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POSITION PAPER

Heart failure in cardiomyopathies: a position paper from the Heart Failure Association of the European Society of Cardiology

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Cardiomyopathies are a heterogeneous group of heart muscle diseases and an important cause of heart failure (HF). Current knowledge on incidence, pathophysiology and natural history of HF in cardiomyopathies is limited, and distinct features of their therapeutic responses have not been systematically addressed. Therefore, this position paper focuses on epidemiology, pathophysiology, natural history and latest developments in treatment of HF in patients with dilated (DCM), hypertrophic (HCM) and restrictive (RCM) cardiomyopathies. In DCM, HF with reduced ejection fraction (HFrEF) has high incidence and prevalence and represents the most frequent cause of death, despite improvements in treatment. In addition, advanced HF in DCM is one of the leading indications for heart transplantation. In HCM, HF with preserved ejection (HFpEF) affects most patients with obstructive, and ~10% of patients with non-obstructive HCM. A timely treatment is important, since development of advanced HF, although rare in HCM, portends a poor prognosis. In RCM, HFpEF is common, while HFrEF occurs later and more frequently in amyloidosis or iron overload/haemochromatosis. Irrespective of RCM aetiology, HF is a harbinger of a poor outcome. Recent advances in our understanding of the mechanisms underlying the development of HF in cardiomyopathies have significant implications for therapeutic decision-making. In addition, new aetiology-specific treatment options (e.g. enzyme replacement therapy, transthyretin stabilizers, immunoadsorption, immunotherapy, etc.) have shown a potential to improve outcomes. Still, causative therapies of many cardiomyopathies are lacking, highlighting the need for the development of effective strategies to prevent and treat HF in cardiomyopathies.

Keywords Heart failure • Dilated cardiomyopathy • Hypertrophic cardiomyopathy • Restrictive cardiomyopathy • Peripartum cardiomyopathy • Epidemiology • Natural history • Pathophysiology • Management

Introduction

Cardiomyopathies are a heterogeneous group of heart muscle diseases, including dilated (DCM), hypertrophic (HCM), restrictive (RCM), arrhythmogenic right ventricular (ARVC), and non-classified cardiomyopathies that frequently present as the syndrome of heart failure (HF).[1] The variety of causes, multiple underlying pathophysiological mechanisms and different phenotypic expressions influence their presentation and response to treatment.[1] Although patients with cardiomyopathies have been represented in clinical trials, distinct features of their therapeutic responses, relative to other aetiologies of HF, remain unknown.

For HF with reduced ejection fraction (< 40%, HFrEF), standard therapy is indicated regardless of the underlying cause. In contrast, for selected cardiomyopathies, specific treatment options have been introduced, targeting specific underlying pathophysiology (e.g. enzyme replacement therapy, transthyretin stabilizers, gene silencing, monoclonal antibodies, immunotherapy, and others), thus increasing the perspectives for improved outcomes. Therefore, this position paper is focused on the incidence, pathophysiology, natural history, outcomes and treatment of HF due to specific heart muscle diseases, including DCM, HCM and RCM. Clinical presentation of ARVC is usually dominated by ventricular arrhythmia, while HF (right heart or biventricular) may occur in the minority of patients with advanced disease. Considering its specific clinical characteristic, ARVC has not been addressed in this document.

Since HF is often the presenting clinical syndrome in DCM, HCM and RCM, a practical stepwise approach has been suggested in *Figure 1*. This approach should aid in clinical assessment of the phenotype [including HFrEF; HF with mid-range ejection fraction (40–49%); HF with preserved ejection fraction (≥ 50%, HFpEF)], and aetiology of HF in cardiomyopathies.

Heart failure in dilated cardiomyopathy

Incidence and prevalence of heart failure in dilated cardiomyopathy

Dilated cardiomyopathy is characterized by ventricular dilatation and systolic dysfunction in the absence of known abnormal loading conditions or significant coronary artery disease.[1] It is considered one of the leading causes of HFrEF worldwide.[2] The reported prevalence of DCM in Europe and North America is ~36 cases per 100 000 population, and the annual incidence ranges between 5 and 7.9 cases per 100 000 population.[3,4] The prevalence of DCM is apparently lower in Eastern Asia (i.e. 14 cases per 100 000 in Japan),[5] and it might be higher in Africa and Latin America compared with Europe.[6,7]

Determining the incidence of HF in DCM is challenging, because of variations in patient selection and underreporting of a specific HF aetiology in many clinical trials and observational studies.

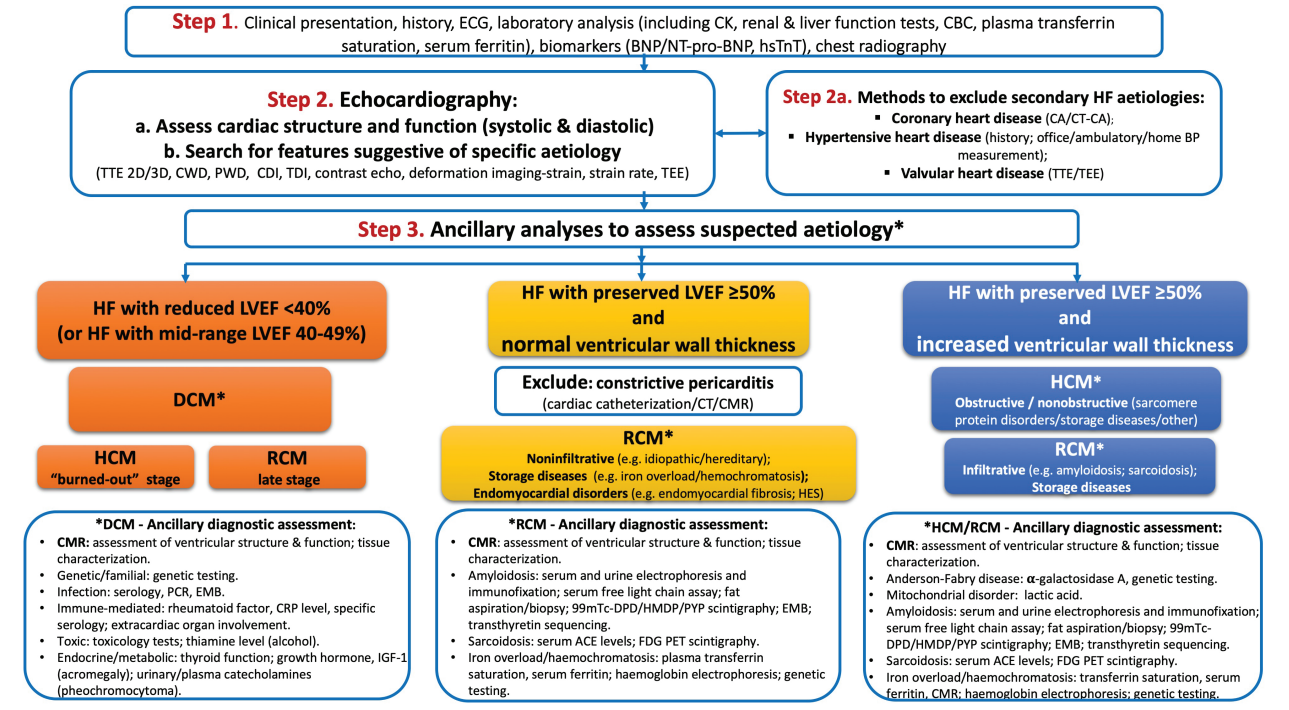

Figure 1 Proposed clinical approach to the assessment of heart failure aetiology in cardiomyopathies. ACE, angiotensin-converting enzyme; BNP, B-type natriuretic peptide; BP, blood pressure; CA, coronary angiography; CBC, complete blood count; CDI, colour Doppler imaging; CK, creatine kinase, CMR, cardiac magnetic resonance; CRP, C-reactive protein; CT-CA, computed tomography coronary angiography; CWD, continuous wave Doppler; DCM, dilated cardiomyopathy; ECG, electrocardiogram; ECV, extracellular volume; EMB, endomyocardial biopsy; FDG, fluorodeoxyglucose; HCM, hypertrophic cardiomyopathy; HES, hypereosinophilic syndrome; HF, heart failure; HMDP, hydroxymethylene diphosphonate; hsTnT, high sensitivity troponin T; IGF-1, insulin-like growth factor-1; LVEF, left ventricular ejection fraction; 99mTc-DPD, technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid; NT-proBNP, N-terminal pro B-type natriuretic peptide; PCR, polymerase chain reaction; PET, positron emission tomography; PYP, pyrophosphate; PWD, pulsed wave Doppler; RCM, restrictive cardiomyopathy; SPECT, single photon emission computed tomography; TDI, tissue Doppler imaging; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

A recent study suggested that among patients with recent-onset (< 6 months) DCM, 32% presented with HF and 66% had at least one HF hospitalization before enrolment.[8] Similarly, in a contemporary cohort of 881 patients with DCM, HF was the most common clinical presentation with a higher incidence in female compared to male patients (i.e. 64% vs. 54%).[9] Compared with men, women presented with more advanced HF as indicated by a higher proportion of the New York Heart Association (NYHA) functional class III–IV symptoms (25% vs. 16%) and had a higher frequency of left bundle branch block (LBBB) at diagnosis (43% vs. 23%).[9] In another study, self-declared black race was associated with a younger age and more severe HF symptoms at diagnosis compared with white race.[10] Furthermore, in a cohort of 3078 patients hospitalized for HF in Denmark and Sweden, individuals with DCM were ~10 years younger (median age, 64 years), and had more severe symptoms and a lower left ventricular ejection fraction (LVEF) (median LVEF, 24%) compared with other HF patients.[11]

There is a broad variation in the reported prevalence of DCM in patients with HF. In trials of HFrEF, DCM has been reported in 12–35% of individuals.[12–14] In observational studies of HF patients, the prevalence of DCM ranged between 8% and 47%.[11,15,16] In a cohort of 156 013 patients hospitalized for HF in the USA, DCM was the stated underlying cause in 31%.[17] These estimates are often approximate because the precise diagnosis of DCM may be lacking in many patients who have not undergone a full diagnostic evaluation.

