ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–124
https://doi.org/10.1093/eurheartj/ehad194

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)

Authors/Task Force Members: Elena Arbelo *†, (Chairperson) (Spain), Alexandros Protonotarios ‡, (Task Force Co-ordinator) (United Kingdom), Juan R. Gimeno ‡, (Task Force Co-ordinator) (Spain), Eloisa Arbustini (Italy), Roberto Barriales-Villa (Spain), Cristina Basso (Italy), Connie R. Bezzina (Netherlands), Elena Biagini (Italy), Nico A. Blom[1] (Netherlands), Rudolf A. de Boer (Netherlands), Tim De Winter (Belgium), Perry M. Elliott (United Kingdom), Marcus Flather (United Kingdom), Pablo Garcia-Pavia (Spain), Kristina H. Haugaa (Sweden), Jodie Ingles (Australia), Ruxandra Oana Jurcut (Romania), Sabine Klaassen (Germany), Giuseppe Limongelli (Italy), Bart Loeys [2] (Belgium), Jens Mogensen (Denmark), Iacopo Olivotto (Italy), Antonis Pantazis (United Kingdom), Sanjay Sharma (United Kingdom), J. Peter Van Tintelen (Netherlands), James S. Ware (United Kingdom), Juan Pablo Kaski *†, (Chairperson) (United Kingdom), and ESC Scientific Document Group

* Corresponding authors: Elena Arbelo, Arrhythmia Section, Cardiology Department, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain, IDIBAPS, Institut d'Investigació August Pi i Sunyer (IDIBAPS), Barcelona, Spain, Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain, and European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart, ERN GUARD-Heart, Barcelona, Spain. Tel: +34 93 22 75 55 11, E-mail: elenaarbelo@secardiologia.es; and Juan Pablo Kaski, Centre for Paediatric Inherited and Rare Cardiovascular Disease, University College London, Institute of Cardiovascular Science, London, United Kingdom and Centre for Inherited Cardiovascular Diseases, Great Ormond Street Hospital, London, United Kingdom. Tel: +44 78 29 88 39, E-mail: j.kaski@ucl.ac.uk

† The two Chairpersons contributed equally to the document and are joint corresponding authors.

‡ The two Task Force Co-ordinators contributed equally to the document.

Author/Task Force Member affiliations are listed in author information.

[1] Representing the Association for European Paediatric and Congenital Cardiology (AEPC)

[2] Representing the European Society of Human Genetics (ESHG)

ESC Clinical Practice Guidelines (CPG) Committee: listed in the Appendix.

ESC subspecialty communities having participated in the development of this document:

Associations: Association of Cardiovascular Nursing & Allied Professions (ACNAP), European Association of Cardiovascular Imaging (EACVI), European Association of Preventive Cardiology (EAPC), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA).

Councils: Council on Cardiovascular Genomics.

Working Groups: Development Anatomy and Pathology, Myocardial and Pericardial Diseases.

Patient Forum

Document Reviewers: Philippe Charron, (CPG Review Co-ordinator) (France), Massimo Imazio, (CPG Review Co-ordinator) (Italy), Magdy Abdelhamid (Egypt), Victor Aboyans (France), Michael Arad (Israel), Folkert W. Asselbergs (Netherlands), Riccardo Asteggiano (Italy), Zofia Bilinska (Poland), Damien Bonnet (France), Henning Bundgaard (Denmark), Nuno Miguel Cardim (Portugal), Jelena Čelutkienė (Lithuania), Maja Cikes (Croatia), Gaetano Maria De Ferrari (Italy), Veronica Dusi (Italy), Volkmar Falk (Germany), Laurent Fauchier (France), Estelle Gandjbakhch (France), Tiina Heliö (Finland), Konstantinos Koskinas (Switzerland), Dipak Kotecha (United Kingdom), Ulf Landmesser (Germany), George Lazaros (Greece), Basil S. Lewis (Israel), Ales Linhart (Czechia), Maja-Lisa Løchen (Norway), Benjamin Meder (Germany), Richard Mindham (United Kingdom), James Moon (United Kingdom), Jens Cosedis Nielsen (Denmark), Steffen Petersen (United Kingdom), Eva Prescott (Denmark), Mary N. Sheppard (United Kingdom), Gianfranco Sinagra (Italy), Marta Sitges (Spain), Jacob Tfelt-Hansen (Denmark), Rhian Touyz (Canada), Rogier Veltrop (Netherlands), Josef Veselka (Czechia), Karim Wahbi (France), Arthur Wilde (Netherlands), and Katja Zeppenfeld (Netherlands)

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.

Keywords Guidelines • Arrhythmia • Arrhythmogenic right ventricular cardiomyopathy • Cardiomyopathies • Diagnosis • Dilated cardiomyopathy • Genetics • Genetic counselling • Genetic testing • Hypertrophic cardiomyopathy • Implantable cardioverter defibrillator • Management • Multimodality imaging • Non-dilated left ventricular cardiomyopathy • Pregnancy • Restrictive cardiomyopathy • Risk stratification • Screening • Sports • Sudden cardiac death

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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;

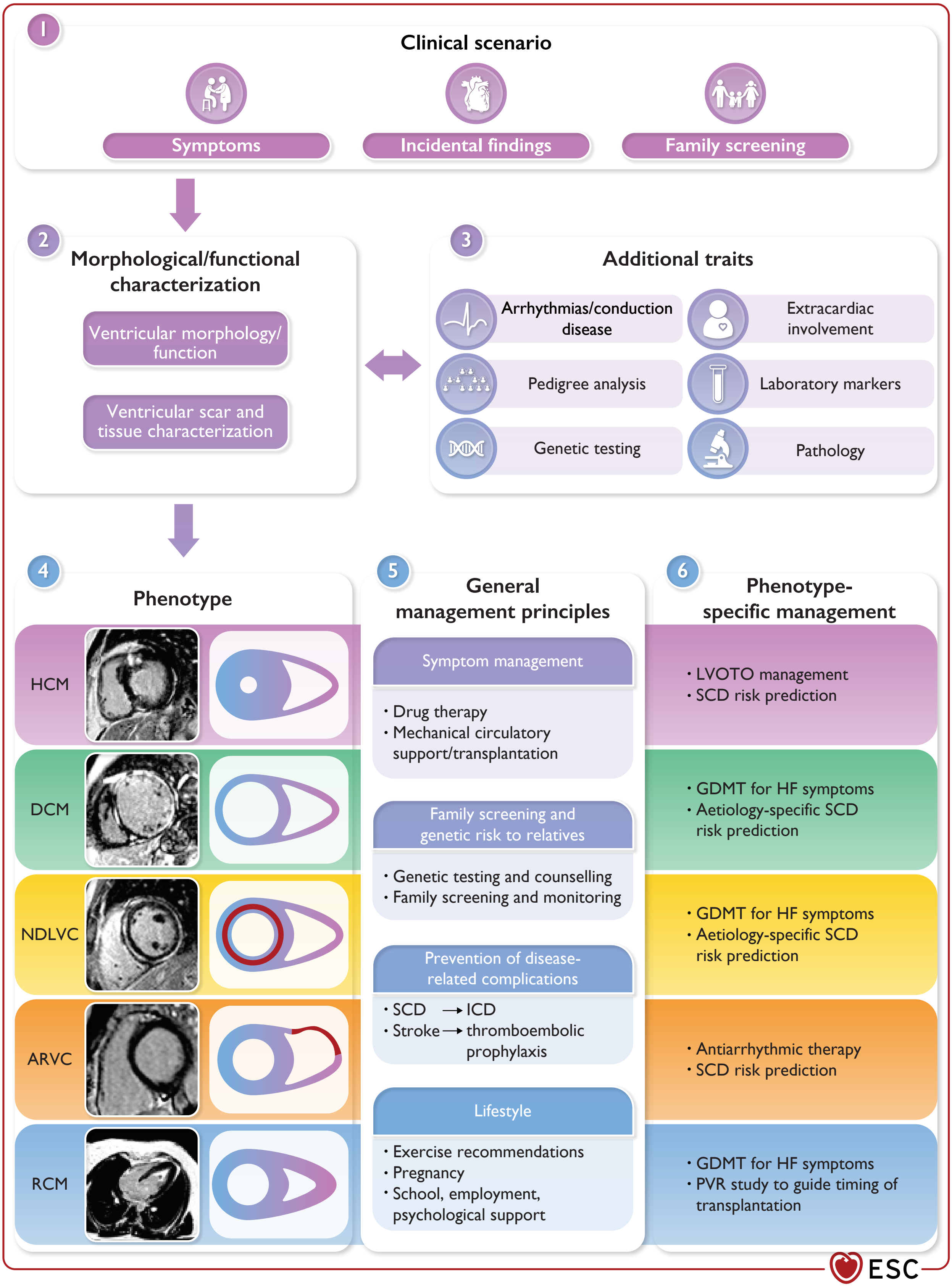

Figure 1 Central illustration. Key aspects in the evaluation and management of cardiomyopathies. ARVC, arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; GDMT, guideline-directed medical therapy; HCM, hypertrophic cardiomyopathy; HF, heart failure 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.

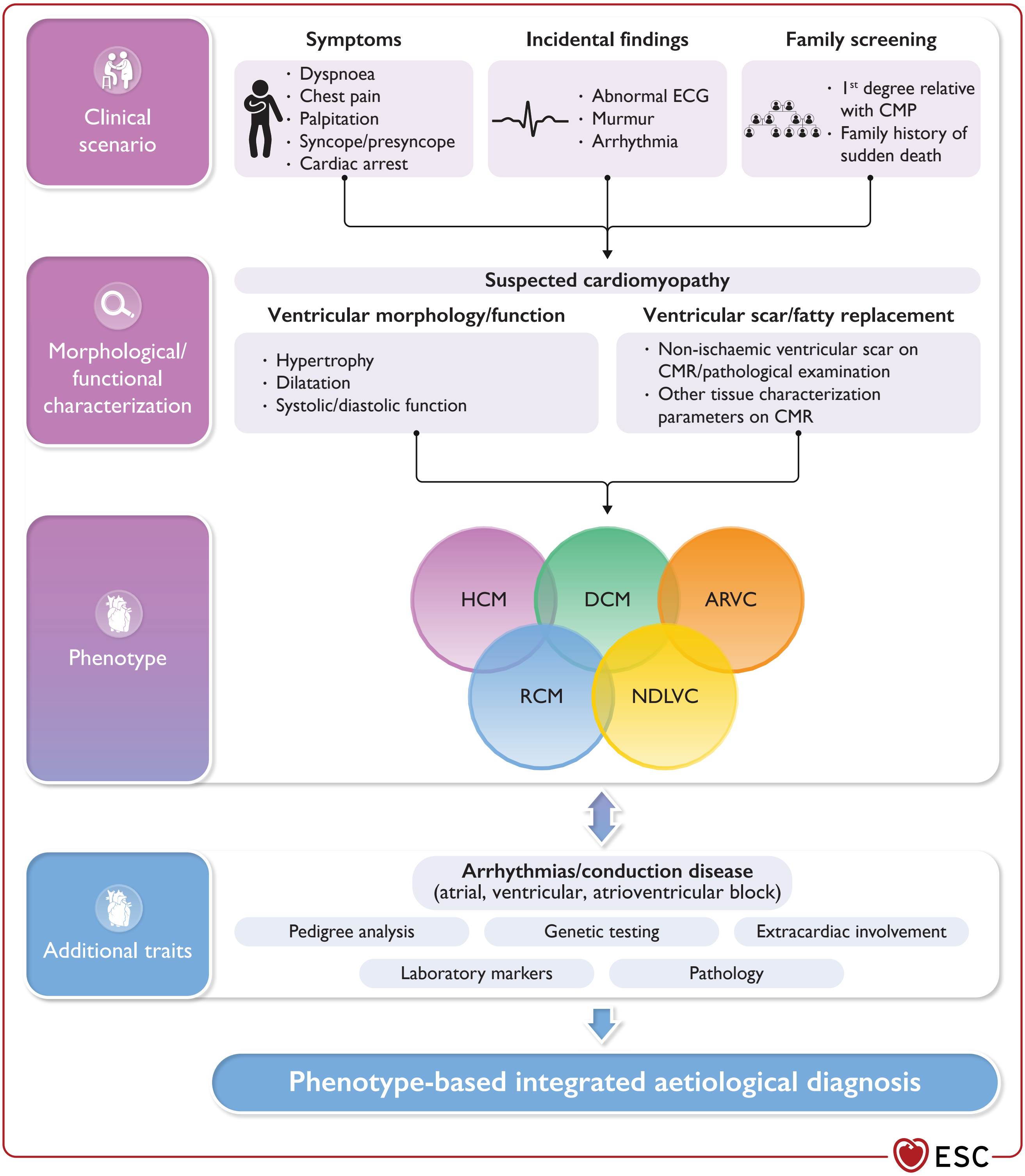

Figure 2 Clinical diagnostic workflow of cardiomyopathy. ARVC, arrhythmogenic right ventricular cardiomyopathy; CMP, cardiomyopathy; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; NDLVC, non-dilated left ventricular cardiomyopathy;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

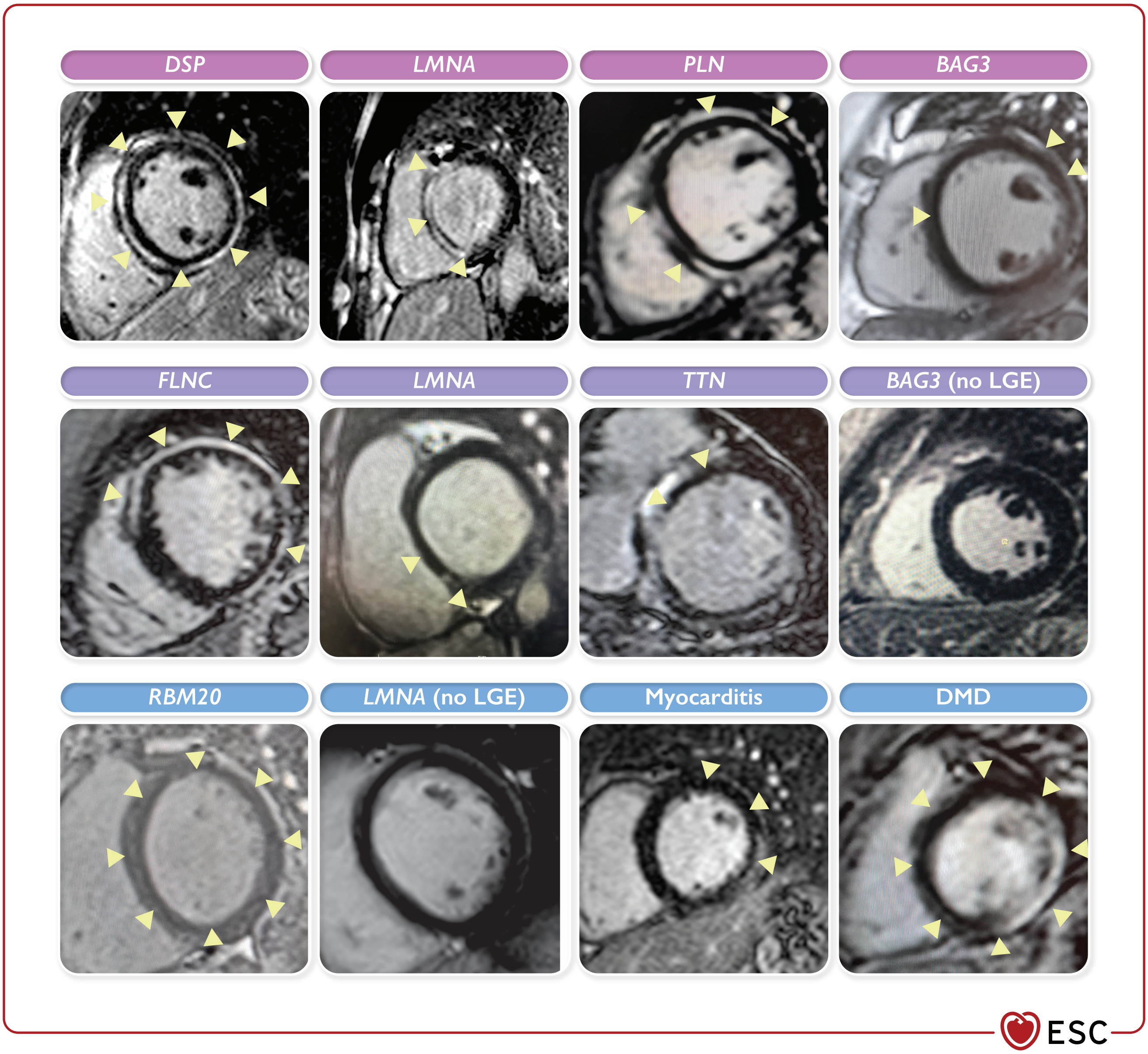

Figure 3 Examples of non-dilated left ventricular cardiomyopathy phenotypes and their aetiological correlates. BAG3, BAG cochaperone-3; DMD, Duchenne muscular dystrophy; DSP, desmoplakin; FLNC, filamin C; LGE, late gadolinium enhancement; LMNA, lamin A/C; NDLVC, non-dilated left ventricular cardiomyopathy; 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.

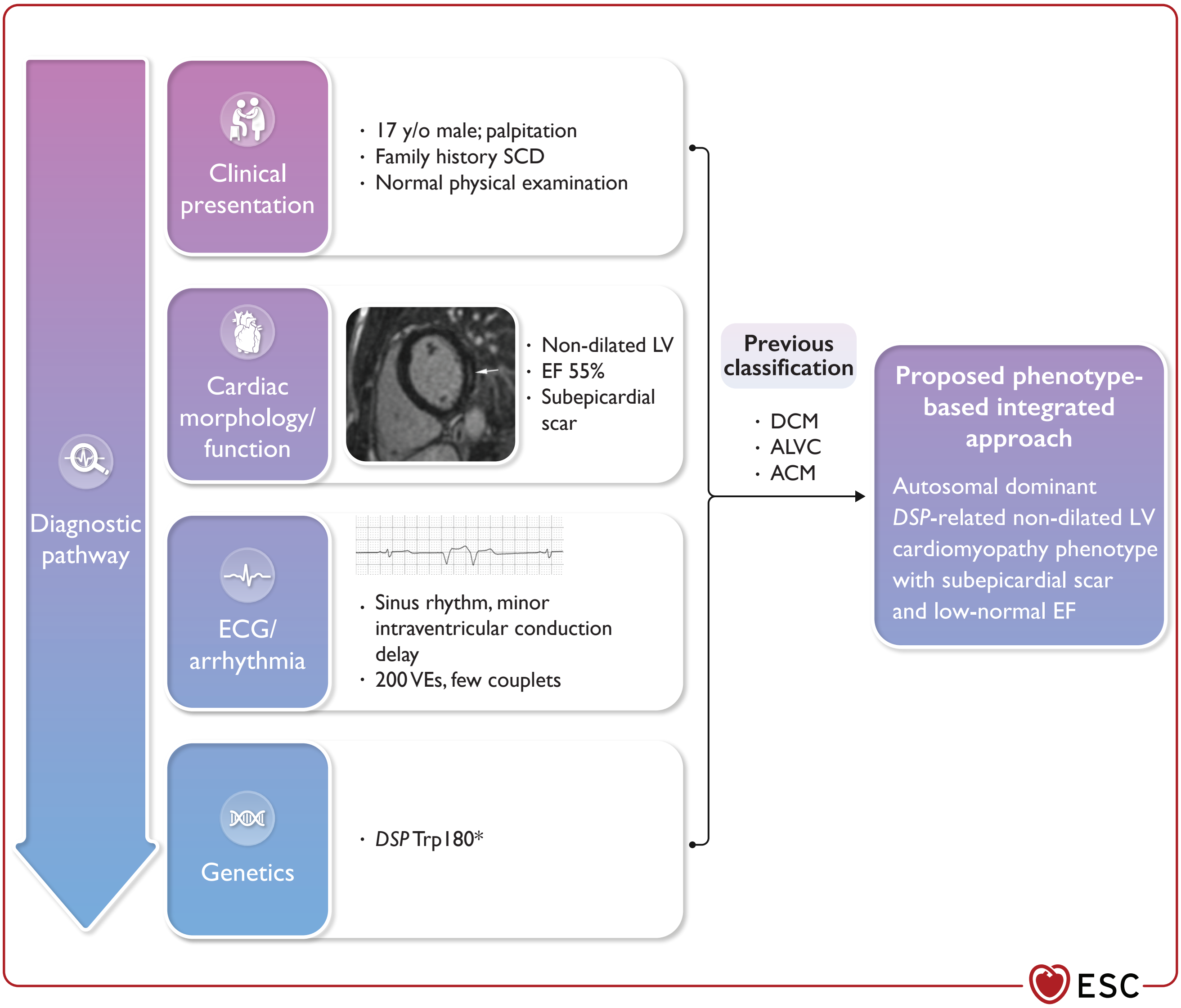

Figure 4 Worked example of the non-dilated left ventricular cardiomyopathy phenotype. ACM, arrhythmogenic cardiomyopathy; ALVC, arrhythmogenic left ventricular cardiomyopathy; DCM, dilated cardiomyopathy; *DSP*, desmoplakin; ECG, electrocardiogram; EF, ejection fraction; LV, left ventricular; NDLVC, 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]

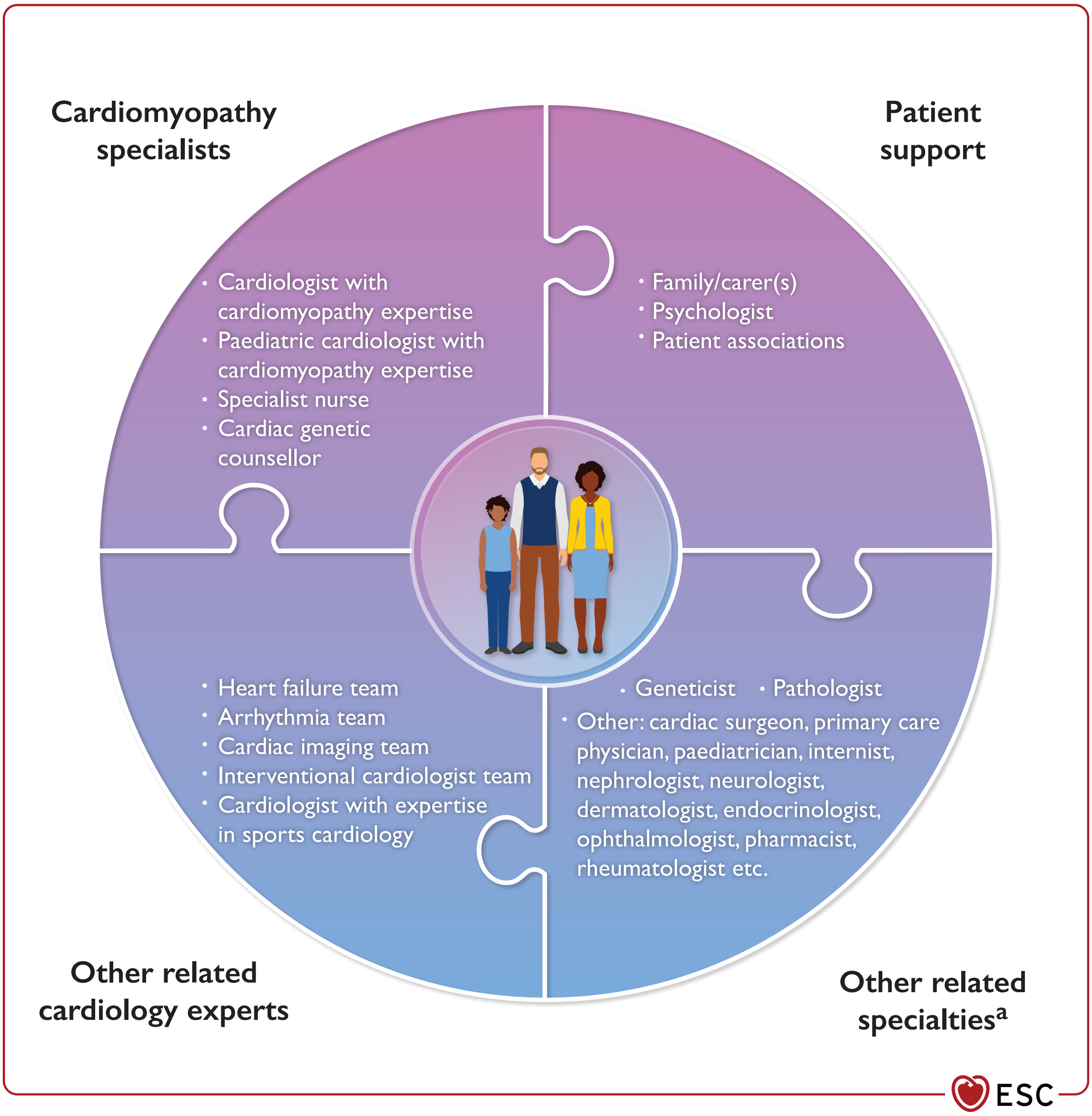

Figure 5 Multidisciplinary care of cardiomyopathies. [a]The list presented is not exhaustive and represents examples of specialties that often interact in the care of cardiomyopathy patients.

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

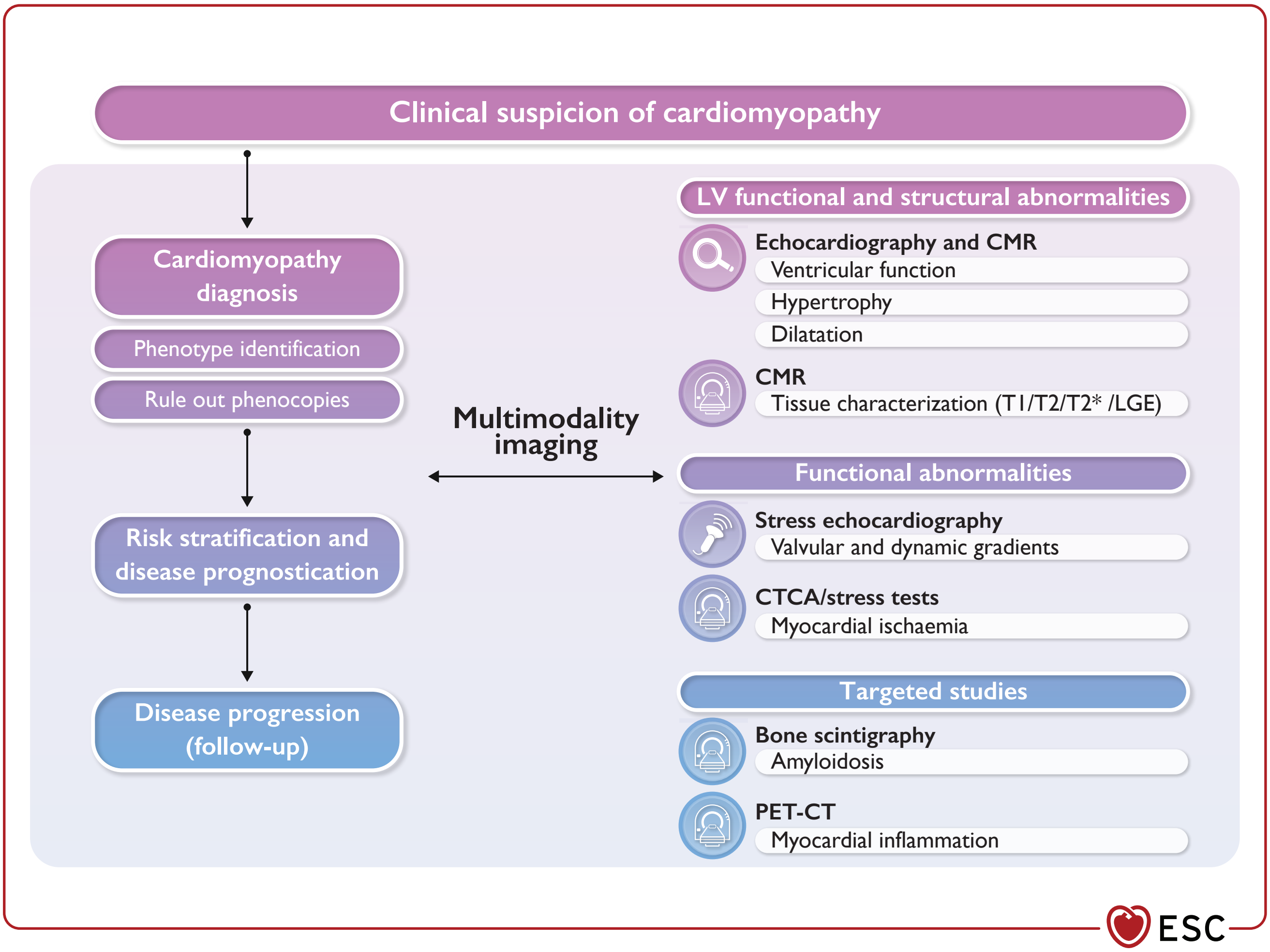

Figure 6 Multimodality imaging process in cardiomyopathies. CMR, cardiac magnetic resonance; CTCA, computed tomography coronary angiography; LGE, late gadolinium enhancement; LV, left ventricular; PET, positron emission tomography.

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.

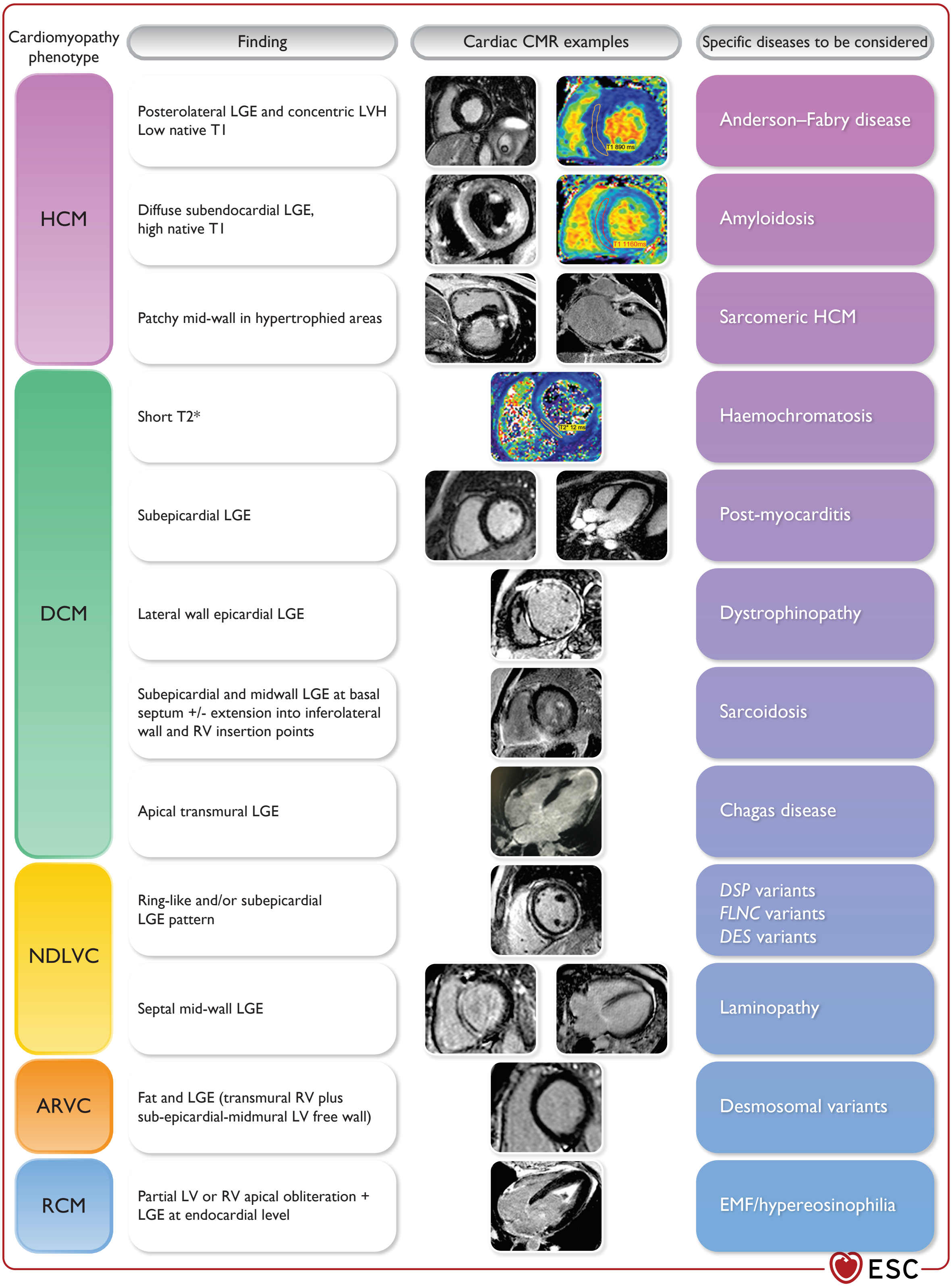

Figure 7 Examples of cardiac magnetic resonance imaging tissue characterization features that should raise the suspicion of specific aetiologies, grouped according to cardiomyopathy phenotype. ARVC, arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; *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)			● (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)		
DSG2		○ (white)		●● (dark blue)		
DSP	○ (white)	●● (dark blue)	● (grey)	● (dark blue)		
DTNA		○ (white)	● (grey)			
EYA4		○ (white)				
FHL1	● (dark blue)[c]					[c] Emery–Dreifuss MD
FLNC	● (dark blue)[c]	●● (dark blue)	● (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		o o 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	o o blue	light blue		white	grey	
TNNI3K		white				
TNNT2	o o o blue	o o blue	grey	white	grey	
TPM1	blue	light blue	grey	white	grey	
TRIM63	light blue					
TTN	white	o o o 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.

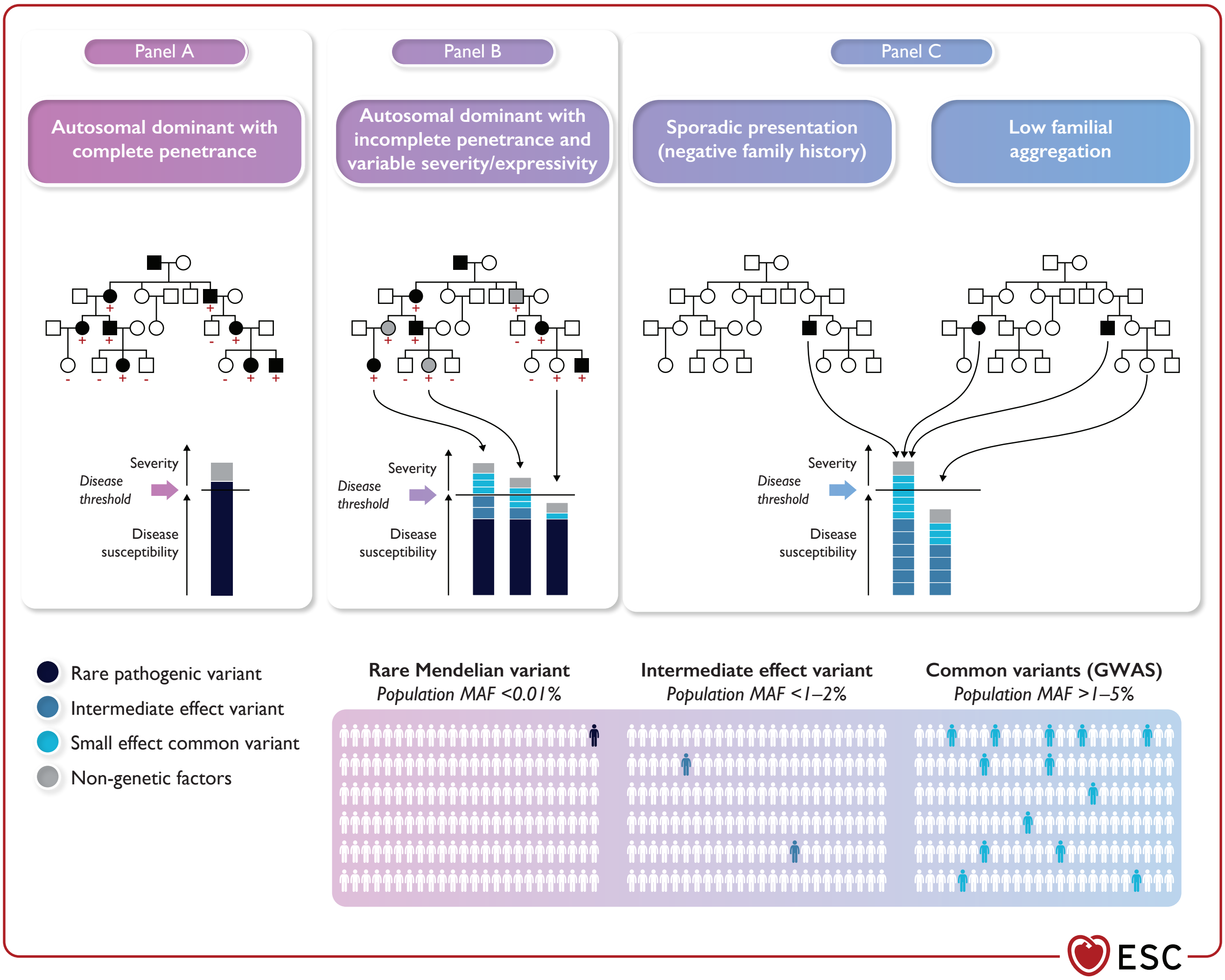

Figure 8 The genetic architecture of the cardiomyopathies. GWAS, genome-wide association studies; MAF, minor allele frequency. Cardiomyopathy can be Mendelian, caused by genetic variants that are ultra-rare in the general population and have large effect sizes. Such variants can display complete penetrance; 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

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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

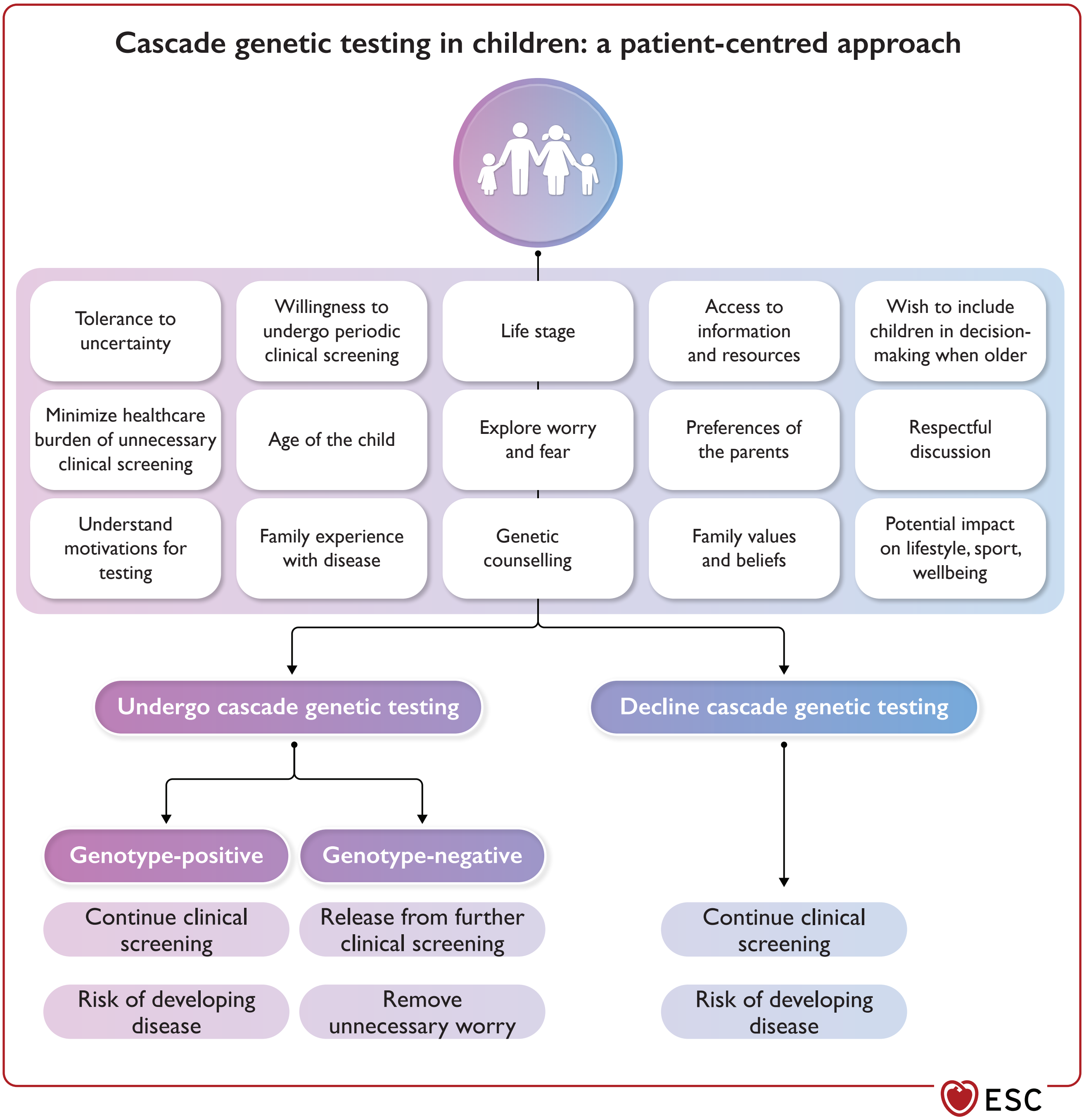

Figure 9 A patient-centred approach to cascade genetic testing of children. Factors to consider when supporting families to decide whether to pursue cascade genetic testing in children.

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

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).

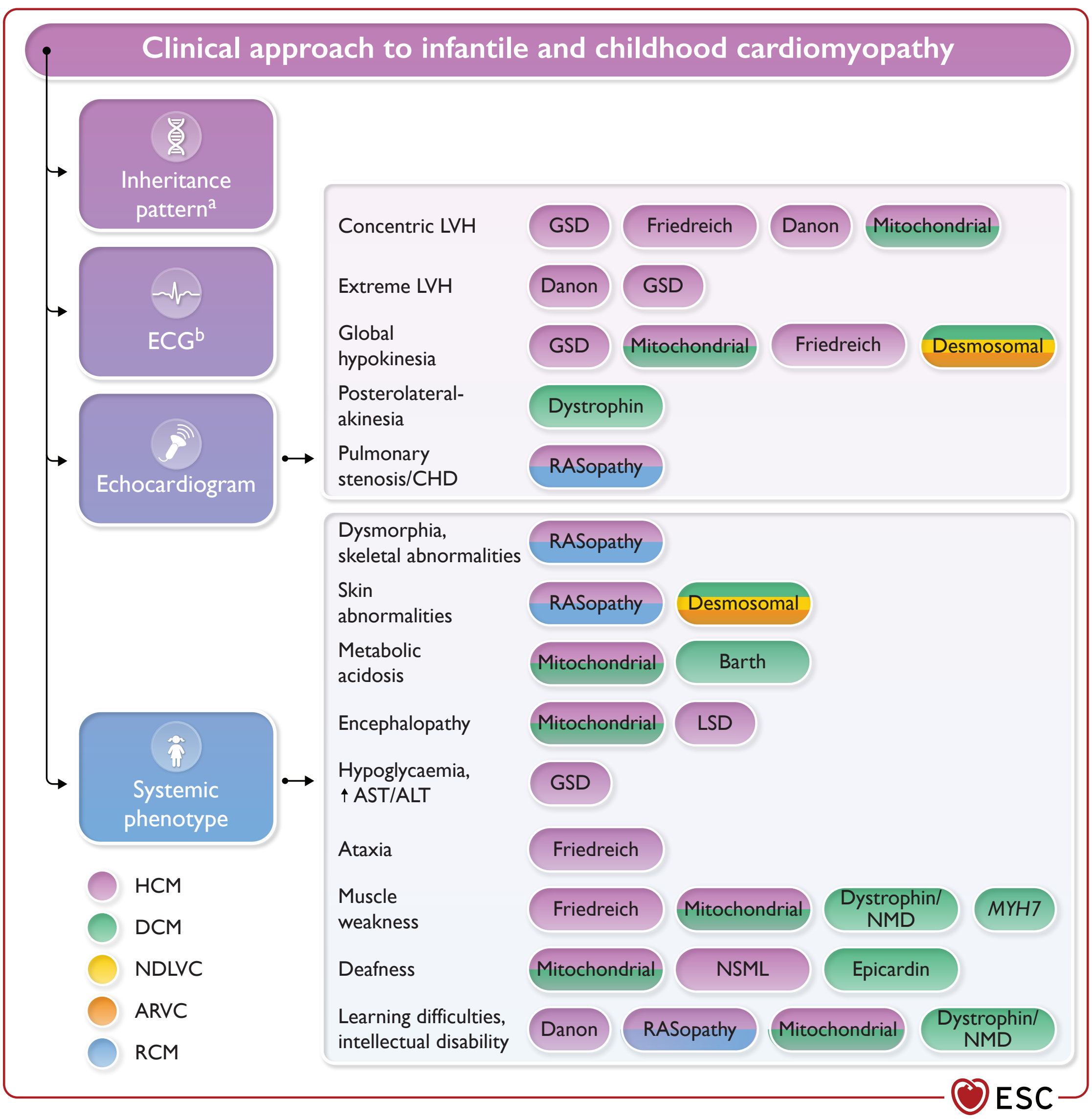

Figure 10 Clinical approach to infantile and childhood cardiomyopathy. ALT, alanine aminotransferase; ARVC, arrhythmogenic right ventricular cardiomyopathy; AST, aspartate transaminase; CHD, congenital heart disease; DCM, dilated cardiomyopathy; ECG, electrocardiogram; GSD, glycogen storage disorder; 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

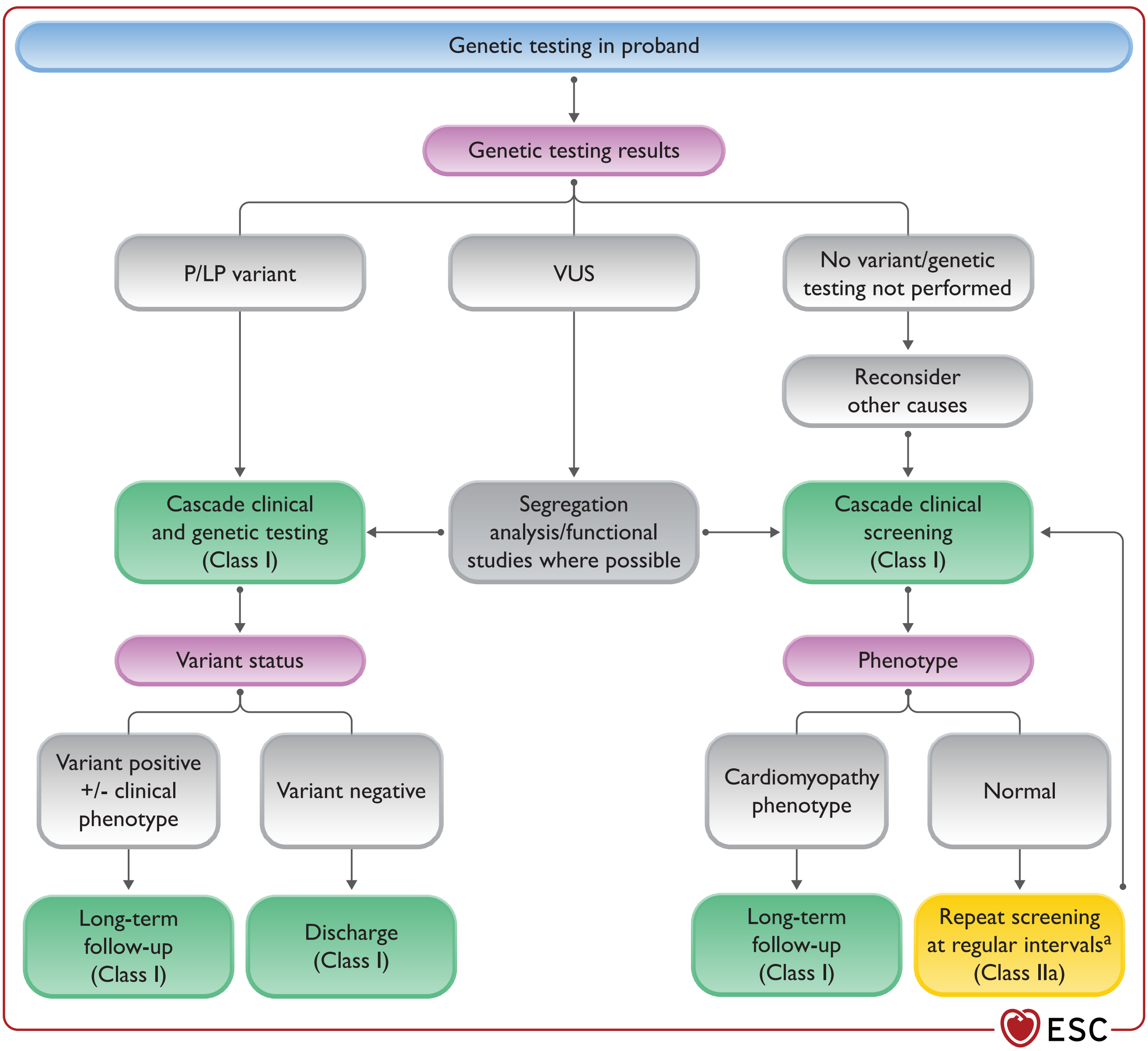

Figure 11 Algorithm for the approach to family screening and follow-up of family members. P/LP, pathogenic/likely pathogenic, VUS, variant of unknown significance. [a]If no additional affected relatives and no variant identified on genetic testing, consider earlier termination of clinical screening.

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]

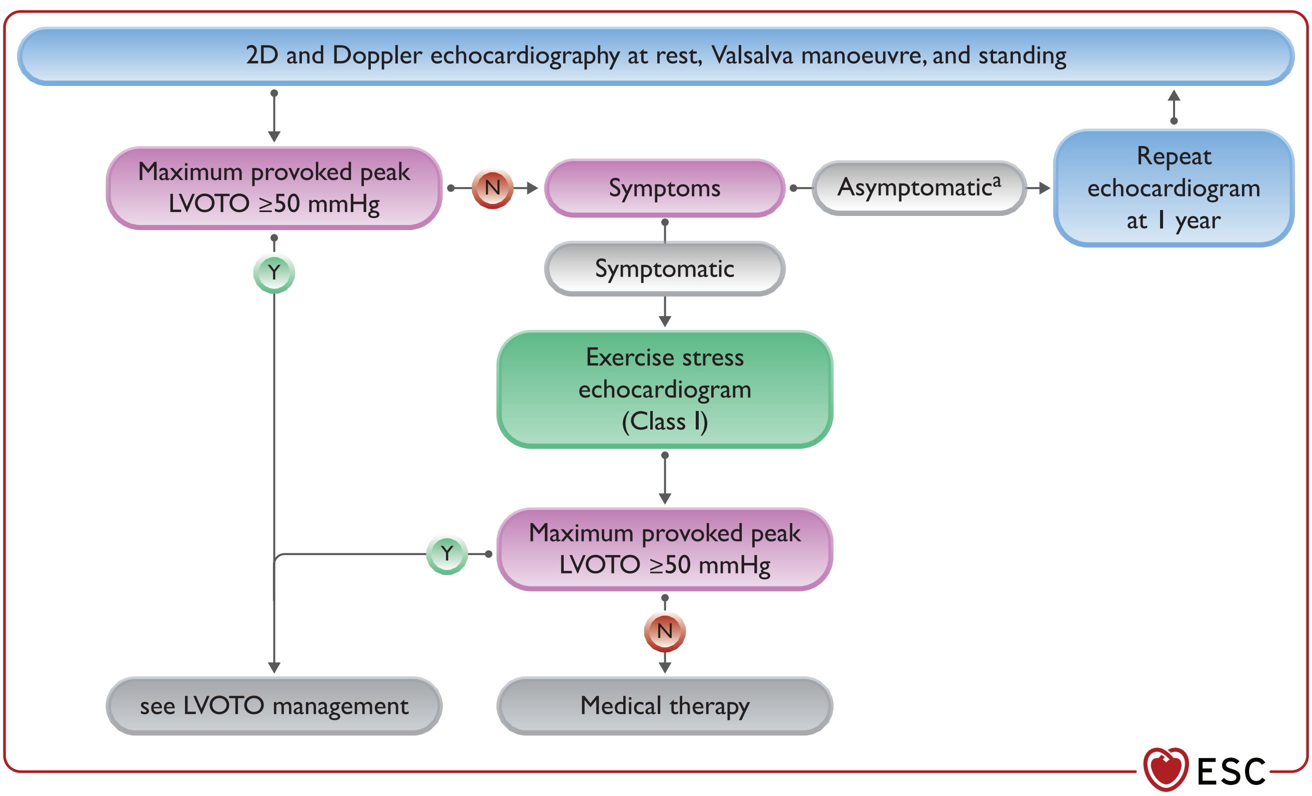

Figure 12 Protocol for the assessment and treatment of left ventricular outflow tract obstruction. 2D, two-dimensional; LVOTO, left ventricular outflow tract obstruction. [a]Exercise echocardiography may be considered in individual patients when the presence of an left ventricular outflow tract gradient 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*).

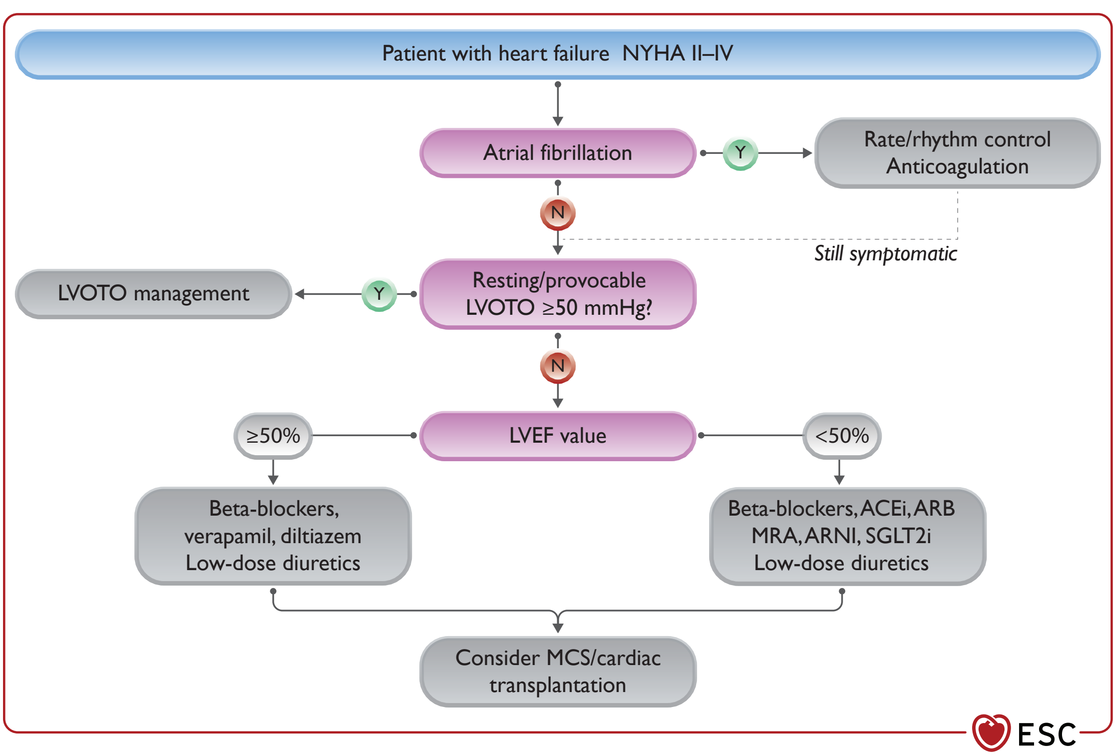

Figure 13 Algorithm for the treatment of heart failure in hypertrophic cardiomyopathy. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction;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

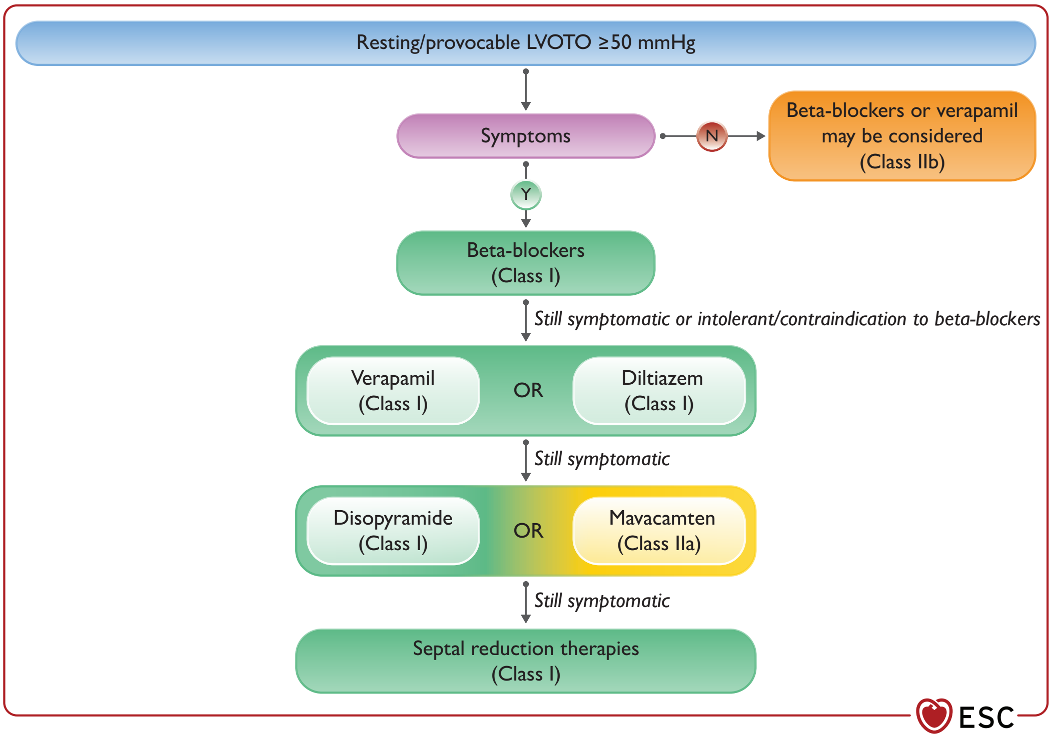

Figure 14 Flow chart on the management of left ventricular outflow tract obstruction. LVOTO, left ventricular outflow tract obstruction.

