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ESC GUIDELINES

2023 ESC Guidelines for the management of cardiomyopathies Supplementary data

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 in the full text.

[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 in the full text.

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), and Heart Failure Association (HFA).

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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)

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Abbreviations and acronyms

3D	Three-dimensional
AFD	Anderson–Fabry disease
AlcCM	Alcoholic cardiomyopathy
AR	Autosomal recessive
ARVC	Arrhythmogenic right ventricular cardiomyopathy
ASA	Alcohol septal ablation
ATTR	Transthyretin amyloidosis
ATTRv	Hereditary transthyretin amyloidosis
ATTRwt	Wild-type OR Acquired transthyretin amyloidosis
AV	Atrioventricular
BNP	Brain natriuretic peptide
CCM	Cancer therapy-induced cardiomyopathy
CGU	Cardiogenetic unit
CMP	Cardiomyopathy
CMR	Cardiac magnetic resonance
CMU	Cardiomyopathy unit
CT	Computed tomography
CV	Cardiovascular
DCM	Dilated cardiomyopathy
DIP	Drug-induced phospholipidosis
ECG	Electrocardiogram
ECV	Extracellular volume
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EORP	EURObservational Research Programme
EU	European Union
FLC	Free light chain
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HH	Hereditary haemochromatosis
HRR	Heart rate reserve
ICC	Inherited cardiac condition
ICD	Implantable cardioverter defibrillator
LAD	Left anterior descending
LGE	Late gadolinium enhancement
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
LVOT	Left ventricular outflow tract
LVOTO	Left ventricular outflow tract obstruction
LVSD	Left ventricular systolic dysfunction
MRI	Magnetic resonance imaging
NAC	National amyloid centre
NCS	Non-cardiac surgery
NSVT	Non-sustained ventricular tachycardia
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PET	Positron emission tomography
PMCR	Paediatric Cardiomyopathy Registry
PPCM	Peripartum cardiomyopathy
RCM	Restrictive cardiomyopathy
RPE	Rate of perceived exertion
SCD	Sudden cardiac death
SRT	Septal reduction therapy
SVD	Small vessel disease
TTNtv	Titin gene truncating variants
VF	Ventricular fibrillation
VO_2max	Maximum oxygen consumption
VT	Ventricular tachycardia
VUS	Variant of uncertain significance

1. Epidemiology

1.1. General epidemiological data

Cardiomyopathies are in many cases inherited cardiac diseases with an identifiable or suspected genetic cause, with variable and often incomplete penetrance throughout life.[1] Geographical differences in the distribution of genetic variants may influence the estimated prevalence of different cardiomyopathy phenotypes in different populations, ethnicities, regions, and countries. The complexity of diagnostic criteria for some conditions, such as arrhythmogenic right ventricular cardiomyopathy (ARVC), limits the evaluation of the true prevalence of the disease in the general population. Moreover, epidemiological data are often not collected systematically at the population level, particularly in children.

Hypertrophic cardiomyopathy (HCM) is the most common cardiomyopathy, with an estimated prevalence taken from a pooled analysis of eight studies of 0.2% (95% confidence interval [CI], 1.44–2.71) or 1/460 population.[2–9] Data from cardiac magnetic resonance (CMR) analysis of a large adult cohort (>45 years of age) suggested that the prevalence may be higher than those derived from early echocardiography-based studies, with up to 1.4% prevalence, or 1/76 population.[10] In contrast, data from the UK Biobank reported a prevalence of 0.11% of left ventricular hypertrophy (LVH) above 15 mm in a population where arterial hypertension and aortic stenosis were excluded (0.22% in men and 0.04% in women).[11] Of note, (likely and definite) pathogenic gene variants have been detected in up to 60% of HCM.[12]

The prevalence of dilated cardiomyopathy (DCM) has been traditionally estimated at 0.036% (95% CI, 0.023–0.050) or 1/2740 based on one large population study.[13] More recent data suggest that the prevalence of DCM may be almost 10 times higher, based on indirect assumptions of the prevalence of genetic variants associated with the disease in general populations[14] and with less stringent diagnostic criteria.[15] Likely and/or definitely pathogenic gene variants occur in up to 40% of DCM,[16] and the prevalence of (likely) pathogenic genetic variants is also over 10% in non-familial DCM.

The true prevalence of ARVC based on the pooled analysis of three relatively large series is estimated at 0.078% (95% CI, 0.077–0.078) or 1/1290.[17–19] However, substantial geographical differences in the estimated population prevalence have been reported.

Data from the EURObservational Research Programme (EORP) Cardiomyopathy and Myocarditis registry with consecutive inclusion of cardiomyopathy cases provide information on the relative burden of cardiomyopathies seen in specialized clinics across Europe.[20] Hypertrophic cardiomyopathy burden in inherited cardiac disease units is 1.4 times higher than DCM, 12.2 times higher than classical ARVC, and 26.3 times higher than restrictive cardiomyopathy (RCM).

1.2. Paediatric cardiomyopathies

Overall, the annual incidence of paediatric cardiomyopathies is estimated to be about 1 per 100 000 children, with the highest incidence in the first year of life, based on population studies in Finland, the United States of America, and Australia.[21–23]

Paediatric cardiomyopathies form a diverse group of uncommon diseases, including genetic causes, metabolic or neuromuscular diseases, toxic causes, and infections. Dilated cardiomyopathy and HCM make up ~50% and 25% of all children with cardiomyopathy, respectively, whereas ARVC rarely presents in the first decade of life.[21,23] Restrictive cardiomyopathy is rare in childhood. The annual incidence of DCM is 0.34–0.58 per 100 000 children, with the highest incidence in infants (<1 year of age) of 3.80–4.58 per 100 000.[21–24] The annual incidence is higher in boys than in girls (0.66 vs. 0.47) and in Blacks than in Whites (0.98 vs. 0.46).[25] Data from the Paediatric Cardiomyopathy Registry (PMCR) suggest that 66% of children have idiopathic disease. Of known causes, myocarditis was the most common (46%), followed by neuromuscular disease (26%), familial DCM (14%), metabolic disease (11%), and malformation syndrome (3%).[25] In the current era, clinical genetic testing detects a genetic cause in about one-third of paediatric DCM cases, including a relatively high percentage of *de novo* mutations.[26,27] The overall annual incidence of HCM is 0.24–0.47 per 100 000 children.[21–23] A large peak in incidence in the first year of life is mainly caused by HCM due to metabolic disorders and malformation syndromes. Another smaller peak in the second decade is mainly due to sarcomeric diseases.[28] Arrhythmogenic right ventricular cardiomyopathy is very rare in early childhood; however, large ARVC registry data show that ~15% of ARVC patients present with paediatric onset disease with mean 15.3 ± 2.4 years of age. Paediatric ARVC patients more often present with sudden cardiac death (SCD).[29,30] Restrictive cardiomyopathy is very rare, with an annual incidence of 0.03–0.04 per 100 000 children.[21,23] Age at diagnosis ranges from infancy to adolescence; however, in contrast with other paediatric cardiomyopathies, RCM shows no peak in infancy and the incidence increases with age.[31]

1.3. Special populations

Direct causes of cardiomyopathies include pathogenic gene variants, toxins (e.g. alcohol, chemotherapy), autoimmunity, storage diseases (e.g. Fabry disease), infiltrative diseases (e.g. amyloidosis), various stressors (e.g. pregnancy, tachyarrhythmias), or infections.

Several forms of DCM previously considered secondary to external factors were recently proved to have genetic contributors, including alcoholic cardiomyopathy (AlcCM), cancer therapy-induced cardiomyopathy (CCM), and peripartum cardiomyopathy (PPCM). Titin gene truncating variants (*TTN*tv) represent a prevalent genetic predisposition for AlcCM (present in 13.5% 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.[32] Unrecognized rare variants in cardiomyopathy-associated genes, particularly *TTN*tv (in 7.5% of cases), appeared to be associated with an increased risk of CCM in children and adults, and adverse cardiac events in adults.[33] Rare truncating variants in eight genes were found in 15% of women with PPCM, and two-thirds were *TTN*tv (10% of patients vs. 1.4% of the reference population).[34,35] Additionally, other truncating variants were identified in the genes *DSP* (1%), *FLNC* (1%), and *BAG3* (0.2%).[35]

Hypertrophic cardiomyopathy can represent the common phenotype for several phenocopies and genocopies.[12] Anderson–Fabry disease was found in 0.94% of males and 0.90% of females in cardiac screening programmes for LVH and HCM.[36] Screening with bone scintigraphy found a high prevalence of transthyretin cardiac amyloidosis in specific populations: 11.4% in aortic stenosis, 4.8% in heart failure with preserved ejection fraction, 12.9% in LVH/HCM, and 2.6% in carpal tunnel syndrome (more if it is bilateral).[37]

The concept that cardiomyopathies are more prevalent than initially thought has generally been accepted by the scientific community, but more work needs to be done to ensure that the classification and detection of these rarer cardiac conditions are carried out in a systematic manner.

