Valvular heart disease and cardiomyopathy: reappraisal of their interplay

Marsan, N.A.; Graziani, F.; Meucci, M.C.; Wu, H.W.; Lillo, R.; Bax, J.J.; ... ; Crea, F.

nature reviews cardiology

https://doi.org/10.1038/s41569-023-00911-0

Review article

Check for updates

Valvular heart disease and cardiomyopathy: reappraisal of their interplay

Nina Ajmone Marsan[1,6] ✉, Francesca Graziani[2,6], Maria Chiara Meucci[1,2], Hoi W. Wu[1], Rosa Lillo[2,3], Jeroen J. Bax[1,4], Francesco Burzotta[2,3], Massimo Massetti[2,3], J. Wouter Jukema[1,5,7] & Filippo Crea[2,3,7]

Abstract

Cardiomyopathies and valvular heart diseases are typically considered distinct diagnostic categories with dedicated guidelines for their management. However, the interplay between these conditions is increasingly being recognized and they frequently coexist, as in the paradigmatic examples of dilated cardiomyopathy and hypertrophic cardiomyopathy, which are often complicated by the occurrence of mitral regurgitation. Moreover, cardiomyopathies and valvular heart diseases can have a shared aetiology because several genetic or acquired diseases can affect both the cardiac valves and the myocardium. In addition, the association between cardiomyopathies and valvular heart diseases has important prognostic and therapeutic implications. Therefore, a better understanding of their shared pathophysiological mechanisms, as well as of the prevalence and predisposing factors to their association, might lead to a different approach in the risk stratification and management of these diseases. In this Review, we discuss the different scenarios in which valvular heart diseases and cardiomyopathies coexist, highlighting the need for an improved classification and clustering of these diseases with potential repercussions in the clinical management and, particularly, personalized therapeutic approaches.

Sections

Introduction

Coexistence of valvular heart disease and cardiomyopathy

Shared pathophysiology of valvular heart disease and cardiomyopathy

Clinical perspectives and conclusions

[1]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands. [2]Department of Cardiovascular Science, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy. [3]Catholic University of the Sacred Heart, Rome, Italy. [4]Heart Center, University of Turku and Turku University Hospital, Turku, Finland. [5]Netherlands Heart Institute, Utrecht, The Netherlands. [6]These authors contributed equally: Nina Ajmone Marsan, Francesca Graziani. [7]These authors jointly supervised this work: J. Wouter Jukema, Filippo Crea. ✉e-mail: n.ajmone@lumc.nl

Key points

- Cardiomyopathies and valvular heart diseases are traditionally considered to be distinct diagnostic categories, but their coexistence is increasingly being recognized in several clinical settings.
- Dilated cardiomyopathy and hypertrophic cardiomyopathy are the paradigmatic examples of the coexistence of valvular heart disease and cardiomyopathy, given that these cardiomyopathies are often associated with mitral regurgitation, which further complicates their management.
- Cardiomyopathies and valvular heart disease can also share specific pathophysiological mechanisms, given that various genetic or acquired diseases can affect both the valves and the myocardium, including storage or immune-mediated disorders and radiation-induced cardiac damage.
- The association between cardiomyopathies and valvular heart diseases can have prognostic implications and can affect clinical decision-making; therefore, a personalized medicine approach is advocated for patients in whom these conditions coexist.

Introduction

Our understanding of cardiovascular disorders is constantly improving, owing to the development and implementation of advanced imaging techniques, big data analysis and genetics and omics studies. Diagnostic assessment of patients with cardiovascular diseases has therefore reached a new level of complexity and has allowed us to improve our comprehension of not only the main disease but also the interplay between different pathological conditions that frequently coexist, which have crucial repercussions on patient risk and the need for customized management. For example, valvular heart diseases and cardiomyopathies have been traditionally regarded as two distinct disorders, with dedicated guidelines for their clinical framework and treatment. Valvular heart disease classification is based on the specific valve lesion, and current guidelines focus on risk stratification and selection of the best timing and type of intevention[1]. Cardiomyopathies are classified by their morpho-functional phenotype and whether they are inherited; therefore, the dedicated guidelines emphasize the need for systematic screening for a genetic origin, but still recommend a treatment predominantly on the basis of the clinical presentation[2]. However, a growing body of evidence has shown that valvular heart diseases and cardiomyopathies share several important aspects, which until now have been largely unrecognized. These conditions can often coexist, as in the paradigmatic case of mitral regurgitation in dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM). Furthermore, such conditions can share specific pathophysiological mechanisms, and a number of genetic or acquired diseases can affect both the cardiac valves and the myocardium. However, the biological links between valvular heart diseases and cardiomyopathies are still largely unknown and future translational research in this direction is of paramount importance, given the potential of identifying novel targets for medical treatment.

In this Review, we discuss the most recent literature on the different clinical scenarios in which valvular heart diseases and cardiomyopathies can be associated, either because they are the cause of one another or because they have a common aetiology (Fig. 1). With this new perspective on valvular heart diseases and cardiomyopathies, we seek to highlight the need for an improved classification of these diseases, with possible relevant repercussions in clinical practice. With the aim of providing a framework for patient management, we clustered valvular heart diseases and cardiomyopathies on the basis of their coexistence and shared pathophysiology, with further distinction between valvular heart diseases with possible concomitant cardiomyopathy; cardiomyopathies with possible concomitant valvular heart disease; and acquired diseases causing valvular heart disease and cardiomyopathy.

Coexistence of valvular heart disease and cardiomyopathy

Cardiomyopathies are disorders of the heart muscle that are not explained by coronary artery disease, congenital abnormalities or loading conditions[2]. Each cardiomyopathy is characterized by specific geometrical and functional abnormalities in either the left or the right chambers or both, which can lead to valvular heart diseases such as mitral regurgitation and tricuspid regurgitation. DCM and HCM account for the large majority of all cardiomyopathies[3] and are the paradigmatic examples of the association between myocardial and valvular heart diseases. Specifically, both cardiomyopathies are often complicated by the presence of mitral regurgitation, which is typically dynamic[4,5] (Fig. 2), depending on a number of geometrical and haemodynamic factors[6]. In this setting, assessment of mitral regurgitation severity and, most importantly, of the relative burden of mitral regurgitation on myocardial function is challenging, although with important consequences on the selection of treatment.

DCM and functional mitral regurgitation

Pathophysiology and prognostic implications. Non-ischaemic DCM is complicated by secondary mitral regurgitation in approximately 50% of the patients[7]. The term secondary or functional means that the mitral valve is not abnormal per se and its dysfunction is related to the myocardial disease, which causes left ventricular (LV) remodelling and/or systolic dysfunction[7]. In patients with non-ischaemic DCM, the main mechanism of secondary mitral regurgitation is an unbalance between tethering forces versus closing forces acting on the mitral valve leaflets in favour of the former[8]. Increased tethering forces are a direct consequence of LV dilatation with lateral displacement of the papillary muscles, whereas LV contractile dysfunction leads to an impairment of the closing forces[8]. Moreover, mitral valve annular dilatation and impaired annular dynamics often contribute to the pathogenesis of DCM-related mitral regurgitation[9]. In secondary mitral regurgitation, the degree of regurgitation can vary substantially between clinical evaluations, depending on the different loading conditions, cardiac rhythm, blood pressure and medications[4]. This dynamic nature further complicates the diagnosis of secondary mitral regurgitation and the understanding of its role in the clinical picture of DCM.

The presence of moderate or severe functional mitral regurgitation has been associated with a twofold excess risk of death in patients with non-ischaemic DCM[10] (Table 1). Nevertheless, whether mitral regurgitation is just a marker of more advanced cardiomyopathy or directly contributes to the adverse outcomes in these patients is still debated[11,12]. The studies reporting the negative prognostic effect of functional mitral regurgitation in patients with non-ischaemic DCM attempted to correct for factors that reflect the severity of the underlying LV remodelling and heart failure[10,13–15]. However, the isolated contribution of mitral regurgitation to the disease process remains

difficult to establish from retrospective investigations and needs to be clarified in randomized, interventional trials that are specifically focused on non-ischaemic functional mitral regurgitation[12].

Therapeutic options. The management of patients with DCM complicated by the presence of secondary mitral regurgitation is complex and requires timely referral to a multidisciplinary heart team[12]. Given that secondary mitral regurgitation is a disease of the left ventricle and not of the valve itself, current treatment strategies are primarily directed towards the underlying cardiomyopathy[12]. Heart failure-targeted medical therapy[16–19] and cardiac resynchronization therapy[20–23] have demonstrated a strong independent effect on decreasing the severity of mitral regurgitation in observational studies. The persistence or worsening of mitral regurgitation despite the use of optimal medical therapy and cardiac resynchronization therapy has been consistently associated with worse outcomes[17,18,20–23].

Evidence supporting surgical intervention for secondary mitral regurgitation is scarce[24,25], and isolated mitral valve surgery is rarely performed, given the substantial procedural risk, high rates of mitral regurgitation recurrence and the absence of a proven survival benefit[1]. In the past decade, transcatheter edge-to-edge repair (TEER) has emerged as a promising alternative for selected patients with functional mitral regurgitation. Conflicting results have been reported by the two currently available randomized clinical trials: MITRA-FR[26] and COAPT[27]. Although the MITRA-FR trial[26] did not show any difference in patient survival with TEER plus medical therapy compared with medical therapy alone in patients with severe secondary mitral regurgitation, the COAPT trial[27] revealed a significant prognostic benefit of TEER in patients with secondary mitral regurgitation, consistently observed in either patients with ischaemic aetiology or patients with non-ischaemic aetiology (61% and 39% of the enrolled population, respectively)[28].

Of interest, the concept of proportionate and disproportionate functional mitral regurgitation (which is based on a modelled relationship between the mitral regurgitation effective regurgitant orifice area and LV end-diastolic volume) has been proposed to explain the discordant results of the two studies and to identify patients who will benefit from the intervention[29]. According to this approach, patients with a COAPT-like phenotype of disproportionate mitral regurgitation, characterized by a greater severity of mitral regurgitation in relation to LV remodelling, might have higher chances of benefit from the mitral valve treatment than patients with a MITRA-FR-like phenotype of proportionate mitral regurgitation, who might be better candidates for an intervention that targets the LV disease. However, although attractive from a pathophysiological perspective, several investigations have demonstrated that the benefit of TEER, as well as the prognostic discrepancy between the two trials, cannot be fully clarified by the proportionate–disproportionate hypothesis[30–32]. Several other factors probably contribute to the clinical outcomes in patients undergoing TEER, including the severity of LV and right ventricular systolic dysfunction, the presence of concomitant severe tricuspid regurgitation and/or pulmonary hypertension and haemodynamic instability[33,34]. Particularly, the presence of severe LV impairment, defined by a LV end-systolic diameter > 70 mm and/or LV ejection fraction < 20%, identified patients with poor long-term outcomes after TEER[33]. To date, European and US guidelines[1,35] provide a class IIa recommendation for TEER in patients who are likely to have a good response to the treatment.

Finally, for patients who still have symptoms and severe functional mitral regurgitation after optimal medical therapy, advanced heart failure therapies including cardiac transplantation and LV assist device implantation should also be considered, given the proven benefit in improving survival in appropriately selected patients[36].

