

Cardiomyopathies in Practice

From Deep Phenotyping
to Precision Medicine

Gianfranco Sinagra
Marco Merlo
Editors

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Springer

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This book is dedicated to Prof. Fulvio Camerini, who, in the 1970s, recognized the importance of this chapter of pathology, fostering curiosity and methodological rigor in the observation of patients, in the systematic collection of data and in a multidisciplinary approach. He remained open to the rapid and far-reaching advances in knowledge, embracing contributions from genetics, multimodal imaging, cardiovascular pathology, and multicenter registry data.

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Evolution of the Approach to Cardiomyopathies with the Implementation of Genetics and Cardiac Magnetic Resonance

1

Marco Merlo  and Gianfranco Sinagra 

The approach to cardiomyopathies has deeply evolved over the past decades, moving from a diagnostic framework largely based on clinical evaluation and conventional imaging to a more integrated approach that incorporates advanced imaging and genetics. Despite these advances, the classification of cardiomyopathies remains fundamentally phenotype-based, encompassing dilated cardiomyopathy (DCM), non-dilated left ventricular cardiomyopathy (NDLVC), hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), restrictive cardiomyopathy (RCM), and related forms. However, phenotype represents the starting point rather than the destination of the diagnostic process; in this perspective, the purpose of this book is to guide the reader through this evolving framework, drawing on the experience of the *Trieste Cardiomyopathy Registry*, which has collected more than 3600 cases of cardiomyopathies (Fig. 1.1), with systematic data acquisition and prolonged longitudinal follow-up. Over the years, the Registry has provided a solid clinical and research platform, contributing meaningful insights into disease evolution, risk stratification, and patient management, while maintaining a rigorous and methodologically sound approach. Building upon the most recent classifications and 2023 ESC guidelines and integrating clinical experience with current scientific evidence, it aims to provide a comprehensive approach to cardiomyopathies. Despite the remarkable technological progress represented by CMR and genetic testing, the diagnostic journey still begins where medicine has always begun with a careful anamnesis and a solid clinical assessment. The first and most crucial diagnostic tool remains the patient's history. A detailed personal and family history provides the foundation upon which every subsequent investigation is built. Symptoms such as dyspnea, palpitations,

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	DCM	Alcohol	ChemoTx	Tachy-CMP	ACM*	NDLVC	HCM	Myocarditis	Amyloidosis
N° of patients	1801	70	78	209	165	132	541	364	282
Mean age (years)	52±15	57±9	57±13	60±14	40±25	38±8	48±20	38±16	67±11 for AL 79±8 for TTR
Follow-up (months)	144±120	132±60	120±60	120±60	185±42	61±43	60±18	77±81	20±19
Years of enrolment	1978-2025	2005-2025	2005-2025	2005-2025	1976-2025	2023-2025	1983-2025	1981-2025	1990-2025

*ACM include ARVC and biventricular ACM

Fig. 1.1 The Trieste Cardiomyopathy Registry

syncope, or reduced exercise tolerance must be interpreted within a broader context that includes familial patterns, premature sudden cardiac death, heart failure of unclear origin, or relatives with implantable devices, especially at a young age. Clinical evaluation flows naturally from anamnesis with a red-flags approach (the so-called “cardiomyopathy mindset”). Attention should also be paid to extracardiac signs, such as skeletal muscle involvement or systemic features, which may suggest a syndromic or specific inherited form of cardiomyopathies. Importantly, the clinician’s role at this stage is not to confirm the disease but to recognize those elements that justify further investigation. Cardiomyopathies often reveal themselves gradually, and early signs may be understated. The ability to identify these early signals remains central to modern practice, both for patients and for family members. ECG and echocardiography represent the first-line instrumental extensions of clinical evaluation. They are accessible, noninvasive, and highly informative. Historically, these two tools formed the backbone of diagnosis; however, the introduction of CMR has significantly expanded diagnostic capabilities. CMR offers superior morphological definition and, more importantly, tissue characterization. The possibility of identifying myocardial fibrosis or subtle structural abnormalities has increased diagnostic sensitivity, allowing recognition of disease even when ECG and echocardiography are normal. In some cases, CMR reveals myocardial “scar” in patients who would previously not have fulfilled criteria for cardiomyopathy. While this has refined our understanding of disease spectrum and improved risk stratification, it also requires careful interpretation to avoid overdiagnosis or misclassification of clinically borderline findings. Parallel to imaging advancements, genetics has profoundly transformed the conceptual framework of cardiomyopathies. The identification of pathogenic variants can clarify etiology, confirm the diagnosis, refine risk stratification, guide decisions regarding sports eligibility, and enable cascade family screening. In selected conditions, it may also have therapeutic implications, and its role is expected to expand further in the next future with the development of targeted and gene-based therapies. Nevertheless, genetics is not merely a confirmatory instrument and may introduce complexity, particularly when variants of uncertain significance are identified or in specific gene-elusive patients with overt phenotype of cardiomyopathy. Such findings can

generate uncertainty and require careful interpretation within the broader clinical and imaging context. Thus, although genetics and CMR have undeniably strengthened our diagnostic armamentarium, enhancing sensitivity and etiological definition, they complement rather than replace the fundamental steps of anamnesis, clinical reasoning, ECG, and echocardiography. Within this integrated framework, the management of cardiomyopathy extends beyond the individual diagnosis to include structured evaluation and longitudinal follow-up of the entire family. Nevertheless, important challenges persist. The optimal management of genotype-positive but phenotype-negative individuals remains unresolved, particularly regarding risk stratification and therapeutic decisions. Likewise, patients with a definite clinical phenotype but no identifiable pathogenic variant—the so-called gene-elusive cases—expose the current limits of genetic testing. Emerging approaches, including polygenic risk scores and other advanced genomic technologies, may further refine etiological classification and support more personalized treatment strategies. Finally, the deep-phenotyping process of all patients with cardiomyopathies, across the entire spectrum of clinical phenotypes, may increasingly benefit from artificial intelligence soon. A more personalized classification and management strategy supported by artificial intelligence represents an important horizon, although it is not yet fully applicable in everyday clinical practice. For this reason, comprehensive clinical evaluation remains the cornerstone in the management of these complex patients and their families. This book aims to accompany the reader through this evolving landscape. Starting from the most recent disease classifications and the latest ESC guidelines, it seeks to integrate scientific evidence, advanced imaging, and genetic insights with consolidated clinical experience.

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Part I

The Bases of Genotype-Phenotype Characterization

General Aspects of Cardiac Magnetic Resonance in Cardiomyopathies

2

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Giancarlo Vitrella, Alessandro Altinier, Annalisa Bernabei,
Massimo Valenti, Lorenzo Pagnan, and Alessandro Sarno

2.1 Indications and Contraindications

Cardiac magnetic resonance (CMR) is a fundamental tool in the management of patients with suspected or confirmed cardiomyopathy. This modality, which does not involve the use of radiation, is widely recognized as the gold standard for the quantification of cardiac chamber volumes, mass, and function [1], providing a precise characterization of the clinical phenotype (i.e., dilated, nondilated, hypertrophic, arrhythmogenic, and restrictive cardiomyopathies), according to the recent 2023 European Guidelines on the management of cardiomyopathies [2]. In addition, CMR enables characterization of myocardial tissue through advanced techniques. Late gadolinium enhancement (LGE) imaging allows assessment of the extent and localization of macroscopic myocardial fibrosis, which has significant diagnostic, therapeutic, and prognostic implications [3]. T1- and T2-weighted images are also used in tissue characterization to respectively identify fatty infiltration or myocardial edema. More recently, parametric mapping techniques have enhanced the accuracy of etiological assessment by CMR. In particular, microscopic fibrosis can be quantified by estimating the extracellular volume fraction

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(ECV) using native and post-contrast T1 mapping [4], while T2 mapping improves the identification of diffuse myocardial edema [5].

According to the ESC Guidelines for the management of cardiomyopathies, CMR is strongly recommended (class I, LOE B) for the initial evaluation of all patients with suspected cardiomyopathy, with the aim of defining the etiology, staging the severity of the disease, stratifying the risk of events, and guiding therapy [2]. Follow-up examinations may be considered every 2–5 years on an individual basis to monitor disease progression, reassess event risk, and evaluate therapeutic efficacy [2].

Absolute contraindications to CMR include the presence of metallic implants or foreign bodies that are incompatible with an MRI scan (e.g., shrapnel fragments) and severe obesity exceeding the scanner table capacity. Severe renal impairment ($\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$) contraindicates the administration of gadolinium-based contrast agents, particularly first-generation linear agents, due to the risk of nephrogenic systemic fibrosis, although this complication is almost unreported with the use of newer macrocyclic gadolinium-based agents [6]. Moreover, gadolinium use is generally discouraged during pregnancy due to potential fetal effects.

Although most contemporary pacemakers and implantable cardioverter-defibrillators (ICDs) are MRI-conditional, safe imaging requires configuring both the device and the MRI scanner to the appropriate safe mode. These devices, especially ICDs, often generate imaging artifacts that can be mitigated through specific strategies to reduce device-related signal inhomogeneity [7]. Although the device may be MRI-compatible, the presence of other elements, such as abandoned leads, can make the overall system unsafe for scanning [8].

2.2 Main Sequences in Cardiac Magnetic Resonance Imaging

Magnetic resonance scanners used for cardiac imaging should have a field strength of at least 1.0 T, with 1.5 T being the most widely employed. A field strength of 3.0 T provides a higher signal-to-noise ratio, which is particularly useful in LGE sequences. However, at this field strength, cine steady-state free precession (SSFP) sequences are more susceptible to artifacts, including off-resonance effects at the lung–heart interface, potentially resulting in dark banding within the posterolateral segments, as well as increased flow artifacts [9].

The evaluation of cardiomyopathies requires imaging protocols tailored to specific clinical indications. For a general overview, CMR sequences can be summarized as morphologic, functional, tissue characterization, and parametric mapping. Morphologic sequences may be further divided into dark blood and bright blood sequences.

Black blood imaging predominantly uses turbo spin echo (TSE) sequences, which can be weighted for T1, proton density (PD), or T2 signals. Adding an inversion-recovery (IR) prepulse, typically applied as a double-IR technique to selectively null the blood signal, enhances the black blood effect.

Fat infiltration in myocardial tissue produces high signal on T1- and PD-weighted sequences, whereas edema is better visualized using T2-weighted imaging. To further enhance myocardial edema delineation, a third inversion recovery (IR) pulse can be applied to suppress epicardial fat signal [short tau inversion recovery (STIR) sequences].

Bright blood sequences, used for morphologic and functional evaluation, are currently based on balanced steady-state free precession (b-SSFP) technique, which generates a signal primarily reflecting the T2/T1 ratio. This T2/T1 weighting produces the characteristic “India Ink” chemical-shift artifact at fat–myocardium interfaces, including regions of fat infiltration or replacement, as observed in arrhythmogenic cardiomyopathy [10].

Balanced SSFP sequences—often designated with vendor-specific terminology—are a cornerstone of CMR, providing a comprehensive assessment of cardiac morphology and function due to their high spatial resolution and excellent intrinsic contrast between blood and myocardium. With retrospective ECG gating and breath-hold, b-SSFP acquisitions typically capture 30 phases per cardiac cycle, enabling reconstruction of cine loops for detailed dynamic functional assessment.

For the assessment of global systolic function, ventricular short-axis images are acquired in parallel slices extending from the atrioventricular plane to the apex, with a fixed slice thickness (typically 8 mm) and a variable interslice gap. These images are used to quantify myocardial mass, as well as end-diastolic and end-systolic volumes, from which the ejection fraction (EF) is derived [11]. In uncooperative patients, b-SSFP sequences can also be acquired in real time under free-breathing conditions, albeit with reduced spatial and temporal resolution.

Flow quantification is performed using gradient echo sequences with velocity encoding (VENC) set near the expected maximal velocity of the target vessel. Typically acquired in an 8 mm slice at the scanner isocenter, the sequence can be oriented through-plane (orthogonal to flow) for assessment of flow direction, forward and backward volumes, and peak velocity, or in-plane (aligned with flow) for the evaluation of flow direction and velocity [12].

LGE sequences for scar imaging are typically acquired using T1 IR gradient-echo (GRE) or phase-sensitive inversion recovery (PSIR) techniques. These sequences are obtained approximately 10 minutes after administration of a gadolinium-based contrast agent. The optimal inversion time is determined using a Look-Locker sequence, which samples myocardial signal recovery to null normal myocardium, thereby enhancing visualization of the expanded extracellular space with contrast retention, such as necrotic or fibrotic tissue [13]. The presence of LGE should be confirmed in two orthogonal planes and described in terms of location, pattern (i.e., nonischemic or ischemic), and extension.

Advanced tissue characterization can be further obtained using parametric sequences, which assign quantitative T1, T2, or T2* values to each myocardial voxel, generating color-coded maps of the heart. These sequences are of paramount importance for differentiating cardiomyopathies and are particularly useful in hypertrophic phenotypes [14]. Typically, three short-axis slices are

acquired to cover the basal, mid, and apical segments. Measurements vary between 1.5 T and 3 T scanners and across centers, requiring local reference ranges [15].

T1 mapping is mostly obtained using the modified Look-Locker inversion recovery (MOLLI) sequence, acquired in diastole in patients with normal heart rates. Source images must be carefully reviewed for motion artifacts. For extracellular volume (ECV) quantification, the MOLLI acquisition is repeated approximately 15 minutes post-contrast administration. Notably, a hematocrit performed within 24 hours is required for accurate calculation.

T2 mapping is performed before contrast administration using either multi-echo spin echo (MESE), gradient spin echo (GraSE), or single-shot T2-prepared balanced SSFP sequences, providing a quantitative assessment of myocardial water content.

T2* mapping employs a gradient-echo, multi-echo acquisition. This technique, together with T1 mapping and extracellular volume (ECV) quantification, is primarily used for quantitative evaluation of myocardial iron overload, such as in patients with hemochromatosis [16–18].

Table 2.1 provides a summary of the study protocols used in the assessment of cardiomyopathies.

Table 2.1 General CMR study protocol for the evaluation of cardiomyopathies, including optional sequences and disease-specific considerations

Sequence	Orientation	Purpose	Notes
Localizer	Multiplanar	Localization of the heart	Initial scout images
b-SSFP	Axial, multislice	Anatomy	Extended from the aortic arch to the diaphragm
b-SSFP	2-, 3-, 4-chamber	Cine imaging	Assessment of regional/global function
T1 mapping	Short-axis	Parametric tissue characterization	Pre-contrast study
T2 mapping	Short-axis	Parametric tissue characterization	Pre-contrast study
b-SSFP	Short-axis, multislice	Cine imaging	From atrioventricular plane to the apex; quantification of biventricular volumes and mass; assessment of regional/global function
Look-locker	Short-axis	Identification of the optimal inversion time for normal myocardium nulling	6–10 minutes after contrast administration
PSIR	Short-axis, multislice	Scar / fibrosis	From atrioventricular plane to the apex; distribution / localization of LGE
PSIR	2-, 3-, 4-chamber	Scar / fibrosis	Distribution / localization of LGE
T1 mapping	Short-axis	ECV quantification	15 minutes after contrast administration

2.2.1 Optional/Disease-Specific Sequences

Cardiomyopathy	Sequence	Notes
DCM / ARVC / HCM / RCM	Phase-contrast of aorta and pulmonary artery	Quantification of transvalvular flow, valvular regurgitation and shunts
DCM / ARVC / HCM / RCM	T2-STIR / T2 mapping	Edema detection
DCM / RCM	T2* mapping	Evaluation of myocardial iron deposition
HCM	Phase-contrast three-chamber in-plane / LVOT through-plane	Assessment of LVOT obstruction
ARVC	b-SSFP multislice four-chamber, multislice RV long axis and RVOT	RV morphology and function
ARVC	Double IR (black blood) T1/PD TSE	Confirmation of fat infiltration
RCM	Real-time cine	Assessment of ventricular interdependence during respiration—for differential diagnosis with constrictive pericarditis

ARVC arrhythmogenic right ventricular cardiomyopathy; *b-SSFP* balance steady-state free precession; DCM dilated cardiomyopathy; ECV extracellular volume; HCM hypertrophic cardiomyopathy; IR inversion recovery; LGE late gadolinium enhancement; LVOT left ventricular outflow tract; PSIR phase-sensitive inversion recovery; RCM restrictive cardiomyopathy; RVOT right ventricular outflow tract; STIR short tau inversion recovery.

2.3 Role of CMR in Dilated Cardiomyopathy

CMR has become an essential tool for the diagnosis and management of DCM patients (Fig. 2.1) [2]. High spatial resolution and unrestricted multiplanar imaging make CMR ideal for comprehensive morphofunctional assessment of the heart, overcoming the limitations of echocardiography related to geometric assumptions and poor cardiac acoustic windows [19].

Beyond the assessment of biventricular volumes and function, CMR can identify the presence of edema, fatty infiltration, iron deposition, and fibrosis by using dedicated sequences [20], thus enabling in vivo myocardial tissue characterization and providing key insights into the disease’s etiology [21]. Moreover, CMR is highly effective in detecting left ventricular (LV) thrombi, a potential complication of severe LV systolic dysfunction, which increases the risk of thromboembolic events [22] through early gadolinium enhancement (EGE) and late gadolinium enhancement (LGE) techniques.

CMR is able to differentiate LV dilatation and dysfunction due to ischemic or nonischemic origin (i.e., idiopathic, genetic, inflammatory, and toxic causes), mainly through the LGE technique. Subendocardial or transmural LGE in a coronary distribution suggests an ischemic etiology, whereas epicardial or intramural involvement is more typical of nonischemic disease [23]. Overall, LGE is detected in approximately half of the patients with DCM. When present, it typically appears

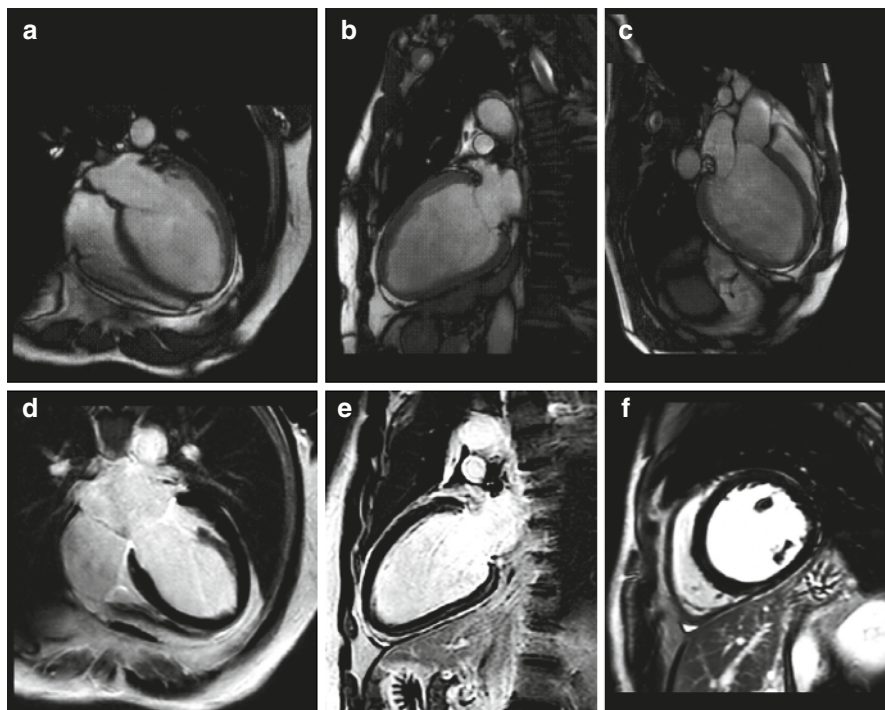


Fig. 2.1 Case of dilated cardiomyopathy (DCM) caused by a pathogenic *FLNC* gene mutation. (a–c) Balanced steady-state free precession cine images, long-axis views, showing severe left ventricular dilatation with increased sphericity. (d–f) Late gadolinium-enhanced images, long-axis and short-axis views, revealing hyperintense intramural stria at the level of the inferior wall, consistent with a nonischemic pattern of fibrosis

as patchy or linear epicardial and/or mid-wall enhancement, most often involving the interventricular septum [24, 25]. Subendocardial LGE may also be observed, even in the absence of coronary artery disease [26]. In some patients, LGE is found in an extensive semi-circumferential or circumferential “ring-like” pattern, often associated with pathogenic variants in *DSP*, *FLNC*, and *LMNA* genes [27]. This pattern correlates with a higher arrhythmic risk and reduced likelihood of reverse remodeling (LVRR) [28–30].

Diffuse interstitial fibrosis can be reliably evaluated through T1 mapping and ECV quantification, regardless of the presence of LGE [31]. Elevated values are independently associated with higher risk of death and heart failure hospitalization [32–34]. Conversely, lower ECV is associated with a higher likelihood of subsequent reverse remodeling [35].

2.3.1 Implications for Patient Management

The presence, distribution, and extent of LGE may support indications to defibrillator implantation in primary prevention [2, 36]. In addition, it may guide decisions in patients considered for cardiac resynchronization therapy (CRT). In particular, the absence of LGE is associated with a higher likelihood of reverse remodeling, significant improvement in left ventricular ejection fraction (LVEF), and better clinical outcomes after CRT [37–39]. Conversely, pacing over scar tissue is linked to a higher incidence of major adverse cardiovascular events [40].

2.3.2 Risk Stratification

The presence of LGE is independently associated with adverse clinical outcomes in patients with DCM. Several meta-analyses consistently demonstrate that the LGE confers an increased risk of all-cause and cardiovascular mortality, hospitalization for heart failure (HF), heart transplantation, major ventricular arrhythmias (MVA), and sudden cardiac death (SCD) [41, 42].

Although severely reduced left ventricular ejection fraction (i.e., LVEF $\leq 35\%$), remains the cornerstone for selecting patients for primary prevention implantable cardioverter-defibrillator (ICD) therapy, it is an imperfect risk stratification marker. Moreover, the prognostic value of LVEF differs according to the imaging modality. CMR-derived LVEF $\leq 35\%$ is associated with a higher risk of adverse events compared with the same threshold measured by standard transthoracic echocardiography [43].

LGE has proven to be a more powerful predictor of arrhythmic events, independent of LVEF [44], with the distribution pattern providing additional prognostic information. In particular, septal location is associated with increased risk of all-cause mortality, MVA, and SCD [24, 45]. The extent of LGE seems less relevant, as even small amounts are associated with an increased risk of events [24].

LGE dispersion, quantified using the Global Dispersion Score (GDS), has recently been proposed as a novel marker to identify DCM patients at higher risk for malignant arrhythmic events, independent of LVEF or LGE extent [46]. An increased GDS is an independent predictor of such events, reflecting higher tissue heterogeneity [46].

Native T1 and ECV are additional markers to identify patients at increased risk for HF and arrhythmias, as higher values are associated with adverse outcomes. Specifically, an ECV fraction exceeding 32% was associated with a fourfold higher risk, with each 1% increment in ECV associated with an additional 17% increase in risk [33, 34].

LV strain analysis assessed with CMR has emerged as a sensitive marker of adverse prognosis in DCM. A decreased GLS is an independent predictor of ventricular arrhythmias and death, providing incremental value to LVEF and LGE [47].

CMR may improve prediction of LVRR, thus improving risk stratification and helping provide tailored therapy. LVRR occurs more frequently in LGE-negative patients and in patients with lower myocardial T2 and ECV values [48].

2.3.3 Screening of Family Members

According to recent European Guidelines, isolated LV dilatation may be an early manifestation of DCM [2]. However, LV enlargement is common in healthy endurance athletes, and distinguishing them from DCM patients may be challenging. A recent study found that endurance athletes did not have LGE and had lower T2 and especially T1 relaxation times [49]. Genotype-positive/phenotype-negative family members exhibit high rates of disease penetrance, and the presence of LGE helps identify those at increased risk of developing overt DCM [50, 51].

2.4 Role of CMR in Nondilated Left Ventricular Cardiomyopathy

Nondilated left ventricular cardiomyopathy (NDLVC) is a recently defined phenotype introduced by the ESC Guidelines, characterized by LV structural and/or functional abnormalities without LV dilatation [2]. A diagnosis of NDLVC can be made in the presence of nonischemic LV scarring or fatty replacement, with or without wall motion abnormalities and global systolic dysfunction, or isolated global LV hypokinesia without scarring, unexplained solely by abnormal loading conditions or coronary artery disease (Fig. 2.2) [2].

NDLVC encompasses a broad spectrum of etiologies, including idiopathic, genetic, inflammatory causes, early-stage dilated cardiomyopathy, and left-dominant variants of arrhythmogenic cardiomyopathy [52].

The prevalence of NDLVC is not yet well established, as this category was recently introduced, although previous studies on hypokinetic nondilated cardiomyopathy suggest that NDLVC may account for approximately 20–50% of cases among patients with nonischemic cardiomyopathy and LV dysfunction [53, 54].

Multimodality imaging plays a central role in the diagnosis, risk stratification, and follow-up of NDLVC patients [2]. With its ability to identify nonischemic myocardial fibrosis and/or fatty replacement through T1-, PD-weighted sequences, and LGE technique, CMR has emerged as the primary imaging modality in NDLVC. CMR also offers valuable insights into the underlying etiology. Myocardial edema suggests an inflammatory cause, while patterns of LGE help differentiate ischemic from nonischemic disease [55–57]. Furthermore, a ring-like pattern of LGE may suggest the presence of high-risk genetic mutations [27]. LGE is observed in 60% of NDLVC patients, predominantly within epicardial and intramural regions, and is associated with MVA [45].

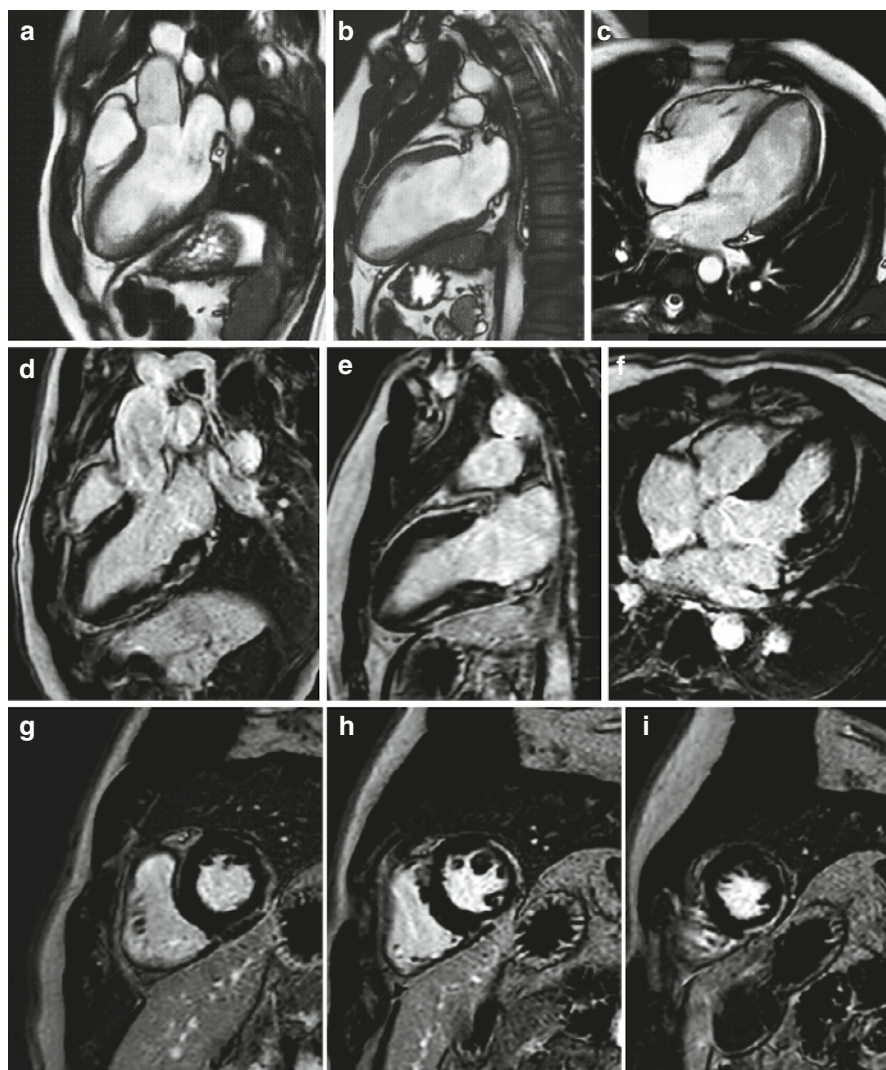


Fig. 2.2 Case of nondilated left ventricular cardiomyopathy (NDLVC) due to a pathogenic DSP gene mutation. (a–c) Cine images show normal chamber size with preserved regional and global systolic function of both ventricles. (d–i) Post-contrast images demonstrate extensive late gadolinium enhancement with a nonischemic pattern involving the inferior, posterior, and lateral walls of the left ventricle (hyperintense areas), consistent with fibrotic replacement

2.4.1 Implications for Patient Management

CMR is strongly recommended at the initial evaluation of all patients with suspected NDLVC to help define the etiology, stratify the risk of events, and guide therapy [2].

In NDLVC patients with an LVEF below 35% and “ring-like” LGE, CMR may support early consideration of primary prevention ICD implantation, as this pattern is associated with reduced likelihood of LVRR and a higher risk of MVA or SCD [30].

CMR can reliably detect changes in LV volumes over time, making it a valuable tool during follow-up. Previous studies suggest that approximately one in five NDLVC patients will progress to DCM within 3 years, accompanied by worse clinical outcomes [58].

2.4.2 Risk Stratification

The association between LGE and adverse major arrhythmic outcome in NDLVC patients is well established. Intramural LGE identifies a subset of NDLVC patients with an increased likelihood of MVA and SCD, comparable to LGE-positive DCM patients [59]. Moreover, septal LGE location is associated with an increased risk of events [45]. A ring-like LGE pattern further elevates the risk of MVA/SCD [30]. A recent externally validated 5-year risk score included septal and ring-like LGE as predictive of arrhythmias in NDLVC patients, along with signs of myocardial inflammation, thus emphasizing the role of CMR in arrhythmic risk stratification in these patients [60].

2.4.3 Screening of Family Members

According to ESC Guidelines, all first-degree relatives of affected patients should undergo a comprehensive clinical evaluation, including cardiac imaging. CMR is the preferred imaging modality for family members of NDLVC patients, according to the ESC diagnostic criteria [2]. Moreover, the indication for CMR may be particularly strong in relatives of patients with extensive LGE or genotype-positive status, especially when the proband carries a pathogenic or likely pathogenic (P/LP) variant associated to ring-like scarring, there is a family history of SCD, or genetic testing results are delayed. In such cases, CMR findings can guide the prioritization of genetic testing and support decisions on primary prevention ICD implantation [2, 61–64].

2.5 Role of CMR in Myocarditis and Inflammatory Cardiomyopathies

Inflammatory cardiomyopathies are a heterogeneous group of diseases characterized by acute or chronic myocardial inflammation of different etiology, encompassing conditions such as myocarditis, cardiac sarcoidosis, and hot-phase cardiomyopathy. CMR is essential for the noninvasive evaluation of these conditions, prognostic stratification, and treatment monitoring.

2.5.1 Myocarditis

Although a definite diagnosis of myocarditis requires EMB, multimodality imaging allows for accurate detection of disease in most cases with infarct-like presentation and, with a lower sensitivity, in myocarditis with new onset HF or arrhythmic presentation [65, 66]. The original Lake Louise Criteria (LLC) for CMR imaging in suspected myocarditis included T2-weighted sequences for the evaluation of edema, and T1-weighted early and late gadolinium enhancement sequences, respectively, for the detection of hyperemia and myocardial tissue damage [67]. The LLC criteria are effective in detecting myocarditis presenting with infarct-like symptoms, often with signal abnormalities in the basal and mid regions of LV inferolateral wall, with a subepicardial or intramural distribution. However, they lack sensitivity and specificity compared to EMB in cases presenting as new-onset HF or arrhythmias. In this setting, T1 and T2 mapping techniques may detect diffuse tissue abnormalities, thus increasing sensitivity and specificity of CMR [66]. LLC criteria were therefore updated to include mapping techniques [55].

CMR findings at presentation and follow-up improve risk prognostication of myocarditis patients (Fig. 2.3). Baseline LV systolic dysfunction and LGE, particularly with septal location, are associated with increased risk of mortality, acute HF, MVA, and myocarditis recurrence [68–70]. Conversely, a normal CMR study is associated with low morbidity and mortality risk [68]. CMR feature tracking and extracellular volume (ECV) quantification were also suggested to further improve risk stratification, as reduced global longitudinal strain (GLS) and increased ECV are independently associated with major adverse cardiovascular events and show incremental prognostic value over LVEF and LGE [71, 72]. Right ventricular involvement, more common than previously recognized, is also associated with a higher incidence of major cardiac events during follow-up [73].

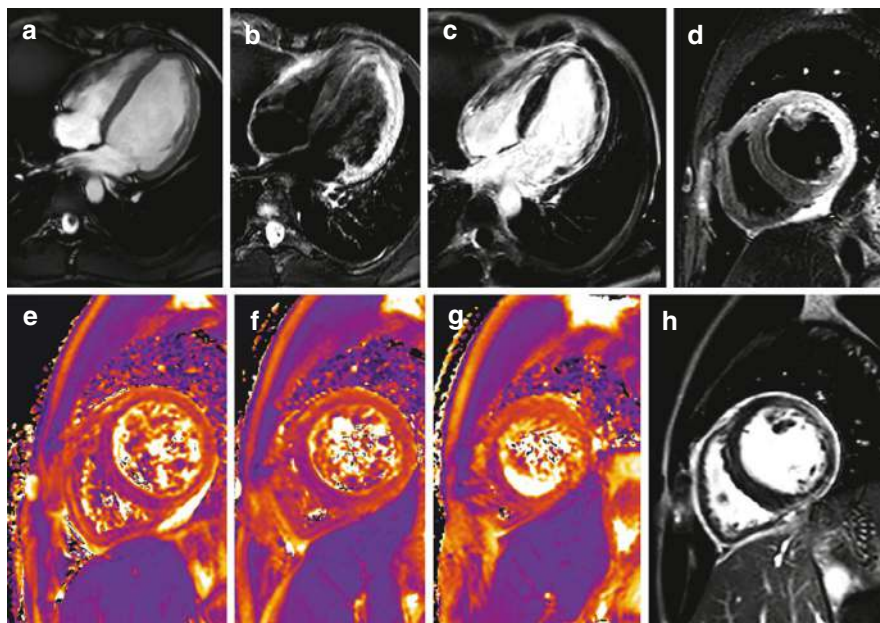


Fig. 2.3 Case of acute myocarditis. (a) Cine SSFP four-chamber view shows apparent left ventricular wall thickening (pseudo-hypertrophy) caused by pronounced myocardial edema. (b, d) T2-weighted STIR images, four-chamber and short-axis views, demonstrate increase of signal intensity of the lateral wall consistent with edema. (e–g) T2 mapping images confirm increased T2 relaxation time in the left ventricular free wall. (c, h) Post-contrast images, four-chamber and short-axis views, reveal extensive late gadolinium enhancement of the lateral wall (nonischemic pattern), consistent with myocardial injury

Finding LGE in the acute setting does not necessarily imply fibrosis, as it may be reduced or absent at follow-up. When found at 6 months' follow-up, LGE is a marker of worse outcomes [74, 75]. The presence of myocardial fat infiltration should also be systematically assessed in follow-up studies, as detection of LV intramyocardial fat after myocarditis is strongly associated with an increased risk of major cardiac events and adverse ventricular remodeling [76].

2.5.2 Cardiac Sarcoidosis

CMR plays a central role in the diagnosis and prognostic stratification of cardiac involvement in systemic sarcoidosis (Fig. 2.4). Cine SSFP sequences effectively detect subtle regional wall motion abnormalities and wall thinning, found typically at the basal interventricular septum [77]. Tissue

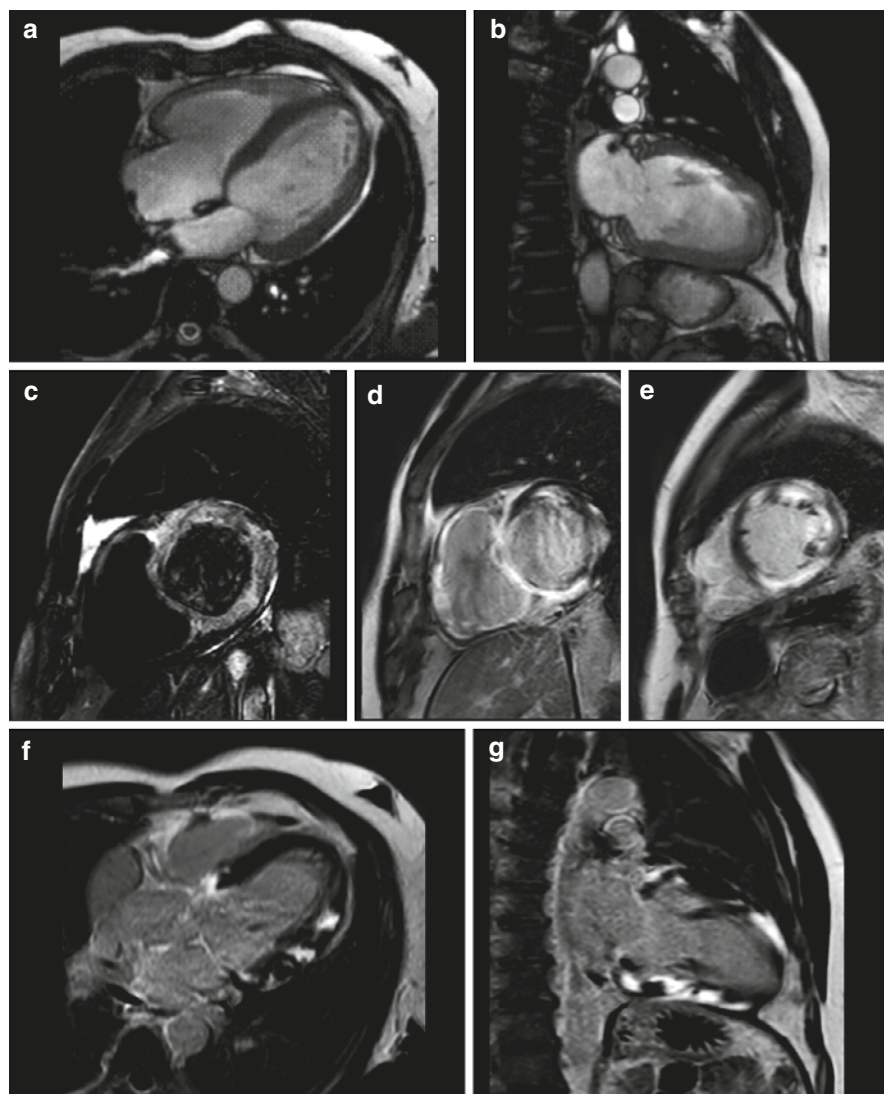


Fig. 2.4 Case of cardiac sarcoidosis. (a, b) Cine SSFP images (four-chamber and two-chamber views) show biventricular dilation and dysfunction with characteristic thinning of the basal interventricular septum. (c) T2-weighted STIR short-axis image shows areas of increased signal intensity consistent with the presence of myocardial edema. (d–g) Post-contrast images demonstrate extensive, multifocal gadolinium enhancement involving both ventricles

characterization identifies edema with T2-weighted sequences and fibrotic burden with LGE sequences [78, 79]. The typical LGE pattern is multifocal, non-ischemic, and commonly involves the right side of the interventricular septum, the basal inferolateral wall, and right ventricular (RV) insertion points [80]. CMR also aids in the differential diagnosis of cardiac sarcoidosis (CS) and ARVC [81], and may improve the detection rate of EMB, by providing information on lesion localization [82].

Although reduced LVEF is a good predictor of outcomes, many CS patients with normal LVEF are at a high risk of cardiac events [83]. Multiple studies have shown that LGE is the strongest independent predictor of mortality and MVA, providing incremental prognostic value over LVEF [84–86]. RV involvement is also associated with a poor prognosis, especially when both RV LGE and systolic dysfunction are present [78, 87]. Therefore, primary prevention ICD implantation may be considered in CS patients with LVEF >35% and extensive LGE, although a definite cutoff is unclear [78, 88, 89].

Patients with CS, as well as those with systemic sarcoidosis who experience a change in their clinical status, require serial cardiac evaluations. Although PET-CT is the gold standard for evaluating disease reactivation and treatment response, CMR may also be considered to assess changes in myocardial involvement [78].

2.5.3 Hot-Phase Cardiomyopathies

CMR is pivotal in the diagnosis of “hot-phase” cardiomyopathy, a recently described form of presentation in some arrhythmogenic cardiomyopathy (ACM) and NDLVC patients [90]. In particular, T2-weighted sequences and T2 mapping allow for the detection of myocardial edema, a hallmark of active disease. Myocardial scarring, as assessed through the LGE technique, is present in up to 90% of “hot-phase” patients, with a typical nonischemic pattern usually located at the LV inferolateral wall and the interventricular septum [91]. A characteristic circumferential subepicardial ring-like LGE pattern is frequently associated with *DSP* and *FLNC* mutations and is associated with worse prognosis [27].

2.6 Role of CMR in Arrhythmogenic Cardiomyopathy

ACM is a primary heart muscle disease characterized by progressive fibro-fatty replacement of the ventricular myocardium, predisposing to ventricular arrhythmias and SCD (Fig. 2.5) [92, 93].

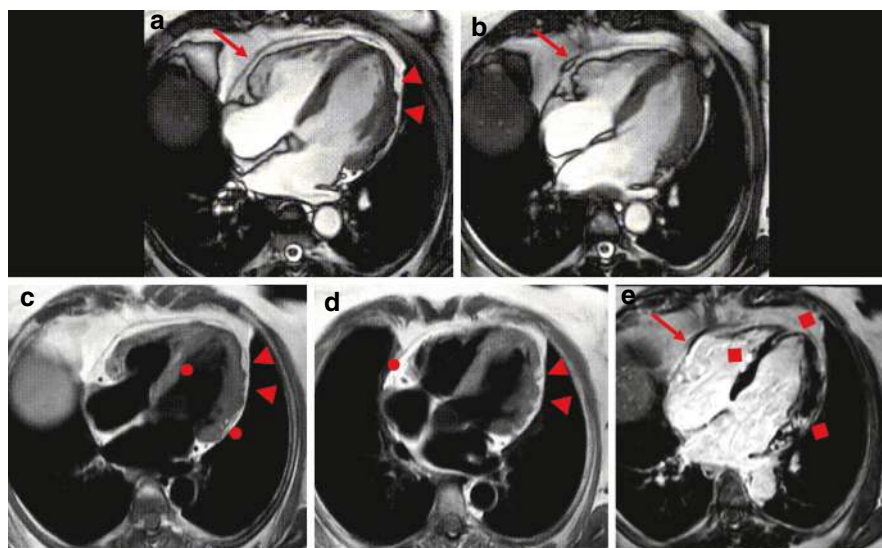


Fig. 2.5 Case of arrhythmogenic right ventricular cardiomyopathy (ARVC) with biventricular involvement caused by a pathogenic DSP gene mutation. (a, b) Cine images demonstrate aneurysmal deformation of the right ventricular free wall (arrows), with corresponding transmurular hyperintensity on late gadolinium enhancement sequences (E, arrow). The left ventricle demonstrates an irregular epicardial contour (“rat-bite sign,” ▲) with multiple areas of India Ink artifact, mainly along the interventricular septum. These regions show high signal intensity on proton density black blood images, consistent with fatty replacement (c, d, ●). Multiple areas of LGE are present, involving the left ventricular epicardial surface, the interventricular septum, and the right ventricle (e, arrow and ◆)

CMR is the optimal imaging modality for the evaluation of ACM. Cine SSFP sequences provide a detailed assessment of the right ventricle with high spatial resolution and unrestricted multiplanar capabilities. CMR can also detect fibro-fatty infiltration, the hallmark feature of the disease [94].

According to the classic diagnostic criteria, the key features of ACM are regional RV wall motion abnormalities (i.e., akinesia, dyskinesia, or dyssynchronous RV contraction), RV dilatation (i.e., major criterion: RV end-diastolic volume ≥ 110 ml/m² for males or ≥ 100 ml/m² for females; minor criterion: RV end-diastolic volume ≥ 100 ml/m² for males or ≥ 90 ml/m² for females), and RV dysfunction (i.e., major criterion: RVEF $\leq 40\%$; minor criterion: RVEF $\leq 45\%$) [95]. The European Task Force recommends assessing RV volumes and function using age- and gender-specific nomograms [96]. Dedicated nomograms considering chamber dilation typical of athlete’s heart should also be applied [97].

Additionally, the European Task Force established specific structural and functional diagnostic criteria for the evaluation of left-sided forms of the disease [96]. In

particular, a ring-like LGE (subepicardial or mid-myocardial stria pattern) in ≥ 3 LV segments is considered a major criterion, whereas nonischemic LGE and global LV systolic dysfunction (with or without dilatation) are regarded as minor criteria [96]. Combining functional assessment with tissue characterization substantially improves diagnostic accuracy in ACM [98].

A comprehensive CMR evaluation is essential for a complete assessment of patients with suspected ACM. Multiplane cine CMR sequences—including extended vertical and horizontal long-axis views as well as short-axis images for a detailed assessment of the RV walls and right ventricular outflow tract (RVOT)—are recommended to evaluate biventricular dimensions, wall thickness, regional wall motion, and global systolic function [9]. Moreover, cine images enable the evaluation of fat infiltration through the “India Ink” artifact, with high diagnostic accuracy [10]. Fatty infiltration or replacement can be confirmed using specific T1- or PD-weighted black blood sequences. CMR phase-contrast imaging provides accurate flow quantification, which is valuable in ruling out RV dilation due to volume overload, such as congenital left-to-right shunts [99]. When inflammatory activation is suspected (i.e., “hot phase”), T2-weighted STIR sequences and T2-mapping should be performed to identify the presence of myocardial edema [90]. LGE imaging is crucial for assessing the presence, location, and extent of fibro-fatty replacement.

CMR may be repeated during follow-up, when clinically indicated, every 2–5 years to monitor disease progression and reassess the risk of adverse events [2]. Lastly, CMR is particularly valuable for family member screening, especially when a pathogenic genotype is present [100], as it may detect early signs of the disease.

2.6.1 Risk Stratification

CMR improves risk stratification of MVA and SCD in ACM. CMR is the preferred method to assess RVEF, a risk predictor in ACM [113]. LGE is strongly associated with a higher risk of mortality and major adverse cardiovascular events, particularly when the LV is involved [101, 102].

Fatty infiltration, the hallmark of the disease, has also been linked to an increased risk of events, although its prognostic impact appears modest. This may reflect the challenges and limited reproducibility of fat detection by CMR [103].

2.7 Role of CMR in Hypertrophic Cardiomyopathy

CMR plays a central role in the evaluation of HCM. In particular, LGE sequences are able to detect and quantify myocardial fibrosis, a well-established predictor of arrhythmic risk and adverse clinical outcomes [104]. In addition, when echocardiographic assessment is limited by suboptimal acoustic windows or when hypertrophy

involves the apical, anterolateral, or inferoseptal segments—areas less accessible to ultrasound evaluation—CMR allows accurate visualization of the hypertrophied segments [2, 105, 106]. Furthermore, CMR minimizes the risk of overestimating wall thickness due to the inclusion of adjacent structures, such as the *crista supra-ventricularis*, or in cases of concomitant RV hypertrophy. Moreover, CMR excels in detecting LV apical aneurysms, a key feature of HCM [107, 108].

Six distinct morphological subtypes of LV hypertrophy have been described in HCM, reflecting considerable variation in both the extent and regional distribution of myocardial thickening (Fig. 2.6). Recognition of these phenotypic subtypes is clinically relevant, as specific patterns may be associated with differing

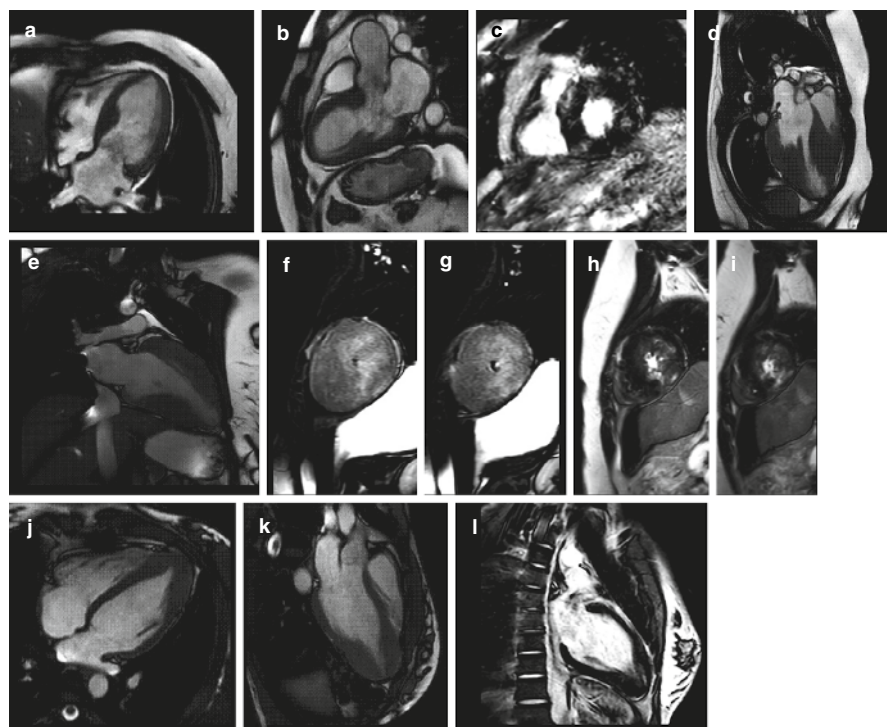


Fig. 2.6 (a, b) Cine images from a case of hypertrophic cardiomyopathy with pronounced basal septal hypertrophy and sigmoidal septal morphology. (c) Multiple areas of intramyocardial late gadolinium enhancement are evident within the interventricular septum and the left ventricular free wall. (d, e) Hypertrophic cardiomyopathy characterized by marked hypertrophy of the mid-left-ventricular segments and the presence of an apical aneurysm. (f, g) T2-weighted STIR short-axis images demonstrate intramyocardial hyperintensity of the left ventricular walls, consistent with myocardial edema. (h, i) Diffuse, mild late gadolinium enhancement involving the hypertrophic walls of the left ventricle. (j-l) Apical hypertrophic cardiomyopathy characterized by hypertrophy and LGE of the apical segments.

hemodynamic consequences and variable risks of adverse outcomes [109]. CMR is also able to identify left ventricular outflow tract (LVOT) obstruction through cine images and estimate LVOT gradient through phase-contrast sequences, although 2D echocardiography remains the gold standard in this settings.

Finally, stress perfusion CMR has demonstrated significant value in detecting coronary microvascular dysfunction in HCM. First-pass perfusion imaging frequently reveals hypoperfused myocardial regions during pharmacological stress, often preceding the development of replacement fibrosis. These perfusion abnormalities may represent early markers of adverse disease progression and could contribute to the pathophysiological cascade, leading to fibrosis, remodeling, and increased arrhythmic risk [110, 111].

2.7.1 Screening of Family Members

In genotype-positive, phenotype-negative individuals, CMR is increasingly recommended to detect subtle structural markers of the disease, such as myocardial crypts, mitral valve abnormalities, and focal LGE, that often precede overt hypertrophy and may predict phenotypic conversion. Contemporary European and American Recommendations suggest the use of CMR in these scenarios, especially when echocardiographic findings are inconclusive or when early tissue characterization is desired [2, 112].

In this setting, CMR feature-tracking parameters represent a promising tool for detecting preclinical disease, as they are consistently reduced in individuals with subclinical hypertrophic cardiomyopathy [113].

2.7.2 Differential Diagnosis

The evaluation of LV hypertrophy requires careful integration of clinical history and CMR phenotypic characterization. In athletes exhibiting LV wall thickness of 13–15 mm, physiological remodeling (“athlete’s heart”) should be considered [114]. Maximum wall thickness exceeding 16 mm is more suggestive of HCM, as physiological hypertrophy seldom surpasses this value. A hallmark of athlete’s heart is regression of wall thickness by ≥ 2 mm after 4–6 weeks of detraining, supporting a benign phenotype [115]. Distinguishing HCM from hypertensive heart disease (HHD) hinges on assessing whether the LV hypertrophy is proportional to the severity of hypertension. Concentric hypertrophy with preserved geometry and mild fibrosis may indicate hypertensive heart disease, whereas asymmetric septal hypertrophy, presence of LVOT obstruction with SAM, and extensive LGE are features that favor HCM. Systematic reviews confirm that native T1, ECV, and maximal wall thickness are significantly higher in HCM,

whereas end-diastolic volume and strain patterns tend to be preserved in HHD [116]. Moreover, effective regression of LVH following long-term antihypertensive therapy further supports a hypertensive etiology. Lastly, broader considerations must include infiltrative and storage disorders—such as cardiac amyloidosis or Anderson–Fabry disease—that may mimic HCM on CMR. These conditions often present with overlapping phenotypic features, including concentric LVH or focal LGE, yet require distinct management.

2.7.3 Risk Stratification for SCD

In addition to precise measurement of maximal LV wall thickness, LGE quantification refines SCD risk stratification and supports decision-making regarding primary prevention ICD implantation. Although LGE is not formally included in the ESC HCM Risk-SCD score, both the European and American Guidelines recognize extensive LGE (>15% of LV mass) as a significant risk modifier that may support ICD consideration [2, 112].

Quantitative assessment of LGE has shown independent prognostic value in predicting arrhythmic events in HCM patients [117]. Recent meta-analyses confirmed that greater LGE burden correlates with higher SCD risk, even in patients with otherwise low-to-intermediate clinical risk profiles [104, 118]. Additionally, CMR enables detection of LV apical aneurysms, a recognized high-risk feature associated with ventricular arrhythmias, thromboembolism, and SCD [119]. In advanced disease stages, adverse ventricular remodeling with wall thinning, extensive fibrosis, and systolic dysfunction (i.e., end-stage HCM) further elevates the risk of life-threatening arrhythmias and generally warrants consideration for ICD implantation [120].

The prognostic significance of T2-weighted imaging has also been demonstrated in small cohorts. T2 hyperintensity and elevated T2 mapping values, indicative of active myocardial injury, have been linked to an increased risk of ventricular arrhythmias and SCD, providing incremental prognostic value beyond LGE positivity [121–124].

2.7.4 Future Perspectives

Reliance on static wall thickness cutoffs in millimeters introduces measurement variability, highlighting the need for a more reproducible diagnostic framework [125]. CMR offers a clear advantage in this context, as it is less operator-dependent than transthoracic echocardiography. In addition, CMR can identify atypical HCM variants that fall outside conventional diagnostic criteria, such as apical hypertrophy associated with giant T-wave inversions but wall thickness < 15 mm

[126]. Recently, investigators have proposed a dedicated diagnostic cutoff for apical hypertrophic cardiomyopathy, emphasizing the lack of normal apical tapering and suggesting an apical wall thickness $> 5.6 \text{ mm/m}^2$ to improve diagnostic accuracy [127].

Both progressive myocardial fibrosis and early small-vessel ischemia, identified through stress perfusion imaging or microvascular indices, are independently associated with adverse prognosis [128, 129]. Routine and consistent use of CMR may therefore enhance diagnostic precision and improve patient monitoring. Furthermore, novel myosin inhibitors have demonstrated reverse remodeling effects on serial CMR, with reductions in both hypertrophy and fibrosis [130–132]. CMR is therefore set to become integral to monitoring treatment response and managing long-term follow-up in HCM.

2.8 Role of CMR in Restrictive and Infiltrative Cardiomyopathies

CMR is essential for differentiating primary restrictive cardiomyopathy from infiltrative conditions such as amyloidosis, Anderson–Fabry disease, Friedreich’s ataxia, hypereosinophilic syndrome, and Danon disease. By detecting early myocardial involvement and defining distinct tissue signatures, CMR supports accurate diagnosis, patient selection for targeted therapies, and longitudinal monitoring of treatment response [133, 134].

2.8.1 Primary Restrictive Cardiomyopathy (RCM)

CMR plays a central role in differentiating RCM from other restrictive pathologies [135]. Ventricular walls are generally of normal thickness, and LGE is absent or limited to patchy mid-wall or subendocardial areas, reflecting focal replacement fibrosis rather than diffuse infiltration. Parametric mapping (i.e., T1 and ECV) values are usually within normal limits or mildly elevated, in contrast to the markedly abnormal profiles observed in amyloidosis or other infiltrative diseases. These findings support the noninfiltrative nature of primary RCM. Cine imaging demonstrates preserved EF, often accompanied by abnormal longitudinal strain. Notably, CMR can distinguish RCM from constrictive pericarditis by identifying normal pericardial thickness, lack of ventricular interdependence, and absence of septal bounce or exaggerated respiratory variation in ventricular filling. Moreover, CMR aids in disease monitoring, particularly in evaluating the progression of fibrosis or the development of ventricular dysfunction over time.

2.8.2 Cardiac Amyloidosis

CMR has become a cornerstone of noninvasive evaluation of cardiac amyloidosis, allowing both morphologic assessment and advanced tissue characterization [136]. Common morphologic features include concentric LV wall thickening, biatrial dilation, and pericardial and pleural effusions—findings that often precede overt systolic dysfunction. In contrast to other causes of hypertrophy, the ventricular cavity becomes small, with a progressive decline in stroke volume and restrictive hemodynamics as the disease advances. Tissue characterization with LGE frequently reveals extensive subendocardial or transmural enhancement, with difficult myocardial nulling, hallmarks of diffuse interstitial expansion due to amyloid deposition (Fig. 2.7). However, LGE alone may underestimate early or diffuse disease, particularly in AL amyloidosis. Consequently, parametric mapping techniques (i.e., native T1 mapping and ECV quantification) have emerged as superior tools for detecting and quantifying amyloid burden [137, 138]. Elevated native T1 times reflect intracellular and interstitial abnormalities, while increased ECV correlates with interstitial expansion and has demonstrated prognostic relevance in both AL and ATTR amyloidosis. These quantitative techniques provide incremental diagnostic value, especially in the early phases of disease when structural abnormalities are subtle or nonspecific. Moreover, serial ECV assessment has shown promise in monitoring therapeutic response to emerging disease-modifying agents, such as transthyretin stabilizers and silencers [139].

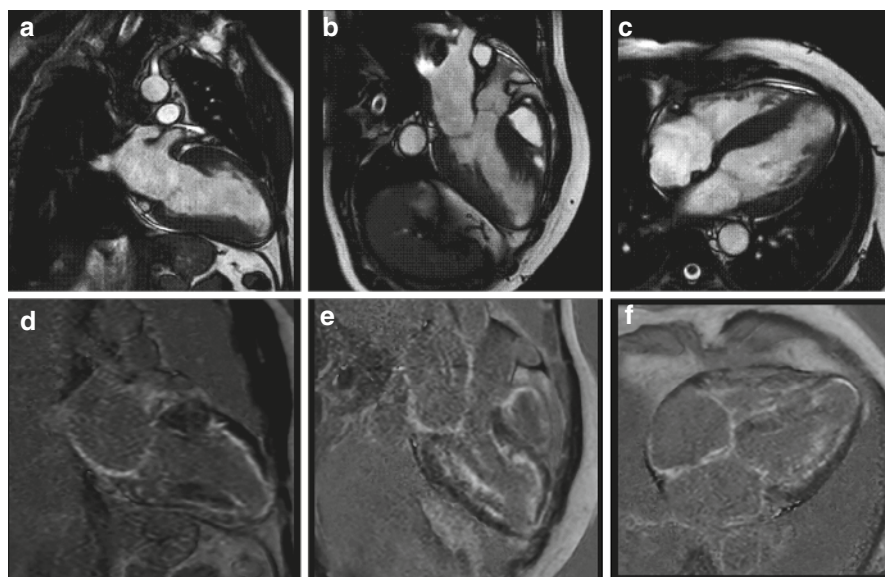


Fig. 2.7 AL cardiac amyloidosis characterized by diffuse thickening of the left ventricular walls (a–c). Contrast-enhanced sequences (d–f) demonstrate poor myocardial nulling, diffuse late gadolinium enhancement, and blood pool early darkening

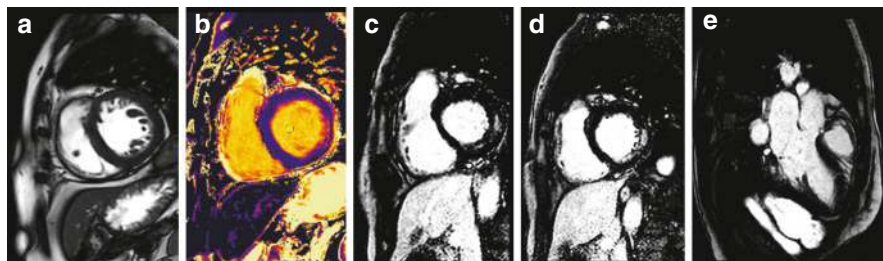


Fig. 2.8 Case of Anderson–Fabry disease. (a) Cine SSFP images demonstrate mild concentric left ventricular hypertrophy of the left ventricle. (b) T1 mapping shows a global reduction in native T1 values, except in the basal posterior segment where late gadolinium enhancement is present (c–e)

2.8.3 Anderson–Fabry Disease

CMR plays a critical role in the early detection, phenotyping, and longitudinal assessment of Anderson–Fabry-related cardiomyopathy (Fig. 2.8) [140, 141]. On CMR, Anderson–Fabry disease typically exhibits mid-wall LGE localized to the basal inferolateral wall. A hallmark diagnostic feature differentiating Anderson–Fabry disease from other hypertrophic phenocopies or sarcomeric hypertrophic cardiomyopathy is a reduction in native myocardial T1 relaxation time—attributed to intracellular glycosphingolipid accumulation—contrasting with the T1 elevation seen in fibrotic or infiltrative processes. Importantly, native T1 mapping has emerged as a sensitive technique for detecting cardiac involvement even in the absence of LV hypertrophy, particularly in heterozygous females and early-stage male patients. Disease progression may follow a three-phase model: an initial storage phase with low native T1 but no hypertrophy, a transition phase characterized by inflammation, increasing wall thickness, and initial LGE, and an advanced fibrotic phase with LGE expansion, wall thinning, and pseudonormalization of T1 values. Timely initiation of disease-specific therapy is crucial, as patients without established fibrosis derive greater benefit, including regression or stabilization of LVH and improvement in global longitudinal strain. Consequently, CMR is invaluable not only for early diagnosis but also for guiding therapeutic decisions and tracking myocardial response to treatment over time.

2.8.4 Friedreich’s Ataxia

CMR plays a critical role in characterizing myocardial involvement in Friedreich’s ataxia, typically revealing patchy mid-wall LGE, particularly in the interventricular septum and inferolateral walls, along with elevated native T1 and ECV values, reflecting diffuse interstitial fibrosis [142]. As the disease progresses, restrictive filling patterns, reduced compliance, and arrhythmias may emerge, leading to HF.

2.8.5 Hypereosinophilic Syndromes

Hypereosinophilic syndromes (HES) result in eosinophilic infiltration of the myocardium and evolve through three histopathological stages: necrotic, thrombotic, and fibrotic. CMR is essential for the staging of HES, with T2 mapping detecting early myocardial edema, EGE identifying thrombi, and LGE revealing diffuse sub-endocardial fibrosis [143, 144]. Even in hematologically controlled patients, serial CMR is recommended, as imaging findings better reflect disease activity than peripheral eosinophil counts.

2.8.6 Danon Disease

In Danon disease, CMR shows massive hypertrophy with extensive, often diffuse LGE, markedly elevated T1 and ECV values, and impaired myocardial strain, particularly in basal and mid-septal segments [133]. The disease may mimic hypertrophic cardiomyopathy but progresses more rapidly and is often accompanied by extracardiac features such as skeletal myopathy and cognitive impairment. Early CMR-based diagnosis is essential for timely referral for advanced HF therapies and genetic confirmation [134].

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General Aspects of Genetics in Cardiomyopathies

3

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3.1 Introduction

Genetic cardiomyopathies represent a major challenge and opportunity in modern cardiology, where early recognition of inherited disease may drastically alter clinical outcomes—not only for the patient, but for entire families. Defined as myocardial disorders characterized by structural and functional abnormalities not fully attributable to coronary artery disease, significant valvular pathology, or congenital heart defects [1], cardiomyopathies (CMPs) encompass a wide spectrum of phenotypes with variable age of onset, severity, and arrhythmic risk. These diseases are among the leading causes of heart failure, sudden cardiac death, and heart transplantation in young adults, often affecting individuals in the most productive years of life.

This chapter aims to provide a comprehensive overview of the genetic basis of cardiomyopathies, including patterns of inheritance, molecular pathways, and genotype–phenotype correlations. We will also examine the clinical implication of genetic testing, the interpretation of variants of uncertain significance (VUS), and the evolving role of genotype in guiding family management, arrhythmic risk stratification, and the development of novel therapeutic strategies.

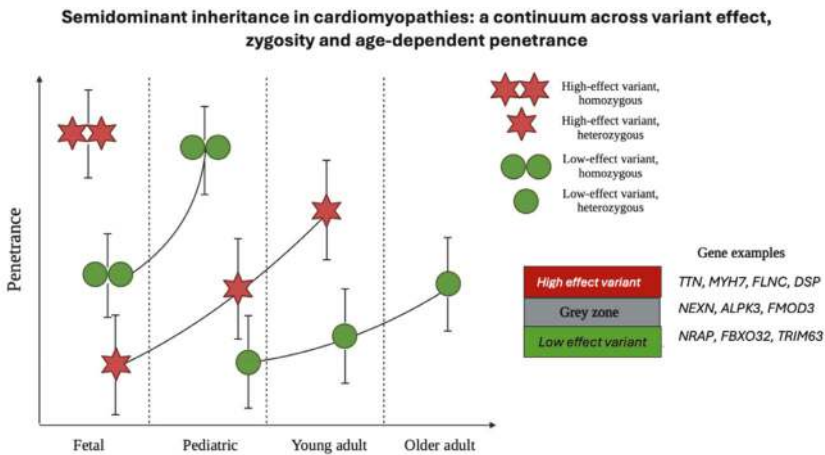
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3.2 Patterns of Inheritance

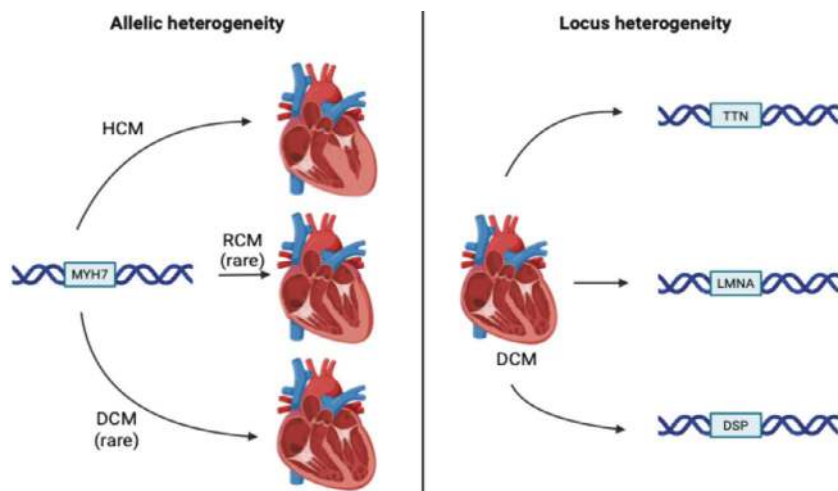
Inherited CMPs are predominantly monogenic disorders, most frequently inherited in an autosomal-dominant pattern [2]. However, autosomal-recessive, X-linked, and mitochondrial forms are also described, particularly in syndromic presentations or early-onset cases [3]. While the classical Mendelian dichotomy of dominant versus recessive inheritance has long served as a conceptual framework, recent evidence suggests that this binary classification oversimplifies the underlying genetic architecture of CMPs.

A growing body of data supports a continuum of dominance and recessiveness, in which the penetrance results are finely tuned by the specific gene, the number of alleles involved (monoallelic vs. biallelic), the class of variants (missense vs. truncating), and their frequency in the general population. This semidominant model is increasingly acknowledged as a more accurate representation of genotype–phenotype correlations in several cardiomyopathy genes.



The figure illustrates how penetrance and cardiomyopathy-associated variants depend on both allele dosage and variant effect size. High-effect biallelic variants are typically associated with fetal or neonatal lethal disease, whereas heterozygous carriers display later onset with age-dependent penetrance. Low-effect variants show a spectrum from pediatric presentation in homozygotes to adult-onset or subclinical manifestations in heterozygotes, highlighting the semidominant nature of many cardiomyopathy genes.

Genetic variation in CMPs is further complicated by pronounced allelic and locus heterogeneity, which greatly impacts both variant interpretation and clinical application. Most CMPs-associated genes contain a wide spectrum of distinct mutations in the same gene (*allelic heterogeneity*) [4]. Indeed, next-generation sequencing studies have shown that 60–90% of rare variants associated with CMPs are “private,” occurring exclusively within single families [5]. Furthermore, all major CMPs’ phenotypes can arise from pathogenic variants in multiple distinct genes (*locus heterogeneity*). This is especially evident in DCM, where mutations span a wide range of genes encoding sarcomeric, nuclear envelope, cytoskeletal, desmosomal, ion channels, and RNA-binding proteins [6].



3.3 Criteria for Variant Interpretation and Gene Validation

Key concepts in genetic interpretation include also incomplete penetrance, where not all individuals carrying a pathogenic variant manifest disease phenotype, and variable expressivity, which accounts for the wide range of clinical presentations observed—even within the same family—ranging from asymptomatic carriers to individuals with end-stage heart failure or sudden cardiac death [7]. This phenotypic variability is influenced not only by variant type and gene context, but also by modifying factors, both genetic and environmental.

Given this complexity, variant interpretation in CMPs relies not only on critical phenotype correlations, but also on rigorous population-based filters.

From a population genetics perspective, the minor allele frequency (MAF) is a critical criterion in determining variant pathogenicity. Disease-causing variants in Mendelian CMPs are expected to be exceedingly rare in the general population (e.g., $MAF < 0.0001$), and databases such as gnomAD [8] are instrumental in establishing whether a variant is too common to be plausibly pathogenic [9, 10]. Moreover, variants observed in homozygosity in healthy individuals are generally considered nonpathogenic in a recessive model. Case-control studies showing the enrichment of specific variants or genes in disease cohorts relative to control populations further support their pathogenic role.

To address the growing complexity in gene-disease relationships and ensure robust clinical translation, expert-driven curation efforts have become indispensable. Notably, the Clinical Genome Resource (ClinGen) [11] has developed a standardized framework to evaluate gene-disease associations based on cumulative genetic and functional evidence. ClinGen panels dedicated to HCM, DCM, and ACM have already validated key CMP-associated genes, ensuring their appropriate inclusion in diagnostic panels and clinical decision-making [12].

Variant interpretation in validated genes, however, remains a major challenge. Classification relies on ACMG/AMP criteria, which stratify variants as pathogenic (P), likely pathogenic (LP), variants of uncertain significance (VUS), likely benign, or benign. The rationale for assigning a variant to the P/LP category typically relies on multiple lines of evidence, including segregation data, functional studies, population frequency, and computational predictions. Conversely, VUS represent a category of uncertainty rather than a true biological intermediate state. In practice, a variant classified as VUS may represent either a benign bystander or a truly causative change, in which the available insufficient evidence prevents a confident classification in either direction. This artificial category underscores the current limitations of our knowledge: VUS are particularly common in genes with high background variation, limited functional characterization, or weaker disease associations, and they pose significant challenges for clinical decision-making. Importantly, a negative or inconclusive result does not rule out a genetic etiology, as it may reflect incomplete gene annotation, limited test sensitivity, or more complex polygenic and non-Mendelian mechanisms.

3.4 Non-Mendelian Contributions

Common genetic polymorphisms can modulate disease penetrance and expressivity in inherited cardiomyopathies, particularly when co-inherited with rare pathogenic variants, supporting a “second-hit” or polygenic model in selected cases. [4] Genome-wide association studies (GWAS) and polygenic risk score analyses further support this interaction, especially in HCM and DCM, and may help explain a part of the marked phenotypic variability observed across individuals with the same primary pathogenic variant [13, 14].

Finally, environmental and lifestyle factors—such as intense physical exertion, alcohol abuse, or exposure to cardiotoxic agents—can modulate the penetrance and severity of the phenotype, highlighting the complex gene–environment interplay in cardiomyopathy pathogenesis [15]. The interplay between rare monogenic variants, common polymorphisms, and environmental exposures underscores the complex, multifactorial, and dynamic nature of inherited cardiomyopathy pathogenesis, challenging the monogenic paradigm and reinforcing the need for integrative, individualized approaches in clinical genetics.

3.5 Genetic Testing: When and How

Genetic testing plays an increasingly central role in the diagnostic and clinical management of inherited CMPs, offering critical insights for confirming a suspected genetic etiology, refining prognosis, tailoring therapeutic strategies, and enabling

cascade screening among relatives. In specific conditions, such as Fabry or Danon disease, the identification of a genetic cause also directs disease-specific treatments, while in sarcomeric CMPs, ongoing research into allele-specific therapies reinforces the future therapeutic relevance of genotype data.

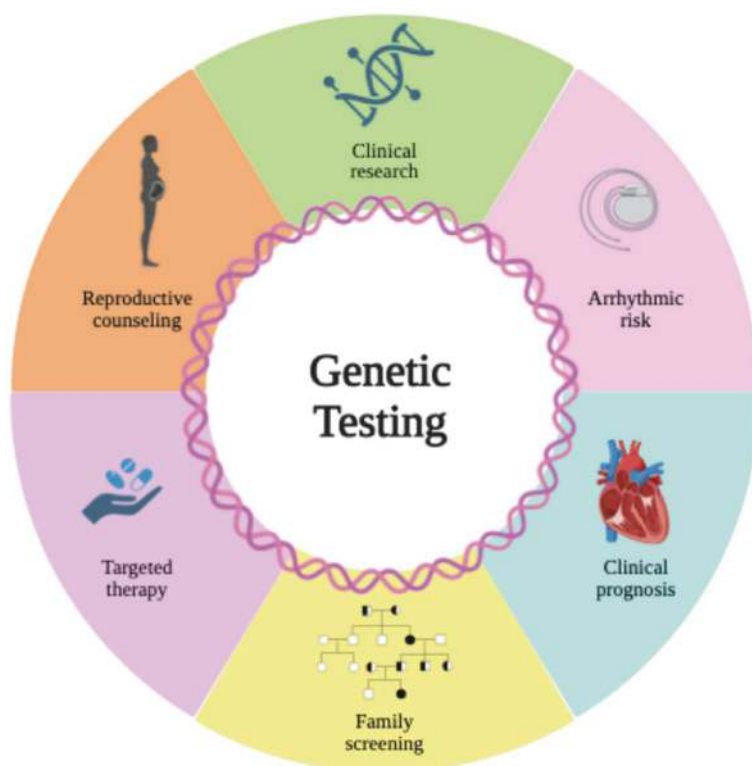
According to current ESC guidelines, genetic testing is recommended in affected individuals when there is a reasonable suspicion of a monogenic disorder and potential clinical utility [1]. When a pathogenic or likely pathogenic variant is identified, targeted testing in first-degree relatives (cascade testing) allows for early identification of at-risk individuals and may exempt noncarriers from surveillance. Predictive testing is also appropriate in asymptomatic minors if a clearly pathogenic familial variant is known.

Diagnostic panels should initially include well-validated disease genes, curated through expert consensus (e.g., ClinGen), and tailored to the presenting phenotype. Broader approaches such as whole-exome sequencing may be appropriate in selected scenarios, especially in early-onset cases or consanguineous families with negative first-line results.

Indeed, emerging data indicate that a subset of CMPs may follow complex inheritance models involving multiple low-effect variants, as suggested by the development of polygenic risk scores (PRS) [16]. Although not yet integrated into routine practice, PRS may, in the future, enhance risk stratification in both affected individuals and asymptomatic carriers.

From an ethical standpoint, the broad application of genetic testing—as supported by recent guidelines [1]—must be balanced against issues of resource allocation and clinical utility. Testing should be prioritized in scenarios with a high probability of actionable findings to ensure appropriate use of public healthcare systems.