2. The patient pathway

2.1. Genetic testing

2.1.1. Variant interpretation

If a variant is identified in a gene known to be associated with the presenting phenotype, the laboratory will classify it according to a 5-tier system. Where there is sufficient evidence to support causation, the variant will be classified as pathogenic or likely pathogenic (P/LP). Conversely, where there is sufficient evidence to support a variant as not being the cause of disease, it is classified as benign or likely benign. Where there is conflicting or insufficient evidence, this will be considered a variant of uncertain significance (VUS). Benign/likely benign variants may not be included in the report. Pathogenic and benign classifications convey high confidence regarding the causal significance of a variant. 'Likely' represents >90% likelihood that a variant is pathogenic or benign, usually sufficient confidence to act on a result. Often there are insufficient data to achieve 90% confidence for or against pathogenicity, and variants are reported as uncertain. There are many rare variants in the genomes of healthy individuals, and many of these, even in well-known disease-associated genes, are innocent bystanders and not causative for the observed disease. VUS should therefore not be used for cascade testing and are seldom actionable in the proband.

It is important for the clinician to recognize when they can contribute additional information that might allow a VUS to be re-interpreted with more confidence, and the laboratory will often flag in the report if extra information might be sufficient to reclassify. For example, if a variant is not inherited from either parent, then it has likely arisen *de novo* in the affected individual and is more likely to be pathogenic. Segregation analysis may reveal that the variant is shared by several affected relatives, providing additional evidence for a role in disease rather than a bystander role. Reclassification of variants can be challenging for patients and families,[38,39] but should be part of pre-test genetic counselling discussions.

2.2. Genetic counselling

2.2.1. What is 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.[40,41] Genetic counselling can include discussion of inheritance risks, provide education, perform pre- and post-genetic test counselling and variant interpretation, obtain a three-generation family history, and provide psychosocial support.[42] The unique psychosocial needs of the inherited cardiomyopathy patient population have shaped the field of cardiac genetic counselling.[43] For those with a new diagnosis, 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. Indeed, in the general setting, genetic counselling can improve knowledge, recall, and patient empowerment; increase satisfaction with decision-making; and reduce anxiety.[44–47]

2.2.2. Who performs genetic counselling?

Genetic counselling is a process that is preferably performed by healthcare professionals with specific training, such as genetic counsellors, genetic nurses, or clinical/medical geneticists. Regardless of who takes on this role, it involves more than simply the provision of information: it requires careful attention to psychosocial needs. A systematic review of genetic counselling communication showed that higher levels of empathic responses, less verbal dominance (ratio of counsellor to patient talk), and the provision of a summary letter were associated with more positive outcomes.[48]

2.2.3. Genetic counselling in paediatrics

Genetic counselling performed by trained healthcare professionals working within a multidisciplinary team is recommended for all children with all types of cardiomyopathies, regardless of whether genetic testing is being considered.

There are specific issues to consider when counselling children and their families and considering clinical screening and predictive genetic testing.[49–51] 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.[50] The psychosocial impact should be considered and counselling should take place in the context of a multidisciplinary setting involving the child and their family.[42,52–54] With appropriate multidisciplinary support in a paediatric setting, psychosocial outcomes in children undergoing clinical screening and predictive genetic testing are no different than those of the general population.[54] Pre- and post-test counselling should be performed,[42,53] and the wishes of the child in terms of testing and disclosure of results should be at the forefront. Although the Task Force acknowledges that different healthcare systems may not allow for this, psychological support should be made available to all children and families with cardiomyopathy or undergoing clinical and/or genetic testing, with a particular focus on those with a recent diagnosis, a family history of SCD, and who are at important points during childhood, such as moving from primary to secondary education and transitioning from paediatric to adult services.[52,54–56]

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

One critical role for genetic counselling is alongside genetic testing. This includes a discussion prior to a decision to undertake genetic testing (pre-test) and when the results are returned (post-test). Pre-test genetic counselling focuses on the collection of a detailed family history, providing genetic education about inheritance risks, the process and logistics of genetic testing and options for return of the results, an explanation of all possible outcomes, clinical and family implications, the risk of reclassification and identification of secondary genetic findings, insurance implications, and an exploration of feelings and understanding of the information provided. Post-test discussions include a review of the key points previously discussed in the pre-test session, return of the result, discussion of the implications of this result to the patient's care, and implications for the family. It can be helpful to provide tailored information from the family history, explicitly noting every family member's inheritance risk, and clinical and genetic testing options. Where a suspicious VUS has been identified, specific explanation of what this means is important, including whether there is a plan for resolving it, such as segregation to other affected relatives in the family, and how often the classification will be reviewed. There should be ample opportunity for questions or clarification at all points in the process.

2.2.5. Cascade genetic 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. 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. Genetic cascade screening should continue for all offspring of relatives who are shown to carry a P/LP variant.

Relatives who do not carry the variant can be dismissed from follow-up, while genotype-positive relatives should continue regular clinical evaluation.

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. Therefore, it is advised that variants should be classified by a specialized multidisciplinary cardiac genetic team with an appropriate level of expertise. In this context, it is important to understand that up to 50% of published variants are wrongly classified. In addition, systematic reclassification of identified variants is crucial, including its communication to families, emphasizing the need for these specialized multidisciplinary cardiogenetic teams.

2.2.6. Uptake of genetic counselling and testing

Several studies have evaluated the uptake of genetic testing and counselling and/or cardiological screening in inherited cardiomyopathies in first-degree relatives of index patients. Roughly 39–45% of at-risk relatives for an inherited cardiomyopathy come for screening within 1–2 years after the identification of the pathogenic variant in the family.[57–60] After a longer follow-up (median 16 years) this increased to 60%.[60] A first-intervention study (more intensive discussion of informing relatives at risk with the index patient, followed by a family letter sent directly to the relatives) did not increase the uptake.[60] This suboptimal uptake leaves room for improvement, and future studies will give guidance on how to do this. Currently, it is recommended to discuss with the index patient how they will reach out to first-degree relatives and how the healthcare provider can help and provide support.

2.2.7. Approaching relatives of the index patient

At-risk relatives are generally informed by the index patient, who is supported with a family letter about the condition, the content of the family screening programme, and links to relevant websites with further information. However, the approach to relatives varies between countries due to differences in tradition and legislation.

The discussion of how to approach family members is an important part of the genetic counselling process with the index patient.

For a variety of reasons, the index patient may refuse to inform at-risk relatives of having inherited the condition and about the offer of family screening. This is a cause for concern, since most inherited cardiac conditions (ICCs) are associated with adverse complications and

SCD, which may be prevented if diagnosed in due time. Depending on the legislation of each country, it may be possible to bypass the index patient and approach at-risk relatives directly. This may be done through a letter informing each relative that a hereditary condition is suspected in the family and that they should contact the ICC unit and obtain more information if they wish. Sometimes, affected relatives may refuse to have their minor children investigated; an issue which may be difficult to solve unless there is legislation in place that outlines how to deal with this issue.

When these kinds of difficult situations occur, it is important to be patient and try to understand the reasons of the affected individuals for withholding information from at-risk relatives. Offering repeated counselling sessions or suggesting a phone call with relatives at a later stage are two possible solutions. Usually, however, the problem resolves once the affected individual has had sufficient time to consider the implications.