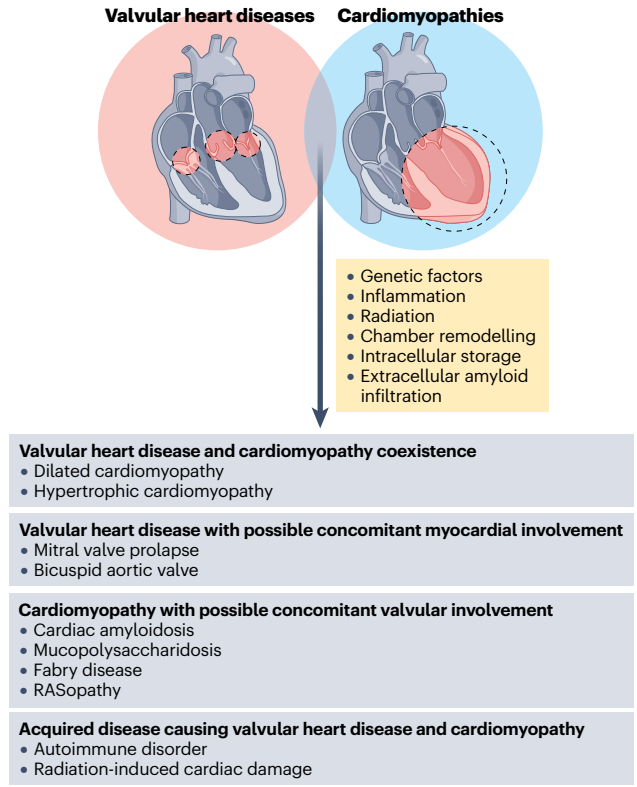

Fig. 1 | Interplay between valvular heart diseases and cardiomyopathies. The figure shows how valvular heart diseases and cardiomyopathies can overlap. The upper panel illustrates the shared specific pathophysiological mechanisms that can affect the myocardium and cardiac valves. The lower panel presents the clinical scenarios in which valvular heart diseases and cardiomyopathies coexist, categorized as valvular heart diseases with possible concomitant cardiomyopathy, cardiomyopathies with possible concomitant valvular heart disease and acquired diseases causing valvular heart disease and cardiomyopathy.

HCM and mitral regurgitation

Pathophysiology and prognostic implications. HCM is the most common genetic cardiac disease, with highly heterogeneous phenotypic expression and natural history[37]. In up to ~75% of the patients, HCM is complicated by obstruction of the LV outflow tract (LVOT), present at rest or by provocation, and defines the obstructive form of the disease[38]. LVOT obstruction is a complex dynamic phenomenon in which the mitral valve has a central role. Septal LV hypertrophy narrows the LVOT, and abnormal dynamic forces act on the mitral valve causing systolic anterior motion (SAM)[39], which, in turn, leads to the loss of leaflet coaptation and consequent mitral regurgitation. Over the past three decades, several studies showed that obstructive HCM-related mitral regurgitation is not a mere result of dragging forces caused by the hypertrophic–hyperdynamic left ventricle, but involves intrinsic abnormalities of the mitral valve apparatus, which include elongation and increased thickness of mitral leaflets[40], displacement of papillary muscles[41], abnormal chordae tendinae, unusual chordal attachments and/or direct attachment of the papillary muscle to the leaflets[42].

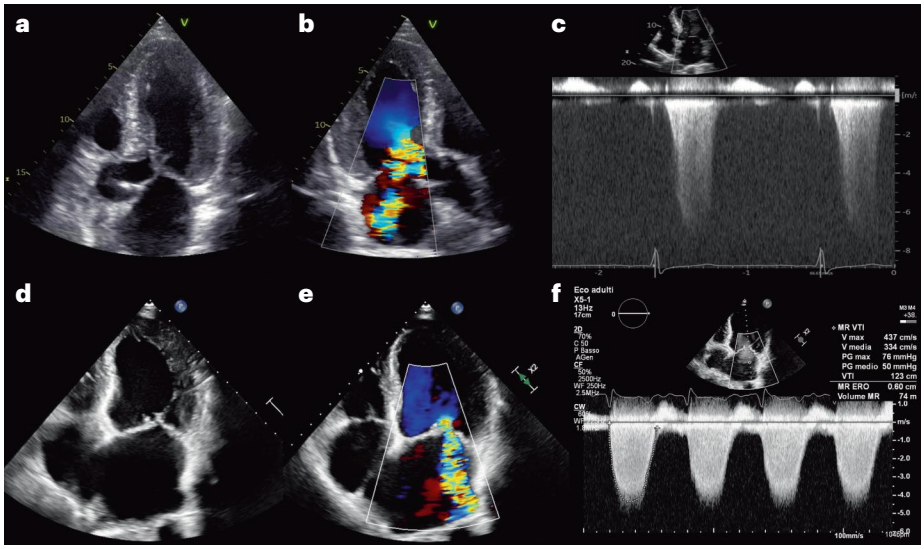

Fig. 2 | Mitral regurgitation in hypertrophic and dilated cardiomyopathy. a–**c**, 2D transthoracic echocardiography of a patient with hypertrophic cardiomyopathy. **a**, Apical five-chamber view showing asymmetric septal hypertrophy and systolic anterior motion (SAM) of the anterior mitral valve leaflet. **b**, Colour Doppler three-chamber view showing SAM-related severe mitral regurgitation. **c**, Continuous-wave Doppler showing SAM-dependent mitral regurgitation signal. **d**–**f**, 2D transthoracic echocardiography of a patient with dilated cardiomyopathy. **d**, Apical four-chamber view showing a dilated left ventricle and left atrium. **e**, Colour Doppler apical four-chamber view showing severe functional mitral regurgitation. **f**, Continuous-wave Doppler showing functional mitral regurgitation signal. CF, color flow; CW, continuous wave; MR ERO, mitral regurgitation effective regurgitant orifice; PG, pressure gradient; VTI, velocity time integral; WF, wave frequencies.

Intriguingly, morphological abnormalities in the mitral valve are not only an expression of the overt form of HCM, but can also be observed in the pre-hypertrophic stage of the disease[40,43]. Whether these abnormalities represent a primary phenotypic expression of HCM has been a matter of debate, and the pathogenetic link between HCM and mitral valve abnormalities remains elusive. A study published in 2020 reported the presence of a long muscular mitral–aortic discontinuity in a high proportion of young patients with obstructive HCM with sarcomeric protein gene mutations[44]. The investigators suggested that postnatal persistence of this congenital abnormality can displace the leaflet towards the apex, potentially favouring the development of LVOT obstruction. Another study proposed the existence of a common cell lineage ancestry from epicardium-derived pluripotent cells to explain the pathogenic relationship between alterations in sarcomere-related genes and the 'extended' HCM phenotypes not involving the cardiomyocytes, including myocardial disarray, interstitial fibrosis, mitral valve abnormalities and microvascular remodelling[45]. Intriguingly, the investigators hypothesized that abnormal embryonic development might account for the heterogeneous disease features of HCM, in line with basic science studies proposing embryological and developmental explanations for coexistent cardiac disorders[46], including cardiomyopathies and valvular heart diseases.

As demonstrated in 1969, the degree of SAM-related mitral regurgitation varies directly with the severity of LVOT obstruction and with the dynamic nature of the obstruction[47]. Therefore, the presence of LVOT obstruction and the severity of mitral regurgitation have to be evaluated not only at rest but also with exercise echocardiography[38]. Exercise echocardiography is a key diagnostic tool in the assessment of patients with HCM and should be considered in all symptomatic patients with HCM, especially when symptoms are not explained or are disproportionate with respect to the degree of LVOT obstruction at rest[38]. Conversely, given that the assessment of symptoms can be challenging, cardiopulmonary testing might be helpful in these patients to provide objective information on the severity of cardiac functional impairment, which has also important prognostic implications[48].

The presence of clinically significant rest or exercise-induced LVOT obstruction has been associated with an increased risk of heart failure and death, including sudden cardiac death[49–51]. The presence of clinically significant SAM-related mitral regurgitation has been demonstrated to contribute to the worse functional capacity of these patients and to lead to structural abnormalities such as left atrial (LA) enlargement[51], with consequent increased risk of atrial fibrillation[52]. A study in 126 patients with HCM undergoing exercise echocardiography proved that moderate or severe exercise-induced mitral regurgitation was a predictor of worse outcomes (composite end point of all-cause death, cardiac arrest and hospitalization for cardiovascular causes)[53]. However, large studies to assess the independent prognostic value of mitral regurgitation in patients with obstructive HCM have not been conducted so far because dissecting the role of mitral regurgitation from that of the LVOT obstruction is challenging.

The spectrum of HCM includes the evolution to the end-stage phase, which is observed in roughly 5% of the patients and characterized by a restrictive or dilated hypokinetic phenotype[54]. Intuitively, as systolic dysfunction and LV dilatation ensue, the 'typical' functional mitral regurgitation can develop. However, no data are available on the prevalence and/or prognostic effect of functional mitral regurgitation in this setting.

Therapeutic options. When a patient with HCM presents with symptoms despite receiving optimal medical therapy, the presence of LVOT obstruction and at least moderate mitral regurgitation has relevant therapeutical implications. Surgical treatment in obstructive HCM is complex[55,56], and a patient-tailored approach is needed to define whether the primary target has to be the muscle or the valve[57].

Septal myectomy is the gold-standard strategy to treat LVOT obstruction, which can also treat SAM-related mitral regurgitation at the same time[51,58]. A large study found that among patients without evidence of preoperative intrinsic mitral valve disease, only 2.1% required concomitant mitral valve surgery at the time of septal myectomy[55]. New surgical techniques of mitral valve repair through transaortic chordal cutting in association with a shallow septal muscular resection have been shown to abolish LVOT obstruction and reduce mitral regurgitation severity, specifically in patients with obstructive HCM and mild LV hypertrophy[59]. In addition, other septal reduction therapies, such as

Table 1 | Studies reporting the prognostic value of valvular heart disease in patients with cardiomyopathies

Study (year)	Inclusion criteria	Number of patients	Covariates considered as confounders	Conclusions	Ref.
Dilated cardiomyopathy					
Trichon et al. (2003)	HFrEF	2,057 (841 with non-ischaemic cardiomyopathy)	Age, sex, ischaemic aetiology, diabetes mellitus, LVEF, NYHA class, ventricular gallop	The severity of functional MR is independently associated with the risk of death in patients with ischaemic or non-ischaemic cardiomyopathy	14
Rossi et al. (2011)	Dilated cardiomyopathy	1,256 (424 with non-ischaemic cardiomyopathy)	Age > 65 years, NYHA class, LVEF < 30%, restrictive mitral filling pattern	Severe functional MR is independently associated with increased risk of the composite of death and hospitalization for heart failure in patients with ischaemic or non-ischaemic cardiomyopathy	10
Kajimoto et al. (2017)	Acutely decompensated heart failure	3,357 (424 with non-ischaemic cardiomyopathy)	Age, sex, hypertension, diabetes, hospital readmission for heart failure, atrial fibrillation, NYHA class, systolic blood pressure, plasma levels of urea nitrogen and creatinine, intravenous administration of diuretics, vasodilators or inotropes during hospitalization and medications at discharge from hospital	Moderate or severe functional MR is independently associated with increased risk of the composite of death and hospitalization for heart failure in patients with ischaemic cardiomyopathy, but not in patients with non-ischaemic cardiomyopathy	13
Goliasch et al. (2018)	HFrEF receiving GDMT	576 (351 with non-ischaemic cardiomyopathy)	Age, sex, ischaemic aetiology, plasma creatinine level, LV end-diastolic diameter, LVEF, severe tricuspid regurgitation, intensified GDMT, implanted cardioverter–defibrillator, response to cardiac resynchronization therapy and a neurohumoral activation cluster (encompassing NT-proBNP, MR-proANP, MR-proADM, CT-proET1 and copeptin)	Severe functional MR is independently associated with worse survival; subanalyses did not reveal differences according to heart failure aetiology (ischaemic versus non-ischaemic); the negative prognostic effect of functional MR was predominantly driven by an intermediate HFrEF phenotype (NYHA class II and III, moderately reduced LVEF and within the second quartile of plasma NT-proBNP levels)	15
Hypertrophic cardiomyopathy					
Feneon et al. (2017)	Hypertrophic cardiomyopathy with preserved LVEF	129	Rest PASP > 50 mmHg, rest LVOT gradient > 50 mmHg	Clinically significant (grade 2 or more) exercise-induced MR is associated with increased risk of the composite of death, cardiorespiratory arrest and hospitalization for cardiovascular causes in patients with hypertrophic cardiomyopathy	53
Cardiac amyloidosis					
Chacko et al. (2020)	ATTR cardiomyopathy	1,240 (766 with wild-type and 474 with hereditary ATTR cardiomyopathy)	Interventricular septum thickness, stroke volume index, left atrial area index, right atrial area index, clinically significant MR, clinically significant tricuspid regurgitation, LV global longitudinal strain, *E*/e′ lat, TAPSE, PASP, right ventricular wall thickness and heart rate	Severe aortic valve stenosis is independently associated with worse survival in patients with ATTR cardiomyopathy	139

ATTR, amyloid transthyretin; CT-proET1, C-terminal pro-endothelin 1; *E*/e′ lat, ratio of transmitral *E* velocity to early diastolic mitral annular velocity at lateral annulus; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MR, mitral regurgitation; MR-proADM, mid-regional proadrenomedullin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PASP, pulmonary arterial systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

alcohol septal ablation, have been shown to improve SAM-related mitral regurgitation in patients with obstructive HCM[60,61]. Conversely, 'direct mitral valve procedures', including several new techniques of mitral valvuloplasty and prosthetic replacement of mitral valve, can also reduce the LVOT obstruction[62–69] and might be indicated in specific cases of coexistence of SAM and intrinsically abnormal mitral valve apparatus.

