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ESC GUIDELINES

2023 ESC Guidelines for the management of cardiomyopathies

Developed by the task force on the management of cardiomyopathies of the European Society of Cardiology (ESC)

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All experts involved in the development of these guidelines have submitted declarations of interest. These have been compiled in a report and simultaneously published in a supplementary document to the guidelines. The report is also available on the ESC website www.escardio.org/Guidelines

See the *European Heart Journal* online for supplementary documents that include background information and evidence tables.

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Abbreviations and acronyms

18F-FDG	18F-fluorodeoxyglucose
2D	Two-dimensional
3D	Three-dimensional
^{99m}Tc	^{99m}Technetium
AAD	Antiarrhythmic drug
ABC	Atrial Fibrillation Better Care approach
ACE	Angiotensin-converting enzyme
ACE-I	Angiotensin-converting enzyme inhibitor
ACM	Arrhythmogenic cardiomyopathy
AD	Autosomal dominant
AED	Automated external defibrillator
AF	Atrial fibrillation
AFD	Anderson–Fabry disease
AHA/ACC	American Heart Association/American College of Cardiology
AL	Monoclonal immunoglobulin light chain amyloidosis
ALCAPA	Anomalous left coronary artery from the pulmonary artery
ALT	Alanine aminotransferase
ALVC	Arrhythmogenic left ventricular cardiomyopathy
APHRS	Asia Pacific Heart Rhythm Society
AR	Autosomal recessive
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
ARVC	Arrhythmogenic right ventricular cardiomyopathy
ASA	Alcohol septal ablation
AST	Aspartate transaminase
ATPase	Adenosine triphosphatase
ATTR	Transthyretin amyloidosis
ATTR-CA	Transthyretin cardiac amyloidosis
ATTR-CM	Transthyretin amyloid cardiomyopathy
ATTRv	Hereditary transthyretin amyloidosis
ATTRwt	Wild-type OR Acquired transthyretin amyloidosis
AV	Atrioventricular
b.p.m.	Beats per minute
BAG3	BAG cochaperone-3
BNP	Brain natriuretic peptide
CAD	Coronary artery disease
CCB	Calcium channel blocker
CHA_2DS_2-VASc	Congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74, sex category (female) (score)
CHD	Congenital heart disease
CK	Creatinine kinase
CMR	Cardiac magnetic resonance
COVID-19	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection
CPET	Cardio-pulmonary exercise testing
CPR	Cardio-pulmonary resuscitation
CRT	Cardiac resynchronization therapy
CrCl	Creatinine clearance
CT	Computed tomography
CTCA	Computed tomography coronary angiography
DBS	Deep brain stimulation
DCM	Dilated cardiomyopathy
DES	Desmin
DMD	Duchenne muscular dystrophy
DOAC	Direct-acting oral anticoagulant
DPD	3,3-diphosphono-1,2-propanodicarboxylic acid
DSP	Desmoplakin
EAST-AFNET	Early Treatment of Atrial Fibrillation for Stroke Prevention Trial
ECG	Electrocardiogram
ECHO	Echocardiogram
ECV	Extracellular volume
EF	Ejection fraction
EHRA	European Heart Rhythm Association
EMB	Endomyocardial biopsy
EMF	Endomyocardial fibrosis
EORP	EURObservational Research Programme
ERN	European Reference Network
ERT	Enzyme replacement therapy
FLNC	Filamin C
FRA	Friedreich ataxia
FTX	Frataxin
Gb3	Globotriaosylceramide
GDMT	Guideline-directed medical therapy
GSD	Glycogen storage disorder
GWAS	Genome-wide association study
HbA1c	Haemoglobin A1C
HBP	His-Bundle pacing
HCM	Hypertrophic cardiomyopathy
HCMR	Hypertrophic Cardiomyopathy Registry
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HMDP	Hydroxymethylene diphosphonate
HR	Hazard ratio
HRS	Heart Rhythm Society
hs-cTnT	High-sensitivity cardiac troponin T
ICD	Implantable cardioverter defibrillator
INR	International normalized ratio
ITFC	International Task Force Consensus statement
IVF	*In vitro* fertilization
LA	Left atrium
LAHRS	Latin American Heart Rhythm Society
LBBB	Left bundle branch block
LGE	Late gadolinium enhancement
LMNA	Lamin A/C
LMWH	Low-molecular-weight heparin
LSD	Lysosomal storage disease
LV	Left ventricular
LVAD	LV assist device
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy

LVNC Left ventricular non-compaction
LVOT Left ventricular outflow tract
LVSD Left ventricular systolic dysfunction
LVOTO Left ventricular outflow tract obstruction
MCS Mechanical circulatory support
MELAS Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (syndrome)
MERRF Mitochondrial epilepsy with ragged-red fibres
MGUS Monoclonal gammopathy of undetermined significance
MICONOS Mitochondrial Protection with Idebenone in Cardiac or Neurological Outcome (study group)
MLVWT Maximum left ventricular wall thickness
MRA Mineralocorticoid receptor antagonist
MRI Magnetic resonance imaging
MV Mitral valve
mWHO Modified World Health Organization (classification)
NCS Non-cardiac surgery
NDLVC Non-dilated left ventricular cardiomyopathy
NGS Next-generation sequencing
NSML Noonan syndrome with multiple lentigines
NSVT Non-sustained ventricular tachycardia
NT-proBNP N-terminal pro-brain natriuretic peptide
NYHA New York Heart Association
OMT Optimal medical therapy
P/LP Pathogenic/likely pathogenic
PES Programmed electrical stimulation
PET Positron emission tomography
PKP2 Plakophilin 2
PLN Phospholamban
PPCM Peripartum cardiomyopathy
PRKAG2 Protein kinase AMP-activated non-catalytic subunit gamma 2
PRS Polygenic risk scores
PTH Parathyroid hormone
PVR Pulmonary vascular resistance
PYP Pyrophosphate
QoL Quality of life
QRS Q, R, and S waves of an ECG
RAS-HCM RASopathy-associated HCM
RBBB Right bundle branch block
RBM20 RNA binding motif protein
RCM Restrictive cardiomyopathy
RCT Randomized controlled trial
RV Right ventricular
RVEF Right ventricular ejection fraction
RVOTO Right ventricular outflow tract obstruction
RWMA Regional wall motion abnormality
SAECG Signal-averaged electrocardiogram
SAM Systolic anterior motion
SCD Sudden cardiac death
SGLT2i Sodium–glucose co-transporter 2 inhibitor
SMVT Sustained monomorphic ventricular tachycardia
SPECT Single-photon emission computed tomography
SRT Septal reduction therapy
TIA Transient ischaemic attack
TMEM43 transmembrane protein 43
TRED-HF Therapy withdrawal in REcovered Dilated cardiomyopathy—Heart Failure
TTE Transthoracic echocardiography
TTN Titin
TTNtv Titin gene truncating variants
TTR Transthyretin
TWI T wave inversion
UFH Unfractionated heparin
VALOR-HCM A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy
VE Ventricular extrasystole
VF Ventricular fibrillation
VKA Vitamin K antagonist
VT Ventricular tachycardia
VUS Variant of unknown significance
WHO World Health Organization

1. Preamble

Guidelines evaluate and summarize available evidence with the aim of assisting health professionals in proposing the best diagnostic or therapeutic approach for an individual patient with a given condition. Guidelines are intended for use by health professionals and the European Society of Cardiology (ESC) makes its Guidelines freely available.

ESC Guidelines do not override the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable in each country to drugs and devices at the time of prescription, and, where appropriate, to respect the ethical rules of their profession.

ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated. ESC Policies and Procedures for formulating and issuing ESC Guidelines can be found on the ESC website (https://www.escardio.org/Guidelines).

The Members of this Task Force were selected by the ESC to represent professionals involved with the medical care of patients with this pathology. The selection procedure aimed to include members from across the whole of the ESC region and from relevant ESC Subspecialty Communities. Consideration was given to diversity and inclusion, notably with respect to gender and country of origin. The Task Force performed a critical evaluation of diagnostic and therapeutic approaches, including assessment of the risk-benefit ratio. The strength of every recommendation and the level of evidence supporting them were weighed and scored according to predefined scales as outlined below. The Task Force followed ESC voting procedures, and all approved recommendations were subject to a vote and achieved at least 75% agreement among voting members.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. Their declarations of interest were reviewed according to the ESC declaration of interest rules and can be found on the ESC website (http://www.escardio.org/Guidelines) and have been compiled in a report published in a supplementary document with the guidelines. The Task Force received its

Table 1 Classes for recommendations

Classes of recommendations	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

Table 2 Levels of evidence

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

entire financial support from the ESC without any involvement from the healthcare industry.

The ESC Clinical Practice Guidelines (CPG) Committee supervises and co-ordinates the preparation of new guidelines and is responsible for the approval process. ESC Guidelines undergo extensive review by the CPG Committee and external experts, including members from across the whole of the ESC region and from relevant ESC Subspecialty Communities and National Cardiac Societies. After appropriate revisions, the guidelines are signed off by all the experts involved in the Task Force. The finalized document is signed off by the CPG Committee for publication in the *European Heart Journal*. The guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their writing. Tables of evidence summarizing the findings of studies informing development of the guidelines are included. The ESC warns readers that the technical language may be misinterpreted and declines any responsibility in this respect.

Off-label use of medication may be presented in this guideline if a sufficient level of evidence shows that it can be considered medically appropriate for a given condition.

However, the final decisions concerning an individual patient must be made by the responsible health professional giving special consideration to:

- The specific situation of the patient. Unless otherwise provided for by national regulations, off-label use of medication should be limited to situations where it is in the patient's interest, with regard to the quality, safety, and efficacy of care, and only after the patient has been informed and has provided consent.
- Country-specific health regulations, indications by governmental drug regulatory agencies, and the ethical rules to which health professionals are subject, where applicable.

2. Introduction

The objective of this European Society of Cardiology (ESC) Guideline is to help healthcare professionals diagnose and manage patients with cardiomyopathies according to the best available evidence. Uniquely for relatively common cardiovascular diseases, there are very few randomized controlled clinical trials in patients with cardiomyopathies. For this reason, the majority of the recommendations in this guideline are based on observational cohort studies and expert consensus opinion. The aim is to provide healthcare professionals with a practical diagnostic and treatment framework for patients of all ages and, as an increasing number of patients have a known genetic basis for their disease, the guideline also considers the implications of a diagnosis for families and provides advice on reproduction and contraception. As cardiomyopathies can present at any age and can affect individuals and families across the entire life course, this guideline follows the principle of considering cardiomyopathies in all age groups as single disease entities, with recommendations applicable to children and adults with cardiomyopathy throughout, while accepting that the evidence base for many of the recommendations is significantly more limited for children. Age-related differences are specifically highlighted.

This is a new guideline, not an update of existing guidelines, with the exception of the section on hypertrophic cardiomyopathy (HCM), in which we have provided a focused update to the *2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy*.[1] As such, most of the recommendations in this guideline are new. It is beyond the scope of this guideline to provide detailed descriptions and recommendations for each individual cardiomyopathy phenotype; instead, the aim is to provide a guide to the diagnostic approach to cardiomyopathies, highlight general evaluation and management issues, and signpost the reader to the relevant evidence base for the recommendations.

Adoption of morphological and functional disease definitions means that the number of possible aetiologies is considerable, particularly in young children. As it is impractical to provide an exhaustive compendium of all possible causes of cardiomyopathy, the guideline focuses on the most common disease phenotypes, but additional references for less common disorders are also provided. Similarly, treatment recommendations focus largely on generic management issues but refer to specific rare diseases when appropriate. The central illustration (*Figure 1*) highlights key aspects in the evaluation and management of cardiomyopathies addressed in this guideline.

This is the first major international guideline to address cardiomyopathies other than HCM. Other major innovations include:

- A new phenotypic description of cardiomyopathies, including updated descriptions of dilated and non-dilated left ventricular (LV) cardiomyopathy phenotypes, and highlighting the key role of ventricular myocardial scar assessment using cardiac magnetic resonance (CMR) imaging.
- A focus on the patient pathway, from presentation, through initial assessment and diagnosis, to management, highlighting the importance of considering cardiomyopathy as a cause of common clinical presentations (e.g. heart failure, arrhythmia) and the importance of utilizing a multiparametric approach following the identification of the presenting phenotype to arrive at an aetiological diagnosis.
- Updated recommendations for clinical and genetic cascade screening for relatives of individuals with cardiomyopathies.
- A focus on cardiomyopathies across the life course, from paediatric to adult age (including transition), and considering the different clinical phases (e.g. concealed, overt, end stage).
- New recommendations on sudden cardiac death (SCD) risk stratification for different cardiomyopathy phenotypes, including in childhood, and highlighting the important role of genotype in the assessment of sudden death risk.
- Updated recommendations for the management of left ventricular outflow tract obstruction (LVOTO) in HCM.
- A multidisciplinary approach to cardiomyopathies that has the patient and their family at its heart.

3. Phenotypic approach to cardiomyopathies

In medicine, classification systems are used to standardize disease nomenclature by grouping disorders according to shared characteristics. In 2008, the ESC promoted a pragmatic system for the clinical description of cardiomyopathies in which a historical focus on ventricular morphology and function was maintained, while signposting aetiological diversity through subdivision into genetic and non-genetic subtypes.[2] Since then, knowledge of cardiomyopathies has increased substantially through the application of new imaging and molecular technologies.

In this guideline, the Task Force took a number of considerations into account when deciding its approach to disease description. These included: (i) a historical legacy which, while still useful, has led to contradictory and confusing terminology in many situations; (ii) the evolving nature of cardiomyopathies over a lifetime; (iii) aetiological complexity with multiple disease processes contributing to disease phenotypes;

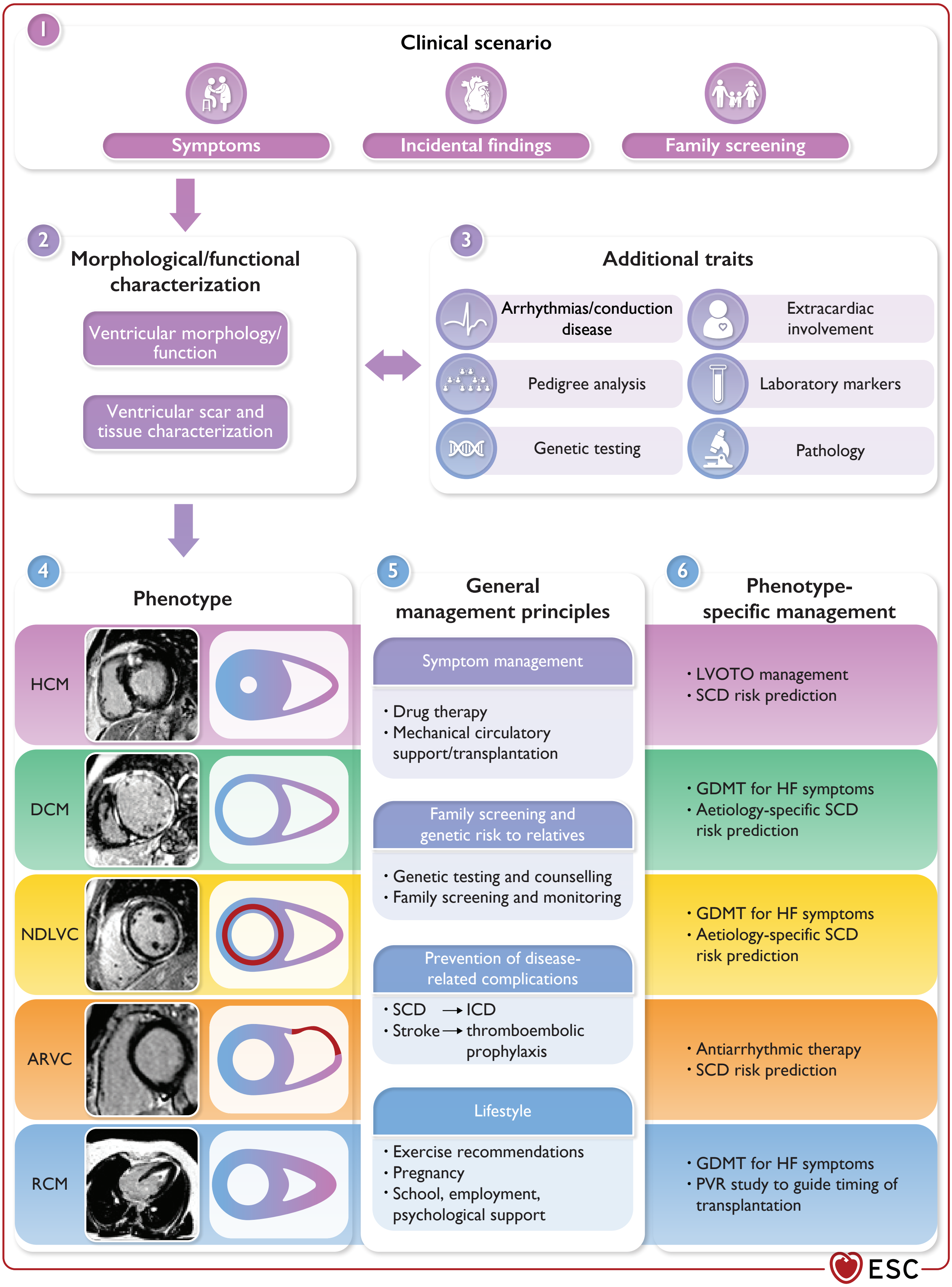

Figure 1 Central illustration. Key aspects in the evaluation and management of cardiomyopathies. ARVC, arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; GDMT, guideline-directed medical therapy; HCM, hypertrophic cardiomyopathy; HF, heart failure ICD, implantable cardioverter defibrillator; LVOTO, left ventricular outflow tract obstruction; MCS, mechanical circulatory support; NDLVC, non-dilated left ventricular cardiomyopathy; PVR, pulmonary vascular resistance; RCM, restrictive cardiomyopathy; SCD, sudden cardiac death.

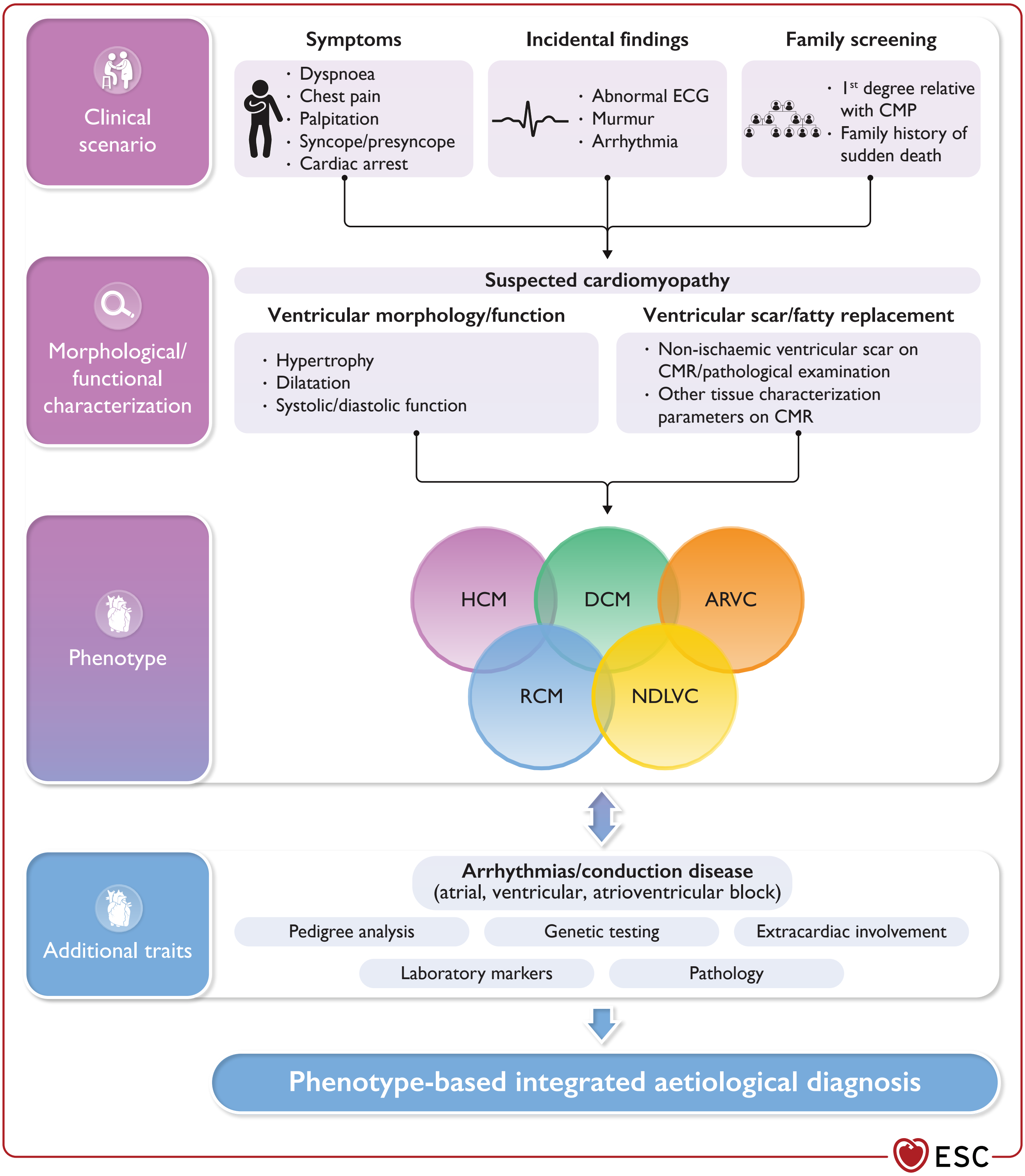

Figure 2 Clinical diagnostic workflow of cardiomyopathy. ARVC, arrhythmogenic right ventricular cardiomyopathy; CMP, cardiomyopathy; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; NDLVC, non-dilated left ventricular cardiomyopathy; RCM, restrictive cardiomyopathy.

(iv) differential disease expression in families; and (v) emerging aetiology-focused therapies.

The Task Force concluded that a single classification system that embraces all possible causes of disease and every clinical scenario remains an aspiration that is outside the scope of this clinical guideline. Instead, the Task Force updated the existing clinical classification to include new phenotypic descriptions and to simplify terminology, while simultaneously providing a conceptual framework for diagnosis and treatment. This nomenclature prompts clinicians to consider cardiomyopathy as the cause of several clinical presentations (e.g. arrhythmia, heart failure), and focuses on morphological and functional characteristics of the myocardium (*Figure 2*). It is important to recognize that different cardiomyopathy phenotypes may coexist in the same family, and that disease progression in an individual patient can include evolution from one cardiomyopathy phenotype to another. Nevertheless, the Task Force recommends an approach to disease nomenclature and diagnosis that is based on the predominant cardiac phenotype at presentation.

While recognizing the fact that genes encoding cardiac ion channels may be implicated in some patients with dilated cardiomyopathy (DCM), conduction disorders, and arrhythmias, the Task Force was not persuaded that there is sufficient evidence to consider cardiac channelopathies as cardiomyopathies, in keeping with the approach taken by other recent ESC Guidelines.[3]

The most important changes in this guideline relate to the group of conditions variously included under the umbrella term 'arrhythmogenic cardiomyopathies'. This term refers to a group of conditions that feature structural and functional abnormalities of the myocardium (identified by cardiac imaging and/or macroscopic and microscopic pathological investigation) and ventricular arrhythmia. This nosology has evolved in response to the recognition of the clinical and genetic overlap between right ventricular (RV) and LV cardiomyopathies, but a lack of a generally accepted definition has meant that the term encompasses a broad range of diverse pathologies and has introduced a number of inconsistencies and contradictions when applied in a clinical setting.[4] The term 'arrhythmogenic right ventricular (dysplasia/) cardiomyopathy' (ARVC) was originally used by physicians who first discovered the disease, in the pre-genetic and pre-CMR era, to describe a new heart muscle disease predominantly affecting the right ventricle, whose cardinal clinical manifestation was the occurrence of malignant ventricular arrhythmias. Subsequently, autopsy investigations, genotype–phenotype correlation studies and the increasing use of contrast-enhancement CMR led to the identification of fibro-fatty replacement of the myocardium as a key phenotypic feature of the disease that affects the myocardium of both ventricles, with LV involvement which may even exceed the severity of RV involvement. This has led to the catch-all term of arrhythmogenic cardiomyopathy (ACM), which represents the evolution of the original term of ARVC.[5] Consistent with its general approach, the Task Force agreed to highlight the vital importance of arrhythmia as a diagnostic red flag and prognostic marker across a range of clinical phenotypes, but did not recommend the use of the term ACM as a *distinct* cardiomyopathy subtype as it lacks a morphological or functional definition consistent with the existing classification scheme. While acknowledging that 'ACM' as an umbrella term that encompasses diverse clinical phenotypes has been previously used, this decision will, it is hoped, help to resolve many of the circular arguments that currently bedevil the field. The fundamental tenet throughout this guideline is that aetiology is vital to the management of patients with heart muscle disease and that a careful and consistent description of the morphological and functional phenotype is a crucial first step in the diagnostic pathway, while the final diagnosis will ideally describe aetiology alongside the phenotype.[6,7]

3.1. Definitions

A cardiomyopathy is defined as 'a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease (CAD), hypertension, valvular disease, and congenital heart disease (CHD) sufficient to cause the observed myocardial abnormality'.[2] This definition applies to both children and adults and makes no a priori assumptions about aetiology (which can be familial/genetic or acquired) or myocardial pathology. While the focus of this guideline is on genetic cardiomyopathies, the systematic approach to diagnosis starting from the phenotype at presentation described in this guideline enables clinicians to reach precise diagnoses that may also include non-genetic (e.g. inflammatory, toxic, and multisystem diseases) causes. It is important to note that cardiomyopathies can coexist with ischaemic, valvular, and hypertensive disease and that the presence of one does not exclude the possibility of the other.

Table 3 Morphological and functional traits used to describe cardiomyopathy phenotypes

Morphological traits	
Ventricular hypertrophy: left and/or right	
Ventricular dilatation: left and/or right	
Non-ischaemic ventricular scar and other myocardial tissue characterization features on cardiac magnetic resonance	
Functional traits	
Ventricular systolic dysfunction (global, regional)	
Ventricular diastolic dysfunction (restrictive physiology)	

The morphological and functional traits used to describe the cardiomyopathy phenotypes are shown in *Table 3*. The major innovation is the specific inclusion of myocardial tissue characterization traits, including non-ischaemic ventricular scarring or fatty replacement, which can occur with and without ventricular dilatation, wall motion abnormalities, or global systolic or diastolic dysfunction. This phenotype is important to recognize, as it may be the sole clue to the diagnosis of a cardiomyopathy and has prognostic significance that varies with the underlying aetiology.

Atrial dilatation (left and/or right) is an important additional clinical finding in the phenotypic description of cardiomyopathies. Ultra-rare, usually autosomal recessive, cases of pure dilated atrial cardiomyopathy are reported,[8] but these are outside the scope of this guideline.

3.2. Cardiomyopathy phenotypes

3.2.1. Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is defined as the presence of increased LV wall thickness (with or without RV hypertrophy) or mass that is not solely explained by abnormal loading conditions.[2]

3.2.2. Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is defined as the presence of LV dilatation and global or regional systolic dysfunction unexplained solely by abnormal loading conditions (e.g. hypertension, valve disease, CHD) or CAD.[2] Very rarely, LV dilatation can occur with normal ejection fraction (EF) in the absence of athletic remodelling or other environmental factors; this is not in itself a cardiomyopathy, but may represent an early manifestation of DCM. The preferred term for this is *isolated left ventricular dilatation.*

Right ventricular dilatation and dysfunction may be present but are not necessary for the diagnosis. When dilatation or wall motion abnormalities are confined or predominant to the right ventricle, the possibility of ARVC should be considered (see *Section 3.2.4*).

3.2.3. Non-dilated left ventricular cardiomyopathy

Hitherto, the definition of DCM had a number of important limitations, most notably the exclusion of genetic and acquired disorders

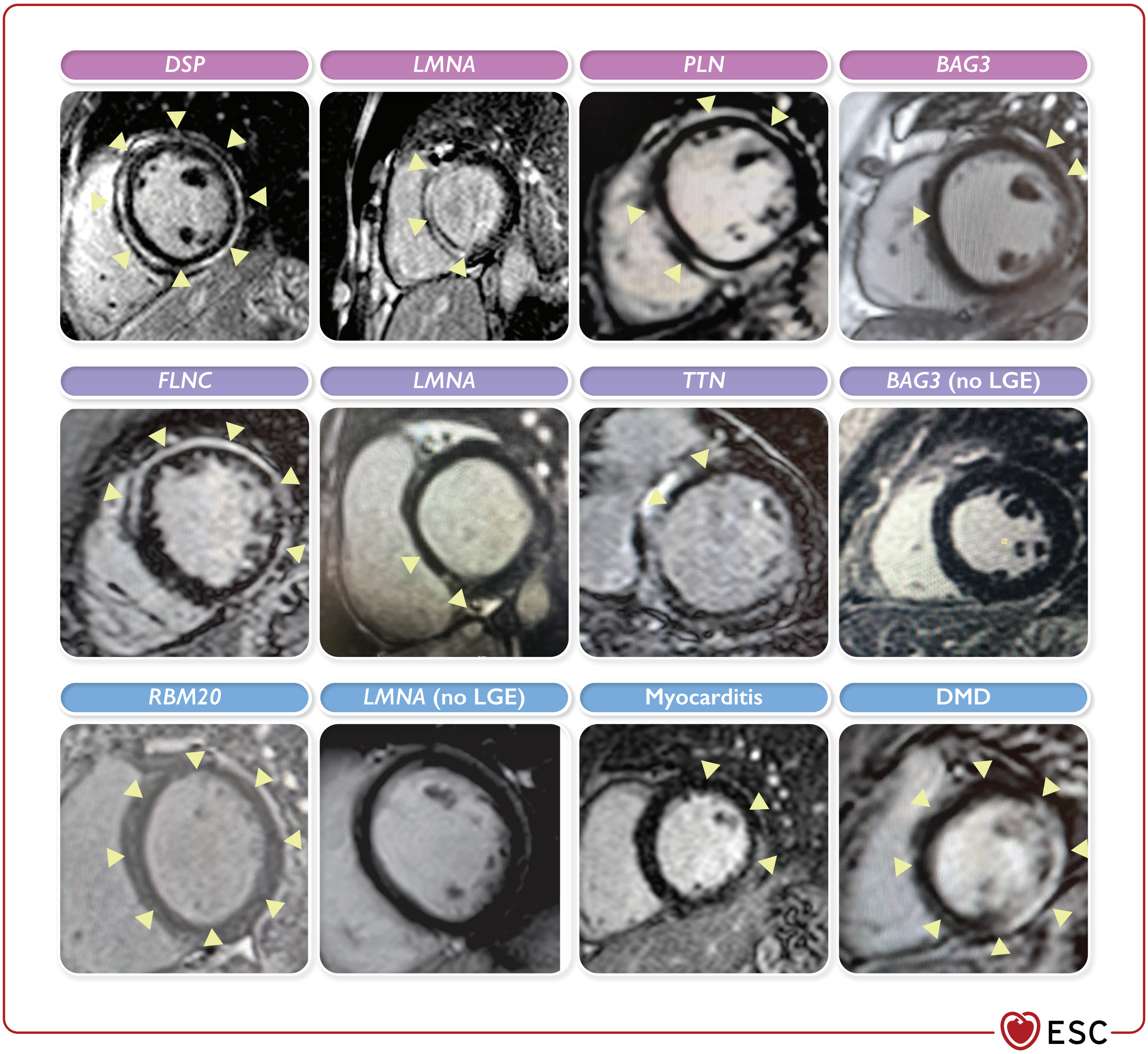

Figure 3 Examples of non-dilated left ventricular cardiomyopathy phenotypes and their aetiological correlates. BAG3, BAG cochaperone-3; DMD, Duchenne muscular dystrophy; DSP, desmoplakin; FLNC, filamin C; LGE, late gadolinium enhancement; LMNA, lamin A/C; NDLVC, non-dilated left ventricular cardiomyopathy; PLN, phospholamban; RBM20, RNA binding motif protein 20; TTN, titin. Distribution of LGE (arrowheads) in NDLVC and aetiological correlates. Desmoplakin (*DSP*), filamin C (*FLNC*) and phospholamban (*PLN*) genotypes show a characteristic subepicardial, ring-like LGE pattern, whereas titin (*TTN*), BAG3 (*BAG3*), lamin A/C (*LMNA*), *DMD*, *RBM20* genotypes and myocarditis are more heterogeneous, but with overall less scar (sometimes without) and lower left ventricular ejection fraction.

that manifest as intermediate phenotypes that do not meet standard disease definitions in spite of the presence of myocardial disease on cardiac imaging or tissue analysis. In a previous ESC statement, this phenomenon inspired the creation of a new disease category, hypokinetic non-dilated cardiomyopathy.[9] In this guideline, we propose replacement of this term with non-dilated left ventricular cardiomyopathy (NDLVC), which can be further characterized by the presence or absence of systolic dysfunction (regional or global). Isolated LV dysfunction (regional or global) without scarring should also be considered under this diagnostic category. The NDLVC phenotype is defined as the presence of non-ischaemic LV scarring or fatty replacement regardless of the presence of global or regional wall motion abnormalities (RWMAs), or isolated global LV hypokinesia without scarring.

The NDLVC phenotype will include individuals that up until now may have variably been described as having DCM (but without LV dilatation), arrhythmogenic left ventricular cardiomyopathy (ALVC), left-dominant ARVC, or arrhythmogenic DCM (but often without fulfilling diagnostic criteria for ARVC) (*Figure 3*). The simple worked example (*Figure 4*) shows how the identification of an NDLVC phenotype should trigger a multiparametric approach that leads to a specific aetiological diagnosis, with implications for clinical treatment.

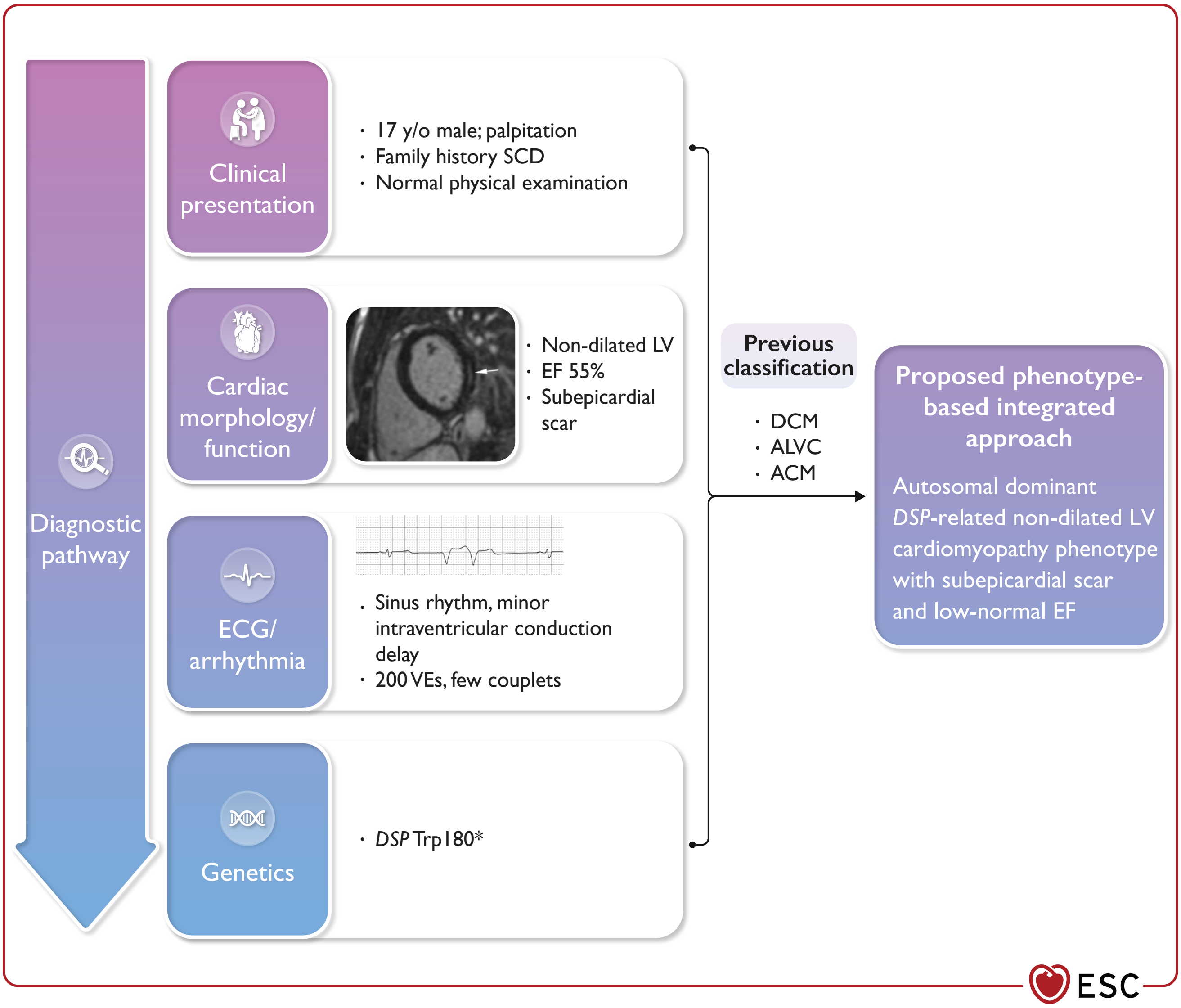

Figure 4 Worked example of the non-dilated left ventricular cardiomyopathy phenotype. ACM, arrhythmogenic cardiomyopathy; ALVC, arrhythmogenic left ventricular cardiomyopathy; DCM, dilated cardiomyopathy; *DSP*, desmoplakin; ECG, electrocardiogram; EF, ejection fraction; LV, left ventricular; NDLVC, non-dilated left ventricular cardiomyopathy; SCD, sudden cardiac death; VE, ventricular extrasystole. Worked example of the NDLVC phenotype showing how a systematic multiparametric approach to clinical phenotyping, starting from the recognition of a clinical phenotype and integrating extended phenotypic information and targeted diagnostics, including genetic testing, can be used to arrive at highly specific phenotypic descriptions that can result in personalized treatment plans. In this worked example, the diagnosis transforms from a simplistic categorization to a complex genetic disorder characterized by myocardial scar and a propensity to ventricular arrhythmia.

3.2.4. Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is defined as the presence of predominantly RV dilatation and/or dysfunction in the presence of histological involvement and/or electrocardiographic abnormalities in accordance with published criteria.[10]

For decades, ARVC has been one of the principal cardiomyopathy subtypes. It has been defined in accordance with published consensus criteria that comprise RV dysfunction (global or regional), histological abnormalities in the form of fibro-fatty replacement of cardiomyocytes, electrocardiographic characteristics, ventricular arrhythmia of RV origin, and the presence of familial disease and/or pathogenic variants in desmosomal protein genes.

Over time, the clinical paradigm of ARVC has moved from a focus on severe RV disease and malignant ventricular arrhythmia to a broader concept that includes concealed or subclinical phenotypes and biventricular or even left-dominant disease. This has led to a plethora of new terms, including 'arrhythmogenic left ventricular cardiomyopathy (ALVC)', 'left and right dominant cardiomyopathy', 'arrhythmogenic dilated cardiomyopathy', and most recently, the catch-all term 'arrhythmogenic cardiomyopathy'. The term ARVC can be used to describe the original variant in which ventricular dilatation or wall motion abnormalities are predominantly confined to the right ventricle, with or without LV involvement, and the 2010 modified Task Force criteria for the diagnosis of ARVC can be applied.[10] Predominant LV disease can also occur in the same family;[5] see *Section 7.3* for recommendations on assessment and management of this phenotype.

3.2.5. Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) is defined as restrictive left and/or RV pathophysiology in the presence of normal or reduced diastolic volumes (of one or both ventricles), normal or reduced systolic volumes, and normal ventricular wall thickness.[2]

Restrictive cardiomyopathy commonly presents as biatrial enlargement. Left ventricular systolic function can be preserved, but it is rare for contractility to be completely normal. Restrictive pathophysiology may not be present throughout the natural history, but only at an initial stage (with an evolution towards a hypokinetic-dilated phase).[11] Restrictive physiology can also occur in patients with end-stage hypertrophic and dilated cardiomyopathy; the preferred terms are 'hypertrophic' or 'dilated cardiomyopathy with restrictive physiology'. Restrictive ventricular physiology can also be caused by endocardial pathology (fibrosis, fibroelastosis, and thrombosis) that impairs diastolic function.

3.3. Other traits and syndromes associated with cardiomyopathy phenotypes

3.3.1. Left ventricular hypertrabeculation (left ventricular non-compaction)

The term 'left ventricular non-compaction' (LVNC) has been used to describe a ventricular phenotype characterized by prominent LV trabeculae and deep intertrabecular recesses. The myocardial wall is often thickened with a thin, compacted epicardial layer and a thicker endocardial layer. In some patients, this abnormal trabecular architecture is associated with LV dilatation and systolic dysfunction. Left ventricular non-compaction is frequently a familial trait and is associated with variants in a range of genes, including those encoding proteins of the sarcomere, Z-disc, cytoskeleton, and nuclear envelope.[12–16]

Left ventricular non-compaction has also been used to describe an acquired and sometimes transient phenomenon of excessive LV trabeculation (e.g. in athletes, during pregnancy, or following vigorous activity)[17–19] that must reflect increased prominence of an otherwise normal myocardial architecture, given that cardiomyocytes are terminally differentiated and the formation of new cardiac structures is impossible.[20]

The Task Force does not consider LVNC to be a cardiomyopathy in the general sense. Instead, it is seen as a phenotypic trait that can occur either in isolation or in association with other developmental abnormalities, ventricular hypertrophy, dilatation, and/or systolic dysfunction. Given the lack of morphometric evidence for ventricular compaction in humans,[21,22] the term 'hypertrabeculation', rather than LVNC, is recommended, particularly when the phenomenon is transient or clearly of adult onset.

3.3.2. Takotsubo syndrome

Transient LV apical ballooning syndrome, or takotsubo syndrome, is characterized, in its most typical variant, by transient regional systolic dysfunction, dilatation, and oedema involving the LV apex and/or mid-ventricle in the absence of obstructive coronary disease on coronary angiography.[23] Patients present with an abrupt onset of angina-like chest pain and have diffuse T wave inversion (TWI), sometimes preceded by ST-segment elevation and mild cardiac enzyme elevation. Most reported cases occur in post-menopausal women. Symptoms are often preceded by emotional or physical stress. Norepinephrine concentration is elevated in most patients and a transient, dynamic outflow tract pressure gradient is reported in some cases. Left ventricular function usually normalizes over a period of days to weeks, and recurrence is rare. The same kind of reversible myocardial dysfunction is occasionally encountered in patients with intracranial haemorrhage or other acute cerebral accidents (neurogenic myocardial stunning).

Takotsubo syndrome is sometimes referred to as takotsubo or stress cardiomyopathy. Given the transient nature of the phenomenon, the Task Force does not recommend its classification as a cardiomyopathy.

4. Epidemiology

Cardiomyopathies have a variable expression throughout life.[24] Geographical distribution of genetic variants influences estimated prevalence in different populations, ethnicities, regions, and countries. The complexity of diagnostic criteria for some conditions, such as ARVC, limits the evaluation of the true prevalence of the disease in the general population. Moreover, epidemiological data are often not collected systematically at population level. For example, the prevalence of idiopathic DCM has been recently estimated to be almost 10 times higher based on several population-based estimates and indirect assumptions of the prevalence of genetic variants associated with the disease in general populations,[25] and with less stringent diagnostic criteria.[9]

There are no specific data on the epidemiology of the NDLVC phenotype, but patients affected by it have previously been included in DCM or ARVC cohorts, from which extrapolations may be possible. Contemporary epidemiological metrics for the main cardiomyopathies are shown in *Table 4*. Further details on the epidemiology of cardiomyopathies can be found in the Supplementary data online, *Section 1*.

Table 4 Key epidemiological metrics in adults and children for the different cardiomyopathy phenotypes

Cardiomyopathy phenotype	Adults	Children
HCM	Prevalence: 0.2%[26–33]	Childhood incidence: 0.002–0.005%[34–36] Childhood prevalence: 0.029%[36]
DCM	Prevalence: 0.036–0.400%[25,37]	Childhood incidence: 0.003–0.006% Childhood prevalence: 0.026%[36] Infantile incidence: 0.038–0.046%[34–36,38]
NDLVC	To be determined	To be determined
ARVC	Prevalence: 0.078%[39–41]	Very rare in infancy and early childhood; to be determined in older children and adolescents
RCM	Rare	Childhood incidence: 0.0003%[34]

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; NDLVC, non-dilated left ventricular cardiomyopathy; RCM, restrictive cardiomyopathy.

4.1. Special populations

Several forms of cardiomyopathy previously considered secondary to external factors were recently proved to have genetic contributors, leading to the 'second hit theory', and a genetic aetiology should be kept in mind for family history taking and genetic testing.

- Titin gene truncating variants (*TTN*tv) represent a prevalent genetic predisposition for alcoholic cardiomyopathy (present in 13.5% of patients vs. 2.9% in controls), as they are associated with a worse left ventricular ejection fraction (LVEF) in DCM patients who consume alcohol above recommended levels.[42]
- Unrecognized rare variants in cardiomyopathy-associated genes, particularly *TTN*tv (in 7.5% of cases), appear to be associated with an increased risk of cancer therapy-induced cardiomyopathy in children and adults.[43]
- Rare truncating variants in eight genes are found in 15% of women with peripartum cardiomyopathy (PPCM), and two-thirds are *TTN*tv (10% of patients vs. 1.4% of the reference population).[44,45] Additionally, other truncating variants are identified in the *DSP* (1%), *FLNC* (1%), and *BAG3* (0.2%) genes.[45]
- Anderson–Fabry disease is found in 0.94% of males and 0.90% of females in cardiac screening programmes for left ventricular hypertrophy (LVH) in selected populations and HCM.[46]
- Screening with bone scintigraphy found a high prevalence of transthyretin cardiac amyloidosis (ATTR-CA) in specific populations: 8% in severe aortic stenosis, 12% in heart failure with preserved ejection fraction (HFpEF) with LVH, 7% in LVH/HCM depending on the age, and 7% in carpal tunnel syndrome undergoing surgery (a higher prevalence if it is bilateral), mainly for the wild-type form.[47,48]
- Disease-causing variants in genes implicated in DCM, NDLVC, and ARVC have been identified in 8–22% of adults and children presenting with acute myocarditis.[49–51] Individuals with an acute myocarditis presentation and desmosomal protein gene variants were shown to have a higher rate of myocarditis recurrence and ventricular arrhythmia compared with myocarditis patients without a desmosomal variant identified.[52]

5. Integrated patient management

The diagnosis, assessment, and management of patients with cardiomyopathy requires a co-ordinated, systematic, and individualized pathway that delivers optimized care by a multidisciplinary and expert team. Central to this approach is not only the individual patient, but also the family as a whole; clinical findings in relatives are essential for understanding what happens to the patient, and vice versa.[53,54]

5.1. Multidisciplinary cardiomyopathy teams

Healthcare professionals encounter diseases affecting the myocardium in many and varied clinical settings. Some may manifest for the first time with an acute event, including sudden unexplained death, whereas others present with progressive symptoms or are detected incidentally. Patients with cardiomyopathy can also have extracardiac manifestations (e.g. neurological, neuromuscular, ophthalmological, nephrological). Patient care requires the collaboration of different specialties.[55] The composition of the multidisciplinary team will depend on the patient's and family's needs and the local availability of services (*Figure 5*). Patients with complex needs benefit from a multidisciplinary team, including relevant specialties as well as the general cardiologist, general practitioner, and the family/carer. In addition, the integration of genetics into mainstream cardiology services requires expertise from different specialties:

- Adult and paediatric cardiologists subspecialized in cardiogenetic conditions.
- Cardiac imaging specialists (technicians, cardiologists, radiologists), including CMR experts.
- Specialist nurses and/or genetic counsellors with skills in family history taking, drawing pedigrees, and patient/family management, particularly when the number of disciplines or the complexity implicated in a patient's/family's care increases.
- Clinical psychologists to support patients and their relatives.
- Geneticists and bioinformaticians to interpret results of genetic investigations.
- Expert pathologists to interpret findings by endomyocardial biopsy (EMB) and autopsy of individuals dying from a suspected inherited cardiac condition. Specialist cardiovascular pathology centres play a crucial role in the autopsy diagnosis of cardiomyopathy when local expertise is not available.[56,57]

Finally, patients' associations should be promoted and integrated into the healthcare process for rare and very rare cardiac conditions.

One particularly important aspect of the multidisciplinary approach to patient care in cardiomyopathies is the need for appropriate transition of care from paediatric to adult services. Children with a genetic cardiomyopathy generally need lifelong cardiac follow-up. The transition to adulthood, including the transfer of care to adult cardiomyopathy services, can be challenging for both the child and the parents. The process of transition should include adequate and timely preparation and joint consultations, taking into consideration the child's wishes, and level of understanding and independence at different life stages. Evidence from the field of CHD highlights the importance of specific interventions that can help the process of transition of clinical care, including adequate and timely preparation for transition and joint consultations.[58,59]

5.2. Co-ordination between different levels of care

A shared care approach between cardiomyopathy specialists and general adult and paediatric cardiology centres is strongly recommended. While referral cardiomyopathy units are essential for complex cases with diagnostic and/or treatment difficulties that require expertise that may only be available in high-volume centres, general adult and paediatric cardiologists have a key role to play in the diagnosis, management, and follow-up of patients with cardiomyopathy (see *Section 9*). A shared approach between cardiomyopathy units and between general cardiologist/paediatric cardiologist is strongly recommended. This approach can be facilitated by the implementation of telemedical contact between units and the use of remote monitoring with patients.[60] The creation of local/regional/national/international networks, such as the European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart (ERN GUARD-Heart) (https://guardheart.ern-net.eu) allows clinicians and health professionals to share information about these pathologies, for the benefit of cardiomyopathy patients.[61]

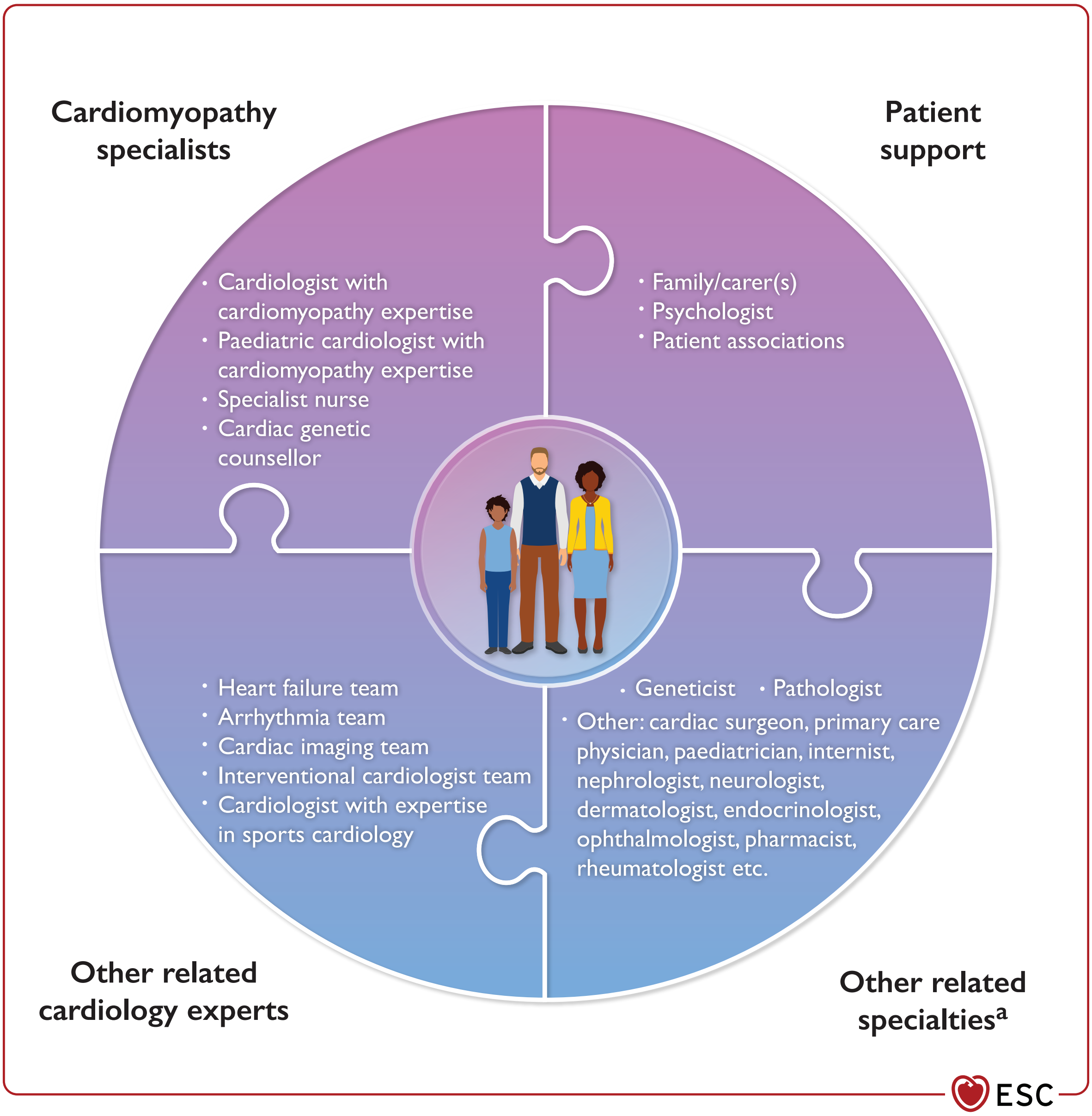

Figure 5 Multidisciplinary care of cardiomyopathies. [a]The list presented is not exhaustive and represents examples of specialties that often interact in the care of cardiomyopathy patients.