2.2.8. Inheritance and family communication

Knowing that one's family is at increased risk of inheriting a genetic condition can create uncertainty and worry for many index patients. Because most inherited cardiomyopathies follow an autosomal dominant inheritance pattern, there is a need to communicate the importance of both clinical and genetic testing of relatives. Conveying this information to at-risk relatives is typically reliant on the proband in the family understanding the information and passing it on to the appropriate relatives. Numerous studies show that effective family communication is an important challenge, and interventions to support communication have so far not yielded favourable results, highlighting the multidimensional nature of the issue.[52,60,61] Common barriers to communication may include poor family relationships; guilt about passing a causative variant on to children; psychosocial factors, including distress; and comprehension of the result.[62,63] A patient will often selectively communicate genetic information to relatives, assessing their ability to understand and cope with the information, their life stage, and risk status.[61] Health literacy is an important barrier to effectively communicating genetic risk information to relatives, highlighting the need for targeted resources and mechanisms for support.[64]

2.2.9. Psychological support

Coming to terms with a diagnosis of an inherited cardiomyopathy can be difficult and have a significant impact on psychological well-being.[43,65–70]

As a patient, being at risk of hereditary cardiomyopathy is not only a matter of facts and test results, but also of perception: while one affected family member can have only mild symptoms that can be treated with medication, others may have a different outcome with a greater impact in terms of the treatment needed (e.g. ICD or transplant). This fact should be considered when treating a family with a hereditary cause of cardiomyopathy, in aspects such as the communication of test results and targeting psychological needs. Not every patient within a family has the same burden of symptoms and/or disease outcome.

The 'estimate of risk' is not only a matter for the professional caretaker in terms of how to treat the patient: the impact on the patient themselves and the consequences of that treatment may necessitate a very thorough and professional need for psychological assistance. The psychological well-being of a patient with cardiomyopathy has a broad range of aspects to consider, from the very personal to specific and practical needs:

- Self-care should be clearly emphasized: from day-to-day blood pressure testing to the importance of a strict medication schedule. This contributes to a patient's feeling of self-control.
- The aspects of treatment (medication, ICD, transplant) that have an effect on daily life should be clearly communicated (e.g. medication schedule, side effects of medication, diet restrictions, exercise restrictions, etc.).
- The significance of the hereditary component of the condition should be made clear, as the possibility of having children with the defect (or the decision not to have children at all) can be a difficult burden to bear for many patients.
- Practical issues should be emphasized (these may vary according to local legislation); e.g. seeking a mortgage, getting a driver's licence, career planning, etc.

Psychological assistance should support and encourage the patient as well as the family, but also give guidance to the patient to try to find answers to the very specific challenges they will face.

3. Specific entities

3.1. Hypertrophic cardiomyopathy

3.1.1. Cardiac magnetic resonance imaging and sudden cardiac death risk in hypertrophic cardiomyopathy

Although current data suggest that the extent of late gadolinium enhancement (LGE) on CMR may be of use in predicting cardiovascular mortality, data in regards to the use of LGE in the prediction of SCD risk are conflicting (Table S1). Similarly, the roles of the presence of LV apical aneurysms (Table S2) and LV systolic dysfunction (Table S3) as additional independent predictors of SCD risk in HCM remain to be determined.

Table S1 **Studies on the role of late gadolinium enhancement in predicting sudden cardiac death in patients with hypertrophic cardiomyopathy**

Study name or first author	Details and quality of evidence			Summary of key findings		
	Study type	Number of patients and follow-up duration	Key inclusion and exclusion criteria	Relevant aims and outcome(s)	Key findings	Conclusions and limitations
Maron *et al.*, 2008[71]	Observational, prospective	$n = 202$ Two centres FU: 681 ± 249 days	**Inclusion:** consecutive HCM pts	**Aim:** describe clinical profile and relation of LGE to CV outcomes	Adverse cardiovascular events in 11/202 pts. Among 7/11 with LGE: • 2 died suddenly; • 2 had appropriate ICD discharge; and • 3 with progressive HF symptoms vs. 4/11 pts without LGE: • 3 with sudden death; and • 1 with progressive HF. Annual cardiovascular event rate in HCM pts with LGE exceeded that of pts without LGE (5.5% vs. 3.3%), but not statistically significant (HR 1.45; 95% CI, 0.43–4.97; $P = 0.5$)	**Conclusions:** LGE was an independent predictor of systolic dysfunction. Data insufficient to consider LGE as an independent risk factor for adverse prognosis
Bruder *et al.*, 2010[72]	Observational, prospective	$n = 243$; 220 in analysis Single centre Mean FU: 1090 days	**Inclusion:** consecutive HCM pts **Exclusion:** Hx of previous septal ablation or myectomy, known coronary artery disease, aortic stenosis, amyloidosis, systemic hypertension, or contraindications to CMR	Primary endpoints: (i) all-cause death; and (ii) cardiac death (death from all cardiac causes, including SCD, heart failure, and aborted SCD)	All-cause mortality: 20/220 SCD: 11/220 among which 2 with ICD discharged **Univariate analysis for SCD:** Presence of LGE: OR 5.14; 95% CI, 0.65–41.0; $P = 0.10$ (non-significant) **Multivariable Cox regression analysis, (presence of LGE, LVEF, and LV mass):** LGE independent predictor of cardiac death (HR 4.81; $P = 0.035$) Not performed in the subgroup of SCD patients ($n = 11$, limited number of events)	**Conclusions:** LGE is a predictor of all-cause and cardiac mortality. Unable to demonstrate statistically significant relation to SCD **Limitations:** single centre, small size, limited number of events

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O'Hanlon *et al.*, 2010[73]	Observational, prospective	$n = 217$ Single centre Mean FU: 3.1 ± 1.7 years	**Inclusion:** consecutive HCM pts **Exclusion:** significant coronary artery disease, or prior SRT	Combined primary endpoint: (i) CV death; (ii) unplanned CV admission; (iii) sustained VT/VF, or (iv) appropriate ICD discharge Secondary outcomes: (i) HF; (ii) arrhythmic	**Primary endpoint:** 40/217 (18.4%) pts • 34/136 (25%) in the LGE group • 6/81 (7.4%) in the non-LGE group (HR 3.4; 95% CI, 1.4–8.1; $P = 0.006$) CV deaths: 9 LGE group: 8 Multivariable analysis: presence and amount of LGE remained independent predictors of the primary endpoint (HR 2.7; 95% CI, 1.01–7.1; $P = 0.046$) **Arrhythmic endpoint:** 12/217 overall • LGE group: 10/136 (7.3%), and • non-LGE group: 2/81 (2.5%) (HR 3.15; 95% CI, 0.69–14.4; $P = 0.138$) Univariate analysis: the amount of LGE was significantly associated with the outcome (HR 1.30; 95% CI, 1.05–1.61; $P = 0.014$), but in the multivariable analysis: NSVT was the strongest predictor. No other variables were added to the model (low event rate)	**Conclusion:** LGE is an independent predictor of adverse outcomes. Longer follow-up in a larger cohort will clarify the role of LGE as a risk factor in SCD prediction **Limitations:** single referral centre, small cohort, underpowered, low event rate, selection bias (pts with ICDs excluded at baseline)
Rubinshtein *et al.*, 2010[74]	Observational, retrospective	$n = 424$ Single centre Mean FU: 43 ± 14 months	**Inclusion:** consecutive HCM pts **Exclusion:** ICD *in situ*, previous hx of SRT	**Aims:** (i) evaluate the relation between LGE and HCM genes status, severity of symptoms, and the degree of ventricular ectopy on Holter ECG; (ii) Outcomes of SCD and appropriate ICD therapies were recorded	Outcome occurred in 8/424 pts • SCD 4 pts; and • ICD discharge: 4 pts All 8 pts had LGE In addition to LGE, the presence of NSVT was another univariate associate of events (HR 6.9; 95% CI, 1.14–52.4; $P = 0.04$) No multivariable Cox model analysis performed (low event rate). On bivariate analysis LGE remained associated with events after controlling for all other parameters	**Conclusion:** LGE remained a significant associate of subsequent SCD or appropriate ICD therapies after controlling for other factors **Limitations:** single centre, selection bias, low event rate, lack of multivariate Cox model, high number of SRT in FU

