# Epidemiology and Clinical Aspects of Genetic Cardiomyopathies

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**KEYWORDS**

• Hypertrophic cardiomyopathy • Nonischemic dilated cardiomyopathy
• Arrhythmogenic right ventricular cardiomyopathy • Restrictive cardiomyopathy • Clinical registry

**KEY POINTS**

- Cardiomyopathies are an increasingly recognized cause of heart failure and sudden death, particularly in young patients.
- Since their original description, major advances were achieved in the phenotype knowledge, natural history, and nosography of cardiomyopathies leading to different classification systems.
- Deeper knowledge of the natural history of the disease and its phases (preclinical, overt disease, and end-stage disease) is needed.
- Large-scale clinical registries provide the opportunity to bridge knowledge gaps and improve risk prediction and management of patients with cardiomyopathies.

## INTRODUCTION

Cardiomyopathies (CMPs) are myocardial disorders in which the heart muscle is structurally and functionally abnormal in the absence of abnormal conditions that can explain the observed myocardial abnormality.[1] Although considered rare diseases, the estimated combined prevalence of all CMPs is at least 3%.[2] Furthermore, their recognition is increasing because of advances in imaging techniques[3] and greater awareness in both the lay and medical communities. CMPs are typified by clinical and genetic heterogeneity and are associated with significant morbidity and mortality.[4] In this article, the authors summarize the classification, epidemiology, and phenotypic spectrum of genetic CMPs. (**Tables 1** and **2**)

## CLASSIFICATION OF CARDIOMYOPATHIES

In 1957, Brigden[5] first used the term *cardiomyopathies* to describe a group of uncommon myocardial diseases not related to coronary artery diseases. Later in the 1960s, Goodwin and colleagues[6] defined CMPs as "*myocardial diseases of unknown cause*"[6] and identified 3 different entities, namely, dilated CMP (DCM), hypertrophic CMP (HCM), and restrictive CMP (RCM).

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**Table 1**
**Classification systems for cardiomyopathies**

| Author/Year | CMP Definition | Classification |
|---|---|---|
| Goodwing/1972 | Myocardial diseases of unknown cause | Hypertrophic CMP<br>Dilated CMP<br>Restrictive CMP |
| WHO/ISFC/1995 | Diseases of the myocardium associated with cardiac dysfunction | Hypertrophic CMP<br>Dilated CMP<br>Restrictive CMP<br>Arrhythmogenic right ventricular CMP<br>Unclassified CMP<br>• Fibroelastosis<br>• Noncompacted myocardium<br>Specific CMPs<br>• Ischemic CMP<br>• Valvular CMP<br>• Hypertensive CMP<br>• Inflammatory CMP<br>• Metabolic CMP<br>• Associated to general system diseases (eg, sarcoidosis)<br>• Associated to muscular dystrophies<br>• Associated to neuromuscular diseases<br>• Caused by toxic reaction (eg, alcoholic CMP)<br>• Peripartal CMP |
| AHA/2006 | A heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic | Genetic<br>• Hypertrophic CMP<br>• Arrhythmogenic right ventricular CMP/dysplasia<br>• Left ventricular noncompaction<br>• Channelopathies<br>Mixed<br>• Dilated CMP<br>• Restrictive CMP<br>Acquired<br>• Inflammatory CMP<br>• Takotsubo CMP<br>• Peripartum CMP<br>• Tachycardia-induced CMP |
| ESC/2008 | A myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease sufficient to cause the observed myocardial abnormality | Hypertrophic CMP<br>• Familial<br>◦ Unknown gene<br>◦ Sarcomeric protein mutation<br>◦ Glycogen storage diseases<br>◦ Lysosomal storage disease<br>◦ Disorder of fatty acid metabolism<br>◦ Carnitine deficiency<br>◦ Mitochondrial cytopathies<br>◦ Noonan syndrome<br>◦ Leopard syndrome<br>◦ Friedreich ataxia<br>◦ Amyloid (mutated TTR)<br>• Nonfamilial<br>◦ Obesity<br>◦ Infants of diabetic mothers<br>◦ Athletic training<br>◦ Amyloid (AL/prealbumin, wild-type TTR) |

(*continued on next page*)

