European Heart Journal Supplements (2025) **27** (Supplement 1), i73–i82
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suae108

ESC
European Society
of Cardiology

The 'Padua classification' of cardiomyopathies into three groups: hypertrophic/restrictive, dilated/hypokinetic, and scarring/arrhythmogenic

Domenico Corrado [1]*, Francesca Graziano [1,2], Barbara Bauce [1], Maria Bueno Marinas[1], Chiara Calore[1], Rudy Celeghin[1], Alberto Cipriani[1], Monica De Gaspari[1], Manuel De Lazzari [1], Federico Migliore [1], Martina Perazzolo Marra [1], Kalliopi Pilichou [1], Ilaria Rigato[1], Stefania Rizzo[1], Annalisa Angelini [1], Alessandro Zorzi[1], Gaetano Thiene [1], and Cristina Basso [1]

[1]*Department of Cardio-Thoraco-Vascular Sciences and Public Health, University of Padova, Padova, Italy; and* [2]*Department of Sports Medicine, Semmelweis University, Budapest, Hungary*

KEYWORDS
Cardiomyopathy;
Cardiac magnetic resonance;
Diagnosis

The newly proposed classification of cardiomyopathies, referred to as 'the Padua Classification', is based on both pathobiological basis (genetics, molecular biology, and pathology) and clinical features (morpho-functional and structural ventricular remodelling as evidenced by cardiac magnetic resonance). Cardiomyopathies are grouped into tree main categories and characterized by a designation combining both 'anatomical' and 'functional' features: hypertrophic/restrictive, dilated/hypokinetic, and scarring/arrhythmogenic; each cardiomyopathy group includes either genetic or non-genetic aetiologic variants. This novel approach aims to enhance the diagnostic accuracy and to support 'disease-specific' therapeutic strategies, with the objective to improve patient management and outcome.

Introduction

The classification of cardiomyopathies has undergone several revisions over the time, reflecting the advances in our understanding on the pathobiology of heart muscle diseases and the evolving imaging technology. In the 1970s, Goodwin and Oakley defined cardiomyopathies as 'disorders of the heart muscle of unknown cause,' distinguishing them from ischemic heart disease.[1] They introduced the first classification system, grouping cardiomyopathies into categories based on functional pathology: (i) Congestive cardiomyopathy, characterized by poor systolic function; (ii) hypertrophic cardiomyopathy (HCM, with or without obstruction), characterized by impaired diastolic compliance; and (iii) obliterative (constrictive) cardiomyopathy. The evolving cardiomyopathy classifications over the last 50 years and the nomenclature of cardiomyopathy phenotypes are summarized in *Figure 1*.[1-7]

In recent years, the scientific advances in molecular biology and genetics, in combination with the increasing use in the clinical setting of contrast-enhanced cardiac magnetic resonance (CMR) for morpho-functional imaging and structural myocardial tissue characterization, have provided important new insights into our understanding of the distinctive aspects of cardiomyopathies, with regard to both the genetic background and the phenotypic features.[2,3] With regard to the development of molecular genetics, the discovery of the genetic cause of cardiomyopathies (previously defined of unknown origin), led the way towards a possible genomic/post-genomic classification based on the underlying gene defects and the

*Corresponding author. Tel: +39 3357766527, Email: domenico.corrado@unipd.it

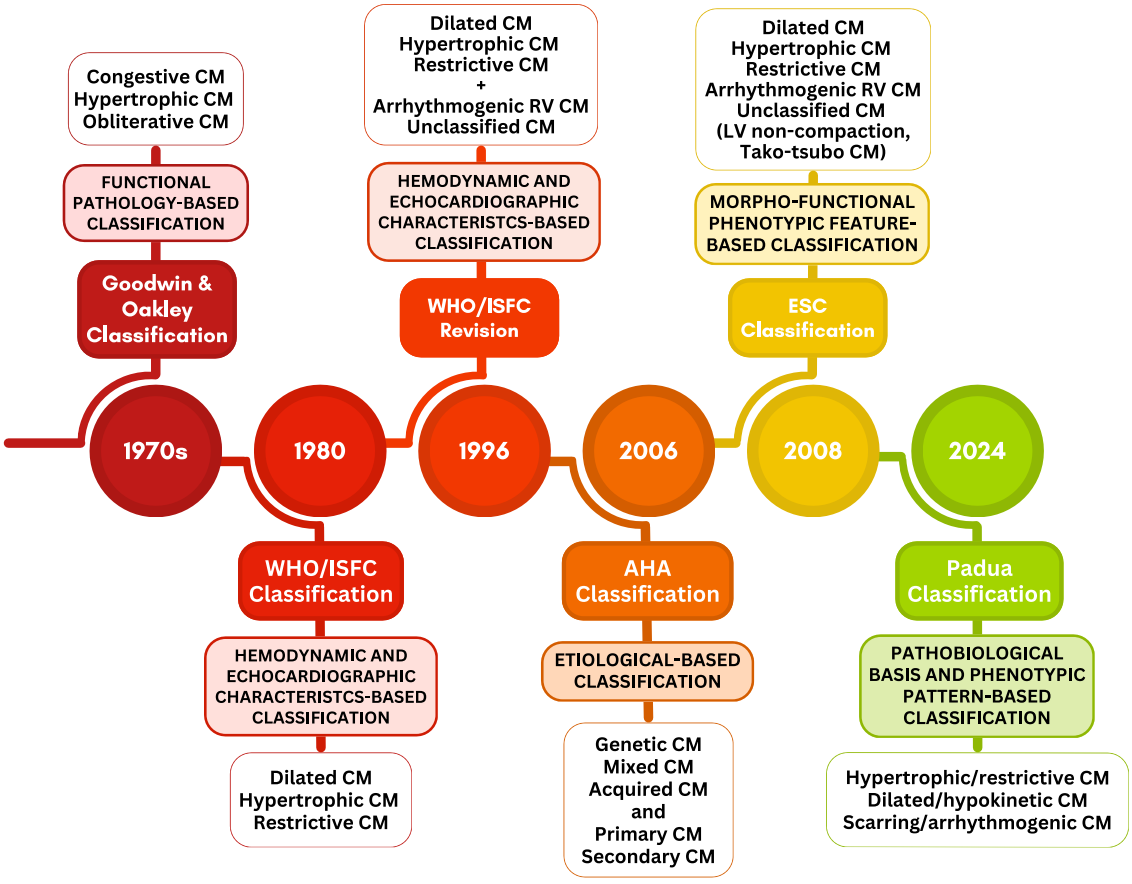

Figure 1 **Evolution of Cardiomyopathy Classification.** This flowchart illustrates the main steps of development of cardiomyopathy classification from the 1970s to 2024. The initial classification of Goodwin and Oakley in the 1970s was followed by those of the World Health Organization (WHO) and International Society and Federation of Cardiology in 1980 and 1996. In 1996, the classification endorsed by the WHO included: dilated, hypertrophic, restrictive, and arrhythmogenic right ventricular cardiomyopathies. In 2006, the American Heart Association task force proposed a classification of cardiomyopathies, which included ion channelopathies and distinguished conditions primarily involving the heart (genetic, acquired, or mixed aetiology) from conditions secondarily affecting the heart in the setting of systemic diseases. In 2008, the European Society of Cardiology proposed a classification of cardiomyopathies, which excluded ion channelopathies, separated familial vs. non-familial conditions, and sub-divided specific disease and idiopathic. The 2024 'Padua Classification' grouped cardiomyopathies into three main categories: *Hypertrophic/Restrictive, Dilated/Hypokinetic and Scarring/Arrhythmogenic, on the basis of distinctive pathobiology* and morpho-functional ventricular remodelling. AHA, American Heart Association; CM, cardiomyopathy; ESC, European Society of Cardiology; ISFC; International Society and Federation of Cardiology; WHO, World Health Organization.

cellular level of expression of abnormal encoded proteins.[4] On the front of cardiac imaging, one of the most remarkable advance was the ability of contrast-enhanced CMR to demonstrate myocardial scar tissue by the late gadolinium enhancement (LGE) technique.[5]

In previous classification of cardiomyopathies heart muscle diseases were separated in categories on the basis of either morphological features (i.e. hypertrophic and dilated) or functional abnormalities (i.e. restrictive and arrhythmogenic), which are not mutually exclusive.[6,7] This approach created confusion because the same condition may pertain to different categories. For instance, HCM with a restrictive physiology can be classified either as 'hypertrophic' or 'restrictive' cardiomyopathy (RCM).