Continued

Green *et al.*, 2012[75]	Systematic review and meta-analysis	$n = 1063$ Pooled HCM pts from 4 studies (1–4) Mean FU: 3.1 years	**Inclusion:** studies of LGE in HCM that reported outcomes of cardiovascular mortality, SCD, aborted SCD, and HF death	**Aim:** association of LGE with CV mortality, SCD, aborted SCD, and HF death	LGE correlated with: • cardiac death (OR 2.92; 95% CI, 1.01–8.42; $P = 0.047$) • HF death (OR 5.68; 95% CI, 1.04–31.07; $P = 0.045$); and • all-cause mortality (OR 4.46; 95% CI, 1.53–13.01; $P = 0.006$), but was not significant for SCD/aborted SCD (OR 2.39; 95% CI, 0.87–6.58; $P = 0.091$)	**Conclusion:** there are significant relationships between LGE and cardiovascular mortality, heart failure death, and all-cause mortality in HCM. Additionally, LGE and SCD/aborted SCD displayed a trend toward significance
Chan *et al.*, 2014[76]	Observational, prospective	$n = 1293$ 7 HCM centres Mean FU: 3.3 years	**Inclusion:** consecutive HCM patients with CMR at first evaluation **Exclusion:** prior ICD implantation or history of sustained VT/ VF, claustrophobia, obstructive coronary artery disease, septal myectomy or alcohol ablation (before CMR), and incomplete follow-up	SCD composite endpoint: HCM-related sudden death, aborted arrest, ICD discharge	Cumulative SCD events incidence: 0.9%/year SCD events in 37/1293 patients (3%): • 14/1293 died suddenly; • 6/1293 aborted cardiac arrest; • 17/1293 appropriate ICD therapy LGE present in 548/1293 pts (42%): • ≤10% of the LV mass ($n = 381$, 29%); • 11–19% ($n = 94$, 7%); • ≥20% ($n = 73$, 6%) Among 37 pts with SCD events, LGE was present in 26 (70%), occupying 13 ± 14% of the LV myocardium Each 10% increase in LGE was associated with 40% increase in relative SCD events risk (adjusted HR 1.46 for 10% increase in LGE; 95% CI, 1.12–1.92; $P = 0.002$) Compared with patients without LGE, the adjusted (for conventional risk factors and EF) HR of SCD events related to %LGE: • 10%, 1.46; • 15%, 1.77; • 20%, 2.14 In low-risk pts SCD event risk increased in direct proportion to extent of LGE (HR 1.66/10% LGE; 95% CI, 1.24–2.23; $P = 0.0007$) The absence of LGE was associated with lower risk of SCD events (adjusted HR 0.39; 95% CI, 0.18–0.84; $P = 0.02$)	**Conclusions:** extensive LGE provides additional information for assessing SCD event risk among HCM patients, particularly patients otherwise judged to be at low risk **Limitations:** selection bias, exclusion of high-risk pts with ICDs, low event rate in HCM. 17 out of 37 ICD shocks potentially non-fatal arrhythmias

Continued

Ismail *et al.*, 2014[77]	Observational, prospective	Size: 711 Median FU: 3.5 years Single HCM centre	**Inclusion:** consecutive HCM pts **Exclusion:** previous myectomy or alcohol septal ablation; previous myocardial infarction; or contraindications to CMR (including prior device implantation) and gadolinium-based contrast agents	Primary endpoint: SCD or aborted SCD	SCD composite endpoint 22/711 pts (3.1%), in detail: • 18 (3.8%) pts with LGE and 4 (1.7%) with no LGE (HR LGE, 2.69; 95% CI, 0.91–7.97, $P = 0.073$) Patients with LGE were more likely to have extreme hypertrophy (LV wall thickness ≥30 mm) and non-sustained VT at baseline. On univariable analysis, the amount of fibrosis was a significant predictor of outcome: (HR per 5% LGE 1.24; 95% CI, 1.06–1.45, $P = 0.007$) On multivariable analysis, only LVEF was an independent predictor (HR 0.92; 95% CI, 0.89–0.95, $P \leq 0.001$) Increasing %LGE was associated with increased risk. However, not statistically significant after adjusting for EF	**Conclusions:** the amount of myocardial fibrosis is an important predictor of outcome in HCM but may not provide information incremental to EF. **Limitations:** single centre. Small size. Low event rate. Selection bias. High-risk pts with ICDs excluded. Methodology of LGE quantification
Briasoulis *et al.*, 2014[78]	Meta-analysis	$n = 3067$ Pooled pts from 6 HCM studies. Mean FU: 3.05 years	**Inclusion:** prospective HCM studies reporting the effects of LGE on clinical outcomes (SCD/aborted SCD, all-cause mortality, cardiac and heart failure death)	**Aim:** assess the utility of CMR on LGE as a prognostic factor of SCD in HCM	SCD/aborted SCD in HCM pts with LGE was significantly increased as compared with pts without LGE (OR 2.52; 95% CI, 1.44–4.4; $P = 0.001$) The extent of LGE was not significantly related to the risk of SCD	**Conclusion:** LGE is significantly associated with SCD risk, cardiac mortality, and all-cause mortality in patients with non-high-risk HCM according to conventional risk factors

Continued

Mentias *et al.*, 2018[79]	Observational, retrospective	*n* = 1423 (458 non-obstructive, 965 obstructive) Single HCM centre Median FU: 4.5 years	**Inclusion:** consecutive low-/ intermediate-risk HCM pts with preserved LVEF undergoing CMR. **Exclusion:** prior device implantation; claustrophobia; high SCD risk pts; ≥moderate aortic/mitral stenosis; subaortic membrane; LGE pattern consistent with ischaemic myocardial damage; LVEF <50%; prior history of alcohol septal ablation or surgical myectomy; and prior mitral and/or aortic valve replacement	Primary composite endpoint: actual SCD, successful resuscitation from cardiac arrest or appropriate ICD shocks	60/1423 (4%) composite primary events: • 40 actual SCD; • 20 appropriate ICD discharges Any LGE on CMR: 717 (50%) pts Risk of primary events increased when %LGE increased ≥15% Entire cohort: 32 pts with primary event of 342 (9%) with %LGE ≥15% vs. 28 pts of 1081 (3%) with %LGE < 15%; $P < 0.001$ **%LGE on univariable analysis:** • >0 to <15% (HR 1.41; 95% CI, 0.87–2.39; $P = 0.39$) • ≥15% (HR 2.34; 95% CI, 1.29–3.31; $P \leq 0.001$) **%LGE on multivariable competing risk regression analysis (Fine Gray method, ESC risk score in the model) for primary composite events:** obstructive group: • >0 to <15% (HR 1.52; 95% CI, 0.91–5.39; $P = 0.21$) • ≥15% (HR 3.04; 95% CI, 1.48–6.10; $P = 0.003$) Non-obstructive group: • >0 to <15% (HR 1.43; 95% CI, 0.87–7.16; $P = 0.32$) • ≥15% (HR 2.84; 95% CI, 1.27–6.34; $P = 0.01$)	**Conclusions:** %LGE ≥15% was associated with increased risk of primary composite events in patients with low/ intermediate SCD risk and preserved EF. **Limitations:** retrospective single centre study. Selection bias, exclusion of high-risk pts, SRT referral centre (high volume of myectomy pts)

CI, confidence interval; CMR, cardiac magnetic resonance; CV, cardiovascular; ECG, electrocardiogram; EF, ejection fraction; ESC, European Society of Cardiology; FU, follow-up; HCM, hypertrophic cardiomyopathy; HF, heart failure; HR, hazard ratio; Hx, history; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; OR, odds ratio; pts, patients; SCD, sudden cardiac death; SRT, septal reduction therapy; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table S2 **Apical aneurysms and sudden death in hypertrophic cardiomyopathy**

Study name or first author	Details and quality of evidence			Summary of key findings		
	Study type	Number of patients and intervention(s)	Key inclusion and exclusion criteria	Relevant outcome(s)	Key findings	Conclusion(s)
Rowin *et al.*, 2017[80]	Retrospective observational	93 pts from 2 centres	**Inclusion:** diagnosis of HCM and apical aneurysm on cardiac MRI and/or echo **Exclusion:** known obstructive coronary artery disease	SCD composite endpoint (actual SCD + resuscitated cardiac arrest + appropriate ICD therapy)	Composite endpoint event rate 4.7%/year vs. 0.9%/year in remaining HCM cohort. SCD composite endpoint 21/93 pts (22.6%), in detail: • Actual SCD: 1.1% (1/93 pts) • Aborted SCD: 2.2% (2/93 pts) • Appropriate ICD therapy 19.4% (18/93 pts). Rhythm was monomorphic VT in 89% (16/18 pts)	**Conclusion:** HCM patients with LV apical aneurysms are at high risk of arrhythmic sudden death **Limitations:** selection bias, high prevalence of confounders in patients with events (previous VT/VF and LV systolic function)
Lee *et al.*, 2022 [81]	Retrospective observational	160 pts from a single centre	**Inclusion:** diagnosis of HCM and apical aneurysm on cardiac MRI and/or echo **Exclusion:** history of anterior infarction or significant LAD stenosis	SCD composite endpoint (actual SCD + resuscitated cardiac arrest + appropriate ICD therapy)	Composite endpoint event rate 1.8%/year SCD composite endpoint 14/160 pts (8.8%), in detail: • actual SCD: none • aborted SCD: 4.4% (7/160 pts) • appropriate ICD therapy 4.4% (7/160 pts). Rhythm not specified	**Conclusion:** LV apical aneurysms in HCM are a high-risk phenotype, associated with increased risk of adverse cardiovascular events, including malignant ventricular arrhythmias **Limitations:** selection bias, high prevalence of confounders in patients with events (previous VT/VF and LV systolic function)

HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LAD, left anterior descending; LV, left ventricular; MRI, magnetic resonance imaging; pts, patients; SCD, sudden cardiac death; VT, ventricular tachycardia; VF, ventricular fibrillation.

