infection. This model helps explain why only a subset of patients with myocarditis progresses to chronic CMP or worse outcomes. Genomic studies have confirmed a higher burden of CMP-associated genetic variants in patients with acute myocarditis who fare worse over time, supporting this hypothesis [29,30]. Genetic predisposition impairs myocardial resilience, making viral insults more damaging. In essence, a two-hit sequence—genetic susceptibility plus environmental stress—underlies the pathogenesis and severity of some iCMPs.

In patients presenting with a non-ischaemic cardiomyopathy or arrhythmic phenotype, a number of clinical, laboratory and imaging features should be regarded as signals of possible ongoing myocardial inflammation, prompting targeted evaluation for iCMP. These red flags suggestive for a possible iCMP are listed in Table 3, while a management algorithm for clinical practice is proposed in Fig. 2. An illustrative case of iCMP with ECG, multimodality imaging and EMB findings is reported in Fig. 3.

Table 3
Clinical, laboratory and instrumental features suggestive of active myocardial inflammation (iCMP red flags).

Type	Features raising suspicion of inflammatory activity
Clinical history	Recent or recurrent viral-like illness (fever, flu-like, GI or respiratory symptoms within preceding 4–6 weeks) Autoimmune or systemic inflammatory disease Recent myocarditis-like episode in a known cardiomyopathy
Symptoms	Acute or subacute worsening of dyspnoea Palpitations or new arrhythmias Syncope Chest pain suggestive of myocardial or pericardial inflammation
ECG abnormalities	New-onset PR prolongation or atrioventricular block New bundle branch block Low QRS voltages or diffuse T-wave inversion Pseudo-infarct patterns
Laboratory tests	Persistent or fluctuating elevation of cardiac troponin Elevated CRP or ESR
Echocardiography	Ventricular dysfunction out of proportion to remodelling Non-dilated or mildly dilated left ventricle with systolic dysfunction Pericardial effusion

AV, atrioventricular; BNP, B-type natriuretic peptide; CRP, c-reactive protein; ECG, electrocardiogram; ESR: erythrocyte sedimentation rate; GI: gastrointestinal; LV, left ventricle; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Recommendation 1. Initial evaluation of a patient with suspected inflammatory cardiomyopathy is strongly advised with a detailed history (including familial cardiomyopathy and sudden cardiac death), physical examination, 12-lead ECG, and transthoracic echocardiography (Level of Evidence-LoE C, expert consensus).

Recommendation 2. A structured "red-flag" assessment is advised in patients with non-ischaemic cardiomyopathy to identify features suggestive of ongoing myocardial inflammation (rather than to exclude genetic or other cardiomyopathies), in order to guide further diagnostic testing for iCMP (LoE C, expert consensus).

Recommendation 3. Cardiovascular magnetic resonance is strongly advised in all patients with suspected iCMP or unexplained non-ischaemic cardiomyopathy using a protocol that includes oedema-sensitive T2-weighted or T2-mapping sequences in addition to LGE and T1 mapping, to allow detection of active myocardial inflammation as well as fibrosis (LoE B).

Recommendation 4. Multimodality imaging, including FDG-PET and CT, is advised when inflammatory or infiltrative diseases (e.g., sarcoidosis) are suspected, or when CMR findings are inconclusive for inflammatory activity (LoE C, expert consensus).

Recommendation 5. Genetic testing is strongly advised in patients with a family history of cardiomyopathy or sudden cardiac death, and in those with clinical or imaging features suggestive of an inherited cardiomyopathy, including patients presenting with inflammatory "hot-phase" phenotypes (LoE B).

Recommendation 6. Endomyocardial biopsy is strongly advised in chronic iCMP with high-risk or complicated features, including progressive ventricular dysfunction despite optimal therapy, recurrent or malignant ventricular arrhythmias, persistent troponin elevation, or CMR/PET evidence of ongoing myocardial inflammation, in order to define the aetiology (immune-mediated vs viral vs genetic-associated) and guide targeted therapy (LoE C).