Advanced HF in DCM accounts for > 40% of patients who receive long-term mechanical circulatory support (MCS), either as a bridge to heart transplantation or for destination therapy.[18,19] DCM is the most common indication for heart transplantation both in the adult and paediatric populations of advanced HF patients and is the third most common indication for heart and lung transplantation in adults.[20–22] The proportion of patients being transplanted for DCM compared with other HF aetiologies has increased in recent years. Currently, in younger (18–39 years) and middle-aged adults (40–59 years), 64% and 51%, respectively, of all heart transplantations are attributable to DCM.[22] After the age of 60 years, DCM is the second most common indication for heart transplantation preceded only by ischaemic heart disease,

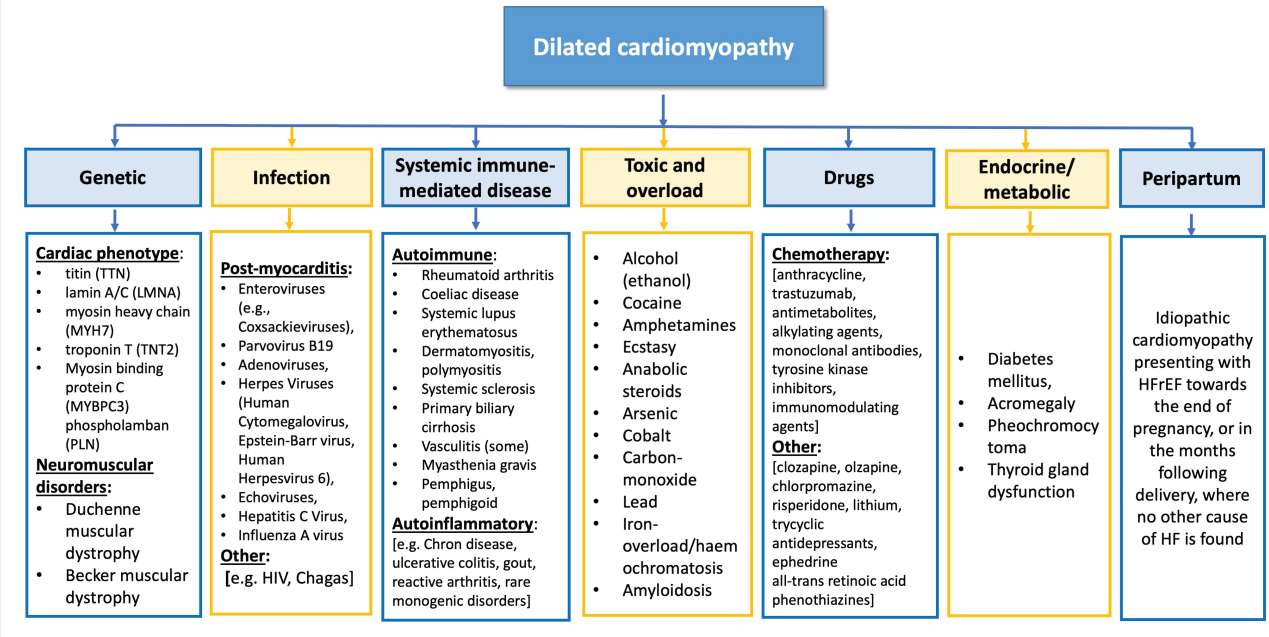

Figure 2 Aetiologies of dilated cardiomyopathy. HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HIV, human immunodeficiency virus.

and accounts for 39% of all heart transplantations. Following transplantation, patients with DCM generally have a favourable short-term and long-term prognosis, with a median survival of 12.2 years.[22]

Pathophysiology of heart failure in dilated cardiomyopathy

The pathophysiology of HF in DCM includes genetic causes, as well as direct myocardial damage caused by infectious or toxic agents, endocrine and metabolic abnormalities, immune-mediated processes and peripartum cardiomyopathy (PPCM)[1] (*Figure 2*). The key morphological alterations underlying the pathophysiology of HF in DCM are summarized in *Figure 3*.

A family history can be detected in 30–50% of cases[23] and a genetic determinant in up to 40% of DCM patients.[1,24] However, this proportion is probably underestimated due to variability in disease penetrance and clinical presentation. To date, more than 60 genes coding for sarcomere proteins, cytoskeleton, nuclear envelope, sarcolemma, ion channels and/or intercellular junction molecules have been implicated in the pathogenesis of DCM.[24,25] Amongst the most common is truncating titin mutation, implicated in the pathogenesis of ~13% and 25% of non-familial and familial cases of DCM, respectively.[26,27] Most mutations have an autosomal dominant inheritance pattern, but there are also X-linked, autosomal recessive and maternal transmission (i.e. mitochondrial disorders) patterns. Routine genetic testing has a relatively low yield (30–35%) and, as yet, few implications for the management of HF in DCM. The exceptions are lamin A/C and phospholamban gene mutations,[28,29] which confer high risk of arrhythmia and sudden cardiac death (SCD) that may lower the threshold for an implantable cardioverter-defibrillator (ICD) implantation.[30] Duchenne muscular dystrophy is an X-linked disorder caused by the absence of a sarcolemmal protein, dystrophin, in the skeletal muscle and the heart, which compromises the link between the cytoskeleton and the extracellular matrix leading to progressive muscle wasting, degeneration of cardiomyocytes and replacement fibrosis.[31] Myocardial fibrosis is associated with deterioration in left ventricular (LV) systolic function and a propensity for adverse outcomes.[32] HF is one of the major causes of death in patients with Duchenne muscular dystrophy; treatment with perindopril and eplerenone has shown a capacity to slow cardiomyopathy progression.[33,34]

Viral infection followed by an (auto)immune activation in the myocardium may play a major role in the development of HF in DCM.[35] Based on small animal studies, a three-phase model of inflammatory heart muscle disease has been proposed. Initially, direct cytotoxic effects can occur within a few days after viral infection (e.g. enterovirus), leading to myocyte necrosis and activation of host innate (i.e. natural killer cells and macrophages) and acquired (i.e. T lymphocytes) immunity. Later, (auto)immune responses can occur in the subacute phase, lasting up to several months. An increased activity of effector T lymphocytes has been described, targeting both the virus and cellular components (heat shock proteins, mitochondrial proteins, cardiac myosin, etc.) by the mechanism of molecular mimicry.[36] In addition to inflammatory myocardial damage, autoantibodies directed against the ADP/ATP carrier may contribute to LV dysfunction.[37] Recently, myocardial inflammation characterized by the presence

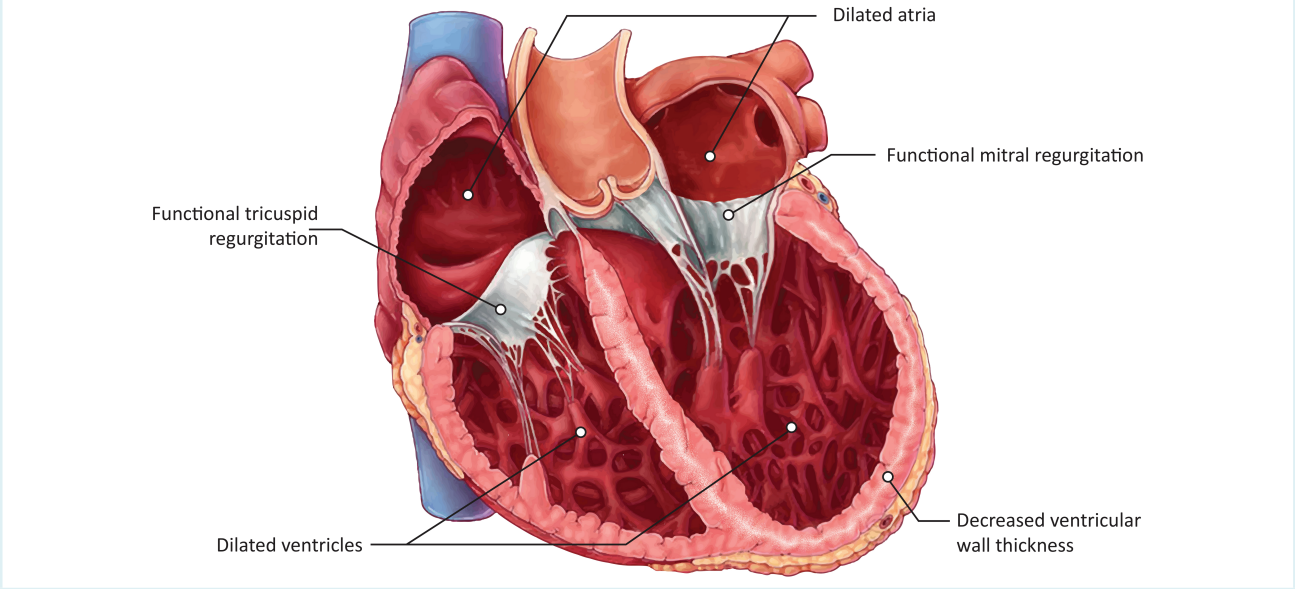

Figure 3 Characteristic alterations in cardiac morphology underlying heart failure in dilated cardiomyopathy.

of cytotoxic perforin-positive T lymphocytes has been shown to predict subsequent deterioration of LV function over the long-term follow-up period.[38] These pathological processes may cause substantial myocardial cell loss and trigger adverse ventricular remodelling and replacement fibrosis, eventually leading to the development of DCM and HF. At the same time, persistent viral genomes have been detected in cardiac tissue without DCM,[39] emphasizing the important role of the host response. Increased susceptibility to the development of DCM has been linked to upregulation of genes for matrix metalloproteinase-9 and type-1 procollagen in mast cells, which may result in pronounced myocardial inflammation and necrosis, followed by replacement fibrosis.[40]

Other infectious causes of DCM may have specific geographic distributions. Most notable examples include human immunodeficiency virus (HIV) infection in sub-Saharan Africa, and Chagas disease (*Trypanosoma cruzi* infection) in South America.[41] The pathogenesis of HIV-mediated DCM and HF is not completely understood, whereas, myocardial damage in Chagas disease results from diffuse fibrosis due to parasitic infestation, microcirculatory damage and autoimmune mechanisms.[42]

Dilated cardiomyopathy may also occur in systemic immune-mediated diseases (SIDs) that include autoimmune and autoinflammatory disorders.[43] In SIDs, autoantibodies may promote inflammatory responses via immune complex formation or may directly participate in cardiac damage, also mediated by aberrant cellular immunity, resulting in myocyte loss, fibrosis and the development of DCM. Genetic susceptibility could be of crucial importance for the progression of HF after autoimmune myocarditis, since evidence suggests that organ-specific autoantibodies predict the development of DCM in asymptomatic relatives of patients with established DCM.[44,45]

The pathogenesis of PPCM is still not elucidated but several contributing factors have been implicated.[46,47] Excessive oxidative stress in the last trimester of pregnancy, possibly caused by insufficient defence mechanisms, can promote activation of cathepsin D and formation of a prolactin fragment with direct cardiotoxic properties.[48] Myocardial inflammation, viral infection, angiogenic imbalance during pregnancy and autoimmune responses characterized by high titres of autoantibodies against the myocardial proteins have been also implicated.[49–52] Susceptibility to PPCM is apparently higher in carriers of DCM-causing sarcomere gene mutations, which supports a notion of a genetic predisposition in some patients.[53]

Direct cardiotoxicity, along with a contribution from neurohormonal activation, altered calcium homeostasis, and oxidative stress have been associated with the development of HF in the setting of chemotherapy (e.g. anthracyclines, trastuzumab, etc.), chronic alcohol abuse (alcoholic cardiomyopathy), and exposure to certain drugs and toxins[54–59] (*Figure 2*). Cardiotoxicity is a relatively common complication of cancer therapy manifesting as LV dysfunction and HF (usually HFrEF).[58] Risk factors for cardiotoxicity include a history of HF or LV dysfunction (including pre-existing DCM/HCM), coronary artery disease, hypertensive or valvular heart disease, as well previous exposure to cardiotoxic drugs (e.g. anthracyclines) or radiotherapy. Depending on the cardiotoxic agent and patients' susceptibility, cardiotoxicity may present soon after exposure, or it may become clinically evident years after treatment (late DCM), as a result of progressive myocardial injury (e.g. 23% of anthracycline-treated patients demonstrated late cardiotoxicity after a median of 7-year follow-up).[60] The prediction of long-term outcomes in cancer patients is hampered by the fact that many patients receive multiple drugs and radiotherapy, which may have a potentiating cardiotoxic effect. Importantly, substantial

reversal of LV dysfunction and recovery from HF may occur with a timely withdrawal of the offending agent(s) and appropriate HF treatment.