Table S3 Studies on the prevalence of and predictors for left ventricular systolic dysfunction in patients with hypertrophic cardiomyopathy

Study name or first author	Number	Specific subset	LVSD prevalence	Annual incidence of HCM-LVSD	Main endpoints	Multivariable analysis for prediction of SCD events
Wasserstrum *et al.*[82]	1328	None	2.8%	0.39%	All-cause mortality or ventricular assist device or transplant	Not available
Biagini *et al.*[83]	222	Both paediatric and adult patients	4.9%	0.53%	Cardiovascular death (SCD, HF-related death, stroke-related death)	LV wall thickness (HR 1.07; 95% CI, 1.01–1.14; $P = 0.03$) and LV end-diastolic diameter (HR 1.08; 95% CI, 1.04–1.11; $P = 0.0001$)[a]
Thaman *et al.*[84]	1080	Serial echocardiography substudy ($n = 462$)	2.4%	0.87%	Composite of SCD and ICD firing; composite of all-cause death, ICD firing, and heart transplantation	Not available
Harris *et al.*[85]	44	None	3.5%	1.12%	Death, SCD, ICD firing, heart transplantation	Not available
Kawarai *et al.*[86]	43	Incident HCM-LVSD	8.7%	0.73%	Sudden death including also non-fatal cardiac arrest and appropriate ICD intervention	Among HCM-LVSD the presence of syncope resulted as an independent predictor of sudden death (HR 6.15; 95% CI, 2.40–15.75; $P < 0.001$)[b]
Rowin *et al.*[87]	2447	None	4.8%	na	SCD events, heart transplant listing, HCM-related death, all-cause death	Not available
SHaRe Consortium[88]	6793	None	8.1%	na	All-cause death, heart transplantation, sudden death, ICD activation	Adjusted[c] HCM-LVSD HR for SCD, 3.9; 95% CI, 2.6–6.3; $P < 0.001$; adjusted HCM-LVSD HR for ICD activation, 1.6; 95% CI, 1.4–1.8; $P < 0.001$

CI, confidence interval; HCM, hypertrophic cardiomyopathy; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LV, left ventricular; LVSD, left ventricular systolic dysfunction; na, not available; pts, patients; SCD, sudden cardiac death; VT, ventricular tachycardia.

[a]Gender, age at first evaluation, family history of sudden death, New York Heart Association (NYHA) functional class I to II or III to IV, medical treatment at first evaluation, non-sustained ventricular tachycardia, LV outflow obstruction, maximum LV wall thickness, posterior wall thickness, LV end-diastolic diameter, end-systolic left atrial diameter, and (as a time-dependant covariate) dilated-hypokinetic evolution.

[b]Multivariable Cox regression including: positive family history, maximum LV wall thickness >30 mm at the initial diagnosis of HCM, non-sustained VT at the diagnosis of end-stage HCM, and unexplained syncope at the diagnosis of end-stage HCM.

[c]Based on a Cox proportional hazards model following patients from initial SHaRe evaluation, adjusted for age, sex, and follow-up time. HR >1 represents an increased risk observed in patients with HCM with LVSD.

3.2. Restrictive cardiomyopathy

The systematic approach to the diagnosis of RCM should include clinical examination, ECG, advance cardiac imaging and genetic testing. Table S4 summarizes the spectrum of restrictive heart disease.

Table S4 Spectrum of restrictive heart disease

Myocardium					Endocardium	Pericardium
Myocytes			ECV			
RCM, primary, genetic	**Genocopies**	**Phenocopies, non-genetic**	**Infiltration**	**Fibrosis/ECV remodelling**		
With or without intramyocyte aggregates of misfolded, mutated proteins: • troponinopathies (1 most common; T; C) • Myosinopathies (*MYH7*) • Desminopathies (*DES*) • BAG30pathies (*BAG3*) • Myotilinopathies (MYOT) Filaminopathies (*FLNC*) • Ab-crystallinopathies (*CRYAB*) • Titinopathies (*TTN*) (rare) • Less common: *ACTCI*, *MYBPC3*, *MYL3*, *TPMI*, *MYL3*, *MYL2*	**Storage diseases with intramyocyte accumulation:** *Lysosomal diseases*[a] • glycogenoses (pompe, Mcardle, Danon, etc.) • Glycosphingolipidoses (AFD) *Iron storage diseases, genetic forms:* • HH (myocytes) • Friedreich ataxia (mitochondria) Heritable haemoglobinopaties and other haematologic diseases may cause myocardial iron storage	**Toxicity:** *intramyocyte accumulation in acquired lysosomal diseases:* • DIP by cationic amphiphilic drugs: e.g. chloroquine-hydroxychloroquine (other cationic amphiphilic drugs) • Less common: • serotonin • methysergide • ergotamine • mercurial agents, busulfan • heavy metals • potentially reversible	**Extramyocyte deposition/ infiltration:** • amyloidosis, genetic and non-genetic[a] (+ myocyte toxicity in primary amyloidosis) • cystinosis, genetic, AR (*CTNS* gene) • hyperoxaluria: primary, genetic: *AGXT* and *GRHPR* genes; secondary (jejunoileal bypass, oxalate poisoning, drug toxicity)	**Non-specific features:** • diabetic heart disease (SVD, fibrosis and myocyte damage) • autoimmune diseases (fibrosis, large and small vessel involvement) e.g. scleroderma • inflammatory, granulomatous (e.g. sarcoidosis: sporadic; rare genetic early-onset sarcoidosis: *CARD15/NOD2* gene	**Diseases affecting endomyocardial layers:** • endomyocardial fibrosis • eosinophilic: tropical and non-tropical forms (myeloproliferative, with hypereosinophilia, Löffler endocarditis, endocardial thrombosis) • Endinger syndrome (carcinoid heart disease) • iatrogenic/drug toxicity • radiation therapy • endocardial neoplasms[a]	**Pericardium diseases affecting pericardium and epicardial fat tissue:** • constrictive pericarditis (panpericardial or segmental; rare, post-pericardiotomy) • pericardial tumours,[a] benign (cysts and lipomas); malignant (primary mesothelioma, most common) • radiation therapy • epicardial steatonecrosis in heart transplantation

AFD, Anderson–Fabry disease; AR, autosomal recessive; DIP, drug-induced phospholipidosis; ECV, extracellular volume; HH, hereditary haemochromatosis; RCM, restrictive cardiomyopathy; SVD, small vessel disease.
[a]Tumours: rhabdomyomas isolated or in tuberous sclerosis 1 and 2, fibromas; angiosarcomas, fibrosarcomas, rhabdomyosarcomas, liposarcomas, fibrosarcomas, rhabdomyosarcomas, liposarcomas, lymphomas.