Until now, the medical management of obstructive HCM has relied on negative inotropic and chronotropic drugs, including β-blockers, calcium channel blockers and disopyramide. Medical therapy is currently recommended by guidelines[38] for symptom relief, given that none of these drugs has been shown to improve the natural history of the disease. No large, randomized trials have specifically investigated the effect of these therapies on mitral regurgitation in obstructive HCM. β-Blockers can blunt exercise-provoked LVOT obstruction and related mitral regurgitation[70], but have demonstrated inconsistent effects on the resting gradient[38,70–73].

The myosin inhibitor mavacamten has been shown to improve symptoms, exercise capacity and LVOT obstruction in patients with obstructive HCM in a phase III, randomized clinical trial[74]. Patients treated with mavacamten in addition to conventional pharmacological

Table 2 | Genetic or congenital valvular heart diseases with possible concomitant cardiac manifestations

Disease	Predominant valve dysfunction	Syndromes	Genetic or chromosomal aetiologies	Associated cardiac manifestations	Refs.
Myxomatous mitral valve disease	Mitral regurgitation	Marfan syndrome	*FBN1* (fibrillin 1)	Aortic aneurysm or dissection	84–87
		Loeys–Dietz syndrome	TGFβ signalling (*SMAD3*, *TGFB2*, *TGFB3*, *TGFBR1*, *TGFBR2*)	Aortic aneurysm or dissection	
		Ehlers–Danlos syndromes	Collagen type I, II, III, V and XI	Aortic aneurysm or dissection	
		Stickler syndrome	Collagen type II, IX and XI	Aortic aneurysm or dissection	
		Osteogenesis imperfecta	Collagen type I	Aortic aneurysm or dissection	
		Non-syndromic	*ADAMTS19*, *ALPK3*, *BAG3*, *DCHS1*, *DZIP1*, *FLNA*, *PLD1*, *RBM20*	Myocardial replacement fibrosis and possible atrial and ventricular arrythmias	
Bicuspid aortic valve disease	Aortic regurgitation and/or aortic stenosis	Turner syndrome	Chromosome X monosomy	Aortic coarctation or aneurism	84,118
		Anderson–Tawil syndrome (LQT7)	*KCNJ2*	Ventricular arrhythmias	
		DiGeorge syndrome	Deletions at 22q11.2	Tetralogy of Fallot, truncus arteriosus and anomalies of the aortic arch	
		William–Beuren syndrome	*ELN* (elastin)	Supravalvular aortic stenosis	
		Down syndrome	Chromosome 21 trisomy	Atrioventricular septal defect	
		Non-syndromic	*GATA4*, *GATA5*, *GATA6*, *NOTCH1*, *SMAD6*	Aortic aneurysm or dissection; LV non-compaction cardiomyopathy	
Congenital pulmonary valve stenosis	Pulmonary valve stenosis	Noonan syndrome, Leopard syndrome and Costello syndrome	RAS–MAPK signalling (*KRAS*, *PTPN11*, *RAF1*, *SOS1*)	Hypertrophic cardiomyopathy	84
		Non-syndromic	*GATA4*	No reported cardiac manifestations	
Ebstein anomaly	Tricuspid regurgitation	Non-syndromic	*MHY7* (myosin heavy chain 7)	LV non-compaction cardiomyopathy, Wolff–Parkinson–White syndrome	84

LV, left ventricular; MAPK, mitogen-activated protein kinase; TGFβ, transforming growth factor-β.

therapies showed improvement in echocardiographic markers of LV filling pressures (LA volume and *E/e'*) and a reduction in SAM and mitral regurgitation severity compared with patients receiving placebo. Mavacamten treatment resolved SAM in 81% of the patients compared with 34% of the patients with placebo. In addition, among patients with mitral regurgitation at baseline, 9% in the mavacamten group had complete resolution of mitral regurgitation compared with no patients in the placebo group[74]. These results need to be confirmed in other specifically designed studies, which will help to assess the role of mavacamten in the therapeutic armamentarium for obstructive HCM[75]. However, whether the resolution of mitral regurgitation provides a prognostic benefit independent from the relief of the LVOT obstruction is currently unknown. Similarly, there are no clear data showing a worse outcome for patients with obstructive HCM with recurrent or residual mitral regurgitation[76–78].

Shared pathophysiology of valvular heart disease and cardiomyopathy

The pathophysiology of valvular heart diseases and cardiomyopathies might have a relevant overlap (Tables 2 and 3). Genetics has a prominent role in most cardiomyopathies and an established prognostic value in some of them[79–83]. Conversely, valvular heart diseases are usually acquired, although for some valvular heart diseases (both left-sided and right-sided), familial segregation and heritability patterns have been described[84–88], supporting an underlying genetic substrate. In addition to a common genetic or congenital background, these diseases can share several other pathogenetic mechanisms. For example, in lysosomal storage disease, a pan-cardiac involvement can be observed, with valvular tissue and myocardium affected by the same mechanisms of damage[89]. Similarly, acquired conditions, such as autoimmune diseases[90,91] (including rheumatic heart disease[92]), and radiation therapy[93] can cause myocardial and valvular injury through abnormally triggered inflammatory pathways and/or direct damage. Irrespective of the mechanism involved, the potential combination of valvular heart disease and cardiomyopathy has relevant clinical implications.

Valvular heart diseases with possible concomitant cardiomyopathy

Mitral valve prolapse. Mitral valve prolapse (MVP) is a common valvular heart disease, affecting 2–3% of the general population[94]. Its clinical presentation can be heterogeneous, ranging from a benign

Table 3 | Genetic or acquired cardiomyopathies with possible concomitant valvular manifestations

Disease	Predominant cardiomyopathy	Specific echocardiographic findings	Genetic defect or pathogenetic mechanism	Associated valvular manifestations[a]	Refs.
Genetic storage or deposit diseases					
Familial ATTR cardiomyopathy	Restrictive and/or hypertrophic cardiomyopathy	Ground-glass appearance of LV myocardium, apical sparing at strain analysis, increased interatrial septum thickness, increased atrioventricular valve thickness, increased RV free wall thickness, mild pericardial effusion	*TTR* (transthyretin)	Degenerative AS (low flow–low gradient) > MR and TR	127,161
Mucopolysaccharidosis	Hypertrophic cardiomyopathy	Mild LV hypertrophy, increased mitral and aortic valve thickness and calcification	α-L-iduronidase (type I), iduronate-2-sulfatase (type II), *N*-acetylgalactosamine-4-sulfatase (type VI)	MR > AR > MS > AS	151,152
Fabry disease	Hypertrophic cardiomyopathy	Concentric LV hypertrophy, disproportionate hypertrophy of papillary muscles, increased atrioventricular valve thickness, increased RV free wall thickness	*GLA* (α-galactosidase A)	MR > AR > TR	89
Acquired diseases					
Wild-type ATTR cardiomyopathy	Restrictive and/or hypertrophic cardiomyopathy	Ground-glass appearance of LV myocardium, apical sparing at strain analysis, increased interatrial septum thickness, increased atrioventricular valve thickness, increased RV free wall thickness and mild pericardial effusion	Amyloid infiltration	Degenerative AS (low flow–low gradient) > MR and TR	127,161
Autoimmune and inflammatory disorders					
Systemic sclerosis	Myocarditis, dilated cardiomyopathy and heart failure	Diffuse hypokinesia and pulmonary hypertension	Inflammation and fibrosis	Degenerative valvular heart disease (primarily MR)	90
Rheumatoid arthritis	Myocarditis, dilated cardiomyopathy and heart failure	Diffuse hypokinesia	Inflammation and fibrosis	Degenerative valvular heart disease (primarily MR)	90
SLE and antiphospholipid syndrome	Myocarditis, dilated cardiomyopathy and heart failure	Libman–Sack endocarditis (verrucous non-bacterial vegetations) and pericardial effusion	Autoimmune reaction mediated by antiphospholipid and anti-SSA/Ro autoantibodies	MR > MS > AR	90
Rheumatic disease	Acute myocarditis	Acute: annular dilatation and chordal elongation, pericardial effusion. Chronic: leaflet thickening and retraction, chordal fusion and shortening, commissural fusion	Autoimmune reaction triggered by infection with group A streptococcus	Acute: MR > AR Chronic: MS > MR > AS > AR > TR and TS > PR and PS[b]	92
Spondyloarthropathies and systemic vasculitis	Acute myocarditis	Diffuse hypokinesia	Inflammation and fibrosis	AR	90
Eosinophilic endomyocardial fibrosis (Loffler endocarditis)	Restrictive cardiomyopathy	Partial LV or RV apical obliteration	Eosinophilic infiltration; stages of disease: (1) acute necrotic stage; (2) thrombotic stage; (3) fibrotic stage (with valvular involvement)	MR > TR	90,156
Sarcoidosis	Dilated cardiomyopathy	Mild or absent dilatation and akinetic or dyskinetic segments with non-coronary distribution	Non-caseating granulomas	MR (related to papillary involvement)[b]	91,156
Radiation-induced	Restrictive and/or ischaemic cardiomyopathy	Leaflet thickening and retraction, calcification of the mitral annulus and aortic–mitral curtain, calcification of the ascending aorta and pericardial thickening	Inflammation and fibrosis	MR and AR > MS and AS > TR and tricuspid stenosis[c]	93

AR, aortic regurgitation; AS, aortic stenosis; ATTR, amyloid transthyretin; LV, left ventricular; MR, mitral regurgitation; MS, mitral stenosis; PR, pulmonary valve regurgitation; PS, pulmonary valve stenosis; RV, right ventricular; SLE, systemic lupus erythematosus; TR, tricuspid regurgitation; TS, tricuspid stenosis. [a]Manifestations are ordered by frequency, from the most to the least common, indicated by >. [b]Uncommon manifestation (<3% of patients). [c]Valvular involvement is common as mixed or multivalvular disease.

