

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

**Petar M. Seferović<sup>1,2\*</sup>, Marija Polovina<sup>1,3</sup>, Johann Bauersachs<sup>4</sup>, Michael Arad<sup>5</sup>, Tuvia Ben Gal<sup>6</sup>, Lars H. Lund<sup>7</sup>, Stephan B. Felix<sup>8</sup>, Eloisa Arbustini<sup>9</sup>, Alida L.P. Caforio<sup>10</sup>, Dimitrios Farmakis<sup>11</sup>, Gerasimos S. Filippatos<sup>11</sup>, Elias Gialafos<sup>12</sup>, Vladimir Kanjuh<sup>2</sup>, Gordana Krljanac<sup>1,3</sup>, Giuseppe Limongelli<sup>13</sup>, Aleš Linhart<sup>14</sup>, Alexander R. Lyon<sup>15</sup>, Ružica Maksimović<sup>1,16</sup>, Davor Miličić<sup>17</sup>, Ivan Milinković<sup>3</sup>, Michel Noutsias<sup>18</sup>, Ali Oto<sup>19</sup>, Öztekin Oto<sup>20</sup>, Siniša U. Pavlović<sup>1,21</sup>, Massimo F. Piepoli<sup>22</sup>, Arsen D. Ristić<sup>1,3</sup>, Giuseppe M.C. Rosano<sup>23</sup>, Hubert Seggewiss<sup>24</sup>, Milika Ašanin<sup>1,3</sup>, Jelena P. Seferović<sup>25,26</sup>, Frank Ruschitzka<sup>27</sup>, Jelena Čelutkienė<sup>28,29</sup>, Tiny Jaarsma<sup>30</sup>, Christian Mueller<sup>31</sup>, Brenda Moura<sup>32</sup>, Loreena Hill<sup>33</sup>, Maurizio Volterrani<sup>34</sup>, Yuri Lopatin<sup>35</sup>, Marco Metra<sup>36</sup>, Johannes Backs<sup>37,38</sup>, Wilfried Mullens<sup>39,40</sup>, Ovidiu Chioncel<sup>41,42</sup>, Rudolf A. de Boer<sup>43</sup>, Stefan Anker<sup>44,45,46</sup>, Claudio Rapezzi<sup>47</sup>, Andrew J.S. Coats<sup>48,49</sup>, and Carsten Tschöpe<sup>50</sup>**

<sup>1</sup>University of Belgrade Faculty of Medicine, Belgrade, Serbia; <sup>2</sup>Serbian Academy of Sciences and Arts, Belgrade, Serbia; <sup>3</sup>Department of Cardiology, Clinical Center of Serbia, Belgrade, Serbia; <sup>4</sup>Department of Cardiology and Angiology, Medical School Hannover, Hannover, Germany; <sup>5</sup>Cardiomyopathy Clinic and Heart Failure Institute, LeVey Heart Center, Sheba Medical Center and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; <sup>6</sup>Department of Cardiology, Rabin Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; <sup>7</sup>Department of Medicine, Karolinska Institutet, and Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden; <sup>8</sup>Department of Internal Medicine B, University Medicine Greifswald, Greifswald, Germany; <sup>9</sup>Centre for Inherited Cardiovascular Diseases, IRCCS Foundation, University Hospital Policlinico San Matteo, Pavia, Italy; <sup>10</sup>Division of Cardiology, Department of Cardiological, Thoracic and Vascular Sciences, University of Padua, Padua, Italy; <sup>11</sup>University of Cyprus Medical School, Nicosia, Cyprus; Heart Failure Unit, Department of Cardiology, Athens University Hospital Attikon, National and Kapodistrian University of Athens, Athens, Greece; <sup>12</sup>Second Department of Cardiology, Heart Failure and Preventive Cardiology Section, Henry Dunant Hospital, Athens, Greece; <sup>13</sup>Department of Cardiothoracic Sciences, Università della Campania 'Luigi Vanvitelli', Monaldi Hospital, AORN Colli, Centro di Ricerca Cardiovascolare, Ospedale Monaldi, AORN Colli, Naples, Italy, and UCL Institute of Cardiovascular Science, London, UK; <sup>14</sup>Second Department of Medicine, Department of Cardiovascular Medicine, General University Hospital, Charles University in Prague, Prague, Czech Republic; <sup>15</sup>National Heart and Lung Institute, Imperial College London and Royal Brompton Hospital, London, UK; <sup>16</sup>Centre for Radiology and Magnetic Resonance Imaging, Clinical Centre of Serbia, Belgrade, Serbia; <sup>17</sup>Department of Cardiovascular Diseases, University Hospital Center Zagreb, University of Zagreb, Zagreb, Croatia; <sup>18</sup>Mid-German Heart Center, Department of Internal Medicine III, Division of Cardiology, Angiology and Intensive Medical Care, University Hospital Halle, Martin-Luther-University Halle, Halle, Germany; <sup>19</sup>Department of Cardiology, Hacettepe University Faculty of Medicine, Ankara, Turkey; <sup>20</sup>Department of Cardiovascular Surgery, Dokuz Eylül University Faculty of Medicine, İzmir, Turkey; <sup>21</sup>Pacemaker Center, Clinical Center of Serbia, Belgrade, Serbia; <sup>22</sup>Heart Failure Unit, Cardiology, G. da Saliceto Hospital, Piacenza, Italy; <sup>23</sup>Centre for Clinical and Basic Research, Department of Medical Sciences, IRCCS San Raffaele Pisana, Rome, Italy; <sup>24</sup>Medizinische Klinik, Kardiologie & Internistische Intensivmedizin, Klinikum Würzburg-Mitte, Würzburg, Germany; <sup>25</sup>Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; <sup>26</sup>Clinic for Endocrinology, Diabetes and Metabolic Disorders, Clinical Center Serbia and Faculty of Medicine, University of Belgrade, Belgrade, Serbia; <sup>27</sup>Department of Cardiology, University Heart Center, Zürich, Switzerland; <sup>28</sup>Clinic of Cardiac and Vascular Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; <sup>29</sup>State Research Institute Centre for Innovative Medicine, Vilnius, Lithuania; <sup>30</sup>Department of Social and Welfare Studies, Faculty of Health Science, Linköping University, Linköping, Sweden; <sup>31</sup>Cardiovascular Research Institute Basel (CRIB) and Department of Cardiology, University Hospital Basel, University of Basel, Basel, Switzerland; <sup>32</sup>Cardiology Department, Centro Hospitalar São João, Porto, Portugal; <sup>33</sup>School of Nursing and Midwifery, Queen's University Belfast, Belfast, UK; <sup>34</sup>Department of Cardiology, IRCCS San Raffaele Pisana, Rome, Italy; <sup>35</sup>Volgograd State Medical University, Regional Cardiology Centre Volgograd, Volgograd, Russia; <sup>36</sup>Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; <sup>37</sup>Department of Molecular Cardiology and Epigenetics, University of Heidelberg, Heidelberg, Germany; <sup>38</sup>DZHK (German Centre for Cardiovascular Research) partner site Heidelberg/Mannheim, Heidelberg, Germany; <sup>39</sup>BIOMED - Biomedical Research Institute, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium; <sup>40</sup>Department of Cardiology, Ziekenhuis Oost-Limburg, Genk, Belgium;

\*Corresponding author. University of Belgrade, Faculty of Medicine and Heart Failure Center, Belgrade University Medical Center, Heart Failure Society of Serbia, 8 Koste Todorovića, 11000 Belgrade, Serbia. Tel/Fax: +381 11 361 47 38, Email: seferovic.petar@gmail.com  
[Correction added on 27 August 2020, after first online publication: the affiliation of the author Giuseppe M.C. Rosano has been corrected to 'Centre for Clinical and Basic Research, Department of Medical Sciences, IRCCS San Raffaele Pisana, Rome, Italy' in this online version.]

<sup>41</sup>University of Medicine Carol Davila, Bucharest, Romania; <sup>42</sup>Emergency Institute for Cardiovascular Diseases, 'Prof. C. C. Iliescu', Bucharest, Romania; <sup>43</sup>Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; <sup>44</sup>Division of Cardiology and Metabolism, Department of Cardiology (CVK), Charité, Berlin, Germany; <sup>45</sup>Berlin-Brandenburg Center for Regenerative Therapies (BCRT), Berlin, Germany; <sup>46</sup>DZHK (German Centre for Cardiovascular Research) partner site Berlin, Charité, Berlin, Germany; <sup>47</sup>Cardiology, Department of Experimental, Diagnostic and Specialty Medicine, Alma Mater Studiorum University of Bologna, Bologna, Italy; <sup>48</sup>Monash University, Australia, and University of Warwick, Coventry, UK; <sup>49</sup>Pharmacology, Centre of Clinical and Experimental Medicine, IRCCS San Raffaele Pisana, Rome, Italy, and St George's University of London, London, UK; and <sup>50</sup>Berlin-Brandenburg Center for Regenerative Therapies, Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK) Berlin, Department of Cardiology, Campus Virchow Klinikum, Charite - Universitaetsmedizin Berlin, Berlin, Germany

Received 15 January 2019; revised 20 February 2019; accepted 28 February 2019; online publish-ahead-of-print 16 April 2019

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).<sup>1</sup> The variety of causes, multiple underlying pathophysiological mechanisms and different phenotypic expressions influence their presentation and response to treatment.<sup>1</sup> 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 ( $\geq 50\%$ , HFpEF)], and aetiology of HF in cardiomyopathies.

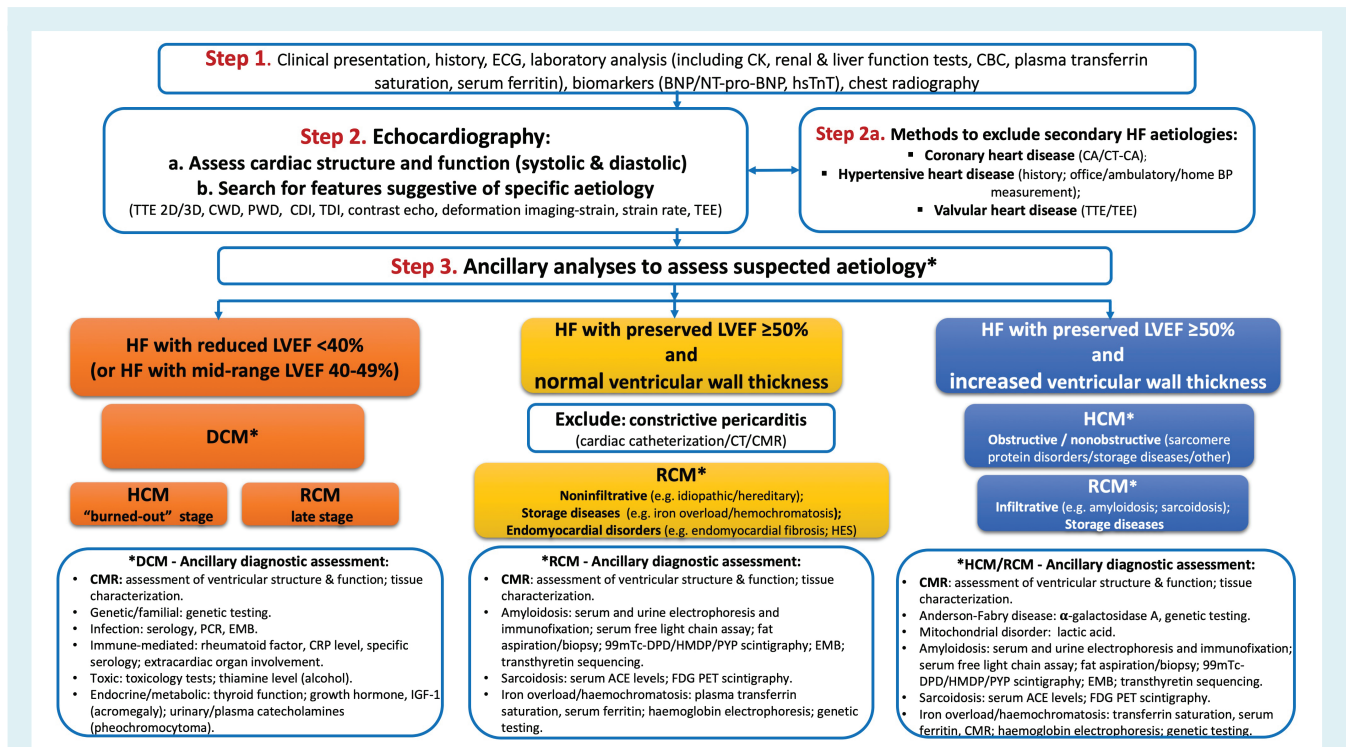
## Heart failure in dilated cardiomyopathy

### 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.<sup>1</sup> It is considered one of the leading causes of HFrEF worldwide.<sup>2</sup> 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.<sup>3,4</sup> The prevalence of DCM is apparently lower in Eastern Asia (i.e. 14 cases per 100 000 in Japan),<sup>5</sup> and it might be higher in Africa and Latin America compared with Europe.<sup>6,7</sup>

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.





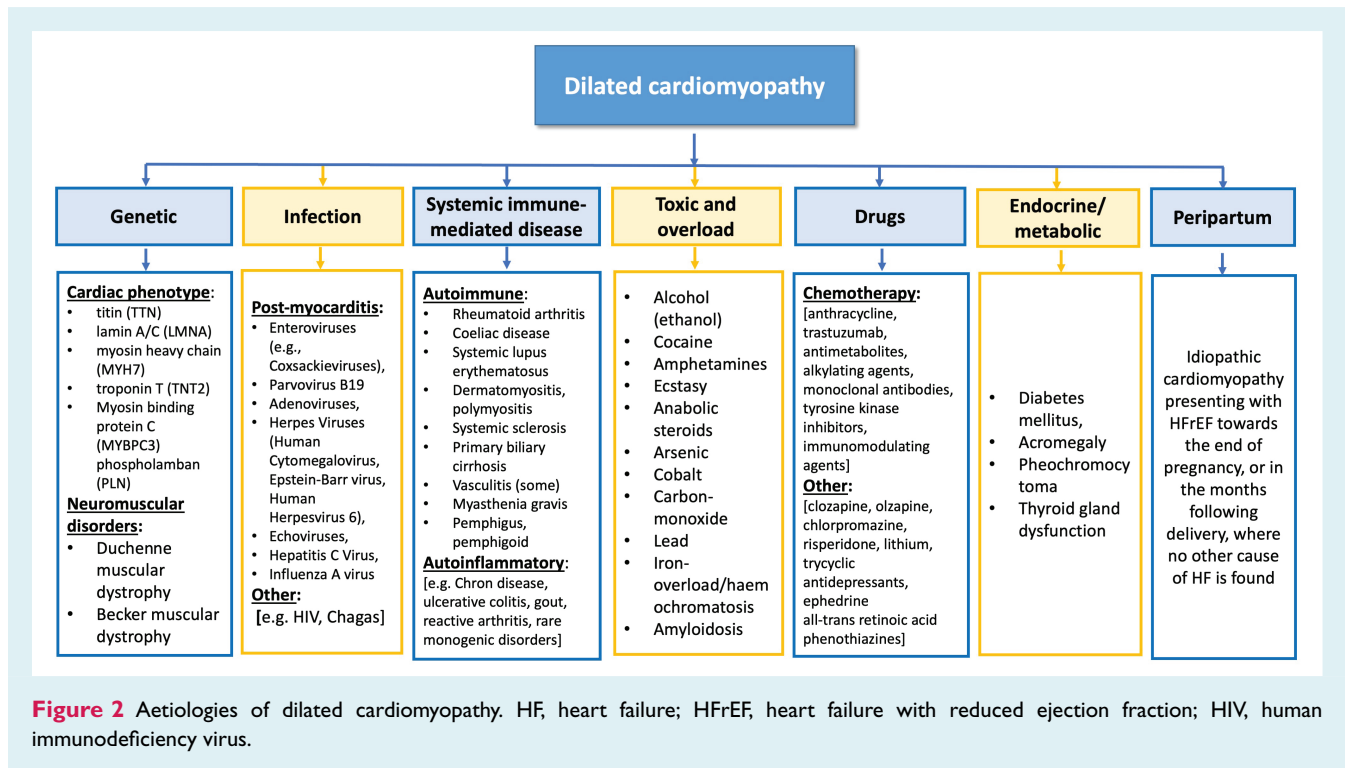
**Figure 1** Proposed clinical approach to the assessment of heart failure aetiology in cardiomyopathies. ACE, angiotensin-converting enzyme; BNP, B-type natriuretic peptide; BP, blood pressure; CA, coronary angiography; CBC, complete blood count; CDI, colour Doppler imaging; CK, creatine kinase, CMR, 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.<sup>8</sup> 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%).<sup>9</sup> 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%).<sup>9</sup> In another study, self-declared black race was associated with a younger age and more severe HF symptoms at diagnosis compared with white race.<sup>10</sup> 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.<sup>11</sup>