Finally, genetic counseling is essential at every stage of the testing process. Delivered by trained professionals, it should encompass pre- and post-test discussions, construction of a multigenerational family history, interpretation of results, and psychosocial support. This is particularly important in emotionally charged contexts, such as pediatric diagnoses, sudden cardiac death in the family, or implantation of defibrillators. Counseling facilitates informed decision-making, promotes patient engagement, and helps mitigate the anxiety associated with genetic risk. Recent evidence from the HeartCare study further reinforces this concept, showing that both patients and clinicians perceived cardiovascular genetic testing as beneficial, informative, and rarely overwhelming, while clinicians reported that results frequently led to meaningful changes in clinical care and family screening strategies [17].



3.6 Epidemiology

Over the past two decades, genetic CMPs have gained increasing attention, both in clinical practice and research. Advances in molecular diagnostics and next-generation sequencing technologies have expanded our ability to detect pathogenic variants, allowing earlier diagnosis, cascade screening, arrhythmic risk stratification, and new opportunities for precision therapies tailored to genotype.

The diagnostic yield of genetic testing varies significantly across cardiomyopathy subtypes, reflecting their distinct pathophysiological and molecular architectures. To date, more than a thousand mutations have been identified in genes involved in diverse biological pathways and structural components of the cardiomyocyte [18]. Among the various forms, hypertrophic cardiomyopathy (HCM) is perhaps the most genetically well-characterized: pathogenic or likely pathogenic variants are detected in approximately 50–60% of familial cases, while the diagnostic yield is significantly lower (around 30%) in apparently sporadic cases [19].

In contrast, dilated cardiomyopathy (DCM) exhibits considerable genetic heterogeneity, with a molecular cause detected in nearly 30–40% of familial cases, most notably in *TNN*, *LMNA*, and other cytoskeletal or nuclear envelope genes [20]. Arrhythmogenic right ventricular cardiomyopathy (ARVC), a disease classically associated with sudden cardiac death in the young, yields a positive genetic, resulting in approximately 50% of cases, predominantly involving desmosomal genes [21]. Although less prevalent, restrictive cardiomyopathy (RCM) also demonstrates a meaningful rate of identifiable genetic variants (around 50%), often overlapping with sarcomeric or infiltrative disease-associated genes [22]. Moreover, nondilated left ventricular cardiomyopathy (NDLVC)—a recently formalized category marked by systolic dysfunction in the absence of chamber enlargement—reveals a molecular etiology in up to 20–40% of cases, frequently involving genes associated with arrhythmogenic and cytoskeletal pathways, in overlap with DCM and ARVC genetic background [23].

3.7 Hypertrophic Cardiomyopathy (HCM)

HCM is the archetype of sarcomeric cardiomyopathies, with *MYH7* and *MYBPC3* accounting for over 70% of genetically confirmed familial cases [24]. These genes encode β -myosin heavy chain and cardiac myosin-binding protein C, respectively, whose pathogenic variants typically enhance myofilament calcium sensitivity and contractility.

Other sarcomeric genes—*TNNT2*, *TNNI3*, *ACTC1*, *MYL2*, and *MYL3*—are implicated in a smaller proportion of cases (1–5%) [25] but may carry significant prognostic implications. For example, *TNNT2* variants are often associated with mild hypertrophy [26], while *MYL2* mutations, especially in compound heterozygosity or homozygosity, have been linked to early-onset, severe phenotypes [27].

Genotype–phenotype correlations are increasingly recognized: *MYH7* variants often lead to early-onset, asymmetric septal hypertrophy, whereas *MYBPC3* P/LP variants are typically associated with later onset and more variable penetrance [28]. Biallelic or compound heterozygous P/PL variants may result in particularly severe presentations, occasionally resembling restrictive or dilated phenotypes. However, incomplete penetrance and variable expressivity are common, influenced by modifier genes, polygenic burden, and environmental factors such as physical activity and hypertension.

Importantly, HCM-like phenotypes may also arise from non-sarcomeric conditions (phenocopies), including infiltrative diseases (e.g., amyloidosis), storage disorders (e.g., Fabry, Danon), mitochondrial dysfunctions, and RASopathies [29]. These entities can mimic sarcomeric HCM but have distinct pathophysiological and therapeutic implications. Therefore, genetic testing is essential to distinguish true sarcomeric HCM from phenocopies, especially when extracardiac features or atypical clinical signs are present.

3.8 Dilated Cardiomyopathy (DCM)

DCM has long been considered genetically heterogeneous, with early studies implicating more than 50 genes across diverse cellular compartments [6]. However, contemporary curation efforts (e.g., ClinGen) have refined this view, and fewer than 20 genes currently have definitive or strong evidence for a causal role. *TTN* truncating variants (TTNtv) are the most prevalent, found in up to 25% of familial DCM cases [30]. These variants predominantly affect the A-band region [31] and are often associated with late-onset, progressive ventricular dilatation and systolic dysfunction. However, their interpretation requires caution, as TTNtv are also found in 1% of the general population [32], highlighting the importance of assessing variant location, clinical and familial context, and enrichment. *LMNA* P/LP variants, affecting nuclear envelope integrity, are present in around 4–6% [33] and associated with early-onset conduction disease and arrhythmic phenotypes, often with rapid progression to severe heart failure [34]. Additional causative genes encode cytoskeletal proteins (*DES*, *FLNC*), ion channels, and RNA-binding proteins, reflecting the complex pathophysiology of this disorder [23]. Notably, desmosome gene variants (*DSP*) may also present with a dilated phenotype, blurring diagnostic boundaries with arrhythmogenic cardiomyopathy [23, 35].

3.9 Nondilated Left Ventricular Cardiomyopathy (NDLVC)

NDLVC exhibits marked heterogeneity, with disease-causing variants frequently identified in genes involved in cytoskeletal (*FLNC*, *DES*), desmosomal (*DSP*), and nuclear envelope (*LMNA*) [35] reflecting a complex interplay between structural and electrical myocardial derangements. In familial cases, the diagnostic yield of genetic testing ranges from 20% to 40%, underscoring the relevance of systematic screening and the frequent overlap with arrhythmogenic cardiomyopathy and dilated phenotypes [23].

3.10 Restrictive Cardiomyopathy (RCM)

RCM is the least common but one of the most severe forms of inherited cardiomyopathy, characterized by normal or near-normal left ventricular size and systolic function, but with marked diastolic dysfunction and biatrial enlargement. The genetic architecture of RCM is heterogeneous, involving both isolated familial forms and RCM as part of multisystem syndromes.

Isolated forms are most frequently associated with mutations in sarcomeric genes such as *TNNI3*, *TNNT2*, and *MYH7*, overlapping genetically with HCM, but presenting a distinct restrictive phenotype, often with early onset and rapid progressions [36].

Systemic or syndromic forms of RCM may be associated with infiltrative diseases (e.g., cardiac amyloidosis), storage disorders (e.g., Fabry disease, Danon disease), and mitochondrial or neuromuscular syndromes.

Mutations in filamin C (*FLNC*) and desmin (*DES*) have also been implicated in familial RCM, often in association with myofibrillar myopathy [37].

3.11 Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

ARVC is a heritable heart muscle disorder primarily affecting the right ventricle and characterized by fibrofatty myocardial replacement, ventricular arrhythmias, and an increased risk of sudden cardiac death, particularly in young individuals.

This CMP is predominantly caused by pathogenic variants in desmosomal genes, especially *PKP2* (plakophilin-2), followed by *DSG2* (desmoglein-2) and *DSP* (desmoplakin) [38]. Mutations in *DSC2* and *JUP* have also been implicated, and biallelic or compound heterozygous variants can lead to more severe, often pediatric-onset disease.

Desmosomal dysfunction contributes to mechanical uncoupling, increased susceptibility to myocyte death under stress and pro-arrhythmic remodeling, often preceding structural abnormalities. This supports the concept that arrhythmogenic cardiomyopathy encompasses a broader spectrum, including left-dominant and biventricular forms, with overlap with other cardiomyopathies.

In recent years, non-desmosomal genes such as *TMEM43*, *PLN*, *FLNC*, and *DES* have also been associated with ARVC or overlapping phenotypes, further highlighting the genetic heterogeneity and expanding the clinical spectrum of the disease [39].

3.12 Genetics and Family

In cardiomyopathies with inherited etiology, genetic information often extends its clinical relevance to apparently healthy family members. Once a pathogenic variant is confirmed in an index case, cascade testing allows early identification of at-risk relatives—even in the absence of clinical signs—enabling timely surveillance and, where appropriate, preventive interventions.

The identification of genotype-positive/phenotype-negative individuals poses unique challenges. While these carriers may remain asymptomatic for years, they are not risk-free. Current guidelines recommend periodic re-evaluation, particularly in childhood-onset forms or in the presence of high-risk genotypes such as *LMNA* or *DSP*.

The psychological impact of genetic risk—especially when clinical implications remain uncertain—requires careful management. Feelings of vulnerability, fear, or family-related guilt are frequent, particularly when results affect reproductive choices or childhood surveillance. In this setting, specialized genetic counseling

becomes a key element in navigating personal and family decisions, reducing anxiety, and fostering informed engagement in long-term care.

3.13 Genetics and Prognosis

Genetic data are increasingly recognized as critical tools for arrhythmic risk stratification in inherited cardiomyopathies [40]. Specific pathogenic variants—such as those in *LMNA*, *FLNC*, or *DSP*—are independently associated with an elevated risk of sudden cardiac death (SCD), even in the absence of severe left ventricular dysfunction or overt clinical markers [41–43]. This has led to the inclusion of genotype as a complementary criterion for implantable cardioverter-defibrillator (ICD) consideration in recent guidelines, particularly in *DCM* and *ARVC*.

The presence of multiple rare variants (i.e., compound heterozygosity or digenic inheritance) has also been linked to more severe phenotypes and earlier disease onset. Moreover, emerging PRS, although not yet integrated into standard practice, show promise in refining individual risk profiles by accounting for the cumulative effect of common genetic modifiers.

Incorporating genetic findings into multivariable risk models—as already explored in *HCM* (e.g., ESC SCD risk calculator with genotype-enhanced versions)—may improve the precision of prognosis and support more tailored preventive strategies.

3.14 Therapies and Future Prospectives

The treatment of inherited cardiomyopathies is entering a new era, where genetic insights increasingly shape clinical decisions. While conventional therapy has long relied on phenotypic expression and functional assessment, current research is shifting the focus toward genotype-informed strategies.

A prime example is mavacamten, a cardiac myosin modulator approved for obstructive HCM, which acts by targeting sarcomeric hypercontractility—a key molecular consequence of specific genetic mutations. Its development, followed by ongoing trials for newer agents like aficamten, represents a milestone in translating pathophysiological mechanisms into targeted therapies.

Beyond pharmacological modulation, molecular therapies are rapidly advancing. Technologies based on RNA silencing—such as antisense oligonucleotides (ASOs) and small interfering RNAs (siRNA)—are being studied to selectively suppress mutant gene expression, thereby reducing the production of pathogenic proteins [44]. These approaches may offer options for cardiomyopathies caused by toxic gain-of-function or dominant-negative variants. At the frontier of innovation, genome-editing platforms like CRISPR/Cas9 and AAV-mediated gene transfer are under investigation for their potential to correct or replace defective genes at the DNA level, although they are still at early developmental stages due to safety, delivery, and ethical constraints.

In parallel, polygenic models are gaining attention. In forms of cardiomyopathy without a clearly identifiable rare pathogenic variant, PRS may improve risk stratification by capturing the contribution of multiple low-effect variants. This could enhance our ability to tailor prevention and monitoring in selected individuals, particularly those with borderline phenotypes or familial history without a clear genetic diagnosis.

Looking forward, the integration of genetic and multi-omics data will be central to personalized therapy in cardiomyopathies—not only guiding diagnosis and prognosis but actively shaping precision interventions aimed at modifying the natural history of disease.

3.15 Conclusion: Clinical–Genetic Integration

Genetic testing has become a fundamental component in the diagnostic and prognostic algorithm of inherited cardiomyopathies. Its clinical relevance extends beyond diagnostic clarification, encompassing arrhythmic risk stratification, family-based preventive strategies, reproductive counseling, and the identification of potential responders to emerging targeted therapies.

Multiple large-scale studies and consensus guidelines now recognize that the presence, type, and combination of genetic variants—particularly in genes with validated pathogenic roles—are independently associated with clinical outcomes, including disease onset, progression, and risk of sudden cardiac death. The implementation of genotype-informed risk models has shown additive prognostic value compared to traditional phenotypic parameters alone.

Moreover, the increasing recognition of incomplete penetrance, variable expressivity, oligogenic inheritance, and polygenic susceptibility underscores the complexity of genetic architecture in cardiomyopathies and challenges the binary interpretation of Mendelian inheritance. In this evolving landscape, genetic testing must be paired with expert variant interpretation and longitudinal clinical correlation.

As precision medicine continues to advance, the integration of genomic data into cardiology is not optional but essential. It enables a transition from reactive to anticipatory care, supports individualized clinical decision-making, and lays the foundation for future disease-modifying therapies.

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Part II

Clinical Approach to Specific Form of CMP

Dilated Cardiomyopathy

4

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4.1 Definition, Epidemiology, and Prognosis

4.1.1 Definition

Dilated cardiomyopathy (DCM) is a primary myocardial disease, characterized by *left ventricular (LV) dilatation* (see Table 4.1) and LV ejection fraction (*LVEF*) $< 50\%$.

These abnormalities occur in the absence of abnormal loading conditions (e.g., chronic hypertension or significant valvular disease) or coronary artery disease of sufficient severity to explain the dysfunction [1]. From a *pathophysiological* perspective, DCM reflects the interplay of chronic myocyte jury, maladaptive extracellular matrix remodeling, and sustained neurohormonal activation, driving progressive chamber dilatation, wall thinning, and contractile impairment. As the disease advances, right ventricular involvement frequently develops, further compromising hemodynamic [2]. Clinically, DCM is a leading cause of *heart failure* with reduced ejection fraction (HFrEF) in young and middle-aged adults and remains one of the most relevant indications for heart transplantation worldwide [3]. For this reason, its socioeconomic impact is substantial, reflecting its prevalence in the working-age population, its chronic course, and the complexity of its long-term management [4]. It is also a recognized cause of *sudden cardiac death* (SCD) in individuals under 50 years of age affected by cardiomyopathies, occasionally occurring in the absence of prior symptoms of HF. Initially described as part of the broad group of “congestive cardiomyopathies,” DCM has undergone progressive redefinition. Current approaches emphasize *etiologic subtyping* (genetic, inflammatory,

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Table 4.1 Left ventricular dilatation criteria

Parameter	Men	Women
LV end-diastolic diameter (adults)	>58 mm	>52 mm
Indexed LV end-diastolic volume (adults)	≥75 mL/m ²	≥62 mL/m ²
LV end-diastolic size or volume (general)	>2 z-scores above the population mean	>2 z-scores above the population mean
Notes	Often biventricular involvement	Often biventricular involvement

toxic, metabolic, idiopathic), in line with the *MOGES classification* (Morpho-functional phenotype, Organ involvement, Genetic inheritance, Etiology, Stage) [5]. The MOGES classification, although not yet routinely applied in clinical practice, is a relatively recent phenotype–genotype-based system that aims to comprehensively characterize all aspects of this complex disease and to facilitate their standardized description. This framework supports both clinical practice and research, paving the way for more targeted interventions.

4.1.2 **Epidemiology**

The epidemiology of DCM is complex and characterized by a wide variability in reported incidence and prevalence rates across different studies and populations. This heterogeneity is largely attributable to recent improvements in disease detection, advances in diagnostic techniques, increased implementation of family screening programs allowing earlier-stage identification, and the ongoing evolution of disease classification systems. Early epidemiological studies reported a wide range of incidence: Torp et al. (1978) estimated an incidence of *3 cases per 100,000 per year* [6], while Williams et al. (1985) reported *8.3 per 100,000* [7]. Codd et al. (1989), in a landmark population-based study from Olmsted County, Minnesota, estimated a prevalence of *36.5 per 100,000* and an incidence of *6 per 100,000 person-years* [8]. Codd’s research was also among the first to highlight important demographic differences: men were more frequently affected than women, with a male-to-female ratio of approximately 3:1. In general, time of disease onset is third-fourth decade. Perhaps, it may be important to report differences in age at presentation, diagnostic modality, and severity of presentation across epidemiological studies, as more recent studies are likely to report younger age at onset and less severe disease due to increased screening. Some studies also reported ethnic disparities: black individuals have a threefold increased risk for developing DCM and a twofold increased risk of death after diagnosis, which were not explained by socioeconomic status and hypertension [9]. In Italy, the first national data emerged from a prospective autopsy study conducted at the University of Trieste between 1987 and 1989: Rakar et al. found a total incidence of *6.95 per 100,000 per year* in Italy—values roughly in line with those of Codd’s study. This investigation revealed

an autopsy-based incidence of 4.5 per 100,000 per year and a clinical incidence of 2.45 per 100,000 per year, leading to a combined total incidence of 6.95 per 100,000 per year [10]. These figures reinforced the findings of Codd and colleagues and highlighted the difficulty of capturing all cases clinically.

A major turning point in the understanding of DCM epidemiology came with the 2008 position statement from the European Working Group on Myocardial and Pericardial Diseases [11]. This classification emphasized morphological and functional phenotypes and recognized both familial and nonfamilial forms.

This shift in perspective led to a more systematic screening of relatives and the recognition that a significant proportion of DCM cases have a familial basis. These insights have allowed multicenter studies with larger, more representative cohorts and have also drawn greater attention to gender differences in disease presentation and outcomes. According to the 2023 ESC Guidelines on Cardiomyopathies, the estimated prevalence of DCM ranges *from 36 to 400 cases per 100,000 individuals* in the general population, reflecting improved diagnostic precision and increased recognition of subclinical and familial forms [12].

4.1.3 Prognosis

The prognosis of DCM encompasses a broad spectrum of clinical event, including all-cause and cardiovascular mortality, HF-related outcomes, and arrhythmic events. These manifestations are frequently interconnected, reflecting the complex and dynamic nature of the disease. Over the years, clinicians have sought to identify baseline predictors of these outcomes to enable individualized risk stratification and to tailor therapeutic strategies and clinical management to the specific characteristics of each patient.

LVEF was among the first parameter identified as a key predictor of adverse outcomes, with values $\leq 35\%$ strongly associated with increased mortality, higher risk of major arrhythmic events and heart transplantation [13].

The extent of *left and right ventricular remodeling* further correlates with poor prognosis, as does the presence of myocardial fibrosis detected through late gadolinium enhancement (*LGE*) on *cardiac magnetic resonance (CMR)*, which indicates a heightened risk of SCD and clinical deterioration (see Chapter 2 CMR) [14].

Renal dysfunction, particularly when the glomerular filtration rate falls below 60 ml/min/1.73m², independently predicts worse outcomes [15]. An advanced *NYHA class* is linked to increased mortality and HF progression. Pulmonary hypertension also represents a negative independent prognostic factor, while elevated biomarkers such as NT-proBNP and troponin levels signal a higher risk of adverse cardiac events [9]. Genetic factors play a pivotal role in risk stratification and will be deeply discussed in a dedicated section. Across large multicenter cohorts, *men* generally show a trend toward worse long-term outcomes, with higher rates of major adverse cardiac events, ventricular arrhythmias, HF progression, and need for transplantation, especially among those carrying pathogenic variants in genes such as *LMNA*, *TTN*, and *FLNC*, which are associated with arrhythmogenic and fibrotic

phenotypes. However, female prognosis is not uniformly benign: outcomes vary according to genotype and women with desmosomal mutations may still experience limited recovery or an increased arrhythmic risk [16].

4.2 Etiology

Current evidence shows that 30–40% of cases have an identifiable genetic basis; the remaining cases result from acquired insults or are idiopathic. Currently, genetic predisposition and environmental triggers are viewed as parts of a continuum, where susceptibility may be unmasked or accelerated by external stressors, commonly referred to as “second hits.” Most familial DCMs exhibit autosomal-dominant inheritance, but recessive, X-linked, and mitochondrial patterns are also described, particularly in syndromic or early-onset presentations. Historically, over 50 genes have been implicated, reflecting the *extreme genetic heterogeneity* of the disease. This diversity explains the variable penetrance and expressivity observed even within the same family and the frequent overlap with other cardiomyopathies, such as hypertrophic (HCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC). However, with the advent of more rigorous gene–disease association studies and the widespread implementation of extensive genotyping, this number has been substantially refined. Current evidence supports fewer than 20 genes with strong, definite, or moderate evidence of association with DCM [17].

The introduction of next-generation sequencing (NGS) has revolutionized the diagnostic approach, allowing simultaneous screening of large gene panels and identification of multiple rare variants. However, interpreting pathogenicity remains challenging: many identified variants are variants of *uncertain significance* (VUS), and up to 13% of patients may *carry two or more mutations*, often associated with worse prognosis and earlier onset of disease [18].

4.2.1 Major Genes and Genotype–Phenotype Correlations

The most frequently involved gene is titin (*TTN*), which encodes the largest human protein and plays a structural and mechanosensory role in the sarcomere. *TTN* truncating variants (*TTN**trv*) occur in 20–25% of familial and up to 18% of sporadic DCM cases, though 2–3% of the healthy population may also harbor such variants, indicating incomplete penetrance. *TTN**trv* most commonly occur within the *A-band region* of the gene, which corresponds to highly constitutively expressed exons integrated with thick filaments. Variants in this domain are strongly associated with the classical DCM phenotype, whereas mutations in other regions—Z-disk, I-band, M-band—may be better tolerated or lead to distinct clinical forms that have not yet been fully described. Indeed, recent autopsy-based data suggest that non-A-band *TTN**trv*—traditionally considered less pathogenic—may still contribute to SCD even in the absence of a significant structural cardiomyopathy, potentially through dominant-negative or electrical instability mechanisms [19]. Patients with *TTN**trv*-related

DCM usually present with *LV dilation and systolic dysfunction* of variable severity. Compared with other genetic forms, the course is generally more favorable, with a *high rate of LV reverse remodeling (LVRR)* under optimized medical therapy—achieved in about 70% of cases, and full normalization in nearly 40%. Atrial fibrillation and nonsustained ventricular tachycardia (NSVT) are common, but *malignant ventricular arrhythmias* typically occur only with severe systolic impairment ($LVEF < 35\%$), rather than mutation site or fibrosis [20]. Penetrance and clinical expression of *TTNv*-DCM are influenced by environmental exposures and additional stressors such as alcohol abuse, chemotherapy, or peripartum hemodynamic stress, which can unmask latent dysfunction in genetically predisposed individuals [18].

LMNA (*lamin*) variants, found in 4–8% of DCM patients, define one of the most distinct and severe phenotypes. *LMNA* encodes a nuclear envelope protein that regulates structural stability and gene transcription. *LMNA*-related DCM manifests with early conduction abnormalities, atrioventricular block, atrial fibrillation, and malignant ventricular arrhythmias, often preceding overt systolic dysfunction. These patients have a rapid disease progression, a high risk of SCD, hypokinetic arrhythmias, and frequently require early heart transplantation [18].

FLNC truncating variants (*FLNC*tv), found in approximately 2–4% of DCM cases, are associated with a *markedly arrhythmogenic phenotype*. CMR typically reveals inferolateral subepicardial fibrosis, and the 5-year incidence of SCD or malignant ventricular arrhythmias reaches about 25–30%, independent of LV systolic function [21].

RBM20 variants, accounting for 1–5% of familial DCM, encode an RNA-binding protein that regulates splicing of *TTN*, *RYR2*, and other calcium-handling genes. Pathogenic variants cause early-onset, highly penetrant arrhythmogenic DCM, typically diagnosed in the third decade of life, with rapid progression to ventricular arrhythmias and HF even at moderate LVEF reductions. The typical LGE distribution is midmyocardial [22].

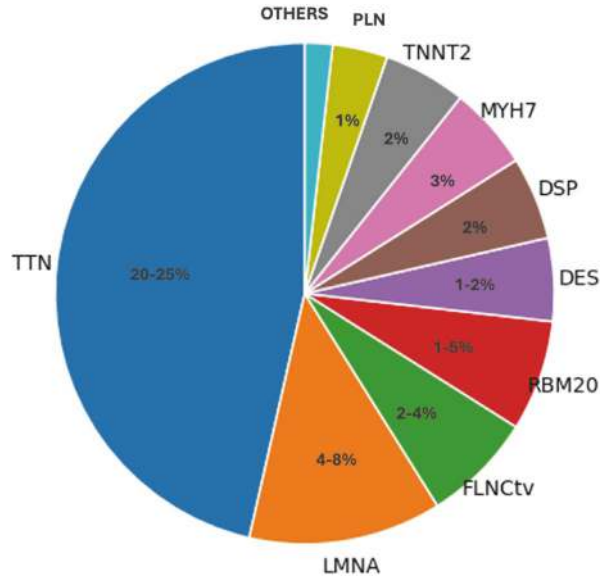
DES (desmin) variants, accounting for about 1–2% of DCM, disrupt the intermediate filament network linking Z-discs, desmosomes, and mitochondria. Carriers often present with atrioventricular conduction defects, arrhythmias, and variable skeletal–muscle involvement, reflecting the overlap between cardiac and skeletal myopathies.

DSP (desmoplakin) variants, originally linked to ARVC, are now recognized as causes of a “left-dominant arrhythmogenic” form of DCM, characterized by fibrosis of the LV, ventricular arrhythmias, and occasional right-sided involvement. These mutations bridge the clinical spectrum between classical DCM and arrhythmogenic cardiomyopathy.

PLN (phospholamban), especially the Arg14del founder variant, leads to early-onset arrhythmogenic DCM marked by malignant ventricular arrhythmias, progressive HF deterioration, and frequent need for heart transplantation (Fig. 4.1).

Finally, *BAG3*, *MYH7*, and *TNNT2* mutations affect sarcomeric and cytoskeletal stability, producing heterogeneous phenotypes and underscoring the overlapping nature of DCM [18]. Beyond single mutations, DCM often reflect a complex

Fig. 4.1 Genetic DCM-weighted distribution



inheritance model: *polygenic risk scores* aggregating the modest effect of common variants, can modify the penetrance of rare variants—for example, increasing the likelihood that *TTN*tv carriers express a DCM phenotype [23].

4.2.2 Acquired and Environmental Causes

Among nongenetic causes, *viral myocarditis* remains a leading mechanism of acquired DCM. Infections by *parvovirus B19*, *Coxsackievirus B*, or *HHV-6* are most frequent, but other agents such as *EBV*, *CMV*, and *Trypanosoma cruzi* can also trigger inflammatory cardiomyopathy. Persistent viral genomes or an autoimmune post-infectious response promote *chronic inflammation and ventricular remodeling*, with up to 20% of patients progressing to DCM within a year [13]. Immune dysregulation also contributes, as systemic immune-mediated diseases such as lupus, sarcoidosis, and rheumatoid arthritis may involve the myocardium through autoimmune and autoinflammatory mechanisms. In these conditions, in a recent study, about one in six patients carried a pathogenic variant in a cardiomyopathy gene, most often *TTN*tv, suggesting that autoimmunity can unmask or accelerate an underlying genetic predisposition, leading to myocardial inflammation, fibrosis, and eventually DCM [24].

Toxic cardiomyopathies constitute another major group. *Chronic alcohol consumption* remains the predominant cause, leading to oxidative stress, apoptosis, myocardial fibrosis, and iron accumulation. Importantly, abstinence can lead to partial or complete recovery; however, accumulating evidence indicated that genetic

susceptibility—often involving *TTN* variants—may modulate individual vulnerability and disease expression in this context as well [25].

Recreational drugs, including *cocaine* and *methamphetamines*, produce direct myocyte toxicity through catecholamine excess, endothelial dysfunction, and inflammation, often resulting in irreversible systolic failure. *Chemotherapeutic agents*, particularly *anthracyclines* and *immune checkpoint inhibitors*, cause dose-dependent myocardial injury mediated by oxidative stress, mitochondrial dysfunction, and immune activation with growing evidence that genetic predisposition, including *TTN**tv*, contributed to interindividual susceptibility [26]. Overall, acquired DCM reflects the interaction between environmental, infectious, and immune triggers acting on a susceptible myocardium. Even when genetic predisposition plays a minor role, inflammatory persistence or immune activation—whether viral, toxic, or systemic—emerges as a central mechanism driving disease progression and remodeling [13, 25].

4.3 Clinical Presentation and Diagnostic Work-Up

DCM presents with a wide clinical spectrum. Some individuals remain asymptomatic for years, identified only through family screening or incidental imaging, while others first present with advanced HF or SCDh. The disease often evolves silently until the onset of overt decompensation.

A thorough *clinical history* is fundamental. Beyond documenting HF symptoms, physicians should investigate potential environmental or iatrogenic exposures such as chronic alcohol intake, recreational drugs, or cardiotoxic chemotherapy. A three-generation family history is essential to identify unrecognized cardiomyopathy, premature HF, or unexplained SCD.

Although *physical findings* may be subtle, they often guide suspicion. *Left-sided failure* manifests with dyspnea, orthopnea, and fatigue, while *right-sided* involvement causes venous congestion with hepatomegaly, ascites, and edema. Hypotension, cool extremities, and dizziness indicate low-output states in advanced disease. Muscle wasting may suggest neuromuscular disease and an irregular pulse often reflects atrial or ventricular arrhythmias. *Arrhythmic manifestations* are common throughout the disease course. Palpitations typically arise from atrial fibrillation or ventricular ectopy, whereas presyncope or syncope may herald malignant ventricular tachyarrhythmias or conduction abnormalities.

Laboratory evaluation provides complementary diagnostic clues. Elevated natriuretic peptides indicate wall stress and prognosis, while persistent troponin elevation suggests ongoing myocardial injury. Tests assessing thyroid status, iron stores, renal function, and autoimmune markers can reveal systemic contributors, and raised creatine kinase may indicate neuromuscular involvement. Such findings are often underappreciated but may uncover reversible causes of DCM.

Certain clinical and laboratory features, called “*red flags*,” should raise suspicion of a genetic or syndromic form. A family history of cardiomyopathy or SCD, early conduction disease, or arrhythmias disproportionate to ventricular dysfunction are

key warning signs. Extracardiac manifestations—such as skeletal muscle weakness, lipodystrophy, or other neuromuscular or metabolic traits—further support this suspicion. Finally, a rapidly progressive course from mild to advanced disease is typical of aggressive genetic subtypes, underscoring the importance of early recognition and genetic evaluation.

A comprehensive evaluation requires the integration of multiple diagnostic tools, including the following:

4.3.1 Electrocardiography

The 12-lead ECG often shows nonspecific abnormalities but provides early diagnostic clues, such as *left bundle branch block (LBBB)* in ~1/3 of patients, with direct implications for cardiac resynchronization therapy (CRT); *low QRS voltage, Q waves, repolarization changes*, reflecting diffuse myocardial damage (Fig. 4.2); *conduction disease, such as AV block or sinus node dysfunction in young individuals*, strongly suggests genetic etiology such as *LMNA* (Fig. 4.3), dystrophin-related cardiomyopathy or myocarditis (sarcoidosis, Chagas disease) [27, 28]. Holter ECG. Monitoring frequently uncovers atrial fibrillation or ventricular arrhythmias; the detection of NSVT has prognostic weight and informs decisions regarding ICDs.

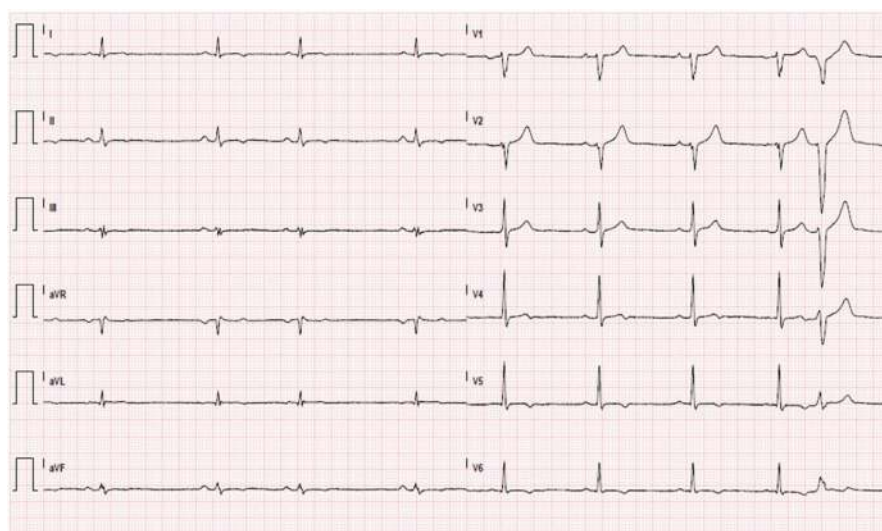


Fig. 4.2 ECG in a *FLNCTV* carrier. Low voltages on peripheral leads and inferolateral negative T waves

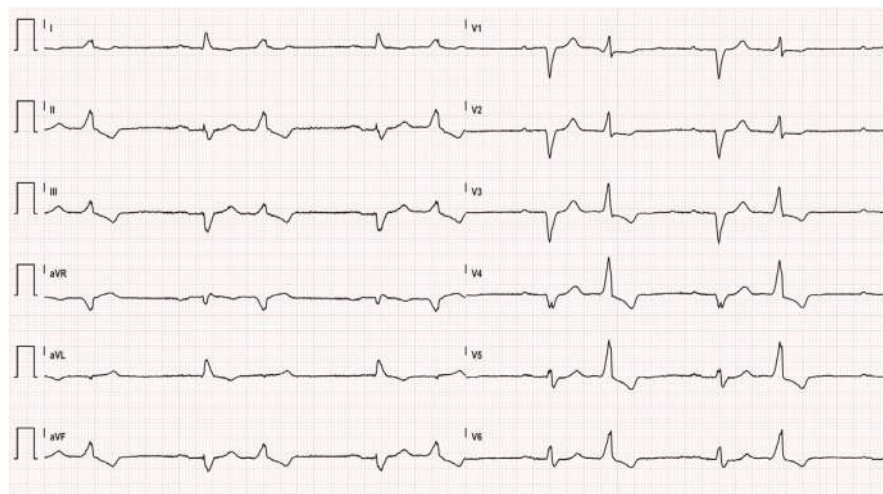


Fig. 4.3 ECG in a *LMNA* variant carrier. First-degree atrioventricular block, intraventricular conduction delay and multiple ventricular ectopic beats

4.3.2 Echocardiography

Echocardiography remains the *first-line imaging tool* in the assessment of DCM, providing a comprehensive evaluation of chamber geometry, global and regional function, and secondary structural abnormalities. It confirms *LV dilatation and systolic dysfunction*, typically defined by an LVEF below 50% and increased *end-diastolic diameter or volume indexed to body surface area*. Characteristically, DCM shows a globular or spherical LV shape with thin walls and reduced contractile thickening, features that help differentiate it from ischemic remodeling. Assessment of *right ventricular function* is equally relevant, as RV involvement strongly influences prognosis. Indices such as TAPSE (<17 mm) and RV fractional area change (<35%) are reliable markers of RV systolic impairment. The quantification of secondary mitral regurgitation, usually due to annular dilatation, contractile desynchrony, and papillary muscle displacement, is critical because it correlates with disease severity and progression, often aggravating symptoms and worsening outcome. In addition, assessment of diastolic function—including restrictive filling patterns, E/E' ratio, and left atrial dilatation—provides important complementary information on filling pressures and disease severity. Given the dynamic nature of DCM, periodic echocardiographic reassessment is essential to monitor ventricular remodeling, functional progression, and response to therapy.

Advanced techniques refine phenotypic characterization. *Global longitudinal strain (GLS)* detects early myocardial dysfunction even when ejection fraction is still preserved, with *GLS values* > −16% considered abnormal. Strain analysis provides incremental prognostic information, as progressive strain reduction often precedes overt systolic failure. *Three-dimensional echocardiography* allows more

accurate quantification of ventricular volumes and ejection fraction than the biplane Simpson method, while *contrast echocardiography* enhances visualization of the endocardial border and facilitates detection of *apical thrombi* in severe dysfunction.

Beyond quantification, echocardiography provides important *prognostic and pathophysiologic insights*. The combination of reduced GLS, right ventricular dysfunction, and moderate-to-severe mitral regurgitation identifies patients at high risk of adverse outcomes and guides timing for advanced therapies. Hence, modern echocardiography offers far more than a static measure of size and ejection fraction: it serves as a *dynamic, multiparametric tool* for diagnosis, risk stratification, and longitudinal follow-up of patients with DCM [29, 30].

4.3.3 Cardiac Magnetic Resonance

CMR allows noninvasive tissue characterization. The hallmark CMR finding in non-ischemic DCM is the presence of *LGE*, typically distributed in a mid-wall or sub-epicardial pattern, reflecting replacement fibrosis (Fig. 4.4). Beyond focal fibrosis detection, *parametric mapping techniques* extend CMR's diagnostic power. Native T1 and ECV mapping allow quantification of diffuse interstitial fibrosis not visible on conventional LGE imaging, while T2 mapping identifies areas of active myocardial inflammation, supporting the distinction between chronic remodeling and acute inflammatory injury. Equally important, CMR helps differentiate idiopathic DCM from phenocopies such as *cardiac sarcoidosis*, *ARVC*, and *myocarditis*, based on the distribution and pattern of tissue abnormalities. In this context, CMR serves not only as a diagnostic tool but also as a *prognostic and pathophysiologic marker*, integrating structural, functional, and tissue-level data to refine risk stratification and therapeutic decisions in patients with DCM [31, 32].

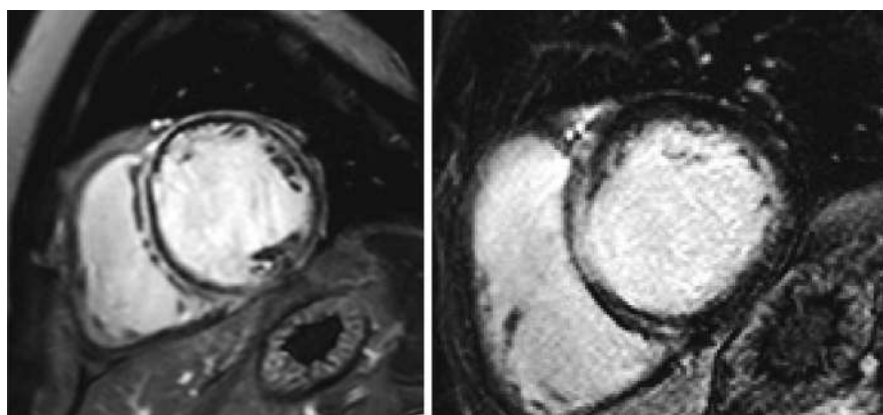


Fig. 4.4 Left panel: extensive ring-like LGE pattern in a *FLNC* variant carrier. Right panel: septal LGE pattern in a *LMNA* variant carrier

4.3.4 Endomyocardial Biopsy

Endomyocardial biopsy (EMB) is not recommended as a routine test in DCM but should be performed in selected patients when the result is expected to change management.

Indications include suspected fulminant or rapidly progressive myocarditis, inflammatory cardiomyopathies such as giant-cell myocarditis or sarcoidosis, unexplained ventricular arrhythmias or conduction disease in the young, and suspected infiltrative or storage disorders not clarified by noninvasive imaging. EMB can also help distinguish active inflammatory cardiomyopathy, where immunosuppression may be considered, from established fibrotic remodeling where standard HF therapy remains the mainstay (Fig. 4.5) [33].

4.3.5 Exercise testing and cardiopulmonary exercise testing (CPET)

Exercise testing may reveal exercise-induced arrhythmias, but cardiopulmonary exercise testing (CPET) provides far more powerful prognostic insights. Key parameters include *peak* VO_2 and the *VE/VCO₂ slope*, both essential for assessing severity and guiding advanced therapies. A peak VO_2 below 12–14 mL/kg/min (or <50% of predicted) and a VE/VCO_2 slope > 35 are classical thresholds supporting heart transplant listing. Integrated scores like the *MECKI score*, which combine CPET data with imaging and biomarkers, further refine risk stratification. Beyond advanced HF, CPET also plays a role in *family screening*: it can unmask subtle abnormalities such as chronotropic incompetence or exercise-induced arrhythmias in genotype-positive relatives before overt ventricular dysfunction develops [34].

4.3.6 Genetic testing

Genetic testing provides diagnostic, prognostic, and family management value across the full etiological spectrum of DCM, including alcohol, chemotherapy, and peripartum-associated disease and is increasingly poised to enable targeted, gene-specific therapies. Pathogenic or likely pathogenic variants are identified in up to ~30–40% of patients overall, in ~10–15% of chemotherapy, alcohol, or pregnancy-associated cases, and in ~20% of apparently nonfamilial presentations. Current 2023 ESC guidance recommends offering genetic testing ideally to all patients with DCM. In resource-limited settings, genetic testing can be prioritized using the *Madrid DCM Genotype Score*, offering testing to index patients who meet clinical predictors for a positive genetic test: (1) documented family history of DCM (three-generation pedigree with prior investigations); (2) skeletal myopathy; (3) absence of hypertension; (4) absence of LBBB; and (5) low ECG voltages [23]. Results should follow *ACMG/AMP standards*, distinguishing pathogenic or likely pathogenic variants from VUS variants, which require periodic re-evaluation. A positive genotype

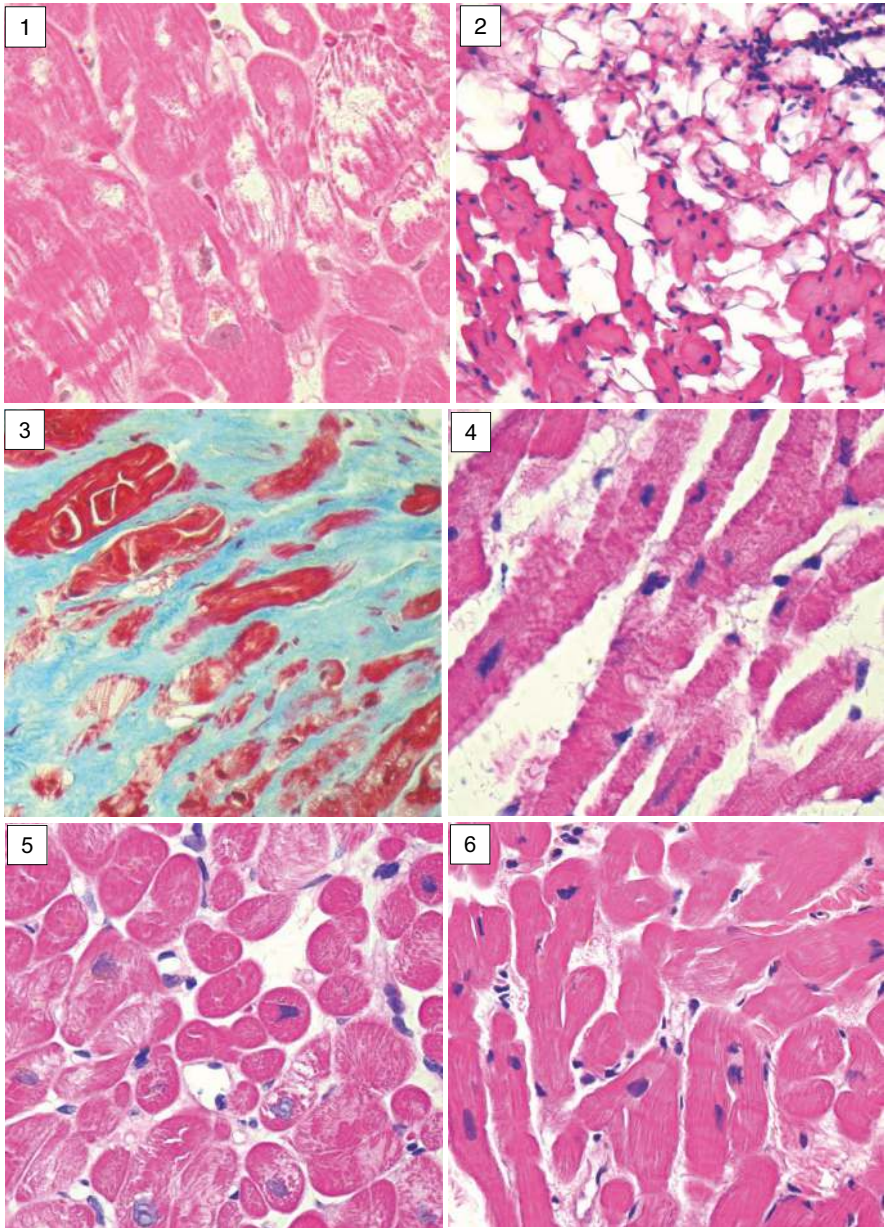


Fig. 4.5 (1) *FLNCRv* carrier. Compacted myocytes, with loss of the “zebra-like” contractile pattern; nuclei are rarefied, with dispersed and cleared chromatin. (2) *DSP* variant carrier. Extensive adipose and fibrous replacement associated with chronic inflammatory infiltrates. Myocytes exhibit markedly irregular and ill-defined peripheral borders with intramyocytic separation. In focal areas, adjacent myocytes appear to collapse against each other. (3) *NEXN* variant carrier. Fibrosis within which scattered residual myocytic elements appear, showing severe dysmorphic features. (4) Severe sarcolemmal alterations with frayed, ill-defined myocytic profiles; nebulization of portions of myocytes with stumps disappearing into the interstitium; abnormal nuclei. (5) *LMNA* carrier. Clearing of the contractile component; ill-defined sarcolemmal profiles; some abnormal nuclei. (6) Frequent features of pseudodisarray, amputations of the myocytic profile and some “ruptured” nuclei

supports etiologic reclassification, informs arrhythmic risk and ICD decisions, and enables cascade family screening. Relatives of carriers should undergo targeted testing, usually from age 10–12 years. VUS findings generally do not warrant family testing unless segregation analysis in affected relatives clarifies pathogenicity [23].

4.4 Arrhythmic Risk and Sudden Cardiac Death

Beyond Left Ventricular Ejection Fraction: Multiparametric Risk The evidence for primary prevention implantable cardioverter-defibrillator (ICD) therapy in DCM begins from landmark randomized trials: the *DEFINITE trial* (2004) enrolled patients with nonischemic cardiomyopathy, reduced LVEF and frequent ventricular ectopy (PVC), or NSVT and demonstrated a significant reduction in SCD, albeit not a statistically significant reduction in all-cause mortality. The *SCD-HeFT* (which included both ischemic and nonischemic HF) showed an overall mortality benefit with ICD therapy (approximately 23% reduction in mortality), thereby establishing the concept of prophylactic ICD in HF populations. More recently, the *DANISH trial* enrolled over 1100 patients with nonischemic systolic dysfunction (mean follow-up ~67 months) and found that while ICD implantation significantly halved SCD, it did not lower all-cause mortality in the overall cohort; benefit on overall mortality was observed in patients aged ≤ 70 years, as subsequently confirmed by *age-stratified* and *extended-follow-up* analyses showing that the reduction in SCD persisted for nearly a decade, whereas competing nonarrhythmic mortality progressively blunted survival benefit in older patients [35–37]. A *meta-analysis* combining these trials reports a hazard ratio for all-cause mortality around 0.78 (95% CI 0.66–0.92) in favor of ICD in nonischemic cohorts, though effect sizes diminish when more contemporary trials (with optimal medical therapy and CRT use) are included [38]. Accordingly, the 2023 ESC Cardiomyopathy Guidelines assign a Class IIa (Level A) indication for ICD implantation in symptomatic nonischemic DCM with LVEF $\leq 35\%$ despite optimal medical therapy, whereas the 2022 AHA/ACC/HFSA Guidelines endorse a Class I (Level A) recommendation for primary prevention in a similar population [39]. However, the ESC document moves beyond an LVEF-centric view, emphasizing the integration of imaging, clinical and genetic markers to refine candidate selection. Episodes of *unexplained syncope* remain among the most consistent clinical harbingers of malignant ventricular arrhythmias or SCD; their prognostic weight increases when accompanied by a family history of SCD or clustering of malignant arrhythmias within the pedigree [40]. Continuous ECG monitoring provides complementary insight: both *12-lead ECG* and *ambulatory Holter recordings* reveal subtle but powerful markers of electrical instability. *Prolonged QRS duration*, *early-onset conduction disease*, and *PVC patterns*—including a high PVC burden or frequent couplets— and frequent NSVT signal an underlying arrhythmogenic substrate. These findings are particularly informative in desmosomal and cytoskeletal genotypes such as *DSP* and

FLNC, where electrical abnormalities frequently precede structural remodeling and identify a high-risk arrhythmogenic phenotype [40–42].

CMR is the reference noninvasive tool to characterize the arrhythmogenic substrate in DCM. The presence of *LGE* correlates directly with ventricular arrhythmic events. Beyond the presence, the *pattern and distribution* of LGE carry specific prognostic weight: a *septal* or *ring-like circumferential* configuration denotes a diffuse fibrotic substrate that disrupts conduction pathways and promotes re-entry, even in patients with relatively preserved LVEF. A greater LGE burden (>3 segments) and an increased LV end-diastolic volume index (LVEDVi) are associated with a higher arrhythmic risk, especially in male patients [43]. Emerging evidence suggests that advanced CMR-derived strain parameters, particularly reductions in longitudinal and radial strain, may reflect diffuse myocardial injury and complement LGE findings, potentially providing additional insights into arrhythmic risk beyond focal fibrosis alone [14, 44, 45]. Moreover, T1 and extracellular volume (ECV) mapping could reveal diffuse interstitial fibrosis and may hold prognostic value even in LGE-negative patients, while T2 elevation may reflect residual inflammation. However, their role in arrhythmic risk stratification remains exploratory and awaits confirmation in prospective studies [46].

Genotype-Specific Risk Certain genetic substrates confer a markedly elevated baseline risk of life-threatening ventricular arrhythmias irrespective of LVEF. Dedicated or emerging risk scores aim to distill multiparametric signals—clinical phenotype, conduction/arrhythmia markers, LVEF, ECG, and CMR features—into individualized estimates of 5-year arrhythmic risk, thereby guiding timely ICD consideration.

LMNA The validated *LMNA* risk score integrates sex, NSVT, atrioventricular block, LVEF, and variant class (missense vs. non-missense). This model captures arrhythmic and conduction phenotypes beyond EF, supporting early ICD decisions [47].

FLNCTv Carriers of truncating *FLNC* variants face high arrhythmic risk, magnified by nonischemic LGE or LVEF <45%. A 19-centre registry produced a predictive model using NSVT, syncope, male sex, age, and LVEF, offering individualized 5-year estimates. Though awaiting external validation, it illustrates the shift toward integrating genotype with clinical phenotype in *FLNC* stratification [48].

DSP DSP variant carriers are prone to malignant arrhythmias, especially with LGE and impaired systolic function. A dedicated DSP risk score for left-dominant arrhythmogenic and “DCM-like” phenotypes incorporates female sex, NSVT, 24-h PVC burden, LVEF <50%, and moderate–severe RV dysfunction—providing practical support for earlier ICD consideration [49].

PLN p. Arg14del The *PLN*-specific calculator integrates LVEF, premature ventricular contraction burden, T-wave inversion, and low-voltage ECG into an individualized 5-year malignant arrhythmia estimate. Additional markers—LVEF <45%, nonischemic LGE, and NSVT—consistently identify particularly high-risk carriers, sharpening ICD selection [50].

TMEM43 Variant carriers are at intrinsically high risk, with malignant arrhythmic events predicted by a simple set of variables: sex (male/female) plus any of the following—LVEF <45%, NSVT, CMR-LGE, or >200 ventricular ectopic on 24-h Holter. These features highlight the strong interaction between genotype, substrate, and arrhythmic phenotype [51, 52].

RBM20 *RBM20* variants carriers display elevated arrhythmic risk largely driven by myocardial substrate. Nonischemic LGE on CMR and LVEF <45% emerge as the key predictors, reinforcing the need for CMR-centered and genotype-informed assessment even when clinical arrhythmic markers are absent [22].

A *multiparametric approach*—integrating clinical phenotype, arrhythmic history, CMR-defined fibrosis, family history of SCD, and high-risk genotypes—represents a major evolution in risk stratification for dilated and arrhythmogenic cardiomyopathies. This strategy transcends the limitations of single-parameter models based solely on LVEF or isolated imaging findings. By combining clinical, ECG, imaging, genetic, and biomarker data, it captures the heterogeneous substrates driving both arrhythmic and nonarrhythmic progression, enabling more refined prediction of outcomes. Emerging applications of *artificial intelligence and machine-learning algorithms* further enhance this framework, allowing automated extraction of subtle imaging features and nonlinear interactions between genetic and clinical variables. Such AI-driven, multiparametric models improve the identification of patients who truly benefit from device implantation while reducing unnecessary ICD exposure in those with predominant heart HF trajectories or potential for reverse remodeling. Ultimately, these gene- and data-informed tools offer a dynamic, continuously adaptive assessment of arrhythmic risk, aligning therapeutic decisions with the evolving phenotype of DCM (Fig. 4.6) [53].

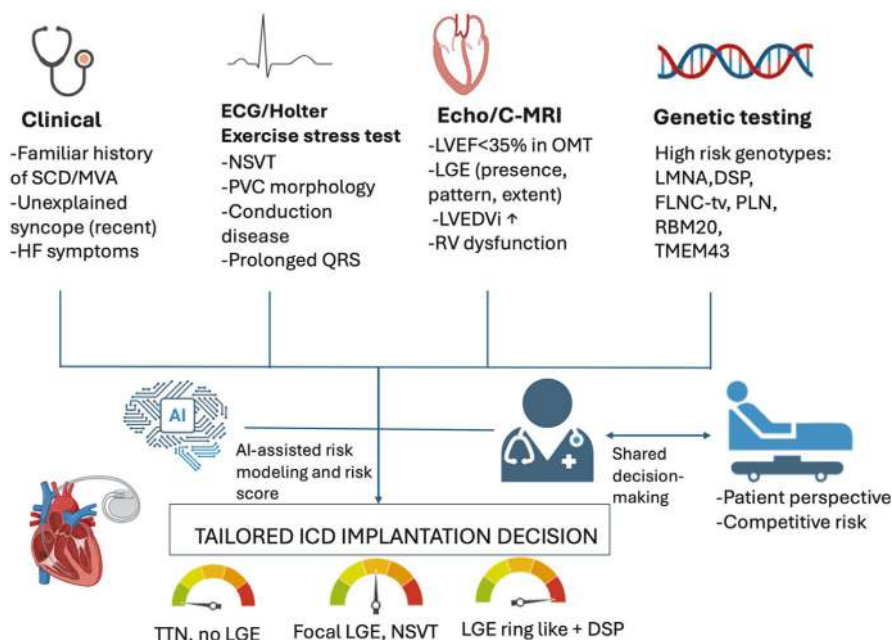


Fig. 4.6 Multiparametric arrhythmic risk stratification for primary prevention ICD in DCM. Created in BioRender. Guarnaccia, A. (2026) <https://BioRender.com/3vflvyo>

4.5 Family Management: Pregnancy and Cascade Screening

4.5.1 Pregnancy Counseling

Women with DCM are at risk of clinical deterioration during pregnancy, especially those with LV systolic dysfunction or advanced HF symptoms. According to the 2025 ESC mWHO 2.0 classification, severe LV impairment (LVEF <30% or NYHA III–IV) and previous peripartum cardiomyopathy with more than mild residual LV dysfunction are classified as *mWHO IV*, indicating *extremely high risk of maternal mortality or severe morbidity*. Patients with moderate LV impairment (EF 30–45%) fall into *mWHO III*, in whom pregnancy carries *very high risk* and management in specialized centers with planned delivery and postpartum monitoring is mandatory.

HF therapy follows standard principles but excludes teratogenic agents: Angiotensin-Converting Enzyme (ACE) inhibitors, Angiotensin 2 Receptor Blockers (ARBs), Angiotensin Receptor Neprilysin Inhibitor (ARNis), Mineralocorticoid-Receptor Antagonists (MRAs), and amiodarone must be avoided, whereas β -blockers may be continued with fetal growth surveillance, and diuretics should be used only for symptomatic congestion. The peripartum and early postpartum periods are associated with peak hemodynamic stress; therefore, monitoring for at least 24–48 hours postpartum (longer in high-risk cases) is recommended. In genetic DCM, inheritance

is in most cases *autosomal dominant*, conferring a 50% transmission risk for pathogenic/likely pathogenic variants. Couples should receive pre-conception genetic counseling, including discussion of *prenatal and pre-implantation genetic testing options* in some specific cases and their ethical implications [54].

4.5.2 Family Screening

Structured family screening enables early disease detection and improves prognosis in relatives of probands with DCM. The screening pathway begins with *12-lead ECG and echocardiography* (including global longitudinal strain analysis), which provide the foundation for detecting early electrical or structural abnormalities. When subtle changes emerge or in carriers of high-risk genotypes, *Holter monitoring and exercise testing* enhance early detection of arrhythmic risk. *CMR* further strengthens this multiparametric approach by characterizing the arrhythmogenic substrate beyond what echocardiography can reveal. In genotype-positive relatives—particularly carriers of DSP or FLNC variants—CMR frequently identifies *ring-like or subepicardial patterns of LGE*, which indicate early fibrotic remodeling and predict ventricular arrhythmias even in the presence of preserved systolic function.

Screening intervals should be tailored to age, genotype, and clinical findings. Current ESC consensus recommends re-evaluation of first-degree relatives of genotype-positive probands—particularly those carrying *LMNA, FLNC, DSP, RBM20, PLN*, or *MYH7* variants—every 1–3 years. Annual follow-up is advised when early disease manifestations, abnormal ECG or imaging findings, or high-risk genotypes are present, or when the family shows early-onset disease. Conversely, older relatives with normal baseline evaluations and no additional risk features may be safely reviewed at longer intervals of up to three years.

Clinical follow-up should also consider *lifestyle and phenotype modifiers*. Relatives engaged in competitive sports or from families with clustering of SCD or arrhythmogenic phenotypes warrant intensified monitoring. Family screening now embraces a comprehensive approach that merges clinical evaluation, advanced imaging, and genetic data to personalize surveillance and management. This strategy enables early preventive action and informed counseling on exercise, pregnancy, and device therapy, while capturing the continuum from silent genetic carriers with subclinical myocardial involvement to overt cardiomyopathy [55–57].

4.6 Treatment Strategies and Advanced Heart Failure Management

4.6.1 Optimal Medical Therapy

In *symptomatic* HFrEF due to DCM, therapy follows the same four disease-modifying drug classes recommended for HFrEF of any etiology: RAS inhibition (ACE-I/ARB) or ARNI; β -blockers; MRAs; SGLT2 inhibitors. Despite limited

evidence, HF therapy is recommended in *asymptomatic LV dysfunction* to delay progression, while the role of early treatment in *genotype-positive/phenotype-negative carriers* remain uncertain owing to scarce trial data and heterogeneous disease trajectories [58]. The 2021 ESC HF guideline advocates early, parallel initiation of all four agents (“rapid quadruple therapy”). Although pivotal trials enrolled mainly mixed ischemic/nonischemic populations, and genotype-stratified DCM data are scarce, defaulting to guideline-directed therapy is essential—waiting for “DCM-only trials” would deny patients therapies already proven to reduce mortality and hospitalizations [59].

ACE-I/ARB or ARNI Early ACE-I studies (CONSENSUS, SOLVD-Treatment, SOLVD-Prevention) demonstrated mortality reduction and prevention of HF progression, with benefits even in asymptomatic LV dysfunction—highly relevant for genotype-positive relatives detected in cascade screening. ARNI (sacubitril/valsartan) displaced ACE-I as first-line RAS blockade after PARADIGM-HF confirmed superiority in reducing CV death and HF hospitalization [60].

β -blockers MERIT-HF, CIBIS-II, and COPERNICUS established survival benefit and reverse remodeling capacity of β -blockers. REVERT documented improvement even in asymptomatic LV dysfunction, reinforcing early use when reduced EF is identified in relatives. While response may vary across genotypes, there is no evidence of harm. Limitations arise in conduction phenotypes (*LMNA* and related genotypes), where pacing or CRT may be prioritized [61, 62].

Mineralocorticoid-Receptor Antagonists RALES and EMPHASIS-HF showed significant reductions in mortality and HF hospitalization. MRAs antifibrotic and anti-arrhythmic properties are particularly appealing in DCM, where myocardial fibrosis is central. Despite the absence of DCM-specific RCTs, MRAs are strongly justified unless contraindicated [62].

SGLT2 Inhibitors DAPA-HF and EMPEROR-Reduced demonstrated rapid reductions in HF hospitalization and CV death, with favorable renal effects and minimal BP impact—making SGLTs inhibitors especially useful in hypotension-limited uptitration. Though trials were mixed etiology and not genotype-specific, their benign hemodynamic profile supports early incorporation, often in the first weeks of therapy [63, 64].

Vericiguat *VICTORIA trial* (2020) tested vericiguat in high-risk patients with recent worsening HF, showing a relative reduction in cardiovascular death or first HF hospitalization. The *VICTOR trial* (2025) evaluated vericiguat in ambulatory, compensated patients without recent decompensation and did not significantly reduce the composite outcome but lowered cardiovascular and all-cause mortality. In the *pooled analysis* of VICTORIA and VICTOR, vericiguat reduced cardiovascular death and HF hospitalizations across disease severities. Thus, vericiguat

appears most beneficial after recent decompensation, but might also have a supportive role in stable, well-treated HFrEF [65–67].

Structured reassessment at 3, 6, and 12 months after therapy optimization is essential, as reverse remodeling may be delayed and treatment withdrawal is unsafe—indeed, the TRED-HF trial demonstrated relapse in ~44% of apparently recovered nonischemic DCM within 6 months of therapy discontinuation [68]. Moreover, even after initial improvement, a substantial proportion of patients experience recurrent LVEF deterioration years later, which is associated with a markedly increased risk of adverse outcomes, reinforcing the need for continued GDMT and long-term follow-up despite apparent recovery [69].

4.6.2 Arrhythmia Management and Cardiac Resynchronization Therapy

Ventricular arrhythmias in DCM span from *PVCs* to sustained *ventricular tachycardia* (VT) and atrial arrhythmias, requiring stepwise management.

Premature Ventricular Contraction β -Blockers are first-line but often insufficient when ectopy is frequent or focal. Suppression of PVCs with *Class Ic agents* is generally avoided due to the lack of solid evidence supporting their safety in this population and to their inotropic negative effect; only highly selected nonischemic cases with preserved function have been cautiously explored as potential exceptions. For PVC-induced cardiomyopathy, *catheter ablation* is preferred, reversing LV dysfunction and outperforming chronic drug therapy [70].

Ventricular Tachycardia β -Blockers remain foundational; amiodarone is the most widely used adjunct, while sotalol offers weaker evidence. Mexiletine may be added to amiodarone for recurrent VT. For recurrent VT, storm, or frequent ICD therapies, *catheter ablation* is recommended. In DCM, arrhythmogenic substrates are often mid-myocardial or epicardial, complicating ablation compared with ischemic disease. CMR is crucial for substrate localization and procedural planning. Achieving noninducibility reduces recurrence, though relapses remain common. Temporary LV support may be required in unstable cases [71, 72].

Atrial Fibrillation and Atrial Flutter (AF/AFL) These are common in DCM and correlate with worse outcomes, reflecting atrial remodeling and elevated filling pressures. Management focuses on symptom control and stroke prevention. Catheter ablation can be effective, but relapse rates are higher than in non-DCM cohorts. The *CASTLE-AF* trial showed that catheter ablation benefits in selected subgroup of HFrEF patients (insufficient response, intolerance, or unwillingness to take antiarrhythmic drugs), while the *CASTLE-HTx* trial extended the benefit of ablation to end-stage HFrEF candidates for transplant or LVAD. Anticoagulation should follow

CHA_2DS_2 -VA, but thresholds are often exceeded, making long-term anticoagulation the rule rather than the exception [73–75].

Cardiac Resynchronization Therapy CRT improves symptoms, reverse remodeling, and survival in selected patients with DCM and HFrEF. The clearest indication is $LVEF \leq 35\%$, *sinus rhythm*, and *LBBB with QRS ≥ 150 ms*. Patients with QRS 130–149 ms or non-LBBB patterns may derive benefit but with weaker evidence. In nonischemic cardiomyopathy, CRT not only alleviates heart failure burden but can also reduce arrhythmic events and unnecessary ICD shocks. Timely implantation before advanced dilation or fibrosis enhances reverse remodeling and long-term outcomes [76].

4.6.3 Advanced Therapies: M-TEER, LVAD, and Transplantation

In DCM, mitral regurgitation is predominantly *ventricular (secondary) in mechanism*, driven by LV dilatation and leaflet tethering. After optimization of GDMT, including CRT when indicated, transcatheter edge-to-edge repair (*M-TEER*) may be considered in persistently symptomatic patients with severe SMR and appropriate anatomy (class I recommendation). The evidence base derives from randomized trials enrolling mixed etiologies, but with differing representation of nonischemic disease: nonischemic cardiomyopathy accounted for ~40% of patients in COAPT and MITRA-FR, and for the large majority in RESHAPE-HF2 (~88%). While COAPT and RESHAPE-HF2 demonstrated reductions in HF hospitalizations (and mortality in COAPT), MITRA-FR was neutral, likely reflecting the importance in patient selection, ventricular remodeling severity, and the proportionality of MR to LV dilatation. These data support a role for M-TEER in carefully selected patients with DCM. [77–80]

For patients with *advanced HF* despite optimal therapy and device therapy, LVADs and transplantation remain life-saving options. *LVADs* are now central to the management of advanced HF in DCM: implantation improves survival, quality of life, and functional capacity, while fostering reverse remodeling and recovery of ejection fraction. LVADs are employed as a *bridge to transplantation/bridge to candidacy* but also represent *destination therapy* in nontransplant candidates (acknowledging that transplant candidacy is a dynamic condition that may evolve over time). Contemporary continuous-flow devices (such as the *HeartMate 3*) achieve excellent survival, with lower rates of thrombosis and stroke compared with earlier designs [81]. *Heart transplantation* remains the definitive therapy for end-stage DCM, with 1-year survival around 90% in modern cohorts and a median survival of 12.5 years (Fig. 4.7) [59]. Appropriate timing and multidisciplinary selection are key to optimizing outcomes. Importantly, *timely referral* to an advanced HF center is crucial to maximize these benefits and should occur within the so-called “golden window” before irreversible end-organ dysfunction develops. Candidates typically present with persistent NYHA III–IV symptoms, severe structural or functional

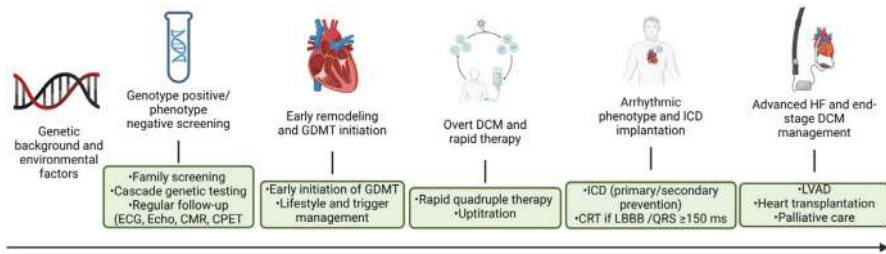


Fig. 4.7 Management of the patient with DCM: from genetic screening to advanced heart failure care. Created in BioRender. Guarnaccia, A. (2026) <https://BioRender.com/sp52x13>

abnormalities (including LVEF $\leq 30\%$ or isolated right ventricular failure), recurrent HF hospitalizations, or low-output episodes requiring intravenous therapies and/or marked exercise intolerance (peak $\text{VO}_2 < 12\text{--}14 \text{ mL/kg/min}$ or 6-minute walk distance $< 300 \text{ m}$) [82].

4.6.4 Precision Medicine and Emerging Therapies

Gene therapy for DCM is rapidly advancing within precision cardiology. Approaches include (1) *gene replacement therapy* with adeno-associated viral (AAV) vectors, aiming to restore functional protein expression. Proof-of-principle was achieved in Danon disease, which was safe and showed biological activity. Early-phase industry programs are targeting *BAG3* and *PKP2* loss-of-function variants; (2) *allele-specific silencing*, such as antisense oligonucleotides or siRNA, with preclinical success in *PLN* p.Arg14del mice and exploratory work in *LMNA* focuses on selectively silencing the mutant allele; (3) *genome editing* with CRISPR–Cas9, showing promising correction of pathogenic variants in preclinical models (notably *RBM20*, *PLN*, and sarcomeric genes). *Challenges* remain—vector immunogenicity, cardiac-specific delivery, limited packaging capacity, durability of expression, and off-target effects. Nonetheless, these strategies mark a shift from supportive therapies to molecularly targeted interventions, with the potential to transform prognosis in selected genetic subsets of DCM [13, 83].

4.7 Future Perspectives

Dilated cardiomyopathy is moving to a model of precision cardiology. Genetics, advanced imaging, and biomarkers are being integrated into risk stratification, moving beyond ejection fraction. Artificial intelligence and machine learning are increasingly applied to CMR, ECG, and multi-omic data to refine arrhythmic risk prediction, enable phenotypic clustering, and identify novel disease trajectories. Gene-specific scores, cascade family screening, and novel targeted therapies—including gene replacement, allele-specific silencing, and genome editing—are

shaping a shift from supportive care to molecularly driven interventions. Together with innovations in LVAD technology and transplantation, these advances are expected to transform the natural history of DCM and enable a truly personalized management path.

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Hypertrophic Cardiomyopathy

5

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5.1 Summary

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disease, with an estimated prevalence of one in every 500 individuals worldwide. Until a few decades ago, the etiology of HCM was unknown and its diagnosis was based primarily on clinical findings. Currently, the diagnosis and characterization of HCM rely on an integrated multiparametric approach encompassing clinical assessment, advanced cardiac imaging modalities, and genetic testing. Cardiac imaging is the cornerstone of HCM diagnosis and risk stratification. In the context of HCM, LVH is mostly asymmetric and predominantly involves the basal septum, but various patterns of hypertrophy are possible. Diagnostic criteria in adults include a maximal end-diastolic wall thickness of ≥ 15 mm (or ≥ 13 mm in relatives of affected patients or genotype-positive individuals) in the absence of other causes of hypertrophy (i.e., chronic hypertension, aortic stenosis). For children, the diagnostic threshold is set at a z-score of at least 2 standard deviations above the mean [1, 2]. Once a clinical diagnosis is established, subsequent management includes genetic testing, risk stratification for sudden cardiac death, assessment of symptom burden, counseling on physical activity, and screening of family members. Although only a small percentage of individuals with HCM develop symptoms and overall mortality

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is relatively low, some patients develop over time serious complications such as heart failure, arrhythmias, and sudden cardiac death (SCD), necessitating careful monitoring and management. In recent years, a substantial evolution in therapeutic strategies has reshaped the management of HCM and significantly reduced the disease-related mortality and morbidity. The development of cardiac myosin inhibitors has introduced a disease-specific approach that targets the underlying pathophysiology, modulating hypercontractility and reducing left ventricular outflow tract (LVOT) obstruction. Given the new treatment perspective, precise diagnosis of HCM and differentiation from its phenocopies, with distinct management and treatment, are now more critical than ever.

5.2 Genetics

HCM is primarily a monogenic disorder with autosomal-dominant inheritance. However, due to the incomplete penetrance of pathogenic genetic variants, positive genotype does not necessarily lead to a clinical phenotype [3]. Consequently, a negative family history does not exclude a genetic etiology. The most common genetic variants involved in the pathogenesis of HCM are found in eight main sarcomere genes encoding contractile proteins of cardiac muscle: MYH7, MYBPC3, TNNI3, TNNT2, TPM1, MYL2, MYL3, and ACTC1 (Table 5.1). MYH7 and MYBPC3 together account for approximately 70% of genetically confirmed cases [4]. Notably, genetic testing cannot detect a pathogenic or likely pathogenic (P/LP) variant in up to 40% of patients diagnosed with HCM, mainly in sporadic cases or small families, usually with late onset and mild clinical phenotype [5, 6]. Given the low probability of identifying a P/LP variant, in patients diagnosed with HCM after the age of 60 genetic testing may be considered optional and can be deferred [5, 6]. These findings suggest that the pathogenesis of HCM is more complex and not fully understood, involving polygenic contributions, epigenetic changes, and environmental factors. The exact role of these modifiers in disease onset and progression is under investigation, and the gene-to-disease relationship remains poorly defined [7].

Table 5.1 Most common genes involved in the pathogenesis of hypertrophic cardiomyopathy

Pathogenic genes	Gene mapping	Genes encoded	Inheritance model
MYH7	14q11.2	Myosin heavy chain 7	AD
MYL2	12q24.11	Myosin light chain 2	AD
MYL3	3q21.31	Myosin light chain 3	AD, minimal AR
MYBPC3	11p11.2	Cardiac myosin binding protein C	AD, minimal AR
TNNT2	1q32.1	Cardiac troponin T2	AD
TNNI3	19q13.42	Cardiac troponin I3	AD
TPM1	15q22.2	Alpha tropomyosin	AD

AD autosomal-dominant, *AR* autosomal-recessive

Table 5.2 Most common hypertrophic cardiomyopathy phenocopies

Disease	Pathogenic genes	Gene mapping	Mutation	Inheritance model
<i>Hereditary hypertrophic cardiomyopathy phenocopies</i>				
Fabry disease	<i>GLA</i>	Xq22.1	Galactosidase alpha	X-linked
Danon disease	<i>LAMP2</i>	Xq24	Lysosomal-associated membrane protein 2	X-linked
Pompe disease	<i>GAA</i>	17q25.3	Acid alpha-glucosidase	AR
PRKAG2 syndrome	<i>AMPK</i>	7q36.1	5' adenosine monophosphate-activated protein kinase	AD
Friedreich's ataxia	<i>FXN</i>	9q21.11	Frataxin	AR
Cardiac amyloidosis ATTRv	<i>TTR</i>	18q12.1	Transthyretin	AD
MELAS	<i>MTTL1</i>	m.3243A > G	mt-tRNA	Matrilineal
RASopathies (e.g., Noonan/LEOPARD syndrome)	<i>PTPN11</i> , <i>RAF1</i> , etc.	12q24.13, 3p25.2	RAS/MAPK signaling pathway	AD
<i>Nonhereditary hypertrophic cardiomyopathy phenocopies</i>				
Cardiac amyloidosis	ATTRwt			
	AL			
Athlete's heart				
Aortic stenosis				

AD autosomal-dominant, AR autosomal-recessive

Genetic testing plays a crucial role in confirming diagnosis, enabling family screening, and supporting the differential diagnosis from HCM phenocopies—conditions that mimic HCM but have distinct etiologies, management, and prognosis [8]. These include metabolic and systemic diseases such as Fabry disease, glycogen storage diseases (e.g., Danon disease, PRKAG2 disease), Friedreich's ataxia, Noonan syndrome, mitochondrial cardiac diseases (e.g., MELAS, Leigh syndrome, MERRF), and cardiac amyloidosis (Table 5.2).

Genetic testing should be preceded by a comprehensive clinical assessment—including detailed family and personal history, physical examination, ECG and multimodal imaging, extending, in selected cases, to histological examination. Deep phenotyping is essential for a rational selection of genetic tests and to ensure accurate interpretation of results. As part of the initial evaluation, a detailed three-generation family history should be obtained to identify patterns of inheritance. Genetic evaluation—including counseling and testing—is then recommended for the first individual diagnosed with HCM in the family, known as the proband or index case. Effective genetic counseling is pivotal to ensure that patients are fully informed about the intrinsic limitations and uncertainties associated with genetic test results. In this context, the development of a multidisciplinary cardiogenetic team appears to be crucial in the future.

Although genotype plays a key diagnostic role in HCM, its value in predicting prognosis and clinical course remains limited [7]. Some studies suggest that patients with P/LP variants may present with earlier disease onset and an increased risk of arrhythmias and heart failure [9, 10]. However, evidence regarding their association with sudden cardiac death (SCD) remains inconclusive. As a result, genotype is not currently used in clinical practice to guide therapeutic decisions such as ICD implantation in adults [1, 2]. An exception applies to the pediatric population, where sarcomeric mutations have been shown to have a more consistent association with adverse outcomes, including SCD, and have been incorporated as a formal component of risk stratification in the North American guidelines [2]. Moreover, while isolated sarcomeric variants offer limited prognostic information, more complex genetic backgrounds—such as compound heterozygosity (multiple variants in the same gene) or digenic heterozygosity (variants in different sarcomeric genes)—have been associated with worse overall prognosis [11].