The natural history and outcome of heart failure in dilated cardiomyopathy

The natural history of HF in DCM can be characterized by three distinct pathways including: (i) a structural and functional recovery following incident HF; (ii) a remission of HF symptoms and improvement/stabilization of LV systolic function; and (iii) progression to advanced HF and heart transplantation/death.[61] Complete functional and structural recovery is infrequent and can occur if an acute insult did not cause significant myocardial loss, which allows normalization of LV function once the insult has resolved. The clinical course of HF in DCM may be variable, but a substantial functional recovery and reverse LV remodelling can on occasion be achieved, especially with the use of guideline-directed medical therapy (GDMT).[62,63]

Observational data prior to GDMT for the management of HF indicate that significant clinical improvement occurred in less than 20% of HF patients with DCM, while 77% died within 2 years of diagnosis, mostly due to progressive pump failure.[64] SCD and systemic embolism, largely attributable to atrial fibrillation (AF), accounted for the remainder of the cardiovascular mortality.[64]

Over the last three decades, outcomes have improved with advances in HF treatment. In a cohort of Japanese DCM patients enrolled between 1982 and 1989, the 5- and 10-year survival rates were 61% and 35%, respectively.[65] In patients assessed between 1990 and 2002, the 5- and 10-year survival rates had increased to 81% and 65%, respectively.[65] A favourable prognosis has been reported with GDMT, demonstrating transplant-free survival at 1, 2, and 4 years of follow-up in 94%, 92%, and 88% of patients, respectively.[10] Over the same period, survival free of HF hospitalization was 88%, 82%, and 78%, respectively.[10] ICD, cardiac resynchronization therapy (CRT), as well as MCS and heart transplantation in advanced HF have all provided further improvements in outcomes, and CRT and MCS in particular have been associated with reverse remodelling and recovery.

However, a recent randomized trial (TRED-HF) of 51 patients with DCM and recovered LV function indicated that withdrawal of GDMT for HF is associated with a 40% relapse of LV dysfunction within 6 months.[66] This strongly supports continuation of HF treatment even in patients with recovered DCM.

Besides GDMT, several additional predictors of reverse LV remodelling have been identified in DCM, which are related to a more favourable long-term prognosis. In the IMPROVE-HF study of 3994 HF patients (32% with a non-ischaemic aetiology), almost 30% experienced a $>10\%$ increase in LVEF over the 2-year follow-up period. Female sex, a non-ischaemic HF aetiology and the absence of digoxin use have been identified as multivariable predictors of LV functional recovery.[67] Several cohort studies have specifically addressed LV functional recovery in recent-onset DCM and observed a $>10\%$ increase in LVEF in 30–70% of patients.[8,10,68] Higher baseline LVEF and lower LV end-diastolic diameter have been recognized as independent predictors of reverse LV remodelling.[10] In addition, a lower extent of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR), indicative of lower interstitial replacement fibrosis, has been shown to provide incremental predictive value for reverse LV remodelling in recent-onset DCM.[8] Importantly, independent of other factors, LV reverse remodelling was associated with ~50% lower mortality rates at 10-year follow-up in DCM patients.[68]

On the other hand, male sex and advanced age (> 60 years) have been associated with a poorer prognosis in patients with DCM and HF.[9,10,69] Self-declared black race has also been related to more severe HF at presentation, a lesser degree of LV reverse remodelling and approximately two-fold higher mortality at follow-up.[10] Other predictors of adverse outcomes include: lower baseline LVEF, higher NYHA class (III–IV), significant mitral regurgitation,[68] the presence of LBBB and higher natriuretic peptide levels.[8,70] Severe functional mitral regurgitation (FMR) has been associated with approximately two-fold increased risk of mortality or worsening HF in DCM.[71] Persistence of severe FMR or worsening of non-severe FMR despite optimal GDMT has been shown to predict adverse prognosis in patients with HFrEF, irrespective of HF aetiology.[72] In addition, a more pronounced mid-wall myocardial LGE on CMR has been associated with higher all-cause and HF mortality and more frequent HF hospitalizations in DCM.[70]

Heart failure in DCM still carries a considerable mortality risk that is similar to, or higher than mortality attributed to other non-ischaemic HF aetiologies (e.g. valvular or hypertensive).[11] Advanced HF remains the most frequent cause of death in DCM, while SCD accounts for $<30\%$ of mortality.[9,70] Importantly, DCM also confers a high risk of non-cardiovascular mortality, as approximately one third of patients die of cancer, infections, pulmonary disease, or haemorrhage.[9,73] The risk of non-cardiovascular death increases with older age and more severe HF.[9,73]

Treatment of heart failure in dilated cardiomyopathy

Both HF-specific and aetiology-related therapies should be considered for the treatment of HF in DCM.

Heart failure-related therapy

Guideline-directed medical therapy and implantable devices provide proven outcome benefit for patients with chronic HF in DCM (*Table 1*)[12,73–85]. In acute/advanced HF, in-hospital treatment with intravenous diuretics, vasodilators, or inotropes may be required, although there is no evidence that these interventions improve outcomes.[74]

Concerns have been raised about the efficacy of certain therapies in patients with DCM, compared with other aetiologies of HF. Suggestions from observational studies of an increased mortality risk with digoxin and amiodarone in DCM patients with HF[65,67] have not been confirmed in clinical trials.[75,86] Prophylactic ICD implantation for primary prevention of SCD is currently recommended in DCM patients with HF (NYHA class II–III) and

Table 1 Outcomes in selected heart failure with reduced ejection fraction clinical trials in patients with idiopathic dilated cardiomyopathy or non-ischaemic heart failure

Clinical trial, publication year	Intervention	Number of patients and characteristics	Idiopathic DCM or non-ischaemic HF	Outcome (treatment vs. comparator)
Medical therapy				
SOLVD,[12] 1991	Enalapril vs. placebo	2569; NYHA class I–IV; LVEF ≤35%	17.9–18.6%	All-cause death: RR ↓27% Death or hospitalization: RR ↓29%; Interaction P = NS according to HF aetiology (ischaemic vs. non-ischaemic)
DIG,[75] 1997	Digoxin vs. placebo	6800; NYHA class I–IV; LVEF ≤45%	14.1–15.5%	Death or HF hospitalization: RR 0.67 (95% CI 0.58–0.77); Interaction P = 0.06 according to HF aetiology (ischaemic vs. non-ischaemic)
MDC,[76] 1993	Metoprolol vs. placebo	383; 94% NYHA class II–III, LVEF <40%	100%	All-cause death: RR ↓34% (95% CI −6% to 62%, P = 0.058). Significant improvement in symptoms, less clinical deterioration with metoprolol
CIBIS,[77] 1994	Bisoprolol vs. placebo	641; NYHA class III (95%) or IV (5%); LVEF <40%	36%	All-cause death: Placebo vs. bisoprolol: 23/115 vs. 11/117; P = 0.01
RALES,[78] 1999	Spironolactone vs. placebo	1663; NYHA class III–IV (NYHA class IV within 6 months before enrolment); LVEF ≤35%	45–46%[a]	All-cause death (overall study population): HR 0.70 (95% CI 0.60–0.82); Interaction P = NS according to HF aetiology (ischaemic. vs. non-ischaemic)
CHARM-Alternative,[79] 2003	Candesartan vs. placebo in patients intolerant to ACE inhibitors	2028; NYHA class II–IV; LVEF ≤40%	18.8–20.3%	CV death or HF hospitalization (overall study population): HR 0.70 (95% CI 0.60–0.81) No reported interaction according to HF aetiology
SHIFT,[80] 2010	Ivabradine vs. placebo	6558; LVEF ≤35%; sinus rhythm >70 b.p.m.; NYHA class II–IV; HF hospitalization within the previous 12 months	32–33%[a]	CV death or HF hospitalization: HR 0.72 (95% CI 0.60–0.85); Interaction P =0.059 according to HF aetiology (ischaemic. vs. non-ischaemic)
EMPHASIS-HF,[81] 2011	Eplerenone vs. placebo	2737; NYHA class II; LVEF <30% (or LVEF 30–35% and QRS >130 ms)	30.1–31.8%[a]	CV death or HF hospitalization (overall study population): HR 0.63 (95% CI 0.54–0.74); Interaction P = 0.73 according to HF aetiology (ischaemic vs. non-ischaemic)
PARADIGM-HF,[82] 2014	Sacubitril/valsartan vs. placebo	10 521; NYHA class II–IV; LVEF ≤35–40%, BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL, or HF hospitalization within the previous 12 months + BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL	39.9–40.1%[a]	CV death or HF hospitalization (overall study population): HR 0.80 (95% CI 0.73–0.87) No reported interaction reported according to HF aetiology

Table 1 continued

Clinical trial, publication year	Intervention	Number of patients and characteristics	Idiopathic DCM or non-ischaemic HF	Outcome (treatment vs. comparator)
Devices				
DEFINITE,[83] 2004	ICD vs. medical therapy	458; LVEF ≤35%; VPC and/or non-sustained VT on GDMT	100%	All-cause death: HR 0.65 (95% CI 0.40–1.06) Sudden cardiac death: HR 0.20 (95% CI 0.06–0.71)
SCD-HeFT,[84] 2005	ICD vs. placebo Amiodarone vs. placebo	2521; NYHA class II–III; LVEF ≤35% on GDMT	48%[a]	All-cause death: ICD vs. placebo, HR 0.73 (95% CI 0.50–1.07) Amiodarone vs. placebo, HR 1.07 (95% CI 0.76–1.51) Interaction P = NS according to HF aetiology (ischaemic vs. non-ischaemic)
COMPANION,[85] 2004	CRT-P/CRT-D vs. medical therapy	1520; NYHA class III–IV; LVEF ≤35% on GDMT; QRS ≥120 ms	44.9%[a]	All-cause death: CRT-P vs. placebo, HR 0.91 (95% CI 0.55–1.49) CRT-D vs. placebo, HR 0.50 (95% CI 0.29–0.88) Interaction P = NS according to HF aetiology (ischaemic vs. non-ischaemic)
DANISH,[73] 2016	ICD vs. medical therapy (58% in both groups received CRT)	1116; NYHA class II–IV with non-ischaemic HF; LVEF ≤35%; NT-proBNP >200 pg/mL	76%	All-cause death: HR 0.87 (95% CI 0.68–1.12) Sudden cardiac death: HR 0.50 (95% CI 0.31–0.82) Interaction P = 0.80 according to HF aetiology (idiopathic vs. valvular vs. hypertension vs. other)

ACE, angiotensin-converting enzyme; BNP, B-type natriuretic peptide; CI, confidence interval; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; CV, cardiovascular; DCM, dilated cardiomyopathy; GDMT, guideline-directed medical therapy; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; RR, relative risk; VPC, ventricular premature complexes; VT, ventricular tachycardia.
[a]Proportion of patients with non-ischaemic HF aetiology.