This article provides the rational for an updated definition and classification of cardiomyopathies that rely on the combination of the distinctive pathobiological basis (genetics, molecular biology, and pathology) and the phenotypic features (morpho-functional and structural ventricular remodelling), leading to the proposal of three different disease categories, each with a combined designation based on both 'anatomic' and 'functional' phenotypic features: hypertrophic/restrictive cardiomyopathy (H/RC), dilated/hypokinetic cardiomyopathy (D/HC) and scarring/arrhythmogenic (S/AC).

Definition and classification

According with the Padua perspectives, cardiomyopathies are defined as 'diseases primarily affecting the myocardium which are characterized by *permanent* structural and functional heart abnormality.' From the definition of cardiomyopathies are excluded those heart diseases in which the myocardial disorder is not a primary event but occurs secondarily to coronary artery disease, hypertensive heart disease, valvular disease, or congenital heart disease. Although the original (prototype) cardiomyopathy phenotype is genetically determined, a number of non-genetic diseases ('phenocopies') may exhibit phenotypic features, which closely resemble those of the inherited aetiologic variant. In a sizeable proportion of cases, the cause of the disease may be not-identifiable

('idiopathic'). Accordingly, each cardiomyopathy phenotype is sub-classified into genetic and non-genetic variants and non-genetic cardiomyopathies are further sub-divided into variants with an identifiable cause and idiopathic forms. The heart muscle involvement may occur in isolation or part of a generalized multi-organ disease.

Beside myocardial involvement secondarily to ischaemia, hypertension, valvular defects, or congenital abnormalities, not included in this definition of are conditions such as acute myocarditis, takotsubo syndrome, and left ventricular non-compaction. Also, the ventricular remodelling caused by electrical dyssynchrony and tachycardiomyopathies does not fit with the proposed definition of cardiomyopathy. Finally, despite their genetic origin, primarily electrical abnormalities such as cardiac ion channel diseases are excluded from this definition that is focused on heart muscle diseases with structural heart abnormalities.

The 'Padua classification' includes three distinctive categories of cardiomyopathies based on updated knowledges on pathobiology, pathophysiology, clinical manifestations, imaging features and outcomes. These categories result from re-grouping cardiomyopathies: (i) by *merging* HCM and RCM into the same cardiomyopathy category; and (ii) by *splitting* dilated cardiomyopathy (DCM) and arrhythmogenic cardiomyopathy (ACM) into two separate cardiomyopathy categories.

The classification includes:

(1) The *hypertrophic/restrictive* (H/RC) cardiomyopathies that include genetic heart muscle disorders from genetically defective sarcomeric and non-sarcomeric proteins (storage and infiltrative diseases) and non-genetic phenocopies, manifesting with the phenotypic pattern of left ventricle (LV) diastolic dysfunction, with no or variable degree of ventricular hypertrophy.[8,9]
(2) The *dilated/hypokinetic* (D/HC) cardiomyopathies that include genetic heart muscle disorders from a variety of defective genes encoding for proteins of cytoskeleton, sarcomere, nuclear envelope and intercalated discs, and non-genetic phenocopies, manifesting with the phenotypic pattern of LV dilatation and/or systolic dysfunction because of intrinsic impairment of myocytes force generation/transmission.[10]
(3) The *scarring/arrhythmogenic* (S/AC) cardiomyopathies that include genetic heart muscle disorders from genetically defective intercalated discs/desmosomal proteins and non-genetic phenocopies, manifesting with the phenotypic pattern of prominent non-ischaemic myocardial scarring of the LV, right ventricle (RV), or both, which underlies scar-related ventricular arrhythmias and may lead to impairment of systolic function because of the underlying loss of myocardium caused by myocyte death.[11,12] It is noteworthy that the proposed classification refers to the original phenotype of the specific condition, because any cardiomyopathy may progress over time from the initial stage to a more advanced disease with the development or worsening of the ventricular systolic function and the ensuing *ventricular dilation* to compensate the decline of heart pump performance with preservation of the stroke volume (Starling's law).

This classification of cardiomyopathies is in agreement with the original definition of 'primary heart muscle disease of unknown aetiology', whose phenotype reproduces the patterns of cardiac remodelling (i.e. changes in the size, shape, structure, and function) caused by conditions of known aetiology such as myocardial infarction, hypertensive heart disease, valvular diseases, and congenital heart diseases (*Figure 2*).

Hypertrophic/restrictive cardiomyopathy (H/RC)

The functional abnormality common to HCM and RCM is the impairment of the LV diastolic filling that causes the increase of end-diastolic ventricular pressure and often underlies symptomatic HF.[8,14,15] Although in patients with HCM the HF can be associated with LV outflow obstruction (with or without mitral insufficiency) or LV systolic dysfunction ('end stage') with reduced ejection fraction (HFrEF), up to half of patients have a non-obstructive disease with preserved ejection fraction and their HF is caused by the diastolic dysfunction (HFpEF).[16]

Across the R/HC spectrum, the restrictive LV filling pattern may show different degree of severity, in combination or independently of the increase of wall thickness. Traditionally, at one end of the spectrum, LV wall thickness ≥15 mm with mild to moderate diastolic dysfunction has been labelled as 'HCM'[8]; at the other end of the spectrum, LV wall thickness <15 mm with restrictive physiology as 'restrictive cardiomyopathy'[14]; and in the middle of the spectrum, LV wall thickness ≥15 mm with severe diastolic dysfunction as 'HCM with restrictive phenotype'.[17] According to the newly proposed classification, HCM and RCM are considered as part of a continuous spectrum of the same sarcomeric heart muscle disease named H/RC, which include HCM, HCM with restrictive physiology, and RCM phenotypes, rather than as separate conditions with different designations based on arbitrary cut-off values of the LV wall thickness (*Figure 3*).

Besides the morpho-functional remodelling, the rationale of unifying H/RCs relies on their common genetic background and histopathologic features. Both genetic HCM and RCM have been classified as 'sarcomeric cardiomyopathies'.[3,4] With the exception of rare non-sarcomeric variants, RCM shares with HCM the disease-causative variants of sarcomeric genes, such as myosin binding protein C (*MYBPC3*), beta myosin heavy chain (*MYH7*), cardiac troponin I (*TNNI3*), and troponin T (*TNNT2*); less frequent defective genes include cardiac alpha actin (*ACTC*), alfa tropomyosin 1 (*TPM1*), and myosin light chain 2 (*MYL2*) and 3 (*MYL3*).[18-23] Of note, *TNNI3*, *MYL7*, and *MYL2* variants were reported as responsible for some familial cases of HCM with 'restrictive phenotype'.[24,25] The coexistence of HCM and RCM phenotypes in the same family with the same disease-causing variant provides additional support to the concept that HCM and RCM represent parts of a continuum phenotypic spectrum of a unique genetic cardiomyopathy.[26,27]

The histopathological features of RCM closely overlap those of HCM, showing a high prevalence of myocardial disarray and interstitial fibrosis.[27-29] Myocyte disarray was reported in around 50% of patients and interstitial fibrosis in the vast majority of cases (80–100%)[20,27,28,30-34] (*Figure 4*). The available evidence indicates that myocardial fibrosis, either interstitial and replacement-type, is the primary cause of diastolic dysfunction and