The identification of a variant of uncertain significance (VUS) is not considered clinically actionable; however, such findings may be updated over time as new evidence emerges. Therefore, periodic re-evaluation of genetic test results is essential, as reclassification of a variant—whether from uncertain to benign or pathogenic—can significantly affect both diagnosis and cascade genetic testing in family members. If the phenotype is atypical or a phenocopy is suspected, extended gene panels should be considered. This requires cardiologists to integrate clinical expertise with an understanding of molecular biology and genetics, and interaction with genetic specialists becomes essential.

For family screening, first-degree relatives of affected individuals should undergo clinical evaluation, including symptom assessment, ECG, and transthoracic echocardiography. In families where a P/LP variant has been identified, cascade genetic testing is recommended. Genotype-positive but phenotype-negative (G+/P−) individuals require ongoing surveillance due to the risk of phenotypic transformation, which occurs in 6–30% of individuals over time [12]. As long as hypertrophy does not develop, the G+/P− status is associated with a favorable prognosis. Cardiac magnetic resonance is recommended in the evaluation of G+/P− individuals, as it can detect subtle structural abnormalities in subclinical HCM [13]. Conversely, in families without an identified disease-causing variant, only clinical follow-up is recommended [1, 2] (Fig. 5.1).

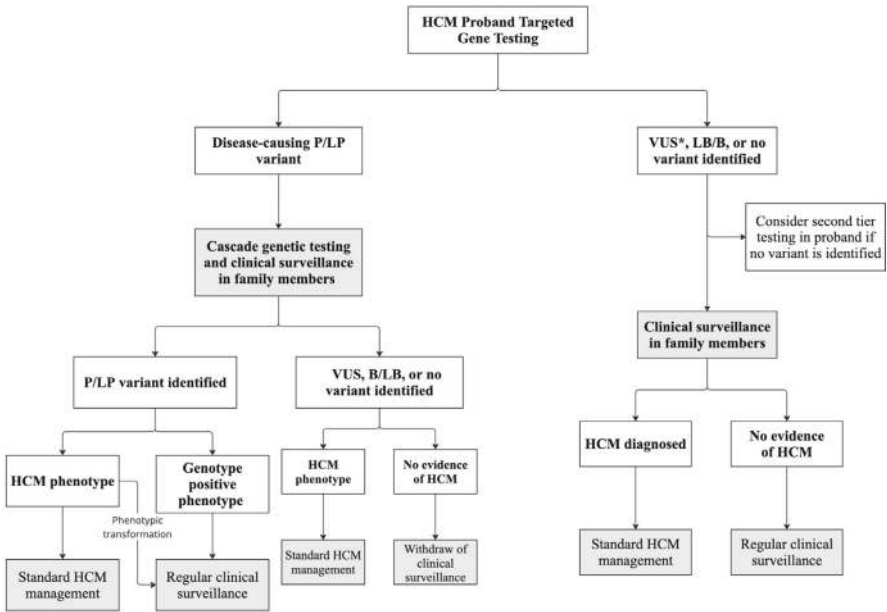


Fig. 5.1 Flow chart for genetic testing and family screening in hypertrophic cardiomyopathy. B/LB benign/likely benign, HCM hypertrophic cardiomyopathy, P/LP pathogenic/likely pathogenic, VUS variant of unknown significance. *Periodical reevaluation for variant reclassification is necessary. (Created in BioRender. Guarnaccia, A. 2026. <https://BioRender.com/2m9ihpj>)

5.3 Natural History and Pathophysiological Moments of Hypertrophic Cardiomyopathy

Contemporary guidelines emphasize that beyond its genetic heterogeneity, the clinical course of HCM is largely driven by a set of interrelated pathophysiological mechanisms, each carrying distinct prognostic implications [1, 2, 14]. Natural course of HCM is marked by four cardinal pathophysiological moments that shape patient trajectories:

1. Dynamic left ventricular outflow tract obstruction (LVOTO) and mitral regurgitation from systolic anterior motion (SAM-MR).
2. Diastolic dysfunction and coronary microvascular ischemia.
3. Arrhythmogenic substrate and its clinical surrogates (e.g., unexplained syncope).
4. Progression to adverse remodeling and end-stage phenotypes.

5.3.1 Epidemiology and the Genotype-Positive/Phenotype-Negative Stage

Population-based imaging and genetic studies converge on a prevalence of 0.2% for phenotypic HCM in adults, with an additional pool of genotype-positive/phenotype-negative relatives who will manifest hypertrophy later in life [1]. Within this spectrum, an apical variant (aHCM) accounts for 8% of Western and up to 25% of Asian cohorts, illustrating geographic heterogeneity in phenotypic expression [2]. The estimated penetrance of HCM in sarcomeric pathogenic/likely pathogenic (P/LP) variant carriers is approximately 60%, and it is modulated by sex, sarcomeric variant class, and extrinsic stressors [15]. Early identification through cascade family screening is therefore central to contemporary care pathways, enabling pre-emptive counseling and rhythm surveillance [1]. In genotype-positive/phenotype-negative (G+/P−) individuals, cardiac MRI is often warranted to ensure that the absence of phenotype is genuine [13].

5.3.2 Age- and Sex-Specific Trajectories

Disease expression is markedly influenced by biological sex and age. In the multinational SHaRe registry, males experienced ventricular tachycardia (VT) or sudden cardiac death (SCD) at nearly twice the incidence of females (HR 1.9) and at a younger median age (29 y.o. vs. 36 y.o.), whereas females accrued a greater burden of heart failure (HF) admissions and atrial fibrillation in mid-life [16]. Pediatric data reflect this dichotomy: of 1010 children diagnosed at ≤18 years of age, left ventricular systolic dysfunction (LVSD, ejection fraction [EF] <50%) developed in 15% of patients with a median age of 32 years at transition. Early-onset LVSD (before 12 years of age) and male sex were independent predictors of LVSD [17].

5.3.3 A Four-Stage Disease Model

Long-term cohort data show that HCM evolves through two common early phases and then may diverge into *either* of two distinct end-stage phenotypes (see Fig. 5.2) [18, 19].

- *Stage 1*
 - Phenotype: concentric or asymmetric LV hypertrophy, preserved or supranormal ejection fraction (EF); dynamic LVOT obstruction (LVOTO) in 70% of patients.
 - Dominant mechanism: hypercontractility with sarcomeric energy wastage.
 - Clinical picture: asymptomatic athlete or mild exertional dyspnea.

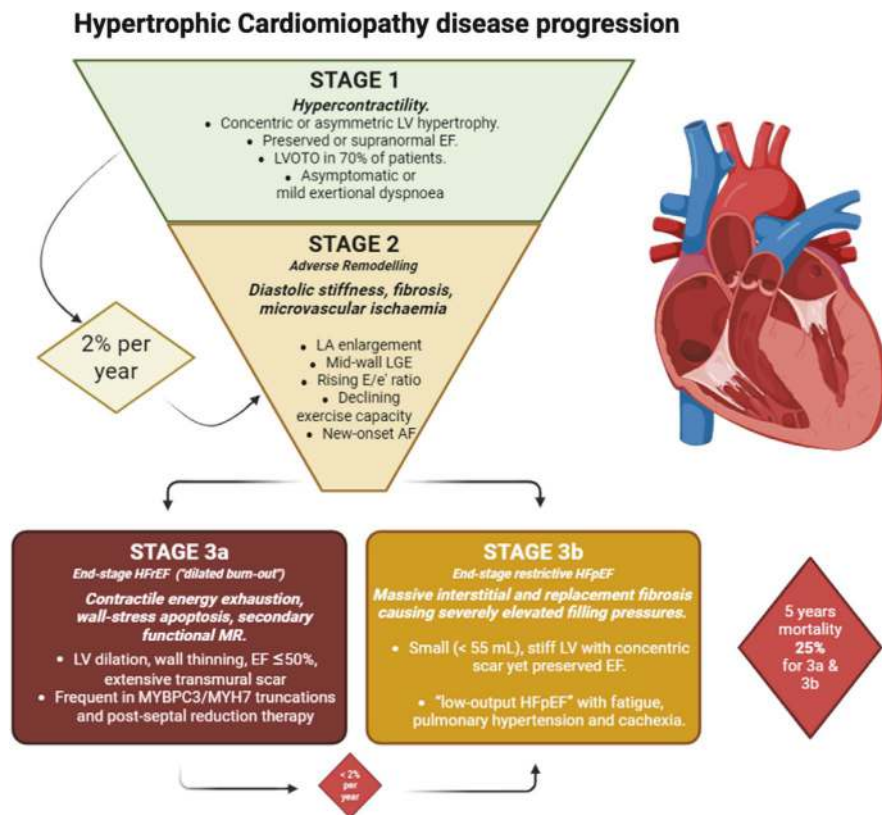


Fig. 5.2 Four-stage HCM funnel: visualizes progression from stage 1 to stage 3a/b, with annual transition probabilities and 5-year mortality for both end-stage types. AF atrial fibrillation, EF ejection fraction, HFpEF heart failure with preserved ejection fraction, HFrEF heart failure with reduced ejection fraction, LA left atrium, LGE late gadolinium enhancement, LV left ventricle, LVOTO left ventricular outflow tract obstruction, MR mitral regurgitation, MYBPC3 myosin binding protein C3, MYH7 myosin heavy chain 7. (Created in BioRender. Guarnaccia, A. 2026. <https://BioRender.com/4qgnrq2>)

- *Stage 2—Adverse remodeling*
 - Phenotype: progressive left atrial (LA) enlargement, rising E/e' ratio, and diffuse mid-wall late gadolinium enhancement (LGE).
 - Pathophysiology: escalating diastolic stiffness, microvascular ischemia, and expansion of interstitial fibrosis.
 - Typical presentation: new-onset atrial fibrillation or declining exercise capacity.
 - Annual transition from stage 1 to stage 2: 2% [18].

After stage 2, the trajectory *bifurcates* rather than proceeds linearly:

- *Stage 3a—End-stage HFrEF (“dilated burn-out”)*
 - About 85% of end-stage HCM.
 - Left ventricular (LV) dilation, wall thinning, EF $\leq 50\%$, and extensive transmural scar.
 - Drivers: contractile energy exhaustion, wall-stress apoptosis, and secondary functional MR.
 - Predominates in males with MYBPC3/MYH7 truncations and in post-septal reduction therapy [19].
 - Clinical phenotype: classic HFrEF with volume-overload symptoms.
- *Stage 3b—End-stage restrictive-HFpEF.*
 - About 15% of end-stage HCM.
 - Small (< 55 mL), stiff LV with concentric scar yet preserved EF.
 - Mechanism: massive interstitial and replacement fibrosis causing severely elevated filling pressures.
 - Over-represented in females and thin-filament variants; cross-over from rEF to restrictive-HFpEF is rare ($< 2\%$) [19].
 - Clinical picture: “low-output HFpEF” with fatigue, pulmonary hypertension, and cachexia.

Both end-stage phenotypes carry a similar 5-year mortality (25%) but diverge therapeutically: LVAD candidacy is limited in restrictive-HFpEF, whereas transplantation is considered for both [19] (Fig. 5.3).

5.3.4 Mortality Trends in the Contemporary Era

Therapeutic advances, implantable cardioverter-defibrillators (ICDs), refined septal-reduction techniques, and stringent rhythm surveillance have lowered all-cause mortality to 0.5% per year in modern observational series [20]. The pattern of fatal events has also evolved: sudden cardiac death (SCD) still predominates in patients < 45 years, whereas progressive HF death and embolic stroke surpass SCD beyond the seventh decade [21]. A further paradigm-shifting development is the introduction of cardiac-myosin inhibitors (e.g., mavacamten, aficamten). In murine models carrying a pathogenic sarcomeric mutation, mavacamten was found to suppress the development of ventricular hypertrophy, cardiomyocyte disorder, and myocardial fibrosis [22]. Short-term treatment in early phase III trials led to consistent reductions in NT-proBNP levels, as well as relief of LVOT obstruction and symptoms, [23, 24] although long-term prognostic data are still being collected. Collectively, these trends underscore that, despite a more benign survival curve, HCM remains a lifelong condition requiring age-specific strategies for arrhythmic prevention, HF management, anticoagulation, and targeted sarcomeric modulation.

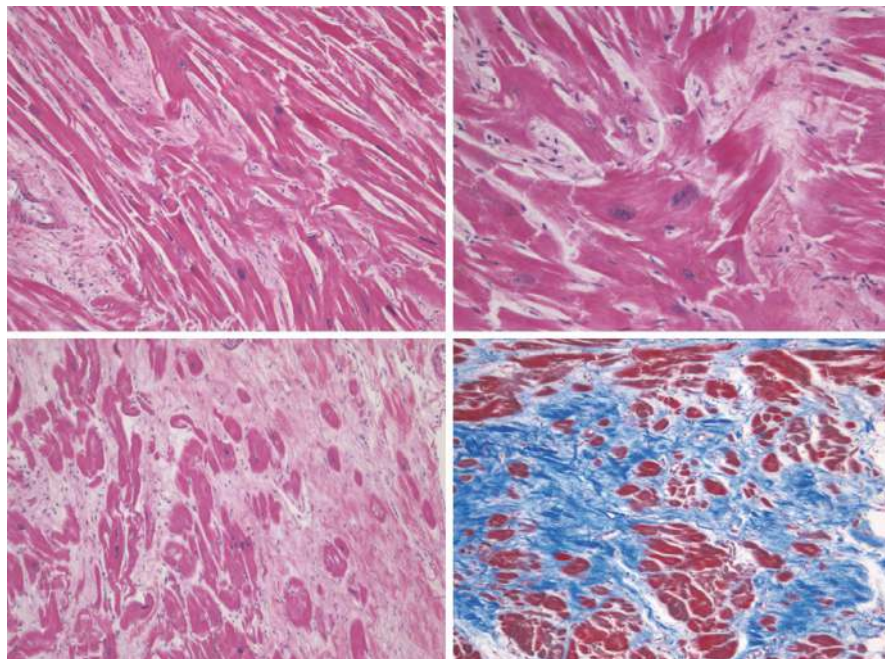


Fig. 5.3 Case of a 24-year-old patient with end-stage hypertrophic cardiomyopathy, who underwent heart transplantation. Hematoxylin–eosin sections show marked cardiomyocyte hypertrophy and extensive architectural disarray of cardiomyocytes, accompanied by replacement fibrosis. Fibrotic changes are further highlighted in the Azan–Mallory stain (lower right panel). (Courtesy of Prof. R. Bussani, Section of Pathological Anatomy, Trieste, Italy)

5.4 Pathophysiological Moments

5.4.1 Dynamic LVOT Obstruction and SAM-Related Mitral Regurgitation

Left ventricular outflow tract obstruction (LVOTO) is present at rest or on provocation in up to 70% of contemporary cohorts [25]. The Venturi and drag forces generated by high-velocity systolic flow pull an elongated anterior mitral leaflet toward a hypertrophied basal septum, producing systolic anterior motion (SAM) and a posteriorly directed eccentric mitral-regurgitant jet (Fig. 5.2) [25, 26]. Histopathological analysis of excised leaflets demonstrates chronic shear-stress injury—expanded spongiosa, attenuated fibrosa, and “curlicue” chordae—suggesting the concept that SAM is both a cause and a consequence of leaflet remodeling [27]. Obstruction imposes a systolic pressure load that augments wall stress, perpetuates hypertrophy, and precipitates subendocardial ischemia. Although obstruction is defined at

≥ 30 mmHg, hemodynamic and outcome data show that a peak gradient ≥ 50 mmHg is the true physiological “*inflection point*”: at this level, outflow impedance doubles systolic wall stress, precipitates clinically relevant SAM-MR and coronary supply–demand mismatch, and correlates with NYHA III–IV symptoms [28]. Surgical or percutaneous reduction from ≥ 50 to < 30 mmHg normalizes forward stroke volume, lowers NT-proBNP, and reduces annual mortality by half, whereas lower baseline gradients confer less consistent benefit [29–32]. For these reasons, the ESC/AHA guidelines set the operating threshold at ≥ 50 mmHg (resting or provoked) [1, 2].

5.4.2 Diastolic Dysfunction and Coronary Microvascular Ischemia

Virtually all HCM patients exhibit impaired relaxation and increased chamber stiffness, reflected by a left-shifted pressure–volume loop [33]. In the apical variant, the “spade-shaped” cavity generates high intraventricular systolic pressures that further elevate diastolic wall stress and accentuate microvascular ischemia, despite the typical absence of LVOTO [34]. In many cases, this lusitropic deficit is exacerbated by coronary microvascular dysfunction (CMD). Advanced imaging data revealed a reduced coronary flow reserve in up to 60% of cases and that correlates with diffuse fibrosis and adverse remodeling [35–37]. CMD intensifies subendocardial ischemia, provoking angina even in the absence of epicardial disease and fostering replacement scar that underpins arrhythmogenic risk. During exercise, chronotropic incompetence ($< 70\%$ predicted HR) further limits cardiac output and independently predicts HF events (HR 2.4) [38]. Collectively, stiff myocardium, ischemic stunning, and inadequate heart rate reserve produce an HFpEF phenotype, unique to HCM.

5.4.3 Arrhythmogenic Substrate and Clinical Surrogates

Patchy mid-wall scar, myocyte disarray, and after-depolarization triggers create a fertile substrate for malignant ventricular arrhythmias [39–41]. In adolescents, LGE $\geq 10\%$ of LV mass was found to be associated with a higher risk of SCD (HR 2.19), thereby improving the performance of pediatric Risk-Kids models [42].

Syncope adds an important clinical layer: a meta-analysis of 57 studies found an unexplained syncope prevalence of 16% and a twofold increase in major arrhythmic events [43]. An expert consensus algorithm recommends distinguishing hemodynamic (LVOTO-mediated) from arrhythmic syncope via sequential Holter, exercise testing, and implantable loop recorders [44].

5.5 Apical Hypertrophic Cardiomyopathy (aHCM)

Anatomically confined apical hypertrophy represents up to 8% of Western HCM phenotypes and up to 25% in Asian cohorts [2]. Regional clustering suggests founder effects and modifier genes rather than sarcomeric variant class alone.

Apical wall thickening remodels the ventricle into a characteristic “*spade shape*”; systolic cavity obliteration creates intraventricular pressure spikes, raising diastolic wall stress, and potentiating microvascular ischemia even in the absence of LVOTO [45]. The confined hypertrophy also shortens longitudinal fibers, accentuating lusitropic delay, and HFPeF physiology.

Resting ECG frequently shows giant negative T-wave inversion ≥ 10 mm in anterolateral leads often preceding sonographic hypertrophy [46]. Chest discomfort mimicking coronary disease is common; true epicardial CAD, however, is no more prevalent than in age-matched controls.

Cardiac MRI accurately quantifies apical wall thickness obscured by near-field echo dropout and detects fibrotic or dyskinetic apical aneurysm in 2–4% of cases, a lesion linked to thrombus formation and monomorphic VT [34]. Routine CMR surveillance every 3–5 years is recommended once apical pouching or late gadolinium enhancement becomes evident [1, 2].

Overall prognosis is generally favorable in aHCM, though outcomes may diverge from classic HCM in the presence of apical aneurysm or extensive scarring [47]. Heart failure admissions are driven by diastolic load rather than LVOTO, and SCD risk remains low unless an aneurysm or extensive scar is present. Anticoagulation is advised for documented apical thrombus or sustained AF; VT arising from aneurysm scar may require catheter ablation [48]. Emerging myosin inhibitors have not yet been systematically studied in aHCM but hold theoretical promise for reverse apical remodeling.

5.6 Diagnostic Workup in Hypertrophic Cardiomyopathy

5.6.1 Electrocardiogram

Standard 12-lead electrocardiogram (ECG) is a fundamental component in the diagnosis of hypertrophic cardiomyopathy (HCM), with abnormalities detected in 94–96% of adult patients and 97% of pediatric patients [49, 50]. An abnormal ECG may also serve as an early marker of HCM in genotype-positive family members, even before structural changes become apparent [51]. P-wave prolongation is commonly observed in advanced stages of the disease and is often associated with atrial fibrillation, particularly in the presence of left atrial enlargement [52]. Atrioventricular (AV) conduction is typically normal in HCM patients; the presence of ventricular pre-excitation or

second- or third-degree AV block should prompt further investigation to exclude phenocopies [53]. Intraventricular conduction delays and QRS fragmentation are frequent findings in advanced disease. Right bundle branch block is commonly seen after septal reduction therapy with alcohol ablation, while left bundle branch block is typically associated with surgical septal myectomy. Pathological Q-waves are present in up to 53% of patients, particularly in the inferior or lateral leads, though they may disappear or evolve with disease progression or aging. Q-waves accompanied by an upright T-wave in the same lead are considered relatively specific for HCM. High QRS voltage is a typical feature, especially when accompanied by other ECG abnormalities [54, 55]. Extremely high QRS voltages should raise suspicion for storage diseases mimicking HCM. Conversely, a mismatch between left ventricular hypertrophy (LVH) confirmed by imaging and low-voltage QRS complexes is more suggestive of infiltrative cardiomyopathy, although it may also be seen in end-stage HCM with extensive myocardial fibrosis [56]. QRS fragmentation, indicating intraventricular conduction delay, may reflect underlying myocardial fibrosis and disease severity [57]. Repolarization abnormalities are common and include ST-segment depression and T-wave inversion. Giant T-wave inversions are particularly suggestive of apical HCM, while tall positive T-waves are more often associated with basal LVH. QTc prolongation is uncommon in HCM but has been linked to appropriate implantable cardioverter-defibrillator (ICD) interventions in affected patients [58].

5.6.2 Echocardiography

Transthoracic echocardiography (TTE) is the first imaging tool used in patients with suspected HCM. The main feature is LVH, although this finding is not exclusive to HCM. LVH should be measured in short-axis views, perpendicular to both the endocardial and epicardial borders. The most typical pattern is asymmetric hypertrophy of the basal septum, where the septal wall is more than 1.3–1.5 times thicker than the posterior wall. Other patterns include sigmoid septum, reverse curvature, concentric, mid-wall, and apical hypertrophy. The shape of the interventricular septum can provide clues about the likelihood of a genetic mutation: a reverse septal contour is more often linked to a positive genetic test, while a sigmoid shape suggests a lower probability [59]. Patients with pathogenic mutations also tend to have thicker walls [10].

Apical HCM refers to hypertrophy that predominantly involves the left ventricular apex, with an apical wall thickness of at least 15 mm (13 mm in first-degree relatives) and an apical/posterior wall thickness ratio ≥ 1.5 [60]. It can be further classified into “pure” (isolated apical involvement), “mixed” (apical and septal), or “relative” (with suggestive ECG changes but apex thickness < 15 mm) [46]. A recent study supports using body-size-indexed apical thickness to identify borderline cases [61].

Massive LVH, defined as wall thickness over 30 mm, is a recognized risk factor for sudden cardiac death (SCD) [40, 41, 62]. Right ventricular (RV) hypertrophy, defined as wall thickness ≥ 5 mm, should also be evaluated, as it is associated with more severe symptoms of heart failure (HF) [63].

Mitral valve abnormalities are common in HCM, affecting over half of the patients. Typical findings include leaflet elongation, prolapse, dysplasia, chordal laxity, and hypermobility [64, 65]. The length of the anterior leaflet plays a key role in the development of left ventricular outflow tract obstruction (LVOTO) [64]. TTE is also the best way to assess mitral regurgitation (MR), usually caused by systolic anterior motion (SAM) of the mitral valve, which usually results in an eccentric, posteriorly directed jet. When 2D imaging is insufficient, 3D TTE or transesophageal echo (TOE) can be helpful.

SAM of the mitral valve is common but nonspecific, as it can be found also in patients with hypovolemia, inotropic drug use, small ventricles, and after mitral valve surgical repair. The presence of SAM is better documented with M-mode, which can categorize its severity [66].

TTE is also essential for identifying and quantifying LVOTO. Pulsed-wave Doppler is used to localize the obstruction, while continuous-wave Doppler measures its severity. A “dagger-shaped,” late-peaking velocity curve is characteristic of dynamic obstruction. A resting gradient of 30 mmHg or more is associated with worse prognosis [31]. It is important to repeat assessment after maneuvers like standing, Valsalva, or light exercise, as some patients develop obstruction only under stress. In the presence of significant MR, LVOT gradient can be estimated using the systolic blood pressure and the MR velocity [67]. In cases of midventricular hypertrophy or abnormal papillary muscle insertion, midventricular obstruction may occur, often resulting in an “hourglass” shaped ventricle. Midventricular obstruction can be associated with apical aneurysm, which is linked to a worse prognosis [34, 68].

Left ventricular ejection fraction (LVEF) is typically normal or even hyperdynamic in HCM [69]. However, when LVEF falls below 50%, outcomes are significantly worse [70]. Tissue Doppler imaging can detect early systolic dysfunction, particularly when lateral mitral annular velocity is <4 cm/s [71–73]. Similarly, reduced global longitudinal strain (GLS) correlates with lower exercise capacity and higher burden of myocardial fibrosis on cardiac magnetic resonance (CMR) [74].

In HCM, diastolic dysfunction is common. A septal E' velocity is often reduced, even in segments without overt hypertrophy, and has been linked to arrhythmias and adverse events in children [73]. Enlargement of the left atrium (LA) and an indexed LA volume ≥ 34 mL/m² are associated with HF, atrial fibrillation, and SCD [73, 75, 76]. Reduced LA strain during the reservoir phase is another typical feature [77]. A difference of ≥ 30 ms between the atrial reversal wave (Ar) in pulmonary venous flow and the A-wave of transmitral flow also indicates elevated filling pressures. To assess elevated left ventricular filling pressure in HCM, current guidelines recommend a multiparametric approach based on four criteria: $E/e' \geq 10$, $Ar-A \geq 30$ ms, $LAVI \geq 34$ mL/m², and estimated systolic pulmonary artery pressure >35 mmHg [78].

5.6.3 Stress Echocardiography

In symptomatic patients without relevant LVOTO (<50 mmHg) at rest or after bedside maneuvers, stress echocardiography is recommended to detect

exercise-induced obstruction [1]. It is best performed with physical exertion, especially during early recovery when preload decreases [79]. Dobutamine stress is not recommended in HCM, while in those unable to exercise, nitrate spray may help unmask latent obstruction [80]. Provoked gradients of 90 mmHg or more are associated with poor prognosis [81]. Notably, obstruction that appears early during exercise is linked to greater functional limitation [82].

Exercise echo also helps assess exercise tolerance, therapy response, MR severity, blood pressure behavior, myocardial ischemia, and arrhythmias [83]. In addition, reduced coronary flow reserve (CFR <2), measured in the left anterior descending artery using Doppler after dipyridamole infusion, indicates microvascular dysfunction and is a strong predictor of adverse events [84].

5.6.4 Cardiac Magnetic Resonance (CMR)

CMR is highly recommended in the initial work-up of HCM [1, 2]. It offers detailed measurements of wall thickness and can detect apical LVH that echocardiography may miss [85]. In the presence of focal LVH, left ventricular (LV) mass is usually not increased [86]. CMR is also superior in assessing mitral valve anatomy, papillary muscle abnormalities (such as apical displacement or direct insertion), and apical aneurysms. Filomena et al. report a high prevalence of apical PM displacement in apical and mixed HCM rather than septal HCM and in healthy controls, while the presence of basal–apical muscle bands is more frequent in the septal and mixed hypertrophy groups. The authors suggest that apical PM displacement may precede apical LVH development [87].

Late gadolinium enhancement (LGE) allows for precise tissue characterization. Fibrosis is found in 50–75% of HCM patients, typically with a mid-wall, patchy pattern in the hypertrophied segments [39, 88–90]. In apical HCM, LGE tends to be subendocardial and localized at the apex, likely due to myocardial ischemia [91, 92]. LGE is associated with a strong and independent adverse outcome in HCM patients [89, 90, 93, 94]. In particular, the extent of LGE is a powerful predictor of adverse outcomes, and a threshold of 15% LGE of the LV mass using the 6-SD technique is the most used in clinical practice [39, 88].

T1 and T2 mapping provide additional diagnostic insights and could help differentiate between HCM and other conditions of LVH such as athletic remodeling, hypertension, inflammation, and infiltration [95, 96]. Elevated native T1 and extracellular volume (ECV) in non-LGE regions are linked to higher risk of HF [97]. Increased T2 values may reflect myocardial injury and are associated with SCD [98].

Importantly, CMR is useful even in genotype-positive/phenotype-negative individuals, as it can reveal subtle hypertrophy, myocardial crypts, papillary muscle

abnormalities, left ventricular myocardial strain abnormalities, and early fibrosis [13, 99–101].

5.6.5 Other Imaging Modalities

Cardiac computed tomography plays a limited role but can be helpful in patients with poor echo windows or contraindications to CMR. It offers high-resolution measurements of wall thickness, function, and coronary anatomy, including detection of myocardial bridges [102].

Single-photon emission computed tomography (SPECT) often shows fixed or reversible perfusion defects even without coronary artery disease and is linked to a worse prognosis [35]. Positron emission tomography imaging has demonstrated that reduced blood flow during pharmacologic stress, in the absence of epicardial CAD, is also a predictor of adverse outcomes in HCM patients [36, 37] (Figs. 5.4 and 5.5).

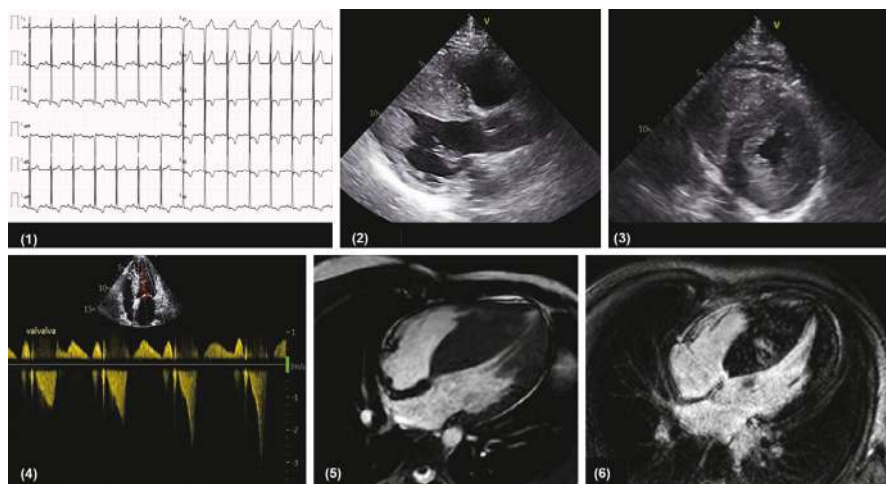


Fig. 5.4 Case of a 36-year-old male patient with obstructive hypertrophic cardiomyopathy and pathogenic mutation in the MYH7 gene. (1) Electrocardiogram shows increased QRS voltages with mild ST segment depression and T-wave inversion in the left-sided leads; (2, 3) transthoracic echocardiography shows severe left ventricular hypertrophy with a reversed curved of the interventricular septum; (4) on continuous-wave Doppler, evidence of significant midventricular obstruction during Valsalva maneuver with the classic dagger-shaped; (5) cardiac magnetic resonance steady-state free precession cine images confirm severe left ventricular hypertrophy with mid-wall late enhancement in the septum on post-gadolinium T1-weighted images (6)

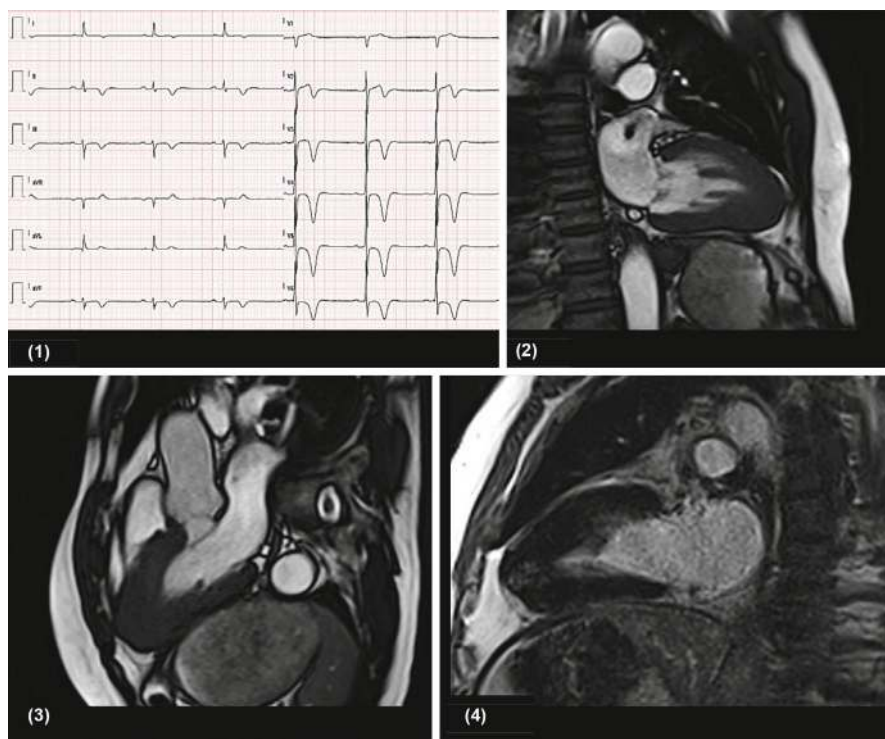


Fig. 5.5 Case of a 65-year-old female patient with apical hypertrophic cardiomyopathy and negative genetic test. (1) Electrocardiogram shows increased QRS voltages with diffuse T-wave inversion and giant T-wave inversion in V_3 - V_5 ; (2, 3) cardiac magnetic resonance steady-state free precession cine images show severe apical hypertrophy with loss of the normal basal-to-apical myocardial wall thickness tapering; and (4) subtle late enhancement in the apical segments on post-gadolinium T1-weighted images

5.7 General Principles of HCM Therapy

Clinical management of HCM involves a personalized approach based on accurate characterization of the disease. The pathophysiological mechanisms of HCM can result not uncommonly in complex clinical scenarios that require referral to highly specialized centers. Therapeutic strategies can schematically be divided into four domains: prevention of sudden cardiac death (SCD), treatment of left ventricular outflow tract obstruction (LVOTO), management of heart failure (HF), and treatment of atrial fibrillation (AF) (Fig. 5.6).

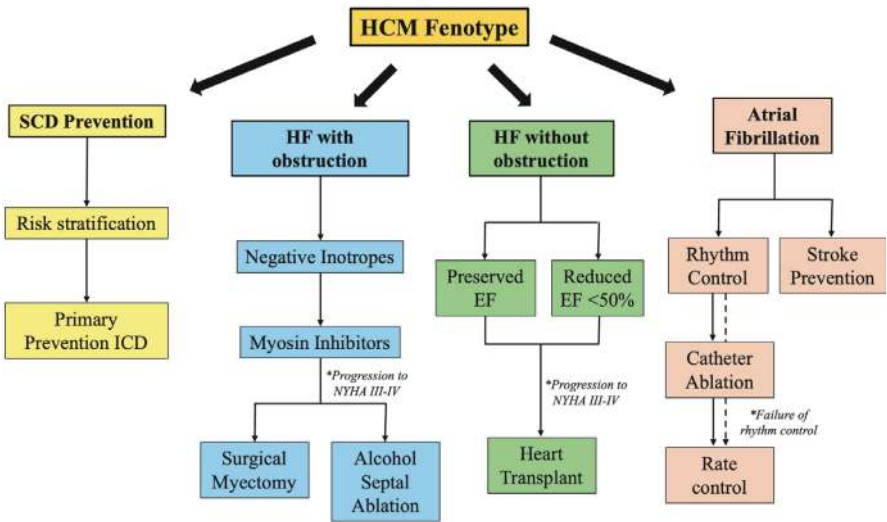


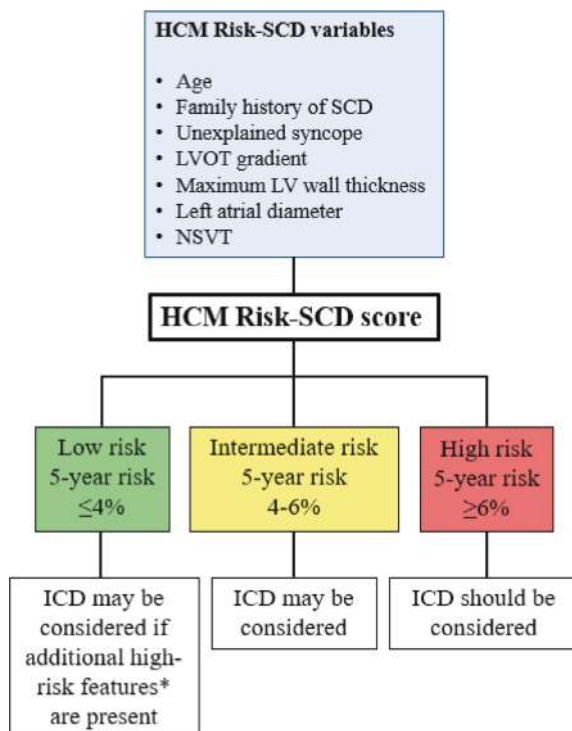
Fig. 5.6 Personalized profiles dictating effective management strategies. HCM hypertrophic cardiomyopathy, HF heart failure, SCD sudden cardiac death, ICD implantable cardioverter defibrillator, EF ejection fraction, NYHA New York Heart Association. (Adapted from Maron et al. “Management of Hypertrophic Cardiomyopathy: JACC State-of-the-Art Review” J Am Coll Cardiol. 2022 Feb).

5.7.1 Prevention of Sudden Cardiac Death (SCD)

The decision to implant an ICD in primary prevention in patients with HCM is often challenging for the clinician. HCM is a relatively common disease that primarily affects young adults, but only a small proportion is at risk of life-threatening arrhythmic events [103, 104]. Moreover, the clinical indication for ICD implantation often falls into a gray area. On the other hand, potential iatrogenic risks (e.g., inappropriate shocks, infections) combined with the psychological and physical burden of living with the ICD should not be overlooked. The latest international guidelines in this regard emphasize the importance of shared decision-making, in which the patient takes an active part in the decision process [1, 2].

Arrhythmic risk stratification is a key step in the management of all patients with HCM. International guidelines, however, have chosen different approaches. European guidelines recommend the use of a score to identify possible candidates for ICD implantation. The HCM Risk-SCD estimates the likelihood of SCD at 5 years through a formula using 7 readily available clinical-instrumental features (Fig. 5.7) [1, 105]. A version designed specifically for the pediatric population is

Fig. 5.7 ESC 2023 flow chart for implantation of ICD for primary prevention. SCD sudden cardiac death, LVOT left ventricular outflow tract, LV left ventricle, NSVT nonsustained ventricular tachycardia. *Clinical risk factors: extensive LGE (>15%) on CMR; LVEF <50%. (Adapted from Arbelo et al. “2023 ESC Guidelines for the management of cardiomyopathies” Eur Heart J. 2023 Oct)



available [106]. Although some known risk factors for SCD, such as systolic dysfunction and an extensive LGE on MRI, are not included in this score, they are taken into account in low-risk scenarios [1].

In contrast, North American guidelines recommend considering ICD in primary prevention even in the presence of only one risk factor for SCD and the HCM Risk-SCD is used only to aid shared decision-making [2]. It is worth emphasizing that according to both the published guidelines, the decision to implant an ICD should not be based on a numerical threshold, but rather on an overall assessment that takes into account the patient's status, life expectancy, and the patient's degree of tolerance to living with an ICD [1, 2].

5.7.2 Management of Left Ventricular Obstruction

Up to 70% of HCM patients present with left ventricular outflow tract obstruction (LVOTO) at rest or during exertion [25]. In patients with LVOTO, the main therapeutic goal is palliation of symptoms and improvement of functional capacity [7]. Some general measures are recommended to reduce abrupt increases in LVOTO such as avoiding dehydration, excessive alcohol consumption, and the use of

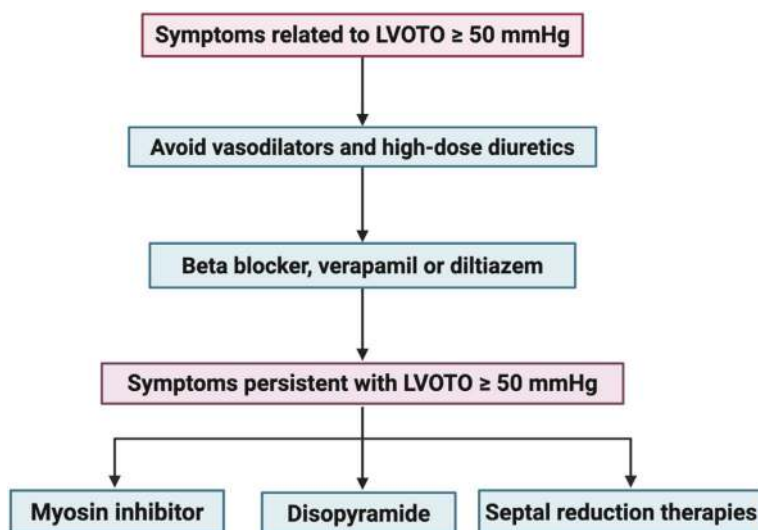


Fig. 5.8 Stepwise management algorithm for symptomatic obstructive hypertrophic cardiomyopathy. LVOTO left ventricular outflow tract obstruction (resting or provoked); oHCM obstructive hypertrophic cardiomyopathy. (Created in BioRender. Guarnaccia, A. 2026. <https://BioRender.com/28xunok>)

vasodilator drugs such as nitrates and phosphodiesterase 5 inhibitors [107]. The drugs classically used to reduce LVOT are negative inotropes (beta blockers, nondihydropyridine calcium antagonists, and disopyramide). Although there is no clear evidence to suggest a slowing of disease progression or a reduction in the incidence of SCD with the use of these drugs, the deleterious effect of a markedly elevated LVOT gradient even in paucisymptomatic patients is known [32, 108]. The overall management strategy for symptomatic obstructive hypertrophic cardiomyopathy is schematically illustrated in Fig. 5.8 [2].

Nonvasodilator beta-blocker (BB) drugs titrated to the maximum tolerated dose are usually the first-line option [109]. The main problem with this class of drugs is the reduction in chronotropic reserve, which may result in a limitation of functional capacity [110, 111]. In patients intolerant to beta-blockers, nondihydropyridine calcium channel blockers (CCB) such as verapamil and diltiazem can be used [1, 2]. Finally, in patients who are symptomatic and have refractory LVOTO despite BB or CCB, disopyramide, a class 1A antiarrhythmic with pronounced negative inotropic effect, may be employed [112, 113]. However, the use of this drug is limited by anticholinergic adverse effects (mucosal dryness, constipation, and urinary retention) and lengthening of the QT interval [113]. Finally, in patients symptomatic for dyspnea, loop diuretics can be used as well, provided they are used at low doses to avoid dehydration.

Cardiac myosin inhibitors, a new class of drugs, represent a major therapeutic breakthrough in the management of obstructive HCM. These drugs act by modulating cardiac myosin activity, thereby reducing actin–myosin interaction, myocardial

contractility, and improving energetics [114, 115]. The most pronounced effect was observed in reducing LVOTO. Mavacamten has been the first myosin inhibitor to be approved for clinical use. In the phase 3 EXPLORER-HCM trial, mavacamten demonstrated significant improvements in NYHA class, peak oxygen consumption (pVO₂), and quality of life (KCCQ) and a marked reduction in LVOTO gradient and natriuretic peptides in patients with obstructive HCM and refractory symptoms who had received optimized standard therapy [24]. These results were maintained over time, and the drug was well tolerated [116]. Mavacamten has also been tested in patients who were eligible for septal reduction therapy (SRT), demonstrating its capacity to reduce this eligibility in up to 82% of patients after 16 weeks [23]. Once again, the results remained stable during the continuation of the study [117]. A second myosin inhibitor, aficamten, has completed a phase 3 trial and is under review by regulatory agencies for approval [118]. Compared with mavacamten, aficamten has a favorable pharmacokinetic and pharmacodynamic profile (e.g., shorter steady-state time and less interaction with hepatic cytochromes), which may confer better safety and tolerance [119].

A relatively small percentage of patients (5–9%) undergoing therapy may experience transient systolic dysfunction [116, 120]. Therefore, echocardiographic monitoring is recommended throughout the course of treatment, particularly during drug titration [26]. According to the latest guidelines, myosin inhibitors are recommended as second-line therapy in patients with refractory LVOTO despite optimized standard therapy to improve symptoms and functional capacity [1, 2].

For patients with LVOTO (≥ 50 mmHg) and severely symptomatic (e.g., NYHA class III or IV, or recurrent syncope), despite optimal medical therapy, invasive options (SRT) should be considered [1, 2]. The timing of referral to SRT is a relevant issue as both advanced age and delayed intervention are independent predictors of heart failure and mortality. This underscores the importance of early referral to SRT where appropriate [121–123]. Septal myectomy is the most performed procedure and consists of a wedge-shaped incision of the interventricular septum to enlarge the left ventricular outflow tract [124]. The procedure is successful in abolishing the obstruction in 90% of cases, but it requires expertise to minimize complications (e.g., advanced AV block, ventricular septal defect, aortic regurgitation) and therefore is usually performed in a limited number of centers [123, 125]. As an alternative to surgery, septal alcohol ablation may be considered in adult patients without major mitral abnormalities [1, 2]. This percutaneous procedure involves the selective injection of alcohol into the septal coronary branches to induce localized scarring and reduce septal hypertrophy [126]. There are no randomized trials that have compared the two SRT approaches; however, observational data have shown similar procedural and safety outcomes [127, 128]. The choice of technique depends on the patient's anatomical features, clinical status, and the experience of the center [1, 2]. Recent real-world data has documented survival rates of 88% over 7 years, and 83% freedom from heart failure (HF) and ventricular arrhythmias over 10 years [123].

Given the higher need for reintervention (8%) and definitive PM implantation post-procedure (10%), septal ablation therapy would be preferable for older patients at high surgical risk [129]. An important consideration in alcohol septal reduction therapy is the theoretical arrhythmic risk induced by iatrogenic scarring. While intramyocardial scar formation may create a potentially arrhythmogenic substrate, available data are somewhat conflicting. Most cohort studies report no significant differences in overall mortality compared with surgical septal myectomy, although some studies suggest a higher incidence of ventricular arrhythmias or major arrhythmic events, particularly in patients with increased septal thickness or residual gradient [128, 130, 131].

Finally, some patients develop unfavorable disease progression to advanced heart failure in the long term after SRT, even in the absence of obstruction [123]. This suggests that the underlying cardiomyopathy may progress despite hemodynamic improvement after SRT.

5.7.3 Other Clinical Scenarios

The management of heart failure in nonobstructive hypertrophic cardiomyopathy (HCM) with preserved ejection fraction (HFpEF) relies on the use of beta-blockers or nondihydropyridine calcium channel blockers to slow the heart rate and improve diastolic filling [132]. Diuretics are used to alleviate congestive symptoms. Although there are no randomized clinical trials on the use of SGLT2 inhibitors in HCM, observational data have shown favorable results regarding mortality and hospitalizations [133].

Patients with microvascular angina may benefit from beta-blockers and calcium channel blockers. In the absence of LVOTO, ranolazine and nitrates may also be considered [1, 2].

However, in restrictive forms without overt ventricular dysfunction, reliance on NYHA class alone may be misleading. Objective assessment using cardiopulmonary exercise testing and right heart catheterization to evaluate pulmonary pressures and vascular resistance should be considered earlier than in other cardiomyopathies to avoid delaying referral for transplantation. Additionally, small ventricular chambers may complicate LVAD function, further challenging clinical management [134, 135].

5.7.4 Atrial Fibrillation

Atrial fibrillation (AF) is the most frequent arrhythmia in patients with HCM with an estimated prevalence of 22% and incidence of 2%/year [136]. AF in patients with HCM is associated with impaired quality of life, excess heart failure mortality, and embolic stroke [136, 137]. Subclinical AF has been detected in 25% of patients with implanted devices [138]. For these reasons, it is crucial

to frame patients at risk of developing AF early and subject them to closer rhythm monitoring so as not to delay stroke protection [139]. All patients after a first episode of AF should be initiated to anticoagulation, as the CHA2DS2-VASc score has limited reliability in HCM [1, 2, 140]. While asymptomatic or mildly symptomatic patients may tolerate rate control, rhythm control should generally be considered first-line in HCM due to the deleterious effects of atrial fibrillation. This includes early initiation of antiarrhythmic drugs (amiodarone, disopyramide, sotalol) and timely transcatheter ablation [1, 2]. Early ablation appears to reduce recurrence of paroxysmal AF and slow progression to permanent AF compared with medical therapy alone [140]. Rate control should be reserved for patients in whom rhythm control is not feasible or has failed.

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Nondilated Left Ventricular Cardiomyopathy

6

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6.1 Introduction and Definition

Nondilated left ventricular cardiomyopathy (NDLVC) is a novel category first introduced by the 2023 ESC Guidelines for the management of cardiomyopathies [1]. It is defined by the presence of nonischemic left ventricular (LV) scarring or fatty replacement (assessed by cardiac magnetic resonance) in the absence of LV dilatation, with or without global or regional wall motion abnormalities, or isolated global LV hypokinesia without scarring that is unexplained solely by abnormal loading conditions (such as hypertension or valve disease) or significant coronary artery disease.

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This novel classification incorporates those previously named as arrhythmogenic LV cardiomyopathy (ALVC) [2], hypokinetic nondilated cardiomyopathy (HNDC) [3], arrhythmogenic cardiomyopathy (ACM) [4], as well as all kinds of primary unexplained sole myocardial scars (Table 6.1). This broad umbrella category was established to encompass all forms of primary myocardial disease that fail to meet the diagnostic criteria of any previously defined specific cardiomyopathies (CMPs).

NDLVC etiology is heterogeneous, complex, and not fully elucidated (Table 6.2). NDLVC represents a *working diagnosis*, and a patient-centered approach should be pursued in order to distinguish different subphenotypes and intercept future

Table 6.1 Comparison between HNDC, ALVC, ACM, and NDLVC definitions

	HNDC (hypokinetic nondilated cardiomyopathy)	ALVC (arrhythmogenic left ventricular cardiomyopathy)	ACM (arrhythmogenic cardiomyopathy)	NDLVC (nondilated left ventricular cardiomyopathy)
References	2016 Position statement, ESC working group on myocardial and pericardial diseases [3]	2023 Consensus report, European Task Force [7]	2019 HRS expert consensus statement [4]	2023 ESC Guidelines, Task Force on the management of cardiomyopathies [1]
<i>Exclusion of LV dilation mandatory for the diagnosis?</i>	Yes	No	No	Yes
<i>LV dysfunction mandatory for the diagnosis?</i>	Yes, LVEF <45% required	No	No	No
Scoring system with major and minor criteria?	No	Yes, divided into six categories: - Morphofunctional ventricular abnormalities - Structural alterations - Repolarization abnormalities - Depolarization and conduction abnormalities Arrhythmias Family history/genetics	No, but it encompasses a broad spectrum of diseases including ALVC ^a	No

(continued)

Table 6.1 (continued)

	HNDC (hypokinetic nondilated cardiomyopathy)	ALVC (arrhythmogenic left ventricular cardiomyopathy)	ACM (arrhythmogenic cardiomyopathy)	NDLVC (nondilated left ventricular cardiomyopathy)
Diagnosis is reached when	LVEF <45% without LV dilation	2 major, 1 major + 2 minor or 4 minor criteria from different categories are present	“An arrhythmogenic heart muscle disorder not explained by ischemic, hypertensive, or valvular heart disease.” Clinical presentation with documented and/ or symptomatic arrhythmia is a distinguishing feature	<i>CMR detected LV scar or fatty replacement and/or LVEF <50% Without LV dilation</i>
Nondefinite diagnosis possible?	No	Yes, borderline and possible ALVC diagnosis can be formulated	Yes ^a	No

ACM arrhythmogenic cardiomyopathy, ALVC arrhythmogenic left ventricular cardiomyopathy, CMR cardiac magnetic resonance, HNDC hypokinetic nondilated cardiomyopathy, LV left ventricle, LVEF left ventricular ejection fraction, NDLVC nondilated left ventricular cardiomyopathy

^aAt least one criterion from the structural category is needed (LGE at CMR)

Table 6.2 List of NDLVC etiologies [8]

NDLVC etiologies	Frequency (%)
Genetic (e.g., <i>DSP</i> , <i>FLNC</i> , <i>PLN</i> , <i>LMNA</i> , <i>DES</i>)	38%
Inflammatory-related scar (post-myocarditis, sarcoidosis, autoimmune)	12%
Neuromuscular disease (e.g., muscular dystrophies, limb-girdle muscular dystrophies, myotonic dystrophies)	10%
Idiopathic	40%

individual disease trajectories. Specific underlying etiologies (such as sarcoidosis or autoimmune disorders) should be investigated, especially if targeted treatments are available. Disease assessment should be dynamic and multiparametric, as with time each individual may shift from NDLVC to other CMPs groups, in particular LV dilatation may eventually occur and thus disease evolves into overt DCM. Furthermore, the same disease phenotypes may subsequently diverge in terms of clinical behavior, with genetic predisposition playing a key role; examples are the prominent arrhythmic properties exerted by some *LMNA* variants [5] and the

myocarditis-like episodes frequent in *DSP* variant carriers [6]. As in other CMPs, genetic predisposition interplays with environmental factors, but the significance of different genetic variants, the role of inflammation, or other external triggers need further study to have a clearer comprehension of this new entity. It is important to note that all the studies mentioned in this chapter are retrospective and observational, often involving heterogeneous patient cohorts and reporting composite endpoints.

6.2 Epidemiology

Specific evidence regarding NDLVC prevalence is lacking due to its recent introduction, although some data may be extrapolated from NDLVC subtypes previously included in other CMP groups. Prevalence of HNDC was estimated to range between 0.9% and 1.9% in a Chinese cohort [9]. ACM has a much lower prevalence, estimated to range between 1:2000 and 1:5000 [10], although this data is derived from studies focused on the classical arrhythmogenic right ventricular cardiomyopathy (ARVC) form.

NDLVC is more frequent in males (with a male-to-female ratio of 2:1), and the mean age at diagnosis is between 37 and 55 years [8, 11–16]. NDLVC patients are usually younger than those with DCM at presentation [13].

6.3 Diagnosis

As indicated by the NDLVC definition, the assessment of LV dimensions, systolic function, and tissue characterization is fundamental for the diagnosis of this new CMP. Imaging tests and, in particular, cardiac magnetic resonance imaging (CMRI) are the cornerstone of a definite diagnosis, but a multiparametric approach is essential to delineate each patient's characteristics. For a precise characterization of CMP, the evaluation of NDLVC patients includes a comprehensive personal and family history, thorough baseline clinical assessment, Holter ECG monitoring, exercise testing, laboratory exams, and genetic testing. The order and necessity of these investigations should be adapted on a case-by-case basis (Fig. 6.1).

6.3.1 Clinical Presentation

NDLVC can manifest with a broad spectrum of clinical presentations (Fig. 6.1). The most common symptom is palpitations, lamented by up to 64% of NDLVC patients [12]. Heart failure (HF)-related symptoms at presentation are rare, with an advanced (III–IV) NYHA class at diagnosis found in less than 10% of cases [11, 16]. From 10% to 20% of NDLVC patients present with chest pain and bursts of troponin release, which can result in a myocardial scar of variable extension [8, 12]. In this context, a differential diagnosis with acute myocarditis is not always possible, as the

How an outpatient enters the NDLVC diagnostic pathway

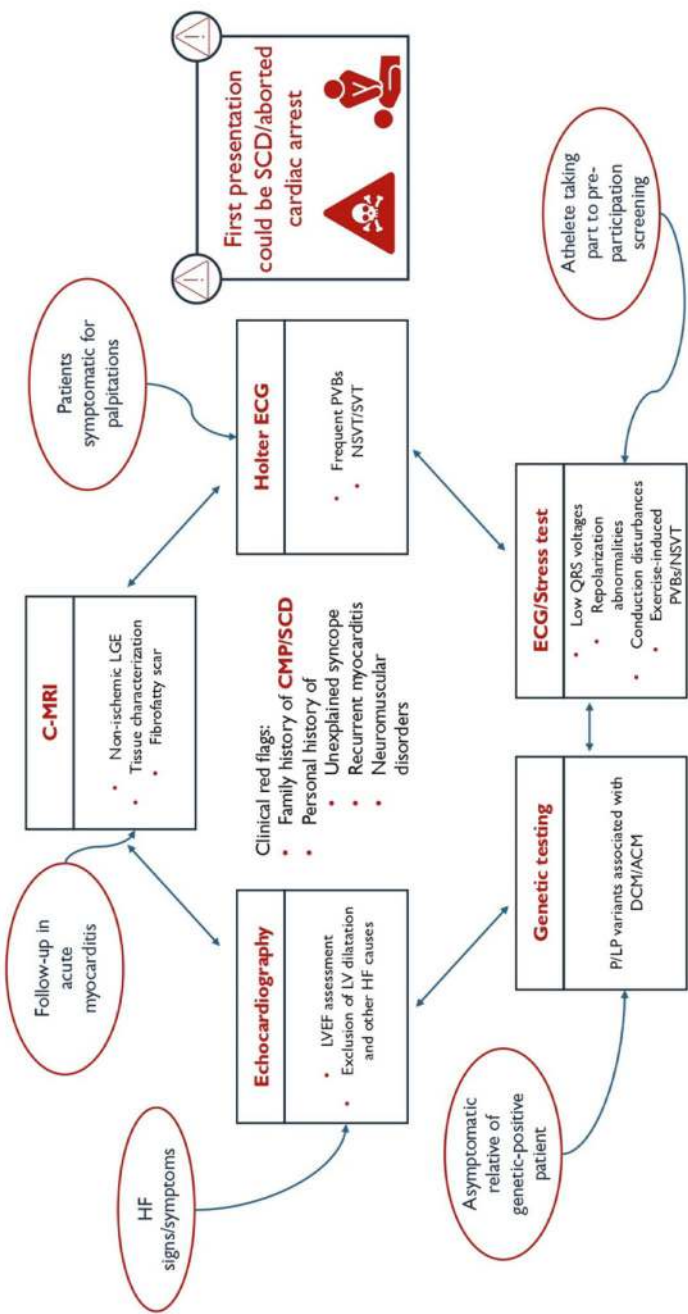


Fig. 6.1 NDLVC clinical presentations and diagnostic pathway. ACM arrhythmic cardiomyopathy, C-MRI cardiac magnetic resonance imaging, CMP cardiomyopathy, DCM dilated cardiomyopathy, HF heart failure, LGE late gadolinium enhancement, LV left ventricle, LVEF left ventricular ejection fraction, NSVT nonsustained ventricular tachycardia, P/LP pathogenic/likely pathogenic, PVBs premature ventricular beats, SCD sudden cardiac death, SVT sustained ventricular tachycardia

two conditions have overlapping features [17–19]. A consistent group of NDLVC patients can be totally asymptomatic and enter the CMPs' diagnostic pathway because of abnormal findings evidenced during pre-participation screening for sport activities, family screening programs, or incidentally.

A family history positive for premature sudden cardiac death (SCD) or CMPs (which is common in NDLVC patients [8, 13, 14, 16]), a personal history of unexplained syncope (which is reported in 6–12% of cases [12, 20]), or neuromuscular disorders [8] should prompt further evaluations and could lead to an NDLVC diagnosis.

It is important to note that NDLVC includes a subgroup of patients with a marked arrhythmic expression, and fatal or aborted SCD due to malignant ventricular arrhythmias (VAs) can be the first presentation of this CMP [12].

6.3.2 ECG

ECG is an easy and available tool that, if carefully evaluated, can provide important information on the underlying disease, and in some cases it can even suggest specific etiology.

Usually sinus rhythm is present, but when atrial arrhythmias are detected an association with *LMNA* variants can be suspected [21]. Conduction disturbances are infrequent and can be related to laminopathies [21], desminopathies [22], as well as to cardiac sarcoidosis [21].

An intraventricular delay and a fragmented QRS morphology can reflect the presence of a fibrotic scar (Fig. 6.2). Low voltages of the QRS complex can be due to extensive fibrosis that causes myocardial mass loss; this pattern is typical of *DSP*, *FLNC*, or *PLN* variants [20, 21] (Fig. 6.2).

It is reported that half of the NDLVC patients present with repolarization abnormalities, typically T-wave inversion in the inferior and/or lateral leads [12, 20, 23] (Fig. 6.3).

A frequent ventricular ectopy could also be detected by standard ECG, and premature ventricular beats (PVB) morphology should be carefully evaluated, as a right-bundle-branch block (RBBB) with a superior axis morphology, for example, might be consistent with an inferior or inferolateral LV wall origin of the arrhythmic focus [4]. It is interesting to note that many of these electrocardiographic characteristics are not exclusive to NDLVC but have been primarily described in other CMPs like DCM and ACM.

6.3.3 Laboratory Testing

Routine laboratory tests need to be assessed, giving relevance to natriuretic peptides, C-reactive protein (CRP), and troponin. Elevated levels of troponin were found in 21% of an NDLVC patient cohort, whereas 39% had high levels of natriuretic peptides and 5% had elevated CRP [12].

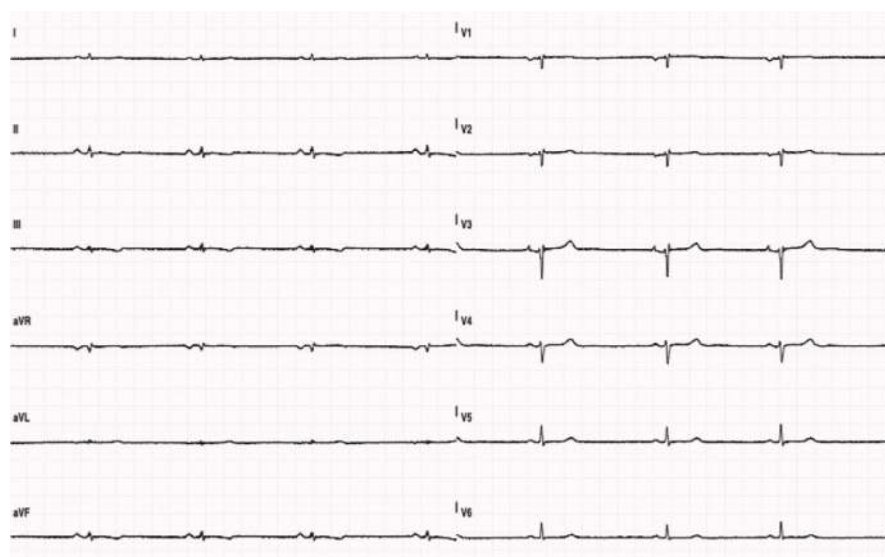


Fig. 6.2 ECG of a 47-year-old patient, carrier of a pathogenic *DSP* variant, presenting with a high arrhythmic burden. ECG shows sinus bradycardia, with a normal atrioventricular conduction, an incomplete right-bundle-branch block, a slow progression of R wave in the precordial leads (suggestive of possible pseudonecrosis), a fragmented QRS in the inferolateral leads, and diffuse low peripheral voltages. Repolarization is mildly altered in the inferior leads. In this patient, the echocardiographic examination was normal, but cardiac magnetic resonance imaging revealed extensive fibrosis, with subepicardial late gadolinium enhancement of the LV free wall and anterior septum

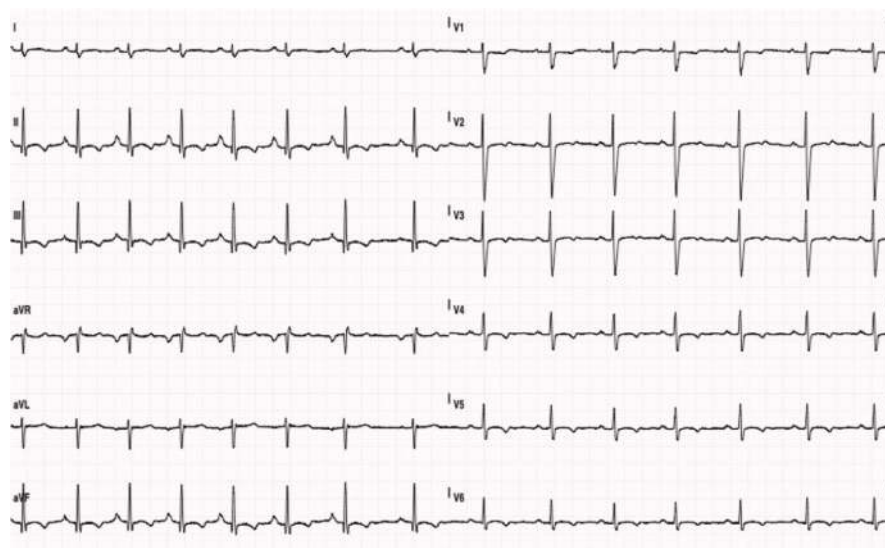


Fig. 6.3 ECG of a 26-year-old woman with a family history positive for arrhythmogenic cardiomyopathy, evaluated in the context of familial screening. ECG shows sinus rhythm with normal atrioventricular and intraventricular conduction, T-wave inversion in the anterior and inferolateral leads. Echocardiography showed mild left ventricular dysfunction. Cardiac magnetic resonance demonstrated extensive subepicardial LGE with a ring-like pattern

Interestingly, CRP was found to have a more significant impact on prognosis in mildly dilated cardiomyopathies than in DCM, whereas the opposite was described for natriuretic peptide levels [24].

Elevated CK levels can be related to neuromuscular disorders such as dystrophinopathies, laminopathies, or desminopathies [25, 26].

6.3.4 Echocardiography

Echocardiography is the first-line assessment that allows a phenotypic classification: it excludes other CMPs and different conditions that can explain a patient's symptoms, such as valvular heart disease.

Compared to DCM, NDLVC patients generally show lower LV dimensions and volumes (as required by NDLVC definition) but also usually a better LVEF [13, 27].

6.3.5 Holter ECG

Holter ECG is a useful tool to assess the burden of VAs, which have prognostic relevance. Nonsustained ventricular tachycardia (NSVTs) are detected in a consistent group of NDLVC patients (16–34%) [14, 16, 20]. Both the number and the morphology of PVBs are clinically relevant; therefore, 12-lead ECG monitoring is recommended whenever feasible [28].

When atrial fibrillation or atrioventricular (AV) blocks are detected, the association with specific genotypes can be suspected (*LMNA*, *DES*) [21, 22].

Holter ECG monitoring in NDLVC patients is recommended at least annually.

6.3.6 Exercise Testing

For a complete characterization of the arrhythmic burden, exercise testing should be incorporated, if feasible. Usually, PVBs are suppressed by exercise, so when VAs are elicited by stress test, there is a consistent risk of an underlying structural heart disease, and in these patients myocardial fibrosis can frequently be found at CMRI [29, 30]. In this context, PVBs with an RBBB morphology and a superior axis or the detection of polymorphic PVBs at exercise testing are stronger predictors of fibrosis at CMRI [29].

6.3.7 Cardiac Magnetic Resonance Imaging

CMRI is essential to diagnose and characterize NDLVC, as it represents the gold standard for volume assessment and allows tissue characterization [31]. The detection of late gadolinium enhancement (LGE), which is related to myocardial fibrosis,

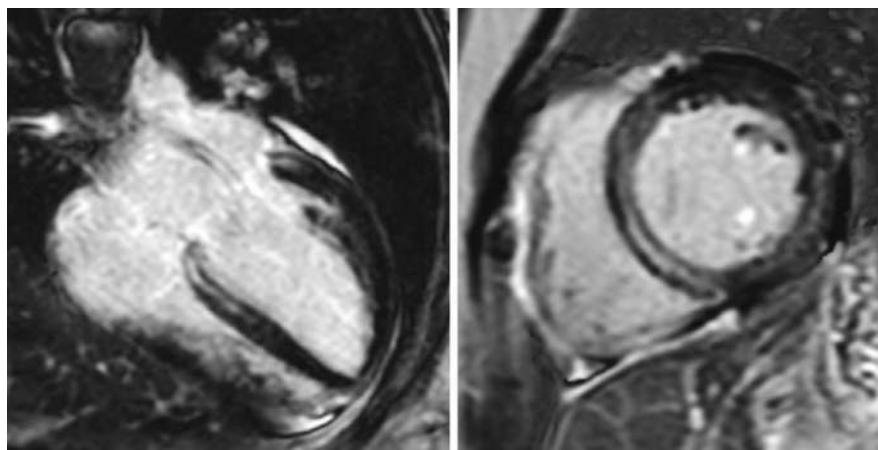


Fig. 6.4 CMRI (four-chamber long-axis and short-axis, LGE sequences) of a 48-year-old carrier of a pathogenic *LMNA* variant, with a family history of DCM and SCD. A septal intramyocardial fibrotic scar is present, as well as subepicardial and intramyocardial fibrosis in the inferolateral segments

is a cornerstone for NDLVC diagnosis, and according to its presence, patients can be divided into two subgroups: those presenting LGE have a fibrotic NDLVC form, and those with no evidence of scar but only LV systolic dysfunction can be referred to as hypokinetic NDLVC [15].

LGE is detected by CMRI in 43–82% of NDLVC patients, and its distribution is consistent with a nonischemic scar, as it usually has an intramyocardial (32–44%) or subepicardial (13–65%) location [12, 14, 15, 32]. LGE septal involvement (Fig. 6.4) tends to be more frequent than LV free wall [12, 14–16], while a ring-like pattern (RLP), defined as LGE presence in at least three contiguous segments in the same short-axis slice (Fig. 6.5), is reported in 9–36% of NDLVC patients [12, 14–16].

The association of some CMRI patterns is related to specific underlying genotypes. *DSP* and *FLNC* variant carriers usually show a subepicardial, inferior/inferolateral LGE distribution or RLP with modest LV systolic impairment, and patients with laminopathies can present with a septal scar, while those with *TTN* variants tend to present with a lower LVEF and a variable, less specific pattern of fibrosis [33].

Compared to DCM, patients affected by NDLVC exhibit a lower burden of myocardial fibrosis and higher LVEF [11, 15, 16, 32], although the evidence is still limited.

Dedicated sequences for edema assessment are not routinely performed in CMRI for CMPs, but Peretto et al. found inflammation evidence at T2-weighted sequences in 36% of NDLVC patients [12]. These findings may justify their broader application in this patient group.

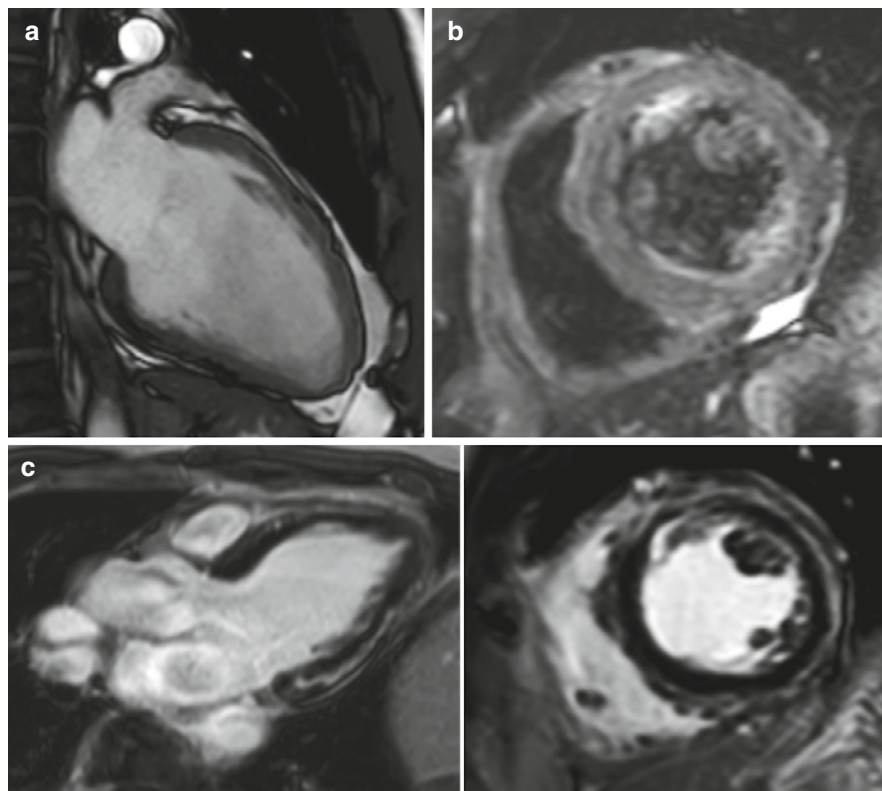


Fig. 6.5 CMRI of a 36-year-old patient, carrier of a pathogenetic *DSP* variant, with a positive family history of arrhythmogenic cardiomyopathy in his mother. A previous perimyocarditic episode that resolved at follow-up examination (absence of edema in T2-weighted sequences, **b**) but exited in mild LV dysfunction with fatty infiltration (which can be noted observing the irregular epicardial profile in cine sequences, **a**) and extensive fibrosis (LGE with a ring-like pattern is present in the post-contrast dedicated sequences, **c**)

6.3.8 Endomyocardial Biopsy

Endomyocardial biopsy (EMB) is an invasive procedure that can be performed in selected symptomatic patients when traditional assessments are inconclusive to reach a definite CMP diagnosis or if other mimicking conditions are suspected [1]. Procedure-related adverse events (including death and other life-threatening complications) have a rate below 1% in experienced centers, but patients' selection still needs to be careful [34]. Risks related to the procedure should be balanced with a clinical impact of the EMB results, which in selected cases can effectively affect the prognostic stratification and treatment decision [34, 35]. Histopathological findings associated with CMPs include hypertrophic, vacuolar and/or atrophic myocytes, interstitial fibrosis, and fibro-fatty myocardial replacement [34] (Fig. 6.6). EMB with immunohistochemical quantification of inflammatory cells represents the gold

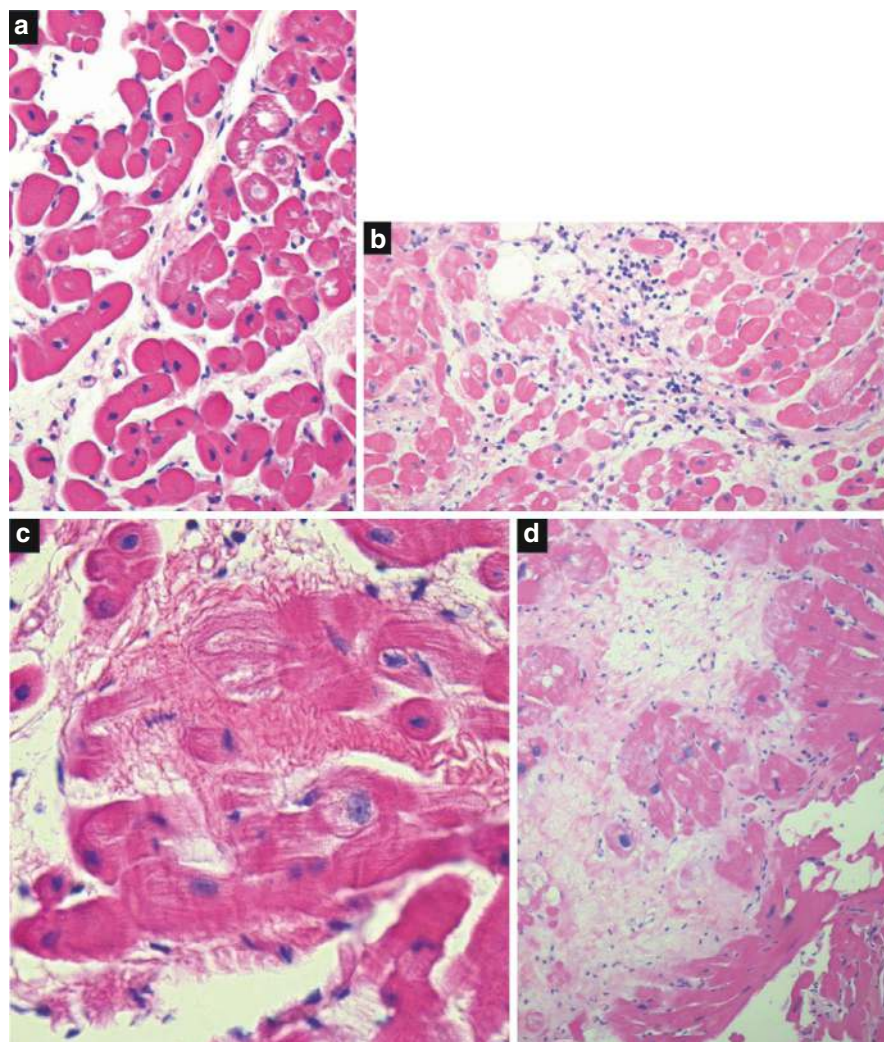


Fig. 6.6 Examples of EMB of NDLVC patients. Anucleated myocytes with rarefaction of the contractile portion. This patient had a history of myocarditis resulting in myocardial scar. **(a)** Areas of fibro-adipose replacement with inflammatory infiltrate. **(b)** Areolas of myocyte fibrotization and amputation of some myocellular profiles. **(c)** Large areas of replacement fibrosis with severely involuted and anucleated myocytes remaining. Small lymphohistiocytic infiltrates coexist. The EMB is suggestive of inflammatory cardiomyopathy **(d)**

standard for myocardial inflammation detection; it can be particularly useful when secondary or specific treatable diseases are suspected, such as myocarditis, autoimmune diseases, or sarcoidosis [19, 36, 37]. An electro-anatomical-guided approach should be considered, as it could help in identifying the areas where to perform the biopsy, increasing the accuracy [20].