There is a broad variation in the reported prevalence of DCM in patients with HF. In trials of HF with reduced ejection fraction (HFrEF), DCM has been reported in

12–35% of individuals.<sup>12–14</sup> In observational studies of HF patients, the prevalence of DCM ranged between 8% and 47%.<sup>11,15,16</sup> In a cohort of 156 013 patients hospitalized for HF in the USA, DCM was the stated underlying cause in 31%.<sup>17</sup> 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.<sup>18,19</sup> 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.<sup>20–22</sup> 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.<sup>22</sup> After the age of 60 years, DCM is the second most common indication for heart transplantation preceded only by ischaemic heart disease,



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.<sup>22</sup>

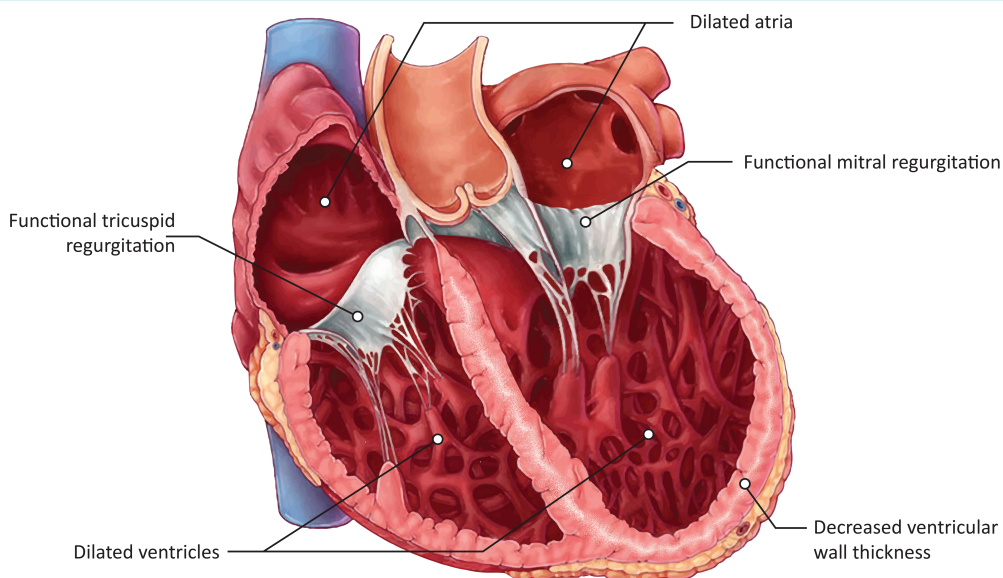
## Pathophysiology of heart failure in dilated cardiomyopathy

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)<sup>1</sup> (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<sup>23</sup> and a genetic determinant in up to 40% of DCM patients.<sup>1,24</sup> 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.<sup>24,25</sup> 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.<sup>26,27</sup> 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,<sup>28,29</sup> which confer high risk of arrhythmia and sudden cardiac death (SCD) that may lower the threshold for an implantable cardioverter-defibrillator (ICD) implantation.<sup>30</sup> 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.<sup>31</sup> Myocardial fibrosis is associated with deterioration in left ventricular (LV) systolic function and a propensity for adverse outcomes.<sup>32</sup> 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.<sup>33,34</sup>

Viral infection followed by an (auto)immune activation in the myocardium may play a major role in the development of HF in DCM.<sup>35</sup> 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.<sup>36</sup> In addition to inflammatory myocardial damage, autoantibodies directed against the ADP/ATP carrier may contribute to LV dysfunction.<sup>37</sup> 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.<sup>38</sup> 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,<sup>39</sup> 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.<sup>40</sup>

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.<sup>41</sup> 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.<sup>42</sup>

Dilated cardiomyopathy may also occur in systemic immune-mediated diseases (SIDs) that include autoimmune and autoinflammatory disorders.<sup>43</sup> 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.<sup>44,45</sup>

The pathogenesis of PPCM is still not elucidated but several contributing factors have been implicated.<sup>46,47</sup> 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.<sup>48</sup> 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.<sup>49–52</sup> 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.<sup>53</sup>

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<sup>54–59</sup> (Figure 2). Cardiotoxicity is a relatively common complication of cancer therapy manifesting as LV dysfunction and HF (usually HFrEF).<sup>58</sup> 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).<sup>60</sup> 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.<sup>61</sup> 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).<sup>62,63</sup>

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.<sup>64</sup> SCD and systemic embolism, largely attributable to atrial fibrillation (AF), accounted for the remainder of the cardiovascular mortality.<sup>64</sup>

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.<sup>65</sup> In patients assessed between 1990 and 2002, the 5- and 10-year survival rates had increased to 81% and 65%, respectively.<sup>65</sup> 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.<sup>10</sup> Over the same period, survival free of HF hospitalization was 88%, 82%, and 78%, respectively.<sup>10</sup> 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.<sup>66</sup> 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.<sup>67</sup> 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.<sup>8,10,68</sup> Higher baseline LVEF and lower LV

end-diastolic diameter have been recognized as independent predictors of reverse LV remodelling.<sup>10</sup> 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.<sup>8</sup> Importantly, independent of other factors, LV reverse remodelling was associated with ~50% lower mortality rates at 10-year follow-up in DCM patients.<sup>68</sup>

On the other hand, male sex and advanced age (>60 years) have been associated with a poorer prognosis in patients with DCM and HF.<sup>9,10,69</sup> 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.<sup>10</sup> Other predictors of adverse outcomes include: lower baseline LVEF, higher NYHA class (III–IV), significant mitral regurgitation,<sup>68</sup> the presence of LBBB and higher natriuretic peptide levels.<sup>8,70</sup> Severe functional mitral regurgitation (FMR) has been associated with approximately two-fold increased risk of mortality or worsening HF in DCM.<sup>71</sup> Persistence of severe FMR or worsening of non-severe FMR despite optimal GDMT has been shown to predict adverse prognosis in patients with HF<sub>rEF</sub>, irrespective of HF aetiology.<sup>72</sup> 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.<sup>70</sup>

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).<sup>11</sup> Advanced HF remains the most frequent cause of death in DCM, while SCD accounts for <30% of mortality.<sup>9,70</sup> 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.<sup>9,73</sup> The risk of non-cardiovascular death increases with older age and more severe HF.<sup>9,73</sup>

## 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)<sup>12,73–85</sup>. 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.<sup>74</sup>

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<sup>65,67</sup> have not been confirmed in clinical trials.<sup>75,86</sup> 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)
<b>Medical therapy</b>				
SOLVD, <sup>12</sup> 1991	Enalapril vs. placebo	2569; NYHA class I–IV; LVEF $\leq$ 35%	17.9–18.6%	All-cause death: RR $\downarrow$ 27%; Death or hospitalization: RR $\downarrow$ 29%; Interaction $P$ = NS according to HF aetiology (ischaemic vs. non-ischaemic)
DIG, <sup>75</sup> 1997	Digoxin vs. placebo	6800; NYHA class I–IV; LVEF $\leq$ 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, <sup>76</sup> 1993	Metoprolol vs. placebo	383; 94% NYHA class II–III, LVEF $<$ 40%	100%	All-cause death: RR $\downarrow$ 34% (95% CI –6% to 62%, $P$ = 0.058). Significant improvement in symptoms, less clinical deterioration with metoprolol
CIBIS, <sup>77</sup> 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, <sup>78</sup> 1999	Spirolactone vs. placebo	1663; NYHA class III–IV (NYHA class IV within 6 months before enrolment); LVEF $\leq$ 35%	45–46% <sup>a</sup>	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, <sup>79</sup> 2003	Candesartan vs. placebo in patients intolerant to ACE inhibitors	2028; NYHA class II–IV; LVEF $\leq$ 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, <sup>80</sup> 2010	Ivabradine vs. placebo	6558; LVEF $\leq$ 35%; sinus rhythm $>$ 70 b.p.m.; NYHA class II–IV; HF hospitalization within the previous 12 months	32–33% <sup>a</sup>	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, <sup>81</sup> 2011	Eplerenone vs. placebo	2737; NYHA class II; LVEF $<$ 30% (or LVEF 30–35% and QRS $>$ 130 ms)	30.1–31.8% <sup>a</sup>	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, <sup>82</sup> 2014	Sacubitril/valsartan vs. placebo	10 521; NYHA class II–IV; LVEF $\leq$ 35–40%, BNP $\geq$ 150 pg/mL or NT-proBNP $\geq$ 600 pg/mL, or HF hospitalization within the previous 12 months + BNP $\geq$ 100 pg/mL or NT-proBNP $\geq$ 400 pg/mL	39.9–40.1% <sup>a</sup>	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)
<b>Devices</b>				
DEFINITE, <sup>83</sup> 2004	ICD vs. medical therapy	458; LVEF $\leq$ 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, <sup>84</sup> 2005	ICD vs. placebo Amiodarone vs. placebo	2521; NYHA class II–III; LVEF $\leq$ 35% on GDMT	48% <sup>a</sup>	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, <sup>85</sup> 2004	CRT-P/CRT-D vs. medical therapy	1520; NYHA class III–IV; LVEF $\leq$ 35% on GDMT; QRS $\geq$ 120 ms	44.9% <sup>a</sup>	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, <sup>73</sup> 2016	ICD vs. medical therapy (58% in both groups received CRT)	1116; NYHA class II–IV with non-ischaemic HF; LVEF $\leq$ 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.

<sup>a</sup>Proportion of patients with non-ischaemic HF aetiology.

LVEF  $\leq$ 35% on GDMT.<sup>74</sup> 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<sup>83,84</sup> (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.<sup>73</sup> However, a recent sub-analysis of the DANISH trial suggested that in patients  $\leq$ 70 years old, ICD implantation reduced all-cause mortality.<sup>87</sup> 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.<sup>88</sup> 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.<sup>68</sup>

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.<sup>85,89,90</sup> Hence, CRT is currently recommended for symptomatic HF patients with LVEF  $<$ 35% and QRS  $\geq$ 130 ms, particularly of LBBB morphology (a surrogate for LV dyssynchrony), treated for  $\geq$ 3 months with GDMT, irrespective of HF aetiology.<sup>74</sup>

Based on the experience from surgical mitral valve repair (MVR) of moderate-to-severe FMR, suggesting reverse LV remodelling and functional improvement,<sup>91</sup> 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.<sup>92</sup>

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.<sup>93</sup> 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.<sup>94</sup>

### 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.<sup>95–97</sup> Accordingly, expert consensus documents have recommended immunosuppression with azathioprine and prednisone for 6–12 months in patients with biopsy-proven, virus-negative DCM,<sup>35</sup> but the exact role of immunosuppression is still unresolved. Immunosuppression is also recommended in acute giant-cell and eosinophilic myocarditis and cardiac sarcoidosis.<sup>7,35,98</sup> 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.<sup>99</sup> 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.<sup>100–102</sup> 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.<sup>103</sup> Treatment with the prolactin inhibitor bromocriptine (accompanied by prophylactic anticoagulation) may provide a disease-specific therapy in patients with acute HF in PPCM.<sup>47,104,105</sup> Further aetiological therapies include cessation of the offending agent(s) (e.g. alcohol) and management of the underlying endocrine or metabolic disorders.<sup>106</sup>

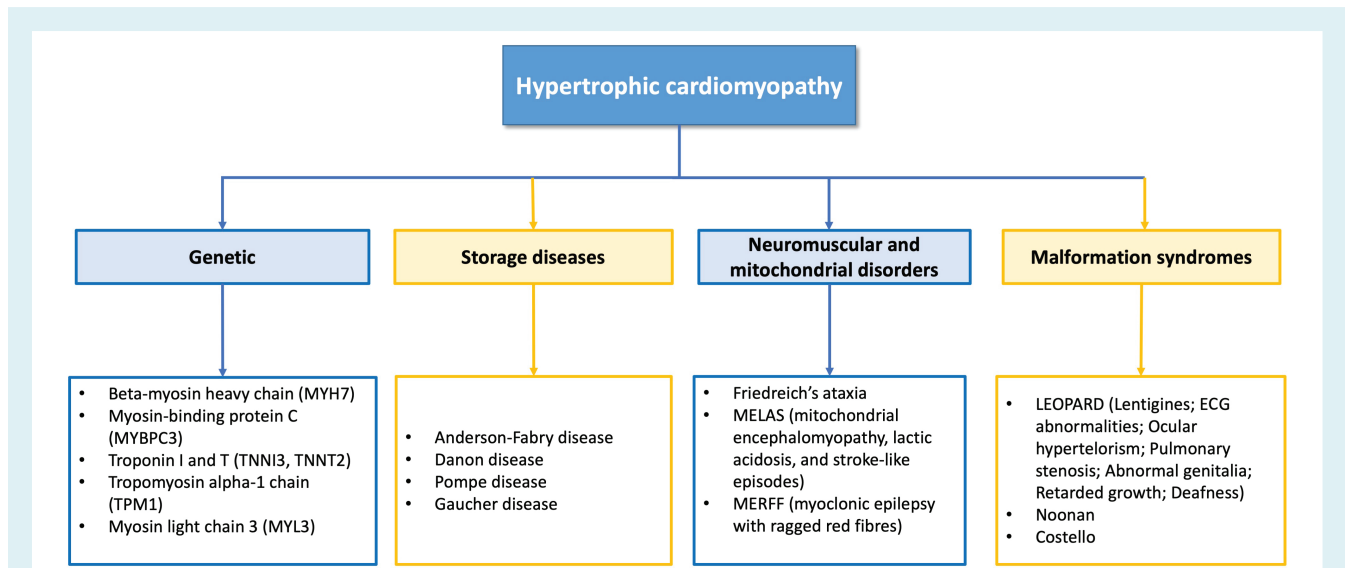
In light of the various monogenetic causes of DCM, gene repair may be a promising target for the causative treatment of HF. Following improvement in skeletal muscle function with CRISPR/Cas9 technology for gene repair in Duchenne muscular dystrophy,<sup>107</sup> this technology is currently under assessment for genome modification in cardiomyopathies.<sup>108</sup> 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