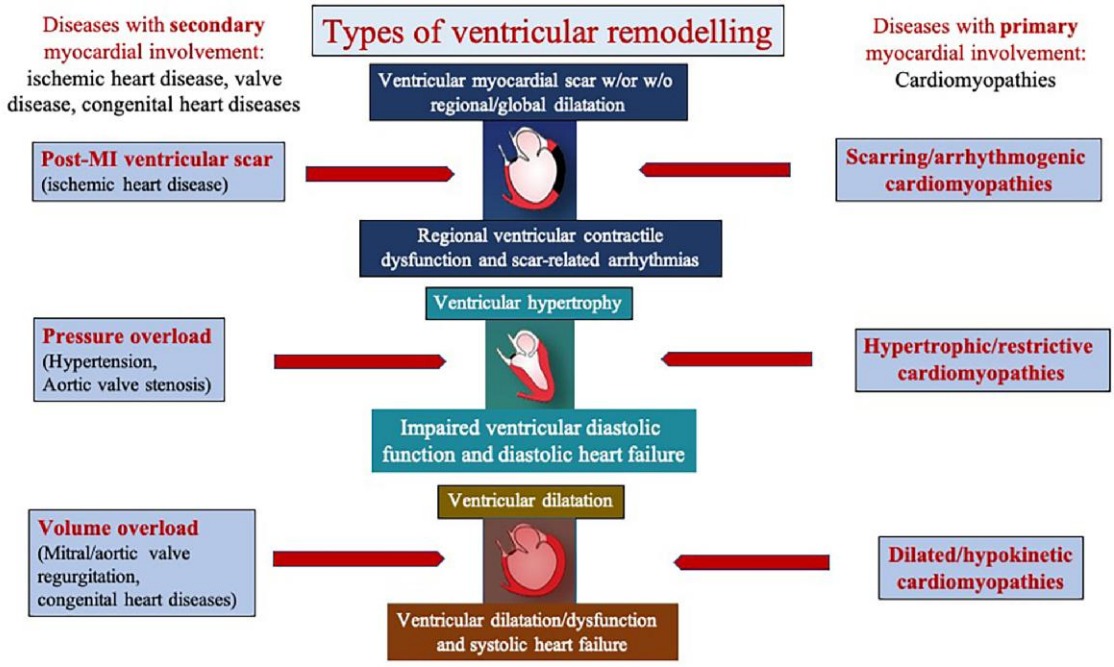

Figure 2 **Cardiomyopathy phenotypes and patterns of cardiac remodelling.** The 'Padua classification' of cardiomyopathy is in agreement with the original definition of 'primary heart muscle disease of unknown aetiology', whose phenotype reproduces the patterns of cardiac remodelling (i.e. changes in the size, shape, structure, and function) caused by conditions of known aetiology such as myocardial infarction, hypertensive heart disease, valvular diseases, and congenital heart diseases. The original phenotype of hypertrophic/restrictive reproduces the cardiac remodelling induced by systemic hypertension or aortic stenosis leading to haemodynamic pressure overload; the phenotype of dilated/hypokinetic the cardiac remodelling induced by mitral or aortic regurgitation leading to haemodynamic volume overload; and the phenotype of scarring/arrhythmogenic the cardiac remodelling of post-infarction myocardial scar leading to ventricular arrhythmias and ventricular systolic dysfunction/dilatation as a function of the amount of the post-necrotic reduction of myocardial mass. Adapted from *Corrado et al.*[13].

account for clinical progression from compensated ventricular hypertrophy to heart failure. The involved pathophysiological mechanisms consist of rising of LV end-diastolic pressure with aggravation of diastolic dysfunction and further reduction of coronary perfusion pressure, which in turn, causes microvascular ischaemia by intramyocardial obstructive small vessels disease, leading to myocyte necrosis and making worse the replacement myocardial fibrosis as a repair process.[36] In a sub-group of patients with advanced disease and large myocardial replacement by myocardial fibrosis, HCM may progress to 'end-stage' LV remodelling characterized by severe wall thinning, systolic dysfunction, and increased cavity size.[8,37]

That HCM and RCM are variants of the same cardiomyopathy phenotype is further supported by the finding that non-sarcomeric aetiologic variants, either infiltrative (cardiac amyloidosis) or storage (Anderson-Fabry disease and glycogen storage diseases) diseases may show either a predominantly hypertrophic or restrictive phenotypic pattern, according to variable degree of LV wall thickness and filling pattern.[38]

It is noteworthy that the restrictive physiology may be induced by other non-genetic conditions specifically leading to endocardial pathology such as Loeffler endocarditis and endomyocardial fibrosis, drug-induced endocardial fibrosis or carcinoid heart disease, and radiations.[29] Moreover, an increase of the restrictive pattern may occur in the late phase of the clinical course of HCM ('end-stage HCM').[17]

Dilated/hypokinetic cardiomyopathy (D/HC)

The phenotype of D/HC is characterized by LV dilatation and systolic dysfunction that are not explained by abnormal LV overload induced by hypertension, valvular disease, and congenital heart disease loading or coronary artery disease.[3,6,7] The primary mechanism involved in the pathogenesis of D/HC is impairment of myocardial contractility, which is a stimulus to compensatory LV remodelling, consisting of ventricular dilatation with eccentric hypertrophy.[10] The genetic aetiology (in ~30% of cases) consists of pathogenic variants of genes that encode components of a large variety of cellular compartments and pathways, predominantly of the cytoskeleton, followed by the sarcomere, the nuclear envelope, and the calcium handling.[10,39] Experimental studies of genetically determined disease phenotype identified several mechanisms potentially involved in the generation of the impaired myocyte contractility. These include disruption of energy production and consumption, abnormal nuclear integrity, transcriptional dysregulation, altered metabolic profiles, altered protein degradation, and abnormal calcium homoeostasis and handling, leading to a final outcome of altered force generation and transmission.[10,39] When present (<50% of cases), patchy myocardial fibrosis occurs in D/HC as a consequence of the primary myocardial dysfunction/ventricular remodelling, due to a superimposed process of focal myocyte death *secondarily* induced by mechanical, ischemic, or metabolic myocardial injuries and impacts marginally the ventricular systolic function.[10,39,40]