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

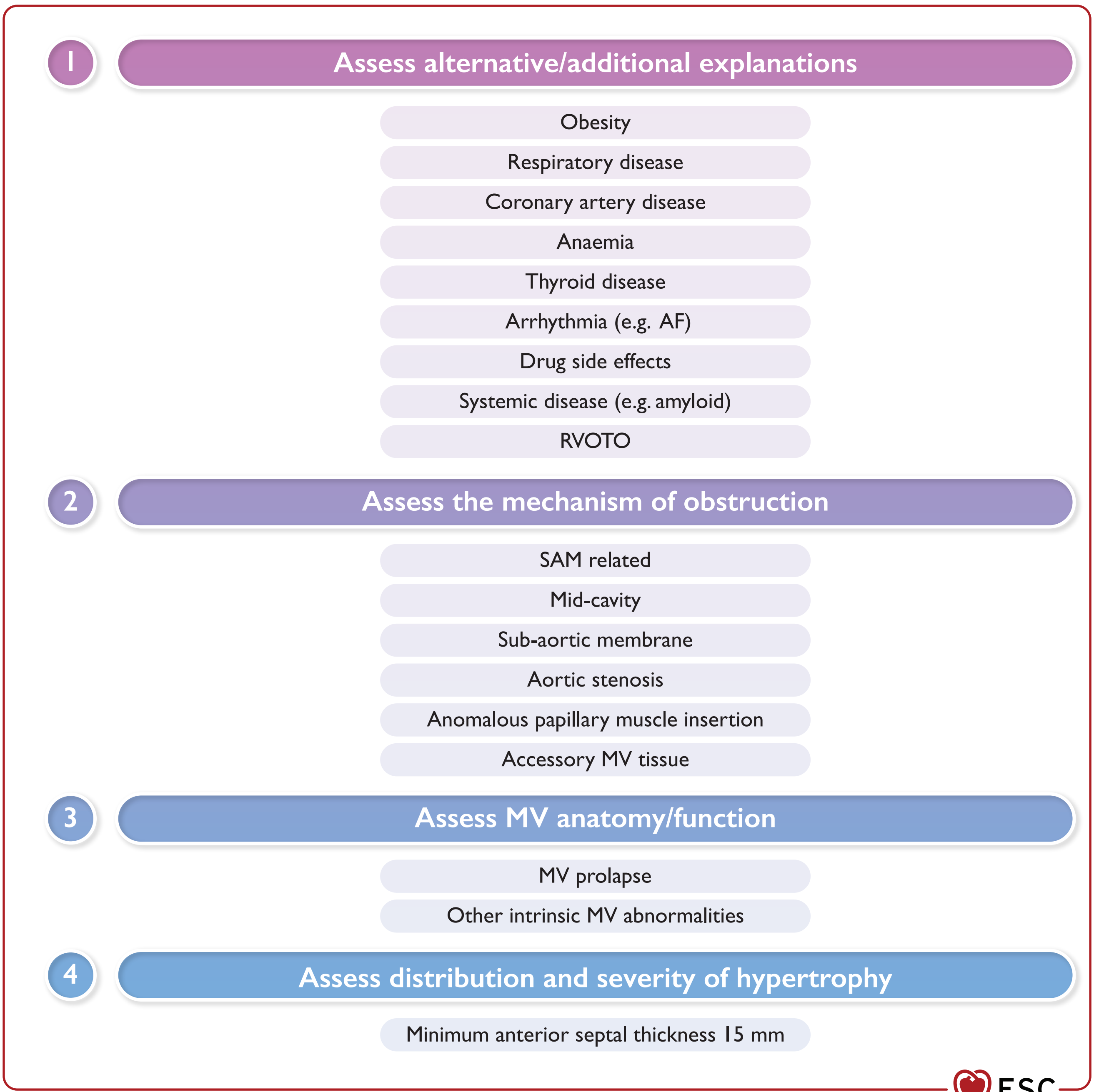

Figure 15 Pre-assessment checklist for patients being considered for invasive septal reduction therapies. AF, atrial fibrillation; MV, mitral valve; RVOTO, right ventricular outflow tract obstruction; SAM, systolic anterior motion.

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]

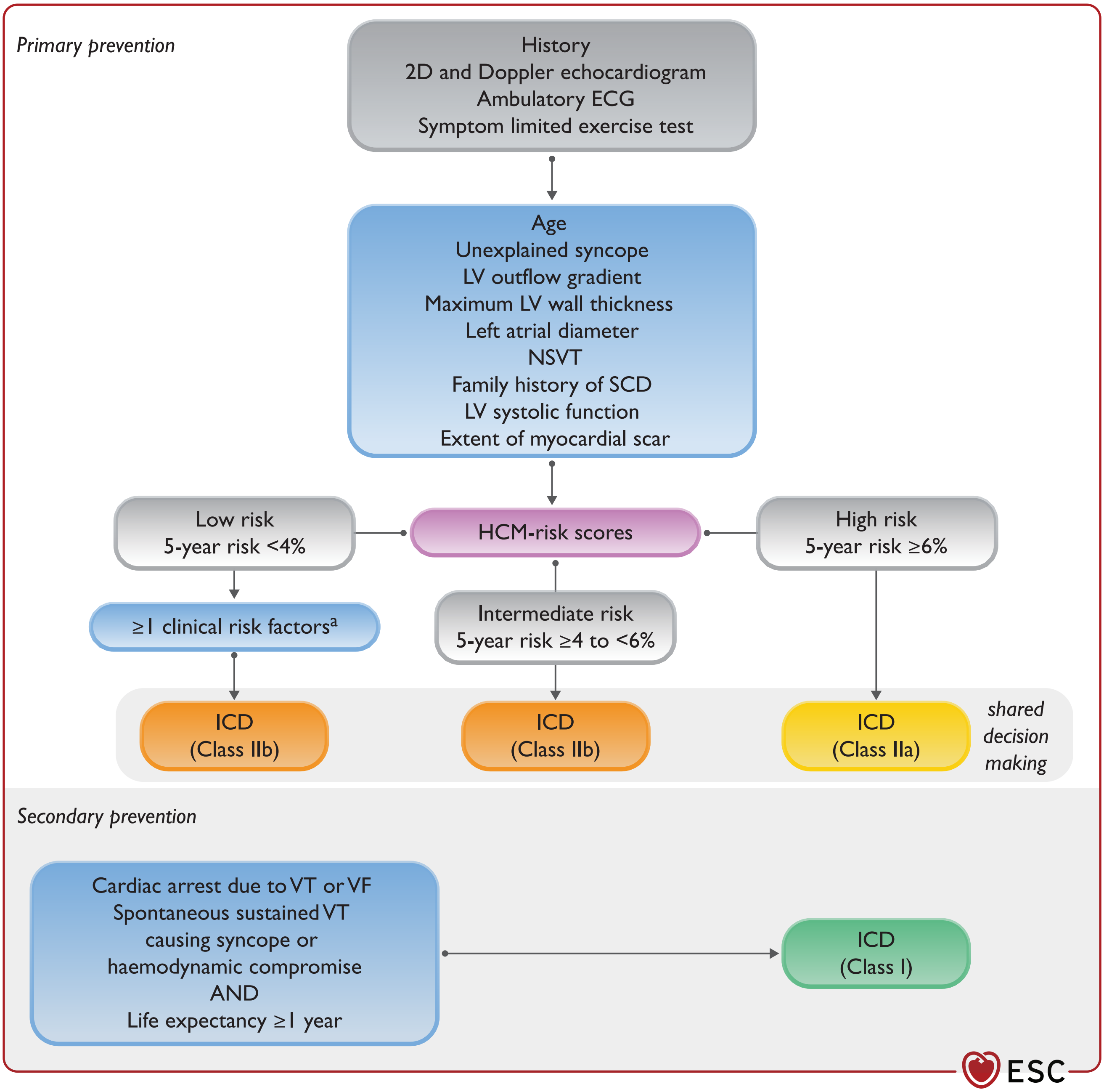

Figure 16 Flow chart for implantation of an implantable cardioverter defibrillator in patients with hypertrophic cardiomyopathy. 2D, two-dimensional; CMR, cardiac magnetic resonance; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LGE, late gadolinium 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

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*

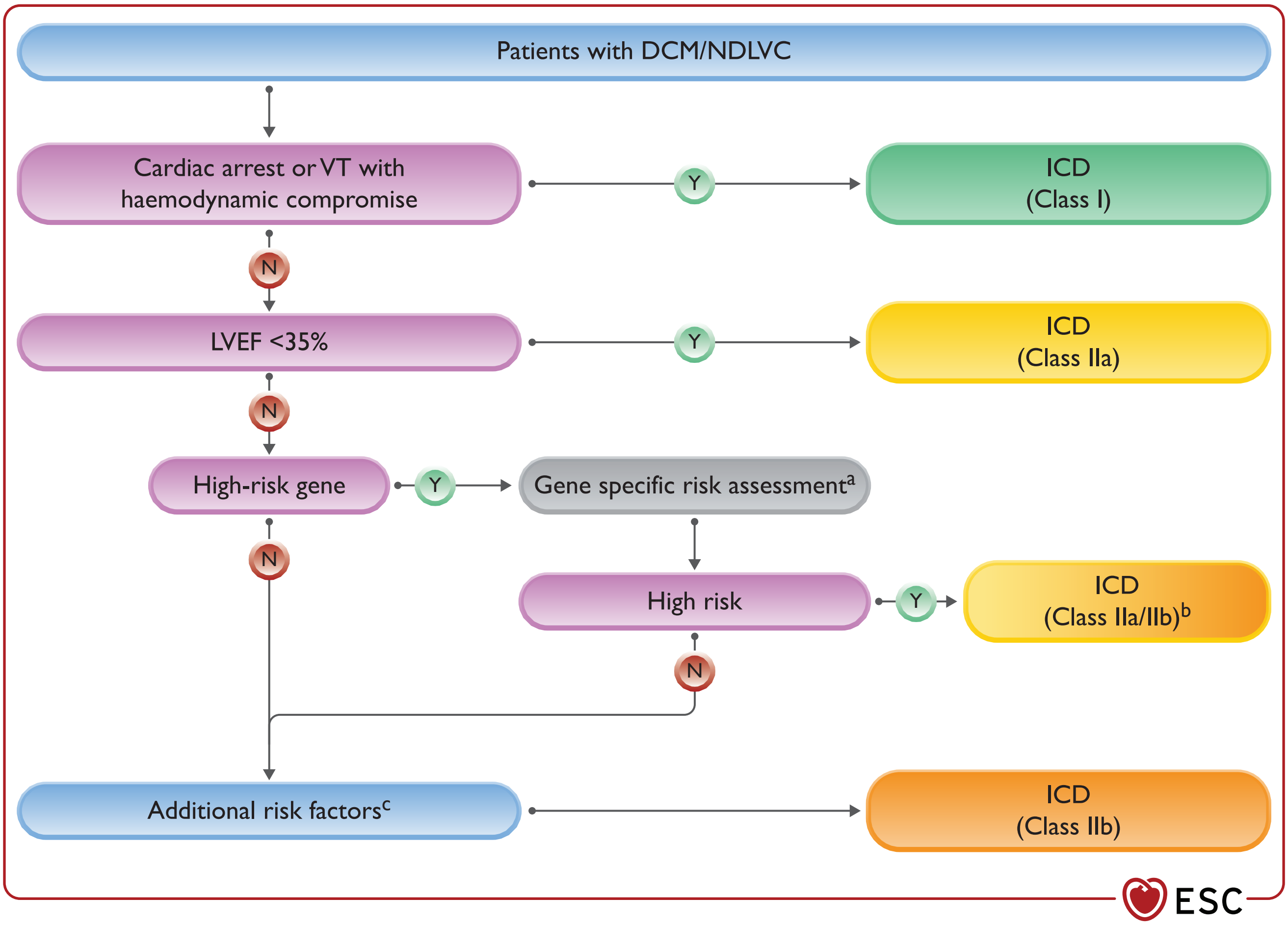

Figure 17 Implantation of implantable cardioverter defibrillators in patients with dilated cardiomyopathy or non-dilated left ventricular cardiomyopathy flowchart. CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; 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

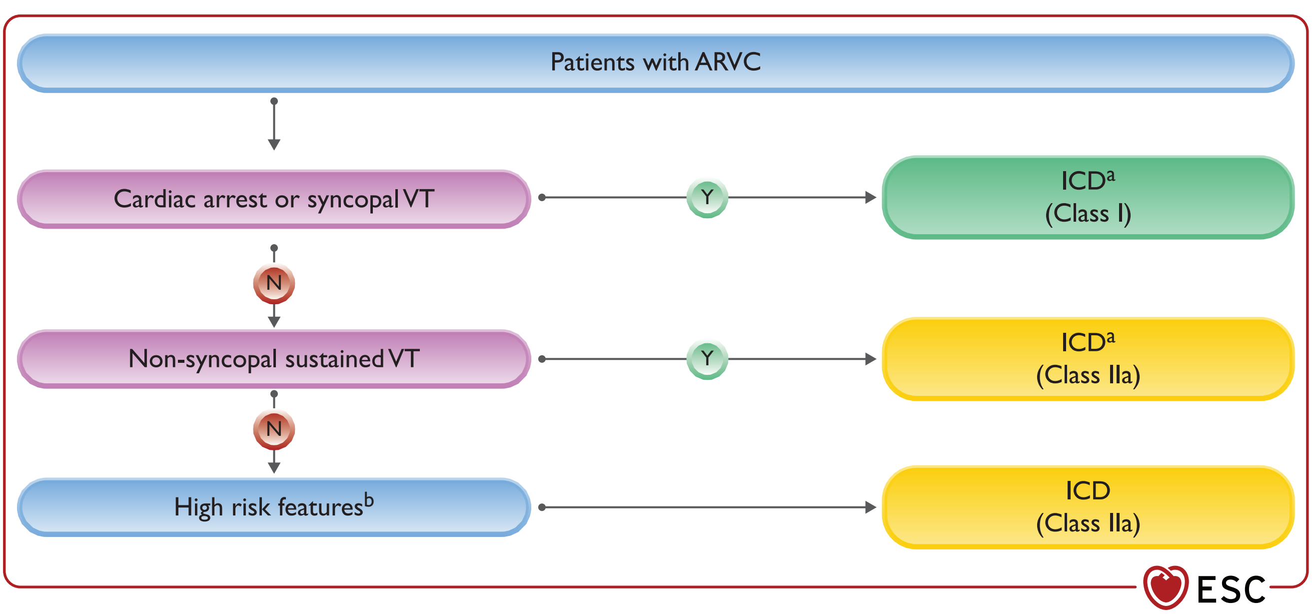

Figure 18 Algorithm to approach implantable cardioverter defibrillator decision-making in patients with arrhythmogenic right ventricular cardiomyopathy. ARVC, arrhythmogenic right ventricular cardiomyopathy; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NSVT, 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]

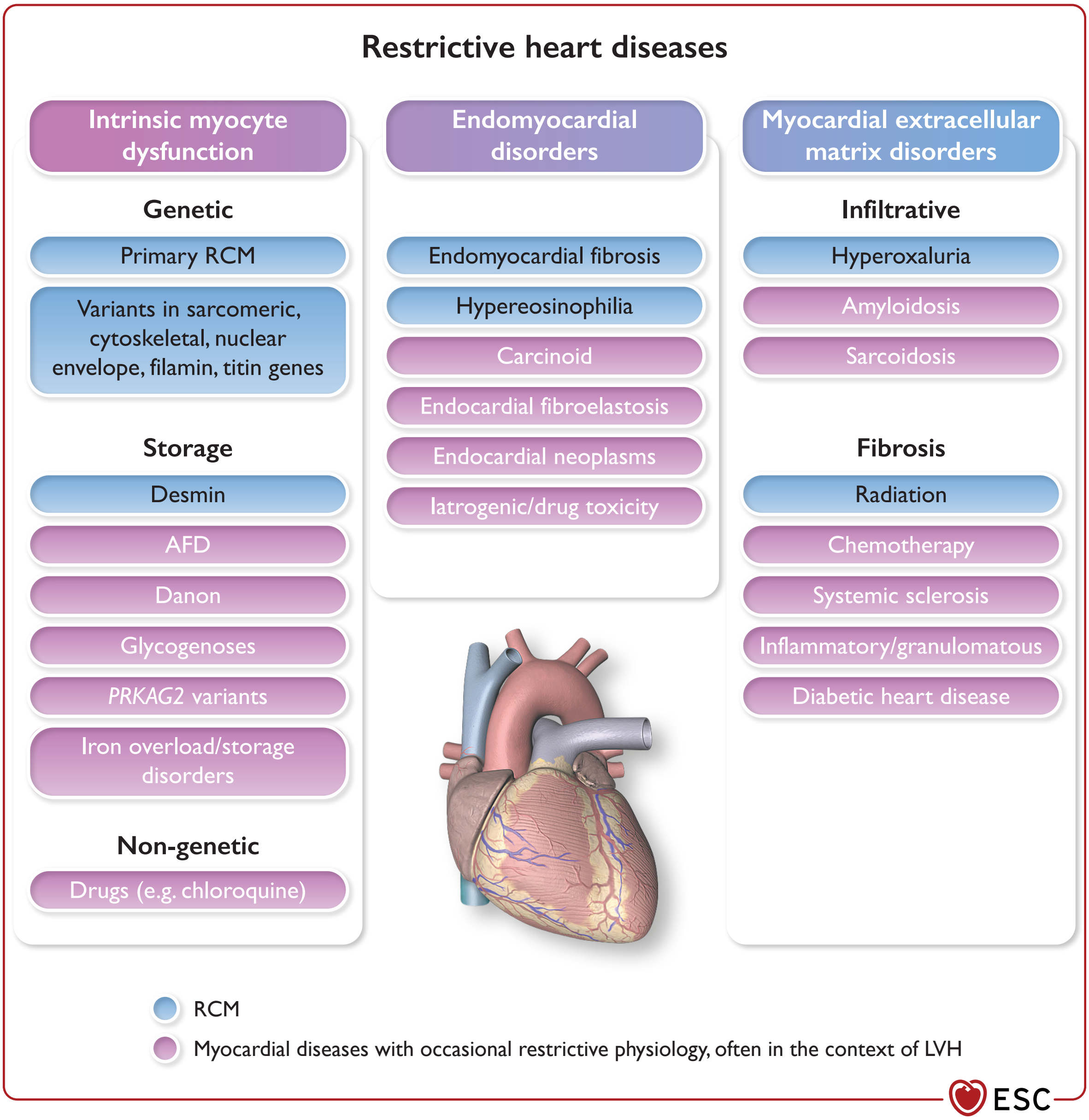

Figure 19 Spectrum of restrictive heart diseases. AFD, Anderson–Fabry disease; LVH, left ventricular hypertrophy; PRKAG2, Protein kinase AMP-activated non-catalytic subunit gamma 2; RCM, restrictive cardiomyopathy. For a more detailed spectrum of restrictive heart disease, please refer to Supplementary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

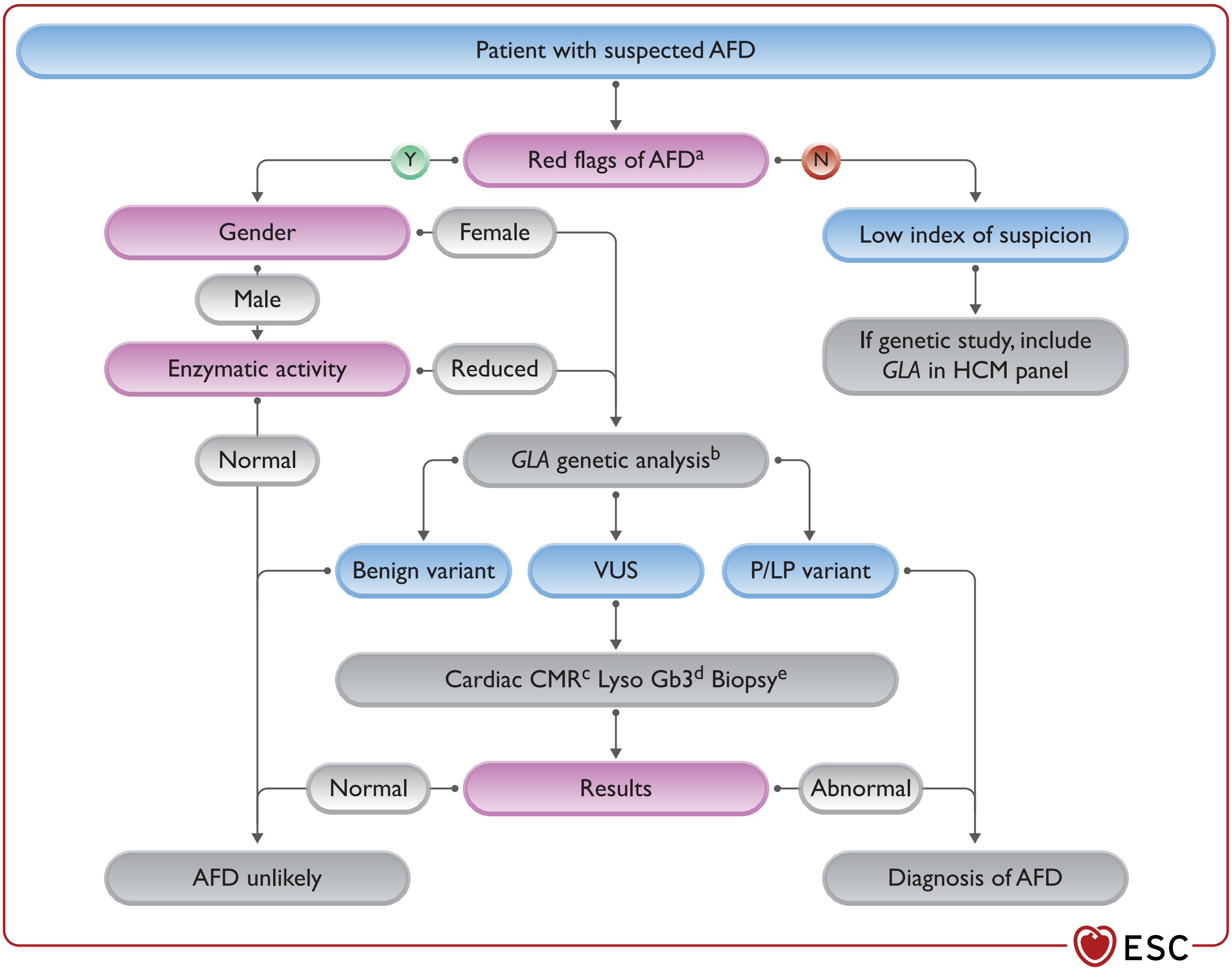

Figure 20 Anderson–Fabry disease diagnostic algorithm. α-Gal A, alpha-galactosidase A; AFD, Anderson–Fabry disease; CMR, cardiac magnetic resonance; Gb3, globotriaosylceramide; HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy; lyso Gb3, globotriaosylsphingosine; P/LP, pathogenic/likely 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

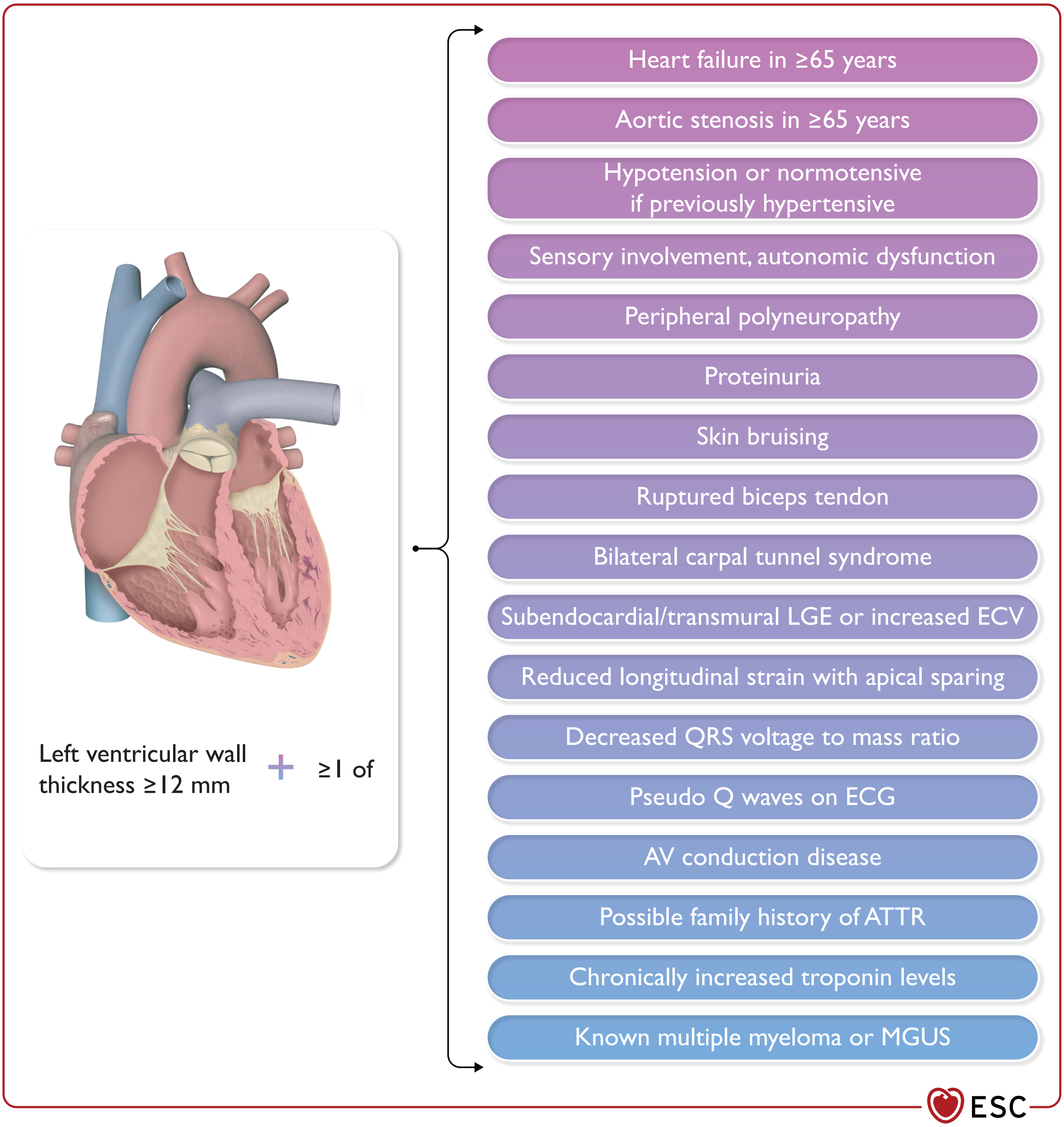

Figure 21 Screening for cardiac amyloidosis. ATTR, transthyretin amyloidosis; AV, atrioventricular; ECG, electrocardiogram; ECV, extracellular volume; LGE, late gadolinium enhancement; MGUS, monoclonal gammopathy of undetermined significance.

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

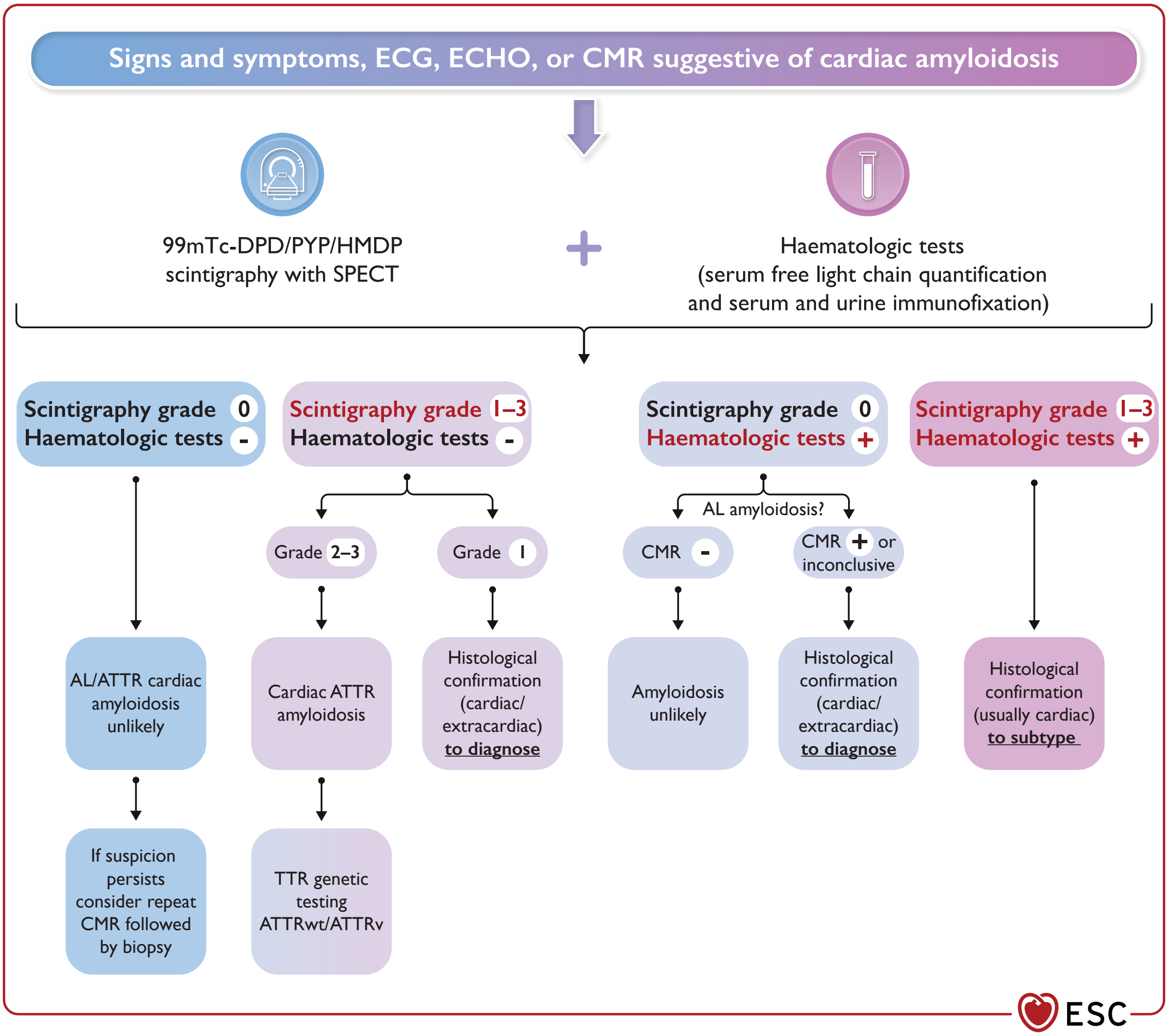

Figure 22 Diagnosis of cardiac amyloidosis. AL, amyloid light chain; ATTR, transthyretin amyloidosis; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CMR, cardiac magnetic resonance; DPD, 3,3-diphosphono-1,2-propanodicarboxylic acid; ECG, electrocardiogram; ECHO,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

19. Author information

Author/Task Force Member Affiliations: Alexandros Protonotarios, Centre for Heart Muscle Disease, UCL Institute of Cardiovascular Science, London, United Kingdom, Inherited Cardiovascular Disease Unit, St Bartholomew's Hospital, London, United Kingdom; **Juan R. Gimeno**, Inherited Heart Diseases Unit (CSUR /ERN), Hospital Universitario Virgen de la Arrixaca- IMIB-Universidad de Murcia, Murcia, Spain, European Reference Networks for rare, low prevalence and complex diseases of the heart, ERN GUARD-Heart, European Commission 6, Amsterdam, Netherlands; **Eloisa Arbustini**, Centre For Inherited Cardiovascular Diseases, IRCCS Foundation Policlinico San Matteo, Piazzale Golgi, 27100 Pavia, Italy; **Roberto Barriales-Villa,** Inherited Cardiovascular Diseases Unit, Cardiology Service, Complexo Hospitalario Universitario A Coruña (CHUAC), A Coruña, Spain, Instituto de Investigación Biomédica de A Coruña (INIBIC), Servizo Galego de Saúde (SERGAS), Universidade da Coruña, A Coruña, Spain, Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares, Instituto de Salud Carlos III, A Coruña, Spain; **Cristina Basso**, Department of Cardiac, Thoracic, Vascular Sciences and Public Health-University of Padua, Cardiovascular Pathology Unit-Azienda Ospedaliera, Padua, Italy; **Connie R. Bezzina**, Amsterdam UMC location University of Amsterdam, Department of experimental cardiology, Heart centre, Meibergdreef 9, Amsterdam, Netherlands, Amsterdam cardiovascular sciences, Heart failure and arrhythmias, Amsterdam, Netherlands, European Reference Networks for rare, low prevalence and complex diseases of the heart, ERN GUARD-Heart; **Elena Biagini,** Cardiology, IRCCS, Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, Cardiology, Centro di riferimento europeo delle malattie cardiovascolari, ERN GUARD-Heart, Bologna, Italy; **Nico A. Blom**, Paediatric Cardiology, Leiden University Medical Center, Leiden, Netherlands, Paediatric Cardiology, Amsterdam University Medical Center, Amsterdam, Netherlands; **Rudolf A. de Boer**, Erasmus Medical

Center, Department of Cardiology, Rotterdam, Netherlands; **Tim De Winter** (Belgium), ESC Patient Forum, Sophia Antipolis, France; **Perry M. Elliott**, UCL Institute of Cardiovascular Science University College London, London, United Kingdom, St. Bartholomew's Hospital, London, United Kingdom; **Marcus Flather**, Norwich Medical School, University of East Anglia, Norwich, United Kingdom, Department of Cardiology, Norfolk and Norwich University Hospital, Norwich, United Kingdom; **Pablo Garcia-Pavia**, Department of cardiology, Hospital Universitario Puerta de Hierro Majadahonda, IDIPHISA, CIBERCV, Madrid, Spain, Centro Nacional de Invstigaciones Cardiovasculares (CNIC), Madrid, Spain, European Reference Networks for rare, low prevalence and complex diseases of the heart, ERN GUARD-Heart, Madrid, Spain; **Kristina H. Haugaa**, Cardiology, Karolinska University Hospital, Stockholm, Sweden, Cardiology, Oslo University Hospital, Oslo, Norway; **Jodie Ingles**, Centre for Population Genomics, Garvan Institute of Medical Research, and UNSW Sydney, Sydney, Australia; **Ruxandra Oana Jurcut**, Expert Center for Rare Genetic Cardiovascular Diseases, Department of Cardiology, Emergency Institute of Cardiovascular Diseases “Prof.dr.C.C.Iliescu”, Bucharest, Romania, Cardiology, University of Medicine and Pharmacy “Carol Davila”, Bucharest, Romania; **Sabine Klaassen,** Experimental and Clinical Research Center, A Cooperation Between the Max Delbrück Center and Charité - Universitätsmedizin Berlin, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany, Congenital Heart Disease - Pediatric Cardiology, Deutsches Herzzentrum der Charité (DHZC), Berlin, Germany, DZHK (German Centre for Cardiovascular Research) partner site Berlin, Berlin, Germany; **Giuseppe Limongelli,** Translational Medical Sciences, University of Campania “Luigi Vanvitelli”, Naples, Italy, Cardiology, Monaldi Hospital - AORN Colli, Naples, Italy, European Reference Network for Rare, Low Prevalence, or Complex Diseases of the Heart (ERN GUARD-Heart); **Bart Loeys**, Center for medical genetics, Antwerp university hospital/university of Antwerp, Antwerp, Belgium, Department of human genetics, Radboud university medical center, Nijmegen, Netherlands; **Jens Mogensen,** Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark; **Iacopo Olivotto**, Meyer Children's Hospital IRCCS, University of Florence, Florence, Italy; **Antonis Pantazis**, Royal Brompton, and Harefield Hospitals, London, United Kingdom; **Sanjay Sharma**, St George's, University of London, London, United Kingdom, St George's University Hospital NHS Foundation Trust, London, United Kingdom; **J. Peter van Tintelen**, Department of Genetics, University Medical Center Utrecht, Utrecht, Netherlands; and **James S. Ware**, National Heart & Lung Institute, Imperial College London, London, United Kingdom, MRC London Institute of Medical Sciences, Imperial College London, London, United Kingdom, Royal Brompton & Harefield Hospitals, Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom.

20. Appendix

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21. Acknowledgements

The Task Force Chairs thank Sebastian Onciul for providing cardiac magnetic resonance images in Figure 7.

22. References

1. Authors/Task Force Members; Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, *et al.* 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;**35**:2733–2779. https://doi.org/10.1093/eurheartj/ehu284
2. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, *et al.* Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2008;**29**:270–276. https://doi.org/10.1093/eurheartj/ehm342
3. Wilde AAM, Semsarian C, Marquez MF, Shamloo AS, Ackerman MJ, Ashley EA, *et al.* 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. *Europace* 2022;**24**:1307–1367. https://doi.org/10.1093/europace/euac030
4. Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC, *et al.* 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm* 2019;**16**:e301–e372. https://doi.org/10.1016/j.hrthm.2019.05.007
5. Corrado D, Perazzolo Marra M, Zorzi A, Beffagna G, Cipriani A, Lazzari M, *et al.* Diagnosis of arrhythmogenic cardiomyopathy: the Padua criteria. *Int J Cardiol* 2020; **319**:106–114. https://doi.org/10.1016/j.ijcard.2020.06.005
6. Biesecker LG, Adam MP, Alkuraya FS, Amemiya AR, Bamshad MJ, Beck AE, *et al.* A dyadic approach to the delineation of diagnostic entities in clinical genomics. *Am J Hum Genet* 2021;**108**:8–15. https://doi.org/10.1016/j.ajhg.2020.11.013
7. Arbustini E, Narula N, Dec GW, Reddy KS, Greenberg B, Kushwaha S, *et al.* The MOGE(S) classification for a phenotype-genotype nomenclature of cardiomyopathy: endorsed by the World Heart Federation. *J Am Coll Cardiol* 2013;**62**:2046–2072. https://doi.org/10.1016/j.jacc.2013.08.1644
8. Disertori M, Quintarelli S, Grasso M, Pilotto A, Narula N, Favalli V, *et al.* Autosomal recessive atrial dilated cardiomyopathy with standstill evolution associated with mutation of Natriuretic Peptide Precursor A. *Circ Cardiovasc Genet* 2013;**6**:27–36. https://doi.org/10.1161/CIRCGENETICS.112.963520
9. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Bohm M, *et al.* Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. *Eur Heart J* 2016;**37**:1850–1858. https://doi.org/10.1093/eurheartj/ehv727
10. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, *et al.* Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. *Eur Heart J* 2010;**31**:806–14. https://doi.org/10.1093/eurheartj/ehq025
11. Rapezzi C, Aimo A, Barison A, Emdin M, Porcari A, Linhart A, *et al.* Restrictive cardiomyopathy: definition and diagnosis. *Eur Heart J* 2022;**43**:4679–4693. https://doi.org/10.1093/eurheartj/ehac543
12. van Waning JI, Caliskan K, Michels M, Schinkel AFL, Hirsch A, Dalinghaus M, *et al.* Cardiac phenotypes, genetics, and risks in familial noncompaction cardiomyopathy. *J Am Coll Cardiol* 2019;**73**:1601–1611. https://doi.org/10.1016/j.jacc.2018.12.085
13. Sedaghat-Hamedani F, Haas J, Zhu F, Geier C, Kayvanpour E, Liss M, *et al.* Clinical genetics and outcome of left ventricular non-compaction cardiomyopathy. *Eur Heart J* 2017;**38**:3449–3460. https://doi.org/10.1093/eurheartj/ehx545
14. Klaassen S, Probst S, Oechslin E, Gerull B, Krings G, Schuler P, *et al.* Mutations in sarcomere protein genes in left ventricular noncompaction. *Circulation* 2008;**117**: 2893–2901. https://doi.org/10.1161/CIRCULATIONAHA.107.746164
15. Probst S, Oechslin E, Schuler P, Greutmann M, Boye P, Knirsch W, *et al.* Sarcomere gene mutations in isolated left ventricular noncompaction cardiomyopathy do not predict clinical phenotype. *Circ Cardiovasc Genet* 2011;**4**:367–374. https://doi.org/10.1161/CIRCGENETICS.110.959270
16. Hoedemaekers YM, Caliskan K, Michels M, Frohn-Mulder I, van der Smagt JJ, Pfefferkorn JE. The importance of genetic counseling, DNA diagnostics, and cardiologic family screening in left ventricular noncompaction cardiomyopathy. *Circ Cardiovasc Genet* 2010;**3**:232–239. https://doi.org/10.1161/CIRCGENETICS.109.903898
17. Gati S, Papadakis M, Papamichael ND, Zaidi A, Sheikh N, Reed M, *et al.* Reversible de novo left ventricular trabeculations in pregnant women: implications for the diagnosis of left ventricular noncompaction in low-risk populations. *Circulation* 2014;**130**: 475–483. https://doi.org/10.1161/CIRCULATIONAHA.114.008554
18. Gati S, Chandra N, Bennett RL, Reed M, Kervio G, Panoulas VF, *et al.* Increased left ventricular trabeculation in highly trained athletes: do we need more stringent criteria for the diagnosis of left ventricular non-compaction in athletes? *Heart* 2013;**99**: 401–408. https://doi.org/10.1136/heartjnl-2012-303418
19. de la Chica JA, Gomez-Talavera S, Garcia-Ruiz JM, Garcia-Lunar I, Oliva B, Fernandez-Alvira JM, *et al.* Association between left ventricular noncompaction and vigorous physical activity. *J Am Coll Cardiol* 2020;**76**:1723–1733. https://doi.org/10.1016/j.jacc.2020.08.030
20. Jensen B, van der Wal AC, Moorman AFM, Christoffels VM. Excessive trabeculations in noncompaction do not have the embryonic identity. *Int J Cardiol* 2017;**227**:325–330. https://doi.org/10.1016/j.ijcard.2016.11.089
21. Faber JW, D'Silva A, Christoffels VM, Jensen B. Lack of morphometric evidence for ventricular compaction in humans. *J Cardiol* 2021;**78**:397–405. https://doi.org/10.1016/j.jjcc.2021.03.006
22. Anderson RH, Jensen B, Mohun TJ, Petersen SE, Aung N, Zemrak F, *et al.* Key questions relating to left ventricular noncompaction cardiomyopathy: is the emperor still wearing any clothes? *Can J Cardiol* 2017;**33**:747–757. https://doi.org/10.1016/j.cjca.2017.01.017
23. Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, *et al.* Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2016;**18**:8–27. https://doi.org/10.1002/ejhf.424
24. McKenna WJ, Maron BJ, Thiene G. Classification, epidemiology, and global burden of cardiomyopathies. *Circ Res* 2017;**121**:722–730. https://doi.org/10.1161/CIRCRESAHA.117.309711
25. Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. *Nat Rev Cardiol* 2013;**10**:531–547. https://doi.org/10.1038/nrcardio.2013.105
26. Hada Y, Sakamoto T, Amano K, Yamaguchi T, Takenaka K, Takahashi H, *et al.* Prevalence of hypertrophic cardiomyopathy in a population of adult Japanese workers as detected by echocardiographic screening. *Am J Cardiol* 1987;**59**:183–184. https://doi.org/10.1016/S0002-9149(87)80107-8
27. Agnarsson UT, Hardarson T, Hallgrimsson J, Sigfusson N. The prevalence of hypertrophic cardiomyopathy in men: an echocardiographic population screening study with a review of death records. *J Intern Med* 1992;**232**:499–506. https://doi.org/10.1111/j.1365-2796.1992.tb00623.x
28. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. *Circulation* 1995;**92**:785–789. https://doi.org/10.1161/01.CIR.92.4.785
29. Maron BJ, Mathenge R, Casey SA, Poliac LC, Longe TF. Clinical profile of hypertrophic cardiomyopathy identified de novo in rural communities. *J Am Coll Cardiol* 1999;**33**: 1590–1595. https://doi.org/10.1016/S0735-1097(99)00039-X
30. Maron BJ, Spirito P, Roman MJ, Paranicas M, Okin PM, Best LG, *et al.* Prevalence of hypertrophic cardiomyopathy in a population-based sample of American Indians aged 51 to 77 years (the Strong Heart Study). *Am J Cardiol* 2004;**93**:1510–1514. https://doi.org/10.1016/j.amjcard.2004.03.007
31. Zou Y, Song L, Wang Z, Ma A, Liu T, Gu H, *et al.* Prevalence of idiopathic hypertrophic cardiomyopathy in China: a population-based echocardiographic analysis of 8080 adults. *Am J Med* 2004;**116**:14–18. https://doi.org/10.1016/j.amjmed.2003.05.009

32. Maro EE, Janabi M, Kaushik R. Clinical and echocardiographic study of hypertrophic cardiomyopathy in Tanzania. *Trop Doct* 2006;**36**:225–227. https://doi.org/10.1258/004947506778604904
33. Basavarajaiah S, Wilson M, Whyte G, Shah A, McKenna W, Sharma S. Prevalence of hypertrophic cardiomyopathy in highly trained athletes: relevance to pre-participation screening. *J Am Coll Cardiol* 2008;**51**:1033–1039. https://doi.org/10.1016/j.jacc.2007.10.055
34. Nugent AW, Daubeney PE, Chondros P, Carlin JB, Cheung M, Wilkinson LC, *et al.* The epidemiology of childhood cardiomyopathy in Australia. *N Engl J Med* 2003;**348**:1639–1646. https://doi.org/10.1056/NEJMoa021737
35. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, *et al.* The incidence of pediatric cardiomyopathy in two regions of the United States. *N Engl J Med* 2003;**348**:1647–1655. https://doi.org/10.1056/NEJMoa021715
36. Arola A, Jokinen E, Ruuskanen O, Saraste M, Pesonen E, Kuusela AL, *et al.* Epidemiology of idiopathic cardiomyopathies in children and adolescents. A nationwide study in Finland. *Am J Epidemiol* 1997;**146**:385–393. https://doi.org/10.1093/oxfordjournals.aje.a009291
37. Codd MB, Sugrue DD, Gersh BJ, Melton LJ III. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy. A population-based study in Olmsted County, Minnesota, 1975–1984. *Circulation* 1989;**80**:564–572. https://doi.org/10.1161/01.CIR.80.3.564
38. Andrews RE, Fenton MJ, Ridout DA, Burch M. New-onset heart failure due to heart muscle disease in childhood: a prospective study in the United Kingdom and Ireland. *Circulation* 2008;**117**:79–84. https://doi.org/10.1161/CIRCULATIONAHA.106.671735
39. Peters S, Trümmel M, Meyners W. Prevalence of right ventricular dysplasia-cardiomyopathy in a non-referral hospital. *Int J Cardiol* 2004;**97**:499–501. https://doi.org/10.1016/j.ijcard.2003.10.037
40. Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. *JAMA* 2006;**296**:1593–1601. https://doi.org/10.1001/jama.296.13.1593
41. Migliore F, Zorzi A, Michieli P, Perazzolo Marra M, Siciliano M, Rigato I, *et al.* Prevalence of cardiomyopathy in Italian asymptomatic children with electrocardiographic T-wave inversion at preparticipation screening. *Circulation* 2012;**125**:529–538. https://doi.org/10.1161/CIRCULATIONAHA.111.055673
42. Ware JS, Amor-Salamanca A, Tayal U, Govind R, Serrano I, Salazar-Mendiguchia J, *et al.* Genetic etiology for alcohol-induced cardiac toxicity. *J Am Coll Cardiol* 2018;**71**:2293–2302. https://doi.org/10.1016/j.jacc.2018.03.462
43. Garcia-Pavia P, Kim Y, Restrepo-Cordoba MA, Lunde IG, Wakimoto H, Smith AM, *et al.* Genetic variants associated with cancer therapy-induced cardiomyopathy. *Circulation* 2019;**140**:31–41. https://doi.org/10.1161/CIRCULATIONAHA.118.037934
44. Ware JS, Li J, Mazaika E, Yasso CM, DeSouza T, Cappola TP, *et al.* Shared genetic predisposition in peripartum and dilated cardiomyopathies. *N Engl J Med* 2016;**374**:233–241. https://doi.org/10.1056/NEJMoa1505517
45. Goli R, Li J, Brandimarto J, Levine LD, Riis V, McAfee Q, *et al.* Genetic and phenotypic landscape of peripartum cardiomyopathy. *Circulation* 2021;**143**:1852–1862. https://doi.org/10.1161/CIRCULATIONAHA.120.052395
46. Doheny D, Srinivasan R, Pagant S, Chen B, Yasuda M, Desnick RJ. Fabry disease: prevalence of affected males and heterozygotes with pathogenic GLA mutations identified by screening renal, cardiac and stroke clinics, 1995–2017. *J Med Genet* 2018;**55**:261–268. https://doi.org/10.1136/jmedgenet-2017-105080
47. Tini G, Sessarego E, Benenati S, Vianello PF, Musumeci B, Autore C, *et al.* Yield of bone scintigraphy screening for transthyretin-related cardiac amyloidosis in different conditions: methodological issues and clinical implications. *Eur J Clin Invest* 2021;**51**:e13665. https://doi.org/10.1111/eci.13665
48. Aimo A, Merlo M, Porcari A, Georgiopoulos G, Pagura L, Vergaro G, *et al.* Redefining the epidemiology of cardiac amyloidosis. A systematic review and meta-analysis of screening studies. *Eur J Heart Fail* 2022;**24**:2342–2351. https://doi.org/10.1002/ejhf.2532
49. Lota AS, Hazebroek MR, Theotokis P, Wassall R, Salmi S, Halliday BP, *et al.* Genetic architecture of acute myocarditis and the overlap with inherited cardiomyopathy. *Circulation* 2022;**146**:1123–1134. https://doi.org/10.1161/CIRCULATIONAHA.121.058457
50. Tiron C, Campuzano O, Fernandez-Falgueras A, Alcalde M, Loma-Osorio P, Zamora E, *et al.* Prevalence of pathogenic variants in cardiomyopathy-associated genes in myocarditis. *Circ Genom Precis Med* 2022;**15**:e003408. https://doi.org/10.1161/CIRCGEN.121.003408
51. Seidel F, Holtgrewe M, Al-Wakeel-Marquard N, Opgen-Rhein B, Dartsch J, Herbst C, *et al.* Pathogenic variants associated with dilated cardiomyopathy predict outcome in pediatric myocarditis. *Circ Genom Precis Med* 2021;**14**:e003250. https://doi.org/10.1161/CIRCGEN.120.003250
52. Ammirati E, Raimondi F, Piriou N, Sardo Infirri L, Mohiddin SA, Mazzanti A, *et al.* Acute myocarditis associated with desmosomal gene variants. *JACC Heart Fail* 2022;**10**:714–727. https://doi.org/10.1016/j.jchf.2022.06.013
53. Cardim N, Freitas A, Brito D. From hypertrophic cardiomyopathy centers to inherited cardiovascular disease centers in Europe. A small or a major step? A position paper from the Nucleus of the Working Group on Myocardial and Pericardial Diseases of the Portuguese Society of Cardiology. *Rev Port Cardiol* 2011;**30**:829–835. https://doi.org/10.1016/j.repc.2011.09.005
54. Barriales-Villa R, Gimeno-Blanes JR, Zorio-Grima E, Ripoll-Vera T, Evangelista-Masip A, Moya-Mitjans A, *et al.* Plan of action for inherited cardiovascular diseases: synthesis of recommendations and action algorithms. *Rev Esp Cardiol* 2016;**69**:300–309. https://doi.org/10.1016/j.recesp.2015.11.031
55. Vriz O, AlSergani H, Elshaer AN, Shaik A, Mushtaq AH, Lioncino M, *et al.* A complex unit for a complex disease: the HCM-Family Unit. *Monaldi Arch Chest Dis* 2021;**92**. https://doi.org/10.4081/monaldi.2021.2147
56. Basso C, Aguilera B, Banner J, Cohle S, d'Amati G, de Gouveia RH, *et al.* Guidelines for autopsy investigation of sudden cardiac death: 2017 update from the Association for European Cardiovascular Pathology. *Virchows Arch* 2017;**471**:691–705. https://doi.org/10.1007/s00428-017-2221-0
57. Fellmann F, van El CG, Charron P, Michaud K, Howard HC, Boers SN, *et al.* European recommendations integrating genetic testing into multidisciplinary management of sudden cardiac death. *Eur J Hum Genet* 2019;**27**:1763–1773. https://doi.org/10.1038/s41431-019-0445-y
58. de Hosson M, Goossens PJJ, De Backer J, De Wolf D, Van Hecke A. Needs and experiences of adolescents with congenital heart disease and parents in the transitional process: a qualitative study. *J Pediatr Nurs* 2021;**61**:90–95. https://doi.org/10.1016/j.pedn.2021.03.016
59. de Hosson M, De Backer J, De Wolf D, De Groote K, Demulier L, Mels S, *et al.* Development of a transition program for adolescents with congenital heart disease. *Eur J Pediatr* 2020;**179**:339–348. https://doi.org/10.1007/s00431-019-03515-4
60. Tini G, Vianello PF, Rizzola G, La Malfa G, Porto I, Canepa M. Telehealth monitoring for hypertrophic cardiomyopathy and amyloid cardiomyopathy patients: lessons from the coronavirus disease 2019 lockdown in Italy. *J Cardiovasc Med* 2020;**21**:622–623. https://doi.org/10.2459/JCM.0000000000001024
61. Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011. In: The European Parliament and the Council of the European Union, (ed); 2011. https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52022DC0210 (5 April 2023 date last accessed).
62. Rapezzi C, Arbustini E, Caforio AL, Charron P, Gimeno-Blanes J, Helio T, *et al.* Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013;**34**:1448–1458. https://doi.org/10.1093/eurheartj/ehs397
63. Elliott P, Charron P, Blanes JR, Tavazzi L, Tendera M, Konte M, *et al.* European cardiomyopathy pilot registry: EURObservational research programme of the European Society of Cardiology. *Eur Heart J* 2016;**37**:164–173. https://doi.org/10.1093/eurheartj/ehv497
64. van Velzen HG, Schinkel AFL, Baart SJ, Oldenburg RA, Frohn-Mulder IME, van Slegtenhorst MA, *et al.* Outcomes of contemporary family screening in hypertrophic cardiomyopathy. *Circ Genom Precis Med* 2018;**11**:e001896. https://doi.org/10.1161/CIRCGEN.117.001896
65. Ranthe MF, Carstensen L, Oyen N, Jensen MK, Axelsson A, Wohlfahrt J, *et al.* Risk of cardiomyopathy in younger persons with a family history of death from cardiomyopathy: a nationwide family study in a cohort of 3.9 million persons. *Circulation* 2015;**132**:1013–1019. https://doi.org/10.1161/CIRCULATIONAHA.114.013478
66. Gimeno JR, Lacunza J, Garcia-Alberola A, Cerdan MC, Oliva MJ, Garcia-Molina E, *et al.* Penetrance and risk profile in inherited cardiac diseases studied in a dedicated screening clinic. *Am J Cardiol* 2009;**104**:406–410. https://doi.org/10.1016/j.amjcard.2009.03.055
67. Ploski R, Rydzanicz M, Ksiazczyk TM, Franaszczyk M, Pollak A, Kosinska J, *et al.* Evidence for troponin C (TNNC1) as a gene for autosomal recessive restrictive cardiomyopathy with fatal outcome in infancy. *Am J Med Genet A* 2016;**170**:3241–3248. https://doi.org/10.1002/ajmg.a.37860
68. Surmacz R, Franaszczyk M, Pyda M, Ploski R, Bilinska ZT, Bobkowski W. Autosomal recessive transmission of familial nonsyndromic dilated cardiomyopathy due to compound desmoplakin gene mutations. *Pol Arch Intern Med* 2018;**128**:785–787. https://doi.org/10.20452/pamw.4365
69. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–3726. https://doi.org/10.1093/eurheartj/ehab368
69a. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2023. https://doi.org/10.1093/eurheartj/ehad195. In press.
70. Bonny A, Lellouche N, Ditah I, Hidden-Lucet F, Yitemben MT, Granger B, *et al.* C-reactive protein in arrhythmogenic right ventricular dysplasia/cardiomyopathy and relationship with ventricular tachycardia. *Cardiol Res Pract* 2010;**2010**:919783. https://doi.org/10.4061/2010/919783
71. Donal E, Delgado V, Bucciarelli-Ducci C, Galli E, Haugaa KH, Charron P, *et al.* Multimodality imaging in the diagnosis, risk stratification, and management of patients with dilated cardiomyopathies: an expert consensus document from the European

Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2019;**20**: 1075–1093. https://doi.org/10.1093/ehjci/jez178
72. Haugaa KH, Basso C, Badano LP, Bucciarelli-Ducci C, Cardim N, Gaemperli O, *et al.* Comprehensive multi-modality imaging approach in arrhythmogenic cardiomyopathy–an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2017;**18**:237–253. https://doi.org/10.1093/ehjci/jew229
73. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**: 233–270. https://doi.org/10.1093/ehjci/jev014
74. Lancellotti P, Nkomo VT, Badano LP, Bergler-Klein J, Bogaert J, Davin L, *et al.* Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2013;**14**:721–740. https://doi.org/10.1093/ehjci/jet123
75. Charron P, Arad M, Arbustini E, Basso C, Bilinska Z, Elliott P, *et al.* Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2010;**31**:2715–2726. https://doi.org/10.1093/eurheartj/ehq271
76. Liu D, Hu K, Nordbeck P, Ertl G, Störk S, Weidemann F. Longitudinal strain bull's eye plot patterns in patients with cardiomyopathy and concentric left ventricular hypertrophy. *Eur J Med Res* 2016;**21**:21. https://doi.org/10.1186/s40001-016-0216-y
77. Haugaa KH, Hasselberg NE, Edvardsen T. Mechanical dispersion by strain echocardiography: a predictor of ventricular arrhythmias in subjects with lamin A/C mutations. *JACC Cardiovasc Imaging* 2015;**8**:104–106. https://doi.org/10.1016/j.jcmg.2014.04.029
78. Haugaa KH, Goebel B, Dahlslett T, Meyer K, Jung C, Lauten A, *et al.* Risk assessment of ventricular arrhythmias in patients with nonischemic dilated cardiomyopathy by strain echocardiography. *J Am Soc Echocardiogr* 2012;**25**:667–673. https://doi.org/10.1016/j.echo.2012.02.004
79. Leren IS, Saberniak J, Haland TF, Edvardsen T, Haugaa KH. Combination of ECG and echocardiography for identification of arrhythmic events in early ARVC. *JACC Cardiovasc Imaging* 2017;**10**:503–513. https://doi.org/10.1016/j.jcmg.2016.06.011
80. Haland TF, Almaas VM, Hasselberg NE, Saberniak J, Leren IS, Hopp E, *et al.* Strain echocardiography is related to fibrosis and ventricular arrhythmias in hypertrophic cardiomyopathy. *Eur Heart J Cardiovasc Imaging* 2016;**17**:613–621. https://doi.org/10.1093/ehjci/jew005
81. Norrish G, Ding T, Field E, Ziolkowska L, Olivotto I, Limongelli G, *et al.* Development of a novel risk prediction model for sudden cardiac death in childhood hypertrophic cardiomyopathy (HCM Risk-Kids). *JAMA Cardiol* 2019;**4**:918–927. https://doi.org/10.1001/jamacardio.2019.2861
82. Lopez L, Frommelt PC, Colan SD, Trachtenberg FL, Gongwer R, Stylianou M, *et al.* Pediatric heart network echocardiographic Z scores: comparison with other published models. *J Am Soc Echocardiogr* 2021;**34**:185–192. https://doi.org/10.1016/j.echo.2020.09.019
83. Adabag AS, Kuskowski MA, Maron BJ. Determinants for clinical diagnosis of hypertrophic cardiomyopathy. *Am J Cardiol* 2006;**98**:1507–1511. https://doi.org/10.1016/j.amjcard.2006.07.029
84. Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. *J Am Coll Cardiol* 1995;**26**:1699–1708. https://doi.org/10.1016/0735-1097(95)00390-8
85. Shapiro LM, McKenna WJ. Distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a two-dimensional echocardiographic study. *J Am Coll Cardiol* 1983;**2**: 437–444. https://doi.org/10.1016/S0735-1097(83)80269-1
86. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA, *et al.* Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 2003;**348**:295–303. https://doi.org/10.1056/NEJMoa021332
87. Nistri S, Olivotto I, Betocchi S, Losi MA, Valsecchi G, Pinamonti B, *et al.* Prognostic significance of left atrial size in patients with hypertrophic cardiomyopathy (from the Italian Registry for Hypertrophic Cardiomyopathy). *Am J Cardiol* 2006;**98**:960–965. https://doi.org/10.1016/j.amjcard.2006.05.013
88. Debonnaire P, Joyce E, Hiemstra Y, Mertens BJ, Atsma DE, Schalij MJ, *et al.* Left atrial size and function in hypertrophic cardiomyopathy patients and risk of new-onset atrial fibrillation. *Circ Arrhythm Electrophysiol* 2017;**10**:e004052. https://doi.org/10.1161/CIRCEP.116.004052
89. Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR, *et al.* Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. *Circulation* 2006;**114**:216–225. https://doi.org/10.1161/CIRCULATIONAHA.105.583500
90. Alba AC, Gaztanaga J, Foroutan F, Thavendiranathan P, Merlo M, Alonso-Rodriguez D, *et al.* Prognostic value of late gadolinium enhancement for the prediction of cardiovascular outcomes in dilated cardiomyopathy: an international, multi-institutional study of the MINICOR group. *Circ Cardiovasc Imaging* 2020;**13**:e010105. https://doi.org/10.1161/CIRCIMAGING.119.010105
91. Leong DP, Chakrabarty A, Shipp N, Molaee P, Madsen PL, Joerg L, *et al.* Effects of myocardial fibrosis and ventricular dyssynchrony on response to therapy in new-presentation idiopathic dilated cardiomyopathy: insights from cardiovascular magnetic resonance and echocardiography. *Eur Heart J* 2012;**33**:640–648. https://doi.org/10.1093/eurheartj/ehr391
92. Yoerger DM, Marcus F, Sherrill D, Calkins H, Towbin JA, Zareba W, *et al.* Echocardiographic findings in patients meeting task force criteria for arrhythmogenic right ventricular dysplasia: new insights from the multidisciplinary study of right ventricular dysplasia. *J Am Coll Cardiol* 2005;**45**:860–865. https://doi.org/10.1016/j.jacc.2004.10.070
93. Pieles GE, Grosse-Wortmann L, Hader M, Fatah M, Chungsomprasong P, Slorach C, *et al.* Association of echocardiographic parameters of right ventricular remodeling and myocardial performance with modified task force criteria in adolescents with arrhythmogenic right ventricular cardiomyopathy. *Circ Cardiovasc Imaging* 2019;**12**:e007693. https://doi.org/10.1161/CIRCIMAGING.118.007693
94. Mehta D, Lubitz SA, Frankel Z, Wisnivesky JP, Einstein AJ, Goldman M, *et al.* Cardiac involvement in patients with sarcoidosis: diagnostic and prognostic value of outpatient testing. *Chest* 2008;**133**:1426–1435. https://doi.org/10.1378/chest.07-2784
95. Skold CM, Larsen FF, Rasmussen E, Pehrsson SK, Eklund AG. Determination of cardiac involvement in sarcoidosis by magnetic resonance imaging and Doppler echocardiography. *J Intern Med* 2002;**252**:465–471. https://doi.org/10.1046/j.1365-2796.2002.01058.x
96. Joyce E, Ninaber MK, Katsanos S, Debonnaire P, Kamperidis V, Bax JJ, *et al.* Subclinical left ventricular dysfunction by echocardiographic speckle–tracking strain analysis relates to outcome in sarcoidosis. *Eur J Heart Fail* 2015;**17**:51–62. https://doi.org/10.1002/ejhf.205
97. Pagourelias ED, Mirea O, Duchenne J, Van Cleemput J, Delforge M, Bogaert J, *et al.* Echo parameters for differential diagnosis in cardiac amyloidosis: a head-to-head comparison of deformation and nondeformation parameters. *Circ Cardiovasc Imaging* 2017; **10**:e005588. https://doi.org/10.1161/CIRCIMAGING.116.005588
98. Phelan D, Collier P, Thavendiranathan P, Popovic ZB, Hanna M, Plana JC, *et al.* Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloidosis. *Heart* 2012;**98**:1442–1448. https://doi.org/10.1136/heartjnl-2012-302353
99. Linhart A, Kampmann C, Zamorano JL, Sunder-Plassmann G, Beck M, Mehta A, *et al.* Cardiac manifestations of Anderson–Fabry disease: results from the international Fabry outcome survey. *Eur Heart J* 2007;**28**:1228–1235. https://doi.org/10.1093/eurheartj/ehm153
100. Boldrini M, Cappelli F, Chacko L, Restrepo-Cordoba MA, Lopez-Sainz A, Giannoni A, *et al.* Multiparametric echocardiography scores for the diagnosis of cardiac amyloidosis. *JACC Cardiovasc Imaging* 2020;**13**:909–920. https://doi.org/10.1016/j.jcmg.2019.10.011
101. Pieroni M, Chimenti C, De Cobelli F, Morgante E, Del Maschio A, Gaudio C, *et al.* Fabry's disease cardiomyopathy: echocardiographic detection of endomyocardial glycosphingolipid compartmentalization. *J Am Coll Cardiol* 2006;**47**:1663–1671. https://doi.org/10.1016/j.jacc.2005.11.070
102. Zemrak F, Ahlman MA, Captur G, Mohiddin SA, Kawel-Boehm N, Prince MR, *et al.* The relationship of left ventricular trabeculation to ventricular function and structure over a 9.5-year follow-up: the MESA study. *J Am Coll Cardiol* 2014;**64**:1971–1980. https://doi.org/10.1016/j.jacc.2014.08.035
103. Steeden JA, Quail M, Gotschy A, Mortensen KH, Hauptmann A, Arridge S, *et al.* Rapid whole-heart CMR with single volume super-resolution. *J Cardiovasc Magn Reson* 2020; **22**:56. https://doi.org/10.1186/s12968-020-00651-x
104. Kiblboeck D, Reiter C, Kammler J, Schmit P, Blessberger H, Kellermair J, *et al.* Artefacts in 1.5 Tesla and 3 Tesla cardiovascular magnetic resonance imaging in patients with leadless cardiac pacemakers. *J Cardiovasc Magn Reson* 2018;**20**:47. https://doi.org/10.1186/s12968-018-0469-4
105. Rajiah P, Kay F, Bolen M, Patel AR, Landeras L. Cardiac magnetic resonance in patients with cardiac implantable electronic devices: challenges and solutions. *J Thorac Imaging* 2020;**35**:W1–W17. https://doi.org/10.1097/RTI.0000000000000462
106. Gandjbakhch E, Dacher JN, Taieb J, Chauvin M, Anselme F, Bartoli A, *et al.* Joint Position Paper of the Working Group of Pacing and Electrophysiology of the French Society of Cardiology and the French Society of Diagnostic and Interventional Cardiac and Vascular Imaging on magnetic resonance imaging in patients with cardiac electronic implantable devices. *Arch Cardiovasc Dis* 2020;**113**:473–484.
107. Nazarian S, Hansford R, Rahsepar AA, Weltin V, McVeigh D, Gucuk Ipek E, *et al.* Safety of magnetic resonance imaging in patients with cardiac devices. *N Engl J Med* 2017;**377**: 2555–2564. https://doi.org/10.1056/NEJMoa1604267
108. Russo RJ, Costa HS, Silva PD, Anderson JL, Arshad A, Biederman RW, *et al.* Assessing the risks associated with MRI in patients with a pacemaker or defibrillator. *N Engl J Med* 2017;**376**:755–764. https://doi.org/10.1056/NEJMoa1603265
109. Gakenheimer-Smith L, Etheridge SP, Niu MC, Ou Z, Presson AP, Whitaker P, *et al.* MRI in pediatric and congenital heart disease patients with CIEDs and epicardial or abandoned leads. *Pacing Clin Electrophysiol* 2020;**43**:797–804. https://doi.org/10.1111/pace.13984

110. Vigen KK, Reeder SB, Hood MN, Steckner M, Leiner T, Dombroski DA, *et al.* Recommendations for imaging patients with cardiac implantable electronic devices (CIEDs). *J Magn Reson Imaging* 2021;**53**:1311–1317. https://doi.org/10.1002/jmri.27320
111. Bhuva AN, Feuchter P, Hawkins A, Cash L, Boubertakh R, Evanson J, *et al.* MRI for patients with cardiac implantable electronic devices: simplifying complexity with a 'one-stop' service model. *BMJ Qual Saf* 2019;**28**:853–858. https://doi.org/10.1136/bmjqs-2018-009079
112. Seewoster T, Lobe S, Hilbert S, Bollmann A, Sommer P, Lindemann F, *et al.* Cardiovascular magnetic resonance imaging in patients with cardiac implantable electronic devices: best practice and real-world experience. *Europace* 2019;**21**:1220–1228. https://doi.org/10.1093/europace/euz112
113. Stühlinger M, Burri H, Vernooy K, Garcia R, Lenarczyk R, Sultan A, *et al.* EHRA consensus on prevention and management of interference due to medical procedures in patients with cardiac implantable electronic devices. *Europace* 2022;**24**: 1512–1537. https://doi.org/10.1093/europace/euac040
114. Primary P, Ian Paterson D, White JA, Butler CR, Connelly KA, Guerra PG, *et al.* 2021 Update on safety of magnetic resonance imaging: joint statement from Canadian Cardiovascular Society/Canadian Society for Cardiovascular Magnetic Resonance/ Canadian Heart Rhythm Society. *Can J Cardiol* 2021;**37**:835–847. https://doi.org/10.1016/j.cjca.2021.02.012
115. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, *et al.* Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: a consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). *J Cardiovasc Magn Reson* 2017;**19**:75. https://doi.org/10.1186/s12968-017-0389-8
116. Baggiano A, Boldrini M, Martinez-Naharro A, Kotecha T, Petrie A, Rezk T, *et al.* Noncontrast magnetic resonance for the diagnosis of cardiac amyloidosis. *JACC Cardiovasc Imaging* 2020;**13**:69–80. https://doi.org/10.1016/j.jcmg.2019.03.026
117. Nordin S, Kozor R, Vijapurapu R, Augusto JB, Knott KD, Captur G, *et al.* Myocardial storage, inflammation, and cardiac phenotype in Fabry disease after one year of enzyme replacement therapy. *Circ Cardiovasc Imaging* 2019;**12**:e009430. https://doi.org/10.1161/CIRCIMAGING.119.009430
118. Ray JG, Vermeulen MJ, Bharatha A, Montanera WJ, Park AL. Association between MRI exposure during pregnancy and fetal and childhood outcomes. *JAMA* 2016;**316**: 952–961. https://doi.org/10.1001/jama.2016.12126
119. Andreini D, Dello Russo A, Pontone G, Mushtaq S, Conte E, Perchinunno M, *et al.* CMR for identifying the substrate of ventricular arrhythmia in patients with normal echocardiography. *JACC Cardiovasc Imaging* 2020;**13**:410–421. https://doi.org/10.1016/j.jcmg.2019.04.023
120. Halliday BP, Baksi AJ, Gulati A, Ali A, Newsome S, Izgi C, *et al.* Outcome in dilated cardiomyopathy related to the extent, location, and pattern of late gadolinium enhancement. *JACC Cardiovasc Imaging* 2019;**12**:1645–1655. https://doi.org/10.1016/j.jcmg.2018.07.015
121. Barison A, Aimo A, Ortalda A, Todiere G, Grigoratos C, Passino C, *et al.* Late gadolinium enhancement as a predictor of functional recovery, need for defibrillator implantation and prognosis in non-ischemic dilated cardiomyopathy. *Int J Cardiol* 2018; **250**:195–200. https://doi.org/10.1016/j.ijcard.2017.10.043
122. Holmstrom M, Kivisto S, Helio T, Jurkko R, Kaartinen M, Antila M, *et al.* Late gadolinium enhanced cardiovascular magnetic resonance of lamin A/C gene mutation related dilated cardiomyopathy. *J Cardiovasc Magn Reson* 2011;**13**:30. https://doi.org/10.1186/1532-429X-13-30
123. Olivotto I, Maron MS, Autore C, Lesser JR, Rega L, Casolo G, *et al.* Assessment and significance of left ventricular mass by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2008;**52**:559–566. https://doi.org/10.1016/j.jacc.2008.04.047
124. Neubauer S, Kolm P, Ho CY, Kwong RY, Desai MY, Dolman SF, *et al.* Distinct subgroups in hypertrophic cardiomyopathy in the NHLBI HCM registry. *J Am Coll Cardiol* 2019;**74**:2333–2345. https://doi.org/10.1016/j.jacc.2019.08.1057
125. Miller RJH, Heidary S, Pavlovic A, Schlachter A, Dash R, Fleischmann D, *et al.* Defining genotype-phenotype relationships in patients with hypertrophic cardiomyopathy using cardiovascular magnetic resonance imaging. *PLoS One* 2019;**14**:e0217612. https://doi.org/10.1371/journal.pone.0217612
126. Quarta G, Husain SI, Flett AS, Sado DM, Chao CY, Tome Esteban MT, *et al.* Arrhythmogenic right ventricular cardiomyopathy mimics: role of cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2013;**15**:16. https://doi.org/10.1186/1532-429X-15-16
127. Menghetti L, Basso C, Nava A, Angelini A, Thiene G. Spin-echo nuclear magnetic resonance for tissue characterisation in arrhythmogenic right ventricular cardiomyopathy. *Heart* 1996;**76**:467–470. https://doi.org/10.1136/hrt.76.6.467
128. Sen-Chowdhry S, Syrris P, Ward D, Asimaki A, Sevdalis E, McKenna WJ. Clinical and genetic characterization of families with arrhythmogenic right ventricular dysplasia/cardiomyopathy provides novel insights into patterns of disease expression. *Circulation* 2007;**115**:1710–1720. https://doi.org/10.1161/CIRCULATIONAHA.106.660241
129. Aquaro GD, Barison A, Todiere G, Grigoratos C, Ait Ali L, Di Bella G, *et al.* Usefulness of combined functional assessment by cardiac magnetic resonance and tissue characterization versus task force criteria for diagnosis of arrhythmogenic right ventricular cardiomyopathy. *Am J Cardiol* 2016;**118**:1730–1736. https://doi.org/10.1016/j.amjcard.2016.08.056
130. Petersen SE, Selvanayagam JB, Wiesmann F, Robson MD, Francis JM, Anderson RH, *et al.* Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. *J Am Coll Cardiol* 2005;**46**:101–105. https://doi.org/10.1016/j.jacc.2005.03.045
131. Masso AH, Uribe C, Willerson JT, Cheong BY, Davis BR. Left ventricular noncompaction detected by cardiac magnetic resonance screening: a reexamination of diagnostic criteria. *Tex Heart Inst J* 2020;**47**:183–193. https://doi.org/10.14503/THIJ-19-7157
132. Grothoff M, Pachowsky M, Hoffmann J, Posch M, Klaassen S, Lehmkuhl L, *et al.* Value of cardiovascular MR in diagnosing left ventricular non-compaction cardiomyopathy and in discriminating between other cardiomyopathies. *Eur Radiol* 2012;**22**:2699–2709. https://doi.org/10.1007/s00330-012-2554-7
133. Jacquier A, Thuny F, Jop B, Giorgi R, Cohen F, Gaubert JY, *et al.* Measurement of trabeculated left ventricular mass using cardiac magnetic resonance imaging in the diagnosis of left ventricular non-compaction. *Eur Heart J* 2010;**31**:1098–1104. https://doi.org/10.1093/eurheartj/ehp595
134. Sado DM, White SK, Piechnik SK, Banypersad SM, Treibel T, Captur G, *et al.* Identification and assessment of Anderson–Fabry disease by cardiovascular magnetic resonance noncontrast myocardial T1 mapping. *Circ Cardiovasc Imaging* 2013;**6**: 392–398. https://doi.org/10.1161/CIRCIMAGING.112.000070
135. Deva DP, Hanneman K, Li Q, Ng MY, Wasim S, Morel C, *et al.* Cardiovascular magnetic resonance demonstration of the spectrum of morphological phenotypes and patterns of myocardial scarring in Anderson–Fabry disease. *J Cardiovasc Magn Reson* 2016;**18**: 14. https://doi.org/10.1186/s12968-016-0233-6
136. Francone M. Role of cardiac magnetic resonance in the evaluation of dilated cardiomyopathy: diagnostic contribution and prognostic significance. *ISRN Radiol* 2014;**2014**: 365404. https://doi.org/10.1155/2014/365404
137. Di Marco A, Anguera I, Schmitt M, Klem I, Neilan TG, White JA, *et al.* Late gadolinium enhancement and the risk for ventricular arrhythmias or sudden death in dilated cardiomyopathy: systematic review and meta-analysis. *JACC Heart Fail* 2017;**5**:28–38. https://doi.org/10.1016/j.jchf.2016.09.017
138. Klem I, Klein M, Khan M, Yang EY, Nabi F, Ivanov A, *et al.* Relationship of LVEF and myocardial scar to long-term mortality risk and mode of death in patients with nonischemic cardiomyopathy. *Circulation* 2021;**143**:1343–1358. https://doi.org/10.1161/CIRCULATIONAHA.120.048477
139. Rastegar N, Te Riele ASJM, James CA, Bhonsale A, Murray B, Tichnell C, *et al.* Fibrofatty changes: incidence at cardiac MR imaging in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Radiology* 2016;**280**:405–412. https://doi.org/10.1148/radiol.2016150988
140. te Riele ASJM, Bhonsale A, James CA, Rastegar N, Murray B, Burt JR, *et al.* Incremental value of cardiac magnetic resonance imaging in arrhythmic risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. *J Am Coll Cardiol* 2013;**62**:1761–1769. https://doi.org/10.1016/j.jacc.2012.11.087
141. Chan RH, Maron BJ, Olivotto I, Pencina MJ, Assenza GE, Haas T, *et al.* Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. *Circulation* 2014;**130**:484–495. https://doi.org/10.1161/CIRCULATIONAHA.113.007094
142. He D, Ye M, Zhang L, Jiang B. Prognostic significance of late gadolinium enhancement on cardiac magnetic resonance in patients with hypertrophic cardiomyopathy. *Heart Lung* 2018;**47**:122–126. https://doi.org/10.1016/j.hrtlng.2017.10.008
143. Weissler-Snir A, Dorian P, Rakowski H, Care M, Spears D. Primary prevention implantable cardioverter-defibrillators in hypertrophic cardiomyopathy–are there predictors of appropriate therapy? *Heart Rhythm* 2021;**18**:63–70. https://doi.org/10.1016/j.hrthm.2020.08.009
144. Raman B, Ariga R, Spartera M, Sivalokanathan S, Chan K, Dass S, *et al.* Progression of myocardial fibrosis in hypertrophic cardiomyopathy: mechanisms and clinical implications. *Eur Heart J Cardiovasc Imaging* 2019;**20**:157–167. https://doi.org/10.1093/ehjci/jey135
145. Ho CY, Abbasi SA, Neilan TG, Shah RV, Chen Y, Heydari B, *et al.* T1 measurements identify extracellular volume expansion in hypertrophic cardiomyopathy sarcomere mutation carriers with and without left ventricular hypertrophy. *Circ Cardiovasc Imaging* 2013;**6**:415–422. https://doi.org/10.1161/CIRCIMAGING.112.000333
146. Moon JC, Fisher NG, McKenna WJ, Pennell DJ. Detection of apical hypertrophic cardiomyopathy by cardiovascular magnetic resonance in patients with non-diagnostic echocardiography. *Heart* 2004;**90**:645–649. https://doi.org/10.1136/hrt.2003.014969
147. Aquaro GD, De Luca A, Cappelletto C, Raimondi F, Bianco F, Botto N, *et al.* Prognostic value of magnetic resonance phenotype in patients with arrhythmogenic right ventricular cardiomyopathy. *J Am Coll Cardiol* 2020;**75**:2753–2765. https://doi.org/10.1016/j.jacc.2020.04.023

148. Martinez-Naharro A, Abdel-Gadir A, Treibel TA, Zumbo G, Knight DS, Rosmini S, *et al.* CMR-verified regression of cardiac AL amyloid after chemotherapy. *JACC Cardiovasc Imaging* 2018;**11**:152–154. https://doi.org/10.1016/j.jcmg.2017.02.012
149. Fontana M, Martinez-Naharro A, Chacko L, Rowczenio D, Gilbertson JA, Whelan CJ, *et al.* Reduction in CMR derived extracellular volume with patisiran indicates cardiac amyloid regression. *JACC Cardiovasc Imaging* 2021;**14**:189–199. https://doi.org/10.1016/j.jcmg.2020.07.043
150. Martinez-Naharro A, Kotecha T, Norrington K, Boldrini M, Rezk T, Quarta C, *et al.* Native T1 and extracellular volume in transthyretin amyloidosis. *JACC Cardiovasc Imaging* 2019;**12**:810–819. https://doi.org/10.1016/j.jcmg.2018.02.006
151. Puntmann VO, Isted A, Hinojar R, Foote L, Carr-White G, Nagel E. T1 and T2 mapping in recognition of early cardiac involvement in systemic sarcoidosis. *Radiology* 2017;**285**: 63–72. https://doi.org/10.1148/radiol.2017162732
152. Pennell DJ, Porter JB, Cappellini MD, Chan LL, El-Beshlawy A, Aydinok Y, *et al.* Deferasirox for up to 3 years leads to continued improvement of myocardial T2* in patients with beta-thalassemia major. *Haematologica* 2012;**97**:842–848. https://doi.org/10.3324/haematol.2011.049957
153. Dalal D, Tandri H, Judge DP, Amat N, Macedo R, Jain R, *et al.* Morphologic variants of familial arrhythmogenic right ventricular dysplasia/cardiomyopathy a genetics–magnetic resonance imaging correlation study. *J Am Coll Cardiol* 2009;**53**:1289–1299. https://doi.org/10.1016/j.jacc.2008.12.045
154. Stokke MK, Castrini AI, Aneq MA, Jensen HK, Madsen T, Hansen J, *et al.* Absence of ECG Task Force Criteria does not rule out structural changes in genotype positive ARVC patients. *Int J Cardiol* 2020;**317**:152–158. https://doi.org/10.1016/j.ijcard.2020.05.095
155. Moon JC, Sachdev B, Elkington AG, McKenna WJ, Mehta A, Pennell DJ, *et al.* Gadolinium enhanced cardiovascular magnetic resonance in Anderson–Fabry disease. Evidence for a disease specific abnormality of the myocardial interstitium. *Eur Heart J* 2003;**24**:2151–2155. https://doi.org/10.1016/j.ehj.2003.09.017
156. Huurman R, van der Velde N, Schinkel AFL, Hassing HC, Budde RPJ, van Slegtenhorst MA, *et al.* Contemporary family screening in hypertrophic cardiomyopathy: the role of cardiovascular magnetic resonance. *Eur Heart J Cardiovasc Imaging* 2022;**23**: 1144–1154. https://doi.org/10.1093/ehjci/jeac099
157. Valente AM, Lakdawala NK, Powell AJ, Evans SP, Cirino AL, Orav EJ, *et al.* Comparison of echocardiographic and cardiac magnetic resonance imaging in hypertrophic cardiomyopathy sarcomere mutation carriers without left ventricular hypertrophy. *Circ Cardiovasc Genet* 2013;**6**:230–237. https://doi.org/10.1161/CIRCGENETICS.113.000037
158. Germans T, Russel IK, Gotte MJ, Spreeuwenberg MD, Doevendans PA, Pinto YM, *et al.* How do hypertrophic cardiomyopathy mutations affect myocardial function in carriers with normal wall thickness? Assessment with cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2010;**12**:13. https://doi.org/10.1186/1532-429X-12-13
159. Germans T, Wilde AA, Dijkmans PA, Chai W, Kamp O, Pinto YM, *et al.* Structural abnormalities of the inferoseptal left ventricular wall detected by cardiac magnetic resonance imaging in carriers of hypertrophic cardiomyopathy mutations. *J Am Coll Cardiol* 2006;**48**:2518–2523. https://doi.org/10.1016/j.jacc.2006.08.036
160. Aziz W, Claridge S, Ntalas I, Gould J, de Vecchi A, Razeghi O, *et al.* Emerging role of cardiac computed tomography in heart failure. *ESC Heart Fail* 2019;**6**:909–920. https://doi.org/10.1002/ehf2.12479
161. Galand V, Ghoshhajra B, Szymonifka J, Das S, Leclercq C, Martins RP, *et al.* Utility of computed tomography to predict ventricular arrhythmias in patients with nonischemic cardiomyopathy receiving cardiac resynchronization therapy. *Am J Cardiol* 2020;**125**: 607–612. https://doi.org/10.1016/j.amjcard.2019.11.003
162. Palmisano A, Vignale D, Peretto G, Busnardo E, Calcagno C, Campochiaro C, *et al.* Hybrid FDG-PET/MR or FDG-PET/CT to detect disease activity in patients with persisting arrhythmias after myocarditis. *JACC Cardiovasc Imaging* 2021;**14**:288–292. https://doi.org/10.1016/j.jcmg.2020.03.009
163. Wicks EC, Menezes LJ, Barnes A, Mohiddin SA, Sekhri N, Porter JC, *et al.* Diagnostic accuracy and prognostic value of simultaneous hybrid 18F-fluorodeoxyglucose positron emission tomography/magnetic resonance imaging in cardiac sarcoidosis. *Eur Heart J Cardiovasc Imaging* 2018;**19**:757–767. https://doi.org/10.1093/ehjci/jex340
164. Youssef G, Leung E, Mylonas I, Nery P, Williams K, Wisenberg G, *et al.* The use of 18F-FDG PET in the diagnosis of cardiac sarcoidosis: a systematic review and metaanalysis including the Ontario experience. *J Nucl Med* 2012;**53**:241–248. https://doi.org/10.2967/jnumed.111.090662
165. Bravo PE, Di Carli MF, Dorbala S. Role of PET to evaluate coronary microvascular dysfunction in non-ischemic cardiomyopathies. *Heart Fail Rev* 2017;**22**:455–464. https://doi.org/10.1007/s10741-017-9628-1
166. Perugini E, Guidalotti PL, Salvi F, Cooke RM, Pettinato C, Riva L, *et al.* Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. *J Am Coll Cardiol* 2005;**46**:1076–1084. https://doi.org/10.1016/j.jacc.2005.05.073
167. Hutt DF, Fontana M, Burniston M, Quigley AM, Petrie A, Ross JC, *et al.* Prognostic utility of the Perugini grading of 99mTc-DPD scintigraphy in transthyretin (ATTR) amyloidosis and its relationship with skeletal muscle and soft tissue amyloid. *Eur Heart J Cardiovasc Imaging* 2017;**18**:1344–1350. https://doi.org/10.1093/ehjci/jew325
168. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, *et al.* Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation* 2016;**133**:2404–2412. https://doi.org/10.1161/CIRCULATIONAHA.116.021612
169. Langer C, Lutz M, Eden M, Ludde M, Hohnhorst M, Gierloff C, *et al.* Hypertrophic cardiomyopathy in cardiac CT: a validation study on the detection of intramyocardial fibrosis in consecutive patients. *Int J Cardiovasc Imaging* 2014;**30**:659–667. https://doi.org/10.1007/s10554-013-0358-8
170. Asferg C, Usinger L, Kristensen TS, Abdulla J. Accuracy of multi-slice computed tomography for measurement of left ventricular ejection fraction compared with cardiac magnetic resonance imaging and two-dimensional transthoracic echocardiography: a systematic review and meta-analysis. *Eur J Radiol* 2012;**81**:e757–e762. https://doi.org/10.1016/j.ejrad.2012.02.002
171. Premaratne M, Shamsaei M, Chow JD, Haddad T, Erthal F, Curran H, *et al.* Using coronary calcification to exclude an ischemic etiology for cardiomyopathy: a validation study and systematic review. *Int J Cardiol* 2017;**230**:518–522. https://doi.org/10.1016/j.ijcard.2016.12.068
172. Dweck MR, Abgral R, Trivieri MG, Robson PM, Karakatsanis N, Mani V, *et al.* Hybrid magnetic resonance imaging and positron emission tomography with fluorodeoxyglucose to diagnose active cardiac sarcoidosis. *JACC Cardiovasc Imaging* 2018;**11**:94–107. https://doi.org/10.1016/j.jcmg.2017.02.021
173. Okumura W, Iwasaki T, Toyama T, Iso T, Arai M, Oriuchi N, *et al.* Usefulness of fasting 18F-FDG PET in identification of cardiac sarcoidosis. *J Nucl Med* 2004;**45**:1989–1998.
174. Besler C, Urban D, Watzka S, Lang D, Rommel KP, Kandolf R, *et al.* Endomyocardial miR-133a levels correlate with myocardial inflammation, improved left ventricular function, and clinical outcome in patients with inflammatory cardiomyopathy. *Eur J Heart Fail* 2016;**18**:1442–1451. https://doi.org/10.1002/ejhf.579
175. Ardehali H, Qasim A, Cappola T, Howard D, Hruban R, Hare JM, *et al.* Endomyocardial biopsy plays a role in diagnosing patients with unexplained cardiomyopathy. *Am Heart J* 2004;**147**:919–923. https://doi.org/10.1016/j.ahj.2003.09.020
176. Ardehali H, Howard DL, Hariri A, Qasim A, Hare JM, Baughman KL, *et al.* A positive endomyocardial biopsy result for sarcoid is associated with poor prognosis in patients with initially unexplained cardiomyopathy. *Am Heart J* 2005;**150**:459–463. https://doi.org/10.1016/j.ahj.2004.10.006
177. Hahn VS, Yanek LR, Vaishnav J, Ying W, Vaidya D, Lee YZJ, *et al.* Endomyocardial biopsy characterization of heart failure with preserved ejection fraction and prevalence of cardiac amyloidosis. *JACC Heart Fail* 2020; **8**:712–724. https://doi.org/10.1016/j.jchf.2020.04.007
178. Lorenzini M, Norrish G, Field E, Ochoa JP, Cicerchia M, Akhtar MM, *et al.* Penetrance of hypertrophic cardiomyopathy in sarcomere protein mutation carriers. *J Am Coll Cardiol* 2020;**76**:550–559. https://doi.org/10.1016/j.jacc.2020.06.011
179. Dalal D, James C, Devanagondi R, Tichnell C, Tucker A, Prakasa K, *et al.* Penetrance of mutations in plakophilin-2 among families with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Am Coll Cardiol* 2006;**48**:1416–1424. https://doi.org/10.1016/j.jacc.2006.06.045
180. Claes GR, van Tienen FH, Lindsey P, Krapels IP, Helderman-van den Enden AT, Hoos MB, *et al.* Hypertrophic remodelling in cardiac regulatory myosin light chain (MYL2) founder mutation carriers. *Eur Heart J* 2016;**37**:1815–1822. https://doi.org/10.1093/eurheartj/ehv522
181. James CA, Bhonsale A, Tichnell C, Murray B, Russell SD, Tandri H, *et al.* Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. *J Am Coll Cardiol* 2013;**62**:1290–1297. https://doi.org/10.1016/j.jacc.2013.06.033
182. Tadros R, Francis C, Xu X, Vermeer AMC, Harper AR, Huurman R, *et al.* Shared genetic pathways contribute to risk of hypertrophic and dilated cardiomyopathies with opposite directions of effect. *Nat Genet* 2021;**53**:128–134. https://doi.org/10.1038/s41588-020-00762-2
183. Harper AR, Goel A, Grace C, Thomson KL, Petersen SE, Xu X, *et al.* Common genetic variants and modifiable risk factors underpin hypertrophic cardiomyopathy susceptibility and expressivity. *Nat Genet* 2021;**53**:135–142. https://doi.org/10.1038/s41588-020-00764-0
184. Pugh TJ, Kelly MA, Gowrisankar S, Hynes E, Seidman MA, Baxter SM, *et al.* The landscape of genetic variation in dilated cardiomyopathy as surveyed by clinical DNA sequencing. *Genet Med* 2014;**16**:601–608. https://doi.org/10.1038/gim.2013.204
185. Escobar-Lopez L, Ochoa JP, Mirelis JG, Espinosa MA, Navarro M, Gallego-Delgado M, *et al.* Association of genetic variants with outcomes in patients with nonischemic dilated cardiomyopathy. *J Am Coll Cardiol* 2021;**78**:1682–1699. https://doi.org/10.1016/j.jacc.2021.08.039
186. Gigli M, Merlo M, Graw SL, Barbati G, Rowland TJ, Slavov DB, *et al.* Genetic risk of arrhythmic phenotypes in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2019; **74**:1480–1490. https://doi.org/10.1016/j.jacc.2019.06.072
187. Garnier S, Harakalova M, Weiss S, Mokry M, Regitz-Zagrosek V, Hengstenberg C, *et al.* Genome-wide association analysis in dilated cardiomyopathy reveals two new players in systolic heart failure on chromosomes 3p25.1 and 22q11.23. *Eur Heart J* 2021;**42**: 2000–2011. https://doi.org/10.1093/eurheartj/ehab030
188. Pua CJ, Tham N, Chin CWL, Walsh R, Khor CC, Toepfer CN, *et al.* Genetic studies of hypertrophic cardiomyopathy in Singaporeans identify variants in TNNI3 and TNNT2

that are common in Chinese patients. *Circ Genom Precis Med* 2020;**13**:424–434. https://doi.org/10.1161/CIRCGEN.119.002823
189. Jordan E, Peterson L, Ai T, Asatryan B, Bronicki L, Brown E, *et al.* Evidence-based assessment of genes in dilated cardiomyopathy. *Circulation* 2021;**144**:7–19. https://doi.org/10.1161/CIRCULATIONAHA.120.053033
190. James CA, Jongbloed JDH, Hershberger RE, Morales A, Judge DP, Syrris P, *et al.* International evidence based reappraisal of genes associated with arrhythmogenic right ventricular cardiomyopathy using the clinical genome resource framework. *Circ Genom Precis Med* 2021;**14**:e003273. https://doi.org/10.1161/CIRCGEN.120.003273
191. Ingles J, Goldstein J, Thaxton C, Caleshu C, Corty EW, Crowley SB, *et al.* Evaluating the clinical validity of hypertrophic cardiomyopathy genes. *Circ Genom Precis Med* 2019;**12**:e002460. https://doi.org/10.1161/CIRCGEN.119.002460
191a. ClinGen Clinical Genome Resource. https://search.clinicalgenome.org/kb/gene-validity (12 July 2023 date last accessed).
192. Miller DT, Lee K, Chung WK, Gordon AS, Herman GE, Klein TE, *et al.* ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 2021;**23**:1381–1390. https://doi.org/10.1038/s41436-021-01172-3
193. Miller DT, Lee K, Gordon AS, Amendola LM, Adelman K, Bale SJ, *et al.* Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 2021;**23**:1391–1398. https://doi.org/10.1038/s41436-021-01171-4
194. Watkins H. Time to think differently about sarcomere-negative hypertrophic cardiomyopathy. *Circulation* 2021;**143**:2415–2417. https://doi.org/10.1161/CIRCULATIONAHA.121.053527
195. Kumuthini J, Zick B, Balasopoulou A, Chalikiopoulou C, Dandara C, El-Kamah G, *et al.* The clinical utility of polygenic risk scores in genomic medicine practices: a systematic review. *Hum Genet* 2022;**141**:1697–1704. https://doi.org/10.1007/s00439-022-02452-x
196. Pirruccello JP, Bick A, Wang M, Chaffin M, Friedman S, Yao J, *et al.* Analysis of cardiac magnetic resonance imaging in 36,000 individuals yields genetic insights into dilated cardiomyopathy. *Nat Commun* 2020;**11**:2254. https://doi.org/10.1038/s41467-020-15823-7
197. Biddinger KJ, Jurgens SJ, Maamari D, Gaziano L, Choi SH, Morrill VN, *et al.* Rare and common genetic variation underlying the risk of hypertrophic cardiomyopathy in a National Biobank. *JAMA Cardiol* 2022;**7**:715–722. https://doi.org/10.1001/jamacardio.2022.1061
198. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, *et al.* Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;**17**:405–424. https://doi.org/10.1038/gim.2015.30
199. Kelly MA, Caleshu C, Morales A, Buchan J, Wolf Z, Harrison SM, *et al.* Adaptation and validation of the ACMG/AMP variant classification framework for MYH7-associated inherited cardiomyopathies: recommendations by ClinGen's Inherited Cardiomyopathy Expert Panel. *Genet Med* 2018;**20**:351–359. https://doi.org/10.1038/gim.2017.218
200. Arbustini E, Behr ER, Carrier L, van Duijn C, Evans P, Favalli V, *et al.* Interpretation and actionability of genetic variants in cardiomyopathies: a position statement from the European Society of Cardiology Council on cardiovascular genomics. *Eur Heart J* 2022;**43**:1901–1916. https://doi.org/10.1093/eurheartj/ehab895
201. National Society of Genetic Counselors Definition Task Force; Resta R, Biesecker BB, Bennett RL, Blum S, Hahn SE. A new definition of genetic counseling: National Society of Genetic Counselors' Task Force report. *J Genet Couns* 2006;**15**:77–83. https://doi.org/10.1007/s10897-005-9014-3
202. Biesecker BB. Goals of genetic counseling. *Clin Genet* 2001;**60**:323–330. https://doi.org/10.1034/j.1399-0004.2001.600501.x
203. Ingles J, Yeates L, Semsarian C. The emerging role of the cardiac genetic counselor. *Heart Rhythm* 2011;**8**:1958–1962. https://doi.org/10.1016/j.hrthm.2011.07.017
204. Bordet C, Brice S, Maupain C, Gandjbakhch E, Isidor B, Palmyre A, *et al.* Psychosocial impact of predictive genetic testing in hereditary heart diseases: the PREDICT study. *J Clin Med* 2020;**9**:1365. https://doi.org/10.3390/jcm9051365
205. Ingles J. Psychological issues in managing families with inherited cardiovascular diseases. *Cold Spring Harb Perspect Med* 2020;**10**:a036558. https://doi.org/10.1101/cshperspect.a036558
206. Edwards A, Gray J, Clarke A, Dundon J, Elwyn G, Gaff C, *et al.* Interventions to improve risk communication in clinical genetics: systematic review. *Patient Educ Couns* 2008;**71**:4–25. https://doi.org/10.1016/j.pec.2007.11.026
207. Austin J, Semaka A, Hadjipavlou G. Conceptualizing genetic counseling as psychotherapy in the era of genomic medicine. *J Genet Couns* 2014;**23**:903–909. https://doi.org/10.1007/s10897-014-9728-1
208. Michie S, Marteau TM, Bobrow M. Genetic counselling: the psychological impact of meeting patients' expectations. *J Med Genet* 1997;**34**:237–241. https://doi.org/10.1136/jmg.34.3.237
209. Ison HE, Ware SM, Schwantes-An TH, Freeze S, Elmore L, Spoonamore KG. The impact of cardiovascular genetic counseling on patient empowerment. *J Genet Couns* 2019;**28**:570–577. https://doi.org/10.1002/jgc4.1050
210. Borry P, Evers-Kiebooms G, Cornel MC, Clarke A, Dierickx K. Public Professional Policy Committee (PPPC) of the European Society of Human Genetics (ESHG). Genetic testing in asymptomatic minors: background considerations towards ESHG recommendations. *Eur J Hum Genet* 2009;**17**:711–719. https://doi.org/10.1038/ejhg.2009.25
211. Ormondroyd E, Oates S, Parker M, Blair E, Watkins H. Pre-symptomatic genetic testing for inherited cardiac conditions: a qualitative exploration of psychosocial and ethical implications. *Eur J Hum Genet* 2014;**22**:88–93. https://doi.org/10.1038/ejhg.2013.81
212. Spanaki A, O'Curry S, Winter-Beatty J, Mead-Regan S, Hawkins K, English J, *et al.* Psychosocial adjustment and quality of life in children undergoing screening in a specialist paediatric hypertrophic cardiomyopathy clinic. *Cardiol Young* 2016;**26**:961–967. https://doi.org/10.1017/S1047951115001717
213. Ingles J, Semsarian C. Conveying a probabilistic genetic test result to families with an inherited heart disease. *Heart Rhythm* 2014;**11**:1073–1078. https://doi.org/10.1016/j.hrthm.2014.03.017
214. Whyte S, Green A, McAllister M, Shipman H. Family communication in inherited cardiovascular conditions in Ireland. *J Genet Couns* 2016;**25**:1317–1326. https://doi.org/10.1007/s10897-016-9974-5
215. Daly MB, Montgomery S, Bingler R, Ruth K. Communicating genetic test results within the family: is it lost in translation? A survey of relatives in the randomized six-step study. *Fam Cancer* 2016;**15**:697–706. https://doi.org/10.1007/s10689-016-9889-1
216. Burns C, McGaughran J, Davis A, Semsarian C, Ingles J. Factors influencing uptake of familial long QT syndrome genetic testing. *Am J Med Genet A* 2016;**170A**:418–425. https://doi.org/10.1002/ajmg.a.37455
217. Kaphingst KA, Blanchard M, Milam L, Pokharel M, Elrick A, Goodman MS. Relationships between health literacy and genomics-related knowledge, self-efficacy, perceived importance, and communication in a medically underserved population. *J Health Commun* 2016;**21**:58–68. https://doi.org/10.1080/10810730.2016.1144661
218. Yeates L, McDonald K, Burns C, Semsarian C, Carter S, Ingles J. Decision-making and experiences of preimplantation genetic diagnosis in inherited heart diseases: a qualitative study. *Eur J Hum Genet* 2022;**30**:187–193. https://doi.org/10.1038/s41431-021-00963-1
219. Landstrom AP, Kim JJ, Gelb BD, Helm BM, Kannankeril PJ, Semsarian C, *et al.* Genetic testing for heritable cardiovascular diseases in pediatric patients: a scientific statement from the American Heart Association. *Circ Genom Precis Med* 2021;**14**:e000086. https://doi.org/10.1161/HCG.0000000000000086
220. Akolekar R, Beta J, Picciarelli G, Ogilvie C, D'Antonio F. Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2015;**45**:16–26. https://doi.org/10.1002/uog.14636
221. Meiser B, Irle J, Lobb E, Barlow-Stewart K. Assessment of the content and process of genetic counseling: a critical review of empirical studies. *J Genet Couns* 2008;**17**:434–451. https://doi.org/10.1007/s10897-008-9173-0
222. Waddell-Smith KE, Donoghue T, Oates S, Graham A, Crawford J, Stiles MK, *et al.* Inpatient detection of cardiac-inherited disease: the impact of improving family history taking. *Open Heart* 2016;**3**:e000329. https://doi.org/10.1136/openhrt-2015-000329
223. Murray B, Tichnell C, Burch AE, Calkins H, James CA. Strength of the genetic counselor: patient relationship is associated with extent of increased empowerment in patients with arrhythmogenic cardiomyopathy. *J Genet Couns* 2022;**31**:388–397. https://doi.org/10.1002/jgc4.1499
224. Ingles J, Lind JM, Phongsavan P, Semsarian C. Psychosocial impact of specialized cardiac genetic clinics for hypertrophic cardiomyopathy. *Genet Med* 2008;**10**:117–120. https://doi.org/10.1097/GIM.0b013e3181612cc7
225. Furqan A, Arscott P, Girolami F, Cirino AL, Michels M, Day SM, *et al.* Care in specialized centers and data sharing increase agreement in hypertrophic cardiomyopathy genetic test interpretation. *Circ Cardiovasc Genet* 2017;**10**:e001700. https://doi.org/10.1161/CIRCGENETICS.116.001700
226. Reuter C, Grove ME, Orland K, Spoonamore K, Caleshu C. Clinical cardiovascular genetic counselors take a leading role in team-based variant classification. *J Genet Couns* 2018;**27**:751–760. https://doi.org/10.1007/s10897-017-0175-7
227. Ingles J, McGaughran J, Scuffham PA, Atherton J, Semsarian C. A cost-effectiveness model of genetic testing for the evaluation of families with hypertrophic cardiomyopathy. *Heart* 2012;**98**:625–630. https://doi.org/10.1136/heartjnl-2011-300368
228. Wordsworth S, Leal J, Blair E, Legood R, Thomson K, Seller A, *et al.* DNA testing for hypertrophic cardiomyopathy: a cost-effectiveness model. *Eur Heart J* 2010;**31**:926–935. https://doi.org/10.1093/eurheartj/ehq067
229. Catchpool M, Ramchand J, Martyn M, Hare DL, James PA, Trainer AH, *et al.* A cost-effectiveness model of genetic testing and periodical clinical screening for the evaluation of families with dilated cardiomyopathy. *Genet Med* 2019;**21**:2815–2822. https://doi.org/10.1038/s41436-019-0582-2
230. Groeneweg JA, Bhonsale A, James CA, te Riele AS, Dooijes D, Tichnell C, *et al.* Clinical presentation, long-term follow-up, and outcomes of 1001 arrhythmogenic right

ventricular dysplasia/cardiomyopathy patients and family members. *Circ Cardiovasc Genet* 2015;**8**:437–446. https://doi.org/10.1161/CIRCGENETICS.114.001003
231. Alfares AA, Kelly MA, McDermott G, Funke BH, Lebo MS, Baxter SB, *et al.* Results of clinical genetic testing of 2,912 probands with hypertrophic cardiomyopathy: expanded panels offer limited additional sensitivity. *Genet Med* 2015;**17**:880–888. https://doi.org/10.1038/gim.2014.205
232. Ingles J, Yeates L, O'Brien L, McGaughran J, Scuffham PA, Atherton J, *et al.* Genetic testing for inherited heart diseases: longitudinal impact on health-related quality of life. *Genet Med* 2012;**14**:749–752. https://doi.org/10.1038/gim.2012.47
233. Friess MR, Marino BS, Cassedy A, Wilmot I, Jefferies JL, Lorts A. Health-related quality of life assessment in children followed in a cardiomyopathy clinic. *Pediatr Cardiol* 2015; **36**:516–523. https://doi.org/10.1007/s00246-014-1042-z
234. Wakefield CE, Hanlon LV, Tucker KM, Patenaude AF, Signorelli C, McLoone JK, *et al.* The psychological impact of genetic information on children: a systematic review. *Genet Med* 2016;**18**:755–762. https://doi.org/10.1038/gim.2015.181
235. Christian S, Somerville M, Taylor S, Atallah J. When to offer predictive genetic testing to children at risk of an inherited arrhythmia or cardiomyopathy. *Circ Genom Precis Med* 2018;**11**:e002300. https://doi.org/10.1161/CIRCGEN.118.002300
236. MacLeod R, Beach A, Henriques S, Knopp J, Nelson K, Kerzin-Storrar L. Experiences of predictive testing in young people at risk of Huntington's disease, familial cardiomyopathy or hereditary breast and ovarian cancer. *Eur J Hum Genet* 2014;**22**:396–401. https://doi.org/10.1038/ejhg.2013.143
237. Knight LM, Miller E, Kovach J, Arscott P, von Alvensleben JC, Bradley D, *et al.* Genetic testing and cascade screening in pediatric long QT syndrome and hypertrophic cardiomyopathy. *Heart Rhythm* 2020;**17**:106–112. https://doi.org/10.1016/j.hrthm.2019.06.015
238. Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, *et al.* Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). *Circulation* 2018;**138**:1387–1398. https://doi.org/10.1161/CIRCULATIONAHA.117.033200
239. Marey I, Fressart V, Rambaud C, Fornes P, Martin L, Grotto S, *et al.* Clinical impact of post-mortem genetic testing in cardiac death and cardiomyopathy. *Open Med (Wars)* 2020;**15**:435–446. https://doi.org/10.1515/med-2020-0150
240. Isbister JC, Nowak N, Butters A, Yeates L, Gray B, Sy RW, *et al.* "Concealed cardiomyopathy" as a cause of previously unexplained sudden cardiac arrest. *Int J Cardiol* 2021;**324**:96–101. https://doi.org/10.1016/j.ijcard.2020.09.031
241. Dellefave-Castillo LM, Cirino AL, Callis TE, Esplin ED, Garcia J, Hatchell KE, *et al.* Assessment of the diagnostic yield of combined cardiomyopathy and arrhythmia genetic testing. *JAMA Cardiol* 2022;**7**:966–974. https://doi.org/10.1001/jamacardio.2022.2455
242. Williams N, Manderski E, Stewart S, Bao R, Tang Y. Lessons learned from testing cardiac channelopathy and cardiomyopathy genes in individuals who died suddenly: a two-year prospective study in a large medical examiner's office with an in-house molecular genetics laboratory and genetic counseling services. *J Genet Couns* 2020;**29**:293–302. https://doi.org/10.1002/jgc4.1157
243. Isbister JC, Nowak N, Yeates L, Singer ES, Sy RW, Ingles J, *et al.* Concealed cardiomyopathy in autopsy-inconclusive cases of sudden cardiac death and implications for families. *J Am Coll Cardiol* 2022;**80**:2057–2068. https://doi.org/10.1016/j.jacc.2022.09.029
244. Michie S, Bobrow M, Marteau TM. Predictive genetic testing in children and adults: a study of emotional impact. *J Med Genet* 2001;**38**:519–526. https://doi.org/10.1136/jmg.38.8.519
245. Rath A, Weintraub R. Overview of cardiomyopathies in childhood. *Front Pediatr* 2021; **9**:708732. https://doi.org/10.3389/fped.2021.708732
246. Lipshultz SE, Law YM, Asante-Korang A, Austin ED, Dipchand AI, Everitt MD, *et al.* Cardiomyopathy in children: classification and diagnosis: a scientific statement from the American Heart Association. *Circulation* 2019;**140**:e9–e68. https://doi.org/10.1161/CIR.0000000000000682
247. Kindel SJ, Miller EM, Gupta R, Cripe LH, Hinton RB, Spicer RL, *et al.* Pediatric cardiomyopathy: importance of genetic and metabolic evaluation. *J Card Fail* 2012;**18**: 396–403. https://doi.org/10.1016/j.cardfail.2012.01.017
248. Norrish G, Field E, McLeod K, Ilina M, Stuart G, Bhole V, *et al.* Clinical presentation and survival of childhood hypertrophic cardiomyopathy: a retrospective study in United Kingdom. *Eur Heart J* 2019;**40**:986–993. https://doi.org/10.1093/eurheartj/ehy798
249. Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, *et al.* Incidence, causes, and outcomes of dilated cardiomyopathy in children. *JAMA* 2006;**296**:1867–1876. https://doi.org/10.1001/jama.296.15.1867
250. Shamszad P, Hall M, Rossano JW, Denfield SW, Knudson JD, Penny DJ, *et al.* Characteristics and outcomes of heart failure-related intensive care unit admissions in children with cardiomyopathy. *J Card Fail* 2013;**19**:672–677. https://doi.org/10.1016/j.cardfail.2013.08.006
251. Pelliccia F, Alfieri O, Calabro P, Cecchi F, Ferrazzi P, Gragnano F, *et al.* Multidisciplinary evaluation and management of obstructive hypertrophic cardiomyopathy in 2020: towards the HCM Heart Team. *Int J Cardiol* 2020;**304**:86–92. https://doi.org/10.1016/j.ijcard.2020.01.021
252. Law SP, Oron AP, Kemna MS, Albers EL, McMullan DM, Chen JM, *et al.* Comparison of transplant waitlist outcomes for pediatric candidates supported by ventricular assist devices versus medical therapy. *Pediatr Crit Care Med* 2018;**19**:442–450. https://doi.org/10.1097/PCC.0000000000001503
253. Ullmo S, Vial Y, Di Bernardo S, Roth-Kleiner M, Mivelaz Y, Sekarski N, *et al.* Pathologic ventricular hypertrophy in the offspring of diabetic mothers: a retrospective study. *Eur Heart J* 2007;**28**:1319–1325. https://doi.org/10.1093/eurheartj/ehl416
254. Yunis KA, Bitar FF, Hayek P, Mroueh SM, Mikati M. Transient hypertrophic cardiomyopathy in the newborn following multiple doses of antenatal corticosteroids. *Am J Perinatol* 1999;**16**:17–21. https://doi.org/10.1055/s-2007-993830
255. Brickman WJ, Silverman BL. Cardiovascular effects of growth hormone. *Endocrine* 2000;**12**:153–161. https://doi.org/10.1385/ENDO:12:2:153
256. Monda E, Rubino M, Lioncino M, Di Fraia F, Pacileo R, Verrillo F, *et al.* Hypertrophic cardiomyopathy in children: pathophysiology, diagnosis, and treatment of non-sarcomeric causes. *Front Pediatr* 2021;**9**:632293. https://doi.org/10.3389/fped.2021.632293
257. Fourey D, Care M, Siminovitch KA, Weissler-Snir A, Hindieh W, Chan RH, *et al.* Prevalence and clinical implication of double mutations in hypertrophic cardiomyopathy: revisiting the gene-dose effect. *Circ Cardiovasc Genet* 2017;**10**:e001685. https://doi.org/10.1161/CIRCGENETICS.116.001685
258. Kaltenecker E, Schleihauf J, Meierhofer C, Shehu N, Mkrtchyan N, Hager A, *et al.* Long-term outcomes of childhood onset Noonan compared to sarcomere hypertrophic cardiomyopathy. *Cardiovasc Diagn Ther* 2019;**9**:S299–S309. https://doi.org/10.21037/cdt.2019.05.01
259. Kishnani PS, Hwu WL, Mandel H, Nicolino M, Yong F, Corzo D, *et al.* A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. *J Pediatr* 2006;**148**:671–676.e2. https://doi.org/10.1016/j.jpeds.2005.11.033
260. Linglart L, Gelb BD. Congenital heart defects in Noonan syndrome: diagnosis, management, and treatment. *Am J Med Genet C Semin Med Genet* 2020;**184**:73–80. https://doi.org/10.1002/ajmg.c.31765
261. Gelb BD, Roberts AE, Tartaglia M. Cardiomyopathies in Noonan syndrome and the other RASopathies. *Prog Pediatr Cardiol* 2015;**39**:13–19. https://doi.org/10.1016/j.ppedcard.2015.01.002
262. Calcagni G, Limongelli G, D'Ambrosio A, Gesualdo F, Digilio MC, Baban A, *et al.* Cardiac defects, morbidity and mortality in patients affected by RASopathies. CARNET study results. *Int J Cardiol* 2017;**245**:92–98. https://doi.org/10.1016/j.ijcard.2017.07.068
263. Lioncino M, Monda E, Verrillo F, Moscarella E, Calcagni G, Drago F, *et al.* Hypertrophic cardiomyopathy in RASopathies: diagnosis, clinical characteristics, prognostic implications, and management. *Heart Fail Clin* 2022;**18**:19–29. https://doi.org/10.1016/j.hfc.2021.07.004
264. Calcagni G, Adorisio R, Martinelli S, Grutter G, Baban A, Versacci P, *et al.* Clinical presentation and natural history of hypertrophic cardiomyopathy in RASopathies. *Heart Fail Clin* 2018;**14**:225–235. https://doi.org/10.1016/j.hfc.2017.12.005
265. Poterucha JT, Johnson JN, O'Leary PW, Connolly HM, Niaz T, Maleszewski JJ, *et al.* Surgical ventricular septal myectomy for patients with Noonan syndrome and symptomatic left ventricular outflow tract obstruction. *Am J Cardiol* 2015;**116**:1116–1121. https://doi.org/10.1016/j.amjcard.2015.06.037
266. Hemmati P, Dearani JA, Daly RC, King KS, Ammash NM, Cetta F, *et al.* Early outcomes of cardiac surgery in patients with Noonan syndrome. *Semin Thorac Cardiovasc Surg* 2019;**31**:507–513. https://doi.org/10.1053/j.semtcvs.2018.12.004
267. Moran AM, Colan SD. Verapamil therapy in infants with hypertrophic cardiomyopathy. *Cardiol Young* 1998;**8**:310–319. https://doi.org/10.1017/S1047951100006818
268. van der Ploeg AT, Reuser AJ. Pompe's disease. *Lancet* 2008;**372**:1342–1353. https://doi.org/10.1016/S0140-6736(08)61555-X
269. Kishnani PS, Corzo D, Nicolino M, Byrne B, Mandel H, Hwu WL, *et al.* Recombinant human acid [alpha]-glucosidase: major clinical benefits in infantile-onset Pompe disease. *Neurology* 2007;**68**:99–109. https://doi.org/10.1212/01.wnl.0000251268.41188.04
270. Tanaka M, Ino H, Ohno K, Hattori K, Sato W, Ozawa T, *et al.* Mitochondrial mutation in fatal infantile cardiomyopathy. *Lancet* 1990;**336**:1452. https://doi.org/10.1016/0140-6736(90)93162-I
271. Holmgren D, Wahlander H, Eriksson BO, Oldfors A, Holme E, Tulinius M. Cardiomyopathy in children with mitochondrial disease; clinical course and cardiological findings. *Eur Heart J* 2003;**24**:280–288. https://doi.org/10.1016/S0195-668X(02)00387-1
272. Arad M, Maron BJ, Gorham JM, Johnson WH Jr, Saul JP, Perez-Atayde AR, *et al.* Glycogen storage diseases presenting as hypertrophic cardiomyopathy. *N Engl J Med* 2005;**352**:362–372. https://doi.org/10.1056/NEJMoa033349
273. Ansong AK, Li JS, Nozik-Grayck E, Ing R, Kravitz RM, Idriss SF, *et al.* Electrocardiographic response to enzyme replacement therapy for Pompe disease. *Genet Med* 2006;**8**:297–301. https://doi.org/10.1097/01.gim.0000195896.04069.5f
274. Schoser B, Attarian S, Borges J, Bouhour F, Chien Y, Choi Y, *et al.* Efficacy and safety results of the avalglucosidase alfa phase 3 COMET trial in late-onset Pompe disease patients. *Eur J Neurol* 2021;**28**:68–68.
275. van der Ploeg AT, Clemens PR, Corzo D, Escolar DM, Florence J, Groeneveld GJ, *et al.* A randomized study of alglucosidase alfa in late-onset Pompe's disease. *N Engl J Med* 2010;**362**:1396–1406. https://doi.org/10.1056/NEJMoa0909859