3.3. Amyloid

Prognosis in cardiac amyloidosis was originally considered poor but this can be further stratified (Table S5). Several multiparametric biomarker-based staging systems have been developed for AL[89,90] and ATTR cardiac amyloidosis.[91–93]

Table S5 Prognostic staging scores in light chain amyloidosis and transthyretin amyloidosis

Kumar *et al.*[89] AL		Lillenes *et al.*[90] AL		Grogan *et al.*[93] ATTRwt		Gillmore *et al.*[92] ATTRv and ATTRwt		Cheng *et al.*[91] ATTRv and ATTRwt	
Staging parameters: FLC-diff >18 mg/dL Troponin T > 0.025 ng/mL NT-proBNP > 1800 pg/mL		Staging parameters: troponin I > 0.1 ng/mL BNP > 81 pg/mL		Staging parameters: troponin T > 0.5 ng/mL NT-proBNP > 3000 pg/mL		Staging parameters: eGFR <45 mL/min NT-proBNP > 3000 pg/mL		Scoring parameters: Mayo or NAC Score (0–2 points) Daily dose of furosemide or equivalent: 0 mg/kg (0 points), >0–0.5 mg/kg (1 point), >0.5–1 mg/kg (2 points), and >1 mg/kg (3 points) NYHA class I–IV (1–4 points)	
Stage	**5-year survival**	**Stage**	**Median survival**	**Stage**	**4-year survival/ median survival**	**Stage**	**Median survival**	**Score**	**Median survival**
Stage I (0 parameters)	68%	Stage I (0 parameters)	Not reached	Stage I (0 parameters)	57% 66 months	Stage I (0 parameters)	69.2 months	Score 1–3	90.5 months
Stage II (1 parameter)	60%	Stage II (1 parameter)	112.8 months	Stage II (1 parameter)	42% 40 months	Stage II (1 parameter)	46.7 months	Score 4–6	38.5 months (Mayo) 36 months (NAC)
Stage III (2 parameters)	28%	Stage III (2 parameters)	51.6 months	Stage III (2 parameters)	18% 20 months	Stage III (2 parameters)	24.1 months	Score 7–9	20.3 months (Mayo) 19.8 months (NAC)
Stage IV (3 parameters)	14%	Stage IIIb (2 parameters and BNP >700 pg/mL)	12 months						

AL, Monoclonal immunoglobulin light chains amyloidosis; ATTRv, Hereditary transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; FLC, free light chain; NAC, national amyloid centre; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.

4. Sports

Exercise recommendations for the different cardiomyopathies are referred to intensity levels that are provided in Table S6.

Table S6 Indices for exercise intensity during sport

Intensity	VO_2max (%)	HRmax (%)	HRR (%)	RPE scale	Training zone
Low-intensity, light exercise	<40	<55	<40	10–11	Aerobic
Moderate-intensity exercise	40–69	55–74	40–69	12–13	Aerobic
High-intensity exercise	70–85	75–90	70–85	14–16	Aerobic + lactate
Very high-intensity exercise	>85	>90	>85	17–19	Aerobic + lactate + anaerobic

HRmax, maximum heart rate; HRR, heart rate reserve; RPE, rate of perceived exertion; VO_2max, maximum oxygen consumption.
Adapted from Vanhees *et al.*[94]

5. Recommendations for non-cardiac interventions

Management of patients with HCM and LVOTO deserves careful evaluation. Objectives and specific actions are summarized in Table S7.

Table S7 Management of a patient with hypertrophic cardiomyopathy and left ventricular outflow tract obstruction for non-cardiac interventions

Objectives	• To maintain normal to high cardiac pre-load. • Afterload control. • To maintain sinus rhythm/AV synchrony at low heart rates (60–65 b.p.m.). • Medication to treat LVOTO should remain on board during NCS.
To avoid	Diuretics and inotropic agents.
If hypotension appears	• Pre-load should be corrected (fluids, Trendelenburg position to favour venous return). • Use drugs that increase systemic vascular resistance without causing greater ventricular obstruction and without increasing contractility and heart rate as phenylephrine or vasopressin.
If LVOTO appears	Consider use of intravenous beta-blockers such as short-acting esmolol, metoprolol, or labetalol.
If rapid atrial fibrillation appears	Rate control with beta-blockers or calcium blockers or electric cardioversion if haemodynamic instability.

AV, atrioventricular; b.p.m., beats per minute; LVOTO, left ventricular outflow tract obstruction; NCS, non-cardiac surgery.
Adapted from Sahoo *et al.*, Dhillon, *et al.*, and Hensley *et al.*[95–97]

6. Requirements for specialized cardiomyopathy units

6.1. Requirements and skills

A cardiogenetic unit/cardiomyopathy unit (CGU/CMU) should have access to both outpatient and inpatient facilities within a healthcare provider structure.[98–101] The activity of a CGU/CMU is based on the availability of multimodality cardiac imaging facilities (echocardiography with advanced analysis, CMR, nuclear medicine), electrocardiographic (including Holter monitoring), and functional evaluation (cardiopulmonary test, electrocardiogram [ECG] exercise testing). Close collaboration with interventional cardiology, electrophysiology, and cardiac surgery departments is necessary. A genetic team with expertise in cardiomyopathies and links to a clinical genetic testing laboratory is also required. These units should also provide a framework for discussing the diagnosis, therapeutic options, and prognosis. Clinical psychologists and genetic counsellors assist with the integration of information by the patients and their families. These units should also collaborate in the management of relatives across different geographic areas. These requirements are summarized in *Table S8*.

7. Living with cardiomyopathy: patient and family education

Our knowledge of both the clinical and genetic basis of cardiomyopathies has been a rapidly evolving area of cardiology over the last 30 years. This poses significant challenges to healthcare professionals who seek to stay abreast of new knowledge and ensure that their patients are receiving the highest standard of care. This can also be difficult for patients who seek to better understand the condition they are being assessed or managed for. For a patient and their at-risk family members, resources to enable understanding and make sense of the tangible impact a diagnosis will have on them should be made available. Patient support groups may also play an important role in supporting patient and family education.

Patient education has been defined as a 'process of assisting consumers of healthcare to learn how to incorporate health-related behaviours (knowledge, skill, attitude) into everyday life with the purpose of achieving the goal of optimal health'.[103] Incorporating patient education into the design and development of healthcare services, as well as clinical guideline documents, can enable greater awareness and appreciation of the need for clear and understandable patient education resources.

Patient education reduces the uncertainty regarding symptoms, management, and prognosis; provides appropriate risk information; and promotes patient empowerment and self-efficacy, whereby the patient plays a leading role in their own health management. This is particularly relevant in the case of paediatric cardiomyopathy patients in which the parent's and child's environment should be appropriately addressed.

The process of patient education can be classified into four components: assessment, planning, implementation, and evaluation.[104] Assessment of the patient, including literacy levels, concerns, priorities, learning preferences, and potential barriers to learning, is crucial to personalizing education. The planning of patient education strategies

involves setting mutual goals for the healthcare provider and the patient, and developing an education plan that uses evidence-based teaching strategies with a focus on patient's needs and priorities. Implementation of the plan should be adjusted according to how the patient responds and their changing learning needs. Finally, the plan should be evaluated to determine where learning has been achieved. The patient education process should be repeated accordingly. A comprehensive approach is shown in *Table S9*.