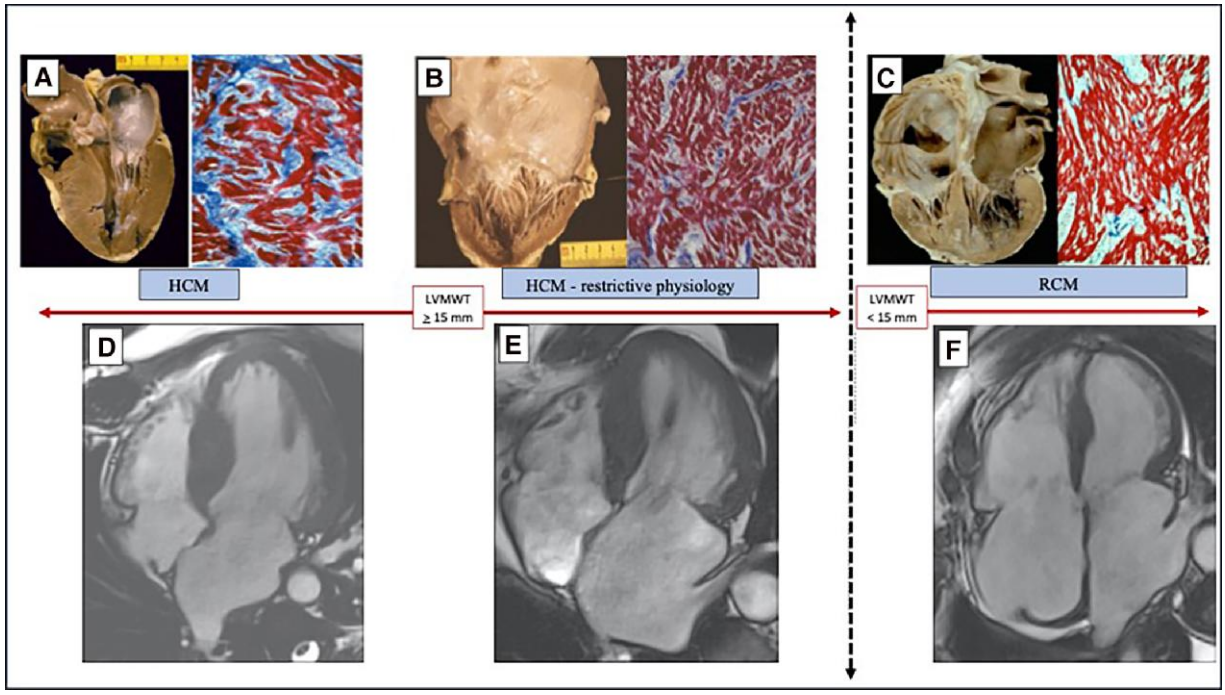

Figure 3 Pathologic and cardiac magnetic resonance (CMR) imaging features of hypertrophic/restrictive (H/RC) phenotypic variants. HCM and RCM are no longer considered two distinct entities on the basis of arbitrary cut offs in the left ventricle (LV) wall thickness (dotted vertical black line), but phenotypic variants of the same genetically determined *sarcomeric* heart muscle disease manifesting with variable degrees of LV hypertrophy and LV diastolic dysfunction. The spectrum of genetically determined H/RC, encompasses HCM with mild to moderate diastolic dysfunction (*A*, *B*), HCM with restrictive physiology (*C*, *D*), and RCM (*E*, *F*) phenotypes (continuous horizontal red line). Note that myocardial disarray and interstitial fibrosis are common histopathologic features to the different phenotypic variants (*A*, *C*, *E*). Note the increasing left atrial dilatation (from *B* to *D* and *F*) as an indirect sign of augmented diastolic filling pressure in the CMR four chamber view sequences of HCM (*B*), HCM with restrictive physiology (*D*) and RCM (*F*). Adapted from Corrado *et al.*[13].

Conditions characterized by LV systolic dysfunction with no (hypokinetic, non-dilated cardiomyopathy; HNDC)[41] or mild (mildly dilated cardiomyopathy)[42] LV dilatation have been reported to account for up to one-third of cases of D/HCs. These phenotypic variants have been considered as early or minor forms of D/HC on the limited basis of morpho-functional features evidenced by echocardiography, without taking into account new and crucial information coming from myocardial tissue characterization by gadolinium-enhanced CMR that leads to re-classify most of cases as arrhythmogenic left ventricular cardiomyopathy (ALVC).[39-41]

The aetiology of D/HC also includes non-genetic causes, which lead to a phenotype closely resembling that of the genetically induced prototype. These include chronic inflammation (infections and autoimmunity), drugs, toxic agents, endocrinology diseases, nutritional deficiency, and 'peripartum' status (*Table 1*).[10,41]

The condition referred to as 'inflammatory DCM' is characterized by LV dilatation and systolic dysfunction due to *chronically* active inflammation of the myocardium that needs to be demonstrated on histopathology/immunocytochemistry investigation by endomyocardial biopsy or at post-mortem.[7,43] Inflammatory D/HC must be distinguished from 'post-inflammatory' disease, characterized by the *sequelae* of myocardial inflammation consisting of sub-epicardial–mid-myocardial fibrosis, which occurs as the healing process of a previous acute myocardial injury with myocardial loss, and thus fulfilling the criteria for appropriate inclusion among phenocopies (i.e. acquired aetiologic variants) of S/AC.[44-46]

Scarring/arrhythmogenic cardiomyopathy (S/AC)

The pathogenesis of scarring/arrhythmogenic cardiomyopathy (S/AC) consists of loss of ventricular myocardium due to myocyte death with subsequent replacement by fibrous (or fibro-fatty) scar tissue (like a post-myocardial infarction scar).[47-51] The myocardial scarring pre-disposes to potentially lethal ventricular arrhythmias and may cause the impairment of ventricular systolic function.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) was the original disease phenotype characterized by early and predominant RV involvement, with no or mild LV disease.[11] Insights arising from post-mortem investigations, genotype–phenotype correlation studies and myocardial tissue characterization by contrast-enhanced CMR showed that the disease often involves the LV.[48-56] Accordingly, the designation of ARVC has been progressively replaced by that of 'arrhythmogenic cardiomyopathy' (ACM), which better reflects the expanding phenotypic disease spectrum, which also includes left-sided variants, i.e. biventricular (ABVC) and predominant-left (also referred to as ALVC).[12,29]

The introduction of myocardial tissue characterization by contrast-enhanced CMR has provided important new insights into our understanding of the different phenotypic