LVEF ≤35% on GDMT.[74] This was based on earlier clinical trials that have demonstrated a decrease in both arrhythmic and all-cause mortality in HF of both ischaemic and non-ischaemic aetiology[83,84] (*Table 1*). The results of the DANISH trial, in which >50% of patients received a CRT on top of GDMT, have shown that ICD implantation reduced the risk of SCD by 50% with no significant effect on all-cause mortality.[73] However, a recent subanalysis of the DANISH trial suggested that in patients ≤70 years old, ICD implantation reduced all-cause mortality.[87] Also, in the COMPANION trial, the addition of a defibrillator function to CRT (i.e. CRT-D) provided a greater reduction in all-cause mortality in patients with DCM on GDMT compared with patients with an ischaemic HF aetiology.[88] This underscores the need for improvement in risk stratification for CRT eligible patients with DCM who might derive most benefit from CRT-D for primary prevention. In addition, approximately one third of patients with DCM may experience reverse LV remodelling and recovery from HF with GDMT, which, in turn, confers a significantly lower risk of SCD.[68] Substantial reverse remodelling is mostly observed with potentially reversible causes of DCM, including alcohol-related, PPCM or tachycardia-induced cardiomyopathy, underlying the importance of aetiological assessment of HF in DCM. Those patients possibly may be protected against SCD during the recovery phase with wearable defibrillators, thus avoiding the requirement for permanent ICD implantation.

Correction of LV mechanical dyssynchrony (15–30% of DCM patients with HF) has a significant positive impact on morbidity and mortality.[85,89,90] Hence, CRT is currently recommend for symptomatic HF patients with LVEF <35% and QRS ≥130 ms, particularly of LBBB morphology (a surrogate for LV dyssynchrony), treated for ≥3 months with GDMT, irrespective of HF aetiology.[74]

Based on the experience from surgical mitral valve repair (MVR) of moderate-to-severe FMR, suggesting reverse LV remodelling and functional improvement,[91] a percutaneous interventional technique has been developed for the correction of FMR. Percutaneous transcatheter MVR with the MitraClip device demonstrated similar efficacy but an improved safety compared with surgery.[92]

Recently, two randomized clinical trials comparing the effectiveness of percutaneous MVR with GDMT have demonstrated diverging results. In the MITRA-FR trial the 1-year risk of death or HF hospitalization did not differ significantly between patients who underwent percutaneous MVR and those who received GDMT alone.[93] Conversely, in the COAPT trial, patients treated with percutaneous edge-to-edge repair experienced markedly lower rates of all-cause mortality and HF hospitalization within 2 years compared with GDMT alone.[94]

Aetiology-related therapy

Aetiology-related treatment of HF in DCM is an evolving field, which needs further evidence from clinical trials. In the case of inflammatory DCM of autoimmune aetiology without viral persistence, this treatment includes immunosuppression and immunoadsorption, whereas, anti-viral agents may be considered in the setting of biopsy-confirmed acute viral myocarditis or viral persistence. Several observational and randomized trials have suggested that in virus-negative post-myocarditis DCM with progressive HF, immunosuppression could be effective in achieving LV reverse remodelling and improvement in HF symptoms.[95–97] Accordingly, expert consensus documents have recommended immunosuppression with azathioprine and prednisone for 6–12 months in patients with biopsy-proven, virus-negative DCM,[35] but the exact role of immunosuppression is still unresolved. Immunosuppression is also recommended in acute giant-cell and eosinophilic myocarditis and cardiac sarcoidosis.[7,35,98] In biopsy-proven chronic enteroviral or adenoviral and/or Parvovirus B19 positive DCM, an immunomodulatory treatment with interferon beta has been recently shown to reduce viral load and improve functional capacity.[99] Small open-label controlled, or observational studies suggested that removal of circulating antibodies in DCM by immunoadsorption, followed by IgG substitution, resulted in improvement in cardiac function, symptom relief and increased exercise tolerance.[100–102] At present, immunoadsorption is considered as an experimental treatment option that requires further evaluation in outcome trials. In anthracycline-induced cardiomyopathy, timely therapy with angiotensin-converting enzyme (ACE) inhibitors and beta-blockers confers a substantial improvement of LVEF.[103] Treatment with the prolactin inhibitor bromocriptine (accompanied by prophylactic anticoagulation) may provide a disease-specific therapy in patients with acute HF in PPCM.[47,104,105] Further aetiologic therapies include cessation of the offending agent(s) (e.g. alcohol) and management of the underlying endocrine or metabolic disorders.[106]

In light of the various monogenetic causes of DCM, gene repair may be a promising target for the causative treatment of HF. Following improvement in skeletal muscle function with CRISPR/Cas9 technology for gene repair in Duchenne muscular dystrophy,[107] this technology is currently under assessment for genome modification in cardiomyopathies.[108] Thus, the emerging CRISPR/Cas9 technology may become an overarching approach to the treatment of primary cause of some cardiomyopathies.

Heart failure in hypertrophic cardiomyopathy

Incidence and prevalence of heart failure in hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is defined by an increase in myocardial wall thickness (≥ 15 mm in adults, or ≥ 13 mm in adults with first degree relatives with HCM) in one or more of the LV wall segments, that cannot be explained by abnormal loading conditions.[109,110] Most patients have an asymmetric septal hypertrophy and approximately 40–70% have an obstructive HCM, diagnosed by a LV intracavitary gradient ≥ 30 mmHg at rest (~25% of patients) or during exercise.[109,111,112] Non-obstructive HCM, demonstrating gradients < 30 mmHg at rest and/or with exercise, is present in 30–60% patients.[109,111,112] In several reports from Europe, Asia and North America, the prevalence of HCM is 2–5 per 1000 of the general population.[113–116] In 60% of patients, HCM results from autosomal dominant sarcomere gene mutations, whereas other aetiologies including hereditary syndromes, neuromuscular disorders and storage diseases characterized by intracellular accumulation of abnormal substrates (e.g. Anderson–Fabry, Pompe, or Danon disease, etc.) account for 5–10% of patients[110,117] (*Figure 4*). In about 30% of patients, the cause of HCM remains unknown.[109] A suggested aetiological assessment of HF in HCM is presented in *Figure 1*.

Heart failure has two distinct clinical features in HCM; in the majority of patients, HF is manifested as a HFpEF phenotype, with specific characteristics in patients with LV obstruction, while only a minority of patients develop HFrEF at a later stage. Due to a substantial aetiological and clinical heterogeneity, ascertaining the incidence of HF in HCM is challenging. Data from a cohort of 1000 patients diagnosed with HCM at mid-adulthood (i.e. 30–59 years of age) reveal HF incidence of ~50%, with symptoms varying from mild to severe (NYHA class II–IV).[118] In a contemporary registry of 3208 individuals with cardiomyopathies in Europe, the prevalence of symptomatic HF in patients with HCM was 67% (NYHA class II and III–IV symptoms, 49.9% and 17.4%, respectively).[119] However, the mentioned prevalence of HF in HCM might be overestimated due to possible under-representation of subjects with mild symptoms or asymptomatic HCM in registries. HF is prevalent in the majority of patients with obstructive HCM and in 10% of patients with non-obstructive HCM.[120] Acute HF is infrequent, however it could be precipitated by conditions such as tachyarrhythmia (e.g. AF), ischaemia, acute or worsening mitral regurgitation (e.g. chordal rupture), or co-morbidity (e.g. thyrotoxicosis).[109,121,122] Progression to advanced HF (e.g. NYHA class III–IV symptoms) occurs in 3.5–17% of individuals, usually as a consequence of severe LV obstruction and hypertrophy, or adverse LV remodelling leading to systolic dysfunction.[123–126] There are no gender or race distinctions in the prevalence of HF in HCM, but patients with sarcomere protein disease tend to develop HF at a younger age and have a higher propensity for progressive HF compared to patients without mutations.[127] Patients with rare inherited disorders (e.g. Anderson–Fabry, Danon, or mitochondrial disease)

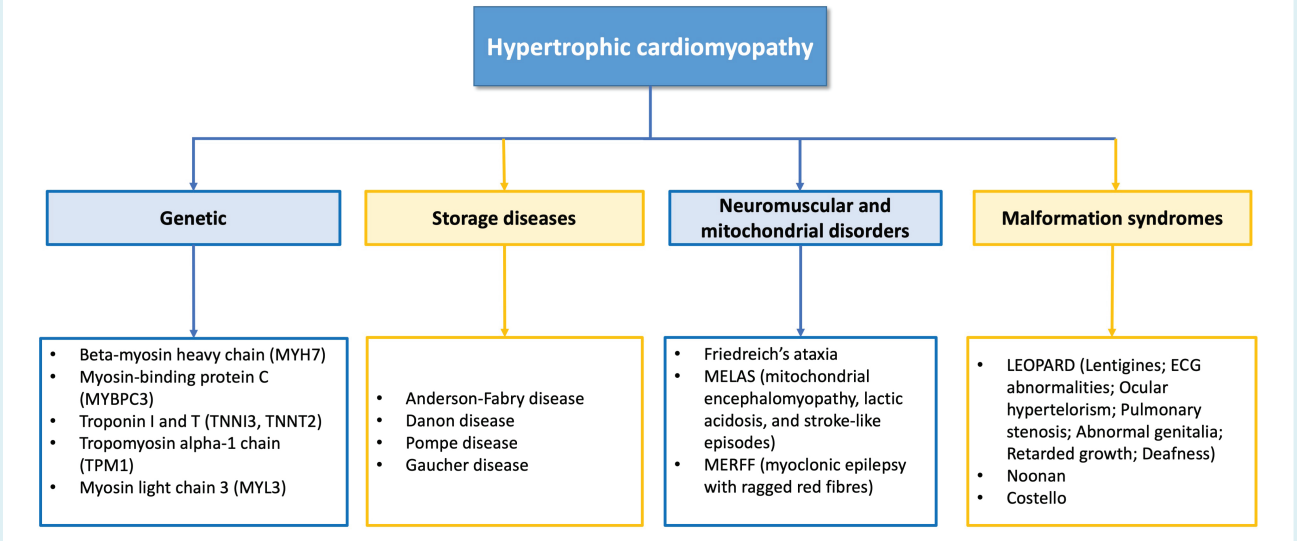

Figure 4 Aetiologies of hypertrophic cardiomyopathy.