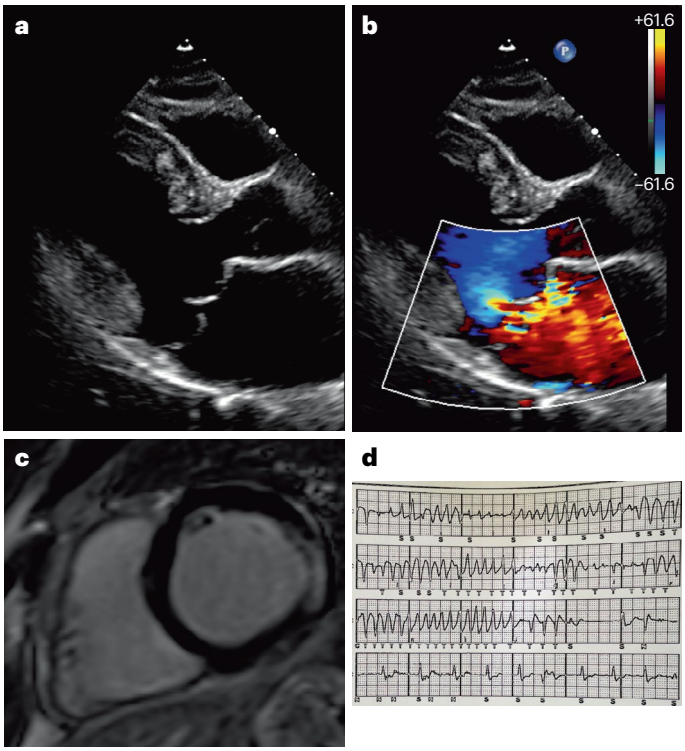

Fig. 3 | Arrhythmic mitral valve prolapse. a,b, Transthoracic echocardiographic long-axis views in end-systole of a patient with arrhythmic mitral valve prolapse show mitral valve prolapse with mitral annular disjunction and severe mitral regurgitation. **c**, Contrast-enhanced cardiac magnetic resonance short axis view of the same patient shows subepicardial late gadolinium enhancement, indicative of myocardial fibrosis, in the left ventricular inferolateral basal wall. **d**, 24-h Holter monitoring showing non-sustained ventricular tachycardia.

condition to life-threatening complications, including development of severe mitral regurgitation and, seldomly, sudden cardiac death[95]. The clinical spectrum of MVP has two major phenotypes: myxomatomous MVP (also known as Barlow disease), which normally affects younger patients and involves the entire mitral valve apparatus; and fibroelastic deficiency, which is typically observed in older patients (aged > 60 years) and characterized by chordal rupture[95]. The majority of MVP cases are sporadic, but a positive family history has been reported in 26% of patients with Barlow disease and in 9% of patients with fibroelastic deficiency undergoing mitral valve surgery[88]. Studies on familial clustering provided knowledge on the genetic background of the disease, identifying specific gene variants that are mostly associated with mitral valve development[84–87,95] (Table 2). Of interest, MVP has been rarely observed in newborn babies, suggesting that it might develop from a combination of genetic alterations with age-dependent penetrance, postnatal disruption of cellular signalling, and environmental factors, including repetitive mechanical stress from physiological wear and tear[96,97]. In addition, a study in probands with Barlow disease identified likely pathogenic variants in cardiomyopathy-related genes (*DSP*, *HCN4*, *MYH6* and *TTN*) in 11% of the patients[98]. Some of these genes, such as *HCN4*, encode proteins involved in the development of both the myocardium and the conduction system[99], suggesting a potential pathogenetic link with the arrhythmic phenotype.

Together, these findings support the hypothesis of a shared genetic background involved in the pathogenesis of MVP and cardiomyopathies and deserve further investigation. However, the presence of a possible underlying cardiomyopathy in patients with MVP was already hypothesized in 1974. Gulotta et al.[100] described abnormal LV contractility in 26 patients with Barlow disease and various degrees of mitral regurgitation, as evaluated by angiography, and postulated the existence of a prolapse cardiomyopathy. This theory has been subsequently supported by imaging studies that reported a disproportionate LA and LV dilatation relative to mitral regurgitation severity in patients with MVP[101,102]. Further supporting the hypothesis of an MVP-related myocardial disease is the observation from studies using cardiac magnetic resonance (CMR) imaging that replacement myocardial fibrosis in the left ventricle was commonly detected in patients with Barlow disease (28–37%) and was mostly located close to the mitral valve annulus, in the basal infero-lateral wall and the adjacent papillary muscle, with a patchy pattern[103–106]. On the basis of the observed typical distribution of myocardial fibrosis and its presence in all degrees of mitral regurgitation, abnormal myocardial stretch and annular alterations have been proposed as the underlying mechanism of myocardial fibrosis in these patients[106]. Among the annular abnormalities (including annular dilatation and early calcifications), mitral annular disjunction (MAD) is frequently found in patients with MVP and particularly those with Barlow disease (pooled rates of 33% and 51%, respectively)[107]. MAD is defined as a systolic separation between the LV myocardium and the mitral annulus supporting the posterior mitral leaflet[107]. The presence of MAD, together with myocardial replacement fibrosis, has been associated with the occurrence of major ventricular arrhythmias and sudden cardiac death[105,108–111] (Fig. 3). However, given that some studies showed that MAD is highly prevalent in healthy individuals[112], its role in the MVP-related arrhythmic risk is still unclear[113].

This growing body of evidence led to the definition of an arrhythmic MVP phenotype and highlighted the importance of the risk stratification of ventricular arrythmias in these patients[107]. To this aim, standard 24-h Holter monitoring is a pivotal tool in clinical practice and is warranted in all patients with MVP, regardless of the presence of symptoms or mitral regurgitation severity. Moreover, multimodality imaging assessment that includes myocardial tissue characterization by CMR has gained a crucial role in this context. However, controversies and important gaps in knowledge remain regarding the arrhythmic risk associated with MVP, and further studies are needed to help clinicians face this conundrum.

Bicuspid aortic valve. Bicuspid aortic valve (BAV) morphology is the most common congenital heart valve condition, with an overall incidence of approximately 0.5–2% in the general population[114,115] and underlying 70–85% of cases of aortic valve stenosis in children and at least 50% of aortic stenosis in adults[116]. A number of reports of familial clustering support the theory that BAV is heritable[117,118], but with a complex genetic heterogeneity. Indeed, BAV can be caused by variations in different genes encoding transcription factors, extracellular matrix proteins and signalling pathways regulating cell proliferation, differentiation, adhesion and apoptosis[117,119,120]. BAV morphology can be sporadic or associated with a specific syndrome (Table 2). In 25% of the patients, BAV is associated with ascending aortic dilatation[121]. In the aortopathy phenotype, genetic factors are likely to have a role, given that the aortic valve and ascending aorta have a common embryogenesis[122]. BAV can also coexist with a number of congenital cardiovascular malformations, primarily coarctation of the aorta

and cardiac septal defects or the hypoplastic left heart syndrome[115]. These data suggest that BAV is not only a disorder of valvulogenesis but also a more complex genetic disease involving aortic and cardiac development. Although a possible association between BAV and specific cardiomyopathies has been proposed on the basis of common genetic traits[123,124], data on the prevalence of coexisting specific cardiomyopathies in individuals with BAV are limited. The strongest association seems to be with LV non-compaction cardiomyopathy[125], but with conflicting results. In a large study that included 1,186 adults with BAV, approximately 6% had concomitant cardiomyopathy; 3.4% of the patients had LV non-compaction cardiomyopathy and 1.4% had HCM, and the presence of cardiomyopathy was independently associated with the occurrence of heart failure[126].

Cardiomyopathies with possible concomitant valvular heart disease

Cardiac ATTR amyloidosis. During the past decade, an epidemiologically significant coexistence of aortic valve stenosis and cardiac wild-type transthyretin amyloid (ATTR) amyloidosis has been observed (Fig. 4), suggesting a pathophysiological link between the two diseases[127]. Given that autopsy studies indicate that ATTR deposits can be found in the heart in almost 25% of octogenarian individuals[128] and that aortic valve stenosis mainly affects people aged > 75 years[129], the association between these two conditions might be purely epidemiological. However, the shared demographic profile as the sole explanation for the coexistence of cardiac ATTR amyloidosis and aortic valve stenosis is not entirely convincing, and some investigators have hypothesized that amyloid infiltration induces or accelerates aortic valve stenosis[127]. Localized dystrophic amyloidosis of heart valves was first described almost 40 years ago[130,131]. A more recent histological study of surgically removed heart valves confirmed a high prevalence of amyloid deposits in patients with aortic valve stenosis, but immunohistochemistry assays did not demonstrate the presence of the most common amyloid proteins and amyloid deposition seemed to be secondary to athero-inflammatory conditions and high shear-stress haemodynamics[132]. However, other histological studies proved the presence of ATTR infiltration of the stenotic aortic valve, suggesting a potential causative role in the progression of aortic valve stenosis severity[133,134]. Another hypothesis is that the pressure overload induced by aortic valve stenosis could have deleterious effects on myocardial hypertrophic remodelling, potentially acting as a mechanical trigger, worsening the ATTR deposits. Moreover, oxidative stress, inflammation and extracellular remodelling have a pivotal role in the ATTR amyloidogenic process[135] and are also involved in the pathophysiology of aortic valve stenosis[136,137]. Therefore, these factors could favour a pathogenetic vicious cycle between the two diseases. However, to date, this 'chicken or the egg' dilemma remains unsolved[127].

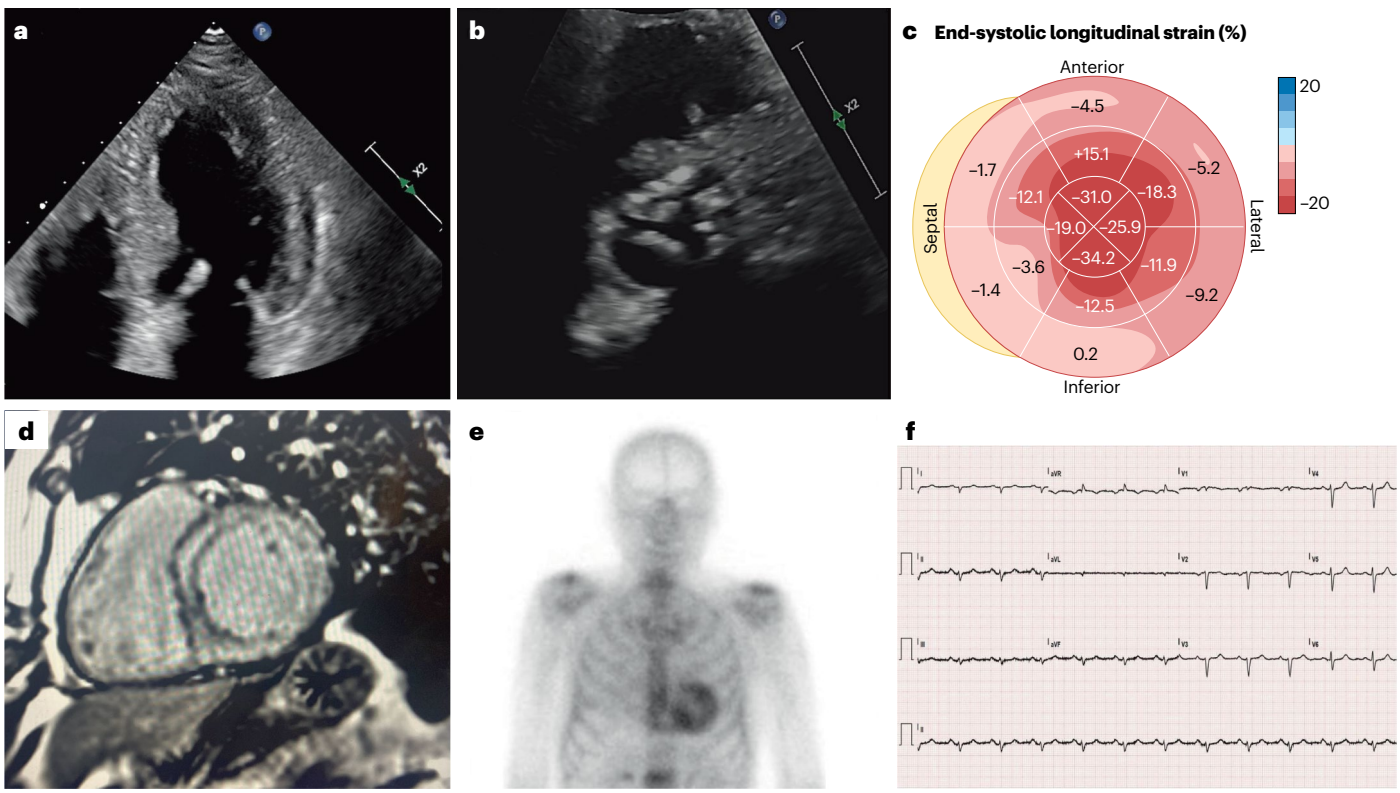

Fig. 4 | Cardiac amyloidosis and aortic stenosis. a–**c**, Transthoracic echocardiography of a patient with concomitant transthyretin cardiac amyloidosis and aortic stenosis. **a**, Four-chamber view showing concentric left ventricular hypertrophy. **b**, Parasternal short-axis view showing calcification and severe narrowing of the aortic valve. **c**, Echocardiographic longitudinal strain bull's-eye plot showing reduced values of strain with characteristic sparing of the apical segments ('apical sparing' pattern, with red colour indicating preserved segmental longitudinal strain and pink colour indicating reduced segmental longitudinal strain). **d**, Contrast-enhanced cardiac magnetic resonance short-axis view showing left ventricular hypertrophy with diffuse transmural enhancement. **e**, Whole-body ^{99}Tc-hydroxymethylene-diphosphonate scintigraphy with evident heart retention with a Perugini visual score of 3. **f**, Twelve-lead electrocardiogram showing low QRS voltages in the peripheral leads and poor R wave progression in the precordial leads (pseudo-infarct pattern).