Table S8 Cardiomyopathy units: requirements and skills

Requirements	Skills
Integrated cardiology/paediatric cardiology unit (should include adult and paediatric cardiovascular specialists with expertise in cardiac genetics and cardiomyopathies)	Ability to perform a family history and draw and interpret a family pedigree Ability to perform or interpret appropriate diagnostic tests and examine diagnostic clues to define the nature of the cardiomyopathy and its underlying aetiology Clinical Nurse Specialists and clinic co-ordinators to facilitate scheduling of new patients and families and arrange appropriate follow-up
Dedicated outpatient clinic	Capacity to see and follow-up cardiomyopathy patients and their families in a dedicated outpatient clinic
Family screening	Ability to carry out a complete clinical screening of relatives (adults and children)
Diagnostic imaging unit (with experience in and capacity to carry out studies on cardiomyopathies, including basal, stress, and transoesophageal echocardiography; CMR; and cardiac CT [whether integrated or not into the cardiology unit])	Performance and interpretation of echocardiography with focus on the evaluation of myocardial morphology, outflow geometry, septum morphology, valve apparatus anatomy, presence of LVOTO, mitral valve and/or papillary muscle anomalies, right ventricle myocardium, Doppler and strain studies, etc. Performance and/or interpretation of CMR with special focus on the characterization of myocardial tissue with parametric mapping methods (quantification of T1, T2, and extracellular volume fraction), LGE, etc. Performance and/or interpretation of cardiac CT scans
Nuclear imaging unit (with experience in cardiac involvement of systemic diseases [amyloidosis, sarcoidosis, etc.]; may not be co-located)	Ability to interpret cardiac scintigraphy studies and PET scans
Genetics unit (with experience in cardiomyopathies and links to a clinical genetic testing laboratory, with access to genetic counselling)	Ability to discuss genetic testing options with patients and their families, as well as the impact on the patient and/or family Access to clinical genetic testing encompassing genes with definitive gene–disease association with the condition tested for Ability to interpret the genetic result and differentiate the clinical implications of different variant classification for the patient and their family Ability to perform cascade genetic testing of at-risk relatives Access to genetic counselling for the patient and all families seen with an inherited cardiomyopathy Access to pre- and post-test genetic counselling for all patients undergoing genetic testing
Catheterization and interventional cardiology unit (diagnostic and therapeutic procedures including structural procedures, with experience in ASA and an adequate number of procedures according to guidelines)	Ability to perform and interpret invasive haemodynamic studies to assess cardiac performance and intracardiac pressures in cardiomyopathies and valve disease as well as coronary angiography to detect haemodynamically significant epicardial coronary disease as contributors to myocardial ischaemia or heart failure Performance and/or interpretation of coronary angiograms of HCM patients that allow for correct identification of a septal perforator branch with compatible anatomy for ASA Ability to contextualize the clinical condition of patients, determine the need for interventions, and the likelihood of safe and effective septal reduction with ASA
Electrophysiology and arrhythmia unit (with experience in electrophysiological studies, ventricular tachycardia and atrial fibrillation ablation, and device implantation [pacemakers, resynchronization devices, and ICDs])	Ability to interpret other arrhythmia screening tools (e.g. implantable loop recorders), perform basic device troubleshooting, and deactivate defibrillator therapy and pacemaker functions Accurate selection of suitable patients for defibrillator therapy/resynchronization based on guidelines

Continued

Cardiac surgery unit (with experience in myectomies and mitral valve repair for the management of obstructive HCM with an adequate number of procedures according to guidelines; may be in another reference centre) **Active heart transplant and ventricular assist device programme** that allows for a response to and continuity for needs derived from the treatment of patients with cardiomyopathies (may be in another reference centre)	Ability to determine the need for effective septal reduction with myectomy and or mitral valve repair Ability to detect patient deterioration and offer referral for heart transplantation when necessary Ability to offer ventricular assist device therapy or access to such a centre
Pathological anatomy unit (with experience in cardiomyopathies) **Forensic pathologist unit** (directly involved in the study of SCDs in the community)	Ability to understand the microscopic study of patient tissue samples in order to arrive at a diagnosis of the disease Ability to develop protocols between forensics and the cardiomyopathy unit for study of SCDs that occur in the community in an out-of-hospital setting
Clinical psychological support (from healthcare professionals with appropriate qualifications in the psychotherapeutic treatment of emotional and behavioural disorders caused by inherited conditions and SCD in relatives)	Psychological support should be offered to the patient or the family, with referral to an appropriately qualified healthcare professional Access to clinical psychological expertise for families with psychological difficulties, e.g. following a young SCD in the family; and patients adjusting to a new diagnosis, ICD therapy, possible medical restrictions on their daily routine, and the psychological aspects of living with a condition for the foreseeable future (aided by medication, ICD, transplant, etc.)
Research, teaching, and educational capacity	Research capacity, and demonstrated research experience in the field of cardiomyopathies, at national and international levels Capacity to carry out teaching and educational activities related to the area of cardiomyopathies, aimed at improving the knowledge and technical capacity of healthcare providers involved in the same chain of care within and outside of the provider facility, such as continuing medical education and distance learning
Telemedicine and other e-health tools	Ability to exchange expertise with other healthcare providers and support them Established procedures and a framework for ensuring the management, safeguarding, and exchange of medical data, including established outcomes, process indicators, and patient registers for the specific area of expertise in accordance with EU data protection legislation Ability to foster the use of telemedicine and other e-health tools within and outside their facilities, by fulfilling the minimum interoperability requirements and, when possible, using agreed standards and recommendations[102]

ASA, alcohol septal ablation; CMR, cardiac magnetic resonance; CT, computed tomography; EU, European Union; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LVOTO, left ventricular outflow tract obstruction; PET, positron emission tomography; SCD, sudden cardiac death.

Table S9 Educational steps

Step	Examples
Assessment	
Demographic data	• Enquire about the patient's level of education, and cultural and religious beliefs and values.
Patient's concerns and priorities	• Enquire what the patient is most concerned about. • Enquire what knowledge the patient has regarding the cardiomyopathy they are being assessed for or affected by. • Ask the patient about level of knowledge of the condition in their close social environment.
Patient's interests	• What does the patient want to understand?
Learning preferences	• Enquire about the patient's preferred mode of learning (e.g. reading, video, verbal, demonstration, app).
Assessment tools	• Questionnaires or other assessment tools can be used to establish the level of knowledge pre- and post-patient education activity.
Planning	
Set mutual goals	• Set goals according to the context. For example, educate the patient so that they are able to inform family members about the condition. • Aim to address individual health literacy needs and consider disabilities that might affect this. • Offer education according to the patient's interests and learning preferences.

Continued

Develop an educational plan	• Avoid medical jargon. • Use simple, direct messaging. • Create objectives and a step-wise approach. • Create communities that promote patient education. • Provide both written material and videos, but also engagement events that allow faster feedback in learning.
Create resources	• Documents. • Videos to watch asynchronously. • Creation of mobile apps, if relevant. • Decision aids to be used in shared decision-making (e.g. decision on genetic testing or ICD implantation). • Illustrations, 3D models. • Accommodate patients who are visually or hearing impaired. • Make available in languages other than English, depending on the location.
Implementation	
Focus on the patient	• Plain language. • Active listening. • Allow for interactive learning (e.g. encourage patients to ask questions). • Be respectful and empathetic.
Follow key educational principles	• Frame the objectives to be clear from the beginning. • Create small educational snippets/segments that are easily understood and digestible. • Create clear summaries and review key points.
Adjust teaching	• Use analogies that make sense in terms of the context and the patient's profile. • Allow enough time to reiterate information on more challenging topics. • Allow for hands-on practice (e.g. have a model of an ICD to demonstrate, and allow the patient to manipulate when discussing ICDs). • Use multiple teaching methods depending on the context.
Evaluation	
Direct patient input	• Have direct conversation with patients to get feedback for any educational activity.
Patient outcomes	• Measure adherence to therapy plans. • Assess re-admission rates. • Assess engagement with genetic counselling. • Assess adherence to lifestyle changes.

3D, three-dimensional; ICD, implantable cardioverter defibrillator.

8. References

1. 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
2. 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
3. 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
4. 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
5. 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
6. 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
7. 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
8. 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
9. 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
10. Massera D, McClelland RL, Ambale-Venkatesh B, Gomes AS, Hundley WG, Kawel-Boehm N, *et al.* Prevalence of unexplained left ventricular hypertrophy by cardiac magnetic resonance imaging in MESA. *J Am Heart Assoc* 2019;**8**:e012250. https://doi.org/10.1161/JAHA.119.012250
11. Lopes LR, Aung N, van Duijvenboden S, Munroe PB, Elliott PM, Petersen SE. Prevalence of hypertrophic cardiomyopathy in the UK biobank population. *JAMA Cardiol* 2021;**6**:852–854. https://doi.org/10.1001/jamacardio.2021.0689
12. 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
13. Codd MB, Sugrue DD, Gersh BJ, Melton LJ 3rd. 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