6.3.9 Genetic Testing

Current guidelines recommend genetic testing in all NDLVC patients, as it helps refine the diagnosis, has prognostic and therapeutic implications for the index case, but also allows cascade family screening [1]. A consistent (23–52%) group of NDLVC patients demonstrated a pathogenic or likely pathogenic (P/LP) variant in CMPs-associated genes, with an overlap between DCM and ARVC genotypes [8, 12, 14, 16, 20]. The most common form of transmission is autosomal dominant. It is known that carriers of P/LP variants in *LMNA*, *FLNC*, *TMEM43*, *PLN*, *DSP*, *RBM20* present a higher risk of malignant VAs [1, 38]. Considered as a whole group, those high-risk genes are found in 9–40% of NDLVC patients, demonstrating a higher prevalence than in DCM [12, 14, 16]. Taken singularly, in NDLVC *DSP*, *TTN*, *LMNA*, *FLNC*, are the most frequently involved genotypes [8, 12, 14, 16].

Precision medicine is focusing on depicting the exact characteristics associated to each specific CMP-involved gene, and it contributes significantly to prognosis stratification and clinical management, in some cases even affecting the decision of implantable cardioverter defibrillator (ICD) insertion [39]. A genotype-centered approach brought even some authors to the definition of distinct disease entities based on the genetic status. An example is the *DSP* cardiomyopathy, which affects predominantly females and that is characterized by episodic myocardial injury, LV fibrosis preceding systolic dysfunction, and a high incidence of VAs [40].

Truncating variants (*tv*) of the *TTN* gene are the cause of the most common form of hereditary DCM (see the DCM chapter), characterized by a favorable response to medical therapy and malignant arrhythmias usually related to a severe impairment of LV function [41]. The early stages of *TTN**tv*-CMP—most often identified through family screening—may present as NDLVC, as observed also in other genetically determined CMPs [42].

LMNA variants are associated with a high prevalence of atrial tachy- and bradyarrhythmias, malignant VAs, the presence of a septal LGE at CMRI, and in general to a worse prognosis in terms of death and need for heart transplantation (HTx) [39].

Patients with *FLNC* truncating variants present a high risk of VAs, tend to develop an overt DCM phenotype, and usually show a considerable fibrotic scar at CMRI [43].

DES variants are an infrequent finding, though recent evidence demonstrates that there is an association with SCD and malignant arrhythmias, especially in males [44].

It has to be noted that genetic result interpretation is not always straightforward, especially when variants of unknown significance or gene mutations not biologically associated with the patient's phenotype are detected. Furthermore, a relevant group of NDLVC patients are gene-elusive, and thus a genotype-oriented approach could not always be feasible.

Genetic assessment is becoming relevant also in defining the relationship between myocarditis and CMPs [19]. Four percent of patients with uncomplicated acute myocarditis present P/LP variants in CMPs-associated genes, with *DSP* being the most involved one. Conversely, acute myocarditis presenting with acute HF, LV dysfunction, or VAs demonstrated P/LP variants in 22% of adults and 45% of

children, and in those cases, sarcomeric gene variants are the most frequent [17]. Finally, the creation of NDLVC as a new entity virtually broadens the number of patients who will be referred for genetic testing significantly, and concerns may arise regarding the sustainability of its wide application. If resources are limited, an integrated multiparametric approach should be pursued to identify those who need to be prioritized. In this context, the development of a *Madrid-like Score* for NDLVC—similar to the Madrid Genotype Score proposed for DCM, which estimates the likelihood of a positive genetic result before testing—could help identify patients at higher pre-test probability of a P/LP variant, thereby optimizing resource allocation and testing efficiency [45].

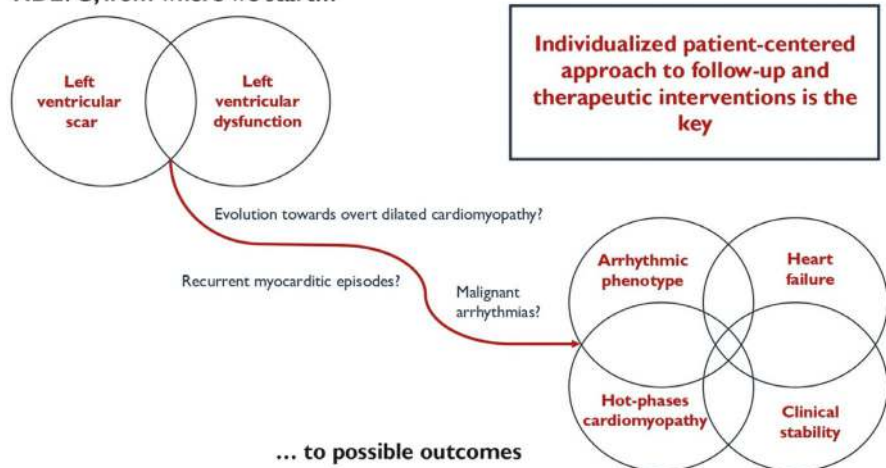
6.3.10 Familiar Screening

Guidelines recommend cascade familiar screening in first-degree relatives of CMP-affected patients, including NDLVC, starting from cardiologic evaluation, echocardiography, and resting ECG. If the index case demonstrates a P/LP variant, genetic testing in asymptomatic relatives should be limited to the investigation of proband's variant. When its presence is excluded, the follow-up program can be terminated; otherwise, a periodic evaluation should be offered in order to possibly allow an early detection of overt phenotypic development. First-degree relatives of genotype-negative-affected patients should also be periodically evaluated. Beyond clinical, ECG, and echocardiographic evaluation, other tests' choice (CMRI, Holter ECG, stress test) as well as their timing should be tailored to the needs of a single individual [1].

The development of LV dysfunction is not rare in NDLVC patients' relatives, with a 10-year incidence rate reported to be of 36% in a large cohort of DCM/NDLVC relatives [42]. In the same study, the genetic status of P/LP variant carrier and positive family history for arrhythmias were reported to be the main risk factors for LV dysfunction development, while LV-GLS and Holter ECG demonstrated a relevant role in predicting LV impairment and adverse outcomes in this cohort. It has relevant implications, as it has been demonstrated that adverse events (death, HTx, HF, major VAs) occurred only in relatives with a depressed LVEF, and familiar screening-detected LV impairment provided better outcomes than occasional LV dysfunction detection [42].

6.4 Natural History and Prognosis

Data on NDLVC natural history and outcomes are still limited and continue to emerge. NDLVC includes heterogeneous groups of patients, with significantly variable risks of mortality, malignant arrhythmias, progressive systolic dysfunction, and cardiac remodeling that can ultimately evolve into overt DCM and HF. Inflammation seems to play a significant role in the natural course of the disease in at least a subset of NDLVC patients, especially in carriers of P/LP *DSP*

NDLVC, from where we start...**Fig. 6.7** NDLVC natural history

variants [6, 12, 46]. A multiparametric baseline evaluation is essential to identify high-risk individuals and tailor the follow-up strategies according to each patient's specific risk profile (Figure 6.7).

6.4.1 Sudden Cardiac Death and Major Arrhythmic Events

NDLVC patients are at considerable risk of malignant VAs and SCD. Reported rates of SCD and major arrhythmic events (MAEs) range between 4% and 6% over a 3-year period [14, 15] and reach 11% at 7 years [16]. In a study including NDLVC probands and symptomatic family members (excluding those who first presented with aborted SCD) [12], the 5-year rates of all-cause and cardiac death were 1%. HTx was required in 2% of patients (1% due to VA storm and 1% due to mechanical failure). The incidence of ventricular fibrillation or SCD, ventricular tachycardia, and appropriate ICD interventions were 1%, 1%, and 14%, respectively. When comparing fibrotic NDLVC with hypokinetic NDLVC, the first group presented a significantly higher incidence of MAEs (8% vs. 0.9%) [15, 16].

Several factors contribute to arrhythmic risk stratification in NDLVC. Among the most accessible parameters, LVEF <45% on echocardiography, frequent PVBs (>1000/24 h), and the presence of NSVTs on baseline Holter monitoring are associated with worse outcomes [12, 16].

CMRI tissue characterization provides additional risk markers.

To date, only a limited number of studies have investigated the prognostic role of the presence, extent, and location of LGE on CMR in NDLVC patients. The presence of LGE [15], the septal location, and the RLP [12, 15] have been consistently associated with MAEs. In addition, a greater extent of LGE has been linked to

adverse outcomes, including all-cause mortality [15] and MAEs, particularly when fatty replacement is also present [14]. A threshold of LGE involvement greater than 9% of the myocardial mass has been proposed as prognostically relevant [14].

The prognostic impact of genetics in NDLVC remains less clearly defined. While some studies reported no significant association between genetic status and adverse outcomes [14, 16], Peretto et al. demonstrated that pathogenic or likely pathogenic variants in high-risk arrhythmogenic genes (*LMNA*, *FLNC*, *TMEM43*, *PLN*, *DSP*, *RBM20*) were independently associated with an increased risk of MAEs [12]. These discrepancies may be explained by differences in study populations, as asymptomatic family members were excluded from the latter cohort [12].

6.4.2 Cardiac Remodeling and Heart Failure

Although most NDLVC patients are in NYHA class I–II at diagnosis, some may present with or develop HF [11, 13, 16]. Unfavorable cardiac remodeling with LV dilation may occur; however, left ventricular reverse remodeling (LVRR) is also possible with optimal medical therapy.

Compared to DCM, some studies suggest that NDLVC patients may have similar outcomes [11], while others report a more favorable prognosis [16]. In a cohort of NDLVC patients presenting with HF, the 3-year rates of HF hospitalization and death due to HF were reported at 10% and 2%, respectively [15]. In NDLVC patients with reduced LVEF, progression to overt DCM occurred in 18%, predominantly within the first year after diagnosis [11]. This group, along with patients who failed to recover LVEF above 50%, showed a higher risk of SCD and HF hospitalization. These findings align with previous reports on mildly DCM [27].

LVRR, evaluated 1 year after the diagnosis and defined as an absolute increase in LVEF $\geq 10\%$ or LVEF normalization ($\geq 50\%$) in patients presenting with LVEF $< 45\%$, was reported in 41% of NDLVC patients with systolic impairment [13]. The presence of P/LP variants in arrhythmogenic genes and RLP at CMRI was both negatively associated with LVRR. Patients who experienced LVRR demonstrated a more favorable clinical course [13].

6.4.3 Inflammation

NDLVC patients may experience recurrent episodes of myocardial injury, characterized by acute chest pain, troponin elevation, and inflammation evidence at CMRI and/or EMB [12]. This inflammatory phenotype has been particularly associated with *DSP* variants, as about 1 in 5 patients with P/LP *DSP* variants experience myocarditis-like episodes [6, 18, 40, 46]. Chronic inflammation may also be present but can be easily overlooked if dedicated T2-weighted CMR sequences or EMB are not performed [12]. The concept of an inflammatory cardiomyopathy phenotype and its overlapping features with NDLVC and DCM have been reinforced by the 2025 ESC myocarditis and pericarditis guidelines [19]. Identification

of inflammation is clinically relevant, as it has been associated with adverse prognosis (in terms of MAEs and HF events) but also represents a possible therapeutic target [6, 12, 46].

6.4.4 Risk Stratification Scores

A recently developed prediction score aims to foresee 5-year risk of MAEs in NDLVC. Predictive factors include male sex, LVEF <45%, NSVTs, septal LGE, RLP, P/LP variants in high-risk arrhythmogenic genes, and evidence of myocardial inflammation on CMRI or EMB. A simplified version of the score, excluding genetic and inflammatory parameters, has also been proposed. This score stratifies patients into four risk classes with predicted event rates of <5%, 5–20%, 20–40%, and >40% [12].

For some genes and variants that can be associated with NDLVC, specific risk scores have previously been developed, although not all have undergone formal validation, and online calculators are available [47]. A worse prognosis in *LMNA* variant carriers is predicted by male sex, nonmissense mutations, presence and grade of AV-blocks, low LVEF, and NSVTs [48]. Patients with *DSP* variants have a higher ventricular arrhythmic risk if female, with NSVTs, a high PVBs burden, and low LVEF and RV systolic dysfunction [49]. When the specific p.Arg14del variant in *PLN* is detected, the risk of malignant VAs is related to the number of negative T waves in the inferior and precordial leads, the presence of low QRS voltages, a low LVEF, and the PVB burden [50]. For *FLNC*-truncating variant carriers, a risk score for life-threatening arrhythmias that takes into consideration age, male sex, history of NSVT, and/or syncope and LVEF has been proposed [51].

6.5 Treatment

Due to the heterogeneity in the clinical presentation of NDLVC patients, an individualized therapeutic approach is essential. Each patient requires an assessment of arrhythmic risk to guide strategies for the prevention of SCD, as well as an evaluation for signs and symptoms of HF, which should be managed according to current clinical guidelines [52].

In NDLVC patients who have experienced cardiac arrest or sustained VAs with hemodynamic compromise, ICD implantation is recommended for secondary prevention of SCD [1]. ICD implantation for primary prevention in NDLVC patients should be considered using a multiparametric approach, including personal and family history evaluation, standard and Holter ECG, echocardiography, CMRI, and genetic testing. Key factors that strongly support ICD implantation include an LVEF below 35%, the presence of a genotype associated with malignant arrhythmias, and extensive myocardial fibrosis detected by CMRI. Arrhythmic risk scores can be helpful tools, although risk threshold to guide ICD implantation is not clearly established. An estimated 5-year risk above 5–10% represents a reasonable cutoff [1, 38].

The introduction of subcutaneous and extravascular ICD systems represents a promising option, particularly in younger patients with a low risk of AV blocks, due to their reduced rate of long-term complications related to transvenous leads [53, 54]. Importantly, ICD implant decision should also consider competing causes of death, patient preferences, and must be periodically reassessed during follow-up.

Patients exhibiting signs and symptoms of HF should receive optimized therapy according to guideline-directed medical treatment, which includes beta-blockers, angiotensin-converting enzyme inhibitors (ACE-Is), or angiotensin receptor–neprilysin inhibitors, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose co-transporter 2 inhibitors [52]. In cases where definite HF is absent but systolic dysfunction or significant myocardial fibrosis is present, early initiation of anti-remodeling therapy, including ACE-I, beta-blockers, and MRAs, may be beneficial, although data on this topic are lacking. Conversely, those with advanced HF need a tailored follow-up to eventually intercept the appropriate timing for HTx or ventricular assist device. Cardiac resynchronization therapy should be considered when appropriate.

If myocardial inflammation is detected, immunosuppressive therapy can be considered in selected patients [55]. In a retrospective, international, large study on P/PL *DSP* variant carriers [46], it was reported that immunosuppressive treatment of myocarditis-like episodes (initial or repeat presentations) was associated with a lower risk of MAEs and HF events, but did not reduce the risk of inflammatory episode recurrence.

6.6 Open Issues

Different aspects of this new CMP deserve further investigation. NDLVC and its subgroup prevalence are still unknown, and data on natural history are scarce. Specific considerations for patients with ARVC and LV involvement (previously referred to as biventricular ACM) are lacking in this phenotypic classification of CMPs. Prognostic stratification (especially in terms of CMRI and genetic testing findings) and the validation of the NDLVC risk score require confirmatory studies. Strong evidence on the therapeutic approach, regarding HF medical treatment for asymptomatic patients, immunosuppressive treatment for the inflammatory-CMP phenotype, and primary prevention ICD implant, is lacking and would be definitively clarified by specific randomized clinical trials. In conclusion, there is space for future research on NDLVC.

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Arrhythmogenic Cardiomyopathy

7

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7.1 Definition and Epidemiology

Arrhythmogenic cardiomyopathy (ACM) is a primary myocardial disease, characterized by progressive fibro-fatty replacement of the ventricular myocardium that predisposes to ventricular arrhythmias (VA) and sudden cardiac death (SCD) [1].

The prevalence of arrhythmogenic right ventricular cardiomyopathy (ARVC) is estimated to range from approximately 1 in 2000 to 1 in 5000 individuals in the general population, with higher rates reported in certain regions of Italy [1].

The disease shows a hereditary transmission in about half of the cases, although incomplete penetrance and variable phenotypic expression may contribute to underestimating the true prevalence of familial forms.

Males are more frequently affected (2–3:1) and often exhibit a more severe phenotype. This may be related to hormonal factors and a higher intensity of physical activity [2].

The clinical onset typically occurs between the ages of 15 and 35, although the disease can also manifest in older adults, albeit less frequently [3].

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Physical activity is the main environmental factor influencing disease progression. Intense and prolonged exercise can result in earlier and more severe phenotypic expression in individuals carrying the genetic variants associated with the disease. Moreover, young athletes with ACM have a fivefold higher risk of SCD, particularly during exercise. In many series, ACM accounts for up to 20% of SCD in young athletes [4].

7.2 Clinical Presentation

The clinical spectrum of ACM is remarkably broad, ranging from asymptomatic forms to heart failure (HF), major VA, and SCD. The initial presentation is often arrhythmic, with palpitations, syncope, or VA. Notably, SCD may be the first manifestation of the disease [5]. HF is more common in the last stages of the disease. ACM can also present with chest pain and elevation of cardiac troponins in the absence of obstructive coronary artery disease, a condition known as “hot phase.” These episodes affect predominantly young carriers of *DSP* variants and present a diagnostic challenge in the differential diagnosis with acute myocarditis [6].

7.3 Diagnostic Criteria

Historically, ACM was first described as ARVC. The classic form of disease is characterised by the presence of dilation, dysfunction, and/or wall motion abnormalities confined to the right ventricle (RV) due to fibro-fatty replacement of cardiomyocytes. This pathological process was originally thought to be limited to the “triangle of dysplasia,” between the pulmonary infundibulum, inferoposterior wall, and apex of the RV. The first diagnostic criteria for the RV phenotype were defined in 1994 and revised in 2010 to improve diagnostic accuracy by including morphofunctional assessment and family history/genetics [7]. The 2010 revision retained the six-category structure and major/minor classification, introducing the diagnostic categories of “borderline” and “possible” ARVC for early stages of the disease. However, the sensitivity of these criteria remained limited.

Over the last decade, the widespread use of cardiac magnetic resonance (CMR) and genetic analysis has contributed to a deeper understanding of the disease, revealing fibro-fatty replacement of the myocardium in both ventricles and a clinical and genetic overlap between LV and RV cardiomyopathies (Fig. 7.1). For many years, the lack of diagnostic criteria for the LV and biventricular phenotype has resulted in underdiagnosis. More in-depth knowledge of the spectrum of disease led to the need for new diagnostic criteria. In 2019, an international expert consensus defined a new broader nosological entity called ACM, incorporating a wide spectrum of genetic, systematic, infectious, and inflammatory disorders. The designation included, but was not limited to, arrhythmogenic right/left ventricular cardiomyopathy [8].

One year later, the Padua criteria were published [9]. The authors focused on the diagnostic role of CMR in detecting myocardial scar to more fully characterize right, left, and biventricular disease variants, reflecting the expanding spectrum of phenotypes.

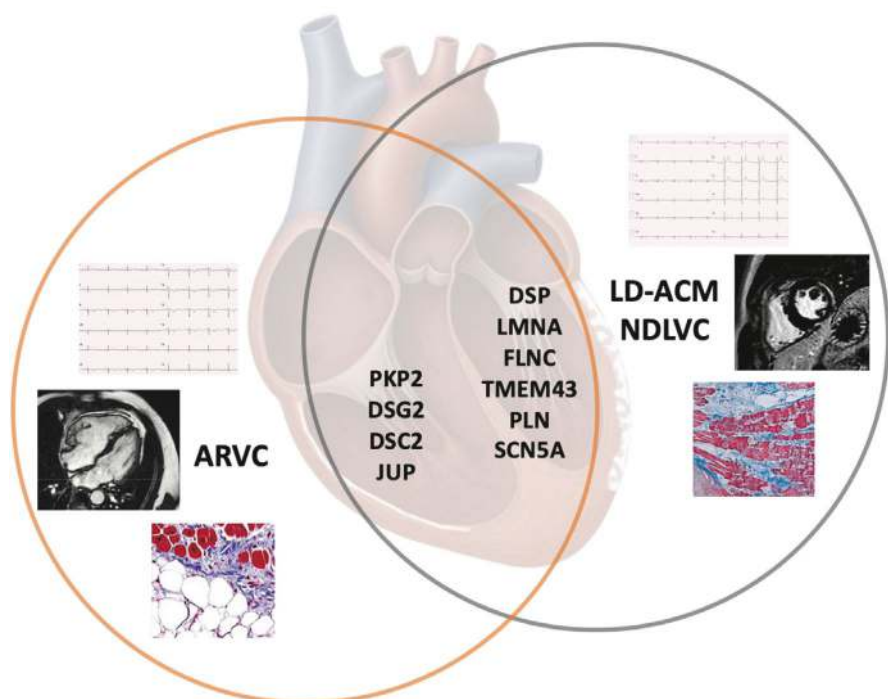


Fig. 7.1 Arrhythmogenic cardiomyopathy (ACM) includes right-dominant (ARVC), left-dominant (now NDLVC), and biventricular forms, with overlapping clinical, imaging, and genetic features. ARVC is defined by RV wall motion abnormalities, dilation, and systolic dysfunction due to fibro-fatty replacement of RV myocardium, commonly linked to PKP2, DSG2, DSC2, and JUP pathogenic variants. NDLVC presents with nonischemic LV scarring or fatty infiltration without dilation, with or without systolic dysfunction, and is often associated with DSP, LMNA, FLNC, TMEM43, PLN, and SCN5A pathogenic variants

Recently, this paradigm shift has also been incorporated into the 2023 European Society of Cardiology (ESC) Guidelines for the management of cardiomyopathies, which created the broader concept of nondilated left ventricular cardiomyopathy (NDLVC) [10]. Nowadays, NDLVC may be considered a heterogeneous group of diseases, which includes, but is not limited to, arrhythmogenic forms with predominant involvement of the left ventricle (LV) and hypokinetic LV cardiomyopathies. For the first time, compared to previous classifications of cardiomyopathies, NDLVC considers nonischemic ventricular scarring and fibro-fatty replacement in the LV as morphological diagnostic criteria, regardless of regional wall motion abnormalities or systolic function. Guidelines underlined that regardless of nomenclature, the starting phenotype must systematically initiate a step-by-step diagnostic–therapeutic approach.

In 2024, the updated European Task Force criteria introduced a comprehensive, multiparametric approach focused on different phenotypes of disease (Table 7.1). The revised criteria significantly improved the diagnostic accuracy of left-dominant and biventricular phenotypes by including CMR-derived scar patterns [e.g.,

Table 7.1 Diagnostic criteria for arrhythmogenic cardiomyopathy

Category	RV phenotype	LV phenotype
Morphofunctional ventricular abnormalities	<i>Major</i> Regional RV akinesia, dyskinesia, or aneurysm <i>plus</i> one of the following: Global RV dilatation (increase of RV EDV according to the imaging test specific nomograms for age, sex, and BSA) ^a or Global RV systolic dysfunction (reduction of RV EF according to the imaging test-specific nomograms for age and sex) ^a	<i>Minor</i> Global LV systolic dysfunction, with or without LV dilatation (increase of LV EDV according to the imaging test-specific nomograms for age, sex, and BSA) ^a
	<i>Minor</i> Regional RV akinesia, dyskinesia, or aneurysm of RV free wall	
Structural alterations	<i>Major</i> Fibrous replacement of the myocardium in ≥1 sample, with or without fatty tissue, at histology <i>Minor</i> Unequivocal RV LGE (confirmed in two orthogonal views) in ≥1 RV region(s) (excluding tricuspid valve)	<i>Major</i> “Ring-like” LV LGE (subepicardial or midmyocardial stria pattern) of ≥3 segments (confirmed in 2 orthogonal views) <i>Minor</i> LV LGE (subepicardial or midmyocardial stria pattern) of one or two bull’s eye segment(s) (in two orthogonal views) of the free wall, septum, or both (excluding patchy, focal or septal junctional LGE)
Repolarization abnormalities	<i>Major</i> Negative T waves in right precordial leads (V ₁ , V ₂ , and V ₃) or beyond in individuals ≥14 years old (in the absence of complete RBBB and not preceded by J-point/ST-segment elevation) <i>Minor</i> Negative T waves in leads V1 and V2 in males ≥14 years old (in the absence of RBBB and not preceded by J-point/ST-segment elevation) Negative T waves beyond V3 in the presence of complete RBBB Negative T waves beyond V3 in individuals <14 years old	<i>Minor</i> Negative T waves in left precordial leads (V ₄ -V ₆) (in the absence of complete LBBB)

Category	RV phenotype	LV phenotype
Depolarization and conduction abnormalities	<i>Minor</i> Epsilon wave (reproducible low-amplitude signals between the end of QRS complex to the onset of the T wave) in the right precordial leads (V1 to V3) Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, or V3 (in the absence of complete RBBB)	<i>Major</i> Low QRS voltages (<0.5 mV peak to peak) in all limb leads in the absence of other causes (e.g., cardiac amyloidosis, obesity, emphysema, or pericardial effusion)
Arrhythmias	<i>Major</i> Frequent ventricular extrasystoles (>500 per 24 h), nonsustained, or sustained ventricular tachycardia of LBBB morphology with noninferior axis <i>Minor</i> Frequent ventricular extrasystoles (>500 per 24 h), nonsustained, or sustained ventricular tachycardia of LBBB morphology with inferior axis ("RVOT pattern") History of cardiac arrest due to ventricular fibrillation or sustained ventricular tachycardia of unknown morphology	<i>Minor</i> Frequent (>500 per 24 h) or exercise-induced ventricular extrasystoles with an RBBB morphology or multiple RBBB morphologies (excluding the "fascicular pattern") Nonsustained or sustained ventricular tachycardia with an RBBB morphology (excluding the "fascicular pattern") History of cardiac arrest due to ventricular fibrillation or sustained ventricular tachycardia of unknown morphology
Family history/ genetics	<i>Major</i> Identification of a pathogenic ACM-gene variant in the patient under evaluation ACM confirmed in a first-degree relative who meets diagnostic criteria ACM confirmed pathologically at autopsy of surgery in a first-degree relative <i>Minor</i> Identification of a likely pathogenic ACM-gene variant in the patient under evaluation History of ACM in a first-degree relative in whom it is not possible or practical to determine whether the family member meets diagnostic criteria Premature sudden death (<35 years of age) due to suspected ACM in a first-degree relative ACM confirmed pathologically or by diagnostic criteria in second-degree relative	

Modified from: Int J Cardiol. 2024 Jan 15;395:131447. Proposed diagnostic criteria for arrhythmogenic cardiomyopathy: European Task Force consensus report
ACM arrhythmogenic cardiomyopathy, *BSA* body surface area, *EDV* end diastolic volume, *EF* ejection fraction, *ITF* International Task Force, *LBBB* left bundle-branch block, *LGE* late gadolinium enhancement, *LV* left ventricle, *RBBB* right bundle-branch block, *RV* right ventricle, *RVOT* right ventricular outflow tract
*CMR cutoff values of EDV and EF for nonathletes (+ or – respectively) derived from S.E. Petersen et al., EACVI expert consensus paper: a comprehensive review of cardiovascular magnetic resonance normal values of cardiac chamber size and aortic root in adults and recommendations for grading severity, EHJ. Cardiovasc. Imaging 20 (2019) 1321–1331 and for athletes (99%CI) from F. D'Ascenzi et al., Cardiac magnetic resonance normal reference values of biventricular size and function in male athlete's heart, JACC Cardiovasc. Imaging 12 (2019) 1756–1765

ring-like late gadolinium enhancement (LGE)] and LV-specific electrocardiographic markers. Genetic testing and, in selected cases, endomyocardial biopsy further enhance diagnostic confidence [11].

7.4 Electrocardiographic Findings

The electrocardiogram (ECG) is a fundamental tool in both the suspicion and diagnosis of ACM [12]. The classic and most frequent findings include

- T-wave inversion in right precordial leads, one of the earliest and most common abnormalities, especially in RV-dominant forms. In more advanced or LV-dominant forms, T-wave inversion may be seen in inferior and lateral leads (Figs. 7.2 and 7.3) [13].

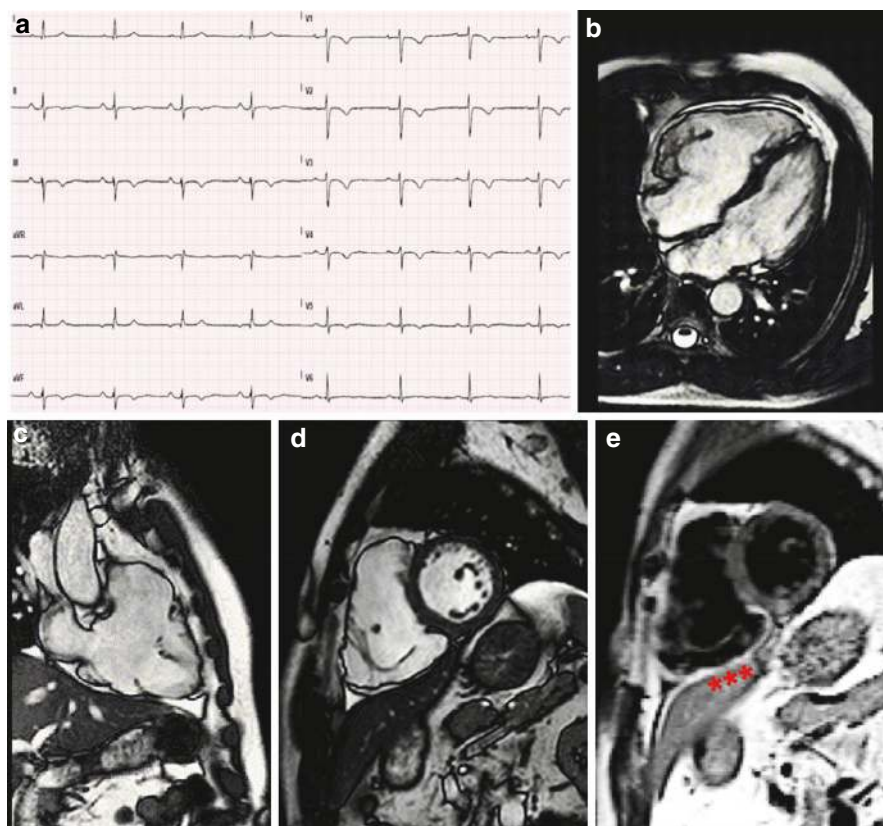


Fig. 7.2 Case of arrhythmogenic right ventricular cardiomyopathy caused by a pathogenic PKP2 mutation. (a) The ECG shows the typical inversion of the T waves in the precordial leads. There is also T-wave inversion in the inferior leads. (b–d) CMR images show right ventricular dilatation, with multiple aneurysms involving both the sub-tricuspid region and the outflow tract. (e) Tissue characterization images (TSE black-blood, T1-weighted) demonstrate extensive fatty replacement of the myocardium (*)

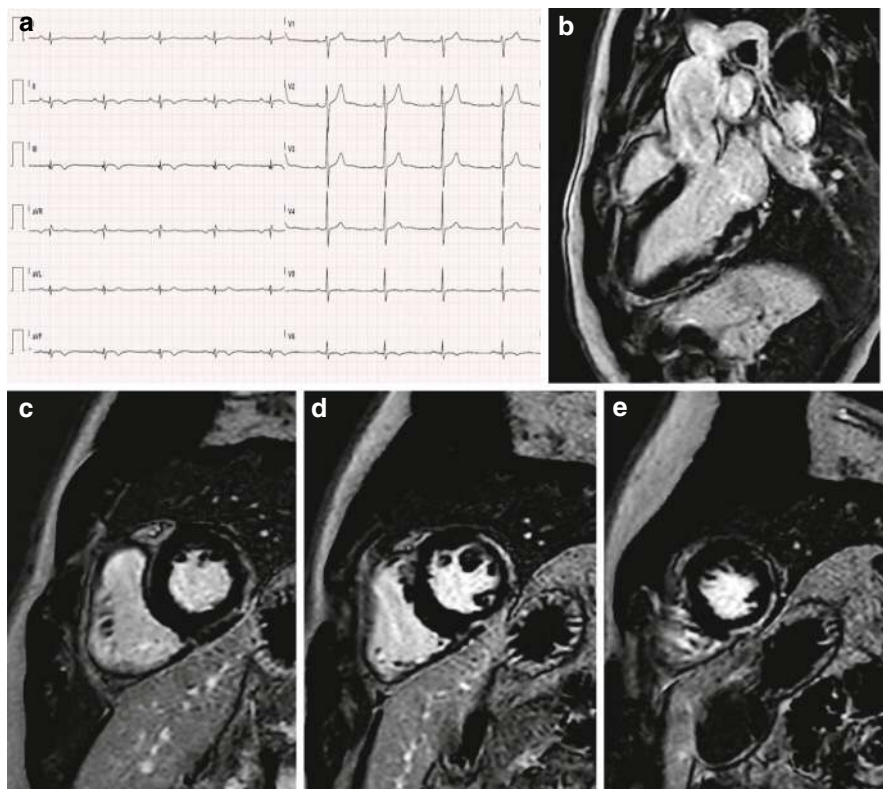


Fig. 7.3 Case of left-dominant arrhythmogenic cardiomyopathy (now included in the nondilated left ventricular cardiomyopathy phenotype) caused by a pathogenic DSP mutation. **(a)** The ECG shows the typical inversion of the T waves in the inferior and lateral leads. **(b–e)** CMR late gadolinium-enhanced images show extensive nonischemic epicardial enhancement—hyperintense areas—in the inferior, posterior, and lateral walls of the left ventricle, consistent with fibro-fatty replacement

- Low QRS voltages, sign of fibro-fatty myocardial replacement.
- Epsilon wave, a small positive deflection at the end of the QRS in V1–V3, representing delayed activation of the RV free wall. While specific, it is not very sensitive.
- Prolonged terminal activation (>55 ms) in V1–V3, reflecting delayed RV conduction.
- VA, including premature ventricular contractions and episodes of ventricular tachycardia (VT), typically with a left bundle-branch block morphology (indicating a RV origin) or right bundle-branch block in ALVC patients, excluding the fascicular pattern [7].

7.5 Role of Multimodality Imaging

Multimodality imaging plays a central role in the diagnosis, risk stratification, and follow-up [10, 14]. First of all, it is essential for an accurate phenotypic characterization.

Echocardiography represents the first-line imaging modality, offering a noninvasive evaluation of cardiac structure and function [14]. The main limitation of this technique is its reliance on adequate acoustic windows. In case of suboptimal image quality the use of ultrasound contrast agents can enhance visualization of the endocardial border, improving the diagnostic performance [14].

Traditional diagnostic criteria for ACM include the detection of regional wall motion abnormalities, alongside the presence of RV dilation or impaired global systolic function [7]. Equal attention must be given to the left ventricle due to its frequent involvement, with careful evaluation of both structural and functional abnormalities [11, 15, 16]. Nonetheless, echocardiography has limited sensitivity in detecting LV involvement, particularly in early-stage disease, as pathological changes—predominantly affecting the epicardial or intramural layers—may not produce significant regional or global functional impairment. In this context, advanced echocardiographic techniques, such as myocardial strain imaging, can improve the detection of subtle myocardial involvement, enhancing diagnostic accuracy and providing significant prognostic information [14, 17, 18]. Given its advantages, myocardial strain imaging is particularly useful for identifying subclinical disease, especially among relatives of affected individuals and asymptomatic carriers of genetic variants associated with the disease [19].

CMR is the gold standard to assess biventricular volumes and function, while also enabling myocardial tissue characterization [20]. Therefore, CMR should be considered the imaging modality of choice for the diagnostic evaluation of ACM [10]. Furthermore, due to the relatively low negative predictive value of echocardiography, CMR remains essential even when echocardiographic findings appear normal [21]. In particular, its superior spatial resolution and unrestricted multiplanar capabilities allow for precise RV assessment, overcoming echocardiography limitations. CMR also enables accurate flow quantification through dedicated sequences (i.e., phase-contrast imaging), aiding in the differential diagnosis of RV dilation caused by congenital anomalies with left-to-right shunting. In some cases, during the active inflammatory episodes called “hot phases,” T2-weighted sequences can effectively detect the presence of myocardial edema.

According to the European Task Force criteria for the diagnosis of ACM, the presence of morphofunctional abnormalities as well as structural alterations of the ventricles should be systematically evaluated [11]. In particular, the presence of LGE in one or more segments of the RV, confirmed in two orthogonal planes, is a minor diagnostic criterion for the RV form. The presence of LGE “ring-like” pattern (i.e., subepicardial or intramyocardial LGE in at least three consecutive segments, confirmed in two orthogonal planes) is a major structural criterion for the diagnosis of the LV forms (included in the definition of nondilated left ventricular cardiomyopathy according to the ESC Guidelines for the management of cardiomyopathies),

whereas the presence of nonischemic LGE in one or more LV segments of the free wall and/or the interventricular septum is considered a minor criterion.

Beyond its diagnostic value, CMR provides critical prognostic insights, with LV involvement serving as an independent predictor of major arrhythmic events [22].

Other cardiac imaging modalities have a limited role in ACM diagnosis. Cardiac computed tomography (CCT), beyond the assessment of coronary anatomy, can offer morphofunctional assessment and tissue characterization by detecting hypodense regions of fat infiltration and areas of fibrosis using the late iodine enhancement technique [14]. However, due to exposure to ionizing radiation and iodinated contrast agents, the use of CCT should be restricted to selected patients with poor echocardiographic windows and contraindications to CMR. The use of positron emission tomography (PET) should be considered case-by-case; it may be particularly useful for the differential diagnosis of inflammatory cardiomyopathies with arrhythmogenic expression, such as cardiac sarcoidosis [23, 24].

7.6 Genetics

Genetics plays a central role in the pathogenesis of ACM. A pathogenic variant can be identified in approximately 50–70% of probands. Current data support a causative role in ACM of pathogenic/likely pathogenic (P/LP) variants involving desmosomal genes and few non-desmosomal genes (Table 7.2).

Among the desmosomal genes, *PKP2* (for Plakophilin-2) is the most implicated, accounting for 40–50% of probands and up to 70% of all desmosomal P/LP variants. Most *PKP2* mutations are truncating loss-of-function (LOF) variants (such as nonsense, splice-site, frameshift mutations, or large deletions). Patients with *PKP2* mutations typically exhibit a classic RV phenotype and a variable lifetime risk of malignant arrhythmias [25].

The second most frequently affected desmosomal gene is *DSP* (encoding Desmoplakin), responsible for approximately 3–15% of cases. *DSP* P/LP variants are usually truncating LOF mutations. The phenotype associated with *DSP* is characterized by frequent predominant LV involvement, high fibrotic burden (often seen as a “ring-like” LGE on CMR), and seemingly higher risk of HF [2, 26].

Other desmosomal genes with a confirmed pathogenic role, in order of prevalence, include Desmoglein-2 (*DSG2*), Desmocollin-2 (*DSC2*), and Plakoglobin (*JUP*).

Among non-desmosomal genes, *TMEM43* (strong supportive evidence), Phospholamban (*PLN*), and Desmin (*DES*) (moderate evidence) have been recognized to have a pathogenic role [27].

Other non-desmosomal genes, including calcium metabolism-related genes, ion channels, and structural sarcomeric components (e.g., *SCN5A*, *TTN*, *FLNC*, *CTNNA3*, *CDH*, *RYR2*), have also been previously investigated as potentially pathogenic, but they were not confirmed either due to paucity of data or due to association with other arrhythmogenic conditions (e.g., CPVT, Brugada syndrome) [27].

ACM causative mutations generally manifest in heterozygous individuals with a dominant pattern. Rarely, *JUP* and *DSP* mutations can be found in homozygous

Table 7.2 Overview of the main genes implicated in arrhythmogenic cardiomyopathy, with their prevalence, inheritance pattern, and most common associated phenotype

Gene	Prevalence	Inheritance	Phenotype
PKP2	50–70% familial ACM	AD; variable penetrance	RV involvement; variable risk of ventricular arrhythmias
DSP	3–15%	AD; variable penetrance (higher than PKP2)	BiV or LV involvement; frequent progression to HF; CMR ring-like LGE pattern; high risk of ventricular arrhythmias
DSG	7–10%	AD; variable penetrance	BiV or LV involvement; progression to HF
DSC	2–7%	AD or AR	BiV involvement
JUP	<1%; Naxos syndrome	AR	RV involvement with palmoplantar keratoderma and woolly hair
DES	1–2%	AD; variable penetrance	BiV involvement; skeletal muscle myopathies
PLN	<1%; highest in the Netherlands (up to 10–15% of cases)	AD; incomplete penetrance	Mostly LV involvement; dilated phenotype
TMEM43	2–5%; highest in Newfoundland	AD; high penetrance	BiV involvement; very aggressive in males; highest risk of ventricular arrhythmias

ACM arrhythmogenic cardiomyopathy, AD autosomal-dominant, RV right ventricle, BiV biventricular, LV left ventricle, AR autosomal-recessive, HF heart failure

subjects associated with peculiar syndromes respectively known as “Naxos disease” and “Carvajal syndrome,” generally associated with skin and hair abnormalities [28].

Up to 16% of ACM patients have a complex phenotype, being carriers of more than one variant. Compound heterozygosity has been associated to higher penetrance of the disease as well as higher risk of heart failure and life-threatening arrhythmias [3].

Ultimately, ACM represents a genetically complex disease where the interplay of Mendelian genetics with polygenic modifiers and environmental exposure (e.g., physical exercise) determines the phenotype.

The incomplete penetrance of ACM causative mutations further confirms the need for collecting different clinical parameters to support the diagnosis besides the genetic finding [9, 29].

Genetics plays a central role in risk stratification, influencing both arrhythmic risk and disease progression. Gene-specific scores have been developed and validated for common mutations and will be discussed further in this chapter [30–32]. These findings support the view that the ACM phenotype represents a heterogeneous group of disorders, each with a distinct clinical course. On this basis, genetic characterization is becoming a critical factor in the clinical management of ACM.

Genetic testing also plays a pivotal role in the screening and early diagnosis of family members. A genotype-driven risk assessment strategy can guide clinical decision-making and optimize resource utilization [33].

A relevant issue arises when a potentially causative variant is identified as an incidental finding. In such cases, the American College of Medical Genetics and Genomics recommends reporting incidental findings related to five ACM-associated genes (*PKP2*, *DSP*, *DSC*, *DSG*, and *TMEM43*), with the primary goal of preventing life-threatening arrhythmic events, including SCD [34]. However, a clear impact of notification of secondary findings has yet to be proven. This is also due to the low penetrance of known variants and their scarce actionability. It is therefore reasonable that these genetic findings are addressed by a multidisciplinary team as a first step for the identification of unacknowledged ACM, who might benefit from lifestyle adjustment even when asymptomatic, and the recognition of phenotype-negative genotype-positive individuals who should undergo a clinical follow-up [35].

7.7 Therapy

Management objectives focus on reducing mortality from arrhythmic SCD or HF, preventing disease progression, and improving symptoms and quality of life [36].

Lifestyle modification is the first nonpharmacological treatment, starting with exercise restriction. Competitive sports and high-intensity activities should be avoided, as they promote phenotypic disease expression and trigger life-threatening VA [37–40]. High-intensity sports are also discouraged in genotype-positive/phenotype-negative individuals, since some evidence demonstrated that exercise could lead to phenotypic expression of the disease, particularly in those with *PKP2* variants [41–43].

Although no prospective clinical trials confirmed beta-blocker impact on SCD or disease progression, they are recommended for patients with arrhythmias, since evidence from retrospective registries suggests their role to reduce exercise-induced arrhythmias [36, 40, 44]. Current evidence does not support the prophylactic use in genotype-positive/phenotype-negative individuals. Cardiospecific beta-blockers should be preferred, titrated to the maximum tolerated dose. Antiarrhythmic drugs did not confer protection from SCD in retrospective studies and are recommended only if beta-blockers fail to control arrhythmia-related symptoms [39, 40, 45]. Amiodarone seems most effective in reducing arrhythmia burden [46], but its use is limited because of long-term side effects, especially in young patients.

Current evidence of flecainide's efficacy and safety is limited to retrospective studies [47]. The ESC Guidelines provide a class IIa recommendation for symptom control without specifying the need for an implantable cardioverter defibrillator (ICD) [10]. Recent real-world data indicated a favorable safety profile and a reduction in arrhythmic event [48]. However, in the absence of randomized controlled trials, class IC AADs should be used cautiously in ACM, especially in patients with extensive fibrosis. Similarly, data on Sotalol use are conflicting [49] and its use should be approached cautiously [46, 50].

Catheter ablation represents a valid option in ACM patients with recurrent sustained VAs. Recent studies have demonstrated that an epicardial or combined epicardial approach is more effective than endocardial ablation alone due to the

epicardial origin of many reentry circuits in the RV myocardium. This approach has been associated with reduced VT recurrence and improved long-term outcomes [51–53]. However, due to the risk of arrhythmia recurrence, catheter ablation is not a definitive therapy and should not be considered as an alternative to ICD [36].

ICD is currently the only strategy proven to reduce SCD [36]. While there is broad consensus that patients with prior sustained VA or aborted SCD should receive a secondary prevention ICD, risk stratification for primary prevention of life-threatening arrhythmias remains challenging [10].

First, arrhythmic risk stratification should be multiparametric and periodically reassessed, considering the progressive nature of the disease [54]. Several high-risk features, such as arrhythmic syncope, RVEF <40%, LVEF <45%, and inducible sustained VT during programmed electrical stimulation (PES), should be considered to aid individualized decision-making for ICD implantation [10, 55]. Additional predictors include young age, male sex, specific ECG findings suggesting extensive myocardial involvement (i.e., number of T-wave inversions and fragmented QRS), frequent (>500/24 h) premature ventricular contractions (PVC), nonsustained VT, and specific LGE patterns [22, 56, 57]. These features were combined in the 2015 ITF consensus document to stratify the risk of SCD in ARVC, but all recommendations were based on expert opinion and did not consider potentially correlated risk factors [36]. In 2019, the “ARVC risk calculator” was developed in order to provide 5-year risk estimates for a composite outcome of life-threatening arrhythmias [56]. The score can be applied at the time of diagnosis in patients with a definitive diagnosis of a classic form of the disease. It includes seven clinical variables [age, sex, number of leads with a negative T wave, 24-h PVC burden, NSVT, history of a recent (<6 months) syncope, and RV ejection fraction from CMR]. Compared to the 2015 TFC consensus, the ARVC risk score resulted in the same protection from VAs, but with approximately 20% reduction in the number of implanted ICDs [56, 58]. The model has been validated in many external cohort [22, 59–61], showing consistent benefit. After the development of the ARVC risk score, several studies aimed to refine its predictive accuracy by assessing the role of variables not originally included. An observational study by Protonotarios et al. [62] confirmed these findings, reporting a better performance in *PKP2* mutation carriers compared to the gene-elusive group. Conversely, Gasparetti et al. [63] recently reported poor performance among a multicentric group of 252 patients with *DSP* variants, highlighting the need for gene-specific risk algorithm [30].

Among patients with ARVC, underlying genotype plays an important role when assessing individual risk for VA [62]. While gene-elusive and *PKP2* variants represent the majority of ARVC cases fulfilling 2010 TFC at the time of their first sustained VA, fewer than half of the patients carrying variants in genes such as *DSP*, *PLN*, and *FLNC* fulfill those criteria [58]. Nevertheless, patients with *DSP*, *LMNA*, and *FLNC* variants experience consistent VA event rates regardless of the fulfillment of the 2010 TFC or their initial clinical diagnosis [64, 65].

Recently, five clinical parameters (NSVT, female sex, natural logarithm of 24-h ventricular premature beats, moderate-to-severe RV dysfunction) were identified as independent predictors of VAs in *DSP* and included in a novel “*DSP* risk score” [30].

A recent multicenter study [66] demonstrated that inducibility during PES is an independent predictor of sustained VA during follow-up beyond the prediction of the calculator. PES inducibility was therefore integrated into the risk predictions from the ARVC risk calculator pre-test probability, improving the performance of the model.

Although debated, the impact of a long history of sport activities does not seem to affect efficiency of the score, presumably because high-level exercise exposure is strongly associated with most of the variables included in the calculator, allowing its use also in athletes [67].

Since risk calculators are validated among ARVC patients fulfilling 2010 ITF criteria [29], new classification could refine their efficiency. Among those with a left-dominant phenotype, Aquaro et al. reported a significant underprediction of ARVC risk calculator-derived VA risk [22]. A new score applied to the NDLVC phenotype has recently been published [68].

7.8 Gene Therapy and Future Directions

Since ACM is often caused by specific Mendelian gene variants, it has recently become a promising field of interest for gene therapy [69]. This approach consists of the introduction of new genes or the modification of existing faulty ones through cardiotropic vectors, respectively called “gene replacement” and “gene editing.” [70] Currently, the standard vectors for cardiac gene therapy delivery are adeno-associated viruses (AAV) [71].

Gene therapies in ACM focus mostly on variants in the *PKP2* gene. In the last 2 years, four different research groups have published encouraging preclinical results of *PKP2* replacement strategy. Kyriakopoulou *et al* [70] showed that delivering a wild-type human *PKP2* gene through an AAV6 vector to induced pluripotent stem cell (iPSC)-derived cardiomyocytes from patients carrying a truncating Plakophilin-2 variant restored normal levels of the protein and also improved the assembly of desmosomes. When tested in human engineered heart tissue or mice, gene delivery also led to an improvement in cardiac function. Similar results were published by a contemporary study by Bradford et al., [72] in which *PKP2* was delivered in an AAV6-vector under the promoter of cardiac troponin T. This latter study also demonstrated that gene replacement rescued phenotype even when administered later in an adult murine model. These findings have been further confirmed by Wu et al [73], proving AAV9-mediated exogenous restoration of *PKP2* in a mouse knockout model. Their human vector construct obtained FDA approval as TN-401 and is now being tested in the first-in-human trial, phase 1b (safety and dosing, trial ID NCT06228924). Other ongoing similar phase 1 clinical trials (NCT06109181, NCT05885412) are testing LX2020 and RP-A601, the latter developed by van Opbergen et al [74] through the use of a recombinant vector to maximize targeting of cardiac cells. Despite differences in the delivery vectors and models used, altogether these studies proved the potential of gene replacement in *PKP2*-ACM and paved the way for clinical research.

Another gene therapy that is being studied focuses on the Dutch *PLN* founding variant (R14del). Building on previous evidence by Karakikes et al. [75], Dave et al. [76], performed in vivo genome editing by AAV9-CRISPR/Cas9 to knock down the mutant *PLN* allele.

In conclusion, the development of gene therapies in ARVC is promising. Further research will have to focus on combining efficacy with safety as well as providing a better understanding of which patients could benefit more from these approaches and validate them across different populations.

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8.1 Introduction

Myocarditis is a highly heterogeneous condition marked by myocardial inflammation and cardiomyocyte injury, arising from a wide range of mechanisms. Clinical presentations range from paucisymptomatic cases to fulminant forms with cardiogenic shock or severe arrhythmias. Myocardial inflammation can be caused by various infectious and noninfectious conditions, and it can be characterized by a wide range of clinical manifestations and evolutions. Diagnosis relies on clinical assessment, imaging, and, in selected cases, endomyocardial biopsy (EMB) [1, 2]. Treatment is tailored based on etiology, ventricular function, and complications.

8.2 Etiopathogenesis

Myocarditis can result from many different causes, such as infections, autoimmune diseases, vasculitis, hypersensitivity, drugs, vaccines, toxins, and physical agents.

It is still debated whether the main pathogenetic factor in the development of myocarditis is imputable directly to the action of cardiotropic or vasculotropic

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viruses, or to an abnormal immune response, mainly determined by autoreactive T cells, following the viral infection [1]. A hypothesis is that an initial damage to the heart from viral infection could act as a trigger and activate inflammation, which is amplified both from the innate and/or adaptive immune response [3–6].

The role of genetic predisposition has not been fully clarified; however, it seems to take part in the development of the myocardial abnormal inflammation that typically characterizes the onset of AM, together with an underlying infectious or autoimmune disease [1]. According to the “two-hit” hypothesis, a patient’s genotype could influence the phenotypic outcome in patients who have been exposed to infectious or toxic agents [7].

8.3 Epidemiology

The incidence and prevalence of the disease can vary according to the diagnostic tools used. While EMB guarantees histological, immunohistochemical, and immunological evidence [8], EMB is not performed on all patients due to the procedure-associated risks. As a result, the diagnosis of AM usually relies on clinical and imaging (CMR) criteria [4]. The highest incidence is found among young men, between the ages of 20 and 40 [9]. The increased use of CMR has determined a rise in the reported cases of myocarditis [10]. Nevertheless, the mortality rate and the rate of performed EMBs have not changed.

This suggests that cases of AM were likely underdiagnosed in the past and may still be underdiagnosed today. The most recent Global Disease Study has estimated a prevalence rate of 7,8/100,000 worldwide [11].

8.4 Clinical Presentation

Two main forms are distinguished according to the interval between symptom onset and diagnosis.

- Acute myocarditis: 1–3 months
- Chronic myocarditis: >3 months

Myocarditis exhibits a broad clinical spectrum—from silent or paucisymptomatic forms with a localized myocardial involvement, to fulminant, life-threatening disease, with systemic impairment [1]. The onset may be preceded by viral prodromes like fever, myalgias, and respiratory or gastrointestinal symptoms [12]. Clinically, three presentation patterns are usually distinguished: (1) acute chest pain, which often mimics an acute coronary syndrome; (2) a predominantly arrhythmic or conduction disturbance presentation; and (3) a de novo heart failure manifestation [13]. Patients presenting with an LVEF<50%, ventricular arrhythmias or low output state are at a higher risk of cardiac events than uncomplicated cases, which usually follow a benign course, and seldom develop persistent systolic dysfunction [14].

Moreover, patients with fulminant myocarditis (FM), defined by a low cardiac output syndrome requiring inotropes and/or mechanical circulatory support [15], have higher rates of cardiac death and heart transplantation both in the short- and long-term compared with patients with no FM presentation [16].

In a study that included 187 patients with acute myocarditis, during the initial hospitalization, 25.5% of patients with FM either died or required heart transplantation, whereas none of the nonfulminant patients experienced these outcomes. Furthermore, transplantation-free survival at 9 years was observed in all nonfulminant patients compared with only 64.5% of those with fulminant disease [16].

8.4.1 Chest Pain

Chest pain represents the most common presentation of AM. An ACS-like clinical presentation is frequently observed and may be attributable to pericarditis (1/3 of cases [17]) or occasionally to coronary artery spasm [12]. Clinical presentation is usually characterized by

- Chest pain, usually 1–4 weeks after an upper respiratory tract infection
- ECG abnormalities that can simulate an acute coronary syndrome
- Increased hs-troponin in the absence of significant occlusive coronary disease [18]

In most cases, the ACS-like syndrome has an uncomplicated course and a good prognosis [1].

8.4.2 Arrhythmias and Conduction Disturbances

Myocarditis is linked to an increased risk of SCD, with an annual incidence of 0.16 per 100,000 person-years and a higher rate among males [19]. Electrical instability related to the lysis of necrotic tissue, gap junction dysfunction, coronary ischemia caused by vasculitis, and the compressive effect of edema on the cardiac conduction system can lead to the development of different types of arrhythmias, both in the acute phase and later in the chronic stage [1]. Supraventricular arrhythmias are more common in the presence of concomitant pericarditis, while atrioventricular blocks and ventricular arrhythmias are more frequent when LV dysfunction and heart failure are present and can occasionally culminate in sudden cardiac death (SCD) [1]. Patients diagnosed with giant cell myocarditis or cardiac sarcoidosis have a high risk of developing ventricular arrhythmias. Lyme carditis frequently manifests as fluctuating AV block, which may rapidly progress to high-degree block. Prompt recognition is essential, as AV conduction disturbances in Lyme infection are often reversible with appropriate antibiotic therapy. Ventricular arrhythmias related to

myocardial scarring can occur at any stage of follow-up, even after inflammation has subsided. Late gadolinium enhancement in antero-septal myocardial segments has been associated with higher rates of major VA, including SCD. Polymorphic and irregular VAs are more commonly encountered during the active inflammatory phase, while monomorphic and regular VAs are generally linked to healed myocarditis with persistent structural sequelae. Nonsustained ventricular arrhythmias, family history of myocarditis, or a ring-like late gadolinium enhancement (LGE) pattern on CMR have been linked to desmosomal gene variants. These patients require further investigations, including genetic testing [20].

8.4.3 Heart Failure

AM may present as de novo acute heart failure or as a worsening of chronic heart failure in the absence of coronary artery disease or other identifiable causes. Patients typically report dyspnea, fatigue, and peripheral edema. Echocardiographic imaging can show reduced LV or biventricular systolic function, with or without ventricular dilatation or increased wall thickness [18]. Rapidly progressive symptoms that lead to hemodynamic compromise and cardiogenic shock define the clinical picture of fulminant acute myocarditis [15].

8.4.4 Fulminant Myocarditis

Fulminant myocarditis represents an emergency, in which hemodynamic status can deteriorate abruptly [21]. A definition of fulminant myocarditis can be framed as follows:

- Recent onset with symptoms beginning less than 4 weeks earlier
- Low cardiac output syndrome requiring inotropes and/or mechanical circulatory support

Fulminant myocarditis can strike across the age spectrum and shows no gender bias. It may arise from any histological variant. Prompt identification of the specific cause of shock is vital because only etiologically targeted therapy can be lifesaving. Early recognition remains the cornerstone for altering its course [21].

8.5 Diagnosis

A first-line assessment, including a detailed patient history, physical examination, 12-lead ECG, transthoracic echocardiography, and laboratory tests (e.g., hs-troponin and CRP), can support the diagnosis of clinically suspected myocarditis, aid in risk stratification, suggest a specific etiology, or point toward an alternative diagnosis. Other

life-threatening conditions must be excluded. A typical example is performing a coronary angiography in patients with an ACS-like presentation. It is also worth noting that some patients with myocarditis may be entirely asymptomatic, with diagnosis initiated by incidental findings. The diagnostic approach to myocardial inflammation should be individualized based on the severity of the clinical presentation and the early response to pharmacological therapy. The abnormalities that can emerge from the first-line evaluation are not pathognomonic, so a definitive diagnosis typically requires second-line investigations. In most cases, CMR imaging is sufficient; however, in selected cases, an invasive assessment such as EMB may be necessary [13, 18, 22]. Family history, including pedigree analysis, is recommended, and genetic testing should be considered in selected cases of recurrent or severe myocarditis. Myocarditis diagnosis has been the subject of considerable debate over the past decades, with various guidelines, position statements, and expert consensus documents proposing differing approaches that have evolved over time, and it remains a field requiring further research.

8.5.1 First-Line Noninvasive Diagnostic Workup

8.5.1.1 ECG

ECG is abnormal in about 85% of cases. However, a normal ECG does not exclude myocardial inflammation. ST-segment and T-wave abnormalities are the most common findings, observed in 58–70% of cases, particularly in the inferior and lateral leads. Less frequent findings, which are associated with a worse prognosis, include Q waves, left and right bundle branch blocks, and varying degrees of AV block. Conduction disturbances are associated with sarcoidosis and Lyme disease; hence, ECG may also suggest a specific etiology. In fulminant myocarditis, ECG may show low voltages due to myocardial edema. As the inflammatory process often involves the pericardium, pericarditis ECG features are commonly observed in patients with myocarditis [14, 15, 23, 24].

8.5.1.2 Laboratory Testing

The standard laboratory panel in the evaluation of suspected acute myocarditis includes hs-cTn, CRP, complete blood count (CBC), and natriuretic peptides. In most patients with myocarditis, hs-cTn levels are elevated. However, a normal troponin value does not rule out the diagnosis. Importantly, there is no direct correlation between the degree of troponin elevation and the severity of clinical presentation or overall prognosis. A chronic, low-level elevation of hs-cTn may support the diagnosis of inflammatory cardiomyopathy, particularly when laboratory evidence of myocardial injury appears disproportionate to the degree of systolic dysfunction and left ventricular remodeling observed on cardiac imaging. In isolated myocarditis, inflammatory markers may remain within normal limits. However, CRP is typically elevated in cases with concomitant pericardial involvement and in systemic inflammatory forms [1, 14, 15, 22]. Routine viral serology testing is not recommended, apart from targeted testing for *Borrelia*, *Rickettsia*, and HIV and HCV,

when clinically indicated. Autoimmune screening should be reserved for selected cases in which there is a clear clinical suspicion [18].

8.5.1.3 Echocardiography

All patients should undergo transthoracic echocardiography as part of the initial diagnostic workup. Given the dynamic nature of the disease, repeated assessments are recommended. Echocardiography is essential for excluding alternative noninflammatory cardiac conditions, contributes to risk stratification, and can reveal findings that support the diagnosis of myocarditis. Echocardiographic abnormalities commonly observed in myocarditis include reduced LVEF, regional wall motion abnormalities often involving the inferolateral wall, pericardial effusion, and diastolic dysfunction [1, 18, 22, 23]. In acute and particularly fulminant forms, echocardiographic features may mimic hypertrophic or restrictive cardiomyopathy, since patients can present with small ventricular cavity size, increased wall thickness with a granular echogenic appearance (reflecting myocardial edema), and both systolic and diastolic impairment [15]. Conversely, pronounced ventricular dilatation and a more spherical ventricular shape may suggest a chronic insult [4]. Left ventricular longitudinal strain may increase sensitivity and help in early diagnosis [22, 25].

8.5.2 Second-Line Diagnostic Workup

8.5.2.1 Cardiac Magnetic Resonance (CMR)

In most cases of clinically suspected myocarditis, CMR is the preferred second-level test to confirm the diagnosis through the application of the 2018 Updated Lake Louise Criteria. A definitive diagnosis of myocarditis requires the presence of at least one T2- and one T1-based criterion. T2-weighted sequences and T2 mapping techniques are useful for identifying and quantifying myocardial edema, whereas T1 mapping, extracellular volume (ECV) estimation, and LGE reflect myocardial injury and fibrosis. The detection of LV dysfunction and a pericardial involvement represent supportive criteria [22, 23, 26]. One of the major advantages of CMR lies in its noninvasive nature and ability to provide detailed tissue characterization with no exposure to ionizing radiation. When performed within 2–3 weeks from the onset of symptoms, CMR offers excellent diagnostic accuracy, with a reported sensitivity and specificity of 88% and 96%, respectively. After 3–4 weeks, the typical imaging findings of edema and acute inflammation tend to diminish, potentially limiting the diagnostic yield [26]. It plays a key role in the differential diagnosis of myocardial injury in patients presenting with chest pain, elevated troponin levels, and angiographically normal coronary arteries [27]. The pattern of LGE distribution becomes essential: ischemic injury typically appears as subendocardial/transmural enhancement confined to a specific coronary territory, while myocarditis usually presents with a non-ischemic pattern, characterized by subepicardial or mid-wall enhancement, not limited to coronary distributions. Despite its many strengths, CMR has several limitations. It cannot determine the histopathological characteristics of the inflammatory process. Its sensitivity is reduced in chronic forms of myocarditis, and technical

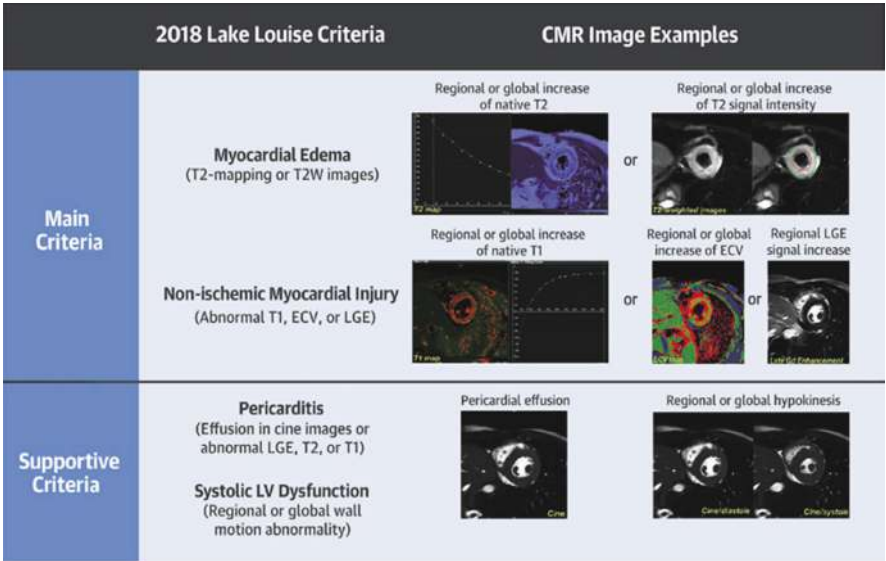


Fig. 8.1 Lake Louise Criteria. (Ferreira, V.M. et al. J Am Coll Cardiol. 2018;72 (24);3158–76)

limitations may arise in patients who are unable to perform breath-holds, have irregular cardiac rhythms, or suffer from claustrophobia. CMR is generally contraindicated in patients who are hemodynamically unstable. In such high-risk patients, EMB should be prioritized during the acute phase, and CMR may be performed once the patient has reached a stable clinical condition [14, 15, 22] (Fig. 8.1).

8.5.2.2 Endomyocardial Biopsy (EMB)

EMB remains the only technique capable of providing a definitive histopathological characterization of myocardial tissue, and it is considered the gold standard for establishing an etiological diagnosis in suspected myocarditis. According to the 1987 Dallas Criteria, *active myocarditis* is defined as the histological presence of inflammatory infiltrates associated with myocyte degeneration and necrosis of non-ischemic origin. The sensitivity and specificity of these criteria are relatively limited, approximately 60% and 80%, respectively [28]. The European Society of Cardiology (ESC) introduced myocarditis criteria that extended beyond conventional histology to include immunohistochemical evaluation of infiltrating immune cells, mainly CD3+ T lymphocytes [18].

To enhance patient care, diagnostic criteria for lymphocytic myocarditis on endomyocardial biopsy have recently been revised to overcome limitations of the Dallas and European Society of Cardiology (ESC) criteria. The “Seaport” criteria incorporate CD3 immunohistochemistry to quantify T lymphocytes and classify disease severity based on the extent of inflammatory infiltrates and myocyte injury, defining three grades (mild, moderate, severe), as well as a category of scattered increased T lymphocytes of undetermined significance (SITUS) [45].

The histological subtype of inflammatory infiltrate bears both prognostic and therapeutic implications [18, 22]. In addition to histopathological assessment, quantitative real time viral PCR and immunohistochemical evaluation are also recommended [28, 49, 50].

The diagnostic yield of EMB depends on several factors: the experience of the operator and pathologist, the number and location of samples obtained, and the timing of the biopsy [1]. Diagnostic sensitivity is highest when the procedure is performed within 2 weeks of symptom onset [29]. The main limitation of EMB is its invasive nature, which invariably carries the risk of procedure-related complications. In experienced centers, the major adverse events rate is usually <1% [28]. EMB should be reserved for selected clinical scenarios where the diagnostic and therapeutic benefits outweigh the risks [51]. According to the 2025 ESC Guidelines, EMB is recommended in high-risk myocarditis and/or hemodynamic instability and/or in patients with intermediate-risk myocarditis not responding to conventional therapy in order to detect a specific histologic subtype and assess the presence of viral genome for treatment [30] (Figs. 8.2, 8.3, and 8.4).

8.5.2.3 Genetic Testing

Genetic testing has gained increasing attention; however, its clinical role remains to be defined. Variants associated with DCM or ACM have been identified in up to 8% of patients presenting with new-onset acute myocarditis, with *DSP* being the most frequently implicated gene [25]. It remains uncertain whether episodes of myocarditis serve as environmental triggers that unmask the phenotypic expression of underlying genetic cardiomyopathies or whether these genetic conditions inherently follow a natural course characterized by recurrent inflammatory “hot-phase” episodes. A worse prognosis has been reported in patients with a pathogenic or likely pathogenic variant in desmosomal genes. Patients with pathogenic *DSP* variants have a 62.3% risk of death, ventricular arrhythmias, and recurrent myocarditis at 5 years, against 17.5% in those with a negative genetic test [20]. Further prospective studies are necessary to determine whether genetic testing can enhance risk stratification in patients with acute myocarditis, who would otherwise be considered at low risk. Based on our experience, genetic testing should be considered in patients with AM when one or more of the following “red flags” are present: recurrent myocarditis episodes; a positive family history of cardiomyopathy, SCD; high-risk late LGE patterns on CMR (e.g., ring-like or septal distribution); high arrhythmic burden; and the development of an overt dilated cardiomyopathy phenotype (Tables 8.1 and 8.2).