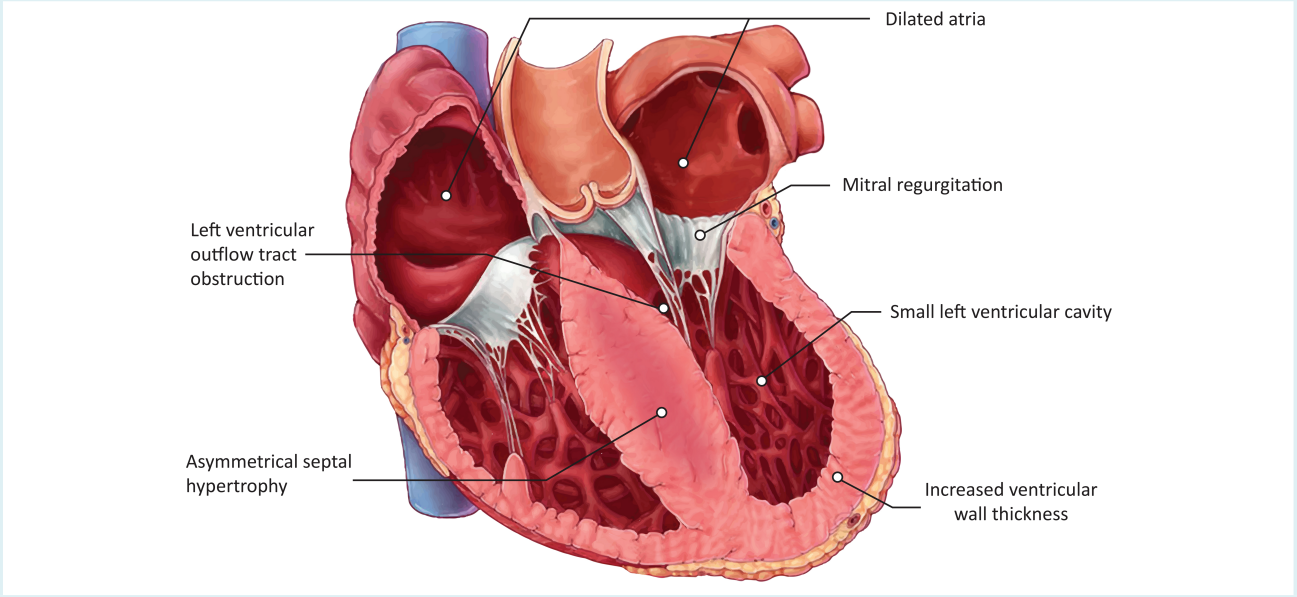

Figure 5 Characteristic alterations in cardiac morphology underlying heart failure in hypertrophic cardiomyopathy.

demonstrate multi-system disease, but their clinical presentation is often (~60%) dominated by symptoms of HF as well as conduction abnormalities.[128]

Amongst HF patients, those with HCM account for 2–3%.[16] Accordingly, the proportion of patients with HCM among all heart transplant recipients for advanced HF is smaller relative to other aetiologies, because HCM is a rare disease.[22] However, compared with other recipients, patients with HCM tend to be younger and with fewer co-morbidities at the time of transplantation. This also accounts for similar or more favourable short-term and long-term prognosis after transplantation.[22]

Pathophysiology of heart failure in hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy due to sarcomere gene mutations

In genetic HCM, myocyte hypertrophy and disarray occur in response to impaired energy balance due to the excessive energy utilization required to generate a hyperdynamic isokinetic tension within the sarcomere.[129,130] Compromised energy balance, coupled with higher oxygen demand of the hypertrophied myocardium result in recurrent episodes of demand ischaemia

(e.g. during exercise or tachycardia) that can explain symptoms of chest pain, exercise intolerance and exertional dyspnoea.[131] In some patients, the underlying pathophysiology may be further aggravated by haemodynamic overload imposed by a dynamic LV outflow tract, mid-cavity or multi-level obstruction.[132] Coronary microvascular dysfunction, characterized by structural abnormalities and decreased blood flow in intramural coronary arterioles, also plays a role in recurrent episodes of myocardial ischaemia and the development of HF.[133] In addition, impaired termination of contraction at low intracellular Ca^{2+} levels produces incomplete myocyte relaxation and diastolic dysfunction, which may both precede and follow the development of overt hypertrophy.[134]

In some patients, a cumulative effect of these factors produces myocyte energy depletion followed by progressive myocyte loss and replacement fibrosis that eventually lead to adverse LV remodelling and progression to systolic dysfunction and HFrEF. Indeed, a meta-analysis of 1063 HCM patients, followed for an average of 3.1 years, demonstrated that replacement fibrosis on LGE-CMR predicted a significantly increased risk of mortality due to HF.[135] In a histologic study of 30 explanted hearts with end-stage evolution of HCM, more than one third of the LV myocardium was replaced by fibrosis, particularly involving the LV apex and the mid-wall.[136] Patients with multiple genetic mutations in sarcomere proteins (up to 5% of the HCM population) are particularly susceptible to accelerated progression to end-stage disease.[137,138] Also, familial clustering of advanced HF has been recognized as a marker of risk for unfavourable outcomes in other family members.[126] In addition, co-morbidities (e.g. myocarditis or epicardial coronary artery disease) may be rarely associated with adverse LV remodelling and development of overt HF.[111]

In patients with obstructive HCM, the severity of HF is principally determined by pressure overload imposed by a dynamic obstruction to LV outflow during systole.[120] The characteristic morphological changes responsible for HF development in HCM are summarized in *Figure 5*. The intracavitary obstruction most commonly involves the outflow tract and is produced by a combination of physical obstruction by the septal hypertrophic tissue, by an abnormal systolic anterior motion (SAM) of the mitral valve, and by diastolic and contractile deficits. In 5–10% of patients, the gradient is exclusively produced by mid-cavity obstruction due to an abnormal apposition of the hypertrophied septum and anterolateral papillary muscle.[120] Dynamic changes in gradients in response to changes in myocardial contractility and loading conditions (e.g. exercise, hydration) explain temporal variability and low reproducibility of HF symptoms in HCM.[120] In patients without a significant gradient at rest, cardiopulmonary exercise testing is the preferred method for provoking obstruction.[109] LV diastolic dysfunction represents another important mechanism underlying the development of HF (i.e. HFpEF) in HCM. It is present in the majority of patients, irrespective of intracavitary obstruction and is characterized by prolonged isometric relaxation and impaired filling patterns.[111] In addition, mitral valve abnormalities, coronary myocardial bridging, apical aneurysms, atrial remodelling and autonomic dysfunction may contribute to the development and severity of HF.[124,139–144] In patients with non-obstructive HCM, HF is mostly caused by diastolic dysfunction, but in a small subset, HF may have a progressive course culminating in end-stage disease and severe HFrEF.

Hypertrophic cardiomyopathy due to storage disorders

In patients with HCM caused by rare storage disorders (e.g. Anderson–Fabry, Danon and Pompe diseases), HF most commonly takes the HFpEF phenotype due to an extensive, concentric increase in LV wall thickness.[145,146] The increased wall thickness is caused partly by myocyte hypertrophy (due to lysosomal accumulation of glycosphingolipids), and partly by interstitial fibrosis stimulated by overproduction of profibrotic cytokines.[146] Asymmetric LV hypertrophy in storage disorders is rare (< 2.5%), while biventricular hypertrophy may occur in up to 25% of patients.[145] In Anderson–Fabry disease, replacement fibrosis (detectable by LGE-CMR or by strain imaging) within the posterolateral wall may contribute to LV dysfunction and FMR.[147] Most patients have preserved LVEF with occasional evidence of subaortic LV obstruction.[148] Overt HF is determined by the degree of LV diastolic dysfunction, which correlates with the extent LV hypertrophy and N-terminal pro B-type natriuretic peptide (NT-proBNP) levels.[149] Rarely, diastolic dysfunction in storage disorders may progress to a restrictive filling pattern, accompanied by a significant biatrial enlargement.[145] In those patients, cardiac involvement may take the characteristics of an RCM; thus, storage disorders need to be considered as underlying aetiology of both HCM and RCM. Development of LV systolic dysfunction and HFrEF invariably occurs in Danon disease and occasionally in patients with other metabolic cardiomyopathies.[150]

The natural course and outcome of heart failure in hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy due to sarcomere gene mutations

Typically, LV hypertrophy in HCM caused by sarcomere disorders develops in adolescence or early adulthood (although it may present from early childhood to the seventh decade), and remains stable with preserved LV systolic function and variable degrees of LV diastolic dysfunction.[151] In patients with obstructive HCM, the severity and prognosis of HF are principally influenced by LV outflow obstruction. This is highlighted by data demonstrating that a gradient ≥ 30 mmHg at rest independently predicted HF progression and increased mortality.[152] Recent findings from a cohort of 324 patients with obstructive HCM and mild HF at baseline, demonstrated progression to NYHA functional class III–IV, at an annual rate of 3.2–7.4% depending on the degree of outflow tract obstruction.[153] As a result, severe HF was prevalent in 20–38% of those patients following a period of 6.5 years.[153] Similarly, in a cohort of 293 HCM patients followed up for a median of 6 years, advanced HF developed in 20% of those with severe obstruction to LV outflow.[123] The distinguishing features of these patients were older age (50 ± 14 years) and a significantly increased LV wall thickness at baseline.[123]

Mid-cavity obstruction is often accompanied by severe HF symptoms and impaired survival. In a cohort of 423 patients, a mid-cavity

obstruction was identified in 8% of patients that were more symptomatic (> 90% with NYHA class ≥ II) and had higher mortality compared with the rest of the cohort.[154]

Severe diastolic dysfunction (i.e. restrictive filling pattern) can be demonstrated in up to 9.2% of patients with HCM, usually in the setting of severe myocardial hypertrophy, with or without LV outflow tract obstruction. These patients generally present with symptoms of low cardiac output (rather than with overt congestion), and they have an independently increased risk of progression to advanced HF and end-stage disease.[123,155] In one study, those patients accounted for 48% of advanced HF cases, and as a result of restrictive filling pattern they had significant left atrial enlargement et entry or during follow-up.