14. 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
15. 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
16. 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
17. Peters S, Trummel 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
18. 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
19. 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
20. 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
21. 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
22. 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
23. 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
24. 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
25. 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
26. Herkert JC, Abbott KM, Birnie E, Meems-Veldhuis MT, Boven LG, Benjamins M, *et al.* Toward an effective exome-based genetic testing strategy in pediatric dilated cardiomyopathy. *Genet Med* 2018;**20**:1374–1386. https://doi.org/10.1038/gim.2018.9
27. Quiat D, Witkowski L, Zouk H, Daly KP, Roberts AE. Retrospective analysis of clinical genetic testing in pediatric primary dilated cardiomyopathy: testing outcomes and the effects of variant reclassification. *J Am Heart Assoc* 2020;**9**:e016195. https://doi.org/10.1161/JAHA.120.016195
28. 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
29. Te Riele A, James CA, Sawant AC, Bhonsale A, Groeneweg JA, Mast TP, *et al.* Arrhythmogenic right ventricular dysplasia/cardiomyopathy in the pediatric population: clinical characterization and comparison with adult-onset disease. *JACC Clin Electrophysiol* 2015;**1**:551–560. https://doi.org/10.1016/j.jacep.2015.08.004
30. Surget E, Maltret A, Raimondi F, Fressart V, Bonnet D, Gandjbakhch E, *et al.* Clinical presentation and heart failure in children with arrhythmogenic cardiomyopathy. *Circ Arrhythm Electrophysiol* 2022;**15**:e010346. https://doi.org/10.1161/CIRCEP.121.010346
31. 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
32. 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
33. 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
34. 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
35. 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
36. 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
37. 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
38. Wong EK, Bartels K, Hathaway J, Burns C, Yeates L, Semsarian C, *et al.* Perceptions of genetic variant reclassification in patients with inherited cardiac disease. *Eur J Hum Genet* 2019;**27**:1134–1142. https://doi.org/10.1038/s41431-019-0377-6
39. 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
40. National Society of Genetic Counselors' Definition Task Force; Resta R, Biesecker BB, Bennett RL, Blum S, Hahn SE, *et al.* 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
41. Biesecker BB. Goals of genetic counseling. *Clin Genet* 2001;**60**:323–330. https://doi.org/10.1034/j.1399-0004.2001.600501.x
42. 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
43. 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
44. 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
45. 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
46. 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
47. 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
48. 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
49. 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
50. 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
51. 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
52. 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
53. Rhodes A, Rosman L, Cahill J, Ingles J, Murray B, Tichnell C, *et al.* Minding the genes: a multidisciplinary approach towards genetic assessment of cardiovascular disease. *J Genet Couns* 2017;**26**:224–231. https://doi.org/10.1007/s10897-016-0017-z
54. 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
55. Last AN, English J, Pote H, Shafran R, Owen T, Kaski JP. Anxiety in children attending a specialist inherited cardiac arrhythmia clinic: a questionnaire study. *BMJ Paediatr Open* 2018;**2**:e000271. https://doi.org/10.1136/bmjpo-2018-000271
56. Meulenkamp TM, Tibben A, Mollema ED, van Langen IM, Wiegman A, de Wert GM, *et al.* Predictive genetic testing for cardiovascular diseases: impact on carrier children. *Am J Med Genet A* 2008;**146A**:3136–3146. https://doi.org/10.1002/ajmg.a.32592

57. Christiaans I, Birnie E, Bonsel GJ, Wilde AA, van Langen IM. Uptake of genetic counselling and predictive DNA testing in hypertrophic cardiomyopathy. *Eur J Hum Genet* 2008;**16**:1201–1207. https://doi.org/10.1038/ejhg.2008.92
58. Charron P, Heron D, Gargiulo M, Richard P, Dubourg O, Desnos M, *et al.* Genetic testing and genetic counselling in hypertrophic cardiomyopathy: the French experience. *J Med Genet* 2002;**39**:741–746. https://doi.org/10.1136/jmg.39.10.741
59. van der Roest WP, Pennings JM, Bakker M, van den Berg MP, van Tintelen JP. Family letters are an effective way to inform relatives about inherited cardiac disease. *Am J Med Genet A* 2009;**149A**:357–363. https://doi.org/10.1002/ajmg.a.32672
60. van den Heuvel LM, van Teijlingen MO, van der Roest W, van Langen IM, Smets EMA, van Tintelen JP, *et al.* Long-term follow-up study on the uptake of genetic counseling and predictive DNA testing in inherited cardiac conditions. *Circ Genom Precis Med* 2020;**13**:524–530. https://doi.org/10.1161/CIRCGEN.119.002803
61. 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
62. 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
63. 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
64. 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
65. O'Donovan C, Ingles J, Broadbent E, Skinner JR, Kasparian NA. How patient perceptions shape responses and outcomes in inherited cardiac conditions. *Heart Lung Circ* 2020;**29**:641–652. https://doi.org/10.1016/j.hlc.2019.11.003
66. Caleshu C, Kasparian NA, Edwards KS, Yeates L, Semsarian C, Perez M, *et al.* Interdisciplinary psychosocial care for families with inherited cardiovascular diseases. *Trends Cardiovasc Med* 2016;**26**:647–653. https://doi.org/10.1016/j.tcm.2016.04.010
67. 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
68. 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
69. Wynn J, Holland DT, Duong J, Ahimaz P, Chung WK. Examining the psychosocial impact of genetic testing for cardiomyopathies. *J Genet Couns* 2018;**27**:927–934. https://doi.org/10.1007/s10897-017-0186-4
70. Christiaans I, van Langen IM, Birnie E, Bonsel GJ, Wilde AA, Smets EM. Quality of life and psychological distress in hypertrophic cardiomyopathy mutation carriers: a cross-sectional cohort study. *Am J Med Genet A* 2009;**149A**:602–612. https://doi.org/10.1002/ajmg.a.32710
71. 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
72. 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
73. 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
74. Rubinshtein R, Glockner JF, Ommen SR, Araoz PA, Ackerman MJ, Sorajja P, *et al.* Characteristics and clinical significance of late gadolinium enhancement by contrast-enhanced magnetic resonance imaging in patients with hypertrophic cardiomyopathy. *Circ Heart Fail* 2010;**3**:51–58. https://doi.org/10.1161/CIRCHEARTFAILURE.109.854026
75. 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
76. 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
77. 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
78. 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
79. 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
80. 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
81. Lee DZJ, Montazeri M, Bataiosu R, Hoss S, Adler A, Nguyen ET, *et al.* Clinical characteristics and prognostic importance of left ventricular apical aneurysms in hypertrophic cardiomyopathy. *JACC Cardiovasc Imaging* 2022;**15**:1696–1711. https://doi.org/10.1016/j.jcmg.2022.03.029
82. Wasserstrum Y, Larranaga-Moreira JM, Martinez-Veira C, Itelman E, Lotan D, Sabbag A, *et al.* Hypokinetic hypertrophic cardiomyopathy: clinical phenotype, genetics, and prognosis. *ESC Heart Fail* 2022;**9**:2301–2312. https://doi.org/10.1002/ehf2.13914
83. Biagini E, Coccolo F, Ferlito M, Perugini E, Rocchi G, Bacchi-Reggiani L, *et al.* Dilated-hypokinetic evolution of hypertrophic cardiomyopathy: prevalence, incidence, risk factors, and prognostic implications in pediatric and adult patients. *J Am Coll Cardiol* 2005;**46**:1543–1550. https://doi.org/10.1016/j.jacc.2005.04.062
84. 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
85. 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
86. 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
87. 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
88. 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
89. 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
90. 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
91. 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
92. 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
93. 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
94. Vanhees L, Geladas N, Hansen D, Kouidi E, Niebauer J, Reiner Z, *et al.* Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular risk factors: recommendations from the EACPR. Part II. *Eur J Prev Cardiol* 2012;**19**:1005–1033. https://doi.org/10.1177/1741826711430926
95. 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
96. 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
97. Hensley N, Dietrich J, Nyhan D, Mitter N, Yee MS, Brady M. Hypertrophic cardiomyopathy: a review. *Anesth Analg* 2015;**120**:554–569. https://doi.org/10.1213/ANE.0000000000000538
98. 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

99. McDonagh TA, Gardner RS, Lainscak M, Nielsen OW, Parissis J, Filippatos G, *et al.* Heart failure association of the European Society of Cardiology specialist heart failure curriculum. *Eur J Heart Fail* 2014;**16**:151–162. https://doi.org/10.1002/ejhf.41
100. 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 (Engl Ed)* 2016;**69**:300–309. https://doi.org/10.1016/j.recesp.2015.11.031
101. 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
102. 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 (Hagerstown)* 2020;**21**: 622–623. https://doi.org/10.2459/JCM.0000000000001024
103. Bastable SB. *Nurse as Educator: Principles of Teaching and Learning for Nursing Practice: Principles of Teaching and Learning for Nursing Practice*. Jones & Bartlett Learning; 2017.
104. Health Care Education Association. https://www.hcea-info.org (25 January 2021, date last accessed).