5. Management and therapy

The diagnostic approach outlined above—integrating clinical

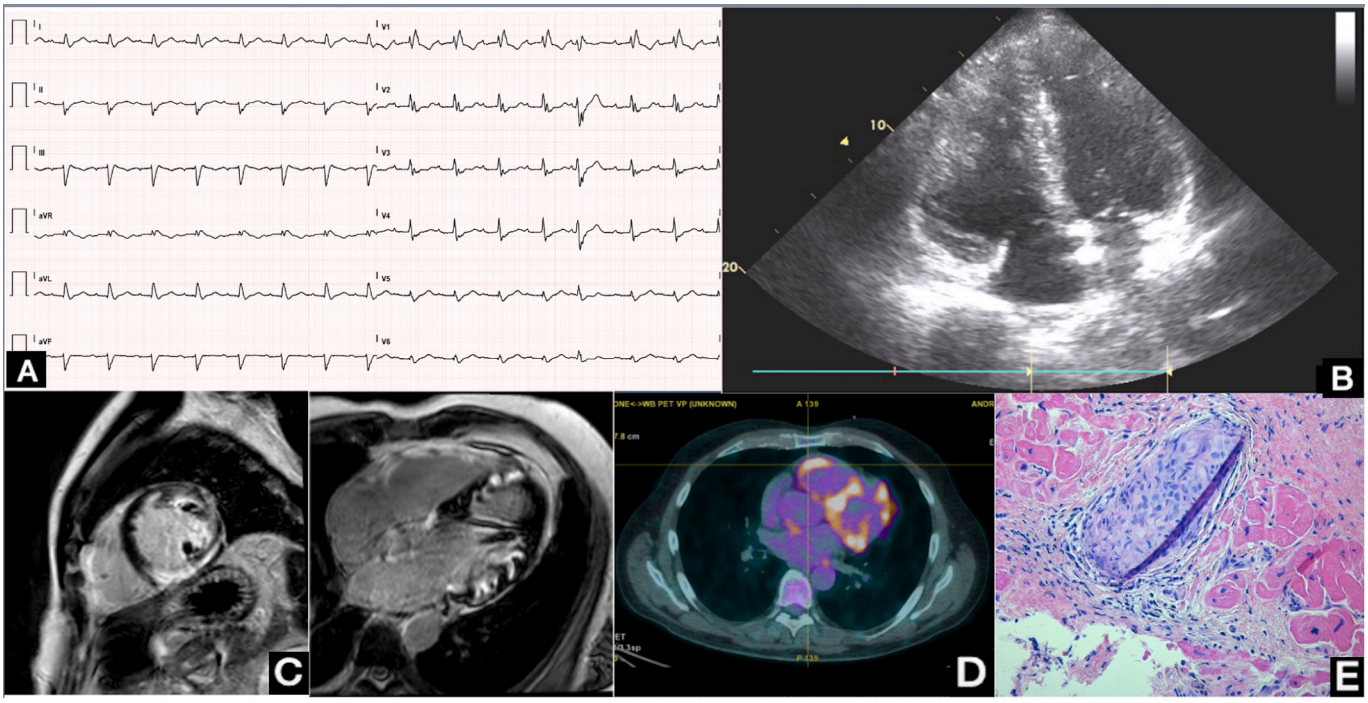

Fig. 3. Representative case of inflammatory cardiomyopathy in cardiac sarcoidosis. (A) ECG showing sinus rhythm with right bundle branch block, left anterior fascicular block, and isolated ventricular ectopy. (B) Transthoracic echocardiography demonstrating a normal-sized left ventricle with mildly reduced systolic function (LVEF 49%) and inferior septal and mid–basal inferior wall hypokinesia, and a hypertrabeculated, dilated, hypokinetic right ventricle with periapical diastolic bulging (RVFAC 28%). (C) Cardiac magnetic resonance showing extensive non-ischaemic late gadolinium enhancement involving both ventricles. (D) ˆ18F-FDG PET demonstrating diffuse myocardial uptake in the right ventricle, interventricular septum, and anterior wall. (E) Endomyocardial biopsy revealing non-necrotizing epithelioid granulomas.

features, multimodal imaging, genetic testing, and endomyocardial biopsy—provides the foundation for a mechanism-based and personalized management strategy in iCMP, which is described in the following section.

Management of iCMP requires a multifaceted approach, combining standard heart failure therapies with aetiology-specific treatments based on clinical, imaging, and biopsy findings (Table 4).

5.1. Heart failure therapies

In patients with reduced ejection fraction due to iCMP, guideline-directed medical therapy (GDMT) is the cornerstone of management [31,32]. In acute or fulminant forms, supportive care in an intensive setting may be required, including inotropes and vasopressors. Timely recognition of myocardial recovery can enable de-escalation of therapy [2].