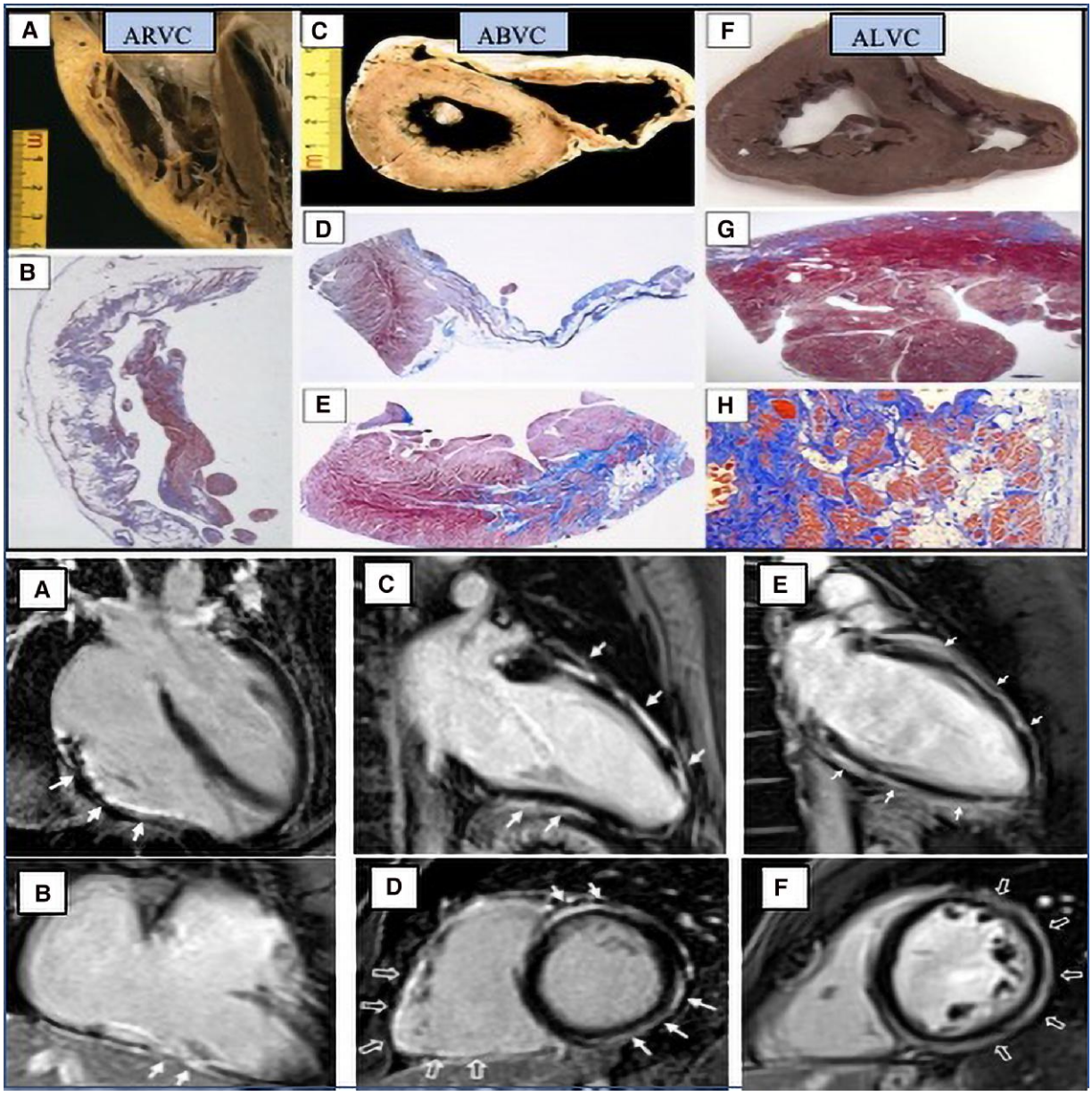

Figure 4 Pathologic and cardiac magnetic resonance (CMR) imaging features of scarring/arrhythmogenic phenotypes. Arrhythmogenic right ventricular cardiomyopathy phenotypic variant. Top left: Macroscopic longitudinal section of the heart showing apicobasal and transmural right ventricular myocardial scarring (*A*). Panoramic histologic view of the right ventricular (RV) free wall showing full-thickness myocardial loss with replacement by fibrous and fatty tissue, with residual myocardium confined to the endocardial trabeculae (trichrome stain) (*B*). Bottom left: Post-contrast CMR images showing late gadolinium enhancement (LGE)/fibrous replacement (solid arrows) of RV free wall in both long-axis 4-chamber view (*A*) and the sagittal view (*B*). ABVC phenotypic variant. Top mid: Macroscopic transverse section of the heart showing infundibular and inferior sub-tricuspidal aneurysms (*C*). Panoramic histological view of the inferior aneurysm showing wall thinning with transmural fibro-fatty myocardial replacement (*D*). Panoramic histological view showing sub-epicardial fibro-fatty scar of the left ventricular free wall (*E*). Bottom mid: Post-contrast images—long-axis 2-chamber view (*C*) and short-axis view (*D*) showing LGE/myocardial fibrosis from basal to apical anterolateral and inferolateral LV wall segments and RV free wall (solid arrows). ALVC phenotypic variant. Top right: Macroscopic transverse section of the heart showing a whitish, thin, linear discoloration in the LV posterior-lateral wall, involving the sub-epicardial and mid-mural myocardial layers (*F*). Histologic examination showing sub-epicardial/mid-myocardial fibrous (*G*) and fibro-fatty (*H*) myocardial replacement. Bottom right: Post-contrast long-axis 2-chamber view (*E*) showing LV sub-epicardial LGE (solid arrows), extending from basal-to-apical segments. Post-contrast short-axis view showing the involvement of the LV free wall and the septum ('ring-like' pattern) (open arrows) (*F*). ACM, arrhythmogenic cardiomyopathy; ALVC, arrhythmogenic left ventricular cardiomyopathy; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement. Adapted from Corrado *et al*.[35].

features of left-sided variant of S/AC vs. D/HC.[39,40,57] The presence, distribution and amount of LGE/myocardial scar differ according to the different inner nature of these heart muscle disorders, that were previously indiscriminately diagnosed as dilated cardiomyopathy on the basis of morpho-functional echocardiographic features, and allow to differentiate the '*scarring*' phenotype of left sided S/AC (ALVC) from the *non-scarring*' one of D/HC.[35,40,44,57-62] The new cardiomyopathy classification was the ideal context to propose the updated designation of 'S/AC' that specifically

Table 1 **Aetiologic classification of cardiomyopathies. Adapted from Corrado *et al.*[13].**

Aetiology	Hypertrophic/restrictive cardiomyopathy	Dilated/hypokinetic cardiomyopathy	Scarring/arrhythmogenic cardiomyopathy
Genetic aetiologies	Sarcomeric gene defects (*MYBPC3*, *MYH7*, *TNNI3*, *TNNT2*, *TPM1*, *ACTC1*, *MYL2*, *MYL3*) Non-sarcomeric gene defects: Glycogen storage diseases (GSD II, 'Pompe's disease'; GSD III, 'Forbes' disease'; AMP kinase, WPW/HCM) Lysosomal storage diseases (Anderson-Fabry disease, Hurler's syndrome) Disorders of fatty acid metabolism Mitochondrial cytopathies (MELAS, MERFF, LHON) Syndromic genetic disease (Noonan's syndrome, LEOPARD syndrome, Friedreich's ataxia) Infiltrative disease (transthyretin amyloidosis) Desminopathy Pseuxanthoma elasticum Inherited haemochromatosis	Sarcomeric gene defects (*TTN*, MYH7, *MYBPC3*, *TNNT2*, *TNNI3*) Nuclear membrane gene defects (*LMNA*) Cytoskeletal gene defects (*PLN*) Myopalladin (*MYPN*) Sodium channel α-unit (*SCN5A*) Mitochondrial cytopathy	Desmosomal gene defects (*PKP2*, *DSP*, *DSC2*, *DSG2*) Non-desmosomal gene defects (*PNL*, *FLNC*, *DES*, *LMNA*) Neuromuscular disorders (*DMD*-Duchenne muscular dystrophy, *DMD*-Becker muscular dystrophy; *DMPK*-Myotonic dystrophy or Steinert)
Non-genetic Aetiologies	Obesity Endocrine (infants of diabetic mothers, acromegaly) Infiltrative disease (AL amyloidosis) Acquired haemochromatosis (high parenteral iron administration) Scleroderma Endomyocardial diseases (Endomyocardial fibrosis, hypereosinophilic syndrome, carcinoid heart disease, metastatic cancers, drugs, radiation)	Chronic Inflammation (viral, autoimmune) Peripartum Drugs (doxorubicin, anthracyclines, and trastuzumab) Endocrine (hypothyroidism /hyperthyroidism, diabetes) Nutritional (Thiamine deficiency 'Beri-Beri') Toxic (alcohol, cocaine)	Post-inflammatory (viral, toxic, and autoimmune) Sarcoidosis Parasitic infectious (Chagas' disease)
Unknown aetiology	Idiopathic	Idiopathic	Idiopathic

reflects the disease phenotype distinctively characterized by fibrous (or fibro-fatty) ventricular scar replacing the post-necrotic myocardial loss, which is common to the disease phenotypic varieties, i.e. involving the RV, the LV, or both ventricles (*Figure 4*).[44]

In 2019, an International Expert report[63] critically reviewed the 2010 Task Force (TF) diagnostic criteria[58] that exclusively targeted the original RV phenotype and did not include findings by gadolinium-enhanced CMR for detection of myocardial scar, which are determinant for an accurate characterization of the LV phenotype.[4,59] In 2020, an International consensus document provided upgraded criteria (the 'Padua criteria') for the diagnosis of the entire phenotypic spectrum of the disease, with the introduction of specific diagnostic criteria for the LV phenotype[60]; in 2023, these upgraded diagnostic criteria were refined by a European Task Force consensus document.[35] According to the 2020 and 2023 upgraded criteria, the diagnosis of both right- and left-sided variants of S/AC is based on the same multi-parametric approach recommended by the 2010 TF scoring system, with six categories of criteria, which encompass morpho-functional ventricular abnormalities, structural myocardial tissue alterations, ECG changes of ventricular depolarization and repolarization, ventricular arrhythmias, and familial and genetic findings.[35,58,60,61]

Similarly to H/RC and D/HC, the 2023 European Task Force consensus document proposed an aetiologic classification based on the clinical evidence that S/ACM is an 'umbrella term', which comprises a spectrum of conditions of different aetiologies, either genetic or non-genetic, involving the RV, the LV or both, whose common denominator is the prominent non-ischaemic ventricular myocardial scarring and the scar-related ventricular arrhythmias (*Table 1*).[35,62]