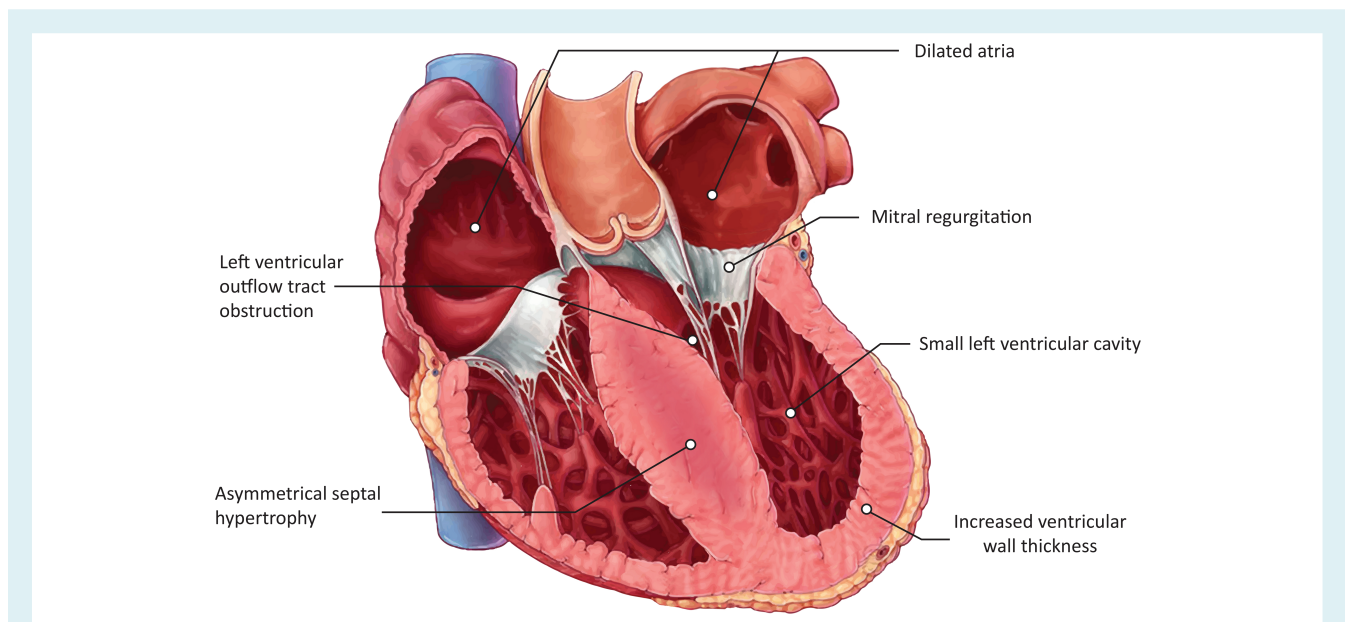
### Incidence and prevalence of heart failure in hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is defined by an increase in myocardial wall thickness ( $\geq 15$  mm in adults, or  $\geq 13$  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.<sup>109,110</sup> Most patients have an asymmetric septal hypertrophy and approximately 40–70% have an obstructive HCM, diagnosed by a LV intracavitary gradient  $\geq 30$  mmHg at rest ( $\sim 25\%$  of patients) or during exercise.<sup>109,111,112</sup> Non-obstructive HCM, demonstrating gradients  $< 30$  mmHg at rest and/or with exercise, is present in 30–60% patients.<sup>109,111,112</sup> In several reports from Europe, Asia and North America, the prevalence of HCM is 2–5 per 1000 of the general population.<sup>113–116</sup> 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<sup>110,117</sup> (Figure 4). In about 30% of patients, the cause of HCM remains unknown.<sup>109</sup> 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 HFrfEF 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  $\sim 50\%$ , with symptoms varying from mild to severe (NYHA class II–IV).<sup>118</sup> 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).<sup>119</sup> 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.<sup>120</sup> 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).<sup>109,121,122</sup> 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.<sup>123–126</sup> 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.<sup>127</sup> 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.<sup>128</sup>

Amongst HF patients, those with HCM account for 2–3%.<sup>16</sup> 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.<sup>22</sup> 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.<sup>22</sup>

## 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.<sup>129,130</sup> 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.<sup>131</sup> 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.<sup>132</sup> 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.<sup>133</sup> 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.<sup>134</sup>

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 HF<sub>rEF</sub>. 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.<sup>135</sup> 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.<sup>136</sup> 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.<sup>137,138</sup> Also, familial clustering of advanced HF has been recognized as a marker of risk for unfavourable outcomes in other family members.<sup>126</sup> 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.<sup>111</sup>

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.<sup>120</sup> 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.<sup>120</sup> 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.<sup>120</sup> In patients without a significant gradient at rest, cardiopulmonary exercise testing is the preferred method for provoking obstruction.<sup>109</sup> LV diastolic dysfunction represents another important mechanism underlying the development of HF (i.e. HF<sub>pEF</sub>) 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.<sup>111</sup> In addition, mitral valve abnormalities, coronary myocardial bridging, apical aneurysms, atrial remodelling and autonomic dysfunction may contribute to the development and severity of HF.<sup>124,139–144</sup> 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 HF<sub>rEF</sub>.

### 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 HF<sub>pEF</sub> phenotype due to an extensive, concentric increase in LV wall thickness.<sup>145,146</sup> 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.<sup>146</sup> Asymmetric LV hypertrophy in storage disorders is rare (< 2.5%), while biventricular hypertrophy may occur in up to 25% of patients.<sup>145</sup> 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.<sup>147</sup> Most patients have preserved LVEF with occasional evidence of subaortic LV obstruction.<sup>148</sup> 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.<sup>149</sup> Rarely, diastolic dysfunction in storage disorders may progress to a restrictive filling pattern, accompanied by a significant biatrial enlargement.<sup>145</sup> 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 HF<sub>rEF</sub> invariably occurs in Danon disease and occasionally in patients with other metabolic cardiomyopathies.<sup>150</sup>

## 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.<sup>151</sup> 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  $\geq 30$  mmHg at rest independently predicted HF progression and increased mortality.<sup>152</sup> 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.<sup>153</sup> As a result, severe HF was prevalent in 20–38% of those patients following a period of 6.5 years.<sup>153</sup> 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.<sup>123</sup> The distinguishing features of these patients were older age ( $50 \pm 14$  years) and a significantly increased LV wall thickness at baseline.<sup>123</sup>

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  $\geq$  II) and had higher mortality compared with the rest of the cohort.<sup>154</sup>

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.<sup>123,155</sup> 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 at 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),<sup>120,156</sup> 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.<sup>151,157</sup> Adverse LV remodelling is subtended by extensive myocardial replacement fibrosis.<sup>151,158</sup> The most advanced, 'burned-out', phase occurs in 3% of patients and carries a considerable risk of mortality (11% per year).<sup>126</sup>

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

### 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.<sup>160</sup> 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.<sup>161</sup> The progression to advanced HF has been observed in 10% of patients over a median period of 7.1 years.<sup>162</sup> 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.<sup>163</sup> 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.<sup>164,165</sup>

## 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.<sup>109</sup>

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.<sup>109</sup> 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.<sup>166</sup> In patients with obstructive HCM, who have a gradient  $\geq$  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.<sup>109</sup> 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.<sup>167,168</sup> Alternatively, alcohol septal ablation has been shown to convey an improvement in outcomes comparable with surgery.<sup>169</sup> Surgery seems less beneficial for older patients and for those with residual AF.<sup>170</sup> Alcohol septal ablation may be less effective in younger patients with higher baseline gradients.<sup>171</sup> The periprocedural complications of both procedures include atrioventricular block (7–20% of patients), bundle branch block, or ventricular septal defect.<sup>109</sup> These treatment modalities are currently available in a small number of experienced centres.

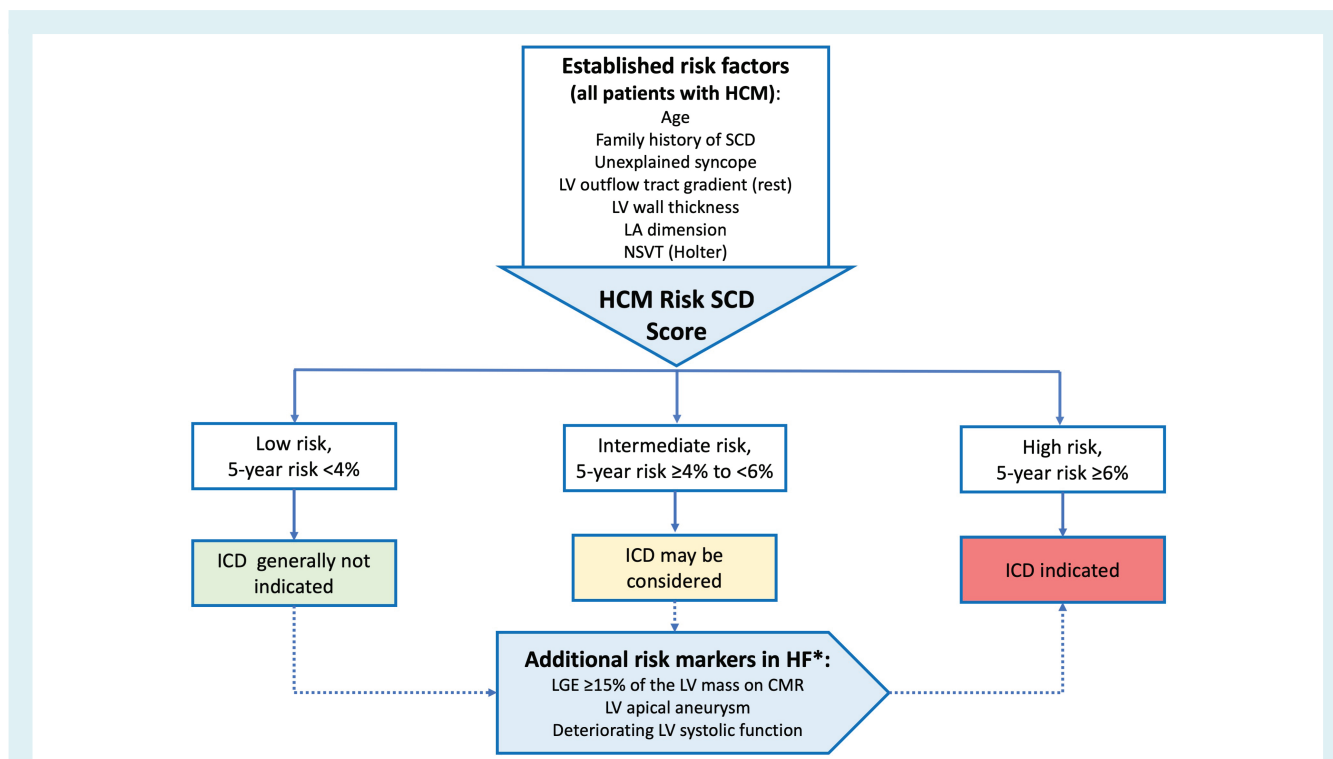
Dual-chamber pacing has failed to demonstrate convincing treatment benefits.<sup>172</sup> It is currently recommended in patients with obstructive HCM (and an indication for antibradycardia pacing), deemed unsuitable for, or unwilling to undergo surgery/alcohol septal reduction.<sup>109</sup>

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<sup>109</sup> (Figure 6). Specifically, in patients with HF due to HCM, additional features may be used to refine risk assessment for SCD,<sup>126,140,173</sup> 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.<sup>109</sup> In a setting of progressive LV dysfunction, refractory HF symptoms and LBBB, limited data supports CRT implantation in patients with LVEF < 50%,<sup>174</sup> whereas patients with LVEF  $\leq$  35% and LBBB should be considered for CRT implantation as per current guidelines for the management of HF.<sup>74</sup>

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- $\alpha$  or agalsidase- $\beta$

Oral chaperon: migalastat

#### Pompe disease

Enzyme replacement therapy:  $\alpha$ -glucosidase

- 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
- Similar effect on a composite renal, cardiovascular and cerebrovascular outcome compared with enzyme replacement therapy
- Possible positive impact on left ventricular fibrosis and hypertrophy

- 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.<sup>175</sup> 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.<sup>157</sup>

#### Treatment of patients with storage disorders

For patients with HCM occurring in Anderson–Fabry disease, there is an effective enzyme replacement therapy

with agalsidase- $\alpha$  and agalsidase- $\beta$ ,<sup>176–178</sup> or with an oral chaperone, migalastat,<sup>179,180</sup> 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  $\alpha$ -glucosidase is available (Table 2).<sup>181,182</sup> 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.<sup>183</sup>

## 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.<sup>110</sup> Ventricular wall thickness is usually normal; however, in infiltrative or storage disease aetiologies of RCM, there is a variable degree of ventricular wall thickening.<sup>184</sup> 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.<sup>110,185</sup>

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.<sup>186,187</sup> These aetiologies need to be considered in differential diagnosis between RCM and DCM (Figure 7). In addition, RCM is characterized by a greater risk of thromboembolism, conduction abnormalities, arrhythmias and SCD.<sup>188</sup>

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).<sup>119</sup> 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.<sup>189</sup> 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.<sup>190</sup> Among individuals > 65 years of age, RCM due to cardiac amyloidosis may be an underrecognized, albeit important cause of unexplained HF.<sup>191</sup> In a series of patients ≥ 90 years of age who died of HF, autopsy revealed RCM in 10%.<sup>192</sup> 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<sup>193</sup> and a 13% prevalence among patients with HFpEF.<sup>194</sup>

### 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.<sup>186</sup> 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.<sup>195</sup> Irrespective of the aetiology, RCM is characterized by severe diastolic dysfunction, presenting with a restrictive filling abnormality.<sup>110</sup> Markedly elevated filling pressure leads to prominent biatrial enlargement, and a predisposition to AF, which further diminishes ventricular filling.<sup>184</sup> 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).