**Table 1**
**(*continued*)**

| Author/Year | CMP Definition | Classification |
|---|---|---|
| | | Dilated CMP<br>• Familial<br>◦ Unknown gene<br>◦ Sarcomeric protein<br>◦ Z-band muscle<br>◦ LIM protein<br>◦ TCAP<br>◦ Cytoskeletal genes dystrophin<br>◦ Desmin<br>◦ Metavinculin<br>◦ Sarcoglycan complex<br>◦ Epicardin<br>◦ Nuclear membrane<br>◦ Lamin A/C<br>◦ Emerin<br>◦ Intercalated disc protein<br>◦ Mitochondrial cytopathy<br>• Nonfamilial<br>◦ Myocarditis<br>◦ Kawasaki disease<br>◦ Eosinophilic<br>◦ Drugs<br>◦ Pregnancy<br>◦ Endocrine<br>◦ Nutritional<br>◦ Hypophosphatemia<br>◦ Hypocalcemia<br>◦ Alcohol<br>◦ Tachycardiomyopathy<br>Restrictive CMP<br>• Familial<br>◦ Tropinin I<br>◦ Desmin<br>◦ HFE<br>◦ Amyloid (mutated TTR)<br>• Nonfamilial<br>◦ Sarcoidosis<br>◦ Carcinoid heart disease<br>◦ Scleroderma<br>◦ Amyloid (AL/prealbumin, wild-type TTR)<br>• Arrhythmogenic right ventricular CMP<br>• Unclassified CMP<br>◦ Left ventricular noncompaction<br>◦ Takotsubo CMP |
| WHF/2013 | Heart muscle disease sufficient to cause structural and functional myocardial abnormality in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease | Descriptive genotype-phenotype nosology system (see text for details) |

*Abbreviations:* AHA, American Heart Association; AL, Light chain; ESC, European Society of Cardiology; ISFC, International Society and Federation of Cardiology; TCAP, Titin cap gene; TTR, Transthyretin; WHF, World Heart Federation; WHO, World Health Organization.

**Table 2**
**Prevalence of adults and pediatric cardiomyopathies**

| | Pediatric | Adult |
|---|---|---|
| Hypertrophic CMP | Not available | Prevalence 1 per 500 to 1 per 200[a] |
| Dilated CMP | Not available | 1 per 2700 to 1 per 250[b] |
| Arrhythmogenic right ventricular CMP | Not available | 1 per 2000–5000 |
| Restrictive CMP | Not available | Not available |

[a] Newer techniques (ie, genetic testing, cardiac MRI) have increased recognition of the hypertrophic CMP (HCM) phenotype and improved clinical diagnosis. For these reasons, the prevalence of HCM in the general population has been estimated to be closer to 1 out of every 200.
[b] The only formal study that estimated the prevalence of dilated CMP (DCM) was the Olmsted study (~1 per 2700). This prevalence was twice the prevalence of hypertrophic cardiomyopathy (HCM), which was estimated at 19.7 per 100,000 (~1 per 5000) from the same cohort during this study period. Subsequently, multiple well-designed epidemiologic studies have shown an HCM prevalence of approximately 1 per 500. It is highly likely that the Olmsted County study also significantly underestimated the prevalence of DCM, so the estimated prevalence generated from the HCM/DCM incidence data is now considered approximately 1 per 500.

In 1996, the World Health Organization and the International Society and Federation of Cardiology[7] redefined CMPs as "*diseases of the myocardium associated with cardiac dysfunction*." A new entity, arrhythmogenic right ventricular CMP (ARVC), was added to the classification, whereas several unclassified CMPs were highlighted, including left ventricular noncompaction (LVNC).

In the new millennium, the classification of CMPs was revisited once more by the American Heart Association (AHA) and the European Society of Cardiology (ESC) in independent initiatives. In 2006, the AHA published a scientific statement in which CMPs were defined as "*a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic.*"[8] The writing committee maintained a distinction between primary CMPs (when disease is solely or predominantly of the heart muscle) and secondary CMPs (when myocardial involvement is associated with a multisystem disorder). In addition, primary CMPs were classified as genetic (HCM, ARVC, LVNC), acquired (peripartum, tachycardia induced, myocarditis, Takotsubo), or mixed (DCM, RCM); ion channel diseases were included as functional (ie, electrophysiologic) disorders of the cardiomyocyte.