Recommendation Table 1 — Recommendations for the provision of service of multidisciplinary cardiomyopathy teams

Recommendations	Class[a]	Level[b]
It is recommended that all patients with cardiomyopathy and their relatives have access to multidisciplinary teams with expertise in the diagnosis and management of cardiomyopathies.	I	C
Timely and adequate preparation for transition of care from paediatric to adult services, including joint consultations, is recommended in all adolescents with cardiomyopathy.[58,59]	I	C

[a]Class of recommendation.
[b]Level of evidence.

6. The patient pathway

The diagnosis of cardiomyopathy rests on the identification of structural and/or functional myocardial abnormalities, including myocardial fibrosis, that are not explained solely by abnormal loading conditions or CAD. However, disease phenotypes can also include arrhythmic and electrocardiographic manifestations, morphological abnormalities of the cardiac valves, and abnormal coronary microcirculatory function. As a key theme throughout this guideline, the Task Force highlights the importance of using a systematic approach to the identification and assessment of patients with a suspected cardiomyopathy. Central to this is the need for clinicians to consider a diagnosis of cardiomyopathy as the cause of several common adult and paediatric clinical presentations. The identification of a cardiomyopathy phenotype is only the beginning of the diagnostic process and should prompt a systematic search for the underlying aetiology, which may be genetic or acquired.

6.1. Clinical presentation

Patients with cardiomyopathy may access health services through several pathways. Referral from primary care (e.g. general practitioners and general paediatricians) may be triggered by symptoms (most commonly dyspnoea, chest pain, palpitation, syncope) or incidental findings (e.g. an abnormal electrocardiogram [ECG] in the context of community, school, work-related medical check-ups, or sports pre-participation screening; the incidental detection of a murmur; or, increasingly, genotype-first identification as a result of secondary findings during research or clinical sequencing for other indications). In secondary and tertiary care (general cardiology and paediatric cardiology), patients with cardiomyopathy may present to the heart failure clinic with symptoms of heart failure with reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF), or preserved ejection fraction (HFpEF); to the arrhythmia clinic with early-onset conduction disease, atrial arrhythmia, or ventricular arrhythmia; or to the emergency department with suspected myocarditis. Frequently, patients enter the cardiomyopathy pathway in primary, secondary, or tertiary care as a result of family screening following the diagnosis of cardiomyopathy or a sudden death in a relative, and may also be identified as part of the work-up for multiorgan disease known to be associated with cardiovascular involvement. Clinicians in all these settings therefore need to consider the possibility of cardiomyopathy as a cause and use a systematic, cardiomyopathy-oriented approach to clinical evaluation.

6.2. Initial work-up

The cardiomyopathy-oriented approach is based on interpreting clinical and instrumental findings to suspect and ultimately generate a phenotype-based aetiological diagnosis to guide disease-specific management.[62] This approach requires deliberate analysis of multiparametric investigations in the individual and their relatives and an integrated probabilistic analysis of clinical investigations. Re-analysis of clinical data is required as new information emerges, and family information can provide important clues to the diagnosis, given the variable expression and incomplete penetrance of most cardiomyopathies, and can result in differences in diagnostic criteria between probands and relatives. In this context, relatives of individuals with cardiomyopathy can have non-diagnostic morphological and electrocardiographic abnormalities that can indicate mild and early phenotypic expression of disease and can increase diagnostic accuracy for predicting disease in genotyped populations. The identification of diagnostic clues, or red flags, is a crucial aspect of the initial work-up.

6.3. Systematic approach to diagnosis of cardiomyopathy

A multiparametric approach to the evaluation of patients with suspected cardiomyopathy is recommended, with the aims of: (i) establishing and characterizing the presence of a cardiomyopathy phenotype; and (ii) identifying the underlying aetiological diagnosis.[62] Clinicians should approach a patient with suspected cardiomyopathy using a 'cardiomyopathy mindset' (*Figure 2*):

- Use multimodality imaging to characterize the phenotype and identify abnormal ventricular morphology (e.g. hypertrophy, dilatation) and function (systolic/diastolic, global/regional), and detect abnormalities of tissue characterization (e.g. non-ischaemic myocardial scar and fatty replacement).
- Use a combination of personal and family history, clinical examination, electrocardiography, and laboratory investigations to achieve an aetiological diagnosis, looking for specific signs and symptoms and laboratory markers suggestive of a specific diagnosis; the presence of ventricular and atrial arrhythmia and conduction disease to aid diagnosis, suggest specific causes, and monitor disease progression and risk stratification; and clues from the pedigree to suggest specific inheritance patterns and identify at-risk relatives. This approach should result in a timely and accurate diagnosis to enable early treatment of symptoms and prevention of disease-related complications.

Recommendation Table 2 — Recommendations for diagnostic work-up in cardiomyopathies

Recommendations	Class[a]	Level[b]
It is recommended that all patients with suspected or established cardiomyopathy undergo systematic evaluation using a multiparametric approach that includes clinical evaluation, pedigree analysis, ECG, Holter monitoring, laboratory tests, and multimodality imaging.[63]	I	C
It is recommended that all patients with suspected cardiomyopathy undergo evaluation of family history and that a three- to four-generation family tree is created to aid in diagnosis, provide clues to underlying aetiology, determine inheritance pattern, and identify at-risk relatives.[64–66]	I	C

ECG, electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.

6.4. History and physical examination

Age is one of the most important factors to take into account when considering the possible causes of cardiomyopathy. For example, inherited metabolic disorders and congenital dysmorphic syndromes are more common in neonates and infants (see *Section 6.9.1*) than in older children or adults, whereas wild-type transthyretin amyloidosis (ATTRwt) is a disease mostly of adults over the age of 65 years (see *Section 7.6*).

Construction of a three- to four-generation family pedigree helps to identify Mendelian forms of inheritance and identifies other family members who may be at risk of disease development.[62] Specific features to note in the family history include premature deaths (taking into account that SCDs may sometimes be reported as accidental deaths, e.g. drowning, unexplained traffic accident, and, rarely, as stillbirth or sudden infant death syndromes), unexplained heart failure, cardiac transplantation, pacemaker and defibrillator implants, and evidence for systemic disease (e.g. stroke at a young age, skeletal muscle weakness, renal dysfunction, diabetes, deafness). Most Mendelian forms of cardiomyopathy are autosomal dominant and are therefore characterized by the presence of affected individuals across generations, with transmission from parents of either sex (including male-to-male) and a 50% risk of allele transmission to offspring (although, due to incomplete penetrance, the proportion of affected individuals in an individual pedigree will be lower). X-linked inheritance should be suspected if males are the most severely affected individuals and there is no male-to-male transmission. Autosomal recessive inheritance, the least common pattern, is likely when both parents of the proband are

Table 5 Examples of inheritance patterns that should raise the suspicion of specific genetic aetiologies, grouped according to cardiomyopathy phenotype

Cardiomyopathy phenotype		AD	AR	X-linked	Matrilineal
HCM	Sarcomeric	X			
	Anderson–Fabry			X	
	Danon			X	
	TTR amyloidosis	X			
	RASopathy	X	(X)		
	Friedreich ataxia		X		
	Mitochondrial				
	Mitochondrial DNA				X
	Nuclear DNA	X	X	X	
DCM	*LMNA*	X			
	RBM20	X			
	Sarcomeric	X			
	Dystrophin			X	
	Emerin			X	
	Barth syndrome			X	
	Mitochondrial				
	Mitochondrial DNA				X
	Nuclear DNA	X	X	X	
NDLVC	*LMNA*	X			
	DES	X	X		
	FLNC	X			
	PLN	X			
	TMEM43	X			
	RBM20	X			
ARVC	*PLN*	X			
	Desmosomal	X	X		
	TMEM43	X			
RCM	Sarcomeric	X			
	DES	X	X		
	FLNC	X			
	BAG3	X			
	RASopathy	X	(X)		

AD, autosomal dominant; AR, autosomal recessive; ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; NDLVC, non-dilated left ventricular cardiomyopathy; RCM, restrictive cardiomyopathy; TTR, transthyretin; DNA, deoxyribonucleic acid; RASopathies, Ras/mitogen-activated protein kinase pathway dysregulation.
(X) indicates the presence of a correlation between a cardiomyopathy and a pattern of inheritance.

unaffected and consanguineous, although severe autosomal recessive cardiomyopathies can also occur in the absence of familial consanguinity.[67,68] When women—but *not* men—transmit the disease to children of either sex, mitochondrial DNA variants should be considered (*Table 5*). It is important to note that the absence of familial disease does not exclude a genetic origin (see *Section 6.8*).

Patients with cardiomyopathy may experience dyspnoea, chest pain, palpitation, and syncope and/or pre-syncope, although many individuals complain of few, if any, symptoms (see *Section 6.4* for assessment of symptoms in specific cardiomyopathy subtypes). A number of non-cardiac symptoms act as pointers for specific diagnoses (*Table 6*). Similarly, general physical examination can provide diagnostic clues in patients with syndromic or metabolic causes of cardiomyopathy.[62]

6.5. Resting and ambulatory electrocardiography

The resting 12-lead ECG is often the first test that suggests the possibility of cardiomyopathy. Although the ECG can be normal in a small proportion of individuals with cardiomyopathy, standard ECG abnormalities are common in all cardiomyopathy subtypes and can precede the development of an overt morphological or functional phenotype by many years; for example, in genotype-positive individuals identified during family screening. When interpreted in conjunction with findings on echocardiography and CMR imaging, features that would normally indicate other conditions, such as myocardial ischaemia or infarction, can—with age at diagnosis, inheritance pattern, and associated clinical features—suggest an underlying diagnosis or provide clues to the

Table 6 Examples of signs and symptoms that should raise the suspicion of specific aetiologies, grouped according to cardiomyopathy phenotype

Finding	Cardiomyopathy phenotype				
	HCM	DCM	NDLVC	ARVC	RCM
Learning difficulties, developmental delay	Mitochondrial diseases	Dystrophinopathies			Noonan syndrome
	Noonan syndrome	Mitochondrial diseases			
	Danon disease	Myotonic dystrophy			
		FKTN variants			
Sensorineural deafness	Mitochondrial diseases	Epicardin variants			
	NSML	Mitochondrial diseases			
Visual impairment	Mitochondrial diseases	*CRYAB*			
	ATTRv or hereditary ATTR	Type 2 myotonic dystrophy			
	Danon disease				
	Anderson–Fabry disease[a]				
Gait disturbance	Friedreich ataxia	Dystrophinopathies	Myofibrillar myopathies		
		Sarcoglycanopathies			
		Myofibrillar myopathies			
Myotonia		Myotonic dystrophy			
Paraesthesia/sensory abnormalities/neuropathic pain	Amyloidosis				Amyloidosis
	Anderson–Fabry disease				
Carpal tunnel syndrome	TTR-related amyloidosis				
Muscle weakness	Mitochondrial diseases	Dystrophinopathies	Laminopathies		Desminopathies
	Glycogenoses	Sarcoglycanopathies	Desminopathies		
	FHL1 variants	Laminopathies			
		Myotonic dystrophy			
		Desminopathies			
Palpebral ptosis	Mitochondrial diseases	Mitochondrial diseases			
		Myotonic dystrophy			
Lentigines	NSML				
Angiokeratomata	Anderson–Fabry disease				
Pigmentation of skin and scars		Haemochromatosis			
Palmoplantar keratoderma and woolly hair		Carvajal syndrome		Naxos and Carvajal syndromes	
		DSP variants	*DSP* variants	*DSP* variants	

ARVC, arrhythmogenic right ventricular cardiomyopathy; ATTR, transthyretin amyloidosis; ATTRv, hereditary transthyretin amyloidosis; DCM, dilated cardiomyopathy; DSP, desmoplakin; HCM, hypertrophic cardiomyopathy; NDLVC, non-dilated left ventricular cardiomyopathy; NSML, Noonan syndrome with multiple lentigines; RCM, restrictive cardiomyopathy; TTR, transthyretin.

[a]Cornea verticillata, characteristic of Anderson–Fabry disease, does not cause visual impairment *per se*.

underlying diagnosis. For this reason, the ECG is recommended at the first clinic visit in all individuals with known or suspected cardiomyopathy and should be repeated whenever there is a change in symptoms in patients with an established diagnosis. Although the ECG is often non-specific, there are particular features that can suggest a certain aetiology or morphological diagnosis, including atrioventricular (AV) block, ventricular pre-excitation pattern, distribution of repolarization abnormalities, and high or low QRS voltages (*Table 7*).

Patients with cardiomyopathy may seek cardiology evaluation due to arrhythmia-related symptoms or documented arrhythmia, including bradyarrhythmias and tachyarrhythmias, ranging from symptomatic atrial/ventricular premature beats to life-threating ventricular arrhythmias. The frequency of arrhythmias detected during ambulatory electrocardiographic monitoring is age related and variable across different cardiomyopathy subtypes. Some arrhythmias are relatively common in the context of cardiomyopathy (e.g. atrial fibrillation [AF] or ventricular premature beats), while others may suggest a specific diagnosis. ECG monitoring is therefore useful at the initial clinical assessment and at regular intervals to assess the risk of SCD and stroke.

Table 7 Examples of electrocardiographic features that should raise the suspicion of specific aetiologies, grouped according to cardiomyopathy phenotype

Cardiomyopathy phenotype	Finding	Specific diseases to be considered
HCM	Short PR interval/pre-excitation	Glycogenosis Danon disease *PRKAG2* cardiomyopathy Anderson–Fabry disease Mitochondrial disease
	AV block	Amyloidosis Anderson–Fabry disease (late stage) Danon disease Sarcoidosis *PRKAG2* cardiomyopathy
	Extreme LVH	Danon disease Glycogenosis (e.g. Pompe disease) *PRKAG2* cardiomyopathy
	Low QRS voltage[a]	Amyloidosis Friedreich ataxia
	Superior QRS axis ('northwest axis')	Noonan syndrome
	Q waves/pseudoinfarction pattern	Amyloidosis
DCM	AV block	Laminopathy Emery–Dreifuss 1 Myocarditis (esp. Chagas disease, Lyme disease, diphtheria) Sarcoidosis Desminopathy Myotonic dystrophy
	Low P wave amplitude	Emery–Dreifuss 1 and 2
	Atrial standstill	Emery–Dreifuss 1 and 2
	Posterolateral infarction pattern	Dystrophinopathy Limb-girdle muscular dystrophy Sarcoidosis
	Extremely low QRS amplitude	*PLN* variant
NDLVC	AV block	Laminopathy Desminopathy
	Extremely low QRS amplitude	*PLN* variant
	Low QRS voltage + atypical RBBB	Desmosomal variants
ARVC	T wave inversion V1-V3 + terminal activation delay +/− low right ventricular voltages +/− atypical RBBB	
RCM	AV block	Desminopathy Amyloidosis

ARVC, arrhythmogenic right ventricular cardiomyopathy; AV, atrioventricular; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; NDLVC, non-dilated left ventricular cardiomyopathy; *PKP2*, plakophilin 2; *PLN*, phospholamban; *PRKAG2*, protein kinase AMP-activated non-catalytic subunit gamma 2; QRS, Q, R, and S waves of an ECG; RBBB, right bundle branch block; RCM, restrictive cardiomyopathy.
[a]In the absence of obesity, pericardial effusion, chronic obstructive pulmonary disease, abnormalities of the chest, or other reasons that may cause low voltage.
Adapted from Rapezzi *et al.*[62]

6.6. Laboratory tests

Routine laboratory testing aids the detection of extracardiac conditions that cause or exacerbate ventricular dysfunction (e.g. thyroid disease, renal dysfunction, and diabetes mellitus) and secondary organ dysfunction in patients with severe heart failure. High levels of brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP), and high-sensitivity cardiac troponin T (hs-cTnT) are associated with cardiovascular events, heart failure, and death, and may have diagnostic, prognostic, and therapeutic monitoring value.[69] Routine blood tests for comorbidities, including full blood count, renal and liver function parameters and electrolytes, thyroid function, fasting glucose, and Haemoglobin A1C (HbA1c) are recommended in all patients with heart failure symptoms.[69] Persistently elevated serum creatinine kinase (CK) levels can be suggestive of myopathies or neuromuscular disorders including dystrophinopathies (e.g. Becker muscular dystrophy or X-linked DCM), laminopathies, desminopathies, or less often, a myofibrillar myopathy.[62] Elevated C-reactive protein levels may be present in patients with ARVC and NDLVC, particularly in the context of recurrent myocarditis-like episodes.[70] Elevated serum levels of iron and ferritin and high transferrin saturation can suggest a diagnosis of haemochromatosis and should trigger further aetiological refinement (primary vs. secondary) based on genetic testing. Lactic acidosis, myoglobinuria, and leucocytopaenia can be suggestive of mitochondrial diseases. A list of recommended laboratory tests in adults and children is shown in *Table 8*. Following specialist evaluation, additional tests to detect rare metabolic causes are often required in children, including measurement of lactate, pyruvate, pH, uric acid, ammonia, ketones, free fatty acids, carnitine profile, urine organic acids, and amino acids (see *Section 6.9*).

Recommendation Table 3 — Recommendations for laboratory tests in the diagnosis of cardiomyopathies

Recommendations	Class[a]	Level[b]
Routine (first-level) laboratory tests[c] are recommended in all patients with suspected or confirmed cardiomyopathy to evaluate aetiology, assess disease severity, and aid in detection of extracardiac manifestations and assessment of secondary organ dysfunction.	I	C
Additional (second-level) tests[c] should be considered in patients with cardiomyopathy and extracardiac features to aid in detection of metabolic and syndromic causes, following specialist evaluation.	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
[c]See *Table 8*.

6.7. Multimodality imaging

6.7.1. General considerations

Non-invasive imaging modalities represent the backbone of diagnosis and follow-up in patients with cardiomyopathies, including ultrasound-based techniques, CMR imaging, computed tomography (CT), and nuclear techniques, such as positron emission tomography (PET) and scintigraphy (*Figure 6*).[1,71,72] Physicians should always consider the yield of actionable results vs. the costs, advantages, and limitations of each technique, as well as patient safety and patient exposure to ionizing radiation and contrast media. Standardized algorithms should be in place to move hierarchically from simpler and cheaper to more complex and expensive tests. A bi-directional flow of information between the clinician and the imager is key to maximizing appropriateness: clinicians should formulate and share clear pre-test hypotheses, based on available information, to aid the interpretation of novel findings. The imager should respond in a similarly focused fashion, assessing the likelihood of alternative diagnoses and refraining from diagnoses that are not compatible/plausible based on the overall clinical context.

6.7.2. Echocardiography

The non-invasive nature and widespread availability of echocardiography make it the main imaging tool, from initial diagnosis to follow-up. Transthoracic echocardiography (TTE) provides relevant information on global and regional RV and LV anatomy and function as well as valve function and the presence of dynamic obstruction, pulmonary hypertension, or pericardial effusions.[71–73] Myocardial deformation imaging (speckle tracking or tissue Doppler) with global longitudinal strain is a more sensitive marker than EF to detect subtle ventricular dysfunction (e.g. in genotype-positive HCM, DCM, and ARVC family members[72,74,75]), and may help discriminate between different aetiologies of hypertrophy[76] (e.g. amyloidosis, HCM, and athlete's heart). Mechanical dispersion is a marker of contraction inhomogeneity and highlights fine structural changes that may be missed by other modalities.[77–80] Three-dimensional echocardiography reliably assesses volumes of cardiac chambers but needs an adequate acoustic window. Contrast agents can be considered for better endocardial delineation to depict the presence of hypertrabeculation, apical HCM, or apical aneurysms, and to exclude thrombus. Stress echocardiography can be helpful in selected patients to evaluate myocardial ischaemia and exercise echocardiography is useful to identify provocable LVOTO in symptomatic patients with HCM (see *Section 7.1.1.3*). Transoesophageal echocardiography is limited to selected indications, such as the exclusion of atrial thrombi related to AF, elucidating the mechanism of mitral regurgitation, or in planning invasive interventions (e.g. septal myectomy in HCM).

When measuring cardiac dimensions and wall thickness in children, it is important to correct for body size, using z-scores (defined as the number of standard deviations from the population mean). Of note, there are inherent limitations with the use of z-scores in the diagnosis of cardiomyopathies, including the fact that there are many different normative data published resulting in significant variation in z-scores for the same patient.[81] In addition, there are no normative data for wall thickness other than at the basal interventricular septum or posterior wall. The Task Force recommends using the normative data from the Paediatric Heart Network consortium.[82]

Recommendation Table 4 — Recommendation for echocardiographic evaluation in patients with cardiomyopathy

Recommendation	Class[a]	Level[b]
A comprehensive evaluation of cardiac dimensions and LV and RV systolic (global and regional) and LV diastolic function is recommended in all patients with cardiomyopathy at initial evaluation, and during follow-up, to monitor disease progression and aid risk stratification and management.[78,83–102]	I	B

LV, left ventricular; RV, right ventricular.
[a]Class of recommendation.
[b]Level of evidence.

Table 8 First-level (to be performed in each patient) and second-level (to be performed in selected patients following specialist evaluation to identify specific aetiologies) laboratory tests, grouped by cardiomyopathy phenotype

Level	HCM	DCM	NDLVC	ARVC	RCM
First	• CK • Liver function • NT-proBNP[a] • Proteinuria • Renal function • Troponin	• Calcium • CK • Ferritin • Full blood count • Liver function • NT-proBNP[a] • Phosphate • Proteinuria • Renal function • Serum iron • Thyroid function • Troponin • Vitamin D (children)	• Calcium • CK • C-reactive protein • Full blood count • Liver function • NT-proBNP[a] • Phosphate • Proteinuria • Renal function • Troponin	• C-reactive protein • Liver function • NT-proBNP[a] • Renal function • Troponin	• CK • Ferritin • Full blood count • Liver function • NT-proBNP[a] • Proteinuria • Renal function • Serum angiotensin-converting enzyme • Serum iron • Troponin • Urine and plasma protein immunofixation, free light chains
Second	• Alpha-galactosidase A levels (males) and lyso-Gb3 • Carnitine profile • Free fatty acids • Immunofixation and free light chains • Lactic acid • Myoglobinuria • Pyruvate • PTH • Urine and plasma protein • Urine organic acids and plasma amino acids	• Carnitine profile • Free fatty acids • Lactic acid • Organ- and non–organ-specific serum autoantibodies • Serum angiotensin-converting enzyme • Thiamine • Viral serology • Urine organic acids and plasma amino acids	• Organ- and non-organ-specific serum autoantibodies • Viral serology		• Organ- and non–organ-specific autoantibodies • Serum angiotensin-converting enzyme

ARVC, arrhythmogenic right ventricular cardiomyopathy; BNP, brain natriuretic peptide; CK, creatinine kinase; DCM, dilated cardiomyopathy; Gb3, globotriaosylceramide; HCM, hypertrophic cardiomyopathy; NDLVC, non-dilated left ventricular cardiomyopathy; NT-proBNP, N-terminal pro-brain natriuretic peptide; PTH, parathyroid hormone; RCM, restrictive cardiomyopathy.
[a]Alternatively, BNP can be considered depending on the local availability.

6.7.3. Cardiac magnetic resonance

Cardiac magnetic resonance imaging (MRI) combines the advantages of non-invasiveness and independence of acoustic window with the ability for tissue characterization. The latter advantage is particularly important in the diagnosis of NDLVC, ARVC, myocarditis, amyloidosis, sarcoidosis and other forms of inflammatory disease, and iron overload/haemochromatosis. Cardiac magnetic resonance is particularly useful if echocardiography provides poor image quality. Initial evaluation should routinely include cine imaging sequences, T2-weighted sequences, pre- and post-contrast T1 mapping, and late gadolinium enhancement (LGE). When suspecting haemochromatosis, T2* mapping should be employed. Cardiac magnetic resonance findings can provide important aetiological clues (*Figure 7*), with potential therapeutic implications (*Table 9*) and should be assessed collectively with genetic results and other clinical features by experienced operators in cardiac imaging and the evaluation of heart muscle disease. Serial follow-up CMR, every 2–5 years depending on initial severity and clinical course, can assist in evaluating disease progression as well as the benefits of therapy (e.g. evaluation of extracellular volume [ECV] in amyloidosis, or of iron deposition in haemochromatosis), and should be considered in all patients with cardiomyopathy.

6.7.3.1. Special considerations

- Recently developed rapid CMR techniques allow scans to be performed without general anaesthesia even in very young children.[103] In children (and adults) unable to undergo CMR without general anaesthesia, the relative risks and benefits of the procedure should be considered.
- Imaging artefacts caused by cardiac implantable electronic devices have posed limitations for CMR imaging in the past.[104–110] A number of solutions are available to reduce artefacts, including reducing inhomogeneity, technical adjustments, and the use of special sequences, which reduce the rate of uninterpretable studies to one in five.[111,112] Cardiac magnetic resonance can therefore be considered in patients with conditional devices and nearly all non-conditional devices provided appropriate protocols are put in place.[113]
- Nephrogenic systemic fibrosis is a rare complication reported in patients with first-generation linear unstable gadolinium chelates and

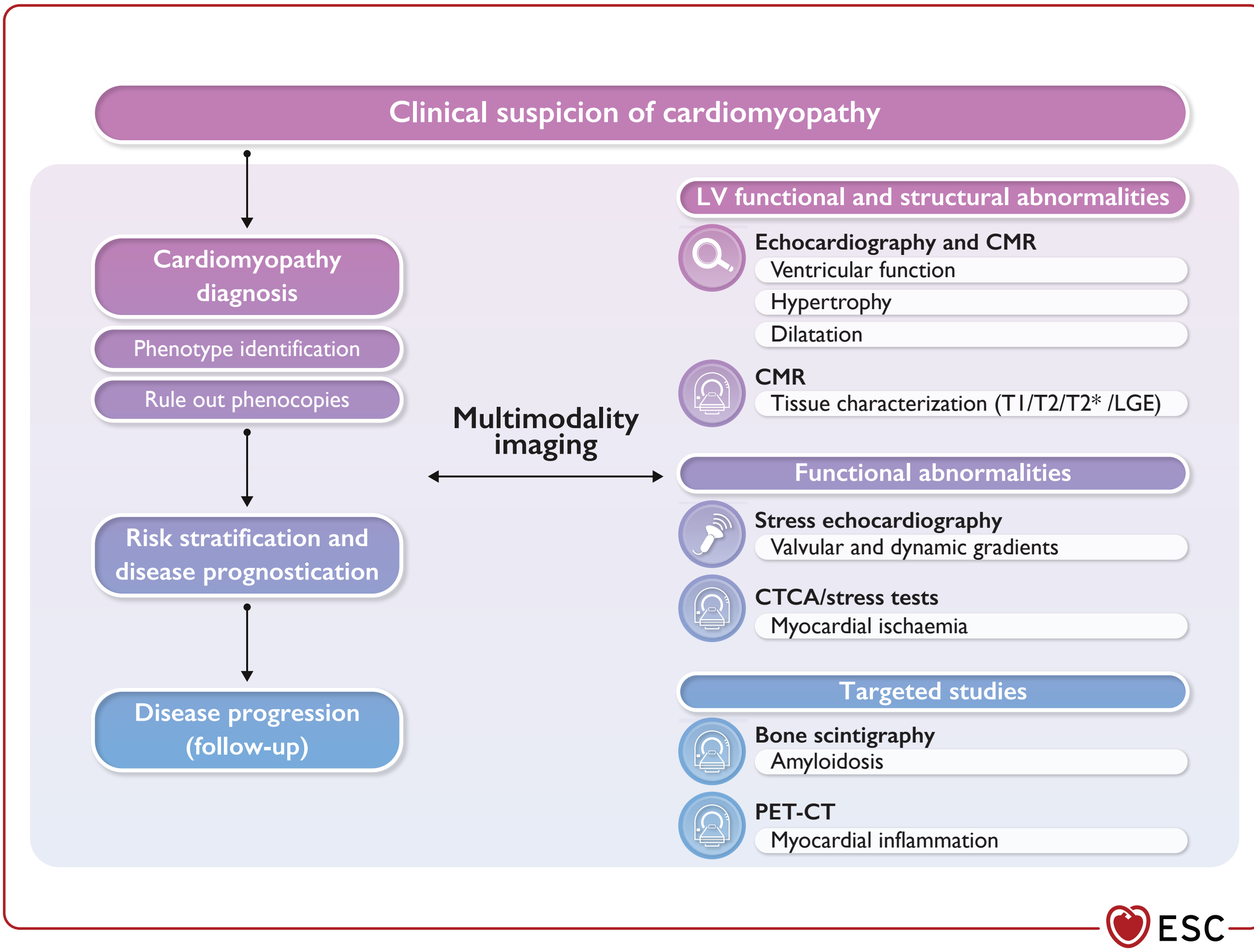

Figure 6 Multimodality imaging process in cardiomyopathies. CMR, cardiac magnetic resonance; CTCA, computed tomography coronary angiography; LGE, late gadolinium enhancement; LV, left ventricular; PET, positron emission tomography.

severe renal disease.[114] However, gadolinium-based contrast agents can be safely administered for patients with an estimated glomerular filtration rate >30 mL/min/1.73 m^2, and nephrogenic systemic fibrosis is virtually unreported with the use of newer linear or macrocyclic gadolinium contrasts. For patients with severe renal impairment, new CMR modalities and mapping procedures, which are very informative and do not require the use of contrast, are particularly valuable when assessing Anderson–Fabry disease and cardiac amyloidosis.[115–117]

- The use of gadolinium contrast is generally not advised in pregnancy due to the potential for adverse outcomes in the foetus and neonate.[118]

Recommendation Table 5 — Recommendations for cardiac magnetic resonance indication in patients with cardiomyopathy

Recommendations	Class[a]	Level[b]
Contrast-enhanced CMR is recommended in patients with cardiomyopathy at initial evaluation.[10,90,116,119–143]	I	B
Contrast-enhanced CMR should be considered in patients with cardiomyopathy during follow-up to monitor disease progression and aid risk stratification and management.[89,90,120–122,127,129,136–147]	IIa	C
Contrast-enhanced CMR should be considered for the serial follow-up and assessment of therapeutic response in patients with cardiac amyloidosis, Anderson–Fabry disease, sarcoidosis, inflammatory cardiomyopathies, and haemochromatosis with cardiac involvement.[148–152]	IIa	C
In families with cardiomyopathy in which a disease-causing variant has been identified, contrast-enhanced CMR should be considered in genotype-positive/phenotype-negative family members to aid diagnosis and detect early disease.[10,122,126,128,129,135–143,145,153–159]	IIa	B
In cases of familial cardiomyopathy without a genetic diagnosis, contrast-enhanced CMR may be considered in phenotype-negative family members to aid diagnosis and detect early disease.[10,128]	IIb	C

Continued

CMR, cardiac magnetic resonance.
[a]Class of recommendation.
[b]Level of evidence.

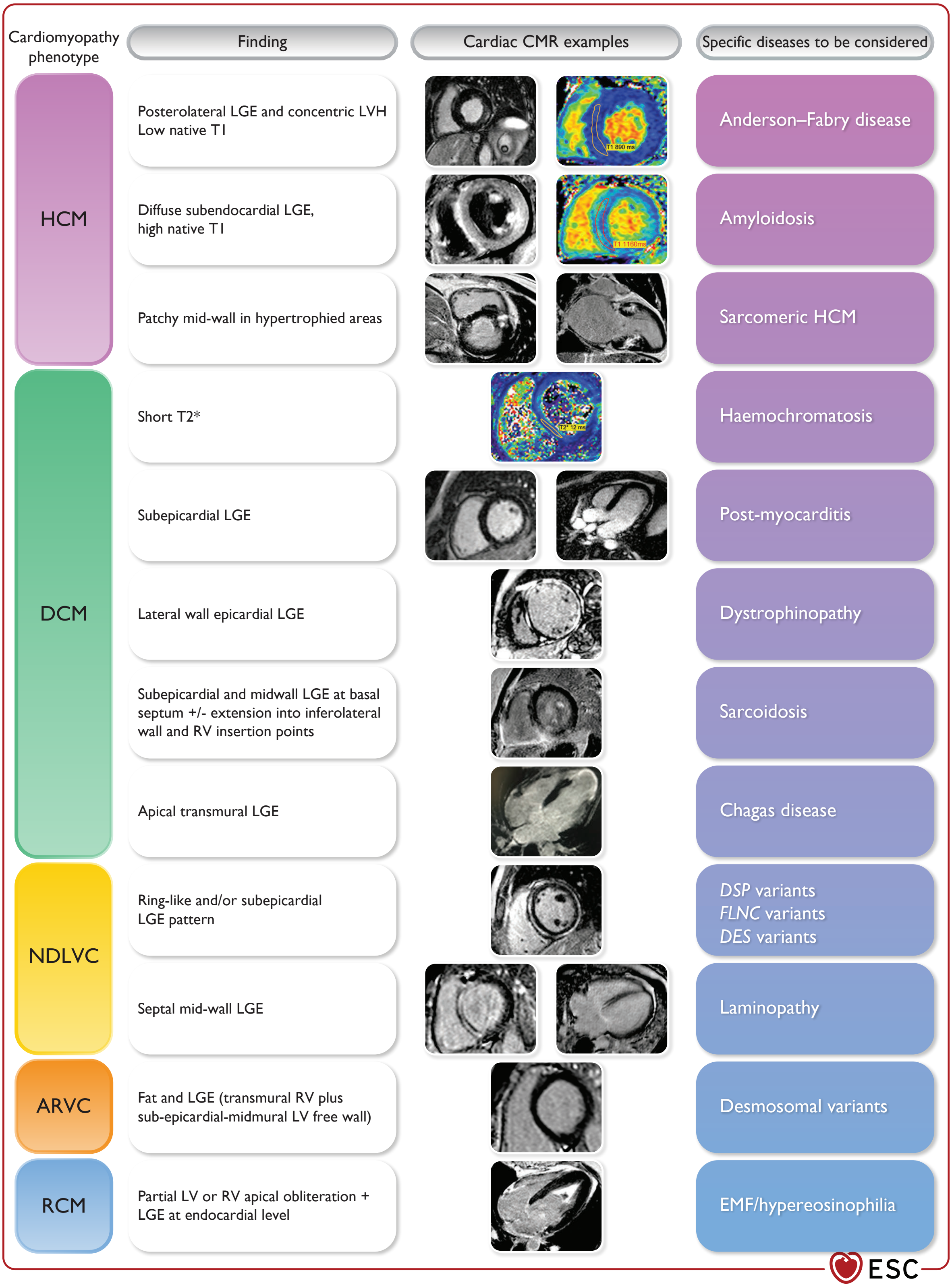

Figure 7 Examples of cardiac magnetic resonance imaging tissue characterization features that should raise the suspicion of specific aetiologies, grouped according to cardiomyopathy phenotype. ARVC, arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; *DES*, desmin; *DSP*, desmoplakin; EMF, endomyocardial fibrosis; *FLNC*, filamin C; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricular; LVH, left ventricular hypertrophy; NDLVC, non-dilated left ventricular cardiomyopathy; RCM, restrictive cardiomyopathy; RV, right ventricular. Examples of CMR tissue characterization features that should raise the suspicion of specific aetiologies (column 4), grouped according to cardiomyopathy phenotype (column 1). CMR images features (column 3) correspond to the listed findings (column 2).

Table 9 Frequently encountered actionable results on multimodality imaging

Parameter/finding	Action
RWMAs on echocardiography or CMR	Raise suspicion of concomitant CAD, myocarditis, ARVC, NDLVC, or sarcoidosis
Systolic impairment on echocardiography or CMR	Assessment of risk in DCM, NDLVC, and ARVC; evaluation of treatment efficacy
Measurement of the wall thickness on echocardiography or CMR	Diagnosis of HCM (when echocardiography is inconclusive); risk stratification in HCM
Diastolic dysfunction on echocardiography	Explain symptoms; evaluation of treatment efficacy
Left atrial size on echocardiography	SCD risk prediction in HCM; systematic screening for AF in case of left atrial enlargement
LVOTO in HCM on resting/ exercise echocardiography	Explain symptoms; guide management
Non-invasive evaluation of pulmonary pressures	Explain symptoms; guide management
Tissue characterization on CMR	Diagnosis; risk assessment
Inflammation on CMR or 18F-FDG-PET	Diagnosis; evaluation of treatment efficacy in inflammatory cardiomyopathies

18F-FDG-PET, fluorodeoxyglucose positron emission tomography; AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; AF, atrial fibrillation; CAD, coronary artery disease; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVOTO, left ventricular outflow tract obstruction; NDLVC, non-dilated left ventricular cardiomyopathy; RWMA, regional wall motion abnormality; SCD, sudden cardiac death.

6.7.4. Computed tomography and nuclear medicine techniques

Other imaging modalities, including nuclear medicine-based techniques and CT, are indicated in selected subsets of patients with cardiomyopathy.[160,161] Indications and the risk-benefit ratio should be evaluated on an individual patient basis, always taking into account radioprotection issues, which are particularly relevant in the young. Nuclear medicine is particularly helpful in the aetiological diagnosis of cardiac amyloidosis (see *Section 7.7*). 18FDG-PET is useful in the identification of myocardial inflammation associated with active sarcoidosis and, potentially, in other atypical forms of myocarditis.[162–164] However, a negative scan does not exclude sarcoidosis in its inactive form. In patients with HCM, DCM, and Anderson–Fabry disease, $H_2^{15}O$ or $^{13}NH_3$ dipyridamole or regadenoson PET has been used to evaluate microvascular dysfunction, an important predictor of adverse outcome.[165] However, this test does not currently have a role in aetiological diagnosis (e.g. in distinguishing phenocopies) and is largely confined to research purposes.

Computed tomography-based imaging is primarily used in patients with a suspicion of cardiomyopathy to rule out CAD, either as an alternative diagnosis (e.g. in individuals with DCM, NDLVC, or ARVC phenotypes) or as a comorbidity affecting clinical manifestations and course. In children and adolescents, CT angiography can be useful to exclude congenital vascular malformations (e.g. anomalous left coronary artery from the pulmonary artery [ALCAPA] or anomalous pulmonary venous return). Standard CT imaging provides additional information regarding concomitant pulmonary disease (e.g. sarcoidosis), pericardial disease, and chest wall deformities affecting the heart.

Recommendation Table 6 — Recommendations for computed tomography and nuclear imaging

Recommendations	Class[a]	Level[b]
DPD/PYP/HMDP bone-tracer scintigraphy is recommended in patients with suspected ATTR-related cardiac amyloidosis to aid diagnosis.[166–168]	I	B
Contrast-enhanced cardiac CT should be considered in patients with suspected cardiomyopathy who have inadequate echocardiographic imaging and contraindications to CMR.[169,170]	IIa	C
In patients with suspected cardiomyopathy, CT-based imaging should be considered to exclude congenital or acquired coronary artery disease as a cause of the observed myocardial abnormality.[171]	IIa	C
18F-FDG-PET scanning should be considered for the diagnostic work-up in patients with cardiomyopathy in whom cardiac sarcoidosis is suspected.[164,172,173]	IIa	C

18F-FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; ATTR, transthyretin amyloidosis; CMR, cardiac magnetic resonance; CT, computed tomography; DPD, 3,3-diphosphono-1,2-propanodicarboxylic acid; HMDP, hydroxymethylene diphosphonate; PYP, pyrophosphate.
[a]Class of recommendation.
[b]Level of evidence.

6.7.5. Endomyocardial biopsy

Endomyocardial biopsy (EMB) with immunohistochemical quantification of inflammatory cells and identification of viral genomes remains the gold standard for the identification of cardiac inflammation. It may confirm the diagnosis of autoimmune disease in patients with unexplained heart failure and suspected giant cell myocarditis, eosinophilic myocarditis, vasculitis, and sarcoidosis. Electron microscopy should be employed when storage or mitochondrial cardiomyopathies are suspected. Endomyocardial biopsy should be reserved for specific situations where its results may affect treatment after careful evaluation of the risk-benefit ratio. Importantly, EMB is not completely risk-free and should be performed by experienced teams. Likewise, the diagnostic work-up of a biopsy should be performed by pathologists with expertise in cardiomyopathies.

Recommendation Table 7 — Recommendation for endomyocardial biopsy in patients with cardiomyopathy

Recommendation	Class[a]	Level[b]
In patients with suspected cardiomyopathy, EMB should be considered to aid in diagnosis and management when the results of other clinical investigations suggest myocardial inflammation, infiltration, or storage that cannot be identified by other means.[174–177]	IIa	C

EMB, endomyocardial biopsy.
[a]Class of recommendation.
[b]Level of evidence.

6.8. Genetic testing and counselling

6.8.1. Genetic architecture

Familial forms of cardiomyopathies show diverse modes of inheritance. Gene identification has, over the last three decades, primarily focused on the identification of Mendelian (monogenic) disease genes that most commonly display autosomal dominant inheritance, although other inheritance patterns including autosomal recessive, X-linked, and mitochondrial (matrilineal) are also observed (*Table 5*). Major genes currently associated with different types of cardiomyopathies are listed in *Table 10*. Cardiomyopathies are characterized by a marked genetic and allelic heterogeneity, that is, many different variants in many different genes can cause the same phenotype. Rare pathogenic variants associated with cardiomyopathies often exhibit the phenomena of incomplete and age-related penetrance, and variable expressivity.[178,179] That is, not all individuals carrying a causative variant manifest the disease and, among those who do, there is broad variability in age of onset and disease severity. Thus, while some individuals may have severe disease necessitating cardiac transplantation at a young age, others may remain unaffected throughout their lives or are only mildly affected. This variability could be due to heterogeneity among causative variants, the additional contribution of non-genetic (clinical, environmental) factors (e.g. hypertension in HCM,[180] exercise in ARVC[181]), and the co-inheritance of additional genetic factors, which act to exacerbate or attenuate the effect of the principal Mendelian genetic variant on the phenotype. This is an active area of research, and recent genome-wide association studies conducted in patients with HCM have provided strong evidence for the modulatory role of common genetic variants of individually small effect that collectively modulate the effects of Mendelian variants (*Figure 8*).[182,183]

Across the different cardiomyopathies, the proportion of cases with a confident genetic diagnosis (that is with identification of a likely causal Mendelian genetic variant) is relatively low (e.g. as low as ∼40% in HCM[124] and ∼30% in DCM[184–186]). Genome-wide association studies of common variants in HCM and DCM have provided empirical evidence for substantial polygenic inheritance in these cardiomyopathies.[182,183,187] Contrary to Mendelian inheritance, where a single, large-effect variant primarily determines susceptibility to the disorder, complex inheritance rests on the co-inheritance of multiple susceptibility variants. Although not yet studied systematically, besides common variants of small effect, intermediate-effect variants with effect sizes and frequencies between common and Mendelian variants are also expected to contribute to such complex inheritance.[188] It is likely that cardiomyopathies span a continuum of genetic complexity, with Mendelian forms at one end, determined primarily by the inheritance of an ultra-rare large-effect genetic variant, and highly polygenic forms at the other (see *Figure 8*). Variants that contribute to disease susceptibility in the setting of complex inheritance likely overlap with those that modulate disease penetrance and expressivity in the Mendelian form of the disease.[182,183]

6.8.2. Genetic testing

Genetic testing of Mendelian cardiomyopathy genes has become a standard aspect of clinical management in affected families.[3] First-line testing should be focused on genes robustly associated with the presenting phenotype. If initial testing does not reveal a cause, but suspicion of a monogenic cause remains high, then more extended sequencing or analysis may be indicated, depending on the family structure and other factors. Once a genetic cause is established in one family member, then other family members may undergo testing for only the causative variant.

Genetic testing in an individual with cardiomyopathy (known as *confirmatory testing* or diagnostic testing) is recommended for their direct benefit: (i) to confirm the diagnosis; (ii) where it may inform prognosis; (iii) where it may inform treatment selection; or (iv) where it may inform their reproductive management. Genetic testing of an affected individual may be indicated, even if it is unlikely to alter their management, if there are *relatives* who may benefit from testing, particularly if there are relatives who will be enrolled in longitudinal surveillance if the genetic aetiology is not established and who may be spared this burden if a genetic diagnosis is made in the family (*Table 11*). Testing may also be helpful in broader contexts, even when not obviously informative for immediate management; for example, a genetic diagnosis may provide psychological benefit in a patient struggling to understand their disease.

Genetic testing in a clinically unaffected relative of an individual with cardiomyopathy may be indicated irrespective of age, even in very young children, if a genetic diagnosis has been established with confidence in the affected individual (known as *cascade testing*, predictive testing, or pre-symptomatic testing). Once a pathogenic/likely pathogenic (P/LP) variant has been identified within an index patient following investigations of relevant disease genes associated with the specific phenotype, it is possible to offer cascade genetic testing of first-degree at-risk relatives, including pre-test genetic counselling (see *Section 6.8.3*). In a scenario where a first-degree relative has died, evaluation of close relatives of the deceased individual (i.e. second-degree relatives of the index patient) should also be considered.

Individuals who are found not to harbour the familial variant can usually be discharged from clinical follow-up; those who do carry the familial variant are recommended to undergo clinical evaluation and usually ongoing surveillance. Cascade testing is not indicated when a variant of uncertain significance is identified in the proband.

Sequencing may also be indicated for segregation analysis (rather than as a diagnostic test) to inform interpretation of a variant of uncertain significance found in an affected individual. This is usually limited to individuals who are clearly affected, or to testing of the parents to identify a *de novo* variant. Genetic counselling in this circumstance would involve clear communication to family members that this is not a diagnostic test, but rather is contributing to clarifying the pathogenicity of the uncertain variant.

Finally, the evaluation of cardiac genes for secondary findings where data are generated in the setting of genetic testing for another clinical indication (also referred to as opportunistic screening) may be reasonable where the balance of benefits and harm is known, and if the cost is acceptable. Broader population screening might also prove reasonable if the balance of benefits and harm proves favourable. At present there is insufficient data to evaluate the balance of benefits and harm in either context, and this should currently only be performed in a research context in order to obtain such data. Careful genetic counselling to fully explain benefits and risks in this setting is critical. At present, there are very little data to evaluate this balance and this is an important evidence gap. In the United States of America, the American College of Medical Genetics and Genomics has recommended that cardiomyopathy-associated genes be evaluated for secondary findings whenever broad clinical sequencing is undertaken, regardless of the initial indication for testing.[192,193] There is currently no international consensus around this recommendation.

Table 10 **Overview of genes associated with monogenic, non-syndromic cardiomyopathies, and their relative contributions to different cardiomyopathic phenotypes**

Gene	Cardiomyopathy phenotype					Associated phenotype
	HCM	DCM	NDLVC	ARVC	RCM	
ABCC9	Dark blue[a]	White				[a] Cantu syndrome
ACTA1	White					
ACTC1	Dark blue	Light blue	Grey	White	Grey	
ACTN2[b]	Light blue	Light blue	Grey			
ALPK3	Dark blue					
ANKRD1	White	White				
BAG3	Dark blue[a]	Dark blue ×2			Grey	[a] Myofibrillar myopathy
CACNA1C	Dark blue[c]					[c] Timothy syndrome
CACNB2	White					
CALR3	White					
CASQ2	White					
CAV3	Dark blue[a]					[a] Caveolinopathy
CDH2				White		
COX15	Dark blue[a]					[a] Leigh syndrome
CRYAB	Dark blue[a]					[a] Alpha-B crystallinopathy
CSRP3	Light blue	White				
CTF1		White				
CTNNA3				White		
DES	Dark blue[c]	Dark blue	Grey	Light blue	Grey	[c] Desminopathy
DMD		Dark blue[c]	Grey			[c] X-linked progressive MD
DMPK			Grey			
DSC2				Dark blue ×2		
DSG2		White		Dark blue ×2		
DSP	White	Dark blue ×2	Grey	Dark blue		
DTNA		White	Grey			
EYA4		White				
FHL1	Dark blue[c]					[c] Emery–Dreifuss MD
FLNC	Dark blue[c]	Dark blue ×2	Grey	Grey	Grey	[c] Myofibrillar myopathy
FHOD3	Grey					
FXN	Dark blue[a]					[a] Friedreich ataxia
GAA	Dark blue[a]					[a] Pompe disease

Continued

GATA4			◌			
GATAD1		○				
GLA	●[c]					[c] Anderson–Fabry disease
HCN4			◌			
ILK		○	◌			
JPH2	◍	◍				
JUP				●[a]		Naxos disease (cardiocutaneous syndrome)
KCNQ1	○					
KLF10	○					
LAMA4		○				
LAMP2	●[c]					[c] Danon disease
LDB3	●[a]	○	◌	○		[a] Myofibrillar myopathy
LMNA		●●	◌	○		
LRRC10		○				
MIB1		○	◌			
MYBPC3	●●●	○	◌	○	◌	
MYH6	○	○				
MYH7	●●●	●●	◌	○	◌	
MYL2	●●	○	◌	○	◌	
MYL3	●●	○	◌	○	◌	
MYLK2	○					
MYOM1	○					
MYOZ2	○					
MYPN	○	○			◌	
NEBL		○				
NEXN	○	◍				
NKX2–5		○	◌			
NNT			◌			
NONO			◌			
NPPA		○				
OBSCN	○	○	◌			
PDLIM3	○	○				
PKP2		○		●●●		
PLEKHM2		○				
PLN[b]	●	●	◌	◍		

Continued

PRDM16		● white	● grey			
PRKAG2	● blue [c]					[c] *PRKAG2* cardiomyopathy
PSEN1		● white				
PSEN2		● white				
PTPN11	● blue [c]					[c] Noonan syndrome
RAF1	● blue [c]					[c] Noonan syndrome
RBM20		●● blue	● grey			
RIT1	● blue [c]					[c] Noonan syndrome
RYR2	● white		● grey	● white		
SCN5A		● blue	● grey	● white		
SGCD		● white				
SLC25A4	● blue [a]					[a] Mitochondrial disease
TAZ			● grey			
TBX5			● grey			
TBX20		● white	● grey			
TCAP	● white	● white				
TGFB3				● white		
TJP1				● white		
TMEM43		● grey	● grey	● blue [a]		
TMEM70			● grey			
TMPO	● white	● white				
TNNC1	● light blue	● blue		● white		
TNNI3	●● blue	● light blue		● white	● grey	
TNNI3K		● white				
TNNT2	●●● blue	●● blue	● grey	● white	● grey	
TPM1	● blue	● light blue	● grey	● white	● grey	
TRIM63	● light blue					
TTN	● white	●●● blue	● grey	● white	● grey	
TTR	● blue [c]					[c] Transthyretin amyloidosis
VCL	● white	● light blue				

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; MD, muscular dystrophy; NDLVC, non-dilated left ventricular cardiomyopathy; RCM, restrictive cardiomyopathy.

Based on ClinGen gene validation efforts;[189–191a] ooo: very common (>10% of tested cases); oo: common (1–10% of tested cases); o: less common (<1% of tested cases); blue circle: definitive/strong evidence; light blue circle: moderate evidence; white circle: limited, no association or refuted/dispute evidence; blank cells: not classified; grey circle: has been described (generally rare, sporadic cases), yet not classified/evaluated by ClinGen. The yield may be higher in subgroups with more specific phenotypes, e.g. the yield of testing *LMNA* is higher in groups with DCM and conduction disease. As NDLVC is a new phenotypic description, genes have not been formally curated for associations with this phenotype. Values shown are based on curations for related cardiomyopathies where the phenotypic spectrum is understood to include NDLVC.

[a] indicates genes associated with syndromic presentations that can include cardiomyopathy as a feature, but where cardiomyopathy is not expected to occur as the only or presenting feature of the syndrome.

[b] *ACTN2* and *PLN* can present a mixed phenotypic picture that may not fit into classical cardiomyopathy descriptions.

[c] indicates genes associated with syndromic presentations that can include cardiomyopathy as a feature, and where cardiomyopathy may be the only or presenting feature of the syndrome. These are sometimes referred to as genocopies. E.g. *GLA* is shown as definitive for HCM, because it causes Anderson–Fabry disease which can present with LVH fulfilling diagnostic criteria for HCM.