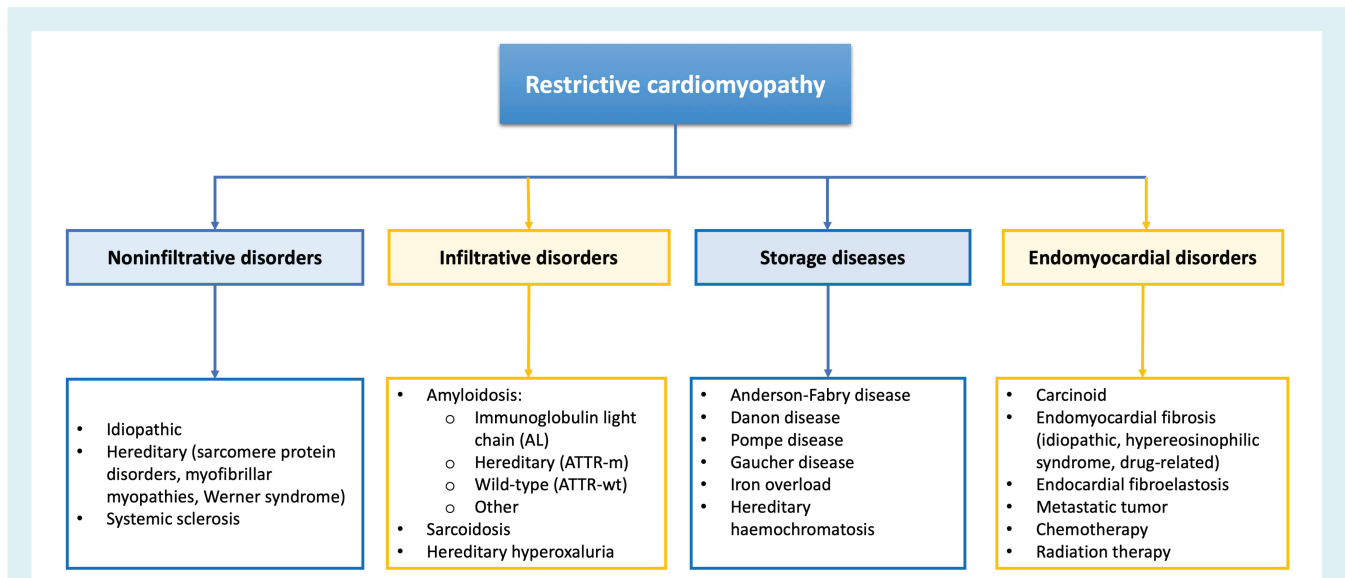
Although cardiac amyloidosis is often considered as a cause of HFpEF since LVEF often remains preserved until the late stage of the disease, in the majority of patients with HF, LV systolic function is also compromised due to a reduction in LV longitudinal function and strain.<sup>196</sup> Furthermore,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

### The natural course and outcome of heart failure in restrictive cardiomyopathy

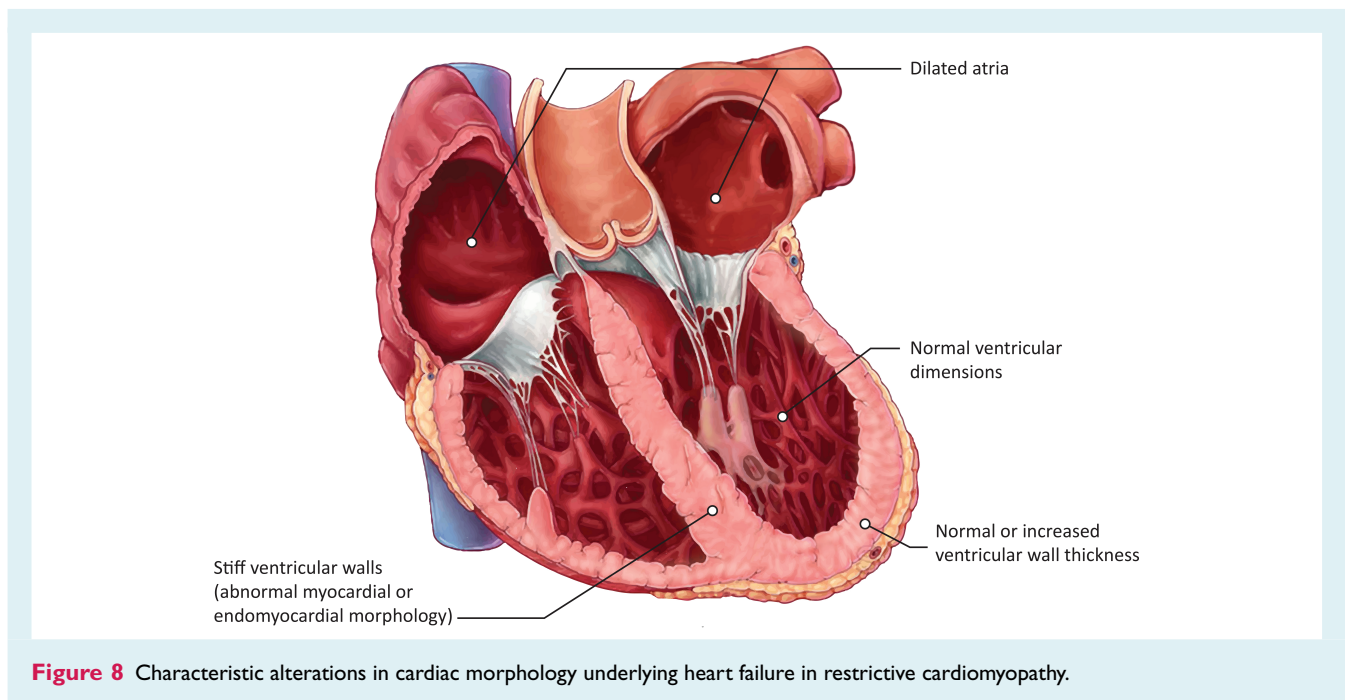
The prognosis of HF in RCM is poor, regardless of the underlying cause of RCM.<sup>195</sup> In a small cohort of paediatric patients with primary RCM, an extraordinary 53% experienced SCD shortly after diagnosis; 75% of the remaining patients had HF, and all had died or underwent heart transplantation within a few years of diagnosis.<sup>199</sup> 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%).<sup>190</sup> 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.<sup>189</sup> The risk of death doubled with each increment in NYHA class, independently of other characteristics.<sup>189</sup>

Caused by intramyocardial deposition of transthyretin-derived amyloid fibrils, transthyretin amyloid cardiomyopathy is the most common cause of the infiltrative form of RCM.<sup>200</sup>

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.<sup>201</sup> 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.<sup>201</sup> This may explain severe and progressive HF in patients with seemingly mild-to-moderate cardiac involvement.<sup>202</sup> 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%.<sup>203,204</sup> In addition to progressive HF, a significant proportion of patients die suddenly, mostly due to pulseless electrical activity for which ICD therapy is ineffective.<sup>202</sup>

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.<sup>186,188</sup> 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.<sup>205,206</sup> 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.<sup>207</sup> 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.<sup>194</sup>

It is frequently accompanied by carpal tunnel syndrome and autonomic neuropathy.<sup>208</sup> 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.<sup>194</sup>

Clinically manifest cardiac involvement occurs in ~5% of patients with sarcoidosis, with a male predominance.<sup>209</sup> However, autopsy findings reveal cardiac involvement in at least 25% of patients with sarcoidosis.<sup>210,211</sup> Isolated cardiac sarcoidosis may precede systemic manifestations.<sup>212</sup> Clinical presentation depends on the burden and location of granulomatous infiltration, which most commonly affects the LV myocardium.<sup>209</sup> 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.<sup>186</sup> Previously undiagnosed sarcoidosis has been identified as an underlying cause of advanced HF in ~3% of patients requiring MCS or heart transplantation.<sup>213,214</sup> There is also a higher risk of high-degree atrioventricular block<sup>215,216</sup> and ventricular tachycardia,<sup>217</sup> and there may be an increased risk of SCD.<sup>209,214</sup> 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.<sup>212,218</sup>

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.<sup>187</sup> Iron excess in the myocardium produces an impairment in transmembrane Ca<sup>2+</sup> flux and diastolic dysfunction, followed by progressive myocyte loss, replacement fibrosis, and chamber dilatation due to direct cytotoxic effects of accumulated iron.<sup>219,220</sup> 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.<sup>187</sup> 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.<sup>221</sup> The occurrence of HF portends a poor prognosis, and < 50% of patients with thalassaemia survive up to 5 years following the onset of HF.<sup>222,223</sup> 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<sup>224–227</sup> (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.<sup>228</sup> Although the aetiology of EMF is still elusive, genetic, dietary, and infectious factors may promote inflammation responsible for endomyocardial damage and fibrosis.<sup>228</sup> 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.<sup>228</sup> Repeated episodes of active disease lead to

a chronic phase, in which RCM prevails, with signs and symptoms of biventricular or right-sided HF.<sup>229</sup> 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.<sup>230</sup> Overt HF carries an ominous prognosis with a 75% mortality rate at 2 years.<sup>231</sup> EMF accounts for 20% of HF hospitalizations and 15% of cardiac deaths in the endemic regions.<sup>232,233</sup>

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.<sup>186</sup> Although occurring outside tropical regions, hypereosinophilic syndrome bears a striking resemblance to EMF with respect to the pathogenesis and clinical presentation of RCM.<sup>186</sup> 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).<sup>188</sup> 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.<sup>234</sup> Heart transplant or heart/liver transplant (in patients with ATTR-m) can be considered in patients with advanced HF unresponsive to medical treatment.<sup>235</sup>

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.<sup>236</sup> 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.<sup>237</sup> 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.<sup>238</sup>

Observational data suggest that ventricular dysfunction and heart rhythm abnormalities can improve with immunosuppression in cardiac sarcoidosis.<sup>239</sup> In a Finnish registry (96% of patients on immunosuppression), transplantation-free survival at 1, 5 and 10 years was 97%, 90%, and 83%, respectively.<sup>212</sup> 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.<sup>240</sup> 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).<sup>241</sup> 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.<sup>242</sup>

In hypereosinophilic syndrome affecting the heart, treatment with corticosteroids alone, or in combination with hydroxyurea or interferon- $\alpha$ , during the acute stage of the disease can result in improvement in LVEF and symptoms.<sup>243</sup> Imatinib may be also useful for the treatment of hypereosinophilic syndrome.<sup>244</sup> 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.<sup>228</sup> 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.<sup>245</sup>

## 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, immunoabsorption, 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.

**Conflict of interest:** none declared.

## References

- Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastakis A, Bohm M, Duboc D, Gimeno J, de Groote P, Imazio M, Heymans S, Klingel K, Komajda M, Limongelli G, Linhart A, Mogensen J, Moon J, Pieper PG, Seferovic PM, Schueler S, Zamorano JL, Caforio AL, Charron P. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2016;**37**:1850–1858.
- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER III, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation* 2016;**133**:e38–e360.
- Codd MB, Sugrue DD, Gersh BJ, Melton LJ 3rd. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy. A population-based study in Olmsted County, Minnesota, 1975–1984. *Circulation* 1989;**80**:564–572.
- Torp A. Incidence of congestive cardiomyopathy. *Postgrad Med J* 1978;**54**:435–439.
- Miura K, Nakagawa H, Morikawa Y, Sasayama S, Matsumori A, Hasegawa K, Ohno Y, Tamakoshi A, Kawamura T, Inaba Y. Epidemiology of idiopathic cardiomyopathy in Japan: results from a nationwide survey. *Heart* 2002;**87**:126–130.
- Falase AO, Ogah OS. Cardiomyopathies and myocardial disorders in Africa: present status and the way forward. *Cardiovasc J Afr* 2012;**23**:552–562.
- Bozkurt B, Colvin M, Cook J, Cooper LT, Deswal A, Fonarow GC, Francis GS, Lenihan D, Lewis EF, McNamara DM, Pahl E, Vasan RS, Ramasubbu K, Rasmussen K, Towbin JA, Yancy C. Current diagnostic and treatment strategies for specific dilated cardiomyopathies: a scientific statement from the American Heart Association. *Circulation* 2016;**134**:e579–e646.
- Kubaneck M, Sramko M, Maluskova J, Kautznerova D, Weichet J, Lupinek P, Vrbska J, Malek I, Kautzner J. Novel predictors of left ventricular reverse remodeling in individuals with recent-onset dilated cardiomyopathy. *J Am Coll Cardiol* 2013;**61**:54–63.
- Halliday BP, Gulati A, Ali A, Newsome S, Lota A, Tayal U, Vassiliou VS, Arzanauskaitė M, Izgi C, Krishnathasan K, Singhal A, Chiew K, Gregson J, Frenneaux MP, Cook SA, Pennell DJ, Collins P, Cleland JG, Prasad SK. Sex- and age-based differences in the natural history and outcome of dilated cardiomyopathy. *Eur J Heart Fail* 2018;**20**:1392–1400.