Pathogenic variants of genes encoding desmosomal proteins are the most frequent cause of inherited S/AC, accounting for up to 50% of disease in probands. Family clinical screening followed by molecular genetic testing in case of proven or suspected inheritable S/AC is a key step to diagnose the genetic defect, either desmosomal or non-desmosomal, or to identify a familial but 'gene elusive' condition. Most of the disease-causing genes encode structural proteins that are involved in the organization of intercellular junctions, most frequently cardiac desmosomal proteins such as plakophilin, desmoplakin, desmoglein, and desmocollin and rarely (<1%) adherens junctional proteins of the 'area composita', such as α-T-catenin and N-cadherin.[19,35] The S/AC phenotype may be caused by non-desmosomal genes defects ('genocopies') including pathogenic variants of

Table 2 Differential diagnosis between ALVC and D/HC

	ALVC	D/HC
Predominant genetic background	Mutations of genes encoding for desmosomal proteins, phospholamban, and filamin C.	Mutations of genes encoding for cytoskeleton, muscular sarcomere, and nuclear envelope proteins.
Main clinical manifestations	Palpitations, syncope, and cardiac arrest.	Heart failure and cardiac arrest.
ECG abnormalities	Low QRS voltages in limb leads; negative T-waves in infero-lateral leads.	Left ventricular hypertrophy with a strain pattern of ST segment; LBBB.
Echocardiography and CMR imaging features	Non-dilated and hypokinetic LV with a large amount of non-ischaemic LGE (sub-epicardial/mediomural) mostly involving the inferolateral LV wall or circumferentially most LV segments ('ring-like' pattern) Regional hypoakinesia w/wo wall thinning Systolic LV dysfunction related to the global extent of LGE.	Dilated and hypokinetic LV with no or patchy non-ischaemic (mid-myocardial) LGE (septum). No regional wall motion abnormalities. Systolic LV dysfunction unrelated to the global extent of LGE.
Histopathological features	Fibrofatty myocardial replacement of myocardial loss because of myocyte death ('gross' myocardial scar).	Preserved myocytes with non-specific abnormalities. Patchy interstitial and or replacement fibrosis (no 'gross' myocardial scar).
Types of ventricular arrhythmias	PVBs, NSVT, and monomorphic sustained VT (RBBB pattern; both LBBB and RBBB patterns in biventricular form); VF.	PVBs and NSVT (RBBB pattern); uncommon sustained VT; VF.
Arrhythmogenic mechanisms	Scar-related re-entry and/or hypersensitivity to catecholamines with adrenergic-dependent ventricular arrhythmias.	Scar-unrelated arrhythmogenesis (hypodynamic impairment or functional branch to branch re-entry).
Most common site of VT origin	Sub-epicardial inferolateral LV free wall.	Intramural septum.

ALVC, arrhythmogenic left ventricular cardiomyopathy; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; D/HC, dilated/hypokinetic; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricle; NSVT, non-sustained ventricular tachycardia; PVBs, premature ventricular beats; RBBB, right bundle branch block; VF, ventricular fibrillation; VT, ventricular tachycardia. Adapted from Corrado *et al.*[63]

phospholamban (*PLN*), filamin C (*FLNC)*, desmin (*DES*), titin (*TTN*), and lamin A/C (*LMNA*) genes; defects of non-desmosomal genes such as transmembrane protein 43 (*TMEM43*) and transforming growth factor beta-3 (*TGFβ-3*) genes are uncommonly identified. The original phenotype expressed by the genetic forms of S/AC may be reproduced by acquired forms (phenocopies) that fulfil the diagnostic criteria for either right or left-sided variants (*Table 1*).[5,35] Inflammatory cardiomyopathies, such as post-viral myocarditis, cardiac sarcoidosis, and cardiomyopathies associated with autoimmune multi-system diseases, may exhibit a phenotype, which closely resembles that of inherited ACM ('phenocopies') and fulfils the diagnostic score. Targeted clinical work-up, based on disease-specific tests and diagnostic criteria is needed for aetiologic characterization of these ACM phenocopies (for instance fludeoxyglucose uptake by positron emission tomography for cardiac sarcoidosis or biochemical and metabolic laboratory investigation for autoimmune disease). In the aetiologic assessment may be of help to evaluate whether the disease is confined to the heart or occurs in the context of multi-organ involvement (for instance, neuromuscular diseases, sarcoidosis, or autoimmune systemic diseases). It is noteworthy that non-genetic S/AC with clinical and imaging findings fulfilling the disease diagnostic criteria cannot be diagnosed presumptively as post-myocarditis in the absence of a prior history of a 'clinically proven' acute myocarditis. Hence, a sizeable proportion of cases showing negative medical history and genetic testing, are diagnosed as 'idiopathic' S/AC, that means a disease phenotype meeting diagnostic criteria, whose aetiology remains unknown after thorough clinical and genetic evaluation. 'Idiopathic' forms may account for more than half of cases of left-sided variants, a finding that further supports the concept that the S/AC diagnosis has to be made on the basis on disease-specific phenotypic features, even in case of unknown aetiology.[35,61]

Differential diagnosis between the ALVC variant of S/AC and D/HC is summarized in *Table 2*.

Therapeutic implications and conclusions

The clinical application of the newly proposed Padua classification may help to design a targeted cardiomyopathy-specific clinical management and evaluation of outcomes of affected patients.

Merging into the unique group of H/RC those cardiomyopathies exhibiting a restrictive functional phenotype associated with variable degree of LV hypertrophy have promising management implications. In this regard, the new pharmacologic treatment with sodium–glucose cotransporter 2 inhibitor (SGLT2i) therapy has been shown to reduce the risk of worsening heart

failure or cardiovascular death among patients with HFpEF due to LV diastolic dysfunction.[62] Moreover, ongoing studies are testing the biologic and clinical benefits of cardiac myosin inhibitors in patients with non-obstructive HCM who have heart failure due to diastolic dysfunction, like that observed in the all phenotypic variants of H/RC.[64,65] The awareness that cardiac transthyretin (ATTR) amyloidosis is a H/RC phenocopy may increase the diagnosis of this condition in the presence of either a predominantly hypertrophic or restrictive phenotypic pattern and lead to successful treatment using the available and future 'disease-modifying' therapies.[66]

The differentiation between left-sided S/AC and D/HC is clinically crucial, because the treatment of patients with S/AC mostly focuses on prevention of life-threatening ventricular arrhythmias and sudden cardiac death (SCD), while management of patients with D/HC mainly aims at relieving heart failure symptoms and improving exercise capacity and outcomes. The cardinal clinical manifestation of DCM is HF; malignant ventricular arrhythmias usually occur in advanced disease in association with severe LV contractile impairment. Instead, the prognosis of S/AC primarily depends on the malignancy of ventricular arrhythmias, which can lead to arrhythmic cardiac arrest and death every time over the disease course.[59,67] At variance with D/HC, the pathogenesis of life-threatening ventricular arrhythmias in the ALVC variant of S/AC extends beyond the severe depression of LV systolic function, being strongly related to the large amount of myocardial fibrosis, which is an independent arrhythmogenic risk factor.[59,60,67] Thus, the implantable defibrillator therapy for primary prevention of SCD in patients with left-sided S/AC should be considered earlier in the disease course, when the degree of LV systolic dysfunction is still mild or moderate.[13,36,59,63,67]

Although current treatment of cardiomyopathies is largely *palliative* and based on drugs, catheter ablation, device or surgical interventions aimed to prevent and manage heart failure and malignant arrhythmias, the proposed classification may stimulate future research to focus on the improvement of our knowledge of the basic mechanisms involved in the onset and progression of pathobiologically different groups of cardiomyopathies, which is an essential condition for the development of disease-specific *curative* therapy.

Funding

None.

Conflict of interest: None declared.