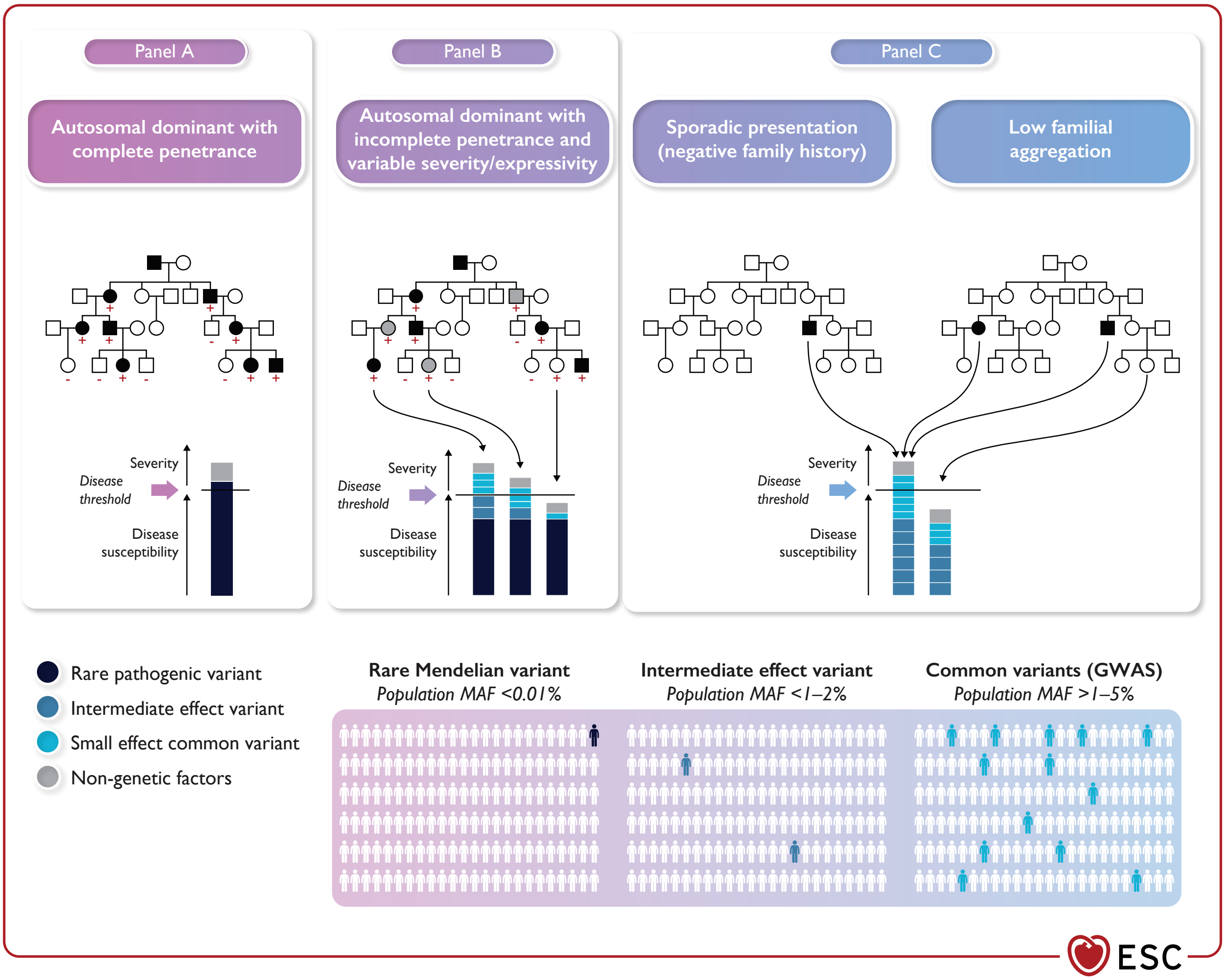

Figure 8 The genetic architecture of the cardiomyopathies. GWAS, genome-wide association studies; MAF, minor allele frequency. Cardiomyopathy can be Mendelian, caused by genetic variants that are ultra-rare in the general population and have large effect sizes. Such variants can display complete penetrance; i.e. all individuals with the variant in the family manifest the disease (panel A). However, individual variants are often insufficient to yield a disease phenotype in isolation, and their effect is modulated by the co-inheritance of modulatory genetic factors and by non-genetic factors (panel B). Besides increasing disease penetrance, such modulatory variants also affect the severity of the disease (panel B). Modulatory genetic factors are thought to comprise common variants with individually small-effect sizes and intermediate-effect variants that have population frequencies and effect sizes between rare and common variants. Some patients have a more complex aetiology (non-Mendelian/polygenic inheritance) in which a substantial number of non-Mendelian genetic factors and non-genetic factors are required to reach the threshold for disease (panel C). Such patients typically have a sporadic presentation or present with a less pronounced familial clustering of the disease. Family trees demonstrate the male (square) and female (circle) family members that are affected (black filled), with incomplete phenotype (grey filled) or unaffected (white filled). The presence or absence of the variant of interest is noted with "+" or "-", respectively.

Table 11 Utility of genetic testing in cardiomyopathies

For the patient
• Diagnosis: for the affected individual, the diagnosis of cardiomyopathy is primarily made on the basis of a phenotypic definition of disease, without reference to genetic aetiology. However, with appropriate genetic counselling and acknowledging the caveat that the finding will only be clinically actionable when a P/LP variant is found, genetic testing may be of value in clarifying borderline cases (e.g. where LVH is observed in the context of mild or controlled hypertension, but the clinician is not able to confidently distinguish between early sarcomeric HCM and a hypertensive phenocopy). Genetic testing can also identify genocopies: distinct genetic conditions that mimic a particular cardiomyopathy. • Prognosis: for an increasing number of conditions, a genetic diagnosis can provide prognostic information. For example, DCM due to variants in *LMNA* has an adverse prognosis requiring more frequent surveillance and shifting therapeutic decision thresholds with a lower threshold for primary prevention ICD implantation. • Therapy: a genetic diagnosis may directly stratify choice of therapy. In addition to decisions on primary prevention ICD implantation, an increasing number of treatments are either established or under trial for a specific molecular subtype of cardiomyopathy. In addition, with an increasingly sophisticated toolbox for

Continued

manipulation of the genome, further waves of therapies aiming to replace, alter, or remove abnormal genes and transcripts responsible for cardiomyopathies are anticipated once a precise molecular aetiology is established in a patient.

- Reproductive advice: a genetic diagnosis informs reproductive advice and management for an affected adult and/or the parents of an affected child, enabling tailored advice on inheritance patterns and the risk of transmission to future children, and opening the door to management of risk; e.g. through pre-natal diagnostics or pre-implantation genetic diagnosis.

For relatives

- Cardiomyopathies display incomplete and age-related penetrance, with great variability, therefore it is very difficult to identify clinically those relatives who are *not* at risk of developing cardiomyopathy. A normal one-off assessment is of limited value, and relatives without cardiomyopathy on initial evaluation may require long-term longitudinal surveillance. Genetic testing can eliminate this uncertainty: an individual who does not carry the genetic variant proved to be responsible for disease in their family can be confidently reassured and discharged without surveillance, while an individual who carries a disease-causing variant can be followed closely, and potentially treated early.

DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; *LMNA*, lamin A/C; LVH, left ventricular hypertrophy; P/LP, pathogenic/likely pathogenic.

6.8.2.1. Non-Mendelian cardiomyopathies and implications for genetic testing

The preceding discussion has focused on genetic testing to identify monogenic forms of cardiomyopathy. The recognition that an important proportion of cardiomyopathies have a more complex genetic architecture has important implications for the use of genetic tests.

The absence of a monogenic disease-causing variant on conventional genetic testing (i.e. sequencing for rare variants of large effect) leaves three possibilities: (i) either there is a monogenic cause that has not been identified (i.e. not detected or recognized as causative by current testing); (ii) the cardiomyopathy does not have a genetic aetiology; or (iii) the cardiomyopathy is attributable to the effects of multiple variants of individually smaller effect (*Figure 8*). Recent data suggest that for many cardiomyopathies, the absence of a rare causative variant on comprehensive testing indicates that the disease is unlikely to have a monogenic aetiology.[182,183,194] This, in turn, implies a different inheritance pattern, with a lower risk to first-degree relatives, such that ongoing surveillance may not be indicated if an initial clinical evaluation is reassuring. The use of genetic testing to identify families in whom the disease is unlikely to be monogenic represents a likely new application of conventional testing, which is gathering evidence but not yet established.

Polygenic risk scores (PRS) (sometimes known as genomic risk scores) are another form of genetic test that may, in the future, have relevance in the management of cardiomyopathies. Instead of trying to identify a single genetic variant that is responsible for disease, many variants across the genome are evaluated, each associated with a small effect on disease risk, and a score representing the aggregate risk is calculated.[182,183,195–197] To date, the value of a PRS in the clinical management of cardiomyopathies has not yet been demonstrated, and access to genetic counselling will be even more important in conveying risks and uncertainties to patients and families.

6.8.2.2. Genetic test reports and variant interpretation

Many genetic diagnostic laboratories use a standardized framework to interpret and report diagnostic genetic test results.[3,198–200] A negative genetic test result in a proband indicates that no causative variant has been found in a known disease-associated gene. This does not necessarily mean the patient does not have a genetic disease, but reflects our limited knowledge of the genetic architecture of inherited cardiomyopathies at this point in time. Aspects concerning the genetic testing approach, genetic testing methods, and variant interpretation are further elaborated in the Supplementary data online, *Section 2*, and in the European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases.[3]

6.8.3. Genetic counselling

Genetic counselling is a process that aims to support patients and their families to understand and adapt to the medical, psychosocial, and familial impact of genetic diseases.[201,202] It should be performed by healthcare professionals with specific training, such as genetic counsellors, genetic nurses, or clinical/medical geneticists, regardless of whether genetic testing is being considered. Genetic counselling can include a discussion of inheritance risks, provide education including the need for clinical evaluation, perform pre- and post-genetic test counselling, review variant classifications, obtain a three-generation family history, and provide psychosocial support.[203–205] For patients with a new diagnosis of cardiomyopathy, there can be difficulty adjusting to life with an inherited cardiomyopathy, challenges living with an implantable cardioverter defibrillator (ICD), and ongoing trauma and grief for those who have experienced a young SCD in their family. Attention to the psychological support needs of patients is therefore critical (see *Section 6.12*). Indeed, in the general setting, genetic counselling can improve knowledge, recall, and patient empowerment; increase satisfaction with decision-making; and reduce anxiety.[206–209]

6.8.3.1. Genetic counselling in children

There are specific issues to be considered when counselling children and their families and considering clinical screening and cascade genetic testing,[75,210,211] (*Table 12*) and a patient-centred approach that takes in

Table 12 Specific issues to consider when counselling children

Issue	Implications
Autonomy	Competence of child to decide on testing
Informed consent	Appropriate to understanding of child
Right to know/not to know the result	Consider wishes of child and family
Confidentiality	Context of family history
Incomplete and age-related penetrance	Symptoms/features of disease may not become apparent for many years
Lifestyle	School, sports, employment
Life stages and transition	Moving from primary to secondary education; transition to adult medical services

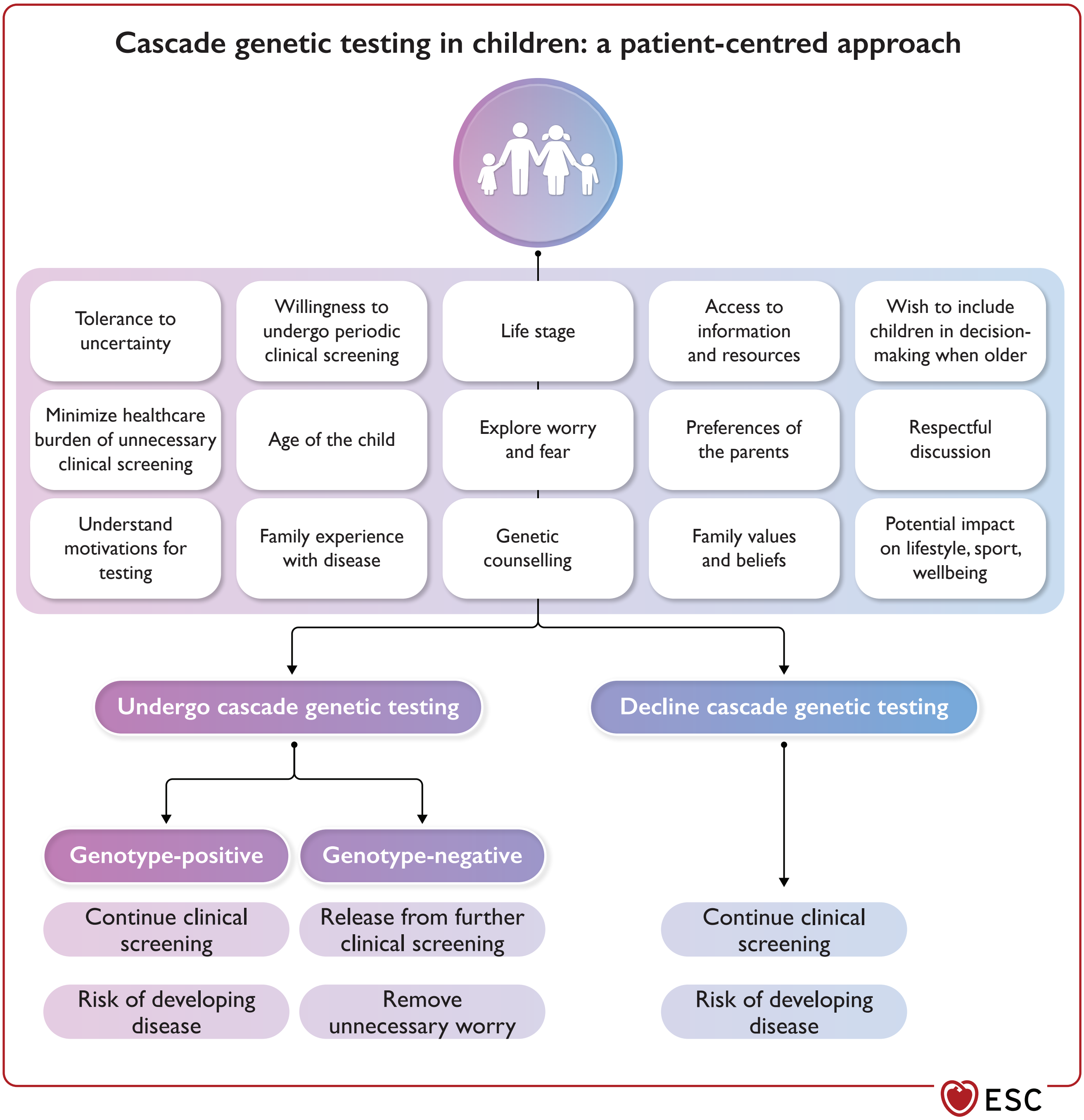

Figure 9 A patient-centred approach to cascade genetic testing of children. Factors to consider when supporting families to decide whether to pursue cascade genetic testing in children.

to account the experiences and values of the family is needed (*Figure 9*). The guiding principle remains that any testing, clinical or genetic, should be in the best interests of the child and have an impact on management, lifestyle, and/or ongoing clinical testing.[75] With appropriate multidisciplinary support in a paediatric setting, psychosocial outcomes in children undergoing clinical screening and cascade genetic testing are no different than those of the general population.[212]

6.8.3.2. Pre- and post-test genetic counselling (proband)

One critical role for genetic counselling is that it should be done alongside genetic testing (see *Section 6.8.2*).[3] This includes a discussion prior to a decision to undertake genetic testing (pre-test), and at the time of the return of the results (post-test). Key discussion points during pre- and post-test counselling are summarized in *Table 13*.

6.8.3.3. Genetic counselling for cascade testing

Once a P/LP variant has been identified within an index patient following investigations of relevant disease genes associated with the specific phenotype, it is possible to offer cascade genetic testing of first-degree at-risk relatives, including pre-test genetic counselling (see *Section 6.8*). In a scenario where a first-degree relative has died, evaluation of close relatives of the deceased individual (i.e. second-degree relatives of the index patient) should also be considered.

Table 13 Key discussion points of pre- and post-test genetic counselling

Pre-test genetic counselling	Detailed family history
	Genetic education
	Process and logistics of genetic testing and return of the result
	Explanation of all possible outcomes
	Implications for clinical care
	Lifestyle implications including sport, exercise, and employment
	Implications for the family
	Risk of reclassification
	Secondary genetic findings
	Potential insurance implications (country dependent)
	Exploration of feelings and understanding
	Psychosocial support
Post-test genetic counselling	Re-cap on key points of pre-test session
	Result disclosure
	Specific implications for clinical care
	Specific implications for the family and how to approach relatives
	Risk of reclassification, plan for resolving uncertain variant status if applicable
	Exploration of feelings and understanding
	Provision of details about how family members can access genetic counselling
	Offer information about reproductive genetic testing options for those with a genetic diagnosis
	Psychosocial support

Modified from Ingles *et al.*[213]

Table 14 Pre-natal and pre-implantation options and implications

Issue	Implications
Chorionic villus sampling	• Transcervical or transabdominal sampling of the placenta at 10–14 weeks of gestation. The procedure-related foetal loss rate is ∼0.2%.[220] • Performed at early gestational age; short testing turnaround time.
Amniocentesis	• Direct sampling of amniotic fluid is performed after 15 weeks of gestation The loss rate is ∼0.1%.[220]
Non-invasive pre-natal testing	• Performed for a single gene disorder. • Cell-free foetal DNA isolated from maternal plasma sample. • Offered in early pregnancy (approximately week 9); miscarriage risk not increased. • Not widely available (method still largely under development and therefore not readily available).
Pre-implantation genetic diagnosis	• IVF procedure with a success rate of 25–30% per embryo transfer though dependent on the mother's age and fertility, followed by biopsy and genetic testing of a single cell of the embryo. • Risks to mother and offspring of IVF, such as multiple birth, premature labour and low birth weight, as well as emotional health effects for those undergoing the procedure. • Availability and methods differ across countries.

IVF, *in vitro* fertilization.

The right assignment of the level of pathogenicity of a variant is crucial for cascade genetic testing. Inappropriate use of genetic testing in a family has the potential to introduce unnecessary worry and fear, as well as potential harm related to the misinterpretation of genetic variants. Variants should therefore be classified by a specialized multidisciplinary cardiac genetic team with an appropriate level of expertise. Systematic reclassification of identified variants and communication to families is crucial. Conveying information on the importance of clinical and genetic testing of at-risk relatives is typically reliant on the proband in the family understanding the information and passing it on to the appropriate relatives. Common barriers to communication can include poor family relationships, guilt regarding passing a causative variant on to children, psychosocial factors including distress, and comprehension of the result.[214,215] A patient will often selectively communicate genetic information to relatives, assessing their ability to understand and cope with the information, their life stage, and their risk status.[216] Poor health literacy is an important barrier to effectively communicating genetic risk information to relatives, highlighting the need for targeted resources and mechanisms for support.[217]

6.8.3.4. Pre-natal or pre-implantation genetic diagnosis

Pre-natal or pre-implantation genetic testing can be offered to parents who have had a previous affected child with an inherited cardiomyopathy due to a single or multiple pathogenic variant(s), or to couples where one or both partners carries a known pathogenic (familial) variant. The decision to pursue pre-natal or pre-implantation genetic testing should consider a spectrum of disease- and parent-related aspects, including cultural, religious, legal, and availability issues.[218] Options for pre-natal or pre-implantation genetic diagnosis should be discussed as part of the genetic counselling process and in a timely manner. If pre-natal diagnostics are performed, it should be done early enough in pregnancy to give the patient options regarding pregnancy continuation, or co-ordination of pregnancy, delivery, and neonatal care.[219]

Options for pre-natal and pre-implantation genetic diagnosis are summarized in *Table 14*. Most reproductive diagnostic testing options are for established pregnancies, except pre-implantation genetic diagnosis which allows for selective implantation of unaffected embryos.

Recommendation Table 8 — **Recommendations for genetic counselling and testing in cardiomyopathies**

Recommendations	Class[a]	Level[b]
Genetic counselling		
Genetic counselling, provided by an appropriately trained healthcare professional and including genetic education to inform decision-making and psychosocial support, is recommended for families with an inherited or suspected inherited cardiomyopathy, regardless of whether genetic testing is being considered.[204,206,208,209,221–224]	I	B
It is recommended that genetic testing for cardiomyopathy is performed with access to a multidisciplinary team, including those with expertise in genetic testing methodology, sequence variant interpretation, and clinical application of genetic testing, typically in a specialized cardiomyopathy service or in a network model with access to equivalent expertise.[222,224–226]	I	B
Pre- and post-test genetic counselling is recommended in all individuals undergoing genetic testing for cardiomyopathy.[204,208,227–236]	I	B
If pre-natal diagnostic testing is to be pursued by the family, it is recommended that this is performed early in pregnancy, to allow decisions regarding continuation or co-ordination of pregnancy to be made.	I	C
A discussion about reproductive genetic testing options with an appropriately trained healthcare professional should be considered for all families with a genetic diagnosis.	IIa	C
Index patients		
Genetic testing is recommended in patients fulfilling diagnostic criteria for cardiomyopathy in cases where it enables diagnosis, prognostication, therapeutic stratification, or reproductive management of the patient, or where it enables cascade genetic evaluation of their relatives who would otherwise be enrolled into long-term surveillance.[227–231,237,238]	I	B
Genetic testing is recommended for a deceased individual identified to have cardiomyopathy at *post-mortem* if a genetic diagnosis would facilitate management of surviving relatives.[239–243]	I	C
Genetic testing may be considered in patients fulfilling diagnostic criteria for cardiomyopathy when it will have a net benefit to the patient, considering the psychological impact and preference, even if it does not enable diagnosis, prognostication, or therapeutic stratification, or cascade genetic screening of their relatives.	IIb	C
Genetic testing in patients with a borderline phenotype not fulfilling diagnostic criteria for a cardiomyopathy may be considered only after detailed assessment by specialist teams.	IIb	C
Family members		
It is recommended that cascade genetic testing, with pre- and post-test counselling, is offered to adult at-risk relatives if a confident genetic diagnosis (i.e. a P/LP variant) has been established in an individual with cardiomyopathy in the family (starting with first-degree relatives if available, and cascading out sequentially).[204,227–232]	I	B
Cascade genetic testing with pre- and post-test counselling should be considered in paediatric at-risk relatives if a confident genetic diagnosis (i.e. a P/LP variant) has been established in an individual with cardiomyopathy in the family (starting with first-degree relatives, if available, and cascading out sequentially), considering the underlying cardiomyopathy, expected age of onset, presentation in the family, and clinical/legal consequences.[233–236,244]	IIa	B
Testing for the presence of a familial variant of unknown significance, typically in parents and/or affected relatives, to determine if the variant segregates with the cardiomyopathy phenotype should be considered if this might allow the variant to be interpreted with confidence.	IIa	C
Diagnostic genetic testing is not recommended in a phenotype-negative relative of a patient with cardiomyopathy in the absence of a confident genetic diagnosis (i.e. a P/LP variant) in the family.	III	C

Continued

P/LP, pathogenic/likely pathogenic.
[a]Class of recommendation.
[b]Level of evidence.

6.9. Diagnostic approach to paediatric patients

Traditionally, cardiomyopathies in children have been considered to be distinct entities from adolescent and adult cardiomyopathies, with different aetiologies, natural history, and management. Although substantially rarer than in adults, contemporary data have shown that, beyond the first year of life, in most cases, paediatric cardiomyopathies represent part of the spectrum of the same diseases that are seen in adolescents and adults.[245] Given their rarity, data on clinical management and outcomes are more limited than in adults, but large population-based or international consortium data have provided important information on clinical presentation, natural history, and outcomes of cardiomyopathies in children.[245] Paediatric-onset cardiomyopathies often represent two opposite ends of the spectrum of heart muscle disease: (i) severe, early-onset disease, with rapid disease progression and poor prognosis, in keeping with the most severe presentations in adults; or (ii) early phenotypic expression of adult cardiomyopathy phenotypes, increasingly identified as a result of family screening. For this reason, the Task Force highlights the principle of considering cardiomyopathies in all age groups as single disease entities, with recommendations applicable to paediatric and adult populations throughout this guideline, accepting that the evidence base for many of the recommendations is significantly more limited for children. Where there are age-related differences, these are specifically highlighted.

The general approach to paediatric and adult cardiomyopathies is based on age of onset, clinical presentation, and cardiac and systemic phenotype.[246] When a syndromic or metabolic disease is suspected, a step-by-step approach taking into consideration age of onset, consanguinity and family history, cardiac and systemic involvement, ECG and imaging, and laboratory work-up is recommended to define phenotype, aetiology, and tailored management.[247] As in adults, clinical presentation varies, from an absence of symptoms to SCD as the first and unique manifestation.[35,81,248,249]

6.9.1. Infantile and early childhood-onset cardiomyopathy

In contrast, the aetiology, natural history, and outcomes of infant-onset (<1 year of age) cardiomyopathies can be substantially different than those seen in older children, adolescents, and adults.

In infantile and early childhood-onset cardiomyopathies, clinical presentation, cardiac phenotype, and aetiology are the main determinants of management.[2] Severe clinical onset of infantile cardiomyopathies is generally managed in intensive or subintensive care units by neonatologists and paediatric cardiologists, for respiratory distress and/or metabolic acidosis, and/or hypoglycaemia, and/or hypotonia.[247,250–252] A comprehensive clinical approach, taking into consideration both the cardiac and systemic phenotype (consanguinity; dysmorphisms or skeletal anomalies; mental retardation; muscle hypotonia and weakness; hypoglycaemia with or without metabolic acidosis; increased CK and transaminases; presence of urine ketones, organic aciduria, acylcarnitine, and free fatty acid profiles; and calcium and vitamin D metabolism), and involving a multidisciplinary team (geneticist and experts in metabolic and neurological diseases), is mandatory to guide management when reversible or specific diseases are present (*Figure 10*).

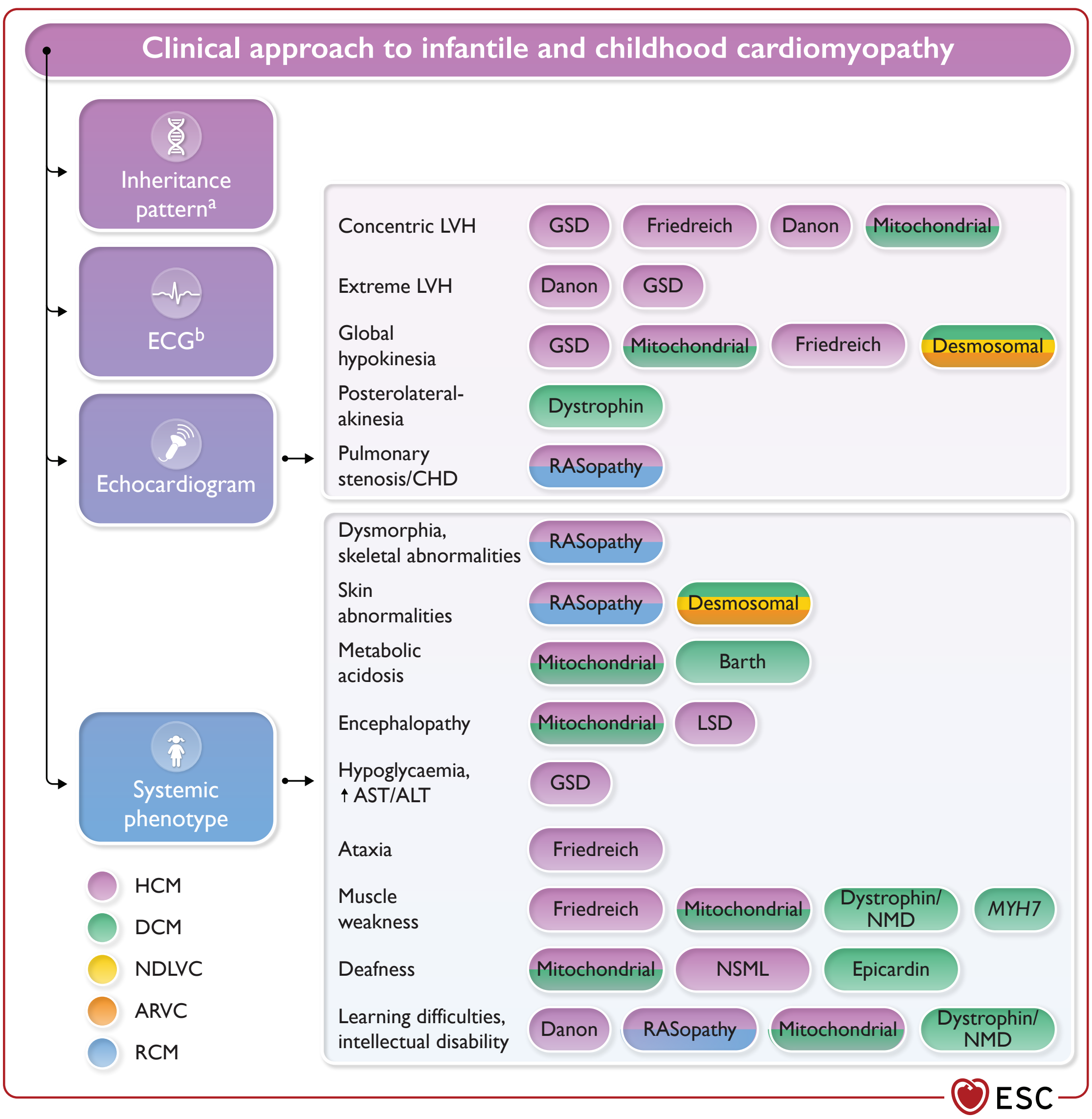

Figure 10 Clinical approach to infantile and childhood cardiomyopathy. ALT, alanine aminotransferase; ARVC, arrhythmogenic right ventricular cardiomyopathy; AST, aspartate transaminase; CHD, congenital heart disease; DCM, dilated cardiomyopathy; ECG, electrocardiogram; GSD, glycogen storage disorder; HCM, hypertrophic cardiomyopathy; LSD, lysosomal storage disease; LVH, left ventricular hypertrophy; MYH7, myosin heavy chain 7; NDLVC, non-dilated left ventricular cardiomyopathy; NSML, Noonan syndrome with multiple lentigines; RCM, restrictive cardiomyopathy. [a]See *Table 5*. [b]See *Table 7*.

In infants with HCM, after exclusion of reversible causes (maternal diabetes,[253] twin–twin syndrome, corticosteroid use[254,255]), it is important to define, along with the pattern of hypertrophy (asymmetric, concentric, biventricular), the presence of LVOTO, diastolic and/or systolic dysfunction,[1,256] and RV involvement. Early-onset sarcomeric disease (including double/compound variants) should be excluded even in the absence of a family history for HCM and SCD; these infants present with severe heart failure symptoms, and survival beyond the first year of life is uncommon.[257] In contrast, clinical presentation with heart failure is rare in infants with heterozygous sarcomeric disease compared with malformation syndromes or metabolic disorders, in whom survival rates are <90% and <70% at 1 year, respectively.[248,258,259] In infants with HCM, in the presence of biventricular outflow tract obstruction and ≥1 red flag for a neurocardiofaciocutaneous syndrome (dysmorphisms, cutaneous abnormalities, skeletal anomalies, etc.), a diagnosis of RASopathies should be strongly suspected.[260–263] Severe LVOTO in RASopathy-related HCM often requires high-dose beta blockade and, in some cases, consideration of septal myectomy.[264–267] In infants with HCM, biventricular hypertrophy, often presenting with signs of heart failure and systolic dysfunction, and ≥1 red flag for metabolic disease (muscle hypotonia, increased CK, and transaminases, consanguinity or matrilineal pattern of inheritance), it is mandatory to exclude inborn errors of metabolism, including glycogenosis type II (Pompe disease), fatty acid oxidation defects, and mitochondrial disorders.[268–272] In infants with Pompe disease, enzyme replacement therapy (ERT) has been shown to result in reversal of LVH.[269,273–275]

In infants with DCM, reversible causes (i.e. hypocalcaemic vitamin D-dependent rickets) and CHD (aortic coarctation and ALCAPA, requiring immediate surgical management) should be ruled out.[249,276,277] Viral myocarditis should also be excluded by non-invasive (i.e. laboratory) and invasive (EMB) investigations, in selected cases.[278,279] Neuromuscular (dystrophin- and sarcoglycan-related cardiomyopathies) should be excluded in patients presenting with muscle hypotonia and increased CK, and a multidisciplinary approach involving a neurologist and experts in metabolic disease is required.[280–282] When a DCM phenotype is associated with LV hypertrabeculation, other mitochondrial/metabolic diseases, including Barth syndrome, should be considered.[283–285]

Isolated RCM is rare in infants, but a mixed RCM/HCM phenotype is more frequently encountered. Familial cases are frequent, particularly in patients with an RCM/HCM phenotype.[286–289] Independently of the phenotype, it is generally associated with poor prognosis, though the RCM/HCM phenotype has significantly better transplant-free survival than isolated RCM.[286]

Arrhythmogenic RV cardiomyopathy and non-dilated LV cardiomyopathy phenotypes are very rare in infants, and are most commonly autosomal recessive forms associated with cutaneous manifestations (e.g. Naxos disease and Carvajal syndrome),[290–292] although this may reflect a lack of systematic clinical screening for these conditions in early childhood. Recent data suggest that ∼15% of ARVC patients present with paediatric-onset disease and paediatric ARVC patients more often present with severe phenotype and higher risk of SCD.[293] Increasingly, children with ARVC and NDLVC phenotypes presenting with acute myocarditic presentations are recognized.[294–297]

6.10. General principles in the management of patients with cardiomyopathy

6.10.1. Assessment of symptoms

Some people with subtle structural abnormalities with cardiomyopathy remain asymptomatic and have a normal lifespan; however, others may develop symptoms, often many years after the appearance of ECG or imaging evidence of disease. In infants, symptoms and signs of heart failure include tachypnoea, poor feeding, excessive sweating, and failure to thrive. Older children, adolescents, and adults complain of fatigue and dyspnoea as well as chest pain, palpitations, and syncope. Because the New York Heart Association (NYHA) classification to grade heart failure is not applicable to children under the age of 5 years, the Ross Heart Failure classification has been adopted in children <5 years of age but has not been validated against outcomes.[298] Systematic two-dimensional (2D) and Doppler echocardiography, resting and ambulatory ECG monitoring, and exercise testing are usually sufficient to determine the most likely cause of symptoms. Additional investigations (e.g. coronary CT scanning or coronary angiography, cardio-pulmonary exercise testing [CPET], electrophysiological study, loop recorder implantation) should be considered to investigate specific symptoms of chest pain, syncope, and palpitation, according to established clinical practice and guidelines.[1,4,69,299–301] Cardiac catheterization to evaluate right and left heart function and pulmonary arterial resistance, and CPET with simultaneous measurement of respiratory gases, is not a standard part of the work-up, but remains recommended in severely symptomatic patients with systolic and/or diastolic LV dysfunction when uncertainty about filling status exists, or for those being considered for heart transplantation or mechanical circulatory support.[69]

6.10.2. Heart failure management

The clinical management of heart failure has been described in the *2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure*.[69] In that document, recommendations are generally independent from the aetiology of heart failure and include current medical therapy, devices, and LV assist device (LVAD)/transplantation. As such, the treatment recommendations must be regarded as generic and not specific to the different forms of cardiomyopathy. Medical therapies for HFrEF based on randomized controlled trials (RCTs) from large cohorts, including angiotensin-converting enzyme inhibitors (ACE-I)/angiotensin receptor neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRA), and sodium–glucose co-transporter 2 inhibitors (SGLT2i), would be mostly applicable to genetic DCM, NDLVC, and other phenotypes associated with LV dysfunction (e.g. end-stage HCM, RCM, and ARVC). Indications for a cardiac resynchronization therapy (CRT) device and heart transplant would also be generally applicable accordingly. Recommendations for management of HFpEF would be mainly applicable to non-obstructive HCM, RCM, and cardiac amyloidosis. A Focused Update is due to be published in 2023.[69a]

Individual response to heart failure therapies may not be the same for different specific genetic causes, as has been demonstrated in several observational studies.[302,303] Further management considerations applicable to specific cardiomyopathy subtypes in adults and children, and in particular contexts, such as pregnancy and rare metabolic genocopies, are rapidly developing[304] and are discussed in the specific cardiomyopathy sections (see *Sections 7.6* and *8.2.2*).

Cardiac amyloidosis and some forms of RCM deserve special consideration regarding heart failure management. Fluid control and maintenance of euvolaemia are central. If heart failure symptoms are present, loop diuretics should be given, although orthostatic hypotension may cause intolerance, and excessive fluid loss may worsen symptoms due to restriction (e.g. in HCM or amyloidosis). The role of beta-blockers, ACE-Is, angiotensin receptor blockers (ARBs), or ARNIs in the treatment of these patients has not been determined and they may not be well tolerated because of hypotension.[305] Moreover, withdrawal of these drugs frequently leads to improvement in symptoms and should be considered.

Heart failure with an LVEF >40–50% recovered from HFrEF or HFmrEF (improved LVEF[306]) is not separately considered in the *2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure*, but is particularly important for genetic DCM, as a substantial proportion of patients with HFrEF or HFmrEF will improve their LVEF with guideline-directed medical therapy (GDMT).[69] Patients and physicians are faced with the dilemma of whether to continue lifelong pharmacotherapy or wean at some point. The TRED-HF (Therapy withdrawal in REcovered Dilated cardiomyopathy—Heart Failure) trial is the only RCT that evaluated if weaning GDMT is safe. The results showed that a large proportion of the patients had recurrent LV dysfunction or heart failure, so current recommendations caution against weaning.[307]

6.10.2.1. Preventive heart failure medical therapy of asymptomatic carriers/early disease expression

Heart failure therapy should be guided according to the *2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure* for HFrEF, HFmrEF, and HFpEF in patients with cardiomyopathy and heart failure symptoms.[69,69a] Evidence for treatment recommendations in asymptomatic LV dysfunction is scarce, which presents a challenge for genetic cardiomyopathies, where a sizeable proportion of the patients are young with no or only mild symptoms, and where asymptomatic patients are frequently discovered through cascade screening. Because heart failure medication has proved to affect LV remodelling in symptomatic patients with LV dysfunction, first-line heart failure therapy may be considered in patients with early forms of DCM/NDLVC to prevent progression of LV dilatation and dysfunction (e.g. ACE-I, ARBs, beta-blockers and MRAs, Class IIb Level C). Biomarkers may help to identify pre-symptomatic patients who might benefit from early neuro-hormonal blockade.[308] The effect of heart failure drugs to prevent progression into overt disease in genetic carriers of DCM-/NDLVC-causing variants is currently unsettled. A placebo-controlled trial (EARLY-Gene trial) is under way to test the utility of candesartan to prevent LV dysfunction/dilatation in this scenario (EudraCT: 2021-004577-30).

Management in other asymptomatic affected patients with diagnoses of HCM, ARVC, and RCM should be decided individually, as medication has not been proved to affect disease expression.

There is no evidence to support the use of current pharmacological agents for the prevention of disease development in non-affected carriers. Randomized controlled trials are warranted in order to address the value of new pharmacologic agents in this scenario.[309]

Heart failure therapies are given to children with cardiomyopathies, applying the evidence from adults to children or based on a limited number of clinical studies.[310] Heart failure therapies routinely used in children with LV dysfunction are ACE-Is, beta-blockers, diuretics, and aldosterone antagonists. Angiotensin receptor blockers are an alternative for ACE-Is. Early results of the multicentric randomized control PANORAMA-HF Trial and the subsequent Food and Drug Administration (FDA) approval for ARNI in children have paved the way for this newer class of drugs for paediatric patients with symptomatic heart failure with systemic left ventricle systolic dysfunction, 1 year of age and older. Dosing recommendations in younger children are currently pending,[311] but for children <40 kg a starting dose of 1.6 mg/kg titrated to a maximum of 3.1 mg/kg has been suggested.[312] There are currently no clinical trial or efficacy data available for SGLT-2 inhibitors in children.

6.10.2.2. Cardiac transplantation

Orthotopic cardiac transplantation should be considered in patients with moderate-to-severe drug-refractory symptoms (NYHA functional class III–IV) who meet standard eligibility criteria (see the *2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure*).[69] This may include patients with RCM and HCM with normal LVEF but severe drug-refractory symptoms (NYHA functional class III–IV) caused by diastolic dysfunction.[313–316] In patients with refractory ventricular arrhythmias that cannot be solely attributed to an acute decompensation in the setting of end-stage heart failure, a comprehensive evaluation of all potential therapeutic options (e.g. pharmacotherapy; ventricular tachycardia [VT] ablation including epicardial access if indicated and feasible; cardiac sympathetic denervation in patients with electrical storm and/or refractory polymorphic VT or rapid monomorphic VT) should be undertaken before recommending cardiac transplantation (see *Section 6.10.4*).

Recommendation Table 9 — Recommendations for cardiac transplantation in patients with cardiomyopathy

Recommendations	Class[a]	Level[b]
Orthotopic cardiac transplantation is recommended for eligible cardiomyopathy patients with advanced heart failure (NYHA class III–IV) or intractable ventricular arrhythmia refractory to medical/invasive/device therapy, and who do not have absolute contraindications.[317–319]	I	C

NYHA, New York Heart Association.
[a]Class of recommendation.
[b]Level of evidence.

6.10.2.3. Left ventricular assist devices

As there are increasing numbers of patients with end-stage heart failure, and the organ donor pool remains limited, mechanical circulatory support (MCS) with an LVAD or biventricular assist device is

Recommendation Table 10 — Recommendation for left ventricular assist device therapy in patients with cardiomyopathy

Recommendation	Class[a]	Level[b]
Mechanical circulatory support therapy should be considered in selected cardiomyopathy patients with advanced heart failure (NYHA class III–IV) despite optimal pharmacological and device treatment, who are otherwise suitable for heart transplantation, to improve symptoms and reduce the risk of heart failure hospitalization from worsening heart failure and premature death while awaiting a transplant.[320–324]	IIa	B
Mechanical circulatory support therapy should be considered in selected cardiomyopathy patients with advanced heart failure (NYHA class III–IV) despite optimal pharmacological and device therapy, who are not eligible for cardiac transplantation or other surgical options, and without severe right ventricular dysfunction, to reduce the risk of death and improve symptoms.[321,325–330]	IIa	B

NYHA, New York Heart Association.
[a]Class of recommendation.
[b]Level of evidence.

increasingly used as a bridge to transplant. Long-term MCS should also be considered as destination therapy for cardiomyopathy patients with advanced heart failure despite optimal medical therapy who are not eligible for transplantation.[69]

6.10.3. Management of atrial arrhythmias

Atrial fibrillation is the most common arrhythmia in all subtypes of cardiomyopathies and is associated with an increased risk of cardio-embolic events, heart failure, and death.[331–333] Data from 3208 consecutive adult patients in the EURObservational Research Programme (EORP) Cardiomyopathy Registry showed an AF prevalence of 28.2% at baseline and 31.1% during follow-up,[331–333] although it differed among cardiomyopathy types (see *Table 15*). Overall, annual incidence in this registry was 3.0%.[332,333] In patients with cardiomyopathies, the presence of AF is associated with more severe symptoms, an increased prevalence of cardiovascular risk factors and comorbidities, and an increased incidence of stroke and death (from any cause and from heart failure).[332,334–336]

Both the *2020 ESC Guidelines for the diagnosis and management of atrial fibrillation* and the *2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure* recommend an integrated and structured approach to facilitate guideline-adherent management. The Atrial Fibrillation Better Care (ABC) approach has been shown to reduce the risk of stroke and systemic embolism, myocardial infarction, and mortality in the general population.[337–361] Although this approach has not been specifically assessed in patients with cardiomyopathies, heart failure was present in ∼20% of the individuals of these studies and, where specified, cardiomyopathy in ∼5.5–6.5%. In particular, two RCTs support integrated care.[347,361] The RACE 3, combining the components of the ABC pathway into structured care, resulted in reduced AF burden and better rhythm control among 245 patients with early persistent AF and stable heart failure (119 randomized to targeted and 126 to conventional therapy).[347] The mobile Atrial Fibrillation App Trial (mAFA-II), which included 714 patients with heart failure (21.5%), 54 with HCM (1.6%), and 105 with DCM (3.2%), showed the superiority of integrated care supported by mobile technology in the composite outcome of 'ischaemic stroke/systemic thrombo-embolism, death, and re-hospitalization' (1.9% vs. 6.0%; hazard ratio [HR] 0.39; 95% confidence interval [CI], 0.22 to 0.67; $P < 0.001$) and re-hospitalization rates (1.2% vs. 4.5%; HR 0.32; 95% CI, 0.17 to 0.60; $P < 0.001$).[361] Adherence to the mobile health technology beyond 1 year was good, and was associated with a reduction in adverse clinical outcomes.[362]

6.10.3.1. Anticoagulation

Thrombo-embolic risk varies in different cardiomyopathy phenotypes (see *Section 7*).[332,363–367] Cardiac amyloidosis, HCM, and RCM[368] are associated with a particularly increased risk of stroke.[332,365,369,370] The EORP registry indicated a worse prognosis for the population with cardiomyopathy and concurrent AF with an annual incidence of stroke/transient ischaemic attack (TIA) about three times higher in the cardiomyopathy group with AF.[332,334] Hence, considering anticoagulation is key in patients with any type of AF or atrial flutter.

Importantly, patients with cardiomyopathy and AF have more cardio-embolic risk factors, including greater age, more advanced NYHA class and more frequent history of stroke/TIA, hypertension, and diabetes mellitus, among others.[332,333] The CHA_2DS_2-VASc (congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 [doubled], diabetes, stroke [doubled]-vascular disease, age 65–74, sex category [female]) score has not been specifically tested in patients with cardiomyopathies,[369] and retrospective evidence suggests that it may perform suboptimally with respect to stroke prediction in HCM and ATTR amyloidosis.[334,365,371–374] For this reason, although there are no RCTs evaluating the role of anticoagulation among patients with HCM, given the high incidence of stroke, prophylactic anticoagulation is recommended in all patients with HCM and AF.[334,371,372,374] A similar recommendation is given in patients with AF and RCM or cardiac amyloidosis.[375] In patients with DCM, NDLVC, or ARVC and AF, chronic oral anticoagulation should be considered on an individual basis, taking into consideration the CHA_2DS_2-VASc score, as proposed by the *2020 ESC Guidelines for the diagnosis and management of atrial fibrillation*.[336] Atrial fibrillation is a rare finding in children with genetic cardiomyopathies and no data are available regarding the performance of CHA_2DS_2-VASc or any other risk stratification score, nor the risk and benefit of prescribing oral anticoagulation. There are no data on long-term prophylactic anticoagulation in children with DCM in sinus rhythm.

In the general population, direct-acting oral anticoagulants (DOACs) are preferred for the prevention of thrombo-embolic events in patients with AF and without severe mitral stenosis and/or mechanical valve prosthesis, as they have similar efficacy to vitamin K antagonists (VKAs) but a lower risk of intracranial haemorrhage.[376] There are no randomized data comparing direct oral anticoagulants with VKAs in patients with cardiomyopathy, although data suggest that they may be used in a similar manner as the general population.[373,374,377–380]

6.10.3.2. Rate control

Rate control should be considered in any patient with cardiomyopathy presenting with AF.[336] A strict rate control (resting heart rate <80 beats per minute [b.p.m.] and heart rate during moderate exercise <110 b.p.m.) did not show any benefit over lenient rate control (resting heart rate <110 b.p.m.) in RACE II[381] and a pooled analysis of RACE II and AFFIRM.[382] However, only 8–12% of patients had a history of cardiomyopathy (type unspecified) in the RACE II trial, and only 10% of the patients in RACE II and 17% of those in the pooled analysis had a history of heart failure hospitalization or NYHA class II or III, respectively.[381,382] No data are available for the different cardiomyopathy subtypes, but observational studies suggest that higher heart rates are associated with worse outcomes in patients with heart failure.[383,384] Accordingly, the *2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure* consider lenient rate control to be acceptable as an initial approach but to target a lower heart rate in case of persistent symptoms or suspicion of associated tachycardia-induced cardiac dysfunction.[69]

Very little data are available regarding the choice of pharmacological treatment for rate control in patients with cardiomyopathies. Beta-blockers are the preferred choice in patients with cardiomyopathies given their long-established safety in the presence of LV dysfunction.[385,386] Digoxin is an alternative, particularly in patients with contraindication or intolerance to beta-blockers and among patients with AF and heart failure symptoms (RATE-AF trial), having shown no difference in quality of life (QoL) at 6 months compared with bisoprolol.[387] When administering digoxin, close monitoring of plasma drug

Table 15 Atrial fibrillation burden and management in cardiomyopathies

Condition	AF epidemiology		AF management			
	Prevalence	Annual incidence	Anticoagulation	Long-term rate control	Long-term rhythm control	
HCM	17–39%[331–334,365,413,421–428]	2.8–4.8%[332,333,365]	Always (if no contraindication)[371,429]	Beta-blockers (preferred) Verapamil or diltiazem (only if preserved LVEF) Digoxin AV node ablation + CRT or physiological pacing[388–390]	Rhythm control is preferred	
					Amiodarone, dofetilide disopyramide, sotalol,[a] dronedarone[b]	Ablation[397,412,415,416,418,430–435]
DCM	25–49%[331–333,426,436,437] LMNA related[438–441]	3.8–5.5%[332,333]	According to cardio-embolic risk (always if HF or reduced LVEF)[c]	Beta-blockers (preferred) Digoxin AV node ablation + CRT or physiological pacing[388–390]	Rhythm control preferred in case of symptoms or/and heart failure or LV dysfunction	
					Amiodarone, sotalol[a]	Ablation
NDLVC	39.2–43.1%[d] [442–444]	4.4–12%[d] [442,444,445]	According to cardio-embolic risk (always if HF or reduced LVEF)	Beta-blockers (preferred) Digoxin Verapamil or diltiazem (only if LVEF ≥40%) AV node ablation + CRT or physiological pacing[388–390]	Rhythm control preferred in case of symptoms or/and heart failure or LV dysfunction	
					Flecainide[e], amiodarone, sotalol[a]	Ablation[446]
ARVC	9–30%[331–333,437,447–451]	2.1–2.8%[332,333]	According to cardio-embolic risk (always if HF or reduced LVEF)	Beta-blockers (preferred) Verapamil or diltiazem (only if LVEF ≥40%) AV node ablation + CRT or physiological pacing[388–390]	Rhythm control preferred in case of symptoms or/and heart failure or LV dysfunction	
					Flecainide[e] (associated with beta-blockers) Amiodarone, sotalol[a]	Ablation
RCM	45–51%[331–333]	4.5–10.3%[332,333]	Always (if no contraindication)	Beta-blockers[d] (preferred) Digoxin[f] Verapamil or diltiazem (only if ≥40%) AV node ablation + CRT or physiological pacing[388–390]	Rhythm control is preferred	
					Amiodarone	No data

AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; AV, atrioventricular; CrCl, creatinine clearance; CRT, cardiac magnetic resonance; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; LMNA, lamin A/C; LV, left ventricular; LVEF, left ventricular ejection fraction; NDLVC, non-dilated left ventricular cardiomyopathy; QRS, Q, R, and S waves of an ECG; RCM, restrictive cardiomyopathy.

[a]Use with caution as evidence suggests that it may be associated with increased all-cause mortality.[452]

[b]Dronedarone is not contraindicated in LV hypertrophy but has no significant studies in HCM.

[c]LMNA-related DCM: increased risk of stroke (8–22%).[368,440]

[d]Extrapolated from studies reporting prevalent and incident AF in HFpEF.

[e]Contraindicated in patients with ischaemic heart disease or reduced LVEF. Should not be used in patients with CrCl <35 mL/min/1.73 m^2 and significant liver disease. Should be discontinued in case of QRS widening >25% above baseline and patients with left bundle branch block or any other conduction block >120 ms. Caution when sinoatrial/atrioventricular conduction disturbances.

[f]In cardiac amyloidosis, beta-blockers in low dosage and digoxin with caution.[453,454] Non-dihydropyridine calcium channel blockers may worsen LV systolic function and heart failure.[455]

levels is needed, as observational data suggest higher mortality in patients with AF, regardless of heart failure; the risk of death was related to serum digoxin concentration and was highest in patients with concentrations ≥1.2 ng/mL. On the contrary, a lower mortality with beta-blocker therapy in AF patients with concomitant heart failure has been observed. Non-dihydropyridine calcium channel blockers (CCBs) (verapamil or diltiazem) may only be used in patients with LVEF ≥40%.[336]

Atrioventricular node ablation is also an alternative in patients with poor ventricular rate control despite medical treatment not eligible for rhythm control by catheter ablation or in patients with biventricular pacing.[336] In patients with symptomatic persistent AF (>6 months) unsuitable for AF ablation or in which AF ablation had failed, narrow QRS and at least one admission for heart failure, AV node ablation in association with CRT has been shown to be superior to rate control with pharmacological therapy, reducing the composite outcome of death due to heart failure, or hospitalization due to heart failure, or worsening heart failure,[388] and all-cause mortality,[389] irrespective of baseline EF (APAF-CRT Trial). Whether conduction system-pacing is a (better) alternative to CRT needs to be further explored with only one small crossover trial (ALTERNATIVE-AF) comparing His-Bundle pacing (HBP) and biventricular pacing in 50 patients with LVEF ≤40% with persistent AF undergoing AV node ablation.[390] In this study, both arms significantly improved LVEF at 9 months, with a small, but statistically significant superiority with HBP.[69,336]

6.10.3.3. Rhythm control

Atrial fibrillation can result in haemodynamic and clinical decompensation due to shortening of the diastolic filling time with rapid heart rates and dependence on atrial contraction for LV filling. Therefore, maintenance of sinus rhythm is highly desirable and a rhythm control strategy is preferred, particularly in the presence of symptoms.