276. Lee TM, Hsu DT, Kantor P, Towbin JA, Ware SM, Colan SD, *et al.* Pediatric cardiomyopathies. *Circ Res* 2017;**121**:855–873. https://doi.org/10.1161/CIRCRESAHA.116.309386
277. Chang RR, Allada V. Electrocardiographic and echocardiographic features that distinguish anomalous origin of the left coronary artery from pulmonary artery from idiopathic dilated cardiomyopathy. *Pediatr Cardiol* 2001;**22**:3–10. https://doi.org/10.1007/s002460010142
278. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, *et al.* The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology. *J Am Coll Cardiol* 2007;**50**:1914–1931. https://doi.org/10.1093/eurheartj/ehm456
279. Law YM, Lal AK, Chen S, Cihakova D, Cooper LT Jr, Deshpande S, *et al.* Diagnosis and management of myocarditis in children: a scientific statement from the American Heart Association. *Circulation* 2021;**144**:e123–e135. https://doi.org/10.1161/CIR.0000000000001001
280. Fatkin D, MacRae C, Sasaki T, Wolff MR, Porcu M, Frenneaux M, *et al.* Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. *N Engl J Med* 1999;**341**:1715–1724. https://doi.org/10.1056/NEJM199912023412302
281. Towbin JA, Hejtmancik JF, Brink P, Gelb B, Zhu XM, Chamberlain JS, *et al.* X-linked dilated cardiomyopathy. Molecular genetic evidence of linkage to the Duchenne muscular dystrophy (dystrophin) gene at the Xp21 locus. *Circulation* 1993;**87**:1854–1865. https://doi.org/10.1161/01.CIR.87.6.1854
282. D'Amario D, Amodeo A, Adorisio R, Tiziano FD, Leone AM, Perri G, *et al.* A current approach to heart failure in Duchenne muscular dystrophy. *Heart* 2017;**103**:1770–1779. https://doi.org/10.1136/heartjnl-2017-311269
283. Towbin JA. Left ventricular noncompaction: a new form of heart failure. *Heart Fail Clin* 2010;**6**:453–469. https://doi.org/10.1016/j.hfc.2010.06.005
284. Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. *Lancet* 2015;**386**:813–825. https://doi.org/10.1016/S0140-6736(14)61282-4
285. Pignatelli RH, McMahon CJ, Dreyer WJ, Denfield SW, Price J, Belmont JW, *et al.* Clinical characterization of left ventricular noncompaction in children: a relatively common form of cardiomyopathy. *Circulation* 2003;**108**:2672–2678. https://doi.org/10.1161/01.CIR.0000100664.10777.B8
286. Webber SA, Lipshultz SE, Sleeper LA, Lu M, Wilkinson JD, Addonizio LJ, *et al.* Outcomes of restrictive cardiomyopathy in childhood and the influence of phenotype: a report from the Pediatric Cardiomyopathy Registry. *Circulation* 2012;**126**:1237–1244. https://doi.org/10.1161/CIRCULATIONAHA.112.104638
287. Pinto JR, Parvatiyar MS, Jones MA, Liang J, Potter JD. A troponin T mutation that causes infantile restrictive cardiomyopathy increases Ca^{2+} sensitivity of force development and impairs the inhibitory properties of troponin. *J Biol Chem* 2008;**283**:2156–2166. https://doi.org/10.1074/jbc.M707066200
288. Peled Y, Gramlich M, Yoskovitz G, Feinberg MS, Afek A, Polak-Charcon S, *et al.* Titin mutation in familial restrictive cardiomyopathy. *Int J Cardiol* 2014;**171**:24–30. https://doi.org/10.1016/j.ijcard.2013.11.037
289. Mogensen J, Kubo T, Duque M, Uribe W, Shaw A, Murphy R, *et al.* Idiopathic restrictive cardiomyopathy is part of the clinical expression of cardiac troponin I mutations. *J Clin Invest* 2003;**111**:209–216. https://doi.org/10.1172/JCI200316336
290. Protonotarios N, Tsatsopoulou A. Naxos disease and Carvajal syndrome: cardiocutaneous disorders that highlight the pathogenesis and broaden the spectrum of arrhythmogenic right ventricular cardiomyopathy. *Cardiovasc Pathol* 2004;**13**:185–194. https://doi.org/10.1016/j.carpath.2004.03.609
291. McKoy G, Protonotarios N, Crosby A, Tsatsopoulou A, Anastasakis A, Coonar A, *et al.* Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). *Lancet* 2000;**355**:2119–2124. https://doi.org/10.1016/S0140-6736(00)02379-5
292. Carvajal-Huerta L. Epidermolytic palmoplantar keratoderma with woolly hair and dilated cardiomyopathy. *J Am Acad Dermatol* 1998;**39**:418–421. https://doi.org/10.1016/S0190-9622(98)70317-2
293. Smedsrud MK, Chivulescu M, Forsa MI, Castrini I, Aabel EW, Rootwelt-Norberg C, *et al.* Highly malignant disease in childhood-onset arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J* 2022;**43**:4694–4703. https://doi.org/10.1093/eurheartj/ehac485
294. Kontorovich AR, Patel N, Moscati A, Richter F, Peter I, Purevjav E, *et al.* Myopathic cardiac genotypes increase risk for myocarditis. *JACC Basic Transl Sci* 2021;**6**:584–592. https://doi.org/10.1016/j.jacbts.2021.06.001
295. Poller W, Haas J, Klingel K, Kuhnisch J, Gast M, Kaya Z, *et al.* Familial recurrent myocarditis triggered by exercise in patients with a truncating variant of the desmoplakin gene. *J Am Heart Assoc* 2020;**9**:e015289. https://doi.org/10.1161/JAHA.119.015289
296. Martins D, Ovaert C, Khraiche D, Boddaert N, Bonnet D, Raimondi F. Myocardial inflammation detected by cardiac MRI in arrhythmogenic right ventricular cardiomyopathy: a paediatric case series. *Int J Cardiol* 2018;**271**:81–86. https://doi.org/10.1016/j.ijcard.2018.05.116
297. Bariani R, Cipriani A, Rizzo S, Celeghin R, Bueno Marinas M, Giorgi B, *et al.* 'Hot phase' clinical presentation in arrhythmogenic cardiomyopathy. *Europace* 2021;**23**:907–917. https://doi.org/10.1093/europace/euaa343
298. Ross RD. The Ross classification for heart failure in children after 25 years: a review and an age-stratified revision. *Pediatr Cardiol* 2012;**33**:1295–1300. https://doi.org/10.1007/s00246-012-0306-8
299. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, *et al.* 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J* 2022;**43**:3997–4126. https://doi.org/10.1093/eurheartj/ehac262
300. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, *et al.* 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407–477. https://doi.org/10.1093/eurheartj/ehz425
301. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, *et al.* 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J* 2018; **39**:1883–1948. https://doi.org/10.1093/eurheartj/ehy037
302. Ahmad F, Seidman JG, Seidman CE. The genetic basis for cardiac remodeling. *Annu Rev Genomics Hum Genet* 2005;**6**:185–216. https://doi.org/10.1146/annurev.genom.6.080604.162132
303. Ferro MD, Stolfo D, Altinier A, Gigli M, Perrieri M, Ramani F, *et al.* Association between mutation status and left ventricular reverse remodelling in dilated cardiomyopathy. *Heart* 2017;**103**:1704–1710. https://doi.org/10.1136/heartjnl-2016-311017
304. de Boer RA, Heymans S, Backs J, Carrier L, Coats AJS, Dimmeler S, *et al.* Targeted therapies in genetic dilated and hypertrophic cardiomyopathies: from molecular mechanisms to therapeutic targets. A position paper from the Heart Failure Association (HFA) and the Working Group on Myocardial Function of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2022;**24**:406–420.
305. Oghina S, Bougouin W, Bezard M, Kharoubi M, Komajda M, Cohen-Solal A, *et al.* The impact of patients with cardiac amyloidosis in HFpEF trials. *JACC Heart Fail* 2021;**9**:169–178. https://doi.org/10.1016/j.jchf.2020.12.005
306. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, *et al.* Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *J Card Fail* 2021;**3**:S1071-9164(21)00050-6. https://doi.org/10.1016/j.cardfail.2021.01.022
307. Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, *et al.* Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet* 2019;**393**:61–73. https://doi.org/10.1016/S0140-6736(18)32484-X
308. Mureddu GF, Tarantini L, Agabiti N, Faggiano P, Masson S, Latini R, *et al.* Evaluation of different strategies for identifying asymptomatic left ventricular dysfunction and pre-clinical (stage B) heart failure in the elderly. Results from 'PREDICTOR', a population based-study in central Italy. *Eur J Heart Fail* 2013;**15**:1102–1112. https://doi.org/10.1093/eurjhf/hft098
309. Green EM, Wakimoto H, Anderson RL, Evanchik MJ, Gorham JM, Harrison BC, *et al.* A small-molecule inhibitor of sarcomere contractility suppresses hypertrophic cardiomyopathy in mice. *Science* 2016;**351**:617–621. https://doi.org/10.1126/science.aad3456
310. Masarone D, Valente F, Rubino M, Vastarella R, Gravino R, Rea A, *et al.* Pediatric heart failure: a practical guide to diagnosis and management. *Pediatr Neonatol* 2017;**58**:303–312. https://doi.org/10.1016/j.pedneo.2017.01.001
311. Loss KL, Shaddy RE, Kantor PF. Recent and upcoming drug therapies for pediatric heart failure. *Front Pediatr* 2021;**9**:681224. https://doi.org/10.3389/fped.2021.681224
312. Arya A, Azad S, Sitaraman R. Angiotensin receptor and neprylisin inhibitor: a new drug in pediatric cardiologist's armamentarium. *Ann Pediatr Cardiol* 2020;**13**:334–336. https://doi.org/10.4103/apc.APC_9_20
313. Biagini E, Spirito P, Leone O, Picchio FM, Coccolo F, Ragni L, *et al.* Heart transplantation in hypertrophic cardiomyopathy. *Am J Cardiol* 2008;**101**:387–392. https://doi.org/10.1016/j.amjcard.2007.09.085
314. Bograd AJ, Mital S, Schwarzenberger JC, Mosca RS, Quaegebeur JM, Addonizio LJ, *et al.* Twenty-year experience with heart transplantation for infants and children with restrictive cardiomyopathy: 1986–2006. *Am J Transplant* 2008;**8**:201–207. https://doi.org/10.1111/j.1600-6143.2007.02027.x
315. Marstrand P, Han L, Day SM, Olivotto I, Ashley EA, Michels M, *et al.* Hypertrophic cardiomyopathy with left ventricular systolic dysfunction: insights from the SHaRe registry. *Circulation* 2020;**141**:1371–1383. https://doi.org/10.1161/CIRCULATIONAHA.119.044366
316. DePasquale EC, Nasir K, Jacoby DL. Outcomes of adults with restrictive cardiomyopathy after heart transplantation. *J Heart Lung Transplant* 2012;**31**:1269–1275. https://doi.org/10.1016/j.healun.2012.09.018
317. Khush KK, Cherikh WS, Chambers DC, Harhay MO, Hayes D Jr, Hsich E, *et al.* The international thoracic organ transplant registry of the International Society for Heart and Lung Transplantation: thirty-sixth adult heart transplantation report – 2019; focus theme: donor and recipient size match. *J Heart Lung Transplant* 2019;**38**:1056–1066. https://doi.org/10.1016/j.healun.2019.08.004

318. Lund LH, Edwards LB, Kucheryavaya AY, Dipchand AI, Benden C, Christie JD, *et al.* The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report–2013; focus theme: age. *J Heart Lung Transplant* 2013;**32**:951–964. https://doi.org/10.1016/j.healun.2013.08.006
319. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, *et al.* The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant* 2016;**35**:1–23. https://doi.org/10.1016/j.healun.2015.10.023
320. Bansal A, Akhtar F, Desai S, Velasco-Gonzalez C, Bansal A, Teagle A, *et al.* Six-month outcomes in postapproval HeartMate3 patients: a single-center US experience. *J Card Surg* 2022;**37**:1907–1914. https://doi.org/10.1111/jocs.16452
321. Mehra MR, Uriel N, Naka Y, Cleveland JC Jr, Yuzefpolskaya M, Salerno CT, *et al.* A fully magnetically levitated left ventricular assist device – final report. *N Engl J Med* 2019; **380**:1618–1627. https://doi.org/10.1056/NEJMoa1900486
322. Mehra MR, Goldstein DJ, Uriel N, Cleveland JC Jr, Yuzefpolskaya M, Salerno C, *et al.* Two-year outcomes with a magnetically levitated cardiac pump in heart failure. *N Engl J Med* 2018;**378**:1386–1395. https://doi.org/10.1056/NEJMoa1800866
323. Zimpfer D, Gustafsson F, Potapov E, Pya Y, Schmitto J, Berchtold-Herz M, *et al.* Two-year outcome after implantation of a full magnetically levitated left ventricular assist device: results from the ELEVATE Registry. *Eur Heart J* 2020;**41**:3801–3809. https://doi.org/10.1093/eurheartj/ehaa639
324. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, *et al.* Seventh INTERMACS annual report: 15,000 patients and counting. *J Heart Lung Transplant* 2015;**34**:1495–1504. https://doi.org/10.1016/j.healun.2015.10.003
325. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, *et al.* Randomized evaluation of mechanical assistance for the treatment of Congestive Heart Failure Study Group. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med* 2001;**345**:1435–1443. https://doi.org/10.1056/NEJMoa012175
326. Rogers JG, Butler J, Lansman SL, Gass A, Portner PM, Pasque MK, *et al.* Chronic mechanical circulatory support for inotrope-dependent heart failure patients who are not transplant candidates: results of the INTrEPID Trial. *J Am Coll Cardiol* 2007;**50**: 741–747. https://doi.org/10.1016/j.jacc.2007.03.063
327. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, *et al.* Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 2009;**361**:2241–2251. https://doi.org/10.1056/NEJMoa0909938
328. Goldstein DJ, Naka Y, Horstmanshof D, Ravichandran AK, Schroder J, Ransom J, *et al.* Association of clinical outcomes with left ventricular assist device use by bridge to transplant or destination therapy intent: the multicenter study of MagLev technology in patients undergoing mechanical circulatory support therapy with HeartMate 3 (MOMENTUM 3) randomized clinical trial. *JAMA Cardiol* 2020;**5**:411–419. https://doi.org/10.1001/jamacardio.2019.5323
329. Theochari CA, Michalopoulos G, Oikonomou EK, Giannopoulos S, Doulamis IP, Villela MA, *et al.* Heart transplantation versus left ventricular assist devices as destination therapy or bridge to transplantation for 1-year mortality: a systematic review and meta-analysis. *Ann Cardiothorac Surg* 2018;**7**:3–11. https://doi.org/10.21037/acs.2017.09.18
330. Jorde UP, Kushwaha SS, Tatooles AJ, Naka Y, Bhat G, Long JW, *et al.* Results of the destination therapy post-food and drug administration approval study with a continuous flow left ventricular assist device: a prospective study using the INTERMACS registry (Interagency Registry for Mechanically Assisted Circulatory Support). *J Am Coll Cardiol* 2014;**63**:1751–1757. https://doi.org/10.1016/j.jacc.2014.01.053
331. Charron P, Elliott PM, Gimeno JR, Caforio ALP, Kaski JP, Tavazzi L, *et al.* The Cardiomyopathy registry of the EURObservational Research Programme of the European Society of Cardiology: baseline data and contemporary management of adult patients with cardiomyopathies. *Eur Heart J* 2018;**39**:1784–1793. https://doi.org/10.1093/eurheartj/ehx819
332. Mizia-Stec K, Caforio ALP, Charron P, Gimeno JR, Elliott P, Kaski JP, *et al.* Atrial fibrillation, anticoagulation management and risk of stroke in the Cardiomyopathy/Myocarditis registry of the EURObservational Research Programme of the European Society of Cardiology. *ESC Heart Fail* 2020;**7**:3601–3609. https://doi.org/10.1002/ehf2.12854
333. Gimeno JR, Elliott PM, Tavazzi L, Tendera M, Kaski JP, Laroche C, *et al.* Prospective follow-up in various subtypes of cardiomyopathies: insights from the ESC EORP Cardiomyopathy Registry. *Eur Heart J Qual Care Clin Outcomes* 2021;**7**:134–142. https://doi.org/10.1093/ehjqcco/qcaa075
334. Fauchier L, Bisson A, Bodin A, Herbert J, Spiesser P, Pierre B, *et al.* Ischemic stroke in patients with hypertrophic cardiomyopathy according to presence or absence of atrial fibrillation. *Stroke* 2022;**53**:497–504. https://doi.org/10.1161/STROKEAHA.121.034213
335. Buckley BJR, Harrison SL, Gupta D, Fazio-Eynullayeva E, Underhill P, Lip GYH. Atrial fibrillation in patients with cardiomyopathy: prevalence and clinical outcomes from real-world data. *J Am Heart Assoc* 2021;**10**:e021970. https://doi.org/10.1161/JAHA.121.021970
336. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, *et al.* 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**: 373–498. https://doi.org/10.1093/eurheartj/ehaa612
337. Lip GYH. The ABC pathway: an integrated approach to improve AF management. *Nat Rev Cardiol* 2017;**14**:627–628. https://doi.org/10.1038/nrcardio.2017.153
338. Proietti M, Romiti GF, Olshansky B, Lane DA, Lip GYH. Improved outcomes by integrated care of anticoagulated patients with atrial fibrillation using the simple ABC (Atrial Fibrillation Better Care) pathway. *Am J Med* 2018;**131**:1359–1366.e6. https://doi.org/10.1016/j.amjmed.2018.06.012
339. Yoon M, Yang P-S, Jang E, Yu HT, Kim T-H, Uhm J-S, *et al.* Improved population-based clinical outcomes of patients with atrial fibrillation by compliance with the simple ABC (Atrial Fibrillation Better Care) pathway for integrated care management: a nationwide cohort study. *Thromb Haemost* 2019;**119**:1695–1703. https://doi.org/10.1055/s-0039-1693516
340. Pastori D, Farcomeni A, Pignatelli P, Violi F, Lip GYH. ABC (Atrial Fibrillation Better Care) pathway and healthcare costs in atrial fibrillation: the ATHERO-AF study. *Am J Med* 2019;**132**:856–861. https://doi.org/10.1016/j.amjmed.2019.01.003
341. Pastori D, Pignatelli P, Menichelli D, Violi F, Lip GYH. Integrated care management of patients with atrial fibrillation and risk of cardiovascular events: the ABC (Atrial Fibrillation Better Care) pathway in the ATHERO-AF study cohort. *Mayo Clin Proc* 2019;**94**:1261–1267. https://doi.org/10.1016/j.mayocp.2018.10.022
342. Proietti M, Lip GYH, Laroche C, Fauchier L, Marin F, Nabauer M, *et al.* Relation of outcomes to ABC (Atrial Fibrillation Better Care) pathway adherent care in European patients with atrial fibrillation: an analysis from the ESC-EHRA EORP Atrial Fibrillation General Long-Term (AFGen LT) Registry. *Europace* 2021;**23**:174–183. https://doi.org/10.1093/europace/euaa274
343. Pastori D, Menichelli D, Violi F, Pignatelli P, Lip GYH; ATHERO-AF study group. The Atrial Fibrillation Better Care (ABC) pathway and cardiac complications in atrial fibrillation: a potential sex-based difference. The ATHERO-AF study. *Eur J Intern Med* 2021; **85**:80–85. https://doi.org/10.1016/j.ejim.2020.12.011
344. Stevens D, Harrison SL, Kolamunnage-Dona R, Lip GYH, Lane DA. The Atrial Fibrillation Better Care pathway for managing atrial fibrillation: a review. *Europace* 2021;**23**:1511–1527. https://doi.org/10.1093/europace/euab092
345. Yao Y, Guo Y, Lip GYH; mAF-App II Trial investigators. The effects of implementing a mobile health-technology supported pathway on atrial fibrillation-related adverse events among patients with multimorbidity: the mAFA-II randomized clinical trial. *JAMA Netw Open* 2021;**4**:e2140071. https://doi.org/10.1001/jamanetworkopen.2021.40071
346. Romiti GF, Pastori D, Rivera-Caravaca JM, Ding WY, Gue YX, Menichelli D, *et al.* Adherence to the 'Atrial Fibrillation Better Care' Pathway in patients with atrial fibrillation: impact on clinical outcomes–a systematic review and meta-analysis of 285,000 patients. *Thromb Haemost* 2022;**122**:406–414. https://doi.org/10.1055/a-1515-9630
347. Rienstra M, Hobbelt AH, Alings M, Tijssen JGP, Smit MD, Brugemann J, *et al.* Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. *Eur Heart J* 2018;**39**:2987–2996. https://doi.org/10.1093/eurheartj/ehx739
348. Wang YF, Jiang C, He L, Du X, Sang CH, Long DY, *et al.* Integrated care of atrial fibrillation using the ABC (Atrial fibrillation Better Care) pathway improves clinical outcomes in Chinese population: an analysis from the Chinese atrial fibrillation registry. *Front Cardiovasc Med* 2021;**8**:762245. https://doi.org/10.3389/fcvm.2021.762245
349. Proietti M, Romiti GF, Olshansky B, Lane DA, Lip GYH. Comprehensive management with the ABC (Atrial fibrillation Better Care) pathway in clinically complex patients with atrial fibrillation: a post hoc ancillary analysis from the AFFIRM trial. *J Am Heart Assoc* 2020;**9**:e014932. https://doi.org/10.1161/JAHA.119.014932
350. Gumprecht J, Domek M, Proietti M, Li YG, Asaad N, Rashed W, *et al.* Compliance of atrial fibrillation treatment with the Atrial fibrillation Better Care (ABC) pathway improves the clinical outcomes in the Middle East population: a report from the Gulf Survey of Atrial Fibrillation Events (SAFE) registry. *J Clin Med* 2020;**9**:1286. https://doi.org/10.3390/jcm9051286
351. Proietti M, Vitolo M, Lip GYH. Integrated care and outcomes in patients with atrial fibrillation and comorbidities. *Eur J Clin Invest* 2021;**51**:e13498. https://doi.org/10.1111/eci.13498
352. Rivera-Caravaca JM, Roldan V, Martinez-Montesinos L, Vicente V, Lip GYH, Marin F. The Atrial Fibrillation Better Care (ABC) pathway and clinical outcomes in patients with atrial fibrillation: the prospective Murcia AF Project Phase II Cohort. *J Gen Intern Med* 2023;**38**:315–323. https://doi.org/10.1007/s11606-022-07567-5
353. Vitolo M, Proietti M, Malavasi VL, Bonini N, Romiti GF, Imberti JF, *et al.* Adherence to the "Atrial fibrillation Better Care" (ABC) pathway in patients with atrial fibrillation and cancer: a report from the ESC-EHRA EURObservational Research Programme in atrial fibrillation (EORP-AF) General Long-Term Registry. *Eur J Intern Med* 2022;**105**: 54–62. https://doi.org/10.1016/j.ejim.2022.08.004
354. Patel SM, Palazzolo MG, Murphy SA, Antman EM, Braunwald E, Lanz HJ, *et al.* Evaluation of the atrial fibrillation better care pathway in the ENGAGE AF-TIMI 48 trial. *Europace* 2022;**24**:1730–1738. https://doi.org/10.1093/europace/euac082

355. Yang PS, Sung JH, Jang E, Yu HT, Kim TH, Lip GYH, *et al.* Application of the simple atrial fibrillation better care pathway for integrated care management in frail patients with atrial fibrillation: a nationwide cohort study. *J Arrhythm* 2020;**36**:668–677. https://doi.org/10.1002/joa3.12364
356. Romiti GF, Proietti M, Vitolo M, Bonini N, Fawzy AM, Ding WY, *et al.* Clinical complexity and impact of the ABC (Atrial fibrillation Better Care) pathway in patients with atrial fibrillation: a report from the ESC-EHRA EURObservational Research Programme in AF General Long-Term Registry. *BMC Med* 2022;**20**:326. https://doi.org/10.1186/s12916-022-02526-7
357. Yang PS, Sung JH, Jang E, Yu HT, Kim TH, Uhm JS, *et al.* The effect of integrated care management on dementia in atrial fibrillation. *J Clin Med* 2020;**9**:1696. https://doi.org/10.3390/jcm9061696
358. Kotalczyk A, Guo Y, Stefil M, Wang Y, Lip GYH, Chi ORI. Effects of the atrial fibrillation better care pathway on outcomes among clinically complex Chinese patients with atrial fibrillation with multimorbidity and polypharmacy: a report from the ChiOTEAF registry. *J Am Heart Assoc* 2022;**11**:e024319. https://doi.org/10.1161/JAHA.121.024319
359. Esteve-Pastor MA, Ruiz-Ortiz M, Muniz J, Roldan-Rabadan I, Otero D, Cequier A, *et al.* Impact of integrated care management on clinical outcomes in atrial fibrillation patients: a report from the FANTASIIA registry. *Front Cardiovasc Med* 2022;**9**:856222. https://doi.org/10.3389/fcvm.2022.856222
360. Guo Y, Imberti JF, Kotalczyk A, Wang Y, Lip GYH, Chi ORI. 4S-AF scheme and ABC pathway guided management improves outcomes in atrial fibrillation patients. *Eur J Clin Invest* 2022;**52**:e13751. https://doi.org/10.1111/eci.13751
361. Guo Y, Lane DA, Wang L, Zhang H, Wang H, Zhang W, *et al.* Mobile health technology to improve care for patients with atrial fibrillation. *J Am Coll Cardiol* 2020;**75**:1523–1534. https://doi.org/10.1016/j.jacc.2020.01.052
362. Guo Y, Guo J, Shi X, Yao Y, Sun Y, Xia Y, *et al.* Mobile health technology-supported atrial fibrillation screening and integrated care: a report from the mAFA-II trial long-term extension cohort. *Eur J Intern Med* 2020;**82**:105–111. https://doi.org/10.1016/j.ejim.2020.09.024
363. Koniaris LS, Goldhaber SZ. Anticoagulation in dilated cardiomyopathy. *J Am Coll Cardiol* 1998;**31**:745–748. https://doi.org/10.1016/S0735-1097(98)00003-5
364. Eapen ZJ, Mi X, Fonarow GC, Setoguchi S, Piccini JP, Mills RM, *et al.* Anticoagulation and clinical outcomes in heart failure patients with atrial fibrillation: findings from the ADHERE registry. *J Atr Fibrillation* 2013;**6**:953.
365. Guttmann OP, Rahman MS, O'Mahony C, Anastasakis A, Elliott PM. Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. *Heart* 2014;**100**:465–472. https://doi.org/10.1136/heartjnl-2013-304276
366. Camm CF, Camm AJ. Atrial fibrillation and anticoagulation in hypertrophic cardiomyopathy. *Arrhythm Electrophysiol Rev* 2017;**6**:63–68. https://doi.org/10.15420/aer.2017:4:2
367. Nasser MF, Gandhi S, Siegel RJ, Rader F. Anticoagulation for stroke prevention in patients with hypertrophic cardiomyopathy and atrial fibrillation: a review. *Heart Rhythm* 2021;**18**:297–302. https://doi.org/10.1016/j.hrthm.2020.09.018
368. van Rijsingen IAW, Bakker A, Azim D, Hermans-van Ast JF, van der Kooi AJ, van Tintelen JP, *et al.* Lamin A/C mutation is independently associated with an increased risk of arterial and venous thromboembolic complications. *Int J Cardiol* 2013;**168**:472–477. https://doi.org/10.1016/j.ijcard.2012.09.118
369. Guttmann OP, Pavlou M, O'Mahony C, Monserrat L, Anastasakis A, Rapezzi C, *et al.* Prediction of thrombo-embolic risk in patients with hypertrophic cardiomyopathy (HCM Risk-CVA). *Eur J Heart Fail* 2015;**17**:837–845. https://doi.org/10.1002/ejhf.316
370. Garcia-Pavia P, Bengel F, Brito D, Damy T, Duca F, Dorbala S, *et al.* Expert consensus on the monitoring of transthyretin amyloid cardiomyopathy. *Eur J Heart Fail* 2021;**23**:895–905. https://doi.org/10.1002/ejhf.2198
371. Jung H, Yang P-S, Sung J-H, Jang E, Yu HT, Kim T-H, *et al.* Hypertrophic cardiomyopathy in patients with atrial fibrillation: prevalence and associated stroke risks in a nationwide cohort study. *Thromb Haemost* 2019;**119**:285–293. https://doi.org/10.1055/s-0038-1676818
372. Jung H, Sung J-H, Yang P-S, Jang E, Yu HT, Kim T-H, *et al.* Stroke risk stratification for atrial fibrillation patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2018;**72**:2409–2411. https://doi.org/10.1016/j.jacc.2018.07.098
373. Vilches S, Fontana M, Gonzalez-Lopez E, Mitrani L, Saturi G, Renju M, *et al.* Systemic embolism in amyloid transthyretin cardiomyopathy. *Eur J Heart Fail* 2022;**24**:1387–1396. https://doi.org/10.1002/ejhf.2566
374. Jung H, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, *et al.* Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation with hypertrophic cardiomyopathy: a nationwide cohort study. *Chest* 2019;**155**:354–363. https://doi.org/10.1016/j.chest.2018.11.009
375. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, *et al.* Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2021;**42**:1554–1568. https://doi.org/10.1093/eurheartj/ehab072
376. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, *et al.* Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;**383**:955–962. https://doi.org/10.1016/S0140-6736(13)62343-0
377. Xiong Q, Lau YC, Senoo K, Lane DA, Hong K, Lip GYH. Non-vitamin K antagonist oral anticoagulants (NOACs) in patients with concomitant atrial fibrillation and heart failure: a systemic review and meta-analysis of randomized trials. *Eur J Heart Fail* 2015;**17**:1192–1200. https://doi.org/10.1002/ejhf.343
378. Noseworthy PA, Yao X, Shah ND, Gersh BJ. Stroke and bleeding risks in NOAC- and warfarin-treated patients with hypertrophic cardiomyopathy and atrial fibrillation. *J Am Coll Cardiol* 2016;**67**:3020–3021. https://doi.org/10.1016/j.jacc.2016.04.026
379. Lee HJ, Kim HK, Jung JH, Han KD, Lee H, Park JB, *et al.* Novel oral anticoagulants for primary stroke prevention in hypertrophic cardiomyopathy patients with atrial fibrillation. *Stroke* 2019;**50**:2582–2586. https://doi.org/10.1161/STROKEAHA.119.026048
380. Lin Y, Xiong H, Su J, Lin J, Zhou Q, Lin M, *et al.* Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in patients with hypertrophic cardiomyopathy with non-valvular atrial fibrillation. *Heart Vessels* 2022;**37**:1224–1231. https://doi.org/10.1007/s00380-022-02021-2
381. Van Gelder IC, Groenveld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, *et al.* Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med* 2010;**362**:1363–1373. https://doi.org/10.1056/NEJMoa1001337
382. Van Gelder IC, Wyse DG, Chandler ML, Cooper HA, Olshansky B, Hagens VE, *et al.* Does intensity of rate-control influence outcome in atrial fibrillation? An analysis of pooled data from the RACE and AFFIRM studies. *Europace* 2006;**8**:935–942. https://doi.org/10.1093/europace/eul106
383. Sartipy U, Savarese G, Dahlstrom U, Fu M, Lund LH. Association of heart rate with mortality in sinus rhythm and atrial fibrillation in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2019;**21**:471–479. https://doi.org/10.1002/ejhf.1389
384. Hess PL, Sheng S, Matsouaka R, DeVore AD, Heidenreich PA, Yancy CW, *et al.* Strict versus lenient versus poor rate control among patients with atrial fibrillation and heart failure (from the Get With The Guidelines – Heart Failure Program). *Am J Cardiol* 2020;**125**:894–900. https://doi.org/10.1016/j.amjcard.2019.12.025
385. Van Gelder IC, Rienstra M, Crijns HJ, Olshansky B. Rate control in atrial fibrillation. *Lancet* 2016;**388**:818–828. https://doi.org/10.1016/S0140-6736(16)31258-2
386. Kotecha D, Flather MD, Altman DG, Holmes J, Rosano G, Wikstrand J, *et al.* Heart rate and rhythm and the benefit of beta-blockers in patients with heart failure. *J Am Coll Cardiol* 2017;**69**:2885–2896. https://doi.org/10.1016/j.jacc.2017.04.001
387. Kotecha D, Bunting KV, Gill SK, Mehta S, Stanbury M, Jones JC, *et al.* Effect of digoxin vs bisoprolol for heart rate control in atrial fibrillation on patient-reported quality of life: the RATE-AF randomized clinical trial. *JAMA* 2020;**324**:2497–2508. https://doi.org/10.1001/jama.2020.23138
388. Brignole M, Pokushalov E, Pentimalli F, Palmisano P, Chieffo E, Occhetta E, *et al.* A randomized controlled trial of atrioventricular junction ablation and cardiac resynchronization therapy in patients with permanent atrial fibrillation and narrow QRS. *Eur Heart J* 2018;**39**:3999–4008. https://doi.org/10.1093/eurheartj/ehy555
389. Brignole M, Pentimalli F, Palmisano P, Landolina M, Quartieri F, Occhetta E, *et al.* AV junction ablation and cardiac resynchronization for patients with permanent atrial fibrillation and narrow QRS: the APAF-CRT mortality trial. *Eur Heart J* 2021;**42**:4731–4739. https://doi.org/10.1093/eurheartj/ehab569
390. Huang W, Wang S, Su L, Fu G, Su Y, Chen K, *et al.* His-bundle pacing vs biventricular pacing following atrioventricular nodal ablation in patients with atrial fibrillation and reduced ejection fraction: a multicenter, randomized, crossover study–The ALTERNATIVE-AF trial. *Heart Rhythm* 2022;**19**:1948–1955. https://doi.org/10.1016/j.hrthm.2022.07.009
391. Guttmann OP, Pavlou M, O'Mahony C, Monserrat L, Anastasakis A, Rapezzi C, *et al.* Predictors of atrial fibrillation in hypertrophic cardiomyopathy. *Heart* 2017;**103**:672–678. https://doi.org/10.1136/heartjnl-2016-309672
392. Andrade JG, Wells GA, Deyell MW, Bennett M, Essebag V, Champagne J, *et al.* Cryoablation or drug therapy for initial treatment of atrial fibrillation. *N Engl J Med* 2021;**384**:305–315. https://doi.org/10.1056/NEJMoa2029980
393. Wazni OM, Dandamudi G, Sood N, Hoyt R, Tyler J, Durrani S, *et al.* Cryoballoon ablation as initial therapy for atrial fibrillation. *N Engl J Med* 2021;**384**:316–324. https://doi.org/10.1056/NEJMoa2029554
394. Freemantle N, Lafuente-Lafuente C, Mitchell S, Eckert L, Reynolds M. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace* 2011;**13**:329–345. https://doi.org/10.1093/europace/euq450
395. Kober L, Torp-Pedersen C, McMurray JJ, Gotzsche O, Levy S, Crijns H, *et al.* Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008;**358**:2678–2687. https://doi.org/10.1056/NEJMoa0800456
396. Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J, *et al.* Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med* 2011;**365**:2268–2276. https://doi.org/10.1056/NEJMoa1109867
397. Providencia R, Elliott P, Patel K, McCready J, Babu G, Srinivasan N, *et al.* Catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Heart* 2016;**102**:1533–1543. https://doi.org/10.1136/heartjnl-2016-309406
398. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, *et al.* Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and

cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019;**321**:1261–1274. https://doi.org/10.1001/jama.2019.0693

399. Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, *et al.* Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device. Results from the AATAC multicenter randomized trial. *Circulation* 2016;**133**:1637–1644. https://doi.org/10.1161/CIRCULATIONAHA.115.019406
400. Packer DL, Piccini JP, Monahan KH, Al-Khalidi HR, Silverstein AP, Noseworthy PA, *et al.* Ablation versus drug therapy for atrial fibrillation in heart failure: results from the CABANA trial. *Circulation* 2021;**143**:1377–1390. https://doi.org/10.1161/CIRCULATIONAHA.120.050991
401. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, *et al.* Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018;**378**:417–427. https://doi.org/10.1056/NEJMoa1707855
402. Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, *et al.* Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;**383**:1305–1316. https://doi.org/10.1056/NEJMoa2019422
403. Rillig A, Magnussen C, Ozga AK, Suling A, Brandes A, Breithardt G, *et al.* Early rhythm control therapy in patients with atrial fibrillation and heart failure. *Circulation* 2021;**144**:845–858. https://doi.org/10.1161/CIRCULATIONAHA.121.056323
404. Khan MN, Jais P, Cummings J, Di Biase L, Sanders P, Martin DO, *et al.* Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med* 2008;**359**:1778–1785. https://doi.org/10.1056/NEJMoa0708234
405. MacDonald MR, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M, *et al.* Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. *Heart* 2011;**97**:740–747. https://doi.org/10.1136/hrt.2010.207340
406. Jones DG, Haldar SK, Hussain W, Sharma R, Francis DP, Rahman-Haley SL, *et al.* A randomized trial to assess catheter ablation versus rate control in the management of persistent atrial fibrillation in heart failure. *J Am Coll Cardiol* 2013;**61**:1894–1903. https://doi.org/10.1016/j.jacc.2013.01.069
407. Hunter RJ, Berriman TJ, Diab I, Kamdar R, Richmond L, Baker V, *et al.* A randomized controlled trial of catheter ablation versus medical treatment of atrial fibrillation in heart failure (the CAMTAF trial). *Circ Arrhythm Electrophysiol* 2014;**7**:31–38. https://doi.org/10.1161/CIRCEP.113.000806
408. Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJA, Voskoboinik A, *et al.* Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI study. *J Am Coll Cardiol* 2017;**70**:1949–1961. https://doi.org/10.1016/j.jacc.2017.08.041
409. Romero J, Gabr M, Alviz I, Briceno D, Diaz JC, Rodriguez D, *et al.* Improved survival in patients with atrial fibrillation and heart failure undergoing catheter ablation compared to medical treatment: a systematic review and meta-analysis of randomized controlled trials. *J Cardiovasc Electrophysiol* 2022;**33**:2356–2366. https://doi.org/10.1111/jce.15622
410. Androulakis E, Sohrabi C, Briasoulis A, Bakogiannis C, Saberwal B, Siasos G, *et al.* Catheter ablation for atrial fibrillation in patients with heart failure with preserved ejection fraction: a systematic review and meta-analysis. *J Clin Med* 2022;**11**:288. https://doi.org/10.3390/jcm11020288
411. Bunch TJ, Munger TM, Friedman PA, Asirvatham SJ, Brady PA, Cha YM, *et al.* Substrate and procedural predictors of outcomes after catheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol* 2008;**19**:1009–1014. https://doi.org/10.1111/j.1540-8167.2008.01192.x
412. Bassiouny M, Lindsay BD, Lever H, Saliba W, Klein A, Banna M, *et al.* Outcomes of nonpharmacologic treatment of atrial fibrillation in patients with hypertrophic cardiomyopathy. *Heart Rhythm* 2015;**12**:1438–1447. https://doi.org/10.1016/j.hrthm.2015.03.042
413. Rowin EJ, Hausvater A, Link MS, Abt P, Gionfriddo W, Wang W, *et al.* Clinical profile and consequences of atrial fibrillation in hypertrophic cardiomyopathy. *Circulation* 2017;**136**:2420–2436. https://doi.org/10.1161/CIRCULATIONAHA.117.029267
414. Chen X, Dong JZ, Du X, Wu JH, Yu RH, Long DY, *et al.* Long-term outcome of catheter ablation for atrial fibrillation in patients with apical hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol* 2018;**29**:951–957. https://doi.org/10.1111/jce.13645
415. Di Donna P, Olivotto I, Delcre SDL, Caponi D, Scaglione M, Nault I, *et al.* Efficacy of catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: impact of age, atrial remodelling, and disease progression. *Europace* 2010;**12**:347–355. https://doi.org/10.1093/europace/euq013
416. Santangeli P, Di Biase L, Themistoclakis S, Raviele A, Schweikert RA, Lakkireddy D, *et al.* Catheter ablation of atrial fibrillation in hypertrophic cardiomyopathy: long-term outcomes and mechanisms of arrhythmia recurrence. *Circ Arrhythm Electrophysiol* 2013;**6**:1089–1094. https://doi.org/10.1161/CIRCEP.113.000339
417. Ha HS, Wang N, Wong S, Phan S, Liao J, Kumar N, *et al.* Catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy patients: a systematic review. *J Interv Card Electrophysiol* 2015;**44**:161–170. https://doi.org/10.1007/s10840-015-0047-8
418. Zhao DS, Shen Y, Zhang Q, Lin G, Lu YH, Chen BT, *et al.* Outcomes of catheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Europace* 2016;**18**:508–520. https://doi.org/10.1093/europace/euv339
419. Lapenna E, Pozzoli A, De Bonis M, La Canna G, Nisi T, Nascimbene S, *et al.* Mid-term outcomes of concomitant surgical ablation of atrial fibrillation in patients undergoing cardiac surgery for hypertrophic cardiomyopathy. *Eur J Cardiothorac Surg* 2017;**51**:1112–1118. https://doi.org/10.1093/ejcts/ezx017
420. Gasperetti A, James CA, Chen L, Schenker N, Casella M, Kany S, *et al.* Efficacy of catheter ablation for atrial arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy–a multicenter study. *J Clin Med* 2021;**10**:4962. https://doi.org/10.3390/jcm10214962
421. Maron BJ, Olivotto I, Bellone P, Conte MR, Cecchi F, Flygenring BP, *et al.* Clinical profile of stroke in 900 patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002;**39**:301–307. https://doi.org/10.1016/S0735-1097(01)01727-2
422. Losi M-A, Betocchi S, Aversa M, Lombardi R, Miranda M, D'Alessandro G, *et al.* Determinants of atrial fibrillation development in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2004;**94**:895–900. https://doi.org/10.1016/j.amjcard.2004.06.024
423. Siontis KC, Geske JB, Ong K, Nishimura RA, Ommen SR, Gersh BJ. Atrial fibrillation in hypertrophic cardiomyopathy: prevalence, clinical correlations, and mortality in a large high-risk population. *J Am Heart Assoc* 2014;**3**:e001002. https://doi.org/10.1161/JAHA.114.001002
424. Klopotowski M, Kwapiszewska A, Kukula K, Jamiolkowski J, Dabrowski M, Derejko P, *et al.* Clinical and echocardiographic parameters as risk factors for atrial fibrillation in patients with hypertrophic cardiomyopathy. *Clin Cardiol* 2018;**41**:1336–1340. https://doi.org/10.1002/clc.23050
425. Choi Y-J, Choi E-K, Han K-D, Jung J-H, Park J, Lee E, *et al.* Temporal trends of the prevalence and incidence of atrial fibrillation and stroke among Asian patients with hypertrophic cardiomyopathy: a nationwide population-based study. *Int J Cardiol* 2018;**273**:130–135. https://doi.org/10.1016/j.ijcard.2018.08.038
426. Yeung C, Enriquez A, Suarez-Fuster L, Baranchuk A. Atrial fibrillation in patients with inherited cardiomyopathies. *Europace* 2019;**21**:22–32. https://doi.org/10.1093/europace/euy064
427. Rowin EJ, Orfanos A, Estes NAM, Wang W, Link MS, Maron MS, *et al.* Occurrence and natural history of clinically silent episodes of atrial fibrillation in hypertrophic cardiomyopathy. *Am J Cardiol* 2017;**119**:1862–1865. https://doi.org/10.1016/j.amjcard.2017.02.040
428. van Velzen HG, Theuns DA, Yap SC, Michels M, Schinkel AF. Incidence of device-detected atrial fibrillation and long-term outcomes in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2017;**119**:100–105. https://doi.org/10.1016/j.amjcard.2016.08.092
429. Robinson K, Frenneaux MP, Stockins B, Karatasakis G, Poloniecki JD, McKenna WJ. Atrial fibrillation in hypertrophie cardiomyopathy: a longitudinal study. *J Am Coll Cardiol* 1990;**15**:1279–1285. https://doi.org/10.1016/S0735-1097(10)80014-2
430. Gaita F, Di Donna P, Olivotto I, Scaglione M, Ferrero I, Montefusco A, *et al.* Usefulness and safety of transcatheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2007;**99**:1575–1581. https://doi.org/10.1016/j.amjcard.2006.12.087
431. Zheng S, Jiang W, Dai J, Li K, Shi H, Wu W, *et al.* Five-year outcomes after catheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol* 2020;**31**:621–628. https://doi.org/10.1111/jce.14349
432. Cao ZJ, Guo XG, Sun Q, Yang JD, Wei HQ, Zhang S, *et al.* Pulmonary vein isolation implemented by second-generation cryoballoon for treating hypertrophic cardiomyopathy patients with symptomatic atrial fibrillation: a case-control study. *J Geriatr Cardiol* 2020;**17**:476–485.
433. Castagno D, Di Donna P, Olivotto I, Frontera A, Calo L, Scaglione M, *et al.* Transcatheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy: long-term results and clinical outcomes. *J Cardiovasc Electrophysiol* 2021;**32**:657–666. https://doi.org/10.1111/jce.14880
434. Dinshaw L, Munkler P, Schaffer B, Klatt N, Jungen C, Dickow J, *et al.* Ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy: treatment strategy, characteristics of consecutive atrial tachycardia and long-term outcome. *J Am Heart Assoc* 2021;**10**:e017451. https://doi.org/10.1161/JAHA.120.017451
435. Creta A, Elliott P, Earley MJ, Dhinoja M, Finlay M, Sporton S, *et al.* Catheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy: a European observational multicentre study. *Europace* 2021;**23**:1409–1417. https://doi.org/10.1093/europace/euab022
436. Grünig E, Tasman JA, Kücherer H, Franz W, Kübler W, Katus HA. Frequency and phenotypes of familial dilated cardiomyopathy. *J Am Coll Cardiol* 1998;**31**:186–194. https://doi.org/10.1016/S0735-1097(97)00434-8
437. Bourfiss M, Riele ASJMT, Mast TP, Cramer MJ, Heijden JF, Veen TABV, *et al.* Influence of genotype on structural atrial abnormalities and atrial fibrillation or flutter in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Cardiovasc Electrophysiol* 2016;**27**:1420–1428. https://doi.org/10.1111/jce.13094
438. Pasotti M, Klersy C, Pilotto A, Marziliano N, Rapezzi C, Serio A, *et al.* Long-term outcome and risk stratification in dilated cardiolaminopathies. *J Am Coll Cardiol* 2008;**52**:1250–1260. https://doi.org/10.1016/j.jacc.2008.06.044
439. Van Rijsingen IAW, Nannenberg EA, Arbustini E, Elliott PM, Mogensen J, Hermans-van Ast JF, *et al.* Gender-specific differences in major cardiac events and mortality in lamin

A/C mutation carriers. *Eur J Heart Fail* 2013;**15**:376–384. https://doi.org/10.1093/eurjhf/hfs191