10. McNamara DM, Starling RC, Cooper LT, Boehmer JP, Mather PJ, Janosko KM, Gorcsan J 3rd, Kip KE, Dec GW. Clinical and demographic predictors of outcomes in recent onset dilated cardiomyopathy: results of the IMAC (Intervention in Myocarditis and Acute Cardiomyopathy)-2 study. *J Am Coll Cardiol* 2011;**58**:1112–1118.
11. Pecini R, Moller DV, Torp-Pedersen C, Hassager C, Kober L. Heart failure etiology impacts survival of patients with heart failure. *Int J Cardiol* 2011;**149**:211–215.
12. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN; SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;**325**:293–302.
13. Cohn JN, Tognoni G, Glazer R, Spormann D. Baseline demographics of the Valsartan Heart Failure Trial. Val-HeFT Investigators. *Eur J Heart Fail* 2000;**2**:439–446.
14. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**:9–13.
15. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005;**149**:209–216.
16. Thorvaldsen T, Benson L, Dahlstrom U, Edner M, Lund LH. Use of evidence-based therapy and survival in heart failure in Sweden 2003–2012. *Eur J Heart Fail* 2016;**18**:503–511.
17. Shore S, Grau-Sepulveda MV, Bhatt DL, Heidenreich PA, Eapen ZJ, Hernandez AF, Yancy CW, Fonarow GC. Characteristics, treatments, and outcomes of hospitalized heart failure patients stratified by etiologies of cardiomyopathy. *JACC Heart Fail* 2015;**3**:906–916.
18. Rose EA, Gelijs AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Ascheim DD, Tierney AR, Levitan RG, Watson JT, Meier P, Ronan NS, Shapiro PA, Lazar RM, Miller LW, Gupta L, Frazier OH, Desvigne-Nickens P, Oz MC, Poirier VL; Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med* 2001;**345**:1435–1443.
19. Yoshioka D, Li B, Takayama H, Garan RA, Topkara VK, Han J, Kurlansky P, Yuzefpolskaya M, Colombo PC, Naka Y, Takeda K. Outcome of heart transplantation after bridge-to-transplant strategy using various mechanical circulatory support devices. *Interact Cardiovasc Thorac Surg* 2017;**25**:918–924.
20. Rossano JW, Dipchand AI, Edwards LB, Goldfarb S, Kucheryavaya AY, Levvey Rn BJ, Lund LH, Meiser B, Yusef RD, Stehlik J. The registry of the International Society for Heart and Lung Transplantation: Nineteenth Pediatric Heart Transplantation Report-2016; focus theme: primary diagnostic indications for transplant. *J Heart Lung Transplant* 2016;**35**:1185–1195.
21. Yusef RD, Edwards LB, Dipchand AI, Goldfarb SB, Kucheryavaya AY, Levvey BJ, Lund LH, Meiser B, Rossano JW, Stehlik J. The registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Lung and Heart-Lung Transplant Report-2016; focus theme: primary diagnostic indications for transplant. *J Heart Lung Transplant* 2016;**35**:1170–1184.
22. Lund LH, Edwards LB, Dipchand AI, Goldfarb S, Kucheryavaya AY, Levvey BJ, Meiser B, Rossano JW, Yusef RD, Stehlik J. The registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Heart Transplantation Report-2016; focus theme: primary diagnostic indications for transplant. *J Heart Lung Transplant* 2016;**35**:1158–1169.
23. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, Olsen E, Thiene G, Goodwin J, Gyarsfas I, Martin I, Nordet P. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the definition and classification of cardiomyopathies. *Circulation* 1996;**93**:841–842.
24. Jefferies JL, Towbin JA. Dilated cardiomyopathy. *Lancet* 2010;**375**:752–762.
25. Japp AG, Gulati A, Cook SA, Cowie MR, Prasad SK. The diagnosis and evaluation of dilated cardiomyopathy. *J Am Coll Cardiol* 2016;**67**:2996–3010.
26. Herman DS, Lam L, Taylor MR, Wang L, Teekakirikul P, Christodoulou D, Conner L, DePalma SR, McDonough B, Sparks E, Teodorescu DL, Cirino AL, Banner NR, Pennell DJ, Graw S, Merlo M, Di Lenarda A, Sinagra G, Bos JM, Ackerman MJ, Mitchell RN, Murry CE, Lakdawala NK, Ho CY, Barton PJ, Cook SA, Mestroni L, Seidman JG, Seidman CE. Truncations of titin causing dilated cardiomyopathy. *N Engl J Med* 2012;**366**:619–628.
27. Roberts AM, Ware JS, Herman DS, Schafer S, Baksi J, Bick AG, Buchan RJ, Walsh R, John S, Wilkinson S, Mazzarotto F, Felkin LE, Gong S, MacCarthy JA, Cunningham F, Flannick J, Gabriel SB, Altschuler DM, Macdonald PS, Heinig M, Keogh AM, Hayward CS, Banner NR, Pennell DJ, O'Regan DP, San TR, de Marvao A, Dawes TJ, Gulati A, Birks EJ, Yacoub MH, Radke M, Gotthardt M, Wilson JG, O'Donnell CJ, Prasad SK, Barton PJ, Fatkin D, Hubner N, Seidman JG, Seidman CE, Cook SA. Integrated allelic, transcriptional, and phenomic dissection of the cardiac effects of titin truncations in health and disease. *Sci Transl Med* 2015;**7**:270ra6.
28. van Rijsingen IA, van der Zwaag PA, Groeneweg JA, Nannenberg EA, Jongbloed JD, Zwinderman AH, Pinto YM, Ditt Prevez RH, Post JG, Tan HL, de Boer RA, Hauer RN, Christiaans I, van den Berg MP, van Tintelen JP, Wilde AA. Outcome in phospholamban R14del carriers: results of a large multicentre cohort study. *Circ Cardiovasc Genet* 2014;**7**:455–465.
29. van der Zwaag PA, van Rijsingen IA, Asimaki A, Jongbloed JD, van Veldhuisen DJ, Wiesfeld AC, Cox MG, van Lochem LT, de Boer RA, Hofstra RM, Christiaans I, van Spaendonck-Zwarts KY, Lekanne dit Deprez RH, Judge DP, Calkins H, Suurmeijer AJ, Hauer RN, Saffitz JE, Wilde AA, van den Berg MP, van Tintelen JP. Phospholamban R14del mutation in patients diagnosed with dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy: evidence supporting the concept of arrhythmogenic cardiomyopathy. *Eur J Heart Fail* 2012;**14**:1199–1207.
30. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhoff P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;**36**:2793–2867.
31. Faysoil A, Nardi O, Orlikowski D, Annane D. Cardiomyopathy in Duchenne muscular dystrophy: pathogenesis and therapeutics. *Heart Fail Rev* 2010;**15**:103–107.
32. Silva MC, Magalhaes TA, Meira ZM, Rassi CH, Andrade AC, Gutierrez PS, Azevedo CF, Gurgel-Giannetti J, Vainzof M, Zatz M, Kaili-Filho R, Rochitte CE. Myocardial fibrosis progression in Duchenne and Becker muscular dystrophy: a randomized clinical trial. *JAMA Cardiol* 2017;**2**:190–199.
33. Duboc D, Meune C, Lerebours G, Devaux JY, Vaksman G, Becane HM. Effect of perindopril on the onset and progression of left ventricular dysfunction in Duchenne muscular dystrophy. *J Am Coll Cardiol* 2005;**45**:855–857.
34. Raman SV, Hor KN, Mazur W, Halnon NJ, Kissel JT, He X, Tran T, Smart S, McCarthy B, Taylor MD, Jefferies JL, Rafael-Fortney JA, Lowe J, Roble SL, Cripe LH. Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2015;**14**:153–161.
35. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Helio T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013;**34**:2636–2648, 48a-48d.
36. Li Y, Heuser JS, Cunningham LC, Kosanke SD, Cunningham MW. Mimicry and antibody-mediated cell signaling in autoimmune myocarditis. *J Immunol* 2006;**177**:8234–8240.
37. Schulze K, Becker BF, Schauer R, Schultheiss HP. Antibodies to ADP-ATP carrier – an autoantigen in myocarditis and dilated cardiomyopathy – impair cardiac function. *Circulation* 1990;**81**:959–969.
38. Escher F, Kuhl U, Lassner D, Stroux A, Westermann D, Skurk C, Tschope C, Poller W, Schultheiss HP. Presence of perforin in endomyocardial biopsies of patients with inflammatory cardiomyopathy predicts poor outcome. *Eur J Heart Fail* 2014;**16**:1066–1072.
39. Nielsen TS, Hansen J, Nielsen LP, Baandrup UT, Banner J. The presence of enterovirus, adenovirus, and parvovirus B19 in myocardial tissue samples from autopsies: an evaluation of their frequencies in deceased individuals with myocarditis and in non-inflamed control hearts. *Forensic Sci Med Pathol* 2014;**10**:344–350.
40. Kitaura-Ienaga K, Hara M, Higuchi K, Yamamoto K, Yamaki A, Ono K, Nakano A, Kinoshita M, Sasayama S, Matsumori A. Gene expression of cardiac mast cell chymase and trypsinase in a murine model of heart failure caused by viral myocarditis. *Circ J* 2003;**67**:881–884.
41. Mendez GF, Cowie MR. The epidemiological features of heart failure in developing countries: a review of the literature. *Int J Cardiol* 2001;**80**:213–219.
42. Rossi MA, Bestetti RB. The challenge of chagasic cardiomyopathy. The pathologic roles of autonomic abnormalities, autoimmune mechanisms and microvascular changes, and therapeutic implications. *Cardiology* 1995;**86**:1–7.
43. Caforio AL, Adler Y, Agostini C, Allanore Y, Anastasakis A, Arad M, Bohm M, Charron P, Elliott PM, Eriksson U, Felix SB, Garcia-Pavia P, Hachulla E, Heymans S, Imazio M, Klingel K, Marcolongo R, Matucci Cerinic M, Pantazis A,

- Plein S, Poli V, Rigopoulos A, Seferovic P, Shoenfeld Y, Zamorano JL, Linhart A. Diagnosis and management of myocardial involvement in systemic immune-mediated diseases: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Disease. *Eur Heart J* 2017;**38**:2649–2662.
44. Caforio AL, Mahon NG, Baig MK, Tona F, Murphy RT, Elliott PM, McKenna WJ. Prospective familial assessment in dilated cardiomyopathy: cardiac autoantibodies predict disease development in asymptomatic relatives. *Circulation* 2007;**115**:76–83.
45. Caforio AL, Keeling PJ, Zachara E, Mestroni L, Camerini F, Mann JM, Bottazzo GF, McKenna WJ. Evidence from family studies for autoimmunity in dilated cardiomyopathy. *Lancet* 1994;**344**:773–777.
46. Sliwa K, Hilfiker-Kleiner D, Petrie MC, Mebazaa A, Pieske B, Buchmann E, Regitz-Zagrosek V, Schaufelberger M, Tavazzi L, van Veldhuisen DJ, Watkins H, Shah AJ, Seferovic PM, Elkayam U, Pankuweit S, Papp Z, Mouquet F, McMurray JJ. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on Peripartum Cardiomyopathy. *Eur J Heart Fail* 2010;**12**:767–778.
47. Bauersachs J, Arrigo M, Hilfiker-Kleiner D, Veltmann C, Coats AJ, Crespo-Leiro MG, De Boer RA, van der Meer P, Maack C, Mouquet F, Petrie MC, Piepoli MF, Regitz-Zagrosek V, Schaufelberger M, Seferovic P, Tavazzi L, Ruschitzka F, Mebazaa A, Sliwa K. Current management of patients with severe acute peripartum cardiomyopathy: practical guidance from the Heart Failure Association of the European Society of Cardiology Study Group on Peripartum Cardiomyopathy. *Eur J Heart Fail* 2016;**18**:1096–1105.
48. Hilfiker-Kleiner D, Kaminski K, Podewski E, Bonda T, Schaefer A, Sliwa K, Forster O, Quint A, Landmesser U, Doerries C, Luchtefeld M, Poli V, Schneider MD, Balligand JL, Desjardins F, Ansari A, Struman I, Nguyen NQ, Zschemisch NH, Klein G, Heusch G, Schulz R, Hilfiker A, Drexler H. A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. *Cell* 2007;**128**:589–600.
49. Forster O, Hilfiker-Kleiner D, Ansari AA, Sundstrom JB, Libhaber E, Tshani W, Becker A, Yip A, Klein G, Sliwa K. Reversal of IFN-gamma, oxLDL and prolactin serum levels correlate with clinical improvement in patients with peripartum cardiomyopathy. *Eur J Heart Fail* 2008;**10**:861–868.
50. Rizeq MN, Rickenbacher PR, Fowler MB, Billingham ME. Incidence of myocarditis in peripartum cardiomyopathy. *Am J Cardiol* 1994;**74**:474–477.
51. Warraich RS, Sliwa K, Damasceno A, Carraway R, Sundrom B, Arif G, Essop R, Ansari A, Fetz J, Yacoub M. Impact of pregnancy-related heart failure on humoral immunity: clinical relevance of G3-subclass immunoglobulins in peripartum cardiomyopathy. *Am Heart J* 2005;**150**:263–269.
52. Patten IS, Rana S, Shahul S, Rowe GC, Jiang C, Liu L, Hacker MR, Rhee JS, Mitchell J, Mahmood F, Hess P, Farrell C, Koullis N, Khankin EV, Burke SD, Tudorache I, Bauersachs J, del Monte F, Hilfiker-Kleiner D, Karumanchi SA, Arany Z. Cardiac angiogenic imbalance leads to peripartum cardiomyopathy. *Nature* 2012;**485**:333–338.
53. Ware JS, Li J, Mazaika E, Yasso CM, DeSouza T, Cappola TP, Tsai EJ, Hilfiker-Kleiner D, Kamiya CA, Mazzarotto F, Cook SA, Halder I, Prasad SK, Pisarcik J, Hanley-Yanez K, Alharethi R, Damp J, Hsieh E, Elkayam U, Sheppard R, Kealey A, Alexis J, Ramani G, Safirstein J, Boehmer J, Pauly DF, Wittstein IS, Thohan V, Zucker MJ, Liu P, Gorcans J III, McNamara DM, Seidman CE, Seidman JG, Arany Z; IMAC-2 and IPAC Investigators. Shared genetic predisposition in peripartum and dilated cardiomyopathies. *N Engl J Med* 2016;**374**:233–241.
54. Ewer MS, Vooletich MT, Durand JB, Woods ML, Davis JR, Valero V, Lenihan DJ. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. *J Clin Oncol* 2005;**23**:7820–7826.
55. Figueredo VM. Chemical cardiomyopathies: the negative effects of medications and nonprescribed drugs on the heart. *Am J Med* 2011;**124**:480–488.
56. Fauchier L, Babuty D, Poret P, Casset-Senon D, Autret ML, Cosnay P, Fauchier JP. Comparison of long-term outcome of alcoholic and idiopathic dilated cardiomyopathy. *Eur Heart J* 2000;**21**:306–314.
57. Ameri P, Canepa M, Anker MS, Belenkov Y, Bergler-Klein J, Cohen-Solal A, Farmakis D, Lopez-Fernandez T, Lainscak M, Pudi R, Ruschitska F, Seferovic P, Filippatos G, Coats A, Suter T, Von Haehling S, Ciardiello F, de Boer RA, Lyon AR, Tocchetti CG. Cancer diagnosis in patients with heart failure: epidemiology, clinical implications and gaps in knowledge. *Eur J Heart Fail* 2018;**20**:879–887.
58. Zamorano JL, Lancellotti P, Rodriguez Munoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GY, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A, Suter TM. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The task force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J* 2016;**37**:2768–2801.
59. Pareek N, Cevallos J, Moliner Borja P, Shah M, Ling Tan L, Chambers V, John Baksi A, Khattar R, Sharma R, Rosen S, Lyon AR. Activity and outcomes of a cardio-oncology service in the United Kingdom – a five-year experience. *Eur J Heart Fail* 2018;**20**:1721–1731.
60. Steinherz LJ, Steinherz PG, Tan CT, Heller G, Murphy ML. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. *JAMA* 1991;**266**:1672–1677.
61. Wilcox JE, Fonarow GC, Ardehali H, Bonow RO, Butler J, Sauer AJ, Epstein SE, Khan SS, Kim RJ, Sabbah HN, Diez J, Gheorghiade M. 'Targeting the Heart' in heart failure: myocardial recovery in heart failure with reduced ejection fraction. *JACC Heart Fail* 2015;**3**:661–669.
62. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, Wu KC, Rade JJ, Bivalacqua TJ, Champion HC. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005;**352**:539–548.
63. Hilfiker-Kleiner D, Sliwa K. Pathophysiology and epidemiology of peripartum cardiomyopathy. *Nat Rev Cardiol* 2014;**11**:364–370.
64. Fuster V, Gersh BJ, Giuliani ER, Tajik AJ, Brandenburg RO, Frye RL. The natural history of idiopathic dilated cardiomyopathy. *Am J Cardiol* 1981;**47**:525–531.
65. Matsumura Y, Takata J, Kitaoka H, Kubo T, Baba Y, Hoshikawa E, Hamada T, Okawa M, Hitomi N, Sato K, Yamasaki N, Yabe T, Furuno T, Nishinaga M, Doi Y. Long-term prognosis of dilated cardiomyopathy revisited: an improvement in survival over the past 20 years. *Circ J* 2006;**70**:376–383.
66. Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, Jackson R, Rahneva T, Wage R, Smith G, Venneri L, Tayal U, Auger D, Midwinter W, Whiffin N, Rajani R, Dungu JN, Pantazis A, Cook SA, Ware JS, Baksi AJ, Pennell DJ, Rosen SD, Cowie MR, Cleland JG, Prasad SK. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet* 2019;**393**:61–73.
67. Wilcox JE, Fonarow GC, Yancy CW, Albert NM, Curtis AB, Heywood JT, Inge PJ, McBride ML, Mehra MR, O'Connor CM, Reynolds D, Walsh MN, Gheorghiade M. Factors associated with improvement in ejection fraction in clinical practice among patients with heart failure: findings from IMPROVE HF. *Am Heart J* 2012;**163**:49–56.e2.
68. Merlo M, Pyxaras SA, Pinamonti B, Barbati G, Di Lenarda A, Sinagra G. Prevalence and prognostic significance of left ventricular reverse remodeling in dilated cardiomyopathy receiving tailored medical treatment. *J Am Coll Cardiol* 2011;**57**:1468–1476.
69. Martinez-Selles M, Doughty RN, Poppe K, Whalley GA, Earle N, Tribouilloy C, McMurray JJ, Swedberg K, Kober L, Berry C, Squire I. Gender and survival in patients with heart failure: interactions with diabetes and aetiology. Results from the MAGGIC individual patient meta-analysis. *Eur J Heart Fail* 2012;**14**:473–479.
70. Gulati A, Jabbar A, Ismail TF, Guha K, Khwaja J, Raza S, Morarji K, Brown TD, Ismail NA, Dweck MR, Di Pietro E, Roughton M, Wage R, Daryani Y, O'Hanlon R, Sheppard MN, Alpendurada F, Lyon AR, Cook SA, Cowie MR, Assomull RG, Pennell DJ, Prasad SK. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. *JAMA* 2013;**309**:896–908.
71. Rossi A, Dini FL, Faggiano P, Agricola E, Ciccoira M, Frattini S, Simioniuc A, Gul-lace M, Ghio S, Enriquez-Sarano M, Temporelli PL. 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* 2011;**97**:1675–1680.
72. Nasser R, Van Assche L, Vorlat A, Vermeulen T, Van Craenenbroeck E, Conraads V, Van der Meiren V, Shivalkar B, Van Herck P, Claeys MJ. Evolution of functional mitral regurgitation and prognosis in medically managed heart failure patients with reduced ejection fraction. *JACC Heart Fail* 2017;**5**:652–659.
73. Kober L, Thune JJ, Nielsen JC, Haerbo J, Videbaek L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjaer H, Brandes A, Thogersen AM, Gustafsson F, Egstrup K, Videbaek R, Hassager C, Svendsen JH, Hof-sten DE, Torp-Pedersen C, Pehrson S; DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;**375**:1221–1230.
74. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Riolope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**:891–975.
75. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;**336**:525–533.
76. Waagstein F, Bristow MR, Swedberg K, Camerini F, Fowler MB, Silver MA, Gilbert EM, Johnson MR, Goss FG, Hjalmarson A. Beneficial effects of