5.2. Immunosuppressive and immunomodulatory therapy

In virus-negative or autoimmune myocarditis (e.g. giant cell myocarditis, cardiac sarcoidosis), immunosuppressive therapy plays a key role [2,11]. In addition to progressive ventricular dysfunction, inflammation-related ventricular arrhythmias represent a clinically relevant manifestation of active myocardial disease and may be reversible with appropriate immunomodulatory treatment [33,34].

Table 4
Treatment approaches by aetiology of inflammatory cardiomyopathy.

Aetiology	Therapy
Autoimmune (e.g. sarcoidosis, giant cell myocarditis)	Corticosteroids ±1 or more additional immunosuppressants (e.g. azathioprine, cyclophosphamide, cyclosporine)
Virus-positive myocarditis	Antivirals or interferon (case-specific); avoid immunosuppression
Virus-negative, idiopathic	Consider immunosuppression guided by endomyocardial biopsy (EMB) findings
Fulminant myocarditis	Supportive care ± immunotherapy; mechanical circulatory support (MCS) or transplant if needed

The landmark TIMIC trial (randomized, double-blind, placebo-controlled) evaluated patients with biopsy-proven, virus-negative iCMP unresponsive to standard heart failure treatment. The immunosuppressive regimen—prednisone followed by taper plus azathioprine for six months—led to significant improvement in left ventricular ejection fraction and reverse remodelling; none in the placebo group improved. No major adverse events were reported [35]. A 20-year follow-up confirmed durable benefits, with approximately 88% of treated patients showing sustained functional improvement [36]. These results are in contrast with the hystorical Myocarditis Treatment Trial (MTT), where adding prednisone plus cyclosporine or azathioprine to standard therapy did not improve left ventricular function or survival compared with conventional therapy alone in an unselcted population of patients [37].

In a meta-analysis including 30 years of studies (1989–2019) on immunosuppressive therapy with 8 randomized trials + 9 observational studies (~1300 patients), immunosuppressive therapy improved left ventricular function and reduced mortality only in biopsy-proven, virus-negative (autoimmune) myocarditis, while providing no benefit—and potential harm—in virus-positive disease [38]. Other reviews and analyses have reported heterogeneous results; therefore, the overall prognostic impact remains debated (Table 5). Nonetheless, in patients with biopsy-proven myocardial inflammation, immunosuppressive therapy may improve left ventricular function, reverse remodelling, and reduce arrhythmic burden, and should be considered when optimal conventional therapy is insufficient [33,34].

However, the clinical evidence supporting immunosuppression in iCMP remains incomplete and partially conflicting, and its efficacy is

Table 5
Evidence summary of immunosuppressive therapy in inflammatory cardiomyopathy.

Study / reference	Design	Population	Intervention	Comparator	Outcomes	Follow-up	Limitations
Frustaci et al. TIMIC [35]	RCT	Virus-negative EMB-proven iCMP	Prednisone + azathioprine	Placebo	↑LVEF, reverse remodelling	6 months	Selected cohort
Chimenti et al. 20y FU [36]	Long-term follow-up	Virus-negative iCMP	Same TIMIC regimen	Matched controls	↓CV death, sustained ↑LVEF	20 years	Observational
Mason et al. MTT [37]	RCT	Myocarditis (mixed viral)	Prednisone ± CsA	Standard therapy	No significant benefit	28 weeks	Virus-positive included
Cheng et al. Meta-analysis [38]	Meta-analysis	30 years studies (1989–2019) RCTs + observational studies on myocarditis/iCMP	Various	Control	Modest ↑LVEF and reduced mortality only in EMB-proven, virus-negative cases	Variable	High heterogeneity

Abbreviations: EMB, endomyocardial biopsy; iCMP, inflammatory cardiomyopathy; LVEF, left ventricular ejection fraction; RCT, randomized controlled trial; CsA, cyclosporine.

largely restricted to carefully selected, biopsy-proven virus-negative cases. Importantly, immunosuppression in virus-positive myocarditis or iCMP remains controversial, as viral persistence may be promoted by immune suppression and no randomized trial has shown clear benefit in this setting. This highlights the critical importance of EMB-based viral and immunohistological characterization before considering immunomodulatory therapy. In addition, while immunosuppressive therapy is traditionally considered in virus-negative myocarditis based on EMB findings, selected patients with myocarditis and the presence of a low viral load—particularly of parvovirus B19 or human herpesvirus 6—may also be candidates for immunosuppression. In such cases, low-level viral persistence is often regarded as an epiphenomenon rather than the primary driver of myocardial injury, whereas immune-mediated inflammation appears to be the dominant pathological mechanism. Consequently, when viral load is low, replication is absent, and EMB demonstrates active myocardial inflammation, immunosuppressive therapy may be considered on an individual basis after careful multidisciplinary evaluation.