440. Kumar S, Baldinger SH, Gandjbakhch E, Maury P, Sellal JM, Androulakis AF, *et al.* Long-term arrhythmic and nonarrhythmic outcomes of lamin A/C mutation carriers. *J Am Coll Cardiol* 2016;**68**:2299–2307. https://doi.org/10.1016/j.jacc.2016.08.058
441. Hasselberg NE, Haland TF, Saberniak J, Brekke PH, Berge KE, Leren TP, *et al.* Lamin A/C cardiomyopathy: young onset, high penetrance, and frequent need for heart transplantation. *Eur Heart J* 2017;**39**:853–860. https://doi.org/10.1093/eurheartj/ehx596
442. Cikes M, Claggett B, Shah AM, Desai AS, Lewis EF, Shah SJ, *et al.* Atrial fibrillation in heart failure with preserved ejection fraction: the TOPCAT trial. *JACC Heart Fail* 2018;**6**:689–697. https://doi.org/10.1016/j.jchf.2018.05.005
443. Zafrir B, Lund LH, Laroche C, Ruschitzka F, Crespo-Leiro MG, Coats AJS, *et al.* Prognostic implications of atrial fibrillation in heart failure with reduced, mid-range, and preserved ejection fraction: a report from 14 964 patients in the European Society of Cardiology Heart Failure Long-Term Registry. *Eur Heart J* 2018;**39**:4277–4284. https://doi.org/10.1093/eurheartj/ehy626
444. Cikes M, Planinc I, Claggett B, Cunningham J, Milicic D, Sweitzer N, *et al.* Atrial fibrillation in heart failure with preserved ejection fraction: the PARAGON-HF trial. *JACC Heart Fail* 2022;**10**:336–346. https://doi.org/10.1016/j.jchf.2022.01.018
445. Ducharme A, Swedberg K, Pfeffer MA, Cohen-Solal A, Granger CB, Maggioni AP, *et al.* Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Am Heart J* 2006;**152**:86–92. https://doi.org/10.1016/j.ahj.2005.06.036
446. Aldaas OM, Lupercio F, Darden D, Mylavarapu PS, Malladi CL, Han FT, *et al.* Meta-analysis of the usefulness of catheter ablation of atrial fibrillation in patients with heart failure with preserved ejection fraction. *Am J Cardiol* 2021;**142**:66–73. https://doi.org/10.1016/j.amjcard.2020.11.039
447. Chu AF, Zado E, Marchlinski FE. Atrial arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and ventricular tachycardia. *Am J Cardiol* 2010;**106**:720–722. https://doi.org/10.1016/j.amjcard.2010.04.031
448. Camm CF, James CA, Tichnell C, Murray B, Bhonsale A, Te Riele ASJM, *et al.* Prevalence of atrial arrhythmias in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Heart Rhythm* 2013;**10**:1661–1668. https://doi.org/10.1016/j.hrthm.2013.08.032
449. Saguner AM, Brunckhorst C, Duru F. Atrial arrhythmias in arrhythmogenic cardiomyopathy: at the beginning or at the end of the disease story? Reply. *Circ J* 2015;**79**:447. https://doi.org/10.1253/circj.CJ-14-1234
450. Müssigbrodt A, Knopp H, Efimova E, Weber A, Bertagnolli L, Hilbert S, *et al.* Supraventricular arrhythmias in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy associate with long-term outcome after catheter ablation of ventricular tachycardias. *Europace* 2018;**20**:1182–1187. https://doi.org/10.1093/europace/eux179
451. Saguner AM, Ganahl S, Kraus A, Baldinger SH, Medeiros-Domingo A, Saguner AR, *et al.* Clinical role of atrial arrhythmias in patients with arrhythmogenic right ventricular dysplasia. *Circ J* 2014;**78**:2854–2861. https://doi.org/10.1253/circj.CJ-14-0474
452. Valembois L, Audureau E, Takeda A, Jarzebowski W, Belmin J, Lafuente-Lafuente C. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. *Cochrane Database Syst Rev* 2019;**9**:CD005049. https://doi.org/10.1002/14651858.CD005049.pub4
453. Muchtar E, Gertz MA, Kumar SK, Lin G, Boilson B, Clavell A, *et al.* Digoxin use in systemic light-chain (AL) amyloidosis: contra-indicated or cautious use? *Amyloid* 2018;**25**:86–92. https://doi.org/10.1080/13506129.2018.1449744
454. Donnelly JP, Sperry BW, Gabrovsek A, Ikram A, Tang WHW, Estep J, *et al.* Digoxin use in cardiac amyloidosis. *Am J Cardiol* 2020;**133**:134–138. https://doi.org/10.1016/j.amjcard.2020.07.034
455. Pollak A, Falk RH. Left ventricular systolic dysfunction precipitated by verapamil in cardiac amyloidosis. *Chest* 1993;**104**:618–620. https://doi.org/10.1378/chest.104.2.618
456. Yang YJ, Yuan JQ, Fan CM, Pu JL, Fang PH, Ma J, *et al.* Incidence of ischemic stroke and systemic embolism in patients with hypertrophic cardiomyopathy, nonvalvular atrial fibrillation, CHA2DS2-VASc score of 1 and without anticoagulant therapy. *Heart Vessels* 2016;**31**:1148–1153. https://doi.org/10.1007/s00380-015-0718-5
457. Lee SE, Park JK, Uhm JS, Kim JY, Pak HN, Lee MH, *et al.* Impact of atrial fibrillation on the clinical course of apical hypertrophic cardiomyopathy. *Heart* 2017;**103**:1496–1501. https://doi.org/10.1136/heartjnl-2016-310720
458. Hirota T, Kubo T, Baba Y, Ochi Y, Takahashi A, Yamasaki N, *et al.* Clinical profile of thromboembolic events in patients with hypertrophic cardiomyopathy in a regional Japanese cohort – results from Kochi RYOMA study. *Circ J* 2019;**83**:1747–1754. https://doi.org/10.1253/circj.CJ-19-0186
459. Tsuda T, Hayashi K, Fujino N, Konno T, Tada H, Nomura A, *et al.* Effect of hypertrophic cardiomyopathy on the prediction of thromboembolism in patients with nonvalvular atrial fibrillation. *Heart Rhythm* 2019;**16**:829–837. https://doi.org/10.1016/j.hrthm.2018.11.029
460. Lozier MR, Sanchez AM, Lee JJ, Donath EM, Font VE, Escolar E. Thromboembolic outcomes of different anticoagulation strategies for patients with atrial fibrillation in the setting of hypertrophic cardiomyopathy: a systematic review. *J Atr Fibrillation* 2019;**12**:2207. https://doi.org/10.4022/jafib.2207
461. Hsu JC, Huang YT, Lin LY. Stroke risk in hypertrophic cardiomyopathy patients with atrial fibrillation: a nationwide database study. *Aging (Albany NY)* 2020;**12**:24219–-24227. https://doi.org/10.18632/aging.104133
462. Komatsu J, Imai RI, Nakaoka Y, Nishida K, Seki SI, Kubo T, *et al.* Importance of paroxysmal atrial fibrillation and sex differences in the prevention of embolic stroke in hypertrophic cardiomyopathy. *Circ Rep* 2021;**3**:273–278. https://doi.org/10.1253/circrep.CR-20-0101
463. Donnellan E, Elshazly MB, Vakamudi S, Wazni OM, Cohen JA, Kanj M, *et al.* No association between CHADS-VASc score and left atrial appendage thrombus in patients with transthyretin amyloidosis. *JACC Clin Electrophysiol* 2019;**5**:1473–1474. https://doi.org/10.1016/j.jacep.2019.10.013
464. El-Am EA, Dispenzieri A, Melduni RM, Ammash NM, White RD, Hodge DO, *et al.* Direct current cardioversion of atrial arrhythmias in adults with cardiac amyloidosis. *J Am Coll Cardiol* 2019;**73**:589–597. https://doi.org/10.1016/j.jacc.2018.10.079
465. Aguilar MI, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev* 2005;**3**:CD001927. https://doi.org/10.1002/14651858.CD001927
466. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;**146**:857–867. https://doi.org/10.7326/0003-4819-146-12-200706190-00007
467. Aguilar MI, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. *Cochrane Database Syst Rev* 2007;**3**:CD006186. https://doi.org/10.1002/14651858.CD006186.pub2
468. Andersen LV, Vestergaard P, Deichgraeber P, Lindholt JS, Mortensen LS, Frost L. Warfarin for the prevention of systemic embolism in patients with non-valvular atrial fibrillation: a meta-analysis. *Heart* 2008;**94**:1607–1613. https://doi.org/10.1136/hrt.2007.135657
469. Dogliotti A, Paolasso E, Giugliano RP. Current and new oral antithrombotics in non-valvular atrial fibrillation: a network meta-analysis of 79 808 patients. *Heart* 2014;**100**:396–405. https://doi.org/10.1136/heartjnl-2013-304347
470. Joundi RA, Cipriano LE, Sposato LA, Saposnik G; Stroke Outcomes Research Working Group. Ischemic stroke risk in patients with atrial fibrillation and CHA2DS2-VASc score of 1: systematic review and meta-analysis. *Stroke* 2016;**47**:1364–1367. https://doi.org/10.1161/STROKEAHA.115.012609
471. Nielsen PB, Larsen TB, Skjoth F, Overvad TF, Lip GY. Stroke and thromboembolic event rates in atrial fibrillation according to different guideline treatment thresholds: a nationwide cohort study. *Sci Rep* 2016;**6**:27410. https://doi.org/10.1038/srep27410
472. Shin SY, Han SJ, Kim JS, Im SI, Shim J, Ahn J, *et al.* Identification of markers associated with development of stroke in "clinically low-risk" atrial fibrillation patients. *J Am Heart Assoc* 2019;**8**:e012697. https://doi.org/10.1161/JAHA.119.012697
473. Krittayaphong R, Raungrattanaamporn O, Bhuripanyo K, Sriratanasathavorn C, Pooranawattanakul S, Punlee K, *et al.* A randomized clinical trial of the efficacy of radiofrequency catheter ablation and amiodarone in the treatment of symptomatic atrial fibrillation. *J Med Assoc Thai* 2003;**86**:S8–16.
474. Stabile G, Bertaglia E, Senatore G, De Simone A, Zoppo F, Donnici G, *et al.* Catheter ablation treatment in patients with drug-refractory atrial fibrillation: a prospective, multi-centre, randomized, controlled study (Catheter Ablation For The Cure Of Atrial Fibrillation Study). *Eur Heart J* 2006;**27**:216–221. https://doi.org/10.1093/eurheartj/ehi583
475. Pappone C, Augello G, Sala S, Gugliotta F, Vicedomini G, Gulletta S, *et al.* A randomized trial of circumferential pulmonary vein ablation versus antiarrhythmic drug therapy in paroxysmal atrial fibrillation: the APAF Study. *J Am Coll Cardiol* 2006;**48**:2340–2347. https://doi.org/10.1016/j.jacc.2006.08.037
476. Oral H, Pappone C, Chugh A, Good E, Bogun F, Pelosi F Jr, *et al.* Circumferential pulmonary-vein ablation for chronic atrial fibrillation. *N Engl J Med* 2006;**354**:934–941. https://doi.org/10.1056/NEJMoa050955
477. Jais P, Cauchemez B, Macle L, Daoud E, Khairy P, Subbiah R, *et al.* Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation* 2008;**118**:2498–2505. https://doi.org/10.1161/CIRCULATIONAHA.108.772582
478. Forleo GB, Mantica M, De Luca L, Leo R, Santini L, Panigada S, *et al.* Catheter ablation of atrial fibrillation in patients with diabetes mellitus type 2: results from a randomized study comparing pulmonary vein isolation versus antiarrhythmic drug therapy. *J Cardiovasc Electrophysiol* 2009;**20**:22–28. https://doi.org/10.1111/j.1540-8167.2008.01275.x
479. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, *et al.* Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA* 2010;**303**:333–340. https://doi.org/10.1001/jama.2009.2029
480. Pappone C, Vicedomini G, Augello G, Manguso F, Saviano M, Baldi M, *et al.* Radiofrequency catheter ablation and antiarrhythmic drug therapy: a prospective, randomized, 4-year follow-up trial: the APAF study. *Circ Arrhythm Electrophysiol* 2011;**4**:808–814. https://doi.org/10.1161/CIRCEP.111.966408

481. Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, *et al.* Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol* 2013;**61**: 1713–1723. https://doi.org/10.1016/j.jacc.2012.11.064
482. Blandino A, Toso E, Scaglione M, Anselmino M, Ferraris F, Sardi D, *et al.* Long-term efficacy and safety of two different rhythm control strategies in elderly patients with symptomatic persistent atrial fibrillation. *J Cardiovasc Electrophysiol* 2013;**24**: 731–738. https://doi.org/10.1111/jce.12126
483. Mont L, Bisbal F, Hernandez-Madrid A, Perez-Castellano N, Vinolas X, Arenal A, *et al.* Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J* 2014;**35**: 501–507. https://doi.org/10.1093/eurheartj/eht457
484. Hummel J, Michaud G, Hoyt R, DeLurgio D, Rasekh A, Kusumoto F, *et al.* Phased RF ablation in persistent atrial fibrillation. *Heart Rhythm* 2014;**11**:202–209. https://doi.org/10.1016/j.hrthm.2013.11.009
485. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, *et al.* Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med* 2015;**372**:1812–1822. https://doi.org/10.1056/NEJMoa1408288
486. Reddy VY, Dukkipati SR, Neuzil P, Natale A, Albenque JP, Kautzner J, *et al.* Randomized, controlled trial of the safety and effectiveness of a contact force-sensing irrigated catheter for ablation of paroxysmal atrial fibrillation: results of the TactiCath Contact Force Ablation Catheter Study for Atrial Fibrillation (TOCCASTAR) study. *Circulation* 2015;**132**:907–915. https://doi.org/10.1161/CIRCULATIONAHA.114.014092
487. Dukkipati SR, Cuoco F, Kutinsky I, Aryana A, Bahnson TD, Lakkireddy D, *et al.* Pulmonary vein isolation using the visually guided laser balloon: a prospective, multicenter, and randomized comparison to standard radiofrequency ablation. *J Am Coll Cardiol* 2015;**66**:1350–1360. https://doi.org/10.1016/j.jacc.2015.07.036
488. Sohara H, Ohe T, Okumura K, Naito S, Hirao K, Shoda M, *et al.* Hot balloon ablation of the pulmonary veins for paroxysmal AF: a multicenter randomized trial in Japan. *J Am Coll Cardiol* 2016;**68**:2747–2757. https://doi.org/10.1016/j.jacc.2016.10.037
489. Bertaglia E, Senatore G, De Michieli L, De Simone A, Amellone C, Ferretto S, *et al.* Twelve-year follow-up of catheter ablation for atrial fibrillation: a prospective, multicenter, randomized study. *Heart Rhythm* 2017;**14**:486–492. https://doi.org/10.1016/j.hrthm.2016.12.023
490. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, *et al.* Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019;**321**:1275–1285. https://doi.org/10.1001/jama.2019.0692
491. Contreras-Valdes FM, Buxton AE, Josephson ME, Anter E. Atrial fibrillation ablation in patients with hypertrophic cardiomyopathy: long-term outcomes and clinical predictors. *J Am Coll Cardiol* 2015;**65**:1485–1487. https://doi.org/10.1016/j.jacc.2014.12.063
492. Rozen G, Elbaz-Greener G, Marai I, Andria N, Hosseini SM, Biton Y, *et al.* Utilization and complications of catheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy. *J Am Heart Assoc* 2020;**9**:e015721. https://doi.org/10.1161/JAHA.119.015721
493. Hodges K, Tang A, Rivas CG, Umana-Pizano J, Chemtob R, Desai MY, *et al.* Surgical ablation of atrial fibrillation in hypertrophic obstructive cardiomyopathy: outcomes of a tailored surgical approach. *J Card Surg* 2020;**35**:2957–2964. https://doi.org/10.1111/jocs.14946
494. Meng Y, Zhang Y, Liu P, Zhu C, Lu T, Hu E, *et al.* Clinical efficacy and safety of Cox-Maze IV procedure for atrial fibrillation in patients with hypertrophic obstructive cardiomyopathy. *Front Cardiovasc Med* 2021;**8**:720950. https://doi.org/10.3389/fcvm.2021.720950
495. Zhang HD, Ding L, Weng SX, Zhou B, Ding XT, Hu LX, *et al.* Characteristics and long-term ablation outcomes of supraventricular arrhythmias in hypertrophic cardiomyopathy: a 10-year, single-center experience. *Front Cardiovasc Med* 2021;**8**:766571. https://doi.org/10.3389/fcvm.2021.766571
496. Cardona-Guarache R, Astrom-Aneq M, Oesterle A, Asirvatham R, Svetlichnaya J, Marcus GM, *et al.* Atrial arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy: prevalence, echocardiographic predictors, and treatment. *J Cardiovasc Electrophysiol* 2019;**30**:1801–1810. https://doi.org/10.1111/jce.14069
497. Zhao L, Xu K, Jiang W, Zhou L, Wang Y, Zhang X, *et al.* Long-term outcomes of catheter ablation of atrial fibrillation in dilated cardiomyopathy. *Int J Cardiol* 2015;**190**: 227–232. https://doi.org/10.1016/j.ijcard.2015.04.186
498. Stollberger C, Gatterer E, Finsterer J, Kuck KH, Tilz RR. Repeated radiofrequency ablation of atrial tachycardia in restrictive cardiomyopathy secondary to myofibrillar myopathy. *J Cardiovasc Electrophysiol* 2014;**25**:905–907. https://doi.org/10.1111/jce.12436
499. Briceno DF, Markman TM, Lupercio F, Romero J, Liang JJ, Villablanca PA, *et al.* Catheter ablation versus conventional treatment of atrial fibrillation in patients with heart failure with reduced ejection fraction: a systematic review and meta-analysis of randomized controlled trials. *J Interv Card Electrophysiol* 2018;**53**:19–29. https://doi.org/10.1007/s10840-018-0425-0
500. Prabhu S, Costello BT, Taylor AJ, Gutman SJ, Voskoboinik A, McLellan AJA, *et al.* Regression of diffuse ventricular fibrosis following restoration of sinus rhythm with catheter ablation in patients with atrial fibrillation and systolic dysfunction: a substudy of the CAMERA MRI trial. *JACC Clin Electrophysiol* 2018;**4**:999–1007. https://doi.org/10.1016/j.jacep.2018.04.013
501. Kuck KH, Merkely B, Zahn R, Arentz T, Seidl K, Schluter M, *et al.* Catheter ablation versus best medical therapy in patients with persistent atrial fibrillation and congestive heart failure: the randomized AMICA trial. *Circ Arrhythm Electrophysiol* 2019;**12**: e007731. https://doi.org/10.1161/CIRCEP.119.007731
502. Wazni OM, Marrouche NF, Martin DO, Verma A, Bhargava M, Saliba W, *et al.* Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. *JAMA* 2005;**293**:2634–2640. https://doi.org/10.1001/jama.293.21.2634
503. Cosedis Nielsen J, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Kongstad O, *et al.* Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med* 2012;**367**:1587–1595. https://doi.org/10.1056/NEJMoa1113566
504. Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J, *et al.* Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA* 2014;**311**:692–700. https://doi.org/10.1001/jama.2014.467
505. Nielsen JC, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Pehrson SM, *et al.* Long-term efficacy of catheter ablation as first-line therapy for paroxysmal atrial fibrillation: 5-year outcome in a randomised clinical trial. *Heart* 2017;**103**:368–376. https://doi.org/10.1136/heartjnl-2016-309781
506. Kuniss M, Pavlovic N, Velagic V, Hermida JS, Healey S, Arena G, *et al.* Cryoballoon ablation vs. antiarrhythmic drugs: first-line therapy for patients with paroxysmal atrial fibrillation. *Europace* 2021;**23**:1033–1041. https://doi.org/10.1093/europace/euab029
507. Parkash R, Wells GA, Rouleau J, Talajic M, Essebag V, Skanes A, *et al.* Randomized ablation-based rhythm-control versus rate-control trial in patients with heart failure and atrial fibrillation: results from the RAFT-AF trial. *Circulation* 2022;**145**: 1693–1704. https://doi.org/10.1161/CIRCULATIONAHA.121.057095
508. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, *et al.* Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol* 2014;**64**:2222–2231. https://doi.org/10.1016/j.jacc.2014.09.028
509. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, *et al.* Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). *J Am Coll Cardiol* 2015;**65**:2159–2169. https://doi.org/10.1016/j.jacc.2015.03.002
510. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, *et al.* Impact of CARDIOrespiratory FITness on arrhythmia recurrence in obese individuals with atrial fibrillation: the CARDIO-FIT study. *J Am Coll Cardiol* 2015;**66**:985–996. https://doi.org/10.1016/j.jacc.2015.06.488
511. Wong CX, Sullivan T, Sun MT, Mahajan R, Pathak RK, Middeldorp M, *et al.* Obesity and the risk of incident, post-operative, and post-ablation atrial fibrillation: a meta-analysis of 626,603 individuals in 51 studies. *JACC Clin Electrophysiol* 2015;**1**:139–152. https://doi.org/10.1016/j.jacep.2015.04.004
512. Trines SA, Stabile G, Arbelo E, Dagres N, Brugada J, Kautzner J, *et al.* Influence of risk factors in the ESC-EHRA EORP atrial fibrillation ablation long-term registry. *Pacing Clin Electrophysiol* 2019;**42**:1365–1373. https://doi.org/10.1111/pace.13763
513. Voskoboinik A, Kalman JM, De Silva A, Nicholls T, Costello B, Nanayakkara S, *et al.* Alcohol abstinence in drinkers with atrial fibrillation. *N Engl J Med* 2020;**382**:20–28. https://doi.org/10.1056/NEJMoa1817591
514. Meng L, Tseng CH, Shivkumar K, Ajijola O. Efficacy of stellate ganglion blockade in managing electrical storm: a systematic review. *JACC Clin Electrophysiol* 2017;**3**: 942–949. https://doi.org/10.1016/j.jacep.2017.06.006
515. Do DH, Bradfield J, Ajijola OA, Vaseghi M, Le J, Rahman S, *et al.* Thoracic epidural anesthesia can be effective for the short-term management of ventricular tachycardia storm. *J Am Heart Assoc* 2017;**6**:e007080. https://doi.org/10.1161/JAHA.117.007080
516. Richardson T, Lugo R, Saavedra P, Crossley G, Clair W, Shen S, *et al.* Cardiac sympathectomy for the management of ventricular arrhythmias refractory to catheter ablation. *Heart Rhythm* 2018;**15**:56–62. https://doi.org/10.1016/j.hrthm.2017.09.006
517. Price J, Mah DY, Fynn-Thompson FL, Tsirka AE. Successful bilateral thoracoscopic sympathectomy for recurrent ventricular arrhythmia in a pediatric patient with hypertrophic cardiomyopathy. *HeartRhythm Case Rep* 2020;**6**:23–26. https://doi.org/10.1016/j.hrcr.2019.10.003
518. Vaseghi M, Barwad P, Malavassi Corrales FJ, Tandri H, Mathuria N, Shah R, *et al.* Cardiac sympathetic denervation for refractory ventricular arrhythmias. *J Am Coll Cardiol* 2017;**69**:3070–3080. https://doi.org/10.1016/j.jacc.2017.04.035
519. Dusi V, Gornbein J, Do DH, Sorg JM, Khakpour H, Krokhaleva Y, *et al.* Arrhythmic risk profile and outcomes of patients undergoing cardiac sympathetic denervation for recurrent monomorphic ventricular tachycardia after ablation. *J Am Heart Assoc* 2021;**10**: e018371. https://doi.org/10.1161/JAHA.120.018371
520. Krug D, Blanck O, Andratschke N, Guckenberger M, Jumeau R, Mehrhof F, *et al.* Recommendations regarding cardiac stereotactic body radiotherapy for treatment refractory ventricular tachycardia. *Heart Rhythm* 2021;**18**:2137–2145. https://doi.org/10.1016/j.hrthm.2021.08.004
521. Lin G, Nishimura RA, Gersh BJ, Phil D, Ommen SR, Ackerman MJ, *et al.* Device complications and inappropriate implantable cardioverter defibrillator shocks in patients

with hypertrophic cardiomyopathy. *Heart* 2009;**95**:709–714. https://doi.org/10.1136/hrt.2008.150656
522. Orgeron GM, James CA, Te Riele A, Tichnell C, Murray B, Bhonsale A, *et al.* Implantable cardioverter-defibrillator therapy in arrhythmogenic right ventricular dysplasia/cardiomyopathy: predictors of appropriate therapy, outcomes, and complications. *J Am Heart Assoc* 2017;**6**:e006242. https://doi.org/10.1161/JAHA.117.006242
523. Corrado D, Calkins H, Link MS, Leoni L, Favale S, Bevilacqua M, *et al.* Prophylactic implantable defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and no prior ventricular fibrillation or sustained ventricular tachycardia. *Circulation* 2010;**122**:1144–1152. https://doi.org/10.1161/CIRCULATIONAHA.109.913871
524. Protonotarios A, Bariani R, Cappelletto C, Pavlou M, Garcia-Garcia A, Cipriani A, *et al.* Importance of genotype for risk stratification in arrhythmogenic right ventricular cardiomyopathy using the 2019 ARVC risk calculator. *Eur Heart J* 2022;**43**:3053–3067. https://doi.org/10.1093/eurheartj/ehac235
525. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, *et al.* Hypertrophic cardiomyopathy outcomes I. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J* 2014;**35**:2010–2020. https://doi.org/10.1093/eurheartj/eht439
526. Jorda P, Bosman LP, Gasperetti A, Mazzanti A, Gourraud JB, Davies B, *et al.* Arrhythmic risk prediction in arrhythmogenic right ventricular cardiomyopathy: external validation of the arrhythmogenic right ventricular cardiomyopathy risk calculator. *Eur Heart J* 2022;**43**:3041–3052. https://doi.org/10.1093/eurheartj/ehac289
527. Masri A, Altibi AM, Erqou S, Zmaili MA, Saleh A, Al-Adham R, *et al.* Wearable cardioverter-defibrillator therapy for the prevention of sudden cardiac death: a systematic review and meta-analysis. *JACC Clin Electrophysiol* 2019;**5**:152–161. https://doi.org/10.1016/j.jacep.2018.11.011
528. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS, *et al.* Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000;**101**:1297–1302. https://doi.org/10.1161/01.CIR.101.11.1297
529. Antiarrhythmics versus Implantable Defibrillators Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;**337**:1576–1583. https://doi.org/10.1056/NEJM199711273372202
530. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000;**102**:748–754. https://doi.org/10.1161/01.CIR.102.7.748
531. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, *et al.* Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. *Eur Heart J* 2000;**21**:2071–2078. https://doi.org/10.1053/euhj.2000.2476
532. Elliott PM, Sharma S, Varnava A, Poloniecki J, Rowland E, McKenna WJ. Survival after cardiac arrest or sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1999;**33**:1596–1601. https://doi.org/10.1016/S0735-1097(99)00056-X
533. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, *et al.* The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–1549. https://doi.org/10.1056/NEJMoa050496
534. Cecchi F, Maron BJ, Epstein SE. Long-term outcome of patients with hypertrophic cardiomyopathy successfully resuscitated after cardiac arrest. *J Am Coll Cardiol* 1989;**13**:1283–1288. https://doi.org/10.1016/0735-1097(89)90302-1
535. Miron A, Lafreniere-Roula M, Steve Fan CP, Armstrong KR, Dragulescu A, Papaz T, *et al.* A validated model for sudden cardiac death risk prediction in pediatric hypertrophic cardiomyopathy. *Circulation* 2020;**142**:217–229. https://doi.org/10.1161/CIRCULATIONAHA.120.047235
536. Aquaro GD, De Luca A, Cappelletto C, Raimondi F, Bianco F, Botto N, *et al.* Comparison of different prediction models for the indication of implanted cardioverter defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy. *ESC Heart Fail* 2020;**7**:4080–4088. https://doi.org/10.1002/ehf2.13019
537. Baudinaud P, Laredo M, Badenco N, Rouanet S, Waintraub X, Duthoit G, *et al.* External validation of a risk prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. *Can J Cardiol* 2021;**37**:1263–1266. https://doi.org/10.1016/j.cjca.2021.02.018
538. Bosman LP, Nielsen Gerlach CL, Cadrin-Tourigny J, Orgeron G, Tichnell C, Murray B, *et al.* Comparing clinical performance of current implantable cardioverter-defibrillator implantation recommendations in arrhythmogenic right ventricular cardiomyopathy. *Europace* 2022;**24**:296–305. https://doi.org/10.1093/europace/euab162
539. Cadrin-Tourigny J, Bosman LP, Nozza A, Wang W, Tadros R, Bhonsale A, *et al.* A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J* 2022;**43**:e1–e9. https://doi.org/10.1093/eurheartj/ehac180
540. Kayvanpour E, Sammani A, Sedaghat-Hamedani F, Lehmann DH, Broezel A, Koelemenoglu J, *et al.* A novel risk model for predicting potentially life-threatening arrhythmias in non-ischemic dilated cardiomyopathy (DCM-SVA risk). *Int J Cardiol* 2021;**339**:75–82. https://doi.org/10.1016/j.ijcard.2021.07.002
541. Wahbi K, Ben Yaou R, Gandjbakhch E, Anselme F, Gossios T, Lakdawala NK, *et al.* Development and validation of a new risk prediction score for life-threatening ventricular tachyarrhythmias in laminopathies. *Circulation* 2019;**140**:293–302. https://doi.org/10.1161/CIRCULATIONAHA.118.039410
542. Verstraelen TE, van Lint FHM, Bosman LP, de Brouwer R, Proost VM, Abeln BGS, *et al.* Prediction of ventricular arrhythmia in phospholamban p.Arg14del mutation carriers-reaching the frontiers of individual risk prediction. *Eur Heart J* 2021;**42**:2842–2850. https://doi.org/10.1093/eurheartj/ehab294
543. Knops RE, Olde Nordkamp LRA, Delnoy PHM, Boersma LVA, Kuschyk J, El-Chami MF, *et al.* Subcutaneous or transvenous defibrillator therapy. *N Engl J Med* 2020;**383**:526–536. https://doi.org/10.1056/NEJMoa1915932
544. Cardim N, Brito D, Rocha Lopes L, Freitas A, Araujo C, Belo A, *et al.* The Portuguese registry of hypertrophic cardiomyopathy: overall results. *Rev Port Cardiol (Engl Ed)* 2018;**37**:1–10. https://doi.org/10.1016/j.repc.2017.08.005
545. McKenna WJ, Judge DP. Epidemiology of the inherited cardiomyopathies. *Nat Rev Cardiol* 2021;**18**:22–36. https://doi.org/10.1038/s41569-020-0428-2
546. Pelliccia F, Limongelli G, Autore C, Gimeno-Blanes JR, Basso C, Elliott P. Sex-related differences in cardiomyopathies. *Int J Cardiol* 2019;**286**:239–243. https://doi.org/10.1016/j.ijcard.2018.10.091
547. Perez-Sanchez I, Romero-Puche AJ, Garcia-Molina Saez E, Sabater-Molina M, Lopez-Ayala JM, Munoz-Esparza C, *et al.* Factors influencing the phenotypic expression of hypertrophic cardiomyopathy in genetic carriers. *Rev Esp Cardiol (Engl Ed)* 2018;**71**:146–154. https://doi.org/10.1016/j.rec.2017.06.002
548. Argiro A, Ho C, Day SM, van der Velden J, Cerbai E, Saberi S, *et al.* Sex-related differences in genetic cardiomyopathies. *J Am Heart Assoc* 2022;**11**:e024947. https://doi.org/10.1161/JAHA.121.024947
549. Shah RA, Asatryan B, Sharaf Dabbagh G, Aung N, Khanji MY, Lopes LR, *et al.* Genotype-first approach I. Frequency, penetrance, and variable expressivity of dilated cardiomyopathy-associated putative pathogenic gene variants in UK Biobank participants. *Circulation* 2022;**146**:110–124. https://doi.org/10.1161/CIRCULATIONAHA.121.058143
550. de Marvao A, McGurk KA, Zheng SL, Thanaj M, Bai W, Duan J, *et al.* Phenotypic expression and outcomes in individuals with rare genetic variants of hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2021;**78**:1097–1110. https://doi.org/10.1016/j.jacc.2021.07.017
551. McGurk KA, Zheng SL, Henry A, Josephs K, Edwards M, de Marvao A, *et al.* Correspondence on "ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG)" by Miller et al. *Genet Med* 2022;**24**:744–746. https://doi.org/10.1016/j.gim.2021.10.020
552. Maron BJ, Casey SA, Olivotto I, Sherrid MV, Semsarian C, Autore C, *et al.* Clinical course and quality of life in high-risk patients with hypertrophic cardiomyopathy and implantable cardioverter-defibrillators. *Circ Arrhythm Electrophysiol* 2018;**11**:e005820. https://doi.org/10.1161/CIRCEP.117.005820
553. Ingles J, Sarina T, Kasparian N, Semsarian C. Psychological wellbeing and posttraumatic stress associated with implantable cardioverter defibrillator therapy in young adults with genetic heart disease. *Int J Cardiol* 2013;**168**:3779–3784. https://doi.org/10.1016/j.ijcard.2013.06.006
554. James CA, Tichnell C, Murray B, Daly A, Sears SF, Calkins H. General and disease-specific psychosocial adjustment in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy with implantable cardioverter defibrillators: a large cohort study. *Circ Cardiovasc Genet* 2012;**5**:18–24. https://doi.org/10.1161/CIRCGENETICS.111.960898
555. Rhodes AC, Murray B, Tichnell C, James CA, Calkins H, Sears SF. Quality of life metrics in arrhythmogenic right ventricular cardiomyopathy patients: the impact of age, shock and sex. *Int J Cardiol* 2017;**248**:216–220. https://doi.org/10.1016/j.ijcard.2017.08.026
556. Sweeting J, Ball K, McGaughran J, Atherton J, Semsarian C, Ingles J. Impact of the implantable cardioverter defibrillator on confidence to undertake physical activity in inherited heart disease: a cross-sectional study. *Eur J Cardiovasc Nurs* 2017;**16**:742–752. https://doi.org/10.1177/1474515117715760
557. Sears SF Jr, Conti JB. Quality of life and psychological functioning of icd patients. *Heart* 2002;**87**:488–493. https://doi.org/10.1136/heart.87.5.488
558. Ingles J, Spinks C, Yeates L, McGeechan K, Kasparian N, Semsarian C. Posttraumatic stress and prolonged grief after the sudden cardiac death of a young relative. *JAMA Intern Med* 2016;**176**:402–405. https://doi.org/10.1001/jamainternmed.2015.7808
559. Stiles MK, Wilde AAM, Abrams DJ, Ackerman MJ, Albert CM, Behr ER, *et al.* 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families. *Heart Rhythm* 2021;**18**:e1–e50. https://doi.org/10.1016/j.hrthm.2020.10.010
560. van den Heuvel LM, Sarina T, Sweeting J, Yeates L, Bates K, Spinks C, *et al.* A prospective longitudinal study of health-related quality of life and psychological wellbeing after an implantable cardioverter-defibrillator in patients with genetic heart diseases. *Heart Rhythm O2* 2022;**3**:143–151. https://doi.org/10.1016/j.hroo.2022.02.003
561. Passman R, Subacius H, Ruo B, Schaechter A, Howard A, Sears SF, *et al.* Implantable cardioverter defibrillators and quality of life: results from the defibrillators in

nonischemic cardiomyopathy treatment evaluation study. *Arch Intern Med* 2007;**167**: 2226–2232. https://doi.org/10.1001/archinte.167.20.2226
562. Ni SQ, Ni J, Yang N, Wang J. Effect of magnetic nanoparticles on the performance of activated sludge treatment system. *Bioresour Technol* 2013;**143**:555–561. https://doi.org/10.1016/j.biortech.2013.06.041
563. von Kanel R, Baumert J, Kolb C, Cho E-Y, Ladwig K-H. Chronic posttraumatic stress and its predictors in patients living with an implantable cardioverter defibrillator. *J Affect Disord* 2011;**131**:344–352. https://doi.org/10.1016/j.jad.2010.12.002
564. Lewis KB, Carroll SL, Birnie D, Stacey D, Matlock DD. Incorporating patients' preference diagnosis in implantable cardioverter defibrillator decision-making: a review of recent literature. *Curr Opin Cardiol* 2018;**33**:42–49. https://doi.org/10.1097/HCO.0000000000000464
565. Luiten RC, Ormond K, Post L, Asif IM, Wheeler MT, Caleshu C. Exercise restrictions trigger psychological difficulty in active and athletic adults with hypertrophic cardiomyopathy. *Open Heart* 2016;**3**:e000488. https://doi.org/10.1136/openhrt-2016-000488
566. Subas T, Luiten R, Hanson-Kahn A, Wheeler M, Caleshu C. Evolving decisions: perspectives of active and athletic individuals with inherited heart disease who exercise against recommendations. *J Genet Couns* 2019;**28**:119–129. https://doi.org/10.1007/s10897-018-0297-6
567. Alpert C, Day SM, Saberi S. Sports and exercise in athletes with hypertrophic cardiomyopathy. *Clin Sports Med* 2015;**34**:489–505. https://doi.org/10.1016/j.csm.2015.03.005
568. Day SM. Exercise in hypertrophic cardiomyopathy. *J Cardiovasc Transl Res* 2009;**2**: 407–414. https://doi.org/10.1007/s12265-009-9134-5
569. Simon NM. Treating complicated grief. *JAMA* 2013;**310**:416–423. https://doi.org/10.1001/jama.2013.8614
570. McDonald K, Sharpe L, Yeates L, Semsarian C, Ingles J. Needs analysis of parents following sudden cardiac death in the young. *Open Heart* 2020;**7**:e001120. https://doi.org/10.1136/openhrt-2019-001120
571. Wisten A, Zingmark K. Supportive needs of parents confronted with sudden cardiac death–a qualitative study. *Resuscitation* 2007;**74**:68–74. https://doi.org/10.1016/j.resuscitation.2006.11.014
572. O'Donovan CE, Waddell-Smith KE, Skinner JR, Broadbent E. Predictors of β-blocker adherence in cardiac inherited disease. *Open Heart* 2018;**5**:e000877. https://doi.org/10.1136/openhrt-2018-000877
573. Cupples S, Dew MA, Grady KL, De Geest S, Dobbels F, Lanuza D, *et al.* Report of the Psychosocial Outcomes Workgroup of the Nursing and Social Sciences Council of the International Society for Heart and Lung Transplantation: present status of research on psychosocial outcomes in cardiothoracic transplantation: review and recommendations for the field. *J Heart Lung Transplant* 2006;**25**:716–725. https://doi.org/10.1016/j.healun.2006.02.005
574. Aatre RD, Day SM. Psychological issues in genetic testing for inherited cardiovascular diseases. *Circ Cardiovasc Genet* 2011;**4**:81–90. https://doi.org/10.1161/CIRCGENETICS.110.957365
575. Burns C, James C, Ingles J. Communication of genetic information to families with inherited rhythm disorders. *Heart Rhythm* 2018;**15**:780–786. https://doi.org/10.1016/j.hrthm.2017.11.024
576. Yeates L, Hunt L, Saleh M, Semsarian C, Ingles J. Poor psychological wellbeing particularly in mothers following sudden cardiac death in the young. *Eur J Cardiovasc Nurs* 2013;**12**:484–491. https://doi.org/10.1177/1474515113485510
577. Karam N, Jabre P, Narayanan K, Sharifzadehgan A, Perier MC, Tennenbaum J, *et al.* Psychological support and medical screening of first-degree relatives of sudden cardiac arrest victims. *JACC Clin Electrophysiol* 2020;**6**:586–587. https://doi.org/10.1016/j.jacep.2020.02.002
578. Kampmann C, Wiethoff CM, Wenzel A, Stolz G, Betancor M, Wippermann CF, *et al.* Normal values of M mode echocardiographic measurements of more than 2000 healthy infants and children in central Europe. *Heart* 2000;**83**:667–672. https://doi.org/10.1136/heart.83.6.667
579. Cardim N, Galderisi M, Edvardsen T, Plein S, Popescu BA, D'Andrea A, *et al.* Role of multimodality cardiac imaging in the management of patients with hypertrophic cardiomyopathy: an expert consensus of the European Association of Cardiovascular Imaging Endorsed by the Saudi Heart Association. *Eur Heart J Cardiovasc Imaging* 2015;**16**:280. https://doi.org/10.1093/ehjci/jeu291
580. Maron MS, Finley JJ, Bos JM, Hauser TH, Manning WJ, Haas TS, *et al.* Prevalence, clinical significance, and natural history of left ventricular apical aneurysms in hypertrophic cardiomyopathy. *Circulation* 2008;**118**:1541–1549. https://doi.org/10.1161/CIRCULATIONAHA.108.781401
581. Weinsaft JW, Kim HW, Crowley AL, Klem I, Shenoy C, Van Assche L, *et al.* LV thrombus detection by routine echocardiography: insights into performance characteristics using delayed enhancement CMR. *JACC Cardiovasc Imaging* 2011;**4**:702–712. https://doi.org/10.1016/j.jcmg.2011.03.017
582. Brouwer WP, Germans T, Head MC, van der Velden J, Heymans MW, Christiaans I, *et al.* Multiple myocardial crypts on modified long-axis view are a specific finding in pre-hypertrophic HCM mutation carriers. *Eur Heart J Cardiovasc Imaging* 2012;**13**: 292–297. https://doi.org/10.1093/ehjci/jes005
583. Maron MS, Rowin EJ, Lin D, Appelbaum E, Chan RH, Gibson CM, *et al.* Prevalence and clinical profile of myocardial crypts in hypertrophic cardiomyopathy. *Circ Cardiovasc Imaging* 2012;**5**:441–447. https://doi.org/10.1161/CIRCIMAGING.112.972760
584. Spirito P, Autore C, Rapezzi C, Bernabo P, Badagliacca R, Maron MS, *et al.* Syncope and risk of sudden death in hypertrophic cardiomyopathy. *Circulation* 2009;**119**: 1703–1710. https://doi.org/10.1161/CIRCULATIONAHA.108.798314
585. Vogelsberg H, Mahrholdt H, Deluigi CC, Yilmaz A, Kispert EM, Greulich S, *et al.* Cardiovascular magnetic resonance in clinically suspected cardiac amyloidosis: non-invasive imaging compared to endomyocardial biopsy. *J Am Coll Cardiol* 2008;**51**: 1022–1030. https://doi.org/10.1016/j.jacc.2007.10.049
586. Syed IS, Glockner JF, Feng D, Araoz PA, Martinez MW, Edwards WD, *et al.* Role of cardiac magnetic resonance imaging in the detection of cardiac amyloidosis. *JACC Cardiovasc Imaging* 2010;**3**:155–164. https://doi.org/10.1016/j.jcmg.2009.09.023
587. Wigle ED, Sasson Z, Henderson MA, Ruddy TD, Fulop J, Rakowski H, *et al.* Hypertrophic cardiomyopathy. The importance of the site and the extent of hypertrophy. A review. *Prog Cardiovasc Dis* 1985;**28**:1–83. https://doi.org/10.1016/0033-0620(85)90024-6
588. Dimitrow PP, Bober M, Michalowska J, Sorysz D. Left ventricular outflow tract gradient provoked by upright position or exercise in treated patients with hypertrophic cardiomyopathy without obstruction at rest. *Echocardiography* 2009;**26**:513–520. https://doi.org/10.1111/j.1540-8175.2008.00851.x
589. Maron BJ, Gottdiener JS, Bonow RO, Epstein SE. Hypertrophic cardiomyopathy with unusual locations of left ventricular hypertrophy undetectable by M-mode echocardiography. Identification by wide-angle two-dimensional echocardiography. *Circulation* 1981;**63**:409–418. https://doi.org/10.1161/01.CIR.63.2.409
590. Elliott P, Gimeno J, Tome M, McKenna W. Left ventricular outflow tract obstruction and sudden death in hypertrophic cardiomyopathy. *Eur Heart J* 2006;**27**:3073; author reply 3073-4. https://doi.org/10.1093/eurheartj/ehl383
591. Wigle ED, Rakowski H, Kimball BP, Williams WG. Hypertrophic cardiomyopathy. Clinical spectrum and treatment. *Circulation* 1995;**92**:1680–1692. https://doi.org/10.1161/01.CIR.92.7.1680
592. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. *N Engl J Med* 2000;**342**:1778–1785. https://doi.org/10.1056/NEJM200006153422403
593. Elliott PM, Gimeno Blanes JR, Mahon NG, Poloniecki JD, McKenna WJ. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. *Lancet* 2001;**357**:420–424. https://doi.org/10.1016/S0140-6736(00)04005-8
594. Kumar S, Van Ness G, Bender A, Yadava M, Minnier J, Ravi S, *et al.* Standardized goal-directed valsalva maneuver for assessment of inducible left ventricular outflow tract obstruction in hypertrophic cardiomyopathy. *J Am Soc Echocardiogr* 2018;**31**: 791–798. https://doi.org/10.1016/j.echo.2018.01.022
595. Maron MS, Olivotto I, Zenovich AG, Link MS, Pandian NG, Kuvin JT, *et al.* Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. *Circulation* 2006;**114**:2232–2239. https://doi.org/10.1161/CIRCULATIONAHA.106.644682
596. Shah JS, Esteban MT, Thaman R, Sharma R, Mist B, Pantazis A, *et al.* Prevalence of exercise-induced left ventricular outflow tract obstruction in symptomatic patients with non-obstructive hypertrophic cardiomyopathy. *Heart* 2008;**94**:1288–1294. https://doi.org/10.1136/hrt.2007.126003
597. Marwick TH, Nakatani S, Haluska B, Thomas JD, Lever HM. Provocation of latent left ventricular outflow tract gradients with amyl nitrite and exercise in hypertrophic cardiomyopathy. *Am J Cardiol* 1995;**75**:805–809. https://doi.org/10.1016/S0002-9149(99)80416-0
598. Reant P, Dufour M, Peyrou J, Reynaud A, Rooryck C, Dijos M, *et al.* Upright treadmill vs. semi-supine bicycle exercise echocardiography to provoke obstruction in symptomatic hypertrophic cardiomyopathy: a pilot study. *Eur Heart J Cardiovasc Imaging* 2018;**19**:31–38. https://doi.org/10.1093/ehjci/jew313
599. Yu EH, Omran AS, Wigle ED, Williams WG, Siu SC, Rakowski H. Mitral regurgitation in hypertrophic obstructive cardiomyopathy: relationship to obstruction and relief with myectomy. *J Am Coll Cardiol* 2000;**36**:2219–2225. https://doi.org/10.1016/S0735-1097(00)01019-6
600. Oki T, Fukuda N, Iuchi A, Tabata T, Tanimoto M, Manabe K, *et al.* Transesophageal echocardiographic evaluation of mitral regurgitation in hypertrophic cardiomyopathy: contributions of eccentric left ventricular hypertrophy and related abnormalities of the mitral complex. *J Am Soc Echocardiogr* 1995;**8**:503–510. https://doi.org/10.1016/S0894-7317(05)80338-4
601. Grigg LE, Wigle ED, Williams WG, Daniel LB, Rakowski H. Transesophageal Doppler echocardiography in obstructive hypertrophic cardiomyopathy: clarification of pathophysiology and importance in intraoperative decision making. *J Am Coll Cardiol* 1992;**20**: 42–52. https://doi.org/10.1016/0735-1097(92)90135-A
602. Marwick TH, Stewart WJ, Lever HM, Lytle BW, Rosenkranz ER, Duffy CI, *et al.* Benefits of intraoperative echocardiography in the surgical management of hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1992;**20**:1066–1072. https://doi.org/10.1016/0735-1097(92)90359-U

603. Geske JB, Cullen MW, Sorajja P, Ommen SR, Nishimura RA. Assessment of left ventricular outflow gradient: hypertrophic cardiomyopathy versus aortic valvular stenosis. *JACC Cardiovasc Interv* 2012;**5**:675–681. https://doi.org/10.1016/j.jcin.2012.01.026
604. Rudolph A, Abdel-Aty H, Bohl S, Boye P, Zagrosek A, Dietz R, *et al.* Noninvasive detection of fibrosis applying contrast-enhanced cardiac magnetic resonance in different forms of left ventricular hypertrophy relation to remodeling. *J Am Coll Cardiol* 2009;**53**: 284–291. https://doi.org/10.1016/j.jacc.2008.08.064
605. Moon JCC, Reed E, Sheppard MN, Elkington AG, Ho SY, Burke M, *et al.* The histologic basis of late gadolinium enhancement cardiovascular magnetic resonance in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2004;**43**:2260–2264. https://doi.org/10.1016/j.jacc.2004.03.035
606. Kwon DH, Smedira NG, Rodriguez ER, Tan C, Setser R, Thamilarasan M, *et al.* Cardiac magnetic resonance detection of myocardial scarring in hypertrophic cardiomyopathy: correlation with histopathology and prevalence of ventricular tachycardia. *J Am Coll Cardiol* 2009;**54**:242–249. https://doi.org/10.1016/j.jacc.2009.04.026
607. White RD, Obuchowski NA, Gunawardena S, Lipchik EO, Lever HM, Van Dyke CW, *et al.* Left ventricular outflow tract obstruction in hypertrophic cardiomyopathy: presurgical and postsurgical evaluation by computed tomography magnetic resonance imaging. *Am J Card Imaging* 1996;**10**:1–13.
608. Richard P, Charron P, Carrier L, Ledeuil C, Cheav T, Pichereau C, *et al.* Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. *Circulation* 2003;**107**:2227–2232. https://doi.org/10.1161/01.CIR.0000066323.15244.54
609. Murphy SL, Anderson JH, Kapplinger JD, Kruisselbrink TM, Gersh BJ, Ommen SR, *et al.* Evaluation of the Mayo Clinic phenotype-based genotype predictor score in patients with clinically diagnosed hypertrophic cardiomyopathy. *J Cardiovasc Transl Res* 2016;**9**: 153–161. https://doi.org/10.1007/s12265-016-9681-5
610. Gruner C, Ivanov J, Care M, Williams L, Moravsky G, Yang H, *et al.* Toronto hypertrophic cardiomyopathy genotype score for prediction of a positive genotype in hypertrophic cardiomyopathy. *Circ Cardiovasc Genet* 2013;**6**:19–26. https://doi.org/10.1161/CIRCGENETICS.112.963363
611. Ingles J, Burns C, Bagnall RD, Lam L, Yeates L, Sarina T, *et al.* Nonfamilial hypertrophic cardiomyopathy: prevalence, natural history, and clinical implications. *Circ Cardiovasc Genet* 2017;**10**:e001620. https://doi.org/10.1161/CIRCGENETICS.116.001620
612. Ko C, Arscott P, Concannon M, Saberi S, Day SM, Yashar BM, *et al.* Genetic testing impacts the utility of prospective familial screening in hypertrophic cardiomyopathy through identification of a nonfamilial subgroup. *Genet Med* 2018;**20**:69–75. https://doi.org/10.1038/gim.2017.79
613. Anan R, Shono H, Kisanuki A, Arima S, Nakao S, Tanaka H. Patients with familial hypertrophic cardiomyopathy caused by a Phe110Ile missense mutation in the cardiac troponin T gene have variable cardiac morphologies and a favorable prognosis. *Circulation* 1998;**98**:391–397. https://doi.org/10.1161/01.CIR.98.5.391
614. Elliott P, Baker R, Pasquale F, Quarta G, Ebrahim H, Mehta AB, *et al.* Prevalence of Anderson–Fabry disease in patients with hypertrophic cardiomyopathy: the European Anderson–Fabry Disease survey. *Heart* 2011;**97**:1957–1960. https://doi.org/10.1136/heartjnl-2011-300364
615. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, *et al.* Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* 2009;**10**:165–193. https://doi.org/10.1093/ejechocard/jep007
616. Kubo T, Gimeno JR, Bahl A, Steffensen U, Steffensen M, Osman E, *et al.* Prevalence, clinical significance, and genetic basis of hypertrophic cardiomyopathy with restrictive phenotype. *J Am Coll Cardiol* 2007;**49**:2419–2426. https://doi.org/10.1016/j.jacc.2007.02.061
617. Biagini E, Spirito P, Rocchi G, Ferlito M, Rosmini S, Lai F, *et al.* Prognostic implications of the Doppler restrictive filling pattern in hypertrophic cardiomyopathy. *Am J Cardiol* 2009;**104**:1727–1731. https://doi.org/10.1016/j.amjcard.2009.07.057
618. Geske JB, Sorajja P, Nishimura RA, Ommen SR. Evaluation of left ventricular filling pressures by Doppler echocardiography in patients with hypertrophic cardiomyopathy: correlation with direct left atrial pressure measurement at cardiac catheterization. *Circulation* 2007;**116**:2702–2708. https://doi.org/10.1161/CIRCULATIONAHA.107.698985
619. Kitaoka H, Kubo T, Okawa M, Takenaka N, Sakamoto C, Baba Y, *et al.* Tissue doppler imaging and plasma BNP levels to assess the prognosis in patients with hypertrophic cardiomyopathy. *J Am Soc Echocardiogr* 2011;**24**:1020–1025. https://doi.org/10.1016/j.echo.2011.05.009
620. Ha J-W, Cho J-R, Kim J-M, Ahn J-A, Choi E-Y, Kang S-M, *et al.* Tissue Doppler-derived indices predict exercise capacity in patients with apical hypertrophic cardiomyopathy. *Chest* 2005;**128**:3428–3433. https://doi.org/10.1378/chest.128.5.3428
621. Spoladore R, Maron MS, D'Amato R, Camici PG, Olivotto I. Pharmacological treatment options for hypertrophic cardiomyopathy: high time for evidence. *Eur Heart J* 2012;**33**:1724–1733. https://doi.org/10.1093/eurheartj/ehs150
622. Olivotto I, Oreziak A, Barriales-Villa R, Abraham TP, Masri A, Garcia-Pavia P, *et al.* Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2020;**396**:759–769. https://doi.org/10.1016/S0140-6736(20)31792-X
623. Dybro AM, Rasmussen TB, Nielsen RR, Ladefoged BT, Andersen MJ, Jensen MK, *et al.* Effects of metoprolol on exercise hemodynamics in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2022;**79**:1565–1575. https://doi.org/10.1016/j.jacc.2022.02.024
624. Wigle ED, Auger P, Marquis Y. Muscular subaortic stenosis. The direct relation between the intraventricular pressure difference and the left ventricular ejection time. *Circulation* 1967;**36**:36–44. https://doi.org/10.1161/01.CIR.36.1.36
625. Wigle ED, Henderson M, Rakowski H, Wilansky S. Muscular (hypertrophic) subaortic stenosis (hypertrophic obstructive cardiomyopathy): the evidence for true obstruction to left ventricular outflow. *Postgrad Med J* 1986;**62**:531–536. https://doi.org/10.1136/pgmj.62.728.531
626. Stauffer JC, Ruiz V, Morard JD. Subaortic obstruction after sildenafil in a patient with hypertrophic cardiomyopathy. *N Engl J Med* 1999;**341**:700–701. https://doi.org/10.1056/NEJM199908263410916
627. Braunwald E, Lambrew CT, Rockoff SD, Ross J Jr, Morrow AG. Idiopathic hypertrophic subaortic stenosis. I. A description of the disease based upon an analysis of 64 patients. *Circulation* 1964;**30**(Suppl 4):3–119. https://doi.org/10.1161/01.cir.29.5s4.iv-3
628. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation* 2001;**104**: 2517–2524. https://doi.org/10.1161/hc4601.097997
629. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, *et al.* 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012; **33**:2719–2747. https://doi.org/10.1093/eurheartj/ehs253
630. European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery; Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, *et al.* Guidelines for the management of atrial fibrillation: the Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;**31**: 2369–2429. https://doi.org/10.1093/eurheartj/ehq278
631. Dybro AM, Rasmussen TB, Nielsen RR, Andersen MJ, Jensen MK, Poulsen SH. Randomized trial of metoprolol in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2021;**78**:2505–2517. https://doi.org/10.1016/j.jacc.2021.07.065
632. Sherrid MV, Barac I, McKenna WJ, Elliott PM, Dickie S, Chojnowska L, *et al.* Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005;**45**:1251–1258. https://doi.org/10.1016/j.jacc.2005.01.012
633. Sherrid MV, Shetty A, Winson G, Kim B, Musat D, Alviar CL, *et al.* Treatment of obstructive hypertrophic cardiomyopathy symptoms and gradient resistant to first-line therapy with beta-blockade or verapamil. *Circ Heart Fail* 2013;**6**:694–702. https://doi.org/10.1161/CIRCHEARTFAILURE.112.000122
634. O'Connor MJ, Miller K, Shaddy RE, Lin KY, Hanna BD, Ravishankar C, *et al.* Disopyramide use in infants and children with hypertrophic cardiomyopathy. *Cardiol Young* 2018;**28**:530–535. https://doi.org/10.1017/S1047951117002384
635. Adler A, Fourey D, Weissler-Snir A, Hindieh W, Chan RH, Gollob MH, *et al.* Safety of outpatient initiation of disopyramide for obstructive hypertrophic cardiomyopathy patients. *J Am Heart Assoc* 2017;**6**:e005152. https://doi.org/10.1161/JAHA.116.005152
636. Epstein SE, Rosing DR. Verapamil: its potential for causing serious complications in patients with hypertrophic cardiomyopathy. *Circulation* 1981;**64**:437–441. https://doi.org/10.1161/01.CIR.64.3.437
637. Rosing DR, Kent KM, Maron BJ, Epstein SE. Verapamil therapy: a new approach to the pharmacologic treatment of hypertrophic cardiomyopathy. II. Effects on exercise capacity and symptomatic status. *Circulation* 1979;**60**:1208–1213. https://doi.org/10.1161/01.CIR.60.6.1208
638. Bonow RO, Rosing DR, Epstein SE. The acute and chronic effects of verapamil on left ventricular function in patients with hypertrophic cardiomyopathy. *Eur Heart J* 1983; **4**(Suppl F):57–65. https://doi.org/10.1093/eurheartj/4.suppl_F.57
639. Spicer RL, Rocchini AP, Crowley DC, Vasiliades J, Rosenthal A. Hemodynamic effects of verapamil in children and adolescents with hypertrophic cardiomyopathy. *Circulation* 1983;**67**:413–420. https://doi.org/10.1161/01.CIR.67.2.413
640. Rosing DR, Idanpaan-Heikkila U, Maron BJ, Bonow RO, Epstein SE. Use of calcium-channel blocking drugs in hypertrophic cardiomyopathy. *Am J Cardiol* 1985;**55**: 185B–195B. https://doi.org/10.1016/0002-9149(85)90630-7
641. Toshima H, Koga Y, Nagata H, Toyomasu K, Itaya K, Matoba T. Comparable effects of oral diltiazem and verapamil in the treatment of hypertrophic cardiomyopathy. Double-blind crossover study. *Jpn Heart J* 1986;**27**:701–715. https://doi.org/10.1536/ihj.27.701
642. Desai MY, Owens A, Geske JB, Wolski K, Naidu SS, Smedira NG, *et al.* Myosin inhibition in patients with obstructive hypertrophic cardiomyopathy referred for septal reduction therapy. *J Am Coll Cardiol* 2022;**80**:95–108. https://doi.org/10.1016/j.jacc.2022.04.048
643. Desai MY, Owens A, Geske JB, Wolski K, Saberi S, Wang A, *et al.* Dose-blinded myosin inhibition in patients with obstructive hypertrophic cardiomyopathy referred for septal reduction therapy: outcomes through 32 weeks. *Circulation* 2023;**147**:850–863. https://doi.org/10.1161/CIRCULATIONAHA.122.062534