- metoprolol in idiopathic dilated cardiomyopathy. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. *Lancet* 1993;**342**:1441–1446.
77. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. *Circulation* 1994;**90**:1765–1773.
  78. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;**341**:709–717.
  79. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;**362**:772–776.
  80. Swedberg K, Komajda M, Bohm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L, SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010;**376**:875–885.
  81. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21.
  82. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004.
  83. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, Calkins H, Hoch D, Goldberger J, Shalaby A, Sanders WE, Schaeffer A, Levine JH; Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prophylactic defibrillator implantation in patients with non-ischemic dilated cardiomyopathy. *N Engl J Med* 2004;**350**:2151–2158.
  84. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;**352**:225–237.
  85. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–2150.
  86. Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, Massie BM, Colling C, Lazzari D. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. *N Engl J Med* 1995;**333**:77–82.
  87. Elming Marie B, Nielsen Jens C, Haarbo J, Videbæk L, Korup E, Signorovitch J, Olesen Line L, Hildebrandt P, Steffensen Flemming H, Bruun Niels E, Eiskjær H, Brandes A, Thøgersen Anna M, Gustafsson F, Egstrup K, Videbæk R, Hassager C, Svendsen Jesper H, Høfsten Dan E, Torp-Pedersen C, Pehrson S, Køber L, Thune Jens J. Age and outcomes of primary prevention implantable cardioverter-defibrillators in patients with nonischemic systolic heart failure. *Circulation* 2017;**136**:1772–1780.
  88. Bristow MR, Saxon LA, Feldman AM, Mei C, Anderson SA, DeMets DL. Lessons learned and insights gained in the design, analysis, and outcomes of the COMPANION trial. *JACC Heart Fail* 2016;**4**:521–535.
  89. Zareba W, Klein H, Cygankiewicz I, Hall WJ, McNitt S, Brown M, Cannom D, Daubert JP, Eldar M, Gold MR, Goldberger JJ, Goldenberg I, Lichstein E, Pitschner H, Rashtian M, Solomon S, Viskin S, Wang P, Moss AJ. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation* 2011;**123**:1061–1072.
  90. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L, Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–1549.
  91. De Bonis M, Taramasso M, Verzini A, Ferrara D, Lapenna E, Calabrese MC, Grimaldi A, Alfieri O. Long-term results of mitral repair for functional mitral regurgitation in idiopathic dilated cardiomyopathy. *Eur J Cardiothorac Surg* 2012;**42**:640–646.
  92. Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, Smalling RW, Siegel R, Rose GA, Engeron E, Loghin C, Trento A, Skipper ER, Fudge T, Letsou GV, Massaro JM, Mauri L; EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011;**364**:1395–1406.
  93. Obadia JF, Messika-Zeitoun D, Leurent G, lung B, Bonnet G, Piriou N, Lefevre T, Piot C, Rouleau F, Carrie D, Nejari M, Ohlmann P, Leclercq F, Saint Etienne C, Teiger E, Leroux L, Karam N, Michel N, Gilard M, Donal E, Trochu JN, Cormier B, Armoiry X, Boutitie F, Maucort-Boulch D, Barnel C, Samson G, Guerin P, Vahanian A, Mewton N; MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018;**379**:2297–2306.
  94. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembock IJ, Brieke A, Marx SO, Cohen DJ, Weissman NJ, Mack MJ; COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;**379**:2307–2318.
  95. Frustaci A, Chimenti C, Calabrese F, Pieroni M, Thiene G, Maseri A. Immunosuppressive therapy for active lymphocytic myocarditis: virological and immunologic profile of responders versus nonresponders. *Circulation* 2003;**107**:857–863.
  96. Frustaci A, Russo MA, Chimenti C. Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. *Eur Heart J* 2009;**30**:1995–2002.
  97. Escher F, Kuhl U, Lassner D, Poller W, Westermann D, Pieske B, Tschope C, Schultheiss HP. Long-term outcome of patients with virus-negative chronic myocarditis or inflammatory cardiomyopathy after immunosuppressive therapy. *Clin Res Cardiol* 2016;**105**:1011–1020.
  98. Cooper LT Jr, Hare JM, Tazelaar HD, Edwards WD, Starling RC, Deng MC, Menon S, Mullen GM, Jaski B, Bailey KR, Cunningham MW, Dec GW. Usefulness of immunosuppression for giant cell myocarditis. *Am J Cardiol* 2008;**102**:1535–1539.
  99. Schultheiss HP, Piper C, Sowade O, Waagstein F, Kapp JF, Wegscheider K, Groetzbach G, Pauschinger M, Escher F, Arbustini E, Siedentop H, Kuehl U. Betaferon in Chronic Viral Cardiomyopathy (BICC) trial: effects of interferon-beta treatment in patients with chronic viral cardiomyopathy. *Clin Res Cardiol* 2016;**105**:763–773.
  100. Felix SB, Staudt A, Dorffle W, Stangl V, Merkel K, Pohl M, Docke WD, Morgera S, Neumayer HH, Wernecke KD, Wallukat G, Stangl K, Baumann G. Hemodynamic effects of immunoadsorption and subsequent immunoglobulin substitution in dilated cardiomyopathy: three-month results from a randomized study. *J Am Coll Cardiol* 2000;**35**:1590–1598.
  101. Ohlow MA, Brunelli M, Schreiber M, Lauer B. Therapeutic effect of immunoadsorption and subsequent immunoglobulin substitution in patients with dilated cardiomyopathy: results from the observational prospective Bad Berka registry. *J Cardiol* 2017;**69**:409–416.
  102. Weinmann K, Werner J, Koenig W, Rottbauer W, Walcher D, Kessler M. Add-on immunoadsorption shortly after optimal medical treatment further significantly and persistently improves cardiac function and symptoms in recent-onset heart failure – a single center experience. *Biomolecules* 2018;**8**:E133.
  103. Farmakis D, Mantzourani M, Filippatos G. Anthracycline-induced cardiomyopathy: secrets and lies. *Eur J Heart Fail* 2018;**20**:907–909.
  104. Hilfiger-Kleiner D, Haghikia A, Berliner D, Vogel-Claussen J, Schwab J, Franke A, Schwarzkopf M, Ehlermann P, Pfister R, Michels G, Westenfeld R, Stangl V, Kindermann I, Kuhl U, Angermann CE, Schlitt A, Fischer D, Podewski E, Böhm M, Sliwa K, Bauersachs J. Bromocriptine for the treatment of peripartum cardiomyopathy: a multicentre randomized study. *Eur Heart J* 2017;**38**:2671–2679.
  105. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomström-Lundqvist C, Cifková R, De Bonis M, lung B, Johnson MR, Kintscher U, Kranke P, Lang IM, Morais J, Pieper PG, Presbitero P, Price S, Rosano GM, Seeland U, Simoncini T, Swan L, Warnes CA. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J* 2018;**39**:3165–3241.
  106. Mirijello A, Tari C, Vassallo GA, Sestito L, Antonelli M, d'Angelo C, Ferrulli A, De Cosmo S, Gasbarrini A, Addolorato G. Alcoholic cardiomyopathy: what is known and what is not known. *Eur J Intern Med* 2017;**43**:1–5.
  107. Amosii L, Hildyard JCW, Li H, Sanchez-Ortiz E, Mireault A, Caballero D, Harron R, Stathopoulou TR, Massey C, Shelton JM, Bassel-Duby R, Piercy RJ, Olson EN. Gene editing restores dystrophin expression in a canine model of Duchenne muscular dystrophy. *Science* 2018;**362**:86–91.
  108. Johansen AK, Molenaar B, Versteeg D, Leitoguinho AR, Demkes C, Spanjaard B, de Ruiter H, Akbari Moqadam F, Kooijman L, Zentilin L, Giacca M, van Rooij E. Postnatal cardiac gene editing using CRISPR/Cas9 with AAV9-mediated delivery of short guide RNAs results in mosaic gene disruption. *Circ Res* 2017;**121**:1168–1181.
  109. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tilmanis C, Watkins H. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the diagnosis and management



- of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;**35**:2733–2779.
110. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, Dubourg O, Kuhl U, Mausch B, McKenna WJ, Monserrat L, Pankuweit S, Rapezzi C, Seferovic P, Tavazzi L, Keren A. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2008;**29**:270–276.
  111. Olivetto I, Girolami F, Nistri S, Rossi A, Rega L, Garbini F, Grifoni C, Cecchi F, Yacoub MH. The many faces of hypertrophic cardiomyopathy: from developmental biology to clinical practice. *J Cardiovasc Transl Res* 2009;**2**:349–367.
  112. Maron MS, Olivetto I, Zenovich AG, Link MS, Pandian NG, Kuvlin JT, Nistri S, Cecchi F, Udelson JE, Maron BJ. Hypertrophic cardiomyopathy is predominantly a disease of left ventricular outflow tract obstruction. *Circulation* 2006;**114**:2232–2239.
  113. Zou Y, Song L, Wang Z, Ma A, Liu T, Gu H, Lu S, Wu P, Zhang dagger Y, Shen dagger L, Cai Y, Zhen double dagger Y, Liu Y, Hui R. Prevalence of idiopathic hypertrophic cardiomyopathy in China: a population-based echocardiographic analysis of 8080 adults. *Am J Med* 2004;**116**:14–18.
  114. Hada Y, Sakamoto T, Amano K, Yamaguchi T, Takenaka K, Takahashi H, Takikawa R, Hasegawa I, Takahashi T, Suzuki J, Sugimoto T, Saito KI. Prevalence of hypertrophic cardiomyopathy in a population of adult Japanese workers as detected by echocardiographic screening. *Am J Cardiol* 1987;**59**:183–184.
  115. Corrado D, Basso C, Schiavon M, Thiene G. Screening for hypertrophic cardiomyopathy in young athletes. *N Engl J Med* 1998;**339**:364–369.
  116. Nistri S, Thiene G, Basso C, Corrado D, Vitolo A, Maron BJ. Screening for hypertrophic cardiomyopathy in a young male military population. *Am J Cardiol* 2003;**91**:1021–1023, a8.
  117. Millat G, Bouvagnet P, Chevalier P, Dauphin C, Jouk PS, Da Costa A, Prieur F, Bresson JL, Faivre L, Eicher JC, Chassaing N, Crehalet H, Porcher R, Rodriguez-Lafrasse C, Rousson R. Prevalence and spectrum of mutations in a cohort of 192 unrelated patients with hypertrophic cardiomyopathy. *Eur J Med Genet* 2010;**53**:261–267.
  118. Maron BJ, Rowin EJ, Casey SA, Link MS, Lesser JR, Chan RH, Garberich RF, Udelson JE, Maron MS. Hypertrophic cardiomyopathy in adulthood associated with low cardiovascular mortality with contemporary management strategies. *J Am Coll Cardiol* 2015;**65**:1915–1928.
  119. Charron P, Elliott PM, Gimeno JR, Caforio AL, Kaski JP, Tavazzi L, Tendera M, Maupaïn C, Laroche C, Rubis P, Jurcut R, Calo L, Helio TM, Sinagra G, Zdravkovic M, Kavaliuniene A, Felix SB, Grzybowski J, Losi MA, Asselbergs FW, Garcia-Pinilla JM, Salazar-Mendiguchia J, Mizia-Stec K, Maggioni AP. The cardiomyopathy registry of the EURObservational Research Programme of the European Society of Cardiology: baseline data and contemporary management of adult patients with cardiomyopathies. *Eur Heart J* 2018;**39**:1784–1793.
  120. Maron BJ, Rowin EJ, Udelson JE, Maron MS. Clinical spectrum and management of heart failure in hypertrophic cardiomyopathy. *JACC Heart Fail* 2018;**6**:353–363.
  121. Olivetto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation* 2001;**104**:2517–2524.
  122. Kuperstein R, Klempfner R, Ofek E, Maor E, Freimark D, Sternik L, Goldenberg I, Raanani E, Arad M. De novo mitral regurgitation as a cause of heart failure exacerbation in patients with hypertrophic cardiomyopathy. *Int J Cardiol* 2018;**252**:122–127.
  123. Melacini P, Basso C, Angelini A, Calore C, Bobbo F, Tokajuk B, Bellini N, Smaniotto G, Zucchetto M, Iliceto S, Thiene G, Maron BJ. Clinicopathological profiles of progressive heart failure in hypertrophic cardiomyopathy. *Eur Heart J* 2010;**31**:2111–2123.
  124. Olivetto I, Cecchi F, Poggesi C, Yacoub MH. Patterns of disease progression in hypertrophic cardiomyopathy: an individualized approach to clinical staging. *Circ Heart Fail* 2012;**5**:535–546.
  125. Thaman R, Gimeno JR, Murphy RT, Kubo T, Sachdev B, Mogensen J, Elliott PM, McKenna WJ. Prevalence and clinical significance of systolic impairment in hypertrophic cardiomyopathy. *Heart* 2005;**91**:920–925.
  126. Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR, Mackey-Bojack S, Manning WJ, Udelson JE, Maron BJ. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. *Circulation* 2006;**114**:216–225.
  127. Olivetto I, Girolami F, Ackerman MJ, Nistri S, Bos JM, Zachara E, Ommen SR, Theis JL, Vaubel RA, Re F, Armentano C, Poggesi C, Torricelli F, Cecchi F. Myofibrillar protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy. *Mayo Clin Proc* 2008;**83**:630–638.
  128. Mehta A, Ricci R, Widmer U, Dehout F, Garcia de Lorenzo A, Kampmann C, Linhart A, Sunder-Plassmann G, Ries M, Beck M. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. *Eur J Clin Invest* 2004;**34**:236–242.
  129. Ferrantini C, Belus A, Piroddi N, Scellini B, Tesi C, Poggesi C. Mechanical and energetic consequences of HCM-causing mutations. *J Cardiovasc Transl Res* 2009;**2**:441–451.
  130. Tardiff JC. Sarcomeric proteins and familial hypertrophic cardiomyopathy: linking mutations in structural proteins to complex cardiovascular phenotypes. *Heart Fail Rev* 2005;**10**:237–248.
  131. Yacoub MH, Olivetto I, Cecchi F. 'End-stage' hypertrophic cardiomyopathy: from mystery to model. *Nat Clin Pract Cardiovasc Med* 2007;**4**:232–233.
  132. Maron BJ, Maron MS, Wigle ED, Braunwald E. The 50-year history, controversy, and clinical implications of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy from idiopathic hypertrophic subaortic stenosis to hypertrophic cardiomyopathy: from idiopathic hypertrophic subaortic stenosis to hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2009;**54**:191–200.
  133. Maron MS, Olivetto I, Maron BJ, Prasad SK, Cecchi F, Udelson JE, Camici PG. The case for myocardial ischemia in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2009;**54**:866–875.
  134. Ho CY. Hypertrophic cardiomyopathy: preclinical and early phenotype. *J Cardiovasc Transl Res* 2009;**2**:462–470.
  135. Green JJ, Berger JS, Kramer CM, Salerno M. Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. *JACC Cardiovasc Imaging* 2012;**5**:370–377.
  136. Galati G, Leone O, Pasquale F, Olivetto I, Biagini E, Grigioni F, Pilato E, Lorenzini M, Corti B, Foa A, Agostini V, Cecchi F, Rapezzi C. Histological and histometric characterization of myocardial fibrosis in end-stage hypertrophic cardiomyopathy: a clinical-pathological study of 30 explanted hearts. *Circ Heart Fail* 2016;**9**:e003090.
  137. Girolami F, Ho CY, Semsarian C, Baldi M, Will ML, Baldini K, Torricelli F, Yeates L, Cecchi F, Ackerman MJ, Olivetto I. Clinical features and outcome of hypertrophic cardiomyopathy associated with triple sarcomere protein gene mutations. *J Am Coll Cardiol* 2010;**55**:1444–1453.
  138. Garcia-Pavia P, Vazquez ME, Segovia J, Salas C, Avellana P, Gomez-Bueno M, Vilches C, Gallardo ME, Garesse R, Molano J, Bornstein B, Alonso-Pulpon L. Genetic basis of end-stage hypertrophic cardiomyopathy. *Eur J Heart Fail* 2011;**13**:1193–1201.
  139. Briguori C, Betocchi S, Romano M, Manganelli F, Angela Losi M, Ciampi Q, Gottilla R, Lombardi R, Condorelli M, Chiariello M. Exercise capacity in hypertrophic cardiomyopathy depends on left ventricular diastolic function. *Am J Cardiol* 1999;**84**:309–315.
  140. Maron MS, Finley JJ, Bos JM, Hauser TH, Manning WJ, Haas TS, Lesser JR, Udelson JE, Ackerman MJ, Maron BJ. Prevalence, clinical significance, and natural history of left ventricular apical aneurysms in hypertrophic cardiomyopathy. *Circulation* 2008;**118**:1541–1549.
  141. Nistri S, Olivetto I, Betocchi S, Losi MA, Valsecchi G, Pinamonti B, Conte MR, Casazza F, Galderisi M, Maron BJ, Cecchi F. Prognostic significance of left atrial size in patients with hypertrophic cardiomyopathy (from the Italian Registry for Hypertrophic Cardiomyopathy). *Am J Cardiol* 2006;**98**:960–965.
  142. Sorajja P, Ommen SR, Nishimura RA, Gersh BJ, Tajik AJ, Holmes DR. Myocardial bridging in adult patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2003;**42**:889–894.
  143. Schafers M, Dutka D, Rhodes CG, Lammertsma AA, Hermansen F, Schober O, Camici PG. Myocardial presynaptic and postsynaptic autonomic dysfunction in hypertrophic cardiomyopathy. *Circ Res* 1998;**82**:57–62.
  144. Sherrid MV, Balam S, Kim B, Axel L, Swistel DG. The mitral valve in obstructive hypertrophic cardiomyopathy: a test in context. *J Am Coll Cardiol* 2016;**67**:1846–1858.
  145. Wu JC, Ho CY, Skali H, Abichandani R, Wilcox WR, Banikazemi M, Packman S, Sims K, Solomon SD. Cardiovascular manifestations of Fabry disease: relationships between left ventricular hypertrophy, disease severity, and alpha-galactosidase A activity. *Eur Heart J* 2010;**31**:1088–1097.
  146. Akhtar MM, Elliott PM. Anderson-Fabry disease in heart failure. *Biophys Rev* 2018;**10**:1107–1119.
  147. Weidemann F, Niemann M, Herrmann S, Kung M, Stork S, Waller C, Beer M, Breunig F, Wanner C, Voelker W, Ertl G, Bijns B, Strotmann JM. A new echocardiographic approach for the detection of non-ischaemic fibrosis in hypertrophic myocardium. *Eur Heart J* 2007;**28**:3020–3026.
  148. Calcagnino M, O'Mahony C, Coats C, Cardona M, Garcia A, Janagaran K, Mehta A, Hughes D, Murphy E, Lachmann R, Elliott PM. Exercise-induced left ventricular outflow tract obstruction in symptomatic patients with Anderson-Fabry disease. *J Am Coll Cardiol* 2011;**58**:88–89.
  149. Torralba-Cabeza MA, Olivera S, Hughes DA, Pastores GM, Mateo RN, Perez-Calvo JL. Cystatin C and NT-proBNP as prognostic biomarkers in Fabry disease. *Mol Genet Metab* 2011;**104**:301–307.
  150. Maron BJ, Roberts WC, Arad M, Haas TS, Spirito P, Wright GB, Almquist AK, Baffa JM, Saul JP, Ho CY, Seidman J, Seidman CE. Clinical outcome and phenotypic expression in LAMP2 cardiomyopathy. *JAMA* 2009;**301**:1253–1259.