In addition, a subset of genetic cardiomyopathies, particularly arrhythmogenic and desmoplakin-related cardiomyopathies, may present with so-called “hot phases” characterized by myocardial injury, inflammation, and myocarditis-like episodes. In these patients, multimodal imaging and biopsy may demonstrate active inflammatory infiltrates, and preliminary studies suggest that targeted immunomodulatory therapy may reduce disease activity and arrhythmic burden in selected cases [39–41]. However, evidence remains limited to small observational series, and no standardized immunosuppressive strategy can currently be recommended; therefore, any immunomodulatory treatment in genetic cardiomyopathies should be individualized and guided by documented myocardial inflammation within a specialized multidisciplinary framework.

The 2025 ESC Guidelines on the management of myocarditis and pericarditis provide a Class IIa, Level of Evidence B recommendation for EMB-guided immunosuppressive therapy in virus-negative iCMP [2]. On this basis, new, adequately powered, aetiology-stratified trials are urgently needed.

5.2.1. Recommendations

Recommendation 1. Guideline-directed heart failure therapy is strongly advised in patients with iCMP to improve and/or stabilize left ventricular function (LoE C).

Recommendation 2. Specific medical therapy for the potentially underlying systemic or immune-mediated disease is strongly advised in patients with iCMP (LoE C).

Recommendation 3. In patients with virus-negative iCMP and documented myocardial inflammation, EMB-guided immunosuppressive therapy is advised when one or more of the following are present (LoE B):

(i) progressive or persistent left-ventricular dysfunction despite optimal heart-failure therapy,
(ii) recurrent or malignant ventricular arrhythmias attributable to inflammatory activity,
(iii) persistent myocardial injury (e.g. elevated troponin), or.
(iv) imaging evidence of active inflammation on CMR (T2-weighted or T2-mapping) and/or FDG-PET.

In these settings, immunosuppression aims to reduce inflammatory myocardial damage, limit adverse remodelling, and improve clinical and arrhythmic outcomes.

5.3. Antiviral therapy

Antiviral or interferon-based therapies may be considered in selected patients with virus-positive myocarditis (e.g. enteroviruses), particularly with high viral loads (e.g. Parvovirus B19, hepatitis C, adenovirus). However, clinical evidence supporting antiviral therapy remains limited, and routine use is not currently recommended. Decisions should be made in conjunction with virological testing and expert input [2].

5.4. Arrhythmia management and device therapy

Arrhythmias are common in iCMP and include ventricular arrhythmias, conduction disturbances, and supraventricular tachyarrhythmias. Management includes guideline-directed heart failure therapy, antiarrhythmic drugs, catheter ablation, and device-based therapies. Catheter ablation should be considered in patients with recurrent or drug-refractory ventricular tachycardia, preferably after control of active myocardial inflammation, as ablation performed during inflammatory phases is associated with high recurrence rates. An implantable cardioverter-defibrillator (ICD) is indicated for secondary prevention in patients with sustained ventricular arrhythmias and for primary prevention in those with severely reduced LVEF according to ESC guidelines. In patients in the “grey zone” (e.g. LVEF >35% but <50%), additional risk factors such as unexplained syncope, extensive LGE, non-sustained ventricular tachycardia, and high-risk genetic background should be considered to individualize ICD decisions. Cardiac resynchronisation therapy (CRT) may benefit selected patients with ventricular dyssynchrony according to ESC recommendations [2,30,31].

Among the heterogeneous forms of iCMP, cardiac sarcoidosis represents a paradigmatic example of the strong interplay between inflammation and arrhythmogenesis. In this setting, monomorphic ventricular tachycardia is frequent and often clusters during phases of active inflammation or corticosteroid tapering. These arrhythmias may require catheter ablation, particularly in ICD carriers, but long-term recurrence remains common (≈46% at 1–5 years), reflecting the progressive inflammatory-fibrotic substrate [42,43]. Importantly, re-intensification of immunosuppressive therapy can reduce arrhythmic burden, highlighting the central role of immunomodulation alongside anti-arrhythmic therapy and ablation [42–44].