In contrast, an ESC position statement in 2008 created a categorization system in which CMPs were still defined as "*myocardial disorders in which the heart muscle is structurally and functionally abnormal in the absence of coronary artery disease, hypertension, valvular or congenital heart disease sufficient to cause the observed myocardial abnormality*."[9] Ion channel diseases were specifically excluded because of their lack of a structural cardiac phenotype.

The aim of the ESC document was to deliberately emphasize the distinction between genetic and nongenetic forms of disease to increase awareness of the spectrum of disorders that result in heart muscle dysfunction. Because the diagnosis of CMPs is based on a clinical phenotype, the 4 classic morphologic subgroups of hypertrophic, dilated, restrictive, and arrhythmogenic CMPs were maintained and a fifth subgroup of unclassified CMPs (including LVNC) was added. Each category was subdivided into familial and nonfamilial subsets.

The most recent classification of CMPs is that proposed by the World Heart Federation in 2013, known as the MOGE(S) classification.[10] In keeping with the ESC position statement, CMPs are defined by the presence of "*heart muscle disease sufficient to cause structural and functional myocardial abnormality in the absence of coronary artery disease, hypertension, valvular disease, and congenital heart disease*."[9] In contrast, however, the MOGE(S) scheme includes both genotype and phenotype in the classification of CMPs.

The MOGE(S) nomenclature system has 5 attributes:

- M: Morpho-functional characteristic
- O: Organ involvement
- G: Genetic or familial inheritance pattern
- E: Etiologic annotation
- S: Functional status using stages A to D of the ACC/AHA staging and classes I to IV using the New York Heart Association (NYHA) functional classification (The descriptor S is optional but may come in handy for the description of early CMP.)
- MD stands for dilated CMP, MH for HCM, MA for ARVC, MR for RCM, and MLNVC for LVNC.
- OH stands for heart only, OH + M for heart and skeletal muscle, OH + A for heart and nervous system, and so on.
- GAD stands for autosomal dominant, GAR for autosomal recessive, GXL for X-linked, and so on.

- EG stands for genetic cause with subgroups like EG-MYH7[p. Arg403Glu] for one variety of HCM.
- $S^{B-I}$ stands for a variety of CMPs in heart failure stage B and functional class I and so on.

For example, $M_H O_H G_{AD} E_{G\text{-}MYH7[p.\ Arg403Glu]} S_{B\text{-}I}$ represents morpho-functional phenotype (M): HCM (H); organ (O) involvement: heart (H); genetic/familial (G) with autosomal dominant (AD) transmission; cause (E): genetic (G) and caused by the p.Arg403Glu mutation of the MYH7 gene, ACC/AHA stage (S) B, NYHA I.

## EPIDEMIOLOGY OF CARDIOMYOPATHIES

It is now clear that most of the CMPs are relatively common in everyday clinical practice. HCM is probably the most common subtype with a prevalence of 1 per 500 to 1 per 200[11,12] in adults of all races. Disease expression usually occurs in adolescents and young adults, whereas it is thought to be less common in young children, in whom other causes, such as metabolic storage diseases, need to be considered.[13] The historical estimated prevalence of DCM is 1 per 2500; however, more recent estimates suggest a substantially higher prevalence of approximately 1 or more in 250 individuals.[14] In children, DCM is less common, with an overall annual incidence of 0.57 cases per 100,000 person-years.[15] In the pediatric age group, the incidence of DCM is greater in the first year of life (4.58 per 100,000) than during childhood and adolescence (0.34 per 100,000); the prevalent causes are myocarditis, neuromuscular disorders, and inborn errors of metabolism.[16]

The prevalence of ARVC has not been systematically studied but is estimated at 1 per 2000 to 5000 in adults,[17] whereas in childhood ARVC is rare and disease expression usually occurs during adolescence and early adulthood.

Finally, RCM represents a very small fraction (less than 5%) of all CMPs in Western countries, both in pediatric[18] and in adult populations, although they are more common in certain regions, for example, endomyocardial fibrosis is a relatively common cause of heart failure in equatorial Africa.

## CLINICAL ASPECTS OF CARDIOMYOPATHIES

CMPs represent a frequent cause of heart failure and sudden death, particularly in children and young adults (**Fig. 1**). In this section, the authors briefly summarize the clinical phenotype of CMPs.