Regarding long-term pharmacological treatment,[336] antiarrhythmic drugs (AADs) have shown limited success in maintaining sinus rhythm over time both in the general population and in patients with cardiomyopathies,[391–393] show high rates of withdrawal due to intolerance,[394] and, most importantly, are associated with significant side effects, including proarrhythmia and extracardiac side effects, and, in some cases (sotalol and class IA drugs, such as quinidine and disopyramide), increased mortality.[394] As a consequence, a degree of caution is recommended when using antiarrhythmic drugs in this population. Data on antiarrhythmic therapy for the specific management of AF in the context of genetic cardiomyopathies other than HCM are scarce. It is important to note the potential for proarrhythmia of class I antiarrhythmics, particularly in the presence of significant structural heart disease; these should therefore be used with caution. Antiarrhythmic drug–drug treatment has mostly been limited to amiodarone or sotalol, as there are no available data regarding other antiarrhythmics such as dofetilide or dronedarone. Importantly, sotalol should not be used in patients with HFrEF, significant LVH, prolonged QT, asthma, hypokalaemia, or creatinine clearance (CrCl) <30 ml/min. Likewise, dronedarone should be avoided in patients with recent decompensated heart failure or permanent AF as it has been shown to increase mortality.[395,396]

Catheter ablation of AF is a safe and superior alternative to AAD therapy for maintenance of sinus rhythm, reducing AF-related symptoms, and improving QoL, and can be considered an alternative to AAD therapy in practically any type and context of AF.[336,397] In patients with AF and normal LVEF, catheter ablation has not been shown to reduce total mortality or stroke.[398] In selected patients with HFrEF,[399–401] ablation has shown a reduction in all-cause mortality and hospitalizations, and should be considered as a first-line option. In the general AF population, the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) randomized 2789 patients with early AF and associated cardiovascular comorbidities to an early rhythm control strategy or usual care (28.6% with heart failure).[402] The trial was stopped early after a median follow-up of 5.1 years for a lower occurrence of the primary outcome of death, stroke, or hospitalization for worsening heart failure or acute coronary syndrome in the patients in the early rhythm control group vs. those assigned to usual care. A pre-specified analysis evaluated the effects in patients with heart failure, showing the benefit of early rhythm control in this subgroup of patients,[403] findings which corroborated those of the CABANA trial.[400] In patients with AF and heart failure, several RCTs have demonstrated an improvement in outcomes with catheter ablation when compared with medical therapy.[399–401,404–409] Some observational studies in patients with HFpEF have also suggested better results in terms of freedom from AF and all-cause mortality,[410] but proper RCTs are warranted.

The role of catheter ablation in patients with cardiomyopathies has been reported in several registries, mainly in HCM patients.[397,411–420] Overall, maintenance is achieved in up to two-thirds of patients, although repeat procedures or continuation of antiarrhythmic medications are often necessary.[397,411,415–419] Patients with cardiomyopathies may have a higher risk of AF recurrence, particularly in the presence of atrial remodelling/dilatation.[397]

6.10.3.4. Comorbidities and risk factor management

Cardiovascular risk factors and comorbidities are also more frequent in patients with cardiomyopathies and AF. These include smoking, alcohol consumption, hypertension, diabetes mellitus type 2, hyperlipidaemia, renal impairment, chronic obstructive pulmonary disease, valvular and ischaemic heart disease, and anaemia.[332,334] Furthermore, these patients have a larger body mass index and report less physical activity than those without AF.[332,334] These risk factors and comorbidities are associated with the risk of AF and its complications and should therefore be appropriately identified and managed to prevent AF progression and the occurrence of adverse outcomes.[336]

Recommendation Table 11 — Recommendations for management of atrial fibrillation and atrial flutter in patients with cardiomyopathy

Recommendations	Class[a]	Level[b]
Anticoagulation		
Oral anticoagulation in order to reduce the risk of stroke and thrombo-embolic events is recommended in all patients with HCM or cardiac amyloidosis and AF or atrial flutter (unless contraindicated).[332,365,369,371,373,378,413,427,428,456–464]	I	B
Oral anticoagulation to reduce the risk of stroke and thrombo-embolic events is recommended in patients with DCM, NDLVC, or ARVC, and AF or atrial flutter with a CHA_2DS_2-VASc score ≥2 in men or ≥3 in women.[465–469]	I	B

Continued

Oral anticoagulation to reduce the risk of stroke and thrombo-embolic events should be considered in patients with RCM and AF or atrial flutter (unless contraindicated).	IIa	C
Oral anticoagulation to reduce the risk of stroke and thrombo-embolic events should be considered in patients with DCM, NDLVC, or ARVC, and AF or atrial flutter with a CHA_2DS_2-VASc score of 1 in men or of 2 in women.[470–472]	IIa	B
Control of symptoms and heart failure		
Atrial fibrillation catheter ablation is recommended for rhythm control after one failed or intolerant class I or III AAD to improve symptoms of AF recurrences in patients with paroxysmal or persistent AF and cardiomyopathy.[335,397–399,412,415–420,430–435,447,451,473–498]	I	B
Atrial fibrillation catheter ablation is recommended to reverse LV dysfunction in AF patients with cardiomyopathy when tachycardia-induced component is highly probable, independent of their symptom status.[405,407,408,499–501]	I	B
Maintenance of sinus rhythm rather than rate control should be considered at an early stage for patients with a cardiomyopathy and AF without major risk factors for recurrence, regardless of symptoms.[402]	IIa	C
Atrial fibrillation catheter ablation should be considered as first-line rhythm control therapy to improve symptoms in selected patients with cardiomyopathy and paroxysmal or persistent AF without major risk factors for recurrences as an alternative to class I or III AADs, considering patient choice, benefit, and risk.[392,393,480,502–506]	IIa	C
Atrial fibrillation catheter ablation should be considered in selected patients with cardiomyopathy, AF, and heart failure and/or reduced LVEF to prevent AF recurrences and improve QoL, LVEF, and survival and reduce heart failure hospitalization.[399–401,403–408,499–501,507]	IIa	B
Comorbidities and associated risk factors management		
Modification of unhealthy lifestyle and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity in patients with cardiomyopathy.[347,508–513]	I	B

AAD, antiarrhythmic drug; AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; CHA_2DS_2-VASc, congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74, sex category (female) (score); DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVEF, left ventricular ejection fraction; NDLVC, non-dilated left ventricular cardiomyopathy; QoL, quality of life; RCM, restrictive cardiomyopathy.
[a]Class of recommendation.
[b]Level of evidence.

6.10.4. Management of ventricular arrhythmias

Ventricular arrhythmias, particularly in the form of electrical storm and/or repetitive appropriate ICD interventions, contribute to a significantly increased risk of morbidity and mortality in patients with cardiomyopathies.[299]

The *2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death* provide detailed recommendations on acute and long-term management of ventricular arrhythmias in patients with cardiomyopathies.[299] Limited data exist addressing ventricular arrhythmia management in patients with specific genetic cardiomyopathies. Nonetheless, some general concepts can be highlighted:

- Any reversible cause and/or precipitating factor, such as electrolyte imbalances, ischaemia, hypoxaemia, or drugs, should be identified and corrected when possible.
- Extensive efforts should be made in the attempt to understand the aetiology (i.e. underlying mechanism and substrate, and their relationship with the underlying cardiomyopathy) as this will influence the choice of treatment.
- Acute termination of sustained ventricular arrhythmias can be achieved with electrical cardioversion, AADs, or pacing. The initial choice of treatment will depend on the haemodynamic tolerance, the underlying aetiology, and the patient profile.
- In patients presenting with electrical storm, mild-to-moderate sedation is recommended to alleviate psychological distress and reduce sympathetic tone. If the electrical storm remains intractable despite antiarrhythmic therapies, deep sedation/intubation should be considered.
- In case of incessant ventricular arrhythmias and electrical storm not responding to antiarrhythmic medication, catheter ablation is recommended. In refractory cases or whenever VT ablation is either not indicated or not immediately available, autonomic modulation (i.e. stellate ganglion block or cardiac sympathetic denervation, depending on the setting) and/or MCS may be considered.
- In patients with cardiomyopathies and scar-related ventricular arrhythmias, the therapeutic arsenal for long-term prevention of recurrent ventricular arrhythmias includes antiarrhythmic medications (mostly limited to beta-blockers, sotalol, and amiodarone) and catheter ablation (particularly in the case of sustained monomorphic VT or in the case of polymorphic VT triggered by a premature ventricular complex of similar morphology). Additional strategies, performed by experienced centres, may be considered, depending on the characteristics of the patient and the ventricular arrhythmia, including acute neuromodulation strategies (stellate ganglion block and thoracic epidural anaesthesia), chronic neuromodulation strategies (cardiac sympathetic denervation), and stereotactic non-invasive VT ablation.[514–520] Limited data are available at present concerning the long-term cardiac and extracardiac safety of stereotactic non-invasive VT ablation, as well as the dose–response relationship, therefore its usage should be limited to compassionate cases or within prospective clinical studies.
- The acute as well as the chronic management of patients with cardiomyopathies and refractory ventricular arrhythmias, particularly in case of concomitant moderate-to-severe ventricular dysfunction, should involve an integrated evaluation by a heart team including cardiomyopathy specialists, electrophysiologists with specific experience in catheter ablation of ventricular arrhythmias and neuromodulation, anaesthesiologists, and cardiac surgeons.

6.10.5. Device therapy: implantable cardioverter defibrillator

Implantable cardioverter defibrillators are effective at correcting potentially lethal ventricular arrhythmias and preventing SCD, but are also associated with complications, particularly in young patients who will require several replacements during their lifetimes. Implantable cardioverter defibrillators reduce mortality in survivors of cardiac arrest and in patients who have experienced haemodynamically compromising sustained ventricular arrhythmias.[521–523] An ICD is recommended in such patients when the intent is to increase survival; the decision to implant should consider the patient's view and their QoL, as well as the absence of other diseases likely to cause death within the following year.

Arrhythmic risk calculators may be useful tools to predict the risk of SCD and, where available, they may provide a clinical benefit compared with a risk factor approach.[524–526] The issue of the threshold for ICD implantation may be a reasonable concern as every cut-off point comes with a trade-off between unnecessary ICDs with their potential complications vs. the potential for unprotected SCD. The relative weight of these opposing undesirable events varies significantly from one person to another and should be part of the individualized decision-making process. Risk stratification strategies in each cardiomyopathy and the role of ICDs for primary prevention are discussed in *Section 7*.

The *2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death* provide detailed recommendations regarding optimal device programming and prevention/treatment of inappropriate therapy. The implantation of conditional devices is reasonable taking into account the expected need for CMR during follow-up. In children, simpler ICD devices (e.g. single chamber/single coil or subcutaneous) should be considered, bearing in mind specific issues of body size/shape and growth. The wearable cardioverter defibrillator has been shown to detect and treat ventricular arrhythmias successfully.[527] However, data on its benefit for primary prevention other than the early phase of myocardial infarction (e.g. myocarditis, PPCM etc.) are scarce and no recommendation can be made at present.

Recommendation Table 12 — Recommendations for implantable cardioverter defibrillator in patients with cardiomyopathy

Recommendations	Class[a]	Level[b]
General recommendations		
Implantation of a cardioverter defibrillator is only recommended in patients who have an expectation of good quality survival >1 year.	I	C
It is recommended that ICD implantation be guided by shared decision-making that: • is evidence-based; • considers a person's individual preferences, beliefs, circumstances, and values; and • ensures that the person understands the benefits, harms, and possible consequences of different treatment options.[c]	I	C
It is recommended that prior to ICD implantation, patients are counselled on the risk of inappropriate shocks, implant complications, and the social, occupational, and driving implications of the device.	I	C
It is not recommended to implant an ICD in patients with incessant ventricular arrhythmias until the ventricular arrhythmia is controlled.	III	C
Secondary prevention		
Implantation of an ICD is recommended:[d]		
• in patients with HCM, DCM, and ARVC who have survived a cardiac arrest due to VT or VF, or who have spontaneous sustained ventricular arrhythmia causing syncope or haemodynamic compromise in the absence of reversible causes.[528–534]	I	B
• in patients with NDLVC and RCM who have survived a cardiac arrest due to VT or VF, or who have spontaneous sustained ventricular arrhythmia causing syncope or haemodynamic compromise in the absence of reversible causes.	I	C
ICD implantation should be considered in patients with cardiomyopathy presenting with haemodynamically tolerated VT, in the absence of reversible causes.	IIa	C
Primary prevention		
Comprehensive SCD risk stratification is recommended in all cardiomyopathy patients who have not suffered a previous cardiac arrest/sustained ventricular arrhythmia at initial evaluation and at 1–2 year intervals, or whenever there is a change in clinical status.	I	C
The use of validated SCD algorithms/scores as aids to the shared decision-making when offering ICD implantation, where available:[e]		
• is recommended in patients with HCM.[81,525,535]	I	B
• should be considered in patients with DCM, NDLVC, and ARVC.[185,186,524,526,536–542]	IIa	B
If a patient with cardiomyopathy requires pacemaker implantation, comprehensive SCD risk stratification to evaluate the need for ICD implantation should be considered.	IIa	C
Choice of ICD		
When an ICD is indicated, it is recommended to evaluate whether the patient could benefit from CRT.[533]	I	A
Subcutaneous defibrillators should be considered as an alternative to transvenous defibrillators in patients with an indication for an ICD when pacing therapy for bradycardia, cardiac resynchronization, or antitachycardia pacing is not anticipated.[543]	IIa	B
The wearable cardioverter defibrillator should be considered for adult patients with a secondary prevention ICD indication who are temporarily not candidates for ICD implantation.	IIa	C

Continued

ARVC, arrhythmogenic right ventricular cardiomyopathy; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; NDLVC, non-dilated left ventricular cardiomyopathy; RCM, restrictive cardiomyopathy; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

[a]Class of recommendation.

[b]Level of evidence.

[c]Shared decision-making is greatly enhanced by patient decision aids tailored specifically to receivers of care as well as more traditional decision-support tools for healthcare practitioners.

[d]The difference in level of evidence reflects the different levels of evidence available for the various cardiomyopathy phenotypes.

[e]The difference in class of recommendation reflects different performance of available models for different cardiomyopathy phenotypes.

6.10.6. Routine follow-up of patients with cardiomyopathy

In general, patients with cardiomyopathy require lifelong follow-up to detect changes in symptoms, risk of adverse events, ventricular function, and cardiac rhythm.

The frequency of monitoring is determined by the severity of disease, age, and symptoms. A clinical examination, including 12-lead ECG and TTE, should be performed every 1–2 years, or sooner should patients complain of new symptoms. Ambulatory electrocardiography is recommended every 1–2 years in most patients to detect asymptomatic atrial and ventricular arrhythmia, and is indicated whenever patients experience syncope or palpitations. Cardiac magnetic resonance evaluation should be considered every 2–5 years or more frequently in patients with progressive disease (see *Section 6.7.3*). Cardio-pulmonary exercise testing can provide objective evidence for worsening disease but need only be performed every 2–3 years unless there is a change in symptoms. Ergometry and treadmill exercise testing may also provide valuable functional information in patients unable to perform CPET.

Recommendation Table 13 — Recommendations for routine follow-up of patients with cardiomyopathy

Recommendations	Class[a]	Level[b]
It is recommended that all clinically stable patients with cardiomyopathy undergo routine follow-up using a multiparametric approach that includes ECG and echocardiography every 1 to 2 years.	I	C
Clinical evaluation with ECG and multimodality imaging is recommended in patients with cardiomyopathy whenever there is a substantial or unexpected change in symptoms.	I	C

ECG, electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.

6.11. Family screening and follow-up evaluation of relatives

All first-degree relatives of patients with cardiomyopathy should be offered clinical screening with ECG and cardiac imaging (echocardiogram [ECHO] and/or CMR). In families in whom a disease-causing genetic variant has been identified, cascade genetic testing should be offered (see *Section 6.8.3*). Individuals found not to carry the familial variant and who do not have a clinical phenotype can usually be discharged, with advice to seek re-assessment if they develop symptoms or when new clinically relevant data emerge in the family. Those relatives harbouring the familial genetic variant(s) should undergo regular clinical evaluation with ECG, multimodality cardiac imaging, and additional investigations (e.g. Holter monitoring) guided by age, family phenotype, and genotype (*Figure 11*). Similarly, if a genetic cause of the disease has not been identified, either because P/LP variants are absent in the proband or because genetic testing has not been performed, clinical follow-up of all first-degree relatives is recommended; in families without a known disease-causing variant, children should be offered ongoing clinical surveillance, due to age-related penetrance, and ongoing surveillance should also be offered to adult relatives dependent on family history and other factors. In families where there is only one affected individual and where no genetic variant has been identified, the frequency and duration of clinical follow-up may be reduced (see *Figure 11*).

Generally, the frequency of the clinical cardiac evaluation in relatives will be based on the inheritance pattern, the risk of events in the affected individual(s), and the quality-adjusted life-year. It would also depend on age, type of cardiomyopathy, and family history (penetrance, phenotype expression, and risk of complications in affected relatives).

Disease-penetrance studies have demonstrated a similar sigmoid shape pattern of phenotypic expression throughout life in families with confirmed genetic cardiomyopathies. The penetrance during childhood is ∼5% during the first decade of life, increasing to 10–20% per decade from the second to the seventh decades, after which the slope flattens to 5–10% in the last decades, although up to 25% of diagnoses can be made in individuals older than 65 years in some populations.[544] The slope in childhood and early adulthood can be steeper (20% per decade) and similar to that in middle age for HCM, where male sex, subtle ECG abnormalities, and particular genes are predictors of disease expression during follow-up.[178]

Penetrance in most cardiomyopathies is incomplete, reaching 70–90% by the age of 70 years in families with cardiomyopathy.[178]

Recommendation Table 14 — Recommendations for family screening and follow-up evaluation of relatives

Recommendations	Class[a]	Level[b]
Following cascade genetic testing, clinical evaluation using a multiparametric approach that includes ECG and cardiac imaging and long-term follow-up is recommended in first-degree relatives who have the same disease-causing variant as the proband.[178,544,547]	I	B
Following cascade genetic testing, it is recommended that first-degree relatives without a phenotype who do not have the same disease-causing variant as the proband are discharged from further follow-up but advised to seek re-assessment if they develop symptoms or when new clinically relevant data emerge in the family.	I	C
It is recommended that when no P/LP variant is identified in the proband or genetic testing is not performed, an initial clinical evaluation using a multiparametric approach that includes ECG and cardiac imaging is performed in first-degree relatives.	I	C
When no P/LP variant is identified in the proband or genetic testing is not performed, regular, long-term clinical evaluation using a multiparametric approach that includes ECG and cardiac imaging should be considered in first-degree relatives.	IIa	C
During cascade screening, where a first-degree relative has died, clinical evaluation of close relatives of the deceased individual (i.e. second-degree relatives of the index patient) should be considered.	IIa	C

ECG, electrocardiogram, P/LP, pathogenic/likely pathogenic.
[a]Class of recommendation.
[b]Level of evidence.

With some exceptions using the current diagnostic criteria, the penetrance of the disease in women has been shown to be delayed (shifted) by 10 years compared with men.[178,545–548]

Cardiac screening in: (i) carriers of genetic P/LP variants associated with cardiomyopathies; or (ii) in those with demonstration of a familial disease should be offered from childhood to old age. The proposed frequency of screening is every 1–3 years with ECG and ECHO (plus additional tests where this is considered appropriate) before the age of 60 years, and then every 3–5 years thereafter.

These recommendations apply to families affected by cardiomyopathy. The penetrance of similar variants identified outside this context is likely to be much lower, and the benefits and harm of screening and surveillance remain under evaluation.[549–551]

6.11.1. Special considerations in family screening

If the comprehensive study of the index cardiomyopathy patient (including negative genetic testing) and first-degree relatives from informative families (i.e. with a large enough pedigree) leads to the conclusion that the cardiomyopathy presents in isolation (i.e. the index patient is the only individual affected), termination of periodic surveillance could be considered in first-degree relatives ≥50 years of age with normal cardiac investigations.

When the pattern of inheritance is likely to be, or is definitively, other than autosomal dominant, consideration for periodic evaluation of relatives should be individualized, e.g. (i) heterozygous carriers from clear recessive forms of cardiomyopathy could be discharged; (ii) heterozygous carriers of X-linked disease may delay cardiac evaluation, as

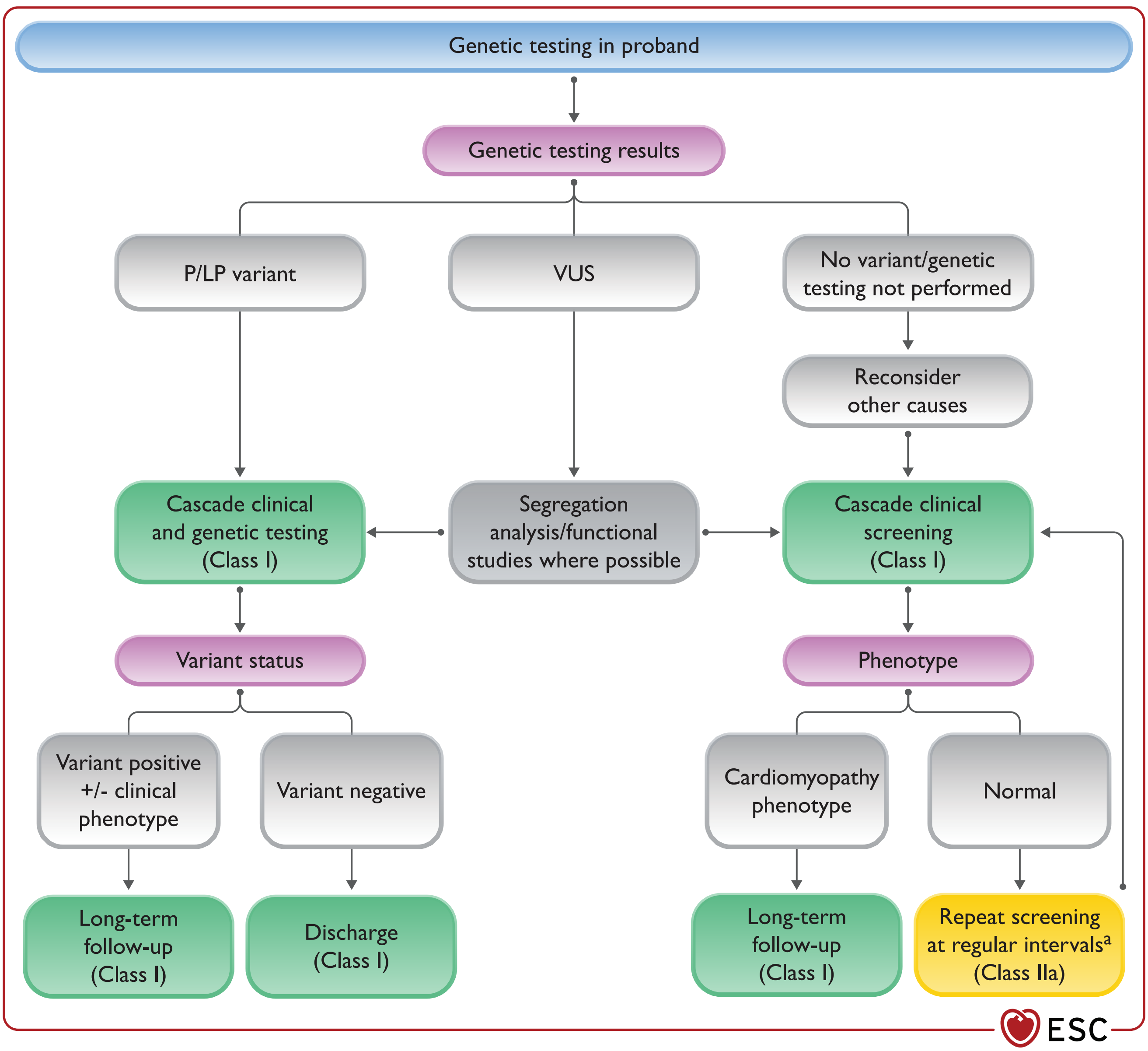

Figure 11 Algorithm for the approach to family screening and follow-up of family members. P/LP, pathogenic/likely pathogenic, VUS, variant of unknown significance. [a]If no additional affected relatives and no variant identified on genetic testing, consider earlier termination of clinical screening.

phenotype may express later in life; and (iii) follow-up in families with more than one likely or definitively pathogenic variant (oligo-polygenicity) should be discussed in the cardiomyopathy team.

6.12. Psychological support in cardiomyopathy patients and family members

Adjusting to a diagnosis of an inherited cardiomyopathy can pose a psychosocial challenge. This includes coming to terms with a new diagnosis, exclusion from competitive sports, or living with the small risk of SCD.[205] While studies show patients with inherited cardiomyopathies adjust well following an ICD, there is an important subgroup who do require additional support.[552–556] The decision to have an ICD, and living with the device, can also pose psychological challenges, especially in those who are young or who have experienced multiple shocks and/or have poor baseline psychosocial functioning.[553,554,557] The SCD of a young relative not only leads to profound grief, but one in two relatives report post-traumatic stress or prolonged grief on average 6 years after the death.[558] Clinical psychological support for patients and their families affected by inherited cardiomyopathies is an important aspect of the multidisciplinary team's care approach and should be available as required.[559] Clinicians should be aware of the potential for poor psychological outcomes and should have a low threshold for referral.

Psychological challenges for patients and their family members are summarized in *Table 16*. While many patients and family members will benefit from psychosocial counselling provided by any number of healthcare professionals, it is important to highlight that for some, treatment by a trained professional such as a clinical psychologist is required.

Table 16 Psychological considerations

Patient group	Psychological considerations
New diagnosis	• Stigma associated with cardiovascular disease and misconception that it only affects older people. • Fear of sudden cardiac death can shake confidence and create anxiety around exercise. • Fear of inheritance risk to other relatives, especially children. • Confidence and self-efficacy to manage their disease. • Direct experience with the disease will affect perceptions about prognosis.[211]
ICD	• Most patients will adjust well following ICD insertion, although there might be an initial decline in health-related quality of life and psychological well-being, this often returns to normal.[552,560,561] • Up to 30% will develop anxiety and/or symptoms of post-traumatic stress and need additional support.[562] • Those who are young, who experience multiple ICD shocks, and/or have poor baseline psychological functioning are at greater risk of poor psychological outcomes.[553–555,561,563] • In young people, especially women, body image concerns can be a major consideration.[554] • Decision-making for those recommended to have an ICD should be patient-centred and include balanced discussion of benefits and risks and careful attention to questions and concerns.[564]
Exercise restrictions	• Physical inactivity is a major determinant of poor health outcomes. • Can reduce health-related quality of life for those who become fearful of performing even low-intensity exercise. • Athletes who are recommended to reduce their activity levels can experience a profound grief and difficulty adjusting to this advice.[565] • Patient-centred discussions and careful attention to concerns is critical in helping to support people make drastic lifestyle changes.[566–568]
Family history of young SCD	• Relatives who experience the SCD of a young relative have significant risk of poor psychological functioning, including post-traumatic stress and prolonged grief.[558] • Grief is a normal response to a loss. Prolonged grief occurs when the grieving process becomes 'stuck'.[569] • Those who witness the death or discover the decedents body have a greater risk of psychological difficulties.[558] • Mothers of the decedent have greater anxiety.[558] • Psychological support for family members is an important and often unmet need following a young SCD.[570,571]
Children and adolescents	• Diagnosis during childhood can raise anxiety especially among parents. Access to resources to support practical issues like information for schools is important. • Navigating transition from paediatric to adult care can be challenging for children and their families. • Decision-making regarding genetic testing of asymptomatic children can often benefit from the inclusion of a clinical psychologist to support adjustment to the result.
Symptomatic disease	• Those managing symptoms will likely perceive a greater impact on their health-related quality of life. Factors influencing self-efficacy will impact on a patient's ability to manage their disease, including medication adherence.[572] • Need for major intervention such as cardiac transplantation can raise significant psychological challenges and clinical psychological support is very important.[573]
Genetic testing	• Despite potential adjustment issues, most patients who undertake genetic testing do not report distress.[574] • Genetic counselling should cover any psychosocial concerns or needs.[204] • Additional support to patients to convey the genetic risk information to at-risk family members should be provided as necessary.[575]

ICD, implantable cardioverter defibrillator; SCD, sudden cardiac death.

Recommendation Table 15 — Recommendations for psychological support in patients and family members with cardiomyopathies

Recommendations	Class[a]	Level[b]
It is recommended that psychological support by an appropriately trained health professional be offered to all individuals who have experienced the premature sudden cardiac death of a family member with cardiomyopathy.[558,570,571,576,577]	I	B
It is recommended that psychological support by an appropriately trained health professional be offered to all individuals with an inherited cardiomyopathy who receive an implantable cardioverter defibrillator.[552–556,561,563]	I	B
Psychological support by an appropriately trained health professional should be considered in all patients and families with an inherited cardiomyopathy and in particular for those issues described in the text.[c]	IIa	C

[a]Class of recommendation.
[b]Level of evidence.
[c]See Table 16.

6.13. The patient pathway

The systematic, multiparametric approach to diagnosis and evaluation of patients with suspected cardiomyopathy described in this section allows clinicians to establish the presence of a cardiomyopathy and identify its aetiology and guides the management of symptoms and prevention of disease-related complications. While many of the aspects of clinical care and the accompanying recommendations are common to all cardiomyopathy phenotypes, achieving an aetiological diagnosis is key to delivering disease-specific management; this is discussed in detail in the subsequent sections of this guideline (see Section 7).

7. Specific cardiomyopathy phenotypes

7.1. Hypertrophic cardiomyopathy

The *2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy* provide detailed recommendations on the assessment and management of patients with HCM.[1] The aim in this guideline is to provide a focused update to the 2014 document, highlighting novel aspects and signposting the reader to the assessment and management of HCM in adults and children. Further details to support the recommendations are available in Supplementary data online, Table S1.

7.1.1. Diagnosis

7.1.1.1. Diagnostic criteria

Adults: in an adult, HCM is defined by an LV wall thickness ≥15 mm in any myocardial segment that is not explained solely by loading conditions. Lesser degrees of wall thickening (13–14 mm) require evaluation of other features including family history, genetic findings, and ECG abnormalities.

Children: the diagnosis of HCM requires an LV wall thickness more than 2 standard deviations greater than the predicted mean (z-score >2).[578]

Relatives: the clinical diagnosis of HCM in adult first-degree relatives of patients with unequivocal disease is based on the presence of LV wall thickness ≥13 mm. In child first-degree relatives with LV wall thickness z-scores of <2, the presence of associated morphological or ECG abnormalities should raise the suspicion but are not on their own diagnostic for HCM.

7.1.1.2. Diagnostic work-up

The initial work-up for HCM includes personal and family history, physical examination, electrocardiography, cardiac imaging, and first-line laboratory tests, as described in Section 6.

7.1.1.3. Echocardiography

As increased ventricular wall thickness can be found at any location (including the right ventricle), the presence, distribution, and severity of hypertrophy should be documented using a standardized protocol for cross-sectional imaging from several projections.[579] Table 17 summarizes the key imaging features to assess in patients with suspected or confirmed HCM. Several imaging features can point to a specific diagnosis (Table 18 and Section 6).[62]

Identification of LVOTO is important in the management of symptoms and assessment of SCD risk (see Section 7.1.5). Two-dimensional and Doppler echocardiography during a Valsalva manoeuvre in the sitting and semi-supine position—and then on standing if no gradient is provoked—is recommended in all patients (Figure 12).[587,588] Exercise stress echocardiography is recommended in *symptomatic* patients if bedside manoeuvres fail to induce LVOTO ≥50 mmHg. Pharmacological provocation with dobutamine is not advised, as it is not physiological and can be poorly tolerated.

Recommendation Table 16 — Recommendation for evaluation of left ventricular outflow tract obstruction

Recommendations	Class[a]	Level[b]
In all patients with HCM, at initial evaluation, transthoracic 2D and Doppler echocardiography are recommended, at rest and during Valsalva manoeuvre in the sitting and semi-supine positions—and then on standing if no gradient is provoked—to detect LVOTO.[84,86,365,525,584,587,589–594]	I	B
In symptomatic patients with HCM and a resting or provoked[c] peak instantaneous LV outflow tract gradient <50 mmHg, 2D and Doppler echocardiography during exercise in the standing, sitting (when possible), or semi-supine position are recommended to detect provocable LVOTO and exercise-induced mitral regurgitation.[588,595–598]	I	B
Transoesophageal echocardiography should be considered in patients with HCM and LVOTO if the mechanism of obstruction is unclear or when assessing the mitral valve apparatus before a septal reduction procedure, or when severe mitral regurgitation caused by intrinsic valve abnormalities is suspected.[599–602]	IIa	C

Continued

In symptomatic patients with HCM and inconclusive non-invasive cardiac imaging, left and right heart catheterization may be considered to assess the severity of LVOTO and to measure LV filling pressures.[603]	IIb	C

2D, two-dimensional; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVOTO, left ventricular outflow tract obstruction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Provocation with Valsalva, standing, or oral nitrate.

7.1.1.4. Cardiac magnetic resonance

Cardiac magnetic resonance is recommended in patients with HCM at their baseline assessment (general recommendations are described in *Section 6.7.3* and Recommendation Table 5). CMR imaging can be particularly helpful in patients with suspected apical or lateral wall hypertrophy or LV apical aneurysm. *Table 17* summarizes the main features to be assessed.

Late gadolinium enhancement is present in 65% of patients (range 33–84%), typically in a patchy mid-wall pattern in areas of hypertrophy and at the anterior and posterior RV insertion points.[604] Late gadolinium enhancement is unusual in non-hypertrophied segments except in advanced stages of disease, when full-thickness LGE in association with wall thinning is common.[604] Late gadolinium enhancement may be associated with increased myocardial stiffness and adverse LV remodelling and the extent of LGE is associated with a higher incidence of RWMAs. Late gadolinium enhancement varies substantially with the quantification method used but the 2-standard deviation technique is the only one validated against necropsy.[605]

Although CMR rarely distinguishes the causes of HCM by their magnetic properties alone, the distribution and severity of interstitial expansion can, in context, suggest specific diagnoses (see *Section 6*). The absence of fibrosis may be helpful in differentiating HCM from physiological adaptation in athletes, but LGE may be absent in people with HCM, particularly young people and those with mild disease.

Recommendation Table 17 — Additional recommendation for cardiovascular magnetic resonance evaluation in hypertrophic cardiomyopathy

Recommendation	Class[a]	Level[b]
Contrast-enhanced CMR may be considered before ASA or myectomy to assess the extent and distribution of hypertrophy and myocardial fibrosis.[606,607]	IIb	C

ASA, alcohol septal ablation; CMR, cardiac magnetic resonance.
[a]Class of recommendation.
[b]Level of evidence.

Table 17 Imaging evaluation in hypertrophic cardiomyopathy

Item to assess	Primary imaging modality	Comments
LV wall thickness	ECHO/CMR	• All LV segments from base to apex examined in end-diastole, preferably in the 2D short-axis view, ensuring that the wall thickness is recorded at mitral, mid-LV, and apical levels. • CMR is superior in the detection of LV apical and anterolateral hypertrophy, aneurysms,[580] and thrombi,[581] and is more sensitive in the detection of subtle markers of disease in patients with sarcomeric protein gene variants (e.g. myocardial crypts, papillary muscle abnormalities).[159,582,583]
Systolic function (global and regional)	ECHO/CMR	• Ejection fraction is a suboptimal measure of LV systolic performance when hypertrophy is present. • Doppler myocardial velocities and deformation parameters (strain and strain rate) are typically reduced at the site of hypertrophy despite a normal EF and may be abnormal before the development of increased wall thickness in genetically affected patients.
Diastolic function	ECHO	• Routine examination should include mitral inflow assessment, tissue Doppler imaging, pulmonary vein flow velocities, pulmonary artery systolic pressure, and LA size/volume.
Mitral valve	ECHO	• Assess presence and degree of SAM and mitral regurgitation. The presence of a central- or anteriorly directed jet of mitral regurgitation should raise suspicion of an intrinsic/primary mitral valve abnormality and prompt further assessment.
LVOT	ECHO	• See *Figure 12*.
LA dimensions	ECHO/CMR	• Provides important prognostic information.[365,525,584] • Most common mechanisms of LA enlargement are SAM-related mitral regurgitation and elevated LV filling pressures.
Myocardial fibrosis/LGE	CMR	• The distribution and severity of interstitial expansion can suggest specific diagnoses. Anderson–Fabry disease is characterized by a reduction in non-contrast T1 signal and the presence of posterolateral LGE.[134,155] In cardiac amyloidosis, there is often global, subendocardial or segmental LGE and a highly specific pattern of myocardial and blood-pool gadolinium kinetics caused by similar myocardial and blood T1 signals.[585,586]

2D, two-dimensional; CMR, cardiac magnetic resonance; ECHO, echocardiogram; EF, ejection fraction; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricular; LVOT, left ventricular outflow tract; SAM, systolic anterior motion; SCD, sudden cardiac death.

Table 18 Echocardiographic features that suggest specific aetiologies in hypertrophic cardiomyopathy

Finding	Specific diseases to be considered
Increased interatrial septum thickness	Amyloidosis
Increased AV valve thickness	Amyloidosis; Anderson–Fabry disease
Increased RV free wall thickness	Amyloidosis, myocarditis, Anderson–Fabry disease, Noonan syndrome, and related disorders
Mild-to-moderate pericardial effusion	Amyloidosis, myocarditis/myopericarditis
Ground-glass appearance of ventricular myocardium on 2D echocardiography	Amyloidosis
Concentric LVH	Glycogen storage disease, Anderson–Fabry disease, *PRKAG2* variants, Friedreich ataxia
Extreme concentric LVH (wall thickness ≥30 mm)	Danon disease, Pompe disease
Global LV hypokinesia (with or without LV dilatation)	Mitochondrial disease, TTR-related amyloidosis, *PRKAG2* variants, Danon disease, myocarditis, advanced sarcomeric HCM, Anderson–Fabry disease, Friedreich ataxia
RVOTO	Noonan syndrome and associated disorders
Apical sparing pattern on longitudinal strain imaging	Amyloidosis

2D, two-dimensional; AV, atrioventricular; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVH, left ventricular hypertrophy; *PRKAG2*, protein kinase AMP-activated non-catalytic subunit gamma 2; RV, right ventricular; RVOTO, right ventricular outflow tract obstruction; TTR, transthyretin.
Modified from Rapezzi *et al.*[62]

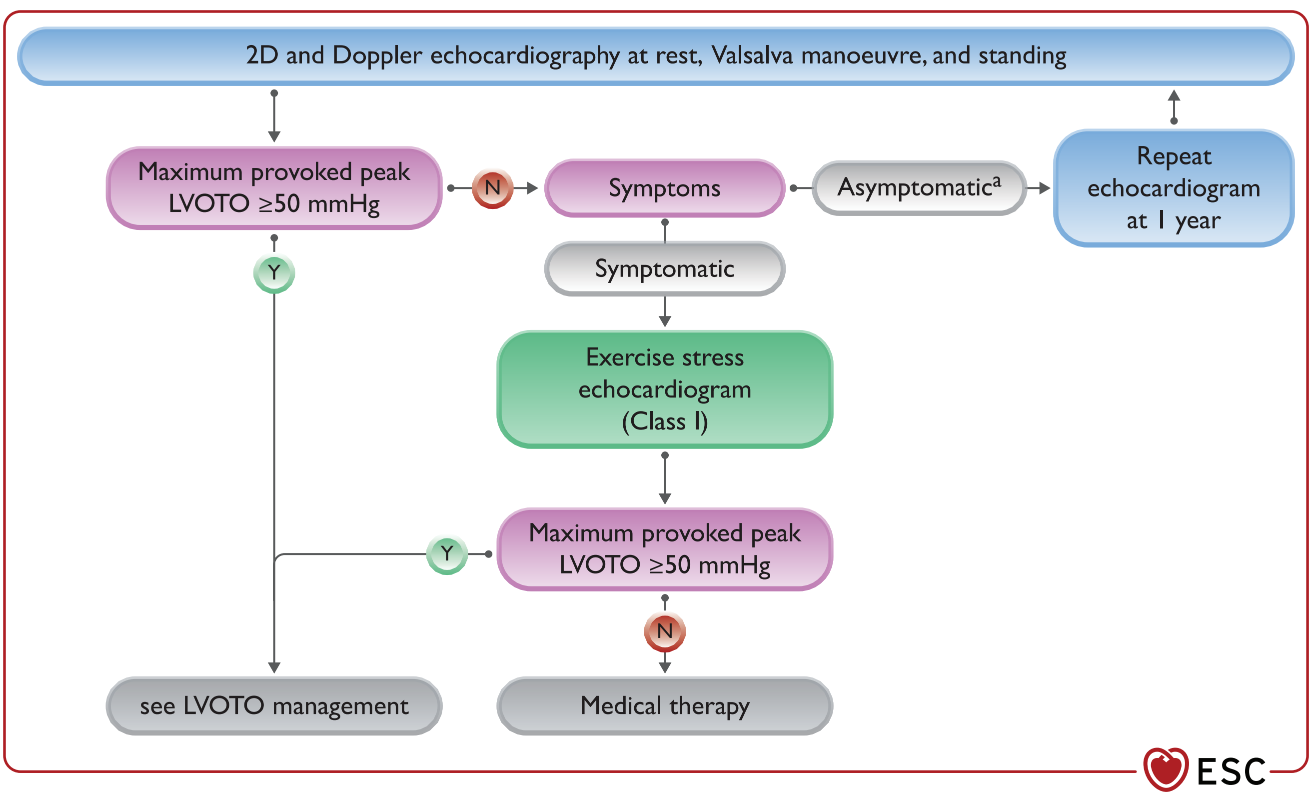

Figure 12 Protocol for the assessment and treatment of left ventricular outflow tract obstruction. 2D, two-dimensional; LVOTO, left ventricular outflow tract obstruction. [a]Exercise echocardiography may be considered in individual patients when the presence of an left ventricular outflow tract gradient is relevant to lifestyle advice and decisions on medical treatment.

7.1.1.5. Nuclear imaging

The major clinical contribution of nuclear imaging in HCM is the detection of TTR-related cardiac amyloidosis (see *Section 7.7*). Recommendations on the utility of bone scintigraphy and cardiac CT are described in *Section 6.7.4*.

7.1.2. Genetic testing and family screening

In about half of cases, HCM is inherited as a Mendelian genetic trait. In such cases, the inheritance is primarily autosomal dominant, i.e. with a 50% risk of transmission to offspring.[608] Apparently sporadic cases can have a monogenic cause, either because of incomplete penetrance of a variant inherited from a parent or due to *de novo* variants that were not carried by the parents or, less commonly, due to autosomal recessive inheritance. In those who undergo genetic testing, ∼40–60% will have a single variant identified as the cause of their disease, although this is influenced by the cohort studied.[124] The likelihood of finding a causal variant is highest in young patients with familial disease and lowest in older patients and individuals with non-classical features. Phenotype-based scores to predict genetic yield in HCM have been developed and may be used to prioritize genetic testing where resources are limited.[609,610] Genes with definitive evidence for gene–disease association with HCM are summarized in *Table 10*. An important subgroup characterized by no identifiable monogenic variant, no family history of disease and often being older, more likely to be male and with a history of hypertension, and less risk of major cardiovascular events is likely to be underlied by complex aetiology.[238,611,612]

Less than 5% of adult patients, but up to 25% of children, with HCM, will have a causative variant in a gene that is known to mimic the HCM phenotype. Such genocopies can have clinically important differences such as altered inheritance risks, and management and therapy options. The aetiology of HCM in childhood is more heterogeneous than that seen in adult populations, and includes inborn errors of metabolism, malformation syndromes, and neuromuscular disorders.[613–615] Most cases of HCM in childhood, however, are caused by variants in the cardiac sarcomere protein genes, inherited as autosomal dominant traits.[616,617] The relative prevalence of different HCM aetiologies varies according to age: HCM related to inborn errors of metabolism and malformation syndromes is most commonly diagnosed in the first 2 years of life, whereas HCM due to neuromuscular disorders (e.g. Friedreich ataxia) most commonly presents in adolescence.[613–615] Outside of infancy, sarcomere protein gene variants account for 55–75% of cases of childhood-onset HCM,[616–619] and even in infancy, sarcomeric disease is present in up to 40% of cases.[616,620] Although rarer, inborn errors of metabolism and malformation syndromes can also present for the first time in older children and adolescents (see *Section 7.6*).[614]

A thorough and comprehensive diagnostic work-up is essential in the diagnosis of childhood-onset HCM in order to confirm the diagnosis, identify the underlying aetiology, and guide treatment (see *Section 6*).

Recommendations for clinical screening, genetic counselling, and testing are described in *Sections 6.8.3* and *6.11*, respectively.

7.1.3. Assessment of symptoms

Most people with HCM are asymptomatic and have a normal lifespan, but some develop symptoms, often many years after the appearance of ECG or echocardiographic evidence of LVH. Assessment of symptoms in patients with cardiomyopathies is described in *Section 6.4*. Assessment of LVOTO, as outlined in *Figure 12*, should be part of the routine evaluation of all symptomatic patients.

7.1.4. Management of symptoms and complications

In the absence of many randomized trials,[621–623] pharmacological therapy is mostly administered on an empirical basis to improve functional capacity and reduce symptoms. In symptomatic patients with LVOTO, the aim is to improve symptoms by using drugs, surgery, or alcohol septal ablation. Therapy in symptomatic patients without LVOTO focuses on management of arrhythmia, reduction of LV filling pressures, and treatment of angina. Patients with progressive LV systolic or diastolic dysfunction refractory to medical therapy may be candidates for cardiac transplantation (*Figure 13*).

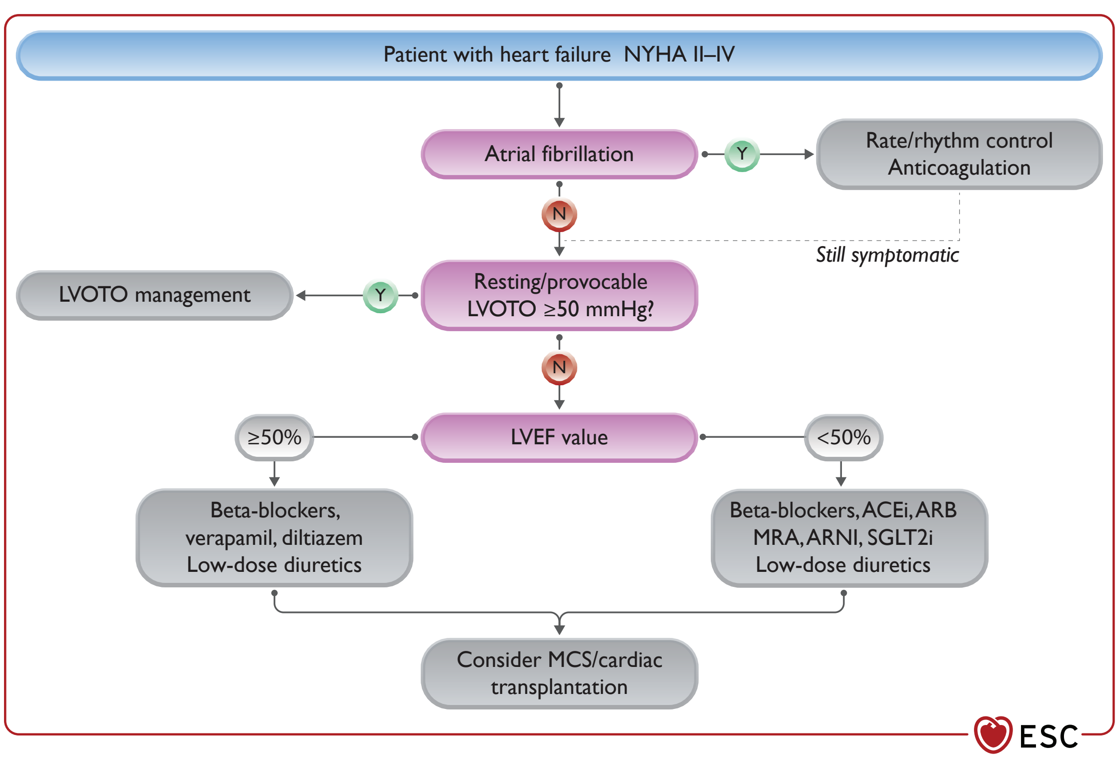

Figure 13 Algorithm for the treatment of heart failure in hypertrophic cardiomyopathy. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

7.1.4.1. Management of left ventricular outflow tract obstruction

By convention, LVOTO is defined as a peak instantaneous Doppler LV outflow tract gradient of ≥30 mmHg, but the threshold for invasive treatment is usually considered to be ≥50 mmHg (the threshold at which theoretical models examining the relationship between the gradient and stroke volume predict that this becomes haemodynamically significant).[587,624,625] Most patients with a maximum resting or provoked LV outflow tract gradient <50 mmHg should be managed in accordance with the recommendations for non-obstructive HCM but, in a very small number of selected cases with LV outflow tract gradients between 30 and 50 mmHg and no other obvious cause of symptoms, invasive gradient reduction may be considered, acknowledging that data covering this group are lacking. Most asymptomatic patients with LVOTO do not require treatment but, in a very small number of selected cases, pharmacological treatment to reduced LV pressures may be considered.[626,627]

7.1.4.1.1. General measures. All patients with LVOTO should avoid dehydration and excess alcohol consumption, and weight loss should be encouraged. Arterial and venous dilators, including nitrates and phosphodiesterase type 5 inhibitors, can exacerbate LVOTO and should be avoided if possible (see *Section 12.2*).[626] New-onset or poorly controlled AF can exacerbate symptoms caused by LVOTO and should be managed by prompt restoration of sinus rhythm or ventricular rate control.[628]

Recommendation Table 18 — Recommendations for treatment of left ventricular outflow tract obstruction (general measures)

Recommendations	Class[a]	Level[b]
Avoidance of digoxin and arterial and venous dilators, including nitrates and phosphodiesterase inhibitors, should be considered, if possible, in patients with resting or provocable LVOTO.[626,627]	IIa	C
Restoration of sinus rhythm or appropriate rate control should be considered before invasive management of LVOTO in patients with new-onset or poorly controlled AF.[629,630]	IIa	C

AF, atrial fibrillation; LVOTO, left ventricular outflow tract obstruction.
[a]Class of recommendation.
[b]Level of evidence.

7.1.4.1.2. Drug therapy. *Figure 14* describes the management of LVOTO in patients with HCM. By consensus, patients with symptomatic LVOTO have been treated initially with non-vasodilating beta-blockers titrated to the maximum tolerated dose, but there are very few studies comparing individual beta-blockers. A recent small, randomized placebo-controlled trial showed reduction of resting and exertional LVOTO, and improvement in symptoms and QoL with metoprolol therapy.[631]

If beta-blockers alone are ineffective, disopyramide, titrated up to a maximum tolerated dose (usually 400–600 mg/day), may be added.[632–634] This class IA AAD can abolish basal LV outflow pressure gradients and improve exercise tolerance and functional capacity with a low risk of proarrhythmic effects and without an increased risk of SCD.[632,633] Dose-limiting anticholinergic side effects include dry eyes and mouth, urinary hesitancy or retention, and constipation.[632,633,635] The QTc interval should be monitored during dose up-titration and the dose reduced if it exceeds 500 ms. Disopyramide should be avoided in patients with glaucoma, in men with prostatism, and in patients taking other drugs that prolong the QT interval, such as amiodarone and sotalol. Disopyramide may be used in combination with verapamil.[633]

Verapamil (starting dose 40 mg three times daily to maximum 480 mg daily) can be used when beta-blockers are contraindicated or ineffective but, based on limited data, should be used cautiously in patients with severe obstruction (≥100 mmHg) or elevated pulmonary artery systolic pressures, as it may provoke pulmonary oedema.[636] Short-term oral administration may increase exercise capacity, improve symptoms, and normalize or improve LV diastolic filling without altering systolic function.[637–640] Similar findings have been demonstrated for diltiazem (starting dose 60 mg three times daily to maximum 360 mg daily),[641] and it should be considered in patients who are intolerant or have contraindications to beta-blockers and verapamil.

Low-dose loop or thiazide diuretics may be used cautiously to improve dyspnoea associated with LVOTO, but it is important to avoid hypovolaemia.

Cardiac myosin ATPase inhibitors. Mavacamten is a first-in-class cardiac myosin adenosine triphosphatase (ATPase) inhibitor that acts by reducing actin–myosin cross-bridge formation, thereby reducing contractility and improving myocardial energetics. In the recently published Clinical Study to Evaluate Mavacamten in Adults with Symptomatic Obstructive Hypertrophic Cardiomyopathy (EXPLORER-HCM) trial, mavacamten reduced the left ventricular outflow tract (LVOT) gradient and improved exercise capacity compared with placebo in patients with HCM and symptomatic LVOTO (NYHA II–III and EF >55%); 27% of patients on mavacamten had an LVOT gradient reduction to <30 mmHg and improved to NYHA class I.[622] The drug was well tolerated and has a good safety profile; only a small subset of patients developed transient LV systolic dysfunction, which resolved after temporary discontinuation of the drug. A second study (A Study to Evaluate Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy [VALOR-HCM]) in adult patients with obstructive HCM referred for septal reduction therapy (SRT) due to intractable symptoms showed that mavacamten significantly reduced the proportion of patients meeting criteria for SRT at 16 and 32 weeks.[642,643] Small CMR and ECHO substudies suggest that mavacamten may also lead to positive myocardial remodelling, with reduction in myocardial mass, LV wall thickness, and left atrial volume.[644–646] Aficamten, a next-in-class cardiac myosin inhibitor, was also recently shown in a Phase II randomized placebo-controlled study (Randomized Evaluation of Dosing With CK-3773274 in Obstructive Outflow Disease in HCM [REDWOOD-HCM]) to significantly reduce LVOT gradients and NT-proBNP levels in adult patients with symptomatic obstructive HCM.[647]

In the absence of a direct head-to-head comparison, the Task Force was unable to recommend the use of cardiac myosin ATPase inhibitors as first-line medical therapy, but did consider the evidence sufficiently robust to support the recommendation that their use as second-line therapy should be considered when optimal medical therapy with beta-blockers, calcium antagonists, and/or disopyramide is ineffective or poorly tolerated. In the absence of evidence to the contrary, cardiac myosin ATPase inhibitors should not be used with disopyramide, but may be coadministered with beta-blockers or calcium antagonists. Up-titration of medication to a maximum dose of 15 mg should be monitored in accordance with licensed recommendations using echocardiography. In patients with contraindications or known sensitivity to beta-blockers, calcium antagonists, and disopyramide, cardiac myosin ATPase inhibitors may be considered as monotherapy.