6. Prognosis and follow-up

6.1. Risk stratification

Identifying early indicators of long-term outcomes is essential for guiding clinical management. Several factors help stratify patients into high, intermediate or low-risk categories, each distinguished by a different prognosis (Table 6).

In this regard, CMR and EMB play a central role in prognostic assessment. The extent and distribution of late gadolinium enhancement (LGE) reflect myocardial fibrosis and are associated with adverse outcomes, including heart failure progression and arrhythmic risk. Patients with minimal or absent LGE tend to show better recovery of ventricular function. In contrast, extensive or transmural LGE—particularly when involving the interventricular septum—identifies patients at higher risk of ventricular arrhythmias, progressive dysfunction, and adverse clinical outcomes, whereas isolated inferolateral LGE, although frequent in myocarditis, carries a less consistent prognostic impact [2,38,45–47]. Moreover, a ring-like pattern of LGE, characterized by circumferential subepicardial or mid-wall enhancement across multiple contiguous segments, has been associated with a high burden of arrhythmic events and adverse prognosis across non-ischemic cardiomyopathies, including inflammatory phenotypes [48]. Data suggest that patients with ring-like LGE have higher rates of ventricular arrhythmias and composite adverse events compared with those with non-ring-like patterns or no LGE, independent of left ventricular ejection fraction, underscoring its potential role as a high-risk imaging phenotype and the importance of multimodal evaluation and targeted therapies in these settings [49,50].

Persistent viral genome detection (e.g. parvovirus B19 or enterovirus) on EMB may be associated with ongoing myocardial injury and a poorer prognosis, particularly in the absence of viral clearance [51,52]. Additionally, a high arrhythmic burden on ECG or Holter monitoring—such as frequent ventricular ectopy or non-sustained ventricular tachycardia—signals a higher risk of sudden cardiac death, necessitating closer surveillance [53,54]. Recurrent myocarditis may be the hot phase presentation of arrhythmogenic CMP [55], and pathogenetic variants associated to CMPs may predispose the patient to a complicated course with persistent/worsening ventricular dysfunction, heart failure, arrhythmic events, and worse outcome [56–59].

6.2. Outcomes

Reported outcomes vary across cohorts. Dedicated studies on iCMP are missing. In acute myocarditis, complete functional recovery has been reported in approximately 50–70% of cases, particularly in self-limiting forms with preserved ventricular function [2]. In contrast, in chronic iCMP the presence of established fibrosis and ventricular remodelling markedly reduces the likelihood of full functional recovery, and improvement is more often partial and dependent on the degree of residual inflammatory activity and scar burden.

However, up to 30–40% of patients may develop chronic heart failure or dilated cardiomyopathy due to progressive remodelling [2,3,6,11]. Long-term observational data showed that patients with biopsy-proven active myocarditis and left ventricular dysfunction have a significantly poorer prognosis compared with those presenting with preserved systolic function, highlighting the prognostic impact of early ventricular impairment [4,60]. The transplant-free survival rate remains high (>85% at 5 years), but selected cases with refractory inflammation or advanced heart failure may require mechanical support or heart transplantation [2]. Arrhythmogenic risk remains a concern, particularly in patients with myocardial fibrosis, even after ejection fraction has improved [2,46,49].

Table 6
Risk factors for adverse outcomes in inflammatory cardiomyopathy.

Risk factor	Implication in iCMP
Extensive LGE (especially septal or ring-like)	Myocardial fibrosis and arrhythmic/HF risk
Persistent myocardial inflammation	Ongoing injury and adverse remodelling
Reduced LVEF	Predictor of HF progression and mortality
High arrhythmic burden	Higher risk of SCD and ICD need
Progressive ventricular remodelling	Poor prognosis
Delayed diagnosis or therapy	Irreversible fibrosis risk
Immune-mediated inflammatory phenotype	May respond to immunosuppression
Pathogenic CMP variants (e.g., DSP, LMNA)	Inflammatory hot phases and arrhythmic risk

6.3. Follow-up plan

A structured follow-up protocol is essential. As a complicated case, a lifelong follow-up is warranted for patients with iCMP [2,4,61]. Repeated CMR is valuable to monitor the evolution of myocardial inflammation, fibrosis, and ventricular remodelling in iCMP. In chronic iCMP, follow-up imaging is typically more informative when performed after a longer interval (e.g., 6–12 months), in order to capture the effects of sustained immunomodulatory and heart-failure therapies and to better assess disease stabilization or progression.