### *Hypertrophic Cardiomyopathy*

The diagnosis of HCM is based on the demonstration of unexplained myocardial hypertrophy, which in practice means a left ventricular (LV) wall thickness of 1.5 cm or greater in an adult of normal size; but less stringent criteria are applied to first-degree relatives of an unequivocally affected individual.[19] Most patients have familial disease, usually with AD inheritance. Mutations in genes encoding proteins of the cardiac sarcomere are the most common cause (~60% of all cases, >90% of genetically defined cases).[20] Symptomatic presentation occurs at any age, with

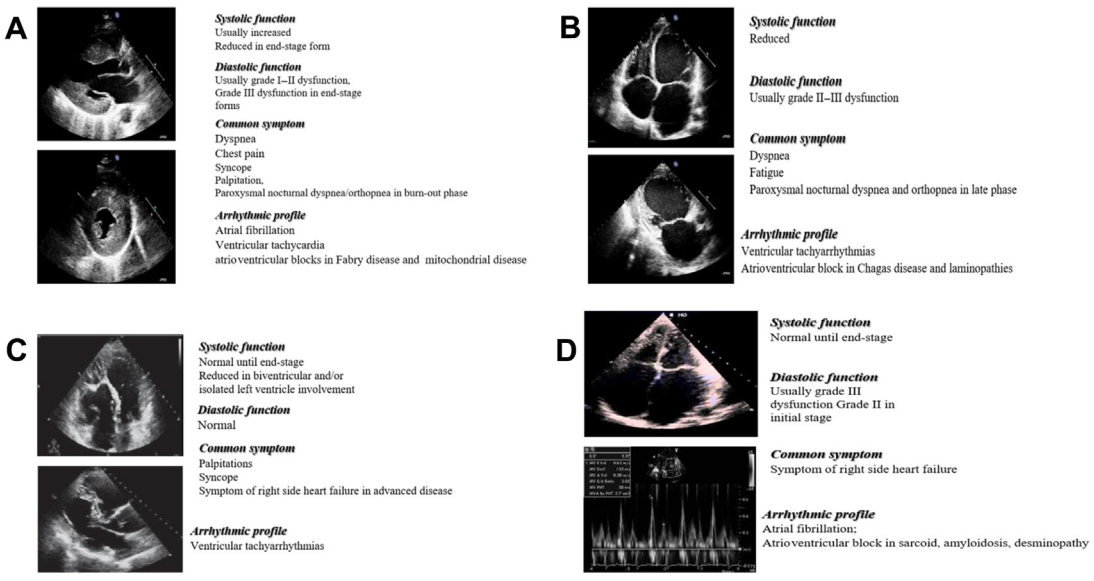


**Fig. 1.** Clinical/echocardiographic profiles of CMPs. (*A*) HCM. (*B*) DCM. (*C*) ARVC. (*D*) RCM.

breathlessness on exertion, chest pain, palpitation, syncope, or sudden death.[21] In children and adolescents, the diagnosis is often made during screening of siblings and offspring of affected family members. The 12-lead electrocardiography (ECG) is a sensitive but nonspecific diagnostic test. Echocardiography reveals LV hypertrophy that is symmetric or asymmetric and localized most commonly to both the septum and free wall with relative sparing of the posterior wall.[22] β-adrenoceptor blockers and non dihydropyridine calcium antagonists are the main symptomatic pharmacologic therapies, particularly for patients with LV outflow tract obstruction.[23] Surgical myectomy via a transaortic approach is considered for patients with symptomatic LV outflow-tract obstruction that is refractory to medical therapy.[24] Injection of alcohol into the septal artery that supplies the septal muscle is an alternative percutaneous technique that can be used in patients with suitable cardiac and coronary anatomy.[25] The overall annual cardiovascular mortality is 1% to 2% per year, with sudden cardiac death (SCD) (1%), heart failure (0.5%), and thromboembolism (0.1%) the main causes.[26,27] Prevention of sudden death relies on risk factor stratification to identify high-risk individuals and targeted therapy with implantable cardioverter defibrillators (ICD).[28] Atrial fibrillation is very common in patients with HCM, affecting approximately 20% to 25% of the population.[29]

### *Dilated Cardiomyopathy*

DCM is defined by dilatation and impaired systolic function of the left or both ventricles not attributable to coronary artery disease, valvular abnormalities, or pericardial disease.[30] Up to 50% of cases are familial, with many disease-causing gene mutations described.[31]

The diagnosis relies on demonstration of an increase in LV end-diastolic dimensions greater than 2 standard deviations greater than the mean and an ejection fraction less than 50%.[32]

The initial presentation is usually with symptoms of cardiac failure, but some individuals may present for the first time with arrhythmia and/or systemic thromboembolism.