In patients with non-obstructive HCM, the disease usually has a benign and stable course and the majority remains free of HF or has mild symptoms due to diastolic dysfunction. However, in 7–10% of patients with non-obstructive HCM (incidence, 1.6% per year),[120,156] the disease can have a progressive course characterized by LV dilatation, wall thinning, and development of LV systolic dysfunction, including an LVEF in the low-normal range.[151,157] Adverse LV remodelling is subtended by extensive myocardial replacement fibrosis.[151,158] The most advanced, 'burned-out', phase occurs in 3% of patients and carries a considerable risk of mortality (11% per year).[126]

In addition, left and right atrial enlargement have been recognized as independent predictors of adverse outcomes in HCM.[123,153,159] Likewise, the occurrence of AF, usually at a younger age than in the general population, significantly increases the risk of a detrimental clinical course.[121,123]

Hypertrophic cardiomyopathy due to storage disorders

In patients with HCM due to hereditary storage disorders, HF may become apparent at any time from childhood to the mature age depending on the extent of cardiac involvement, in relation to the severity of enzyme deficit.[160] In Anderson–Fabry disease, the development of overt HF has been reported in 23% of patients usually between the third and the fifth decade of life.[161] The progression to advanced HF has been observed in 10% of patients over a median period of 7.1 years.[162] Increased levels of cardiac biomarkers (troponin T, NT-proBNP) and higher extent of fibrosis have been associated with a reduction in LVEF during the follow-up.[163] Cardiac disease may progress to LV systolic dysfunction and HFrEF in 6–8% (in particular in the absence of enzyme replacement therapy) and confers a great risk of HF-related mortality.[164,165]

Treatment of heart failure in hypertrophic cardiomyopathy

Treatment of HF in patients with HCM encompasses general HF and aetiology-related treatment.

The first-line therapy of patients with HCM should include non-vasodilating beta-blockers to reduce contractility and alleviate the consequences of LV diastolic dysfunction by lowering heart rate, in combination with low-dose loop diuretics to control symptoms of HF, while avoiding hypovolaemia. In patients with an intolerance or a contraindication to beta-blockers, verapamil or diltiazem could be an alternative. However, there is a paucity of evidence on how these medications influence the natural course and outcomes in HCM.[109]

In patients with obstructive HCM and preserved LVEF, who remain symptomatic despite maximal tolerated doses of beta-blockers, disopyramide could be considered as a second-line, add-on therapy.[109] Disopyramide exerts a negative inotropic effect that can reduce LV outflow tract gradient in the majority of patients and improve HF symptoms, without affecting mortality, or causing proarrhythmia.[166] In patients with obstructive HCM, who have a gradient ≥ 50 mmHg at rest, or during exercise, and remain symptomatic (NYHA class III–IV) despite GDMT, invasive gradient reduction with surgical septal myectomy or septal alcohol ablation should be considered.[109] Surgical septal myectomy has been shown to abolish or significantly reduce obstruction in > 90% of patients treated in experienced centres, followed by a long-term improvement in HF symptoms and extended survival.[167,168] Alternatively, alcohol septal ablation has been shown to convey an improvement in outcomes comparable with surgery.[169] Surgery seems less beneficial for older patients and for those with residual AF.[170] Alcohol septal ablation may be less effective in younger patients with higher baseline gradients.[171] The periprocedural complications of both procedures include atrioventricular block (7–20% of patients), bundle branch block, or ventricular septal defect.[109] These treatment modalities are currently available in a small number of experienced centres.

Dual-chamber pacing has failed to demonstrate convincing treatment benefits.[172] It is currently recommended in patients with obstructive HCM (and an indication for antibradycardia pacing), deemed unsuitable for, or unwilling to undergo surgery/alcohol septal reduction.[109]

Patients with HCM are at an increased risk of SCD. For primary prevention, European Society of Cardiology guidelines recommend the use of a validated prediction model (i.e. HCM Risk-SCD) to estimate an individual 5-year risk of SCD[109] (*Figure 6*). Specifically, in patients with HF due to HCM, additional features may be used to refine risk assessment for SCD,[126,140,173] but their incremental prognostic value compared with HCM Risk-SCD remains unknown (*Figure 6*). Of note, HCM Risk-SCD has not been validated in patients with storage/metabolic causes of HCM, or following myectomy/septal ablation.

Patients with non-obstructive HCM and reduced LVEF (< 50%) should be treated with GDMT for HFrEF.[109] In a setting of progressive LV dysfunction, refractory HF symptoms and LBBB, limited data supports CRT implantation in patients with LVEF < 50%,[174] whereas patients with LVEF ≤ 35% and LBBB should be considered for CRT implantation as per current guidelines for the management of HF.[74]

In patients with HCM and advanced HF, long-term MCS is rarely considered suitable as a bridge to transplantation due to small LV cavity dimensions and severely impaired filling. However, a small study suggested an improvement in outcomes in HCM patients with an LV assist device comparable to patients

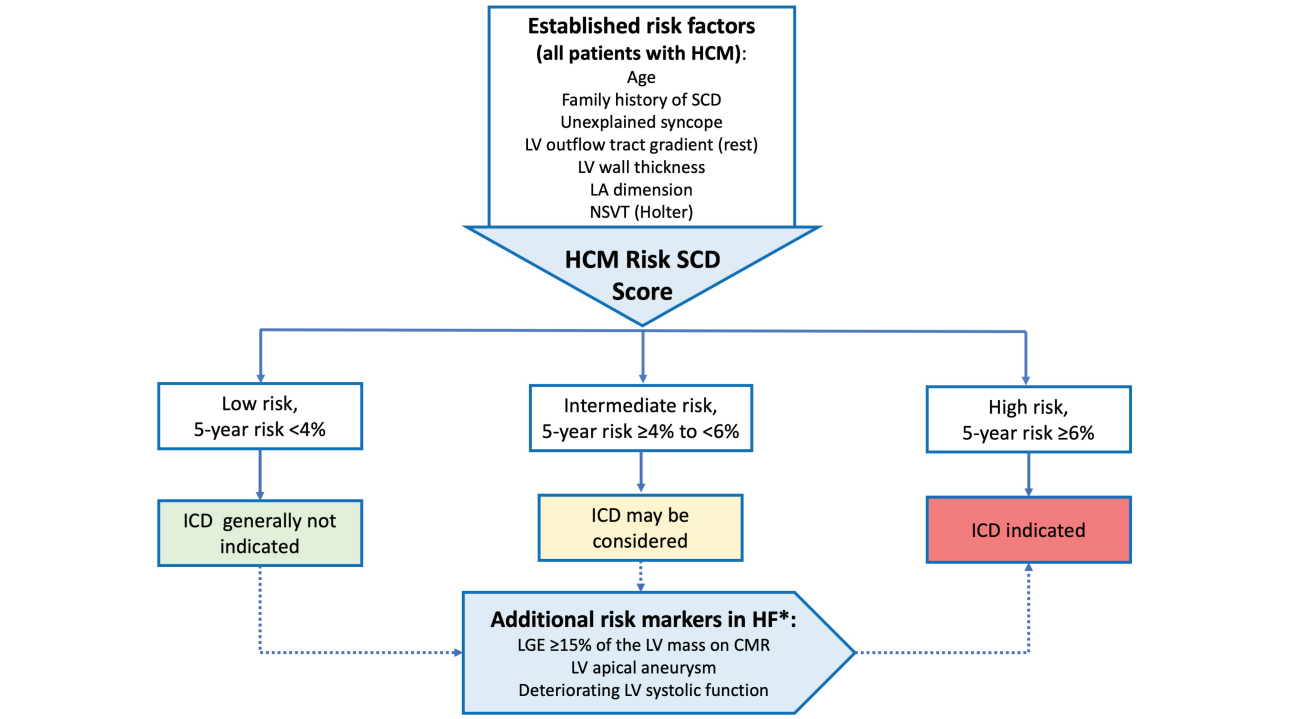

Figure 6 Sudden cardiac death (SCD) risk assessment in patients with heart failure (HF) and hypertrophic cardiomyopathy (HCM). ICD, implantable cardioverter-defibrillator; LA, left atrial; LGE, late gadolinium enhancement; LV, left ventricular; NSVT, non-sustained ventricular tachycardia. *In selected low-to-moderate risk patients based on HCM Risk SCD assessment, an ICD may be recommended in the presence of additional markers of increased SCD risk, following careful consideration of potential complications.

Table 2 Therapies of lysosomal storage disorders: relevance for the management of heart failure

Anderson–Fabry disease	
Enzyme replacement therapy: agalsidase-α or agalsidase-β	• Reduction in left ventricular mass index and a significant increase in mid-wall fractional shortening • Improvement in a composite cardiac, renal and cerebrovascular outcome or mortality • Partial loss of therapeutic effectiveness due to antibody formation may be alleviated by immunomodulators or a combination with an oral chaperone
Oral chaperon: migalastat	• Similar effect on a composite renal, cardiovascular and cerebrovascular outcome compared with enzyme replacement therapy • Possible positive impact on left ventricular fibrosis and hypertrophy
Pompe disease	
Enzyme replacement therapy: α-glucosidase	• Regression of left ventricular hypertrophy (if administered early in the course of the disease)

According to ref. 176, 177, 179–182

with DCM, but with a higher risk of complications.[175] Heart transplantation should be considered in patients who progress to advanced HF despite GDMT. At the time of transplantation most patients demonstrate significant LV systolic dysfunction (i.e. 'burned-out' phase). A small proportion of HCM patients may require heart transplantation for advanced HF despite preserved LVEF.[157]

Treatment of patients with storage disorders

For patients with HCM occurring in Anderson–Fabry disease, there is an effective enzyme replacement therapy with agalsidase-α and agalsidase-β,[176–178] or with an oral chaperone, migalastat,[179,180] that should be instituted as early as possible (*Table 2*). For patients with Pompe disease (glycogen storage disease type II), enzyme replacement therapy with recombinant human α-glucosidase is available (*Table 2*).[181,182] Since no specific therapy is available for patients with Danon disease, a close follow-up is recommended due to the malignant nature of the disease, including low threshold for ICD implantation and early listing for heart transplantation in appropriate candidates.[183]