Echocardiography is used more frequently for serial monitoring of ventricular function [2]. Exercise restriction should be individualized in patients with iCMP based on the activity of myocardial inflammation, the degree of ventricular dysfunction, and the presence of arrhythmias. During phases of active disease, physical activity should be limited to reduce arrhythmic risk and prevent further myocardial injury. Return to exercise or competitive sports should only be considered after resolution of myocardial oedema on CMR (T2-weighted or T2-mapping), stabilization or improvement of ventricular function, and absence of clinically relevant arrhythmias on ambulatory ECG monitoring and exercise testing.

Circulating biomarkers should be assessed longitudinally, including cardiac troponin as a marker of ongoing myocardial injury, natriuretic peptides (BNP or NT-proBNP) to track haemodynamic stress and ventricular dysfunction, and inflammatory markers (e.g. C-reactive protein) to monitor systemic and myocardial inflammatory activity. Persistent or rising values should prompt reassessment with imaging and consideration of recurrent or progressive disease.

During follow-up, serial CMR provides important prognostic and therapeutic guidance. Changes in the extent and pattern of late gadolinium enhancement (LGE) reflect irreversible myocardial fibrosis and arrhythmic substrate, whereas normalization or persistence of T2-based oedema and T1-mapping abnormalities indicate resolved or ongoing inflammatory activity, respectively. These parameters help differentiate active disease from residual scar and guide decisions on immunomodulatory therapy, arrhythmia risk stratification, and return-to-activity.

Patient education and psychosocial support are essential components of long-term management. Patients should receive counselling on physical activity, smoking cessation, and cardiovascular risk modification, as well as the importance of vaccination (including influenza and SARS-CoV-2) to reduce the risk of inflammatory triggers. Women of child-bearing age should be offered dedicated pregnancy counselling, as iCMP and its treatments may influence maternal and fetal outcomes. Given the chronic and potentially relapsing nature of iCMP, psychological support and structured follow-up programs are recommended to improve adherence, quality of life, and long-term outcomes.

Recommendation 1. A lifelong follow-up is strongly advised in patients with iCMP, particularly in those with complicated disease (persistent ventricular dysfunction, myocardial fibrosis, arrhythmias, or recurrent inflammatory activity). *(Level of Evidence C)*.

Recommendation 2. It is strongly advised to individualize exercise restriction according to the activity of myocardial inflammation, degree of ventricular dysfunction, arrhythmic burden, and CMR and biomarker

findings, with return to physical activity guided by resolution of inflammation, stable ventricular function, and rhythm stability *(Level of Evidence C)*.

7. Comparison with international guidelines

7.1. ESC guidelines

The 2013 ESC Working Group position statement established a foundation for the modern management of myocarditis by defining clinical suspicion criteria and strongly supporting EMB in high-risk presentations (e.g., acute heart failure with haemodynamic compromise or malignant arrhythmias) [5]. The 2023 ESC cardiomyopathy guidelines subsequently expanded this framework by emphasizing systematic evaluation of non-ischaemic cardiomyopathy using CMR and genetic testing, while recognizing that definitive aetiologic diagnosis often requires tissue characterization [1].

The 2025 ESC myocarditis and pericardial disease guidelines provide, for the first time, a formal definition of iCMP, as chronic myocarditis associated with systolic ventricular dysfunction and remodelling, with either dilated or non-dilated hypokinetic phenotypes and possible arrhythmogenic substrate [2]. These guidelines establish strong alignment between imaging-based detection of inflammation (CMR) and EMB-guided aetiologic stratification, recommending standard heart-failure therapy for all patients and targeted immunosuppressive treatment in virus-negative immune-mediated iCMP.

While ESC guidance provides the regulatory and diagnostic framework for iCMP, it does not fully operationalize how to detect inflammation in routine cardiomyopathy pathways or how to integrate genetic, imaging, and EMB findings into a unified management algorithm. This position paper builds on ESC recommendations by proposing a practical, inflammation-driven workflow (Figs. 1 and 2) to identify and treat iCMP within everyday cardiomyopathy practice.

7.2. AHA/ACC guidelines

Contemporary AHA/ACC documents recognize myocarditis as an important cause of non-ischaemic cardiomyopathy and strongly support CMR for diagnosis and longitudinal assessment [11,62]. There is therefore broad consensus between ESC and AHA/ACC on the value of non-invasive imaging and standard heart-failure therapy.