Symptomatic therapy is with diuretics, mineralocorticoid receptor antagonists, angiotensin-converting enzyme inhibitors, and β-blockers.[33] Anticoagulation with warfarin is advised in patients in whom an intracardiac thrombus is identified or those with a history of thromboembolism. ICDs are warranted if sustained or symptomatic ventricular arrhythmias are documented and for primary prophylaxis in selected high-risk patients.[34] Cardiac resynchronization therapy can improve symptoms and the prognosis in selected patients with broad QRS duration,[35] and cardiac transplantation may be necessary for adults and pediatric patients with progressive deterioration.[36,37]

### *Restrictive Cardiomyopathy*

RCMs are defined by restrictive ventricular physiology in the presence of normal or reduced diastolic volumes of one or both ventricles, normal or reduced systolic volumes, and normal ventricular wall thickness.[38] In developed countries amyloidosis is the most common cause, whereas in the tropics it is endomyocardial fibrosis. Familial RCM is usually caused by sarcomere protein gene mutations.[39]

The presentation is usually insidious with symptoms of pulmonary congestion and/or mitral regurgitation, hepatomegaly, ascites, and tricuspid regurgitation.[40] Atrial fibrillation is common. Echocardiography typically shows that ventricular dimensions and wall thickness are normal but the atria are grossly enlarged. Congestive symptoms from increased right atrial pressure can be improved with diuretics, but the prognosis of advanced disease is poor.[41]

### *Arrhythmogenic Cardiomyopathy*

Arrhythmogenic cardiomyopathy (AC) is a heart muscle disease characterized by progressive fibrofatty replacement of right ventricular (RV) and LV myocardium associated with ventricular arrhythmia, heart failure, and SCD.[42] Because the originally described disease phenotype was characterized by predominant RV involvement, this disease was first named ARVC. The current term, *AC*, encompasses not only right predominant but also left predominant and biventricular involvement that have been increasingly recognized variants over the last several years.[43] AC is caused by mutations in desmosomal genes in at least 50% of cases.[44] The symptomatic presentation is usually with palpitations or syncope from sustained ventricular arrhythmia, but the first presentation of the disease may be with SCD. There is no single diagnostic test; the diagnosis is based on the presence of criteria encompassing structural, histologic, electrocardiographic, arrhythmic, and genetic parameters.[45–47] Risk stratification for SCD is critical for the management of patients with AC, but it is challenging to identify those who should have an ICD implanted. Patients with aborted SCD, sustained ventricular tachycardia (VT), or severe RV or LV dysfunction are high risk and warrant implantation of an ICD. Syncope, nonsustained VT, and moderate ventricular dysfunction are major risk factors for which an ICD should be strongly considered. Those with minor risk factors (abnormal ECG,

male sex, proband status, positive electrophysiology study, complex genotype) may also warrant consideration of an ICD. Healthy gene carriers without any risk factors are low risk and should have an ICD implanted.[48]

## REGISTRIES ON CARDIOMYOPATHIES

Until recently, most information about the presentation and natural history of individual disorders came from cohort studies in a small number of single centers in Europe and the United States. In order to derive data from less selected cohorts and expand the diversity and scope of the effort, new initiatives based on large longitudinal disease registries and national electronic health records are being conducted in several countries. Large-scale collaboration and comprehensive prospective data gathering provide the power needed to appreciate cumulative disease burden, define accurate risk estimates for adverse events, and determine how genotype impacts disease. Here, the authors highlight a few of the multicenter, international ongoing efforts on this front.

### *Pediatric Cardiomyopathy Registry*

In 1994, the Pediatric Cardiomyopathy Registry (PCMR; https://clinicaltrials.gov/ct2/show/NCT00005391), a large, multicenter, observational study of primary and idiopathic CMPs in children, was funded by the National Heart, Lung, and Blood Institute to study the epidemiology and clinical presentation of pediatric CMPs (<18 years old). The registry has evolved, adding a retrospective cohort of children, with the aim to describe the clinical course and predictors of outcomes. Expanding the potential goals, a collaboration with the Pediatric Heart Transplant Study Group was formed to examine the effect of cardiac transplantation on the clinical course of CMP. The collection of blood and cardiac tissue specimens was added to investigate the relationship of a genetic and viral disease background to clinical outcomes.[49] Currently, data from more than 3500 pediatric patients have been collected.[50] PCMR has provided insight into the incidence of, and risk factors for, pediatric CMP, the prevalence of heart failure at diagnosis, survival and transplant outcomes, and determinants of functional status.[50]