151. Olivetto I, Maron BJ, Appelbaum E, Harrigan CJ, Salton C, Gibson CM, Udelson JE, O'Donnell C, Lesser JR, Manning WJ, Maron MS. Spectrum and clinical significance of systolic function and myocardial fibrosis assessed by cardiovascular magnetic resonance in hypertrophic cardiomyopathy. *Am J Cardiol* 2010;**106**:261–267.
152. Maron MS, Olivetto I, Betocchi S, Casey SA, Lesser JR, Losi MA, Cecchi F, Maron BJ. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 2003;**348**:295–303.
153. Maron MS, Rowin EJ, Olivetto I, Casey SA, Arretini A, Tomberli B, Garberich RF, Link MS, Chan RHM, Lesser JR, Maron BJ. Contemporary natural history and management of nonobstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2016;**67**:1399–1409.
154. Efthimiadis GK, Pagourelis ED, Parcharidou D, Gossios T, Kamperidis V, Theoflogiannakos EK, Pappa S, Meditskou S, Hadjimiltiades S, Pliakos C, Karvounis H, Styliadis IH. Clinical characteristics and natural history of hypertrophic cardiomyopathy with midventricular obstruction. *Circ J* 2013;**77**:2366–2374.
155. Biagini E, Spirito P, Rocchi G, Ferlito M, Rosmini S, Lai F, Lorenzini M, Terzi F, Bacchi-Reggiani L, Boriani G, Branzi A, Boni L, Rapezzi C. Prognostic implications of the Doppler restrictive filling pattern in hypertrophic cardiomyopathy. *Am J Cardiol* 2009;**104**:1727–1731.
156. Pasqualucci D, Fornaro A, Castelli G, Rossi A, Arretini A, Chiriatti C, Targetti M, Girolami F, Corda M, Orru P, Matta G, Stefano P, Cecchi F, Porcu M, Olivetto I. Clinical spectrum, therapeutic options, and outcome of advanced heart failure in hypertrophic cardiomyopathy. *Circ Heart Fail* 2015;**8**:1014–1021.
157. Rowin EJ, Maron BJ, Kiernan MS, Casey SA, Feldman DS, Hryniewicz KM, Chan RH, Harris KM, Udelson JE, DeNofrio D, Roberts WC, Maron MS. Advanced heart failure with preserved systolic function in nonobstructive hypertrophic cardiomyopathy: under-recognized subset of candidates for heart transplant. *Circ Heart Fail* 2014;**7**:967–975.
158. O'Hanlon R, Grasso A, Roughton M, Moon JC, Clark S, Wage R, Webb J, Kulkarni M, Dawson D, Sulaiibeekh L, Chandrasekaran B, Bucciarelli-Ducci C, Pasquale F, Cowie MR, McKenna WJ, Sheppard MN, Elliott PM, Pennell DJ, Prasad SK. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2010;**56**:867–874.
159. Limongelli G, Masarone D, Frisso G, Iacomino M, Ferrara I, Rea A, Gravino R, Bossone E, Salvatore F, Calabro R, Elliott P, Pacileo G. Clinical and genetic characterization of patients with hypertrophic cardiomyopathy and right atrial enlargement. *J Cardiovasc Med (Hagerstown)* 2017;**18**:249–254.
160. Losi MA, Nistri S, Galderisi M, Betocchi S, Cecchi F, Olivetto I, Agricola E, Ballo P, Burralli S, D'Andrea A, D'Errico A, Mele D, Sciomer S, Mondillo S; Working Group of Echocardiography of the Italian Society of Cardiology. Echocardiography in patients with hypertrophic cardiomyopathy: usefulness of old and new techniques in the diagnosis and pathophysiological assessment. *Cardiovasc Ultrasound* 2010;**8**:7.
161. Linhart A, Kampmann C, Zamorano JL, Sunder-Plassmann G, Beck M, Mehta A, Elliott PM. Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry outcome survey. *Eur Heart J* 2007;**28**:1228–1235.
162. Patel V, O'Mahony C, Hughes D, Rahman MS, Coats C, Murphy E, Lachmann R, Mehta A, Elliott PM. Clinical and genetic predictors of major cardiac events in patients with Anderson-Fabry disease. *Heart* 2015;**101**:961–966.
163. Seydelmann N, Liu D, Kramer J, Drechsler C, Hu K, Nordbeck P, Schneider A, Stork S, Bijmens B, Ertl G, Wanner C, Weidemann F. High-sensitivity troponin: a clinical blood biomarker for staging cardiomyopathy in Fabry disease. *J Am Heart Assoc* 2016;**5**:e002839.
164. Rosmini S, Biagini E, O'Mahony C, Bulluck H, Ruozi N, Lopes LR, Guttman O, Reant P, Quarta CC, Pantazis A, Tome-Esteban M, McKenna WJ, Rapezzi C, Elliott PM. Relationship between aetiology and left ventricular systolic dysfunction in hypertrophic cardiomyopathy. *Heart* 2017;**103**:300–306.
165. Shah JS, Lee P, Hughes D, Thaman R, Sachdev B, Pellerin D, Mehta A, Elliott PM. The natural history of left ventricular systolic function in Anderson-Fabry disease. *Heart* 2005;**91**:533–534.
166. Sherrid MV, Barac I, McKenna WJ, Elliott PM, Dickie S, Chojnowska L, Casey S, Maron BJ. Multicenter study of the efficacy and safety of disopyramide in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005;**45**:1251–1258.
167. Ommen SR, Maron BJ, Olivetto I, Maron MS, Cecchi F, Betocchi S, Gersh BJ, Ackerman MJ, McCully RB, Dearani JA, Schaff HV, Danielson GK, Tajik AJ, Nishimura RA. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2005;**46**:470–476.
168. Rastegar H, Boll G, Rowin EJ, Dolan N, Carroll C, Udelson JE, Wang W, Carpino P, Maron BJ, Maron MS, Chen FY. Results of surgical septal myectomy for obstructive hypertrophic cardiomyopathy: the Tufts experience. *Ann Cardiothorac Surg* 2017;**6**:353–363.
169. Kuhn H, Lawrenz T, Lieder F, Leuner C, Strunk-Mueller C, Obergassel L, Bartelsmeier M, Stellbrink C. Survival after transcatheter ablation of septal hypertrophy in hypertrophic obstructive cardiomyopathy (TASH): a 10 year experience. *Clin Res Cardiol* 2008;**97**:234–243.
170. Desai MY, Bhonsale A, Smedira NG, Naji P, Thamilarasan M, Lytle BW, Lever HM. Predictors of long-term outcomes in symptomatic hypertrophic obstructive cardiomyopathy patients undergoing surgical relief of left ventricular outflow tract obstruction. *Circulation* 2013;**128**:209–216.
171. Faber L, Welge D, Fassbender D, Schmidt HK, Horstkotte D, Seggewiss H. One-year follow-up of percutaneous septal ablation for symptomatic hypertrophic obstructive cardiomyopathy in 312 patients: predictors of hemodynamic and clinical response. *Clin Res Cardiol* 2007;**96**:864–873.
172. Qintar M, Morad A, Alhawasli H, Shorbajji K, Firwana B, Essali A, Kadro W. Pacing for drug-refractory or drug-intolerant hypertrophic cardiomyopathy. *Cochrane Database Syst Rev* 2012;CD008523.
173. Chan RH, Maron BJ, Olivetto I, Pencina MJ, Assenza GE, Haas T, Lesser JR, Gruner C, Crean AM, Rakowski H, Udelson JE, Rowin E, Lombardi M, Cecchi F, Tomberli B, Spirito P, Formisano F, Biagini E, Rapezzi C, De Cecco CN, Autore C, Cook EF, Hong SN, Gibson CM, Manning WJ, Appelbaum E, Maron MS. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. *Circulation* 2014;**130**:484–495.
174. Rogers DP, Marazia S, Chow AW, Lambiasi PD, Lowe MD, Frenneaux M, McKenna WJ, Elliott PM. Effect of biventricular pacing on symptoms and cardiac remodelling in patients with end-stage hypertrophic cardiomyopathy. *Eur J Heart Fail* 2008;**10**:507–513.
175. Topilsky Y, Pereira NL, Shah DK, Boilson B, Schirger JA, Kushwaha SS, Joyce LD, Park SJ. Left ventricular assist device therapy in patients with restrictive and hypertrophic cardiomyopathy. *Circ Heart Fail* 2011;**4**:266–275.
176. Mehta A, Beck M, Elliott P, Giugliani R, Linhart A, Sunder-Plassmann G, Schiffmann R, Barbey F, Ries M, Clarke JT. Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data. *Lancet* 2009;**374**:1986–1996.
177. Banikazemi M, Bultas J, Waldek S, Wilcox WR, Whitley CB, McDonald M, Finkel R, Packman S, Bichet DG, Warnock DG, Desnick RJ. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. *Ann Intern Med* 2007;**146**:77–86.
178. El Dib R, Gooma H, Ortiz A, Politei J, Kapoor A, Barreto F. Enzyme replacement therapy for Anderson-Fabry disease: a complementary overview of a Cochrane publication through a linear regression and a pooled analysis of proportions from cohort studies. *PLoS One* 2017;**12**:e0173358.
179. Hughes DA, Nicholls K, Shankar SP, Sunder-Plassmann G, Koeller D, Nedd K, Vockley G, Hamazaki T, Lachmann R, Ohashi T, Olivetto I, Sakai N, Deegan P, Dimmock D, Eyskens F, Germain DP, Goker-Alpan O, Hachulla E, Jovanovic A, Lourenco CM, Narita I, Thomas M, Wilcox WR, Bichet DG, Schiffmann R, Ludington E, Viereck C, Kirk J, Yu J, Johnson F, Boudes P, Benjamin ER, Lockhart DJ, Barlow C, Skuban N, Castelli JP, Barth J, Feldt-Rasmussen U. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. *J Med Genet* 2017;**54**:288–296.
180. Muntze J, Salinger T, Gensler D, Wanner C, Nordbeck P. Treatment of hypertrophic cardiomyopathy caused by cardiospecific variants of Fabry disease with chaperone therapy. *Eur Heart J* 2018;**39**:1861–1862.
181. Prater SN, Banugaria SG, DeArmedy SM, Botha EG, Stege EM, Case LE, Jones HN, Phornphutkul C, Wang RY, Young SP, Kishnani PS. The emerging phenotype of long-term survivors with infantile Pompe disease. *Genet Med* 2012;**14**:800–810.
182. van Capelle CI, Poelman E, Frohn-Mulder IM, Koopman LP, van den Hout JM, Regal L, Cools B, Helbing WA, van der Ploeg AT. Cardiac outcome in classic infantile Pompe disease after 13 years of treatment with recombinant human acid alpha-glucosidase. *Int J Cardiol* 2018;**269**:104–110.
183. D'Souza RS, Levandowski C, Slavov D, Graw SL, Allen LA, Adler E, Mestroni L, Taylor MR. Danon disease: clinical features, evaluation, and management. *Circ Heart Fail* 2014;**7**:843–849.
184. Geske JB, Anavekar NS, Nishimura RA, Oh JK, Gersh BJ. Differentiation of constriction and restriction: complex cardiovascular hemodynamics. *J Am Coll Cardiol* 2016;**68**:2329–2347.
185. Kushwaha SS, Fallon JT, Fuster V. Restrictive cardiomyopathy. *N Engl J Med* 1997;**336**:267–276.
186. Pereira NL, Grogan M, Dec GW. Spectrum of restrictive and infiltrative cardiomyopathies: Part 1 of a 2-Part Series. *J Am Coll Cardiol* 2018;**71**:1130–1148.
187. Murphy CJ, Oudit GY. Iron-overload cardiomyopathy: pathophysiology, diagnosis, and treatment. *J Card Fail* 2010;**16**:888–900.
188. Muchtart E, Blauwet LA, Gertz MA. Restrictive cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. *Circ Res* 2017;**121**:819–837.