Irrespective of the aetiology, the coexistence of cardiac ATTR amyloidosis and aortic stenosis is the ideal example of the prognostic influence of the association between valve and myocardial disease. Indeed, the presence of severe aortic valve stenosis is independently associated with increased morbidity and reduced survival in patients with cardiac ATTR amyloidosis[138–140]. Conversely, patients with aortic stenosis and features suggestive of infiltrative cardiomyopathy, such as severe LV hypertrophy, increased LV filling pressures and low stroke volume, have poor outcome, and an unrecognized cardiac ATTR amyloidosis might be present in this subset of patients[139–141].

For the diagnostic assessment, electrocardiogram abnormalities (atrioventricular and interventricular conduction delay, low-voltage despite LV hypertrophy and Q waves without a history of myocardial infarction) and a disproportionate elevation in the plasma levels of N-terminal pro-brain natriuretic peptide or troponins are typical red flags for cardiac ATTR amyloidosis[142]. In the diagnostic framework of patients with aortic valve stenosis, when coexistent cardiac ATTR amyloidosis is suspected, second-level investigations to confirm myocardial involvement (such as CMR and cardiac scintigraphy with bone tracers) are strongly recommended, given that cardiac ATTR amyloidosis complicates the clinical management and has therapeutic implications. Conversely, cardiac ATTR amyloidosis is commonly associated with a pattern of low-flow, low-gradient aortic valve stenosis, which necessitates additional investigations to confirm aortic stenosis severity, including dobutamine stress echocardiography (although often inconclusive because of a negative flow response in these patients) or aortic valve calcium scoring by CT[142].

When considering treatment options, a study suggests that patients with aortic valve stenosis and suspected cardiac amyloidosis who are undergoing transcatheter aortic valve implantation (TAVI) have an increased risk of operative complications and derive less benefit in terms of symptom improvement and survival compared with patients without suspected cardiac amyloidosis[143]. Therefore, concerns were raised about the futility of aortic valve stenosis relief in patients with cardiac amyloidosis[143]. However, in the past decade, observational studies and meta-analyses have proven that TAVI improves prognosis in this subset of patients compared with medical therapy, with a similar safety profile to that in patients with aortic valve stenosis alone, except for a trend towards a higher risk of permanent pacemaker implantation[144–146]. Therefore, TAVI might be the preferred option for patients with cardiac ATTR amyloidosis and aortic valve stenosis and should not be denied[144–146]. Nevertheless, therapeutical decisions must be discussed in a multidisciplinary heart team from a perspective of personalized medicine[147].

Whether patients with concomitant cardiac ATTR amyloidosis could benefit from earlier intervention (when aortic valve stenosis is moderate) is unknown. We can speculate that the myocardium affected by cardiac ATTR amyloidosis would not be able to face the increased afterload as a normal heart would and thus could benefit from an earlier intervention. Of note, the mitral valve apparatus can also be affected in cardiac ATTR amyloidosis. Mild-to-moderate mitral regurgitation is a common finding, but severe mitral regurgitation can also occur, owing to local amyloid infiltration nodularity (leaflets amyloidoma) causing chordal rupture and mitral valve flail[148,149]. In the clinical scenario of patients with cardiac ATTR amyloidosis and severe mitral regurgitation, TEER can be a reasonable option. A study published in 2022 found no significant difference in procedural success and periprocedural complications with TEER between patients with cardiac ATTR amyloidosis and mitral regurgitation and patients with mitral regurgitation alone[150]. However, patients with dual pathology had worse outcomes driven by a higher rate of hospitalizations for heart failure[150].

Mucopolysaccharidoses. In mucopolysaccharidoses (MPS), glycosaminoglycan deposition affects both the heart muscle and valve tissue, and cardiac involvement is a strong determinant of prognosis[151–153]. Progressive cardiac valve disease is the most prominent cardiac manifestation (60–90%) (Table 3) and valve thickening with associated dysfunction has been reported in >80% of the patients with MPS I (ref. 151). Enzyme replacement therapy can prevent LV hypertrophy from worsening, but the valve disease, once started, is usually not reversible[151]. Interventions that target valvular heart disease are usually associated with high, if not prohibitive, risk of perioperative complications in patients with MPS, owing to the presence of concomitant skeletal and respiratory complications, but valvular heart interventions can be a game-changer, lengthening the life expectancy of these patients[151–153].

In Fabry disease, deposition of glycosphingolipids has also been reported, affecting mostly mitral and aortic valves[89]. However, unlike in MPS, moderate or severe valvular regurgitation is rare[89,154] and seldomly leads to clinically significant outcomes. By contrast, LV hypertrophy is the main determinant of prognosis in patients with Fabry disease[89].

RASopathies. In RASopathies, variants in genes encoding proteins of the RAS–mitogen-activated protein kinase signal transduction pathway can cause heterogenous clinical phenotypes, among which Noonan syndrome is the most prevalent[84]. Approximately 80–90% of the patients with Noonan syndrome show cardiac involvement, with pulmonary valve stenosis and HCM being the main manifestations[84]. According to data from the CArdiac Rasopathy NETwork, almost 50% of the patients with RASopathies and cardiac defects need valvular heart surgery, and even if the overall mortality in these patients is low, the association between valvular heart disease and HCM increases the risk of cardiac-related death[155].

Acquired conditions causing valvular heart disease and cardiomyopathy

Autoimmune rheumatic diseases. Rheumatic diseases are characterized by loss of immune tolerance, resulting in systemic inflammation involving multiple organs. All cardiac structures can be affected during the course of systemic autoimmune diseases (valves, conduction system, myocardium, endocardium, pericardium and coronary arteries), and cardiovascular involvement is strongly associated with a poor prognosis in these patients[90,91]. Although challenging, it is thus essential to detect potential cardiac abnormalities even if they are subclinical, alongside extensive screening of asymptomatic patients to provide proper management and possible early treatment[156].

These diseases can directly affect the myocardium, in the form of myocarditis, or myocardial dysfunction or heart failure mediated by various inflammatory and autoimmune mechanisms[90] (Table 3). Cardiomyopathy is particularly prevalent in patients with systemic sclerosis, rheumatoid arthritis or, although less frequent, systemic lupus erythematosus[90]. Inflammation and scarring of the endocardium, which constitutes the inner surface of the cardiac valves, can also result in valvular thickening and progressive dysfunction[90]. Rheumatic heart disease mainly determines valvular damage (predominantly left-sided) secondary to rheumatic fever triggered by group A streptococcal infection but can also include acute myocarditis[92]. Libman–Sacks endocarditis, a form of non-bacterial thrombotic endocarditis, has been

described in up to 30–50% of patients with systemic lupus erythematosus (depending on the diagnostic approach), and thromboembolic complications, such as cerebrovascular occlusions, are associated with a serious risk of morbidity in these patients[90]. Valvular heart diseases are also described in patients with spondyloarthropathies or systemic vasculitis[90]. Moreover, patients with antiphospholipid syndrome have an increased risk of valvular heart disease and thrombotic complications[90]. Considering these different cardiac manifestations and the complexity of the management of these patients, a multidisciplinary assessment, including a cardiologist with specific competence and a rheumatologist, is of crucial importance to guarantee a timely diagnosis and proper treatment of both valvular heart disease and cardiomyopathy[157].

Radiation-induced cardiac damage. The use of radiation therapy in the management of thoracic malignancies has led to a new spectrum of cardiovascular disorders induced by radiation injury, including coronary, myocardial, pericardial and valvular heart diseases[93]. Histological studies showed that radiation treatment can cause diffuse and progressive myocardial fibrosis, possibly leading to restrictive cardiomyopathy[93]. Moreover, among radiation-related cardiac damages, valvular heart disease occurs in up to 40% of the patients at 10 years and 60% of the patients at 20 years after mediastinal radiation therapy, with a predominant involvement of the mitral and aortic valves[93]. Postactinic valvular heart disease is characterized by progressive valve thickening, calcification and damage to the surrounding structures, including the annulus, subvalvular apparatus and the aortomitral curtain, that generally result in valve stenosis or regurgitation[93].

The isolated prognostic value of the presence of valvular heart disease in patients receiving radiation treatment is difficult to assess owing to the frequent overlap with other cardiovascular complications and/or additional radiation-induced damage on the lung parenchyma. In addition, the management of radiation-associated valvular heart disease is particularly challenging, with a high morbidity and mortality[158,159].

Clinical perspectives and conclusions

Valvular heart diseases and cardiomyopathies have more in common than previously thought and a personalized medicine approach is advocated in patients in whom these conditions coexist. Some patients with valvular heart disease could benefit from being evaluated by a cardiomyopathy expert, who is able to recognize an inheritable condition, which has potential implications in family screening[160] and management, but also guarantees the best treatment for the myocardial disease. Conversely, patients with cardiomyopathy could often benefit from the evaluation of a valvular heart disease specialist, who is able to precisely diagnose and estimate the burden of the valvular lesion on their clinical picture and to refer the patient in a timely manner to the most appropriate intervention. Therefore, the clustering proposed in this Review might improve awareness of the interplay between these two conditions and provide clinicians with a framework for patient management. Detailed personal and family history, symptom assessment and physical examination, together with first-line instrumental investigations, such electrocardiogram and echocardiography, are the starting point to assess the coexistence of valvular heart disease and cardiomyopathy. Clinical assessment should also include the search for systemic or laboratory 'red flags' for specific aetiologies[161] and thereby

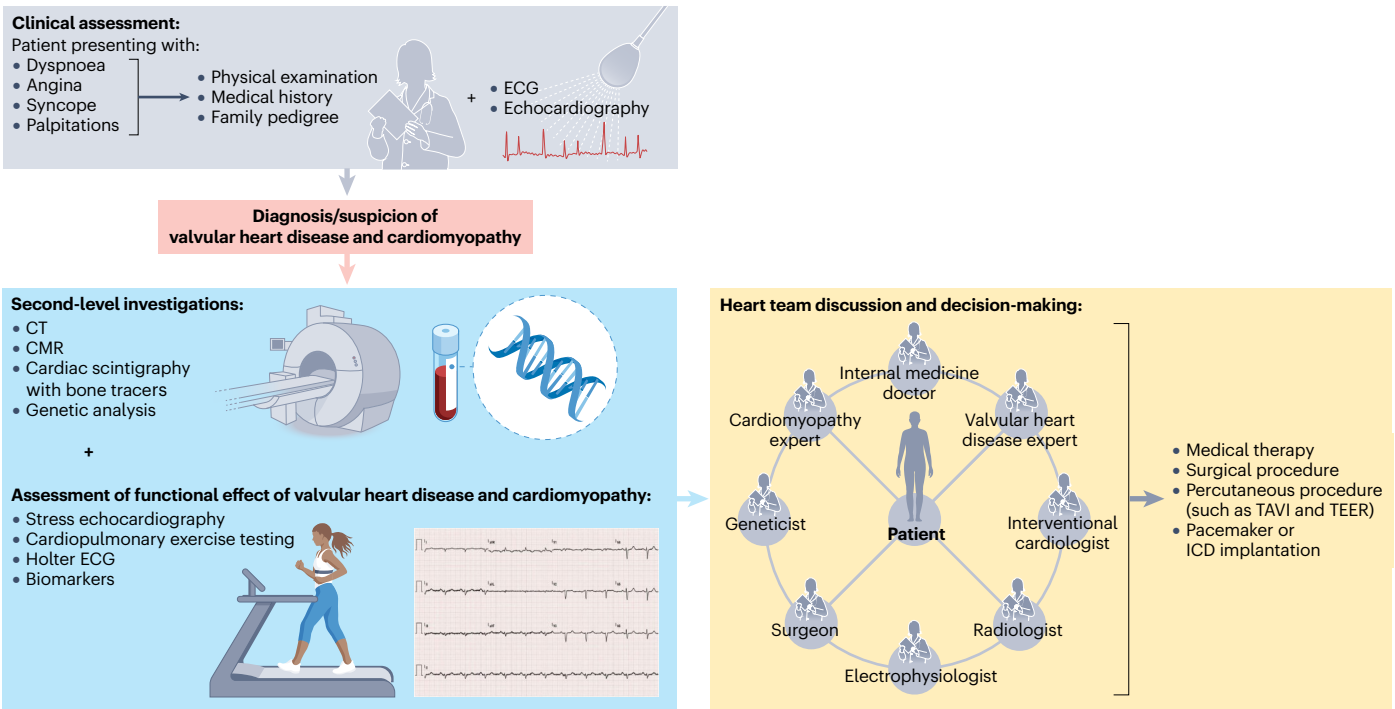

Fig. 5 | Workflow for the assessment and management of patients with concomitant cardiomyopathy and valvular heart disease. If the initial clinical assessment (detailed medical and family history plus physical examination) with first-line diagnostic tools (electrocardiogram (ECG) and echocardiography) leads to suspicion of valvular heart disease and cardiomyopathy, second-level investigations should be performed to complete the diagnostic framework and to assess their functional effect. The final step involves discussion by a multidisciplinary heart team for treatment decision-making. CMR, cardiac magnetic resonance; ICD, implantable cardioverter–defibrillator; TAVI, transcatheter aortic valve implantation; TEER, transcatheter edge-to-edge repair.