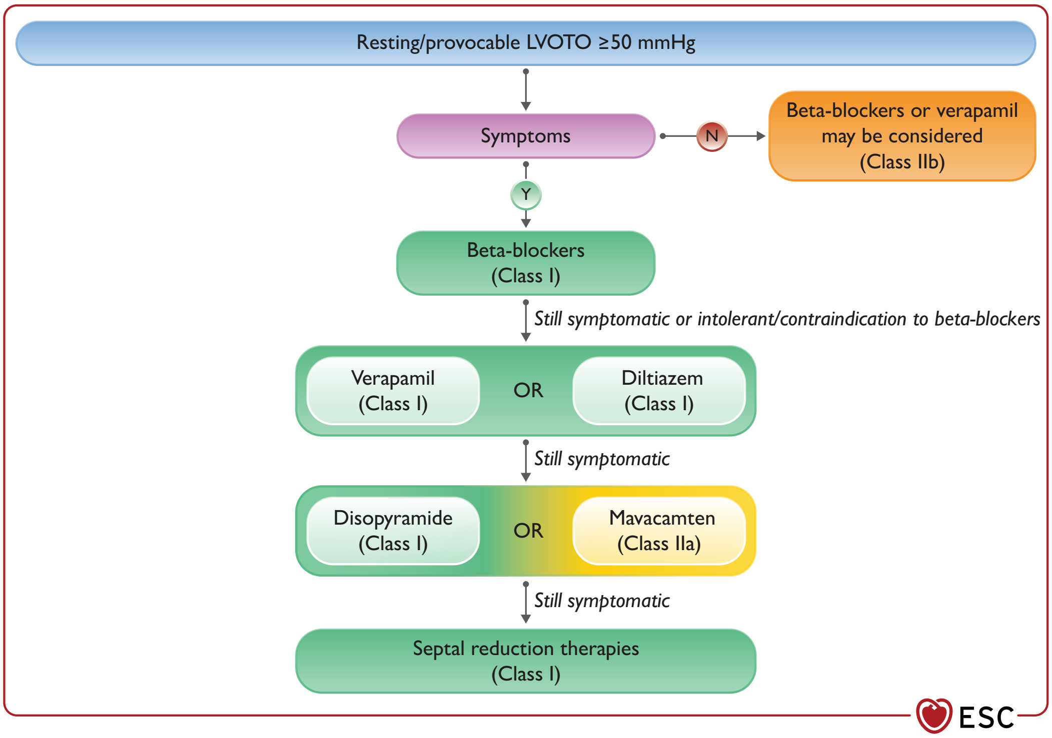

Figure 14 Flow chart on the management of left ventricular outflow tract obstruction. LVOTO, left ventricular outflow tract obstruction.

Recommendation Table 19 — Recommendations for medical treatment of left ventricular outflow tract obstruction

Recommendations	Class[a]	Level[b]
Non-vasodilating beta-blockers, titrated to maximum tolerated dose, are recommended as first-line therapy to improve symptoms in patients with resting or provoked[c] LVOTO.[631–633,648–650]	I	B
Verapamil or diltiazem, titrated to maximum tolerated dose, are recommended to improve symptoms in symptomatic patients with resting or provoked[c] LVOTO who are intolerant or have contraindications to beta-blockers.[633,637–641]	I	B
Disopyramide,[d] titrated to maximum tolerated dose, is recommended in addition to a beta-blocker (or, if this is not possible, with verapamil or diltiazem) to improve symptoms in patients with resting or provoked[c] LVOTO.[632–634]	I	B
Cardiac myosin ATPase inhibitor (mavacamten), titrated to maximum tolerated dose with echocardiographic surveillance of LVEF, should be considered in addition to a beta-blocker (or, if this is not possible, with verapamil or diltiazem) to improve symptoms in adult patients with resting or provoked[c] LVOTO.[622,642–646]	IIa	A
Cardiac myosin ATPase inhibitor (mavacamten), titrated to maximum tolerated dose with echocardiographic surveillance of LVEF, should be considered as monotherapy in symptomatic adult patients with resting or provoked[c] LVOTO (exercise or Valsalva manoeuvre) who are intolerant or have contraindications to beta-blockers, verapamil/diltiazem, or disopyramide.[622,644–646]	IIa	B
Oral or i.v. beta-blockers and vasoconstrictors should be considered in patients with severe provocable[c] LVOTO presenting with hypotension and acute pulmonary oedema who do not respond to fluid administration.[627]	IIa	C
Disopyramide, titrated to maximum tolerated dose, may be considered as monotherapy in patients who are intolerant to or have contraindications to beta-blockers and verapamil/diltiazem to improve symptoms in patients with resting or provoked[c] LVOTO.[632]	IIb	C
Beta-blockers or verapamil may be considered in selected cases in *asymptomatic* patients with resting or provoked[c] LVOTO to reduce LV pressures.[623,639]	IIb	C
The cautious use of low-dose diuretics may be considered in symptomatic LVOTO to improve exertional dyspnoea.	IIb	C

Continued

ATPase, adenosine triphosphatase; i.v., intravenous; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Provocation with Valsalva manoeuvre, upright exercise, or oral nitrates if unable to exercise.
[d]QTc interval should be monitored during up-titration of disopyramide and the dose reduced if it exceeds 500 ms.

7.1.4.1.3. Invasive treatment of left ventricular outflow tract (septal reduction therapy). There are no data to support the use of invasive procedures to reduce LVOTO in asymptomatic patients, regardless of its severity. However, some retrospective data suggest that individuals with high LVOT gradients, even if minimally symptomatic, have a higher mortality than those without markedly elevated gradients.[651] Delay in SRT may have an impact on long-term outcomes, particularly when >5 years from first detection of gradient, even when successful relief of symptoms and gradient is achieved. Earlier interventions may be associated with lower complication rates and better prognosis.[652]

Invasive treatment (SRT) to reduce LVOTO should be considered in patients with a LVOTO gradient ≥50 mmHg, severe symptoms (NYHA functional class III–IV), and/or exertional or unexplained recurrent syncope in spite of maximally tolerated drug therapy. Invasive therapy may also be considered in patients with mild symptoms (NYHA class II) refractory to medical therapy who have a resting or maximum provoked gradient of ≥50 mmHg (exercise or Valsalva) and moderate-to-severe systolic anterior motion-related mitral regurgitation, AF, or moderate-to-severe left atrial dilatation in expert centres with demonstrable low procedural complication rates.[653]

Surgery. The most commonly performed surgical procedure to treat LVOTO is ventricular septal myectomy, in which a rectangular trough that extends distally to beyond the point of the mitral leaflet–septal contact is created in the basal septum below the aortic valve.[654] This

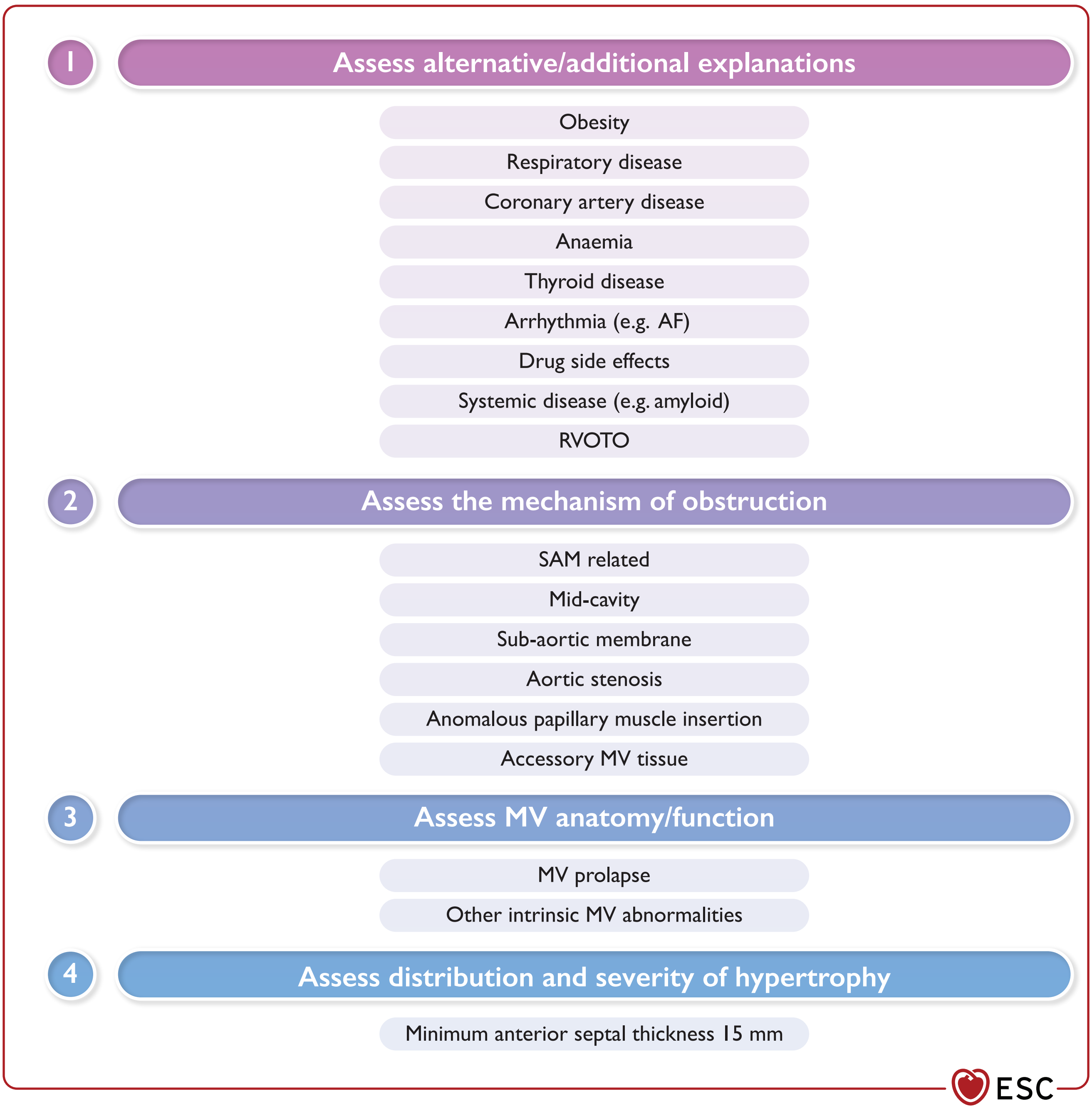

Figure 15 Pre-assessment checklist for patients being considered for invasive septal reduction therapies. AF, atrial fibrillation; MV, mitral valve; RVOTO, right ventricular outflow tract obstruction; SAM, systolic anterior motion.

abolishes or substantially reduces LV outflow tract gradients in over 90% of cases, reduces systolic anterior motion-related mitral regurgitation, and improves exercise capacity and symptoms. Long-term symptomatic benefit is achieved in >80% of patients with a long-term survival comparable to that of the general population.[655–665] Pre-operative determinants of a good long-term outcome are age <50 years, left atrial size <46 mm, absence of AF, and male sex.[663]

The main surgical complications are AV nodal block, left bundle branch block (LBBB), ventricular septal defect, and aortic regurgitation, but these are uncommon (except LBBB) in experienced centres using intra-operative transoesophageal echocardiography guidance.[662,666,667] When there is coexisting mid-cavity obstruction, the standard myectomy can be extended distally into the mid-ventricle around the base of the papillary muscles; however, data on the efficacy and long-term outcomes of this approach are limited.[668]

In patients with intrinsic/primary mitral valve disease or marked mitral leaflet elongation and/or moderate-to-severe mitral regurgitation, septal myectomy can be combined with mitral valve repair or replacement.[669–675] In patients with AF, concomitant ablation using the Cox–Maze procedure can also be performed.[676] In infants and very young children, the modified Konno procedure may be an alternative to myectomy when the aortic annulus is too small.[677]

Alcohol septal ablation (ASA). In experienced centres, selective injection of alcohol into a septal perforator artery to create a localized septal scar has outcomes similar to surgery in terms of gradient reduction, symptom improvement, and exercise capacity, including in younger adults.[678–685] In many centres, ASA has become the primary SRT modality. The main non-fatal complication is AV block in 7–20% of patients, and the procedural mortality is lower than isolated myectomy.[679–683,686,687]

Due to the variability of the septal blood supply, myocardial contrast echocardiography is essential prior to alcohol injection. Injection of large volumes of alcohol in multiple septal branches—with the aim of gradient reduction—in the catheter laboratory is generally not recommended, as it can be associated with a high risk of complications and arrhythmic events.[688]

Alternative methods have been reported in small numbers of patients, including non-ASA techniques (coils,[689,690] polyvinyl alcohol foam particles,[691] cyanoacrylate[692]) and direct endocavitary and intramuscular ablation (radiofrequency, cryotherapy).[693,694] These alternative methods have not been directly compared with other septal reduction therapies and long-term outcome/safety data are not available. Alcohol septal ablation and alternative methods should not be used in children with HCM outside experimental settings, due to a lack of medium- to long-term safety and efficacy data.

Surgery vs. alcohol septal ablation. Because of specific anatomic features of the LVOT and the mitral valve, some patients with HCM will be more suitable candidates for septal myectomy than ASA. Experienced multidisciplinary teams should assess all patients before intervention, as morbidity and mortality are highly dependent on the available level of expertise (see *Section 9*).[687,695,696] A summary of the key points in pre-operative assessment is shown in *Figure 15*.

There are no randomized trials comparing surgery and ASA, but several meta-analyses have shown that both procedures improve functional status with a similar procedural mortality.[697–703] Alcohol septal ablation is associated with a higher risk of AV block, requiring permanent pacemaker implantation, and larger residual LV outflow tract gradients.[697–702] The risk of AV block following surgery and ASA is highest in patients with pre-existing conduction disease, and prophylactic permanent pacing before intervention has been advocated,[704] although recent data suggest that the long-term outcome of patients after ASA with implanted permanent pacemaker is similar to those without pacemaker.[705] Repeat ASA or myectomy procedure is reported in 7–20% of patients after ASA, which is higher than reported following surgical myectomy.[702] Septal ablation may be less effective in patients with very severe hypertrophy (≥30 mm), but systematic data are limited.[706] In general, the risk of ventricular septal defect following septal myectomy is very small and could be higher in patients with mild hypertrophy (≤16 mm) at the point of the mitral leaflet–septal contact. This risk is exceedingly rare with ASA, but alternatives such as dual-chamber pacing or mitral valve repair/replacement may also be considered in such cases.[707]

Recommendation Table 20 — Recommendations for septal reduction therapy

Recommendations	Class[a]	Level[b]
It is recommended that SRT be performed by experienced operators working as part of a multidisciplinary team expert in the management of HCM.[664,665,687,695,696,708–710]	I	C
SRT to improve symptoms is recommended in patients with a resting or maximum provoked LVOT gradient of ≥50 mmHg who are in NYHA/Ross functional class III–IV, despite maximum tolerated medical therapy.[697–702]	I	B
Septal myectomy, rather than ASA, is recommended in children with an indication for SRT, as well as in adult patients with an indication for SRT and other lesions requiring surgical intervention (e.g. mitral valve abnormalities).[673]	I	C
SRT should be considered in patients with recurrent exertional syncope caused by a resting or maximum provoked LVOTO gradient ≥50 mmHg despite optimal medical therapy.[686,711–713]	IIa	C
Mitral valve repair or replacement should be considered in symptomatic patients with a resting or maximum provoked LVOTO gradient ≥50 mmHg and moderate-to-severe mitral regurgitation that cannot be corrected by SRT alone.[661,669–672,714]	IIa	C
Mitral valve repair should be considered in patients with a resting or maximum provoked LVOTO gradient ≥50 mmHg when there is moderate-to-severe mitral regurgitation following isolated myectomy.	IIa	C
SRT may be considered in expert centres with demonstrable low procedural complication rates in patients with mild symptoms (NYHA class II) refractory to medical therapy who have a resting or maximum provoked (exercise or Valsalva) gradient of ≥50 mmHg and: • moderate-to-severe SAM-related mitral regurgitation; or • AF; or • moderate-to-severe left atrial dilatation.[653,715]	IIb	C

Continued

Mitral valve replacement may be considered in patients with a resting or maximum provoked LVOTO gradient ≥50 mmHg when there is moderate-to-severe mitral regurgitation following isolated myectomy.[661,674,714,716]	IIb	C
Surgical AF ablation and/or left atrial appendage occlusion procedures during septal myectomy may be considered in patients with HCM and symptomatic AF.[717,718]	IIb	C

AF, atrial fibrillation; ASA, alcohol septal ablation; HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction; NYHA, New York Heart Association; SAM, systolic anterior motion; SRT, septal reduction therapy.
[a]Class of recommendation.
[b]Level of evidence.

Dual-chamber pacing. Three small, randomized, placebo-controlled studies of dual-chamber pacing and several long-term observational studies have reported reductions in LV outflow tract gradients and variable improvement in symptoms and QoL, including one paediatric study.[719–724] A Cochrane review concluded that the data on the benefits of pacing are based on physiological measures and lack information on clinically relevant endpoints.[725]

Recommendation Table 21 — Recommendations for indications for cardiac pacing in patients with obstruction

Recommendations	Class[a]	Level[b]
Sequential AV pacing, with optimal AV interval to reduce the LV outflow tract gradient or to facilitate medical treatment with beta-blockers and/or verapamil, may be considered in selected patients with resting or provocable LVOTO ≥50 mmHg, sinus rhythm, and drug-refractory symptoms, who have contraindications for ASA or septal myectomy or are at high risk of developing heart block following ASA or septal myectomy.[633,719–724]	IIb	C
In patients with resting or provocable LVOTO ≥50 mmHg, sinus rhythm, and drug-refractory symptoms, in whom there is an indication for an ICD, a dual-chamber ICD (instead of a single-lead device) may be considered, to reduce the LV outflow tract gradient or to facilitate medical treatment with beta-blockers and/or verapamil.[633,719–724,726]	IIb	C

ASA, alcohol septal ablation; AV, atrioventricular; ICD, implantable cardioverter defibrillator; LV, left ventricular; LVOTO, left ventricular outflow tract obstruction.
[a]Class of recommendation.
[b]Level of evidence.

Left ventricular mid-cavity obstruction and apical aneurysms. Left ventricular mid-cavity obstruction occurs in ∼10% of patients with HCM.[727,728] Patients with mid-cavity obstruction tend to be very symptomatic and, in a number of studies, have shown an increased risk of progressive heart failure and SCD.[727–729] Approximately 25% of patients also have an LV apical aneurysm (see *Section 7.1.5*).[580,727,728,730] Patients with LV mid-cavity obstruction should be treated with high-dose beta-blockers, verapamil, or diltiazem, but the response is often suboptimal. Limited experience, mostly from single centres, suggests that mid-ventricular obstruction can be relieved by transaortic myectomy, a transapical approach, or combined transaortic and transapical incisions, with good short-term outcomes but uncertain long-term survival.[731,732]

Left ventricular apical aneurysms by themselves rarely need treatment. A few patients develop monomorphic ventricular tachycardia related to adjacent apical scarring, which may be amenable to mapping and ablation (see *Section 7.1.5*).[730,733] Rarely, thrombi are present within the aneurysm and should be treated with long-term oral anticoagulation.[734,735] Anticoagulation may also be considered in patients with HCM and apical aneurysms in the absence of documented thrombi.[736,737]

7.1.4.2. Management of symptoms in patients without left ventricular outflow tract obstruction

7.1.4.2.1. Heart failure and chest pain. Management of heart failure in patients without LVOTO should follow the recommendations of the *2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure*, summarized in *Section 6.10.2*. The aim of drug therapy is to reduce LV diastolic pressures and improve LV filling by slowing the heart rate with beta-blockers, verapamil, or diltiazem (ideally monitored by ambulatory ECG recording), and cautious use of loop diuretics. Beta-blockers or calcium antagonists should be considered in patients with exertional or prolonged episodes of angina-like pain even in the absence of resting or provocable LVOTO or obstructive CAD. In the absence of LVOTO, cautious use of oral nitrates may be considered. Ranolazine may also be considered to improve symptoms in patients with angina-like chest pain and no evidence for LVOTO.[738,739]

Recommendation Table 22 — Recommendations for chest pain on exertion in patients without left ventricular outflow tract obstruction

Recommendations	Class[a]	Level[b]
Beta-blockers and calcium antagonists (verapamil or diltiazem) should be considered to improve symptoms in patients with angina-like chest pain even in the absence of LVOTO or obstructive CAD.[740–744]	IIa	C
Oral nitrates may be considered to improve symptoms in patients with angina-like chest pain, even in the absence of obstructive CAD, if there is no LVOTO.	IIb	C
Ranolazine may be considered to improve symptoms in patients with angina-like chest pain even in the absence of LVOTO or obstructive CAD.[738,739]	IIb	C

CAD, coronary artery disease; LVOTO, left ventricular outflow tract obstruction.
[a]Class of recommendation.
[b]Level of evidence.

7.1.4.2.2. Cardiac resynchronization therapy. Regional heterogeneity of LV contraction and relaxation can be seen in patients with HCM, and LV dyssynchrony may be a marker of poor prognosis.[745] Data on the impact of CRT on symptoms, LV function, and prognosis in patients with non-obstructive HCM remain limited, but new evidence has emerged since the *2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy*.[746,747] There is one small study using a blinded crossover design of biventricular and sham pacing and a pre-specified analysis stratified by changes in LV end-diastolic volume (LVEDV) with exercise at baseline.[748] Biventricular pacing was associated with significant increases in LVEDV and stroke volume in patients who had a reduction in exercise LVEDV pre-pacing (consistent with the relief of diastolic ventricular interaction). This translated into improvements in peak maximum oxygen consumption (VO_2) (1.4 mL/kg/min) and QoL scores.[748] Together, they suggest that symptomatic responses to CRT may occur in individual patients, but that these are not associated with consistent changes in LVEF or evidence for a reduction in progression to end-stage heart failure.

The *2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy* recommend that standard criteria for CRT are used in patients with HCM.[724] The Task Force considered these of limited utility in HCM, as the unique pathology of this disease means that patients with contractile impairment rarely have an LVEF ≤35%. While acknowledging this as an area of unmet research need, the Task Force suggests a more pragmatic approach in which CRT might be considered in individual symptomatic patients with LV impairment (LVEF <50%) that meet current ESC ECG criteria (LBBB, QRS 130–149 ms). Cardiac resynchronization therapy might also be considered in patients with HCM and impaired systolic function who require permanent ventricular pacing.[746] In keeping with the *2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy*, the Task Force did not include these as specific recommendations, given the limited evidence base.

7.1.5. Sudden cardiac death prevention in hypertrophic cardiomyopathy

Most contemporary series of adult patients with HCM report an annual incidence for cardiovascular death of 1–2%, with SCD, heart failure, and thrombo-embolism being the main causes of death.[749] The most commonly recorded fatal arrhythmic event is spontaneous ventricular fibrillation (VF), but asystole, AV block, and pulseless electrical activity are described.[532,750–754] In children with HCM, although initial studies, usually from small, highly selected cohorts, reported SCD rates of up to 10% per year,[755–757] more recent, larger, population-based studies have shown SCD rates in the region of 1.2–1.5% per year.[81,535,758] While much lower than previously thought, this is still >50% higher than reported in adult HCM populations. Sudden cardiac death appears to be very rare below the age of 6 years.[81,759]

Estimation of SCD risk is an integral part of clinical management. Clinical features that are associated with an increased SCD risk and that have been used in previous guidelines to estimate risk are shown in *Table 19*.

Table 19 Major clinical features associated with an increased risk of sudden cardiac death

Risk factor	Comment
Age	• The effect of age on SCD has been examined in a number of studies[86,525,584,760–764] and two have shown a significant association, with an increased risk of SCD in younger patients.[525,584] • Some risk factors appear to be more important in younger patients, most notably NSVT,[765] severe LVH,[766] and unexplained syncope.[584] • Sudden cardiac death is very rare below the age of 6 years,[535,767] and there are some data to suggest a peak of SCD in childhood HCM between 9 and 15 years;[757] however, the association between age at diagnosis and SCD risk in childhood HCM remains unclear.
NSVT	• NSVT (defined as ≥3 consecutive ventricular beats at ≥120 b.p.m. lasting <30 s) occurs in 20–30% of patients during ambulatory ECG monitoring and is an independent predictor of SCD.[81,525,535,590,764,765,768–773] • There is no evidence that the frequency, duration, or rate of NSVT influences the risk of SCD.[765,774] • NSVT occurring during or immediately following exercise is very rare, but may be associated with a high risk of SCD.[768]
Maximum LV wall thickness	• The severity and extent of LVH measured by TTE are associated with the risk of SCD.[81,535,592,593,763,765,770–772,775–780] • Several studies have shown the greatest risk of SCD in patients with a maximum wall thickness of ≥30 mm; however, there are few data in patients with extreme hypertrophy (≥35 mm).[525,592,763,765,769,781–784]
Family history of sudden cardiac death at a young age	• While definitions vary,[525,592,762,782] a family history of SCD is usually considered clinically significant when one or more first-degree relatives have died suddenly aged <40 years with or without a diagnosis of HCM, or when SCD has occurred in a first-degree relative at any age with an established diagnosis of HCM. • Family history of SCD does not appear to be an independent risk factor for SCD in childhood HCM.[81,535] This may be due to a higher prevalence of *de novo* variants in childhood HCM, the inclusion of non-sarcomeric disease, and/or under-reporting of family history in paediatric cohorts.
Syncope	• Syncope is common in patients with HCM but is challenging to assess, as it has multiple causes.[785] • Non-neurocardiogenic syncope for which there is no explanation after investigation is associated with an increased risk of SCD.[81,525,535,584,590,755,761,768,769,781,786–788] • Episodes within 6 months of evaluation may be more predictive of SCD.[584]
Left atrial diameter	• Several studies have reported a positive association between LA size and SCD.[81,525,535,584,772,789] There are no data on the association between SCD and LA area or volume. Measurement of LA size is also important in assessing the risk of AF (see *Section 6.10.3*).
LV outflow tract obstruction	• A number of studies have reported a significant association between LVOTO and SCD risk.[86,525,590,762,768,790] Several unanswered questions remain, including the prognostic importance of provocable LVOTO and the impact of treatment (medical or invasive) on SCD. • In childhood HCM, there are conflicting data on the association between LVOTO and SCD risk.[81,535,772,777]

AF, atrial fibrillation; b.p.m., beats per minute; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; LA, left atrium; LV, left ventricular; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; NSVT, non-sustained ventricular tachycardia; SCD, sudden cardiac death; TTE, transthoracic echocardiogram.

7.1.5.1. *Left ventricular apical aneurysms*

Left ventricular apical aneurysms are defined as a discrete thin-walled dyskinetic or akinetic segment of the most distal portion of the left ventricle and are often associated with a mid-cavity gradient. Their prevalence in unselected patients is uncertain but they were reported in 3% of individuals in the prospective Hypertrophic Cardiomyopathy Registry (HCMR).[124] The first descriptions of LV apical aneurysms in HCM suggested an association with sustained monomorphic ventricular tachycardia (SMVT)[730]—a relatively rare occurrence in HCM—and a number of studies have suggested that they are a useful marker of SCD risk.[580,728,736,737,791,792] Based on these data, LV aneurysms were included in the recent 2020 American Heart Association/American College of Cardiology (AHA/ACC) HCM guideline as a major independent SCD risk factor and were considered a reasonable sole indication for an ICD.[793] In a review for this guideline, the data from two published studies and a meta-analysis were evaluated (see Supplementary data online, *Table S2*). All these studies were retrospective and the absolute number of events is too small to assess the independent predictive value of apical aneurysms. In two small series that described a selected subgroup of HCM patients with mid-ventricular obstruction, there was no increase in incidence of SCD events. In the only series that provides a detailed analysis of SCD events, the majority were appropriate ICD interventions for monomorphic VT, suggesting significant inclusion bias.[737] Finally, a large proportion of individuals with events had other important risk markers including prior sustained ventricular arrhythmia. Based on the current data, the Task Force recommends that individualized ICD decisions should be based using well-established risk factors and not solely on the presence of an LV apical aneurysm.

7.1.5.2. *Left ventricular systolic dysfunction*

A small number of retrospective studies and two larger registries have examined the relation between prognosis in patients with HCM and LV systolic dysfunction (most frequently defined by a LVEF <50%) (see Supplementary data online, *Table S3*). All studies consistently show an increased rate of SCD events in patients with left ventricular systolic dysfunction (LVSD) ranging from 7 to 20% compared with that of patients with normal LV systolic function. However, the independent and additional value of LVSD compared with current risk stratification tools has not been investigated. There is only one multivariable model that investigates the independent relation of LVSD to the risk of SCD events but the covariables examined were limited (age, sex, and follow-up time).[315] As with other recently proposed risk markers in HCM, the Task Force maintains its recommendation to first estimate SCD risk using the HCM-SCD Risk and HCM Risk-Kids tools, and then to use the presence of an LVEF <50% in shared decision-making about prophylactic ICD implantation, with full disclosure of the lack of robust data on its impact on prognosis.

7.1.5.3. *Late gadolinium enhancement on cardiac magnetic resonance imaging*

In the *2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy*, the extent of LGE on CMR was considered helpful in predicting cardiovascular mortality, but data at that time were felt insufficient to support the use of LGE in prediction of SCD risk. Since then, more studies have been published (see Supplementary data online, *Table S1*). In aggregate, the data show that LGE is common and, that when extensive (expressed as a percentage of LV mass), is associated with an increase in SCD risk and other events, particularly in the presence of other markers of disease severity including LV systolic impairment. A meta-analysis of nearly 3000 patients from several studies suggests that the presence of LGE is associated with a 2.32-fold increased risk of SCD/aborted SCD/appropriate ICD discharge, and a 2.1-fold increase in all-cause mortality.[794] It has been suggested that the addition of LGE to the current AHA/ACC sudden death algorithm or the HCM-SCD risk model improves stratification of patients who are otherwise considered low or intermediate risk.[793]

As in 2014, a number of uncertainties persist. These include the inevitable confounders in the retrospective studies that bias towards high-risk patients or patients referred specifically for septal myectomy. There also remains some debate about the methods used to quantify LGE with the 2-standard deviation technique; the only one that is validated against necropsy.[605] Retrospective CMR series also report relatively high event rates suggesting that they are not representative of the broad spectrum of disease. In HCMR, a prospective CMR study of 2755 patients, LGE was present in 50% of patients based on visual criteria and in 60% based on >6 SCD signal criteria, but only 2% of patients had LGE >15% of LV mass.[124] In the most recent report from the registry, there have been 24 deaths from any cause after a mean follow-up of 33.5 ± 12.4 months (median: 36 months and range 1–64 months); the relation with LGE is not reported.[795] There are very limited data on the role of CMR over and above validated risk algorithms in SCD risk prediction in children with HCM.[796,797]

On balance, the Task Force maintains the recommendation to first estimate SCD risk using the HCM-SCD Risk calculators. For patients who are in the low to intermediate risk category, the presence of extensive LGE (≥15%) may be used in shared decision-making with patients about prophylactic ICD implantation, acknowledging the lack of robust data on the impact of scar quantification on the personalized risk estimates generated by the HCM-SCD Risk calculators.

7.1.5.4. *Abnormal exercise blood pressure response*

Approximately one-third of adult patients with HCM have an abnormal systolic blood pressure response to exercise characterized by progressive hypotension or a failure to augment the systolic blood pressure that is caused by an inappropriate drop in systemic vascular resistance and a low cardiac output reserve.[798,799] Various definitions for abnormal blood pressure response in patients with HCM have been reported;[590,765,768,782] for the purposes of this guideline, an abnormal blood pressure response is defined as a failure to increase systolic pressure by at least 20 mmHg from rest to peak exercise or a fall of >20 mmHg from peak pressure.[590,765,768,782,800]

Abnormal exercise blood pressure response may be associated with a higher risk of SCD in adult patients aged ≤40 years, but it has a low positive predictive accuracy and its prognostic significance in patients >40 years of age is unknown, and recent data have suggested that, although it may be associated with increased overall mortality largely related to heart failure, it is not consistently associated with an increased risk of ventricular arrhythmia or SCD.[800,801] There is no evidence to suggest that abnormal blood pressure response to exercise is associated with a higher risk of SCD in children with HCM.[802] The Task Force, therefore, does not recommend the use of abnormal blood pressure response to exercise as an indication for primary prevention ICD implantation in patients with a low or intermediate risk category.

7.1.5.5. Sarcomeric variants

A small number of studies have explored the prognostic value of sarcomeric variants in HCM. Despite initial attempts to classify variants as 'malignant' or 'benign',[803–807] no studies have shown an independent role for specific sarcomeric variants in SCD risk prediction. Variants initially classified as 'malignant' or 'benign' can have very different phenotypic expression, even in members of the same family,[808–810] and, as variants are often found in individual families, evaluation of their prognostic implications is problematic. Similarly, while the presence of multiple sarcomeric variants in an individual has been suggested to be associated with a worse prognosis,[608,811–813] other cohorts have not consistently reported this association.[807,814–816] Recent studies have evaluated the potential prognostic role of the presence of any sarcomeric variant. The largest of these, comprising 2763 patients, showed a statistically significant impact on overall prognosis in those with vs. without a sarcomeric variant, but did not assess its association specifically with SCD.[238] A smaller study of 512 probands and 114 relatives, of whom 327 had a disease-causing sarcomeric variant, suggested that the presence of a pathogenic variant was independently associated with all-cause, cardiovascular, and heart failure mortality as well as SCD/aborted SCD (HR 2.88; 95% CI, 1.23–6.71).[817] Patients with a sarcomeric variant were younger and were more likely to have NSVT, syncope, and LVOTO and the association with SCD lost statistical significance (HR 2.44; 95% CI, 0.99–6.01; $P = 0.052$) after adjusting for ≥2 major clinical risk factors. The role of sarcomeric variants as a predictor of SCD independent of SCD risk-prediction models (e.g. HCM Risk-SCD and HCM Risk-Kids) remains to be demonstrated. Based on the available data, the Task Force does not recommend the use of the presence of sarcomeric variant(s) to guide decisions around ICD implantation for primary prevention in individuals with a low or intermediate SCD risk score.

7.1.5.6. Prevention of sudden cardiac death

There are no randomized, controlled data to support the use of AADs for the prevention of SCD in HCM. Amiodarone was associated with a lower incidence of SCD in one small observational study of patients with non-sustained ventricular tachycardia (NSVT) on Holter monitoring, but observational data suggest that amiodarone often fails to prevent SCD.[818,819] Disopyramide does not appear to have a significant impact on the risk of SCD.[632] However, beta-blockers and/or amiodarone are recommended in patients with an ICD who continue to have symptomatic ventricular arrhythmias, paroxysmal AF, or recurrent shocks despite optimal treatment and device re-programming.[820]

There are no randomized trials or statistically validated prospective prediction models that can be used to guide ICD implantation in patients with HCM. Recommendations are instead based on observational, retrospective cohort studies that have determined the relationship between clinical characteristics and prognosis. The *2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy* recommended a risk-prediction model—HCM Risk-SCD (https://qxmd.com/calculate/calculator_303/hcm-risk-scd)—that provides individualized, quantitative risk estimates using an enhanced phenotypic approach.[525] This approach has since been validated in independent cohorts and a meta-analysis of available published data, relevant to the *2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy* performance, for SCD prevention has shown that pooled estimates are concordant with the observed SCD risk in patients designated as high or low risk.[821–824] In children, risk stratification for SCD has traditionally been based on risk factors extrapolated from adults with HCM, but this approach does not identify the children most at risk of SCD. In 2019, the first validated paediatric-specific risk model for SCD was developed (HCM Risk-Kids; https://hcmriskkids.org), using a similar approach to HCM Risk-SCD,[81,825] and has since been independently externally validated.[535,797,826] A similar paediatric risk-prediction model (PRIMaCY Childhood HCM Sudden Cardiac Death Risk Prediction tool) has also been developed, using similar clinical parameters and with similar reported accuracy to HCM Risk-Kids (https://primacy.shinyapps.io/calculator/).[535]

In this update, the Task Force maintains the principle of risk estimation using the validated HCM Risk-SCD tool as the first step in sudden death prevention in patients aged 16 years or more, and recommends the use of a validated risk score (e.g. HCM Risk-Kids tool) for children and adolescents <16 years. This is in contrast to the *2020 AHA/ACC Guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy*,[793] in which the tool is considered an aid to a shared decision-making process for ICD placement in patients with clinical risk markers. This approach by the AHA/ACC, in part, reflected concerns that reliance on a risk tool does not account for individual patient perception and acceptance of pre-determined thresholds for medical intervention, as well as the omission of clinical risk markers such as LV systolic impairment from the HCM Risk-SCD model.

The Task Force acknowledges the challenges associated with defining universal thresholds for acceptable risk, but feels that reliance on an unquantified estimate of risk does nothing to resolve this dilemma. Instead, the Task Force recommends more overt shared decision-making based on real-world data as well as individual preferences, beliefs, circumstances, and values. Gaps in evidence are acknowledged and should be shared with patients. Similarly, competing risks related to the disease (heart failure, stroke) and to age and comorbidity, as well as device-related complications, should be discussed.[726,827,828] Critically, the Task Force calls for development of enhanced patient decision aids tailored specifically to receivers of care as well as more traditional decision-support tools for healthcare practitioners.

Figure 16 summarizes the recommendations for primary prevention ICD implantation in HCM in each risk category. These take into account not only the absolute statistical risk, but also the age and general health of the patient, socioeconomic factors, and the psychological impact of therapy. The recommendations are meant to be sufficiently flexible to account for scenarios that are not encompassed by the HCM Risk-SCD or HCM Risk-Kids models. These models should not be used in elite athletes or in individuals with metabolic/infiltrative diseases (e.g. Anderson–Fabry disease) and syndromes (e.g. Noonan syndrome). The models do not use exercise-induced LV outflow tract gradients and have not been validated before and after myectomy. The HCM Risk-SCD model has been validated in one study of adult patients following ASA,[829] and a recent study has suggested that severe LVH and residual LVOTO are associated with an increased risk of SCD following ASA, with a modest C-statistic of 0.68.[830]

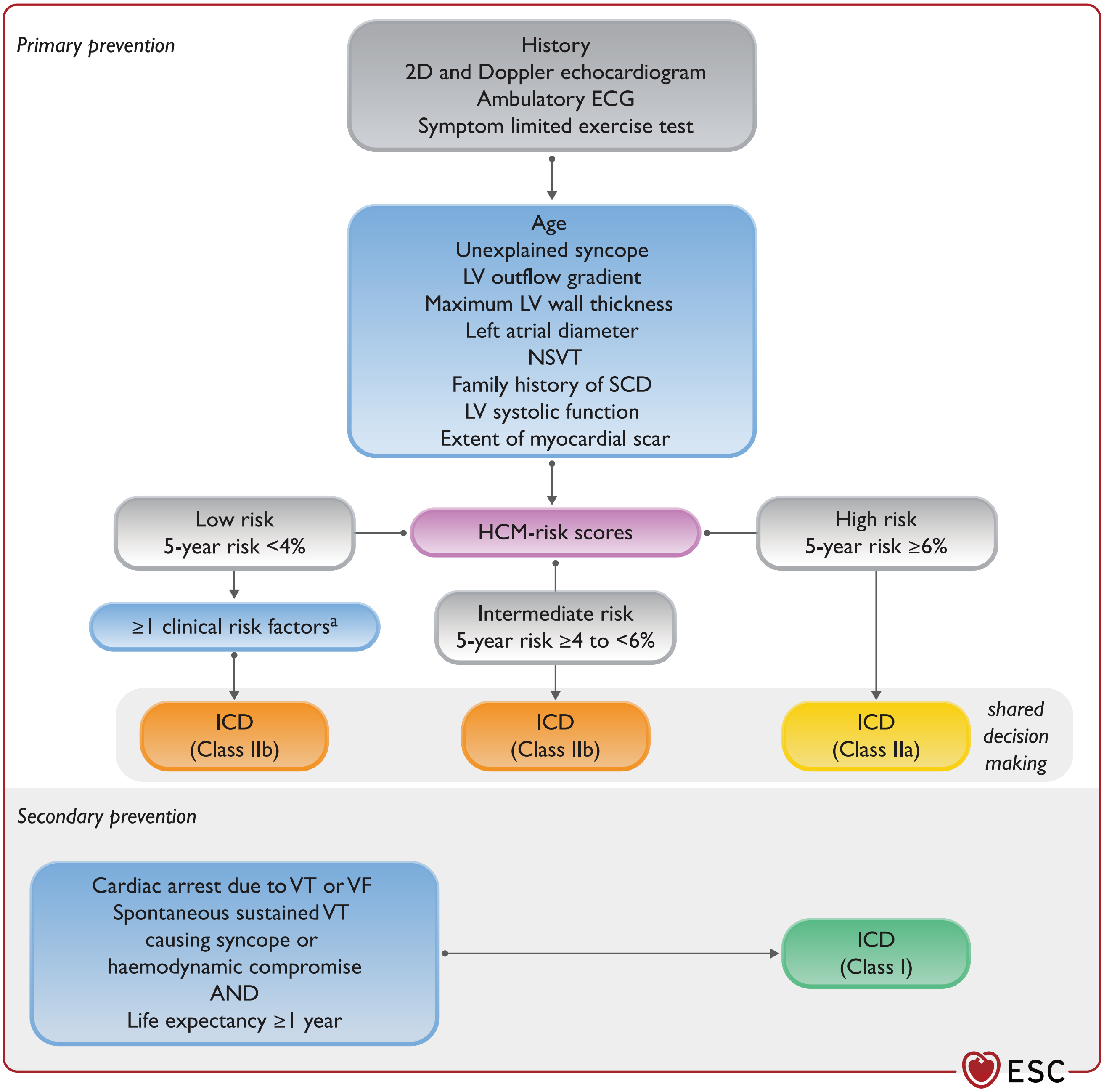

Figure 16 Flow chart for implantation of an implantable cardioverter defibrillator in patients with hypertrophic cardiomyopathy. 2D, two-dimensional; CMR, cardiac magnetic resonance; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia. [a]Clinical risk factors: extensive LGE (>15%) on CMR; LVEF <50%.

Recommendation Table 23 — Additional recommendations for prevention of sudden cardiac death in patients with hypertrophic cardiomyopathy

Recommendations	Class[a]	Level[b]
Secondary prevention		
Implantation of an ICD is recommended in patients who have survived a cardiac arrest due to VT or VF, or who have spontaneous sustained VT with haemodynamic compromise.[532,534,726,831,832]	I	B
Primary prevention		
The HCM Risk-SCD calculator is recommended as a method of estimating risk of sudden death at 5 years in patients aged ≥16 years for primary prevention.[525,821–824]	I	B
Validated paediatric-specific risk prediction models (e.g. HCM Risk-Kids) are recommended as a method of estimating risk of sudden death at 5 years in patients aged <16 years for primary prevention.[81,833]	I	B

Continued

Continued

It is recommended that the 5-year risk of SCD be assessed at first evaluation and re-evaluated at 1–2 year intervals or whenever there is a change in clinical status.[525]	I	B
Implantation of an ICD should be considered in patients with an estimated 5-year risk of sudden death of ≥6%, following detailed clinical assessment that considers: (i) the lifelong risk of complications; (ii) competing mortality risk from the disease and comorbidities; AND (iii) the impact of an ICD on lifestyle, socio-economic status, and psychological health.[81,521,525,726,832,833]	IIa	B
In patients with LV apical aneurysms, decisions about primary prevention ICD based on an assessment of risk using the HCM Risk-SCD or a validated paediatric risk-prediction (e.g. HCM Risk-Kids) tool and not solely on the presence of the aneurysm should be considered.[580,728,737,791,792]	IIa	B
Implantation of an ICD may be considered in individual patients with an estimated 5-year risk of SCD of between ≥4% and <6%, following detailed clinical assessment that takes into account the lifelong risk of complications and the impact of an ICD on lifestyle, socio-economic status, and psychological health.[81,521,525,726,832,833]	IIb	B
For patients who are in the low-risk category (<4% estimated 5-year risk of SCD), the presence of extensive LGE (≥15%) on CMR may be considered in shared decision-making with patients about prophylactic ICD implantation, acknowledging the lack of robust data on the impact of scar quantification on the personalized risk estimates generated by HCM Risk-SCD or a validated paediatric model (e.g. HCM Risk-Kids).[141,796,797,834–841]	IIb	B
For patients who are in the low-risk category (<4% estimated 5-year risk of SCD), the presence of LVEF <50% may be considered in shared decision-making with patients about prophylactic ICD implantation, acknowledging the lack of robust data on the impact of systolic dysfunction on the personalized risk estimates generated by HCM Risk-SCD or a validated paediatric model (e.g. HCM Risk-Kids).[89,315,841–844]	IIb	B

CMR, cardiac magnetic resonance; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.

7.2. Dilated cardiomyopathy

7.2.1. Diagnosis

7.2.1.1. Index case

Dilated cardiomyopathy is defined by the presence of LV dilatation and systolic dysfunction unexplained solely by abnormal loading conditions or CAD. Left ventricular dilatation is defined by LV end-diastolic dimensions or volumes >2 z-scores above population mean values corrected for body size, sex, and/or age. For adults this represents an LV end-diastolic diameter >58 mm in males and >52 in females and an LVEDV index of ≥75 mL/m^2 in males and ≥62 mL/m^2 in females by ECHO.[9,845,846] Left ventricular global systolic dysfunction is defined by LVEF <50%.[9]

7.2.1.2. Relatives

Clinical testing in relatives often reveals mild non-diagnostic abnormalities that overlap with normal variation or mimic changes seen in other more common diseases such as hypertension and obesity. In this context, the presence of isolated LV dilatation with preserved systolic function or in the presence of a familial causative variant is sufficient for a diagnosis of DCM in a relative. Additional electrocardiographic or imaging abnormalities in the context of a family history of DCM are suggestive of disease and warrant close follow-up.[9,75,817] In the absence of conclusive genetic information in a family, DCM is considered familial if: (i) one or more first- or second-degree relatives have DCM; or (ii) when an otherwise unexplained SCD has occurred in a first-degree relative at any age with an established diagnosis of DCM.

7.2.1.3. Diagnostic work-up

The key elements of the diagnostic work-up for all patients with DCM are described in *Section 6* and include clinical and family history, laboratory tests, ECG, Holter monitoring, cardiac imaging, and genetic testing. Echocardiography is central for the diagnosis and CMR provides more detailed morphological and prognostic information. Additional laboratory tests, exercise testing, EMB, cardiac CT, and cardiac catheterization should also be considered, as detailed in *Section 6*.

7.2.1.4. Echocardiography

Comprehensive TTE is recommended for all DCM patients as it provides all the relevant information on the global and regional LV anatomy, function and haemodynamics, valvular heart disease, right heart function, pulmonary pressure, atrial geometry, and associated features.[71] Advanced echocardiographic techniques (tissue Doppler and speckle tracking deformation imaging) can allow the early detection of subclinical myocardial dysfunction in specific situations (e.g. genetic DCM carriers, recipients of known cardiotoxic chemotherapy).[71,74]

Contrast agents may be considered for better endocardial delineation, to better depict the presence of hypertrabeculation, or to exclude intraventricular thrombus. Transoesophageal echocardiography is rarely necessary except for when atrial thrombi are present in patients with AF, or for assessing valvular function and guiding transcatheter therapy in patients with concomitant secondary mitral or tricuspid regurgitation.

7.2.1.5. Cardiac magnetic resonance

Cardiac magnetic resonance provides additional information on tissue characterization in patients with DCM, including the presence of myocardial oedema, which may suggest a myocarditic or inflammatory cause, and LGE, to determine the presence and extent of fibrosis, as well as its distribution, which may allow exclusion of myocardial infarction and also point towards specific aetiologies (e.g. subepicardial distribution in post-myocarditis forms, patchy in sarcoidosis, extensive inferolateral in dystrophinopathies, septal mid-wall in *LMNA* carriers, and ring-like in *DSP* and *FLNC*-truncating variant carriers) (see *Section 7.3*).[71,847] Late gadolinium enhancement distribution and extent hold prognostic value both for arrhythmia and heart failure severity.[137,848] Dedicated T2* sequences describe myocardial iron deposition, which is useful for the diagnosis of haemochromatosis.[71]

7.2.1.6. Nuclear medicine

There is a limited role for radionuclide imaging in DCM. Measurement of 18F-fluorodeoxyglucose (18F-FDG) uptake using PET, with focal or focal-on-diffuse FDG uptake patterns especially if there is concomitant abnormal 18F-FDG-PET uptake in extracardiac tissues, can be useful in suspected cardiac sarcoidosis.[849]

7.2.2. Genetic testing and family screening

The aetiology of DCM is highly heterogeneous and includes inherited (genetic/familial) and acquired causes.[9,545,850,851] Direct causes of DCM include pathogenic gene variants, toxins, auto-immunity, infections, storage diseases, and tachyarrhythmias. Monogenic gene variants causing DCM are highly heterogeneous, implicating many genes and diverse pathways. Moreover, only 30–40% of DCM cases are attributable to pathogenic rare variants, with a substantial polygenic/common variant contribution in this population. Furthermore, disease modifiers can play a role in the acceleration of the DCM phenotype.[7,9,850] This includes conditions that may aggravate or trigger DCM, including epigenetic factors and acquired modifiers, such as pregnancy, hypertension, excessive alcohol use, and other toxins.[42–44] It is important to consider the interplay between genetic and acquired causes during the diagnostic work-up. Identification of an acquired cause does not exclude an underlying causative gene variant, whereas the latter may require an additional acquired cause and/or disease modifier to manifest. Within the genes that can cause DCM, there are genes robustly associated with classical DCM that have been recently curated,[189] and also others classically associated with ARVC but that very commonly can present with LV dilatation and predominantly LV dysfunction. Moreover, genes described in the context of hypertrabeculation/LVNC (e.g. *NKX2.5* and *PRDM16*), or that can cause DCM with or without skeletal involvement (such as *DMD* or *EMD*), should also be considered DCM-associated genes and examined, particularly if phenotype is concordant. The most common genetic and acquired causes of DCM are shown in *Table 10* and *Table 20*. Detailed lists of causes of DCM have been previously published.[9,852]

7.2.2.1. Genetic testing

Causative gene variants occur in up to 40% of DCM patients in contemporary cohorts,[185,186,853,854] and between 10 and 15% in chemotherapy-induced, alcoholic, or peripartum DCM.[42–44] Although the prevalence of genetic variants is higher in familial DCM, causative genetic variants are also identified in over 20% of non-familial DCM cases.[185,854,855] Finding a causative gene variant in a patient with DCM allows better prediction of the disease outcome and progression,

Table 20 Non-genetic causes of dilated cardiomyopathy

Infection (post-myocarditis)	
Viral (enteroviruses, adenoviruses, echoviruses, herpes viruses, parvovirus B19, HIV, SARS-CoV-2, etc.)	
Bacterial (Lyme disease)	
Mycobacterial	
Fungal	
Parasitic (Chagas disease)	
Toxic and overload	
Alcohol (ethanol)	
Cocaine, amphetamines, ecstasy	
Cobalt	
Anabolic/androgenic steroids	
Haemochromatosis and other causes of iron overload	
Endocrinology	
Hypo- and hyperthyroidism	
Cushing/Addison disease	
Phaeochromocytoma	
Acromegaly	
Diabetes mellitus	
Nutritional deficiency	
Selenium deficiency	
Thiamine deficiency (Beri-Beri)	
Zinc and copper deficiency	
Carnitine deficiency	
Electrolyte disturbance	
Hypocalcaemia	
Hypophosphataemia	
Peripartum	
Autoimmune diseases	
Giant cell myocarditis	
Inflammatory (biopsy-proven, non-infectious myocarditis)	
Eosinophilic granulomatosis with polyangiitis	
Systemic lupus erythematosus	
Sarcoidosis	
Rheumatoid arthritis	
Coeliac disease	
Primary biliary cirrhosis	
Myasthenia gravis	
Pemphigus pemphigoid	
Crohn disease	
Ulcerative colitis	
Polymyositis/dermatomyositis	
Reactive arthritis	
Drugs	
Antineoplastic drugs	Anthracyclines; antimetabolites; alkylating agents; Taxol; hypomethylating agent; monoclonal antibodies; tyrosine kinase inhibitors; immunomodulating agents
Psychiatric drugs	Clozapine, olanzapine; chlorpromazine, risperidone, lithium; methylphenidate; tricyclic antidepressants
Other drugs	All-trans retinoic acid; antiretroviral agents; phenothiazines

HIV, human immunodeficiency virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

may contribute to the indications for device implantation, informs genetic counselling, and allows familial screening for relatives. Moreover, genetic testing in DCM has long-term implications in terms of cost-effectiveness by identifying at-risk family members with positive genotypes, and thus reducing the number of family members requiring serial clinical follow-up.[229] Genetic testing can therefore be beneficial in all patients with DCM, including children[856,857] and those with alcohol-/chemotherapy-induced and peripartum DCM. Where resources are limited, scores designed to identify DCM patients with a high probability of a positive genotype (e.g. the Madrid DCM Genotype Score [https://madridDCMscore.com]) may be considered to prioritize genetic testing.[858] Of note, age should not be a limiting factor when deciding which DCM patients should undergo genetic testing.[185,858,859]

Recommendations for clinical screening, genetic counselling, and testing are described in *Sections 6.8.3* and *6.11*. More detailed evaluation of conduction defects or arrhythmia, which may be an early presentation of certain genetic DCM subtypes, should be considered in the context of certain gene variants (e.g. *LMNA*, *EMD*, *DES*). Cardiac MRI should also be considered in relatives with normal cardiac function who carry causative genetic variants associated with increased risk of SCD (e.g. *FLNC*, *DES*, *DSP*, *PLN*, *LMNA*, *TMEM43*, *RMB20*). If there are no additional family members with DCM, other than the proband, periodic evaluation of first-degree relatives should follow the same intervals according to age (see *Section 6.11*), but termination of periodic surveillance in families in whom a genetic variant has not been identified could be considered in first-degree relatives ≥50 years of age with normal ECG and normal cardiac imaging tests.