189. Ammash NM, Seward JB, Bailey KR, Edwards WD, Tajik AJ. Clinical profile and outcome of idiopathic restrictive cardiomyopathy. *Circulation* 2000;**101**:2490–2496.
190. Kubo T, Gimeno JR, Bahl A, Steffensen U, Steffensen M, Osman E, Thaman R, Mogensen J, Elliott PM, Doi Y, McKenna WJ. Prevalence, clinical significance, and genetic basis of hypertrophic cardiomyopathy with restrictive phenotype. *J Am Coll Cardiol* 2007;**49**:2419–2426.
191. Rich MW. Epidemiology, pathophysiology, and etiology of congestive heart failure in older adults. *J Am Geriatr Soc* 1997;**45**:968–974.
192. Waller BF, Roberts WC. Cardiovascular disease in the very elderly. Analysis of 40 necropsy patients aged 90 years or over. *Am J Cardiol* 1983;**51**:403–421.
193. Castano A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, Rubin J, Chiuzan C, Nazif T, Vahl T, George I, Kodali S, Leon MB, Hahn R, Bokhari S, Maurer MS. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. *Eur Heart J* 2017;**38**:2879–2887.
194. Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, Bornstein B, Salas C, Lara-Pezzi E, Alonso-Pulpon L, Garcia-Pavia P. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. *Eur Heart J* 2015;**36**:2585–2594.
195. Mogensen J, Arbustini E. Restrictive cardiomyopathy. *Curr Opin Cardiol* 2009;**24**:214–220.
196. Maurer MS, Elliott P, Comenzo R, Semigran M, Rapezzi C. Addressing common questions encountered in the diagnosis and management of cardiac amyloidosis. *Circulation* 2017;**135**:1357–1377.
197. Rubin J, Steidley DE, Carlsson M, Ong ML, Maurer MS. Myocardial contraction fraction by M-mode echocardiography is superior to ejection fraction in predicting mortality in transthyretin amyloidosis. *J Card Fail* 2018;**24**:504–511.
198. Clemmensen TS, Molgaard H, Sorensen J, Eiskjaer H, Andersen NF, Mellekjaer S, Andersen MJ, Tolbod LP, Harms HJ, Poulsen SH. Inotropic myocardial reserve deficiency is the predominant feature of exercise haemodynamics in cardiac amyloidosis. *Eur J Heart Fail* 2017;**19**:1457–1465.
199. Rivenes SM, Kearney DL, Smith EO, Towbin JA, Denfield SW. Sudden death and cardiovascular collapse in children with restrictive cardiomyopathy. *Circulation* 2000;**102**:876–882.
200. Rammos A, Meladinis V, Vovas G, Patsouras D. Restrictive cardiomyopathies: the importance of noninvasive cardiac imaging modalities in diagnosis and treatment – a systematic review. *Radiol Res Pract* 2017;**2017**:2874902.
201. Brenner DA, Jain M, Pimentel DR, Wang B, Connors LH, Skinner M, Apstein CS, Liao R. Human amyloidogenic light chains directly impair cardiomyocyte function through an increase in cellular oxidant stress. *Circ Res* 2004;**94**:1008–1010.
202. Falk RH, Alexander KM, Liao R, Dorbala S. AL (light-chain) cardiac amyloidosis: a review of diagnosis and therapy. *J Am Coll Cardiol* 2016;**68**:1323–1341.
203. Skinner M, Anderson J, Simms R, Falk R, Wang M, Libbey C, Jones LA, Cohen AS. Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine only. *Am J Med* 1996;**100**:290–298.
204. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin Hematol* 1995;**32**:45–59.
205. Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C, Laumann K, Zeldenrust SR, Leung N, Dingli D, Greipp PR, Lust JA, Russell SJ, Kyle RA, Rajkumar SV, Gertz MA. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. *J Clin Oncol* 2012;**30**:989–995.
206. Banyersad SM, Fontana M, Maestrini V, Sado DM, Captur G, Petrie A, Piechnik SK, Whelan CJ, Herrey AS, Gillmore JD, Lachmann HJ, Wechalekar AD, Hawkins PN, Moon JC. T1 mapping and survival in systemic light-chain amyloidosis. *Eur Heart J* 2015;**36**:244–251.
207. Castano A, Drachman BM, Judge D, Maurer MS. Natural history and therapy of TTR-cardiac amyloidosis: emerging disease-modifying therapies from organ transplantation to stabilizer and silencer drugs. *Heart Fail Rev* 2015;**20**:163–178.
208. Gertz MA, Benson MD, Dyck PJ, Grogan M, Coelho T, Cruz M, Berk JL, Plante-Bordeneuve V, Schmidt HH, Merlini G. Diagnosis, prognosis, and therapy of transthyretin amyloidosis. *J Am Coll Cardiol* 2015;**66**:2451–2466.
209. Birnie DH, Nery PB, Ha AC, Beanlands RS. Cardiac sarcoidosis. *J Am Coll Cardiol* 2016;**68**:411–421.
210. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. *Circulation* 1978;**58**:1204–1211.
211. Martusewicz-Boros MM, Boros PW, Wiatr E, Kempisty A, Piotrowska-Kownacka D, Roszkowski-Sliz K. Cardiac sarcoidosis: is it more common in men? *Lung* 2016;**194**:61–66.
212. Kandolin R, Lehtonen J, Airaksinen J, Vihinen T, Miettinen H, Ylitalo K, Kaikkonen K, Tuohinen S, Haataja P, Kerola T, Kokkonen J, Pelkonen M, Pietila-Effati P, Utrianen S, Kupari M. Cardiac sarcoidosis: epidemiology, characteristics, and outcome over 25 years in a nationwide study. *Circulation* 2015;**131**:624–632.
213. Segura AM, Radovancevic R, Demirozu ZT, Frazier OH, Buja LM. Granulomatous myocarditis in severe heart failure patients undergoing implantation of a left ventricular assist device. *Cardiovasc Pathol* 2014;**23**:17–20.
214. Roberts WC, Chung MS, Ko JM, Capehart JE, Hall SA. Morphologic features of cardiac sarcoidosis in native hearts of patients having cardiac transplantation. *Am J Cardiol* 2014;**113**:706–712.
215. Kandolin R, Lehtonen J, Kupari M. Cardiac sarcoidosis and giant cell myocarditis as causes of atrioventricular block in young and middle-aged adults. *Circ Arrhythm Electrophysiol* 2011;**4**:303–309.
216. Nery PB, Beanlands RS, Nair GM, Green M, Yang J, McArdle BA, Davis D, Ohira H, Gollob MH, Leung E, Healey JS, Birnie DH. Atrioventricular block as the initial manifestation of cardiac sarcoidosis in middle-aged adults. *J Cardiovasc Electrophysiol* 2014;**25**:875–881.
217. Nery PB, McArdle BA, Redpath CJ, Leung E, Lemery R, Dekemp R, Yang J, Keren A, Beanlands RS, Birnie DH. Prevalence of cardiac sarcoidosis in patients presenting with monomorphic ventricular tachycardia. *Pacing Clin Electrophysiol* 2014;**37**:364–374.
218. Yazaki Y, Isoe M, Hiroe M, Morimoto S, Hiramitsu S, Nakano T, Izumi T, Sekiguchi M. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. *Am J Cardiol* 2001;**88**:1006–1010.
219. Oudit GY, Sun H, Trivieri MG, Koch SE, Dawood F, Ackerley C, Yazdanpanah M, Wilson GJ, Schwartz A, Liu PP, Backx PH. L-type Ca<sup>2+</sup> channels provide a major pathway for iron entry into cardiomyocytes in iron-overload cardiomyopathy. *Nat Med* 2003;**9**:1187–1194.
220. Liu P, Olivieri N. Iron overload cardiomyopathies: new insights into an old disease. *Cardiovasc Drugs Ther* 1994;**8**:101–110.
221. Kremastinos DT. Heart failure in beta-thalassemia. *Congest Heart Fail* 2001;**7**:312–314.
222. Zurlo MG, De Stefano P, Borgna-Pignatti C, Di Palma A, Piga A, Melevendi C, Di Gregorio F, Burattini MG, Terzoli S. Survival and causes of death in thalassaemia major. *Lancet* 1989;**2**:27–30.
223. Kremastinos DT, Tsetsos GA, Tsiapras DP, Karavolias GK, Ladis VA, Kattamis CA. Heart failure in beta thalassemia: a 5-year follow-up study. *Am J Med* 2001;**111**:349–354.
224. Kremastinos DT, Tsiapras DP, Kostopoulou AG, Hamodraka ES, Chaidaroglou AS, Kapsali ED. NT-proBNP levels and diastolic dysfunction in beta-thalassaemia major patients. *Eur J Heart Fail* 2007;**9**:531–536.
225. Palka P, Lange A, Atherton J, Stafford WJ, Burstow DJ. Biventricular diastolic behaviour in patients with hypertrophic and hereditary hemochromatosis cardiomyopathies. *Eur J Echocardiogr* 2004;**5**:356–366.
226. Hamdy AM. Use of strain and tissue velocity imaging for early detection of regional myocardial dysfunction in patients with beta thalassemia. *Eur J Echocardiogr* 2007;**8**:102–109.
227. Anderson LJ, Holden S, Davis B, Prescott E, Charrier CC, Bunce NH, Firmin DN, Wonke B, Porter J, Walker JM, Pennell DJ. Cardiovascular T2-star (T2\*) magnetic resonance for the early diagnosis of myocardial iron overload. *Eur Heart J* 2001;**22**:2171–2179.
228. Grimaldi A, Mocumbi AO, Freers J, Lachaud M, Mirabel M, Ferreira B, Narayanan K, Celermajer DS, Sidi D, Jouven X, Marijon E. Tropical endomyocardial fibrosis: natural history, challenges, and perspectives. *Circulation* 2016;**133**:2503–2515.
229. Mocumbi AO, Ferreira MB, Sidi D, Yacoub MH. A population study of endomyocardial fibrosis in a rural area of Mozambique. *N Engl J Med* 2008;**359**:43–49.
230. Tharakan JA. Electrocardiogram in endomyocardial fibrosis. *Indian Pacing Electrophysiol J* 2011;**11**:129–133.
231. D'Arbela PG, Mutazindwa T, Patel AK, Somers K. Survival after first presentation with endomyocardial fibrosis. *Br Heart J* 1972;**34**:403–407.
232. Ellis J, Martin R, Wilde P, Tometzki A, Senkungu J, Nansera D. Echocardiographic, chest X-ray and electrocardiogram findings in children presenting with heart failure to a Ugandan paediatric ward. *Trop Doct* 2007;**37**:149–150.
233. Urhoghide GE, Falase AO. Degranulated eosinophils, eosinophil granule basic proteins and humoral factors in Nigerians with endomyocardial fibrosis. *Afr J Med Sci* 1987;**16**:133–139.
234. Grupper A, Park SJ, Pereira NL, Schettle SD, Gerber Y, Topilsky Y, Edwards BS, Daly RC, Stulak JM, Joyce LD, Kushwaha SS. Role of ventricular assist therapy for patients with heart failure and restrictive physiology: improving outcomes for a lethal disease. *J Heart Lung Transplant* 2015;**34**:1042–1049.
235. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, Danziger-Isakov L, Kirklin JK, Kirk R, Kushwaha SS, Lund LH, Potena L, Ross HJ, Taylor DO, Verschuuren EA, Zuckerman A. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant* 2016;**35**:1–23.

236. Sperry BW, Ikram A, Hachamovitch R, Valent J, Vranian MN, Phelan D, Hanna M. Efficacy of chemotherapy for light-chain amyloidosis in patients presenting with symptomatic heart failure. *J Am Coll Cardiol* 2016;**67**:2941–2948.
237. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C; ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med* 2018;**379**:1007–1016.
238. Solomon SD, Adams D, Kristen A, Grogan M, González-Duarte A, Maurer MS, Merlini G, Damy T, Slama MS, Brannagan TH 3rd, Dispenzieri A, Berk JL, Shah AM, Garg P, Vaishnav A, Karsten V, Chen J, Gollob J, Vest J, Suhr O. Effects of patisiran, an RNA interference therapeutic, on cardiac parameters in patients with hereditary transthyretin-mediated amyloidosis. *Circulation* 2019;**139**:431–443.
239. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, Judson MA, Kron J, Mehta D, Cosedis Nielsen J, Patel AR, Ohe T, Raatikainen P, Soejima K. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm* 2014;**11**:1305–1323.
240. Rivers J, Garrahy P, Robinson W, Murphy A. Reversible cardiac dysfunction in hemochromatosis. *Am Heart J* 1987;**113**:216–217.
241. Borgna-Pignatti C, Rugolotto S, De Stefano P, Zhao H, Cappellini MD, Del Vecchio GC, Romeo MA, Forni GL, Gamberini MR, Ghilardi R, Piga A, Cnaan A. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. *Haematologica* 2004;**89**:1187–1193.
242. Brittenham GM. Iron-chelating therapy for transfusional iron overload. *N Engl J Med* 2011;**364**:146–156.
243. Helbig G. Imatinib for the treatment of hypereosinophilic syndromes. *Expert Rev Clin Immunol* 2018;**14**:163–170.
244. Butterfield JH, Weiler CR. Treatment of hypereosinophilic syndromes – the first 100 years. *Semin Hematol* 2012;**49**:182–191.
245. Bertrand E, Chauvet J, Assamoi MO, Charles D, Ekra E, Dienot BB, Caileau G, Burdin J, Longechaud A, Millet P. Results, indications and contra-indications of surgery in restrictive endomyocardial fibrosis: comparative study on 31 operated and 30 non-operated patients. *East Afr Med J* 1985;**62**:151–160.