guide further diagnostic tests. Similarly, a detailed family pedigree and assessment of patterns of inheritance can aid in the differential diagnosis of genetic conditions. Second-level investigations with multimodality imaging and genetic analysis are necessary to complete the diagnostic framework and to assess the functional effect of the valvular heart disease and cardiomyopathy (Fig. 5). However, an important gap in knowledge exists regarding the exact effect that each disease has on each other. In addition, it can be difficult to dissect in everyday clinical practice the role that these conditions have on patient clinical status, as well as their relationship with prognosis. In this complex scenario, multidisciplinary discussion in which different experts offer their competencies is mandatory for proper therapeutic decision-making.

Both valvular heart diseases and cardiomyopathies are diseases with wide phenotypic heterogeneity, resulting from the complex interplay among genotype, epigenetic factors and environmental factors. A better understanding of the shared pathophysiological mechanisms of valvular heart diseases and cardiomyopathies, as well as of the prevalence and predisposing factors to their coexistence, is needed to further optimize the risk stratification and treatment of these patients. Indeed, fundamental research studies aimed at identifying the pathogenic molecular pathways with a holistic approach are of outmost importance, because they are the starting point for developing medical treatments that target the heart muscle and valves at the same time. Moreover, prospective studies aimed at evaluating the safety and efficacy of a specific treatment approach when the two diseases coexist are warranted and might contribute to improve the systematic research of a myocardial disorder among patients with valvular heart disease and vice versa, from the perspective of patient-tailored care.

Published online: 10 August 2023

References

1. Vahanian, A. et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur. Heart J.* **43**, 561–632 (2022).
2. Elliott, P. et al. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology working group on myocardial and pericardial diseases. *Eur. Heart J.* **29**, 270–276 (2008).
3. McKenna, W. J., Maron, B. J. & Thiene, G. Classification, epidemiology, and global burden of cardiomyopathies. *Circ. Res.* **121**, 722–730 (2017).
4. Lancellotti, P., Zamorano, J. L. & Vannan, M. A. Imaging challenges in secondary mitral regurgitation: unsolved issues and perspectives. *Circ. Cardiovasc. Imaging* **7**, 735–746 (2014).
5. Wigle, E. D. Cardiomyopathy: the diagnosis of hypertrophic cardiomyopathy. *Heart* **86**, 709–714 (2001).
6. Milleron, O. et al. Eclipsed mitral regurgitation: an unusual cause of acute heart failure. *Eur. Heart J. Cardiovasc. Imaging* **18**, 1163–1169 (2017).
7. Agricola, E. et al. Non-ischemic dilated cardiopathy: prognostic value of functional mitral regurgitation. *Int. J. Cardiol.* **146**, 426–428 (2010).
8. He, S., Fontaine, A. A., Schwammenthal, E., Yoganathan, A. P. & Levine, R. A. Integrated mechanism for functional mitral regurgitation: leaflet restriction versus coapting force: in vitro studies. *Circulation* **96**, 1826–1834 (1997).
9. Levack, M. M. et al. Three-dimensional echocardiographic analysis of mitral annular dynamics: implication for annuloplasty selection. *Circulation* **126**, S183–S188 (2012).
10. Rossi, A. et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. *Heart* **97**, 1675–1680 (2011).
11. Mack, M. & Grayburn, P. Guideline-directed medical therapy for secondary mitral regurgitation: more questions than answers! *JACC Heart Fail.* **5**, 660–662 (2017).
12. El Sabbagh, A., Reddy, Y. N. V. & Nishimura, R. A. Mitral valve regurgitation in the contemporary era: insights into diagnosis, management, and future directions. *JACC Cardiovasc. Imaging* **11**, 628–643 (2018).
13. Kajimoto, K., Minami, Y., Otsubo, S. & Sato, N. Ischemic or nonischemic functional mitral regurgitation and outcomes in patients with acute decompensated heart failure with preserved or reduced ejection fraction. *Am. J. Cardiol.* **120**, 809–816 (2017).
14. Trichon, B. H., Felker, G. M., Shaw, L. K., Cabell, C. H. & O'Connor, C. M. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. *Am. J. Cardiol.* **91**, 538–543 (2003).
15. Goliasch, G. et al. Refining the prognostic impact of functional mitral regurgitation in chronic heart failure. *Eur. Heart J.* **39**, 39–46 (2018).
16. Seneviratne, B., Moore, G. A. & West, P. D. Effect of captopril on functional mitral regurgitation in dilated heart failure: a randomised double blind placebo controlled trial. *Br. Heart J.* **72**, 63–68 (1994).
17. Nasser, R. et al. Evolution of functional mitral regurgitation and prognosis in medically managed heart failure patients with reduced ejection fraction. *JACC Heart Fail.* **5**, 652–659 (2017).
18. Pagnesi, M. et al. Clinical impact of changes in mitral regurgitation severity after medical therapy optimization in heart failure. *Clin. Res. Cardiol.* **111**, 912–923 (2022).
19. Kang, D. H. et al. Angiotensin receptor neprilysin inhibitor for functional mitral regurgitation. *Circulation* **139**, 1354–1365 (2019).
20. Cabrera-Bueno, F. et al. Persistence of secondary mitral regurgitation and response to cardiac resynchronization therapy. *Eur. J. Echocardiogr.* **11**, 131–137 (2010).
21. Verhaert, D. et al. Impact of mitral regurgitation on reverse remodeling and outcome in patients undergoing cardiac resynchronization therapy. *Circ. Cardiovasc. Imaging* **5**, 21–26 (2012).
22. Van Bommel, R. J. et al. Cardiac resynchronization therapy as a therapeutic option in patients with moderate–severe functional mitral regurgitation and high operative risk. *Circulation* **124**, 912–919 (2011).
23. Spartera, M. et al. Role of cardiac dyssynchrony and resynchronization therapy in functional mitral regurgitation. *Eur. Heart J. Cardiovasc. Imaging* **17**, 471–480 (2016).
24. Acker, M. A. et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. *N. Engl. J. Med.* **370**, 23–32 (2014).
25. Smith, P. K. et al. Cardiothoracic Surgical Trials Network Investigators. Surgical treatment of moderate ischemic mitral regurgitation. *N. Engl. J. Med.* **371**, 2178–2188 (2014).
26. Obadia, J. F. et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N. Engl. J. Med.* **379**, 2297–2306 (2018).
27. Stone, G. W. et al. Transcatheter mitral-valve repair in patients with heart failure. *N. Engl. J. Med.* **379**, 2307–2318 (2018).
28. Chiarito, M. et al. Edge-to-edge percutaneous mitral repair for functional ischaemic and non-ischaemic mitral regurgitation: a systematic review and meta-analysis. *Esc. Heart Fail.* **9**, 3177–3187 (2022).
29. Grayburn, P. A., Sannino, A. & Packer, M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. *JACC Cardiovasc. Imaging* **12**, 353–362 (2019).
30. Lindenfeld, J. et al. Association of effective regurgitation orifice area to left ventricular end-diastolic volume ratio with transcatheter mitral valve repair outcomes: a secondary analysis of the COAPT trial. *JAMA Cardiol.* **6**, 427–443 (2021).
31. Ooms, J. F. et al. Transcatheter edge-to-edge repair in proportionate versus disproportionate functional mitral regurgitation. *J. Am. Soc. Echocardiogr.* **35**, 105–115e8 (2022).
32. Orban, M. et al. Impact of proportionality of secondary mitral regurgitation on outcome after transcatheter mitral valve repair. *JACC Cardiovasc. Imaging* **14**, 715–725 (2021).
33. Adamo, M. et al. COAPT-like profile predicts long-term outcomes in patients with secondary mitral regurgitation undergoing mitraclip implantation. *JACC Cardiovasc. Interv.* **14**, 15–25 (2021).
34. Brener, M. I. et al. Right ventricular–pulmonary arterial coupling in patients with HF secondary MR: analysis from the COAPT trial. *JACC Cardiovasc. Interv.* **14**, 2231–2242 (2021).
35. Otto, C. M. et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* **143**, e72–e227 (2021).
36. Rose, E. A. et al. Long-term use of a left ventricular assist device for end-stage heart failure. *N. Engl. J. Med.* **345**, 1435–1443 (2001).
37. Maron, B. J. et al. Diagnosis and evaluation of hypertrophic cardiomyopathy: JACC state-of-the-art review. *J. Am. Coll. Cardiol.* **79**, 372–389 (2022).
38. Ommen, S. R. et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary: a report of The American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J. Am. Coll. Cardiol.* **76**, 3022–3055 (2020).
39. Woo, A. & Jedrzkiewicz, S. The mitral valve in hypertrophic cardiomyopathy: it's a long story. *Circulation* **124**, 9–12 (2011).
40. Maron, M. S. et al. Mitral valve abnormalities identified by cardiovascular magnetic resonance represent a primary phenotypic expression of hypertrophic cardiomyopathy. *Circulation* **124**, 40–47 (2011).
41. Levine, R. A. et al. Papillary muscle displacement causes systolic anterior motion of the mitral valve. Experimental validation and insights into the mechanism of subaortic obstruction. *Circulation* **91**, 1189–1195 (1995).
42. Klues, H. G., Roberts, W. C. & Maron, B. J. Anomalous insertion of papillary muscle directly into anterior mitral leaflet in hypertrophic cardiomyopathy. Significance in producing left ventricular outflow obstruction. *Circulation* **84**, 1188–1197 (1991).
43. Groarke, J. D. et al. Intrinsic mitral valve alterations in hypertrophic cardiomyopathy sarcomere mutation carriers. *Eur. Heart J. Cardiovasc. Imaging* **19**, 1109–1116 (2018).
44. Ferrazzi, P. et al. Congenital muscular mitral-aortic discontinuity identified in patients with obstructive hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **76**, 2238–2247 (2020).
45. Olivotto, I., Cecchi, F., Poggesi, C. & Yacoub, M. H. Developmental origins of hypertrophic cardiomyopathy phenotypes: a unifying hypothesis. *Nat. Rev. Cardiol.* **6**, 317–321 (2009).
46. Djenoune, L., Berg, K., Brueckner, M. & Yuan, S. A change of heart: new roles for cilia in cardiac development and disease. *Nat. Rev. Cardiol.* **19**, 211–227 (2022).