644. Spertus JA, Fine JT, Elliott P, Ho CY, Olivotto I, Saberi S, *et al.* Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): health status analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2021;**397**:2467–2475. https://doi.org/10.1016/S0140-6736(21)00763-7
645. Saberi S, Cardim N, Yamani M, Schulz-Menger J, Li W, Florea V, *et al.* Mavacamten favorably impacts cardiac structure in obstructive hypertrophic cardiomyopathy: EXPLORER-HCM cardiac magnetic resonance substudy analysis. *Circulation* 2021; **143**:606–608. https://doi.org/10.1161/CIRCULATIONAHA.120.052359
646. Chuang C, Collibee S, Ashcraft L, Wang W, Vander Wal M, Wang X, *et al.* Discovery of Aficamten (CK-274), a next-generation cardiac myosin inhibitor for the treatment of hypertrophic cardiomyopathy. *J Med Chem* 2021;**64**:14142–14152. https://doi.org/10.1021/acs.jmedchem.1c01290
647. Maron MS, Masri A, Choudhury L, Olivotto I, Saberi S, Wang A, *et al.* Phase 2 study of aficamten in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2023;**81**:34–45. https://doi.org/10.1016/j.jacc.2022.10.020
648. Adelman AG, Shah PM, Gramiak R, Wigle ED. Long-term propranolol therapy in muscular subaortic stenosis. *Br Heart J* 1970;**32**:804–811. https://doi.org/10.1136/hrt.32.6.804
649. Flamm MD, Harrison DC, Hancock EW. Muscular subaortic stenosis. Prevention of outflow obstruction with propranolol. *Circulation* 1968;**38**:846–858. https://doi.org/10.1161/01.CIR.38.5.846
650. Monda E, Lioncino M, Palmiero G, Franco F, Rubino M, Cirillo A, *et al.* Bisoprolol for treatment of symptomatic patients with obstructive hypertrophic cardiomyopathy. The BASIC (bisoprolol AS therapy in hypertrophic cardiomyopathy) study. *Int J Cardiol* 2022;**354**:22–28. https://doi.org/10.1016/j.ijcard.2022.03.013
651. Sorajja P, Nishimura RA, Gersh BJ, Dearani JA, Hodge DO, Wiste HJ, *et al.* Outcome of mildly symptomatic or asymptomatic obstructive hypertrophic cardiomyopathy: a long-term follow-up study. *J Am Coll Cardiol* 2009;**54**:234–241. https://doi.org/10.1016/j.jacc.2009.01.079
652. Cavigli L, Fumagalli C, Maurizi N, Rossi A, Arretini A, Targetti M, *et al.* Timing of invasive septal reduction therapies and outcome of patients with obstructive hypertrophic cardiomyopathy. *Int J Cardiol* 2018;**273**:155–161. https://doi.org/10.1016/j.ijcard.2018.09.004
653. Menon SC, Ackerman MJ, Ommen SR, Cabalka AK, Hagler DJ, O'Leary PW, *et al.* Impact of septal myectomy on left atrial volume and left ventricular diastolic filling patterns: an echocardiographic study of young patients with obstructive hypertrophic cardiomyopathy. *J Am Soc Echocardiogr* 2008;**21**:684–688. https://doi.org/10.1016/j.echo.2007.11.006
654. Morrow AG, Reitz BA, Epstein SE, Henry WL, Conkle DM, Itscoitz SB, *et al.* Operative treatment in hypertrophic subaortic stenosis. Techniques, and the results of pre and postoperative assessments in 83 patients. *Circulation* 1975;**52**:88–102. https://doi.org/10.1161/01.CIR.52.1.88
655. Krajcer Z, Leachman RD, Cooley DA, Coronado R. Septal myotomy-myomectomy versus mitral valve replacement in hypertrophic cardiomyopathy. Ten-year follow-up in 185 patients. *Circulation* 1989;**80**:I57–I64.
656. Heric B, Lytle BW, Miller DP, Rosenkranz ER, Lever HM, Cosgrove DM. Surgical management of hypertrophic obstructive cardiomyopathy. Early and late results. *J Thorac Cardiovasc Surg* 1995;**110**:195–206;discussion 206-8. https://doi.org/10.1016/S0022-5223(05)80026-1
657. Robbins RC, Stinson EB. Long-term results of left ventricular myotomy and myectomy for obstructive hypertrophic cardiomyopathy. *J Thorac Cardiovasc Surg* 1996;**111**: 586–594. https://doi.org/10.1016/S0022-5223(96)70310-0
658. Schonbeck MH, Brunner-La Rocca HP, Vogt PR, Lachat ML, Jenni R, Hess OM, *et al.* Long-term follow-up in hypertrophic obstructive cardiomyopathy after septal myectomy. *Ann Thorac Surg* 1998;**65**:1207–1214. https://doi.org/10.1016/S0003-4975(98)00187-8
659. Schulte HD, Borisov K, Gams E, Gramsch-Zabel H, Losse B, Schwartzkopff B. Management of symptomatic hypertrophic obstructive cardiomyopathy–long-term results after surgical therapy. *Thorac Cardiovasc Surg* 1999;**47**:213–218. https://doi.org/10.1055/s-2007-1013146
660. Ommen SR, Maron BJ, Olivotto I, Maron MS, Cecchi F, Betocchi S, *et al.* Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005;**46**:470–476. https://doi.org/10.1016/j.jacc.2005.02.090
661. Woo A, Williams WG, Choi R, Wigle ED, Rozenblyum E, Fedwick K, *et al.* Clinical and echocardiographic determinants of long-term survival after surgical myectomy in obstructive hypertrophic cardiomyopathy. *Circulation* 2005;**111**:2033–2041. https://doi.org/10.1161/01.CIR.0000162460.36735.71
662. Smedira NG, Lytle BW, Lever HM, Rajeswaran J, Krishnaswamy G, Kaple RK, *et al.* Current effectiveness and risks of isolated septal myectomy for hypertrophic obstructive cardiomyopathy. *Ann Thorac Surg* 2008;**85**:127–133. https://doi.org/10.1016/j.athoracsur.2007.07.063
663. Desai MY, Bhonsale A, Smedira NG, Naji P, Thamilarasan M, Lytle BW, *et al.* Predictors of long-term outcomes in symptomatic hypertrophic obstructive cardiomyopathy patients undergoing surgical relief of left ventricular outflow tract obstruction. *Circulation* 2013;**128**:209–216. https://doi.org/10.1161/CIRCULATIONAHA.112.000849
664. Hodges K, Rivas CG, Aguilera J, Borden R, Alashi A, Blackstone EH, *et al.* Surgical management of left ventricular outflow tract obstruction in a specialized hypertrophic obstructive cardiomyopathy center. *J Thorac Cardiovasc Surg* 2019;**157**:2289–2299. https://doi.org/10.1016/j.jtcvs.2018.11.148
665. Nguyen A, Schaff HV, Nishimura RA, Dearani JA, Geske JB, Lahr BD, *et al.* Does septal thickness influence outcome of myectomy for hypertrophic obstructive cardiomyopathy? *Eur J Cardiothorac Surg* 2018;**53**:582–589. https://doi.org/10.1093/ejcts/ezx398
666. Altarabsheh SE, Dearani JA, Burkhart HM, Schaff HV, Deo SV, Eidem BW, *et al.* Outcome of septal myectomy for obstructive hypertrophic cardiomyopathy in children and young adults. *Ann Thorac Surg* 2013;**95**:663–669;discussion 669. https://doi.org/10.1016/j.athoracsur.2012.08.011
667. Iacovoni A, Spirito P, Simon C, Iascone M, Di Dedda G, De Filippo P, *et al.* A contemporary European experience with surgical septal myectomy in hypertrophic cardiomyopathy. *Eur Heart J* 2012;**33**:2080–2087. https://doi.org/10.1093/eurheartj/ehs064
668. Dearani JA, Ommen SR, Gersh BJ, Schaff HV, Danielson GK. Surgery insight: septal myectomy for obstructive hypertrophic cardiomyopathy–the Mayo Clinic experience. *Nat Clin Pract Cardiovasc Med* 2007;**4**:503–512. https://doi.org/10.1038/ncpcardio0965
669. Kofflard MJ, van Herwerden LA, Waldstein DJ, Ruygrok P, Boersma E, Taams MA, *et al.* Initial results of combined anterior mitral leaflet extension and myectomy in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1996;**28**:197–202. https://doi.org/10.1016/0735-1097(96)00103-9
670. McIntosh CL, Maron BJ, Cannon RO III, Klues HG. Initial results of combined anterior mitral leaflet plication and ventricular septal myotomy-myectomy for relief of left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy. *Circulation* 1992;**86**(5 Suppl):II60–II7.
671. Reis RL, Bolton MR, King JF, Pugh DM, Dunn MI, Mason DT. Anterion-superior displacement of papillary muscles producing obstruction and mitral regurgitation in idiopathic hypertrophic subaortic stenosis. Operative relief by posterior-superior realignment of papillary muscles following ventricular septal myectomy. *Circulation* 1974;**50**(2 Suppl):II181–II188.
672. Schoendube FA, Klues HG, Reith S, Flachskampf FA, Hanrath P, Messmer BJ. Long-term clinical and echocardiographic follow-up after surgical correction of hypertrophic obstructive cardiomyopathy with extended myectomy and reconstruction of the subvalvular mitral apparatus. *Circulation* 1995;**92**(9 Suppl):II122–II127. https://doi.org/10.1161/01.CIR.92.9.122
673. Kaple RK, Murphy RT, DiPaola LM, Houghtaling PL, Lever HM, Lytle BW, *et al.* Mitral valve abnormalities in hypertrophic cardiomyopathy: echocardiographic features and surgical outcomes. *Ann Thorac Surg* 2008;**85**:1527–1535,1535.e1-2. https://doi.org/10.1016/j.athoracsur.2008.01.061
674. Stassano P, Di Tommaso L, Triggiani D, Contaldo A, Gagliardi C, Spampinato N. Mitral valve replacement and limited myectomy for hypertrophic obstructive cardiomyopathy: a 25-year follow-up. *Tex Heart Inst J* 2004;**31**:137–142.
675. Minakata K, Dearani JA, Nishimura RA, Maron BJ, Danielson GK. Extended septal myectomy for hypertrophic obstructive cardiomyopathy with anomalous mitral papillary muscles or chordae. *J Thorac Cardiovasc Surg* 2004;**127**:481–489. https://doi.org/10.1016/j.jtcvs.2003.09.040
676. Boll G, Rowin EJ, Maron BJ, Wang W, Rastegar H, Maron MS. Efficacy of combined Cox-Maze IV and ventricular septal myectomy for treatment of atrial fibrillation in patients with obstructive hypertrophic cardiomyopathy. *Am J Cardiol* 2020;**125**:120–126. https://doi.org/10.1016/j.amjcard.2019.09.029
677. Laredo M, Khraiche D, Raisky O, Gaudin R, Bajolle F, Maltret A, *et al.* Long-term results of the modified Konno procedure in high-risk children with obstructive hypertrophic cardiomyopathy. *J Thorac Cardiovasc Surg* 2018;**156**:2285–2294.e2. https://doi.org/10.1016/j.jtcvs.2018.06.040
678. Sigwart U. Non-surgical myocardial reduction for hypertrophic obstructive cardiomyopathy. *Lancet* 1995;**346**:211–214. https://doi.org/10.1016/S0140-6736(95)91267-3
679. Faber L, Welge D, Fassbender D, Schmidt HK, Horstkotte D, Seggewiss H. One-year follow-up of percutaneous septal ablation for symptomatic hypertrophic obstructive cardiomyopathy in 312 patients: predictors of hemodynamic and clinical response. *Clin Res Cardiol* 2007;**96**:864–873. https://doi.org/10.1007/s00392-007-0578-9
680. Fernandes VL, Nielsen C, Nagueh SF, Herrin AE, Slifka C, Franklin J, *et al.* Follow-up of alcohol septal ablation for symptomatic hypertrophic obstructive cardiomyopathy the Baylor and Medical University of South Carolina experience 1996 to 2007. *JACC Cardiovasc Interv* 2008;**1**:561–570. https://doi.org/10.1016/j.jcin.2008.07.005
681. Kuhn H, Lawrenz T, Lieder F, Leuner C, Strunk-Mueller C, Obergassel L, *et al.* Survival after transcoronary ablation of septal hypertrophy in hypertrophic obstructive cardiomyopathy (TASH): a 10 year experience. *Clin Res Cardiol* 2008;**97**:234–243. https://doi.org/10.1007/s00392-007-0616-7
682. Sorajja P, Valeti U, Nishimura RA, Ommen SR, Rihal CS, Gersh BJ, *et al.* Outcome of alcohol septal ablation for obstructive hypertrophic cardiomyopathy. *Circulation* 2008; **118**:131–139. https://doi.org/10.1161/CIRCULATIONAHA.107.738740
683. Sorajja P, Ommen SR, Holmes DR Jr, Dearani JA, Rihal CS, Gersh BJ, *et al.* Survival after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. *Circulation* 2012; **126**:2374–2380. https://doi.org/10.1161/CIRCULATIONAHA.111.076257

684. Veselka J, Krejci J, Tomasov P, Zemanek D. Long-term survival after alcohol septal ablation for hypertrophic obstructive cardiomyopathy: a comparison with general population. *Eur Heart J* 2014;**35**:2040–2045. https://doi.org/10.1093/eurheartj/eht495
685. Liebregts M, Faber L, Jensen MK, Vriesendorp PA, Januska J, Krejci J, *et al.* Outcomes of alcohol septal ablation in younger patients with obstructive hypertrophic cardiomyopathy. *JACC Cardiovasc Interv* 2017;**10**:1134–1143. https://doi.org/10.1016/j.jcin.2017.03.030
686. Veselka J, Jensen MK, Liebregts M, Januska J, Krejci J, Bartel T, *et al.* Long-term clinical outcome after alcohol septal ablation for obstructive hypertrophic cardiomyopathy: results from the Euro-ASA registry. *Eur Heart J* 2016;**37**:1517–1523. https://doi.org/10.1093/eurheartj/ehv693
687. Kim LK, Swaminathan RV, Looser P, Minutello RM, Wong SC, Bergman G, *et al.* Hospital volume outcomes after septal myectomy and alcohol septal ablation for treatment of obstructive hypertrophic cardiomyopathy: US Nationwide Inpatient Database, 2003–2011. *JAMA Cardiol* 2016;**1**:324–332. https://doi.org/10.1001/jamacardio.2016.0252
688. ten Cate FJ, Soliman OI, Michels M, Theuns DA, de Jong PL, Geleijnse ML, *et al.* Long-term outcome of alcohol septal ablation in patients with obstructive hypertrophic cardiomyopathy: a word of caution. *Circ Heart Fail* 2010;**3**:362–369. https://doi.org/10.1161/CIRCHEARTFAILURE.109.862359
689. Durand E, Mousseaux E, Coste P, Pilliere R, Dubourg O, Trinquart L, *et al.* Non-surgical septal myocardial reduction by coil embolization for hypertrophic obstructive cardiomyopathy: early and 6 months follow-up. *Eur Heart J* 2008;**29**:348–355. https://doi.org/10.1093/eurheartj/ehm632
690. Iacob M, Pinte F, Tintoiu I, Cotuna L, Caroescu M, Popa A, *et al.* Microcoil embolisation for ablation of septal hypertrophy in hypertrophic obstructive cardiomyopathy. *Kardiol Pol* 2004;**61**:350–355.
691. Gross CM, Schulz-Menger J, Kramer J, Siegel I, Pilz B, Waigand J, *et al.* Percutaneous transluminal septal artery ablation using polyvinyl alcohol foam particles for septal hypertrophy in patients with hypertrophic obstructive cardiomyopathy: acute and 3-year outcomes. *J Endovasc Ther* 2004;**11**:705–711. https://doi.org/10.1583/03-1171MR.1
692. Oto A, Aytemir K, Okutucu S, Kaya EB, Deniz A, Cil B, *et al.* Cyanoacrylate for septal ablation in hypertrophic cardiomyopathy. *J Interv Cardiol* 2011;**24**:77–84. https://doi.org/10.1111/j.1540-8183.2010.00605.x
693. Lawrenz T, Borchert B, Leuner C, Bartelsmeier M, Reinhardt J, Strunk-Mueller C. Endocardial radiofrequency ablation for hypertrophic obstructive cardiomyopathy: acute results and 6 months' follow-up in 19 patients. *J Am Coll Cardiol* 2011;**57**:572–576. https://doi.org/10.1016/j.jacc.2010.07.055
694. Keane D, Hynes B, King G, Shiels P, Brown A. Feasibility study of percutaneous transvalvular endomyocardial cryoablation for the treatment of hypertrophic obstructive cardiomyopathy. *J Invasive Cardiol* 2007;**19**:247–251.
695. Panaich SS, Badheka AO, Chothani A, Mehta K, Patel NJ, Deshmukh A, *et al.* Results of ventricular septal myectomy and hypertrophic cardiomyopathy (from Nationwide Inpatient Sample [1998–2010]). *Am J Cardiol* 2014;**114**:1390–1395. https://doi.org/10.1016/j.amjcard.2014.07.075
696. Bourque C, Reant P, Bernard A, Leroux L, Bonnet G, Pernot M, *et al.* Comparison of surgical ventricular septal reduction to alcohol septal ablation therapy in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2022;**172**:109–114. https://doi.org/10.1016/j.amjcard.2022.02.033
697. Agarwal S, Tuzcu EM, Desai MY, Smedira N, Lever HM, Lytle BW, *et al.* Updated meta-analysis of septal alcohol ablation versus myectomy for hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2010;**55**:823–834. https://doi.org/10.1016/j.jacc.2009.09.047
698. Alam M, Dokainish H, Lakkis NM. Hypertrophic obstructive cardiomyopathy–alcohol septal ablation vs. myectomy: a meta-analysis. *Eur Heart J* 2009;**30**:1080–1087. https://doi.org/10.1093/eurheartj/ehp016
699. Zeng Z, Wang F, Dou X, Zhang S, Pu J. Comparison of percutaneous transluminal septal myocardial ablation versus septal myectomy for the treatment of patients with hypertrophic obstructive cardiomyopathy–a meta analysis. *Int J Cardiol* 2006;**112**:80–84. https://doi.org/10.1016/j.ijcard.2005.10.009
700. Leonardi RA, Kransdorf EP, Simel DL, Wang A. Meta-analyses of septal reduction therapies for obstructive hypertrophic cardiomyopathy: comparative rates of overall mortality and sudden cardiac death after treatment. *Circ Cardiovasc Interv* 2010;**3**:97–104. https://doi.org/10.1161/CIRCINTERVENTIONS.109.916676
701. Batzner A, Pfeiffer B, Neugebauer A, Aicha D, Blank C, Seggewiss H. Survival after alcohol septal ablation in patients with hypertrophic obstructive cardiomyopathy. *J Am Coll Cardiol* 2018;**72**:3087–3094. https://doi.org/10.1016/j.jacc.2018.09.064
702. Nguyen A, Schaff HV, Hang D, Nishimura RA, Geske JB, Dearani JA, *et al.* Surgical myectomy versus alcohol septal ablation for obstructive hypertrophic cardiomyopathy: a propensity score-matched cohort. *J Thorac Cardiovasc Surg* 2019;**157**:306–315.e3. https://doi.org/10.1016/j.jtcvs.2018.08.062
703. Bytyci I, Nistri S, Morner S, Henein MY. Alcohol septal ablation versus septal myectomy treatment of obstructive hypertrophic cardiomyopathy: a systematic review and meta-analysis. *J Clin Med* 2020;**9**:3062. https://doi.org/10.3390/jcm9103062
704. Faber L, Welge D, Fassbender D, Schmidt HK, Horstkotte D, Seggewiss H. Percutaneous septal ablation for symptomatic hypertrophic obstructive cardiomyopathy: managing the risk of procedure-related AV conduction disturbances. *Int J Cardiol* 2007;**119**:163–167. https://doi.org/10.1016/j.ijcard.2006.07.179
705. Veselka J, Liebregts M, Cooper R, Faber L, Januska J, Kashtanov M, *et al.* Outcomes of patients with hypertrophic obstructive cardiomyopathy and pacemaker implanted after alcohol septal ablation. *JACC Cardiovasc Interv* 2022;**15**:1910–1917. https://doi.org/10.1016/j.jcin.2022.06.034
706. Veselka J, Jensen M, Liebregts M, Cooper RM, Januska J, Kashtanov M, *et al.* Alcohol septal ablation in patients with severe septal hypertrophy. *Heart* 2020;**106**:462–466. https://doi.org/10.1136/heartjnl-2019-315422
707. Veselka J, Faber L, Liebregts M, Cooper R, Januska J, Kashtanov M, *et al.* Short- and long-term outcomes of alcohol septal ablation for hypertrophic obstructive cardiomyopathy in patients with mild left ventricular hypertrophy: a propensity score matching analysis. *Eur Heart J* 2019;**40**:1681–1687. https://doi.org/10.1093/eurheartj/ehz110
708. Tumiene B, Graessner H, Mathijssen IM, Pereira AM, Schaefer F, Scarpa M, *et al.* European reference networks: challenges and opportunities. *J Community Genet* 2021;**12**:217–229. https://doi.org/10.1007/s12687-021-00521-8
709. Veselka J, Faber L, Jensen MK, Cooper R, Januska J, Krejci J, *et al.* Effect of institutional experience on outcomes of alcohol septal ablation for hypertrophic obstructive cardiomyopathy. *Can J Cardiol* 2018;**34**:16–22. https://doi.org/10.1016/j.cjca.2017.10.020
710. Cui H, Schaff HV, Wang S, Lahr BD, Rowin EJ, Rastegar H, *et al.* Survival following alcohol septal ablation or septal myectomy for patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2022;**79**:1647–1655. https://doi.org/10.1016/j.jacc.2022.02.032
711. McCully RB, Nishimura RA, Tajik AJ, Schaff HV, Danielson GK. Extent of clinical improvement after surgical treatment of hypertrophic obstructive cardiomyopathy. *Circulation* 1996;**94**:467–471. https://doi.org/10.1161/01.CIR.94.3.467
712. Orme NM, Sorajja P, Dearani JA, Schaff HV, Gersh BJ, Ommen SR. Comparison of surgical septal myectomy to medical therapy alone in patients with hypertrophic cardiomyopathy and syncope. *Am J Cardiol* 2013;**111**:388–392. https://doi.org/10.1016/j.amjcard.2012.10.014
713. Geske JB, Driver CN, Yogeswaran V, Ommen SR, Schaff HV. Comparison of expected and observed outcomes for septal myectomy in hypertrophic obstructive cardiomyopathy. *Am Heart J* 2020;**221**:159–164. https://doi.org/10.1016/j.ahj.2019.11.020
714. Ferrazzi P, Spirito P, Iacovoni A, Calabrese A, Migliorati K, Simon C, *et al.* Transaortic chordal cutting: mitral valve repair for obstructive hypertrophic cardiomyopathy with mild septal hypertrophy. *J Am Coll Cardiol* 2015;**66**:1687–1696. https://doi.org/10.1016/j.jacc.2015.07.069
715. Veselka J, Faber L, Liebregts M, Cooper R, Januska J, Krejci J, *et al.* Outcome of alcohol septal ablation in mildly symptomatic patients with hypertrophic obstructive cardiomyopathy: a long-term follow-up study based on the Euro-alcohol septal ablation registry. *J Am Heart Assoc* 2017;**6**:e005735. https://doi.org/10.1161/JAHA.117.005735
716. Cooley DA, Wukasch DC, Leachman RD. Mitral valve replacement for idiopathic hypertrophic subaortic stenosis. Results in 27 patients. *J Cardiovasc Surg (Torino)* 1976;**17**:380–387.
717. Chen MS, McCarthy PM, Lever HM, Smedira NG, Lytle BL. Effectiveness of atrial fibrillation surgery in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2004;**93**:373–375. https://doi.org/10.1016/j.amjcard.2003.10.025
718. Whitlock RP, Belley-Cote EP, Paparella D, Healey JS, Brady K, Sharma M, *et al.* Left atrial appendage occlusion during cardiac surgery to prevent stroke. *N Engl J Med* 2021;**384**:2081–2091. https://doi.org/10.1056/NEJMoa2101897
719. Slade AK, Sadoul N, Shapiro L, Chojnowska L, Simon JP, Saumarez RC, *et al.* DDD pacing in hypertrophic cardiomyopathy: a multicentre clinical experience. *Heart* 1996;**75**:44–49. https://doi.org/10.1136/hrt.75.1.44
720. Nishimura RA, Trusty JM, Hayes DL, Ilstrup DM, Larson DR, Hayes SN, *et al.* Dual-chamber pacing for hypertrophic cardiomyopathy: a randomized, double-blind, crossover trial. *J Am Coll Cardiol* 1997;**29**:435–441. https://doi.org/10.1016/S0735-1097(96)00473-1
721. Kappenberger L, Linde C, Daubert C, McKenna W, Meisel E, Sadoul N, *et al.* Pacing in hypertrophic obstructive cardiomyopathy. A randomized crossover study. *Eur Heart J* 1997;**18**:1249–1256. https://doi.org/10.1093/oxfordjournals.eurheartj.a015435
722. Maron BJ, Nishimura RA, McKenna WJ, Rakowski H, Josephson ME, Kieval RS. Assessment of permanent dual-chamber pacing as a treatment for drug-refractory symptomatic patients with obstructive hypertrophic cardiomyopathy. A randomized, double-blind, crossover study (M-PATHY). *Circulation* 1999;**99**:2927–2933. https://doi.org/10.1161/01.CIR.99.22.2927
723. Mickelsen S, Bathina M, Hsu P, Holmes J, Kusumoto FM. Doppler evaluation of the descending aorta in patients with hypertrophic cardiomyopathy: potential for assessing the functional significance of outflow tract gradients and for optimizing pacemaker function. *J Interv Card Electrophysiol* 2004;**11**:47–53. https://doi.org/10.1023/B:JICE.0000035929.84238.2f
724. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, *et al.* 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Eur Heart J* 2021;**42**:3427–3520. https://doi.org/10.1093/eurheartj/ehab364
725. Qintar M, Morad A, Alhawasli H, Shorbaji K, Firwana B, Essali A, *et al.* Pacing for drug-refractory or drug-intolerant hypertrophic cardiomyopathy. *Cochrane Database Syst Rev* 2012;**2012**:CD008523. https://doi.org/10.1002/14651858.CD008523.pub2

726. O'Mahony C, Lambiase PD, Quarta G, Cardona M, Calcagnino M, Tsovolas K, *et al.* The long-term survival and the risks and benefits of implantable cardioverter defibrillators in patients with hypertrophic cardiomyopathy. *Heart* 2012;**98**:116–125. https://doi.org/10.1136/hrt.2010.217182
727. Minami Y, Kajimoto K, Terajima Y, Yashiro B, Okayama D, Haruki S, *et al.* Clinical implications of midventricular obstruction in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2011;**57**:2346–2355. https://doi.org/10.1016/j.jacc.2011.02.033
728. Efthimiadis GK, Pagourelias ED, Parcharidou D, Gossios T, Kamperidis V, Theofilogiannakos EK, *et al.* Clinical characteristics and natural history of hypertrophic cardiomyopathy with midventricular obstruction. *Circ J* 2013;**77**:2366–2374. https://doi.org/10.1253/circj.CJ-12-1561
729. Shah A, Duncan K, Winson G, Chaudhry FA, Sherrid MV. Severe symptoms in mid and apical hypertrophic cardiomyopathy. *Echocardiography* 2009;**26**:922–933. https://doi.org/10.1111/j.1540-8175.2009.00905.x
730. Alfonso F, Frenneaux MP, McKenna WJ. Clinical sustained uniform ventricular tachycardia in hypertrophic cardiomyopathy: association with left ventricular apical aneurysm. *Br Heart J* 1989;**61**:178–181. https://doi.org/10.1136/hrt.61.2.178
731. Said SM, Schaff HV, Abel MD, Dearani JA. Transapical approach for apical myectomy and relief of midventricular obstruction in hypertrophic cardiomyopathy. *J Card Surg* 2012;**27**:443–448. https://doi.org/10.1111/j.1540-8191.2012.01475.x
732. Kunkala MR, Schaff HV, Nishimura RA, Abel MD, Sorajja P, Dearani JA, *et al.* Transapical approach to myectomy for midventricular obstruction in hypertrophic cardiomyopathy. *Ann Thorac Surg* 2013;**96**:564–570. https://doi.org/10.1016/j.athoracsur.2013.04.073
733. Gao X-J, Kang L-M, Zhang J, Dou K-F, Yuan J-S, Yang Y-J. Mid-ventricular obstructive hypertrophic cardiomyopathy with apical aneurysm and sustained ventricular tachycardia: a case report and literature review. *Chin Med J (Engl)* 2011;**124**:1754–1757.
734. Takeda I, Sekine M, Matsushima H, Hosomi N, Nakamura T, Ohtsuki T, *et al.* Two cases of cerebral embolism caused by apical thrombi in midventricular obstructive cardiomyopathy. *Intern Med* 2011;**50**:1059–1060. https://doi.org/10.2169/internalmedicine.50.5079
735. Sato Y, Matsumoto N, Matsuo S, Yoda S, Tani S, Kasamaki Y, *et al.* Mid-ventricular obstructive hypertrophic cardiomyopathy associated with an apical aneurysm: evaluation of possible causes of aneurysm formation. *Yonsei Med J* 2007;**48**:879–882. https://doi.org/10.3349/ymj.2007.48.5.879
736. Papanastasiou CA, Zegkos T, Kokkinidis DG, Parcharidou D, Karamitsos TD, Efthimiadis GK. Prognostic role of left ventricular apical aneurysm in hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Int J Cardiol* 2021;**339**:108. https://doi.org/10.1016/j.ijcard.2021.07.025
737. Rowin EJ, Maron BJ, Haas TS, Garberich RF, Wang W, Link MS, *et al.* Hypertrophic cardiomyopathy with left ventricular apical aneurysm: implications for risk stratification and management. *J Am Coll Cardiol* 2017;**69**:761–773. https://doi.org/10.1016/j.jacc.2016.11.063
738. Ammirati E, Contri R, Coppini R, Cecchi F, Frigerio M, Olivotto I. Pharmacological treatment of hypertrophic cardiomyopathy: current practice and novel perspectives. *Eur J Heart Fail* 2016;**18**:1106–1118. https://doi.org/10.1002/ejhf.541
739. Olivotto I, Camici PG, Merlini PA, Rapezzi C, Patten M, Climent V, *et al.* Efficacy of ranolazine in patients with symptomatic hypertrophic cardiomyopathy: the RESTYLE-HCM randomized, double-blind, placebo-controlled study. *Circ Heart Fail* 2018;**11**:e004124. https://doi.org/10.1161/CIRCHEARTFAILURE.117.004124
740. Bourmayan C, Razavi A, Fournier C, Dussaule JC, Baragan J, Gerbaux A, *et al.* Effect of propranolol on left ventricular relaxation in hypertrophic cardiomyopathy: an echographic study. *Am Heart J* 1985;**109**:1311–1316. https://doi.org/10.1016/0002-8703(85)90357-6
741. Alvares RF, Goodwin JF. Non-invasive assessment of diastolic function in hypertrophic cardiomyopathy on and off beta adrenergic blocking drugs. *Br Heart J* 1982;**48**:204–212. https://doi.org/10.1136/hrt.48.3.204
742. Wilmshurst PT, Thompson DS, Juul SM, Jenkins BS, Webb-Peploe MM. Effects of verapamil on haemodynamic function and myocardial metabolism in patients with hypertrophic cardiomyopathy. *Br Heart J* 1986;**56**:544–553. https://doi.org/10.1136/hrt.56.6.544
743. Udelson JE, Bonow RO, O'Gara PT, Maron BJ, Van Lingen A, Bacharach SL, *et al.* Verapamil prevents silent myocardial perfusion abnormalities during exercise in asymptomatic patients with hypertrophic cardiomyopathy. *Circulation* 1989;**79**:1052–1060. https://doi.org/10.1161/01.CIR.79.5.1052
744. Pacileo G, De Cristofaro M, Russo MG, Sarubbi B, Pisacane C, Calabro R. Hypertrophic cardiomyopathy in pediatric patients: effect of verapamil on regional and global left ventricular diastolic function. *Can J Cardiol* 2000;**16**:146–152.
745. Cappelli F, Morini S, Pieragnoli P, Targetti M, Stefano P, Marchionni N, *et al.* Cardiac resynchronization therapy for end-stage hypertrophic cardiomyopathy: the need for disease-specific criteria. *J Am Coll Cardiol* 2018;**71**:464–466. https://doi.org/10.1016/j.jacc.2017.11.040
746. Killu AM, Park J-Y, Sara JD, Hodge DO, Gersh BJ, Nishimura RA, *et al.* Cardiac resynchronization therapy in patients with end-stage hypertrophic cardiomyopathy. *Europace* 2018;**20**:82–88. https://doi.org/10.1093/europace/euw327
747. Gu M, Jin H, Hua W, Fan X-H, Niu H-X, Tian T, *et al.* Clinical outcome of cardiac resynchronization therapy in dilated-phase hypertrophic cardiomyopathy. *J Geriatr Cardiol* 2017;**14**:238–244. https://doi.org/10.11909/j.issn.1671-5411.2017.04.002
748. Ahmed I, Loudon BL, Abozguia K, Cameron D, Shivu GN, Phan TT, *et al.* Biventricular pacemaker therapy improves exercise capacity in patients with non-obstructive hypertrophic cardiomyopathy via augmented diastolic filling on exercise. *Eur J Heart Fail* 2020;**22**:1263–1272. https://doi.org/10.1002/ejhf.1722
749. Elliott PM, Gimeno JR, Thaman R, Shah J, Ward D, Dickie S, *et al.* Historical trends in reported survival rates in patients with hypertrophic cardiomyopathy. *Heart* 2006;**92**:785–791. https://doi.org/10.1136/hrt.2005.068577
750. Barriales-Villa R, Centurion-Inda R, Fernandez-Fernandez X, Ortiz MF, Perez-Alvarez L, Rodriguez Garcia I, *et al.* Severe cardiac conduction disturbances and pacemaker implantation in patients with hypertrophic cardiomyopathy. *Rev Esp Cardiol* 2010;**63**:985–988. https://doi.org/10.1016/S0300-8932(10)70210-4
751. Nicod P, Polikar R, Peterson KL. Hypertrophic cardiomyopathy and sudden death. *N Engl J Med* 1988;**318**:1255–1257. https://doi.org/10.1056/NEJM198805123181907
752. Stafford WJ, Trohman RG, Bilsker M, Zaman L, Castellanos A, Myerburg RJ. Cardiac arrest in an adolescent with atrial fibrillation and hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1986;**7**:701–704. https://doi.org/10.1016/S0735-1097(86)80484-3
753. Krikler DM, Davies MJ, Rowland E, Goodwin JF, Evans RC, Shaw DB. Sudden death in hypertrophic cardiomyopathy: associated accessory atrioventricular pathways. *Br Heart J* 1980;**43**:245–251. https://doi.org/10.1136/hrt.43.3.245
754. Joseph S, Balcon R, McDonald L. Syncope in hypertrophic obstructive cardiomyopathy due to asystole. *Br Heart J* 1972;**34**:974–976. https://doi.org/10.1136/hrt.34.9.974
755. McKenna WJ, Deanfield JE. Hypertrophic cardiomyopathy: an important cause of sudden death. *Arch Dis Child* 1984;**59**:971–975. https://doi.org/10.1136/adc.59.10.971
756. McKenna WJ, Franklin RC, Nihoyannopoulos P, Robinson KC, Deanfield JE. Arrhythmia and prognosis in infants, children and adolescents with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1988;**11**:147–153. https://doi.org/10.1016/0735-1097(88)90181-7
757. Ostman-Smith I, Wettrell G, Keeton B, Holmgren D, Ergander U, Gould S, *et al.* Age- and gender-specific mortality rates in childhood hypertrophic cardiomyopathy. *Eur Heart J* 2008;**29**:1160–1167. https://doi.org/10.1093/eurheartj/ehn122
758. Lipshultz SE, Orav EJ, Wilkinson JD, Towbin JA, Messere JE, Lowe AM, *et al.* Risk stratification at diagnosis for children with hypertrophic cardiomyopathy: an analysis of data from the Pediatric Cardiomyopathy Registry. *Lancet* 2013;**382**:1889–1897. https://doi.org/10.1016/S0140-6736(13)61685-2
759. Marston NA, Han L, Olivotto I, Day SM, Ashley EA, Michels M, *et al.* Clinical characteristics and outcomes in childhood-onset hypertrophic cardiomyopathy. *Eur Heart J* 2021;**42**:1988–1996. https://doi.org/10.1093/eurheartj/ehab148
760. Sorajja P, Ommen SR, Nishimura RA, Gersh BJ, Berger PB, Tajik AJ. Adverse prognosis of patients with hypertrophic cardiomyopathy who have epicardial coronary artery disease. *Circulation* 2003;**108**:2342–2348. https://doi.org/10.1161/01.CIR.0000097110.55312.BF
761. Kofflard MJ, Ten Cate FJ, van der Lee C, van Domburg RT. Hypertrophic cardiomyopathy in a large community-based population: clinical outcome and identification of risk factors for sudden cardiac death and clinical deterioration. *J Am Coll Cardiol* 2003;**41**:987–993. https://doi.org/10.1016/S0735-1097(02)03004-8
762. Maki S, Ikeda H, Muro A, Yoshida N, Shibata A, Koga Y, *et al.* Predictors of sudden cardiac death in hypertrophic cardiomyopathy. *Am J Cardiol* 1998;**82**:774–778. https://doi.org/10.1016/S0002-9149(98)00455-X
763. Autore C, Bernabo P, Barilla CS, Bruzzi P, Spirito P. The prognostic importance of left ventricular outflow obstruction in hypertrophic cardiomyopathy varies in relation to the severity of symptoms. *J Am Coll Cardiol* 2005;**45**:1076–1080. https://doi.org/10.1016/j.jacc.2004.12.067
764. D'Andrea A, Caso P, Severino S, Cuomo S, Capozzi G, Calabro P, *et al.* Prognostic value of intra-left ventricular electromechanical asynchrony in patients with hypertrophic cardiomyopathy. *Eur Heart J* 2006;**27**:1311–1318. https://doi.org/10.1093/eurheartj/ehi688
765. Monserrat L, Elliott PM, Gimeno JR, Sharma S, Penas-Lado M, McKenna WJ. Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. *J Am Coll Cardiol* 2003;**42**:873–879. https://doi.org/10.1016/S0735-1097(03)00827-1
766. Maron BJ, Casey SA, Hurrell DG, Aeppli DM. Relation of left ventricular thickness to age and gender in hypertrophic cardiomyopathy. *Am J Cardiol* 2003;**91**:1195–1198. https://doi.org/10.1016/S0002-9149(03)00266-2
767. Norrish G, Cleary A, Field E, Cervi E, Boleti O, Ziolkowska L, *et al.* Clinical features and natural history of preadolescent nonsyndromic hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2022;**79**:1986–1997. https://doi.org/10.1016/j.jacc.2022.03.347
768. Gimeno JR, Tome-Esteban M, Lofiego C, Hurtado J, Pantazis A, Mist B, *et al.* Exercise-induced ventricular arrhythmias and risk of sudden cardiac death in patients with hypertrophic cardiomyopathy. *Eur Heart J* 2009;**30**:2599–2605. https://doi.org/10.1093/eurheartj/ehp327
769. Dimitrow PP, Chojnowska L, Rudzinski T, Piotrowski W, Ziolkowska L, Wojtarowicz A, *et al.* Sudden death in hypertrophic cardiomyopathy: old risk factors re-assessed in a

new model of maximalized follow-up. *Eur Heart J* 2010;**31**:3084–3093. https://doi.org/10.1093/eurheartj/ehq308
770. Maron BJ, Spirito P, Ackerman MJ, Casey SA, Semsarian C, Estes NA III, *et al.* Prevention of sudden cardiac death with implantable cardioverter-defibrillators in children and adolescents with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2013;**61**: 1527–1535. https://doi.org/10.1016/j.jacc.2013.01.037
771. Ostman-Smith I, Sjoberg G, Rydberg A, Larsson P, Fernlund E. Predictors of risk for sudden death in childhood hypertrophic cardiomyopathy: the importance of the ECG risk score. *Open Heart* 2017;**4**:e000658. https://doi.org/10.1136/openhrt-2017-000658
772. Ziolkowska L, Turska-Kmiec A, Petryka J, Kawalec W. Predictors of long-term outcome in children with hypertrophic cardiomyopathy. *Pediatr Cardiol* 2016;**37**: 448–458. https://doi.org/10.1007/s00246-015-1298-y
773. Yetman AT, Hamilton RM, Benson LN, McCrindle BW. Long-term outcome and prognostic determinants in children with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1998;**32**:1943–1950. https://doi.org/10.1016/S0735-1097(98)00493-8
774. Cecchi F, Olivotto I, Montereggi A, Squillatini G, Dolara A, Maron BJ. Prognostic value of non-sustained ventricular tachycardia and the potential role of amiodarone treatment in hypertrophic cardiomyopathy: assessment in an unselected non-referral based patient population. *Heart* 1998;**79**:331–336. https://doi.org/10.1136/hrt.79.4.331
775. Jensen MK, Jacobsson L, Almaas V, van Buuren F, Hansen PR, Hansen TF, *et al.* Influence of septal thickness on the clinical outcome after alcohol septal alation in hypertrophic cardiomyopathy. *Circ Cardiovasc Interv* 2016;**9**:e003214. https://doi.org/10.1161/CIRCINTERVENTIONS.115.003214
776. Nakajima S, Morioka S. [Effects of plasminogen activator on epidermal cell migration]. *Nihon Hifuka Gakkai Zasshi* 1990;**100**:1199–1201.
777. Balaji S, DiLorenzo MP, Fish FA, Etheridge SP, Aziz PF, Russell MW, *et al.* Risk factors for lethal arrhythmic events in children and adolescents with hypertrophic cardiomyopathy and an implantable defibrillator: an international multicenter study. *Heart Rhythm* 2019;**16**:1462–1467. https://doi.org/10.1016/j.hrthm.2019.04.040
778. Bharucha T, Lee KJ, Daubeney PE, Nugent AW, Turner C, Sholler GF, *et al.* Sudden death in childhood cardiomyopathy: results from a long-term national population-based study. *J Am Coll Cardiol* 2015;**65**:2302–2310. https://doi.org/10.1016/j.jacc.2015.03.552
779. McMahon CJ, Nagueh SF, Pignatelli RH, Denfield SW, Dreyer WJ, Price JF, *et al.* Characterization of left ventricular diastolic function by tissue Doppler imaging and clinical status in children with hypertrophic cardiomyopathy. *Circulation* 2004;**109**: 1756–1762. https://doi.org/10.1161/01.CIR.0000124723.16433.31
780. Ostman-Smith I, Wettrell G, Keeton B, Riesenfeld T, Holmgren D, Ergander U. Echocardiographic and electrocardiographic identification of those children with hypertrophic cardiomyopathy who should be considered at high-risk of dying suddenly. *Cardiol Young* 2005;**15**:632–642. https://doi.org/10.1017/S1047951105001824
781. Efthimiadis GK, Parcharidou DG, Giannakoulas G, Pagourelias ED, Charalampidis P, Savvopoulos G, *et al.* Left ventricular outflow tract obstruction as a risk factor for sudden cardiac death in hypertrophic cardiomyopathy. *Am J Cardiol* 2009;**104**:695–699. https://doi.org/10.1016/j.amjcard.2009.04.039
782. Elliott PM, Poloniecki J, Dickie S, Sharma S, Monserrat L, Varnava A, *et al.* Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. *J Am Coll Cardiol* 2000;**36**:2212–2218. https://doi.org/10.1016/S0735-1097(00)01003-2
783. Louie EK, Maron BJ. Hypertrophic cardiomyopathy with extreme increase in left ventricular wall thickness: functional and morphologic features and clinical significance. *J Am Coll Cardiol* 1986;**8**:57–65. https://doi.org/10.1016/S0735-1097(86)80092-4
784. Norrish G, Ding T, Field E, Cervi E, Ziolkowska L, Olivotto I, *et al.* Relationship between maximal left ventricular wall thickness and sudden cardiac death in childhood onset hypertrophic cardiomyopathy. *Circ Arrhythm Electrophysiol* 2022;**15**:e010075. https://doi.org/10.1161/CIRCEP.121.010075
785. Williams L, Frenneaux M. Syncope in hypertrophic cardiomyopathy: mechanisms and consequences for treatment. *Europace* 2007;**9**:817–822. https://doi.org/10.1093/europace/eum093
786. Sediva H, Hnat T, Bonaventura J, Slesarenko J, Veselka J. Head-up tilt test in risk stratification of patients with hypertrophic cardiomyopathy. *Int J Angiol* 2019;**28**:245–248. https://doi.org/10.1055/s-0039-1688983
787. Moak JP, Leifer ES, Tripodi D, Mohiddin SA, Fananapazir L. Long-term follow-up of children and adolescents diagnosed with hypertrophic cardiomyopathy: risk factors for adverse arrhythmic events. *Pediatr Cardiol* 2011;**32**:1096–1105. https://doi.org/10.1007/s00246-011-9967-y
788. Romeo F, Cianfrocca C, Pelliccia F, Colloridi V, Cristofani R, Reale A. Long-term prognosis in children with hypertrophic cardiomyopathy: an analysis of 37 patients aged less than or equal to 14 years at diagnosis. *Clin Cardiol* 1990;**13**:101–107. https://doi.org/10.1002/clc.4960130208
789. Maskatia SA, Decker JA, Spinner JA, Kim JJ, Price JF, Jefferies JL, *et al.* Restrictive physiology is associated with poor outcomes in children with hypertrophic cardiomyopathy. *Pediatr Cardiol* 2012;**33**:141–149. https://doi.org/10.1007/s00246-011-0106-6
790. Olivotto I, Maron MS, Adabag AS, Casey SA, Vargiu D, Link MS, *et al.* Gender-related differences in the clinical presentation and outcome of hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005;**46**:480–487. https://doi.org/10.1016/j.jacc.2005.04.043
791. Yan L-R, Zhao S-H, Wang H-Y, Duan F-J, Wang Z-M, Yang Y-J, *et al.* Clinical characteristics and prognosis of 60 patients with midventricular obstructive hypertrophic cardiomyopathy. *J Cardiovasc Med (Hagerstown)* 2015;**16**:751–760. https://doi.org/10.2459/JCM.0000000000000163
792. Minami Y, Haruki S, Hagiwara N. Phenotypic overlap in hypertrophic cardiomyopathy: apical hypertrophy, midventricular obstruction, and apical aneurysm. *J Cardiol* 2014;**64**: 463–469. https://doi.org/10.1016/j.jjcc.2014.03.003
793. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, *et al.* 2020 AHA/ACC Guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2020;**142**:e558–e631. https://doi.org/10.1161/CIR.0000000000000937
794. Kamp NJ, Chery G, Kosinski AS, Desai MY, Wazni O, Schmidler GS, *et al.* Risk stratification using late gadolinium enhancement on cardiac magnetic resonance imaging in patients with hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Prog Cardiovasc Dis* 2021;**66**:10–16. https://doi.org/10.1016/j.pcad.2020.11.001
795. Kramer CM, DiMarco JP, Kolm P, Ho CY, Desai MY, Kwong RY, *et al.* Predictors of major atrial fibrillation endpoints in the National Heart, Lung, and Blood Institute HCMR. *JACC Clin Electrophysiol* 2021;**7**:1376–1386. https://doi.org/10.1016/j.jacep.2021.04.004
796. Raja AA, Farhad H, Valente AM, Couce JP, Jefferies JL, Bundgaard H, *et al.* Prevalence and progression of late gadolinium enhancement in children and adolescents with hypertrophic cardiomyopathy. *Circulation* 2018;**138**:782–792. https://doi.org/10.1161/CIRCULATIONAHA.117.032966
797. Petryka-Mazurkiewicz J, Ziolkowska L, Kowalczyk-Domagala M, Mazurkiewicz L, Boruc A, Spiewak M, *et al.* LGE for risk stratification in primary prevention in children with HCM. *JACC Cardiovasc Imaging* 2020;**13**:2684–2686. https://doi.org/10.1016/j.jcmg.2020.06.009
798. Frenneaux MP, Counihan PJ, Caforio AL, Chikamori T, McKenna WJ. Abnormal blood pressure response during exercise in hypertrophic cardiomyopathy. *Circulation* 1990; **82**:1995–2002. https://doi.org/10.1161/01.CIR.82.6.1995
799. Counihan PJ, Frenneaux MP, Webb DJ, McKenna WJ. Abnormal vascular responses to supine exercise in hypertrophic cardiomyopathy. *Circulation* 1991;**84**:686–696. https://doi.org/10.1161/01.CIR.84.2.686
800. Sadoul N, Prasad K, Elliott PM, Bannerjee S, Frenneaux MP, McKenna WJ. Prospective prognostic assessment of blood pressure response during exercise in patients with hypertrophic cardiomyopathy. *Circulation* 1997;**96**:2987–2991. https://doi.org/10.1161/01.CIR.96.9.2987
801. Smith ED, Tome J, McGrath R, Kumar S, Concannon M, Day SM, *et al.* Exercise hemodynamics in hypertrophic cardiomyopathy identify risk of incident heart failure but not ventricular arrhythmias or sudden cardiac death. *Int J Cardiol* 2019;**274**:226–231. https://doi.org/10.1016/j.ijcard.2018.07.110
802. Norrish G, Cantarutti N, Pissaridou E, Ridout DA, Limongelli G, Elliott PM, *et al.* Risk factors for sudden cardiac death in childhood hypertrophic cardiomyopathy: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2017;**24**:1220–1230. https://doi.org/10.1177/2047487317702519
803. Watkins H, Rosenzweig A, Hwang DS, Levi T, McKenna W, Seidman CE, *et al.* Characteristics and prognostic implications of myosin missense mutations in familial hypertrophic cardiomyopathy. *N Engl J Med* 1992;**326**:1108–1114. https://doi.org/10.1056/NEJM199204233261703
804. Anan R, Greve G, Thierfelder L, Watkins H, McKenna WJ, Solomon S, *et al.* Prognostic implications of novel beta cardiac myosin heavy chain gene mutations that cause familial hypertrophic cardiomyopathy. *J Clin Invest* 1994;**93**:280–285. https://doi.org/10.1172/JCI116957
805. Moolman JC, Corfield VA, Posen B, Ngumbela K, Seidman C, Brink PA, *et al.* Sudden death due to troponin T mutations. *J Am Coll Cardiol* 1997;**29**:549–555. https://doi.org/10.1016/S0735-1097(96)00530-X
806. Ackerman MJ, VanDriest SL, Ommen SR, Will ML, Nishimura RA, Tajik AJ, *et al.* Prevalence and age-dependence of malignant mutations in the beta-myosin heavy chain and troponin T genes in hypertrophic cardiomyopathy: a comprehensive outpatient perspective. *J Am Coll Cardiol* 2002;**39**:2042–2048. https://doi.org/10.1016/S0735-1097(02)01900-9
807. Garcia-Giustiniani D, Arad M, Ortiz-Genga M, Barriales-Villa R, Fernandez X, Rodriguez-Garcia I, *et al.* Phenotype and prognostic correlations of the converter region mutations affecting the beta myosin heavy chain. *Heart* 2015;**101**:1047–1053. https://doi.org/10.1136/heartjnl-2014-307205
808. Van Driest SL, Maron BJ, Ackerman MJ. From malignant mutations to malignant domains: the continuing search for prognostic significance in the mutant genes causing hypertrophic cardiomyopathy. *Heart* 2004;**90**:7–8. https://doi.org/10.1136/heart.90.1.7
809. Fananapazir L, Epstein ND. Genotype-phenotype correlations in hypertrophic cardiomyopathy. Insights provided by comparisons of kindreds with distinct and identical beta-myosin heavy chain gene mutations. *Circulation* 1994;**89**:22–32. https://doi.org/10.1161/01.CIR.89.1.22