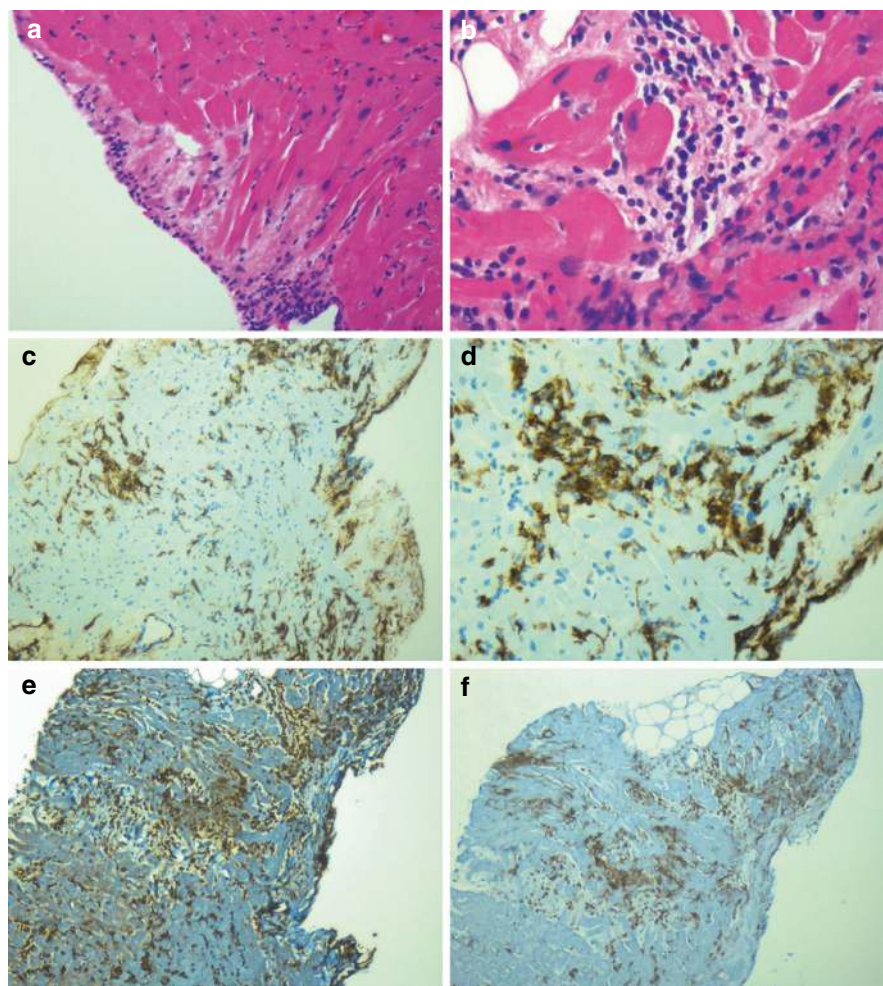


Fig. 8.2 Endomyocardial biopsy of a 40-year-old man admitted with cardiogenic shock due to fulminant myocarditis. Panels A and B show hematoxylin and eosin staining revealing severe inflammatory infiltrates. Panels C ($\times 10$ original magnification) and D ($\times 20$ original magnification) show immunohistochemical analysis demonstrating a dominant population of natural killer CD16+ lymphocytes. Panel E ($\times 10$ original magnification) shows HLA-DR expression, indicating immune activation. Panel F ($\times 10$ original magnification) shows immunohistochemical analysis demonstrating a population of activated T lymphocytes (CD45RO+)

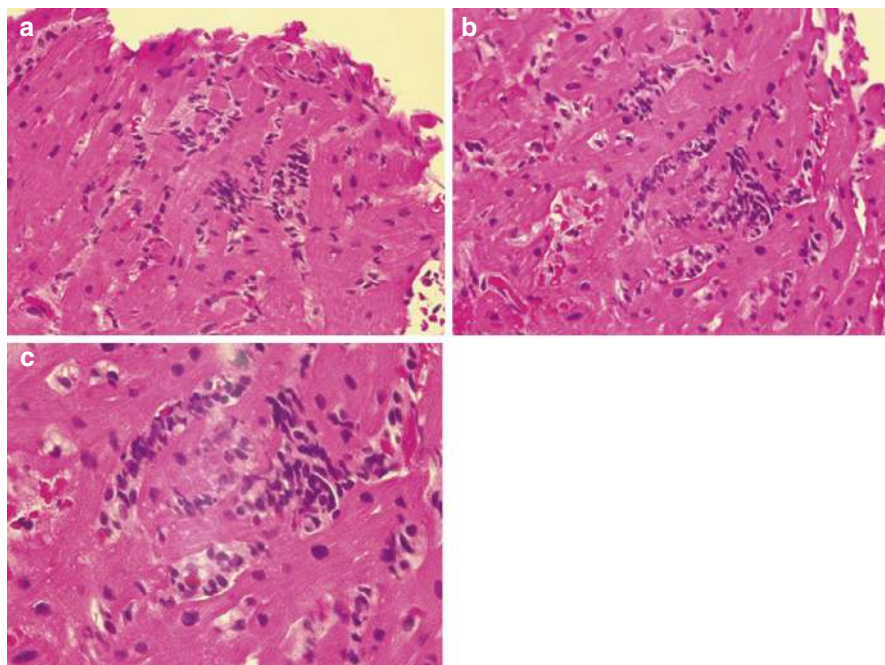


Fig. 8.3 Endomyocardial biopsy of a 1-year-old female admitted with cardiogenic shock due to fulminant myocarditis. Hematoxylin and eosin staining (panels A and B $\times 40$ original magnification; panel C $\times 63$ original magnification) reveals severe inflammatory infiltrates

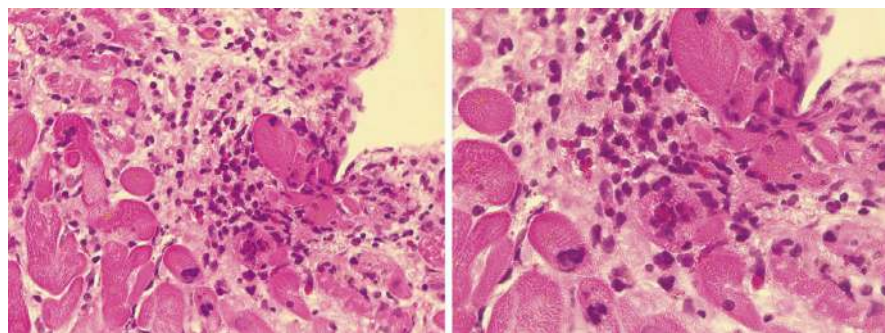


Fig. 8.4 Endomyocardial biopsy (hematoxylin and eosin staining; left panel at $\times 40$ original magnification, right panel at $\times 63$ original magnification) of a young man with acute myocarditis showing eosinophilic endomyocarditis, with a significant proportion of eosinophilic granulocytes, some of which are undergoing active degranulation

Table 8.1 Diagnostic workup for myocarditis (Sinagra et al. [13])

Role and Typical Findings of Noninvasive Testing and Endomyocardial Biopsy in the Diagnostic Work-up of Myocarditis			
Variable	Low risk	Intermediate risk	High risk
Personal history	Should always be thoroughly investigated [4, 10, 11] Flulike symptoms, insect bite (for <i>Borrelia</i> or <i>Rickettsia</i> suspicion), timing of symptoms onset, family history of cardiomyopathy, drugs or toxic substance assumption		
Biomarkers	Troponin: typically elevated (no prognostic value) [12, 13]	Troponin: low accuracy for detection of myocardial inflammation [14]	
	Antimicrobial serology: • low accuracy for detection of microbial infection [15] • not to be routinely considered in the diagnostic work-up • may be useful to detect infections by <i>Borrelia</i> or <i>Rickettsia</i> in clinical suspicion for bradyarrhythmias and advanced AV blocks • Serologic analyses for autoimmune diseases should be considered only in the presence of clinical suspicion		
Electrocardiography	Diffuse and saddle-shaped ST-segment elevation Bradyarrhythmias or advanced AV conduction defects in the absence of LV dysfunction may be suggestive of infections by <i>Borrelia</i> or <i>Rickettsia</i>	Low voltages Discordance between the severity of the clinical scenario and the scarcity of electrocardiographic alterations (absence of left atrial dilation and intraventricular conduction delay) Bradyarrhythmias or advanced AV conduction defects in the presence of LV dysfunction may be suggestive of sarcoidosis or giant cell myocarditis	
Echocardiography	Normal ventricular dimensions, morphologic features, wall motion, and global function Transient wall motion anomalies Transient mild ventricular dysfunction Pericardial effusion [4, 12, 13]	Global impairment of LV or biventricular function without major remodeling Diastolic dysfunction Patchy alterations of the wall motion not responsive to coronary distribution or electrocardiographic alterations Pericardial effusion Transient pseudohypertrophy of the ventricular wall Alteration of the echocardiographic myocardial texture [4, 16, 17]	
Cardiac magnetic resonance imaging	Good accuracy [11, 18–20] Distinction between myocarditis and acute coronary syndromes (subepicardial vs subendocardial/transmural LGE distribution) [18]	Modest accuracy [14, 21] May be considered a conclusive diagnostic test	Modest accuracy [14, 21] Cannot be considered a conclusive diagnostic test in the context of a major clinical syndrome

(continued)

Table 8.1 (continued)

Role and Typical Findings of Noninvasive Testing and Endomyocardial Biopsy in the Diagnostic Work-up of Myocarditis			
Variable	Low risk	Intermediate risk	High risk
Coronary angiography/ computed tomography	In the presence of risk factors for coronary artery disease	In the presence of risk factors for coronary artery disease	Indicated
Endomyocardial biopsy	Not indicated	May be considered (case by case selection)	Indicated in the presence of refractoriness to medical therapy in the short term

Table 8.2 Comparison between the “2025 ESC Guidelines for the management of myocarditis and pericarditis” (Schulz-Menger et al. [30]) and “2024 ACC Expert Consensus Decision Pathway on Strategies and Criteria for the Diagnosis and Management of Myocarditis” (Drazner et al. [22])

	ESC Guidelines, 2025 [30]	ACC Expert Consensus, 2024
Possible presentations	Chest pain Heart failure Arrhythmias Sudden cardiac death Potential genetic background	Chest pain Heart failure Arrhythmias
Initial assessment	12-lead ECG Markers of myocardial injury (TnI, TnT) Erythrocyte sedimentation rate, CRP CBC (including eosinophilic count) Heart failure markers (NT-proBNP) Echocardiography (including strain imaging) Routine viral serology testing not recommended	12-lead ECG hs-cTn CBC with differentials, CRP Transthoracic echocardiography, with global longitudinal strain
CMR	Updated Lake Louis Criteria (LLC) <i>CMR-proven myocarditis</i> (2 LLC main criteria) ≥ 1 T2-based criterion, myocardial edema (T2W imaging or T2 map) ≥ 1 T1-based criterion (LGE, T1 map or ECV) <i>CMR-uncertain myocarditis</i> (1 LLC main criterion) ≥ 1 T1-based criterion, nonischemic myocardial injury (LGE, T1 map or ECV)	2018 Updated Lake Louise Criteria (LLC) <i>Main criteria</i> ≥ 1 T2-based criterion (T2W imaging or T2 map) and ≥ 1 T1-based criterion (LGE, T1 map or ECV) <i>Supportive criteria</i> Pericardial abnormalities (concomitant pericarditis) Systolic LV dysfunction

(continued)

Table 8.2 (continued)

	ESC Guidelines, 2025 [30]	ACC Expert Consensus, 2024
Diagnostic criteria	For <i>possible</i> myocarditis Clinical presentation with at least 1 additional criterion (ST-T changes, troponin elevation, wall motion or strain abnormalities, reduced EF, or CMR findings) For <i>unlikely/rejected</i> myocarditis Only clinical presentation	For symptomatic myocarditis (<i>stage C</i>) ≥ 1 presentation + ≥ 1 diagnostic criteria Histopathology consistent with myocarditis CMR consistent with myocarditis Elevated hs-cTn with additional supportive evidence
EMB indications	High-risk myocarditis Hemodynamic instability 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 Generally indicated in selected cases, to establish a differential diagnosis and to guide etiology-driven therapy	Asymptomatic myocarditis (<i>stage B</i>) in the context of ICI therapy Symptomatic myocarditis (<i>stage C</i>) with ≥ 1 between: LV dysfunction Symptomatic HF Advanced AV block and/or ventricular arrhythmias Peripheral Eosinophilia Uncertain diagnosis and inability to undergo CMR Advanced myocarditis (<i>stage D</i>)
Definite diagnosis	Clinical presentation and CMR or EMB-proven myocarditis	EMB and/or CMR
Genetic testing	Recommendation IC To obtain family history including pedigrees in cases of recurrent IMPS to provide clues to the underlying etiology, determine inheritance pattern, and identify a relative risk Recommendation IIaB Patients with “red flags” (<i>see Genetic testing</i>)	Suggested in all patients with myocarditis. In case of limited resources, prioritize patients with: Recurrent myocarditis Family history of CMPs, myocarditis, sudden cardiac death Ring-like or septal LGE at CMR

8.6 Natural History and Prognosis

Myocarditis is considerably heterogeneous when assessing its evolution. Mortality in acute myocarditis is approximately 1–7% [14, 31]. The in-hospital mortality rate for low-risk syndromes is close to 0% compared with a 12–15% of mortality or heart transplant rate for intermediate and high-risk syndromes [14].

8.6.1 Low-Risk Myocarditis

Patients presenting with chest pain, normal LVEF without wall motion abnormalities, no significant ventricular arrhythmias, and ECG alterations that normalize within 4 weeks of onset are considered at low risk of future cardiovascular events. After normalization of the ECG and echocardiographic findings, patients generally have a good prognosis. The elevation of blood troponin values is not considered relevant in the prognostic stratification and does not justify a more in-depth follow-up.

CMR imaging is useful for risk stratification, as certain features, such as a mid-wall anteroseptal pattern, extensive involvement, or persistent LGE over time, may indicate a higher risk of major cardiovascular events [32, 33]. Younger age and prior episodes of myocarditis are predictors of relapsing myocarditis [34].

8.6.2 Intermediate-Risk Myocarditis

The intermediate-risk category identifies a “gray zone” of prognostic uncertainty. The clinical evaluation and follow-up should be assessed case-by-case to identify the possible progression to heart failure. These patients have a mild-to-moderate LVEF dysfunction, persistent ECG or wall motion alterations, diffus or basal anteroseptal LGE, or frequent nonsustained ventricular tachycardia [2].

8.6.3 High-Risk Myocarditis

High-risk syndromes include cases with arrhythmic presentation or a severe heart failure at onset. This subgroup of patients has both a short-term and long-term worse prognosis, with a 10% rate of heart transplantation at 1 year and a 40% rate at 10 years [35]. The most significant negative prognostic factors are acute hemodynamic instability, intraventricular conduction anomalies, and extended LGE associated with left ventricular remodeling [2]. EMB is indicated in these cases. Fulminant myocarditis with cardiogenic shock has a 28% risk of death or need for

Table 8.3 Follow-up in acute myocarditis

	Low-risk	Intermediate-risk	High-risk
Clinical reassessment	6 months 1 year 2 years	3 months 6 months 1 year Yearly	1 month 3 months 6 months 12 months Yearly
Noninvasive testing	Clinical assessment ECG and echocardiogram CMR after 6 months recommended when LGE is present	Clinical assessment ECG and echocardiogram Holter monitoring Exercise test to detect arrhythmias CMR after 6 months to evaluate LGE and wall motion evolution	
EMB	Not recommended	EMB repetition in selected cases of: Worsening heart failure Significant EF reduction Significant or recurrent troponin release Persistent or recurrent electrical instability	
Physical activity restraint	Yes, for at least for 3–6 months	Yes, for at least 6 months and decision should be individualized	
Lifetime follow-up	No if normalized within 2 years	Yes	

heart transplant after 60 days, and a 48% risk after 7 years [36]. Ventricular arrhythmias during acute myocarditis may be self-limiting; therefore, an accurate risk stratification of future major arrhythmic events (MAE) remains challenging. The risk of MAEs during follow-up for patients presenting with life-threatening arrhythmias is 25%; generally occurring within the first year of follow-up [37]. Persistent ECG or wall motion abnormalities, severe ventricular functional impairment, or extensive LGE appear to be associated with a higher risk of MAEs [13, 37]. Two other prognostic factors are etiology and histopathological features [35]. GCM has a significantly poorer prognosis compared to the eosinophilic and lymphocytic types [36] (Table 8.3).

8.7 Treatment

The management of acute myocarditis should be individualized based on disease severity, hemodynamic stability, underlying etiology, and clinical presentation. Therapeutic decisions should be guided by risk stratification and histopathological findings, where available (Fig. 8.5).

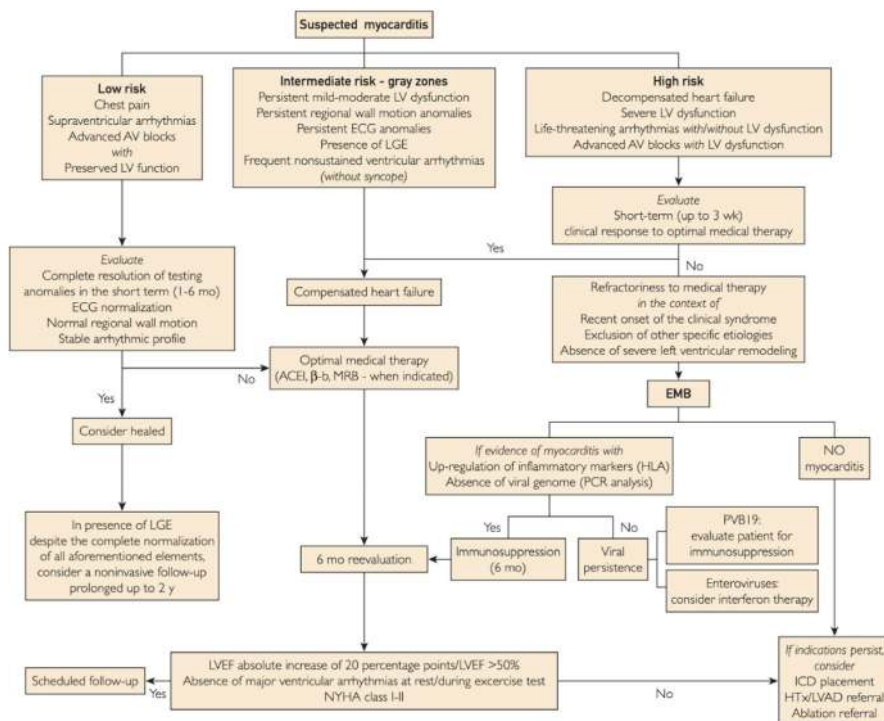


Fig. 8.5 Clinical management of myocarditis. (Sinagra et al. [13])

8.7.1 Medical Therapy

Pharmacological therapy is used to control symptom severity, prevent adverse myocardial remodeling, and reduce the occurrence or recurrence of arrhythmias.

8.7.1.1 Acute Ventricular Dysfunction

In hemodynamically stable patients, standard heart failure pharmacotherapy should be employed, including beta-blockers, angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors (SGLT2i) [38], following ESC and AHA guidelines for heart failure with reduced ejection fraction. Loop diuretics may be added for volume overload. The early initiation of neurohormonal therapy in patients with EF >50% remains debated [23], particularly in the absence of left ventricular dilation or LGE on CMR. In these cases, therapy is individualized and may be discontinued if myocardial function remains stable after 6–12 months.

Inotropic agents, such as norepinephrine, epinephrine, or milrinone, are usually required when treating an acute severe LV systolic dysfunction with hemodynamic instability [14]. The best setting for the treatment of this condition is a hub center with mechanical cardiopulmonary support facilities [23].

8.7.1.2 Arrhythmias

There are no disease-specific recommendations for arrhythmias associated with myocarditis. Nonsustained arrhythmias may require treatment only if symptomatic. Amiodarone remains the agent of choice for ventricular arrhythmias during the acute phase. Other treatment options are sotalol (for LVEF >40%) and mexiletine.

After stabilization, beta-blockers are preferred for chronic suppression, given the long-term toxicity of amiodarone. In cases of high-grade atrioventricular block or sustained ventricular arrhythmias, temporary pacing or defibrillation may be necessary.

When appropriate, implantable cardioverter-defibrillators (ICDs) are generally deferred until at least 3–6 months post-onset, unless arrhythmias persist. Wearable cardioverter-defibrillators may serve as a bridge during this period [7].

Athletes diagnosed with myocarditis should refrain from competitive sports for a minimum of 3–6 months and decision must be individualized. Return to play should be based on normalization of imaging, ECG, biomarkers, and clinical recovery [39]. After the acute phase, clinicians should follow the current guidelines for the management of ventricular arrhythmias and sudden cardiac death [40].

8.7.2 Mechanical Circulatory Assistance and Heart Transplant

When systolic dysfunction is refractory to medical therapy and low-cardiac output syndromes occur, mechanical circulatory support may be needed. Temporary devices, such as intra-aortic balloon pump (IABP), an axial flow pump, or venoarterial ECMO, should be taken into consideration. This treatment can be considered a bridge to recovery, heart transplantation, or implantation of a durable device [23]. Multicenter studies show a short-term rate of transplant-free survival of 66–76% in fulminant myocarditis, who were treated with temporary mechanical circulatory support. Given the absence of protocols for temporary MCS management, the choice of therapy pertains to the clinicians, according to their experience [7].

8.7.3 Immunosuppression

The use of immunosuppressive agents remains controversial in acute myocarditis. The original Myocarditis Treatment Trial (1995) failed to demonstrate a significant benefit of corticosteroids and azathioprine in unselected patients [41]. However,

acute myocarditis associated with systemic autoimmune disorders is generally treated with corticosteroids as first-line therapy with higher dosages or additional immunosuppressive therapies reserved for patients with complicated presentation [23]. The immunosuppressive therapy is currently indicated in specific etiologic subtypes [23, 41]. In these settings, high-dose corticosteroids are typically administered, often in combination with other immunosuppressants such as azathioprine, mycophenolate mofetil, or cyclosporine.

In patients with virus-negative myocarditis confirmed by endomyocardial biopsy, immunosuppressive therapy with corticosteroids and azathioprine has been confirmed as both effective and safe, leading to sustained improvement in clinical status and a significant increase in left ventricular ejection fraction over long-term follow-up [42]. Treated patients experienced a marked reduction in heart failure symptoms and hospitalizations compared with those managed with standard heart failure. A multicenter randomized study (IMPROVE-MC) on immunosuppression in virus-negative myocarditis is ongoing (patients with biopsy-proven myocarditis and reduced LVEF $\leq 45\%$ randomized to a 12-month treatment with prednisone and azathioprine vs. placebo in addition to optimized medical therapy). The ongoing MYTHS trial (MYocarditis THERapy with Steroids) is evaluating a short course of high-dose intravenous methylprednisolone administered over three consecutive days in patients with acute myocarditis and reduced left ventricular systolic function (LVEF $< 41\%$) while the ongoing MYTHS-MR trial (MYocarditis THERapy with Steroids in Patients with Mildly Reduced Ejection Fraction) is evaluating pulsed IV methylprednisolone in patients with acute myocarditis and mildly reduced EF (LVEF $< 50\%$). In both studies, treatment response is assessed with clinical and functional follow-up at 6 months.

In selected cases of virus-negative, biopsy-proven B-cell-mediated autoimmune myocarditis, rituximab has emerged as a therapeutic option, with case reports demonstrating histological resolution and improvement in left ventricular function following anti-CD20 therapy [42]. Other targeted biologic agents have been reported in refractory cases, although evidence remains limited to small series and registry data. Beyond established immunosuppressive regimens, novel therapeutic strategies are being explored in fulminant or refractory myocarditis. Ruxolitinib has shown promising outcomes in cytokine-driven myocardial inflammation, with recent reports describing recovery of cardiac function under combined immunomodulation and mechanical support [42].

The main immunosuppressive strategies tailored to myocarditis etiology and clinical presentation are summarized in Table 8.4.

Table 8.4 Aetiology-driven immunosuppressive regimens based on the latest scientific evidence [22, 30, 42, 44]

Myocarditis subtype	First-line agents	Second-line agents	Rescue therapies	Notes
Lymphocytic autoimmune	<i>Prednisone</i> 1 mg/kg/day (nonsevere presentation) ^a <i>Methylprednisolone</i> i.v. 7–14 mg/kg/day for 3 days, then 1 mg/kg/day p.o. (severe presentation) ^a	<i>Oral corticosteroids + immunosuppressive therapy (IST): azathioprine^b or mycophenolate mofetil^c, cyclosporine^d, methotrexate^e</i>	<i>Intravenous immunoglobulins (IVIG)^f or plasmapheresis</i> (3–5 sessions in 5–10 days)	Viral genome must be excluded (PCR on EMB); response and tapering assessed based on symptoms and LVEF.
Eosinophilic	<i>Prednisone</i> 1 mg/kg/day (nonsevere presentation) ^a <i>Methylprednisolone</i> i.v. 7–14 mg/kg/day for 3 days, then 1 mg/kg/day p.o. (severe presentation) ^a	<i>Oral corticosteroids + IST</i>	–	In addition to immunosuppressive therapy, targeted treatment of the underlying condition associated with eosinophilic myocarditis should be implemented when identified. Given the reported occurrence of intracavitary thrombi in a substantial proportion of eosinophilic myocarditis cases (≈12%), anticoagulation may be considered during the acute phase [47]. Typical treatment duration ≥6 months.

(continued)

Table 8.4 (continued)

Myocarditis subtype	First-line agents	Second-line agents	Rescue therapies	Notes
Giant cell myocarditis	<i>Prednisone</i> 1 mg/kg/day p.o. then tapered (nonsevere presentation) ^a <i>Methylprednisolone</i> i.v. 7–14 mg/kg/day for 3 days, then 1 mg/kg/day p.o. (severe presentation) ^a + <i>IST</i> (azathioprine ^b or mycophenolate mofetil ^c , cyclosporine ^d)	<i>Antihymocyte globulin (ATG)</i> ^g , <i>cyclophosphamide</i> ^h , <i>rituximab</i> ⁱ	–	Based on multicenter experience, combined immunosuppression is often life-saving. Typical treatment duration of at least 12 months.
Sarcoid-associated	<i>Prednisone</i> 1 mg/kg/day p.o., tapering from 40–60 mg daily (non-severe presentation) <i>Methylprednisolone</i> i.v. 7–14 mg/kg/day for 3 days, then 1 mg/kg/day p.o. (severe presentation)	<i>Methotrexate</i> ^e (first choice) or <i>azathioprine</i> ^b , <i>mycophenolate mofetil</i> ^f , <i>cyclophosphamide</i> ^a	<i>Infliximab</i> ^j or <i>adalimumab</i> ^k , <i>rituximab</i> ⁱ	Taper steroids after 3–6 months; adjust based on cardiac MRI/PET. Long-term maintenance therapy (>12 months).

(ICI)-associated myocarditis	Discontinue ICI therapy and perform clinical reassessment <i>Methylprednisolone</i> i.v. 500–1000 mg/day × 3 days, then taper with oral prednisone (nonsevere presentation) <i>Methylprednisolone</i> i.v. 7–14 mg/kg/day × 3 days, then 1 mg/kg/day (severe presentation)	No response at 24–48 h: consider <i>mycophenolate mofetil</i> ^f , <i>ATG</i> ^g , <i>abatacept</i> , or <i>alemtuzumab</i>	<i>Infliximab</i> ⁱ or <i>adalimumab</i> ^k , <i>rituximab</i> ^l	Early initiation of corticosteroids (within 24 h) is recommended; up to 50% of the patients may be steroid-refractory. According to cardio-oncology consensus documents, rapid escalation of therapy is essential for survival [48]. Infliximab should be used with extreme caution, particularly in patients with heart failure [46]. Typical treatment duration ≥4–6 weeks and longer in selected cases. In a prospective registry, combined ruxolitinib and high-dose abatacept, together with screening for concomitant respiratory muscle failure, was associated with improved survival.
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ICI immune checkpoint inhibitor

^aSevere presentation myocarditis is defined by hemodynamic compromise, malignant arrhythmias, advanced conduction disturbances, or severe ventricular dysfunction; all other stable presentations are considered nonsevere presentations

Immunosuppressive regimen (IS):

^b Azathioprine: 1–2 mg/kg per day p.o. (typically 100–150 mg daily, in 1–2 divided doses)

^c Mycophenolate mofetil: 500–1000 mg p.o. b.i.d. (total 1–2 g/day)

^d Cyclosporine: ~3–5 mg/kg/day p.o. (divided b.i.d.) adjusted to target trough levels ~150–250 ng/mL

^e Methotrexate: 15–20 mg/week p.o. or s.c. (low-dose weekly, with folic acid supplementation)

^f IVIG = standard dose off-label 2 g/kg total dose, typically administered over 1 to 2 days

^g Antithymocyte globulin: ~1 mg/kg i.v., often given daily for 3–5 days

^h Cyclophosphamide: 600 mg/m² i.v. bolus on days 1, 15, and 30 (pulse therapy)

ⁱ Rituximab: 375 mg/m² i.v. weekly × 4 doses (1 month)

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

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

^l Abatacept: 500 mg i.v. every 2 weeks × 5 doses (approximately 10 weeks)

^m Alemtuzumab: 30 mg i.v. once (alternative: 15 mg i.v. daily for 2 days)

8.7.4 Anti-Inflammatory Therapy

Nonsteroidal anti-inflammatory drugs (NSAIDs), particularly ibuprofen, indomethacin, and aspirin, may be used for symptom control in low-risk patients with chest pain or pericardial involvement. Colchicine may be considered in cases of myopericarditis, although randomized data are still lacking. The ongoing CMP-MYTHiC (CardioMyoPathy With MYocarditis THERapy With Colchicine) is assessing colchicine for chronic inflammatory cardiomyopathy.

8.7.5 Post-Discharge and Long-Term Therapy

Patients with residual systolic dysfunction after discharge should continue guideline-directed medical therapy for heart failure. In a longitudinal study [45], the beta-blocker group was associated with better outcomes compared to the non-beta-blocker cohort. The evidence from this analysis is not strong enough to suggest any specific indications for the use beta-blockers or RAASi after discharge in patients with a preserved ejection fraction (>50%), even if there is evidence of fibrosis (LGE) at CMR. The decision to administer these drugs is made on a case-to-case basis. In patients with complete functional recovery, therapy may be tapered after 6–12 months, particularly in the absence of residual LGE or arrhythmias [1]. However, patients with mid-wall or anteroseptal LGE, or with desmosomal gene variants, require closer surveillance due to their elevated risk of recurrence, sudden cardiac death, or progression to DCM.

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Phenocopies and Restrictive Cardiomyopathies

9

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9.1 Introduction

Within the spectrum of cardiomyopathies, several conditions can resemble the phenotypic features of a genetic cardiomyopathy while having a different underlying cause—these are known as *phenocopies*. Significant overlap exists in the clinical presentation of different myocardial diseases at various stages of their pathophysiological evolution. This is particularly relevant for hypertrophic cardiomyopathy

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(HCM), as increased wall thickness is a common feature across a wide range of cardiac disorders. Differentiating true HCM from its phenocopies can be challenging and often requires a comprehensive, multimodality imaging and multiparametric approach, with endomyocardial biopsy reserved for selected cases. This distinction is crucial, given the substantial implications for prognosis, therapeutic decision-making, and family screening.

Restrictive cardiomyopathy (RCM) encompasses a heterogeneous group of myocardial diseases characterized by increased myocardial stiffness and reduced diastolic compliance, leading to fixed diastolic volumes. Restrictive ventricular filling is the hemodynamic hallmark of RCM. Patients may present with advanced diastolic dysfunction from onset or develop a restrictive phenotype in the later stages of disease. This chapter will review the main phenocopies of HCM and RCM, highlighting their pathophysiology as well as their clinical and imaging characteristics. Of note, significant phenotypic and genetic overlap can be observed between these two forms of cardiomyopathies: most HCM phenocopies can develop restrictive physiology at some point, once myocardial fibrosis progresses to the point of causing severe diastolic dysfunction.

9.2 Phenocopies of Sarcomeric HCM

9.2.1 Cardiac Amyloidosis: Transthyretin (TTR) and Light-Chain (AL) Subtypes

Amyloid cardiomyopathy is an infiltrative cardiomyopathy caused by the deposition of insoluble protein in the form of amyloid fibrils within the myocardial extracellular space.

More than 30 proteins are known to form amyloid deposits *in vivo*; however, only nine have been identified as capable of accumulating within the myocardium and causing clinically relevant cardiac disease. Among these, certain forms (AApoAI, AApoAII, AApoAIV, A β 2M, AFib, AGel) are very rare, while cardiac amyloidosis secondary to chronic inflammatory or infectious conditions (AA type) has become increasingly uncommon. Consequently, over 98% of currently diagnosed cases of cardiac amyloidosis are attributable to fibrils derived from monoclonal immunoglobulin light chains (AL) or transthyretin (ATTR), either in its hereditary variant (ATTRv) or acquired wild-type form (ATTRwt) [1].

AL amyloidosis results from a plasma cell clone producing misfolded immunoglobulin free light chains (FLCs) (predominantly of λ type) that deposit in multiple organs, where they cause both toxic and infiltrative damage [2, 3]. Cardiac involvement is the most critical determinant of prognosis. The kidney, liver, spleen, and peripheral nervous system are commonly involved [4].

ATTR amyloidosis—either wild-type (non-hereditary form, ATTRwt) or variant (hereditary form, ATTRv)—results from dissociation of the circulating TTR tetramer, a protein synthesized by the liver responsible for transporting thyroxine and retinol-binding protein [4]. ATTRwt amyloidosis typically develops in older

patients, predominantly males, and presents with specific osteoarticular disorders, such as carpal tunnel syndrome (CTS) or lumbar stenosis. ATTRv amyloidosis, caused by single-gene mutations (Table 9.1), often presents in young adults with a heterogeneous phenotype involving predominantly the heart (cardiomyopathy), the nerve (neuropathy), or both (mixed phenotype) [4]. The main mechanism of damage in ATTR amyloidosis is progressive amyloid deposition leading to increased stiffness and restrictive physiology [5], conduction abnormalities, and systolic dysfunction [4].

The diagnosis of amyloidosis has historically been delayed due to multiple factors: a) lack of disease awareness, b) nonspecific signs and symptoms (i.e., increased wall thickness common in hypertensive heart disease or aortic stenosis), and c) need of histological proof of amyloid deposition [5]. Identification of typical cardiac and extracardiac clinical, laboratory, and imaging features of amyloidosis (red flags) has exponentially increased the number of patients diagnosed with ATTR-CM and AL amyloidosis (Table 9.2).

Among clinical features, CTS is the earliest marker of disease that can precede by 5–10 years the development of ATTR-CM [7]. In prospective studies, 10% of patients undergoing carpal tunnel release already harbor amyloid (mostly ATTR) in their tenosynovial tissues, and 20% of them already show evidence of ATTR-CM [8]. Identification of unexplained ventricular hypertrophy at the time of surgery has been associated with subsequent development of symptomatic HF and ATTR-CM [9].

Amyloid deposition in the heart results in progressive cardiac injury reflected by elevation in cardiac biomarkers, predominantly N-terminal pro-brain natriuretic peptide (NT-proBNP) and troponin. The toxic effect of AL oligomers is reflected by significantly higher concentrations of cardiac biomarkers in patients with AL amyloidosis compared to those with ATTR amyloidosis [2]. A monoclonal gammopathy can be found in 20–25% of patients aged 70 years or above and does not exclude the presence of ATTR-CM in a suggestive clinical context [10]. Of note, normal serum protein electrophoresis has a sensitivity of only 60–70%, which cannot accurately rule out the presence of a monoclonal component. Missing the diagnosis of AL

Table 9.1 Most common TTR mutations identified in patients with symptomatic amyloidosis

TTR mutation	Mayo Clinic	TTR amyloidosis outcomes survey
T60A	26.0	1.7
V30M	16.0	73.3
V122I	11.0	4.4
S77T	6.0	1.6
L111M	0.0	1.9
E89Q	0.0	2.1
All others	41.0	16.7

Values are %. Data from Swiecicki et al. [11] (a single center retrospective study on 266 patients with the diagnosis of hereditary TTR amyloidosis) and Coelho et al. [12] (a multicenter, longitudinal, observational survey on patients with the diagnosis of TTR amyloidosis including 885 patients with the mutated form)

Table 9.2 Clinical, laboratory, and imaging red flags for amyloidosis

Clinical	Hypertrophic cardiomyopathy diagnosed after the sixth decade of life Hypertensive cardiomyopathy diagnosed in elderly patients with normal BP and no valvular disease Need for down-titration or discontinuation of antihypertensive therapy due to poor tolerability intolerance of β -blockade in newly diagnosed heart failure Bowel dysfunction (constipation, diarrhea) Heart failure with preserved ejection fraction Aortic valve stenosis in the elderly Periorbital purpura and macroglossia Bilateral CTS, atraumatic rupture of biceps tendon, and LS stenosis. Unexplained neuropathic pain, mostly in non-diabetic patients Orthostatic hypotension and erectile dysfunction due to autonomic neuropathy. Vitreous deposits
Laboratory	Persistent mild increase in troponin levels on repeated tests Increased NT-proBNP values (> 5000 pg/mL) in non-advanced heart failure Low serum transthyretin values Low QRS voltages (peripheral and/or precordial leads)
ECG	Discrepancies between the degree of wall thickening and QRS voltages AV delay and/or blocks Pseudonecrosis
Echocardiography	Diffuse left ventricular wall thickening Coexisting right ventricle hypertrophy Restrictive diastolic filling pattern Paradoxical low-flow, low-gradient aortic valve stenosis Pericardial effusion Increased thickness of the interatrial septum and atrioventricular valves Granular sparkling appearance of the myocardium Reduced left ventricular longitudinal strain with “apical sparing” pattern
CMR	Diffuse late gadolinium enhancement with subendocardial or transmural distribution Significant elevation in native T1 values Increased extracellular volume fraction (>0.30)
Bone scintigraphy	Cardiac uptake of bone tracers
PET	Cardiac uptake of tracers

Source: Reproduced from Porcari et al. [6]

ATTR transthyretin amyloidosis, *AV* Atrioventricular, *BP* blood pressure, *CMR* cardiac magnetic resonance, *CTS* carpal tunnel syndrome, *LS* lumbar spine, *PET* positron emission tomography

amyloidosis has detrimental consequences. Therefore, the combined assessment of serum FLCs assay, serum immunofixation (SPIE), and urine immunofixation (UPIE) is recommended to achieve a 99% sensitivity for identifying monoclonal proteins and guide subsequent clinical management [10].

A wall thickness >12 mm on echocardiogram is the cornerstone of an algorithm for raising suspicion of disease recommended by the European Society of Cardiology (ESC). Typical echocardiographic features include granular sparkling appearance of the myocardium, biatrial enlargement, interatrial septum thickening, valvular thickening, restrictive filling pattern, pericardial effusion, and apical sparing pattern (“cherry-on-top”) using speckle-tracking analysis (Fig. 9.1) [5, 1]. Thickened

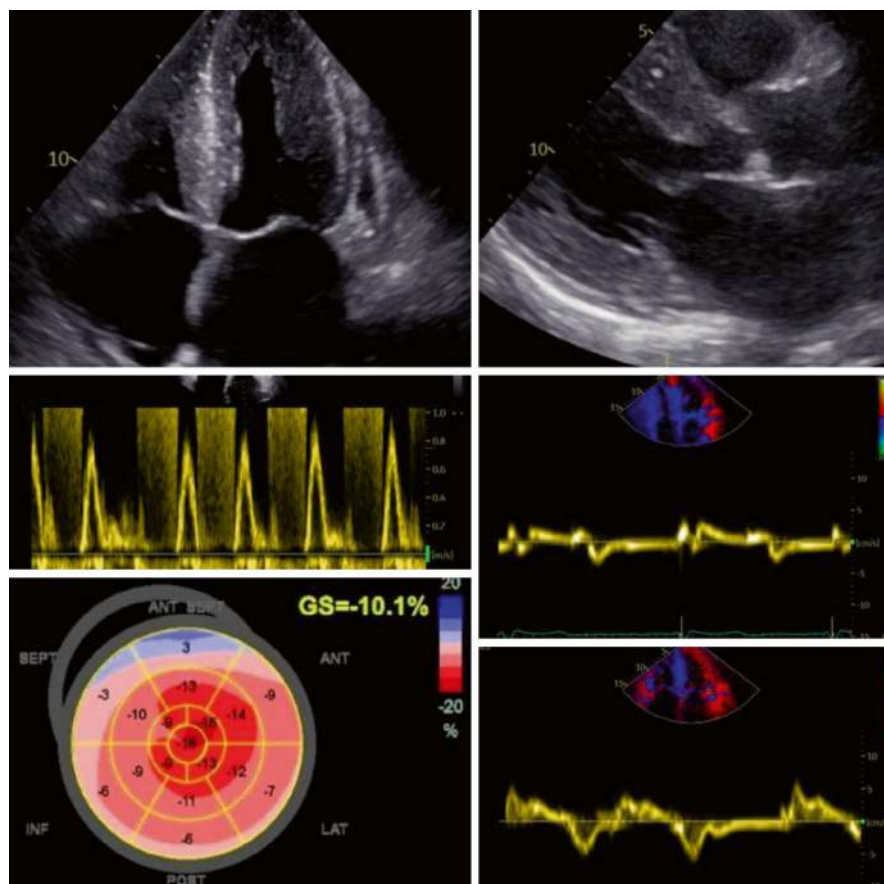


Fig. 9.1 Typical ECG and echocardiographic red flags of cardiac amyloidosis. (a) Apical four-chamber view: biventricular wall thickness and biatrial dilation. (b) Parasternal long axis view. (c) Mitral inflow demonstrates a high E-wave velocity and short deceleration time. (d, e) Lateral annular tissue Doppler imaging at the septal and lateral parts of the annulus are reduced. (f) GLS map showing the typical apical sparing pattern

interatrial septum has emerged as the least specific red flag in patients with increased wall thickness [13].

CMR imaging cannot distinguish AL- from ATTR-CM, but has the unique ability to characterize myocardial tissue composition by demonstrating increased native T1, diffuse subendocardial, or transmural late gadolinium enhancement (LGE), with abnormal myocardial nulling, and increased extracellular volume (ECV), which is particularly useful for detection of early disease and assessment of amyloid burden [10].

Bone tracer scintigraphy with planar imaging and SPECT/CT can demonstrate abnormal myocardial uptake. The presence of cardiac uptake should always prompt further testing. Three tracers are validated for use in amyloidosis, with significant

differences in kinetic and dynamics [14]. While AL amyloidosis often shows no or mild cardiac uptake, ATTR-CM most commonly presents with moderate to intense cardiac uptake. However, the degree of cardiac uptake cannot inform on the specific type of amyloidosis as Perugini grade 2 and 3 can be found in 40% of patients with ALCA [10, 15]. In recent years, major advances in cardiac imaging along with repurposed bone scintigraphy have heralded a non-biopsy diagnosis of ATTR amyloid cardiomyopathy (ATTR-CM), without need for tissue biopsy in nearly 70% of cases. In patients with suggestive echocardiographic or CMR findings, the presence of Perugini grade 2 or 3 in the absence of monoclonal proteins in serum and urine identifies ATTR-CM with a diagnostic accuracy approaching 99–100% [10] (Fig. 9.2).

The diagnostic performance of this algorithm in settings at lower pre-test probability of disease has to be tested. Tissue biopsy, either cardiac (EMB) or extracardiac, may be required in selected cases, particularly when imaging is not conclusive.

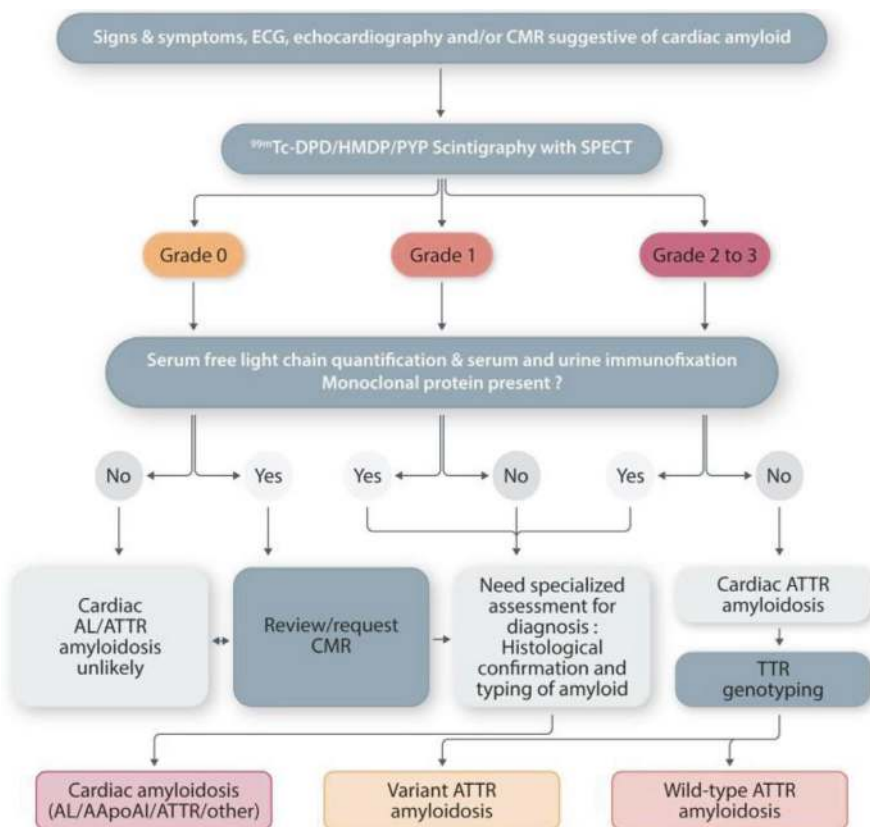


Fig. 9.2 Diagnostic algorithm for patients with suspected cardiac amyloidosis. ^{99m}Tc -DPD, ^{99m}Tc -3,3-diphosphono-1,2-propanodicarboxylic acid; ^{99m}Tc -HMDP, ^{99m}Tc -hydroxymethylene diphosphonate; ^{99m}Tc -PYP, ^{99m}Tc -pyrophosphate; *AApoA1*, apolipoprotein A-I; *AL*, light chain; *CMR*, cardiac magnetic resonance; *SPECT*, single-photon emission tomography imaging; *TTR*, transthyretin. (Reproduced from Porcari et al. [6])

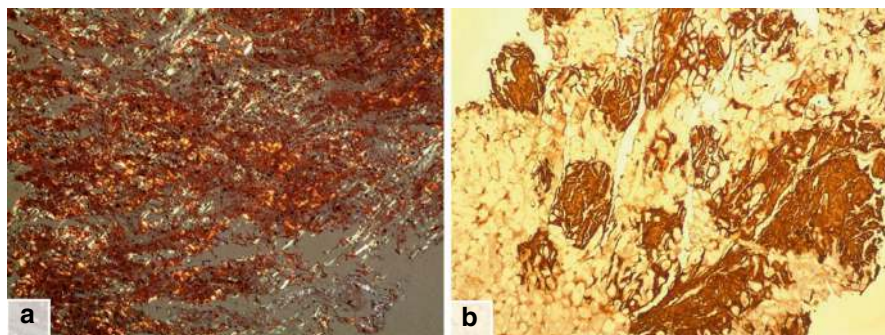


Fig. 9.3 Histological analysis of endomyocardial biopsy samples. (a) Congo Red binding to amyloid fibrils showing the typical apple-green birefringence; (b) Immunohistochemistry for transthyretin, positivity in an advanced case of cardiac infiltration

Histological analysis can confirm the presence of amyloid infiltration via Congo red staining (apple-green birefringence under polarized light) and type the amyloid deposit by immunohistochemistry or mass spectrometry (Fig. 9.3a, b). Biopsy of easily accessible tissues (e.g., abdominal fat pad, minor salivary gland, or rectum) is often diagnostic in AL amyloidosis (70–80% of cases) [3] as opposed to ATTR, where biopsy is less sensitive (<15–20% in ATTRwt, 20–25% in ATTRv) and EMB may be required [16]. All confirmed cases of ATTR-CM require TTR gene sequencing to distinguish wild-type from hereditary forms. Identification of a variant prompts cascade testing in family members and may influence disease progression and treatment options [4, 17].

9.2.2 Cardiac Sarcoidosis

Sarcoidosis is a multisystem granulomatous disease of unknown cause, affecting predominantly young to middle-aged adults, with a peak incidence between 25 and 45 years of age [1]. Sarcoidosis is hypothesized to result from environmental exposure to unidentified antigens in genetically predisposed individuals leading to a dysregulated immune response which causes the formation of noncaseating granulomas in affected organs, most commonly involving the lungs, lymph nodes, skin, and eyes [1]. Although pulmonary involvement is seen in over 90% of cases, cardiac sarcoidosis (CS) is a potentially life-threatening manifestation, found histologically in up to 25% patients [18, 19]. Myocardial infiltration by noncaseating granulomas leads to inflammation, edema, and progressive fibrosis (Fig. 9.4a–c). The inflammatory phase may cause conduction abnormalities and arrhythmias, while the fibrotic phase contributes to myocardial scarring, systolic dysfunction, and heart failure (HF) [19, 20]. Genetic susceptibility, particularly HLA class II alleles, is linked to disease risk and severity [21]. Black individuals and Japanese patients are at higher risk, and sex-related differences in presentation have also been reported [21]. Furthermore, given the morbidity and mortality associated with cardiac involvement of

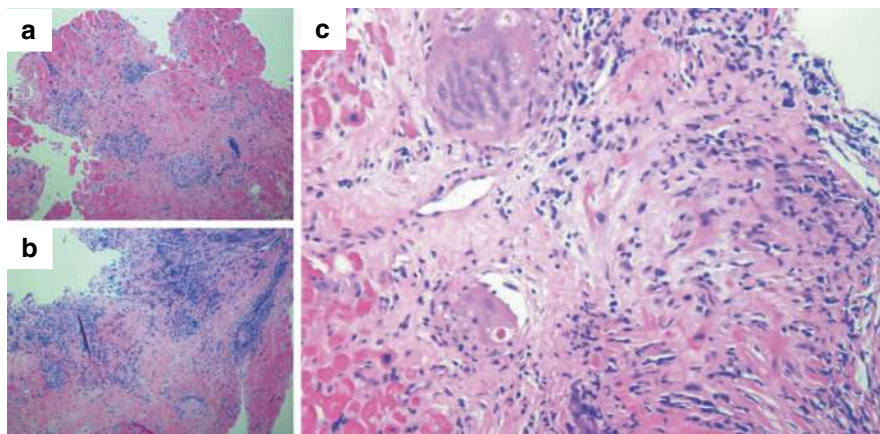


Fig. 9.4 Histological analysis of endomyocardial biopsy samples of a patient with cardiac sarcoidosis. (a, b) Diffuse myocardial inflammation characterized by a dense interstitial inflammatory cell infiltrate between cardiomyocytes. (c) Oval epithelioid granuloma composed of multinucleated histiocytic aggregates, without necrosis, within a markedly fibrotic stroma

sarcoidosis, timely and accurate diagnosis to enable prompt tailored management is essential [21].

CS presents with a wide spectrum of manifestations:

- Conduction abnormalities: High-degree atrioventricular block, often in patients younger than 60 years without known risk factors.
- Ventricular arrhythmias: Sustained or non-sustained ventricular tachycardia due to reentrant circuits around scarred myocardium.
- HF: Systolic or diastolic dysfunction due to granulomatous infiltration or fibrosis.
- Sudden cardiac death: May be the first manifestation in undiagnosed cases.
- Systemic features: Hilar lymphadenopathy, uveitis, erythema nodosum, and pulmonary involvement (cough, dyspnea) may provide diagnostic context.

Importantly, CS may also be clinically isolated, without overt systemic disease, complicating diagnosis. Diagnosis requires a high index of suspicion, especially in patients with unexplained conduction disease, arrhythmias, or cardiomyopathy [22] (Table 9.3). Initial evaluation includes 12-lead ECG, which may show AV block, bundle branch block, fragmented QRS complexes or ventricular ectopy, and an echocardiogram which may demonstrate reduced systolic function, regional wall aneurysm, basal septal thinning, and abnormal global longitudinal strain. Findings are often nonspecific but may support further investigation [21].

9.2.2.1 Advanced Imaging

CMR Imaging: Detects myocardial edema and fibrosis using T2-weighted imaging and late gadolinium enhancement (LGE). Typical LGE patterns are patchy, mid-myocardial, or subepicardial, often in the basal interventricular septum,

Table 9.3 Clinical, laboratory, and imaging red flags for cardiac sarcoidosis

Clinical	Shortness of breath Irregular heartbeat Chest pain Legs and/or ankles swelling Presyncope or syncope Sudden cardiac death
Laboratory	Hypercalcemia
ECG	AV conduction delays or blocks Right or left bundle-branch blocks Fragmented QRS complexes Frequent ventricular arrhythmias
Echocardiography	Reduced LVEF Akinetic and dyskinetic regional wall motion abnormalities (not in a coronary artery distribution) Chamber dilation, with or without regional wall aneurysm, and basal septal thinning
CMR	Wall thinning, aneurysm, or chamber dilation LV patchy, multifocal LGE in the mid-myocardium and sub-epicardium Septal LGE RV free wall involvement
FDG-PET	Focal, diffuse, or patchy FDG uptake with or without perfusion abnormalities

AV atrioventricular, *CMR* cardiac magnetic resonance, *ECG* electrocardiography, *FDG-PET* fluoro-deoxyglucose F 18 positron emission tomography, *LGE* late gadolinium enhancement, *LV* left ventricular, *LVEF* left ventricular ejection fraction, *RV* right ventricular

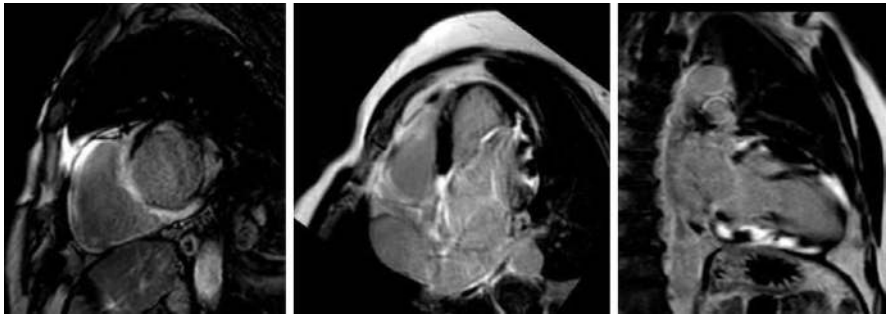


Fig. 9.5 Cardiac magnetic resonance in a patient with cardiac sarcoidosis. Multifocal and biven-tricular late gadolinium enhancement with typical thinning of the basal segment of the interven-tricular septum

inferolateral walls or RV free wall (present in >90% of cases) (Fig. 9.5). However, no specific LGE pattern is accurate enough to diagnose CS and the absence of LGE does not fully exclude CS [20].

18F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET): Identifies active inflammation by detecting glucose uptake and requires myocardial suppres-sion protocols to differentiate physiological from pathological uptake. The hallmark

of CS on FDG-PET imaging is the presence of multifocal FDG uptake, particularly when associated with resting perfusion defects (e.g., perfusion-metabolism mismatch) or in association with extracardiac inflammation [19].

Combining CMR and PET increases diagnostic yield by detecting both inflammation and fibrosis.

Histological confirmation may be achieved via extracardiac or cardiac biopsy. Extracardiac biopsies (e.g., lymph nodes, lungs, or skin) are often preferred when systemic involvement is observed [22]. EMB has high specificity but very low sensitivity (20–30%) due to the patchy nature of myocardial infiltration. Consensus guidelines from the Heart Rhythm Society (HRS), Japanese Circulation Society (JCS), and WASOG provide frameworks integrating histologic, imaging, and clinical data [23, 24]. In clinical practice, diagnosis is often based on a probabilistic approach—ranging from definite to low-probability CS—depending on findings from multimodality imaging and systemic evaluation.

9.3 Storage Disorders

9.3.1 Anderson–Fabry Disease

Anderson–Fabry disease (AFD) is a rare, progressive genetic disorder classified under lysosomal storage diseases. Its incidence ranges from 1 in 117,000 to 1 in 2500, according to neonatal screening studies [25]. It is caused by mutations in the *GLA* gene, inherited with an X-linked pattern. This condition leads to deficiency or absence of the enzyme α -galactosidase A, resulting in the accumulation of globotriaosylceramide (Gb3) in various cells, which activates detrimental cellular pathways and causes multi-organ damage [26]. AFD typically involves the heart, kidneys, the nervous system, the gastrointestinal system, the skin, and the eyes. There are two main clinical phenotypes:

1. Early-onset (classic phenotype): mostly affects males during childhood or adolescence with severe multi-organ involvement.
2. Late-onset (non-classic phenotype): generally milder, often seen in adult females, with limited organ damage.

Clinical variability depends on factors like the specific *GLA* mutation (over 900 known) and the X chromosome lyonization in females, which can cause milder disease due to mosaic expression. In children, early indicators include neuropathic pain, especially in limbs, thermoregulation issues (heat/cold intolerance, hypohidrosis), angiokeratomas (typically on the lower body), and cornea verticillata. Cardiac symptoms usually appear in the 30 s–40 s and significantly impact prognosis. Gb3 accumulation in cardiomyocytes leads to hypertrophic cardiomyopathy, which presents as HF with preserved ejection fraction (HFpEF), conduction abnormalities, malignant arrhythmias, and infarct-like chest pain with normal coronary arteries. ECG findings may include high QRS voltages, negative T waves, and short

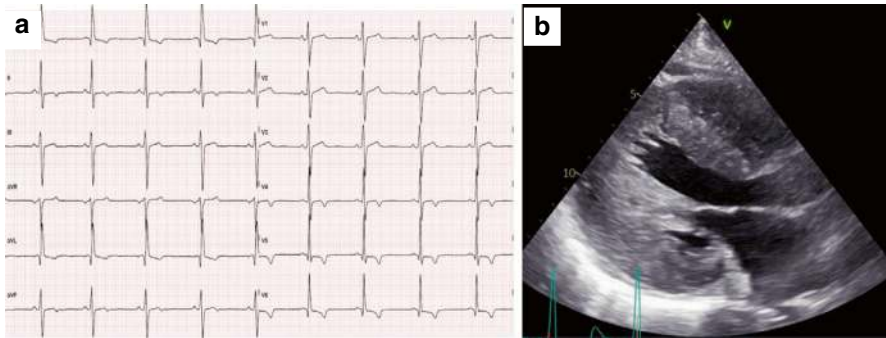


Fig. 9.6 A patient with Anderson–Fabry disease. (a) AFD electrocardiogram showing sinus rhythm with short PR interval, left ventricle hypertrophy with secondary repolarization abnormalities. (b) Echocardiogram showing diffuse increase in wall thickness with thickened papillary muscles

Table 9.4 Cardiac and extracardiac red flags for Anderson–Fabry disease

Clinical	ECG	Imaging	Laboratory
<i>Cardiac</i>	High QRS voltages	Concentric LVH	Elevated Nt-proBNP
HFpEF	Short PQ interval	Hypertrophy of papillary muscles	Elevated high sensitivity troponin
Chest pain	Inferolateral negative T waves	Thickening of mitral and aortic valves	Reduced eGFR
Arrhythmias	AV blocks	RVH with normal function	Proteinuria
<i>Extracardiac</i>	Bradycardia	GLS reduction	Microalbuminuria
Juvenile stroke	Chronotropic incompetence	Inferolateral basal LGE on CMR	
Angiokeratomas	Reduced P wave duration	Low T1 on CMR	
Renal failure	Reduced T wave ratio		
Cornea verticillata			
Neuropathic pain			
Gastrointestinal symptoms			
Hearing loss			
Heat/cold intolerance			
Hypohidrosis			

AV atrioventricular, CMR cardiac magnetic resonance, GFR glomerular filtration rate, GLS global longitudinal strain, HFpEF heart failure with preserved ejection fraction, LGE late gadolinium enhancement, LVH left ventricle hypertrophy, RVH right ventricle hypertrophy

PR intervals (Fig. 9.6a). Echocardiography shows concentric biventricular hypertrophy, papillary muscle thickening, reduced global longitudinal strain, and diastolic dysfunction (Fig. 9.6b). CMR imaging can demonstrate key features including low T1 mapping, specific to AFD, and typical LGE pattern in the basal posterolateral LV segments. For a comprehensive summary of cardiac and extracardiac red flags see Table 9.4.

Diagnostic confirmation requires plasma α -galactosidase A measurement (typically absent in affected males) and GLA gene sequencing, which is essential for confirming diagnosis in females and guiding treatment strategy [26].

There are no validated risk scores for sudden cardiac death (SCD) in AFD. Current guidelines recommend implantable cardioverter-defibrillator (ICD) in secondary prevention (e.g., after cardiac arrest). Primary prevention decisions are individualized, based on risk factors such as unexplained syncope, rapidly progressing ventricular hypertrophy, and the extent of myocardial fibrosis on CMR [27].

9.3.2 Pompe Disease

Pompe disease is an autosomal recessive genetic disorder caused by pathogenic variants in the gene encoding acid alpha-glucosidase (GAA), resulting in lysosomal glycogen accumulation primarily in skeletal and cardiac muscles. The infantile form is marked by muscular hypotonia (“floppy baby” syndrome), macroglossia, hepatomegaly, and severe left ventricular hypertrophy (LVH), which may be complicated by left ventricular outflow tract obstruction. ECG findings often include high QRS voltage, pre-excitation patterns, repolarization abnormalities, bundle branch blocks, and atrioventricular blocks. In adult-onset patients, cardiac involvement is rare, with progressive skeletal muscle and respiratory failure being the predominant features. The disease course can be improved with enzyme replacement therapy, and emerging gene therapy strategies are currently under investigation [28].

9.3.3 Danon Disease

Danon disease is a rare X-linked genetic cardiomyopathy caused by a critical deficiency of the lysosomal-associated membrane protein 2 (LAMP-2), encoded by the LAMP2 gene. Deficiency of LAMP-2 leads to accumulation of intracellular vacuoles containing glycogen and other materials, resulting in cardiomyocyte hypertrophy, oxidative stress, cell death and diffuse fibrosis [29] (Fig. 9.7a, b).

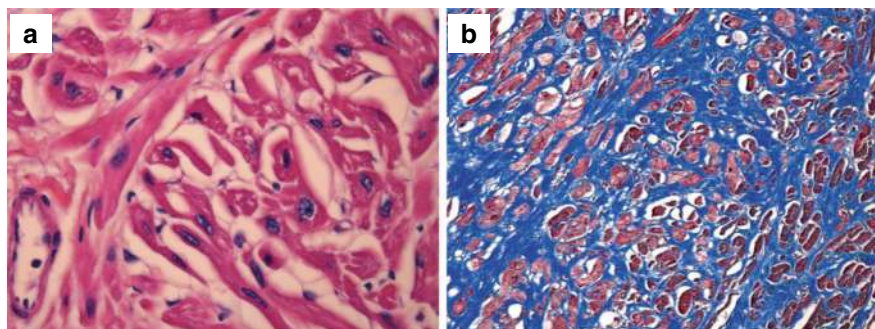


Fig. 9.7 Endomyocardial biopsy sample in a patient with Danon disease. (a) Prominent myocyte hypertrophy and cytoplasmic vacuolization. (b) Trichrome staining showing extensive fibrosis in blue and the cardiomyocytes in red

Danon disease presents with a classic triad of severe cardiomyopathy, skeletal myopathy, and cognitive impairment. Cardiac manifestations are prominent and include left ventricular hypertrophy, HF signs and symptoms, conduction abnormalities, and malignant ventricular arrhythmias. Male patients typically present earlier with more severe disease. Currently, the only available treatment option for Danon disease is cardiac transplantation [29].

9.3.4 PRKAG2 Disease

PRKAG2 disease is caused by pathogenic variants in the *PRKAG2* gene, which encodes the gamma2 regulatory subunit of AMP-activated protein kinase. It follows an autosomal dominant inheritance pattern and leads to early-onset cardiac hypertrophy and pre-excitation syndromes. Clinically, it presents with left ventricular hypertrophy, atrioventricular block, atrial fibrillation, bundle branch blocks, and ventricular pre-excitation. Unlike Danon disease, PRKAG2 disease often has less severe.

LVH, a higher prevalence of AV block, and rarely causes muscle weakness or mental impairment. Disease progression is generally milder than in Danon disease, with fewer cases of systolic dysfunction, heart transplantation, or sudden cardiac death [30].

9.3.5 Rasopathies

Rasopathies are genetic disorders caused by mutations in genes of the RAS/MAPK pathway, including Noonan syndrome, cardiofaciocutaneous syndrome, Noonan syndrome with multiple lentigines, and Costello syndrome. These conditions involve multiple systems, presenting with facial dysmorphism, short stature, skin changes such as café-au-lait spots, and various organ abnormalities. Cardiovascular issues are common, especially congenital heart defects such as pulmonary valve stenosis, atrial septal defects, and cardiac hypertrophy typically diagnosed in infancy. Hypertrophic cardiomyopathy occurs in up to 80% of cases [31].

9.3.6 Mitochondrial Disease

Mitochondrial diseases (MDs) are a heterogeneous group of disorders primarily affecting tissues with high energy demands, such as the nervous system, heart, muscles, kidneys, and endocrine organs. They result from pathogenic variants in mitochondrial or nuclear DNA. Cardiac hypertrophy occurs in about 40% of patients (Fig. 9.8a, b). Arrhythmias and atrioventricular block are common. Prognosis varies by age, with pediatric cases having high mortality, while adults generally experience fewer major cardiac events. Cognitive impairment is also frequent. Treatment focuses on dietary supplements and supportive care [32].

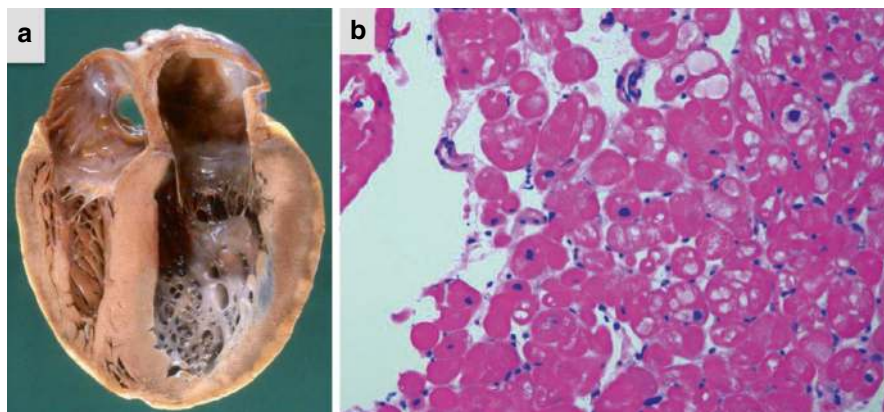


Fig. 9.8 Gross evaluation of fixed heart and histological characterization in a patient with a mitochondrial disease involving the heart. **(a)** Diffuse cardiac hypertrophy with pale areas of myocardial scarring. **(b)** Cardiomyocytes showing multifocal perinuclear halo-like optically empty area. Intramyocellular halos demonstrate Alcian Blue–PAS positivity, appearing as small multicentric alcianophilic deposits

9.3.7 Gaucher Disease

Gaucher disease is a genetic lysosomal storage disorder caused by mutations in the GBA gene, leading to a deficiency of the enzyme glucocerebrosidase. This results in the accumulation of glucocerebroside within macrophages, called Gaucher cells, primarily affecting the spleen, liver, bone marrow, and sometimes the lungs and brain. Cardiomyopathy is a rare manifestation of Gaucher disease, but it can manifest with restrictive cardiomyopathy and valvular calcifications. Diagnosis is based on enzyme activity assays and genetic testing. Treatments include ERT and substrate reduction therapy, which can improve symptoms and quality of life [33].

9.3.8 Hemochromatosis

Hemochromatosis cardiomyopathy results from excess iron deposition in the myocardium due to hereditary hemochromatosis or secondary causes of systemic iron overload. Initially, iron accumulation causes a restrictive pattern, which later progresses to dilated cardiomyopathy with systolic HF (Fig. 9.9a, b). Cardiac MRI with *T2 imaging** is the gold standard for detecting myocardial iron overload. Early diagnosis is essential, as iron chelation therapy or phlebotomy can significantly improve or even reverse cardiac dysfunction in the early stages. If left untreated, prognosis is poor due to progressive HF and arrhythmias [34].

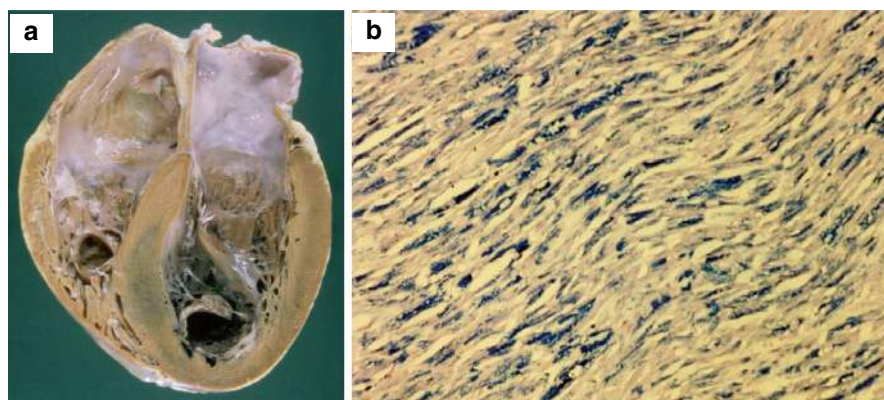


Fig. 9.9 Gross evaluation of fixed heart and histological characterization in a patient with hemochromatosis. (a) Diffuse cardiac hypertrophy associated with ventricle dilatation. (b) Prussian blue iron staining of the myocardium showing iron deposition

9.4 Intrinsic Myocyte Dysfunction and Interstitial Fibrosis

Primary RCMs include both genetically determined forms and idiopathic forms, in which a familial aggregation might be noted, but genetic tests are negative for a specific gene mutation. Mutations associated with RCM have been described in various genes, encoding for both sarcomeric and nonsarcomeric proteins (Table 9.5) [35].

Most of the gene variants associated with primary RCM are also known to cause HCM, accounting for the significant phenotypic and genetic overlap between these two types of cardiomyopathies: some patients with HCM develop a restrictive phenotype in later stages of their disease, in others LV hypertrophy and restrictive hemodynamics coexist from the beginning [5, 35]. Interstitial fibrosis can be triggered by several processes; the proliferation of fibroelastic tissues leads to increased myocardial stiffness and progressive restrictive filling.

Radiation-induced myocardial fibrosis is a late-stage clinical complication of chest radiotherapy among individuals treated for chest tumors. Ionizing radiation triggers myocardial damage through direct genetic damage, oxidative stress, and endothelial dysfunction; reactive hypertrophy and fibroblast activation follow myocardial injury. Radiation damage is dose dependent: a cumulative dose >20Gy/year is significantly linked to higher risk of developing heart fibrosis over 5–15 years [5, 36]. Changes in radiation delivery and dose have reduced the incidence of cardiac complications following radiation [5, 36]. Several chemotherapy drugs as well as anti-malarial drugs used to treat systemic autoimmune diseases have been linked to the development of progressive interstitial fibrosis, although the exact pathogenetic mechanism is yet to be fully elucidated [5, 35, 37].

Table 9.5 Primary restrictive cardiomyopathies and associated genes

Genetic cardiomyopathies that can present as primary RCM	Associated gene
Troponinopathies	TNN-T; TNN-C
Myosinopathies	MYH7
Desminopathies	DES
BAG3opathies	BAG3
Myotilinopathies	MYOT
Filaminopathies	FLNC
Ab-crystallinopathies	CRYAB
Titinopathies	TTN
Less common forms	ACTC1; MYBPC3; MYL3; TPM1; MYL3; MYL2

Systemic diseases associated with myocardial hypertrophy and fibrosis can occasionally develop progressive diastolic dysfunction and, ultimately, restrictive physiology.

Systemic sclerosis (SSc) is a systemic fibrosing autoimmune disease associated with high disease-related mortality, heart involvement being one of the leading causes of mortality in patients. Myocardium damage in SSc can either be direct or be the indirect result of other SSc-associated organ damage, such as interstitial lung disease, pulmonary arterial hypertension, and renal involvement. The prevalence of primary heart involvement ranges from 7% to 39%, manifesting as arrhythmias, HF, pericardial disease, valvular abnormalities, myocardial inflammation, and varying degrees of fibrosis. The disease has a long subclinical course, posing a diagnostic challenge; when clinically manifest, SSc primary heart involvement is associated with a 5-year mortality of 75% [38, 39].

Diabetic myocardial disorder, defined as systolic and/or diastolic dysfunction in the presence of diabetes, is an established cause of HF. Direct myocardial damage from diabetes often acts in association with obesity, hypertension, kidney disease, and coronary artery disease to cause systolic dysfunction. Overproduction of AGEs, microvascular disease, lipotoxicity as well as epigenetic changes and post-translational modification of key proteins contribute to the decrease of extracellular matrix turnover and the promotion of cardiomyocyte hypertrophy, myocardial stiffness, and interstitial fibrosis, resulting in progressive systo-diastolic dysfunction [40].

9.5 Endomyocardial Disorders

Several forms of RCM primarily result from endocardial involvement. These include conditions in which RCM is the main phenotypic manifestation (such as endomyocardial fibrosis and hypereosinophilic syndrome with cardiac involvement) as well as myocardial diseases in which endocardial fibrosis is an accompanying feature that may lead to restrictive physiology (such as carcinoid, endocardial fibroelastosis, endocardial neoplasms, and iatrogenic damage) [5, 35].

Endomyocardial fibrosis and hypereosinophilic syndrome are two forms of RCM associated with proteotoxic damage produced by eosinophils followed by fibroelastic substitution of endomyocardial tissue. Hypereosinophilia, defined as a sustained absolute eosinophil count in peripheral blood $\geq 1.5 \times 10^9/L$, can be associated with eosinophilic infiltration into tissues and organ damage. Hypereosinophilia is most frequently secondary to other conditions (allergic conditions, infections, endocrine disorders, hematological and autoimmune disorders), whereas neoplastic (clonal hypereosinophilia), hereditary, and idiopathic forms are rarer [5, 41].

Hypereosinophilic syndrome (HES) affecting the endocardium, formerly known as Loeffler's endocarditis, is a rare condition caused by eosinophil degranulation damaging the endothelium and myocardium as well as contributing to the dysregulation of blood coagulation homeostasis (Fig. 9.10a–d). Pathogenesis is characterized by three distinct phases: acute tissue necrosis, formation of acute mural thrombi, and fibrotic tissue replacement [41, 42].

Endomyocardial fibrosis (EMF) is an idiopathic disorder characterized by diffuse thickening of the endocardium secondary to proliferation of fibroelastic tissue leading to progressive diastolic dysfunction (Figs. 9.11a, b and 9.12). Most EMF cases are clustered in sub-Saharan Africa, South Asia, and Latin America; cases in Europe and North America are sporadic and mainly related to migration [5, 43]. Etiology of EMF remains unknown, although several potential etiological factors or

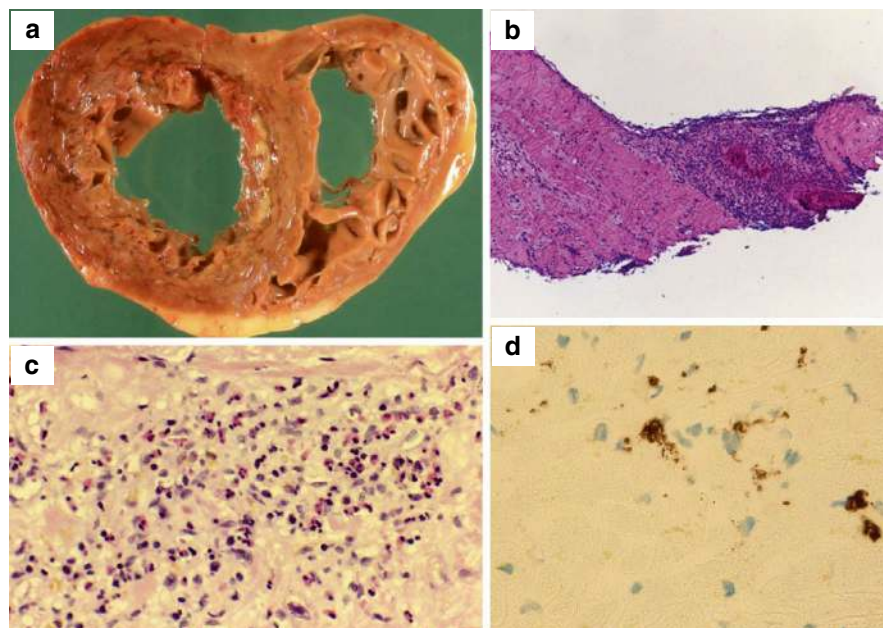


Fig. 9.10 Postmortem examination of a patient with hypereosinophilic syndrome. (a) Gross evaluation of unfixed heart showing diffuse structural abnormalities with areas of myocardial necrosis. (b) Severe myocardial infiltration of inflammatory cells. (c) Inflammatory infiltrates of lymphocytes and eosinophils. (d) Eosinophils showing active degranulation

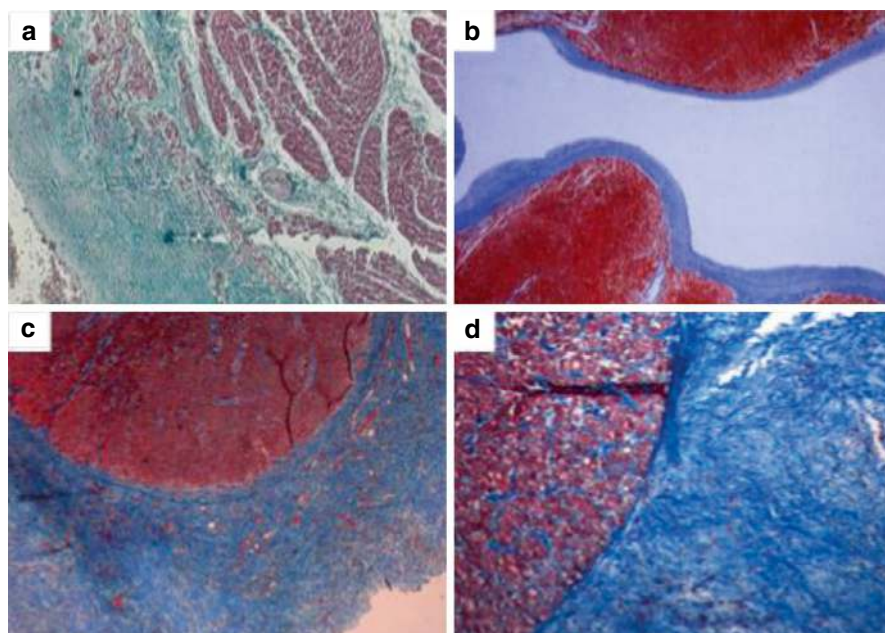


Fig. 9.11 A patient with endomyocardial fibrosis presenting with massive right ventricle thrombosis. (a) Azan–Mallory staining showing extensive fibrosis in blue and the cardiomyocytes in red. (b) Endomyocardial fibrosis shown in blue. (c, d) A large thrombus is tightly attached to the ventricular myocardium, which appears severely permeated by fibrotic tissue branches. (d) There are numerous apoptotic/necrotic myocytes with loss of the contractile apparatus

triggers have been suggested (such as hypersensitivity, autoimmunity, hypereosinophilia, genetic susceptibility, infectious agents, dietary factors) [43, 44]. Blood eosinophilia is a common finding in EMF patients; however, several distinctive features distinguish EMF from HES: patients with EMF are more frequently younger, originating from poor and malnourished populations and present with heavy parasite loads; fibrosis is more frequently biventricular in EMF; moreover, despite the presence of hypereosinophilia, tissue eosinophilia is rarely found in the established EMF [43].

Both EMF and HES are associated with significant morbidity and mortality; clinical manifestations include HF, intracardiac thrombosis, myocardial infarction, arrhythmias, and pericardial effusion. Echocardiography shows varying degrees of diastolic dysfunction, endomyocardial hyperechogenicity, and mural thrombus formation, particularly at the apex of both ventricles, and apical obliteration in later stages; the involvement of subvalvular and valvular structures is also common. CMR might show hyperintensity in T2-weighted sequences during the active phases of eosinophilic damage and subendocardial LGE pattern. Endomyocardial biopsy is currently the gold standard for diagnosis of both conditions [35, 41–44]. Early

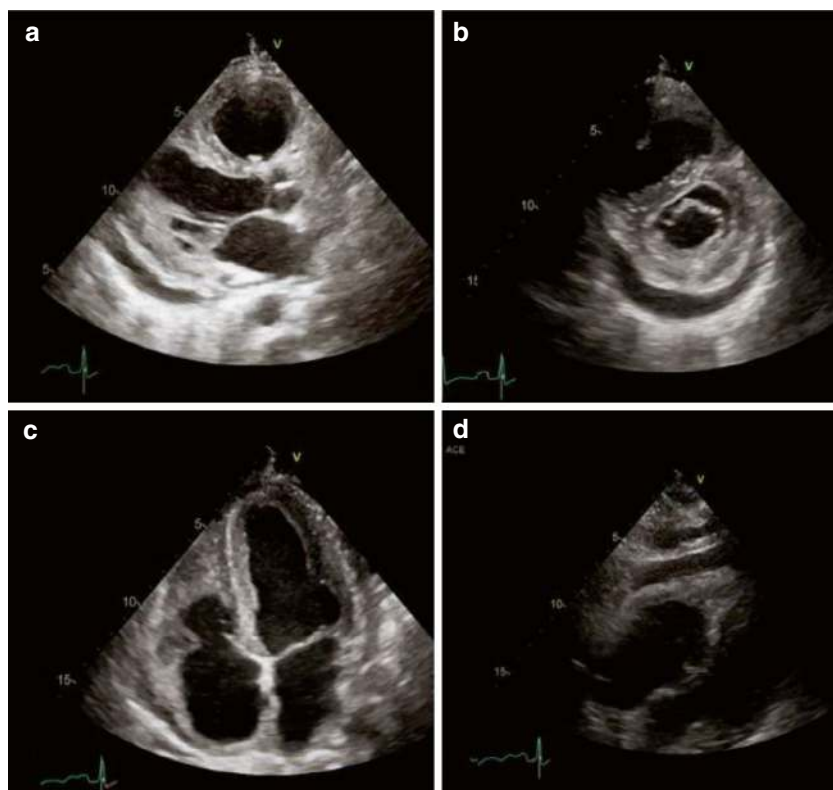


Fig. 9.12 Echocardiography showing mild hypertrophy with hyperechoic endomyocardium (a–c), right ventricle apical obliteration (c, d) and pericardial effusion (a, b, d)

stages of HES may require immune modulation therapy, while medical management of the fibrotic stage may include diuretics to control symptoms and anticoagulation to prevent intracardiac thrombosis [41, 42].