47. Wigle, E. D., Adelman, A., Auger, P. & Marquis, Y. Mitral regurgitation in muscular subaortic stenosis. *Am. J. Cardiol.* **24**, 698–706 (1969).
48. Rowin, E. J., Maron, B. J., Olivotto, I. & Maron, M. S. Role of exercise testing in hypertrophic cardiomyopathy. *JACC Cardiovasc. Imaging* **10**, 1374–1386 (2017).
49. Maron, M. S. et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N. Engl. J. Med.* **348**, 295–303 (2003).
50. Maron, B. J., Rowin, E. J., Udelson, J. E. & Maron, M. S. Clinical spectrum and management of heart failure in hypertrophic cardiomyopathy. *JACC Heart Fail.* **6**, 353–363 (2018).
51. Elliott, P. M. 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.* **35**, 2733–2779 (2014).
52. Maron, B. J. et al. Left atrial remodeling in hypertrophic cardiomyopathy and susceptibility markers for atrial fibrillation identified by cardiovascular magnetic resonance. *Am. J. Cardiol.* **113**, 1394–1400 (2014).
53. Feneon, D. et al. Impact of exercise-induced mitral regurgitation on hypertrophic cardiomyopathy outcomes. *Eur. Heart J. Cardiovasc. Imaging* **17**, 1110–1117 (2016).
54. Olivotto, I., Cecchi, F., Poggesi, C. & Yacoub, M. H. Patterns of disease progression in hypertrophic cardiomyopathy: an individualized approach to clinical staging. *Circ. Heart Fail.* **5**, 535–546 (2012).
55. Hong, J. H. et al. Mitral regurgitation in patients with hypertrophic obstructive cardiomyopathy: implications for concomitant valve procedures. *J. Am. Coll. Cardiol.* **68**, 1497–1504 (2016).
56. Iacovoni, A. et al. A contemporary European experience with surgical septal myectomy in hypertrophic cardiomyopathy. *Eur. Heart J.* **33**, 2080–2087 (2012).
57. Pelliccia, F. et al. Multidisciplinary evaluation and management of obstructive hypertrophic cardiomyopathy in 2020: towards the HCM Heart Team. *Int. J. Cardiol.* **304**, 86–92 (2020).
58. Maron, B. J. et al. The case for surgery in obstructive hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **44**, 2044–2053 (2004).
59. Ferrazzi, P. et al. Transaortic chordal cutting: mitral valve repair for obstructive hypertrophic cardiomyopathy with mild septal hypertrophy. *J. Am. Coll. Cardiol.* **66**, 1687–1696 (2015).
60. Morcos, M., Strobel, A., Messenger, J. & Gill, E. Treatment of severe left ventricular outflow tract obstruction and mitral regurgitation with alcohol septal ablation. *CASE* **6**, 387–391 (2022).
61. Nielsen, C. D., Fernandes, V. & Spencer, W. H. III Alcohol septal ablation for obstructive hypertrophic cardiomyopathy. *Am. Heart Hosp. J.* **1**, 83–90 (2003).
62. Krajcer, Z., Leachman, R. D., Cooley, D. A. & Coronado, R. Septal myotomy-myomectomy versus mitral valve replacement in hypertrophic cardiomyopathy. Ten-year follow-up in 185 patients. *Circulation* **80**, I57–I64 (1989).
63. Sherrid, M. V., Balaram, S., Kim, B., Axel, L. & Swistel, D. G. The mitral valve in obstructive hypertrophic cardiomyopathy: a test in context. *J. Am. Coll. Cardiol.* **67**, 1846–1858 (2016).
64. Afanasyev, A. V. et al. Edge-to-Edge repair versus secondary cord cutting during septal myectomy in patients with hypertrophic obstructive cardiomyopathy: a pilot randomised study. *Heart Lung Circ.* **30**, 438–445 (2021).
65. Thomas, F., Rader, F. & Siegel, R. J. The use of mitraclip for symptomatic patients with hypertrophic obstructive cardiomyopathy. *Cardiology* **137**, 58–61 (2017).
66. van der Lee, C., Kofflard, M. J. & van Herwerden, L. A. Sustained improvement after combined anterior mitral leaflet extension and myectomy in hypertrophic obstructive cardiomyopathy. *Circulation* **108**, 2088–2092 (2003).
67. Rankin, J. S. et al. A new mitral valve repair strategy for hypertrophic obstructive cardiomyopathy. *J. Heart Valve Dis.* **17**, 642–647 (2008).
68. Delmo Walter, E. M., Siniawski, H. & Hetzer, R. Sustained improvement after combined anterior mitral valve leaflet retention plasty and septal myectomy in preventing systolic anterior motion in hypertrophic obstructive cardiomyopathy in children. *Eur. J. Cardiothorac. Surg.* **36**, 546–552 (2009).
69. Nasseri, B. A. et al. Combined anterior mitral valve leaflet retention plasty and septal myectomy in patients with hypertrophic obstructive cardiomyopathy. *Eur. J. Cardiothorac. Surg.* **40**, 1515–1520 (2011).
70. Nistri, S. et al. β-Blockers for prevention of exercise-induced left ventricular outflow tract obstruction in patients with hypertrophic cardiomyopathy. *Am. J. Cardiol.* **110**, 715–719 (2012).
71. Cohen, L. S. & Braunwald, E. Amelioration of angina pectoris in idiopathic hypertrophic subaortic stenosis with beta-adrenergic blockade. *Circulation* **35**, 847–851 (1967).
72. Dybro, A. M. et al. Randomized trial of metoprolol in patients with obstructive hypertrophic cardiomyopathy. *J. Am. Coll. Cardiol.* **78**, 2505–2517 (2021).
73. Maron, B. J. Clinical course and management of hypertrophic cardiomyopathy. *N. Engl. J. Med.* **379**, 655–668 (2018).
74. Olivotto, I. et al. EXPLORER-HCM_Study Investigators. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* **396**, 759–769 (2020).
75. Maron, M. S. & Ommen, S. R. Exploring new and old therapies for obstructive hypertrophic cardiomyopathy: mavacamten in perspective. *Circulation* **143**, 1181–1183 (2021).
76. Schönbeck, M. H. et al. Long-term follow-up in hypertrophic obstructive cardiomyopathy after septal myectomy. *Ann. Thorac. Surg.* **65**, 1207–1214 (1998).
77. Sun, D. et al. Posterior wall thickness associates with survival following septal myectomy for obstructive hypertrophic cardiomyopathy. *JACC Heart Fail.* **10**, 831–837 (2022).
78. Woo, A. et al. Clinical and echocardiographic determinants of long-term survival after surgical myectomy in obstructive hypertrophic cardiomyopathy. *Circulation* **111**, 2033–2041 (2005).
79. Gigli, M. et al. Genetic risk of arrhythmic phenotypes in patients with dilated cardiomyopathy. *J. Am. Coll. Cardiol.* **74**, 1480–1490 (2019).
80. De Frutos, F. et al. Natural history of MYH7-related dilated cardiomyopathy. *J. Am. Coll. Cardiol.* **80**, 1447–1461 (2022).
81. Paldino, A. et al. Prognostic prediction of genotype vs phenotype in genetic cardiomyopathies. *J. Am. Coll. Cardiol.* **80**, 1981–1994 (2022).
82. Ho, C. Y. et al. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe). *Circulation* **138**, 1387–1398 (2018).
83. Arends, M. et al. Characterization of classical and nonclassical fabry disease: a multicenter study. *J. Am. Soc. Nephrol.* **28**, 1631–1641 (2017).
84. LaHaye, S., Lincoln, J. & Garg, V. Genetics of valvular heart disease. *Curr. Cardiol. Rep.* **16**, 487 (2014).
85. Durst, R. et al. Mutations in DCHS1 cause mitral valve prolapse. *Nature* **525**, 109–113 (2015).
86. Ta-Shma, A. et al. Congenital valvular defects associated with deleterious mutations in the PLD1 gene. *J. Med. Genet.* **54**, 278–286 (2017).
87. Wünnemann, F. et al. Loss of ADAMTS19 causes progressive non-syndromic heart valve disease. *Nat. Genet.* **52**, 40–47 (2020).
88. Hiemstra, Y. L. et al. Familial occurrence of mitral regurgitation in patients with mitral valve prolapse undergoing mitral valve surgery. *Eur. J. Prev. Cardiol.* **27**, 272–280 (2020).
89. Lillo, R. et al. Echocardiography in Anderson–Fabry disease. *Rev. Cardiovasc. Med.* **23**, 201 (2022).
90. Prasad, M. et al. Cardiorheumatology: cardiac involvement in systemic rheumatic disease. *Nat. Rev. Cardiol.* **12**, 168–176 (2015).
91. Shammas, R. L. & Movahed, A. Sarcoidosis of the heart. *Clin. Cardiol.* **16**, 462–472 (1993).
92. Remenyi, B. et al. Valvular aspects of rheumatic heart disease. *Lancet* **387**, 1335–1346 (2016).
93. Desai, M. Y., Jellis, C. L., Kotecha, R., Johnston, D. R. & Griffin, B. P. Radiation-associated cardiac disease: a practical approach to diagnosis and management. *JACC Cardiovasc. Imaging* **11**, 1132–1149 (2018).
94. Freed, L. A. et al. Mitral valve prolapse in the general population: the benign nature of echocardiographic features in the Framingham Heart Study. *J. Am. Coll. Cardiol.* **40**, 1298–1304 (2002).
95. Van Wijngaarden, A. L., Kruithof, B. P. T., Vinella, T., Barge-Schaapveld, D. Q. C. M. & Ajmone Marsan, N. Characterization of degenerative mitral valve disease: differences between fibroelastic deficiency and Barlow's disease. *J. Cardiovasc. Dev. Dis.* **8**, 23 (2021).
96. Nascimento, R. et al. Is mitral valve prolapse a congenital or acquired disease? *Am. J. Cardiol.* **79**, 226–227 (1997).
97. Kruithof, B. P. T. et al. Stress-induced remodelling of the mitral valve: a model for leaflet thickening and superimposed tissue formation in mitral valve disease. *Cardiovasc. Res.* **5**, 931–943 (2020).
98. Van Wijngaarden, A. L. et al. Identification of known and unknown genes associated with mitral valve prolapse using an exome slice methodology. *J. Med. Genet.* **57**, 843–850 (2020).
99. Delwarde, C. et al. Genetics and pathophysiology of mitral valve prolapse. *Front. Cardiovasc. Med.* **10**, 1077788 (2023).
100. Gulotta, S. J., Gulco, L., Padmanabhan, V. & Miller, S. The syndrome of systolic click, murmur, and mitral valve prolapse — a cardiomyopathy? *Circulation* **49**, 717–728 (1974).
101. Yang, L. T. et al. Mitral valve prolapse patients with less than moderate mitral regurgitation exhibit early cardiac chamber remodeling. *J. Am. Soc. Echocardiogr.* **33**, 815–825 (2020).
102. Romero Daza, A. et al. Mitral valve prolapse morphofunctional features by cardiovascular magnetic resonance: more than just a valvular disease. *J. Cardiovasc. Magn. Reson.* **23**, 107 (2021).
103. Kitkungvan, D. et al. Myocardial fibrosis in patients with primary mitral regurgitation with and without prolapse. *J. Cardiovasc. Magn. Reson.* **72**, 823–834 (2018).
104. Han, Y. et al. Cardiovascular magnetic resonance characterization of mitral valve prolapse. *JACC Cardiovasc. Imaging* **1**, 294–303 (2008).
105. Bui, A. H. et al. Diffuse myocardial fibrosis in patients with mitral valve prolapse and ventricular arrhythmia. *Heart* **103**, 204–209 (2017).
106. Constant Dit Beaufils, A. L. et al. Replacement myocardial fibrosis in patients with mitral valve prolapse: relation to mitral regurgitation, ventricular remodeling, and arrhythmia. *Circulation* **143**, 1763–1774 (2021).
107. Sabbag, A. et al. EHRA expert consensus statement on arrhythmic mitral valve prolapse and mitral annular disjunction complex in collaboration with the ESC Council on Valvular Heart Disease and the European Association of Cardiovascular Imaging endorsed by the Heart Rhythm Society, by the Asia Pacific Heart Rhythm Society, and by the Latin American Heart Rhythm Society. *Europace* **24**, 1981–2003 (2022).
108. Perazzolo Marra, M. et al. Morphofunctional abnormalities of mitral annulus and arrhythmic mitral valve prolapse. *Circ. Cardiovasc. Imaging* **9**, e005030 (2016).
109. Basso, C. et al. Arrhythmic mitral valve prolapse and sudden cardiac death. *Circulation* **132**, 556–566 (2015).
110. Van Wijngaarden, A. L. et al. Parameters associated with ventricular arrhythmias in mitral valve prolapse with significant regurgitation. *Heart* **107**, 411–418 (2021).