7.2.3. Assessment of symptoms

Patients with DCM often develop symptoms of heart failure, although this can occur many years after the appearance of ECG or echocardiographic abnormalities. Assessment of symptoms in patients with cardiomyopathies is described in *Section 6.10.1*.

7.2.4. Management

The clinical management of heart failure and other manifestations of DCM has been described in the *2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure*, the *2020 ESC Guidelines for the diagnosis and management of atrial fibrillation*, and the *2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy*.[69,336,724] In these guidelines, recommendations are generally independent of the aetiology of heart failure, AF, and other clinical presentations. As such, although they summarize large and robust datasets and trials, the treatment recommendations must be regarded as generic and not specific to the different forms of genetic DCM. However, as large cohorts of genetic DCMs with uniform genetic features are relatively rare, adequately powered RCTs in cardiomyopathies are scarce. The Task Force therefore recommends applying the *2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure*, which contain treatment guidelines for patients with signs and symptoms of heart failure, for symptom management of patients with DCM.[69] Treatment recommendations for asymptomatic LV dysfunction or dilatation are scarce, which presents a challenge for genetic DCM, where a sizeable proportion of the patients are young with no or mild symptoms, and where asymptomatic patients are frequently discovered through cascade screening. Recommendations for the pharmacological management of heart failure symptoms in patients with cardiomyopathies are described in *Section 6.10.2*.

7.2.5. Sudden cardiac death prevention in dilated cardiomyopathy

Predicting SCD is a challenging aspect of the clinical care of patients with DCM. Implantable cardioverter defibrillators are effective at treating potentially lethal ventricular arrhythmias and preventing SCD, but are also associated with complications, particularly in young patients, who will require several replacements during their lifetimes (see *Section 6.10.5*).

7.2.5.1. Secondary prevention of sudden cardiac death

Implantable cardioverter defibrillators reduce mortality in survivors of cardiac arrest and in patients who have experienced sustained symptomatic ventricular arrhythmias with haemodynamic compromise.[531] An ICD is recommended in such patients when the intent is to increase survival; the decision to implant should consider the patient's view and their QoL, as well as the absence of other diseases likely to cause death within the following year.

7.2.5.2. Primary prevention of sudden cardiac death

Available RCTs examining the usefulness of ICDs to prevent SCD and improve survival have included only patients with LVEF ≤35%, with conflicting results. While a trial including both ischaemic and non-ischaemic symptomatic heart failure patients showed reduction in mortality,[860] trials including only patients without CAD did not significantly improve the overall risk of mortality despite the fact that there was an absolute reduction in SCD with ICDs, and subgroup analysis suggested that there was a survival benefit in patients ≤70 years.[861,862] Nevertheless, in a recent meta-analysis of studies that examined the effect of ICDs in DCM, a survival benefit was observed, although the effect was modest compared with LVEF ≤35% patients with CAD.[863]

Although LVEF ≤35% has been reported as an independent risk marker of all-cause and cardiac death in DCM, it has also shown only modest ability in identifying DCM patients with higher risk of SCD, suggesting that additional factors should be taken into consideration when deciding on ICD implantation in a disease with significant aetiological heterogeneity. Recent natural history studies suggest that phenotype plays a role a role in SCD risk, with patients harbouring disease-causing variants in *PLN*, *DSP*, *LMNA*, *FLNC*, *TMEM43*, and *RBM20* having a substantially higher rate of major arrhythmic events than other causes of DCM regardless of LVEF.[440,542,864–870] A recent retrospective study of 1161 individuals with DCM has shown that DCM patients with P/LP DCM-causing genetic variants have a worse clinical evolution and higher rate of major arrhythmic events than genotype-negative DCM patients and particularly in DCM patients with LVEF ≤35%.[185] The study also observed a higher risk of major arrhythmic events in DCM patients affected by DCM-causing variants in certain genotypes regardless of LVEF. Genes associated with higher arrhythmic risk included genes coding for nuclear envelope (*LMNA*, *EMD*, *TMEM43*), desmosomal (*DSP*, *DSG2*, *DSC2*, *PKP2*), and certain cytoskeletal proteins.[185] Together, these data suggest that DCM patients harbouring DCM-causing variants in high-risk genes (*LMNA*, *EMD*, *TMEM43*, *DSP*, *RBM20*, *PLN*, *FLNC*-truncating variants) should be considered as patients with a high-risk genetic background for SCD and primary prevention ICD implantation should be considered with LVEF thresholds higher than 35%, particularly in the presence of additional risk factors (e.g. NSVT, increased ventricular ectopic beats, male sex, significant LGE, specific gene variant). For some high-risk genotypes (e.g. *LMNA* [https://lmna-risk-vta.fr][541]), gene-specific (or, in the case of the *PLN*

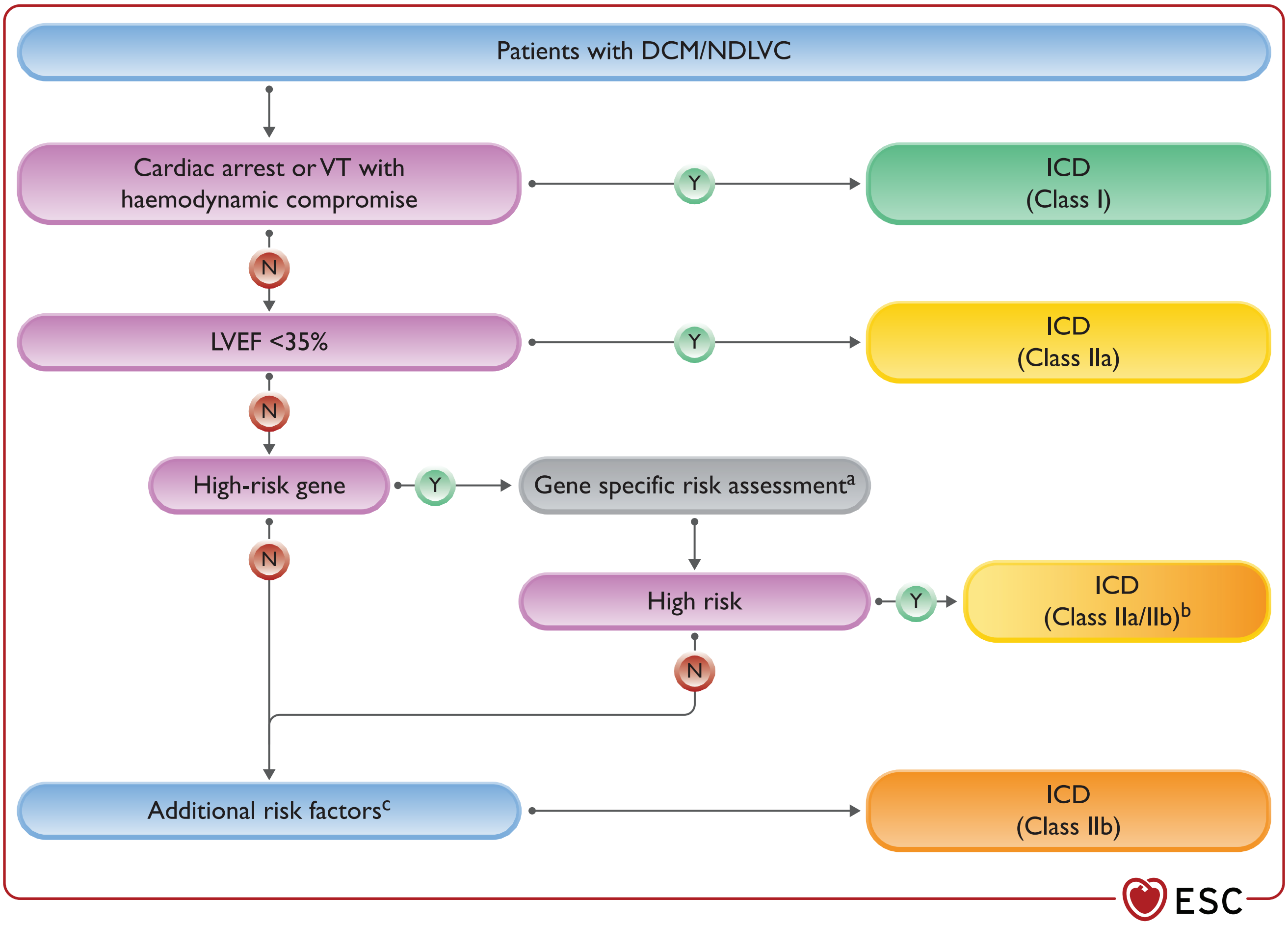

Figure 17 Implantation of implantable cardioverter defibrillators in patients with dilated cardiomyopathy or non-dilated left ventricular cardiomyopathy flowchart. CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NDLVC, non-dilated left ventricular cardiomyopathy; VE, ventricular ectopic beats; VT, ventricular fibrillation. [a]See *Table 21*. [b]Strength of recommendation depends on gene and context. [c]Additional risk factors include syncope, LGE presence on CMR.

p.Arg14del variant, variant-specific [https://plnriskcalculator.shinyapps.io/final_shiny])[542] risk-prediction scores have been developed that consider genotype characteristics and additional phenotypic features. Where such scores are available, they should be used to guide primary prevention ICD implantation (*Figure 17*). As discussed in *Section 7.1.5*, the Task Force acknowledges the challenges associated with defining universal thresholds for acceptable risk across different cardiomyopathy phenotypes, but is of the opinion that a similar approach to that taken in risk stratification for HCM is reasonable. Although the *2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death* have suggested a higher threshold of 10% risk at 5 years to guide primary prevention ICD implantation in patients with DCM and *LMNA* variants,[3] this Task Force recommends shared decision-making based on real-world data as well as individual preferences, beliefs, circumstances, and values. Gaps in evidence should be shared with patients, and competing risks related to the disease (heart failure, stroke), and to age and comorbidity, as well as device-related complications, should be discussed. In support of this, a recent study validating the LMNA-risk VTA calculator overestimated arrhythmic risk when using ≥7% predicted 5-year risk as threshold (specificity 26%, C-statistic 0.85), despite a high sensitivity.[871]

Importantly, there are also data to suggest that other genotypes (e.g. *TTN* truncating variants) are associated with recovery of LVEF with standard heart failure criteria from the *2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.*[185,867,872]

In patients without a high-risk genotype and LVEF >35%, the presence and extent of myocardial scarring determined by LGE on CMR imaging can be helpful in risk stratification in patients with DCM.[873,874] Late gadolinium enhancement is observed in 25–35% of patients with DCM and its presence is a strong risk marker for all-cause mortality and ventricular arrhythmias, both in retrospective and prospective studies. A recent prospective study of 1020 DCM patients with a median follow-up of 5.2 years showed that myocardial scar had a strong and incremental prognostic value for predicting SCD, while LVEF ≤35% was not associated with SCD.[138] In another study, a risk calculator was developed that among others, incorporated the presence of LGE on CMR imaging[540], although this has not yet been externally validated. There are at least two ongoing trials of ICD therapy according to the presence of scar on CMR imaging, including DCM patients (NCT04558723 and NCT03993730), but the Task Force's opinion is that the existing level of evidence can support using LGE to guide ICD implantation in subgroups of patients with DCM (*Figure 17*). Additional risk factors, such as syncope or the presence of NSVT and burden of ventricular ectopy (VE), may also help guide ICD implantation. There are no data currently to support a specific threshold for VE burden, and this will depend on the underlying genotype and other clinical factors.[542,867,872] In patients with unexplained syncope, programmed electrical stimulation (PES) may provide additional information on the underlying cause.[875] There are no definitive data supporting the routine use of PES for primary prevention risk stratification in patients with DCM, but this may be beneficial in patients with DCM and myotonic dystrophy with an independent indication to electrophysiological study to assess conduction disturbances,[876] although the clinical value of this approach has not been consistently demonstrated.[877]

Recommendation Table 24 — Recommendations for an implantable cardioverter defibrillator in patients with dilated cardiomyopathy

Recommendations	Class[a]	Level[b]
Secondary prevention		
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with DCM who have survived a cardiac arrest or have recovered from a ventricular arrhythmia causing haemodynamic instability.[530,531,884]	I	B
Primary prevention		
An ICD should be considered to reduce the risk of sudden death and all-cause mortality in patients with DCM, symptomatic heart failure, and LVEF ≤35% despite >3 months of OMT.[861,885]	IIa	A
The patient's genotype should be considered in the estimation of SCD risk in DCM.[185,186,869,886]	IIa	B
An ICD should be considered in patients with DCM with a genotype associated with high SCD risk and LVEF >35% in the presence of additional risk factors (see *Table 21*).[541,542,867,869,873,878,881,886]	IIa	C
An ICD may be considered in selected patients with DCM with a genotype associated with high SCD risk and LVEF >35% without additional risk factors (see *Table 21*).[869,873,881,886]	IIb	C
An ICD may be considered in patients with DCM without a genotype associated with high SCD risk and LVEF >35% in the presence of additional risk factors.[c,138,873,874]	IIb	C

CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; OMT, optimal medical therapy; SCD, sudden cardiac death.
[a]Class of recommendation.
[b]Level of evidence.
[c]Additional risk factors include syncope, LGE presence on CMR.

7.3. Non-dilated left ventricular cardiomyopathy

7.3.1. Diagnosis

7.3.1.1. Index case

The non-dilated LV cardiomyopathy phenotype is defined by the presence of non-ischaemic LV scarring or fatty replacement in the absence of LV dilatation, with or without global or regional wall motion abnormalities, or isolated global LV hypokinesia without scarring (as assessed by the presence of LGE on CMR) that is unexplained solely by abnormal loading conditions (hypertension, valve disease) or CAD. Global LV systolic dysfunction is defined by abnormal LVEF (i.e. <50%).[9]

Table 21 High-risk genotypes and associated predictors of sudden cardiac death

Gene	Annual SCD rate	Predictors of SCD
LMNA[185,186,438,541,865,878,879]	5–10%	Estimated 5-year risk of life-threatening arrhythmia using *LMNA* risk score (https://lmna-risk-vta.fr)
FLNC-truncating variants[866,867,880]	5–10%	LGE on CMR LVEF < 45%
TMEM43[868,881]	5–10%	Male Female and any of the following: LVEF <45%, NSVT, LGE on CMR, >200 VE on 24h Holter ECG
PLN[542,882,883]	3–5%	Estimated 5-year risk of life-threatening arrhythmia using *PLN* risk score (https://plnriskcalculator.shinyapps.io/final_shiny) LVEF < 45% LGE on CMR NSVT
DSP[185,186]	3–5%	LGE on CMR LVEF < 45%
RBM20[869]	3–5%	LGE on CMR LVEF < 45%

CMR, cardiac magnetic resonance; DSP, desmoplakin; ECG, electrocardiogram; FLNC, filamin C; LGE, late gadolinium enhancement; LMNA, lamin A/C; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; PLN, phospholamban; RMB, RNA binding motif protein; SCD, sudden cardiac death; VE, ventricular ectopic beats.

7.3.1.2. Relatives

Clinical testing in relatives may reveal non-diagnostic abnormalities. In this context, the presence of LV systolic global or regional dysfunction, or additional electrocardiographic abnormalities (e.g. repolarization abnormalities, low QRS voltages, frequent ventricular extrasystoles [>500 per 24 h] or NSVT) in a first-degree relative of an individual with NDLVC (or a first-degree relative with autopsy-proven NDLVC) is highly suggestive of NDLVC and warrants close follow-up.

In the absence of conclusive genetic information in the family, NDLVC should be considered familial if one or more first- or second-degree relatives have NDLVC, or when SCD has occurred in a first-degree relative at any age with an established diagnosis of NDLVC. Familial disease should also be suspected if a first-degree relative has sudden death at <50 years of age and autopsy findings suggestive of the NDLVC phenotype.

7.3.1.3. Diagnostic work-up

The key elements of the diagnostic work-up for all patients with NDLVC are described in *Section 6* and include clinical history, laboratory tests, Holter monitoring and cardiac imaging, and genetic testing.

Echocardiography and CMR are both central to the diagnosis. Additional laboratory tests, exercise testing, EMB, and cardiac catheterization may also be considered (see *Section 6*).

7.3.1.4. Electrocardiographic features

Recommendations on resting and ambulatory ECG testing are described in *Section 6.5* and are of particular importance in patients with NDLVC, as specific features can indicate the underlying genetic cause. Prolonged PR interval or AV block is frequent in neuromuscular causes of NDLVC and in sarcoidosis. Laminopathies are characterized by prolonged PR interval, AF, and ventricular ectopics (VEs), and frequently show low voltage in pre-cordial leads.[887] Depolarization abnormalities such as low QRS voltage are also a common finding in NDLVC caused by *DSP* and *PLN* variants.[542] Ambulatory ECG monitoring is useful in NDLVC patients to reveal supraventricular and ventricular arrhythmias or bradycardias due to AV conduction block and is recommended at least yearly, or when there is a change in clinical status. In some patients with NDLVC at high risk of developing conduction disease and/or arrhythmias (including laminopathies, neuromuscular disease, *PLN*, and *FLNC*-truncating variants), Holter monitoring may be considered more frequently.

Recommendation Table 25 — Recommendation for resting and ambulatory electrocardiogram monitoring in patients with non-dilated left ventricular cardiomyopathy

Recommendation	Class[a]	Level[b]
Ambulatory ECG monitoring is recommended in patients with NDLVC annually or when there is a change in clinical status, to aid in management and risk stratification.	I	C

ECG, electrocardiogram; NDLVC, non-dilated left ventricular cardiomyopathy.
[a]Class of recommendation.
[b]Level of evidence.

7.3.1.5. Echocardiography

Comprehensive TTE is recommended for all patients with NDLVC as it provides all relevant information on the global and regional LV anatomy, function, and haemodynamics; valvular heart disease; right heart function; pulmonary pressure; atrial geometry; and other features.[71,73] Advanced echocardiographic techniques (including deformation imaging using tissue Doppler and speckle tracking) can allow the early detection of subclinical myocardial dysfunction in specific situations (e.g. genetic NDLVC carriers).[71,74]

7.3.1.6. Cardiac magnetic resonance

Cardiac magnetic resonance with LGE is the foremost imaging modality in NDLVC as it provides confirmation of the presence of non-ischaemic myocardial fibrosis that is essential for the diagnosis in most cases. Cardiac magnetic resonance can also be useful to detect the presence of myocardial oedema, which may suggest an inflammatory or myocarditic aetiology, and to describe the extent and pattern of fibrosis distribution. This can provide clues to the underlying aetiology (e.g. subepicardial distribution in post-myocarditis forms, patchy in sarcoidosis, extensive inferolateral in dystrophinopathies, septal mid-wall in *LMNA* carriers, and ring-like in *DSP* and *FLNC* variant carriers),[71] and may provide additional prognostic value both for arrhythmia and heart failure severity.[137,848]

7.3.1.7. Nuclear medicine

The role of radionuclide imaging in NDLVC is limited. Measurement of 18F-FDG uptake using PET, with focal or focal-on-diffuse FDG uptake patterns, especially if concomitant abnormal 18F-FDG-PET uptake in extracardiac tissues, can be useful in suspected cardiac sarcoidosis.[849] Isolated cardiac uptake has also been described in patients with NDLVC caused by *DSP* variants.[888]

7.3.1.8. Endomyocardial biopsy

Endomyocardial biopsy (EMB) with immunohistochemical quantification of inflammatory cells remains the gold standard investigation for the identification of cardiac inflammation. It may confirm the diagnosis of autoimmune disease in patients with unexplained heart failure and suspected giant cell myocarditis, eosinophilic myocarditis, vasculitis, and sarcoidosis. In experienced centres, electroanatomical voltage mapping-guided EMB may improve the yield of diagnosis of NDLVC.[889] The risks and benefits of EMB should be evaluated and this procedure should be reserved for specific situations where its results may affect diagnosis or treatment (see *Section 6.7.5*).

7.3.2. Genetic testing

The genes most commonly implicated in NDLVC are *DSP*, *FLNC* (truncating variants), *DES*, *LMNA*, or *PLN*, but there is substantial overlap with the genetic background of both DCM and ARVC (*Table 10*). Desmoplakin (*DSP*) variants, in particular, cause a unique form of cardiomyopathy with a high prevalence of LV fibrosis and myocardial inflammatory episodes.[864]

The identification of a P/LP gene variant in a patient with NDLVC allows better prediction of the disease outcome and progression, may contribute to the indications for device implantation, informs genetic counselling, and allows familial screening for relatives (see *Section 6.8.3*). Therefore, genetic testing is recommended in all patients with NDLVC.

Recommendations for clinical screening, genetic counselling, and testing are described in *Sections 6.8.3* and *6.11*. Evaluation of conduction disease, and atrial and ventricular arrhythmia, is of particular importance in patients with NDLVC, as these may often be early phenotypic features. There are very few data on the natural history of phenotype-negative variant carriers or on the clinical yield of familial cascade screening in NDLVC, but cross-sectional studies suggest age-related increases in penetrance.[9] Precautionary long-term evaluation of first-degree relatives is therefore recommended.

7.3.3. Assessment of symptoms

Most patients with NDLVC are asymptomatic, but some develop symptoms related to arrhythmia or conduction disease (e.g. syncope, palpitation) or diastolic heart failure (e.g. dyspnoea). Sustained ventricular arrhythmia, cardiac arrest, or SCD can be the initial presentation in a proportion of patients. Assessment of symptoms in patients with cardiomyopathies is described in *Section 6.10.1*.

7.3.4. Management

The clinical management of heart failure and other manifestations of NDLVC (atrial tachyarrhythmia, conduction disease) has been described in the *2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure*, the *2020 ESC Guidelines for the diagnosis and management of atrial fibrillation*, the *2021 ESC Guidelines on cardiac* *pacing and cardiac resynchronization therapy*, and the *2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death*,[69,299,336,724] and are discussed in *Section 6.10.2*.

7.3.5. Sudden cardiac death prevention in non-dilated left ventricular cardiomyopathy

The prediction and prevention of SCD is the cornerstone of the clinical care of patients with NDLVC.

7.3.5.1. Secondary prevention of sudden cardiac death

As in other cardiomyopathy subtypes, ICD implantation is recommended in survivors of cardiac arrest and in patients who have experienced sustained ventricular arrhythmias with haemodynamic compromise;[531] the decision to implant should consider the patient's view and their QoL, as well as the absence of other diseases likely to cause death within 1 year.

7.3.5.2. Primary prevention of sudden cardiac death

There are no available RCTs examining the usefulness of ICDs to prevent SCD in patients with mild or moderate LV dysfunction. Recommendations for ICD implantation in DCM individuals with LVEF <35% are discussed in *Section 6.10.2* and also apply to patients with NDLVC and LVEF <35%. Most patients with NDLVC, however, have either normal or mildly impaired LV systolic function. Much of the data on the natural history and risk prediction in NDLVC are derived from cohorts that include either patients with DCM or with ARVC (see *Sections 7.2* and *7.4*), and data on patients with NDLVC are therefore necessarily very limited. However, the available data suggest that genotype is a major determinant of SCD risk, with patients harbouring variants in *PLN*, *TMEM43*, *DES*, *DSP*, *LMNA*, *FLNC* (truncating variants), and *RBM20* having a substantially higher rate of major arrhythmic events than other causes regardless of LVEF.[440,542,864–869] For some high-risk genotypes (e.g. *LMNA* [https://lmna-risk-vta.fr][541]), gene-specific (or, in the case of the *PLN* p.Arg14del variant, variant-specific [https://plnriskcalculator.shinyapps.io/final_shiny])[542] risk-prediction scores have been developed that consider genotype characteristics and additional phenotypic features. Where such scores are available, they should be used to guide primary prevention ICD implantation (*Figure 12*). As discussed in *Sections 7.1.5* and *7.2.5*, the Task Force acknowledges the challenges associated with defining universal thresholds for acceptable risk across different cardiomyopathy phenotypes, but is of the opinion that a similar approach to that taken in risk stratification for HCM is reasonable, although the *2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death* have suggested a higher threshold of 10% risk at 5 years to guide primary prevention ICD implantation in patients with NDLVC and *LMNA* variants.[3] This Task Force recommends more overt shared decision-making based on real-world data as well as individual preferences, beliefs, circumstances, and values. Gaps in evidence are acknowledged and should be shared with patients, and competing risks related to the disease (heart failure, stroke) and to age and comorbidity, as well as device-related complications, should be discussed.

There are very few data to guide risk stratification in patients with NDLVC without a known causative gene variant, but on the basis of the existing literature, the Task Force suggests that it may be reasonable to consider primary prevention ICD implantation in patients with NSVT, a family history of SCD, or significant LGE. Additional risk factors, such as the burden of VE, may also help guide ICD implantation, but there are no data currently to support a specific threshold for VE burden, and this will depend on the underlying genotype and other clinical factors.[542,867,872] In patients with unexplained syncope, PES may provide additional information on the underlying cause.[875] There are no definitive data supporting the regular use of PES for primary prevention risk stratification in patients with NDLVC, but may be beneficial in patients with NDLVC and myotonic dystrophy with an independent indication to EP study to assess conduction disturbances,[876] although the clinical value of this approach has not been consistently demonstrated.[877] Given the overlap with DCM and available data, and in keeping with the *2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death*, the Task Force agreed that the recommendations for primary prevention ICD implantation in NDLVC should be the same as those for DCM (*Figure 17*), but the level of evidence is necessarily lower.

Recommendation Table 26 — Recommendations for an implantable cardioverter defibrillator in patients with non-dilated left ventricular cardiomyopathy

Recommendations	Class[a]	Level[b]
Secondary prevention		
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with NDLVC who have survived a cardiac arrest or have recovered from a ventricular arrhythmia causing haemodynamic instability.	I	C
Primary prevention		
An ICD should be considered to reduce the risk of sudden death and all-cause mortality in patients with NDLVC, heart failure symptoms, and LVEF ≤35% despite >3 months of OMT.[861,885]	IIa	A
The patient's genotype should be considered in the estimation of SCD risk in NDLVC.	IIa	C
An ICD should be considered in patients with NDLVC with a genotype associated with high SCD risk and LVEF >35% in the presence of additional risk factors (see *Table 21*).[185,186,438,541,542,865–869,878–883]	IIa	C
An ICD may be considered in selected patients with NDLVC with a genotype associated with high SCD risk and LVEF >35% without additional risk factors (see *Table 21*).	IIb	C
An ICD may be considered in patients with NDLVC without a genotype associated with high SCD risk and LVEF >35% in the presence of additional risk factors.[c]	IIb	C

ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NDLVC, non-dilated left ventricular cardiomyopathy; OMT, optimal medical therapy; SCD, sudden cardiac death.
[a]Class of recommendation.
[b]Level of evidence.
[c]Additional risk factors include syncope, LGE presence on CMR.

7.4. Arrhythmogenic right ventricular cardiomyopathy

7.4.1. Diagnosis

7.4.1.1. Index case

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized structurally by a progressive myocardial atrophy with fibro-fatty replacement of the RV myocardium.[890] Lesions can also be present in the LV myocardium; predominant LV disease can coexist in the same family. Arrhythmogenic right ventricular cardiomyopathy usually manifests in the second to fourth decade of life.[891] Men are affected more frequently than women and an age-related penetrance has been demonstrated, with high clinical and genetic variability.

An ARVC diagnosis should be suspected in adolescents or young adults with palpitations, syncope, or aborted sudden death. Frequent VEs or VT of LBBB morphology are among the most common clinical presentation. The presence of right pre-cordial TWI (V1–V3) in routine ECG testing should also be suspected for ARVC.[10,892] Less common ECG changes include low QRS voltages in the peripheral leads and terminal activation delay in the right pre-cordial leads.[893] Right ventricular dilatation on 2D echocardiography is also a frequent reason for patient referral. Less common presentations are RV or biventricular heart failure that can mimic DCM or NDLVC.[894] Patients with multiple variants are thought to develop a more severe phenotype, and patients with a *DSP* or *DSG2* variant are more prone to develop heart failure.[895,896]

In children and young adults, syncope, palpitations, and ventricular arrhythmias are also the usual presenting symptoms.[897] However, chest pain, dynamic ST-T wave changes on basal 12-lead ECG, and myocardial enzymes release in the setting of normal coronary arteries are often reported, requiring differential diagnosis with myocarditis or acute myocardial infarction.[898]

7.4.1.2. Relatives

Clinical testing in relatives often reveals non-diagnostic abnormalities. In this context, the presence of RV systolic global or regional dysfunction, or additional electrocardiographic abnormalities (e.g. repolarization abnormalities, prolonged terminal activation duration, low QRS voltages, frequent ventricular extrasystoles [>500 per 24 h], or NSVT) in a first-degree relative of an individual with ARVC (or a first-degree relative with autopsy-proven ARVC) is highly suggestive of ARVC and warrants close follow-up.

7.4.1.3. Diagnostic work-up

The key elements of the diagnostic work-up for all patients with ARVC are defined by the diagnostic criteria used for the identification of affected individuals. The revised Task Force criteria for the diagnosis of ARVC published by Marcus *et al.* in 2010 have been used for the diagnosis of ARVC for more than a decade.[10] More recently, the Padua criteria have offered an updated iteration to include LV involvement but are yet to be externally validated.[5] Key elements of the diagnostic work-up include ECG, Holter monitoring, cardiac imaging, genetic testing, and, in specific circumstances, EMB.[4,10,892] Additional laboratory tests, exercise testing, and cardiac catheterization should also be considered, as detailed in *Section 6*.

7.4.1.4. Electrocardiography and Holter monitoring

Abnormalities of the repolarization and depolarization as well as arrhythmias are key to the diagnosis of ARVC.[5] The diagnostic utility of late potentials on signal-averaged electrocardiogram (SAECG) has been challenged in patients with ARVC for showing poor sensitivity and specificity.[5,899] It has been noted that epsilon waves are frequently overdiagnosed and that there is poor agreement even between experts regarding their presence.[900] Furthermore, it has been demonstrated that they occur in the presence of severe structural disease and thus add little to the diagnosis.[900,901] Therefore, epsilon waves and SAECG should be utilized for diagnostic purposes with caution.

Recommendation Table 27 — Recommendation for resting and ambulatory electrocardiogram monitoring in patients with arrhythmogenic right ventricular cardiomyopathy

Recommendation	Class[a]	Level[b]
Annual ambulatory ECG monitoring is recommended in patients with ARVC to aid in diagnosis, management, and risk stratification.[902]	I	C

ARVC, arrhythmogenic right ventricular cardiomyopathy; ECG, electrocardiogram.
[a]Class of recommendation.
[b]Level of evidence.

7.4.1.5. Echocardiography and cardiac magnetic resonance

A comprehensive cardiac imaging assessment is recommended for all ARVC patients.[71,73] Structural and functional alterations assessed by echocardiography and CMR are key to ARVC diagnosis.[10] The key feature is the presence of wall motional abnormalities such as RV akinesia, dyskinesia, or bulging, and the determinant of the diagnostic performance is the level of RV dilatation or dysfunction (major and minor criteria). Cardiac magnetic resonance should be considered the first-line test for assessment of the RV functional structural abnormalities criterion as it has demonstrated superior sensitivity.[10] Contrast-enhanced CMR is the only tool allowing the detection of LV involvement which remains otherwise underestimated by applying the 2010 Task Force Criteria. Tissue characterization by CMR or indirectly by electroanatomical voltage mapping may show signs of fibro-fatty replacement that can be present in either ventricle.[889,903,904]

7.4.1.6. Endomyocardial biopsy

Differential diagnosis in patients with suspected ARVC includes inflammatory processes affecting the right ventricle such as myocarditis and sarcoidosis. In some instances, especially when dealing with probands with a sporadic form, EMB may be helpful to rule out myocarditis and sarcoidosis.[72,892,905] Endomyocardial biopsy can also be useful in selected patients in whom non-invasive assessment is inconclusive.[4,72] Electroanatomic voltage mapping-guided EMB may be considered in selected cases, particularly in case of negative CMR.[906]

7.4.1.7. Nuclear medicine

Measurement of 18F-FDG uptake using PET, with focal or focal-on-diffuse FDG uptake patterns, can be useful in suspected cardiac sarcoidosis.[849] However, it has been demonstrated that patients with ARVC can also show myocardial 18F-FDG-PET uptake.[888,907] Therefore, there is a limited role for radionuclide imaging in ARVC unless there is concomitant abnormal 18F-FDG-PET uptake in extracardiac tissues, or other clinical features suggestive of cardiac sarcoidosis.[904,908]

7.4.1.8. Arrhythmogenic right ventricular cardiomyopathy phenocopies

In suspicion of ARVC, a systematic approach to investigation of phenocopies should be undertaken. Differential diagnosis in patients with suspected ARVC includes myocarditis, sarcoidosis, RV infarction, DCM, Chagas disease, pulmonary hypertension, and CHD with volume overload (such as Ebstein anomaly, atrial septal defect, and partial anomalous venous return, left-to-right shunt, and pericardial agenesis).[909,910] Disease phenocopies also include non-structural diseases. In fact, one of the main diagnostic dilemmas is to distinguish ARVC from idiopathic RV outflow tract VT, since the latter is usually benign.[4] The idiopathic nature of VT is supported by the absence of family history, a normal basal 12-lead ECG, a normal ventricular structure by cardiac imaging and electroanatomic mapping, a single VT morphology, and the non-inducibility at programmed ventricular stimulation.

In highly trained competitive athletes, differential diagnosis with physiological adaptation to training needs to be considered.[911] Right ventricular enlargement, ECG abnormalities, and arrhythmias reflect the increased haemodynamic load during exercise. While global RV systolic dysfunction and/or RWMAs, such as bulgings or aneurysms, are more in keeping with ARVC, the absence of overt structural changes of the right ventricle, frequent VEs, or inverted T waves in pre-cordial leads all support a benign nature (so-called athlete's heart).[72,912,913]

7.4.2. Genetic testing and family screening

The genes underlying ARVC mainly encode proteins of the cardiac desmosome: plakophilin-2 (*PKP2*), desmoplakin (*DSP*), desmoglein-2 (*DSG2*), desmocollin-2 (*DSC2*), and plakoglobin (*JUP*). In addition to desmosomal genes, P/LP variants have also been described in other genes, including *DES*,[914] *TMEM43*,[915] and *PLN*.[190,882] Pathogenic or likely pathogenic variants can be identified in up to 60% of patients with a diagnosis of ARVC.[230] Given the diagnostic importance of genetic testing in ARVC, it is important that genetic variants are frequently reappraised in terms of their pathogenicity.[916] The pattern of inheritance in the majority of ARVC families is autosomal dominant. The penetrance of the disease in genetic carriers is age, gender, and physical activity dependent.[892,917]

Recommendations for clinical screening, genetic counselling, and testing are described in *Sections 6.8.3* and *6.11*. Cardiac evaluation should be adapted to the particular risk of complications in the family. Evaluation every 1–2 years including ECG, ECHO, and Holter/ECG monitoring is generally recommended for relatives at risk of developing the disease. Cardiac magnetic resonance should be considered at the baseline evaluation.

7.4.3. Assessment of symptoms

Patients with ARVC commonly experience palpitations and can develop symptoms of heart failure, although this may occur many years after the appearance of the initial abnormalities. Assessment of symptoms in patients with cardiomyopathies is described in *Section 6.10.1*.

7.4.4. Management

The aim of the clinical management of ARVC relies on the improvement of symptoms, the reduction of the pace of disease progression, and the prevention of complications. Recommendations for the pharmacological management of atrial arrhythmias and heart failure symptoms in patients with cardiomyopathies are described in *Sections 6.10.2* and *6.10.3*.

7.4.4.1. Antiarrhythmic therapy

Beta-blockers constitute the first option to reduce arrhythmic burden via a reduction in adrenergic tone, particularly on exercise. Titration to the maximal tolerated dose has been associated with an improvement in survival from major ventricular arrhythmias in retrospective observational studies.[918]

Amiodarone is often used when other beta-blockers fail to control arrhythmias.[917,919,920] It should, however, be used with caution for the long-term management of ventricular arrhythmias, especially in young patients. Sotalol has been used for many years, but evidence regarding its efficacy remain limited and conflicting.[921,922] Flecainide should be considered when single agent treatment has failed to control arrhythmia-related symptoms in patients with ARVC or when autonomic side effects limit the use of beta-blockers.[923,924] Experience with other antiarrhythmics (dofetilide, ranolazine) is limited to very small case series.[919,923]

A proportion of patients require invasive arrhythmic procedures and/or ICD implantation. Complex endocardial and/or epicardial approach guided by three-dimensional (3D) electroanatomical mapping can be recommended but with a high recurrence rate (30–50% in experienced centres).[919,925–927] Sympathetic denervation has also been used.[928] Such procedures do not confer adequate protection against SCD, but may be very useful in reducing the VT burden and the risk of electrical storm.[917] Discontinuation of intense physical exercise has shown a potential to slow the pace of disease progression and reduce the ventricular arrhythmia burden.[917,919]

Recommendation Table 28 — Recommendations for the antiarrhythmic management of patients with arrhythmogenic right ventricular cardiomyopathy

Recommendations	Class[a]	Level[b]
Beta-blocker therapy is recommended in ARVC patients with VE, NSVT, and VT.[920–922]	I	C
Amiodarone should be considered when regular beta-blocker therapy fails to control arrhythmia-related symptoms in patients with ARVC.[921,922]	IIa	C
Flecainide in addition to beta-blockers should be considered when single agent treatment has failed to control arrhythmia-related symptoms in patients with ARVC.[923,924]	IIa	C
Catheter ablation with availability for epicardial approach guided by 3D electroanatomical mapping of VT should be considered in ARVC patients with incessant VT or frequent appropriate ICD interventions for VT despite pharmacological therapy with beta-blockers.[925,929–934]	IIa	C

3D, three-dimensional; ARVC, arrhythmogenic right ventricular cardiomyopathy; ICD, implantable cardioverter defibrillator; NSVT, non-sustained ventricular tachycardia; VE, ventricular ectopic beats; VT, ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.

7.4.5. Sudden cardiac death prevention in arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy is characterized by its high propensity for ventricular arrhythmias and SCD.[919] Although estimated to be a rare disease, it has been consistently reported as one of the most common causes of SCD in registries around the world.[935–937] Sudden cardiac death seems to be more prevalent in young athletic individuals affected by the disease.[935,938]

7.4.5.1. Secondary prevention of sudden cardiac death

Implantable cardioverter defibrillators reduce mortality in survivors of cardiac arrest and in patients who have experienced sustained symptomatic ventricular arrhythmias.[531] An ICD is recommended in such patients when the intent is to increase survival; the decision to implant should consider the patient's view and their QoL, as well as the absence of other diseases likely to cause death within the following year.

7.4.5.2. Primary prevention of sudden cardiac death

Most of the current evidence on the outcomes of patients with ARVC and their predictors is limited to observational retrospective cohort studies that are typically of small size.[939] Thus, the number of clinical predictors that can be studied using multivariate models is very limited, and most studies cannot be compared with one another. A systematic review and meta-analysis ($n = 18$ studies) has shown that the average risk of ventricular arrhythmia ranges from 3.7 to 10.6% per year and that male sex, RV dysfunction, and prior non-sustained or sustained VT/VF consistently predict ventricular arrhythmias in populations with ARVC.[939]

The first comprehensive effort to offer an approach to risk stratification in the context of decision-making for ICD implantation was made in the 2015 International Task Force consensus statement (ITFC) on the treatment of ARVC/dysplasia, where recommendations were made according to the presence of risk factors that would characterize the risk level of each patient.[919] A follow-up study ($n = 365$) offered a modification on the International Task Force approach that resulted in better discrimination.[940] The *2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death*[941] and the *2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy*[4] have also offered alternative approaches to this issue. A risk-prediction model was developed from a multicentre collaboration ($n = 528$); it utilizes sex, age, recent syncope, NSVT, VE count, number of leads with TWI, and right ventricular ejection fraction (RVEF) as predictors to provide an individualized estimate of sustained ventricular arrhythmias in patients with ARVC (arvcrisk.com).[539]

A study ($n = 617$) comparing the previous approaches to risk stratify patients has revealed that the modified ITFC approach provides the highest net benefit, up to an estimated 5-year risk of 25%, whereas AHA and HRS perform best in patients with an estimated 5-year risk >25%.[538] In the same study, an estimated 5-year risk of 12.5% seems to be the optimal threshold, beyond which the risk-prediction model has the best performance. An external comparison ($n = 140$) of the different ARVC risk levels showed that the highest net benefit was seen with a 10% cut-off, using the 2019 ARVC risk calculator.[536] In the same study, the 10% cut-off was superior to the HRS and ITFC approaches.[536] Another external validation study ($n = 128$) of the 2019 ARVC risk model showed that although discriminative ability is excellent (c-index 0.84), the model seems to significantly overestimate the risk of patients below the 50% 5-year risk threshold.[537] Recently, a correction to the 2019 ARVC risk calculator was issued.[539] Two large external validation studies of the updated 2019 ARVC risk calculator have been published, suggesting a good discriminative performance, but the latter study revealed overestimation of risk.[524,526] This raises concerns regarding the accuracy of the model in offering an individualized prediction that can help inform patients during decision-making; however, it can remain informative due to its excellent discriminative performance. Furthermore, one study suggested that the updated 2019 ARVC risk calculator performs best in *PKP2* patients, but its performance is more limited in gene-negative individuals.[524]

Therefore, a combination of these approaches is recommended to individualize risk quantification that can aid clinicians in balancing the risks and benefits of ICD implantation. The final decision should be made together with the patient, considering other competing risks and the patient's risk tolerance. As discussed in *Section 7.1.5*, the Task Force acknowledges the challenges associated with defining universal thresholds for acceptable risk across different cardiomyopathy phenotypes, but is of the opinion that a similar approach to that taken in risk stratification for HCM, DCM, and NDLVC is reasonable. In this context, the Task Force recommends shared decision-making based on real-world data as well as individual preferences, beliefs, circumstances, and values. Gaps in evidence should be shared with patients, and competing risks related to the disease (heart failure, stroke) and to age and comorbidity, as well as device-related complications, should be discussed. The suggested approach is summarized in *Figure 18*.

Patients with ARVC are known to suffer from sustained VTs that can be well tolerated without leading to SCD. Using appropriate ICD interventions as surrogate for SCD outcome has been shown to overestimate SCD.[942] Considering that, in most centres, a high ratio of ARVC patients will be implanted with an ICD, it is conceivable why this may hamper risk stratification for SCD in patients with ARVC. Efforts to address this have been made within several studies,[522,523,943–947] where

Recommendation Table 29 — Recommendations for sudden cardiac death prevention in patients with arrhythmogenic right ventricular cardiomyopathy

Recommendations	Class[a]	Level[b]
Secondary prevention		
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with ARVC who have survived a cardiac arrest or have recovered from a ventricular arrhythmia causing haemodynamic instability.[939,943,944,948,949]	I	A
An ICD should be considered in ARVC patients who have suffered a haemodynamically tolerated VT.[522,939,943–945,948–950]	IIa	B
Primary prevention		
High-risk features[c] should be considered to aid individualized decision-making for ICD implantation in patients with ARVC.[538,939]	IIa	B
The updated 2019 ARVC risk calculator should be considered to aid individualized decision-making for ICD implantation in patients with ARVC.[d,524,526,536–539]	IIa	B

ARVC, arrhythmogenic right ventricular cardiomyopathy; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; PES, programmed electrical stimulation; RVEF, right ventricular ejection fraction; SMVT, sustained monomorphic ventricular tachycardia; VT, ventricular tachycardia.

[a]Class of recommendation.

[b]Level of evidence.

[c]High-risk features: arrhythmic syncope, NSVT, RVEF <40%, LVEF <45%, SMVT at PES.

[d]See text for discussion of gene-specific differences in the performance of the updated 2019 ARVC risk calculator.

the outcome of interest is fast VT (>250 b.p.m.) rather than any sustained VT. The largest of these studies (*n* = 864) has led to the development of a separate score for the prediction of unstable VT/VF.[945] Due to the lack of any external validation studies, there is insufficient information to support the applicability of this risk score outside of its development cohorts. Furthermore, a specific rate cut-off is also not well evidence-based and its performance to predict SCD remains unclear. Although it is likely that slower sustained VTs per se are not life-threatening, it remains unknown how frequently they would degenerate to faster VTs or VF. It is therefore reasonable to suggest that all patients at risk of any sustained ventricular arrhythmia should be offered primary prevention ICDs.

The role of PES in risk stratification of ARVC patients is not well defined, particularly in those who are asymptomatic.[523,939] However, current practice suggests that inducibility of SMVT at PES might add value in patients with symptoms consistent with sustained ventricular arrhythmia and this is further supported in this guideline[3]

7.5. Restrictive cardiomyopathy

7.5.1. Diagnosis

Patients with overt RCM manifest signs and symptoms typical of HFpEF.[306] The systematic approach to diagnosis should include clinical examination, ECG, echocardiography, and CMR.[951] Physical examination may show a prominent jugular venous pulse. In the advanced phases, the pulse volume is low, the stroke volume declines, and the heart rate may increase. Hepatomegaly, ascites, and peripheral oedema are common in decompensated patients. Echocardiography is the gold standard diagnostic tool; criteria for diagnosing and grading diastolic dysfunction have been previously described.[951,952] Importantly, the degree of diastolic dysfunction in patients with RCM is often only truly restrictive in advanced stages and most patients show milder grades of diastolic impairment at diagnosis.[951] Cardiac catheterization should be performed in cases where the diagnosis is in doubt and to aid in the assessment for and timing of cardiac transplantation.[953] Cardiac MRI distinguishes RCM from constrictive pericarditis, provides information on the presence and extent of myocardial fibrosis, and contributes to distinguishing metabolic from inflammatory diseases.[951,954] Endomyocardial biopsy is a precision diagnostic tool in restrictive cardio-desminopathies;[955] iron myocardial overload, both intramyocyte in haemochromatosis[956] and mitochondrial in Friedreich ataxia cardiomyopathy;[957] cystinosis;[958] generalized arterial calcification of infancy;[955,959] and lysosomal storage diseases (LSDs).[960,961] Deep phenotyping in probands should go beyond cardiac traits and explore extracardiac manifestations in syndromic diseases and in RCM associated with neuromuscular disorders (see *Section 6*).[962]

7.5.2. Genetic testing

When inherited, RCM most commonly presents as an autosomal dominant disorder and, less commonly, autosomal recessive or sporadic. Genes associated with RCM encode sarcomeric structural and regulatory proteins and cytoskeletal intermediate filaments (*Table 10*). Although all major sarcomeric genes may cause RCM,[963] the most common disease gene is *TNNI3*, which encodes the thin filament troponin I.[964] Other less commonly involved genes include *TNNT2*, *ACTC1*, *MYH7*, *MYBPC3*, *TTN*, *TPM1*, *MYPN*, *MYL3*, and *MYL2*. Restrictive cardiomyopathy can be associated with intramyocyte accumulation of unfolded defective proteins, a feature that is increasingly demonstrated in carriers of defects in *DES*, *FLNC*, and *BAG3*. These diseases have significant implications for prognosis and timely decision-making, both in children and adults. Restrictive cardiomyopathy may also occur in individuals with a family history of HCM[289] or DCM.[965] The observation of different cardiomyopathy phenotypes within families suggests a variable response to the variant, and

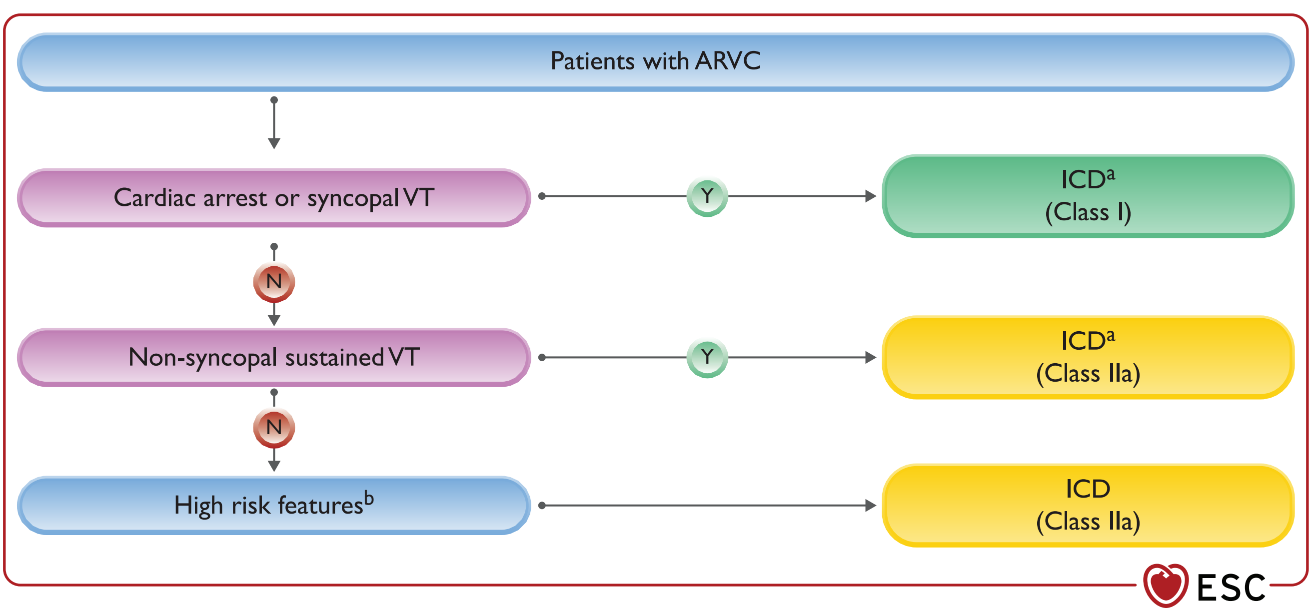

Figure 18 Algorithm to approach implantable cardioverter defibrillator decision-making in patients with arrhythmogenic right ventricular cardiomyopathy. ARVC, arrhythmogenic right ventricular cardiomyopathy; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; PES, programmed electrical stimulation; RVEF, right ventricular ejection fraction; SMVT, sustained monomorphic ventricular tachycardia; VT, ventricular tachycardia. [a]Clinicians should aim to control ventricular arrhythmia with pharmacological or invasive antiarrhythmic therapies in addition to offering an ICD. [b]High-risk features are defined as either cardiac syncope, NSVT, RVEF <40%, LVEF <45%, SMVT at PES or as per the updated 2019 ARVC risk calculator.[539]

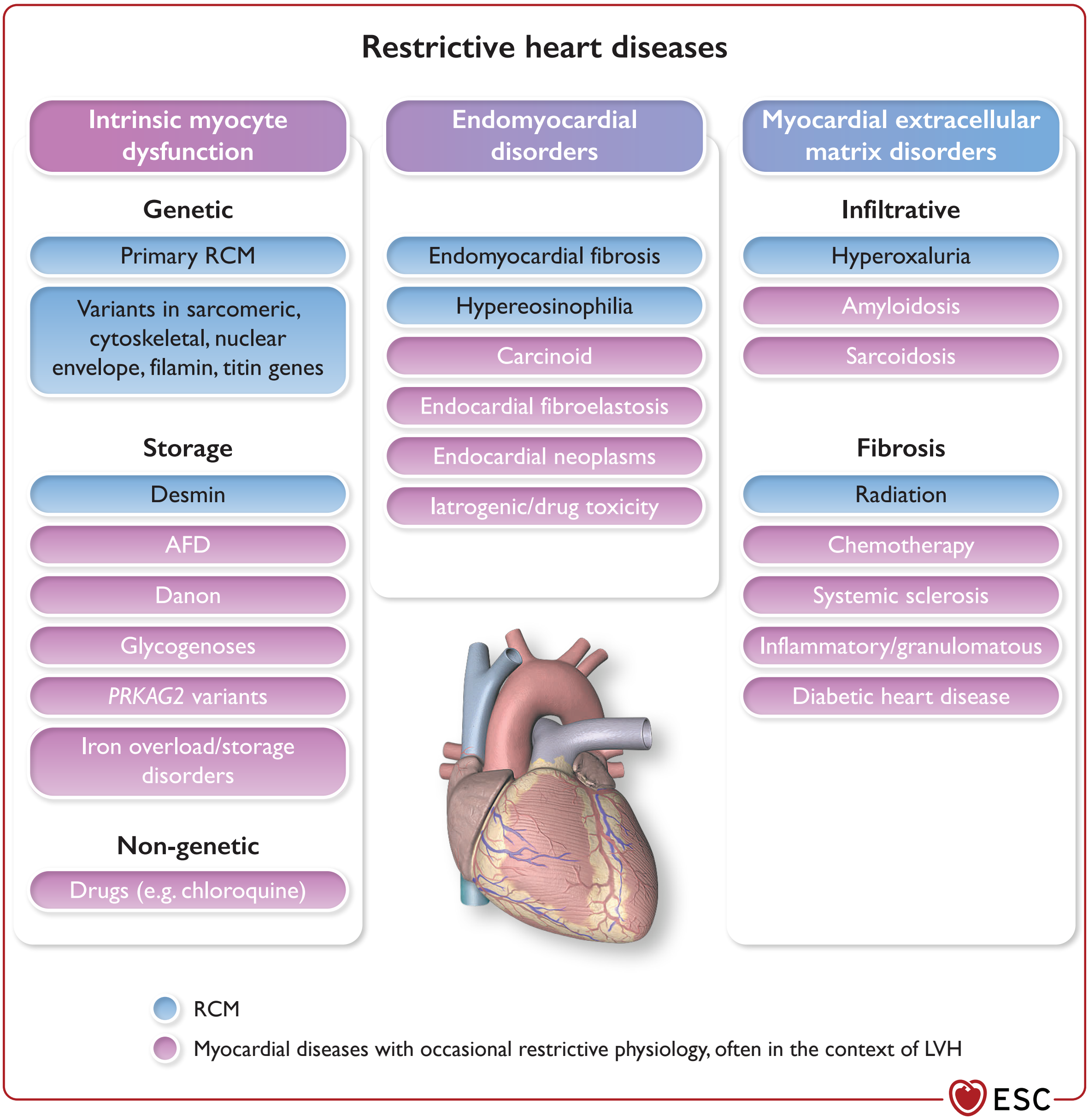

Figure 19 Spectrum of restrictive heart diseases. AFD, Anderson–Fabry disease; LVH, left ventricular hypertrophy; PRKAG2, Protein kinase AMP-activated non-catalytic subunit gamma 2; RCM, restrictive cardiomyopathy. For a more detailed spectrum of restrictive heart disease, please refer to Supplementary data online, *Table S4*.

implicates factors beyond the specific variant in the determination of ultimate clinical manifestation of disease.[966] Hereditary infiltrative diseases can also cause RCM, the most common of which is amyloidosis caused by pathogenic variants in the *TTR* gene, although this is usually in the presence of LVH (see *Section 7.7*).