Carcinoid heart disease (CHD) is a rare manifestation of advanced neuroendocrine tumors, caused by vasoactive substances secreted by the tumor (prominently serotonin) stimulating fibroblast growth and fibrogenesis, which can lead to valvular and endocardial fibrosis inducing valve regurgitation/stenosis. Although rare, restrictive physiology may ultimately lead to right HF [45].

Endocardial fibroelastosis (EFE) is a proliferation of fibroelastic tissue in the endocardium usually in response to a concomitant stressor (flow turbulence, LVOT obstruction, valve disease) primarily affecting young individuals. Both a primary form of EFE (familial, autoimmune) and a form secondary to structural heart disease have been described. EFE can manifest both in a dilated phenotype and in a restrictive one [46].

9.6 Restrictive Cardiomyopathy

RCM represents the most heterogeneous forms among cardiomyopathies, encompassing a wide range of etiologies with different histological substrates and it is primarily identified by its hemodynamic rather than morphological features [5]. Key pathophysiological element of RCM is increased myocardial stiffness, which reduces diastolic compliance, consequently, to fixed diastolic volumes. These features, along with a systolic function that may appear preserved (i.e., LVEF) but is often impaired, lead to fixed stroke volume and elevated filling pressures. The cardiac output then depends heavily on preserved atrial systole and heart rate. Biatrial enlargement is frequent and predisposes to atrial fibrillation [5]. Most disorders involve both the right and left ventricles and can lead to signs and symptoms of right-sided, left-sided, or biventricular HF [47]. Cardiac catheterization classically shows elevated and rapidly equalized diastolic pressures across all four chambers, with the typical dip-and-plateau (also referred as “square root sign”) pattern in early diastolic pressure tracings [5, 48].

Current Limitations to Achieve a Unifying Definition for Such a Heterogeneous Group of Diseases Despite RCM remains difficult to define due to great heterogeneity, a general definition of RCM is essential for clinical practice. According to the ESC [35], along with a restrictive pathophysiology, the other features of RCM are “normal or reduced systolic and diastolic volumes (of one or both ventricles)” and “normal ventricular wall thickness.” While this definition is conceptually accurate, it has some limitations that would lead to the exclusion of many disorders with a common restrictive physiology [37, 5]:

- Myocardial wall thickness may be increased due to hypertrophy, interstitial infiltration (e.g. cardiac amyloidosis) or intracellular storage (e.g., Fabry).
- The “restrictive phenotype” may be variably expressed, in a cause-specific manner, depending on the evolution of the underlying pathology, potentially being evident at disease onset or emerge as a terminal evolutionary phase.
- Systolic dysfunction may result from concomitant conditions (i.e., previous myocardial infarction) or from advanced cardiomyopathy (i.e., late stages of cardiac amyloidosis). To overcome the limitation of the ESC criteria, Rapezzi et al. [5] recently proposed the following revised the definition: “RCM is characterized by the coexistence of persistent restrictive pathophysiology, commonly with atrial dilatation, and nondilated ventricles, regardless of ventricular wall thickness and systolic function” (Fig. 9.13).

9.6.1 Main Causes and Diagnostic Work-Up

An age-based epidemiological approach can help guide the diagnosis. In younger patients (<30 years), the most common causes are genetic (i.e., sarcomeric genes myosin heavy chain 7, cardiac troponin I, mainly) and metabolic disorders, including abnormalities of iron, glycogen, or protein metabolism [47]. In older individuals

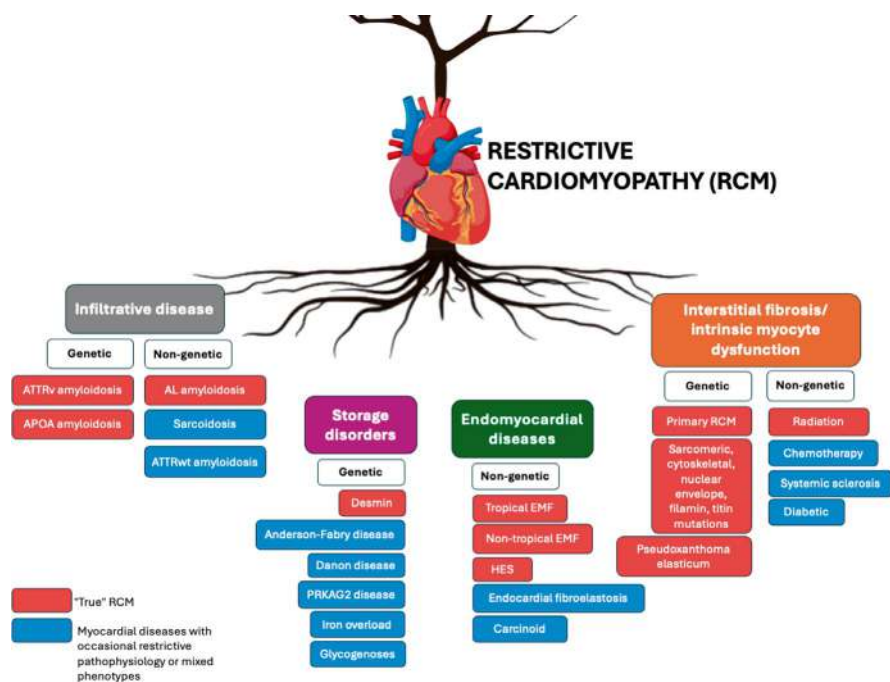


Fig. 9.13 Proposed classification of restrictive cardiomyopathy based on myocardial histology, genetics, and the reversible or persistent character of restriction. *APOA* apolipoprotein A, *ATTRv* variant amyloid transthyretin amyloidosis, *EMF* endomyocardial fibrosis, *HES* hypereosinophilic syndrome, *PRKAG2* protein kinase AMP-activated non-catalytic subunit gamma 2. (Adapted from Rapezzi et al. [5])

(>60–65 years), conditions such as cardiac amyloidosis, iron overload cardiomyopathy, radiation-induced heart disease, and sarcoidosis become increasingly prevalent [35, 49].

Because of the heterogeneous nature of RCM and the major therapeutic implications of an accurate diagnosis, the work-up often requires a broader range of investigations than for other cardiomyopathies. This may include invasive procedures such as cardiac catheterization in challenging cases, while multimodality imaging (echocardiography, CMR, and nuclear imaging) plays a central role in assessing morphology, function, and tissue characteristics [35, 47, 48]. Genetic testing is gaining importance, and RCM remains one of the main indications for endomyocardial biopsy, given the critical role of histological characterization in establishing the diagnosis [50].

9.6.2 Differentiation from Constrictive Pericarditis

RCM may need to be differentiated from constrictive pericarditis (CP), as both may present with right-sided HF, preserved LVEF, and impaired diastolic filling [50]. In CP, echocardiography typically demonstrates exaggerated ventricular

interdependence, leading to respirophasic ventricular septal shift and variations in ventricular filling [47, 48, 51]—findings absent in RCM. These hemodynamic features can be confirmed cardiac catheterization [52]. Tissue Doppler imaging (TDI) further aids differentiation: in CP, septal e' is often preserved or even higher than lateral e' (annulus reversus), whereas in RCM both septal and lateral e' are reduced [47, 48, 51]. Advanced imaging with cardiac CT or MRI may also reveal pericardial thickening in CP, a feature not seen in RCM [48].

9.6.3 Overlap Between HCM Phenocopies and RCM

Sarcomeric HCM can evolve into a restrictive physiology in end-stage disease; however, the overlap is more commonly seen in HCM phenocopies in which there is a typical evolution and progression toward the “restrictive phenotype.” For example, thin filament sarcomeric variants typically present with milder hypertrophy but greater diastolic dysfunction at diagnosis, with progressive deterioration over time [53]. Similarly, ATTR-CM may have varying degree of wall thickness and almost always impaired diastolic function, that progress toward restrictive physiology. A similar trajectory is seen in AFD. These examples highlight the dynamic nature of cardiomyopathies and the need for serial phenotypic reassessment over time.

9.7 Management and Therapeutic Implications

9.7.1 General Principles of HF Management in RCM

Patients with HCM phenocopies and RCM most often present with HFpEF, and only a minority develop reduced EF (HFrEF). While LVEF remains clinically relevant, it is a poor marker of disease progression in these settings. For instance, in amyloid cardiomyopathy, progressive reduction in ventricular cavity size leads to reduced volumes, while maintaining a normal LVEF. A hemodynamic approach—focusing on stroke volume and cardiac output rather than LVEF—is more informative. Three pathophysiological features strongly influence treatment:

1. *Fixed stroke volume*—Cardiac output depends almost entirely on heart rate, making patients poorly tolerant of bradycardia.
2. *Reverse remodeling is not a target*—Clinical improvement may be accompanied by increased LV volumes and stroke volume.
3. *Beta-blockers are often poorly tolerated*—Due to negative chronotropic effects and, to a lesser extent, inotropic impact.

As congestion drives most symptoms, loop diuretics remain the cornerstone therapy, often requiring combination diuretic strategies in refractory cases. The limited diastolic compliance and stiffness of the “HFpEF heart” make these patients highly sensitive to even small changes in volume status. In RCM or infiltrative cardiomyopathies, congestion typically progresses slowly, necessitating gradual dose

escalation and multi-agent diuretic regimens. Kidney function is a critical player in diuretic treatment: as soon as kidney dysfunction progresses, hemodynamic balance becomes more fragile and increased diuretic dosages are needed.

Patients are typically poorly tolerant of bradycardia, and bradyarrhythmias may require the implantation of an atrioventricular pacemaker. Drugs acting on the renin-angiotensin-aldosterone system have not demonstrated prognostic benefit and may cause hypotension. Most recently, SGLT2i have demonstrated benefit on hard cardiovascular outcomes in cardiomyopathies that were believed to be only responsive to disease-modifying therapies. In a contemporary cohort of ATTR-CM patients, SGLT2i showed a net reduction in cardiovascular mortality and HF hospitalizations, and were associated with attenuated rise in natriuretic peptide [54].

Atrial fibrillation (AF) is a common complication of this group of diseases. AF prevalence in HCM is approximately 21% and 42% in RCM but has different clinical significance. In HCM, it is associated with higher all-cause mortality, whereas in RCM the association with outcome is controversial. Management focuses on stroke prevention, symptom control through rate and rhythm strategies, and modification of risk factors. Anticoagulation is always recommended in HCM and RCM with AF, given the high thromboembolic risk and the poor predictive performance of conventional thromboembolic risk scores in these populations. In HCM and phenocopies, a lenient rate control is typically achieved with β -blockers, and non-dihydropyridine calcium channel blockers may be an alternative. In RCM, rate control can be challenging due to a fixed cardiac output highly dependent on heart rate. In refractory cases, atrioventricular node ablation with CRT pacing may be considered. For rhythm control, sotalol and amiodarone are recommended, with the former to be preferred in HCM and young patients because of its lower side effects. Catheter ablation is an alternative, but evidence about its efficacy is conflicting [55–57].

9.7.2 Phenotyping Impacts Treatment Decisions

Timely differentiation between HCM and its phenocopies is critical, as diagnostic delays can adversely affect prognosis. Current management of cardiomyopathies encompasses a broad range of disease-modifying therapies that demand accurate phenotyping of the underlying cardiomyopathy:

- Amyloid cardiomyopathy: treatment options include transthyretin stabilizers, TTR protein synthesis inhibitors, gene-editing approaches, or chemotherapy, depending on the amyloidosis subtype, all of which can improve both quality of life and survival [58, 59].
- CS: highly responsive to immunomodulatory therapy, with corticosteroids as first-line agents, often combined with steroid-sparing immunosuppressants [21].
- AFD: early initiation of enzyme replacement therapy (ERT) with intravenous infusion of recombinant α -galactosidase A every 2 weeks is crucial to prevent or

slow organ damage; chaperone therapy offers comparable efficacy in patients with amenable mutations; gene-editing therapies are under investigation [60].

- Glycogen storage diseases: prognosis is poor without treatment; currently, ERT is only available for Pompe disease, with gene therapies in development for other subtypes [35].

All HCM phenocopies present with extracardiac involvement which may limit advanced treatment such as heart transplant (HT) and/or left ventricle assist device (LVAD). A comprehensive assessment of multi-organ involvement is mandatory, and the risks of long-term immunosuppression must be carefully weighed. In CS, 14% of patients progress to terminal stage in 15-year follow-up and require HT, reaching similar HT outcomes to non-sarcoidotic recipients. Precapillary pulmonary hypertension should be excluded, and potential immunosuppression-related complications assessed. AL cardiac amyloidosis and hereditary ATTR-CM more frequently require HT: renal, gastrointestinal, and neurological involvement may be the great limitations to candidacy. In AL amyloidosis, suppression of pathogenic light chains after transplant is essential, whereas in hereditary ATTR-CM with neuropathy, disease-specific therapies can be initiated post-HT to prevent extracardiac progression [61].

9.8 Conclusions

Distinguishing sarcomeric HCM from its phenocopies and accurately diagnosing RCM is crucial, given the profound implications for prognosis, therapeutic strategies, and family screening. Phenocopies often mimic HCM in early stages but may evolve into a restrictive phenotype over time, as seen in ATTR-CM or AFD. Likewise, primary RCM encompasses a heterogeneous group of disorders with diverse etiologies, frequently overlapping phenotypically with hypertrophic and infiltrative cardiomyopathies.

In this complex diagnostic landscape, a comprehensive and integrated approach is essential. Diagnostic algorithms should incorporate clinical evaluation, advanced multimodality imaging, histological confirmation when appropriate, and increasingly, genetic testing. The use of artificial intelligence-driven tools to manage and interpret large datasets—including imaging, genomic, and clinical data—may offer valuable support in refining diagnostic accuracy and stratifying patient risk. Future progress will depend on technological innovation and on the establishment of multidisciplinary care models that unite cardiologists, geneticists, imaging specialists, and organ-specific experts. Such an approach is crucial to addressing the multisystemic nature of many of these conditions, and to tailoring therapeutic strategies to the individual needs of each patient.

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Part III

Role of Environmental Factors

Role of Inflammation in Genetically Determined Cardiomyopathies

10

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Recent advances in genetics and cardioimmunology have shed new light on the complex interplay between genetic background and inflammation in myopericardial diseases. Conditions such as arrhythmogenic cardiomyopathy with hot phases and cases of biopsy-proven myocarditis with mutations in genes like TTN or DSP are examples of the overlap between genetic backgrounds and the immune system, influencing both disease development and prognosis.

Collectively, these observations support the view that inflammation may act as a “second hit,” which, in synergy with a “first hit” represented by genetic predisposition, leads to myocardial injury. This concept aligns with the so-called “second hit theory” [7].

In fact, myocardial damage causes the release of molecules, such as heat shock proteins (Hsp), mitochondrial DNA, and cellular debris, called DAMPs [1].

DAMPs are recognized by pattern recognition receptors (PRRs) on the surface of cardiac immune cells (Toll-like receptors—TLRs) and intracellular ones (NOD-like receptors—NLRs), activating the nuclear factor kappa B (NF-KB) and the NLRP3 inflammasome pathways [2].

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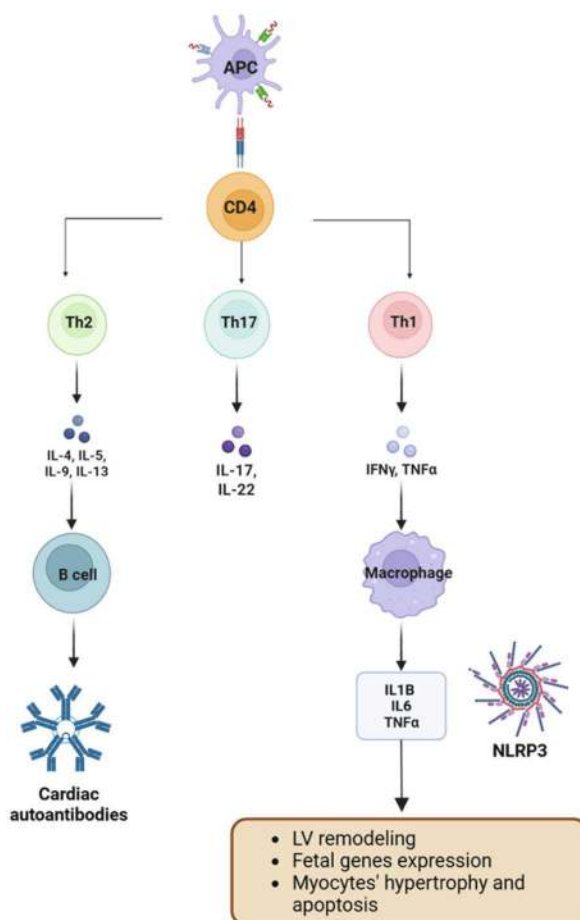
This cascade results in the release of pro-inflammatory cytokines, such as TNF- α , IL1B, and IL6, amplifying the inflammatory milieu [3].

In case of persistent activation of the immune system, an initially protective response activates a vicious cycle, leading to tissue fibrosis and progression of the myocardial damage [4] (Fig. 10.1).

Understanding these mechanisms is increasingly relevant, as inflammation has emerged as a key player in the progression of various cardiovascular diseases, acting alongside genetic predisposition and autoimmunity.

This chapter summarizes the current state of knowledge on cardioimmunology, an emerging multidisciplinary field focused on the interactions between the cardiovascular and immune systems, in cardiomyopathies. This discipline is expected to play a pivotal role in current and future practice, not only in atherosclerotic and pericardial diseases but also in heart failure and cardiomyopathies.

Fig. 10.1 Innate and adaptive response in myocardial diseases. (Created in BioRender. Bassetto, G. (2026) <https://BioRender.com/g21q266>)



10.1 Dilated Cardiomyopathy

The interaction of inflammatory triggers in the aetiology of dilated cardiomyopathy (DCM) and the overlap of DCM with myocarditis and inflammatory cardiomyopathy are well-known in clinical practice. Nonetheless, knowledge of how this interaction happens and progresses is still very limited, in spite of a growing research interest.

In a context in which clinical, laboratory, and histopathological data often coincide, the substantial overlap between DCM and myocarditis often poses diagnostic challenges to the clinician. This overlap is two-faced: on one side, it is documented in the literature that 6–30% of patients diagnosed with acute myocarditis can progress to DCM [5–7], either with or without an initial remission phase (persistent left ventricular (LV) dysfunction vs adverse LV remodelling). On the other hand, for many years, in both preclinical [8] and clinical [9] studies, there has been evidence of myocardial inflammation in DCM patients.

The progression from myocarditis to DCM is yet not fully elucidated and still the subject of controversies on the mechanisms that drive the initial trigger to myocardial inflammation, from acute injury to chronic cardiac dysfunction. It has been attributed to ongoing inflammatory processes, either due to the persistence of the viral genome in the myocardium [10], inefficiently cleared by the immune system, or due to a chronic autoimmune response triggered by the failure of T cell tolerance to cardiac autoantigens [11–13].

Genetic predisposition plays a crucial role in determining which patients are most vulnerable to this transition: growing evidence suggests that a significant proportion of patients have an underlying cardiomyopathy-associated genetic variant. The largest study to date investigating the genetics of acute myocarditis patients identified rare protein-altering variants in up to 23% of the enrolled patients [14], a proportion similar to other reports in smaller cohorts [15].

This has given rise to a “second hit” hypothesis, supposing that a genetically susceptible myocardium, when exposed to environmental triggers like viral infections, is more likely to manifest overt disease. In this framework, inflammation acts as both a trigger and a perpetuator of myocardial dysfunction. In mouse models, multiple genes have been linked to increased cardiac inflammation [16, 17], but in real-world patients, a certain causative link between inflammation as a *primum movens* for DCM development remains to be established.

The diagnosis of inflammatory DCM relies on imaging and invasive tissue characterization: cardiac magnetic resonance imaging (CMR) and endomyocardial biopsy (EMB) are invaluable tools for detecting myocardial inflammation, even in the absence of classic myocarditis-like symptoms. Increasingly, genetic testing is recommended, especially in patients with a family history of cardiomyopathy or atypical clinical features, as it can reveal underlying variants that may influence both prognosis and management [18].

10.2 Arrhythmogenic Cardiomyopathy (ACM) and “Hot Phases”

Arrhythmogenic cardiomyopathy (ACM) is another condition where inflammation and genetics intersect in clinically meaningful ways. ACM is most associated with mutations in desmosomal proteins, such as desmoplakin (DSP), plakophilin-2 (PKP2), and desmoglein-2 (DSG2). These genetic defects compromise the structural integrity of cardiac myocytes, predisposing them to detachment, apoptosis, and subsequent replacement by fibrofatty tissue [19].

Activation of the immune system has been described in ACM patients: histopathological studies have consistently demonstrated the presence of lymphocytic and macrophagic infiltrates within the myocardium, and activation of innate immunity mediated by GSK3B and the NFkB pathway seems to have a role in disease development [20, 21].

Potentials physiopathological mechanisms in ACM have been identified in autoimmunity and molecular mimicry, since autoantibodies targeting intercalated disks (AIDA), DSG2 (anti-DSG2), and TTN (anti-TTN) have been found in the blood of ACM patients and seem to associate with disease severity (higher TVNS burden and lower LVEF), although larger studies are needed to strengthen this hypothesis [22].

A particularly dramatic manifestation of the interplay between genetics and inflammation in ACM is the so-called “hot phase.” These episodes are characterized by acute chest pain, elevation of cardiac biomarkers (such as troponin), and the absence of obstructive coronary artery disease [23]. Clinically, they are often indistinguishable from classic myocarditis but occur in patients with an underlying genetic predisposition.

Hot phases predominantly affect younger patients and are associated with a heightened risk of arrhythmia. The pathophysiology of these episodes has not yet been described, although it appears to be influenced by both genetic and immunological factors. Mutations in DSP are most commonly implicated, but other genes, such as FLNC and LMNA, can also be involved [24–26].

Diagnosing hot phases requires a multimodal approach. Electrocardiography, echocardiography, cardiac MRI, positron emission tomography, and endomyocardial biopsy are all valuable tools for assessing myocardial inflammation and structural changes.

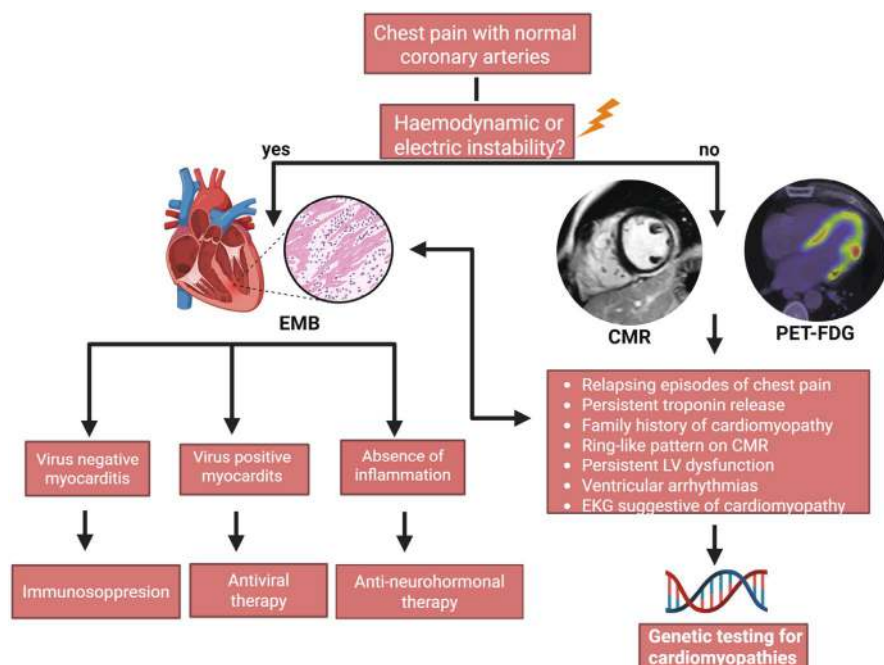


Fig. 10.2 Recognizing red flags for hot phases in the multiparametric workup of suspected myocardial syndrome. (Created in BioRender. Bassetto, G. (2026) <https://BioRender.com/v7mbxwz>)

Indeed, in these patients, recognizing some red flags, such as recurrent episodes of myocarditis, chronic troponin release, family history of cardiomyopathy, ECG features such as low voltages, T wave inversion, presence of ring-like LGE pattern on CMR, and persistent severe left ventricular dysfunction despite optimized medical therapy, should raise the suspicion of a cardiomyopathic background [27] (Fig. 10.2).

Genetic testing is strongly recommended when clinical red flags are present, as identifying a pathogenic variant can have significant implications for management and family screening [14]. While biomarkers such as troponin are elevated during hot phases, there remains a need for more specific markers to guide diagnosis and therapy.

Management of hot phases is multifaceted. Tailored immunosuppressive therapy might help to reduce inflammation and prevent adverse outcomes, although robust evidence is still lacking and treatment decisions should be made by multidisciplinary teams [28, 29]. Recently, a multicentric study focusing on DSP carriers reported a reduced risk of ventricular arrhythmias and heart failure in patients treated with immunosuppressive therapy, although this approach did not seem to reduce recurrences. Interestingly, colchicine and nonsteroidal anti-inflammatory therapies did not show the same efficacy [30]. A pilot study focusing on histological characterization of hot-phase patients observed that, when apoptosis was prevalent on EMB, LV reverse remodelling was achieved more frequently following treatment with anti-neurohormonal therapy [24]. This finding laid the path for research focusing on cardiac histology to unravel the underlying physiopathological mechanism.

10.3 Non-Dilated Left Ventricular Cardiomyopathy

NDLVC, a new entity described by the 2023 ESC guidelines, presents multiple overlaps with ACM and DCM, and ongoing studies are analyzing the role of genetics and inflammation in this subset of patients [31]. Interestingly, a large retrospective study of suspected NDLVC with arrhythmic presentation showed a worse prognosis, defined as cardiovascular death, heart transplantation, and ventricular VA, when inflammation was present on EMB [32]. Similarly, histological evidence of myocardial inflammation- together with male sex, NSVTs, LVEF<45%, septal and ring-like LGE, and arrhythmic genotypes- predicted malignant ventricular arrhythmias in NDLVC patients with no previous history of arrhythmic events. These data support once more a comprehensive diagnostic workup, including CMR, genetic testing, and, in selected cases, endomyocardial biopsy [33]. Nevertheless, research focusing on multicentric and prospective data is needed in order to better characterize the prevalence and role of inflammation in NDLVC (Fig. 10.3).

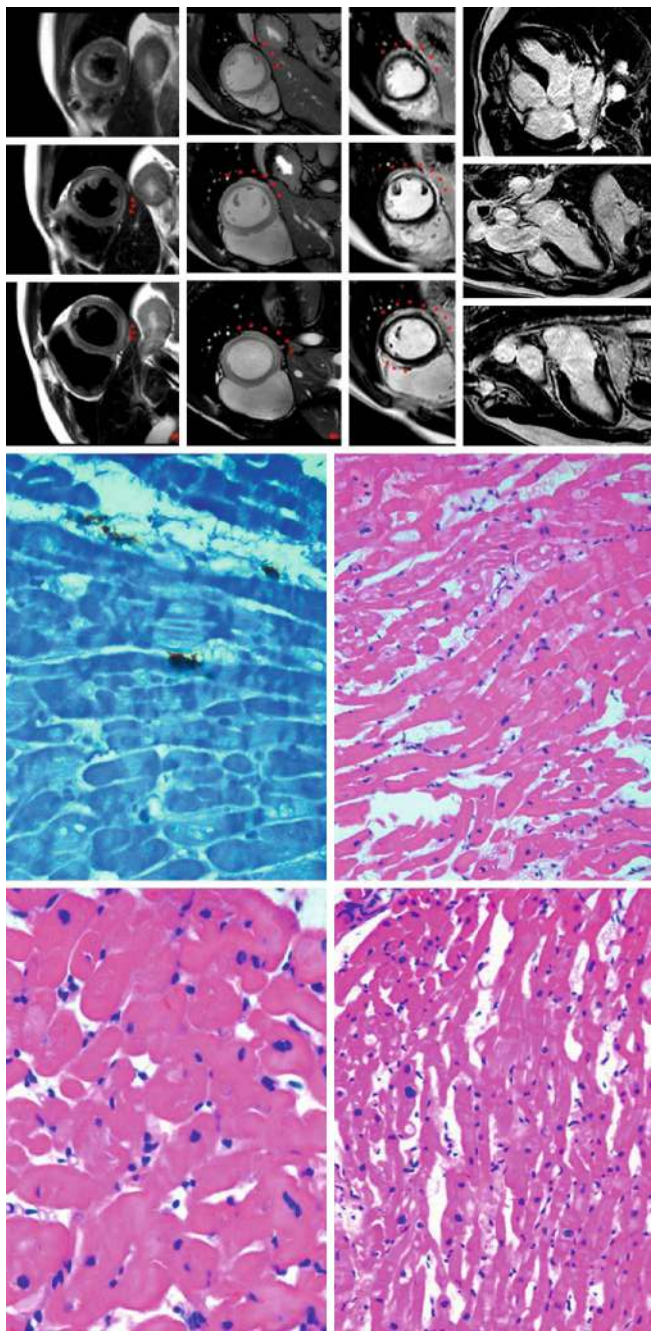


Fig. 10.3 Case of NDLVC and hot phases. Twenty-nine-year-old patient presenting with multiple episodes of chest pain and persistent troponin release. Hematoxylin-eosin stain of EMB showing edema, myocardial damage, and lymphocytic infiltrates. Immunohistochemistry showing CD4+ elements in the myocardium. CMR images showing a nondilated ventricle with extensive subepicardial circumferential LGE (ring-like pattern). Genetic testing was positive for a pathogenic variant in DSP

10.4 Hypertrophic Cardiomyopathy

Classically, cardiac hypertrophy and HCM have not been associated with inflammation. Some studies have reported low-grade inflammatory infiltrates in myectomy tissues [34], or others have detected upregulated inflammatory pathways in proteomic analysis of HCM [35]. Also, elevated hsCRP and proinflammatory cytokines (IL1B, IL6, TNFa) have been described to be linked to the severity of LGE on CMR [36]. While probably not involved in the canonical pathogenic pathway, inflammation in HCM may play a role in later stages of disease when heart failure ensues, and as such, it is being investigated as a potential marker of disease progression [37].

10.5 Anderson-Fabry Disease

In Anderson-Fabry disease, there is growing evidence suggesting that inflammation has a key role in disease progression.

The inflammatory response in Fabry disease can be conceptualized in stages: early, chronic, and resolving. The early phase is characterized by the acute response of the innate immune system: the accumulation of Gb3 and Lyso-Gb3 leads to a cascade of signaling events that trigger both innate and adaptive immune responses. Glycosphingolipids act as danger-associated molecular patterns (DAMPs), activating pattern-recognition receptors (PRRs) such as Toll-like receptors on immune cells. As the disease progresses, chronic low-grade inflammation becomes established, manifesting as persistent activation of the immune system even in the absence of overt organ damage. This chronic inflammation is detectable before traditional clinical markers of organ failure are evident and shares similarities with systemic autoinflammatory and autoimmune conditions, suggesting overlapping immune pathways. Immune dysregulation is further evidenced by the development of anti-drug antibodies during enzyme replacement therapy, which can diminish therapeutic efficacy and complicate management.

Resolution of inflammation is increasingly acknowledged as a distinct, active biological stage (the so-called latent or “resolving” phase), and recent studies suggest that the failure to adequately resolve inflammation may contribute to the ongoing tissue injury observed in Fabry disease.

Early identification of inflammation, possibly through novel biomarkers, might be an opportunity for timely intervention before irreversible organ fibrosis occurs.

Concerning therapeutic implications, while enzyme replacement, pharmacological chaperones, and substrate reduction therapies remain central to medical management, there is growing recognition of the potential value of adjunctive immunomodulatory and anti-inflammatory therapies, such as B-cell-targeted agents and regulators of pro-resolution pathways. Still, the interplay between inflammation, glycosphingolipid accumulation, and disease progression is not fully understood, and addressing inflammatory pathways in Fabry disease remains a challenge in contemporary medicine [38].

10.6 Therapeutic Approaches and Future Directions

Cardioimmunology is rapidly advancing with new therapeutic frontiers targeting both innate and adaptive immune pathways in cardiovascular disease. Over the past few decades, the growing understanding of how inflammation contributes to cardiovascular diseases has sparked intense efforts to develop therapies that can modify or suppress harmful immune responses in the heart [39]. At the moment, immunosuppression is recommended by current guidelines in endomyocardial biopsy-proven myocarditis refractory to optimal medical therapy and fulminant myocarditis (after ruling out viral etiology), other than in specific high-risk cases such as giant cell, eosinophilic myocarditis and sarcoid myocarditis. Fewer data are available on the role of inflammation and the immune system in HF and myopericardial diseases, although systemic inflammation has been recognized in the pathophysiology and progression of both acute and chronic heart failure (HF). These insights have inspired therapeutic strategies, especially for HF with reduced ejection fraction (HFrEF), but also HF with preserved ejection fraction (HFpEF), where elevation of inflammatory biomarkers and systemic inflammation are increasingly targeted in ongoing clinical trials.

These therapies counteract inflammation through:

- Anti-inflammatory strategies
- Targeted anti-cytokines
- Immunomodulation

10.7 Anti-Inflammatory and Immunosuppressive Therapies

In this category are included drugs that suppress the production (transcription) or block the activity (translation) of inflammatory mediators. One of the first clear therapeutic strategies explored was the use of general anti-inflammatory drugs. Steroids like prednisone were among the earliest treatments tested for inflammatory cardiomyopathies. An early, influential trial showed that prednisone could improve heart function in patients whose dilated cardiomyopathy was driven by clear evidence of myocardial inflammation (evaluated as inflammatory cell infiltration on biopsy) [40]. However, this benefit was not seen in patients without signs of active inflammation, underlining that indiscriminate immunosuppression does not help all heart failure patients. Similar findings were reported in the TIMIC study [41], in which patients with resolved myocarditis with no evidence of myocardial viral activity and chronic HF symptomatology unresponsive to conventional therapy were randomized to receive high-dose prednisone (1 mg/kg) for 1 month daily, followed by tapering doses for 5 months on top of daily azathioprine (2 mg/kg) for 6 months or placebo. The results showed that there was a significant improvement described by clinical and imaging endpoints. These early studies, although small, suggest that the degree of chronic myocardial inflammation in patients with HF is functionally important.

10.8 Targeted Anti-Cytokines

As researchers understood more about the specific harmful cytokines driving inflammation in heart failure, therapies shifted to more precise, targeted approaches. Early enthusiasm was focused on tumor-necrosis factor (TNF), a potent proinflammatory cytokine found at elevated levels in patients with heart failure. Unfortunately, blocking TNF with drugs like etanercept or infliximab did not deliver the expected benefit [42]. In large, well-conducted trials, these treatments not only failed to improve outcomes but, in the case of infliximab, even increased the risk of worse heart failure or death at higher doses. These disappointing results highlighted that blocking certain cytokines can have unpredictable effects, highlighting the fact that cytokines often play double roles, sometimes helping repair tissue while also contributing to damage. In contrast, more recent efforts to block interleukin-1 β (IL-1 β) have been more promising. The landmark CANTOS trial tested canakinumab, an anti-IL-1 β antibody, in patients with a history of prior myocardial infarction and inflammatory atherosclerosis, as denoted by a high-sensitivity C-reactive protein [43]. The trial showed that canakinumab reduced cardiovascular events overall and hinted at a possible reduction in heart failure hospitalizations. Although this was not its primary aim, the result gave hope that carefully selected patients (overt inflammation) could benefit from targeted cytokine therapy. Furthermore, it also raised the interesting idea that timing matters: targeting inflammation earlier in the disease process may be more effective than waiting until advanced heart failure develops.

Another cytokine under investigation is interleukin-6 (IL-6). Unlike TNF, IL-6 was initially overlooked because its main receptor was thought to be absent on heart muscle cells. Later, scientists discovered that IL-6 can act indirectly through other pathways. This has restored interest in drugs like tocilizumab, an IL-6 receptor blocker already used for rheumatoid arthritis. While not yet tested in heart failure specifically, tocilizumab has shown early promise in myocardial infarction settings, suggesting potential for future trials [44]. Newer agents targeting IL-6 are currently being evaluated in patients with heart failure and preserved ejection fraction, another major area of unmet need.

10.9 Immunomodulation

Beyond blocking specific inflammatory molecules, some strategies try to influence the immune system more broadly. One example is intravenous immunoglobulin (IVIG), which can dampen excessive immune responses. While IVIG has shown encouraging results in some small trials, it remains expensive, logistically challenging, and has not yet demonstrated clear benefit in large studies with meaningful outcomes like survival [45]. Another option is directly targeting the immune cells rather than just the messengers they produce (cytokines). For example, there is a way to prevent harmful immune cells from migrating to the injured heart, consequently interrupting their activation signals. It is the case of abatacept (a T cell

activation blocker), which is now being tested for serious conditions like myocarditis triggered by cancer immunotherapies.

In conclusion, the therapies discussed in this chapter illustrate both the promise and the complexity of trying to modulate the immune system to treat heart disease. On one hand, the evidence is clear that inflammation plays a harmful role in many forms of heart failure, but completely blocking it can be counterproductive as it disrupts the body's necessary repair processes. Successful approaches will likely require selecting the right patients, targeting the right pathways at the right time, in order to establish a careful balance between suppressing harmful inflammation and preserving the heart's capacity to heal. In this direction, the field of cardioimmunology is still an exciting challenge. It has moved from broad-range attempts to suppress inflammation without distinction, to increasingly precise strategies shaped by insights from immunology, genetics, and advanced imaging. The next decade will likely bring more comprehensive trials that match patients to therapies based on more reliable biomarkers of inflammation and immune activation. If these efforts succeed, they may finally unlock the ambitious aim of truly personalized treatments for heart failure, considering not only the mechanics of the failing pump, but also a deep understanding of the immune system that drives it.

10.10 Conclusions

The interplay of genetics and the immune system in cardiomyopathies—especially in DCM and ACM—and their management is currently a hot topic in cardiology. Despite advances in diagnostic tools, overlapping clinical and imaging features between inherited cardiomyopathies and myocarditis can be a challenge for the clinician, particularly during acute “hot phases,” and multiple gaps are left in the multimodal approach for diagnosing and treating patients.

Existing biomarkers, such as troponin and CRP, lack specificity in the differential diagnosis, and the gold standard in the diagnosis of inflammatory cardiomyopathies, EMB, has limited availability, as well as intrinsic risks and low sensitivity, especially in the setting of patchy or focal disease.

Genetic testing remains underused and, even when performed, the clinical interpretation of some genetic variants—i.e., variants of uncertain significance (VUS)—is not fully established.

As for risk stratification, no parameters have been identified to predict arrhythmic events, heart failure progression, or sudden cardiac death with accuracy in this special patient cohort.

Therapeutically, the optimal patient selection and timing of immunosuppressive therapy are not known, often extrapolated from small observational studies, and randomized controlled trials are urgently needed, while targeted therapies—such as gene therapy, novel biologics, or precision immunomodulators—are currently understudied. Comprehension of the pathophysiological interactions between the immune system and genetic variants is of the uttermost importance to achieve results in this field.

Meanwhile, a multidisciplinary approach, involving cardiologists, geneticists, immunologists, and pathologists, should be implemented in these cases, aiming to reach a patient-tailored approach.

In summary, the convergence of genetic and inflammatory factors in cardiomyopathies represents a fascinating field and a frontier in cardiovascular medicine characterized by diagnostic complexity, therapeutic uncertainty, and significant research gaps. Addressing these challenges will require advances in biomarkers, imaging, genetic and molecular diagnostics, and multicentric clinical research.

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Sport and Exercise (Including CPET Evaluation)

11

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11.1 Introduction

11.1.1 Overview of the Interplay Between Physical Activity and Cardiomyopathies

The relationship between exercise and cardiomyopathies is complex, and it has been studied since the first nomenclature of cardiomyopathies (CMPs) [1]. The interaction between physical activity and CMPs is bidirectional, influenced by both patient-specific and exercise-specific factors. Each patient with cardiomyopathy presents a unique combination of risk profile, symptoms, and sporting preferences. Before prescribing or recommending physical activity, clinicians should thoroughly assess the CMP clinical phenotype (e.g., dilated cardiomyopathy [DCM], hypertrophic cardiomyopathy [HCM], arrhythmogenic right ventricular cardiomyopathy [ARVC], the presence and stage of heart failure (subclinical versus advanced), cardiovascular risk factors (e.g., obesity, hypertension, hypercholesterolemia), sudden cardiac death risk markers, drug medications, and any specific considerations for implantable cardioverter-defibrillator (ICD) carriers [2, 3].

Cardiomyopathies encompass a broad and highly heterogeneous group of disorders with a clinical course that can change over time [4]. The same type of

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physical exercise may be well tolerated by one patient yet excessive for another, even when they share the same cardiomyopathy phenotype. Likewise, an individual patient's tolerance to exercise may vary depending on the phase of clinical stability of the disease. For this reason, exercise prescription should follow a rigorous clinical approach, with a training program tailored to each patient as precisely as a custom-made suit [5, 6].

From the exercise perspective, the potential benefits and risks depend on the type, intensity, frequency, and duration of the activity, as well as whether it is performed in a competitive or recreational setting [7].

High-intensity or endurance sports may exacerbate myocardial stress, provoke arrhythmias, or accelerate disease progression in certain phenotypes (e.g., ARVC), while moderate, individualized programs can improve functional capacity, cardiovascular health, and quality of life [8]. On the other hand, complete abstention from physical activity leads to muscle mass loss, weight gain, subsequent cardiac deconditioning, and ultimately a further decline in functional capacity (VO_2 peak), which may already be compromised [9, 10] (see Fig. 11.1).

Cardiopulmonary exercise testing (CPET) is the recognized gold standard tool for objective quantification of exercise tolerance and aerobic functional capacity. Furthermore, CPET provides a safe, accurate, and reproducible source of diagnostic and prognostic data, essential for tailoring exercise prescriptions and monitoring improvements during follow-up and throughout the training protocol [11, 12].

When major concerns remain regarding the safety of a specific sport, an initial supervised, monitored, and protected training protocol can be useful to promptly identify potential risks [13].

Despite its many advantages, CPET is still underused in routine clinical practice, and, as it remains largely confined to specialized laboratories, it is unfortunately not accessible to all patients with cardiomyopathy [14].

Another limitation that often concerns clinicians is that CPET and cardiac rehabilitation protocols are typically conducted in a hospital. Consequently, we lack information on how, for example, a patient with exertional dyspnea affected with DCM and HF performs during his activities of daily living (ADLs). In this context, emerging portable ergospirometry systems (e.g., the K5) offer the potential to quantify and assess the physiological burden of daily physical activities over a typical day [15].

This chapter will explore the pathophysiological mechanisms and clinical implications of physical activity in cardiomyopathies, examining the boundary between physiological adaptation and pathological remodeling, disease-specific considerations, and strategies for risk assessment and clinical management. It will then conclude with practical recommendations and future perspectives in sports cardiology.

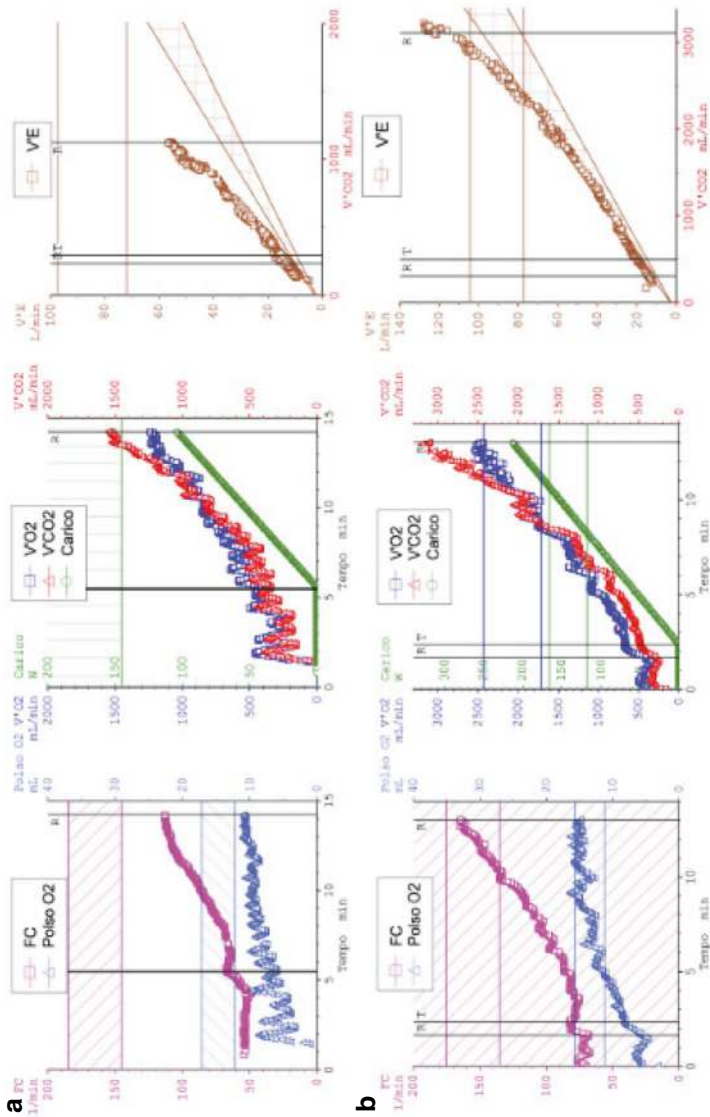


Fig. 11.1 CPET-based comparison of two patients with dilated cardiomyopathy and severe systolic dysfunction. This figure shows a comparison between two age-matched male patients, both affected by dilated cardiomyopathy with severe systolic dysfunction (LVEF <35%). The three upper plots (a) depict a patient with severely reduced peak $\dot{V}O_2$ and a markedly elevated $\dot{V}E/\dot{V}CO_2$ slope, indicative of advanced heart failure. In contrast, the lower plots (b) represent a patient who, despite the underlying cardiomyopathy, remains largely pauci-symptomatic, maintains an active lifestyle, and follows personalized exercise training protocols. In this second case, peak $\dot{V}O_2$, O_2 pulse (defined as the ratio between peak $\dot{V}O_2$ and heart rate), and $\dot{V}E/\dot{V}CO_2$ slope are within normal ranges

11.2 Pathophysiological Mechanism

11.2.1 Cardiovascular Effects of Exercise: Physiological Adaptation vs. Pathological Remodeling

Physical exercise can lead to cardiac remodeling, which may manifest either as a physiological adaptation or as pathological change. The nature of the physiological adaptation depends largely on the type, intensity, and duration of training.

- *Endurance training* typically induces eccentric hypertrophy, characterized by an enlargement of the left ventricular cavity with proportional wall thickening. This results in increased left ventricular mass and volume, accompanied by dilation of the atria and the right ventricle. Such remodeling supports augmented stroke volume and cardiac output during exercise, while systolic and diastolic function are preserved or even enhanced. The remodeling is balanced, with normal or improved myocardial strain and ejection fraction [16, 17].
- *Resistance training*, by contrast, is more often associated with concentric hypertrophy, defined by an increase in left ventricular wall thickness with relatively little chamber enlargement. This pattern reflects an adaptation to pressure overload [16, 18].

In practice, many athletes develop a mixed phenotype depending on their specific training regimen. Importantly, these exercise-induced changes differ fundamentally from pathological remodeling: they are generally symmetric, accompanied by preserved or enhanced cardiac performance, and, most critically, are reversible upon detraining.

Beyond structural and functional changes, exercise is also associated with electrophysiological adaptations. Increased vagal tone may manifest as sinus bradycardia, first-degree atrioventricular block, and early repolarization patterns. Athletes may also meet voltage criteria for ventricular hypertrophy, display incomplete right bundle branch block, or exhibit benign T-wave inversions, particularly in leads V1–V4 among Black athletes. These findings are typically asymptomatic, stable over time, and reversible with detraining, reflecting physiological rather than pathological remodeling [16, 19]. In contrast, cardiomyopathies are often associated with abnormal ECG features, including pathologic Q waves, low limb-lead voltages, lateral T-wave inversions, ventricular ectopy, and conduction abnormalities such as complete bundle branch block. Unlike the athlete's heart, these abnormalities are frequently accompanied by symptoms (e.g., syncope, palpitations) and arrhythmias and are not reversible with detraining [20, 21].

Distinguishing physiological from pathological cardiac remodeling relies on a combination of clinical, imaging, biomarker, and functional parameters [22, 23]. The principal discriminating features are summarized in Table 11.1.

This comparative framework highlights how the integration of multimodal assessment is essential to avoid misclassification between athlete's heart and

Table 11.1 Key features distinguishing physiological exercise adaptation from pathological remodeling [22, 23]

	Physiological adaptation	Pathological remodeling
History and clinical features	No family history of cardiomyopathy or sudden cardiac death; absence of symptoms or only exercise-related bradycardia/fatigue	Positive family history of cardiomyopathy or sudden cardiac death; symptoms such as syncope, palpitations, dyspnea
Electrocardiography	Sinus bradycardia, first-degree AV block, early repolarization; voltage criteria for LV hypertrophy; incomplete right bundle branch block; benign T-wave inversions (particularly V1–V4 in Black athletes)	Pathologic Q waves; low limb-lead voltages; lateral T-wave inversions; ventricular ectopy; complete bundle branch block
Imaging (echocardiography/CMR)	Mild-to-moderate, symmetric LV wall thickening; increased LV cavity size; balanced atrial/ventricular enlargement; normal or enhanced systolic/diastolic function	Asymmetric septal hypertrophy or marked wall thickness; reduced cavity size or dilation with systolic dysfunction; RV involvement or fibrofatty replacement; presence of LGE
Biomarkers (troponin, BNP/NT-proBNP)	Transient, mild elevations after strenuous exercise, normalizing within 24–48 h	Pathological elevations, typically higher and persistent over time
Functional tests (CPET)	Normal or supranormal VO_2 max; efficient ventilatory response (normal VE/VCO_2 slope); preserved exercise tolerance	Reduced VO_2 max; elevated VE/VCO_2 slope; early anaerobic threshold; impaired exercise tolerance

BNP B-type natriuretic peptide, *CPET* cardiopulmonary exercise testing, *CMR* cardiovascular magnetic resonance, *LGE* late gadolinium enhancement, *LV* left ventricle, *NT-proBNP*

N-terminal pro-B-type natriuretic peptide, *RV* right ventricle, *VE/VCO₂ slope* minute ventilation versus carbon dioxide production slope, *VO₂ max* maximum oxygen consumption

cardiomyopathy, thereby guiding both clinical management and recommendations for sports participation.

11.2.2 Exercise in Genetically Predisposed Individuals: Trigger or Modulator of Cardiomyopathy?

Individuals carrying pathogenic variants without overt structural disease, as well as those in early or subclinical stages of cardiomyopathy, pose a particular challenge. They are often young and physically active, for whom regular exercise provides important cardiovascular and psychosocial benefits. At the same time, there is concern that vigorous training may increase arrhythmic vulnerability, anticipate disease expression, or accelerate progression toward heart failure and sudden cardiac death (SCD).

Vigorous physical activity imposes a substantial hemodynamic and adrenergic load that, in genetically predisposed hearts, can interact with a vulnerable substrate,

promote electrical instability, trigger ventricular arrhythmias, and drive adverse remodeling [24]. Exercise thus acts as a double-edged factor: while intense training may precipitate arrhythmias or hasten disease progression, moderate activity is generally considered safe and may even improve functional capacity and long-term outcomes.

This dual role is particularly evident in arrhythmogenic cardiomyopathy (ACM), regarded as the paradigm of exercise-sensitive cardiomyopathies. Several observational studies have shown a dose–response relationship, with higher volumes of vigorous or competitive endurance exercise linked to earlier phenotypic expression, faster ventricular dysfunction, and greater arrhythmic risk, especially in men and in individuals with high lifetime exposure [8, 25–27].

Beyond ACM, evidence in other inherited cardiomyopathies is less consistent. In hypertrophic cardiomyopathy (HCM), evidence is more heterogeneous. Some cohorts reported a higher prevalence of non-sustained ventricular tachycardia in highly active patients—possibly influenced by selection and surveillance bias—whereas larger contemporary series did not demonstrate increased risk of major cardiovascular events or sustained arrhythmias in those engaged in vigorous activity, suggesting that moderate exercise is safe and vigorous activity may be acceptable in carefully selected low-risk patients [28–32].

In dilated cardiomyopathy (DCM), the effect seems genotype-specific: carriers of LMNA (and possibly TMEM43) variants appear particularly prone to exercise-related arrhythmic and functional deterioration, whereas evidence in titin truncating variant (TTNtv) carriers is more reassuring, with no clear signal of harm from moderate or even higher training volumes [33–35].

Overall, the impact of exercise in genetically predisposed individuals is not uniform but depends on both genetic substrate and cumulative intensity of training. Moderate activity is generally beneficial, while sustained vigorous exercise may foster maladaptive remodeling and increase arrhythmic risk, particularly in cardiomyopathies involving impaired cellular coupling or mechanosensory pathways [7].

11.2.2.1 Genotype-Positive/Phenotype-Negative (G+/P–) Individuals

The concern that intense physical activity might accelerate phenotypic expression has not been confirmed in genotype-positive but phenotype-negative (G+P–) relatives of patients with hypertrophic cardiomyopathy (HCM). On the contrary, observational studies indicate that greater exercise participation in youth is associated with better diastolic function later in life, regardless of hypertrophy severity [29, 36, 37]. These findings support current recommendations, which no longer impose universal restrictions on asymptomatic G+P– individuals [38].

In contrast, exercise load is a major determinant of penetrance in ACM. Up to one-third of clinically diagnosed cases are “gene-elusive,” often lacking identifiable desmosomal variants but sharing a history of intense endurance training [39–41]. Both overt ACM and the G+P– stage display a clear dose–response relationship:

higher volumes of high-intensity exercise correlate with earlier phenotypic expression, greater ventricular remodeling, and increased arrhythmic risk [42, 43].

Observational studies of G+P− carriers confirm these trends, showing faster disease progression and more frequent arrhythmias in those engaged in sustained vigorous sports [44].

Thus, while moderate exercise may be neutral or even favorable in G+P− HCM, in ACM cumulative high-intensity activity acts as a strong driver of disease development and arrhythmic events [45].

11.2.2.2 Progression or Protection? Exercise as a Disease Modifier

The historical link between vigorous exercise, SCD, and inherited cardiomyopathies led to uniform restrictions, irrespective of genotype or disease stage. Yet physical activity is essential for cardiovascular health, and excessive caution has fostered physician-driven inactivity. Exercise should therefore be viewed not only as a trigger of arrhythmias but also as a modifiable determinant of disease trajectory, with effects that vary by intensity, timing, and genetic background.

In HCM, individuals engaging in intensive activity often have milder hypertrophy and no left ventricular outflow tract obstruction, features associated with lower risk. The absolute incidence of exercise-related SCD is low ($\approx 0.06/1000$ person-years), although still higher than in the general population [46]. Data on exercise and myocardial fibrosis are conflicting, with some studies showing no link and others suggesting a dose–response with training volume [28, 47, 48]. Imaging indicates that active disease with myocardial edema may predispose to fibrotic progression [49]. Structured programs are generally safe, modestly improving peak VO_2 and ventilatory efficiency, changes associated with better prognosis [30, 32, 50].

In ACM, particularly with *PKP2* or *DSP* variants, vigorous or endurance exercise consistently accelerates phenotypic conversion and arrhythmic risk, even in G+P− carriers [41, 51]. Exercise restriction reduces arrhythmic events and delays heart failure progression. A robust dose–response effect supports strict avoidance of high-intensity or competitive sports in this setting [52].

In DCM, moderate exercise improves functional capacity and LVEF in stable patients. Evidence according to genetic background in DCM is more limited and genotype-dependent. *TTN* truncating variants, found in up to 25% of familial cases, often follow a relatively mild course, and moderate-to-high exercise did not worsen outcomes in one cohort [35, 53]. Conversely, *LMNA* mutations are associated with early conduction disease and high arrhythmic risk, with observational data linking sustained vigorous activity to adverse events, thereby reinforcing early ICD implantation and limitation of intense sports [54].

Overall, across cardiomyopathies, the balance between progression and protection is shaped by genotype, sex, cumulative load, and age at training. Moderate exercise appears generally safe and may confer functional benefits, whereas chronic high-intensity exposure accelerates maladaptive remodeling and arrhythmogenesis, particularly in disorders affecting structural or mechanosensory proteins.

In this regard, Fig. 11.2 illustrates a conceptual J-shaped relationship between cumulative exercise dose and prognosis. Physical inactivity is associated with

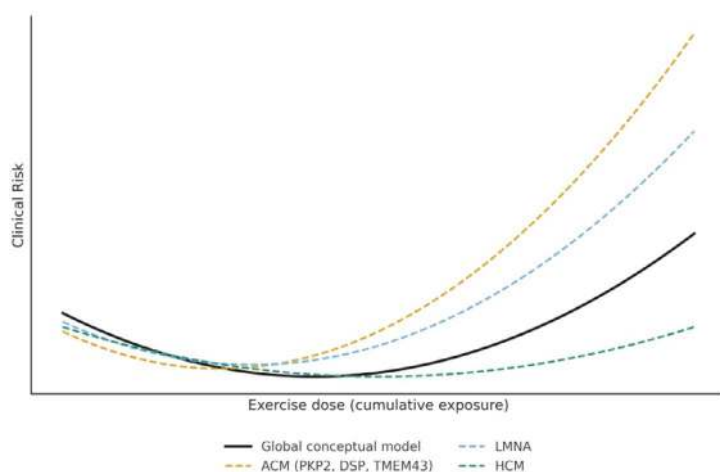


Fig. 11.2 Dose–response relationship between exercise exposure and clinical risk in inherited cardiomyopathies. The figure illustrates a conceptual J-shaped relationship between cumulative exercise dose and prognosis. This is a conceptual model and does not represent a quantitative risk estimate

increased clinical risk due to deconditioning, whereas moderate individualized exercise is associated with the lowest risk. Excessive or high-intensity endurance activity can be linked to accelerated disease progression and arrhythmic burden in selected genetic substrates, particularly in arrhythmogenic cardiomyopathy (PKP2, DSP, TMEM43) and LMNA-related disease, while HCM shows a flatter response curve.

11.2.2.3 The Importance of Quantifying the Effort

The influence of exercise on inherited cardiomyopathies is not binary but determined by cumulative burden—integrating frequency, duration, intensity, and type of activity—together with genetic background and host factors such as sex, age at sport initiation, and epigenetic modifiers. Endurance disciplines, characterized by sustained isotonic contractions and high cardiac output, impose particular hemodynamic and adrenergic stress. Quantifying this load is challenging: absolute thresholds (e.g., Borg scale for exertional dyspnea, METs) suggest comparability but neglect interindividual fitness variability, whereas relative measures (i.e., VO_2 peak, heart rate reserve, watt peak) more accurately capture the strength of the effort. On the other hand, the definitions of “moderate” and “vigorous” training are vague and often differ across studies, making risk interpretation more difficult.

In HCM, evidence is heterogeneous. In one cohort of 188 *MYBPC3* carriers, high-dynamic activity >22 MET-h/week tripled the risk of malignant arrhythmias versus ≤ 7.5 MET-h/week, despite no excess in major adverse cardiovascular events (MACE) [36]. Other data are more reassuring: in athletes with mild HCM, no deaths or sustained arrhythmias occurred over 4.5 years, and multicenter analyses did not confirm a consistent genotype–exercise interaction [50, 55]. Prospective trials

indicate that individualized programs up to ~85% heart rate reserve are generally safe, improving exercise capacity and diastolic function without increasing MACE [56].

ACM remains the prototype of exercise-sensitive disease. Truncating variants in *PKP2* and *DSP* confer high vulnerability, with even modest vigorous activity (~14–15 MET-h/week) linked to ventricular dysfunction and arrhythmias [57]. *DSP* carriers also display higher rates of myocarditis, left ventricular impairment, and arrhythmias when exposed to moderate-to-vigorous exercise. Restriction reduces arrhythmic events but does not reverse established dysfunction [51]. Non-desmosomal forms such as *TMEM43* and *PLN* also show dose-dependent vulnerability, with markedly higher arrhythmic risk during exertion. Overall, ACM demonstrates the clearest genotype- and dose-dependent association, strongly supporting strict avoidance of competitive or high-intensity training, while low-to-moderate activity may be acceptable in selected patients.

In DCM and NDLVC, effects appear genotype-specific. *LMNA* and *TMEM43* variants consistently predict early arrhythmias and rapid dysfunction, potentially aggravated by sustained vigorous training [58]. Evidence for *FLNC* and other genes is limited and largely extrapolated from ACM, warranting caution but leaving uncertainties.

Taken together, exercise-related outcomes in inherited cardiomyopathies are shaped by mutation type, sex, age, and cumulative load. While moderate exercise is safe and beneficial for many patients, carriers of high-risk genotypes—particularly *PKP2*, *DSP*, *LMNA*, and *TMEM43*—require careful restriction and individualized counseling.

11.3 Disease-Specific Considerations

11.3.1 Focus on Arrhythmic and Hemodynamic Risks Related to Physical Activity

11.3.1.1 Hypertrophic Cardiomyopathy (HCM)

Hypertrophic cardiomyopathy (HCM) is considered a leading cause of sudden cardiac death (SCD) in young athletes and is more frequently linked to high-intensity or competitive sports that involve sudden movements, like football or basketball [59]. The circumstantial link between sport and SCD in HCM patients has resulted in prohibitive exercise recommendations, leading to the exclusion from any competitive or high-intensity physical activities and sports [60]. However, recent data suggest that the absolute risk of SCD in HCM patients participating in sports may be lower than previously thought. Nevertheless, there are major risk factors that must be taken into appropriate consideration: family history of sudden cardiac death, history of unexplained syncope, sustained ventricular arrhythmias, systolic dysfunction (LVEF <50%), severe outflow tract obstruction not controlled by medical therapy, extensive LGE on CMR, and sarcomeric genetic variant [5].

Regarding competitive sports, patients who present with symptoms or have high-risk profiles should refrain from engaging in high-intensity exercise and competitive athletic activities. However, participation in disciplines that require primarily technical skills and involve low cardiovascular effort may be considered appropriate. In individuals who are genotype-positive but phenotype-negative, the risk of arrhythmias is generally low, and therefore participation in competitive sports can be permitted.

As for recreational physical activity, in the absence of major risk factors, light to moderate aerobic exercise can be safely performed, provided the patient is clinically stable and undergoes regular medical follow-up. It is recommended to engage in physical activity three to five times per week, with the training heart rate gradually increasing to reach 60–70% of the heart rate reserve.

Hemodynamic risk is more significant in patients with obstructive HCM, where left ventricular outflow tract obstruction may cause syncope, hypotension, or symptom exacerbation during exertion. Beta-blocker therapy and the presence of obstruction are associated with reduced exercise capacity but do not necessarily increase the risk of fatal events during sports [61].

11.3.1.2 Dilated Cardiomyopathy (DCM)

Dilated cardiomyopathy (DCM) predisposes to heart failure and ventricular arrhythmias [62]. The arrhythmic risk is significant, especially in patients with reduced ejection fraction (EF), higher fibrosis burden detected with CMR, and genetic subtypes, such as lamin A/C (LMNA), desmoplakin (DSP), and filamin C (FLNC) genes [5]. Recent evidence support the safety of moderate-to-high levels of physical activity in many patients with DCM, though high-risk patients require more restrictive supervised regimens [7].

Asymptomatic individuals with an LVEF of at least 45%, no history of unexplained syncope, and no documented ventricular tachyarrhythmias may safely participate in sports, provided there is no family history of sudden cardiac death. Conversely, competitive sports should be avoided in patients with an LVEF below 45%, in those who are symptomatic, or in the presence of extensive myocardial fibrosis, ventricular tachyarrhythmias, unexplained syncope, or high-risk genetic mutations such as LMNA or FLNC variants. These individuals should limit themselves to leisure-time physical activity and undergo regular follow-up. Exercise is strictly contraindicated in cases of unstable or decompensated heart failure, active arrhythmias, or severe comorbid conditions.

Beyond arrhythmic risk, during exertion there is also a hemodynamic risk, which can manifest as worsening heart failure, syncope, or arrhythmias [63]. Nevertheless, regular moderate physical activity and exercise training are recommended in DCM. Aerobic exercise at 50–80% of oxygen uptake reserve, 3–5 times per week (for up to 45 min), is both safe and effective for improving exercise capacity and quality of life, provided the patient is clinically stable [64].

11.3.1.3 Non-Dilated Left Ventricular Cardiomyopathy

The arrhythmic risk in NDLCV is highest among patients with certain features: male sex, left ventricular ejection fraction (LVEF) less than 45%, septal or ring-like late gadolinium enhancement (LGE) seen on CMR, non-sustained ventricular tachycardia, and pathogenic variants in high-risk genotypes (LMNA, DSP, or PKP2) [65]. The increased arrhythmia risk is thought to be mediated by beta-adrenergic stimulation, which modulates disease expression and arrhythmic susceptibility [66].

11.3.1.4 ARVC

These patients are more likely to present with sudden cardiac death, suggesting the importance of careful arrhythmic risk stratification. Understanding a patient's genetic background is crucial in arrhythmogenic cardiomyopathy (ACM), as specific variants—such as those in the plakophilin-2 (*PKP2*) gene—can increase susceptibility to the harmful effects of high-intensity exercise. While high-intensity activity and competitive sports should be avoided, recreational exercise may be considered, and low- to moderate-intensity exercise is a safe option in patients with a mild phenotypic expression [38].

11.3.1.5 Restrictive Cardiomyopathy (RCM)

The hemodynamic stress and neurohormonal activation associated with high-intensity exercise may precipitate arrhythmias or worsen diastolic dysfunction. RCM is generally associated with restriction from competitive sports due to the risk of arrhythmias and heart failure exacerbation, but individualized recommendations for recreational activity may be appropriate in select stable patients [5].

11.4 Risk Assessment and Clinical Management

11.4.1 Pre-Participation Screening

Routine ECG screening in young athletes—some of whom enter competitive activity as early as 8 years of age (e.g., rhythmic gymnastics)—enables the early detection of abnormalities suggestive of cardiomyopathies typically manifesting with ECG alterations [67]. Exercise testing, whether by step test, cycle ergometer, treadmill, or rowing ergometer, together with postexercise ECG, allows evaluation of repolarization dynamics and facilitates the identification of exercise-induced ventricular ectopy [19, 20, 68]. Such findings may represent the initial expression of genetically determined cardiomyopathies or myocardial scarring, both potential substrates for life-threatening arrhythmias. This systematic approach has been associated with a reduction in sudden cardiac death among young competitive athletes, with rates now lower than in the general age-matched population [69].

The standard pre-participation assessment includes family and personal history, clinical examination, spirometry, urinalysis, and visual acuity testing. Particular attention is paid to red flags such as a family history of premature

myocardial infarction, exercise-related palpitations, chest pain, syncope, or pre-syncope, which warrant second-level investigations [70, 71]. These may include echocardiography, ambulatory 12-lead Holter ECG monitoring during habitual training, and, when indicated, cardiac magnetic resonance imaging (CMR) to detect nonischemic fibrosis [24]. The identification of frequent or complex ventricular arrhythmias, despite a normal echocardiogram, often justifies CMR to assess for structural abnormalities such as scarring or fibro-fatty replacement [66, 72, 73].

Genetic testing is not considered a first-line tool for eligibility assessment, as results may be negative or of uncertain significance. It is generally reserved for athletes with a positive family history of pathogenic variants, in which case it may confirm the diagnosis of an inherited cardiomyopathy. However, variable penetrance and expressivity limit its role in determining fitness for competition [74, 75].

Ultimately, the decision regarding eligibility rests with the sports physician or cardiologist, who must balance diagnostic findings against the risks of allowing continued competitive activity.

11.4.2 Return-to-Play Decisions

When evaluating an athlete with cardiomyopathy, it is essential to determine their risk of experiencing a fatal or potentially fatal event over time. There are risk scores validated by international scientific societies that assist in decision-making for several conditions—such as hypertrophic cardiomyopathy—helping clinicians define the most appropriate course of action while always prioritizing the athlete's health. Expert recommendations from international guidelines are available, though they do not always fully agree on eligibility criteria for competitive sports participation [2, 24, 66].

Return-to-play decisions are based on the presence or absence of high-risk features (e.g., history of ventricular arrhythmias, syncope, severe LV dysfunction, heart failure symptoms, or ICD placement) [76]. The AHA/ACC and ESC both recommend that universal sport restriction should not be applied; instead, eligibility for competitive or vigorous exercise should be determined through annual comprehensive evaluation and shared decision-making with an expert provider [5]. Clinical decisions in sports cardiology must consider the psychological impact on athletes, as misclassification may create “false patients.” Detraining may aid diagnostic clarity: regression of ECG abnormalities, in the absence of other pathological findings (normal echocardiogram, Holter, family history, and clinical history), suggests benign athlete's heart adaptations rather than cardiomyopathy. In such cases, continuation of competitive sport, even at higher intensity, is generally safe.

In summary, return-to-play decisions in cardiomyopathies require a structured, individualized approach incorporating history, ECG, imaging, genetic

testing, and expert-led shared decision-making, as recommended by the AHA/ACC and ESC.

11.4.3 Differences Between Competitive and Recreational Physical Activity

Competitive physical activity in patients with cardiomyopathies is defined as systematic training with the primary goal of excelling in sports and competing against others, often at high intensity and with greater physical demands. Recreational physical activity is performed for leisure, without systematic training or the intent to compete, and typically involves mild to moderate intensity [5].

Individuals practicing non-competitive sports must undergo an annual medical evaluation. The procedure includes history, physical examination, and blood pressure measurement; a resting ECG is recommended once before age 60 and annually in adults, though exercise testing is not required. These visits, often performed by general practitioners, pediatricians, or sports physicians, serve as a population screening tool, enabling the detection of familial risk of sudden cardiac death, ECG abnormalities, or early signs of myocardial disease, thereby prompting further investigation. This broader and more heterogeneous population is assessed primarily for health protection rather than competitive eligibility [77].

In summary, competitive physical activity carries higher risk and requires individualized assessment and shared decision-making, while recreational activity is generally safe and beneficial for most patients with cardiomyopathies, provided disease-specific considerations are addressed [6, 78].

11.5 Clinical Recommendations and Future Perspectives

11.5.1 Overview of Current Guidelines

Current guidelines (ESC, AHA/ACC) recommend that regular aerobic exercise and physical activity are beneficial and should be encouraged in most patients with cardiomyopathies, including those with heart failure, to improve functional status, exercise performance, and quality of life. For heart failure, the AHA/ACC/HFSA guidelines specifically recommend exercise training or regular physical activity for eligible patients, with a goal of 30 min of moderate activity 5 days per week, including warm-up and cool-down periods [79, 80]. Supervised exercise is preferred initially, especially for those with advanced symptoms or comorbidities. Cardiac rehabilitation is also endorsed for improving exercise tolerance and health-related quality of life in heart failure [24].

All major guidelines agree in recommending physical activity for everyone, provided it is performed safely. Regular exercise is a cornerstone of health promotion,

whereas sedentary behavior is associated with increased morbidity. Individualized exercise prescription is increasingly emphasized, particularly for patients excluded from competitive sports. Following the principle of “*no one left behind*,” physical activity is prescribed as a therapeutic intervention, ideally after cardiopulmonary exercise testing (CPET) and individualized risk stratification [14, 64, 78]. Medical therapy may be optimized to facilitate safe participation, usually involving light-to-moderate aerobic exercise, complemented by resistance, flexibility, and balance training. Shared decision-making with the athlete and, when applicable, their family is essential to ensure both safety and quality of life during the transition out of competitive sport.

11.5.2 Future Perspectives

Research is an ally of athletes: increasingly sophisticated techniques help physicians in complex situations, such as artificial intelligence (AI) or wearable devices that enable data analysis, and investigations often lead to positive outcomes, sometimes even allowing athletes to return to competitive sports [81]. Precision medicine in sports cardiology is increasingly driven by the integration of artificial intelligence (AI) and wearable monitoring technologies. AI enables the analysis of complex, multimodal datasets—including imaging, electrophysiological, and behavioral data—facilitating individualized risk stratification, diagnosis, and management for athletes [82]. Deep learning models can synthesize features from ECG, CMR, and clinical data to predict arrhythmic risk and guide interventions, as demonstrated by multimodal approaches such as the DEEP RISK model [83]. The AI-enhanced CMR interpretation further improves diagnostic accuracy and efficiency, supporting personalized care.

Wearable devices, including smartwatches and sensor patches, continuously capture physiological and activity data, enabling real-time arrhythmia detection, monitoring of training loads, and early identification of cardiac events. AI algorithms process these large datasets to deliver actionable insights, optimize training, and reduce the risk of sudden cardiac death. The European Heart Rhythm Association, Heart Rhythm Society, and ESC Working Group on E-Cardiology highlight the importance of integrating wearable and telemonitoring data with AI for dynamic, personalized risk prediction [83].

The limitations of wearable monitoring devices for detecting cardiovascular abnormalities in athletes and continuous physiological data include troubles regarding data and signal quality, limited clinical validation in athletes, lack of standardization, potential data overload, and finally privacy and security concerns. Ongoing research and large-scale trials are needed to establish clinical utility and ensure equitable, secure implementation [84].

11.6 From Past to Present: The Dynamic Evolution of Clinical Recommendations on Physical Activity

Clinical recommendations regarding physical activity and exercise prescription for cardiac patients are continuously evolving. This dynamic trend is even more pronounced in individuals with cardiomyopathy, for whom, considering recent scientific evidence, a progressive shift has been observed in recent years—from an almost absolute restriction from exercise to the promotion of physical activity through personalized protocols developed by multidisciplinary professional teams [13, 24].

An illustrative example is obstructive hypertrophic cardiomyopathy (OHCM), which until 2024 was regarded as a relative contraindication to CPET, particularly in patients with a significant resting gradient. Today, CPET is not only considered broadly safe when performed with appropriate precautions but is also employed, thanks to its strong diagnostic and prognostic value, as a primary endpoint in major randomized clinical trials investigating novel myosin inhibitor therapies [3, 28, 47, 50, 60, 85].

Similarly, until 2015, exercise was considered absolutely contraindicated in arrhythmogenic cardiomyopathy (ACM), particularly competitive and high-intensity endurance sports. Since the 2019 Heart Rhythm Society consensus, guidelines have adopted a more nuanced view: while vigorous and competitive activity remains discouraged, individualized low-intensity exercise may be permitted under supervision in selected low-risk patients. The update reinforces risk stratification and shared decision-making, allowing moderate recreational activity only in carefully chosen cases [5, 7, 38, 45, 66].

The cessation or temporary reduction of physical activity (“detraining”) was once recommended in earlier American Heart Association (AHA) and American College of Cardiology (ACC) guidelines as a possible tool to differentiate physiological athlete’s hypertrophy from hypertrophic cardiomyopathy (HCM) [3, 86]. To be fair, this approach was never truly considered a diagnostic or therapeutic strategy in suspected HCM, as it was not associated with any formal recommendation given the low level of evidence. In current guidelines, detraining is no longer recommended [2, 3, 63]. The diagnosis of HCM is now based on imaging, genetics, and clinical phenotype, rather than on the response to detraining, even in patients with borderline morphology or athletes with left ventricular hypertrophy [87]. Consequently, exercise suspension is not indicated to clarify the diagnosis, since it does not improve risk stratification or prognosis. On the contrary, physical inactivity is associated with reduced functional capacity, increased cardiometabolic risk, and lower quality of life, without evidence of specific benefits from detraining in any subgroup. In other words, the concept has shifted from *deconditioning to diagnosing to monitoring and risk stratification* on a case-by-case basis.