However, a key divergence lies in the use of EMB and aetiology-guided therapy. While ESC guidelines explicitly define iCMP and recommend EMB-guided immunosuppression in virus-negative iCMP, AHA/ACC guidance limits EMB mainly to selected refractory or unexplained cases and does not provide a dedicated management pathway for chronic iCMP beyond heart-failure treatment. As a result, aetiology-driven therapy and systematic inflammation-based phenotyping remain less explicitly implemented in U.S. guidance.

This position paper therefore seeks to bridge this gap by translating ESC concepts into a clinically actionable framework that integrates CMR, EMB, genetic testing, and targeted immunomodulation, with the aim of improving risk stratification, arrhythmia management, and long-term outcomes in patients with inflammatory cardiomyopathy.

A comparison of the ESC and ACC key recommendation is summarized in Table 7.

Table 7
ESC vs AHA/ACC perspectives on chronic inflammatory cardiomyopathy.

Aspect	ESC 2025	AHA/ACC
Disease concept	Chronic myocarditis with remodelling	Myocarditis as CMP cause
Diagnostic approach	CMR + EMB if needed	CMR + EMB if needed
Biopsy	Intermediate/high risk iCMP	Selected refractory cases
Immunotherapy	Virus-negative iCMP	Selected immune cases
Risk stratification	LGE, inflammation, LVEF, arrhythmias genetics	LVEF, arrhythmias
Follow-up	CMR and rhythm surveillance	HF-oriented follow-up

8. Hot phases in inflammatory cardiomyopathy

Hot phases are acute, myocarditis-like inflammatory flares—characterized by chest pain, troponin release, and myocardial oedema with unobstructed coronaries—that can represent the earliest clinical expression of a genetic cardiomyopathy (often but not always desmosomal) and may herald the trajectory towards iCMP, even left ventricular ejection fraction is preserved for long time [55]. Recurrent flares are increasingly recognized as pivotal events in the disease course, as their occurrence can accelerate myocardial remodelling and drive progression to ventricular dysfunction [55,57]. Many patients alternate “hot” episodes with intervals of apparently normal systolic function before developing chronic dysfunction consistent with iCMP. In iCMP, episodic active inflammatory “hot phases” can occur as acute flares of myocarditis during the chronic disease course. These episodes have been observed in arrhythmogenic and dilated cardiomyopathies as well, and are associated with adverse outcomes. Pathogenetically, hot phases often result from an interplay between environmental triggers and a susceptible genetic background [55,57]. Patients experiencing these flares frequently carry pathogenic variants in cardiomyopathy-related genes, especially desmosomal proteins like desmoplakin (DSP) [56]. Such inflammatory bursts contribute to disease progression and have emerged as a strong predictor of major arrhythmic events (MAE), as recently shown in a multicentre study identifying myocardial inflammation as a major determinant of adverse arrhythmic outcomes, with MAE occurring at a shorter term than in individuals carrying high-risk genotypes in the absence of active inflammation [59]. Clinically, prompt recognition of a “hot phase” in genetic and iCMP is crucial, as distinguishing a hot phase from isolated myocarditis often requires a multimodal evaluation—including CMR to assess oedema and fibrosis, inflammatory imaging with FDG-PET when appropriate, EMB with histology and immunohistology, and genetic testing to identify underlying variants such as desmoplakin (DSP)-associated disease (which is frequently associated with inflammatory hot phases). Emerging evidence suggests that targeted therapy during hot phases, including immunosuppressive or anti-inflammatory treatments, may mitigate acute myocardial damage and influence disease progression; small series in DSP cardiomyopathy describe attenuation of inflammatory activity and arrhythmic events with such strategies, supporting a personalized approach guided by imaging and biopsy findings [57–59,63].

9. Gaps in current knowledge and future directions

Despite advances in cardiac imaging, molecular diagnostics, and immunopathology, major knowledge gaps remain in iCMP. These gaps directly affect how the recommendations in this position paper should be applied in practice—favouring individualized, mechanism-based decision-making over rigid treatment algorithms.

9.1. Epidemiology

Reliable data on the true incidence and prevalence of iCMP remain scarce. While myocarditis is increasingly recognized with modern imaging and biopsy techniques, the lack of large prospective registries limits our ability to quantify how often acute myocarditis evolves into chronic iCMP or dilated cardiomyopathy. This uncertainty reinforces the need for lifelong follow-up and systematic imaging surveillance, as recommended earlier in this manuscript.