7.5.3. Assessment of symptoms

Patients with RCM often develop symptoms of heart failure, although this can occur some years after the appearance of the initial abnormalities. Assessment of symptoms in patients with cardiomyopathies is described in *Section 6.10.1*.

7.5.4. Management

The administration of heart failure medications and device implantation, including ventricular assist device as a bridge-to-candidacy is guided by symptoms and heart failure phenotype and severity,[967] and is described in *Section 6.10.2*. Precision diagnosis (phenotype and cause) is key to timely planning of heart transplantation as it guarantees the exclusion of all genetic and acquired phenocopies that may be amenable to alternative treatment. Prevention of heart transplantation in all RCM patients with alternative treatments is a major goal for all adult and paediatric RCM.

Precise diagnosis is also essential for genetic phenocopies with available target treatments: ERT for Anderson–Fabry disease or glycogenosis such as Pompe disease; therapeutic phlebotomy for haemochromatosis; immunosuppressive therapeutics for sarcoidosis; new biological drugs for systemic diseases (e.g. autoimmune diseases with cardiac involvement that can reverse or stabilize by treating the disease itself); and removal of the toxic causes (see *Figure 19* and Supplementary data online, *Table S4*). Precision diagnosis today is essential due to the increasing availability of disease-specific treatments and diagnostic tools to exclude geno/phenocopies.

Restrictive cardiomyopathy is associated with the worst prognosis of all the cardiomyopathy phenotypes. Survival data are limited to small windows of observation. The prognosis of RCM largely depends on the restrictive physiology, regardless of the underlying cause.[968–971] More than 50% of children with RCM are at risk of death (including SCD) or transplantation shortly after diagnosis; clinical features putatively associated with increased risk of death or transplantation include: heart failure symptoms; reduced LV systolic function; increased left atrial size; syncope; ischaemia; and impaired LV diastolic function on echocardiography.[286,969,972,973] Up to 75% of surviving patients demonstrate heart failure, and the outcome is either death or heart transplantation within a few years of diagnosis.[968,969] Elevated pulmonary vascular resistance (PVR) is present in up to 40% of children with RCM, and can rise quickly even in the absence of other clinical changes, which has an impact on suitability for and timing of cardiac transplantation.[953] Cardiac catheterization with an assessment of PVR is therefore recommended in all children at diagnosis and every 6 to 12 months.[953] In adult patients with genetic RCM, the main cause of death is heart failure (more than 40%), with a 5-year survival rate of ∼50% in cohorts that include patients with HCM and restrictive physiology.[616]

Recommendation Table 30 — Recommendations for the management of patients with restrictive cardiomyopathy

Recommendations	Class[a]	Level[b]
It is recommended that multimodality imaging be used to differentiate RCM from HCM or DCM with restrictive physiology.	I	C
It is recommended that baseline cardiac and non-cardiac investigations are performed to assess involvement of the neuromuscular system or other syndromic disorders.	I	C
Cardiac catheterization is recommended in all children with RCM to measure pulmonary artery pressures and PVR at diagnosis and at 6–12 monthly intervals to assess change in PVR.[953]	I	B
ICD implantation is recommended to reduce the risk of sudden death and all-cause mortality in patients with RCM who have survived a cardiac arrest or have recovered from a ventricular arrhythmia causing haemodynamic instability.	I	C
Endomyocardial biopsy should be considered in patients with RCM to exclude specific diagnoses (including iron overload, storage disorders, mitochondrial cytopathies, amyloidosis, and granulomatous myocardial diseases) and to diagnose restrictive myofibrillar disease caused by desmin variants.	IIa	C
ICD implantation may be considered in *children* with RCM who have evidence of myocardial ischaemia and syncope.[969]	IIb	C

DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; PVR, pulmonary vascular resistance; RCM, restrictive cardiomyopathy.
[a]Class of recommendation.
[b]Level of evidence.

7.6. Syndromic and metabolic cardiomyopathies

It is beyond the scope of these guidelines to provide a detailed review and recommendations on specific cardiomyopathy genocopies and phenocopies. Instead, the Task Force refers the reader to detailed position statements and consensus documents published on behalf of the ESC Working Group on Myocardial and Pericardial Diseases (e.g. on Anderson–Fabry Disease and amyloidosis).[370,375,974] This section highlights only the key diagnostic and management issues. *Table 22* summarizes the clinical features and management of syndromic and metabolic cardiomyopathies.

7.6.1. Anderson–Fabry disease

7.6.1.1. Definition

Anderson–Fabry disease is an inborn error of metabolism where a deficient or absent enzyme, alpha-galactosidase A (α-Gal A), due to a pathogenic genetic variant in the *GLA* gene, causes the storage of some degradation cell products, mainly globotriaosylceramide (Gb3) in a patient's lysosomes.[975] This storage causes cell dysfunction in its own right and activates cellular hypertrophy pathways, common to other causes of HCM, as well as inflammation and immune activation.[976] It is a multisystem disorder affecting particularly the heart, kidney, and brain. [975] It is inherited in an X-linked manner; males are therefore always affected, while females' organ involvement usually develops later in life but can become similar to males due to the lyonization phenomena.[977,978]

Two Anderson–Fabry phenotypes can be distinguished, depending on the gender, lyonization phenomena, and pathogenic genetic variant:[976,979]

- A severe clinical phenotype, known as 'classic' Anderson–Fabry characterized by absent or severely reduced (<1% of mean normal) α-Gal A activity, marked Gb3 accumulation, and childhood or adolescent onset of symptoms followed by progressive multiorgan failure, is most often seen in males (but not exclusively) without residual enzyme activity.
- A 'non-classical' Anderson–Fabry phenotype or later-onset phenotype with incomplete systemic involvement, which is seen in both males and females, with some level of residual enzyme activity, and in most cases manifesting as isolated cardiac involvement.

7.6.1.2. Diagnosis, clinical work-up, and differential diagnosis

Anderson–Fabry disease should be suspected in patients with LVH and additional cardiac and extracardiac red flags (see *Table 23*) sought (*Figure 20*). The diagnosis is established by assessment of α-GalA activity and lyso-Gb3 measurement in male patients; in females, genetic testing is usually required to confirm the diagnosis. Severe LVH (>15 mm) is unlikely to be seen in patients <20 years of age.[980] In children and adolescents, diagnosis is made by family history or based on other extracardiac symptoms, but overt LVH is usually not present.[981]

7.6.1.3. Clinical course, outcome, and risk stratification

Cardiovascular involvement usually manifests as LVH, myocardial fibrosis, inflammation, heart failure, and arrhythmias, which limit QoL and are the most common cause of death. Clinical monitoring is essential to assess disease progression and requires a multidisciplinary approach.[980]

Table 22 Clinical features and management of syndromic and metabolic cardiomyopathies

Clinical red flags	Diagnosis	Specific cause	Multidisciplinary team	Management
Abnormal facial features Cryptorchidism Pulmonary valve stenosis Congenital heart disease Extreme right-axis deviation at ECG Lymphangectasis Bleeding diathesis Café au lait spots Lentigines Growth retardation Sensorineural deafness	NGS panel testing for RASopathy	Noonan syndrome Costello syndrome Cardiofaciocutaneous syndrome Noonan syndrome with multiple lentigines	Cardiologist Geneticist Endocrinologist Paediatrician Dermatologist Radiologist	Beta-blockers/CCBs Selective management of RVOTO/ pulmonary valvuloplasty SCD risk stratification
Short PR interval End-stage, hypokynetic HCM AV block (Kearns–Sayre syndrome) Lactic acidosis Sensorineural deafness Neutropenia (Barth syndrome) Diabetes Stroke-like lesions at brain MRI	NGS panel for mtDNA and nuclear DNA Skeletal muscle biopsy/ endomyocardial biopsy	MELAS syndrome MERRF syndrome Leigh syndrome Other mitochondrial disease Beta-oxidation disorders	Cardiologist Neurologist Endocrinologist Paediatrician Metabolism expert Radiologist	Avoiding drugs or situational stressors Beta-oxidation disorders: nutritional management, avoidance of fasting, aggressive treatment during increased metabolic stress Carnitine supplementation (selected cases)
Hepatomegaly Increased aminotransferase enzymes Delayed motor milestones Hypotonia Short PR interval ECG criteria for extreme LVH	Screening: GAA activity in DBS or leucocytes/Glc_4 dosing Diagnostic confirmation: acid alpha-glucosidase assay performed on skin fibroblasts (preferred method) or muscle biopsy	Type II glycogen storage disease (Pompe disease)	Cardiologist General Paediatrician/ neonatologist Gastroenterologist Neuromuscular disease specialist	Enzyme replacement therapy
Short PR interval Massive LVH Skeletal myopathy Increased serum CK enzyme Intellectual disability X-linked inheritance	NGS or target testing for *LAMP-2* variants	Danon disease	Cardiologist Neuromuscular disease specialist Pneumologist Advanced heart failure specialist	No treatment
Short PR interval Early-onset atrial fibrillation AV block Increased serum CK enzyme Autosomal dominant inheritance pattern	NGS or target testing for *PRKAG2*	PRKAG2 syndrome	Cardiologist Neuromuscular disease expert	No treatment

Continued

Progressive limb ataxia Diabetes mellitus Pes cavus Reduced native T1 at CMR imaging	NGS testing for bi-allelic expansion of GAA repeats in the *FXN* gene	Friedreich ataxia	Cardiologist Neurologist Endocrinologist Orthopaedic surgeon Neuromuscular disease expert	No specific treatment
Bilateral carpal tunnel syndrome Lumbar spinal stenosis Autonomic dysfunction Peripheral neuropathy Relative apical sparing pattern Ejection fraction/strain ratio >5 Pseudonecrosis Q waves Low ECG voltages OR Positive serum or urine monoclonal chain at immunofixation	DPD/HMDP Tc^{99} scintigraphy Free light chain/serum and urine immunofixation Endomyocardial biopsy	Cardiac amyloidosis (AL or ATTR) (see *Section 7.7*)	Cardiologist Neurologist Nephrologist Haematologist (AL amyloidosis) Ophthalmologist	Tafamidis Patisiran[a] Inotersen[a] (ATTR-CA) OR Specific chemotherapy (AL amyloidosis)
Gastrointestinal symptoms Angiokeratoma Cornea verticillata Chronic kidney disease Proteinuria Sensorineural hypoacusia Stroke/TIA Neuropathic pain X-linked inheritance pattern Short PR interval Low native T1 at cardiac CMR	Screening in males: lyso-Gb3 dosing Screening in females/diagnostic confirmation: genetic testing for *GLA* variants	Anderson–Fabry disease	Cardiologist Nephrologist Neurologist Ophthalmologist Audiologist Gastroenterologist Dermatologist	Enzyme replacement therapy (agalsidase alfa/beta) Migalastat
Skeletal myopathy Posterolateral pseudonecrosis pattern Posterolateral or inferolateral akinesia	Genetic testing for dystrophinopathies	*DMD*	Neurologist Cardiologist Pneumologist Neuromuscular disease expert	Steroids (prednisone or deflazacort)
Skeletal myopathy AV block Premature atrial fibrillation Malignant ventricular arrhythmias	NGS testing	*LMNA* cardiomyopathy Emery–Dreifuss muscular dystrophy	Cardiologist Neurologist	SCD risk prevention Pacing if indicated
Bilateral hilar lymphadenopathy Pulmonary infiltrates Uveitis Gastrointestinal involvement High-degree AV block Frequent VEs Thinned basal interventricular septum Extended LGE at CMR imaging	18F-FDG-PET Endomyocardial biopsy Lung biopsy	Sarcoidosis	Cardiologist Pneumologist Neurologist Gastroenterologist	Steroids Steroid-sparing immunosuppressant drugs

Continued

Previous transfusions Chronic liver disease Skin pigmentation Diabetes Hypogonadotropic hypogonadism Elevated ferritin AV block	Iron status Complete blood count Increased T2* values at CMR imaging Genetic test for *HFE*, *HJV*, hepcidin receptor, ferroportin, *HAMP* gene Peripheral blood smear Haemoglobin electrophoresis Genetic testing for hereditary haemoglobinopathies	Iron overload cardiomyopathy	Cardiologist Haematologist Endocrinologist Paediatrician Gastroenterologist	Iron-chelating drugs Phlebotomy

18F-FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; AL, amyloid light chain; ATTR, transthyretin amyloidosis; ATTR-CA: transthyretin cardiac amyloidosis; AV, atrioventricular; CCB, calcium channel blocker; CK, creatinine kinase; CMR, cardiac magnetic resonance; DBS, deep brain stimulation; DMD, Duchenne muscular dystrophy; DPD, 3,3-diphosphono-1,2-propanodicarboxylic acid; ECG, electrocardiogram; Gb3, globotriaosylceramide; HCM, hypertrophic cardiomyopathy; HMDP, hydroxymethylene diphosphonate; LGE, late gadolinium enhancement; LMNA, lamin A/C; LVH, left ventricular hypertrophy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (syndrome); MERRF, mitochondrial epilepsy with ragged-red fibres; MRI, magnetic resonance; mtDNA, mitochondrial DNA; NGS, next-generation sequencing; PRKAG2, protein kinase AMP-activated non-catalytic subunit gamma 2; RVOTO, right ventricular outflow tract obstruction; SCD, sudden cardiac death; TIA, transient ischaemic attack; VE, ventricular ectopic beats.
[a]Patisiran and inotersen approved for treatment of familial polyneuropathy with/without cardiomyopathy.

Table 23 Anderson–Fabry disease red flags

Extracardiac red flags	
No male-to-male transmission in pedigree	
Renal involvement (dialysis, renal transplantation) or LVH in relatives	
Neuropathic pain	
Angiokeratomas	
Albuminuria	
Cornea verticillata	
Hypohidrosis, heat/cold and exercise intolerance	
Gastrointestinal symptoms (nausea, vomiting, non-specific abdominal pain, constipation, diarrhoea)	
Hearing loss (either progressive or sudden), tinnitus, vertigo	
Cardiac red flags	
ECG	Short PQ interval in young patients
	Atrioventricular blocks in adult patients
	Bradycardia
	Chronotropic incompetence
	LVH
Echocardiogram	LVH with normal systolic function
	Hypertrophy of papillary muscles
	Mitral and aortic valve thickening with mild-to-moderate regurgitation
	Reduced global longitudinal strain
CMR	Basal-inferolateral late gadolinium enhancement
	Low native T1 (caution with 'pseudonormalization' in areas affected by fibrosis)
	High focal/global T2
Laboratory	Elevated high-sensitivity troponin Elevated NT-proBNP

CMR, cardiac magnetic resonance; ECG, electrocardiogram; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal pro-brain natriuretic peptide.

7.6.1.4. Management

Specific treatment strategies, including enzyme replacement or pharmacological chaperone, have limited efficacy in advanced cases with irreversible organ damage, so early initiation appears to be important. Enzyme replacement therapy is indicated in all symptomatic patients with classical disease, including children, at the earliest signs of organ involvement.[974] Therapeutic strategies currently in development include second-generation ERTs, substrate-reduction therapies, and gene and mRNA therapies.[980]

7.6.2. RASopathies

7.6.2.1. Definition

The RASopathies constitute a group of multisystemic syndromes caused by variants in the RAS-mitogen-activated kinase (RAS-MAPK) cascade,[984–986] including Noonan syndrome,[987–989] Noonan syndrome with multiple lentigines;[990,991] Costello syndrome,[992,993] and cardiofaciocutaneous syndrome.[994–996]

7.6.2.2. Diagnosis, clinical work-up, and differential diagnosis

The suspicion of an underlying RASopathy should be raised in infant- and childhood-onset HCM with coexisting CHD[262,263,991,997–1000] or extracardiac abnormalities (see *Table 22*). Gene testing is recommended for diagnosis when phenotypic features are present. Compared with sarcomeric HCM, RASopathy-associated HCM (RAS-HCM) shows earlier age at diagnosis,[261,999] increased prevalence and severity of left or biventricular obstruction,[258,262,1001] and higher rates of early hospitalizations for heart failure or need for interventional procedures or surgery.[258] Pulmonary stenosis is the most commonly associated CHD, with a prevalence ranging between 25% and 70%, and unfavourable outcomes for pulmonary valvuloplasty.[256,1002–1004]

7.6.2.3. Clinical course, management, and sudden death risk stratification

Data from the North American Pediatric Cardiomyopathy Registry[1005] cohort show poorer survival rates among patients with RAS-HCM compared with non-syndromic HCM, particularly in patients who have been diagnosed before 1 year of age. Disease-specific risk factors for SCD are currently an area of debate, and may include the degree of LV hypertrophy, prolonged QTc interval, ECG risk score for HCM,[771] and the HCM Risk-Kids score >6%.[81,826]

7.6.2.4. Management

Non-vasodilating beta-blockers should be titrated to maximum tolerated dose in patients with RAS-HCM, particularly in cases of severe

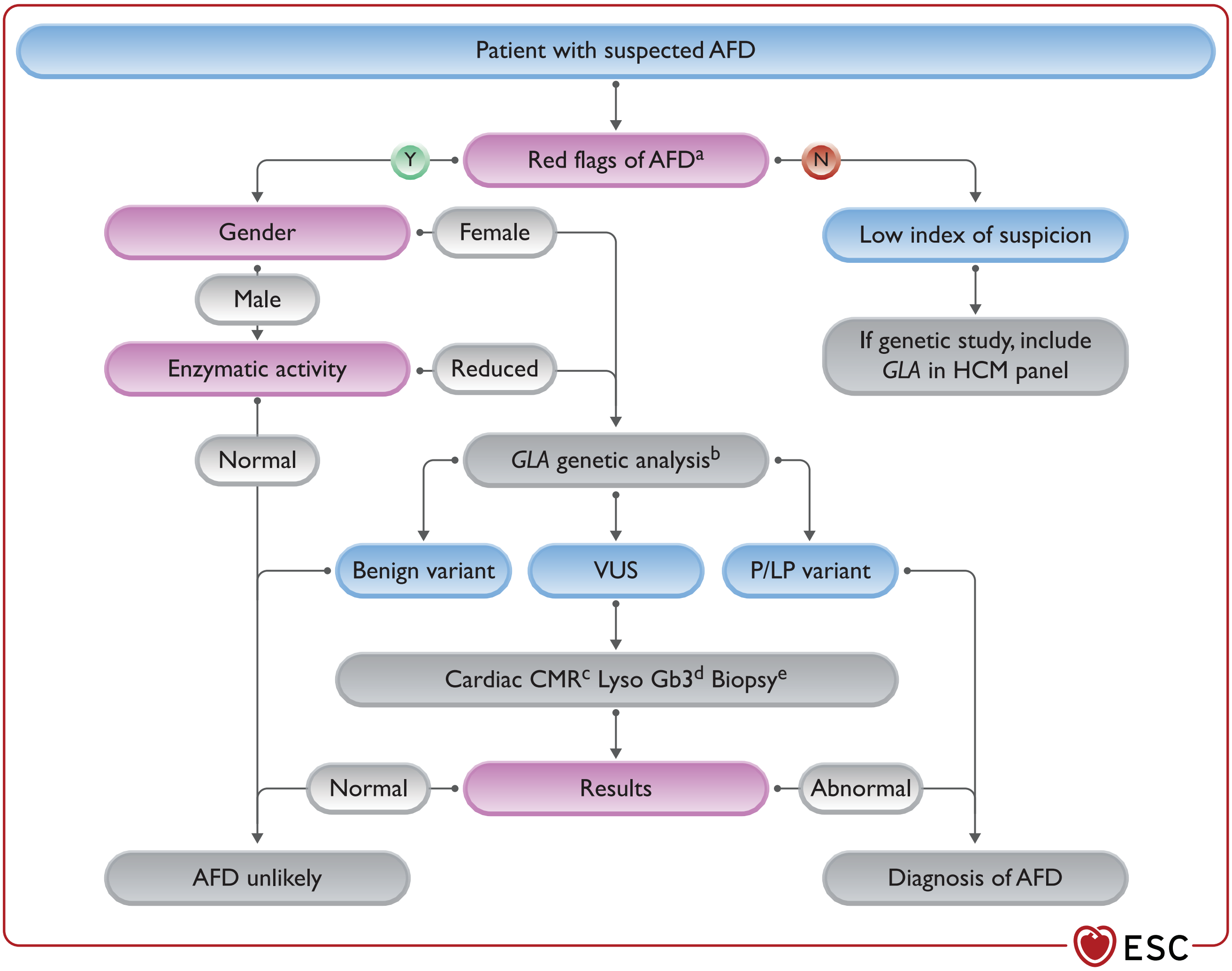

Figure 20 Anderson–Fabry disease diagnostic algorithm. α-Gal A, alpha-galactosidase A; AFD, Anderson–Fabry disease; CMR, cardiac magnetic resonance; Gb3, globotriaosylceramide; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; lyso Gb3, globotriaosylsphingosine; P/LP, pathogenic/likely pathogenic; VUS, variant of unknown significance. [a]See *Table 23*. [b]Genetic analysis must include the study of possible large deletions or a copy number variation not detected by the Sanger method. [c]The finding of increased plasma and/or urinary Gb3, or plasma lyso Gb3 and its analogues in the evaluation of male or female patients with a VUS and normal (in female patients) or lowered α-Gal A activity provides additional diagnostic information, but the role of biomarkers in such patients still requires validation. [d]Low native T1 values reinforce or generate suspicion of Fabry disease. Normal native T1 values do not exclude Fabry disease, as they are rarely observed in untreated patients with mild LVH (mostly females), or in advanced disease due to pseudonormalization. [e]An endomyocardial biopsy is recommended, but could be done in other affected organs such as the kidneys and skin. It should be evaluated by expert pathologists and always include electron microscopy studies to detect lamellar bodies and intracellular inclusions. Of note, some drugs may produce drug-induced phospholipidosis with an intracellular accumulation of phospholipids in different organs that can mimic zebra bodies on electron microscopy.[982,983]

biventricular obstruction.[248,1002,1006–1008] Calcium channel blockers may be considered as a second-line option in patients >6 months of age when beta-blocker therapy is ineffective or not tolerated.[267,639] Surgical myectomy and orthotopic heart transplantation may be considered in high-volume centres after multidisciplinary assessment by the heart team.[265,266,1009–1011] Pulmonary valvuloplasty may be considered in children and infants with severe RV outflow tract obstruction (RVOTO).[1012–1015]

7.6.3. Friedreich ataxia

7.6.3.1. Definition

Friedreich ataxia is an autosomal recessive disorder caused by a homozygous GAA triplet repeat expansion in the frataxin (*FTX*) gene,[1016–1019] leading to HCM, progressive neuromuscular symptoms, and extracardiac manifestations, including diabetes mellitus.[1016,1020,1021]

7.6.3.2. Diagnosis, clinical work-up, and differential diagnosis

Although several diagnostic criteria have been proposed to suspect Friedreich ataxia,[1022,1023] genetic testing with identification of bi-co-allelic GAA expansion in the first intron of the *FTX* gene or compound heterozygosis is required for diagnosis.[1024,1025]

Cardiovascular involvement usually manifests as hypertrophic non-obstructive cardiomyopathy, with hypokinetic end-stage disease progression and impaired perfusion reserve,[1026] leading to advanced heart failure and death.[248,1005,1027–1029] There appears to be no specific relationship between the extent of neurological involvement and cardiac phenotype.[248,1005,1027–1029,1005,1027–1030,1030] Mitochondrial iron storage is the pathologic hallmark of the disease.[1031]

7.6.3.3. Clinical course, management, and risk stratification

Supraventricular arrhythmias, particularly AF, are commonly detected.[1027] Despite the lack of long-term follow-up longitudinal studies, the risk of ventricular arrhythmias and SCD seems low compared with sarcomeric HCM.[1027,1032,1033] The Mitochondrial Protection with Idebenone in Cardiac or Neurological Outcome (MICONOS) study group[1034] has proposed a staging of cardiac involvement based on LVEF and end-diastolic wall thickness. The extent of TWI at ECG, LVEF, LV end-diastolic posterior wall thickness, fibrosis on CMR, and hs-TnT have been proposed as negative prognostic factors.[1035]

7.6.3.4. Management

No specific treatment is currently available for Friedreich ataxia. Treatment with idebenone, a coenzyme Q_{10} analogue, showed the potential to improve LV mass and cardiac outcomes in open-label studies;[1036] nevertheless, four RCTs[1037–1040] showed no significant benefit on cardiac or neurologic outcomes.

7.6.4. Glycogen storage disorders

7.6.4.1. Definition

Glycogen storage disorders (GSDs) represent a heterogeneous group of metabolic diseases, including infantile-onset Pompe disease (GSD, type IIa), Danon disease (GSD, type IIb), and PRKAG2 disease.[272]

7.6.4.2. Diagnosis, clinical work-up, and differential diagnosis

Despite wide clinical heterogeneity, a presentation within the first few months of life, hypotonia, failure to thrive, generalized muscle weakness, and severe non-obstructive HCM with concentric pattern followed by hypokinetic end-stage cardiomyopathy, usually within the first year of life, are typical of GSD IIa.[259,268,1041,1042] Short PR interval and increased ECG voltages may represent useful diagnostic clues for GSDs.[1042,1043] PRKAG2 syndrome should be suspected in the setting of autosomal dominant transmission and association with conduction system disease including ventricular pre-excitation, sick sinus syndrome, AF, AV block, intraventricular conduction delays or sinoatrial blocks.[1043–1047] An X-linked pattern of inheritance is typical of Danon disease (GSD IIb). Skeletal myopathy, in association with learning disability, retinal involvement and ventricular pre-excitation, has been detected in males affected by Danon disease, while the cardiac phenotype can be isolated in affected females.[1048–1052]

7.6.4.3. Clinical course, management, and risk stratification

In the absence of therapeutic intervention, Pompe disease has a poor prognosis, mainly due to end-stage heart failure.[268,1041] Recently, data from a large multicentre European registry have shown that Danon disease runs a malignant phenotype, but there are insufficient data to identify candidate risk factors for sudden death.[1049] Sudden cardiac death occurs in almost 10% of patients with PRKAG2 syndrome, mainly as a consequence of advanced AV block, supraventricular tachycardia degenerated to VF, or massive hypertrophy.[1044,1053,1054]

7.6.4.4. Management

Enzyme replacement therapy is recommended in patients with GSD IIa.[269,274,275,1055,1056] To date, there are no approved aetiological therapies for PRKAG2 syndrome and Danon disease. Heart failure therapy, antiarrhythmic therapy, and indications for the implantation of devices are included in *Section 6.10*.

7.7. Amyloidosis

It is beyond the scope of this document to provide specific recommendations for the assessment and management of cardiac amyloidosis. Instead, the Task Force refers the reader to the 2021 position statement of the ESC Working Group on Myocardial and Pericardial Diseases on Diagnosis and Treatment of Cardiac Amyloidosis.[375] This section highlights only the key diagnostic and management issues.

7.7.1. Definition

Cardiac amyloidosis is characterized by the extracellular deposition of misfolded proteins in the ventricular myocardium with the pathognomonic histological property of green birefringence when viewed under cross-polarized light after staining with Congo Red.[375]

Although once considered a rare disease, data obtained in the last decade suggest that cardiac amyloidosis is underappreciated as a cause of common cardiac diseases or syndromes such as HFpEF, aortic stenosis, or unexplained LVH, particularly in the elderly.[1057–1059] Although nine different types of cardiac amyloidosis have been described, most cases correspond to monoclonal immunoglobulin light chain amyloidosis (AL) or transthyretin amyloidosis (ATTR), either in its hereditary (ATTRv) or acquired (ATTRwt) form.[375] The ATTRwt form, which is associated with ageing, is currently considered the most frequent form of cardiac amyloidosis worldwide.

7.7.2. Diagnosis, clinical work-up, and differential diagnosis

Cardiac amyloidosis should be suspected in patients with increased LV wall thickness in the presence of cardiac or extracardiac red flags and/or in specific clinical situations, as detailed in *Figure 21*, particularly in patients >65 years of age.[375]

Cardiac amyloidosis can be diagnosed using both invasive and non-invasive diagnostic criteria.[375] Invasive diagnostic criteria apply to all forms of cardiac amyloidosis, whereas non-invasive criteria are accepted only for ATTR. Invasive criteria include demonstration of amyloid fibrils within cardiac tissue or, alternatively, demonstration of amyloid deposits in an extracardiac biopsy accompanied either by characteristic features of cardiac amyloidosis on echocardiography or CMR.[375] Non-invasive criteria include typical echocardiographic/CMR findings combined with planar and single-photon emission computed tomography (SPECT) grade 2 or 3 myocardial radiotracer uptake in ^{99m}technetium-pyrophosphate (^{99m}Tc-PYP) or 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) or hydroxymethylene diphosphonate (HMDP) scintigraphy and exclusion of a clonal dyscrasia by all the following tests: serum free light chain assay, serum and urine protein electrophoresis with immunofixation.[168] Tomographic scintigraphy should be considered in order to reduce the number of misclassifications.[1060] False negative scans may rarely occur in certain ATTRv genotypes; false positives may be due to AL, recent myocardial infarction, or long-term chloroquine use.[370] Therefore, planar and SPECT scintigraphy coupled with assessment for monoclonal proteins followed by CMR and/or cardiac/extracardiac biopsy if necessary allows appropriate diagnosis in patients with suggestive signs/symptoms, as described in *Figure 22*.[375] However, the DPD/PYP/HMDP scan cannot distinguish between wild-type and mutated ATTR, and therefore TTR genetic testing is required. Of note, TTR genetic testing is recommended in all transthyretin amyloid cardiomyopathy (ATTR-CM) patients regardless of age, as 5% of

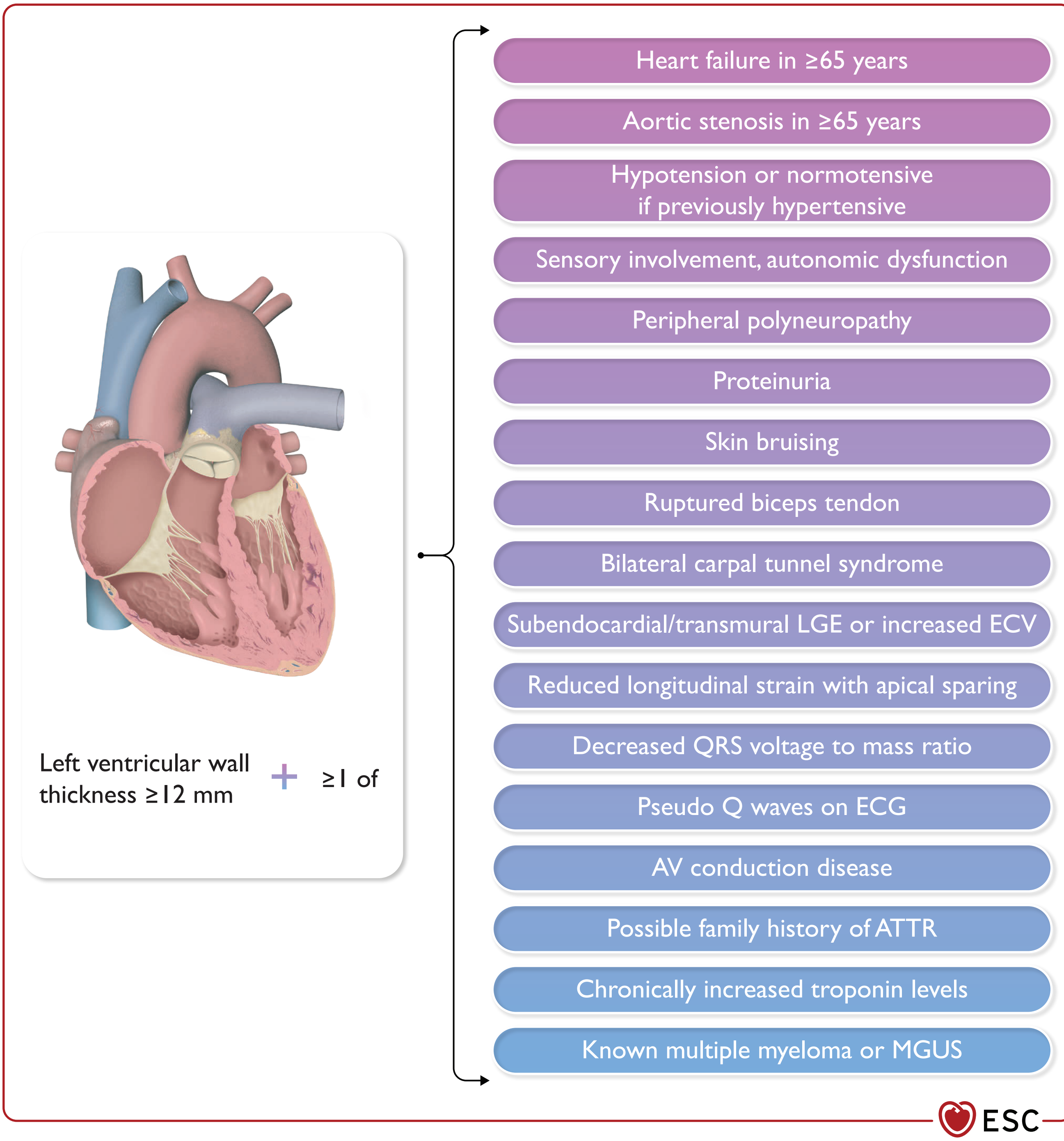

Figure 21 Screening for cardiac amyloidosis. ATTR, transthyretin amyloidosis; AV, atrioventricular; ECG, electrocardiogram; ECV, extracellular volume; LGE, late gadolinium enhancement; MGUS, monoclonal gammopathy of undetermined significance.

ATTR-CM patients ≥70 years (and 10% among females) have ATTRv.[375,1061]

7.7.3. Clinical course and risk stratification

Cardiac amyloidosis is a progressive disease with poor outcomes if left untreated. Amyloid light chain cardiac amyloidosis is associated with more rapid progression of heart failure and worse prognosis than ATTR.[1058,1062,1063] Fortunately, the prognosis of AL amyloidosis has significantly improved with the introduction of very effective therapies capable of dramatically reducing the production of the cardiotoxic light chains.[1064] Prognosis in ATTR depends on the variant, degree of cardiac involvement, and neurologic phenotype.[1065–1068] Several multiparametric biomarker-based staging systems have been developed for AL[1069,1070] and ATTR cardiac amyloidosis[1066–1068] (see Supplementary data online, *Table S5*).

7.7.4. Management

The treatment of cardiac amyloidosis includes treating and preventing complications and stopping or delaying amyloid deposition by specific treatment.[375,1071] There is no evidence to support the use of standard

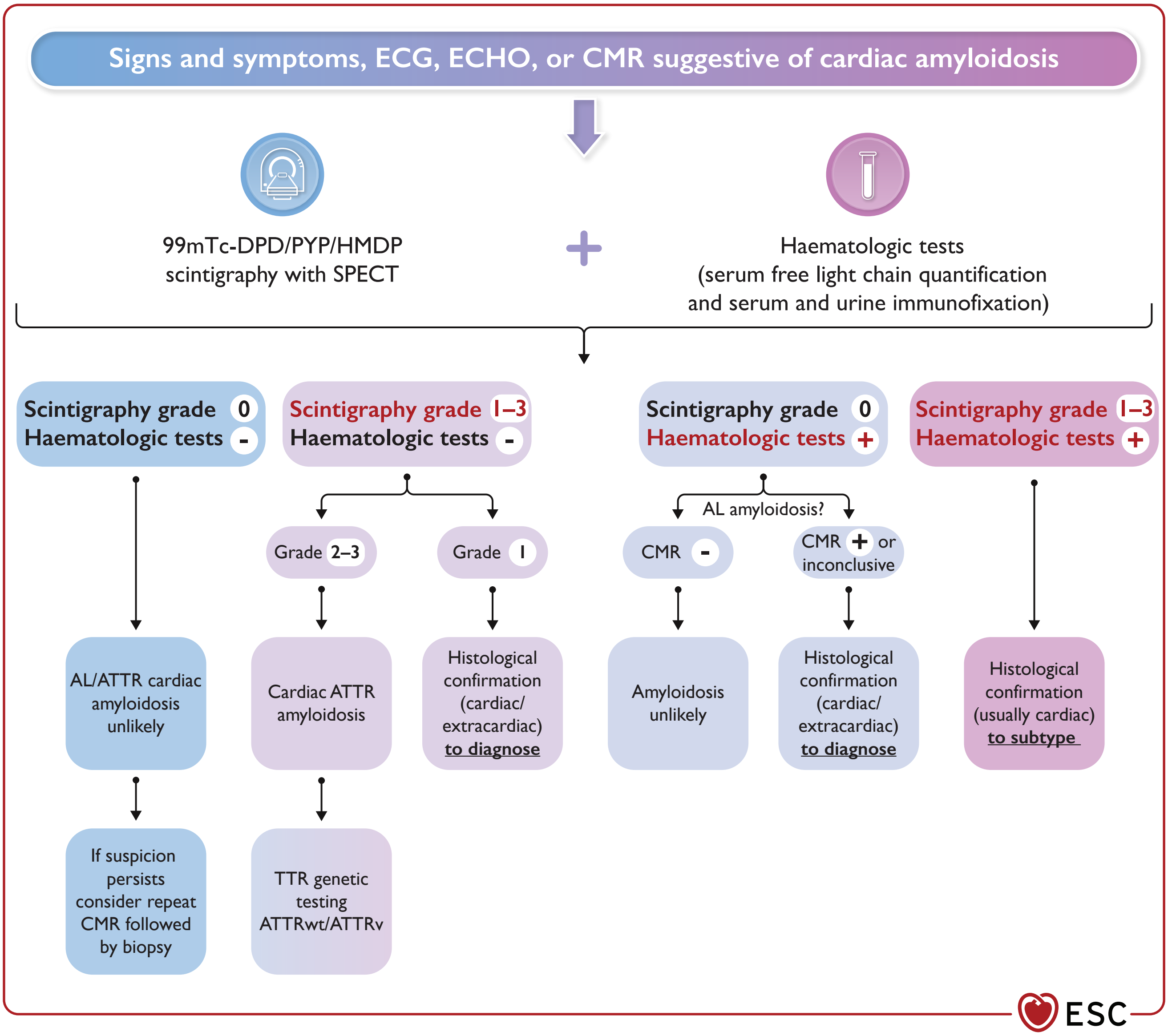

Figure 22 Diagnosis of cardiac amyloidosis. AL, amyloid light chain; ATTR, transthyretin amyloidosis; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CMR, cardiac magnetic resonance; DPD, 3,3-diphosphono-1,2-propanodicarboxylic acid; ECG, electrocardiogram; ECHO, echocardiogram; HMDP, hydroxymethylene diphosphonate; PYP, pyrophosphate; TTR, transthyretin.

heart failure therapy, which often is not well tolerated, apart from diuretics (see *Section 6.10.2*).[1072,1073]

The natural history of cardiac amyloidosis associates electrical conduction disease of the heart with symptomatic bradycardia and advanced AV block.[375,1074,1075] The clinical threshold for pacemaker indication should be low, as the disease progresses and implantation of the device allows rate response to exercise and medication adjustment.[375,1074] The role of ICD in cardiac amyloidosis for SCD prevention is not clearly known, but available data do not support their use in primary prevention.[1076,1077]

7.7.4.1. Specific therapies

Therapy for AL cardiac amyloidosis is based on treatment of the underlying haematological problem with chemotherapy or autologous stem-cell transplant.[1064]

Transthyretin stabilization and reduction of its production are the basis of TTR cardiac amyloidosis treatment. Tafamidis reduced all-cause mortality and cardiovascular hospitalizations in ATTR, with the largest effect achieved in patients at NYHA functional class I and II.[1078] Additional studies are being conducted with other stabilizing agents and other molecules that reduce TTR production.[1078a]

8. Other recommendations

8.1. Sports

8.1.1. Cardiovascular benefits of exercise

Regular physical activity and systematic exercise confer several cardiovascular, psychological, and QoL benefits. Through curbing risk factors for atherosclerosis, such as obesity and insulin resistance,[1079] hypertension,[1080] and hyperlipidaemia,[1081] regular physical activity is associated with an up to 50% risk reduction in an adverse event from CAD in middle-aged and older individuals.[1082,1083] Individuals who exercise regularly live 5–7 years longer than their sedentary counterparts,[1084] and have a lower risk of cerebrovascular accidents[1085] and certain malignancies.[1085–1087] These benefits that can be derived later in life also apply to individuals with established cardiovascular disease. For a definition of exercise intensity levels, please refer to Supplementary data online, *Table S6*.

8.1.2. Exercise-related sudden cardiac death and historical exercise recommendations for patients with cardiomyopathy

Rigorous exercise may trigger myocardial infarction and fatal arrhythmias among individuals with an underlying cardiovascular disease.[1088–1091] Superimposed on the pathological substrate of the disease entity itself, exercise may induce sudden cardiac arrest through mechanical shearing forces within the coronary arteries, effects of high concentrations of circulating catecholamines, increased cardiac loading conditions, raised core temperature, electrolyte shifts, and acid-base disturbance.

Cardiomyopathies are the leading cause of exercise-related SCD in young people in the Western world.[40,1092–1095] The established link between exercise and SCD from cardiomyopathy, and the finding that, in some cardiomyopathy phenotypes, exercise may accelerate progression of the underlying cardiomyopathic disease process, has historically resulted in restrictive exercise recommendations in all affected patients regardless of pathology, disease severity, symptomatic status, general risk profile, or prior therapeutic interventions, including an ICD.[1096–1098] As a result, individuals with cardiomyopathy often confine themselves to a relatively sedentary lifestyle through fear of potential SCD and accrue risk factors for atherosclerotic CAD, which confer a worse prognosis.[1099–1102,1096,1097]

8.1.3. Exercise recommendations in hypertrophic cardiomyopathy

Recent pre-clinical[1103] and clinical data suggest that moderate exercise may be beneficial and safe in patients with HCM.[1098–1102] Information on a safe dose of vigorous exercise is still limited, but the heterogeneous morphology and pathophysiology of HCM means that some individuals are capable of participating in vigorous exercise, including high-intensity competitive sports.[760] Most athletes capable of exercising intensively have mild LV hypertrophy, normal-sized or enlarged LV, normal diastolic function, and no evidence of LVOTO.[1104,1105] Currently available data indicate that participation in vigorous exercise and competitive sport may be considered in a select group of predominantly adult patients who have mild morphology and a low-risk profile.[1106–1108] However, studies examining the effect of vigorous exercise or moderate-to-high-intensity competitive sport on the natural history of HCM were not designed or powered adequately to address the question and there are potential issues of selection bias. Nevertheless, based on emerging evidence, the Task Force agreed to adopt a comparatively liberal approach, advocating that, after appropriate selection, some individuals with a low-risk profile may participate in high-intensity exercise and competitive sport after comprehensive expert evaluation and shared discussion, which highlights the unpredictable nature of exercise-related SCD in HCM. Sporting disciplines in which syncope may result in fatal accidental injury or danger to others are not recommended.

Genotype-positive/phenotype-negative patients may engage in all competitive sport; however, annual assessment is recommended to check for developing phenotypic features of disease.[1109]

8.1.4. Exercise recommendations in arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy is a recognized cause of exercise-related SCD in young asymptomatic individuals,[40,890] postulated to result from ventricular stretch leading to myocyte detachment with subsequent inflammation and fibro-fatty replacement of the ventricular myocardium. Fatal arrhythmias may occur during the inflammatory process or because of myocardial scar. In addition, there are data to suggest that high-intensity exercise is associated with acceleration of disease phenotype in individuals with ARVC, including those who are genotype positive/phenotype negative, and particularly those with *PKP2* variants.[181,1110–1114] Furthermore, exercise restriction has been shown to improve clinical outcomes in patients with ARVC.[40,1111,1115–1117] Based on these data, the Task Force recommends against intensive exercise or competitive sports in individuals with ARVC as part of a shared decision-making process. The evidence on the impact of exercise in genotype-positive/phenotype-negative individuals is more limited. In these cases, the Task Force recommends a cautious approach in the context of shared decision-making when discussing competitive sports participation. Mild-to-moderate physical activity for up to 150 min per week is considered safe and is recommended in able phenotype-negative individuals.[1118]

8.1.5. Exercise recommendations in dilated cardiomyopathy and non-dilated left ventricular cardiomyopathy

There is evidence that moderate exercise in optimally treated patients with DCM improves functional capacity, ventricular function, and QoL;[1119] however, intensive exercise and competitive sports may also trigger fatal arrhythmias in DCM and NDLVC.[1093,1120–1122]

In general, symptomatic individuals with DCM and NDLVC should abstain from most competitive and leisure sports, or recreational exercise associated with moderate or high exercise intensity. A select group of asymptomatic individuals with DCM and NDLVC who have mildly impaired LV function without exercise-induced arrhythmias or significant myocardial fibrosis may participate in most competitive sports.

Although the natural history of most pathogenic variants capable of causing DCM and NDLVC is unknown, it would be reasonable to permit intensive exercise and competitive sports in most individuals with pathogenic variants in the absence of overt features of DCM or NDLVC. Special consideration, however, should be given to individuals with pathogenic variants in genes that are associated with an increased risk of life-threatening arrhythmias, such as lamin A/C[181,1123] or *TMEM43* variants, for which there is emerging evidence that exercise may have an adverse effect on cardiac function and risk of potentially fatal arrhythmias. The impact of vigorous exercise in patients with pathogenic variants in other high-risk genes, such as filamin C variants[1112] exhibiting DCM or NDLVC phenotypes, is not fully understood; however, extrapolating our understanding of the effect of exercise on some ARVC and DCM phenotypes necessitates a cautious approach.

Recommendation Table 31 — Exercise recommendations for patients with cardiomyopathy

Recommendations	Class[a]	Level[b]
All cardiomyopathies		
Regular low- to moderate-intensity exercise is recommended in all able individuals with cardiomyopathy.	I	C

Continued

An individualized risk assessment for exercise prescription is recommended in all patients with cardiomyopathy.	I	C
HCM		
High-intensity exercise and competitive sport should be considered in genotype-positive/phenotype-negative individuals who seek to do so.[1124]	IIa	C
High-intensity exercise and competitive sport may be considered in asymptomatic low-risk[c] individuals with morphologically mild hypertrophic cardiomyopathy in the absence of resting or inducible left ventricular outflow obstruction and exercise-induced complex ventricular arrhythmias.[1107,1113,1125,1126]	IIb	B
High-intensity exercise, including competitive sport, is not recommended in high-risk individuals and in individuals with left ventricular outflow tract obstruction and exercise-induced complex ventricular arrhythmias.	III	C
ARVC		
Avoidance of high-intensity exercise, including competitive sport, may be considered in genotype-positive/phenotype-negative individuals in families with ARVC.[1111,1116,1117]	IIb	C
Moderate- and/or high-intensity exercise, including competitive sport, is not recommended in individuals with ARVC.[181,1111–1114]	III	B
DCM and NDLVC		
Moderate- and high-intensity exercise should be considered in individuals who are gene positive and phenotype negative (with the exception of pathogenic variants in *LMNA* and *TMEM43*) who seek to do so.[1123]	IIa	C
High-intensity exercise and competitive sport may be considered in a select group of asymptomatic and optimally treated individuals with a left ventricular ejection fraction ≥50% in the absence of exercise-induced complex arrhythmias.	IIb	C
Moderate-intensity exercise may be considered in asymptomatic and optimally treated individuals with a left ventricular ejection fraction of 40–49% in the absence of exercise-induced complex arrhythmias.	IIb	C
High-intensity exercise, including competitive sport, is not recommended in symptomatic individuals, those with a left ventricular ejection fraction ≤40%, exercise-induced arrhythmias or pathogenic variants in *LMNA* or *TMEM43*.	III	C

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LMNA, lamin A/C; NDLVC, non-dilated left ventricular cardiomyopathy; TMEM43, transmembrane protein 43.
[a]Class of recommendation.
[b]Level of evidence.
[c]See *Section 7.1.5* for risk assessment in HCM.

8.2. Reproductive issues

Pregnancy and the post-partum period constitute periods of increased risk of cardiovascular complications in women with cardiomyopathy.[1127–1130] Cardiomyopathy can also be first diagnosed in pregnancy or arise during pregnancy as PPCM.[1131]

The risk associated with pregnancy in a patient with a cardiomyopathy is estimated using the modified World Health Organization (mWHO) classification.[1130] Pregnancy is contraindicated in women with WHO class IV, including patients with EF <30% or NYHA class III–IV or previous PPCM with persisting impairment of the LV function.

8.2.1. Contraception, *in vitro* fertilization, and hormonal treatment

Counselling on safe and effective contraception is indicated in all women of fertile age. Ethinyloestradiol-containing contraceptives have the greatest risk of thrombosis[1132] and are not advised in women with a high risk of thrombo-embolic disease. Progestin-only contraceptives are an alternative, as they have little or no effect on coagulation factors, blood pressure, and lipid levels. Levonorgestrel-based long-acting reversible contraception implants or intrauterine devices are the safest and most effective contraceptives and have few side effects affecting cardiomyopathies.

Medically assisted procreation adds risks beyond those of pregnancy alone; superovulation is pro-thrombotic and can be complicated by ovarian hyperstimulation syndrome, with marked fluid shifts and an even greater risk of thrombosis. Hormonal stimulation should be carefully considered in women who have WHO class III disease (VT or HCM) or who are anticoagulated.

8.2.2. Pregnancy management

8.2.2.1. Pre-pregnancy

Patients with a known cardiomyopathy and at risk of developing cardiomyopathy should receive pre-pregnancy counselling by a multidisciplinary team: the pregnancy heart team. The individual risk of the woman by pregnancy should be discussed using the WHO classification, in addition to discussing the likelihood of transmission of the disease to the offspring and how to reduce the transgenerational risk of transmitting the disorder.

For individual risk estimation, at a minimum, an ECG, echocardiography, and exercise test should be performed. Several aspects must be discussed with the woman, including long-term prognosis, drug therapy, estimated maternal risk and outcome, and plans for pregnancy care and delivery.

8.2.2.2. Pregnancy

In women with mWHO class II–III, III, and IV (including women with HCM, VTs, and EF <35%), management during pregnancy and around delivery should be conducted in an expert centre by a multidisciplinary team: the pregnancy heart team, including cardiologists with expertise in cardiomyopathies and arrhythmias; obstetricians; and anaesthetists. Depending on the individual case, other specialists may be included (geneticist, cardio-thoracic surgeon, paediatric cardiologist, foetal medicine specialist, neonatologist, etc.). A delivery plan should be created that includes the details of induction; the management of labour and delivery; and post-partum surveillance.