810. Landstrom AP, Ackerman MJ. Mutation type is not clinically useful in predicting prognosis in hypertrophic cardiomyopathy. *Circulation* 2010;**122**:2441–2449;discussion 2450. https://doi.org/10.1161/CIRCULATIONAHA.110.954446
811. Richard P, Charron P, Leclercq C, Ledeuil C, Carrier L, Dubourg O, *et al.* Homozygotes for a R869G mutation in the beta-myosin heavy chain gene have a severe form of familial hypertrophic cardiomyopathy. *J Mol Cell Cardiol* 2000;**32**:1575–1583. https://doi.org/10.1006/jmcc.2000.1193
812. Richard P, Isnard R, Carrier L, Dubourg O, Donatien Y, Mathieu B, *et al.* Double heterozygosity for mutations in the beta-myosin heavy chain and in the cardiac myosin binding protein C genes in a family with hypertrophic cardiomyopathy. *J Med Genet* 1999;**36**:542–545. https://doi.org/10.1136/jmg.36.7.542
813. Jeschke B, Uhl K, Weist B, Schroder D, Meitinger T, Dohlemann C, *et al.* A high risk phenotype of hypertrophic cardiomyopathy associated with a compound genotype of two mutated beta-myosin heavy chain genes. *Hum Genet* 1998;**102**:299–304. https://doi.org/10.1007/s004390050695
814. Kaski JP, Syrris P, Esteban MT, Jenkins S, Pantazis A, Deanfield JE, *et al.* Prevalence of sarcomere protein gene mutations in preadolescent children with hypertrophic cardiomyopathy. *Circ Cardiovasc Genet* 2009;**2**:436–441. https://doi.org/10.1161/CIRCGENETICS.108.821314
815. Morita H, Rehm HL, Menesses A, McDonough B, Roberts AE, Kucherlapati R, *et al.* Shared genetic causes of cardiac hypertrophy in children and adults. *N Engl J Med* 2008;**358**:1899–1908. https://doi.org/10.1056/NEJMoa075463
816. Lopes LR, Syrris P, Guttmann OP, O'Mahony C, Tang HC, Dalageorgou C, *et al.* Novel genotype-phenotype associations demonstrated by high-throughput sequencing in patients with hypertrophic cardiomyopathy. *Heart* 2015;**101**:294–301. https://doi.org/10.1136/heartjnl-2014-306387
817. van Velzen HG, Vriesendorp PA, Oldenburg RA, van Slegtenhorst MA, van der Velden J, Schinkel AFL, *et al.* Value of genetic testing for the prediction of long-term outcome in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2016;**118**:881–887. https://doi.org/10.1016/j.amjcard.2016.06.038
818. McKenna WJ, Oakley CM, Krikler DM, Goodwin JF. Improved survival with amiodarone in patients with hypertrophic cardiomyopathy and ventricular tachycardia. *Br Heart J* 1985;**53**:412–416. https://doi.org/10.1136/hrt.53.4.412
819. Melacini P, Maron BJ, Bobbo F, Basso C, Tokajuk B, Zucchetto M, *et al.* Evidence that pharmacological strategies lack efficacy for the prevention of sudden death in hypertrophic cardiomyopathy. *Heart* 2007;**93**:708–710. https://doi.org/10.1136/hrt.2006.099416
820. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, *et al.* ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace* 2006;**8**:746–837. https://doi.org/10.1093/europace/eul108
821. Vriesendorp PA, Schinkel AF, Liebregts M, Theuns DA, van Cleemput J, Ten Cate FJ, *et al.* Validation of the 2014 European Society of Cardiology guidelines risk prediction model for the primary prevention of sudden cardiac death in hypertrophic cardiomyopathy. *Circ Arrhythm Electrophysiol* 2015;**8**:829–835. https://doi.org/10.1161/CIRCEP.114.002553
822. Choi Y-J, Kim H-K, Lee SC, Park J-B, Moon I, Park J, *et al.* Validation of the hypertrophic cardiomyopathy risk-sudden cardiac death calculator in Asians. *Heart* 2019;**105**:1892–1897. https://doi.org/10.1136/heartjnl-2019-315160
823. O'Mahony C, Jichi F, Ommen SR, Christiaans I, Arbustini E, Garcia-Pavia P, *et al.* International external validation study of the 2014 European Society of Cardiology Guidelines on sudden cardiac death prevention in hypertrophic cardiomyopathy (EVIDENCE-HCM). *Circulation* 2018;**137**:1015–1023. https://doi.org/10.1161/CIRCULATIONAHA.117.030437
824. Fernandez A, Quiroga A, Ochoa JP, Mysuta M, Casabe JH, Biagetti M, *et al.* Validation of the 2014 European Society of Cardiology sudden cardiac death risk prediction model in hypertrophic cardiomyopathy in a reference center in South America. *Am J Cardiol* 2016;**118**:121–126. https://doi.org/10.1016/j.amjcard.2016.04.021
825. Norrish G, Ding T, Field E, McLeod K, Ilina M, Stuart G, *et al.* A validation study of the European Society of Cardiology guidelines for risk stratification of sudden cardiac death in childhood hypertrophic cardiomyopathy. *Europace* 2019;**21**:1559–1565. https://doi.org/10.1093/europace/euz118
826. Ostman-Smith I, Sjoberg G, Alenius Dahlqvist J, Larsson P, Fernlund E. Sudden cardiac death in childhood hypertrophic cardiomyopathy is best predicted by a combination of electrocardiogram risk-score and HCMRisk-Kids score. *Acta Paediatr* 2021;**110**:3105–3115. https://doi.org/10.1111/apa.16045
827. Magnusson P, Gadler F, Liv P, Morner S. Hypertrophic cardiomyopathy and implantable defibrillators in Sweden: inappropriate shocks and complications requiring surgery. *J Cardiovasc Electrophysiol* 2015;**26**:1088–1094. https://doi.org/10.1111/jce.12750
828. Norrish G, Chubb H, Field E, McLeod K, Ilina M, Spentzou G, *et al.* Clinical outcomes and programming strategies of implantable cardioverter-defibrillator devices in paediatric hypertrophic cardiomyopathy: a UK National Cohort Study. *Europace* 2021;**23**:400–408. https://doi.org/10.1093/europace/euaa307
829. Liebregts M, Faber L, Jensen MK, Vriesendorp PA, Hansen PR, Seggewiss H, *et al.* Validation of the HCM Risk-SCD model in patients with hypertrophic cardiomyopathy following alcohol septal ablation. *Europace* 2018;**20**:f198–f203. https://doi.org/10.1093/europace/eux251
830. Veselka J, Liebregts M, Cooper R, Faber L, Januska J, Kashtanov M, *et al.* Prediction of sudden cardiac arrest after alcohol septal ablation for hypertrophic obstructive cardiomyopathy: ASA-SCARRE risk score. *Am J Cardiol* 2022;**184**:120–126. https://doi.org/10.1016/j.amjcard.2022.08.028
831. Maron BJ, Spirito P, Shen WK, Haas TS, Formisano F, Link MS, *et al.* Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA* 2007;**298**:405–412. https://doi.org/10.1001/jama.298.4.405
832. Syska P, Przybylski A, Chojnowska L, Lewandowski M, Sterlinski M, Maciag A, *et al.* Implantable cardioverter-defibrillator in patients with hypertrophic cardiomyopathy: efficacy and complications of the therapy in long-term follow-up. *J Cardiovasc Electrophysiol* 2010;**21**:883–889. https://doi.org/10.1111/j.1540-8167.2009.01716.x
833. Norrish G, Qu C, Field E, Cervi E, Khraiche D, Klaassen S, *et al.* External validation of the HCM Risk-Kids model for predicting sudden cardiac death in childhood hypertrophic cardiomyopathy. *Eur J Prev Cardiol* 2022;**29**:678–686. https://doi.org/10.1093/eurjpc/zwab181
834. Maron MS, Appelbaum E, Harrigan CJ, Buros J, Gibson CM, Hanna C, *et al.* Clinical profile and significance of delayed enhancement in hypertrophic cardiomyopathy. *Circ Heart Fail* 2008;**1**:184–191. https://doi.org/10.1161/CIRCHEARTFAILURE.108.768119
835. Bruder O, Wagner A, Jensen CJ, Schneider S, Ong P, Kispert EM, *et al.* Myocardial scar visualized by cardiovascular magnetic resonance imaging predicts major adverse events in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2010;**56**:875–887. https://doi.org/10.1016/j.jacc.2010.05.007
836. O'Hanlon R, Grasso A, Roughton M, Moon JC, Clark S, Wage R, *et al.* Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2010;**56**:867–874. https://doi.org/10.1016/j.jacc.2010.05.010
837. Green JJ, Berger JS, Kramer CM, Salerno M. Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. *JACC Cardiovasc Imaging* 2012;**5**:370–377. https://doi.org/10.1016/j.jcmg.2011.11.021
838. Ismail TF, Jabbour A, Gulati A, Mallorie A, Raza S, Cowling TE, *et al.* Role of late gadolinium enhancement cardiovascular magnetic resonance in the risk stratification of hypertrophic cardiomyopathy. *Heart* 2014;**100**:1851–1858. https://doi.org/10.1136/heartjnl-2013-305471
839. Briasoulis A, Mallikethi-Reddy S, Palla M, Alesh I, Afonso L. Myocardial fibrosis on cardiac magnetic resonance and cardiac outcomes in hypertrophic cardiomyopathy: a meta-analysis. *Heart* 2015;**101**:1406–1411. https://doi.org/10.1136/heartjnl-2015-307682
840. Mentias A, Raeisi-Giglou P, Smedira NG, Feng K, Sato K, Wazni O, *et al.* Late gadolinium enhancement in patients with hypertrophic cardiomyopathy and preserved systolic function. *J Am Coll Cardiol* 2018;**72**:857–870. https://doi.org/10.1016/j.jacc.2018.05.060
841. Rowin EJ, Maron MS, Adler A, Albano AJ, Varnava AM, Spears D, *et al.* Importance of newer cardiac magnetic resonance-based risk markers for sudden death prevention in hypertrophic cardiomyopathy: an international multicenter study. *Heart Rhythm* 2022;**19**:782–789. https://doi.org/10.1016/j.hrthm.2021.12.017
842. Rowin EJ, Maron BJ, Carrick RT, Patel PP, Koethe B, Wells S, *et al.* Outcomes in patients with hypertrophic cardiomyopathy and left ventricular systolic dysfunction. *J Am Coll Cardiol* 2020;**75**:3033–3043. https://doi.org/10.1016/j.jacc.2020.04.045
843. Thaman R, Gimeno JR, Murphy RT, Kubo T, Sachdev B, Mogensen J, *et al.* Prevalence and clinical significance of systolic impairment in hypertrophic cardiomyopathy. *Heart* 2005;**91**:920–925. https://doi.org/10.1136/hrt.2003.031161
844. Kawarai H, Kajimoto K, Minami Y, Hagiwara N, Kasanuki H. Risk of sudden death in end-stage hypertrophic cardiomyopathy. *J Card Fail* 2011;**17**:459–464. https://doi.org/10.1016/j.cardfail.2011.01.015
845. Pettersen MD, Du W, Skeens ME, Humes RA. Regression equations for calculation of z scores of cardiac structures in a large cohort of healthy infants, children, and adolescents: an echocardiographic study. *J Am Soc Echocardiogr* 2008;**21**:922–934. https://doi.org/10.1016/j.echo.2008.02.006
846. Chubb H, Simpson JM. The use of Z-scores in paediatric cardiology. *Ann Pediatr Cardiol* 2012;**5**:179–184. https://doi.org/10.4103/0974-2069.99622
847. Sepehrkhouy S, Gho J, van Es R, Harakalova M, de Jonge N, Dooijes D, *et al.* Distinct fibrosis pattern in desmosomal and phospholamban mutation carriers in hereditary cardiomyopathies. *Heart Rhythm* 2017;**14**:1024–1032. https://doi.org/10.1016/j.hrthm.2017.03.034
848. Chen W, Qian W, Zhang X, Li D, Qian Z, Xu H, *et al.* Ring-like late gadolinium enhancement for predicting ventricular tachyarrhythmias in non-ischaemic dilated cardiomyopathy. *Eur Heart J Cardiovasc Imaging* 2021;**22**:1130–1138. https://doi.org/10.1093/ehjci/jeab117
849. Writing Group, Document Reading Group, EACVI Reviewers: this document was reviewed by members of the EACVI Scientific Documents Committee for 2014–2016

and 2016–2018. A joint procedural position statement on imaging in cardiac sarcoidosis: from the Cardiovascular and Inflammation & Infection Committees of the European Association of Nuclear Medicine, the European Association of Cardiovascular Imaging, and the American Society of Nuclear Cardiology. *Eur Heart J Cardiovasc Imaging* 2017;**18**:1073–1089. https://doi.org/10.1093/ehjci/jex146
850. Fatkin D, Huttner IG, Kovacic JC, Seidman JG, Seidman CE. Precision medicine in the management of dilated cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol* 2019;**74**:2921–2938. https://doi.org/10.1016/j.jacc.2019.10.011
851. Merlo M, Cannata A, Sinagra G. Dilated cardiomyopathy: a paradigm of revolution in medicine. *J Clin Med* 2020;**9**:3385. https://doi.org/10.3390/jcm9113385
852. Seferovic PM, Polovina M, Bauersachs J, Arad M, Gal TB, Lund LH, *et al.* Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:553–576. https://doi.org/10.1002/ejhf.1461
853. Verdonschot JAJ, Hazebroek MR, Krapels IPC, Henkens M, Raafs A, Wang P, *et al.* Implications of genetic testing in dilated cardiomyopathy. *Circ Genom Precis Med* 2020;**13**:476–487. https://doi.org/10.1161/CIRCGEN.120.003031
854. Hey TM, Rasmussen TB, Madsen T, Aagaard MM, Harbo M, Molgaard H, *et al.* Clinical and genetic investigations of 109 index patients with dilated cardiomyopathy and 445 of their relatives. *Circ Heart Fail* 2020;**13**:e006701. https://doi.org/10.1161/CIRCHEARTFAILURE.119.006701
855. Cuenca S, Ruiz-Cano MJ, Gimeno-Blanes JR, Jurado A, Salas C, Gomez-Diaz I, *et al.* Genetic basis of familial dilated cardiomyopathy patients undergoing heart transplantation. *J Heart Lung Transplant* 2016;**35**:625–635. https://doi.org/10.1016/j.healun.2015.12.014
856. van der Meulen MH, Herkert JC, den Boer SL, du Marchie Sarvaas GJ, Blom N, Ten Harkel ADJ, *et al.* Genetic evaluation of a nation-wide Dutch pediatric DCM cohort: the use of genetic testing in risk stratification. *Circ Genom Precis Med* 2022;**15**:e002981. https://doi.org/10.1161/CIRCGEN.120.002981
857. Ware SM, Wilkinson JD, Tariq M, Schubert JA, Sridhar A, Colan SD, *et al.* Genetic causes of cardiomyopathy in children: first results from the pediatric cardiomyopathy genes study. *J Am Heart Assoc* 2021;**10**:e017731. https://doi.org/10.1161/JAHA.120.017731
858. Escobar-Lopez L, Ochoa JP, Royuela A, Verdonschot JAJ, Dal Ferro M, Espinosa MA, *et al.* Clinical risk score to predict pathogenic genotypes in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2022;**80**:1115–1126. https://doi.org/10.1016/j.jacc.2022.06.040
859. Cannata A, Merlo M, Dal Ferro M, Barbati G, Manca P, Paldino A, *et al.* Association of titin variations with late-onset dilated cardiomyopathy. *JAMA Cardiol* 2022;**7**:371–377. https://doi.org/10.1001/jamacardio.2021.5890
860. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, *et al.* Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225–237. https://doi.org/10.1056/NEJMoa043399
861. Kober L, Thune JJ, Nielsen JC, Haarbo J, Videbaek L, Korup E, *et al.* Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;**375**:1221–1230. https://doi.org/10.1056/NEJMoa1608029
862. Elming MB, Nielsen JC, Haarbo J, Videbaek L, Korup E, Signorovitch J, *et al.* Age and outcomes of primary prevention implantable cardioverter-defibrillators in patients with nonischemic systolic heart failure. *Circulation* 2017;**136**:1772–1780. https://doi.org/10.1161/CIRCULATIONAHA.117.028829
863. Alba AC, Foroutan F, Duero Posada J, Battioni L, Schofield T, Alhussein M, *et al.* Implantable cardiac defibrillator and mortality in non-ischaemic cardiomyopathy: an updated meta-analysis. *Heart* 2018;**104**:230–236. https://doi.org/10.1136/heartjnl-2017-311430
864. Smith ED, Lakdawala NK, Papoutsidakis N, Aubert G, Mazzanti A, McCanta AC, *et al.* Desmoplakin cardiomyopathy, a fibrotic and inflammatory form of cardiomyopathy distinct from typical dilated or arrhythmogenic right ventricular cardiomyopathy. *Circulation* 2020;**141**:1872–1884. https://doi.org/10.1161/CIRCULATIONAHA.119.044934
865. Barriales-Villa R, Ochoa JP, Larranaga-Moreira JM, Salazar-Mendiguchia J, Diez-Lopez C, Restrepo-Cordoba MA, *et al.* Risk predictors in a Spanish cohort with cardiac laminopathies. The REDLAMINA registry. *Rev Esp Cardiol (Engl Ed)* 2021;**74**:216–224. https://doi.org/10.1016/j.recesp.2020.03.002
866. Gigli M, Stolfo D, Graw SL, Merlo M, Gregorio C, Nee Chen S, *et al.* Phenotypic expression, natural history, and risk stratification of cardiomyopathy caused by filamin C truncating variants. *Circulation* 2021;**144**:1600–1611. https://doi.org/10.1161/CIRCULATIONAHA.121.053521
867. Akhtar MM, Lorenzini M, Pavlou M, Ochoa JP, O'Mahony C, Restrepo-Cordoba MA, *et al.* Association of left ventricular systolic dysfunction among carriers of truncating variants in filamin C with frequent ventricular arrhythmia and end-stage heart failure. *JAMA Cardiol* 2021;**6**:891–901. https://doi.org/10.1001/jamacardio.2021.1106
868. Hodgkinson KA, Howes AJ, Boland P, Shen XS, Stuckless S, Young T-L, *et al.* Long-term clinical outcome of arrhythmogenic right ventricular cardiomyopathy in individuals with a p.S358L mutation in TMEM43 following implantable cardioverter defibrillator therapy. *Circ Arrhythm Electrophysiol* 2016;**9**:e003589. https://doi.org/10.1161/CIRCEP.115.003589
869. Hey TM, Rasmussen TB, Madsen T, Aagaard MM, Harbo M, Molgaard H, *et al.* Pathogenic RBM20-variants are associated with a severe disease expression in male patients with dilated cardiomyopathy. *Circ Heart Fail* 2019;**12**:e005700. https://doi.org/10.1161/CIRCHEARTFAILURE.118.005700
870. Ebert M, Wijnmaalen AP, de Riva M, Trines SA, Androulakis AFA, Glashan CA, *et al.* Prevalence and prognostic impact of pathogenic variants in patients with dilated cardiomyopathy referred for ventricular tachycardia ablation. *JACC Clin Electrophysiol* 2020;**6**:1103–1114. https://doi.org/10.1016/j.jacep.2020.04.025
871. Rootwelt-Norberg C, Christensen AH, Skjolsvik ET, Chivulescu M, Vissing CR, Bundgaard H, *et al.* Timing of cardioverter-defibrillator implantation in patients with cardiac laminopathies–external validation of the LMNA-risk ventricular tachyarrhythmia calculator. *Heart Rhythm* 2023;**20**:423–429. https://doi.org/10.1016/j.hrthm.2022.11.024
872. Akhtar MM, Lorenzini M, Cicerchia M, Ochoa JP, Hey TM, Sabater Molina M, *et al.* Clinical phenotypes and prognosis of dilated cardiomyopathy caused by truncating variants in the TTN gene. *Circ Heart Fail* 2020;**13**:e006832. https://doi.org/10.1161/CIRCHEARTFAILURE.119.006832
873. Mirelis JG, Escobar-Lopez L, Ochoa JP, Espinosa MA, Villacorta E, Navarro M, *et al.* Combination of late gadolinium enhancement and genotype improves prediction of prognosis in non-ischaemic dilated cardiomyopathy. *Eur J Heart Fail* 2022;**24**:1183–1196. https://doi.org/10.1002/ejhf.2514
874. Di Marco A, Brown PF, Bradley J, Nucifora G, Claver E, de Frutos F, *et al.* Improved risk stratification for ventricular arrhythmias and sudden death in patients with nonischemic dilated cardiomyopathy. *J Am Coll Cardiol* 2021;**77**:2890–2905. https://doi.org/10.1016/j.jacc.2021.04.030
875. Brilakis ES, Shen WK, Hammill SC, Hodge DO, Rea RF, Lexvold NY, *et al.* Role of programmed ventricular stimulation and implantable cardioverter defibrillators in patients with idiopathic dilated cardiomyopathy and syncope. *Pacing Clin Electrophysiol* 2001;**24**:1623–1630. https://doi.org/10.1046/j.1460-9592.2001.01623.x
876. Merino JL, Carmona JR, Fernandez-Lozano I, Peinado R, Basterra N, Sobrino JA. Mechanisms of sustained ventricular tachycardia in myotonic dystrophy: implications for catheter ablation. *Circulation* 1998;**98**:541–546. https://doi.org/10.1161/01.CIR.98.6.541
877. Russo V, Papa AA, Rago A, Ciardiello C, Martino AM, Stazi A, *et al.* Arrhythmic CArdiac DEath in MYotonic dystrophy type 1 patients (ACADEMY 1) study: the predictive role of programmed ventricular stimulation. *Europace* 2022;**24**:1148–1155. https://doi.org/10.1093/europace/euab282
878. van Rijsingen IA, Arbustini E, Elliott PM, Mogensen J, Hermans-van Ast JF, van der Kooi AJ, *et al.* Risk factors for malignant ventricular arrhythmias in lamin a/c mutation carriers a European cohort study. *J Am Coll Cardiol* 2012;**59**:493–500. https://doi.org/10.1016/j.jacc.2011.08.078
879. Thuillot M, Maupain C, Gandjbakhch E, Waintraub X, Hidden-Lucet F, Isnard R, *et al.* External validation of risk factors for malignant ventricular arrhythmias in lamin A/C mutation carriers. *Eur J Heart Fail* 2019;**21**:253–254. https://doi.org/10.1002/ejhf.1384
880. Ader F, De Groote P, Reant P, Rooryck-Thambo C, Dupin-Deguine D, Rambaud C, *et al.* FLNC pathogenic variants in patients with cardiomyopathies: prevalence and genotype-phenotype correlations. *Clin Genet* 2019;**96**:317–329. https://doi.org/10.1111/cge.13594
881. Hodgkinson KA, Connors SP, Merner N, Haywood A, Young T-L, McKenna WJ, *et al.* The natural history of a genetic subtype of arrhythmogenic right ventricular cardiomyopathy caused by a p.S358L mutation in TMEM43. *Clin Genet* 2013;**83**:321–331. https://doi.org/10.1111/j.1399-0004.2012.01919.x
882. van der Zwaag PA, van Rijsingen IA, Asimaki A, Jongbloed JD, van Veldhuisen DJ, Wiesfeld AC, *et al.* Phospholamban R14del mutation in patients diagnosed with dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy: evidence supporting the concept of arrhythmogenic cardiomyopathy. *Eur J Heart Fail* 2012;**14**:1199–1207. https://doi.org/10.1093/eurjhf/hfs119
883. van Rijsingen IA, van der Zwaag PA, Groeneweg JA, Nannenberg EA, Jongbloed JD, Zwinderman AH, *et al.* Outcome in phospholamban R14del carriers: results of a large multicentre cohort study. *Circ Cardiovasc Genet* 2014;**7**:455–465. https://doi.org/10.1161/CIRCGENETICS.113.000374
884. Hallstrom AP, Greene HL, Wyse DG, Zipes D, Epstein AE, Domanski MJ, *et al.* Antiarrhythmics Versus Implantable Defibrillators (AVID)–rationale, design, and methods. *Am J Cardiol* 1995;**75**:470–475. https://doi.org/10.1016/S0002-9149(99)80583-9
885. Beggs SAS, Jhund PS, Jackson CE, McMurray JJV, Gardner RS. Non-ischaemic cardiomyopathy, sudden death and implantable defibrillators: a review and meta-analysis. *Heart* 2018;**104**:144–150. https://doi.org/10.1136/heartjnl-2016-310850
886. Jorda P, Toro R, Diez C, Salazar-Mendiguchia J, Fernandez-Falgueras A, Perez-Serra A, *et al.* Malignant arrhythmogenic role associated with RBM20: a comprehensive interpretation focused on a personalized approach. *J Pers Med* 2021;**11**:130. https://doi.org/10.3390/jpm11020130
887. Hasselberg NE, Edvardsen T, Petri H, Berge KE, Leren TP, Bundgaard H, *et al.* Risk prediction of ventricular arrhythmias and myocardial function in Lamin A/C mutation positive subjects. *Europace* 2014;**16**:563–571. https://doi.org/10.1093/europace/eut291

888. Protonotarios A, Wicks E, Ashworth M, Stephenson E, Guttmann O, Savvatis K, *et al.* Prevalence of (18)F-fluorodeoxyglucose positron emission tomography abnormalities in patients with arrhythmogenic right ventricular cardiomyopathy. *Int J Cardiol* 2019; **284**:99–104. https://doi.org/10.1016/j.ijcard.2018.10.083
889. Casella M, Gasperetti A, Sicuso R, Conte E, Catto V, Sommariva E, *et al.* Characteristics of patients with arrhythmogenic left ventricular cardiomyopathy: combining genetic and histopathologic findings. *Circ Arrhythm Electrophysiol* 2020;**13**:e009005. https://doi.org/10.1161/CIRCEP.120.009005
890. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomyopathy and sudden death in young people. *N Engl J Med* 1988;**318**:129–133. https://doi.org/10.1056/NEJM198801213180301
891. Protonotarios A, Anastasakis A, Panagiotakos DB, Antoniades L, Syrris P, Vouliotis A, *et al.* Arrhythmic risk assessment in genotyped families with arrhythmogenic right ventricular cardiomyopathy. *Europace* 2016;**18**:610–616. https://doi.org/10.1093/europace/euv061
892. Corrado D, van Tintelen PJ, McKenna WJ, Hauer RNW, Anastastakis A, Asimaki A, *et al.* Arrhythmogenic right ventricular cardiomyopathy: evaluation of the current diagnostic criteria and differential diagnosis. *Eur Heart J* 2020;**41**:1414–1429. https://doi.org/10.1093/eurheartj/ehz669
893. Cipriani A, Bauce B, De Lazzari M, Rigato I, Bariani R, Meneghin S, *et al.* Arrhythmogenic right ventricular cardiomyopathy: characterization of left ventricular phenotype and differential diagnosis with dilated cardiomyopathy. *J Am Heart Assoc* 2020;**9**:e014628. https://doi.org/10.1161/JAHA.119.014628
894. Sen-Chowdhry S, Syrris P, Prasad SK, Hughes SE, Merrifield R, Ward D, *et al.* Left-dominant arrhythmogenic cardiomyopathy: an under-recognized clinical entity. *J Am Coll Cardiol* 2008;**52**:2175–2187. https://doi.org/10.1016/j.jacc.2008.09.019
895. Bhonsale A, Groeneweg JA, James CA, Dooijes D, Tichnell C, Jongbloed JD, *et al.* Impact of genotype on clinical course in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated mutation carriers. *Eur Heart J* 2015;**36**:847–855. https://doi.org/10.1093/eurheartj/ehu509
896. Hermida A, Fressart V, Hidden-Lucet F, Donal E, Probst V, Deharo JC, *et al.* High risk of heart failure associated with desmoglein-2 mutations compared to plakophilin-2 mutations in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Eur J Heart Fail* 2019;**21**:792–800. https://doi.org/10.1002/ejhf.1423
897. DeWitt ES, Chandler SF, Hylind RJ, Beausejour Ladouceur V, Blume ED, VanderPluym C, *et al.* Phenotypic manifestations of arrhythmogenic cardiomyopathy in children and adolescents. *J Am Coll Cardiol* 2019;**74**:346–358. https://doi.org/10.1016/j.jacc.2019.05.022
898. Protonotarios A, Elliott PM. Arrhythmogenic right ventricular cardiomyopathy as a hidden cause of paediatric myocarditis presentation. *Int J Cardiol* 2018;**271**:113–114. https://doi.org/10.1016/j.ijcard.2018.06.117
899. Bosman LP, Cadrin-Tourigny J, Bourfiss M, Aliyari Ghasabeh M, Sharma A, Tichnell C, *et al.* Diagnosing arrhythmogenic right ventricular cardiomyopathy by 2010 Task Force Criteria: clinical performance and simplified practical implementation. *Europace* 2020; **22**:787–796. https://doi.org/10.1093/europace/euaa039
900. Platonov PG, Calkins H, Hauer RN, Corrado D, Svendsen JH, Wichter T, *et al.* High interobserver variability in the assessment of epsilon waves: implications for diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Heart Rhythm* 2016;**13**:208–216. https://doi.org/10.1016/j.hrthm.2015.08.031
901. Protonotarios A, Anastasakis A, Tsatsopoulou A, Antoniades L, Prappa E, Syrris P, *et al.* Clinical significance of epsilon waves in arrhythmogenic cardiomyopathy. *J Cardiovasc Electrophysiol* 2015;**26**:1204–1210. https://doi.org/10.1111/jce.12755
902. Gasperetti A, Cappelletto C, Carrick R, Targetti M, Tichnell C, Martino A, *et al.* Association of premature ventricular contraction burden on serial Holter monitoring with arrhythmic risk in patients with arrhythmogenic right ventricular cardiomyopathy. *JAMA Cardiol* 2022;**7**:378–385. https://doi.org/10.1001/jamacardio.2021.6016
903. Corrado D, Basso C, Leoni L, Tokajuk B, Bauce B, Frigo G, *et al.* Three-dimensional electroanatomic voltage mapping increases accuracy of diagnosing arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circulation* 2005;**111**:3042–3050. https://doi.org/10.1161/CIRCULATIONAHA.104.486977
904. Hoogendoorn JC, Sramko M, Venlet J, Siontis KC, Kumar S, Singh R, *et al.* Electroanatomical voltage mapping to distinguish right-sided cardiac sarcoidosis from arrhythmogenic right ventricular cardiomyopathy. *JACC Clin Electrophysiol* 2020;**6**:696–707. https://doi.org/10.1016/j.jacep.2020.02.008
905. Avella A, d'Amati G, Pappalardo A, Re F, Silenzi PF, Laurenzi F, *et al.* Diagnostic value of endomyocardial biopsy guided by electroanatomic voltage mapping in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *J Cardiovasc Electrophysiol* 2008;**19**:1127–1134. https://doi.org/10.1111/j.1540-8167.2008.01228.x
906. Casella M, Dello Russo A, Bergonti M, Catto V, Conte E, Sommariva E, *et al.* Diagnostic yield of electroanatomic voltage mapping in guiding endomyocardial biopsies. *Circulation* 2020;**142**:1249–1260. https://doi.org/10.1161/CIRCULATIONAHA.120.046900
907. Tessier R, Marteau L, Vivien M, Guyomarch B, Thollet A, Fellah I, *et al.* 18F-Fluorodeoxyglucose positron emission tomography for the detection of myocardial inflammation in arrhythmogenic left ventricular cardiomyopathy. *Circ Cardiovasc Imaging* 2022;**15**:e014065. https://doi.org/10.1161/CIRCIMAGING.122.014065
908. Gasperetti A, Rossi VA, Chiodini A, Casella M, Costa S, Akdis D, *et al.* Differentiating hereditary arrhythmogenic right ventricular cardiomyopathy from cardiac sarcoidosis fulfilling 2010 ARVC Task Force Criteria. *Heart Rhythm* 2021;**18**:231–238. https://doi.org/10.1016/j.hrthm.2020.09.015
909. Laredo M, Duthoit G, Gandjbakhch E, Redheuil A, Hebert J-L. Total pericardium agenesis mistaken for arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J Cardiovasc Imaging* 2018;**19**:120. https://doi.org/10.1093/ehjci/jex251
910. Castelletti S, Crotti L, Dagradi F, Rella V, Salerno S, Parati G, *et al.* Partial pericardial agenesis mimicking arrhythmogenic right ventricular cardiomyopathy. *Clin J Sport Med* 2020;**30**:e159–e162. https://doi.org/10.1097/JSM.0000000000000733
911. Brosnan MJ, Te Riele A, Bosman LP, Hoorntje ET, van den Berg MP, Hauer RNW, *et al.* Electrocardiographic features differentiating arrhythmogenic right ventricular cardiomyopathy from an athlete's heart. *JACC Clin Electrophysiol* 2018;**4**:1613–1625. https://doi.org/10.1016/j.jacep.2018.09.008
912. D'Ascenzi F, Solari M, Corrado D, Zorzi A, Mondillo S. Diagnostic differentiation between arrhythmogenic cardiomyopathy and athlete's heart by using imaging. *JACC Cardiovasc Imaging* 2018;**11**:1327–1339. https://doi.org/10.1016/j.jcmg.2018.04.031
913. Rossi VA, Niederseer D, Sokolska JM, Kovacs B, Costa S, Gasperetti A, *et al.* A novel diagnostic score integrating atrial dimensions to differentiate between the athlete's heart and arrhythmogenic right ventricular cardiomyopathy. *J Clin Med* 2021;**10**:4094. https://doi.org/10.3390/jcm10184094
914. van Tintelen JP, Van Gelder IC, Asimaki A, Suurmeijer AJH, Wiesfeld ACP, Jongbloed JDH, *et al.* Severe cardiac phenotype with right ventricular predominance in a large cohort of patients with a single missense mutation in the DES gene. *Heart Rhythm* 2009;**6**:1574–1583. https://doi.org/10.1016/j.hrthm.2009.07.041
915. Merner ND, Hodgkinson KA, Haywood AFM, Connors S, French VM, Drenckhahn JD, *et al.* Arrhythmogenic right ventricular cardiomyopathy type 5 is a fully penetrant, lethal arrhythmic disorder caused by a missense mutation in the TMEM43 gene. *Am J Hum Genet* 2008;**82**:809–821. https://doi.org/10.1016/j.ajhg.2008.01.010
916. Costa S, Medeiros-Domingo A, Gasperetti A, Akdis D, Berger W, James CA, *et al.* Impact of genetic variant reassessment on the diagnosis of arrhythmogenic right ventricular cardiomyopathy based on the 2010 Task Force Criteria. *Circ Genom Precis Med* 2021;**14**:e003047. https://doi.org/10.1161/CIRCGEN.120.003047
917. Elliott PM, Anastasakis A, Asimaki A, Basso C, Bauce B, Brooke MA, *et al.* Definition and treatment of arrhythmogenic cardiomyopathy: an updated expert panel report. *Eur J Heart Fail* 2019;**21**:955–964. https://doi.org/10.1002/ejhf.1534
918. Gasperetti A, Targetti M, Olivotto I. Anti-arrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: the importance of optimal beta-blocker dose titration. *Int J Cardiol* 2021;**338**:150–151. https://doi.org/10.1016/j.ijcard.2021.06.009
919. Corrado D, Wichter T, Link MS, Hauer R, Marchlinski F, Anastasakis A, *et al.* Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement. *Eur Heart J* 2015;**36**:3227–3237. https://doi.org/10.1093/eurheartj/ehv162
920. Cappelletto C, Gregorio C, Barbati G, Romani S, De Luca A, Merlo M, *et al.* Antiarrhythmic therapy and risk of cumulative ventricular arrhythmias in arrhythmogenic right ventricle cardiomyopathy. *Int J Cardiol* 2021;**334**:58–64. https://doi.org/10.1016/j.ijcard.2021.04.069
921. Marcus GM, Glidden DV, Polonsky B, Zareba W, Smith LM, Cannom DS, *et al.* Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: a report from the North American ARVC Registry. *J Am Coll Cardiol* 2009;**54**:609–615. https://doi.org/10.1016/j.jacc.2009.04.052
922. Wichter T, Borggrefe M, Haverkamp W, Chen X, Breithardt G. Efficacy of antiarrhythmic drugs in patients with arrhythmogenic right ventricular disease. Results in patients with inducible and noninducible ventricular tachycardia. *Circulation* 1992;**86**:29–37. https://doi.org/10.1161/01.CIR.86.1.29
923. Ermakov S, Gerstenfeld EP, Svetlichnaya Y, Scheinman MM. Use of flecainide in combination antiarrhythmic therapy in patients with arrhythmogenic right ventricular cardiomyopathy. *Heart Rhythm* 2017;**14**:564–569. https://doi.org/10.1016/j.hrthm.2016.12.010
924. Rolland T, Badenco N, Maupain C, Duthoit G, Waintraub X, Laredo M, *et al.* Safety and efficacy of flecainide associated with beta-blockers in arrhythmogenic right ventricular cardiomyopathy. *Europace* 2022;**24**:278–284. https://doi.org/10.1093/europace/euab182
925. Daimee UA, Assis FR, Murray B, Tichnell C, James CA, Calkins H, *et al.* Clinical outcomes of catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular cardiomyopathy: insights from the Johns Hopkins ARVC Program. *Heart Rhythm* 2021;**18**:1369–1376. https://doi.org/10.1016/j.hrthm.2021.04.028
926. Mathew S, Saguner AM, Schenker N, Kaiser L, Zhang P, Yashuiro Y, *et al.* Catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia: a sequential approach. *J Am Heart Assoc* 2019;**8**:e010365. https://doi.org/10.1161/JAHA.118.010365
927. Gandjbakhch E, Laredo M, Berruezo A, Gourraud JB, Sellal JM, Martins R, *et al.* Outcomes after catheter ablation of ventricular tachycardia without implantable cardioverter-defibrillator in selected patients with arrhythmogenic right ventricular cardiomyopathy. *Europace* 2021;**23**:1428–1436. https://doi.org/10.1093/europace/euab172

928. Assis FR, Krishnan A, Zhou X, James CA, Murray B, Tichnell C, *et al.* Cardiac sympathectomy for refractory ventricular tachycardia in arrhythmogenic right ventricular cardiomyopathy. *Heart Rhythm* 2019;**16**:1003–1010. https://doi.org/10.1016/j.hrthm.2019.01.019
929. Shen L-S, Liu L-M, Zheng L-H, Hu F, Hu Z-C, Liu S-Y, *et al.* Ablation strategies for arrhythmogenic right ventricular cardiomyopathy: a systematic review and meta-analysis. *J Geriatr Cardiol* 2020;**17**:694–703. https://doi.org/10.11909/j.issn.1671-5411.2020.11.001
930. Romero J, Patel K, Briceno D, Alviz I, Gabr M, Diaz JC, *et al.* Endo-epicardial ablation vs endocardial ablation for the management of ventricular tachycardia in arrhythmogenic right ventricular cardiomyopathy: a systematic review and meta-analysis. *J Cardiovasc Electrophysiol* 2020;**31**:2022–2031. https://doi.org/10.1111/jce.14593
931. Christiansen MK, Haugaa KH, Svensson A, Gilljam T, Madsen T, Hansen J, *et al.* Incidence, predictors, and success of ventricular tachycardia catheter ablation in arrhythmogenic right ventricular cardiomyopathy (from the Nordic ARVC Registry). *Am J Cardiol* 2020;**125**:803–811. https://doi.org/10.1016/j.amjcard.2019.11.026
932. Briceno DF, Liang JJ, Shirai Y, Markman TM, Chahal A, Tschabrunn C, *et al.* Characterization of structural changes in arrhythmogenic right ventricular cardiomyopathy with recurrent ventricular tachycardia after ablation: insights from repeat electroanatomic voltage mapping. *Circ Arrhythm Electrophysiol* 2020;**13**:e007611. https://doi.org/10.1161/CIRCEP.119.007611
933. Laredo M, Da Silva L, Extramiana F, Lellouche N, Varlet E, Amet D, *et al.* Catheter ablation of electrical storm in patients with arrhythmogenic right ventricular cardiomyopathy. *Heart Rhythm* 2020;**17**:41–48. https://doi.org/10.1016/j.hrthm.2019.06.022
934. Berruezo A, Acosta J, Fernandez-Armenta J, Pedrote A, Barrera A, Arana-Rueda E, *et al.* Safety, long-term outcomes and predictors of recurrence after first-line combined endoepicardial ventricular tachycardia substrate ablation in arrhythmogenic cardiomyopathy. Impact of arrhythmic substrate distribution pattern. A prospective multicentre study. *Europace* 2017;**19**:607–616. https://doi.org/10.1093/europace/euw212
935. Finocchiaro G, Papadakis M, Robertus JL, Dhutia H, Steriotis AK, Tome M, *et al.* Etiology of sudden death in sports: insights from a United Kingdom regional registry. *J Am Coll Cardiol* 2016;**67**:2108–2115. https://doi.org/10.1016/j.jacc.2016.02.062
936. de Noronha SV, Sharma S, Papadakis M, Desai S, Whyte G, Sheppard MN. Aetiology of sudden cardiac death in athletes in the United Kingdom: a pathological study. *Heart* 2009;**95**:1409–1414. https://doi.org/10.1136/hrt.2009.168369
937. D'Silva A, Papadakis M. Sudden cardiac death in athletes. *Eur Cardiol* 2015;**10**:48–53. https://doi.org/10.15420/ecr.2015.10.01.48
938. Corrado D, Basso C, Rizzoli G, Schiavon M, Thiene G. Does sports activity enhance the risk of sudden death in adolescents and young adults? *J Am Coll Cardiol* 2003;**42**:1959–63. https://doi.org/10.1016/j.jacc.2003.03.002
939. Bosman LP, Sammani A, James CA, Cadrin-Tourigny J, Calkins H, van Tintelen JP, *et al.* Predicting arrhythmic risk in arrhythmogenic right ventricular cardiomyopathy: a systematic review and meta-analysis. *Heart Rhythm* 2018;**15**:1097–1107. https://doi.org/10.1016/j.hrthm.2018.01.031
940. Orgeron GM, Te Riele A, Tichnell C, Wang W, Murray B, Bhonsale A, *et al.* Performance of the 2015 International Task Force Consensus Statement risk stratification algorithm for implantable cardioverter-defibrillator placement in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circ Arrhythm Electrophysiol* 2018;**11**:e005593. https://doi.org/10.1161/CIRCEP.117.005593
941. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, *et al.* 2017 AHA/ACC/HRS Guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2018;**72**:e91–e220. https://doi.org/10.1016/j.jacc.2017.10.054
942. Ellenbogen KA, Levine JH, Berger RD, Daubert JP, Winters SL, Greenstein E, *et al.* Are implantable cardioverter defibrillator shocks a surrogate for sudden cardiac death in patients with nonischemic cardiomyopathy? *Circulation* 2006;**113**:776–782. https://doi.org/10.1161/CIRCULATIONAHA.105.561571
943. Corrado D, Leoni L, Link MS, Della Bella P, Gaita F, Curnis A, *et al.* Implantable cardioverter-defibrillator therapy for prevention of sudden death in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circulation* 2003;**108**:3084–3091. https://doi.org/10.1161/01.CIR.0000103130.33451.D2
944. Link MS, Laidlaw D, Polonsky B, Zareba W, McNitt S, Gear K, *et al.* Ventricular arrhythmias in the North American multidisciplinary study of ARVC: predictors, characteristics, and treatment. *J Am Coll Cardiol* 2014;**64**:119–125. https://doi.org/10.1016/j.jacc.2014.04.035
945. Cadrin-Tourigny J, Bosman LP, Wang W, Tadros R, Bhonsale A, Bourfiss M, *et al.* Sudden cardiac death prediction in arrhythmogenic right ventricular cardiomyopathy: a multinational collaboration. *Circ Arrhythm Electrophysiol* 2021;**14**:e008509. https://doi.org/10.1161/CIRCEP.120.008509
946. Platonov PG, Haugaa KH, Bundgaard H, Svensson A, Gilljam T, Hansen J, *et al.* Primary prevention of sudden cardiac death with implantable cardioverter-defibrillator therapy in patients with arrhythmogenic right ventricular cardiomyopathy. *Am J Cardiol* 2019;**123**:1156–1162. https://doi.org/10.1016/j.amjcard.2018.12.049
947. Bhonsale A, James CA, Tichnell C, Murray B, Gagarin D, Philips B, *et al.* Incidence and predictors of implantable cardioverter-defibrillator therapy in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy undergoing implantable cardioverter-defibrillator implantation for primary prevention. *J Am Coll Cardiol* 2011;**58**:1485–1496. https://doi.org/10.1016/j.jacc.2011.06.043
948. Watkins DA, Hendricks N, Shaboodien G, Mbele M, Parker M, Vezi BZ, *et al.* Clinical features, survival experience, and profile of plakophylin-2 gene mutations in participants of the arrhythmogenic right ventricular cardiomyopathy registry of South Africa. *Heart Rhythm* 2009;**6**(11 Suppl):S10–S17. https://doi.org/10.1016/j.hrthm.2009.08.018
949. Hulot J-S, Jouven X, Empana J-P, Frank R, Fontaine G. Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circulation* 2004;**110**:1879–1884. https://doi.org/10.1161/01.CIR.0000143375.93288.82
950. Mazzanti A, Ng K, Faragli A, Maragna R, Chiodaroli E, Orphanou N, *et al.* Arrhythmogenic right ventricular cardiomyopathy: clinical course and predictors of arrhythmic risk. *J Am Coll Cardiol* 2016;**68**:2540–2550. https://doi.org/10.1016/j.jacc.2016.09.951
951. Habib G, Bucciarelli-Ducci C, Caforio ALP, Cardim N, Charron P, Cosyns B, *et al.* Multimodality imaging in restrictive cardiomyopathies: an EACVI expert consensus document in collaboration with the "Working Group on myocardial and pericardial diseases" of the European Society of Cardiology Endorsed by The Indian Academy of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2017;**18**:1090–1121. https://doi.org/10.1093/ehjci/jex034
952. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF III, Dokainish H, Edvardsen T, *et al.* Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016;**29**:277–314. https://doi.org/10.1016/j.echo.2016.01.011
953. Fenton MJ, Chubb H, McMahon AM, Rees P, Elliott MJ, Burch M. Heart and heart-lung transplantation for idiopathic restrictive cardiomyopathy in children. *Heart* 2006;**92**:85–89. https://doi.org/10.1136/hrt.2004.049502
954. Saeed M, Liu H, Liang C-H, Wilson MW. Magnetic resonance imaging for characterizing myocardial diseases. *Int J Cardiovasc Imaging* 2017;**33**:1395–1414. https://doi.org/10.1007/s10554-017-1127-x
955. Arbustini E, Morbini P, Grasso M, Fasani R, Verga L, Bellini O, *et al.* Restrictive cardiomyopathy, atrioventricular block and mild to subclinical myopathy in patients with desmin-immunoreactive material deposits. *J Am Coll Cardiol* 1998;**31**:645–653. https://doi.org/10.1016/S0735-1097(98)00026-6
956. Arbustini E, Grasso M, Rindi G, Arosio P, Gavazzi A, Diegoli M, *et al.* H and L ferritins in myocardium in iron overload. *Am J Cardiol* 1991;**68**:1233–1236. https://doi.org/10.1016/0002-9149(91)90202-V
957. Koeppen AH, Ramirez RL, Becker AB, Bjork ST, Levi S, Santambrogio P, *et al.* The pathogenesis of cardiomyopathy in Friedreich ataxia. *PLoS One* 2015;**10**:e0116396. https://doi.org/10.1371/journal.pone.0116396
958. Dixit MP, Greifer I. Nephropathic cystinosis associated with cardiomyopathy: a 27-year clinical follow-up. *BMC Nephrol* 2002;**3**:8. https://doi.org/10.1186/1471-2369-3-8
959. Giovannoni I, Callea F, Travaglini L, Amodeo A, Cogo P, Secinaro A, *et al.* Heart transplant and 2-year follow up in a child with generalized arterial calcification of infancy. *Eur J Pediatr* 2014;**173**:1735–1740. https://doi.org/10.1007/s00431-014-2447-7
960. Gambarin FI, Disabella E, Narula J, Diegoli M, Grasso M, Serio A, *et al.* When should cardiologists suspect Anderson–Fabry disease? *Am J Cardiol* 2010;**106**:1492–1499. https://doi.org/10.1016/j.amjcard.2010.07.016
961. Ben-Ami R, Puglisi J, Haider T, Mehta D. The Mount Sinai Hospital clinicalpathological conference: a 45-year-old man with Pompe's disease and dilated cardiomyopathy. *Mt Sinai J Med* 2001;**68**:205–212.
962. Kawano H, Kawamura K, Kanda M, Ishijima M, Abe K, Hayashi T, *et al.* Histopathological changes of myocytes in restrictive cardiomyopathy. *Med Mol Morphol* 2021;**54**:289–295. https://doi.org/10.1007/s00795-021-00293-7
963. Kaski JP, Syrris P, Burch M, Tome-Esteban MT, Fenton M, Christiansen M, *et al.* Idiopathic restrictive cardiomyopathy in children is caused by mutations in cardiac sarcomere protein genes. *Heart* 2008;**94**:1478–1484. https://doi.org/10.1136/hrt.2007.134684
964. Mogensen J, van Tintelen JP, Fokstuen S, Elliott P, van Langen IM, Meder B, *et al.* The current role of next-generation DNA sequencing in routine care of patients with hereditary cardiovascular conditions: a viewpoint paper of the European Society of Cardiology working group on myocardial and pericardial diseases and members of the European Society of Human Genetics. *Eur Heart J* 2015;**36**:1367–1370. https://doi.org/10.1093/eurheartj/ehv122
965. Menon SC, Michels VV, Pellikka PA, Ballew JD, Karst ML, Herron KJ, *et al.* Cardiac troponin T mutation in familial cardiomyopathy with variable remodeling and restrictive physiology. *Clin Genet* 2008;**74**:445–454. https://doi.org/10.1111/j.1399-0004.2008.01062.x
966. Burke MA, Cook SA, Seidman JG, Seidman CE. Clinical and mechanistic insights into the genetics of cardiomyopathy. *J Am Coll Cardiol* 2016;**68**:2871–2886. https://doi.org/10.1016/j.jacc.2016.08.079

967. Muchtar E, Blauwet LA, Gertz MA. Restrictive cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. *Circ Res* 2017;**121**:819–837. https://doi.org/10.1161/CIRCRESAHA.117.310982
968. Mori H, Kogaki S, Ishida H, Yoshikawa T, Shindo T, Inuzuka R, *et al.* Outcomes of restrictive cardiomyopathy in Japanese children–a retrospective cohort study. *Circ J* 2022;**86**:1943–1949. https://doi.org/10.1253/circj.CJ-21-0706
969. Rivenes SM, Kearney DL, Smith EO, Towbin JA, Denfield SW. Sudden death and cardiovascular collapse in children with restrictive cardiomyopathy. *Circulation* 2000;**102**: 876–882. https://doi.org/10.1161/01.CIR.102.8.876
970. Mogensen J, Arbustini E. Restrictive cardiomyopathy. *Curr Opin Cardiol* 2009;**24**: 214–220. https://doi.org/10.1097/HCO.0b013e32832a1d2e
971. Ammash NM, Seward JB, Bailey KR, Edwards WD, Tajik AJ. Clinical profile and outcome of idiopathic restrictive cardiomyopathy. *Circulation* 2000;**101**:2490–2496. https://doi.org/10.1161/01.CIR.101.21.2490
972. Anderson HN, Cetta F, Driscoll DJ, Olson TM, Ackerman MJ, Johnson JN. Idiopathic restrictive cardiomyopathy in children and young adults. *Am J Cardiol* 2018;**121**: 1266–1270. https://doi.org/10.1016/j.amjcard.2018.01.045
973. Walsh MA, Grenier MA, Jefferies JL, Towbin JA, Lorts A, Czosek RJ. Conduction abnormalities in pediatric patients with restrictive cardiomyopathy. *Circ Heart Fail* 2012;**5**:267–273. https://doi.org/10.1161/CIRCHEARTFAILURE.111.964395
974. Linhart A, Germain DP, Olivotto I, Akhtar MM, Anastasakis A, Hughes D, *et al.* An expert consensus document on the management of cardiovascular manifestations of Fabry disease. *Eur J Heart Fail* 2020;**22**:1076–1096. https://doi.org/10.1002/ejhf.1960
975. Aerts JM, Groener JE, Kuiper S, Donker-Koopman WE, Strijland A, Ottenhoff R, *et al.* Elevated globotriaosylsphingosine is a hallmark of Fabry disease. *Proc Natl Acad Sci USA* 2008;**105**:2812–2817. https://doi.org/10.1073/pnas.0712309105
976. Germain DP. Fabry disease. *Orphanet J Rare Dis* 2010;**5**:30. https://doi.org/10.1186/1750-1172-5-30
977. Ortiz A, Germain DP, Desnick RJ, Politei J, Mauer M, Burlina A, *et al.* Fabry disease revisited: management and treatment recommendations for adult patients. *Mol Genet Metab* 2018;**123**:416–427. https://doi.org/10.1016/j.ymgme.2018.02.014
978. Echevarria L, Benistan K, Toussaint A, Dubourg O, Hagege AA, Eladari D, *et al.* X-chromosome inactivation in female patients with Fabry disease. *Clin Genet* 2016; **89**:44–54. https://doi.org/10.1111/cge.12613
979. Schiffmann R, Hughes DA, Linthorst GE, Ortiz A, Svarstad E, Warnock DG, *et al.* Screening, diagnosis, and management of patients with Fabry disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney Int* 2017;**91**:284–293. https://doi.org/10.1016/j.kint.2016.10.004
980. Pieroni M, Moon JC, Arbustini E, Barriales-Villa R, Camporeale A, Vujkovac AC, *et al.* Cardiac involvement in Fabry disease: JACC review topic of the week. *J Am Coll Cardiol* 2021;**77**:922–936. https://doi.org/10.1016/j.jacc.2020.12.024
981. Germain DP, Fouilhoux A, Decramer S, Tardieu M, Pillet P, Fila M, *et al.* Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients. *Clin Genet* 2019;**96**:107–117. https://doi.org/10.1111/cge.13546
982. Bracamonte ER, Kowalewska J, Starr J, Gitomer J, Alpers CE. Iatrogenic phospholipidosis mimicking Fabry disease. *Am J Kidney Dis* 2006;**48**:844–850. https://doi.org/10.1053/j.ajkd.2006.05.034
983. Politei J, Frabasil J, Durand C, Di Pietrantonio S, Fernandez A, Alberton V, *et al.* Incidental finding of cornea verticillata or lamellar inclusions in kidney biopsy: measurement of lyso-Gb3 in plasma defines between Fabry disease and drug-induced phospholipidosis. *Biochim Biophys Acta Mol Basis Dis* 2021;**1867**:165985. https://doi.org/10.1016/j.bbadis.2020.165985
984. Mendez HM, Opitz JM. Noonan syndrome: a review. *Am J Med Genet* 1985;**21**: 493–506. https://doi.org/10.1002/ajmg.1320210312
985. Tartaglia M, Gelb BD, Zenker M. Noonan syndrome and clinically related disorders. *Best Pract Res Clin Endocrinol Metab* 2011;**25**:161–179. https://doi.org/10.1016/j.beem.2010.09.002
986. Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. *Lancet* 2013;**381**: 333–342. https://doi.org/10.1016/S0140-6736(12)61023-X
987. Tartaglia M, Gelb BD. Disorders of dysregulated signal traffic through the RAS-MAPK pathway: phenotypic spectrum and molecular mechanisms. *Ann NY Acad Sci* 2010; **1214**:99–121. https://doi.org/10.1111/j.1749-6632.2010.05790.x
988. Romano AA, Allanson JE, Dahlgren J, Gelb BD, Hall B, Pierpont ME, *et al.* Noonan syndrome: clinical features, diagnosis, and management guidelines. *Pediatrics* 2010;**126**: 746–759. https://doi.org/10.1542/peds.2009-3207
989. Tartaglia M, Mehler EL, Goldberg R, Zampino G, Brunner HG, Kremer H, *et al.* Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. *Nat Genet* 2001;**29**:465–468. https://doi.org/10.1038/ng772
990. Limongelli G, Pacileo G, Marino B, Digilio MC, Sarkozy A, Elliott P, *et al.* Prevalence and clinical significance of cardiovascular abnormalities in patients with the LEOPARD syndrome. *Am J Cardiol* 2007;**100**:736–741. https://doi.org/10.1016/j.amjcard.2007.03.093
991. Limongelli G, Sarkozy A, Pacileo G, Calabro P, Digilio MC, Maddaloni V, *et al.* Genotype-phenotype analysis and natural history of left ventricular hypertrophy in LEOPARD syndrome. *Am J Med Genet A* 2008;**146A**:620–628. https://doi.org/10.1002/ajmg.a.32206
992. Gripp KW, Morse LA, Axelrad M, Chatfield KC, Chidekel A, Dobyns W, *et al.* Costello syndrome: clinical phenotype, genotype, and management guidelines. *Am J Med Genet A* 2019;**179**:1725–1744. https://doi.org/10.1002/ajmg.a.61270
993. Gripp KW, Hopkins E, Sol-Church K, Stabley DL, Axelrad ME, Doyle D, *et al.* Phenotypic analysis of individuals with Costello syndrome due to HRAS p.G13C. *Am J Med Genet A* 2011;**155A**:706–716. https://doi.org/10.1002/ajmg.a.33884
994. Pierpont ME, Magoulas PL, Adi S, Kavamura MI, Neri G, Noonan J, *et al.* Cardio-facio-cutaneous syndrome: clinical features, diagnosis, and management guidelines. *Pediatrics* 2014;**134**:e1149–e1162. https://doi.org/10.1542/peds.2013-3189
995. Allanson JE, Anneren G, Aoki Y, Armour CM, Bondeson ML, Cave H, *et al.* Cardio-facio-cutaneous syndrome: does genotype predict phenotype? *Am J Med Genet C Semin Med Genet* 2011;**157C**:129–135. https://doi.org/10.1002/ajmg.c.30295
996. Niihori T, Aoki Y, Narumi Y, Neri G, Cave H, Verloes A, *et al.* Germline KRAS and BRAF mutations in cardio-facio-cutaneous syndrome. *Nat Genet* 2006;**38**:294–296. https://doi.org/10.1038/ng1749
997. Calcagni G, Gagliostro G, Limongelli G, Unolt M, De Luca E, Digilio MC, *et al.* Atypical cardiac defects in patients with RASopathies: updated data on CARNET study. *Birth Defects Res* 2020;**112**:725–731. https://doi.org/10.1002/bdr2.1670
998. Hickey EJ, Mehta R, Elmi M, Asoh K, McCrindle BW, Williams WG, *et al.* Survival implications: hypertrophic cardiomyopathy in Noonan syndrome. *Congenit Heart Dis* 2011;**6**:41–47. https://doi.org/10.1111/j.1747-0803.2010.00465.x
999. Wilkinson JD, Lowe AM, Salbert BA, Sleeper LA, Colan SD, Cox GF, *et al.* Outcomes in children with Noonan syndrome and hypertrophic cardiomyopathy: a study from the Pediatric Cardiomyopathy Registry. *Am Heart J* 2012;**164**:442–448. https://doi.org/10.1016/j.ahj.2012.04.018
1000. Prendiville TW, Gauvreau K, Tworog-Dube E, Patkin L, Kucherlapati RS, Roberts AE, *et al.* Cardiovascular disease in Noonan syndrome. *Arch Dis Child* 2014;**99**:629–634. https://doi.org/10.1136/archdischild-2013-305047
1001. Cerrato F, Pacileo G, Limongelli G, Gagliardi MG, Santoro G, Digilio MC, *et al.* A standard echocardiographic and tissue Doppler study of morphological and functional findings in children with hypertrophic cardiomyopathy compared to those with left ventricular hypertrophy in the setting of Noonan and LEOPARD syndromes. *Cardiol Young* 2008;**18**:575–580. https://doi.org/10.1017/S104795110800320X
1002. Colquitt JL, Noonan JA. Cardiac findings in Noonan syndrome on long-term follow-up. *Congenit Heart Dis* 2014;**9**:144–150. https://doi.org/10.1111/chd.12102
1003. Ishizawa A, Oho S, Dodo H, Katori T, Homma SI. Cardiovascular abnormalities in Noonan syndrome: the clinical findings and treatments. *Acta Paediatr Jpn* 1996;**38**: 84–90. https://doi.org/10.1111/j.1442-200X.1996.tb03444.x
1004. Bertola DR, Castro MAA, Yamamoto GL, Honjo RS, Ceroni JR, Buscarilli MM, *et al.* Phenotype-genotype analysis of 242 individuals with RASopathies: 18-year experience of a tertiary center in Brazil. *Am J Med Genet C Semin Med Genet* 2020;**184**: 896–911. https://doi.org/10.1002/ajmg.c.31851
1005. Colan SD, Lipshultz SE, Lowe AM, Sleeper LA, Messere J, Cox GF, *et al.* Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. *Circulation* 2007;**115**:773–781. https://doi.org/10.1161/CIRCULATIONAHA.106.621185
1006. Ostman-Smith I, Wettrell G, Riesenfeld T. A cohort study of childhood hypertrophic cardiomyopathy: improved survival following high-dose beta-adrenoceptor antagonist treatment. *J Am Coll Cardiol* 1999;**34**:1813–1822. https://doi.org/10.1016/S0735-1097(99)00421-0
1007. Jackson G, Anand IS, Oram S. Asymmetric septal hypertrophy and propranolol treatment in a case of Ullrich–Noonan syndrome. *Br Heart J* 1979;**42**:611–614. https://doi.org/10.1136/hrt.42.5.611
1008. Chen H, Li X, Liu X, Wang J, Zhang Z, Wu J, *et al.* Clinical and mutation profile of pediatric patients with RASopathy-associated hypertrophic cardiomyopathy: results from a Chinese cohort. *Orphanet J Rare Dis* 2019;**14**:29. https://doi.org/10.1186/s13023-019-1010-z
1009. McCallen LM, Ameduri RK, Denfield SW, Dodd DA, Everitt MD, Johnson JN, *et al.* Cardiac transplantation in children with Noonan syndrome. *Pediatr Transplant* 2019;**23**:e13535. https://doi.org/10.1111/petr.13535
1010. Chen S, Chen L, Jiang Y, Xu H, Sun Y, Shi H, *et al.* Early outcomes of septal myectomy for obstructive hypertrophic cardiomyopathy in children with Noonan syndrome. *Semin Thorac Cardiovasc Surg* 2022;**34**:655–665. https://doi.org/10.1053/j.semtcvs.2021.07.027
1011. Schleihauf J, Cleuziou J, Pabst von Ohain J, Meierhofer C, Stern H, Shehu N, *et al.* Clinical long-term outcome of septal myectomy for obstructive hypertrophic cardiomyopathy in infants. *Eur J Cardiothorac Surg* 2018;**53**:538–544. https://doi.org/10.1093/ejcts/ezx369
1012. Holzmann J, Tibby SM, Rosenthal E, Qureshi S, Morgan G, Krasemann T. Results of balloon pulmonary valvoplasty in children with Noonan's syndrome. *Cardiol Young* 2018;**28**:647–652. https://doi.org/10.1017/S1047951117002827
1013. Shaw AC, Kalidas K, Crosby AH, Jeffery S, Patton MA. The natural history of Noonan syndrome: a long-term follow-up study. *Arch Dis Child* 2007;**92**:128–132. https://doi.org/10.1136/adc.2006.104547