These are just a few examples of the changes that exercise prescription has undergone for patients with cardiomyopathy in recent years. Overall, for all major

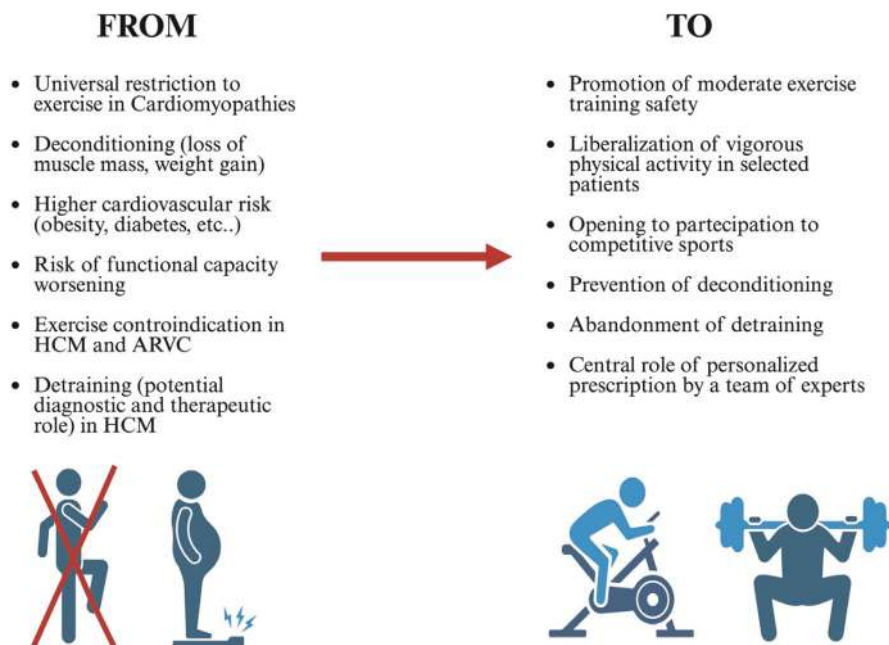


Fig. 11.3 The most significant variations in exercise prescription adopted by the scientific community over the last years. Abbreviations: ARVC arrhythmogenic right ventricular cardiomyopathy, HCM hypertrophic cardiomyopathy

inherited cardiomyopathies, the paradigm has shifted from universal restriction and detraining to the promotion of moderate exercise, individualized prescription, and shared decision-making, with restrictions targeted only to high-risk subgroups regarding high-intensity activity [3, 5, 24, 45].

Figure 11.3 summarizes the most significant variations adopted by the scientific community.

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Modifiers of Cardiomyopathy Expressivity: The Role of Intrinsic and Environmental Factors

12

Marco Bressan, Gioacchino Di Carlo, Alessandro De Rosa, Elena Bertarelli, and Alessia Paldino

As outlined in previous chapters, cardiomyopathies are characterized by significant heterogeneity in disease onset, clinical presentation, and prognosis—even among individuals carrying identical pathogenic variants. This variability is largely attributable to the complex interplay between genetic background and a variety of modifying factors, both intrinsic and extrinsic [1–3]. These factors act as modulators of gene penetrance and disease expressivity and may, in some cases, represent critical “second hits” that trigger or exacerbate clinical manifestations.

These triggers may be classified into three main groups (see Table 12.1): intrinsic factors and two main extrinsic factors—heart failure comorbidities and environmental factors.

The impact of these promoting factors may differ according to the underlying genotype.

12.1 Intrinsic Factors

Age is a major determinant of cardiomyopathy expression, with penetrance often increasing over time. For example, in genotype-positive relatives, age-related penetrance has been well-documented, particularly for *TTN* truncating variants, which tend to manifest later than sarcomeric gene mutations typically associated with hypertrophic cardiomyopathy (HCM) in adolescents or young adults [4–7].

Sex also plays a crucial role in disease expressivity and progression. In most cardiomyopathies, male patients tend to exhibit earlier onset, more severe phenotypes, and worse long-term outcomes. This has been reported across multiple subtypes,

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Table 12.1 Triggers classification

Main category	Subcategory	Examples
Intrinsic factors	Demographic characteristics	Age, sex, ethnicity
Heart failure-related comorbidities	Cardiovascular and metabolic conditions	Systemic hypertension, diabetes mellitus, obesity
	Renal disease	Chronic kidney disease
Environmental factors	Toxic exposures	Alcohol, chemotherapeutic agents
	Paraphysiological stressors	Pregnancy, sustained tachyarrhythmias, intense physical activity
	Inflammatory triggers	Myocarditis, systemic inflammatory conditions

including dilated (DCM), hypertrophic (HCM), and arrhythmogenic cardiomyopathy (ACM). Conversely, specific genetic contexts may reveal exceptions to this trend—for instance, in *DSP*-related ACM, male sex appears to be protective, with a reduced arrhythmic burden compared to females [8–10]. Disease-specific aspects are addressed in detail in the chapters focusing on each cardiomyopathy.

12.2 Extrinsic Factors: The “Second-Hit” Hypothesis

In cardiomyopathies, the “second-hit” model, adapted from oncology, explains how genetic predisposition alone might be, in some cases, insufficient for disease development, requiring an additional stressor to trigger phenotypic expression.

This framework provides a compelling explanation for the incomplete penetrance, variable expressivity, and heterogeneous age of onset observed in familial cardiomyopathy cohorts. The impact of “second hits” can vary based on the type, duration, and intensity of exposure, as well as the underlying genetic architecture [11].

Extrinsic factors can be broadly categorized into two subgroups [12]:

- Heart failure comorbidities, which alter hemodynamic load and myocardial stress but do not directly affect genetic penetrance. These include common cardiovascular and metabolic disorders such as systemic hypertension, diabetes, obesity, and chronic kidney disease.
- Disease-promoting factors, which can directly impair myocardial structure or function (e.g., alcohol, chemotherapeutic agents, chronic inflammation, pregnancy, intense exercise, tachyarrhythmias).

This chapter aims to explore how the “second-hit” model can deepen our understanding of the pathogenesis, clinical variability, and therapeutic opportunities in both inherited and acquired cardiomyopathies.

Identifying and managing modifiable “second hits” may not only delay disease onset in individuals with a genetic predisposition but also mitigate disease progression in those already affected. The integration of lifestyle interventions, risk factor

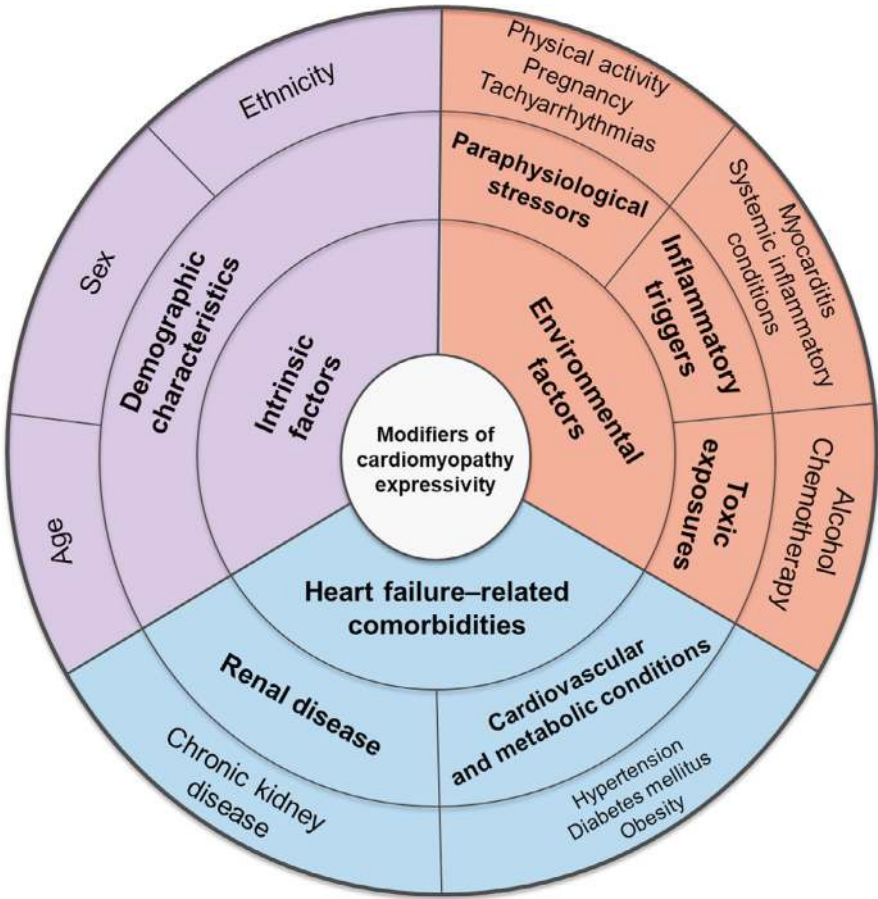


Fig. 12.1 The impact of promoting factors (Intrinsic factors, environmental factors, heart failure-related comorbidities)

surveillance, and personalized counseling becomes essential, particularly in the context of family-based management strategies.

Furthermore, recognizing these modifiers can help refine risk stratification models and guide therapeutic decisions, especially in cases where the penetrance or severity of cardiomyopathy appears disproportionate to the known genotype (Fig. 12.1).

12.3 Pregnancy

Pregnancy is a dynamic process that induces major physiological changes, requiring progressive cardiovascular adaptation. It can be considered a prolonged natural stress test. While pregnant women without heart disease usually tolerate these hemodynamic changes well, women with preexisting cardiomyopathies may face significantly increased risks of adverse cardiac events, such as heart failure, arrhythmias, and even maternal death [13, 14].

After conception, a considerable reduction in peripheral vascular resistance occurs, driven by nitric oxide release and consequent RAAS pathway activation, which increases plasma volume and Cardiac Output (CO). The increase in CO is achieved through a rise in stroke volume during the first half of pregnancy, followed by a steady increase in heart rate thereafter. Hemodynamic changes persist during labor and delivery. Moreover, the emotional burden of delivery may increase sympathetic tone, raising blood pressure and heart rate. These changes may overwhelm the cardiovascular reserve in patients with heart disease [15, 16].

Moreover, physiological changes can affect the pharmacokinetics and pharmacodynamics of cardiac medications [17, 18] and some HF medications, such as ACEi, ARBs, ARNIs, SGLT2i, and ivabradine, are contraindicated during pregnancy and should be stopped or replaced to ensure fetal safety, potentially increasing the risk of decompensation [18].

When analyzing the interaction between cardiomyopathies and pregnancy, two distinct clinical scenarios must be considered: (1) pregnancy in women with a pre-existing cardiomyopathy and (2) new-onset cardiomyopathy first diagnosed during pregnancy.

Within the second scenario, a further distinction should be made between peripartum cardiomyopathy and the unmasking of a previously silent (typically dilated) cardiomyopathy where pregnancy acts as a “second hit.”

12.3.1 Pregnancy in Women with a Preexisting Cardiomyopathy

Cardiovascular disease is the leading cause of indirect maternal mortality. All women with known or suspected heart disease planning pregnancy should receive preconception counseling [19] to estimate individual risk, optimize medical therapy, and improve both maternal and fetal outcomes. A comprehensive evaluation should incorporate a complete history (including relevant family history), physical examination, electrocardiography, echocardiography, natriuretic peptide levels, and functional testing as needed—ideally while temporarily discontinuing medications that would need to be stopped if pregnancy were to occur [14].

Cardio-obstetric risk stratification tools such as the modified WHO 2.0 (mWHO 2.0) classification and CARPREG II can guide risk assessment [20]. For congenital heart disease, the ZAHARA score should be used [21]. Counseling by a clinical geneticist is recommended in women with a diagnosis of inherited cardiovascular disease to guide risk stratification and prenatal genetic testing.

CARPREG II risk score	
Risk predictors	Points
High-risk left-sided obstructive lesion (e.g., severe MS, severe AS, LVOT obstruction)	2
Pulmonary hypertension (PASP ≥50 mmHg)	2
Coronary artery disease	2

CARPREG II risk score	
Risk predictors	Points
No prior cardiac intervention (if intervention indicated)	2
Late pregnancy assessment (>20 weeks gestation)	1

Total score	Risk of cardiac event
0–1	~5%
2	~10%
3	~15%
4	~22%
≥5	~40%

Initially proposed in the 2018 ESC Guidelines, the Pregnancy Heart Team has been further established in the 2025 ESC Guidelines [18, 22]. The Pregnancy Heart Team should encompass a core team—cardiologist, anesthesiologist, clinical nurse specialist and midwife obstetrician—that can be expanded with other experts, tailored to women’s physical and mental health or emerging complications. The primary responsibilities of the Pregnancy Heart Team encompass risk assessment, collaborative care plan development, continuous progress monitoring, coordination, patient education, and psychological counseling.

The presence of high-risk features requires a discussion by the Pregnancy Heart Team, including a shared decision-making process for contraceptive options or pregnancy termination, involving psychological support.

Signs of extremely high risk of maternal mortality or severe morbidity
A. Pulmonary arterial hypertension
B. Severe symptomatic systemic ventricular dysfunction (LVEF <30%, NYHA class III/IV)
C. Previous peripartum cardiomyopathy with more than mild left ventricular impairment
D. HCM with symptomatic severe outflow tract obstruction (>50 mmHg) or with severely symptomatic left ventricular dysfunction (LVEF<50%)
E. Severe mitral stenosis or severe symptomatic aortic stenosis
F. Systemic RV with moderate or severely decreased ventricular function, Fontan with any complication, Eisenmenger syndrome
G. Marfan syndrome with aortic dilation >45 mm, aortic dilation >50 mm in patients with bicuspid aortic valve, or aortic (re)coarctation, previous aortic dissection with increasing diameter

The cardiovascular adaptations of pregnancy carry different clinical implications depending on the underlying cardiomyopathy phenotype.

12.3.1.1 Pregnancy in Women with Hypertrophic Cardiomyopathy (HCM)

Pregnant women with HCM may experience worsening obstruction due to decreased afterload, increased heart rate, and enhanced LV contractility. Therefore, women with preexisting LVOT gradients are considered at higher risk. LVOT obstruction, defined as a subaortic gradient >30 mmHg, has been associated with a 10% incidence of maternal adverse events. Due to increased adrenergic tone, arrhythmias may become more frequent and less well tolerated [23, 24].

Nonetheless, despite higher maternal mortality in women with HCM compared with the general population, absolute maternal mortality is low (0.5%) and confined to women with a very high risk [25].

In patients with known HCM who are planning to or who become pregnant, the medication regimen should be carefully reviewed to minimize fetal effects. Disopyramide should be avoided as it can induce uterine contractions and premature delivery [26]. Beta-blockers are the first-line therapy and should be continued or started if symptoms arise (e.g., AF, ventricular arrhythmias). Verapamil may be used as second-line therapy. Myosin inhibitors (e.g., mavacamten) have not been tested in pregnancy, and animal studies have shown fetal toxicity [27]. Cardioversion should be considered for poorly tolerated persistent AF [22].

12.3.1.2 Pregnancy in Women with Dilated Cardiomyopathy (DCM) and Non-Dilated Left Ventricle Cardiomyopathy (NDLVC)

Pregnancy is generally less well tolerated in women with preexisting DCM.

Therapy should be modified before pregnancy. ACE-Is, ARBs, mineralocorticoid receptor antagonists (MRAs), sacubitril/valsartan, and SGLT2 inhibitors are all contraindicated during pregnancy. Prepregnancy risk stratification should include temporary withdrawal of contraindicated medication with close monitoring.

Cardiac complications are common and mainly related to heart failure driven by impaired left ventricular systolic function and discontinuation of disease-modifying therapies [28]. Highly symptomatic patients and women with severe left ventricular dysfunction are considered at higher risk [29]. Other high-risk criteria include the following: right ventricular failure, sustained ventricular arrhythmias, atrial fibrillation and/or severe mitral regurgitation.

Genetically determined dilated cardiomyopathies show different clinical courses depending on the underlying genetic variation. For example, *TTN* truncating variants—the most common genetic cause of idiopathic dilated cardiomyopathy and also implicated in peripartum cardiomyopathy—are associated with an increased risk of heart failure during or after pregnancy [28]. Although left ventricular recovery is possible, it is often delayed, requiring prolonged follow-up.

In contrast, available data suggest that pregnancy is generally well tolerated in women with *LMNA* mutations. Observational studies have shown no significant increase in arrhythmic events, left ventricular dysfunction, or adverse outcomes compared to nulliparous women [30].

12.3.1.3 Pregnancy in Women with Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Data from available studies have shown that pregnancy is well tolerated in women with ARVC.

Events are mostly represented by ventricular arrhythmia and appropriate ICD interventions, while HF is rare [31–33]. The arrhythmic risk seems poorly predictable and more related to the phenotypic expression than the pregnancy itself.

12.3.1.4 Pregnancy in Women with Other Cardiomyopathies

- Left ventricular non-compaction should be considered in the differential diagnosis for peripartum cardiomyopathy (PPCM).
However, isolated hypertrabeculation identified during pregnancy can be the simple consequence of an increased preload, can resolve after pregnancy, and cannot be used to make a diagnosis of cardiomyopathy.
- Pregnancy in patients with restrictive cardiomyopathy is rare. The restrictive pattern may be exacerbated by the physiological changes that occur during pregnancy.
- Pregnancy in women with Chemotherapy-induced Cardiomyopathy: cancer survivors of reproductive age, especially those exposed to cardiotoxic therapies (e.g., anthracyclines or chest radiation), face increased risk of left ventricular dysfunction or heart failure during or after pregnancy. Risk factors include younger age at cancer diagnosis, longer time to first pregnancy, lower baseline left ventricular function, and higher anthracycline dose. Most cardiac events occurred in those treated with anthracyclines [34]. Guidelines recommend surveillance in early pregnancy for women with prior exposure, though no clear guidance exists for ongoing monitoring if left ventricle function is normal pre-pregnancy.

12.3.1.5 Pregnancy in Gene-Positive Phenotype-Negative Women

Data on asymptomatic gene carriers are limited and often contradictory. Several cohort studies have supported the hypothesis that pregnancy can unmask cardiomyopathy in those with genetic predisposition, with rare dilatative cardiomyopathy (DCM) variants found in up to 22% of females with PPCM [35, 36]. However, the extent to which pregnancy modifies DCM onset and progression remains unknown. A retrospective study of women with pathogenic or likely pathogenic DCM variants revealed that most asymptomatic females with rare DCM variants had uneventful pregnancies [29]. Although limited by the retrospective design, these results provide some reassurance that pregnancy in females with rare DCM variants who are confirmed to be clinically unaffected before conception can be well tolerated. Careful pre-conceptional workup (ECG, echocardiogram, exercise testing, Holter, MRI) and risk stratification are essential. For low-risk patients, monitoring every 2–3 months is advised; closer follow-up is advised for high-risk genotypes.

12.3.2 De Novo Heart Failure During Pregnancy

During pregnancy, signs and symptoms of heart failure, such as lower extremity edema and shortness of breath, can overlap with those common in normal pregnancy. However, when associated with other worrying features (chest pain, orthopnea, syncope, hypertension or hypotension, elevated JVP, gallop rhythm), further evaluation should be considered [37]. Suspicion of heart failure should prompt confirmatory examination, made up of ECG, chest radiography, echocardiography, and laboratory testing, including N-terminal pro-brain-type peptide (NT pro-BNP) [38]. During pregnancy, levels of NT pro-BNP can be increased even in the absence of heart failure or hypertension.

New-diagnosed DCM must be differentiated from PPCM. Although they are distinct diseases, they may share a genetic predisposition, and distinction could be impossible [29, 35, 36].

12.3.3 Peripartum Cardiomyopathy (PPCM)

PPCM is defined as an idiopathic cardiomyopathy presenting with heart failure secondary to left ventricular dysfunction (ejection fraction <45%) toward the end of pregnancy or in the months following delivery, where no other cause of heart failure is found [39]. It was previously defined as symptomatic heart failure presenting in the last month of pregnancy and up to 5 months postpartum; however, the definition has been broadened because no clinical differences were found with women who developed the condition prior to the last month of gestation. Risk factors include hypertension, preeclampsia, multiparity, maternal age > 30 years, twin pregnancy, and African-American race [14, 40]. A genetic contribution to PPCM is suggested by the presence of shared genetic predisposition in peripartum and Dilated Cardiomyopathies (DCMP), as some gene variants, including *TTN*, have been identified in both conditions [35].

Therefore, genetic counseling and testing should be considered in women with PPCM.

PPCM is associated with adverse outcomes, including pulmonary edema, thromboembolic complications, brain injury, cardiopulmonary arrest, mechanical circulatory support, cardiac transplantation, and death. The most reliable prognostic factor is systolic function of the left ventricle at the time of diagnosis, with a significant association between an ejection fraction <30% and an increased risk of adverse events and a lower rate of recovery [41]. Other factors associated with worse outcomes include left ventricle dilation, left ventricle thrombus, right ventricular systolic dysfunction, and obesity. Higher troponin and NT-proBNP levels are also associated with less favorable outcomes. Mortality at 1 year ranges from 4% in the “Investigations of Pregnancy-Associated Cardiomyopathy” study 18–11% in a population of 96 African-American women [42]. Less data are available about long-term outcomes (defined as >5 years), but in the United States, mortality estimates have ranged from 7% to 20% [43]. When recovery occurs, it usually does so in the

first 3–6 months [30, 41] and even up to 2 years following diagnosis. Left ventricle systolic function recovery and normalization are not protective factors from PPCM in subsequent pregnancies and in women with persistent left ventricle dysfunction [43].

Current management is largely derived from guideline-directed medical treatment for nonischemic heart failure with reduced ejection fraction [18, 39]. Loop diuretics should be used to treat fluid overload and beta blockers for standard heart failure treatment. Nitrates can be used to treat hypertension. RAAS inhibitors, MRAs, and ARNIs are contraindicated during pregnancy [44]. New treatment options include bromocriptine, a dopamine agonist and prolactin inhibitor, which received a Class 2b recommendation in the ESC guidelines, based on a small clinical trial [18]. The ongoing REBIRTH Trial (Impact of Bromocriptine on Clinical Outcomes for Peripartum Cardiomyopathy) will evaluate the efficacy of bromocriptine. Given the higher risk of thromboembolic events during pregnancy, therapeutic anticoagulation should be considered in case of severe left ventricle systolic dysfunction. Warfarin should be avoided during pregnancy, while low-molecular-weight heparin can be used. Both are safe during lactation. Direct oral anticoagulants are not recommended in pregnancy and should only be used when no other option is viable, in consultation with the Pregnancy Heart Team and the hematology team.

12.3.4 Labor and Delivery in Cardiomyopathies

Labor and delivery are often accompanied by significant pain, adrenergic stimulation, and the potential need for urgent anesthetic intervention; consequently, close hemodynamic and continuous telemetry monitoring during and after delivery is frequently indicated. When no obstetric contraindications exist, vaginal delivery is generally preferred. Neuraxial anesthesia can effectively alleviate pain, thereby limiting adrenergic activation and reducing the risk of arrhythmias [45, 46]. However, in women with HCM and severe LVOTO, peripheral vasodilation is poorly tolerated, and epidural or spinal anesthesia should therefore be administered with caution [27]. Women with low-risk LVOTO may undergo spontaneous labor and vaginal delivery, whereas caesarean section may be the preferred mode of delivery in those with severe LVOTO [27].

12.3.5 Postpartum

Women with newly diagnosed or preexisting heart failure should be monitored closely during postpartum. The American College of Obstetrics and Gynecologists recommends a visit with an internist or cardiology within 7–14 days from delivery [47]. Breastfeeding is generally safe in most cardiomyopathies but may be discouraged with certain high-excretion medications (e.g., sotalol) or in NYHA class

III–IV due to metabolic demand. In PPCM, recovery is possible, but the postpartum risk of malignant arrhythmias remains high. A wearable defibrillator is recommended if ejection fraction $\leq 35\%$ persists for 3–6 months. Anticoagulation should be considered in those with severely reduced left ventricle ejection fraction during late pregnancy and up to 6–8 weeks postpartum.

12.4 Chemotherapeutic Agents

Cancer patients receiving chemotherapy have an increased risk of developing cardiovascular complications. Cardiotoxic effects from antineoplastic therapies are detectable in over a third of treated patients, although only a minority are severe and prognostically relevant. Antineoplastic therapy has multiple negative effects leading to heart failure, myocarditis, hypertension, arrhythmias, and vascular toxicity.

Cancer therapy-related cardiac dysfunction (CTRCD) is a dynamic process, and both the risk of clinical events and the potential for reversibility will depend on several factors, including age, sex, genetics, preexisting cardiovascular risk factors or cardiovascular disease, previous cancer treatments, and the type, intensity, and duration of new cancer treatment.

Patients undergoing chemotherapy should have careful clinical evaluation and assessment of cardiovascular risk factors and comorbidities before initiating the treatment.

The 2022 ESC cardio-oncology guidelines support the use of baseline risk stratification (*HFA-ICOS* score) as the starting point for determining strategies for the prevention, monitoring, and management of CTRCD [48]. The *HFA-ICOS* predicts the development of symptomatic or severe/ moderate asymptomatic CTRCD in patients classified as low-moderate risk vs. high-very high risk. It has also been shown that symptomatic heart failure or a reduction in left ventricular ejection fraction to $<40\%$ adversely affects the prognosis of cancer patients, with a tenfold increase in all-cause mortality [49].

Based on the risk profile, personalized baseline assessments and surveillance must be performed. Baseline echocardiographic evaluation of left ventricular ejection fraction and global longitudinal strain (GLS) is recommended in all patients before cardiotoxic cancer treatment initiation to stratify CRT-CVT risk and to identify significant changes during treatment. Current CTRCD is based on reduction of left ventricular ejection fraction and/or relative changes in GLS, particularly in moderate- and high-risk patients. Baseline GLS can predict left ventricle dysfunction in patients receiving anthracyclines and/or trastuzumab [50]. A relative GLS reduction of 13.6% predicted a subsequent decline in left ventricular ejection fraction, with an upper limit of GLS reduction of 15% at the 95th percentile [51]. Consistently, current ESC guidelines recommend a 15% cutoff when monitoring GLS during cancer therapy.

12.4.1 Role of Genetics

Candidate gene and genome-wide association studies have identified more than 40 genes and single nucleotide polymorphisms associated with anthracycline-related cardiovascular toxicity. The most frequently implicated genes encode proteins involved in anthracycline metabolism (e.g., CBR3, SCL isoforms), protection against reactive oxygen species (e.g., GSTM1, CBR3), DNA damage response and repair (e.g., RARG), and sarcomeric regulation, including troponin T-related pathways (e.g., CELF4) [52–55]. Unrecognized rare variants in cardiomyopathy-associated genes, particularly *TTN* truncating variants (in 7.5% of cases), appear to be associated with an increased risk of CTRCD in children and adults [52–55].

However, to date, no studies have demonstrated an increased risk of cancer therapy-related cardiac dysfunction in patients carrying pathogenic variants or with a family history of CTRCD.

12.4.2 Anthracyclines

Anthracycline-based chemotherapeutic agents (including doxorubicin, epirubicin, and idarubicin) can induce CTRCD in a dose-dependent manner. The risk of CTRCD also varies according to the cumulative dose of the drug, reaching up to 25% for doses greater than 400 mg/m² [56]. Cardiac injury may occur during both the early and late phases of chemotherapy. Early cardiotoxicity is traditionally classified into acute cardiotoxicity, occurring within days to weeks after anthracycline exposure and predominantly manifesting as arrhythmias, and early-onset chronic cardiotoxicity, developing within the first year after treatment and typically associated with heart failure. Late-onset cardiotoxicity usually emerges more than 1 year after completion of anthracycline therapy and is most often characterized by a slow progressive and insidious cardiac dysfunction [57].

Anthracyclines exert multiple deleterious effects on cardiomyocytes, including dysregulation of calcium homeostasis, mitochondrial dysfunction, and activation of apoptotic pathways. Mitochondrial injury, partly mediated by inactivation of iron-regulatory proteins, leads to intracellular iron overload and excessive production of reactive oxygen species, promoting lipid peroxidation and depletion of intracellular ATP. In addition, anthracyclines induce opening of the mitochondrial permeability transition pore and binding to topoisomerase II β , resulting in DNA double-strand breaks and subsequent cardiomyocyte apoptosis [58]. Dexrazoxane is the only approved drug for prevention of anthracycline-induced cardiotoxicity [59]. Dexrazoxane interferes with anthracycline binding to topoisomerase 2 β , which prevents cardiac damage without disturbing the antitumor efficacy and reduces intracellular iron accumulation. Moreover, liposomal anthracyclines, due to their different pharmacokinetics and tissue distribution, offer equivalent antitumor efficacy with reduced cardiotoxicity [60].

12.4.2.1 HER2-Targeted Therapy

It is recognized that anti-HER2 therapies (i.e., *Trastuzumab*) may lead to left ventricular systolic dysfunction in up to 15–20% of patients [61]. They can increase mitochondrial ROS production and decrease intracellular calcium levels, leading to impaired cardiomyocyte contraction. Cardiotoxicity typically manifests during therapy but is reversible. The 2022 ESC cardio-oncology guidelines recommend left ventricle function surveillance based on left ventricle ejection fraction and GLS prior to and every 3 months during HER2-targeted therapies and within 12 months after completing treatment [50]. Baseline NP and cTn measurement are recommended in high- and very high-risk patients prior to anti-HER-targeted therapies.

12.4.2.2 Immune Checkpoint Inhibitors (ICI)

Block key T cell regulatory pathways, thereby enhancing antitumor T cell activation. However, disinhibited T cells may also cause direct cardiomyocyte injury, leading to immune-mediated cardiac complications, most notably myocarditis. Although ICI-associated myocarditis is rare (<1% of treated patients), it carries a high mortality rate of approximately 40% [62]. Studies show that in patients with ICI-associated myocarditis, selective clonal populations of T cells infiltrating the myocardium were identical to those found in tumors and skeletal muscles, with ribonucleic acid sequencing studies revealing the expression of heart-specific genes in the tumor, raising the possibility that somatic mutations in the tumor itself may contribute to CTR-CVTICI [63]. ICI-associated cardiotoxicity also includes pericarditis, arrhythmias, heart failure, acute coronary syndromes, thromboembolism and vasculitis. According to 2022 ESC guidelines, ICI-associated myocarditis therapy is based on high-dose corticosteroids in clinically unstable patients, while using second-line immunosuppression treatment in patients with steroid-refractory disease. Caution is advised against the use of infliximab for steroid-refractory myocarditis and HF.

12.4.2.3 VEGF Inhibitors (VEGFi) and Multi-Targeted Kinase Inhibitors (multi-TKI)

Cardiomyocyte growth, coronary and systemic vascular integrity, and diastolic function can be affected by VEGFi and multi-TKI. They contribute to the development of hypertension, thromboembolism, ventricular dysfunction, and QTc prolongation. Hypertension is a class-dose-dependent effect and is the most reported adverse event under VEGFi treatment. About 80% of patients have a sharp rise in blood pressure; the overall incidence of VEGFR-TKI-associated high-grade and all-grade hypertensive events was 23.0% and 4.4%, respectively [64]. The VEGFi decrease microvessel density, reduce the bioavailability of nitric oxide NO, and inhibit the production of endothelin-1, causing vasoconstriction and increased peripheral vascular resistance [58]. According to 2022 ESC guidelines, an intensive home blood pressure monitoring should be assessed during the treatment. Patients with blood pressure $\geq 140/90$ mmHg should start ACEIs or ARBs as first-line anti-hypertensive drugs.

12.4.3 Bcr-Abl Tyrosine-Kinase Inhibitor (TKI)

In a prospective study, the incidence of cardiovascular toxicity was evaluated in 531 patients treated with first-line TKIs. Overall, 45% of patients experienced cardiovascular adverse events, and 9% developed atherothrombotic adverse events. Among TKIs, ponatinib (a third-generation TKI) was associated with the highest rates of cardiovascular and atherothrombotic events [65]. Dasatinib has been associated with the development of pulmonary hypertension [66]. Second-generation BCR-ABL TKI may induce QTc prolongation [67]. The 2022 ESC guidelines recommend baseline electrocardiography in all patients, QTc monitoring in patients treated with second-generation BCR-ABL TKIs, discontinuation of TKI therapy in patients with confirmed pulmonary hypertension, and consideration of aspirin and statin therapy in patients with peripheral arterial disease.

12.4.4 Taxanes

Taxanes are primarily associated with arrhythmias, which often manifest as sinus bradycardia, ventricular tachycardia, and atrioventricular block. The mechanism of cardiotoxicity is associated with abnormal changes in calcium ion concentration. [50] Also, CRTCD is reported in patients treated with combined regimens of paclitaxel and doxorubicin with a cumulative dose much lower than would be expected with doxorubicin alone [68]. The use of cortisol and antihistamines may reduce paclitaxel-induced cardiotoxicity.

12.4.4.1 Radiotherapy

Irradiation of organs near the heart is widely used in cancer treatment and often forms an integral part of a multimodal therapeutic strategy. It can cause heart failure, ischemia, pericardial effusion, valvular disease, and arrhythmias. They show up in 23–32% (with high-dose irradiation close to the organ). Subclinical cardiac toxicity can occur within months after finishing radiotherapy, and many symptomatic cardiac events occur within just 2 years after completing treatment. Radiation exposure to cardiac tissues first results in endothelial cell damage leading to fibrosis. In addition to fibrosis, radiation also leads to DNA damage and increased oxidative stress and can cause focal ischemia. Radiation-induced heart failure is more likely to occur with preserved ejection fraction, rather than reduced [69].

12.4.5 Therapy of CTRCD

Early identification of CTRCD and initiation of cardioprotective therapy (CPT) are associated with better cardiac function recovery and fewer adverse cardiac events [70]. Recent evidence suggests that continuing CPT even after recovery from DCM is crucial [71].

Whether CPT should be continued after the recovery of left ventricle function in CTRCD patients is still unclear. Patients who withdrew CPT experienced worse clinical outcomes. Notably, a significant decrease in left ventricle ejection fraction after CPT withdrawal was observed in patients with a baseline normal ejection fraction. According to the 2022 ESC guidelines, for the primary prevention of cardiotoxicity in high- or very-high-risk patients, ACEI or ARB and beta-blockers are recommended [72–74].

Additionally, statins are recommended for all adult cancer patients at high- or very-high-risk of cardiotoxicity due to their pleiotropic effects, reducing the incidence of cardiotoxicity, although there was no significant change in left ventricle ejection fraction [75]. Moreover, sacubitril/valsartan in the SARAH trial showed a lower percentage of patients developing a $\geq 15\%$ reduction in GLS, compared to the placebo [76], and empagliflozin (an SGLT2 inhibitor) in the EMPACARD-PILOT trial significantly reduced the incidence of CTRCD [77].

To date, no studies involving either neurohormonal therapies or statins have demonstrated a benefit in reducing the incidence of heart failure.

12.5 Alcoholic Cardiomyopathy

Excessive alcohol intake is one of the leading causes of DCM. Alcoholic cardiomyopathy (AC) is a form of acquired DCM caused by prolonged and heavy alcohol intake—commonly defined as the consumption of >80 g/day over 5 years, even if there is still some controversy regarding this definition—in the absence of other causes of DCM [78]. AC occurs in 1–2% of all individuals who consume alcohol heavily, predominantly in men [1]. However, women might be more vulnerable, because they require a lower daily dose and shorter duration of ethanol exposure than men to develop AC [79].

Genetic factors may predispose to the disease. *TTN* variants represent an important genetic predisposition to AC, and the combination of these variants and excess alcohol consumption is associated with worse left ventricular ejection fraction in patients affected by DCM [80], paving the way to support the “second hits” hypothesis of DCM arising from the combination of genetics with environmental factors. On the other hand, most individuals with *TTN* variants do not develop AC and just as healthy individuals can consume excessive amounts of alcohol without developing cardiomyopathy [81]. These findings indicate that additional environmental, epigenetic, or genetic factors might be involved.

Recently, an angiotensin-converting enzyme gene polymorphism has also been reported as associated with vulnerability to AC [82].

The pathogenesis of cardiac damage includes a combination of direct toxic effects of alcohol on the myocardium (causing cell death, fibrosis, and impaired contractility), oxidative stress, mitochondrial dysfunction, and modified calcium homeostasis due to both ethanol and acetaldehyde damage, leading to cellular injury and myocardial dysfunction [78]. Ethanol consumption also activates the renin-angiotensin system, causing progressive cardiac dysfunction [83].

Moreover, AC patients exhibit a high prevalence of hypertension, atrial fibrillation, and chronic obstructive pulmonary disease [84] and, because of that, the diagnosis is even more challenging.

AC is characterized by depressed cardiac output, reduced myocardial contractility, and dilatation of all the chambers of the heart, causing signs and symptoms of heart failure. Alcohol consumption is related to an increased incidence of arrhythmia: both supraventricular (mostly triggered by binge drinking in younger patients) and ventricular tachycardia (in heavier drinkers) [78]. Atrial fibrillation is the most common arrhythmia in AC. Moreover, chronic alcohol abuse produces multiple physiologic aberrancies in the heart, including effects on the QT interval and heart rate variability [85].

The effect of alcohol on left ventricle ejection fraction is dose-dependent and progressive, causing, initially, a subclinical diastolic dysfunction associated with increased left ventricular mass and preserved left ventricle ejection fraction [86] and then to systolic dysfunction. In particular, several studies have described increased left ventricular end-diastolic volume as an early cardiac abnormality related to alcohol abuse, as well as decreased E/A ratio and prolonged isovolumic relaxation time, indicating impaired left ventricle relaxation [87]. Moreover, speckle tracking analysis has reported a subclinical decrease of systolic function in alcohol abusers, presenting lower values of left ventricular GLS and global circumferential strain in alcohol abusers compared with controls [88].

Although abstinence from alcohol is the primary step in treating AC, it has been reported an increase in left ventricle ejection fraction even within patients who kept drinking alcohol moderately (<80 g/day) [89]. In the same study, it was found that AC was associated with a favorable outcome with a higher heart transplantation-free survival compared with idiopathic DCM (15% in AC vs 35% in idiopathic DCM during a median follow-up of 59 months). Moreover, atrial fibrillation, QRS >120 ms, and lack of beta-blocker therapy were independent predictors of death or heart transplantation. Beta-blocker treatment, QRS < 120 ms, and absence of diuretics were independent predictors of ejection fraction recovery [90].

Medical therapy is no different from that for other etiologies of heart failure. As said before, the absence of beta-blockers is a marker of worse prognosis in AC. Moreover, any nutritional deficiencies should be corrected (i.e., vitamin supplements, in particular B complex vitamins). If needed, the use of some drugs can help to achieve abstinence in alcohol use disorders (i.e., disulfiram, naltrexone, and acamprosate). It is recommended to manage arrhythmia, if necessary.

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Role of Polygenic Risk Scores and Artificial Intelligence

13

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13.1 Polygenic Risk Scores

In the last decades, a growing body of evidence has made genetic testing a standard aspect of clinical management of cardiomyopathies (CMPs)-affected patients and families, as the identification of a specific mutated gene has progressively become essential in their etiological definition, therapeutic management and prognostic assessment.

Despite CMPs having been traditionally regarded as Mendelian inheritance's models, genetic testing can identify an underlying causative monogenic variant in no more than 30–50% cases [1], even after the recent advances in knowledges and technologies (i.e., the introduction of next-generation sequencing—NGS). The majority of affected patients turn out to be negative to genetic testing even in familial CMPs, where a genetic etiology should be highly likely. Moreover, data from families and population cohorts confirm incomplete penetrance and variable expressivity of Mendelian pathogenic variants, with a non-negligible number of individuals harboring rare CMPs-associated variants in the absence of overt disease [2]. This complexity can be only partially explained by the interaction between genetic background and environmental factors.

Interestingly, in the last few years, exome- and genome-wide association studies (EWAS, GWAS) have increasingly contributed to better understanding the genetic underpinnings of complex diseases, unveiling that *common genetic variations* can

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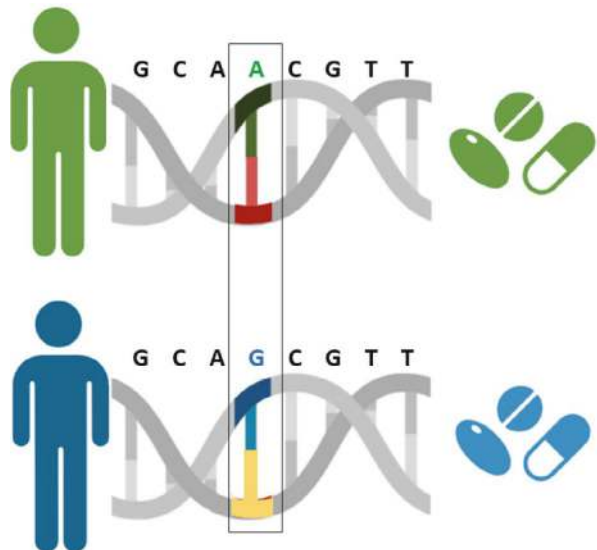
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play a nonnegligible role in CMPs susceptibility, as described for other common pathologies (i.e., cancer, coronary artery disease [3]) whose multifaceted polygenic architecture has already been described.

13.1.1 Single Nucleotide Polymorphisms, Genome-Wide Association Studies and Polygenic Risk Scores: A Brief Overview

Single nucleotide polymorphisms (*SNPs*) are defined as variations in a nucleotide base pair (i.e., compared with what is expected at that location in the reference human genome) with a minor allele frequency (MAF) of more than 1% (i.e., present in at least 1% of the population) and therefore called “common variants” [4] (Fig. 13.1). Given their relatively high frequency in the general population, SNPs usually contribute to phenotypic expression and variability with no or only weak, subtle additive effects, hampering their links with a phenotype of interest. This is the aim of *GWAS*, in which large cohorts of patients and non-affected individuals (in terms of thousands of individuals, usually derived from large biorepository datasets such as UK Biobank) undergo genotyping array (a DNA microarray analyzing SNPs across the genome), systematically testing millions of common variants’ sites. By comparing the frequency of an allele at a given variant site between cases and controls or within a continuous variable, it is possible to assess if and which different alleles significantly covary with an outcome of interest [5]. Of note, the genome-wide statistical significance threshold corresponds to a Bonferroni-corrected p -value of $P < 5 \times 10^{-8}$ [6]. All these variants, each carrying an individually small but statistically significant risk, can collectively account for substantial

Fig. 13.1 Single nucleotide polymorphisms (SNPs): these are positions in a genome where some individuals have one nucleotide (i.e., A, adenine) and others have a different nucleotide (i.e., G, guanine). There are roughly 4 to five million such genomic variants in an individual’s genome



disease-development risk, properly named polygenic risk. This concept can be mathematically expressed in polygenic risk scores (*PRSs*), the weighted summations of those SNPs found to be significantly associated with the disease, each with its own weight derived from the effect size obtained in GWAS. As shown in the mathematical formula below for an individual j , the score is obtained by the weighted sum of trait-associated SNPs, where N is the total number of SNPs, β_i is the effect size of SNP $_i$, and dosage $_{ij}$ is the allelic dosage for the allele effect in SNP $_i$ for the individual j .

$$PRS_j = \sum_i^N \beta_i * \text{dosage}_{ij}$$

Once developed, the performance of any PRS has to be evaluated in an out-of-sample population (i.e., independent of the population on which it is based) (Fig. 13.2).

More recently, Turley et al. introduced multi-trait analysis of GWAS (*MTAG*) [7], a method for conducting meta-analysis of GWAS for different traits. The underlying key idea is that, when different traits are supposed to be genetically linked (i.e., DCM and cardiac volumes, HCM and left ventricular thickness), the GWAS-derived effect estimates for each trait can be improved by appropriately incorporating information contained in the GWAS estimates for the other traits. The MTAG method, which can be applied downstream to GWAS summary statistics from an arbitrary number of traits, has proven to lead to substantial improvements in the number of *loci* identified and the predictive power of associated PRSs and has therefore been increasingly used.

In the last 15 years, various GWAS/MTAG have contributed to better characterize the polygenic bases of dilated and hypertrophic CMPs (DCM, HCM), leading to the validation of specific PRSs (Fig. 13.3). In this chapter we will review this growing body of evidence, also highlighting potential clinical implications and associated limits.

Notably, as of the time of writing, neither GWAS nor PRSs have been developed for arrhythmogenic right ventricular cardiomyopathy (ARVC).

13.1.2 Polygenic Risk Scores in Dilated Cardiomyopathy

The very first large-scale SNP analysis in DCM patients was carried out by Stark et al. in 2010, in a small pioneering work revealing just one SNP significantly associated with the disease [8]. The following year, in the first DCM-GWAS (enrolling 1179 patients with DCM diagnosis), Villard et al. identified two DCM-associated SNPs [9], then confirmed in a larger EWAS together with other six novel *loci*, many of which near DCM-associated genes (i.e., *TTN*, *FLNC*, *BAG3*...) [10]. Moving from these studies, in 2021 Tadros et al., in a work focused on HCM, also performed a DCM EWAS/GWAS meta-analysis, identifying a total of 13 *loci* significantly associated with DCM, as will be discussed in the following paragraph [11]. The derived genetic risk was then

POSSIBLE CLINICAL APPLICATIONS OF PRSs

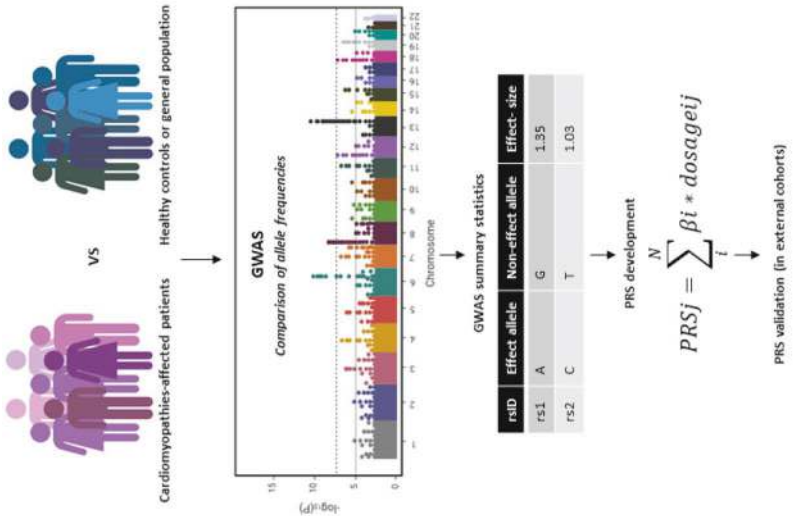


Fig. 13.2 General overview of genome-wide association studies and consequent PRS's development (on the left). Possible future clinical perspectives for PRSs (on the right). CMTs cardiomyopathies, HCM hypertrophic cardiomyopathy, GWAS genome-wide association studies, PRSs polygenic risk scores

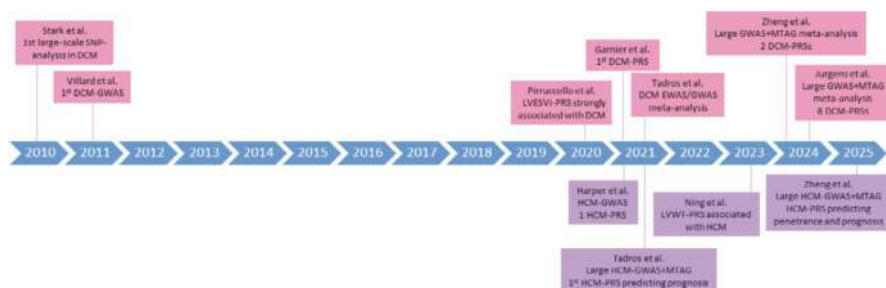


Fig. 13.3 Timeline of DCM and HCM GWAS and PRSs's development. DCM dilated cardiomyopathy, EWAS exome wide association studies, GWAS genome-wide association studies, HCM hypertrophic cardiomyopathy, LVESVi left ventricle end-systolic volume indexed, LVWT left ventricular wall thickness, MTAG multi-trait analysis of GWAS, PRSs polygenic risk scores, SNP single nucleotide polymorphisms

found to correlate with the risk of nonischemic CMP in the general population [12]. However, while all the abovementioned studies have contributed to point out and better characterize the polymorphic genetic architecture of DCM, uncovering the until-then-unknown polygenic contribution, none of them provided a DCM-PRS.

It was only in 2021 that Garnier et al. developed an eight risk-alleles DCM-PRS, described to confer a threefold increased risk of disease. This first PRS, however, was not validated outside the cohort of development, raising methodological concerns [13]. At the same time, given the limited sample size of these previous studies and their subsequent modest yield, other groups preferred to focus on the link between SNPs and structural and functional cardiac traits, usually disrupted in DCM phenotype [14–16]. Moving from cardiac magnetic resonance (CMR) imaging data of UK Biobank participants without diagnosis of heart failure (HF) or DCM at the time of enrollment, Pirruccello et al. developed seven PRSs, one of which, the 28-SNPs LV end-systolic indexed-volume (LVESVi) PRS showed the single strongest relationship with DCM diagnosis and was significantly associated with incident disease even adjusted for age, sex and genotyping batch, influencing cardiac size and function even among *TTN* truncating mutations carriers [14]. Data from this and similar analyses have been further used to increase GWAS finding in DCM by applying MTAG approaches, exploiting genetic correlations among various traits and phenotypes. In 2024 the results of the two largest GWAS meta-analyses studies for DCM have been released by Zheng et al. [17] and Jurgens et al. [18], who both performed large-scale GWAS of clinical and biobank cohorts and then a MAG for CMR-derived traits, identifying many new *loci* and genes significantly associated with the disease. The first study, comprising a population of 14,256 DCM cases (defined as LV systolic dysfunction with or without LV dilatation in the absence of secondary causes) and 1,199,156 controls, identified 80 genomic risk *loci* and prioritized 62 putative effector genes, including several with rare variant DCM associations [17]. The second, enrolling 9365 DCM cases and 946,368 controls, identified 70 genome-wide significant *loci* mapped to 63 prioritized genes [18]. In these two studies many PRSs, taking into account hundreds of

thousands of SNPs, were developed and then systematically compared in three datasets of European ancestry, demonstrating a significant—despite weakly—power of discrimination between DCM patients and controls, with the one based on MTAG summary statistics from both studies showing the best predictive performance. Interestingly, Jurgens et al. reported that, although the DCM-PRS was enriched significantly in genotype-positive as well as genotype-negative patients compared with controls in the Amsterdam UMC dataset, the former exhibited a significantly lower PRS, suggesting that polygenic burden could contribute to disease risk in both, but genotype-negative ones might need more polygenic burden to reach disease state [18].

13.1.3 Polygenic Risk Scores in Hypertrophic Cardiomyopathy

In 2021 two large-scale GWAS demonstrated that there was place for polygenic contribution also in the HCM risk. Harper et al. identified 12 significant susceptibility *loci* for HCM, pointing out a strong polygenic influence especially for sarcomere-negative HCM, and developed a genetic risk score that showed a significant influence on the HCM's odds in a validation cohort and on the phenotypic severity in sarcomere-variant's carriers [19]. Another PRS derived from the same GWAS was found to be significantly associated with the risk of HCM in two biobanks, with an increasing risk across PRS strata and a strong effect among genotype-negative patients (while it did not reach statistical significance in genotype-positive ones) [20].

At the same time, Tadros et al. conducted a GWAS and MTAG study in HCM (1733 cases), DCM (5521 cases), and 19,260 UK Biobank participants with structurally normal hearts, identifying new *loci* for LV traits with opposing effects in the two CMPs (i.e., two *loci* associated with LVEF in the general population increased the risk of HCM, decreasing the risk of DCM) [11]. Their HCM-PRS was then demonstrated to correlate with the severity of phenotypic expression in carriers of HCM—causing rare variants and, above all, with adverse clinical events (each standard deviation increase in PRS associated with a 28% relative risk increase in a composite of septal reduction therapy, cardiac transplantation, sustained ventricular arrhythmias, sudden cardiac death, appropriate defibrillator therapy, atrial fibrillation/flutter), providing the first evidence that polygenic background could influence outcomes and so that a PRS might play a prognostic role, stratifying event-free survival [11].

A larger GWAS from the same group recently identified 50 *loci* and a novel HCM causative Mendelian gene, supervillin (*SVIL*), showing that its rare truncating variants conferred a tenfold increased risk of disease [21].

More recently another PRS was shown to be associated with a significant higher HCM-risk in the general population (also among genotype-positive patients—with HCM penetrance differing tenfold between those in the highest and lowest PGS quintiles) [22], with the risk of adverse outcomes and death among HCM patients and with the risk of developing HCM and adverse events among relatives of HCM probands [22].

Interestingly, a PRS of CMR-derived inferoseptal LV regional wall thickness exhibited a notable association with incident HCM [23], confirming the relationship between common genetic variants, cardiac imaging phenotypes and risk for CMPs development, as previously described in DCM [14]. Similarly, a GWAS analysis identified 11 *loci* (one of them in myosin heavy chain 7B—*MYH7B* gene) associated with CMR-detected native myocardial T1 time (a marker of fibrosis), which was then proven to be associated with CMPs and HF in UK Biobank participants [24].

13.1.4 Polygenic Risk Scores in a Clinical Perspective

In just over 10 years, GWAS yielded unexpected insights into genetics and biological basis of CMPs, shedding light on a non-negligible polygenic contribution, besides and over the well-known Mendelian pathways. Common variants have been proposed as the genetic backbone of CMPs in gene-elusive patients and, on the other hand, as modulators of the risk of disease development and severity in genotype-positive individuals, accounting for incomplete penetrance and variable expressivity. In fact, many SNPs that turned out to be significantly associated with CMPs are located near genes harboring rare CMP-causing variants. This suggests their possible role as expression quantitative trait *loci* (eQTL), acting as modulators of the transcription of the diseased allele [25]. However, the interaction between monogenic and polygenic variants, as well as with environmental factors, remains largely unknown and deserves further investigation.

Consistently, despite several PRSs have been developed, they have not found a place in clinical practice yet. Nonetheless, there are some scenarios in which they promise to be used in the future, improving our diagnostic and risk-stratification tools.

In *CMPs-affected patients*, PRSs could be of potential value for a deeper characterization of the disease and a baseline prediction of its severity but also for a comprehensive risk stratification for adverse outcomes and a tailored therapy.

First of all, PRS assessment might become part of the systematic search for an underlying etiology in the diagnostic process [1], as finding a higher DCM- or HCM-PRS in gene-elusive patients could justify the disease development and contribute to predict its expected severity (in terms of structural and functional remodeling) also in carriers of well-known monogenic rare variants. Moreover there is evidence that two HCM-PRSs could predict adverse CMP-related composite events [11, 22], paving the way to PRSs' use in HCM prognostic stratification, as it has already been proposed for higher-prevalence diseases (i.e., ischemic heart disease). Obviously, they will need to be used together with established clinical risk models, as the HCM-risk score. Among patients with a conventionally-assessed borderline risk, PRSs could be tested on its capability to reclassify ICD prescriptions, or prompt more intensive follow-up and earlier treatment strategies, improving the decision-making process. On the other side, none of DCM-PRSs has ever been tested for adverse outcomes' prediction. The intrinsic nature of PRSs, developed with respect to a specific phenotype or target diagnosis, may nonetheless be

inadequate for capturing the complexity and temporal dynamics of DCM more than HCM, thereby limiting the validity of their prognostic applications. Therefore, studies are needed in order to evaluate PRSs' potential weight and their interactions with the other determinants of prognosis in DCM, whose comprehensive arrhythmic stratification remains, still today, a clinical unmet need.

Finally there is a possibility that polygenic background may influence the response to pharmacological therapy, as demonstrated for statins [26]. The first evidence in this regard comes from a GWAS of 686 patients with recent-onset DCM, which identified a highly suggestive SNP (mapped to the 5'-flanking region of the *CDCP1* gene) for improved LVEF after 6 months of HF-therapy, implicating its possible role in myocardial reverse remodeling [27].

Additionally, PRSs promise to be a useful tool in the evaluation of *subjects at risk of CMPs*, as genotype-positive phenotype-negative individuals diagnosed during family screening or unaffected individuals with a family history of CMPs without known genetic background. Their stratification for disease-development remains complex, time- and resources-consuming. In a recent study enrolling a cohort of DCM families (the half of which gene-elusive), the LVESVi-PRS developed by Pirruccello et al. [14] for DCM demonstrated a significant difference in disease's odds ratios between DCM patients (proband or non-proband) and unaffected individuals (family members of DCM probands or healthy controls, these two cohorts showing indistinguishable values) [28]. Moreover Zheng et al. reported that, among relatives of HCM probands, their PRS was able to stratify the risk of developing HCM and adverse outcomes [22]. These data, if further and substantially confirmed, suggest PRS assessment as a useful tool to identify those family members at higher risk for CMPs.

13.1.5 Limitations and Future Challenges

It's only in the past decade that the concept of polygenic risk has entered our horizon of knowledge, therefore there are still many knots to untangle and limitations to overcome before a PRSs' real-world practical implementation becomes feasible. The main question remains how to interpret the values, which is the threshold to classify individuals as high or low polygenic risk, given that the available PRSs are reported in percentiles according to the cohorts studied (in terms of ethnicity, genotyping platform and internal calibration), thus limiting the ability to yield universal raw scores. Further efforts should now shift toward the universal harmonization and the consequent generalizations of PRSs' applicability.

Another key issue is the underrepresentation of ethnic diversity in most GWAS, whose populations are predominantly of European ancestry, potentially generating misinterpretation and misapplication in individuals of non-European descent, raising care disparities [4]. For instance, Jurgens et al. tested PRSs in African and Admixed-American ancestry cohorts, reporting lower odds ratios compared to those in Europeans [18]. Of note, just one DCM-GWAS in African ancestry—patients has

been conducted, reporting a novel DCM-associated *locus* then not confirmed in the replication analysis [29].

An additional not negligible limitation is that all the available polygenic risk models include only common variants, while their performance would definitely be improved by incorporating well-characterized rare high-risk variants, as it is likely to be achieved with the increasing use of whole-genome sequencing. As there is still uncertainty about the interplay of common, rare variants, epigenetic, and environmental factors, the incremental value of PRSs over clinical scores should be investigated, allowing a more comprehensive assessment.

Moreover, the implications of PRSs have not yet been sufficiently studied in real-world clinical settings. Of note, the efficacy of PRSs for coronary artery disease (the most studied phenotype to date) has been examined in numerous studies producing mixed results, highlighting challenges concerning reproducibility and transferability and, consequently, clinical efficacy.

Finally, the cost-effectiveness of a large-scale application of PRSs has yet to be fully explored, especially because it might involve a significantly broader group of individuals than carriers of monogenic variants, with healthcare costs rising exponentially.

13.2 Applications of Artificial Intelligence

The greatest benefit of machine learning may ultimately be not what the machines learn but what we learn by teaching them [30]

Thanks to the digitization process that has permeated healthcare, the amount and variety of data collected in medical contexts have reached unprecedented volumes and continues to grow. The rapidly evolving technology of artificial intelligence (AI), with its capacity to analyze large and complex datasets and provide sophisticated models, is interestingly impacting cardiovascular (CV) medicine, promising to offer novel tools for (earlier) diagnosis, risk stratification, and patient-tailored treatment also in the field of CMPs, whose management requires a systematic, multiparametric and time-evolving approach, integrating a multitude of different data.

13.2.1 Big Data, Electronic Health Records, and Biobanks

The umbrella term *big data* is used to indicate massive datasets (too large and complex to be processed by traditional software) and the analytic approaches used to identify associations, detect trends, and uncover hidden patterns. As such data are generated for clinical purposes, different from those for which they are later extracted, their analyses present several challenges, particularly in terms of quality (data inaccuracy, missingness, systematic biases) and heterogeneity of modalities (numerical data, images, video, signals, free text).

The most significant example of big data in medicine are electronic health records (EHRs), generated during routine provision of patient care and collected primarily for clinical and administrative purposes. EHRs consist of longitudinal (repeated encounters) heterogeneous structured and unstructured data including demographic, administrative, clinical, behavioral, claims (medical and pharmacy), vital signs, laboratory results, and imaging or instrumental information.

At population level, EHRs offer valuable insights into disease onset, progression and responses to treatments or interventions. At the individual level, EHRs can capture patient trajectories and promote the use of person-specific data to tailor treatments to an individual's unique health profile. At research level, fundamental discoveries about the genetic determinants of disease over the last two decades have been made possible thanks to the establishment of several nation biobanks combining EHRs and genomic data (e.g., K Biobank [31], All of Us Research Program [32], FINNgen [33]). These large-scale resources offer a powerful approach, allowing to test genetic variants against a wide array of phenotypes and enabling both hypothesis-driven and hypothesis-generating research [34]. In the context of CMP, in addition to what is reported in the previous paragraph, recent studies have highlighted novel insights into the prevalence and penetrance of rare variants in DCM [35] and HCM [36] and a shared genetic background between HCM and DCM [37].

Population-based cohorts also allow researchers to examine how findings from clinical studies translate to general real-world populations, often revealing important differences in outcomes [38]. In fact, both clinical cohorts and population-based biobanks come with inherent biases. The first often overrepresent individuals with more severe disease, while biobanks are typically affected by a “healthy volunteer” bias, tending to underreport disease prevalence [39]. Strategies that combine population-based biobanks with clinical cohorts will be necessary to advance our understanding of diseases affected by ascertainment bias related to age or prevalence.

13.2.2 Machine Learning, Deep Learning, and Main Applications

The key to understanding big data and the diverse data modalities present in EHRs and biobanks is the use of *machine learning* (ML) and *deep learning* (DL) algorithms, capable of capturing complex patterns.

The term ML reflects the fact that in these algorithms much of the model structure (such as input variables and their interactions) is learned directly from the data, rather than being explicitly specified by the analyst. Consequently, compared to traditional models, ML can account for non-linear relationships, providing a better fitting where complex relationships between predictors and outcomes exist and so being particularly suitable when prior knowledge about the variables under study is limited—representing a *data-driven* rather than a *hypothesis-driven* approach. Nonetheless, in the context of structured, tabular data, the extent to which ML models consistently outperform conventional statistical approaches remains debated [40, 41].

Instead, there is little doubt that ML—and particularly DL—can achieve remarkable results when applied to unstructured, complex data. DL is a subfield of ML that relies on artificial neural networks (mathematical architectures composed of interconnected nodes organized in multiple layers—hence the term “deep”). These layered structures enable models to progressively learn increasingly complex representations of data while remaining highly scalable, making them suitable for the analysis of nonstandard data like images and raw signals. Of note, although neural networks are often regarded as “black-box” models—because the operations of their intermediate layers are not directly interpretable to humans—various explainability techniques have been recently developed to shed light on the relationship between input data and model output.

In the context of CMPs, the most relevant implementations have been based on ECG signals, echocardiography signatures and cardiac magnetic resonance imaging.

ECG waveforms, as numeric time series recorded from single or multiple leads, have been a particularly fertile ground for innovation. In fact one of the earliest successes of DL was the application of recurrent neural networks—specifically designed to process sequential data—for arrhythmia classification [42, 43]. Moreover, several studies recently demonstrated that AI-guided ECG’s reading can detect subtle structural heart disease through electrocardiographic signatures preceding overt echocardiographic signs. This evidence has been provided for HCM [44, 45], ARVC [46], LV systolic dysfunction [47, 48] and transthyretin amyloid cardiomyopathy (AC) [49, 50] and, more recently, extended to single-lead ECG acquisitions (i.e., smartwatches) [51], promising an easy and accessible cost-effective screening tool, especially for first-degree relatives of CMPs’ patients. Of note, in August 2023, the US Food and Drug Administration granted its first approval of an AI software in cardiology, namely, a HCM detection ECG-algorithm [52].

ECG has also demonstrated considerable promise in predictive tasks—usually more challenging than classifications—such as forecasting the onset of paroxysmal atrial fibrillation [53, 54] or predicting malignant VAs in patients with ICD [55].

Besides diagnostics, using ML, baseline ECG variables were found to effectively identify two DCM subgroups differing in disease progression upon their initial evaluation [56]. Moreover, two independently developed AI-ECG algorithms were demonstrated to longitudinally correlate with changes in echocardiographic and laboratory markers during mavacamten treatment in obstructive HCM, suggesting a potential role in noninvasive monitoring of treatment response [57].

In the field of noninvasive cardiac imaging, which remains the cornerstone in CMPs’ pathway, AI-powered algorithms could enable automated chamber quantification, EF, and strain measurement, reducing interobserver variability and so ensuring a wider and faster access to diagnostic tests that are still limited by the need for specific training. For instance, a ML framework (using cardiac tissue deformation’s features) showed good sensitivity and specificity in discriminating LV hypertrophy in athletes versus HCM patients [58], and an ECG and echocardiography-based human-interpretation-free ML pipeline was even found to outperform cardiologists in diagnosing AC [59]. Moreover, a cognitive ML algorithm enabled to differentiate constrictive pericarditis from restrictive CMP [60].

As neural networks were showed to perform as well as or even better than cardiologists in biventricular volumes and mass measurements, in the coming years, AI will be increasingly used also in the field of CMR, aiming to accelerate image acquisition and analysis [61] (whose long processing times remain a major limitation for clinical application) and leading to new opportunities, as in detecting and quantifying myocardial fibrosis without the need for gadolinium, just applying DL automated analysis to standard non-contrast CMR and generating synthetic late gadolinium enhancement (LGE) images, whose correlation with conventional LGE has been already demonstrated in HCM [62].

AI models have been also proposed to improve clinical CV genetics, contributing to predict variant pathogenicity and estimate genotype-positivity, for which a DL model has already been shown to outperform conventional HCM-risk scores [63]. It might support cardiologists in identifying which patients to refer for genetic testing.

Moreover, AI-frameworks could refine risk stratification, which remains a major challenge in the long-term management of CMPs' affected patients, carrying a life-long and heterogeneous risks of adverse events from a young age. Indeed, while traditional stratification tools can rely on a limited number of simplified human-interpretable variables, partially overlooking the intricate interactions in biological systems, complex AI-based models can account for all the time-varying inputs in electronic health records and enable the extension of prognostication to unstructured data. Through multimodal merging of a huge amount of different data (i.e., clinical, imaging, ECG, genetic), AI tools may define the patient's unique disease trajectory and risk, also taking into account competitive risks in a highly personalized assessment. Despite evidence remains scarce, a data-driven ML method demonstrated a good performance (compared with currently employed SCD prediction algorithms) in predicting ventricular arrhythmias in HCM patients [64].

One of the main barriers to the widespread adoption of medical AI is the limited availability of large, annotated datasets. As highlighted in the examples above, most existing approaches rely on supervised machine learning, which requires labeled data specifying the characteristic of interest (e.g. disease status, phenotype value). However, when the target trait is rare or depends on costly examinations—as in the case of cardiomyopathies—assembling such datasets is difficult and expensive.

Foundation models offer a potential solution. Instead of relying solely on labeled data, they are pretrained on vast amounts of unlabeled data using self-supervised learning, producing informative vector-based representations that can then be fine-tuned for downstream tasks with much smaller labeled datasets [65, 66]. As in other domains, foundation models are emerging as a paradigm shift in medical AI, moving from task-specific models toward more general, deep representations of data.

13.2.3 Artificial Intelligence-Derived Phenotypes

Emerging AI algorithms are also powering disease profiling, a framework based on the identification of endophenotypes—intermediate measurable traits bridging genetic variations and clinical diseases (i.e., LVEF as endophenotype for HF and

aortic stiffness as endophenotype for aortic dissection) that may be abnormal even in otherwise healthy individuals. A central premise in the field is that genetic drivers of population-level variation in these cardiac traits are also relevant to the risk of developing cardiovascular disease. As outlined earlier in this chapter, GWAS and MTAG have capitalized on such quantitative traits—particularly within large-scale biobanks—to identify genetic loci associated with cardiac structure, function, and disease susceptibility.

The advent of DL has opened new possibilities in this field. Taking the LV as an example, large-scale CMR datasets have been used to segment LV pixels, reconstruct the structure in three-dimensional space, and measure its volumes, enabling the definition of novel quantitative traits, such as LV sphericity [67] and fractal dimension of trabecular morphology [68]. Notably, DL makes it possible to move beyond purely physical measures and derive higher-order biological characteristics. For instance, it has been developed a model to predict chronological age from CMR data and calculate the deviation from expected age, termed “cardiac age acceleration” [69], a novel supervised trait—resembling a well-established biological concept—that the authors were able to link with CMP-related genes and adverse clinical outcomes.

This framework defines a spectrum that ranges from well-established clinical cardiac traits to engineered imaging-derived features, to supervised traits, and, ultimately, to unsupervised, data-driven phenotypes [70] (Fig. 13.4). At the far end of this spectrum, foundation models enable extraction of latent phenotypes (“digital biomarkers” [71]) that can be genetically characterized and associated with cardio-metabolic outcomes and other traits [72].

Despite integration of AI-based decision support systems in clinical practice promises to empower cardiologists in crafting patient-specific management plans, despite a rapidly-increasing number of studies investigating CV applications of AI-technologies, evidence of improvement in CV outcomes is not available yet. Further research is required to validate findings, test real-world effectiveness, ensure equity, and assess long-term reliability.

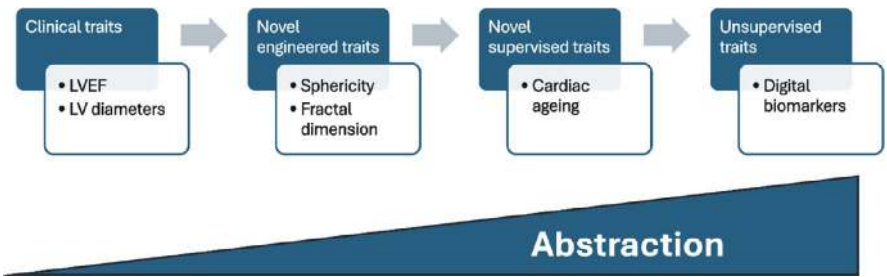


Fig. 13.4 From clinically observable traits to AI-derived traits. The figure illustrates the spectrum of cardiac traits, ranging from well-established clinical measures to increasingly abstract, data-driven representations, with examples provided at each level. (Inspired from J. Pirruccello at ESHG 2025). LV left ventricle, LVEF left ventricle ejection fraction

PRSs and AI represent the cutting edge of modern CV medicine, two transformative tools that are widening our knowledge, promising to help cardiologists better navigate the complexities of diseases and providing unprecedented opportunities to enhance care for patients with CMPs. However, despite encouraging progress, several challenges remain to be addressed before their widespread clinical implementation. Collaborative efforts among clinicians, data scientists, and regulators are essential to ensure safe and effective translation of these innovations in clinical practice, ultimately improving patient outcomes.

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Emerging Evidence on Molecular Dysregulation Driving Cardiomyopathies and Heart Failure

14

Alberto Guarnaccia, Davide Miglietta, Maria Perotto, Matteo Dal Ferro, Serena Zacchigna, Marco Merlo , and Gianfranco Sinagra 

14.1 Historical Overview: From Haemodynamic and Neurohormonal to Molecular Circuitry

Key Message Heart failure has transitioned from a haemodynamic and neurohormonal disorder to a cardiomyocyte-centred disease driven by metabolic stress, mitochondrial dysfunction, and imbalances in the AMPK-mTOR nutrient-sensing hub—a paradigm reinforced by the rapid, phenotype-agnostic efficacy of SGLT2 inhibitors.

Heart failure was long viewed through the lens of impaired pump mechanics, congestion, and altered fluid distribution. Therapeutic strategies accordingly focused on preload, afterload, and sodium-water balance, providing symptomatic relief but limited effects on long-term survival. A decisive conceptual pivot came with the neurohormonal hypothesis, which reframed heart failure as a condition sustained by maladaptive activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system. Landmark trials with ACE inhibitors, beta-blockers, and later neprilysin inhibition established, for the first time, that interrupting maladaptive neurohormonal drive (RAAS/SNS and, later, neprilysin-related pathways) could alter the natural history of the disease [1–3].

A second paradigm shift emerged, unexpectedly, from cardiovascular outcome trials in type 2 diabetes. In these studies, SGLT2 inhibitors produced rapid and substantial reductions in heart-failure hospitalisations, despite minimal influence on blood pressure, intravascular volume, or classical haemodynamic parameters. The early onset and consistency of benefit across diverse patient groups pointed to

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mechanisms operating beyond glucose lowering or natriuresis [4, 5]. Dedicated heart-failure trials subsequently demonstrated diabetes-independent efficacy across the spectrum of ejection fraction, from HFrEF to HFpEF [6–9]. These findings collectively challenged the prevailing centrality of haemodynamic unloading and suggested that heart-failure biology might be anchored in a shared cell-intrinsic metabolic stress circuitry, operating downstream of diverse clinical triggers (Fig. 14.1).

In this context, the term ‘upstream’ refers to two distinct biological levels: systemic neurohormonal drivers (RAAS and sympathetic activation), on one hand, and a convergent, cell-intrinsic stress circuitry centred on nutrient sensing and mitochondrial quality control, on the other. As mechanistic studies and omics analyses expanded, a new explanatory framework took shape: chronic cardiomyocyte stress induces a partial re-engagement of a foetal-like metabolic programme. This state is characterised by increased reliance on GLUT1-driven glycolysis, reduced fatty-acid oxidation, and diminished mitochondrial throughput. Mitochondrial quality-control pathways—particularly autophagy and mitophagy—lose their physiological oscillatory behaviour, while nutrient-sensing signals become chronically unbalanced. Across diverse forms of cardiac stress, the AMPK-mTOR hub shifts from an energy-deficit, catabolic configuration towards a persistent anabolic, nutrient-surplus mode, suppressing organelle turnover, impairing proteostasis, and promoting energetic inefficiency [10, 11].

This integrated cellular-stress paradigm provides a unifying interpretation for several observations that previously appeared disconnected. The rapid improvement seen with SGLT2 inhibitors corresponds to early upregulation of AMPK/SIRT1-linked nutrient-deprivation pathways and reduced mTORC1 output, as reflected by

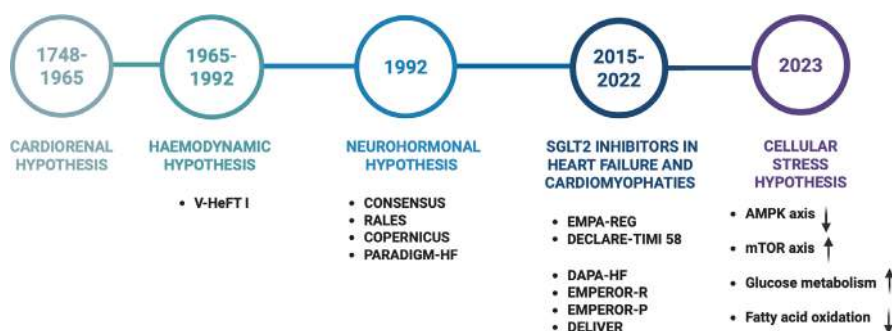


Fig. 14.1 Paradigm shifts in the understanding and treatment of heart failure. Evolution from the early cardiorenal era (1748–1965) to the haemodynamic era (1965–1992), the neurohormonal model (1992), the SGLT2 inhibitor era (2015–2022), and the current intracellular-stress paradigm (2023–present). The figure illustrates how therapeutic innovation has mirrored conceptual progress, culminating in a cardiomyocyte-centred framework driven by metabolic and mitochondrial mechanisms

proteomic signatures observed across major heart-failure programmes (ref?). These molecular shifts recapitulate biological patterns found in models of caloric restriction and mitochondrial stress recovery, highlighting the centrality of metabolic housekeeping in determining cardiomyocyte resilience.

Ultimately, this evolving understanding reframes heart failure not simply as a disease of haemodynamic overload or neurohormonal dysregulation but as a disorder rooted in disrupted intracellular homeostasis. Defective mitochondrial quality control, maladaptive nutrient sensing, and reactivation of developmental metabolic patterns converge to drive energetic decline and structural progression. This perspective sets the foundation for the mechanistic narrative developed throughout the chapter and underpins the increasingly translational view that cardiomyocyte metabolic health is the primary determinant of therapeutic reversibility in modern heart-failure care.

This evolving view naturally leads to the question of how cardiomyocytes revert to a foetal metabolic logic under chronic stress, a process explored in the next section.

14.2 Foetal Molecular Signature vs Adult Metabolic Homeostasis

Key Message Under chronic stress, the adult cardiomyocyte reactivates a foetal-like, glycolytic, and nutrient-surplus metabolic programme dominated by GLUT1 and PI3K-Akt-mTOR signalling, antagonising AMPK/SIRT1-driven oxidative maturation and priming the myocardium for mitochondrial dysfunction and maladaptive remodelling.