8.2.2.3. Timing and mode of delivery

The timing and mode of delivery should be personalized according to the type of cardiomyopathy, ventricular function, NYHA class, arrhythmic risk, and thrombo-embolic risk. Vaginal delivery is associated with less blood loss and lower risk of infection, venous thrombosis, and embolism than caesarean section and should be advised for most women. Caesarean section should be considered for obstetric indications, patients with severe outflow tract obstruction, or in cases of severe acute/intractable heart failure, or in cases at high risk of threatening arrhythmia and for patients presenting in labour on oral anticoagulants.[1130] During delivery, patients with cardiomyopathy should be circulatory and heart rhythm monitored on an individualized basis.

8.2.2.4. Post-partum

The post-partum period is associated with significant haemodynamic changes and fluid shifts, particularly in the first 24–48 h after delivery, which may precipitate heart failure. Haemodynamic monitoring should therefore be continued for at least 24–48 h in patients at risk. Most drugs enter the milk and could thus contraindicate breastfeeding (see *Section 8.2.2.5*).

8.2.2.5. Pharmacological treatment: general aspects

Pharmacological treatment in pregnant women should be the same as in non-pregnant patients, with an avoidance of drugs contraindicated in pregnancy, such as ACE-Is, ARBs, and renin inhibitors.[1130] The first trimester is associated with the greatest teratogenic risk. Pharmacologic therapy is advised to begin as late as possible in pregnancy and at the lowest effective dose. Drug exposure later in pregnancy may confer adverse effects on foetal growth and development. It is recommended to check drug and safety data before initiation of a new drug in pregnancy; see Table 7 in the *2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy*.[1130] From this list, antiarrhythmics can be summarized as follows:

- Well tolerated: sotalol, oral verapamil.
- While the benefits and risks should be evaluated in each case, the following drugs can often be continued if there is a clear indication for use during pregnancy: bisoprolol, carvedilol, digoxin, diltiazem (possible teratogenic effects), disopyramide (uterine contractions), flecainide, lidocaine, metoprolol, nadolol, propranolol, verapamil, quinidine.
- Insufficient data: ivabradine, mexiletine, propafenone, vernakalant.
- Contraindicated: amiodarone, atenolol, dronedarone, ACE-Is, ARBs, renin inhibitors, and spironolactone.[1130]

Ongoing beta-blocker treatment in cardiomyopathies should be continued during pregnancy, with close monitoring of foetal growth. After delivery, it is advised to heart rhythm monitor the infant for 48 h. The use of beta-blockers and anticoagulation during pregnancy is described in the *2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy*.[1130]

Vitamin K antagonist use in the first trimester results in embryopathy (limb defects, nasal hypoplasia) in 0.6–10% of cases.[1133,1134] In contrast, unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) do not cross the placenta; therefore, substitution of VKA with UFH or LMWH in weeks 6–12 almost eliminates the risk of embryopathy. This risk is also dose dependent (0.45–0.9% with low-dose warfarin). Vaginal delivery while the mother is on VKAs is contraindicated because of the risk of foetal intracranial bleeding. Haemorrhagic complications in the mother occur with all regimens, but the incidence is lower with VKA than with LMWH/UFH throughout pregnancy.[1130]

VKA should be continued until pregnancy is achieved. Continuation of VKAs throughout pregnancy should be considered when the dose is low (see Table 7 in the *2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy*[1130]). The target international normalized ratio (INR) should be chosen according to current guidelines, with INR monitoring weekly or every 2 weeks. Self-monitoring of INR in suitable patients is recommended. Alternatively, depending on the indication, a switch to LMWH from weeks 6–12 under strict monitoring may be considered in patients with a low dose requirement. When a higher dose of VKAs is required, discontinuation of VKAs between weeks 6 and 12 and replacement with adjusted-dose i.v. UFH or LMWH twice daily with dose adjustment according to peak anti-Xa (for LMWH) levels should be considered.

In case of delivery in anticoagulated women (not including mechanical valves) with a planned caesarean section, therapeutic LMWH dosing can be simply omitted for 24 h prior to surgery. If delivery has to be performed earlier, anti-Xa activity can guide the timing of the procedure.

Antiarrhythmic therapy in pregnancy other than medication. Implantation of an ICD and catheter ablation should ideally be considered prior to pregnancy in patients with a high risk of ventricular arrhythmias to avoid implantations and interventions during pregnancy.[1135] If an ICD is indicated in pregnancy, ICD implantation should be performed beyond 8 weeks of gestation with radiation protection[1136] and the indication should be weighed against the limited experience available. In pregnant patients with existing ICD, routine ICD interrogation and advice are recommended prior to delivery.

8.2.2.6. Specific cardiomyopathies

Most women with HCM tolerate pregnancy well.[1137] Complications during pregnancy most often occur in women who have symptoms, arrhythmias, or impaired LV function before pregnancy. Left ventricular outflow tract gradients may increase slightly during pregnancy and high gradients before pregnancy are associated with more complications.[1137] Women should be assessed according to WHO risk class, indicating at trimester for low-risk patients (class II) and monthly or bi-monthly for higher-risk patients (class III). Therapeutic anticoagulation with LMWH or VKAs according to the stage of pregnancy is recommended for patients with AF. Cardioversion in pregnancy should be considered for poorly tolerated persistent AF. Hypovolaemia is poorly tolerated. Caesarean section should be considered in patients with severe LVOTO, pre-term labour while on oral anticoagulants, or severe heart failure.[1130] Epidural and spinal anaesthesia must be applied cautiously, especially with severe LVOTO, due to potential hypovolaemia, and single-shot spinal anaesthesia should be avoided.

Pregnancy in ARVC seems to be relatively tolerable, as shown in several studies, with no excess mortality and no clear negative long-term outcome.[1138–1141] Previous VTs represent a WHO risk class III, indicating bi-monthly or monthly follow-up at an expert centre.

Women with DCM are at risk of further deterioration of LV function in pregnancy. Data suggest that pregnancy might not be associated with long-term adverse disease progression or event-free survival in LMNA genotype-positive women.[1142] Predictors of maternal mortality are NYHA class III/IV and EF <40%. Highly adverse risk factors include

EF <20%, severe mitral regurgitation, RV failure, AF, and/or hypotension.[1143]

8.2.2.7. Peripartum cardiomyopathy

Genetic studies in patients with PPCM have revealed genetic similarity between PPCM and DCM. Specifically, an overrepresentation of truncating variants has been demonstrated in *TTN*, *FLNC*, *BAG3*, and *DSP*, with *TTN* truncating variants most commonly involved (found in ∼10% of patients).[44,45] It has been suggested that approaches to genetic testing in PPCM should mirror those taken in DCM.[45] Medications used to treat heart failure during pregnancy require special considerations as discussed above. In the presence of persistant cardiac dysfunction, medication should be continued. Use of bromocriptine as disease-specific therapy in patients with PPCM as an addition to standard heart failure therapy has shown promising results in two clinical trials.[1144,1145] In severe cases of PPCM, temporary MCS has been used successfully and should be considered in patients with haemodynamic instability despite inotropic support.[1146] In patients with PPCM, thresholds for early ICD implantations should be higher than in other conditions because of a high rate of spontaneous recovery after delivery.[1147]

Recommendation Table 32 — Recommendations for reproductive issues in patients with cardiomyopathy

Recommendations	Class[a]	Level[b]
Pre-pregnancy risk assessment and counselling are recommended in all women using the mWHO classification of maternal risk.	I	C
Counselling on safe and effective contraception is recommended in all women of fertile age and their partners.	I	C
Counselling on the risk of disease inheritance is recommended for all men and women before conception.	I	C
Vaginal delivery is recommended in most women with cardiomyopathies, unless there are obstetric indications for caesarean section, severe heart failure (EF <30% or NYHA class III–IV), or severe outflow tract obstructions, or in women presenting in labour on oral anticoagulants.	I	C
It is recommended that medication be carefully reviewed for safety in advance of pregnancy and adjusted according to tolerability in pregnancy.	I	C
Therapeutic anticoagulation with LMWH or VKAs according to the stage of pregnancy is recommended for patients with AF.	I	C
Continuation of beta-blockers should be considered during pregnancy in women with cardiomyopathies, with close follow-up of foetal growth and of the condition of the neonate, and if benefits outweigh risks.	IIa	C
Genetic counselling and testing should be considered in patients with peripartum cardiomyopathy.	IIa	C

AF, atrial fibrillation; EF, ejection fraction; LMWH, low-molecular-weight heparin; mWHO, modified World Health Organization; NYHA, New York Heart Association; VKA, vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.

8.3. Recommendations for non-cardiac surgery

Cardiomyopathies, in general, are associated with an increased incidence of peri-operative heart failure and arrhythmias, although the significant variability in the phenotypic expression of cardiomyopathies must be considered. Special attention should be given to the clinical status, LVEF, volume overload, and increased levels of natriuretic peptides. In the period after non-cardiac surgery (NCS), fluids given during the operation may be mobilized, causing hypervolaemia and pulmonary congestion. Careful attention to fluid balance is therefore essential.[1148,1149] Obstructive HCM deserves specific consideration due to its peculiar pathophysiology, with adequate intra-operative vigilance, avoiding factors and medication that may increase LVOTO and prompt pharmacological treatment and intravascular fluid therapy if needed (see Supplementary data online, *Table S7*).[1150,1151]

Natriuretic peptide concentrations are quantitative plasma biomarkers for the presence and severity of haemodynamic cardiac stress and heart failure, and elevated NT-proBNP concentrations may facilitate detection of heart failure, optimal intra-operative monitoring, and initiation or optimization of heart failure therapy after surgery.[1152] Moreover, in cardiomyopathy patients elevated NT-proBNP values are strong predictors of overall prognosis.[1153–1156]

Patients with a first-degree relative with a genetic cardiomyopathy should be evaluated with an ECG and an echocardiographic examination to rule out the presence of the disease, irrespective of age (see *Section 6.11*). There are no specific data on risks of NCS in phenotype-negative family members; however, they are at risk of developing the disease, which may be subclinical at the time of the NCS.[1157] Data in children with HCM undergoing general anaesthesia for cardiac and non-cardiac procedures show that, in a specialist setting with multidisciplinary involvement, peri-operative morbidity and mortality are extremely low.[1158]

Recommendation Table 33 — Recommendations for non-cardiac surgery in patients with cardiomyopathy

Recommendations	Class[a]	Level[b]
Peri-operative ECG monitoring is recommended for all patients with cardiomyopathy undergoing surgery.	I	C
In patients with cardiomyopathy and suspected or known HF scheduled for intermediate or high-risk NCS, it is recommended to re-evaluate LV function with echocardiography (assessing LVOTO in HCM patients) and measurement of NT-proBNP/BNP levels, unless this has recently been performed.[1151,1153–1156,1158–1165]	I	B
It is recommended that cardiomyopathy patients with high-risk genotypes or associated factors for arrhythmic or heart failure complications or severe LVOTO be referred for additional specialized investigations to a cardiomyopathy unit before undergoing elective NCS.	I	C
In patients aged <65 years with a first-degree relative with a cardiomyopathy, it is recommended to perform an ECG and TTE before NCS, regardless of symptoms.	I	C

ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; HF, heart failure; LV, left ventricular; LVOTO, left ventricular outflow tract obstruction; NCS, non-cardiac surgery; NT-proBNP, N-terminal pro-brain natriuretic peptide; TTE, transthoracic echocardiography.
[a]Class of recommendation.
[b]Level of evidence.

9. Requirements for specialized cardiomyopathy units

As genomic tests and information are incorporated into strategies for the routine diagnosis and management of cardiomyopathies and the estimation of disease risk, cardiologists need to familiarize themselves with the general principles underlying the interpretation of test results and must be able to convey the implications to patients. They also need to be able to make informed judgments about which tests are appropriate for different patients and clinical situations. The risk of SCD and the possibility that family members could inherit the condition makes multidisciplinary expertise, including genetic counselling, psychological care, and patient support associations, a critical aspect of care.[1166] As a result, there is a growing need for clinicians to develop their understanding of the basic principles of clinical genetics and the diverse clinical manifestations of individual genetic disorders.[54,964,1166,1167]

Cardiomyopathies have a highly heterogeneous clinical presentation and an evolution that sometimes is difficult to predict. Disease phenotype can be the result of various acquired factors or genetic backgrounds. Mixed phenotypes or two conditions within the same patient or among a family can coexist. Genetic diagnosis raises common logistical and ethical problems in its execution, as well as in the interpretation and communication of the results.[1166] Diagnostic process, the management of symptoms, and risk stratification often require comprehensive evaluation of the patient and their family, with the participation of multidisciplinary teams. On the other hand, interventional procedures (septal ablation, myectomies, etc.) require an expertise that only centres that treat many patients can achieve. Specialization in this area also requires permanent updating to accurately characterize the disease prognosis, ensure the choice of the best therapeutic option in each case, and guarantee the implementation of that choice by a team with experience in the field.

These characteristics imply that the adequate management of these diseases requires specific tools, extensive experience, and a multidisciplinary basic-clinical approach that are difficult to achieve.

The cardiomyopathy unit is usually integrated into a general cardiogenetic (or inherited cardiac conditions) unit, where other professionals involved in hereditary cardiac and vascular conditions, such as channelopathies, genetic aortopathies, familial dyslipidaemias, and a number of genetic metabolic and syndromic diseases with cardiac involvement, are co-ordinated. They represent an organizational model aimed at providing comprehensive cardiovascular and genetic assessment and personalized management in patients with inherited cardiovascular diseases. Specialized multidisciplinary clinics have long been advocated as the ideal model for the management of patients and families with inherited cardiac conditions.[4,53,559,1166] Such a model of care supports the holistic care of patients and their at-risk family members, taking a patient-centred approach and valuing clinical, genetic, and psychosocial outcomes. The benefit of a specialized clinic for management of HCM has been previously reported, with patients showing better adjustment and less worry than those who did not attend.[53,224] Besides expertise in the field of inherited cardiac conditions, the presence of a multidisciplinary team, access to good technical resources, participation in dedicated research projects, availability of genetic counselling, and family screening are all pre-requisites for organizing a cardiogenetic clinic. The ability to provide education and training for medical professionals and collaboration with patients' associations is of utmost importance.

Supplementary data online, *Table S8* synthesizes the requirements and skills and recommendations for professional education/training needed for a cardiogenetic clinic as proposed by international expert associations.

10. Living with cardiomyopathy: advice for patients

Most people with cardiomyopathy lead normal and productive lives, but a small number experience significant symptoms and are at risk of disease-related complications. Regardless of the severity of their disease, it is important that individuals receive support and accurate advice from cardiomyopathy specialists and other healthcare professionals, and that they are encouraged to understand and manage the disease themselves (see the Supplemental Data online, *Table S9*, for a description of the patient education process).

Table 24 General guidance for daily activity for patients with cardiomyopathies

Topic	General guidance
Exercise	• See earlier section on exercise recommendations.
Diet, alcohol use, and weight	• Patients should be encouraged to maintain a recommended body mass index. • Avoid dehydration, excess alcohol intake, and drugs consumption.
Smoking	• There are no data that show an interaction between tobacco smoking and cardiomyopathy, but patients should be provided with general advice on the health risks associated with smoking, including pro-arrhythmic and pro-inflammatory effects and, when available, information on smoking cessation.[1168–1171]
Reproductive issues	• Patients should be given the opportunity to discuss their concerns about reproductive issues. Anxiety and depression following a diagnosis are frequent, and some patients may express guilt or fear about their genetic diagnosis and the risk of transmission to offspring.
Sexual activity	• Patients should be counselled on the potential effect of their medication on sexual performance. • Most people with cardiomyopathy will be able to undertake normal sexual activity. Individualized advice should be provided regarding its safety and the possible impact of sexual activity on the risk of disease progression, ventricular arrhythmias, and/or ICD shocks.
Medication	• Patients should be provided with information about their medication, including potential side and teratogenic effects and interactions with prescribed medications, over-the-counter remedies, and other complementary therapies.
Vaccination	• In the absence of contraindications, patients should be advised to have regular recommended vaccinations (e.g. yearly influenza and SARS-CoV-2 vaccination).

Continued

Driving	• Most patients should be eligible for an ordinary driving licence and can continue driving unless they experience distracting or disabling symptoms. • Advice on driving licences for heavy goods or passenger-carrying vehicles should be in line with local legislation. • For further information on driving with ICDs, see local rules.
Occupation	• Most people with cardiomyopathy will be able to accomplish their normal jobs. The implications of heavily manual jobs that involve strenuous activity should be discussed with the appropriate specialist. • For some occupations, such as pilots, military personnel, and emergency services personnel, there are strict guidelines or rules on eligibility. • The social and financial implications of a diagnosis of cardiomyopathy should be included in the counselling of relatives before clinical or genetic screening.
Holidays and travel insurance	• Most asymptomatic or mildly symptomatic patients can fly safely. For further information on flying with ICD, see 'Fitness to fly for passengers with cardiovascular disease'.[1172] • Insurance companies may charge more for travel insurance. In some countries, patient support organizations can provide advice about obtaining reasonable insurance.
Life insurance	• The diagnosis of cardiomyopathy will result in difficulty obtaining life insurance or mortgages. Advice on the rules that apply in different countries should be provided to patients at diagnosis.
Pregnancy and childbirth	See *Section 8.2*
Education/schooling	• Teachers and other carers should be provided with advice and written information relevant to the care of children with cardiomyopathy. • In the absence of symptoms and risk factors, children should be allowed to perform low- to moderate-level aerobic physical activity, in accordance with advice from their paediatric cardiologist. Advice on high-intensity exercise in children should be guided by cardiomyopathy phenotype and the presence of symptoms and risk factors within a specialist paediatric cardiomyopathy setting. • Provision should be made for children with learning difficulties and other special needs. • Parents, teachers, and staff at sports facilities should be trained in CPR and in the use of AEDs.

AED, automated external defibrillator; CPR, cardio-pulmonary resuscitation; ICD, implantable cardioverter defibrillator; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 24 summarizes some of the key issues that should be discussed with patients, relatives, and carers. When appropriate (e.g. when considering pregnancy, see *Section 8.2*), patients should be referred to other specialist services.

11. Sex differences in cardiomyopathies

Sex differences in phenotypic expression and outcomes are well documented across cardiovascular medicine. Differences in clinical presentation, progression, and outcome in cardiomyopathies between females and males can be attributable to genetic and hormonal differences, but also to variations in management, access to healthcare, or response to specific therapies.[546,1173] Eliminating these variations represents a major unmet need in the care of cardiomyopathies.

Cardiomyopathies are typically inherited as an autosomal dominant trait. Therefore, the prevalence would be expected to be equal among the sexes. Women are consistently less represented than men in clinical studies across different cardiomyopathies (30–40%). Despite this, the difference may be explained by bias in interaction with healthcare facilities or by diagnosis criteria based on unadjusted cardiac imaging measurements; data from large pedigrees seem to support the hypothesis that there is a real delay in the age of phenotypic expression in female carriers (at least for HCM).[178,1174–1176]

Females with HCM are diagnosed later than males (8–13 years later), are more severely affected, more often have LVOTO, have more severe symptoms at baseline, and more commonly develop advanced heart failure during follow-up.[1177,1178] Women with LVOTO and indication for invasive procedures are often older and more symptomatic than males.[1179–1181] Females and males appear to show similar survival benefit from invasive SRT.[705,1181] Cardiomyopathy-related death has shown to be increased in middle-aged females with HCM compared with men and the general population; this is due to a higher rate of death from heart failure. No difference in SCD has been demonstrated in HCM regarding sex.[1182,1183]

Females with DCM may have a better response to therapy and seem to have a more favourable clinical course than males.[186,1184] Male sex has been reported to be consistently associated with an increased SCD rate in DCM (general cohorts and particular genotypes series),[186,541,872,878,1185–1187] and death from heart failure or transplant in general DCM cohorts.[1188,1189]

Male sex and sports have been traditionally identified as variables associated with an earlier phenotypic penetrance and a more severe disease expression in genetic carriers, and are independent predictors of malignant ventricular arrhythmic events in ARVC.[522,950,1190–1195] As in HCM, females with ARVC may have an increased risk of developing heart failure.[1193]

Reports on sex differences in familial or genetic RCM are scarce.[331,546] Compared with other types of cardiomyopathies, females seem to be as equally represented as males in RCM series.[331]

12. Comorbidities and cardiovascular risk factors in cardiomyopathies

12.1. Cardiovascular risk factors

The penetrance of the disease in genetic carriers of cardiomyopathy-associated variants is incomplete. Gene–environment interactions can explain part of the heterogeneity of the phenotypic expression of all cardiomyopathy phenotypes, although published data focus primarily on HCM, DCM, and ARVC.

12.2. Dilated cardiomyopathy

Individual genetic predisposition favours a dilated phenotype in the presence of trigger factors, such as inflammation, infection, toxic insults from alcohol or drugs, and tachyarrhythmias.

12.3. Hypertrophic cardiomyopathy

Hypertension and obesity have been associated with penetrance and phenotypic expression of HCM.[1196] Results from the EORP Cardiomyopathy/Mycarditis Registry showed that patients with HCM had a high prevalence of cardiovascular risk factors, comparable with data from the general population.[1196] Hypertension, diabetes, and obesity were associated with older age at presentation, a lower prevalence of family history of HCM and SCD, more symptoms, frequent AF, and worse LV diastolic function.[1197] Hypertension and obesity were also associated with higher provocable LVOT gradients and LVH.[1198]

12.4. Arrhythmogenic right ventricular cardiomyopathy

The role of intense exercise in disease expression and outcomes has been studied in HCM and DCM, but the impact has shown to be particularly relevant in ARVC (*Table 25*). Despite significant research, the pathophysiology of ARVC is complex and not well understood. The search for genetic or environmental triggers, such as viruses and immune response, has failed to identify actionable factors. The role of inflammation on the pathophysiology is thought to be key.[1199]

Recommendation Table 34 — Recommendation for management of cardiovascular risk factors in patients with cardiomyopathy

Recommendation	Class[a]	Level[b]
Identification and management of risk factors and concomitant diseases is recommended as an integral part of the management of cardiomyopathy patients.	I	C

[a]Class of recommendation.
[b]Level of evidence.

13. Coronavirus disease (COVID-19) and cardiomyopathies

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, known as COVID-19, is characterized by a high variability of clinical presentation and outcomes with an adverse association between underlying cardiac disease, including heart failure, and SARS-CoV-2-related mortality.[1200–1202] However, examination of SARS-CoV-2 infection in underlying causes of heart failure, particularly cardiomyopathies, has been limited.

Analyses of international registries on cardiomyopathies and SARS-CoV-2 from the pre-vaccine period have identified several markers of adverse outcomes.[1203] Prior history of heart failure and particular phenotypes (amyloidosis and DCM) were significantly associated with intensive care unit admission and death compared with HCM, ARVC, and the general population. For HCM, age, baseline functional class, LVOTO, and systolic impairment were independent predictors of death.[1204]

SARS-CoV-2 vaccination has been demonstrated to be safe in large population studies and reports on complications related to the vaccination in patients with cardiomyopathy are anecdotal. Given this, and the potential for worse outcomes in cardiomyopathy patients who contract COVID-19, vaccination is encouraged in all cardiomyopathy patients and, in particular, in those with signs or symptoms of heart failure.

14. Key messages

(1) Cardiomyopathies are more common than previously thought and they typically require nuanced management that may differ from the conventional approach to patients with arrhythmia or heart failure.
(2) Aetiology is fundamental to the management of patients with heart muscle disease and careful and systematic description of the morphological and functional phenotype is a crucial first step in the diagnostic pathway.
(3) An approach to nomenclature and diagnosis of cardiomyopathies that is based on the predominant phenotype at presentation is recommended.
(4) Patients with cardiomyopathy may seek medical attention due to symptoms onset (HF or arrhythmia related), incidental abnormal findings, or as a result of family screening following the diagnosis in a relative.

Table 25 Modulators of the phenotypic expression of cardiomyopathies

Condition	HCM	DCM	ARVC	Expression
Hypertension	+++	++	?	Hypertrophy, dilatation, dysfunction, AF
Diabetes	++	+	?	Hypertrophy, dysfunction, AF
Obesity	++	+	?	Hypertrophy, LVOTO, AF
Toxic	–	+++	?	Dilatation, dysfunction
Sports	+	+	+++	Dilatation, dysfunction, ventricular arrhythmia
Virus	–	++	+	Dilatation, dysfunction, ventricular arrhythmia
Pregnancy	–	++	–	Dilatation, dysfunction

AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVOTO, left ventricular outflow tract obstruction.
+, degree of positive association; –, absence of definitive association; ?, unknown association.

(5) Multimodality imaging to characterize the cardiac phenotype (morphology and function)—including tissue characterization for non-ischaemic myocardial scar detection—is necessary, in combination with a detailed personal and family history, clinical examination, electrocardiography, and laboratory investigations.
(6) Imaging results should always be interpreted in the overall clinical context, including genetic testing results, rather than in isolation.
(7) Tissue characterization by CMR is of value in diagnosis, monitoring of disease progression and risk stratification in each of the main cardiomyopathy phenotypes.
(8) DPD/PYP/HMDP bone-tracer scintigraphy or SPECT represent the gold standard for the diagnosis of ATTR-related cardiac amyloidosis.
(9) The presence of non-ischaemic ventricular scar or fatty replacement on cardiac CMR and/or pathological examination, which can occur with or without ventricular dilatation and/or systolic dysfunction, can be the sole clue to the diagnosis of a cardiomyopathy and can have prognostic significance that varies with aetiology.
(10) The aim of this multiparametric and systemic approach is to generate a phenotype-based aetiological diagnosis, interpreting available data with a cardiomyopathy-oriented mindset that combines cardiological assessment with non-cardiac parameters.
(11) A multidisciplinary approach to patient care and appropriate transition of care from paediatric to adult cardiomyopathy services is needed.
(12) Genetic testing should be performed in patients with cardiomyopathy and may influence risk stratification and management.
(13) Genetic counselling, including pre- and post-test counselling, and psychological support are an essential aspect of the multidisciplinary care of patients with cardiomyopathy and their relatives.
(14) Paediatric cardiomyopathies largely represent part of the same clinical spectrum as those seen in older adolescents and adults, but infant-onset (in the first year of life) cardiomyopathies are often associated with severe phenotypes and a high rate of heart failure-related morbidity and mortality.
(15) Beyond the first year of life, genetic causes of childhood-onset cardiomyopathies are similar to those in adults.
(16) Symptom management, identification, and prevention of disease-related complications (including SCD, heart failure, and stroke) are the cornerstone of management of all cardiomyopathies.
(17) Cardiac myosin inhibitors (Mavacamten) should be considered in patients with HCM and LVOTO who remain symptomatic despite optimal medical therapy.
(18) Validated SCD risk-prediction tools (HCM Risk-SCD and HCM Risk-Kids) are the first step in sudden death prevention in patients with HCM.
(19) Additional risk markers may be of use in patients with low or intermediate risk, but there is a lack of robust data on the impact of these parameters on the personalized risk estimates generated by the risk-prediction tools.
(20) Pharmacological treatment of DCM patients does not differ from those recommended in chronic heart failure.
(21) SCD risk of DCM and NDLVC patients varies depending on the underlying cause and genetic subtype.
(22) CMR findings play an important role in guiding ICD implantation for patients with DCM and NDLVC.
(23) In DCM and NDLVC patients, ICD should be considered for certain genetic forms even if LVEF is >35%.
(24) It is of importance to define aetiology for a tailored management in patients with syndromic and metabolic cardiomyopathies (i.e. ERT/chaperone in lysosomal storage disease; tafamidis in ATTRwt, etc.).
(25) Pregnancy and the post-partum period are associated with increased cardiovascular risk in women with known cardiomyopathy.
(26) A multidisciplinary team should evaluate the patient with cardiomyopathy to assess the risk associated with pregnancy.
(27) Beta-blocker therapy on arrhythmic indication can safely be continued during pregnancy; safety data should be checked before initiation of new drugs in pregnancy.
(28) Healthy adults of all ages and individuals with known cardiac disease should exercise with moderate intensity, totalling at least 150 min per week.
(29) All patients with cardiomyopathy should have an individualized risk assessment for exercise prescription. Evaluation should be guided by three principles: (i) preventing life-threatening arrhythmias during exercise; (ii) symptom management to allow sports; and (iii) preventing sports-induced progression of the arrhythmogenic condition.
(30) Individuals who are genotype positive/phenotype negative or have a mild cardiomyopathy phenotype and absence of symptoms or any risk factors, may be able to participate in competitive sports. In some high-risk patients with HCM, ARVC, and NDLVC, high-intensity exercise and competitive sports should be discouraged.
(31) Patients with high-risk genotypes or associated factors for arrhythmic or heart failure complications or severe LVOTO should be referred for specialized investigations before undergoing elective NCS.
(32) Identification and management of risk factors and concomitant diseases is recommended as an integral part of the management of cardiomyopathy patients.

15. Gaps in evidence

Although there have been major advances in the genetics, diagnosis, and treatments of patients with cardiomyopathy over the last few years, there are a number of areas where robust evidence is still lacking and deserve to be addressed in future clinical research.

(1) Cardiomyopathy phenotypes.
(2) Epidemiology:
  (a) Prevalence of NDLVC phenotype (children and adults).
  (b) Systematic assessment of prevalence of cardiomyopathy phenotypes in childhood.
(3) Integrated patient management:
  (a) Embedding of telemedicine into cardiomyopathy networks.
(4) Patient pathway:
  (a) Laboratory tests:
    (i) Studies on novel 'omic' biomarkers (proteomics, metabolomics, and transcriptomics) are needed to assess their potential value for diagnostic and prognostic purposes in cardiomyopathies.
  (b) Multimodality imaging:
    (i) Advanced echocardiographic techniques, including speckle tracking deformation imaging, are promising but lack robust validation in the setting of cardiomyopathies.

  - (ii) A universally accepted, standardized method for the quantification of myocardial fibrosis by CMR is lacking.
  - (iii) CMR scans may be performed in patients with compatible implantable devices, but the quality is limited by artefacts.
  - (iv) Artificial intelligence enhanced electrocardiography and imaging for cardiomyopathy evaluation has been proving a novel tool to dramatically improve diagnosis and prognosis; further studies are needed for routine introduction in clinical practice.
  - (v) Impact of CMR on screening in genotype-positive relatives of individuals with cardiomyopathy and in gene-elusive families.
- (c) Genetics:
  - (i) Penetrance is poorly characterized for most pathogenic variants. This is true both for variants found through cascade screening of relatives of a patient with cardiomyopathy, and also for variants found in the wider population who may have clinical sequencing for another indication or may choose to have genome sequencing as a screening test.
  - (ii) The benefits, harm, and costs of screening of cardiomyopathy-associated genes in individuals without a personal or family history of cardiomyopathy is not known.
- (d) General principles in management:
  - (i) Management of RV failure remains largely non-evidence-based.
  - (ii) Large-scale studies are required to guide ventricular arrhythmia management in patients with genetic cardiomyopathies.
  - (iii) Optimal rate control and AADs per subtype of cardiomyopathy.
  - (iv) The role of ICDs in patients with well tolerated VT.
  - (v) All risk calculators are developed using baseline data. Therefore, the utility of their application during follow-up visits of patients remains unclear and needs to be studied.
  - (vi) Risk prediction in childhood cardiomyopathies other than HCM remains empirical—multicentre approach required to understand and develop SCD risk models in childhood.
  - (vii) Lack of controlled studies on the effect of ablation in patients with AF and cardiomyopathy.
  - (viii) Models to predict AF recurrence have not been validated in cardiomyopathy patients.
  - (ix) Lack of randomized studies assessing the efficacy of cardiac sympathetic denervation for the prevention of VT/VF recurrences.
- (e) Approach to paediatric cardiomyopathies:
  - (i) Lack of randomized studies or large registries addressing the benefit and optimal dosing of drug therapy in paediatric population.

(5) Hypertrophic cardiomyopathy:
- (a) Epidemiology:
  - (i) Imaging and genotype studies suggest a population prevalence of up to 1 in 200 of the population. However, HER-based studies suggest a much lower number of 3–4/10 000. Further studies into the prevalence of clinically important diseases are necessary.
- (b) Aetiology:
  - (i) Aetiology of gene-elusive disease.
  - (ii) The role of polygenic risk.
  - (iii) Interaction between comorbidity and disease outcomes.
  - (iv) Genetic and environmental determinants of disease expression in variant carriers.
- (c) Symptom management:
  - (i) Optimal timing of LVOTO management and its impact on disease progression.
  - (ii) Prevention of AF and heart failure.
- (d) Sudden death prevention:
  - (i) Impact of genetics (Mendelian and complex) on risk of disease-related outcomes.
  - (ii) Improved prediction models that reduce residual risk and prevent unnecessary ICD implantation.
  - (iii) Refinement of risk-prediction models to include serial data.
  - (iv) Role of LVOTO in risk prediction in children (apparent discrepancy compared with adults).
- (e) New therapies:
  - (i) Clinical utility of myosin inhibitors, other small molecules, and emerging genetic therapies.

(6) Dilated cardiomyopathy:
- (a) Genetic basis of familial DCM is still unknown in a high number of cases.
- (b) Detailed data about the specific clinical course in diverse genetic and non-genetic DCM forms are not available.
- (c) It is unknown if patients with DCM respond differently to pharmacological treatment according to underlying aetiology.
- (d) Optimized SCD prevention strategy remains unsolved. There are not data from prospective clinical trials in modern cohorts with contemporary medical treatment. This gap is knowledge is particularly relevant for DCM patients with LVEF > 35%.
- (e) Sport recommendations and utility of prophylactic pharmacological therapy to prevent DCM onset in genetic carriers.

(7) Non-dilated left ventricular cardiomyopathy:
- (a) Prevalence of disease.
- (b) Natural history and response to treatment.
- (c) SCD prevention.
- (d) Sports recommendations.

(8) Arrhythmogenic right ventricular cardiomyopathy:
- (a) RCTs for therapies for the management of arrhythmias and heart failure are lacking.
- (b) Studies on the effect of exercise remain largely retrospective.
- (c) Studies on the incidence and prognostication of heart failure remain limited.
- (d) Studies on the frequency and mode of clinical screening for asymptomatic family members are lacking.

(9) Restrictive cardiomyopathy:
- (a) SCD prevention.

(10) Syndromic and metabolic cardiomyopathies:
- (a) Lack of randomized trials or large observational cohort studies assessing the role of new target therapies addressing the RAS/MAPK pathway (i.e trametinib).
- (b) There are few long-term outcome studies addressing ventricular remodelling in RAS-HCM.
- (c) HCM Risk-Kids has not been validated in paediatric patients with RAS-HCM. Data regarding SCD risk stratification are lacking, although candidate risk factors have been identified.

(d) Lack of studies addressing the optimal timing to start ERT in adolescents and adults with late-onset Pompe disease.
(e) Lack of standardized protocols to treat cross-reactive immunologic material-negative patients.
(f) Lack of standardization of clinical endpoints in ERT/chaperone therapy trials.
(g) Lack of head-to-head comparisons between agalsidase alpha and beta.
(h) Optimal time to begin treatment in asymptomatic female patients with non-classic disease.

(11) Amyloid:
(a) Further studies are needed to assess the efficacy and safety of tafamidis in NYHA class III patients.
(b) SCD risk stratification and indications for ICD implantation should be carefully defined, taking into account the estimated life expectancy, competitive non-cardiovascular mortality, and the high rate of pulseless electrical activity.
(c) The need for drug therapy in patients with cardiac amyloidosis and subclinical cardiac involvement (i.e asymptomatic patients, positive scintigraphy with negative ECHO) has not been clearly defined.

(12) Sports:
(a) 'Return to play' for patients with low-risk cardiomyopathies (and how to define low risk in relation to exercise).
(b) SCD risk and exercise recommendations in phenotype-negative gene carriers.
(c) Role of exercise in disease expression and progression.
(d) Large, adequately powered randomized prospective studies are necessary to provide evidence-based recommendations for optimal exercise prescription without compromising safety.

(13) Reproductive issues:
(a) Several cardiomyopathies lack specific outcome data regarding pregnancy.
(b) There is a lack of randomized trials on the use of AADs, heart failure drugs, and interventions during pregnancy.

(14) Non-cardiac interventions:
(a) There is a lack specific outcome data regarding risks of non-cardiac interventions.

(15) Management of cardiovascular risk factors in patients with cardiomyopathies:
(a) There is a lack of data on the impact of comorbidities on penetrance, severity, and outcome of cardiomyopathies.

16. 'What to do' and 'What not to do' messages from the Guidelines

Recommendations	Class[a]	Level[b]
Recommendations for the provision of service of multidisciplinary cardiomyopathy teams		
It is recommended that all patients with cardiomyopathy and their relatives have access to multidisciplinary teams with expertise in the diagnosis and management of cardiomyopathies.	I	C
Timely and adequate preparation for transition of care from paediatric to adult services, including joint consultations, is recommended in all adolescents with cardiomyopathy.	I	C
Recommendations for diagnostic work-up in cardiomyopathies		
It is recommended that all patients with suspected or established cardiomyopathy undergo systematic evaluation using a multiparametric approach that includes clinical evaluation, pedigree analysis, ECG, Holter monitoring, laboratory tests, and multimodality imaging.	I	C
It is recommended that all patients with suspected cardiomyopathy undergo evaluation of family history and that a three- to four-generation family tree is created to aid in diagnosis, provide clues to underlying aetiology, determine inheritance pattern, and identify at-risk relatives.	I	C
Recommendations for laboratory tests in the diagnosis of cardiomyopathies		
Routine (first-level) laboratory tests are recommended in all patients with suspected or confirmed cardiomyopathy to evaluate aetiology, assess disease severity, and aid in detection of extracardiac manifestations and assessment of secondary organ dysfunction.	I	C
Recommendation for echocardiographic evaluation in patients with cardiomyopathy		
A comprehensive evaluation of cardiac dimensions and LV and RV systolic (global and regional) and LV diastolic function is recommended in all patients with cardiomyopathy at initial evaluation, and during follow-up, to monitor disease progression and aid risk stratification and management.	I	B
Recommendations for cardiac magnetic resonance indication in patients with cardiomyopathy		
Contrast-enhanced CMR is recommended in patients with cardiomyopathy at initial evaluation.	I	B
Recommendations for computed tomography and nuclear imaging		
DPD/PYP/HMDP bone-tracer scintigraphy is recommended in patients with suspected ATTR-related cardiac amyloidosis to aid diagnosis.	I	B
Recommendations for genetic counselling and testing in cardiomyopathies		
Genetic counselling		
Genetic counselling, provided by an appropriately trained healthcare professional and including genetic education to inform decision-making and psychosocial support, is recommended for families with an inherited or suspected inherited cardiomyopathy, regardless of whether genetic testing is being considered.	I	B

Continued

It is recommended that genetic testing for cardiomyopathy is performed with access to a multidisciplinary team, including those with expertise in genetic testing methodology, sequence variant interpretation, and clinical application of genetic testing, typically in a specialized cardiomyopathy service or in a network model with access to equivalent expertise.	I	B
Pre- and post-test genetic counselling is recommended in all individuals undergoing genetic testing for cardiomyopathy.	I	B
If pre-natal diagnostic testing is to be pursued by the family, it is recommended that this is performed early in pregnancy, to allow decisions regarding continuation or co-ordination of pregnancy to be made.	I	C
Index patients		
Genetic testing is recommended in patients fulfilling diagnostic criteria for cardiomyopathy in cases where it enables diagnosis, prognostication, therapeutic stratification, or reproductive management of the patient, or where it enables cascade genetic evaluation of their relatives who would otherwise be enrolled into long-term surveillance.	I	B
Genetic testing is recommended for a deceased individual identified to have cardiomyopathy at *post-mortem* if a genetic diagnosis would facilitate management of surviving relatives.	I	C
Family members		
It is recommended that cascade genetic testing, with pre- and post-test counselling, is offered to adult at-risk relatives if a confident genetic diagnosis (i.e. a P/LP variant) has been established in an individual with cardiomyopathy in the family (starting with first-degree relatives if available, and cascading out sequentially).	I	B
Diagnostic genetic testing is not recommended in a phenotype-negative relative of a patient with cardiomyopathy in the absence of a confident genetic diagnosis (i.e. a P/LP variant) in the family.	III	C
Recommendations for cardiac transplantation in patients with cardiomyopathy		
Orthotopic cardiac transplantation is recommended for eligible cardiomyopathy patients with advanced heart failure (NYHA class III–IV) or intractable ventricular arrhythmia refractory to medical/invasive/device therapy, and who do not have absolute contraindications.	I	C
Recommendations for management of atrial fibrillation and atrial flutter in patients with cardiomyopathy		
Anticoagulation		
Oral anticoagulation in order to reduce the risk of stroke and thromboembolic events is recommended in all patients with HCM or cardiac amyloidosis and AF or atrial flutter (unless contraindicated).	I	B
Oral anticoagulation to reduce the risk of stroke and thrombo-embolic events is recommended in patients with DCM, NDLVC, or ARVC, and AF or atrial flutter with a CHA_2DS_2-VASc score ≥2 in men or ≥3 in women.	I	B
Control of symptoms and heart failure		
Atrial fibrillation catheter ablation is recommended for rhythm control after one failed or intolerant class I or III AAD to improve symptoms of AF recurrences in patients with paroxysmal or persistent AF and cardiomyopathy.	I	B
Atrial fibrillation catheter ablation is recommended to reverse LV dysfunction in AF patients with cardiomyopathy when a tachycardia-induced component is highly probable, independent of their symptom status.	I	B
Comorbidities and associated risk factor management		
Modification of an unhealthy lifestyle and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity in patients with cardiomyopathy.	I	B
Recommendations for implantable cardioverter defibrillator in patients with cardiomyopathy		
General recommendations		
Implantation of a cardioverter defibrillator is only recommended in patients who have an expectation of good quality survival >1 year.	I	C
It is recommended that ICD implantation be guided by shared decision-making that: • is evidence-based; • considers a person's individual preferences, beliefs, circumstances, and values; and • ensures that the person understands the benefits, harm, and possible consequences of different treatment options.	I	C
It is recommended that prior to ICD implantation, patients are counselled on the risk of inappropriate shocks, implant complications, and the social, occupational, and driving implications of the device.	I	C
It is not recommended to implant an ICD in patients with incessant ventricular arrhythmias until the ventricular arrhythmia is controlled.	III	C
Secondary prevention		
Implantation of an ICD is recommended:		
• in patients with HCM, DCM, and ARVC who have survived a cardiac arrest due to VT or VF, or who have spontaneous sustained ventricular arrhythmia causing syncope or haemodynamic compromise in the absence of reversible causes.	I	B
• in patients with NDLVC and RCM who have survived a cardiac arrest due to VT or VF, or who have spontaneous sustained ventricular arrhythmia causing syncope or haemodynamic compromise in the absence of reversible causes.	I	C

Continued

Primary prevention		
Comprehensive SCD risk stratification is recommended in all cardiomyopathy patients who have not suffered a previous cardiac arrest/sustained ventricular arrhythmia at initial evaluation and at 1–2 year intervals, or whenever there is a change in clinical status.	I	C
The use of validated SCD algorithms/scores as aids to the shared decision-making when offering ICD implantation, where available is recommended in patients with HCM.	I	B
Choice of ICD		
When an ICD is indicated, it is recommended to evaluate whether the patient could benefit from CRT.	I	A
Recommendations for routine follow-up of patients with cardiomyopathy		
It is recommended that all clinically stable patients with cardiomyopathy undergo routine follow-up using a multiparametric approach that includes ECG and echocardiography every 1–2 years.	I	C
Clinical evaluation with ECG and multimodality imaging is recommended in patients with cardiomyopathy whenever there is a substantial or unexpected change in symptoms.	I	C
Recommendations for family screening and follow-up evaluation of relatives		
Following cascade genetic testing, clinical evaluation using a multiparametric approach that includes ECG and cardiac imaging and long-term follow-up is recommended in first-degree relatives who have the same disease-causing variant as the proband.	I	B
Following cascade genetic testing, it is recommended that first-degree relatives without a phenotype who do not have the same disease-causing variant as the proband are discharged from further follow-up but advised to seek re-assessment if they develop symptoms or when new clinically relevant data emerge in the family.	I	C
It is recommended that when no P/LP variant is identified in the proband or genetic testing is not performed, an initial clinical evaluation using a multiparametric approach that includes ECG and cardiac imaging is performed in first-degree relatives.	I	C
Recommendations for psychological support in patients and family members with cardiomyopathies		
It is recommended that psychological support by an appropriately trained health professional be offered to all individuals who have experienced the premature sudden cardiac death of a family member with cardiomyopathy.	I	B
It is recommended that psychological support by an appropriately trained health professional be offered to all individuals with an inherited cardiomyopathy who receive an implantable cardioverter defibrillator.	I	B
Recommendation for evaluation of left ventricular outflow tract obstruction		
In all patients with HCM, at initial evaluation, transthoracic 2D and Doppler echocardiography are recommended, at rest and during Valsalva manoeuvre in the sitting and semi-supine positions—and then on standing if no gradient is provoked—to detect LVOTO.	I	B
In symptomatic patients with HCM and a resting or provoked peak instantaneous LV outflow tract gradient <50 mmHg, 2D and Doppler echocardiography during exercise in the standing, sitting (when possible), or semi-supine position are recommended to detect provocable LVOTO and exercise-induced mitral regurgitation.	I	B
Recommendations for medical treatment of left ventricular outflow tract obstruction		
Non-vasodilating beta-blockers, titrated to maximum tolerated dose, are recommended as first-line therapy to improve symptoms in patients with resting or provoked LVOTO.	I	B
Verapamil or diltiazem, titrated to maximum tolerated dose, are recommended to improve symptoms in symptomatic patients with resting or provoked LVOTO who are intolerant or have contraindications to beta-blockers.	I	B
Disopyramide, titrated to maximum tolerated dose, is recommended in addition to a beta-blocker (or, if this is not possible, with verapamil or diltiazem) to improve symptoms in patients with resting or provoked LVOTO.	I	B
Recommendations for septal reduction therapy		
It is recommended that SRT be performed by experienced operators working as part of a multidisciplinary team expert in the management of HCM.	I	C
SRT to improve symptoms is recommended in patients with a resting or maximum provoked LVOT gradient of ≥50 mmHg who are in NYHA/Ross functional class III–IV, despite maximum tolerated medical therapy.	I	B
Septal myectomy, rather than ASA, is recommended in children with an indication for SRT, as well as in adult patients with an indication for SRT and other lesions requiring surgical intervention (e.g. mitral valve abnormalities).	I	C
Additional recommendations for prevention of sudden cardiac death in patients with hypertrophic cardiomyopathy		
Secondary prevention		
Implantation of an ICD is recommended in patients who have survived a cardiac arrest due to VT or VF, or who have spontaneous sustained VT with haemodynamic compromise.	I	B

Continued

Primary prevention		
The HCM Risk-SCD calculator is recommended as a method of estimating risk of sudden death at 5 years in patients aged ≥16 years for primary prevention.	I	B
Validated paediatric-specific risk-prediction models (e.g. HCM Risk-Kids) are recommended as a method of estimating risk of sudden death at 5 years in patients aged <16 years for primary prevention.	I	B
It is recommended that the 5-year risk of SCD be assessed at first evaluation and re-evaluated at 1–2 year intervals or whenever there is a change in clinical status.	I	B
Recommendations for an implantable cardioverter defibrillator in patients with dilated cardiomyopathy		
Secondary prevention		
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with DCM who have survived a cardiac arrest or have recovered from a ventricular arrhythmia causing haemodynamic instability.	I	B
Recommendation for resting and ambulatory electrocardiogram monitoring in patients with non-dilated left ventricular cardiomyopathy		
Ambulatory ECG monitoring is recommended in patients with NDLVC annually or when there is a change in clinical status, to aid in management and risk stratification.	I	C
Recommendations for an implantable cardioverter defibrillator in patients with non-dilated left ventricular cardiomyopathy		
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with NDLVC who have survived a cardiac arrest or have recovered from a ventricular arrhythmia causing haemodynamic instability.	I	C
Recommendation for resting and ambulatory electrocardiogram monitoring in patients with arrhythmogenic right ventricular cardiomyopathy		
Annual ambulatory ECG monitoring is recommended in patients with ARVC to aid in diagnosis, management, and risk stratification.	I	C
Recommendations for the antiarrhythmic management of patients with arrhythmogenic right ventricular cardiomyopathy		
Beta-blocker therapy is recommended in ARVC patients with VE, NSVT, and VT.	I	C
Recommendations for sudden cardiac death prevention in patients with arrhythmogenic right ventricular cardiomyopathy		
Secondary prevention		
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with ARVC who have survived a cardiac arrest or have recovered from a ventricular arrhythmia causing haemodynamic instability.	I	A
Recommendations for the management of patients with restrictive cardiomyopathy		
It is recommended that multimodality imaging be used to differentiate RCM from HCM or DCM with restrictive physiology.	I	C
It is recommended that baseline cardiac and non-cardiac investigations are performed to assess involvement of the neuromuscular system or other syndromic disorders.	I	C
Cardiac catheterization is recommended in all children with RCM to measure pulmonary artery pressures and PVR at diagnosis and at 6–12 monthly intervals to assess change in PVR.	I	B
ICD implantation is recommended to reduce the risk of sudden death and all-cause mortality in patients with RCM who have survived a cardiac arrest or have recovered from a ventricular arrhythmia causing haemodynamic instability.	I	C
Exercise recommendations for cardiomyopathy patients		
All cardiomyopathies		
Regular low- to moderate-intensity exercise is recommended in all able individuals with cardiomyopathy.	I	C
An individualized risk assessment for exercise prescription is recommended in all patients with cardiomyopathy.	I	C
HCM		
High-intensity exercise, including competitive sport, is not recommended in high-risk individuals and in individuals with left ventricular outflow tract obstruction and exercise-induced complex ventricular arrhythmias.	III	C
ARVC		
Moderate- and/or high-intensity exercise, including competitive sport, is not recommended in individuals with ARVC.	III	B
DCM and NDLVC		
High-intensity exercise, including competitive sport, is not recommended in symptomatic individuals, those with a left ventricular ejection fraction ≤40%, exercise-induced arrhythmias, or pathogenic variants in *LMNA* or *TMEM43.*	III	C
Recommendations for reproductive issues in patients with cardiomyopathy		
Pre-pregnancy risk assessment and counselling are recommended in all women using the mWHO classification of maternal risk.	I	C

Continued

Counselling on safe and effective contraception is recommended in all women of fertile age and their partners.	I	C
Counselling on the risk of disease inheritance is recommended for all men and women before conception.	I	C
Vaginal delivery is recommended in most women with cardiomyopathies, unless there are obstetric indications for caesarean section, severe heart failure (EF <30% or NYHA class III–IV), or severe outflow tract obstructions, or in women presenting in labour on oral anticoagulants.	I	C
It is recommended that medication be carefully reviewed for safety in advance of pregnancy and adjusted according to tolerability in pregnancy.	I	C
Therapeutic anticoagulation with LMWH or VKAs according to the stage of pregnancy is recommended for patients with AF.	I	C
Recommendations for non-cardiac surgery in patients with cardiomyopathy		
Peri-operative ECG monitoring is recommended for all patients with cardiomyopathy undergoing surgery.	I	C
In patients with cardiomyopathy and suspected or known HF scheduled for intermediate or high-risk NCS, it is recommended to re-evaluate LV function with echocardiography (assessing LVOTO in HCM patients) and measurement of NT-proBNP/BNP levels, unless this has recently been performed.	I	B
It is recommended that cardiomyopathy patients with high-risk genotypes or associated factors for arrhythmic or heart failure complications or severe LVOTO be referred for additional specialized investigations to a cardiomyopathy unit before undergoing elective NCS.	I	C
In patients aged <65 years with a first-degree relative with a cardiomyopathy, it is recommended to perform an ECG and TTE before NCS, regardless of symptoms.	I	C
Recommendation for management of cardiovascular risk factors in patients with cardiomyopathy		
Identification and management of risk factors and concomitant diseases is recommended as an integral part of the management of cardiomyopathy patients.	I	C

2D, two-dimensional; AAD, antiarrhythmic drug; AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; ASA, alcohol septal ablation; ATTR, transthyretin amyloidosis; BNP, brain natriuretic peptide; CHA_2DS_2-VASc, congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74, sex category (female) (score); CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; DPD, 3,3-diphosphono-1,2-propanodicarboxylic acid; ECG, electrocardiogram; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; HMDP, hydroxymethylene diphosphonate; ICD, implantable cardioverter defibrillator; LMWH, low-molecular-weight heparin; LV, left ventricular; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction; mWHO, modified World Health Organization; NCS, non-cardiac surgery; NDLVC, non-dilated left ventricular cardiomyopathy; NSVT, non-sustained ventricular tachycardia; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; P/LP, pathogenic/likely pathogenic; PVR, pulmonary vascular resistance; PYP, pyrophosphate; RCM, restrictive cardiomyopathy; RV, right ventricular; SCD, sudden cardiac death; SRT, septal reduction therapy; TTE, transthoracic echocardiogram; VE, ventricular ectopic beats; VF, ventricular fibrillation; VKA, vitamin K antagonist; VT, ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.

17. Supplementary data

Supplementary material is available at *European Heart Journal* online.

18. Data availability statement

No new data were generated or analysed in support of this research.

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20. Appendix

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22. References

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