Data availability

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

References

1. Goodwin JF, Oakley CM. The cardiomyopathies. *Br Heart J* 1972;**34**:545–552.
2. Braunwald E. Cardiomyopathies: an overview. *Circ Res* 2017;**121**:711–721.
3. McKenna WJ, Maron BJ, Thiene G. Classification, epidemiology, and global burden of cardiomyopathies. *Circ Res* 2017;**121**:722–730.
4. Thiene G, Corrado D, Basso C. Revisiting definition and classification of cardiomyopathies in the era of molecular medicine. *Eur Heart J* 2008;**29**:144–146.
5. Kramer CM. Role of cardiac MR imaging in cardiomyopathies. *J Nucl Med* 2015;**56 Suppl 4**:39S–45S.
6. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D *et al*. Contemporary definitions and classification of the cardiomyopathies. An American Heart Association scientific statement from the council on clinical cardiology, heart failure and transplantation committee; quality of care and outcomes research and functional genomics and translational biology interdisciplinary working groups; and council on epidemiology and prevention. *Circulation* 2006;**113**:1807–1816.
7. Elliott P, Anderson B, Arbustini E, Bilinska Z, Cecchi F, Charron P *et al*. Classification of cardiomyopathies: a position statement from the European working group on myocardial and pericardial diseases. *Eur Heart J* 2008;**29**:270–276.
8. Marian AJ, Braunwald E. Hypertrophic cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. *Circ Res* 2017;**121**:749–770.
9. Muchtar E, Blauwet LA, Gertz MA. Restrictive cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. *Circ Res* 2017;**121**:819–837.
10. Weintraub RG, Semsarian C, Macdonald P. Dilated cardiomyopathy. *Lancet* 2017;**390**:400–414.
11. Corrado D, Link MS, Calkins H. Arrhythmogenic right ventricular cardiomyopathy. *N Engl J Med* 2017;**376**:61–72.
12. Corrado D, Basso C, Judge DP. Arrhythmogenic cardiomyopathy. *Circ Res* 2017;**121**:784–802.
13. Corrado D, Thiene G, Bauce B, Calore C, Cipriani A, De Lazzari M *et al*. The "Padua classification" of cardiomyopathies: combining pathobiological basis and morpho-functional remodeling. *Int J Cardiol* 2024;**418**:132571.
14. Sen-Chowdhry S, Jacoby D, Moon JC, McKenna WJ. Update on hypertrophic cardiomyopathy and a guide to the guidelines. *Nat Rev Cardiol* 2016;**13**:651–675.
15. Rapezzi C, Aimo A, Barison A, Emdin M, Porcari A, Linhart A *et al*. Restrictive cardiomyopathy: definition and diagnosis. *Eur Heart J* 2022;**43**:4679–4693.
16. Melacini P, Basso C, Angelini A, Calore C, Bobbo F, Tokajuk B *et al*. Clinicopathological profiles of progressive heart failure in hypertrophic cardiomyopathy. *Eur Heart J* 2010;**31**:2111–2123.
17. Kubo T, Gimeno JR, Bahl A, Steffensen U, Steffensen M, Osman E *et al*. Prevalence, clinical significance, and genetic basis of hypertrophic cardiomyopathy with restrictive phenotype. *J Am Coll Cardiol* 2007;**49**:2419–2426.
18. García-Hernández S, de la Higuera Romero L, Ochoa JP, McKenna WJ. Emerging themes in genetics of hypertrophic cardiomyopathy. Current status and clinical application. *Can J Cardiol* 2024;**40**:742–753.
19. Wilde AAM, Semsarian C, Márquez MF, Shamloo AS, Ackerman MJ, Ashley EA *et al*. Developed in partnership with and endorsed by the European heart rhythm association (EHRA), a branch of the European Society of Cardiology (ESC), the heart rhythm society (HRS), the Asia pacific heart rhythm society (APHRS), and the Latin American heart rhythm society (LAHRS). European heart rhythm association (EHRA)/heart rhythm society (HRS)/Asia pacific heart rhythm society (APHRS)/Latin American heart rhythm society (LAHRS) expert consensus statement on the state of genetic testing for cardiac diseases. *Europace* 2022;**24**:1307–1367.
20. Kaski JP, Syrris P, Burch M, Tomé-Esteban MT, Fenton M, Christiansen M *et al*. Idiopathic restrictive cardiomyopathy in children is caused by mutations in cardiac sarcomere protein genes. *Heart* 2008;**94**:1478–1484.
21. Wu W, Lu CX, Wang YN, Liu F, Chen W, Liu YT *et al*. Novel phenotype-genotype correlations of restrictive cardiomyopathy with myosin-binding protein c (mybpc3) gene mutations tested by next-generation sequencing. *J Am Heart Assoc* 2015;**4**:e001879.
22. Menon SC, Michels VV, Pellikka PA, Ballew JD, Karst ML, Herron KJ *et al*. Cardiac troponin T mutation in familial cardiomyopathy with variable remodeling and restrictive physiology. *Clin Genet* 2008;**74**:445–454.
23. Caleshu C, Sakhuja R, Nussbaum RL, Schiller NB, Ursell PC, Eng C *et al*. Furthering the link between the sarcomere and primary cardiomyopathies: restrictive cardiomyopathy associated with multiple mutations in genes previously associated with hypertrophic or dilated cardiomyopathy. *Am J Med Genet A* 2011;**155A**:2229–2235.
24. Mogensen J, Kubo T, Duque M, Uribe W, Shaw A, Murphy R *et al*. Idiopathic restrictive cardiomyopathy is part of the clinical expression of cardiac troponin I mutations. *J Clin Invest* 2003;**111**:209–216.