111. Dejgaard, L. A. et al. The mitral annulus disjunction arrhythmic syndrome. *J. Am. Coll. Cardiol.* **72**, 1600–1609 (2018).
112. Toh, H. et al. Prevalence and extent of mitral annular disjunction in structurally normal hearts: comprehensive 3D analysis using cardiac computed tomography. *Eur. Heart J. Cardiovasc. Imaging* **22**, 614–622 (2021).
113. Faletra, F. F. et al. Morphology of mitral annular disjunction in mitral valve prolapse. *J. Am. Soc. Echocardiogr.* **35**, 176–186 (2022).
114. Basso, C. et al. An echocardiographic survey of primary school children for bicuspid aortic valve. *Am. J. Cardiol.* **93**, 661–663 (2004).
115. Siu, S. C. & Silversides, C. K. Bicuspid aortic valve disease. *J. Am. Coll. Cardiol.* **55**, 2789–2800 (2010).
116. Roberts, W. C. & Ko, J. M. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation* **111**, 920–925 (2005).
117. Padang, R., Bagnall, R. D. & Semsarian, C. Genetic basis of familial valvular heart disease. *Circ. Cardiovasc. Genet.* **5**, 569–580 (2012).
118. Glick, B. N. & Roberts, W. C. Congenitally bicuspid aortic valve in multiple family members. *Am. J. Cardiol.* **73**, 400–404 (1994).
119. Martin, L. J. et al. Evidence in favor of linkage to human chromosomal regions 18q, 5q and 13q for bicuspid aortic valve and associated cardiovascular malformations. *Hum. Genet.* **121**, 275–284 (2007).
120. Fedak, P. W. et al. Clinical and pathophysiological implications of a bicuspid aortic valve. *Circulation* **106**, 900–904 (2002).
121. Yassine, N. M., Shahram, J. T. & Body, S. C. Pathogenic mechanisms of bicuspid aortic valve aortopathy. *Front. Physiol.* **8**, 687 (2017).
122. Owens, G. K., Kumar, M. S. & Wamhoff, B. R. Molecular regulation of vascular smooth muscle cell differentiation in development and disease. *Physiol. Rev.* **84**, 767–801 (2004).
123. Feizi, O., Farrer Brown, G. & Emanuel, R. Familial study of hypertrophic cardiomyopathy and congenital aortic valve disease. *Am. J. Cardiol.* **41**, 956–964 (1978).
124. Brown, P. S. Jr, Roberts, C. S., McIntosh, C. L., Roberts, W. C. & Clark, R. E. Combined obstructive hypertrophic cardiomyopathy and stenotic congenitally bicuspid aortic valve. *Am. J. Cardiol.* **66**, 1273–1275 (1990).
125. Agarwal, A. et al. Left ventricular noncompaction in patients with bicuspid aortic valve. *J. Am. Soc. Echocardiogr.* **26**, 1306–1313 (2013).
126. Jeong, H. et al. Prevalence, characteristics, and clinical significance of concomitant cardiomyopathies in subjects with bicuspid aortic valves. *Yonsei Med. J.* **60**, 816–823 (2019).
127. Galat, A. et al. Aortic stenosis and transthyretin cardiac amyloidosis: the chicken or the egg? *Eur. Heart J.* **37**, 3525–3531 (2016).
128. Tanskanen, M. et al. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: a population based autopsy study. *Ann. Med.* **40**, 232–239 (2008).
129. Osnabrugge, R. L. et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J. Am. Coll. Cardiol.* **62**, 1002–1012 (2013).
130. Cooper, J. H. Localized dystrophic amyloidosis of heart valves. *Hum. Pathol.* **14**, 649–653 (1983).
131. Conte, M. et al. Isolated valve amyloidosis in aortic stenosis: a new clinical scenario? *J. Am. Coll. Cardiol.* **79**, 3476 (2022).
132. Kristen, A. V. et al. High prevalence of amyloid in 150 surgically removed heart valves — a comparison of histological and clinical data reveals a correlation to atheroinflammatory conditions. *Cardiovasc. Pathol.* **19**, 228–235 (2010).
133. Fujimoto, T. et al. Case with transthyretin amyloid cardiomyopathy complicated with rapidly progressive aortic stenosis possibly caused by amyloid deposition in the aortic valve. *Circ. Cardiovasc. Imaging* **14**, e013357 (2021).
134. Singal, A. K. et al. Concomitant transthyretin amyloidosis and severe aortic stenosis in elderly Indian population: a pilot study. *JACC CardioOncol* **3**, 565–576 (2021).
135. Merlini, G. & Bellotti, V. Molecular mechanisms of amyloidosis. *N. Engl. J. Med.* **349**, 583–596 (2003).
136. Henderson, B. C. et al. Oxidative remodeling in pressure overload induced chronic heart failure. *Eur. J. Heart Fail.* **9**, 450–457 (2007).
137. Park, J. Y. et al. Association of inflammation, myocardial fibrosis and cardiac remodelling in patients with mild aortic stenosis as assessed by biomarkers and echocardiography. *Clin. Exp. Pharmacol. Physiol.* **41**, 185–191 (2014).
138. Rosenblum, H. et al. Unveiling outcomes in coexisting severe aortic stenosis and transthyretin cardiac amyloidosis. *Eur. J. Heart Fail.* **23**, 250–258 (2021).
139. Chacko, L. et al. Echocardiographic phenotype and prognosis in transthyretin cardiac amyloidosis. *Eur. Heart J.* **41**, 1439–1447 (2020).
140. Ricci, F. et al. Prognostic significance of cardiac amyloidosis in patients with aortic stenosis: a systematic review and meta-analysis. *JACC Cardiovasc. Imaging* **14**, 293–295 (2021).
141. Myasoedova, V. A. et al. Red flags, prognostic impact, and management of patients with cardiac amyloidosis and aortic valve stenosis: a systematic review and meta-analysis. *Front. Med.* **9**, 858281 (2022).
142. Ternacle, J. et al. Aortic stenosis and cardiac amyloidosis: JACC review topic of the week. *J. Am. Coll. Cardiol.* **74**, 2638–2651 (2019).
143. Dahl Pedersen, A. L. et al. Prevalence and prognostic implications of increased apical-to-basal strain ratio in patients with aortic stenosis undergoing transcatheter aortic valve replacement. *J. Am. Soc. Echocardiogr.* **33**, 1465–1473 (2020).
144. Cannata, F. et al. Transcatheter aortic valve replacement in aortic stenosis and cardiac amyloidosis: a systematic review and meta-analysis. *ESC Heart Fail.* **9**, 3188–3197 (2022).
145. Nitsche, C. et al. Prevalence and outcomes of concomitant aortic stenosis and cardiac amyloidosis. *J. Am. Coll. Cardiol.* **77**, 128–139 (2021).
146. Scully, P. R. et al. Prevalence and outcome of dual aortic stenosis and cardiac amyloid pathology in patients referred for transcatheter aortic valve implantation. *Eur. Heart J.* **41**, 2759–2767 (2020).
147. Burzotta, F. et al. Clinical impact of heart team decisions for patients with complex valvular heart disease: a large, single-center experience. *J. Am. Heart Assoc.* **11**, e024404 (2022).
148. Ammar, K. A. et al. Cardiac amyloidosis presenting as severe mitral regurgitation. *JACC Cardiovasc. Imaging* **9**, 1003–1006 (2016).
149. Krishnaswamy, A., Hanna, M., Goodman, A. & Kapadia, S. R. First reported case of mitraclip placement due to mitral valve flail in the setting of cardiac amyloidosis. *Circ. Heart Fail.* **9**, e003069 (2016).
150. Donà, C. et al. Unveiling cardiac amyloidosis, its characteristics, and outcomes among patients with MR undergoing transcatheter edge-to-edge MV repair. *JACC Cardiovasc. Interv.* **15**, 1748–1758 (2022).
151. Braunlin, E. A. et al. Cardiac disease in patients with mucopolysaccharidosis: presentation, diagnosis and management. *J. Inherit. Metab. Dis.* **34**, 1183–1197 (2011).
152. Rosser, B. A., Chan, C. & Hoschtitzky, A. Surgical management of valvular heart disease in mucopolysaccharidoses: a review of literature. *Biomedicines* **10**, 375 (2022).
153. Mori, N. et al. Transcatheter aortic valve implantation for severe aortic stenosis in a patient with mucopolysaccharidosis type II (Hunter syndrome) accompanied by severe airway obstruction. *J. Cardiol. Cases* **25**, 49–51 (2021).
154. Lillo, R., Ingrasciotta, G., Locorotondo, G., Lombardo, A. & Graziani, F. An unusual case of mitral valve chordal rupture. *Echocardiography* **38**, 2109–2111 (2021).
155. Calcagni, G. et al. Cardiac defects, morbidity and mortality in patients affected by RASopathies. CARNET study results. *Int. J. Cardiol.* **245**, 92–98 (2017).
156. Sade, L. E. & Akdogan, A. Imaging for screening cardiovascular involvement in patients with systemic rheumatologic diseases: more questions than answers. *Eur. Heart J. Cardiovasc. Imaging* **20**, 967–978 (2019).
157. Donnellan, E. et al. Outcomes of patients with mediastinal radiation-associated severe aortic stenosis undergoing transcatheter aortic valve replacement. *Circulation* **138**, 1752–1754 (2018).
158. Donnellan, E. et al. Longterm outcomes of patients with mediastinal radiation-associated severe aortic stenosis and subsequent surgical aortic valve replacement: a matched cohort study. *J. Am. Heart Assoc.* **6**, e005396 (2017).
159. Donnellan, E. et al. Outcomes of patients with mediastinal radiation-associated mitral valve disease undergoing cardiac surgery. *Circulation* **140**, 1288–1290 (2019).
160. Wilde, A. A. M. et al. Expert consensus statement on the state of genetic testing for cardiac diseases. *Europace* **24**, 1307–1367 (2022).
161. Rapezzi, C. et al. Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC working group on myocardial and pericardial diseases. *Eur. Heart J.* **34**, 1448–1458 (2013).

Author contributions

N.A.M., F.G., M.C.M., H.W.W. and R.L. researched data for the article. N.A.M., F.G., M.C.M. and R.L. provided substantial contribution to the discussion of content. All the authors wrote the manuscript and reviewed and/or edited it before submission.

Competing interests

N.A.M. received speaker fees from Abbott Vascular, GE Healthcare and Philips Ultrasound and a research grant from Alnylam and Pfizer. F.G. received honoraria for board meetings; speaker fees from Sanofi-Genzyme, Shire, Takeda and Pfizer and research grants from Takeda and Pfizer. R.L. received honoraria for board meetings from Sanofi-Genzyme and Shire. J.J.B. received speaker fees from Abbott Vascular. F.B. received speaker fees from Abiomed, Abbott, Medtronic and Terumo. J.W.J. and his department received research grants from and/or was a speaker (with or without lecture fees) at meetings sponsored or supported by Abbott, Amarin, Amgen, Athera, Biotronik, Boston Scientific, Dalcor, Daiichi Sankyo, Edwards Lifesciences, GE Healthcare, Johnson and Johnson, Lilly, Medtronic, Merck-Schering-Plough, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi Aventis, the Netherlands Heart Foundation, CardioVascular Research the Netherlands, the Netherlands Heart Institute and the European Community Framework KP7 Programme. F.C. received personal fees from Amgen, Astra Zeneca, BMS, GlyCardial Diagnostics and Servier. The other authors declare no competing interests.

Additional information

Peer review information *Nature Reviews Cardiology* thanks Christopher Semsarian and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.