1014. Anderson K, Cnota J, James J, Miller EM, Parrott A, Pilipenko V, *et al.* Prevalence of Noonan spectrum disorders in a pediatric population with valvar pulmonary stenosis. *Congenit Heart Dis* 2019;**14**:264–273. https://doi.org/10.1111/chd.12721
1015. Ko S, Komuro J, Katsumata Y, Shiraishi Y, Kawakami T, Yamada Y, *et al.* Peripheral pulmonary stenosis with Noonan syndrome treated by balloon pulmonary angioplasty. *Pulm Circ* 2020;**10**:2045894020954310. https://doi.org/10.1177/2045894020954310
1016. Durr A, Cossee M, Agid Y, Campuzano V, Mignard C, Penet C, *et al.* Clinical and genetic abnormalities in patients with Friedreich's ataxia. *N Engl J Med* 1996;**335**:1169–1175. https://doi.org/10.1056/NEJM199610173351601
1017. Campuzano V, Montermini L, Molto MD, Pianese L, Cossee M, Cavalcanti F, *et al.* Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. *Science* 1996;**271**:1423–1427. https://doi.org/10.1126/science.271.5254.1423
1018. Cai K, Frederick RO, Tonelli M, Markley JL. Interactions of iron-bound frataxin with ISCU and ferredoxin on the cysteine desulfurase complex leading to Fe-S cluster assembly. *J Inorg Biochem* 2018;**183**:107–116. https://doi.org/10.1016/j.jinorgbio.2018.03.007
1019. Filla A, De Michele G, Cavalcanti F, Pianese L, Monticelli A, Campanella G, *et al.* The relationship between trinucleotide (GAA) repeat length and clinical features in Friedreich ataxia. *Am J Hum Genet* 1996;**59**:554–560.
1020. Delatycki MB, Paris DB, Gardner RJ, Nicholson GA, Nassif N, Storey E, *et al.* Clinical and genetic study of Friedreich ataxia in an Australian population. *Am J Med Genet* 1999;**87**:168–174.https://doi.org/10.1002/(sici)1096-8628(19991119)87:2<168::AID-AJMG8>3.0.CO;2-2
1021. Ackroyd RS, Finnegan JA, Green SH. Friedreich's ataxia. A clinical review with neurophysiological and echocardiographic findings. *Arch Dis Child* 1984;**59**:217–221. https://doi.org/10.1136/adc.59.3.217
1022. Harding AE. Friedreich's ataxia: a clinical and genetic study of 90 families with an analysis of early diagnostic criteria and intrafamilial clustering of clinical features. *Brain* 1981;**104**:589–620. https://doi.org/10.1093/brain/104.3.589
1023. Geoffroy G, Barbeau A, Breton G, Lemieux B, Aube M, Leger C, *et al.* Clinical description and roentgenologic evaluation of patients with Friedreich's ataxia. *Can J Neurol Sci* 1976;**3**:279–286. https://doi.org/10.1017/S0317167100025464
1024. Hoffman-Zacharska D, Mazurczak T, Zajkowski T, Tataj R, Gorka-Skoczylas P, Polatynska K, *et al.* Friedreich ataxia is not only a GAA repeats expansion disorder: implications for molecular testing and counselling. *J Appl Genet* 2016;**57**:349–355. https://doi.org/10.1007/s13353-015-0331-4
1025. de Silva R, Greenfield J, Cook A, Bonney H, Vallortigara J, Hunt B, *et al.* Guidelines on the diagnosis and management of the progressive ataxias. *Orphanet J Rare Dis* 2019;**14**:51. https://doi.org/10.1186/s13023-019-1013-9
1026. Raman SV, Phatak K, Hoyle JC, Pennell ML, McCarthy B, Tran T, *et al.* Impaired myocardial perfusion reserve and fibrosis in Friedreich ataxia: a mitochondrial cardiomyopathy with metabolic syndrome. *Eur Heart J* 2011;**32**:561–567. https://doi.org/10.1093/eurheartj/ehq443
1027. Pousset F, Legrand L, Monin ML, Ewenczyk C, Charles P, Komajda M, *et al.* A 22-year follow-up study of long-term cardiac outcome and predictors of survival in Friedreich ataxia. *JAMA Neurol* 2015;**72**:1334–1341. https://doi.org/10.1001/jamaneurol.2015.1855
1028. Meyer C, Schmid G, Gorlitz S, Ernst M, Wilkens C, Wilhelms I, *et al.* Cardiomyopathy in Friedreich's ataxia–assessment by cardiac MRI. *Mov Disord* 2007;**22**:1615–1622. https://doi.org/10.1002/mds.21590
1029. Casazza F, Morpurgo M. The varying evolution of Friedreich's ataxia cardiomyopathy. *Am J Cardiol* 1996;**77**:895–898. https://doi.org/10.1016/S0002-9149(97)89194-1
1030. Child JS, Perloff JK, Bach PM, Wolfe AD, Perlman S, Kark RA. Cardiac involvement in Friedreich's ataxia: a clinical study of 75 patients. *J Am Coll Cardiol* 1986;**7**:1370–1378. https://doi.org/10.1016/S0735-1097(86)80159-0
1031. Koeppen AH. Friedreich's ataxia: pathology, pathogenesis, and molecular genetics. *J Neurol Sci* 2011;**303**:1–12. https://doi.org/10.1016/j.jns.2011.01.010
1032. Payne RM, Peverill RE. Cardiomyopathy of Friedreich's ataxia (FRDA). *Ir J Med Sci* 2012;**181**:569–570. https://doi.org/10.1007/s11845-012-0808-7
1033. Payne RM, Wagner GR. Cardiomyopathy in Friedreich ataxia: clinical findings and research. *J Child Neurol* 2012;**27**:1179–1186. https://doi.org/10.1177/0883073812448535
1034. Weidemann F, Rummey C, Bijnens B, Stork S, Jasaityte R, Dhooge J, *et al.* The heart in Friedreich ataxia: definition of cardiomyopathy, disease severity, and correlation with neurological symptoms. *Circulation* 2012;**125**:1626–1634. https://doi.org/10.1161/CIRCULATIONAHA.111.059477
1035. Weidemann F, Liu D, Hu K, Florescu C, Niemann M, Herrmann S, *et al.* The cardiomyopathy in Friedreich's ataxia – new biomarker for staging cardiac involvement. *Int J Cardiol* 2015;**194**:50–57. https://doi.org/10.1016/j.ijcard.2015.05.074
1036. Rustin P, von Kleist-Retzow JC, Chantrel-Groussard K, Sidi D, Munnich A, Rotig A. Effect of idebenone on cardiomyopathy in Friedreich's ataxia: a preliminary study. *Lancet* 1999;**354**:477–479. https://doi.org/10.1016/S0140-6736(99)01341-0
1037. Di Prospero NA, Baker A, Jeffries N, Fischbeck KH. Neurological effects of high-dose idebenone in patients with Friedreich's ataxia: a randomised, placebo-controlled trial. *Lancet Neurol* 2007;**6**:878–886. https://doi.org/10.1016/S1474-4422(07)70220-X
1038. Lynch DR, Perlman SL, Meier T. A phase 3, double-blind, placebo-controlled trial of idebenone in Friedreich ataxia. *Arch Neurol* 2010;**67**:941–947. https://doi.org/10.1001/archneurol.2010.168
1039. Lagedrost SJ, Sutton MS, Cohen MS, Satou GM, Kaufman BD, Perlman SL, *et al.* Idebenone in Friedreich ataxia cardiomyopathy–results from a 6-month phase III study (IONIA). *Am Heart J* 2011;**161**:639–645.e1. https://doi.org/10.1016/j.ahj.2010.10.038
1040. Cook A, Boesch S, Heck S, Brunt E, Klockgether T, Schols L, *et al.* Patient-reported outcomes in Friedreich's ataxia after withdrawal from idebenone. *Acta Neurol Scand* 2019;**139**:533–539. https://doi.org/10.1111/ane.13088
1041. van den Hout HM, Hop W, van Diggelen OP, Smeitink JA, Smit GP, Poll-The BT, *et al.* The natural course of infantile Pompe's disease: 20 original cases compared with 133 cases from the literature. *Pediatrics* 2003;**112**:332–340. https://doi.org/10.1542/peds.112.2.332
1042. Gillette PC, Nihill MR, Singer DB. Electrophysiological mechanism of the short PR interval in Pompe disease. *Am J Dis Child* 1974;**128**:622–6. https://doi.org/10.1001/archpedi.1974.02110300032005
1043. Gollob MH, Green MS, Tang AS, Gollob T, Karibe A, Ali Hassan A-S, *et al.* Identification of a gene responsible for familial Wolff-Parkinson-White syndrome. *N Engl J Med* 2001;**344**:1823–1831. https://doi.org/10.1056/NEJM200106143442403
1044. Sternick EB, Oliva A, Magalhaes LP, Gerken LM, Hong K, Santana O, *et al.* Familial pseudo-Wolff-Parkinson-White syndrome. *J Cardiovasc Electrophysiol* 2006;**17**:724–732. https://doi.org/10.1111/j.1540-8167.2006.00485.x
1045. Arad M, Benson DW, Perez-Atayde AR, McKenna WJ, Sparks EA, Kanter RJ, *et al.* Constitutively active AMP kinase mutations cause glycogen storage disease mimicking hypertrophic cardiomyopathy. *J Clin Invest* 2002;**109**:357–362. https://doi.org/10.1172/JCI0214571
1046. Porto AG, Brun F, Severini GM, Losurdo P, Fabris E, Taylor MRG, *et al.* Clinical spectrum of PRKAG2 syndrome. *Circ Arrhythm Electrophysiol* 2016;**9**:e003121. https://doi.org/10.1161/CIRCEP.115.003121
1047. Lopez-Sainz A, Dominguez F, Lopes LR, Ochoa JP, Barriales-Villa R, Climent V, *et al.* Clinical features and natural history of PRKAG2 variant cardiac glycogenosis. *J Am Coll Cardiol* 2020;**76**:186–197. https://doi.org/10.1016/j.jacc.2020.05.029
1048. Maron BJ, Roberts WC, Arad M, Haas TS, Spirito P, Wright GB, *et al.* Clinical outcome and phenotypic expression in LAMP2 cardiomyopathy. *JAMA* 2009;**301**:1253–1259. https://doi.org/10.1001/jama.2009.371
1049. Lotan D, Salazar-Mendiguchia J, Mogensen J, Rathore F, Anastasakis A, Kaski J, *et al.* Clinical profile of cardiac involvement in Danon disease: a multicenter European registry. *Circ Genom Precis Med* 2020;**13**:e003117. https://doi.org/10.1161/CIRCGEN.120.003117
1050. Stevens-Lapsley JE, Kramer LR, Balter JE, Jirikowic J, Boucek D, Taylor M. Functional performance and muscle strength phenotypes in men and women with Danon disease. *Muscle Nerve* 2010;**42**:908–914. https://doi.org/10.1002/mus.21811
1051. D'Souza RS, Levandowski C, Slavov D, Graw SL, Allen LA, Adler E, *et al.* Danon disease: clinical features, evaluation, and management. *Circ Heart Fail* 2014;**7**:843–849. https://doi.org/10.1161/CIRCHEARTFAILURE.114.001105
1052. Nishino I, Fu J, Tanji K, Yamada T, Shimojo S, Koori T, *et al.* Primary LAMP-2 deficiency causes X-linked vacuolar cardiomyopathy and myopathy (Danon disease). *Nature* 2000;**406**:906–910. https://doi.org/10.1038/35022604
1053. Sternick EB, Oliva A, Gerken LM, Magalhaes L, Scarpelli R, Correia FS, *et al.* Clinical, electrocardiographic, and electrophysiologic characteristics of patients with a fasciculoventricular pathway: the role of PRKAG2 mutation. *Heart Rhythm* 2011;**8**:58–64. https://doi.org/10.1016/j.hrthm.2010.09.081
1054. Murphy RT, Mogensen J, McGarry K, Bahl A, Evans A, Osman E, *et al.* Adenosine monophosphate-activated protein kinase disease mimicks hypertrophic cardiomyopathy and Wolff-Parkinson-White syndrome: natural history. *J Am Coll Cardiol* 2005;**45**:922–930. https://doi.org/10.1016/j.jacc.2004.11.053
1055. Hahn SH, Kronn D, Leslie ND, Pena LDM, Tanpaiboon P, Gambello MJ, *et al.* Efficacy, safety profile, and immunogenicity of alglucosidase alfa produced at the 4,000-liter scale in US children and adolescents with Pompe disease: ADVANCE, a phase IV, open-label, prospective study. *Genet Med* 2018;**20**:1284–1294. https://doi.org/10.1038/gim.2018.2
1056. Nicolino M, Byrne B, Wraith JE, Leslie N, Mandel H, Freyer DR, *et al.* Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease. *Genet Med* 2009;**11**:210–219. https://doi.org/10.1097/GIM.0b013e31819d0996
1057. Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, *et al.* Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J* 2015;**36**:2585–2594. https://doi.org/10.1093/eurheartj/ehv338
1058. Damy T, Costes B, Hagege AA, Donal E, Eicher J-C, Slama M, *et al.* Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in patients

with increased left ventricular wall thickness. *Eur Heart J* 2016;**37**:1826–1834. https://doi.org/10.1093/eurheartj/ehv583

1059. Castano A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, *et al.* Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J* 2017;**38**:2879–2887. https://doi.org/10.1093/eurheartj/ehx350
1060. Asif T, Gomez J, Singh V, Doukky R, Nedeltcheva A, Malhotra S. Comparison of planar with tomographic pyrophosphate scintigraphy for transthyretin cardiac amyloidosis: perils and pitfalls. *J Nucl Cardiol* 2021;**28**:104–111. https://doi.org/10.1007/s12350-020-02328-5
1061. Maestro-Benedicto A, Vela P, de Frutos F, Mora N, Pomares A, Gonzalez-Vioque E, *et al.* Frequency of hereditary transthyretin amyloidosis among elderly patients with transthyretin cardiomyopathy. *Eur J Heart Fail* 2022;**24**:2367–2373. https://doi.org/10.1002/ejhf.2658
1062. Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, *et al.* Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. *Circulation* 2009; **120**:1203–1212. https://doi.org/10.1161/CIRCULATIONAHA.108.843334
1063. Lopez-Sainz A, Hernandez-Hernandez A, Gonzalez-Lopez E, Dominguez F, Restrepo-Cordoba MA, Cobo-Marcos M, *et al.* Clinical profile and outcome of cardiac amyloidosis in a Spanish referral center. *Rev Esp Cardiol (Engl Ed)* 2021;**74**: 149–158. https://doi.org/10.1016/j.rec.2019.12.020
1064. Bianchi G, Zhang Y, Comenzo RL. AL amyloidosis: current chemotherapy and immune therapy treatment strategies: JACC: CardioOncology State-of-the-Art Review. *JACC CardioOncol* 2021;**3**:467–487. https://doi.org/10.1016/j.jaccao.2021.09.003
1065. Ruberg FL, Maurer MS, Judge DP, Zeldenrust S, Skinner M, Kim AY, *et al.* Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). *Am Heart J* 2012;**164**:222–228.e1. https://doi.org/10.1016/j.ahj.2012.04.015
1066. Grogan M, Scott CG, Kyle RA, Zeldenrust SR, Gertz MA, Lin G, *et al.* Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. *J Am Coll Cardiol* 2016;**68**:1014–1020. https://doi.org/10.1016/j.jacc.2016.06.033
1067. Gillmore JD, Damy T, Fontana M, Hutchinson M, Lachmann HJ, Martinez-Naharro A, *et al.* A new staging system for cardiac transthyretin amyloidosis. *Eur Heart J* 2018;**39**: 2799–2806. https://doi.org/10.1093/eurheartj/ehx589
1068. Cheng RK, Levy WC, Vasbinder A, Teruya S, De Los Santos J, Leedy D, *et al.* Diuretic dose and NYHA functional class are independent predictors of mortality in patients with transthyretin cardiac amyloidosis. *JACC CardioOncol* 2020;**2**:414–424. https://doi.org/10.1016/j.jaccao.2020.06.007
1069. Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C, *et al.* Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. *J Clin Oncol* 2012;**30**:989–995. https://doi.org/10.1200/JCO.2011.38.5724
1070. Lilleness B, Ruberg FL, Mussinelli R, Doros G, Sanchorawala V. Development and validation of a survival staging system incorporating BNP in patients with light chain amyloidosis. *Blood* 2019;**133**:215–223. https://doi.org/10.1182/blood-2018-06-858951
1071. Griffin JM, Rosenthal JL, Grodin JL, Maurer MS, Grogan M, Cheng RK. ATTR amyloidosis: current and emerging management strategies: JACC: CardioOncology State-of-the-Art Review. *JACC CardioOncol* 2021;**3**:488–505. https://doi.org/10.1016/j.jaccao.2021.06.006
1072. Aimo A, Vergaro G, Castiglione V, Rapezzi C, Emdin M. Safety and tolerability of neurohormonal antagonism in cardiac amyloidosis. *Eur J Intern Med* 2020;**80**:66–72. https://doi.org/10.1016/j.ejim.2020.05.015
1073. Mitrani LR, De Los Santos J, Driggin E, Kogan R, Helmke S, Goldsmith J, *et al.* Anticoagulation with warfarin compared to novel oral anticoagulants for atrial fibrillation in adults with transthyretin cardiac amyloidosis: comparison of thromboembolic events and major bleeding. *Amyloid* 2021;**28**:30–34. https://doi.org/10.1080/13506129.2020.1810010
1074. Rehorn MR, Loungani RS, Black-Maier E, Coniglio AC, Karra R, Pokorney SD, *et al.* Cardiac implantable electronic devices: a window into the evolution of conduction disease in cardiac amyloidosis. *JACC Clin Electrophysiol* 2020;**6**:1144–1154. https://doi.org/10.1016/j.jacep.2020.04.020
1075. Rapezzi C, Lorenzini M, Longhi S, Milandri A, Gagliardi C, Bartolomei I, *et al.* Cardiac amyloidosis: the great pretender. *Heart Fail Rev* 2015;**20**:117–124. https://doi.org/10.1007/s10741-015-9480-0
1076. Higgins AY, Annapureddy AR, Wang Y, Minges KE, Lampert R, Rosenfeld LE, *et al.* Survival following implantable cardioverter-defibrillator implantation in patients with amyloid cardiomyopathy. *J Am Heart Assoc* 2020;**9**:e016038. https://doi.org/10.1161/JAHA.120.016038
1077. Kim EJ, Holmes BB, Huang S, Lugo R, Al Aboud A, Goodman S, *et al.* Outcomes in patients with cardiac amyloidosis and implantable cardioverter-defibrillator. *Europace* 2020;**22**:1216–1223. https://doi.org/10.1093/europace/euaa094
1078. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, *et al.* Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018;**379**:1007–1016. https://doi.org/10.1056/NEJMoa1805689
1078a. Garcia-Pavia P, Aus dem Siepen F, Donal E, Lairez O, van der Meer P, Kristen AV, *et al.* Phase 1 Trial of Antibody NI006 for Depletion of Cardiac Transthyretin Amyloid. *N Engl J Med* 2023. https://doi.org/10.1056/NEJMoa2303765. Online ahead of print.
1079. Boule NG, Haddad E, Kenny GP, Wells GA, Sigal RJ. Effects of exercise on glycemic control and body mass in type 2 diabetes mellitus: a meta-analysis of controlled clinical trials. *JAMA* 2001;**286**:1218–1227. https://doi.org/10.1001/jama.286.10.1218
1080. Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA, Ray CA, *et al.* Exercise and hypertension. *Med Sci Sports Exerc* 2004;**36**:533–553. https://doi.org/10.1249/01.MSS.0000115224.88514.3A
1081. Kelley GA, Kelley KS, Tran ZV. Walking, lipids, and lipoproteins: a meta-analysis of randomized controlled trials. *Prev Med* 2004;**38**:651–661. https://doi.org/10.1016/j.ypmed.2003.12.012
1082. Morris JN, Heady JA, Raffle PA, Roberts CG, Parks JW. Coronary heart-disease and physical activity of work. *Lancet* 1953;**262**:1053–1057. https://doi.org/10.1016/S0140-6736(53)90665-5
1083. Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. *JAMA* 2002;**288**: 1994–2000. https://doi.org/10.1001/jama.288.16.1994
1084. Clausen JSR, Marott JL, Holtermann A, Gyntelberg F, Jensen MT. Midlife cardiorespiratory fitness and the long-term risk of mortality: 46 years of follow-up. *J Am Coll Cardiol* 2018;**72**:987–995. https://doi.org/10.1016/j.jacc.2018.06.045
1085. Kyu HH, Bachman VF, Alexander LT, Mumford JE, Afshin A, Estep K, *et al.* Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. *BMJ* 2016;**354**:i3857. https://doi.org/10.1136/bmj.i3857
1086. Kim K, Choi S, Hwang SE, Son JS, Lee J-K, Oh J, *et al.* Changes in exercise frequency and cardiovascular outcomes in older adults. *Eur Heart J* 2020;**41**:1490–1499. https://doi.org/10.1093/eurheartj/ehz768
1087. Lee IM. Physical activity and cancer prevention–data from epidemiologic studies. *Med Sci Sports Exerc* 2003;**35**:1823–1827. https://doi.org/10.1249/01.MSS.0000093620.27893.23
1088. Siscovick DS, Weiss NS, Fletcher RH, Lasky T. The incidence of primary cardiac arrest during vigorous exercise. *N Engl J Med* 1984;**311**:874–877. https://doi.org/10.1056/NEJM198410043111402
1089. Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of Myocardial Infarction Onset Study Investigators. *N Engl J Med* 1993;**329**:1677–1683. https://doi.org/10.1056/NEJM199312023292301
1090. Marijon E, Tafflet M, Celermajer DS, Dumas F, Perier M-C, Mustafic H, *et al.* Sports-related sudden death in the general population. *Circulation* 2011;**124**: 672–681. https://doi.org/10.1161/CIRCULATIONAHA.110.008979
1091. Kim JH, Malhotra R, Chiampas G, d'Hemecourt P, Troyanos C, Cianca J, *et al.* Cardiac arrest during long-distance running races. *N Engl J Med* 2012;**366**:130–140. https://doi.org/10.1056/NEJMoa1106468
1092. Maron BJ, Rowin EJ, Maron MS. Letter by Maron *et al*. regarding article, "Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe)". *Circulation* 2019;**139**: 1557–1558. https://doi.org/10.1161/CIRCULATIONAHA.118.038189
1093. Peterson DF, Siebert DM, Kucera KL, Thomas LC, Maleszewski JJ, Lopez-Anderson M, *et al.* Etiology of sudden cardiac arrest and death in US competitive athletes: a 2-year prospective surveillance study. *Clin J Sport Med* 2020;**30**:305–314. https://doi.org/10.1097/JSM.0000000000000598
1094. Corrado D, Basso C, Schiavon M, Thiene G. Screening for hypertrophic cardiomyopathy in young athletes. *N Engl J Med* 1998;**339**:364–369. https://doi.org/10.1056/NEJM199808063390602
1095. Holst AG, Winkel BG, Theilade J, Kristensen IB, Thomsen JL, Ottesen GL, *et al.* Incidence and etiology of sports-related sudden cardiac death in Denmark–implications for preparticipation screening. *Heart Rhythm* 2010;**7**:1365–1371. https://doi.org/10.1016/j.hrthm.2010.05.021
1096. Maron BJ, Isner JM, McKenna WJ. 26th Bethesda conference: recommendations for determining eligibility for competition in athletes with cardiovascular abnormalities. Task Force 3: hypertrophic cardiomyopathy, myocarditis and other myopericardial diseases and mitral valve prolapse. *J Am Coll Cardiol* 1994;**24**:880–885. https://doi.org/10.1016/0735-1097(94)90844-3
1097. Maron BJ, Zipes DP. Introduction: eligibility recommendations for competitive athletes with cardiovascular abnormalities–general considerations. *J Am Coll Cardiol* 2005;**45**:1318–1321. https://doi.org/10.1016/j.jacc.2005.02.006
1098. Maron BJ, Harris KM, Thompson PD, Eichner ER, Steinberg MH. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 14: Sickle Cell Trait: A Scientific Statement From the

American Heart Association and American College of Cardiology. *J Am Coll Cardiol* 2015;**66**:2444–2446. https://doi.org/10.1016/j.jacc.2015.09.046

1099. Reineck E, Rolston B, Bragg-Gresham JL, Salberg L, Baty L, Kumar S, *et al.* Physical activity and other health behaviors in adults with hypertrophic cardiomyopathy. *Am J Cardiol* 2013;**111**:1034–1039. https://doi.org/10.1016/j.amjcard.2012.12.018
1100. Sweeting J, Ingles J, Timperio A, Patterson J, Ball K, Semsarian C. Physical activity in hypertrophic cardiomyopathy: prevalence of inactivity and perceived barriers. *Open Heart* 2016;**3**:e000484. https://doi.org/10.1136/openhrt-2016-000484
1101. Olivotto I, Maron BJ, Tomberli B, Appelbaum E, Salton C, Haas TS, *et al.* Obesity and its association to phenotype and clinical course in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2013;**62**:449–457. https://doi.org/10.1016/j.jacc.2013.03.062
1102. Fumagalli C, Maurizi N, Day SM, Ashley EA, Michels M, Colan SD, *et al.* Association of obesity with adverse long-term outcomes in hypertrophic cardiomyopathy. *JAMA Cardiol* 2020;**5**:65–72. https://doi.org/10.1001/jamacardio.2019.4268
1103. Pelliccia A, Fagard R, Bjornstad HH, Anastassakis A, Arbustini E, Assanelli D, *et al.* Recommendations for competitive sports participation in athletes with cardiovascular disease: a consensus document from the Study Group of Sports Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. *Eur Heart J* 2005;**26**:1422–1445. https://doi.org/10.1093/eurheartj/ehi325
1104. Sorajja P, Allison T, Hayes C, Nishimura RA, Lam CS, Ommen SR. Prognostic utility of metabolic exercise testing in minimally symptomatic patients with obstructive hypertrophic cardiomyopathy. *Am J Cardiol* 2012;**109**:1494–1498. https://doi.org/10.1016/j.amjcard.2012.01.363
1105. Desai MY, Bhonsale A, Patel P, Naji P, Smedira NG, Thamilarasan M, *et al.* Exercise echocardiography in asymptomatic HCM: exercise capacity, and not LV outflow tract gradient predicts long-term outcomes. *JACC Cardiovasc Imaging* 2014;**7**:26–36. https://doi.org/10.1016/j.jcmg.2013.08.010
1106. Konhilas JP, Watson PA, Maass A, Boucek DM, Horn T, Stauffer BL, *et al.* Exercise can prevent and reverse the severity of hypertrophic cardiomyopathy. *Circ Res* 2006;**98**:540–548. https://doi.org/10.1161/01.RES.0000205766.97556.00
1107. Pelliccia A, Borrazzo C, Caselli S, Lemme E, Musumeci MB, Maestrini V, *et al.* Neither athletic training nor detraining affects LV hypertrophy in adult, low-risk patients with HCM. *JACC Cardiovasc Imaging* 2022;**15**:170–171. https://doi.org/10.1016/j.jcmg.2021.08.012
1108. Klempfner R, Kamerman T, Schwammenthal E, Nahshon A, Hay I, Goldenberg I, *et al.* Efficacy of exercise training in symptomatic patients with hypertrophic cardiomyopathy: results of a structured exercise training program in a cardiac rehabilitation center. *Eur J Prev Cardiol* 2015;**22**:13–19. https://doi.org/10.1177/2047487313501277
1109. Kwon S, Lee H-J, Han K-D, Kim DH, Lee S-P, Hwang I-C, *et al.* Association of physical activity with all-cause and cardiovascular mortality in 7666 adults with hypertrophic cardiomyopathy (HCM): more physical activity is better. *Br J Sports Med* 2021;**55**:1034–1040. https://doi.org/10.1136/bjsports-2020-101987
1110. Benito B, Gay-Jordi G, Serrano-Mollar A, Guasch E, Shi Y, Tardif J-C, *et al.* Cardiac arrhythmogenic remodeling in a rat model of long-term intensive exercise training. *Circulation* 2011;**123**:13–22. https://doi.org/10.1161/CIRCULATIONAHA.110.938282
1111. Saberniak J, Hasselberg NE, Borgquist R, Platonov PG, Sarvari SI, Smith H-J, *et al.* Vigorous physical activity impairs myocardial function in patients with arrhythmogenic right ventricular cardiomyopathy and in mutation positive family members. *Eur J Heart Fail* 2014;**16**:1337–1344. https://doi.org/10.1002/ejhf.181
1112. Ruwald AC, Marcus F, Estes NA, Link M, McNitt S, Polonsky B, *et al.* Association of competitive and recreational sport participation with cardiac events in patients with arrhythmogenic right ventricular cardiomyopathy: results from the North American multidisciplinary study of arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J* 2015;**36**:1735–1743. https://doi.org/10.1093/eurheartj/ehv110
1113. Lampert R, Olshansky B, Heidbuchel H, Lawless C, Saarel E, Ackerman M, *et al.* Safety of sports for athletes with implantable cardioverter-defibrillators: long-term results of a prospective multinational registry. *Circulation* 2017;**135**:2310–2312. https://doi.org/10.1161/CIRCULATIONAHA.117.027828
1114. Lie OH, Rootwelt-Norberg C, Dejgaard LA, Leren IS, Stokke MK, Edvardsen T, *et al.* Prediction of life-threatening ventricular arrhythmia in patients with arrhythmogenic cardiomyopathy: a primary prevention cohort study. *JACC Cardiovasc Imaging* 2018;**11**:1377–1386. https://doi.org/10.1016/j.jcmg.2018.05.017
1115. Costa S, Koch K, Gasperetti A, Akdis D, Brunckhorst C, Fu G, *et al.* Changes in exercise capacity and ventricular function in arrhythmogenic right ventricular cardiomyopathy: the impact of sports restriction during follow-up. *J Clin Med* 2022;**11**:1150. https://doi.org/10.3390/jcm11051150
1116. Sawant AC, Te Riele AS, Tichnell C, Murray B, Bhonsale A, Tandri H, *et al.* Safety of American Heart Association-recommended minimum exercise for desmosomal mutation carriers. *Heart Rhythm* 2016;**13**:199–207. https://doi.org/10.1016/j.hrthm.2015.08.035
1117. Lie OH, Dejgaard LA, Saberniak J, Rootwelt C, Stokke MK, Edvardsen T, *et al.* Harmful effects of exercise intensity and exercise duration in patients with arrhythmogenic cardiomyopathy. *JACC Clin Electrophysiol* 2018;**4**:744–753. https://doi.org/10.1016/j.jacep.2018.01.010
1118. Pelliccia A, Sharma S, Gati S, Back M, Borjesson M, Caselli S, *et al.* 2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease. *Eur Heart J* 2021;**42**:17–96. https://doi.org/10.1093/eurheartj/ehaa605
1119. Cruz FM, Sanz-Rosa D, Roche-Molina M, Garcia-Prieto J, Garcia-Ruiz JM, Pizarro G, *et al.* Exercise triggers ARVC phenotype in mice expressing a disease-causing mutated version of human plakophilin-2. *J Am Coll Cardiol* 2015;**65**:1438–1450. https://doi.org/10.1016/j.jacc.2015.01.045
1120. Maron BJ, Haas TS, Murphy CJ, Ahluwalia A, Rutten-Ramos S. Incidence and causes of sudden death in U.S. college athletes. *J Am Coll Cardiol* 2014;**63**:1636–1643. https://doi.org/10.1016/j.jacc.2014.01.041
1121. Malhotra A, Dhutia H, Finocchiaro G, Gati S, Beasley I, Clift P, *et al.* Outcomes of cardiac screening in adolescent soccer players. *N Engl J Med* 2018;**379**:524–534. https://doi.org/10.1056/NEJMoa1714719
1122. Harmon KG, Drezner JA, Maleszewski JJ, Lopez-Anderson M, Owens D, Prutkin JM, *et al.* Pathogeneses of sudden cardiac death in national collegiate athletic association athletes. *Circ Arrhythm Electrophysiol* 2014;**7**:198–204. https://doi.org/10.1161/CIRCEP.113.001376
1123. Skjolsvik ET, Hasselberg NE, Dejgaard LA, Lie OH, Andersen K, Holm T, *et al.* Exercise is associated with impaired left ventricular systolic function in patients with lamin A/C genotype. *J Am Heart Assoc* 2020;**9**:e012937. https://doi.org/10.1161/JAHA.119.012937
1124. Dejgaard LA, Haland TF, Lie OH, Ribe M, Bjune T, Leren IS, *et al.* Vigorous exercise in patients with hypertrophic cardiomyopathy. *Int J Cardiol* 2018;**250**:157–163. https://doi.org/10.1016/j.ijcard.2017.07.015
1125. Pelliccia A, Caselli S, Pelliccia M, Musumeci MB, Lemme E, Di Paolo FM, *et al.* Clinical outcomes in adult athletes with hypertrophic cardiomyopathy: a 7-year follow-up study. *Br J Sports Med* 2020;**54**:1008–1012. https://doi.org/10.1136/bjsports-2019-100890
1126. Saarel EV, Law I, Berul CI, Ackerman MJ, Kanter RJ, Sanatani S, *et al.* Safety of sports for young patients with implantable cardioverter-defibrillators: long-term results of the multinational ICD sports registry. *Circ Arrhythm Electrophysiol* 2018;**11**:e006305. https://doi.org/10.1161/CIRCEP.118.006305
1127. Siu SC, Sermer M, Colman JM, Alvarez AN, Mercier LA, Morton BC, *et al.* Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation* 2001;**104**:515–521. https://doi.org/10.1161/hc3001.093437
1128. Roos-Hesselink JW, Ruys TP, Stein JI, Thilén U, Webb GD, Niwa K, *et al.* Outcome of pregnancy in patients with structural or ischaemic heart disease: results of a registry of the European Society of Cardiology. *Eur Heart J* 2013;**34**:657–665. https://doi.org/10.1093/eurheartj/ehs270
1129. Linde C, Bongiorni MG, Birgersdotter-Green U, Curtis AB, Deisenhofer I, Furokawa T, *et al.* Sex differences in cardiac arrhythmia: a consensus document of the European Heart Rhythm Association, endorsed by the Heart Rhythm Society and Asia Pacific Heart Rhythm Society. *Europace* 2018;**20**:1565–1565ao. https://doi.org/10.1093/europace/euy067
1130. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomström-Lundqvist C, Cífková R, De Bonis M, *et al.* 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J* 2018;**39**:3165–3241. https://doi.org/10.1093/eurheartj/ehy340
1131. Sliwa K, Mebazaa A, Hilfiker-Kleiner D, Petrie MC, Maggioni AP, Laroche C, *et al.* Clinical characteristics of patients from the worldwide registry on peripartum cardiomyopathy (PPCM): EURObservational Research Programme in conjunction with the Heart Failure Association of the European Society of Cardiology Study Group on PPCM. *Eur J Heart Fail* 2017;**19**:1131–1141. https://doi.org/10.1002/ejhf.780
1132. Lidegaard Ø, Løkkegaard E, Jensen A, Skovlund CW, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med* 2012;**366**:2257–2266. https://doi.org/10.1056/NEJMoa1111840
1133. D'Souza R, Ostro J, Shah PS, Silversides CK, Malinowski A, Murphy KE, *et al.* Anticoagulation for pregnant women with mechanical heart valves: a systematic review and meta-analysis. *Eur Heart J* 2017;**38**:1509–1516. https://doi.org/10.1093/eurheartj/ehx032
1134. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. *Arch Intern Med* 2000;**160**:191–196. https://doi.org/10.1001/archinte.160.2.191
1135. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, *et al.* 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;**36**:2793–2867. https://doi.org/10.1093/eurheartj/ehv316
1136. Miyoshi T, Kamiya CA, Katsuragi S, Ueda H, Kobayashi Y, Horiuchi C, *et al.* Safety and efficacy of implantable cardioverter-defibrillator during pregnancy and after delivery. *Circ J* 2013;**77**:1166–1170. https://doi.org/10.1253/circj.CJ-12-1275
1137. Krul SP, van der Smagt JJ, van den Berg MP, Sollie KM, Pieper PG, van Spaendonck-Zwarts KY. Systematic review of pregnancy in women with inherited

cardiomyopathies. *Eur J Heart Fail* 2011;**13**:584–594. https://doi.org/10.1093/eurjhf/hfr040
1138. Castrini AI, Lie OH, Leren IS, Estensen ME, Stokke MK, Klaeboe LG, *et al.* Number of pregnancies and subsequent phenotype in a cross-sectional cohort of women with arrhythmogenic cardiomyopathy. *Eur Heart J Cardiovasc Imaging* 2019;**20**:192–198. https://doi.org/10.1093/ehjci/jey061
1139. Platonov PG, Castrini AI, Svensson A, Christiansen MK, Gilljam T, Bundgaard H, *et al.* Pregnancies, ventricular arrhythmias, and substrate progression in women with arrhythmogenic right ventricular cardiomyopathy in the Nordic ARVC Registry. *Europace* 2020;**22**:1873–1879. https://doi.org/10.1093/europace/euaa136
1140. Gandjbakhch E, Varlet E, Duthoit G, Fressart V, Charron P, Himbert C, *et al.* Pregnancy and newborn outcomes in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Int J Cardiol* 2018;**258**:172–178. https://doi.org/10.1016/j.ijcard.2017.11.067
1141. Wu L, Liang E, Fan S, Zheng L, Hu F, Liu S, *et al.* Effect of pregnancy in arrhythmogenic right ventricular cardiomyopathy. *Am J Cardiol* 2020;**125**:613–617. https://doi.org/10.1016/j.amjcard.2019.11.008
1142. Castrini AI, Skjolsvik E, Estensen ME, Almaas VM, Skulstad H, Lyseggen E, *et al.* Pregnancy and progression of cardiomyopathy in women with LMNA genotypepositive. *J Am Heart Assoc* 2022;**11**:e024960. https://doi.org/10.1161/JAHA.121.024960
1143. Grewal J, Siu SC, Ross HJ, Mason J, Balint OH, Sermer M, *et al.* Pregnancy outcomes in women with dilated cardiomyopathy. *J Am Coll Cardiol* 2009;**55**:45–52. https://doi.org/10.1016/j.jacc.2009.08.036
1144. Sliwa K, Blauwet L, Tibazarwa K, Libhaber E, Smedema JP, Becker A, *et al.* Evaluation of bromocriptine in the treatment of acute severe peripartum cardiomyopathy: a proof-of-concept pilot study. *Circulation* 2010;**121**:1465–1473. https://doi.org/10.1161/CIRCULATIONAHA.109.901496
1145. Hilfiker-Kleiner D, Haghikia A, Berliner D, Vogel-Claussen J, Schwab J, Franke A, *et al.* Bromocriptine for the treatment of peripartum cardiomyopathy: a multicentre randomized study. *Eur Heart J* 2017;**38**:2671–2679. https://doi.org/10.1093/eurheartj/ehx355
1146. Davis MB, Arany Z, McNamara DM, Goland S, Elkayam U. Peripartum cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;**75**:207–221. https://doi.org/10.1016/j.jacc.2019.11.014
1147. Bauersachs J, König T, van der Meer P, Petrie MC, Hilfiker-Kleiner D, Mbakwem A, *et al.* Pathophysiology, diagnosis and management of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Study Group on peripartum cardiomyopathy. *Eur J Heart Fail* 2019; **21**:827–843. https://doi.org/10.1002/ejhf.1493
1148. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, *et al.* ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2002;**105**:1257–1267. https://doi.org/10.1161/circ.105.10.1257
1149. Kristensen SD, Knuuti J, Saraste A, Anker S, Botker HE, Hert SD, *et al.* 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). *Eur Heart J* 2014;**35**:2383–2431. https://doi.org/10.1093/eurheartj/ehu282
1150. Sahoo RK, Dash SK, Raut PS, Badole UR, Upasani CB. Perioperative anesthetic management of patients with hypertrophic cardiomyopathy for noncardiac surgery: a case series. *Ann Card Anaesth* 2010;**13**:253–256. https://doi.org/10.4103/0971-9784.69049
1151. Dhillon A, Khanna A, Randhawa MS, Cywinski J, Saager L, Thamilarasan M, *et al.* Perioperative outcomes of patients with hypertrophic cardiomyopathy undergoing non-cardiac surgery. *Heart* 2016;**102**:1627–1632. https://doi.org/10.1136/heartjnl-2016-309442
1152. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, *et al.* Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail* 2019;**21**:715–731. https://doi.org/10.1002/ejhf.1494
1153. Coats CJ, Gallagher MJ, Foley M, O'Mahony C, Critoph C, Gimeno J, *et al.* Relation between serum N-terminal pro-brain natriuretic peptide and prognosis in patients with hypertrophic cardiomyopathy. *Eur Heart J* 2013;**34**:2529–2537. https://doi.org/10.1093/eurheartj/eht070
1154. D'Amato R, Tomberli B, Castelli G, Spoladore R, Girolami F, Fornaro A, *et al.* Prognostic value of N-terminal pro-brain natriuretic peptide in outpatients with hypertrophic cardiomyopathy. *Am J Cardiol* 2013;**112**:1190–1196. https://doi.org/10.1016/j.amjcard.2013.06.018
1155. van der Meulen M, den Boer S, du Marchie Sarvaas GJ, Blom N, Ten Harkel ADJ, Breur H, *et al.* Predicting outcome in children with dilated cardiomyopathy: the use of repeated measurements of risk factors for outcome. *ESC Heart Fail* 2021;**8**:1472–1481. https://doi.org/10.1002/ehf2.13233
1156. Cheng H, Lu M, Hou C, Chen X, Wang J, Yin G, *et al.* Relation between N-terminal pro-brain natriuretic peptide and cardiac remodeling and function assessed by cardiovascular magnetic resonance imaging in patients with arrhythmogenic right ventricular cardiomyopathy. *Am J Cardiol* 2015;**115**:341–347. https://doi.org/10.1016/j.amjcard.2014.10.040
1157. Chivulescu M, Lie OH, Popescu BA, Skulstad H, Edvardsen T, Jurcut RO, *et al.* High penetrance and similar disease progression in probands and in family members with arrhythmogenic cardiomyopathy. *Eur Heart J* 2020;**41**:1401–1410. https://doi.org/10.1093/eurheartj/ehz570
1158. Norrish G, Forshaw N, Woo C, Avanis MC, Field E, Cervi E, *et al.* Outcomes following general anaesthesia in children with hypertrophic cardiomyopathy. *Arch Dis Child* 2019;**104**:471–475. https://doi.org/10.1136/archdischild-2018-315366
1159. Kazmers A, Cerqueira MD, Zierler RE. Perioperative and late outcome in patients with left ventricular ejection fraction of 35% or less who require major vascular surgery. *J Vasc Surg* 1988;**8**:307–315. https://doi.org/10.1016/0741-5214(88)90283-2
1160. Healy KO, Waksmonski CA, Altman RK, Stetson PD, Reyentovich A, Maurer MS. Perioperative outcome and long-term mortality for heart failure patients undergoing intermediate- and high-risk noncardiac surgery: impact of left ventricular ejection fraction. *Congest Heart Fail* 2010;**16**:45–49. https://doi.org/10.1111/j.1751-7133.2009.00130.x
1161. Barbara DW, Hyder JA, Behrend TL, Abel MD, Schaff HV, Mauermann WJ. Safety of noncardiac surgery in patients with hypertrophic obstructive cardiomyopathy at a tertiary care center. *J Cardiothorac Vasc Anesth* 2016;**30**:659–664. https://doi.org/10.1053/j.jvca.2015.08.017
1162. Huelsmann M, Neuhold S, Resl M, Strunk G, Brath H, Francesconi C, *et al.* PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease): a prospective randomized controlled trial. *J Am Coll Cardiol*. 2013;**62**:1365–1372. https://doi.org/10.1016/j.jacc.2013.05.069
1163. Ledwidge M, Gallagher J, Conlon C, Tallon E, O'Connell E, Dawkins I, *et al.* Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. *JAMA* 2013;**310**:66–74. https://doi.org/10.1001/jama.2013.7588
1164. Rodseth RN, Biccard BM, Le Manach Y, Sessler DI, Lurati Buse GA, Thabane L, *et al.* The prognostic value of pre-operative and post-operative B-type natriuretic peptides in patients undergoing noncardiac surgery: B-type natriuretic peptide and N-terminal fragment of pro-B-type natriuretic peptide: a systematic review and individual patient data meta-analysis. *J Am Coll Cardiol* 2014;**63**:170–180. https://doi.org/10.1016/j.jacc.2013.08.1630
1165. Karthikeyan G, Moncur RA, Levine O, Heels-Ansdell D, Chan MT, Alonso-Coello P, *et al.* Is a pre-operative brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide measurement an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery? A systematic review and meta-analysis of observational studies. *J Am Coll Cardiol* 2009;**54**:1599–1606. https://doi.org/10.1016/j.jacc.2009.06.028
1166. Ahmad F, McNally EM, Ackerman MJ, Baty LC, Day SM, Kullo IJ, *et al.* Establishment of specialized clinical cardiovascular genetics programs: recognizing the need and meeting standards: a scientific statement from the American Heart Association. *Circ Genom Precis Med* 2019;**12**:e000054. https://doi.org/10.1161/HCG.0000000000000054
1167. Burton H, Alberg C, Stewart A. *Heart to Heart: Inherited Cardiovascular Conditions Services*. Cambridge, UK: PHG Foundation, 2009.
1168. Chamberlain AM, Agarwal SK, Folsom AR, Duval S, Soliman EZ, Ambrose M, *et al.* Smoking and incidence of atrial fibrillation: results from the Atherosclerosis Risk in Communities (ARIC) study. *Heart Rhythm* 2011;**8**:1160–1166. https://doi.org/10.1016/j.hrthm.2011.03.038
1169. Kamimura D, Cain LR, Mentz RJ, White WB, Blaha MJ, DeFilippis AP, *et al.* Cigarette smoking and incident heart failure: insights from the Jackson Heart Study. *Circulation* 2018;**137**:2572–2582. https://doi.org/10.1161/CIRCULATIONAHA.117.031912
1170. Gottdiener JS, Buzkova P, Kahn PA, DeFilippi C, Shah S, Barasch E, *et al.* Relation of cigarette smoking and heart failure in adults >/=65 years of age (from the Cardiovascular Health Study). *Am J Cardiol* 2022;**168**:90–98. https://doi.org/10.1016/j.amjcard.2021.12.021
1171. Park J, Lee H-J, Kim SK, Yi J-E, Shin DG, Lee JM, *et al.* Smoking aggravates ventricular arrhythmic events in non-ischemic dilated cardiomyopathy associated with a late gadolinium enhancement in cardiac MRI. *Sci Rep* 2018;**8**:15609. https://doi.org/10.1038/s41598-018-34145-9
1172. Smith D, Toff W, Joy M, Dowdall N, Johnston R, Clark L, *et al.* Fitness to fly for passengers with cardiovascular disease. *Heart* 2010;**96**(Suppl 2):ii1–ii16. https://doi.org/10.1136/hrt.2010.203091
1173. Fumagalli C, Olivotto I. The importance of sex differences in patients with hypertrophic cardiomyopathy – tailoring management and future perspectives. *Am J Med Sci* 2020;**360**:433–434. https://doi.org/10.1016/j.amjms.2020.07.004
1174. Terauchi Y, Kubo T, Baba Y, Hirota T, Tanioka K, Yamasaki N, *et al.* Gender differences in the clinical features of hypertrophic cardiomyopathy caused by cardiac myosin-binding protein C gene mutations. *J Cardiol* 2015;**65**:423–428. https://doi.org/10.1016/j.jjcc.2014.07.010

1175. Sabater-Molina M, Saura D, Garcia-Molina Saez E, Gonzalez-Carrillo J, Polo L, Perez-Sanchez I, *et al.* A novel founder mutation in MYBPC3: phenotypic comparison with the most prevalent MYBPC3 mutation in Spain. *Rev Esp Cardiol (Engl Ed)* 2017; **70**:105–114. https://doi.org/10.1016/j.recesp.2016.06.025
1176. Adalsteinsdottir B, Burke M, Maron BJ, Danielsen R, Lopez B, Diez J, *et al.* Hypertrophic cardiomyopathy in myosin-binding protein C (MYBPC3) Icelandic founder mutation carriers. *Open Heart* 2020;**7**:e001220. https://doi.org/10.1136/openhrt-2019-001220
1177. Lakdawala NK, Olivotto I, Day SM, Han L, Ashley EA, Michels M, *et al.* Associations between female sex, sarcomere variants, and clinical outcomes in hypertrophic cardiomyopathy. *Circ Genom Precis Med* 2021;**14**:e003062. https://doi.org/10.1161/CIRCGEN.120.003062
1178. Lorenzini M, Anastasiou Z, O'Mahony C, Guttman OP, Gimeno JR, Monserrat L, *et al.* Mortality among referral patients with hypertrophic cardiomyopathy vs the general European population. *JAMA Cardiol* 2020;**5**:73–80. https://doi.org/10.1001/jamacardio.2019.4534
1179. Batzner A, Aicha D, Pfeiffer B, Neugebauer A, Seggewiss H. Sex-related differences in symptomatic patients with hypertrophic obstructive cardiomyopathy – time for a new definition? *Int J Cardiol* 2021;**328**:117–121. https://doi.org/10.1016/j.ijcard.2020.12.039
1180. Sreenivasan J, Khan MS, Kaul R, Bandyopadhyay D, Hooda U, Aronow WS, *et al.* Sex differences in the outcomes of septal reduction therapies for obstructive hypertrophic cardiomyopathy. *JACC Cardiovasc Interv* 2021;**14**:930–932. https://doi.org/10.1016/j.jcin.2020.10.002
1181. Meghji Z, Nguyen A, Fatima B, Geske JB, Nishimura RA, Ommen SR, *et al.* Survival differences in women and men after septal myectomy for obstructive hypertrophic cardiomyopathy. *JAMA Cardiol* 2019;**4**:237–245. https://doi.org/10.1001/jamacardio.2019.0084
1182. Butters A, Lakdawala NK, Ingles J. Sex differences in hypertrophic cardiomyopathy: interaction with genetics and environment. *Curr Heart Fail Rep* 2021;**18**:264–273. https://doi.org/10.1007/s11897-021-00526-x
1183. Rowin EJ, Maron MS, Wells S, Patel PP, Koethe BC, Maron BJ. Impact of sex on clinical course and survival in the contemporary treatment era for hypertrophic cardiomyopathy. *J Am Heart Assoc* 2019;**8**:e012041. https://doi.org/10.1161/JAHA.119.012041
1184. D'Amario D, Camilli M, Migliaro S, Canonico F, Galli M, Arcudi A, *et al.* Sex-related differences in dilated cardiomyopathy with a focus on cardiac dysfunction in oncology. *Curr Cardiol Rep* 2020;**22**:102. https://doi.org/10.1007/s11886-020-01377-z
1185. Vissing CR, Rasmussen TB, Dybro AM, Olesen MS, Pedersen LN, Jensen M, *et al.* Dilated cardiomyopathy caused by truncating titin variants: long-term outcomes, arrhythmias, response to treatment and sex differences. *J Med Genet* 2021;**58**:832–841. https://doi.org/10.1136/jmedgenet-2020-107178
1186. Dominguez F, Cuenca S, Bilinska Z, Toro R, Villard E, Barriales-Villa R, *et al.* Dilated cardiomyopathy due to BLC2-associated athanogene 3 (BAG3) mutations. *J Am Coll Cardiol* 2018;**72**:2471–2481. https://doi.org/10.1016/j.jacc.2018.08.2181
1187. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, *et al.* Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004;**350**:2151–2158. https://doi.org/10.1056/NEJMoa033088
1188. Halliday BP, Gulati A, Ali A, Newsome S, Lota A, Tayal U, *et al.* Sex- and age-based differences in the natural history and outcome of dilated cardiomyopathy. *Eur J Heart Fail* 2018;**20**:1392–1400. https://doi.org/10.1002/ejhf.1216
1189. Herman DS, Lam L, Taylor MR, Wang L, Teekakirikul P, Christodoulou D, *et al.* Truncations of titin causing dilated cardiomyopathy. *N Engl J Med* 2012;**366**: 619–628. https://doi.org/10.1056/NEJMoa1110186
1190. Calkins H, Corrado D, Marcus F. Risk stratification in arrhythmogenic right ventricular cardiomyopathy. *Circulation* 2017;**136**:2068–2082. https://doi.org/10.1161/CIRCULATIONAHA.117.030792
1191. Choudhary N, Tompkins C, Polonsky B, McNitt S, Calkins H, Mark Estes NA, *et al.* Clinical presentation and outcomes by sex in arrhythmogenic right ventricular cardiomyopathy: findings from the North American ARVC registry. *J Cardiovasc Electrophysiol* 2016;**27**:555–562. https://doi.org/10.1111/jce.12947
1192. Akdis D, Saguner AM, Shah K, Wei C, Medeiros-Domingo A, von Eckardstein A, *et al.* Sex hormones affect outcome in arrhythmogenic right ventricular cardiomyopathy/dysplasia: from a stem cell derived cardiomyocyte-based model to clinical biomarkers of disease outcome. *Eur Heart J* 2017;**38**:1498–1508. https://doi.org/10.1093/eurheartj/ehx011
1193. Kimura Y, Noda T, Otsuka Y, Wada M, Nakajima I, Ishibashi K, *et al.* Potentially lethal ventricular arrhythmias and heart failure in arrhythmogenic right ventricular cardiomyopathy: what are the differences between men and women? *JACC Clin Electrophysiol* 2016;**2**:546–555. https://doi.org/10.1016/j.jacep.2016.02.019
1194. Hoorntje ET, Te Rijdt WP, James CA, Pilichou K, Basso C, Judge DP, *et al.* Arrhythmogenic cardiomyopathy: pathology, genetics, and concepts in pathogenesis. *Cardiovasc Res* 2017;**113**:1521–1531. https://doi.org/10.1093/cvr/cvx150
1195. Rootwelt-Norberg C, Lie OH, Chivulescu M, Castrini AI, Sarvari SI, Lyseggen E, *et al.* Sex differences in disease progression and arrhythmic risk in patients with arrhythmogenic cardiomyopathy. *Europace* 2021;**23**:1084–1091. https://doi.org/10.1093/europace/euab077
1196. Lopes LR, Losi MA, Sheikh N, Laroche C, Charron P, Gimeno J, *et al.* Association between common cardiovascular risk factors and clinical phenotype in patients with hypertrophic cardiomyopathy from the European Society of Cardiology (ESC) EurObservational Research Programme (EORP) Cardiomyopathy/Myocarditis registry. *Eur Heart J Qual Care Clin Outcomes* 2022;**9**:42–53. https://doi.org/10.1093/ehjqcco/qcac006
1197. Wasserstrum Y, Barriales-Villa R, Fernandez-Fernandez X, Adler Y, Lotan D, Peled Y, *et al.* The impact of diabetes mellitus on the clinical phenotype of hypertrophic cardiomyopathy. *Eur Heart J* 2019;**40**:1671–1677. https://doi.org/10.1093/eurheartj/ehy625
1198. Limongelli G, Monda E, D'Aponte A, Caiazza M, Rubino M, Esposito A, *et al.* Combined effect of Mediterranean diet and aerobic exercise on weight loss and clinical status in obese symptomatic patients with hypertrophic cardiomyopathy. *Heart Fail Clin* 2021;**17**:303–313. https://doi.org/10.1016/j.hfc.2021.01.003
1199. Asatryan B, Asimaki A, Landstrom AP, Khanji MY, Odening KE, Cooper LT, *et al.* Inflammation and immune response in arrhythmogenic cardiomyopathy: state-of-the-art review. *Circulation* 2021;**144**:1646–1655. https://doi.org/10.1161/CIRCULATIONAHA.121.055890
1200. Guan W-J, Liang W-H, Zhao Y, Liang H-R, Chen Z-S, Li Y-M, *et al.* Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J* 2020;**55**:2000547. https://doi.org/10.1183/13993003.00547-2020
1201. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, *et al.* Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;**382**:1708–1720. https://doi.org/10.1056/NEJMoa2002032
1202. Capacity-Covid Collaborative Consortium, Leoss Study Group. Clinical presentation, disease course, and outcome of COVID-19 in hospitalized patients with and without pre-existing cardiac disease: a cohort study across 18 countries. *Eur Heart J* 2022;**43**: 1104–1120. https://doi.org/10.1093/eurheartj/ehab656
1203. Omidi F, Hajikhani B, Kazemi SN, Tajbakhsh A, Riazi S, Mirsaeidi M, *et al.* COVID-19 and cardiomyopathy: a systematic review. *Front Cardiovasc Med* 2021;**8**:695206. https://doi.org/10.3389/fcvm.2021.695206
1204. Gimeno JR, Olivotto I, Rodriguez AI, Ho CY, Fernandez A, Quiroga A, *et al.* Impact of SARS-Cov-2 infection in patients with hypertrophic cardiomyopathy: results of an international multicentre registry. *ESC Heart Fail* 2022;**9**:2189–2198. https://doi.org/10.1002/ehf2.13964