25. De Bortoli M, Vio R, Basso C, Calore M, Minervini G, Angelini A *et al*. Novel missense variant in MYL2 gene associated with hypertrophic cardiomyopathy showing high incidence of restrictive physiology. *Circ Genomic Precis Med* 2020;**13**:e002824.
26. Burke MA, Cook SA, Seidman JG, Seidman CE. Clinical and mechanistic insights into the genetics of cardiomyopathy. *J Am Coll Cardiol* 2016; **68**:2871–2886.
27. Angelini A, Calzolari V, Thiene G, Boffa GM, Valente M, Daliento L *et al*. Morphologic spectrum of primary restrictive cardiomyopathy. *Am J Cardiol* 1997;**80**:1046–1050.
28. Thiene G, Basso C, Calabrese F, Angelini A, Valente M. Twenty years of progress and beckoning frontiers in cardiovascular pathology: cardiomyopathies. *Cardiovasc Pathol* 2005;**14**:165–169.
29. Sheppard MN, van der Wal AC, Banner J, d'Amati G, De Gaspari M, De Gouveia R *et al*. Association for European cardiovascular pathology (AECVP). genetically determined cardiomyopathies at autopsy: the pivotal role of the pathologist in establishing the diagnosis and guiding family screening. *Virchows Arch* 2023;**482**:653–669.
30. Gewillig M, Mertens L, Moerman P, Dumoulin M. Idiopathic restrictive cardiomyopathy in childhood. A diastolic disorder characterized by delayed relaxation. *Eur Heart J* 1996;**17**:1413–1420.
31. Ammash NM, Seward JB, Bailey KR, Edwards WD, Tajik AJ. Clinical profile and outcome of idiopathic restrictive cardiomyopathy. *Circulation* 2000; **101**:2490–2496.
32. Hayashi T, Tsuda E, Kurosaki K, Ueda H, Yamada O, Echigo S *et al*. Electrocardiographic and clinical characteristics of idiopathic restrictive cardiomyopathy in children. *Circ J* 2007;**71**:1534–1539.
33. Russo LM, Webber SA. Idiopathic restrictive cardiomyopathy in children. *Heart* 2005;**91**:1199–1202.
34. Gambarin FI, Tagliani M, Arbustini E. Pure restrictive cardiomyopathy associated with cardiac troponin I gene mutation: mismatch between the lack of hypertrophy and the presence of disarray. *Heart* 2008;**94**: 1257.
35. Corrado D, Anastasakis A, Basso C, Bauce B, Blomström-Lundqvist C, Bucciarelli-Ducci C *et al*. Proposed diagnostic criteria for arrhythmogenic cardiomyopathy: European task force consensus report. *Int J Cardiol* 2024;**395**:131447.
36. Bariani R, Rigato I, Celeghin R, Marinas MB, Cipriani A, Zorzi A *et al*. Phenotypic expression and clinical outcomes in patients with arrhythmogenic cardiomyopathies. *J Am Coll Cardiol* 2024;**83**:797–807.
37. Olivotto I, Maron BJ, Appelbaum E, Harrigan CJ, Salton C, Gibson CM *et al*. Spectrum and clinical significance of systolic function and myocardial fibrosis assessed bycardiovascular magnetic resonance in hypertrophic cardiomyopathy. *Am J Cardiol* 2010;**106**:261–267.
38. Pereira NL, Grogan M, Dec GW. Spectrum of restrictive and infiltrative cardiomyopathies: part 1 of a 2-part series. *J Am Coll Cardiol* 2018;**71**: 1130–1148.
39. Cipriani A, Bauce B, De Lazzari M, Rigato I, Bariani R, Meneghin S *et al*. Arrhythmogenic right ventricular cardiomyopathy: characterization of left ventricular phenotype and differential diagnosis with dilated cardiomyopathy. *J Am Heart Assoc* 2020;**9**:e014628.
40. McNally EM, Mestroni L. Dilated cardiomyopathy: genetic determinants and mechanisms. *Circ Res* 2017;**121**:731–748.
41. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Böhm 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 myocardial and pericardial diseases. *Eur Heart J* 2016;**37**:1850–1858.
42. Gigli M, Stolfo D, Merlo M, Barbati G, Ramani F, Brun F *et al*. Insights into mildly dilated cardiomyopathy: temporal evolution and long-term prognosis. *Eur J Heart Fail* 2017;**19**:531–539.
43. Tschöpe C, Ammirati E, Bozkurt B, Caforio ALP, Cooper LT, Felix SB *et al*. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol* 2021;**18**:169–193.
44. Corrado D, Zorzi A, Cipriani A, Bauce B, Bariani R, Brunetti G *et al*. Scarring/arrhythmogenic cardiomyopathy. *Eur Heart J Suppl* 2023; **25**:C144–C154.
45. Thiene G, Corrado D, Nava A, Rossi L, Poletti A, Boffa GM *et al*. Right ventricular cardiomyopathy: is there evidence of an inflammatory aetiology? *Eur Heart J* 1991;**12**:22–25.
46. Vio R, Zorzi A, Corrado D. Myocarditis in the athlete: arrhythmogenic substrates, clinical manifestations, management, and eligibility decisions. *J Cardiovasc Transl Res* 2020;**13**:284–295.
47. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomyopathy and sudden death in young people. *N Engl J Med* 1988;**318**:129–133.
48. Basso C, Thiene G, Corrado D, Angelini A, Nava A, Valente M. Arrhythmogenic right ventricular cardiomyopathy. Dysplasia, dystrophy, or myocarditis? *Circulation* 1996;**94**:983–991.
49. Corrado D, Basso C, Thiene G, McKenna WJ, Davies MJ, Fontaliran F *et al*. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. *J Am Coll Cardiol* 1997;**30**:1512–1520.
50. Basso C, Bauce B, Corrado D, Thiene G. Pathophysiology of arrhythmogenic cardiomyopathy. *Nat Rev Cardiol* 2011;**9**:223–233.
51. Corrado D, Basso C, Pilichou K, Thiene G. Molecular biology and clinical management of arrhythmogenic right ventricular cardiomyopathy/ dysplasia. *Heart* 2011;**97**:530–539.
52. Miles C, Finocchiaro G, Papadakis M, Gray B, Westaby J, Ensam B *et al*. Sudden death and left ventricular involvement in arrhythmogenic cardiomyopathy. *Circulation* 2019;**139**:1786–1797.
53. Elliott PM, Anastasakis A, Asimaki A, Basso C, Bauce B, Brooke MA *et al*. Definition and treatment of arrhythmogenic cardiomyopathy: an updated expert panel report. *Eur J Heart Fail* 2019;**21**:955–964.
54. Sen-Chowdhry S, Syrris P, Ward D, Asimaki A, Sevdalis E, McKenna WJ *et al*. Clinical and genetic characterization of families with arrhythmogenic right ventricular dysplasia/cardiomyopathy provides novel insights into patterns of disease expression. *Circulation* 2007; **115**:1710–1720.
55. Sen-Chowdhry S, Syrris P, Prasad SK, Hughes SE, Merrifield R, Ward D et al Left-dominant arrhythmogenic cardiomyopathy: an under-recognized clinical entity. *J Am Coll Cardiol* 2008;**52**:2175–2187.
56. Marra MP, Leoni L, Bauce B, Corbetti F, Zorzi A, Migliore F *et al*. Imaging study of ventricular scar in arrhythmogenic right ventricular cardiomyopathy: comparison of 3D standard electroanatomical voltage mapping and contrast-enhanced cardiac magnetic resonance. *Circ Arrhythm Electrophysiol* 2012;**5**:91–100. 86. Marcus FI, Fontaine GH, Guiraudon G, et al. Right ventricular dysplasia: a report of 24 adult cases. *Circulation* 1982;65:384-98.
57. Cipriani A, Mattesi G, Bariani R, Cecere A, Martini N, De Michieli L *et al*. Cardiac magnetic resonance imaging of arrhythmogenic cardiomyopathy: evolving diagnostic perspectives. *Eur Radiol* 2023;**33**: 270–282.
58. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA *et al*. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/ dysplasia: proposed modification of the task force criteria. *Circulation* 2010;**121**:1533–1541.
59. Corrado D, Basso C. Arrhythmogenic left ventricular cardiomyopathy. *Heart* 2022;**108**:733–743.
60. Corrado D, Marra MP, Zorzi A, Beffagna G, Cipriani A, Lazzari M *et al*. Diagnosis of arrhythmogenic cardiomyopathy: the Padua criteria. *Int J Cardiol* 2020;**319**:106–114.
61. Corrado D, Zorzi A, Cipriani A, Bauce B, Bariani R, Beffagna G *et al*. Evolving diagnostic criteria for arrhythmogenic cardiomyopathy. *J Am Heart Assoc* 2021;**10**:e021987.
62. Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF *et al*. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *Lancet* 2022;**400**:757–767.
63. Corrado D, van Tintelen PJ, McKenna WJ, Hauer RNW, Anastastakis A, Asimaki A *et al*. Arrhythmogenic right ventricular cardiomyopathy: evaluation of the current diagnostic criteria and differential diagnosis. *Eur Heart J* 2020;**41**:1414–1429.
64. Saberi S, Cardim N, Yamani M, Schulz-Menger J, Li W, Florea V *et al*. Mavacamten favorably impacts cardiac structure in obstructive hypertrophic cardiomyopathy: eXPLORER-HCM cardiac magnetic resonance substudy analysis. *Circulation* 2021;**143**:606–608.
65. Ho CY, Mealiffe ME, Bach RG, Bhattacharya M, Choudhury L, Edelberg JM *et al*. Evaluation of mavacamten in symptomatic patients with nonobstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2020; **75**:2649–2660.
66. Mallus MT, Rizzello V. Treatment of amyloidosis: present and future. *Eur Heart J* 2023;**25**:B99–B103.
67. Corrado D, Wichter T, Link MS, Hauer R, Marchlinski F, Anastasakis A *et al*. Treatment of arrhythmogenic right ventricular cardiomyopathy/ dysplasia: an international task force consensus statement. *Eur Heart J* 2015;**36**:3227–3237.