During foetal life, cardiomyocytes rely predominantly on glycolysis and lactate uptake through insulin-independent GLUT1 transport. This profile supports rapid tissue growth while operating within an environment of low oxygen tension and limited mitochondrial density. High PI3K-Akt-mTOR activity sustains anabolic growth and DNA and protein synthesis and restrains autophagy, all of which are features of a nutrient-surplus developmental state [12]. After birth, the abrupt rise in circulating fatty acids, thyroid hormone, glucocorticoids, and mechanical workload triggers a programmed metabolic shift. AMPK tone rises, mitochondrial biogenesis accelerates, and oxidative phosphorylation supplants glycolysis as the principal ATP source. This transition also establishes oscillatory autophagy and mitophagy as essential components of mitochondrial quality control and long-term energetic stability [13–15].

Experimental systems highlight the plasticity of this developmental transition. Human iPSC-derived cardiomyocytes maintain an immature phenotype with sparse mitochondria and high glycolytic flux when exposed to glucose-rich conditions. In contrast, switching to long-chain fatty-acid-enriched media induces structural and bioenergetic maturation, activating SIRT1/AMPK-PGC-1 α pathways and

improving calcium handling and sarcomere organisation [12, 16]. Regenerative species such as zebrafish and neonatal mammals display the same metabolic logic: transient glycolysis supports proliferation and tissue regrowth, whereas premature exposure to fatty acids or sustained mTOR activation curtails regenerative capacity, indicating that the timing and intensity of nutrient signals help determine whether cardiomyocytes prioritise proliferation, differentiation, or stress resistance [17].

In the adult heart, chronic stressors—including genetic mutations, mechanical overload, metabolic excess, inflammation, or ischaemia—can reactivate key components of the foetal programme. GLUT1 is upregulated, pyruvate dehydrogenase kinase activity increases, and glycolytic intermediates accumulate. In parallel, enzymes involved in fatty-acid oxidation and PPAR α -dependent transcription become downregulated, leading to an expanding mismatch between cytosolic substrate delivery and mitochondrial oxidative capacity [11, 12]. Sustained PI3K-Akt-mTOR activity further suppresses autophagy and mitophagy, leading to accumulation of dysfunctional mitochondria and impaired protein turnover. A progressive decline in SIRT1/AMPK signalling reduces the ability of the cell to sense energy deficit and restore oxidative metabolism, creating a state in which nutrient-surplus cues remain chronically switched on.

Metabolic intermediates amplify this maladaptive reversion. Increased O-GlcNAcylation, a hallmark of chronic glucose and hexosamine flux, re-engages developmental transcriptional programmes and interferes with excitation-contraction coupling [11]. Post-translational acylations—malonylation, succinylation, and widespread lysine acetylation—impair mitochondrial enzyme efficiency, weaken β -oxidation, and further constrain oxidative throughput [18]. These mechanisms establish a vicious cycle in which nutrient-surplus signalling suppresses the very pathways required to restore energetic balance, reinforcing mitochondrial dysfunction and foetal-like metabolic dependence.

Therapeutic insights from SGLT2 inhibitor studies illustrate the reversibility of this state. Proteomic data show early activation of AMPK/SIRT1 pathways, reduction of mTORC1 output, restoration of oscillatory autophagy, and coherent improvements in mitochondrial turnover and substrate routing. These shifts resemble adaptations observed with caloric restriction and exercise, where intermittent nutrient deprivation signalling promotes metabolic flexibility, organelle renewal, and stress resistance [10, 12, 19, 20]. The capacity to re-establish the postnatal oxidative phenotype suggests that the foetal-like metabolic reversion seen in cardiomyopathy is not fixed but represents a modifiable stress programme maintained by persistent signalling imbalance. Consistent metabolic reorientation is similarly observed with LVAD unloading, where recovery is predicted by mitochondrial enrichment and suppression of

ECM-glycolytic modules [21]. An analogous shift toward physiological fatty-acid and ketone handling emerges with CRT, linking restored metabolic flexibility to reverse remodelling [22].

Taken together, these findings position the foetal-adult metabolic transition as a central axis in cardiomyopathy biology (Fig. 14.2). When the balance tilts toward sustained mTOR-driven nutrient surplus and reduced AMPK/SIRT1 activity, the cardiomyocyte loses its oxidative resilience, accumulates proteotoxic and metabolic stress, and becomes vulnerable to progressive structural disease. Restoring this balance is therefore a rational target for therapies aiming to stabilise mitochondrial function, enhance metabolic flexibility, and slow the trajectory towards overt heart failure.

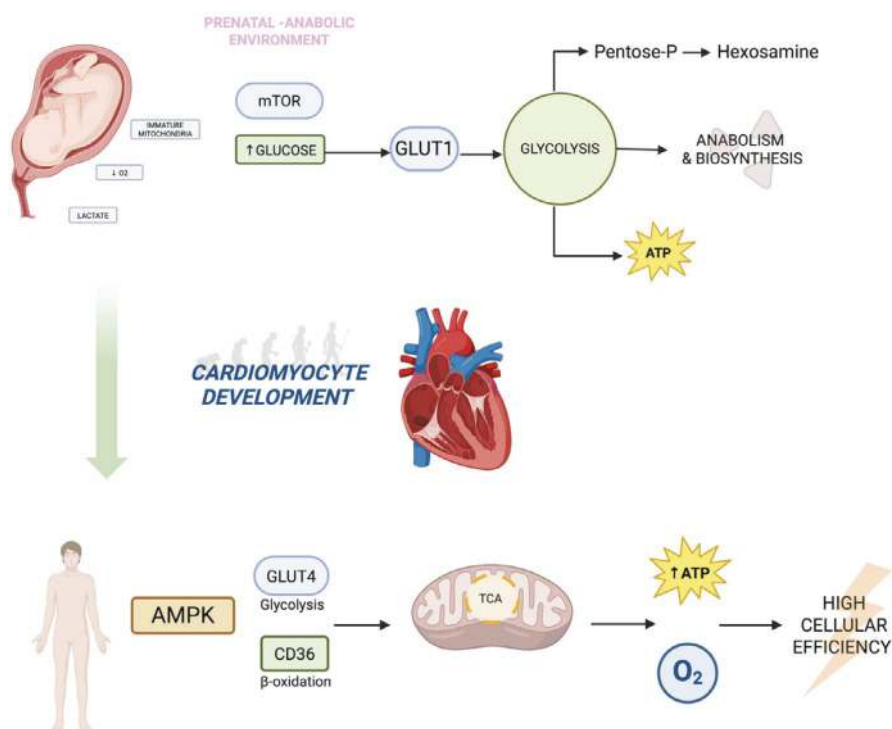


Fig. 14.2 Metabolic transition from the foetal glycolytic state to postnatal oxidative homeostasis. Schematic representation of how cardiomyocytes shift from a GLUT1- and mTOR-driven glycolytic programme during foetal life to a fatty-acid-oxidation and AMPK/SIRT1-directed oxidative phenotype after birth. The figure highlights key regulatory pathways, including mitochondrial biogenesis, autophagy-mitophagy, and the maturation of excitation-contraction coupling

14.3 Anabolic Overdrive Versus Energy Guardianship: The AMPK-mTOR Regulatory Hub in Cardiomyopathy

Key Message Sustained nutrient-surplus and growth-factor signalling chronically tip the AMPK-mTOR hub toward mTOR-dominant anabolism, suppressing autophagy and mitophagy, disrupting proteostasis, and undermining mitochondrial integrity; this imbalance represents a shared mechanistic node across cardiomyopathies and a central target for therapeutic modulation.

Cardiomyocytes rely on a tightly regulated nutrient-sensing network to coordinate growth, energy production, and organelle quality control. At its core lies the reciprocal interplay between AMPK and mTORC1, two evolutionarily conserved regulators that determine whether the cardiomyocyte prioritises anabolic expansion or energy preservation. AMPK, activated under conditions of energy deficit, promotes mitochondrial biogenesis, enhances oxidative phosphorylation, stimulates ULK1-dependent autophagy, and restrains protein synthesis by inhibiting mTORC1 via phosphorylation of TSC2 and Raptor. In contrast, mTORC1 responds to amino acids, insulin, IGF-1, and mechanical cues by accelerating protein translation through S6K and 4EBP1, promoting ribosome production, and repressing autophagic flux. Under physiological conditions, cardiomyocyte health relies on the oscillatory balance between these two nodes, allowing transient switching between nutrient-deprivation and nutrient-surplus states [13, 14].

Chronic pathological stress disrupts this balance. Persistent activation of PI3K-Akt, heightened growth-factor drive, inflammation, and metabolic excess all bias the AMPK-mTOR axis toward sustained mTORC1 dominance. AMPK signalling declines, reducing the cell's ability to sense energy deficit and activate compensatory pathways, while phosphorylated S6 increases and ULK1 remains inhibited, effectively blocking autophagy and mitophagy. As mitochondrial quality control falters, dysfunctional organelles accumulate, respiratory efficiency decreases, and oxidative stress rises, reinforcing the energetic deficit that initiated the maladaptive response [10, 12, 23].

The consequences extend beyond energy metabolism. Anabolic overdrive causes widespread disturbances in proteostasis. Chronic mTOR activation suppresses the autophagic removal of misfolded or damaged proteins, while increased acetyl-CoA availability promotes pervasive protein acetylation within mitochondria and the cytosol. Post-translational acylations—such as malonylation and succinylation—further impair mitochondrial enzyme activity, reducing β -oxidation efficiency and narrowing the cell's metabolic flexibility [18]. Hexosamine flux and O-GlcNAcylation amplify the nutrient-surplus signature, reactivating components of the foetal metabolic programme and perturbing excitation-contraction coupling [11]. Together, these processes create a self-reinforcing loop in which growth cues remain chronically switched on despite worsening energetic and proteostatic stress.

Evidence from genetic and pharmacologic interventions provides direct support for causality within this regulatory hub. In models of pressure-overload hypertrophy, mTOR inhibition with rapamycin not only halts pathological growth but reverses established hypertrophy and improves left ventricular performance, illustrating that restraining sustained anabolic signalling can restore autophagic flux and

mitochondrial turnover [24]. Conversely, mice lacking AMPK α 2 develop exaggerated hypertrophy and accelerated dysfunction under pressure overload, supporting a cardioprotective role for AMPK in stress adaptation [25]. In lamin A/C cardiomyopathy, late mTOR inhibition prolongs survival even when initiated after disease onset, suggesting that the maladaptive signalling state remains reversible if the intervention selectively restores autophagy and avoids excessive autophagic activation [26].

Human studies have mirrored these mechanistic insights. Proteomic analyses from large heart-failure programmes consistently reveal a shift toward nutrient-deprivation signatures with therapies such as SGLT2 inhibitors. Increased AMPK/SIRT1 activity, reduced pS6, and enhanced markers of mitochondrial renewal indicate a coordinated rebalancing of the nutrient-sensing axis rather than a non-specific diuretic effect [19, 20]. These molecular shifts occur early after treatment initiation and are coherent with adaptations seen in caloric restriction and endurance exercise, where intermittent activation of nutrient-deprivation pathways promotes resilience against metabolic and oxidative stress [27, 28].

This unified framework suggests that the AMPK-mTOR regulatory hub is a final common node through which diverse cardiomyopathic stimuli exert their deleterious effects. Genetic mutations in sarcomeric, cytoskeletal, and nuclear-envelope proteins; mechanical overload; metabolic excess; inflammatory signalling; and mitochondrial dysfunction all converge on sustained mTOR activation and suppressed AMPK tone. Whether triggered internally or externally, the downstream phenotype-impaired mitochondrial quality control, proteostasis disruption, and substrate-oxidation mismatch appears remarkably consistent across cardiomyopathies [12].

Taken together, these observations identify the AMPK-mTOR axis not merely as a signalling pathway but as a mechanistic integrator of cardiomyocyte health. Its dynamic oscillatory behaviour is essential for matching energetic demand with growth and repair processes, and its chronic imbalance provides a compelling explanation for the convergence of molecular patterns seen across heart-failure phenotypes. As such, restoring appropriate AMPK-mTOR balance represents a rational target for disease modification, informing both current therapies and future metabolic and mitochondrial interventions.

14.4 Mitochondrial Dysfunction and Substrate-Oxidation Mismatch

Key Message Heart failure with reduced ejection fraction is marked by a mismatch between relatively preserved cytosolic substrate delivery and limited mitochondrial oxidative capacity, creating a fuel-rich but energy-poor myocardium; despite this bottleneck, non-ischaemic HFrEF retains metabolic flexibility that can be restored by interventions rebalancing the AMPK-mTOR regulatory axis.

In heart failure with reduced ejection fraction (HFrEF), a recurring molecular signature is the presence of substantial cytosolic substrate availability alongside impaired mitochondrial oxidative function. Multiple metabolic studies have shown that glycolytic pathways, fatty-acid activation, and cytosolic handling of substrates

remain relatively intact. However, mitochondrial respiration, ATP production, and phosphocreatine buffering capacity are significantly impaired, suggesting that the principal energetic limitation lies downstream of substrate delivery. This condition has been described as a ‘fuel-rich, energy-poor’ myocardium, in which the mismatch between substrate supply and oxidative throughput drives inefficiency and contributes to contractile failure [23, 29].

A constrained oxidative machinery promotes the accumulation of toxic metabolic intermediates. Elevated glucose flux increases hexosamine pathway activity and O-GlcNAcylation, which re-engage foetal-like transcriptional programmes and disrupt excitation-contraction coupling. Reduced β -oxidation exacerbates the accumulation of diacylglycerols, ceramides, and long-chain acylcarnitines, which exert arrhythmogenic, pro-inflammatory, and lipotoxic effects, further impairing mitochondrial efficiency. Within mitochondria, post-translational acylations –particularly malonylation and succinylation of key enzymes– diminish oxidative capacity and perpetuate the bottleneck in fatty-acid oxidation [18]. Together, these biochemical disturbances deepen the energy deficit, perturb proteostasis, and contribute to structural remodelling.

Despite these abnormalities, non-ischaemic HFrEF exhibits a surprising degree of metabolic flexibility. In controlled physiological studies, acute re-engagement of fatty-acid oxidation improves phosphocreatine-to-ATP ratio and enhances left ventricular performance without triggering lactate accumulation. These findings indicate that the failing myocardium is not irreversibly committed to glycolysis; rather, it possesses a reversible oxidative bottleneck that can be relieved when substrate routing and mitochondrial function are appropriately modulated [22, 30]. This residual metabolic adaptability provides an important therapeutic opportunity and suggests that the observed oxidative impairment reflects a modifiable imbalance rather than a fixed structural defect [31].

The AMPK-mTOR nutrient-sensing hub provides a mechanistic explanation for the coexistence of oxidative limitation and retained flexibility. Under physiological conditions, AMPK activation relieves malonyl-CoA inhibition of CPT1, facilitates mitochondrial biogenesis and turnover via PGC-1 α , and promotes ULK1-mediated autophagy and mitophagy. mTORC1, in contrast, promotes anabolic growth and suppresses autophagic clearance. In HFrEF, chronic nutrient-surplus cues shift the axis toward mTOR dominance, leading to inadequate mitochondrial renewal, accumulation of dysfunctional organelles, and impaired oxidative throughput. The resulting state is one in which oxidative capacity is constrained not by substrate availability but by defective organelle quality control and maladaptive signalling [32].

Proteomic and metabolomic datasets from heart-failure cohorts offer translational support for this model. Trials involving SGLT2 inhibitors, for instance, demonstrate reproducible shifts toward nutrient-deprivation signatures, including increased AMPK/SIRT1 activity, reduced mTORC1 output as reflected by lower pS6, and improved markers of mitochondrial turnover [19, 20]. Metabolomic analyses further reveal modest rises in short- and medium-chain acylcarnitines and occasional low-grade β -hydroxybutyrate, interpreted not as ketone-driven metabolism but as evidence of improved mitochondrial trafficking and enhanced oxidative routing [33]. These adaptations are coherent with early rebalancing of the AMPK-mTOR axis and restoration of substrate-oxidation matching.

Viewed through this integrative framework, HFrEF emerges as a disorder of impaired oxidative processing rather than one of simple substrate shortage. The myocardium remains capable of metabolic recovery when mitochondrial quality control is restored, and nutrient-sensing pathways are rebalanced. This interpretation reconciles the paradox of a glucose-tilted, oxidation-limited metabolic state that nonetheless retains the ability to improve oxidative performance under targeted interventions. It also highlights a coherent therapeutic rationale centred on restoring metabolic flexibility, re-establishing efficient organelle turnover, and reactivating the physiological AMPK-mTOR oscillatory balance that underpins cardiomyocyte energetic stability. Altogether, these mechanisms converge on a shared goal: recovering mitochondrial throughput and correcting maladaptive nutrient sensing-principles that directly motivate the therapeutic strategies outlined in the next section.

14.5 Therapeutic and Research Implications: ‘Mitohormesis’

Key Message Durable modification of heart-failure biology requires sustained engagement of nutrient-sensing pathways, restoration of autophagy and mitochondrial quality control, and improved substrate-oxidation coupling. SGLT2 inhibitors act as *in vivo* fasting-mimetic probes of this axis, demonstrating that rebalancing AMPK-mTOR signalling yields clinically meaningful benefit.

A growing body of mechanistic and translational evidence indicates that therapies capable of shifting the cardiomyocyte away from chronic nutrient-surplus signalling and towards a nutrient-deprivation, AMPK-dominant state can modify the course of heart failure. The most consistent human data come from proteomic analyses performed in large clinical programmes, where SGLT2 inhibitors have shown a reproducible capacity to reset nutrient sensing at the AMPK-mTOR hub. Shortly after treatment initiation, circulating signatures reveal increased AMPK and SIRT1 activation, reduced mTORC1 output as reflected by lower pS6, and enhanced markers of autophagy and mitochondrial renewal. These shifts appear in both HFrEF and HFpEF and correlate poorly with changes in haemodynamics or natriuresis [34], suggesting a more fundamental metabolic reorganisation rather than a diuretic-mediated effect [19, 20].

The metabolic adjustments observed with SGLT2 inhibition extend beyond modest elevations in β -hydroxybutyrate. Although low-grade increases in ketone bodies are detectable, the dominant signal is a coherent realignment of substrate use and oxidative flux. Targeted metabolomic programmes have consistently shown modest rises in short- and medium-chain acylcarnitines, together with occasional elevations of C2-associated β -oxidation intermediates. Rather than indicating frank ketosis, these changes reflect improved mitochondrial trafficking and a restoration of substrate routing towards oxidative pathways that had become restricted under chronic nutrient-surplus conditions [10, 33]. This broader framework aligns with the concept of ‘mitohormesis’: interventions that stress the cell and the mitochondria by simulating aspects of caloric restriction and intermittent nutrient deprivation, ultimately promoting metabolic flexibility, mitochondrial turnover, and proteostasis.

One of the most reproducible systemic correlates of these molecular changes is the Hb-EPO-iron programme activated by SGLT2 inhibitors. Short-term increases in

haemoglobin and haematocrit consistently observed after drug initiation have traditionally been attributed to haemoconcentration, but mechanistic analyses argue for a more complex biology. In both renal and hepatic tissues, SGLT2 inhibition enhances erythropoietin synthesis and activates a stress-erythropoiesis programme characterised by increased transferrin receptor 1, reduced hepcidin and ferritin, and enhanced iron mobilisation [35, 36]. The temporal association between these changes and improvements in exercise capacity and health status suggests that the erythropoietic response may serve as a pragmatic biomarker of upstream engagement of the AMPK-SIRT axis. If this interpretation is correct, early haemoglobin and EPO increments could represent an accessible surrogate for the metabolic rebalancing that underlies clinical benefit.

The dependence of therapeutic efficacy on continuous pharmacological engagement further strengthens the mechanistic link. The blinded withdrawal study showed that stopping empagliflozin was followed within approximately 30 days by deterioration in health status and reversal of several physiological and laboratory effects, including changes in body weight, blood pressure, NT-proBNP, haemoglobin, and haematocrit. Molecular signatures revert towards nutrient-surplus patterns, with rising inflammatory and growth-factor signals, reduced AMPK/SIRT1 activity, and reappearance of congestion. This mirror-image pattern—improvement during treatment, deterioration upon withdrawal—suggests that the maladaptive cellular programme characteristic of heart failure remains actively suppressed only while the therapeutic ‘brake’ is applied [37]. Although the precise temporal kinetics vary, the overall trajectory supports the idea that persistent activation of nutrient-deprivation pathways is necessary to maintain disease modification (Fig. 14.3).

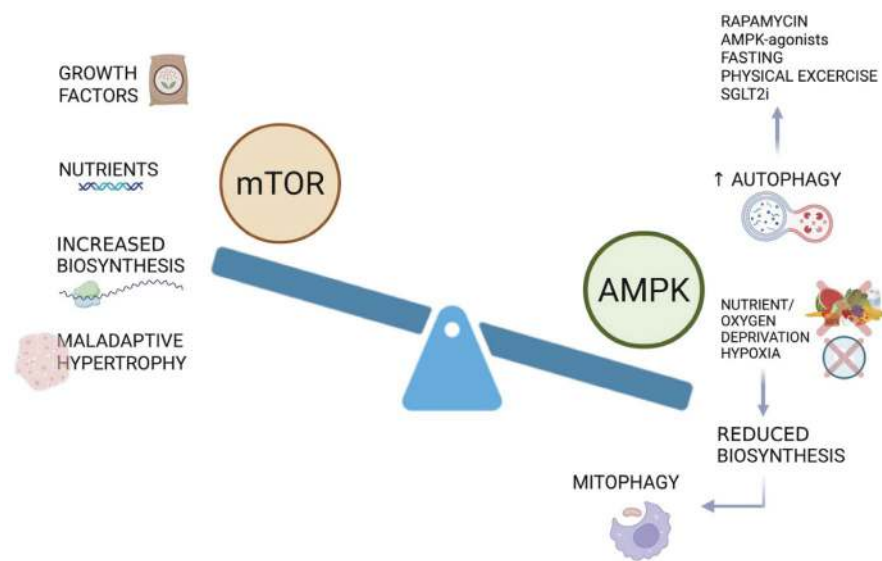


Fig. 14.3 Conceptual model of the proposed effects of SGLT2 inhibition on nutrient sensing, mitochondrial quality control, and substrate handling

Table 14.1 Targetable molecular nodes and corresponding biomarkers for translational monitoring

Node (priority)	Representative agent(s)	Evidence tier	Biomarker(s) of response
AMPK–mTOR regulatory hub & proteostasis	SGLT2i; metformin; rapalogs; caloric restriction; physical exercise	Preclinical mechanistic evidence plus circulating proteomics	-p-AMPK↑ and p-S6↓ in tissue or phosphoproteomic samples where available; circulating IGFBP1, HSPA8, GDF15, and FGF21
GLUT1 → GLUT4/FAO recoupling & mitochondrial ATP	SGLT2i; FAO-supportive strategies; CRT; LVAD	Translational + metabolomics	Acylcarnitine profile, including C2 and C8–C10 species; low-grade β-hydroxybutyrate; PCr/ATP by ³¹ P-MRS where available
Hb–EPO–iron programme (HF stress-erythropoiesis)	SGLT2i;	Mechanistic + clinical	EPO↑, Hb/Hct↑, Tfr1↑; hepcidin↓, ferritin↓

Overview of key regulatory pathways relevant to metabolic and mitochondrial interventions, matched with pharmacological examples and feasible biomarkers for early mechanistic readouts
Abbreviations: AMPK AMP-activated protein kinase, mTOR mechanistic target of rapamycin, p-phosphorylated, pS6 phosphorylated ribosomal protein S6, IGFBP-1 insulin-like growth factor binding protein 1, HSPA8 heat shock protein family A (Hsp70) member 8, LC3 microtubule-associated protein 1A/1B-light chain 3, GLUT glucose transporter, FAO fatty-acid oxidation, CRT cardiac resynchronisation therapy, LVAD left ventricular assist device, PCr/ATP phosphocreatine-to-ATP ratio (31P-MRS), Hb haemoglobin, Hct haematocrit, EPO erythropoietin, Tfr1 transferrin receptor 1

Taken together, these findings suggest that therapies targeting nutrient sensing and mitochondrial housekeeping share a mechanistic coherence that transcends their pharmacological classes. Interventions as diverse as caloric restriction, endurance training, metformin, and SGLT2 inhibitors—and likewise device-based strategies such as CRT [22] and LVAD unloading [21]—converge on restoring AMPK–mTOR balance, enhancing autophagy, and improving mitochondrial efficiency. The clinical success of SGLT2 inhibition across the heart-failure spectrum reinforces the concept that cardiomyocyte metabolic health is central to disease reversibility, and that restoring substrate-oxidation matching is a viable route to structural and functional improvement.

This mechanistic clarity opens opportunities for future research. Short-term mechanistic studies can use proteomic markers, mitokines, or slopes of metabolic readouts to gauge pathway engagement, while longer-term outcome trials can assess whether sustained metabolic rebalancing translates into disease modification. The cumulative evidence positions ‘mitohormesis’ as a functional lens through which to design next-generation therapies aimed at stabilising mitochondrial turnover, preserving proteostasis, and supporting the energetic resilience of the failing heart (Table 14.1).

14.6 Future Perspectives: Ageing Biomarkers and Very-Early Disease Predictors

Key Message Mitochondrial stress mitokines—GDF-15, FGF-21, and ATF-4-linked ISR signatures—and age-related clonal haematopoiesis (CHIP) offer a promising route to identify early cellular vulnerability and to test AMPK-mTOR-centred interventions before structural cardiomyopathy becomes established.

The search for biomarkers capable of detecting heart failure before the onset of structural disease is gaining momentum, supported by evidence that many molecular abnormalities precede clinical expression by years. Among the most compelling candidates are circulating mitokines such as GDF-15, FGF-21, and ATF-4-related integrated stress response (ISR) signatures and clonal haematopoiesis of indeterminate potential (CHIP). Together, they reflect distinct yet converging dimensions of cellular ageing, mitochondrial stress, and nutrient-sensing imbalance, forming a biologically coherent platform for early stratification and mechanistic intervention.

CHIP represents an age-associated process in which haematopoietic stem cells acquire somatic mutations that impart a growth advantage to specific clones. Once considered incidental, even small clones have been shown to modulate inflammatory tone, metabolic signalling, and immune behaviour. Several clinical studies have now demonstrated that individuals with CHIP have higher rates of heart-failure development, faster progression of dilated cardiomyopathy, and worse outcomes, independent of age and traditional risk factors. Clone size and mutated gene strongly influence risk, with *DNMT3A*, *TET2*, and *ASXL1* carrying particularly robust associations [38–40]. In this sense, CHIP functions both as a biological ageing marker and as an active driver of low-grade inflammatory-metabolic stress, making it an attractive anchor for pre-phenotypic risk stratification.

Complementary insight is provided by circulating mitokines. When mitochondrial proteostasis, redox balance, or electron-transport capacity falter, cardiomyocytes engage the integrated stress response—a conserved pathway initiated by phosphorylation of eIF2 α , which selectively enhances translation of ATF4. This shift promotes a compensatory programme aimed at restoring amino-acid supply, redox buffering, and organelle stability. In early stages, such ISR activation is protective rather than damaging [41]. Downstream, ATF-4 induces the secretion of GDF-15 and FGF-21, which act as systemic reporters of mitochondrial strain. GDF-15 rises in proportion to ISR intensity, is highly responsive to cardiac stress, and has shown prognostic value across heart-failure phenotypes. Importantly, individuals with higher baseline GDF-15 appear to derive greater benefit from SGLT2 inhibition, and short-term changes in its concentration—‘slopes’—emerge as practical mechanistic readouts [42]. FGF-21 provides complementary information by

indexing metabolic overload and mitohormetic adaptation, broadening the interpretation of mitochondrial housekeeping.

The convergence between CHIP and mitokine biology suggests a feasible strategy for early-stage, mechanism-oriented trials. Populations enriched for CHIP positivity or elevated GDF-15/FGF-21 levels represent groups in whom cellular stress is already active despite the absence of structural disease. Interventions that rebalance the AMPK-mTOR axis, enhance mitochondrial turnover, or improve substrate-oxidation matching could therefore be tested in smaller, shorter studies using biomarker trajectories as primary mechanistic endpoints. Because mitokines respond rapidly to shifts in nutrient sensing and mitochondrial stress, serial mitokine trajectories could therefore be explored as candidate readouts of pathway engagement in short, mechanism-oriented studies [43].

Importantly, the heterogeneity of these biomarkers dissolves when viewed through the common mechanistic lens developed throughout this chapter. External stressors (pressure overload, metabolic excess, inflammation, toxins, and ischaemia) and internal genetic causes (nuclear and mitochondrial mutations within the cardiomyocyte) all converge on a shared intracellular programme characterised by mitochondrial dysfunction, impaired proteostasis, maladaptive nutrient sensing, and partial reactivation of foetal-like glycolytic dependency. --- CHIP can act not only as a biomarker of biological ageing and disease risk but also as an amplifier of inflammatory and metabolic signals that feed into this final common pathway; GDF-15, FGF-21, and ATF-4-related signatures may reveal its early activation [10, 32].

In this framework, a combined CHIP-GDF-15/FGF-21-ATF-4 panel interpreted as trajectories rather than static measurements could define a new class of pre-phenotypic risk stratification tools. Such an approach would not only identify vulnerable individuals long before conventional markers appear but also provide a rapid, biologically meaningful means to test nutrient-sensing interventions aimed at restoring mitochondrial health and metabolic balance. As the therapeutic era shifts increasingly towards metabolic and mitochondrial strategies, these early biomarkers may become indispensable for designing future prevention trials and for mapping the earliest detectable steps that lead towards cardiomyopathy (Table 14.2).

Table 14.2 Ageing-linked biomarkers as very-early disease predictors and short-term mechanistic trial readouts

Biomarker	What it signals	How it’s measured	How to use it in early trials
<i>CHIP (quantitative VAF burden; DNMT3A, TET2, ASXL1, JAK2 genes)</i>	Age-linked clonal inflammation; higher HF/DCM risk; risk scales with clone size (VAF) and differs by gene	NGS panel with quantitative clone size	Enrich very-early risk cohorts; track outcomes with molecular readouts
GDF-15	Circulating mitokine of mitochondrial/ISR stress; prognostic; higher baseline may predict larger benefit	Serial immunoassay	Candidate serial endpoint over weeks–months; exploratory readout for ISR-targeted interventions
FGF-21	Complementary mitokine of metabolic stress/mitohormesis	Serial immunoassay	sCandidate adjunct serial endpoint with GDF-15
ATF-4 signature	Upstream ISR transcriptional activity	Targeted transcriptomic/proteomic signature	Exploratory targeted transcriptomic/proteomic readout

Key biomarkers involved in biological ageing and early cardiomyocyte stress—CHIP, GDF-15, FGF-21, and ATF-4 signatures—summarised by signal type, measurement modality, and recommended applications in short-term slope-based mechanistic trials and very-early risk enrichment

Abbreviations: *CHIP* clonal haematopoiesis of indeterminate potential, *VAF* variant allele fraction, *NGS* next-generation sequencing, *HF* heart failure, *DCM* dilated cardiomyopathy, *GDF-15* growth differentiation factor 15, *FGF-21* fibroblast growth factor 21, *ISR* integrated stress response, *ATF4* activating transcription factor 4

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Translational Cardiology in Genetic Cardiomyopathies

15

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15.1 Introduction

Translational medicine embodies the “bench-to-bedside and back” paradigm, connecting clinical observations with laboratory discoveries and returning them to patients as personalized approaches to diagnosis, follow-up, and therapy. Cardiovascular research has been among the most dynamic areas of translational medicine, where sustained collaboration between clinicians and scientists has clarified links between genetics, molecular mechanisms, and disease phenotypes [1]. Within this context, genetic cardiomyopathies have emerged as a distinct domain. What began as clinical descriptions of enlarged, thickened, or dysfunctional hearts has evolved into a molecularly grounded understanding of inherited

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mechanisms. Genetic studies established familial clustering and pathogenic variants as robust criteria to distinguish inherited from acquired disease, refining classification and enabling early identification of at-risk, asymptomatic carriers through cascade screening [2]. Despite these advances, a key barrier remains: most available therapies mitigate downstream consequences rather than correcting the primary molecular defect. Optimal medical therapy according to ESC guidance is essential for managing heart failure and arrhythmic risk, but it is typically initiated after myocardial injury is established [3]. While the heart remains a challenging target for regenerative and gene-based interventions, multiple strategies, including gene therapy, tissue engineering, and cell-based approaches, have been explored; limited efficacy and publication bias against negative results have likely slowed progress and translation [4]. Looking forward, translational cardiology should aim both to stabilize or reverse pathological phenotypes in symptomatic patients and to enable preventive interventions in asymptomatic carriers before clinical disease onset. Achieving this goal requires improved biological models and integrative platforms that bridge molecular biology and clinical medicine, accelerating the development of gene-targeted and cell-based therapies [5].

15.2 Translational Medicine in Cardiomyopathies

Cardiomyopathies comprise a heterogeneous group of myocardial disorders in which disease progression reflects interacting cellular processes, including impaired cardiomyocyte proliferation and cell-cycle control, activation of programmed cell death pathways (e.g., apoptosis and necroptosis), cardiomyocyte–fibroblast crosstalk, and transdifferentiation, and maladaptive extracellular matrix expansion driven by canonical and noncanonical profibrotic signaling. Collectively, these mechanisms compromise contractile reserve, mechano-electrical coupling, and chamber geometry, promoting heart failure and arrhythmogenesis [6]. Genetics has been the first major translational contribution to clinical cardiomyopathy care, with direct implications for diagnosis and prognosis. Integration of high-resolution genetic data with deep clinical phenotyping remains central to mechanistic insight and risk prediction [3, 7]. For example, truncating variants in *TTN* are the most frequent monogenic contributors to adult dilated cardiomyopathy (DCM), whereas *LMNA* and *DSP* variants are classically associated with DCM phenotypes featuring conduction-system disease and high arrhythmic risk [8]. In hypertrophic cardiomyopathy (HCM), sarcomeric genes (e.g., *MYH7*, *MYBPC3*, *TNNT2*) predominate and are associated with shared histopathological features such as myofibrillar disarray, interstitial fibrosis,

and microvascular remodeling. Variable penetrance and intra-familial heterogeneity arise from additional rare variants, polygenic background, epigenetic modulation (DNA methylation, chromatin remodeling, and non-coding RNAs), and environmental modifiers (e.g., exercise, alcohol exposure, metabolic stress). These “second hits” seem to influence disease expression and may partly explain why carriers of the same pathogenic variant experience divergent trajectories [9–11]. Molecular characterization is increasingly informing tailored therapies across platforms. Gene-targeted approaches include antisense oligonucleotides and RNA interference to correct splicing or suppress toxic transcripts, AAV-mediated replacement strategies for haploinsufficiency advancing toward early clinical studies, and genome editing approaches (CRISPR/Cas systems) with growing translational momentum [12]. Delivery and dosing remain key constraints for several RNA-based approaches in cardiac tissue; nonetheless, AAV programs and editing technologies are progressing steadily. Complementary strategies target downstream disease pathways, including selective p38/MAPK inhibition in LMNA-related cardiomyopathy. Calcium-handling interventions, including SERCA2a gene therapy (CUPID program) and RyR2 stabilization, aim to restore contractility, while metabolic modulators (e.g., perhexiline, trimetazidine) and SGLT2 inhibitors offer pleiotropic benefits, from improved energetics to antifibrotic effects [13, 14].

Finally, the recent acceleration of modeling and discovery is rooted in organized data collection and rigorous data governance. Harmonized biobanking that links DNA, plasma, peripheral blood mononuclear cells (PBMCs), and myocardial tissue to longitudinal, deeply phenotyped clinical datasets is essential. Incomplete or inconsistent data capture can introduce bias, reduce predictive accuracy, and limit the reliability of AI-driven insights; likewise, models trained on insufficiently diverse populations may not generalize across demographic and clinical groups. Well-curated repositories enable genome-wide and transcriptomic discovery, epigenomic and spatial proteomic mapping, single-cell profiling, and metabolomics pipelines, and they seed experimental platforms used for mechanistic validation and preclinical therapeutic testing. These infrastructures accelerate target prioritization, biomarker validation, and the translation of mechanism-based therapies into genotype-stratified clinical trials [15, 16] (Fig. 15.1).

Schematic overview of the translational continuum from patient recruitment and data acquisition to molecular analysis, disease modeling, patient stratification, and therapeutic intervention. The bidirectional feedback loop highlights the iterative nature of translational cardiology.

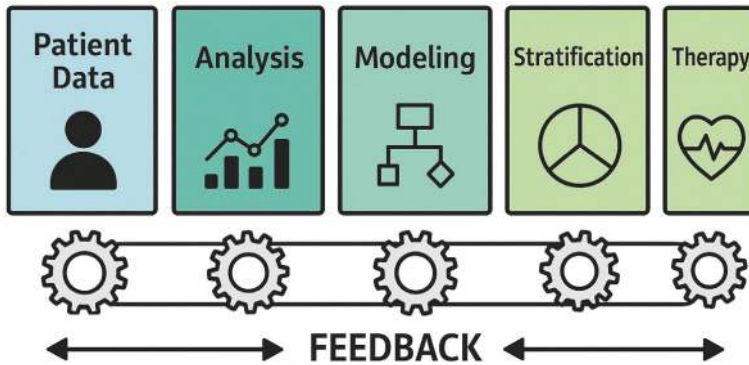


Fig. 15.1 Translational pipeline in genetic cardiomyopathies

15.3 Cellular and In Vitro Models

In vitro models of cardiomyopathies use various cellular systems, from isolated cells to complex three-dimensional (3D) organoids and engineered tissues, to both study mechanisms of disease and test therapies. These models offer personalized insights into disease progression and enable patient-specific drug testing. At the same time, they suffer from some challenges, including cellular immaturity and limited intercellular crosstalk, which hamper their capacity to fully recapitulate human diseases [17].

15.3.1 iPSC-Derived Cardiomyocytes

The most promising and widely used in vitro models rely on human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) [18], which incorporate patient-specific mutations and mimic various aspects of human disease. Protocols to obtain human CMs with good efficiency and maturity are continuously evolving [19, 20]. More recent developments have focused on enhancing hiPSC-CM maturation through metabolic and hormonal modulation [21], electrical and mechanical stimulation [22, 23], and co-culture with non-myocyte cardiac cells [24]. These improvements have led to more mature electrophysiological and contractile properties, thereby increasing the physiological relevance of hiPSC-based disease models. Patient-specific hiPSC-CMs have been used to model different forms of inherited cardiomyopathy, including hypertrophic [25], dilated [26], and arrhythmogenic cardiomyopathy [27, 28] (Fig. 15.2).

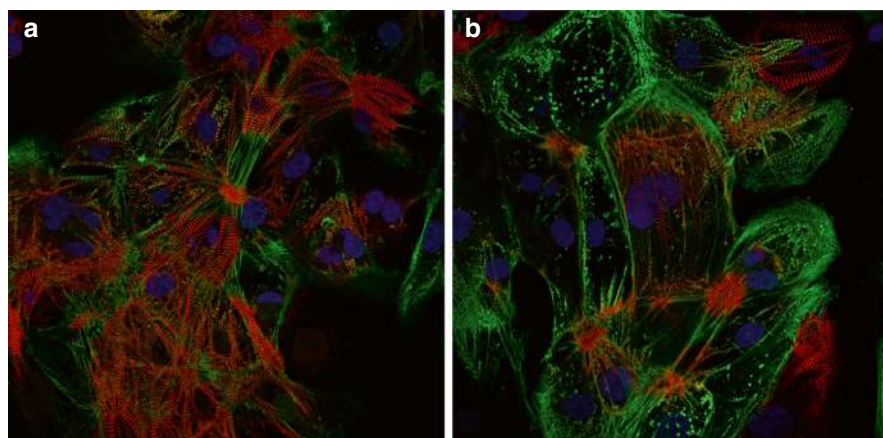


Fig. 15.2 Immunostaining of cardiomyocytes differentiated from control (left) and TTNtv (right) human iPSCs, showing disorganized and destructured sarcomeric myofibrils in TTNtv cells. Red = titin (M band), green = alpha-actinin, blue = DAPI

15.3.2 3D Models

Cardiac organoids are 3D models containing multiple cardiac cell types that reproduce key aspects of cardiac development, fibrosis, and remodeling [29–31]. Their usefulness is limited by poor standardization and lack of vascularization, which prevent full CM [32]. The immaturity of hiPSC-CMs within cardiac organoids [33, 34] has prompted the use of tissue engineering approaches, including cardiac microtissues, engineered myocardium, and microfluidic devices (heart-on-a-chip), often integrating sensors and environmental cues to improve maturation [22, 24]. Among these, engineered heart tissues (EHTs) are particularly valuable, as they enable force measurement, also under electrical or mechanical stimulation, providing insights into contractile dysfunction, arrhythmias, and remodeling [25, 35]. Patient-derived and genome-edited EHTs have been extensively used to model cardiomyopathies due to various genetic defects, leading to dilated, hypertrophic, and restrictive cardiomyopathies, including titin truncating variants (TTNtv), mutations in the TTN splicing regulator RBM20, filamin C variants, and β -myosin mutations [36–38].

On the other hand, microfluidic platforms recreate other features of the cardiac environment, including perfusion and mechanical stress, in miniaturized devices [22, 39]. They appear particularly useful to investigate aspects related to mechanobiology, cardiotoxicity, and drug response [22, 40]. However, their fabrication is complex, and protocols are not yet standardized [41]. Overall, 3D cellular models of inherited cardiomyopathies have provided key insights into how specific genetic defects translate into contractile dysfunction. By enabling quantitative assessment of force generation, calcium handling, and tissue remodeling, these systems bridge molecular and functional phenotypes. Beyond their role in disease modeling, these systems offer a platform for testing gene- and drug-based therapeutic strategies, representing a critical step toward functional precision medicine in cardiomyopathies (Fig. 15.3).

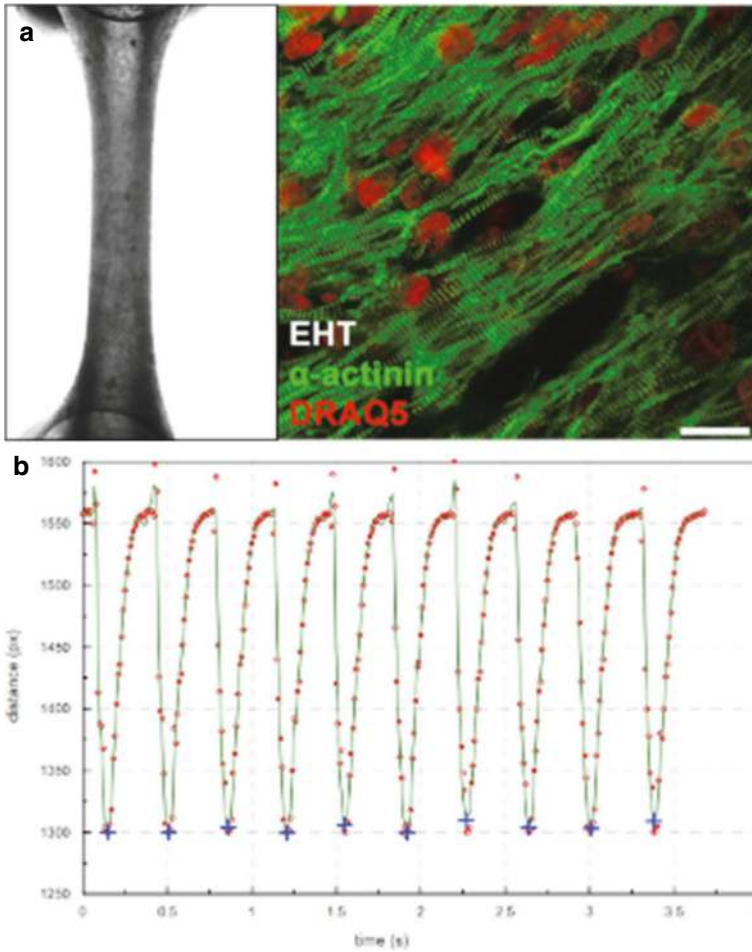


Fig. 15.3 (a) EHT model with immunostaining on the right side of the panel. Image (b) shows a study of EHT shortening during pacing

15.4 In Vivo Models for Cardiomyopathies

In vivo models remain essential for bridging clinical outcomes and therapeutic strategies in cardiomyopathies, because they capture systemic manifestations that isolated cells cannot reproduce, including ventricular remodeling, fibrosis, arrhythmias, and progression to heart failure. They support genotype–phenotype investigation and help address a central question in inherited disease: why do some individuals carrying the same mutation develop severe cardiomyopathy while others remain asymptomatic? Zebrafish provide scalability, rapid genetic manipulation, and optical access to early cardiac phenotypes. TTN truncating variant (TTNtv)-driven DCM models demonstrate that titin heterozygosity alone can induce DCM and hemodynamic

stress intolerance [42, 43]. Contemporary zebrafish resources and reviews further highlight their utility for precision modeling and screening [44]. A key strength is rapid genetics using CRISPR/Cas9 and transgenic approaches in transparent embryos, enabling live imaging and functional assays; recent examples include nexilin knockout models with impaired contractile function, and LMNA-targeted mutants that reveal muscle pathology with transient cardiac defects and implicate PKC α pathways [45, 46]. However, zebrafish limitations include a two-chambered heart and lack of a ventricular septum, restricting modeling of septal defects and aspects of conduction-system disease; adult-onset DCM modeling can be challenging due to late presentation and variable penetrance. Mouse models have been invaluable for mechanistic studies and preclinical testing due to genetic tractability and conserved cardiac pathways. Nonetheless, differences in heart rate, excitation–contraction coupling, calcium handling, and sarcomeric isoform composition can limit direct translation [47, 48]. Additionally, certain human mutations may be embryonic or perinatal lethal in mice, restricting longitudinal disease studies (e.g., FLNC loss-of-function) [49]. Small heart size also complicates imaging and electrophysiology. Titin has been intensively studied in murine cardiomyopathy models. Haploinsufficiency is a major mechanism in TTNv-mediated DCM: human myocardium shows reduced full-length titin protein despite mRNA upregulation, [50, 51] consistent with impaired sarcomere assembly and reduced contractile reserve in experimental systems. Truncated titin may also exert dominant-negative (“poison peptide”) effects by incorporating into sarcomeres or accumulating when proteostasis is impaired [52, 53]. Exon context modulates pathogenicity; for example, variants in exon 327 may escape nonsense-mediated decay and yield highly pathogenic truncated proteins [54]. Domain-specific deletions have clarified how titin’s elastic regions regulate passive stiffness and sarcomere length. N2B deletion causes diastolic dysfunction with increased passive tension, [55] and deletions involving tandem Ig or PEVK segments increase diastolic stiffness and may model HFpEF-like remodeling [56–58]. Additional studies manipulating titin’s spring properties support a mechanistic link between altered passive mechanics and hypertrophic remodeling [59]. More recent approaches, including inducible titin cleavage models, demonstrate acute sarcomere disruption followed by fibroblast activation and reactive fibrosis [60, 61]. Beyond titin, murine models capture diverse pathogenic pathways: desmin knockout mice show myofibrillar disorganization and mitochondrial abnormalities; [62] LMNA mutants reveal nuclear envelope fragility and conduction disease; [63] MYBPC3 truncation models exhibit disarray and diastolic dysfunction; [64] and MYH7 knock-in models recapitulate hypercontractility and increased energetic demand [65]. Cardiomyopathies are complex diseases, driven by a combination of genetic variants and environmental stressors. In vitro models preserve patients’ genetic background and enable the study of disease mechanisms in a controlled setting [66]; however, they fail to reproduce disease progression in the long-term and environmental interactions. In contrast, in vivo models of cardiomyopathies, namely animals carrying disease-causing genetic mutations, overcome these major limitations, reproducing the complex interplay between autonomous CM-specific defects due to the mutation, other cell types, and external factors that contribute to the pathological phenotype.

15.4.1 Zebrafish

Zebrafish offer scalability, rapid genetic manipulation, and optical access to early cardiac phenotypes in transparent embryos, enabling the use of fluorescent reporter transgenes and genetic fate-mapping strategies in combination with cardiac imaging. This model allows the identification and functional characterization of cardiomyopathy-associated genes, largely by transgenic techniques to either introduce or modify gene expression, including morpholino-mediated knockdown to transiently block mRNA translation or splicing and CRISPR/Cas9 genome editing to create precise, heritable mutations. This allows screening high number of genes and specific mutations at a relatively low cost and in a short time and leads to cardiac phenotypes that reproduce those of human cardiomyopathies. For example, hypertrophic cardiomyopathy (HCM) in zebrafish usually presents with increased trabecular density, whereas dilated cardiomyopathy (DCM) shows reduced trabeculation, clearly distinguishable by histological analysis [44]. Mutations in genes associated with human cardiomyopathies, including titin (TTN), cardiac myosin-binding protein C (MYBPC3), and lamin A (LMNA), have been modeled in zebrafish, recapitulating phenotypes such as ventricular dilation, contractile dysfunction, and arrhythmias. A paradigmatic example is titin cardiomyopathy, as TTN is the largest known human protein, representing the most frequently mutated gene in DCM). Over fifteen different zebrafish titin mutants have been generated either using morpholino knockdown to inhibit gene expression or introducing genetic mutations in regions that interact with different sarcomeric structures, including the Z-disc, I-band, A-band, and the I/A junction [67–69]. More recently, CRISPR/Cas9 has been used to generate a Nexilin knockout model, which exhibited reduced contractility and compensatory sarcomeric protein upregulation, [45] and LMNA mutants, showing early skeletal muscle damage with mild and transient cardiac defects [46]. Similar approaches, using either morpholino knockdown or the knock-in of mutations identified in families, have been used to generate zebrafish models of filamin C (FLNC) DCM, which have pointed to *FLNC* haploinsufficiency as a major mechanism of DCM [70]. A few studies generated zebrafish models of HCM due to mutations in sarcomere and non-sarcomeric genes, connected to either metabolism or mitochondrial function [71]. For instance, fish with *Mybpc3* mutations show hypertrophy and disarray early after postfertilization [72]. While zebrafish provide a powerful model to study isoform-specific functions of several sarcomeric proteins, several limitations remain, including the redundancy of sarcomeric genes (i.e., *ttna* and *ttnb*) and differences in isoform expression. In addition, zebrafish hearts are two-chambered, thus not suitable to model septal defects or conduction system disorders; their developmental timing differs from humans, and they remain regenerative in adulthood, limiting their relevance for adult-onset cardiac phenotypes.

15.4.2 Mouse

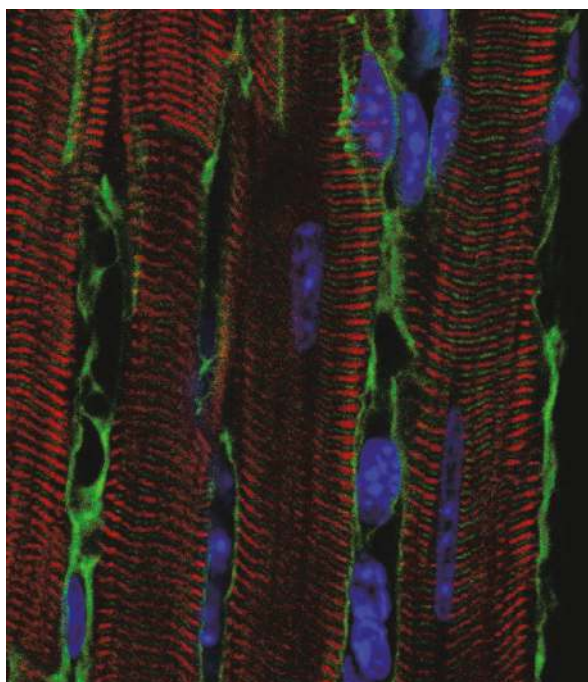
Multiple advantages make mouse models attractive for both mechanistic and translational studies, testing novel therapies for cardiomyopathies. These include the structural similarity with the human heart, genomic homology, small size, and relatively short animal lifespan. At the same time, limitations remain, related to costs, differences in heart rate (500–600 bpm in mice vs. 60–80 bpm in humans), as well as differences in excitation–contraction kinetics, calcium handling, and sarcomeric protein isoforms (e.g., titin N2B/N2BA ratio) [47, 48]. Moreover, some human mutations are embryonically or perinatally lethal in mice, as in the case of filamin C [49] (Fig. 15.4).

Gene function can be studied by transgenic knock-in (humanized models) and knockout strategies, conditional gene targeting (tissue-specific and inducible transgene expression), or precise genome editing by CRISPR/Cas9.

15.4.2.1 Dilated Cardiomyopathy

Available mouse models include mutations in several genes encoding cytoskeletal, sarcomeric, and Z-disk proteins, such as titin, LMNA, sarcoglycan, tropomyosins, nebulin, and nexilin [73–76]. Titin remains one of the most studied cardiomyopathy genes, with knockouts and domain-specific deletions showing how its elastic regions regulate passive stiffness and sarcomere length [56–58, 77] and the pathogenetic role of TTN truncating variants (TTNtvs) exerting dominant-negative or “poison peptide” effects by integrating into sarcomeres [43, 52, 53]. In the case of

Fig. 15.4 Immunostaining of in vivo adult mouse normal cardiac tissue, showing adult cardiomyocytes with mature, organized sarcomeric myofibrils. Red = titin (M band), green = alpha-actinin (Z disk), blue = DAPI



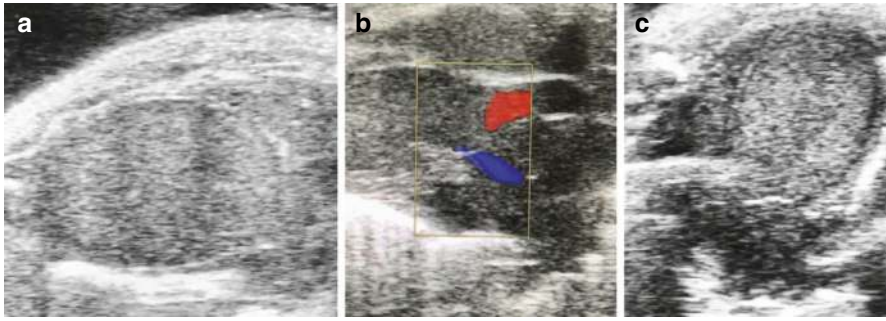


Fig. 15.5 Echocardiography in a neonatal-juvenile murine model of dilated cardiomyopathy (DCM) induced by titin downregulation. DCM was induced by AAV-mediated delivery of an shRNA targeting titin. (a) Parasternal long-axis view showing severe left ventricular dilation with a spherical remodeling pattern. (b) Color Doppler imaging demonstrating significant mitral regurgitation (blue). (c) Apical view of the same model, confirming left ventricular dilation

LMNA-related DCM, the ubiquitous expression of LMNA makes it difficult to distinguish cardiac-specific from systemic mechanisms in germline mutated mouse lines [63, 78]. Cardiac-specific transgenic models were generated by expressing mutant LMNA under a cardiomyocyte-specific promoter [79].

In general, most DCM models display ventricular dilation and wall thinning, associated with loss of cardiac muscle mass. These models highlighted novel DCM mechanisms, including impaired Z-disk assembly, altered apoptotic responses, disrupted myofibrillogenesis, and protein aggregation [73, 80] and the contribution of non-myocyte populations [81] (Fig. 15.5).

15.4.2.2 Hypertrophic Cardiomyopathy

HCM genes predominantly encode for sarcomeric proteins, including α -myosin heavy chain (α -MHC), α -tropomyosin, troponins, and myosin-binding protein C (MYBPC3). Both MYBPC3 KO and truncation models reproduce the hypertrophic phenotype, diastolic dysfunction, fibrosis, and sarcomere disarray [64, 82]. In contrast, DCM-associated MYH7 mutations remain challenging to model in mice, as they predominantly express a different myosin isoform in adulthood (Myh6). Existing models either introduce human Myh7 mutations (i.e., R403Q) into the endogenous *Myh6* gene, or express mutant *MYH7* as a transgene. In both cases, mice exhibited hypercontractility and increased ATP demand, [65] and they contributed to demonstrating that myocardial hypertrophy is a direct consequence of hypercontractility rather than a compensatory response to impaired contractile function. Most HCM models exhibit abnormal Ca^{2+} handling in cardiomyocytes well before structural alterations, pointing to diastolic dysfunction as an early and direct effect of HCM mutations. Progressive myocardial fibrosis, a hallmark of human HCM, develops later in these models, and it leads to cardiac arrhythmias and sudden cardiac death.

15.4.2.3 Restrictive Cardiomyopathy

Restrictive cardiomyopathy (RCM) is a less common but most severe form of cardiomyopathy, characterized by impaired ventricular relaxation due to increased myocardial stiffness and elevated ventricular pressure, with minimal alterations in myofibrillar organization and structural CM abnormalities. Mouse models able to reproduce the human disease phenotype have been generated with mutations in genes encoding for sarcomeric proteins, including troponins, [83] myosin, and myopalladin (MYPN) [84].

15.4.2.4 Arrhythmogenic Cardiomyopathy

Models of arrhythmogenic ventricular cardiomyopathy (ARVC) were generated in mice by introducing mutations in genes encoding desmosomal (DSP, PKP, DSC, DSG, and JUP) and non-desmosomal (RYR2, TMEM43, and ZASP) proteins [85, 86]. Major structural and functional alterations include progressive loss of cardiomyocytes, probably due to their apoptosis or necrosis, and replacement by fibrofatty tissue, primarily in the right ventricle (RV), with left ventricle (LV) involvement in later stages of the disease.

15.4.3 Large Animals

Large animals offer the best physiological, genetic and anatomical parallels to human heart disease. Naturally occurring cardiomyopathies are commonly observed in both canine and feline species. HCM is prevalent in pet cats, whereas DCM is more frequent in dogs [87]. Maine Coon and Ragdoll cats frequently harbor MYBPC3 mutations [88]. On the other hand, canine DCM models, recapitulating the human disease, have mutations in phospholamban (PLN), titin (TTN), dystrophin (DMD), RNA-binding motif protein 20 (RBM20), and desmin (DES) [29, 39–41] [81, 89–91].

Naturally occurring HCM and DCM have been reported also in pigs. Spontaneous HCM in pigs is characterized by hypertrophy and fibrosis [92]. However, most information has been obtained in transgenic pigs carrying mutations in MYBPC3 or MYH7, the most frequently mutated genes in human HCM. For instance, the introduction of the R723G mutation in MYH7 by gene or base editing resulted in perinatal death and classic HCM features, including myocyte disarray and abnormal nuclear morphology [93, 94]. DCM pig models were also generated, as in the case of gene-edited pigs with the pathogenic R636S RBM20 variants, [95] which showed massive granule accumulation in the sarcoplasm, as observed in patient myocardium and their iPS-CMs.

Nonhuman primate (NHP) models remain limited. Rarely, MYBPC3 mutations have been observed in macaques with spontaneous HCM. Recently, the first gene-edited NHP model of DCM was generated via base editing in cynomolgus monkeys carrying a splice-site LMNA mutation (equivalent to the human 357-2A > G

variant). These animals were followed for 4 years, showing phenotypes closely resembling human LMNA-associated DCM [96].

Despite their translational relevance, the high costs and long experimental timelines continue to limit the widespread use of large animal models for studying cardiomyopathy mechanisms or testing novel therapies.

Conclusions

Recent research in genetic cardiomyopathies has relied on a variety of experimental models, each offering distinct advantages and limitations. Animal models, particularly mice, have been historically considered crucial for *in vivo* investigation, providing a unique opportunity to study complex organ-level physiology, long-term disease progression, and therapeutic interventions. Despite the invaluable mechanistic insights, species-specific differences in cardiac physiology and genetics can limit the direct translation of animal findings to humans [97]. Moreover, adherence to the principles of the three Rs (Replacement, Reduction, and Refinement) encourages researchers to minimize animal use [17]. Complementation of animal models and human cell systems stands as the most reliable framework to fully understand cardiomyopathy mechanisms and assess the efficacy of novel therapies.

15.5 A Virtuous Example: Mavacamten

Mavacamten exemplifies a successful translational pathway in hypertrophic cardiomyopathy. Preclinical work identified excessive myosin cross-bridge formation as a driver of hypercontractility, and selective myosin inhibition was shown to normalize sarcomeric mechanics by stabilizing the super-relaxed state of myosin [98]. Mechanistic and structural studies of cardiac myosin modulation further supported translation of sarcomere-targeted therapies [99, 100].

In isolated cardiomyocytes from HCM models, mavacamten reduces contractile tension and restores calcium sensitivity [98, 100]. In animal models carrying pathogenic sarcomere mutations, it improves diastolic relaxation, reduces hypertrophy, and attenuates fibrosis, providing a compelling rationale for clinical translation.

The pivotal EXPLORER-HCM trial demonstrated significant improvements in exercise capacity, symptoms, and left ventricular outflow tract gradient reduction [101]. Long-term extension studies (MAVA-LTE) reported sustained efficacy and safety over several years, [102] while real-world registries confirmed symptomatic improvement in a substantial proportion of treated patients [103]. These data informed incorporation of mavacamten into international guidance for symptomatic obstructive HCM.

Importantly, patient selection remains critical. In nonobstructive HCM, the phase III ODYSSEY-HCM trial did not show significant benefit in exercise capacity or patient-reported outcomes, underscoring phenotype-specific therapeutic effects [104].

Beyond HCM, translational cardiology is rapidly expanding disease-modifying options. In transthyretin amyloid cardiomyopathy (ATTR-CM), stabilizers such as acoramidis have shown clinically meaningful benefit [105]. Gene therapy programs

using AAV vectors and antisense oligonucleotides are progressing in selected genetic cardiomyopathies, whereas genome-editing approaches remain largely pre-clinical with promising yet still uncertain clinical applicability [12]. Together, these advances illustrate the future potential of precision cardiology built on mechanistic understanding, robust models, and data-driven patient stratification.

15.6 Innovative Therapeutic Approaches for Cardiomyopathies

In recent years, several innovative therapeutic strategies have emerged, aiming at modifying disease progression. These approaches were initially focused on cell-based therapies to replace the lost myocardium, while they are currently evolving towards gene therapies, RNA-targeted strategies, such as exon skipping, and genome editing technologies, like CRISPR, base editing, and prime editing. These groundbreaking interventions offer the prospect of disease-modifying or even curative treatments for inherited cardiomyopathies, moving the field closer to precision and regenerative cardiology [106].

15.6.1 Cell Therapies

Cell-based therapies for cardiac repair involve transplantation of either autologous or allogeneic cells, including induced pluripotent stem cells (iPSCs) or embryonic stem cells (ESCs), bone-marrow-derived hematopoietic and mesenchymal stem cells, and cardiac progenitors [107]. To what extent these strategies induce direct myocardial remuscularization and/or act in a paracrine manner to stimulate endogenous repair remains a matter of debate.

Riding the wave of initial excitement on stem cell plasticity, in the early 2000s, several studies used different types of stem cells to induce cardiac regeneration, prompting numerous clinical trials [108, 109]. However, the ability of the transplanted cells to repopulate the cardiac tissue, their transdifferentiation, and regenerative capacity were rapidly disproved [110, 111]. In recent years, multiple studies have established that these cells release a range of bioactive factors (cytokines, growth factors, lipids, etc.) that exert cardioprotective actions on surrounding myocardium, possibly enhancing repair and improving contractile function [112].

While cell therapy has been mainly proposed and tested for ischemic heart disease, a few applications targeted either DCM or HCM, with inconsistent outcomes. Several meta-analyses [113, 114] concluded that randomized controlled trials have shown only modest improvements in LVEF without significant benefits in long-term clinical outcomes, consistent with the rapid cell loss after transplantation. A major problem in interpreting these results lies in the heterogeneity of the patient populations, in terms of age, disease severity, comorbidities, and genetic background, and the type of stem cells used. While most systematic reviews report

favorable profiles for stem cell therapy, with low incidence of adverse effects, the long-term efficacy and potential risks remain inadequately studied, possibly associated with the tumorigenic potential of pluripotent stem cells and the immature phenotype of iPSC-derived cardiomyocytes, posing a high risk of arrhythmia [107, 115].

15.6.1.1 Gene Therapy

As inherited cardiomyopathies are due to specific genetic mutations/variants, the possibility of restoring the missing cellular function using gene therapy stands as a unique curative opportunity.

Historically, vectors of choice for cardiac gene therapy have been based on Adeno-Associated Virus (AAV), due to their high tropism for cardiomyocytes and long-term transgene expression [116]. Recent advances in LNP formulations are paving the way to innovative mRNA-based approaches for gene replacement.

In haploinsufficiency, therapeutic strategies aim to restore normal protein levels through gene supplementation, as in the case of AAV-mediated delivery of *MYBPC3*, *LMNA*, or *DES* in mice. In knockout mouse models, a single administration of the therapeutic vector restored protein levels and cardiac function, with durable effects persisting for over a year [117–119].

Another example is arrhythmogenic right ventricular cardiomyopathy (ARVC), an inherited disorder characterized by ventricular arrhythmias and progressive cardiac dysfunction. The most frequent genetic cause (~40% of cases) is a heterozygous mutation in the desmosomal gene *PKP2* (plakophilin-2), leading to haploinsufficiency, disrupted desmosomes and other intercalated disc structures, and impaired cardiomyocyte electrical coupling. In mutant mice, AAV9-mediated *PKP2* restoration increased desmosomal protein levels and improved cardiac function [120].

The limited cargo size of AAV vectors represents a major limitation in several instances. As mentioned, truncating mutations in the titin (*TTN*) gene are the most common genetic cause of dilated cardiomyopathy (DCM), but its size is not compatible with AAV encapsidation. To solve this limitation, truncated but functional protein isoforms can be used, as in the case of mini- and micro-dystrophins for Duchenne muscular dystrophy (DMD). After demonstration of partial restoration of dystrophin expression and function in small and large animal models, several companies have invested many resources in pushing DMD gene therapy forward, leading to several phase 2/3 clinical trials and regulatory approval [121–123]. Future studies are needed to clarify whether similar approaches can be applied to other large genes, whose mutations lead to inherited cardiomyopathies.

In addition to cDNAs to replace missing cellular functions, therapeutic nucleic acids also include short stretches of DNA/RNA (oligonucleotides) designed to induce the skipping of a mutated exon or the silencing of mutated alleles. This latter approach aims to mitigate the deleterious effects of dominant-negative mutations. Indeed, allele-specific silencing via ASOs or siRNAs/shRNA has proven effective in cardiomyopathies, as in the case of *PLN* and *Myh6* variants [124]. *PLN* regulates SERCA2a-mediated Ca^{2+} cycling within the sarcoplasmic reticulum. The R14del *PLN* variant induces protein aggregation and fibrosis, causing severe dilated

cardiomyopathy [125]. In a PLN mouse model, silencing of the mutated allele via ASO therapy prevented protein aggregation, preserved cardiac function, and improved survival [126]. Similarly, AAV-mediated RNA interference reduced the expression of the pathogenic allele by ~25% and prevented HCM development for at least six months in the Myh6 R403Q mutant mouse [127].

Exon skipping, by chemically modified oligonucleotides, has been proposed and used to restore the expression of functional, yet shorter, variants of mutated proteins. This approach has been successfully used to restore MYBPC3 expression and ameliorate cardiac dysfunction in a MYBPC3 knock-in mouse model of HCM [128]. In the case of *dystrophin*, four different oligonucleotides, targeting exons 51, 53 and 45 of the *dystrophin* gene, have been recently approved by the Food and Drug Administration, based on their ability to increase dystrophin protein levels in DMD patients. Major limitations include the high cost of production, which is linked to the need to design mutation-specific therapies (less than 30% of DMD mutations are currently covered by available oligonucleotides targeting exons 51, 53 and 45), and by the requirement for repeated systemic administration due to the transient therapeutic effect. Additionally, skipping efficiency varies across different muscle groups, with cardiac muscle posing a particularly significant challenge [129].

More recently, mRNA-based delivery of a wild-type copy of the mutated gene has been proposed and proven to be feasible and effective in a mouse model of ARVC. In desmocollin-2-KO (*Dsc2*) mice, which recapitulate the ventricular dilation and dysfunction characteristic of the disease, a single administration of *Dsc2* mRNA restored normal cardiac size and function for up to three months [130]. mRNA delivery is particularly attractive in the case of defects in large genes, difficult to pack into viral vectors. However, the lack of tissue specificity and the transient expression of mRNA remain major barriers to the widespread use of these approaches [131–133].

15.6.1.2 Gene Editing

Gene editing holds promise for the permanent correction of mutations underlying genetic cardiomyopathies. CRISPR/Cas9-based gene editing has demonstrated restoration of dystrophin expression in both patient-derived iPSCs and DMD animal models [134]. However, precise correction via homology-directed repair is largely inaccessible in terminally differentiated cardiomyocytes, leaving the error-prone non-homologous end-joining as the dominant way of DNA repair.

Emerging approaches such as base editing (BE) and prime editing (PE) avoid the need for double-stranded breaks and offer higher precision [135]. BE combines a deaminase enzyme with either a Cas9 nickase or an inactivated Cas9 to enable precise, sgRNA-guided nucleotide conversion in the genome. Cytosine base editors (CBEs) convert C to T, while adenine base editors (ABEs) convert A to G at the target site [136]. This approach is particularly suited for correcting point mutations, as in the case of the MYH7 R403Q substitution involved in HCM [137]. Using both iPSCs and a humanized mouse model carrying the MYH7 mutation, Chai et al. demonstrated ABE efficacy in correcting the genetic defect, normalizing contractile function and ameliorating the hypertrophic phenotype [138]. Despite its efficacy,

unintended editing events, targetability, and delivery remain a challenge [134, 139]. PE employs a Cas9 nickase–reverse transcriptase complex and a prime-editing guide RNA to enable versatile and targeted sequence correction, not limited to point mutations but also including short deletions and insertions [140]. This approach was proved effective in iPSCs, repairing the Δ Ex51 DMD mutation (exon 51 deletion) by restoring the normal open reading frame, resulting in the expression of the wild-type DMD protein. This repair rescued the arrhythmic phenotype in mutant cardiomyocytes, as demonstrated by normalized calcium transients following editing [141]. PE editing flexibility and capacity to correct indels, along with minimized off-target effects compared to other gene-editing methods, make it a promising therapeutic approach. Its application to inherited cardiomyopathies is constrained by the low efficiency, possible safety issues, and limited delivery to cardiomyocytes [142].

Efficient delivery of editing components into target cells is essential for the success of the therapy. While AAV vectors have been extensively used, their limited cargo size precludes them from carrying BE and PE components [143]. In contrast, lipid nanoparticles offer the potential to deliver large cargos, while displaying lower immunogenicity and easier large-scale manufacturing. LNPs usually consist of four main lipid components, such as ionizable lipids, helper lipids, cholesterol, and polyethylene glycol (PEG) [143]. The natural tendency of LNPs to accumulate in hepatocytes via APOE-mediated uptake importantly limits their application to the heart [144]. Efforts to modify lipid composition, incorporate tissue-specific ligands, or bypass liver uptake to enhance cardiomyocyte targeting are currently ongoing [145]. While the transient gene expression conferred by LNPs represents a limitation for traditional gene therapy, which requires sustained gene expression to achieve therapeutic benefit, [146] it represents an advantage in the case of gene editing, as the single-shot correction of the mutation is expected to lead to permanent restoration of protein expression.

Conclusion

The development of novel techniques, together with advances in genetic and molecular research, necessitates a multimodal approach to patient evaluation and management. After defining the genetic substrate, comprehensive patient characterization and individualized risk stratification require multimodal data integration, including the following: (i) circulating biomarkers (high-sensitivity troponin and NT-proBNP, as well as emerging markers, such as circulating miRNAs and extracellular vesicle proteomes); (ii) advanced imaging (strain echocardiography; cardiac magnetic resonance with native T1/T2 mapping, extracellular volume quantification, and emerging microstructural methods); and (iii) integrated genomic and multi-omics analyses (variant-burden testing, polygenic scores, single-cell transcriptomics, and spatial proteomics). Such multimodal approaches enable more accurate predictive modeling, refine the timing of interventions, and improve trial enrichment.

Artificial intelligence (AI) represents an additional translational layer, moving insights from *in silico* models to clinical practice. Algorithms for ECG interpretation and early detection of left ventricular dysfunction are already entering real-world workflows [147, 148]. In cardiomyopathies, AI can support diagnosis, differential diagnosis, risk stratification, and therapeutic personalization. In

imaging, AI-based tools can reduce underdiagnosis of uncommon conditions and accelerate specialist-level interpretation; for example, deep-learning models have demonstrated robust performance for echocardiographic detection of cardiac amyloidosis [149, 150]. Multimodal approaches integrating ECG and imaging can improve discrimination between HCM and other causes of left ventricular hypertrophy, such as hypertensive heart disease [151].

An emerging paradigm is the concept of the “digital twin,” which integrates genetic, molecular, imaging, clinical, and environmental data into a patient-specific computational model capable of simulating disease progression and therapeutic response [152]. Such platforms aim to move beyond static risk prediction toward dynamic, individualized decision support. Initiatives such as SMASH-HCM exemplify early efforts to implement hybrid digital twin solutions in inherited cardiomyopathies, with the long-term goal of guiding personalized surveillance strategies and treatment selection.

Translational cardiology in genetic cardiomyopathies is evolving from phenotype-driven management toward mechanism-based, personalized intervention. Advances in genetics, experimental modeling, multi-omics integration, and artificial intelligence are converging to enable earlier diagnosis, improved risk stratification, and disease-modifying therapies. Sustained integration of these approaches will be essential to realize the full promise of precision cardiology.

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Critical Clinical Approach and Future Perspectives

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Marco Merlo  and Gianfranco Sinagra 

The rapid expansion of imaging technologies and genetic testing has undeniably transformed the field of cardiomyopathies. The modern challenge is no longer simply recognizing the disease but interpreting complex and sometimes discordant information in a coherent and patient-centered way. The abundance of data—structural, functional, molecular—requires synthesis. Advanced tools can identify subtle abnormalities, borderline phenotypes, and genetic variants whose meaning is not always straightforward. The risk of overdiagnosis, unnecessary anxiety, or inappropriate restriction of lifestyle—particularly in young individuals—must be carefully balanced against the risk of under-recognition. Clinical judgment remains the compass that guides interpretation. In this evolving landscape, multidisciplinary collaboration is becoming increasingly important. Cardiologists, geneticists, radiologists, and specialized nurses must work together in structured pathways. Cardiomyopathies often require shared decision-making, especially when choices involve defibrillator implantation, sports participation or family screening. The future of care lies not only in technological progress but in integrated expertise.

Looking ahead, artificial intelligence (AI) is poised to play a growing role in the field. Machine learning algorithms are already being applied to ECG interpretation, echocardiographic quantification, and CMR image analysis, with the potential to detect patterns invisible to the human eye. AI may enhance early diagnosis, improve risk stratification and support personalized prognostic models by integrating clinical, imaging, and genetic data. Large-scale data analysis could refine our understanding of genotype–phenotype correlations and help reclassify variants currently considered uncertain. However, AI should be viewed as a support system rather than a replacement for clinical reasoning. Algorithms depend on the quality of the data

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on which they are trained and may reproduce existing biases or limitations. The future challenge will be to integrate AI outputs into clinical workflows without diminishing the role of critical interpretation. Another promising perspective lies in precision medicine. As knowledge of molecular pathways expands, targeted therapies—already a reality in selected genetic conditions—are likely to increase. Gene-based and RNA-targeted treatments represent a frontier that may redefine management in the coming decades. In parallel, earlier identification of at-risk individuals through family screening and improved phenotypic characterization may allow preventive strategies before overt disease develops. Ultimately, the future of cardiomyopathy management will not be defined solely by technological innovation. The integration of advanced imaging, genetics, artificial intelligence, and emerging therapies must be guided by a disciplined clinical mindset. The goal is not simply to detect more abnormalities but to improve outcomes, quality of life and family care. In this sense, the most important future perspective remains constant: a critical, thoughtful, and patient-centered approach capable of transforming complex data into meaningful clinical decisions.

This book reflects four decades of clinical work and scientific progress driven by the Cardiomyopathy Registry of the University of Trieste, founded by Professor Fulvio Camerini. Our gratitude goes to the researchers and clinicians, as well as to the patients and their families, who have contributed in various ways to the collection of data and clinical events that form the foundation for advancing knowledge and fostering progress in medicine, for the benefit of patients and their families.

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