### *EURObservational Research Programme–European Society of Cardiology*

In 2009, the ESC launched the EURObservational Research Programme (EORP; https://www.escardio.org/Research/Registries-&-surveys/Observational-registry-programme) with the aim of improving the understanding of medical practice by collecting observational data using robust methodologic procedures. The EORP CMP registry is a prospective, multicenter, observational study of patients presenting to referral CMP centers in European countries. Consistent with published data, HCM is the most frequently recorded CMP in the registry, followed by DCM, ARVC, and RCM. Although rare, LVNC was most commonly reported in patients with DCM. In the 3 most common CMP subtypes, most patients were diagnosed before 50 years of age, a trend that was most evident for ARVC. The age trend was reversed in patients with RCM, reflecting the high proportion of patients in this group with amyloidosis. There was a skew toward an earlier diagnosis in men for HCM, DCM, and ARVC and in women for RCM.

A major finding in EORP is the large proportion of patients in whom familial disease is reported. This finding is particularly striking given that only 15% of patients were diagnosed as the result of family screening, illustrating the delay in referring individuals with a family history for further evaluation. A large proportion of patients in the registry underwent genetic testing with a high diagnostic yield showing that, at least within specialist CMP centers, genetic evaluation is an established part of routine practice.[51]

More than a quarter of all patients in the EORP had an ICD at enrollment, but the proportion in ARVC was 60% (predominantly for primary prophylaxis). This high rate of ICD implantation might reflect a bias toward patients with more severe disease in the registry but may also reflect the lack of clear guidelines on ICD implantation in this disease.

The EORP registry has now been extended to include pediatric patients and individuals with clinically suspected myocarditis.

### *Sarcomeric Human Cardiomyopathy Registry*

The Sarcomeric Human Cardiomyopathy Registry (SHaRe; https://thesharegistry.org/) is the first example of a multicenter international registry aiming to create a translational, personalized approach, from basic to clinic, on the specific theme of sarcomeric CMPs. Highly curated data sets from experienced centers were harmonized to create a comprehensive, collaborative registry, currently including greater than 12,000 patients and family members and spanning greater than 24,000 patient-years. Prospective longitudinal clinical and genetic data on probands and families with HCM and DCM are collected.[52] SHaRe is funded by research grants from MyoKardia, Inc (http://www.myokardia.com/), bringing together the world's leading cardiologists and geneticists

from the United States, Europe, and South America.

SHaRe has provided insight into the considerable cumulative burden of adverse outcomes in HCM, largely dominated by heart failure and atrial fibrillation (Day Sharlene, unpublished data, 2018). However, complications are typically delayed for one or more decades following diagnosis. Younger age at diagnosis and the presence of a pathogenic sarcomere gene mutation were identified as powerful multivariate predictors of adverse outcomes, including heart failure, atrial fibrillation, and ventricular arrhythmias. Even patients with sarcomere variants of uncertain significance (~9% of genotype cohort) were found to have an increased risk of adverse outcomes compared with those patients without identified variants (genotype negative), highlighting the importance of genotyping in clinical risk prediction. Future analyses of the SHaRe cohort will focus on specific clinical and genetic HCM subpopulations, refining risk prediction for adverse outcomes, and expanding to the DCM cohort.

Other CMP registries include the Hypertrophic Cardiomyopathy Registry,[53] which will incorporate a core-protocol cardiac MRI in addition to standard clinical factors for risk prediction in HCM; a Canadian national ARVC registry (NCT01804699); a European ARVC registry[54]; an ARVC patient registry at Johns Hopkins[55]; and an ARVC registry at the Mayo Clinic and Cambridge University (NCT03049254).

## SUMMARY

CMPs represent a fascinating but complex area in the wide panorama of heart disorders.

Recent advances have led to an understanding of the natural history and to some effective therapies for CMPs; however, a deeper knowledge of the natural history of the disease and its phases (preclinical, overt disease, and end-stage disease) is needed. Clinical registries provide the opportunity to bridge knowledge gaps and improve risk prediction and management of patients with CMPs and their family members in the future.

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