Heart failure in restrictive cardiomyopathy

Incidence and prevalence of heart failure in restrictive cardiomyopathy

Restrictive cardiomyopathy is defined by the presence of restrictive physiology in patients with normal or reduced diastolic volumes of one or both ventricles, and normal or reduced systolic volumes.[110] Ventricular wall thickness is usually normal; however, in infiltrative or storage disease aetiologies of RCM, there is a variable degree of ventricular wall thickening.[184] The aetiology of RCM is heterogeneous, including idiopathic, hereditary and acquired cases of non-infiltrative and infiltrative myocardial disorders, storage diseases and endomyocardial disorders (*Figure 7*). Importantly, the clinical phenotype of cardiomyopathy due to specific aetiologies may demonstrate and overlap between HCM and RCM (e.g. in Anderson–Fabry, Pompe and Danon diseases), or a transformation from an RCM to DCM due to progressive nature of the underlying disorder (e.g. haemochromatosis/iron overload, amyloidosis). The prevalence of RCM is currently unknown, but it is the least frequent amongst the cardiomyopathies.[110,185]

The principal clinical manifestation of RCM is HFpEF, with signs and symptoms of right, left or biventricular HF. HFrEF may present at the late stage of the disease, and is more prevalent in cardiac amyloidosis and iron overload/haemochromatosis.[186,187] These aetiologies need to be considered in differential diagnosis between RCM and DCM (*Figure 1*). In addition, RCM is characterized by a greater risk of thromboembolism, conduction abnormalities, arrhythmias and SCD.[188]

The prevalence of HF in patients with RCM is high, as evidenced by a large European registry of cardiomyopathies, in which HF was prevalent in 83% of patients with RCM (NYHA class II, III, and IV present in 41%, 40% and 1.6%, respectively).[119] Similarly, in a cohort of 97 patients with primary RCM, 81% had overt HF, with 53% of patients demonstrating symptoms in NYHA class II, and 28% in NYHA class III–IV.[189] In adults with echocardiographically confirmed RCM (performed for screening because of a family history of HCM), 63% of patients presented with HF, while incident HF occurred in 89% of those patients during the 5-year follow-up.[190] Among individuals >65 years of age, RCM due to cardiac amyloidosis may be an underrecognized, albeit important cause of unexplained HF.[191] In a series of patients ≥ 90 years of age who died of HF, autopsy revealed RCM in 10%.[192] Studies using a scintigraphy to diagnose transthyretin amyloidosis (ATTR) demonstrated a 16% prevalence among patients undergoing percutaneous aortic valve replacement for severe low-flow, low-gradient aortic stenosis[193] and a 13% prevalence among patients with HFpEF.[194]

Pathophysiology of heart failure in restrictive cardiomyopathy

The hallmark of RCM is increased ventricular wall stiffness caused by abnormalities intrinsic to the myocardium, or to the endomyocardial layer (*Figure 8*). In primary RCM, abnormal ventricular stiffness has been attributed to increased myofilament sensitivity to calcium, increased deposition of collagen type III, and intracellular aggregates of the mutant protein such as desmin or filamin C.[186] In infiltrative and storage diseases, extracellular or intracellular accumulation of the pathological material in the myocardium accompanied by cardiomyocyte hypertrophy and variable interstitial and/or replacement fibrosis are responsible for increased myocardial stiffness. Endomyocardial fibrosis (EMF) caused by hypereosinophilic syndrome, carcinoid and exposure to chemo/radiotherapy may also result in restrictive pathophysiology.[195] Irrespective of the aetiology, RCM is characterized by severe diastolic dysfunction, presenting with a restrictive filling abnormality.[110] Markedly elevated filling pressure leads to prominent biatrial enlargement, and a predisposition to AF, which further diminishes ventricular filling.[184] Although ventricular systolic function is preserved in RCM, stroke volume may be decreased because impaired diastolic filling fails to provide sufficient preload. Consequently, patients with RCM typically have low-to-normal blood pressure, and may suffer from orthostatic hypotension and hypoperfusion if volume is depleted (e.g. due to excessive diuresis).

Although cardiac amyloidosis is often considered as a cause of HFpEF since LVEF often remains preserved until the late stage of the disease, in the majority of patients with HF, LV systolic function is also compromised due to a reduction in LV longitudinal function and strain.[196] Furthermore, myocardial contractility and inotropic reserve during exercise are also reduced in almost all patients with HF.[197,198]

The natural course and outcome of heart failure in restrictive cardiomyopathy

The prognosis of HF in RCM is poor, regardless of the underlying cause of RCM.[195] In a small cohort of paediatric patients with primary RCM, an extraordinary 53% experienced SCD shortly after diagnosis; 75% of the remaining patients had HF, and all had died or underwent heart transplantation within a few years of diagnosis.[199] In adult patients with RCM and a confirmed genetic background, the 5-year survival rate was 56%, and the main cause of death was HF (42%).[190] Likewise, in a study of patients with idiopathic RCM (10–90 years of age), the 5-year mortality rate was 50%, and 68% of patients died of cardiovascular causes, including HF.[189] The risk of death doubled with each increment in NYHA class, independently of other characteristics.[189]

Caused by intramyocardial deposition of transthyretin-derived amyloid fibrils, transthyretin amyloid cardiomyopathy is the most common cause of the infiltrative form of RCM.[200]

Although there are >30 amyloidogenic proteins, the two most common types of amyloidosis are the immunoglobulin light chain amyloidosis (AL) and ATTR amyloidosis; the latter comprises a mutant transthyretin form (ATTR-m) and a 'wild-type' transthyretin form (ATTR-wt). Cardiac involvement is the principal determinant of mortality in AL amyloidosis due to rapid loss of contractile function and a transition from HFpEF to HFrEF.[201] A direct toxicity of amyloidogenic light chains by increased oxidative stress has been implicated in myocardial damage, which is often out of

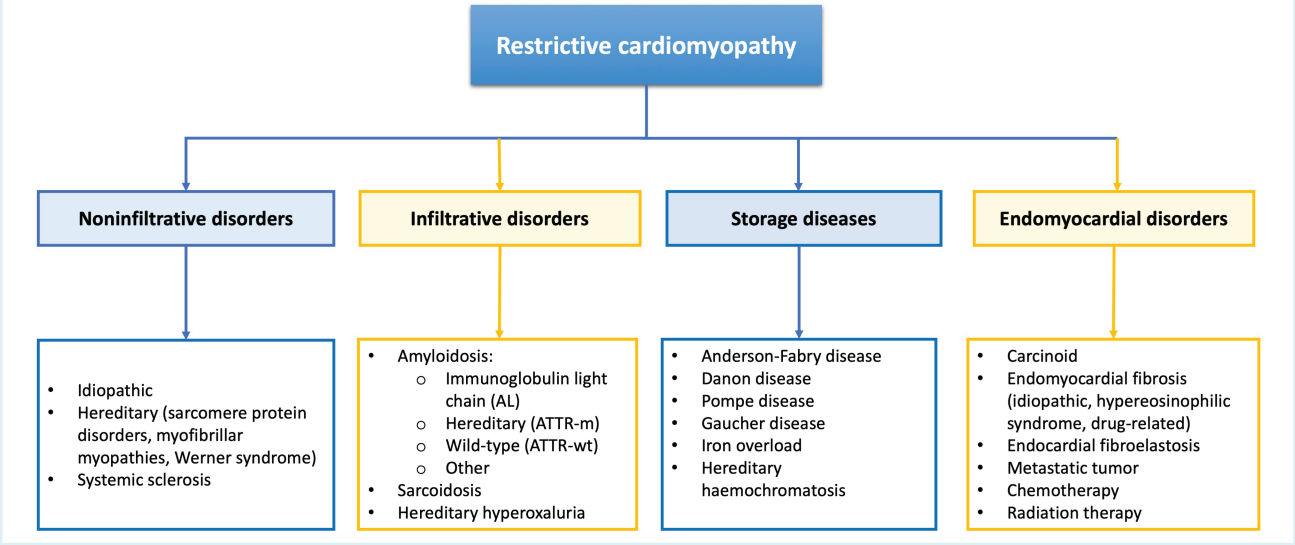

Figure 7 Aetiologies of restrictive cardiomyopathy.

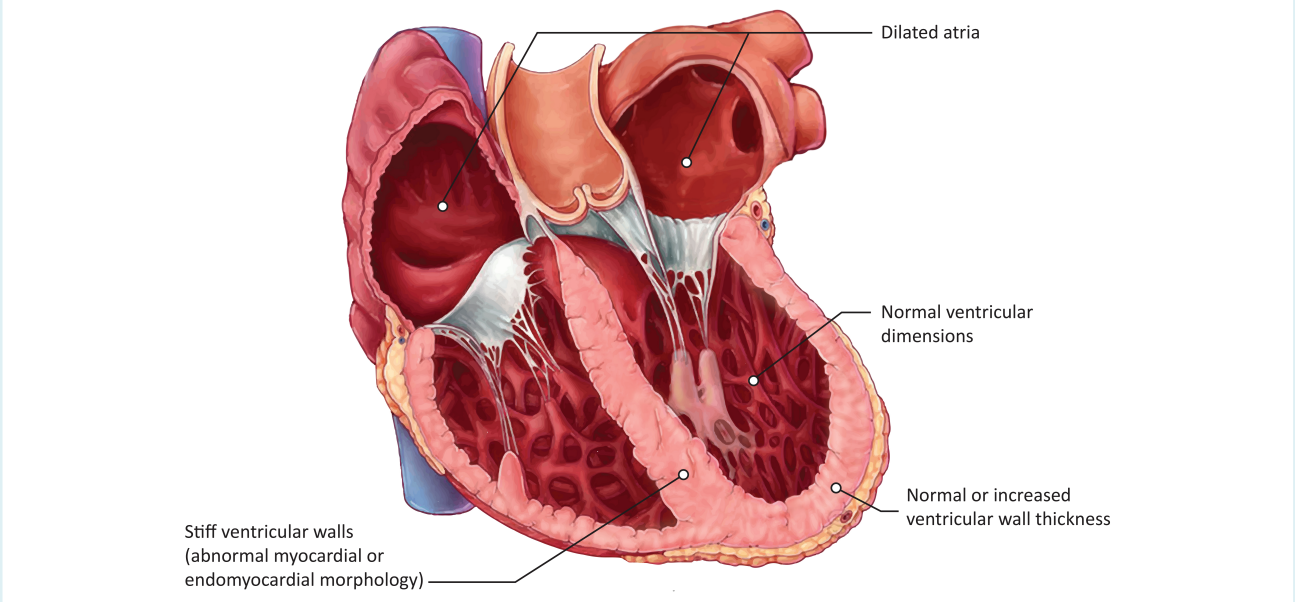

Figure 8 Characteristic alterations in cardiac morphology underlying heart failure in restrictive cardiomyopathy.

proportion to amyloid deposition.[201] This may explain severe and progressive HF in patients with seemingly mild-to-moderate cardiac involvement.[202] HF in AL amyloidosis is often manifested as right HF and frequently unresponsive to conventional treatment; a median survival of patients is approximately 6 months, whilst the 5-year survival rate is < 10%.[203,204] In addition to progressive HF, a significant proportion of patients die suddenly, mostly due to pulseless electrical activity for which ICD therapy is ineffective.[202]