9.2. Pathogenesis

Although the two-hit hypothesis (genetic susceptibility plus environmental or infectious trigger) provides a useful conceptual framework, the relative contributions of viral persistence, immune dysregulation, and autoimmunity remain incompletely defined. This biological uncertainty underpins the manuscript's emphasis on multimodal phenotyping (CMR, EMB, genetics) rather than reliance on clinical phenotype alone to guide therapy.

9.3. Therapeutics and clinical trials

The most critical gap remains the absence of adequately powered RCTs in iCMP. Evidence supporting immunosuppressive therapy is strongest in virus-negative, immune-mediated disease but is derived from small trials and single-centre cohorts. Consequently, the recommendation to use immunosuppression in this manuscript is deliberately conditional and EMB-guided, targeting patients with persistent inflammation, progressive dysfunction, or inflammation-related arrhythmias rather than applied broadly.

In virus-positive disease, particularly when transcriptionally active virus is present, immunosuppression remains controversial, which further supports the recommendation for routine viral PCR on EMB before treatment decisions.

Emerging therapies—including IL-1 blockade, immune pathway–specific biologics, and antiviral or RNA-based approaches—highlight the need for phenotype-stratified trials based on viral, immune, and imaging markers. Until such trials are completed, treatment must balance potential benefit against uncertainty, guided by disease activity and risk profile.

9.4. Outcomes

Long-term outcome data remain heterogeneous, and prognostic markers such as LGE burden, arrhythmic activity, and viral persistence are not yet prospectively validated. This limitation supports the manuscript's recommendations for serial CMR, biomarker monitoring, and arrhythmia surveillance rather than reliance on single-time-point assessments.

9.5. Specific populations

The lack of age-stratified data, particularly in paediatric iCMP and post-MIS-C myocardial disease, means that most recommendations are extrapolated from adult cohorts. This reinforces the need for dedicated paediatric registries and trials, and for cautious, individualized application of immunomodulatory therapies in younger patients.

9.6. Artificial intelligence

Artificial intelligence–based analysis of CMR, including automated quantification of myocardial oedema, fibrosis, and LGE patterns, as well as integration with clinical, genetic, and biomarker data, holds promise for the development of iCMP-specific risk prediction models and more precise, personalized management strategies in the future.

10. Conclusions

This position paper by the Italian Society of Cardiology Working Group offers a comprehensive framework for the diagnosis and management of iCMP, aiming to improve clinical recognition and standardise care pathways. Key recommendations include early suspicion in patients with unexplained heart failure or arrhythmias, the strategic use of CMR and especially EMB for the recognition of the histologic type and develop targeted therapies.

Implementing these evidence-based strategies has substantial potential to improve patient outcomes. Accurate risk stratification, guided by imaging, biopsy, and biomarker data, can help identify patients at risk of further progression. Personalized therapy—particularly immunosuppressive treatment for virus-negative or autoimmune myocarditis—can limit adverse remodelling, promote recovery, and reduce the need for advanced interventions such as mechanical circulatory support or transplantation.

Ultimately, this document reinforces the importance of early recognition, multidisciplinary collaboration, and precise diagnostic work-up to ensure optimal care. While many therapeutic options are already established, significant uncertainties remain—particularly in viral-positive cases and long-term follow-up strategies. Future research, including multicentre trials and registry-based studies, is essential to address these gaps and evolve towards precision medicine in iCMP. Until then, clinicians are encouraged to adopt a nuanced, evidence-informed approach that balances clinical urgency with diagnostic certainty.

CRediT authorship contribution statement

Massimo Imazio: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Valentina Jahnsen:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Data curation. **Marco Merlo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Data curation. **Alberto Aimo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Camillo Autore:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Data curation, Conceptualization. **Andrea Barison:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Barbara Bauce:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Data curation, Conceptualization. **Elena Biagini:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Data curation, Conceptualization. **Emanuele Bobbio:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Francesco Cappelli:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Silvia Castelletti:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Valentino Collini:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Flavio D'Ascenzi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Cesare De Gregorio:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Santo Dellegrottaglie:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Francesca Marzo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Beatrice Musumeci:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Fabrizio Ricci:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Francesco Venturelli:** Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Roberto Pedrinelli:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization. **Stefania Paolillo:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization. **Pasquale Perrone-Filardi:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization. **Giuseppe Limongelli:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Data curation, Conceptualization. **Gianfranco Sinagra:** Writing – review & editing, Visualization, Validation, Supervision, Formal analysis, Data curation, Conceptualization.

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