Amyloid deposits may also cause conduction system abnormalities, ventricular and supraventricular arrhythmia, valvular dysfunction, coronary ischaemia due to small vessel disease and pericardial effusion, which all contribute to significant morbidity and mortality.[186,188] Increased levels of NT-proBNP and troponin T, and extracellular volume expansion on CMR T1 mapping have been shown to strongly predict poor survival in AL amyloidosis.[205,206] Patients with ATTR amyloidosis (particularly those with ATTR-wt or 'senile amyloidosis') have a longer median survival of 24–66 months compared with AL amyloidosis; nevertheless, the prognosis is poor.[207] ATTR-wt has become increasingly recognized as a cause of unexplained HFpEF in elderly patients with biatrial enlargement, mild mitral or tricuspid regurgitation, AF and/or conduction abnormalities.[194]

It is frequently accompanied by carpal tunnel syndrome and autonomic neuropathy.[208] A worse survival has been demonstrated with increasing levels of NT-proBNP and troponin T, and a risk stratification scheme based on cardiac biomarkers has been proposed.[194]

Clinically manifest cardiac involvement occurs in ~5% of patients with sarcoidosis, with a male predominance.[209] However, autopsy findings reveal cardiac involvement in at least 25% of patients with sarcoidosis.[210,211] Isolated cardiac sarcoidosis may precede systemic manifestations.[212] Clinical presentation depends on the burden and location of granulomatous infiltration, which most commonly affects the LV myocardium.[209] The resulting cardiomyopathy is either of a DCM type (more common) or an RCM type (less common) and overt HF is present in 10–40% of patients with cardiac sarcoidosis.[186] Previously undiagnosed sarcoidosis has been identified as an underlying cause of advanced HF in ~3% of patients requiring MCS or heart transplantation.[213,214] There is also a higher risk of high-degree atrioventricular block[215,216] and ventricular tachycardia,[217] and there may be an increased risk of SCD.[209,214] The presence and severity of HF have been identified as important predictors of mortality in patients with sarcoidosis, with the expected 10-year transplantation-free survival of only 53% in individuals with overt HF.[212,218]

Increased gastrointestinal iron absorption in haemochromatosis, and chronic blood transfusions in hereditary anaemias (e.g. thalassaemia, sickle cell anaemia), advanced renal insufficiency, and several haematological disorders (e.g. myelodysplastic syndrome), produce an iron overload state characterized by excessive cellular uptake of non-transferrin bound iron.[187] Iron excess in the myocardium produces an impairment in transmembrane Ca^{2+} flux and diastolic dysfunction, followed by progressive myocyte loss, replacement fibrosis, and chamber dilatation due to direct cytotoxic effects of accumulated iron.[219,220] If left untreated, cardiac involvement in iron overload/haemochromatosis advances from an early stage of an RCM with a HFpEF phenotype, to a late stage of a DCM with a HFrEF phenotype.[187] Less frequently, in elderly patients with severe iron overload, restrictive LV pathophysiology promotes the development of pulmonary hypertension, right ventricular remodelling and failure, without LV dilatation.[221] The occurrence of HF portends a poor prognosis, and < 50% of patients with thalassaemia survive up to 5 years following the onset of HF.[222,223] Early identification and follow-up of cardiac involvement with NT-proBNP levels, echocardiography (in particular tissue Doppler and strain rate imaging) and CMR is highly relevant for the management of patients with iron overload syndromes[224–227] (*Figure 1*).

Endomyocardial fibrosis is the most frequently encountered endomyocardial disorder and is the leading cause of RCM in tropical regions of Africa, Asia and South America.[228] Although the aetiology of EMF is still elusive, genetic, dietary, and infectious factors may promote inflammation responsible for endomyocardial damage and fibrosis.[228] The disease affects young and middle-aged individuals, beginning with an active phase of eosinophilic inflammation, followed by scar formation and a high risk for intracavitary thrombosis.[228] Repeated episodes of active disease lead to a chronic phase, in which RCM prevails, with signs and symptoms of biventricular or right-sided HF.[229] The clinical presentation of HF is often dominated by massive ascites, which is out of proportion to peripheral oedema. As a result of increased filling pressures, significant mitral and tricuspid regurgitation and AF are frequently encountered.[230] Overt HF carries an ominous prognosis with a 75% mortality rate at 2 years.[231] EMF accounts for 20% of HF hospitalizations and 15% of cardiac deaths in the endemic regions.[232,233]

In hypereosinophilic syndrome (formerly, Loeffler's endocarditis), which is characterized by persistently elevated eosinophil blood count ($> 1.5 \times 10^9$/L), cardiac morbidity is caused by the release of biologically active substances that damage the endothelium and myocardium.[186] Although occurring outside tropical regions, hypereosinophilic syndrome bears a striking resemblance to EMF with respect to the pathogenesis and clinical presentation of RCM.[186] In rare cases, carcinoid heart disease and cardiac fibroelastosis need to be considered as underlying causes of RCM.

Treatment of heart failure in restrictive cardiomyopathy

Conventional treatment of HF in RCM includes recommendations on fluid and sodium restriction (particularly in patients with hyponatremia) and judicious use of loop diuretics and mineralocorticoid receptor antagonists since over-diuresis may lead to low output hypotension in the presence of restrictive filling abnormalities. Similarly, ACE inhibitors, or angiotensin receptor blockers may cause hypotension even at low-to-moderate doses, whereas beta-blockers may be poorly tolerated due to an increased risk of worsening HF (because a fixed stroke volume requires a higher heart rate to maintain cardiac output).[188] Therefore, in patients with RCM, these medications need to be used with caution. Tachyarrhythmias are often poorly tolerated and require prompt rate or rhythm control. There is an unresolved issue of an ICD implantation for primary prevention in patients with RCM and preserved LVEF. At present, pending clinical trial evidence, expert consensus suggests an individualized assessment of arrhythmic risk, aetiology, multi-organ involvement and survival expectancy. There is limited experience with MCS in RCM patients with advanced HF. However, data from a small cohort of RCM patients treated with MCS demonstrate improved survival irrespective of aetiology (i.e. amyloidosis vs. other aetiologies), especially among patients with larger LV dimensions.[234] Heart transplant or heart/liver transplant (in patients with ATTR-m) can be considered in patients with advanced HF unresponsive to medical treatment.[235]

Specific therapies should be considered after the aetiology of RCM has been established. The major goal of treatment for cardiac amyloidosis is to inhibit the production, and to reduce the burden of amyloid protein infiltration. For AL amyloidosis, the established treatment strategy is chemotherapy, potentially combined with autologous stem cell transplantation. A recent retrospective study has reported that a combination of bortezomib, dexamethasone, and an alkylating agent has been associated with improved

survival in patients with HF due to AL amyloidosis.[236] Recently, a significant breakthrough in the treatment of cardiac amyloidosis (ATTR-m and ATTR-wt) has been observed with an oral acting transthyretin stabilizer, tafamidis. In the ATTR-ACT randomized trial, tafamidis has been associated with 30% reductions in all-cause mortality and cardiovascular-related hospitalizations and a reduction in the decline in functional capacity and quality of life compared with placebo.[237] Currently, tafamidis is approved in Europe for the treatment of ATTR amyloidosis in adult patients with polyneuropathy. Another strategy including pharmacological inhibition of transthyretin gene expression with patisiran has shown promising results in decreasing adverse cardiac outcomes compared with placebo in a subset of patients with cardiac ATTR-m amyloidosis.[238]

Observational data suggest that ventricular dysfunction and heart rhythm abnormalities can improve with immunosuppression in cardiac sarcoidosis.[239] In a Finnish registry (96% of patients on immunosuppression), transplantation-free survival at 1, 5 and 10 years was 97%, 90%, and 83%, respectively.[212] The choice of the most effective immunosuppressive therapy and the duration of treatment remain yet to be determined. Importantly, a regular follow-up to detect possible relapses is recommended.

In iron overload/haemochromatosis, improvement in cardiac function has been noted with timely and sustained iron removal.[240] In patients with haemochromatosis, phlebotomy removes 200 to 250 mg of iron at each session, and should be performed once or twice weekly to reduce serum ferritin to < 1000 ng/mL (or < 1000 μg/L).[241] Chelation therapy is an effective alternative option when phlebotomy is not feasible, such as in patients with chronic anaemia or malignancy. Iron chelation treatment can improve prognosis and survival in patients with iron overload.[242]

In hypereosinophilic syndrome affecting the heart, treatment with corticosteroids alone, or in combination with hydroxyurea or interferon-α, during the acute stage of the disease can result in improvement in LVEF and symptoms.[243] Imatinib may be also useful for the treatment of hypereosinophilic syndrome.[244] By analogy, corticosteroids and immunosuppressive drugs may be used in the early stages of EMF, but there are no randomized trials to support this approach.[228] There is also evidence that cardiac surgery (endocardectomy with or without valve repair/replacement) performed in experienced centres can increase survival compared with medical treatment in EMF.[245]

Summary

Comprehensive understanding of the epidemiology, underlying mechanisms, natural course and recent therapeutic advances can have a far-reaching impact on the management and prognosis of patients with HF in cardiomyopathies. Amongst cardiomyopathies, DCM is the most prevalent cause of HF. HFrEF is the most frequent presenting manifestation, as well as the predominant cause of death in DCM. Also, advanced HF in DCM is one of the leading indications for heart transplantation. In HCM, HF occurs less frequently than in DCM and usually takes the phenotype of HFpEF. Nevertheless, HF affects most patients with obstructive, and ~10% of patients with non-obstructive HCM. A timely recognition and treatment of patients at risk of progressive HF is important, since development of advanced HF, although rare in HCM, confers a poor prognosis. Although RCM is the least common amongst the cardiomyopathies, the majority of patients present with HFpEF, while HFrEF usually occurs at a later stage and is more frequent in amyloidosis or iron overload/haemochromatosis. Regardless of the underlying aetiology, HF in RCM is a predictor of a poor outcome.

Recently, new insights have occurred into the initiating causes and prevailing mechanisms of HF development in several cardiomyopathies. In addition, novel aetiology-specific therapies, including transthyretin stabilizers in cardiac amyloidosis, enzyme replacement therapies in Anderson–Fabry and Pompe diseases, immunoadsorption, immunotherapy, and selective administration of antiviral agents in DCM, as well as bromocriptine in PPCM, have shown a potential to improve outcomes beyond GDMT of HF. Still, causative therapies of many cardiomyopathies are lacking, which emphasizes the importance of developing evidence-based management that would improve outcomes in a majority of patients with HF in cardiomyopathies.

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