

# State-of-the-art document on optimal contemporary management of cardiomyopathies

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The document represents an expert consensus reached at the online Heart Failure Association Workshop (Belgrade, 18 March 2021).

Cardiomyopathies represent significant contributors to cardiovascular morbidity and mortality. Over the past decades, a progress has occurred in characterization of the genetic background and major pathophysiological mechanisms, which has been incorporated into a more nuanced diagnostic approach and risk stratification. Furthermore, medications targeting core disease processes and/or their downstream adverse effects have been introduced for several cardiomyopathies. Combined with standard care and prevention of sudden cardiac death, these novel and emerging targeted therapies offer a possibility of improving the outcomes in several cardiomyopathies. Therefore, the aim of this document is to summarize practical approaches to the treatment of cardiomyopathies, which includes the evidence-based novel therapeutic concepts and established principles of care, tailored to the individual patient aetiology and clinical presentation of the cardiomyopathy. The scope of the document encompasses contemporary treatment of dilated, hypertrophic, restrictive and arrhythmogenic cardiomyopathy. It was based on an expert consensus reached at the Heart Failure Association online Workshop, held on 18 March 2021.

## Keywords

Aetiology • Arrhythmogenic cardiomyopathy • Dilated cardiomyopathy • Hypertrophic cardiomyopathy • Management • Mortality • Restrictive cardiomyopathy • Treatment

## Introduction

Cardiomyopathies represent a group of heterogeneous myocardial disorders characterized by diverse aetiologies, multiple underlying mechanisms and complex clinical phenotypes. Over the past decades a considerable progress has been made in in-depth characterization of the genetic background and key pathophysiological pathways, which have been integrated into the diagnostic assessment of cardiomyopathies. This has advanced the management of several cardiomyopathies with the introduction of medications that target core disease mechanisms or mitigate their downstream adverse effects. In combination with standard care, involving the treatment of heart failure (HF), strategies for prevention of complications and sudden cardiac death (SCD), these novel and emerging therapies have significantly improved the prognosis in several cardiomyopathies. Therefore, the aim of this review is to summarize practical approaches to the treatment of cardiomyopathies, the framework of which combines the novel therapeutic concepts with established principles of care, tailored to the individual patient aetiology and clinical presentation of the cardiomyopathy. The focus of discussion is on the existing therapeutic approaches in specific aetiologies, pointing to the quality of evidence, as well as on the gaps in knowledge and emerging treatment options. This review is not intended to be a substitute for practical guidelines or consensus documents, which provide a more detailed summary of evidence on specific topics. The scope of this review encompasses optimized contemporary treatment of the four major types of cardiomyopathies, including the dilated, hypertrophic, restrictive and arrhythmogenic phenotypes. It is based on the summary of available data from randomized trials (when available) or observational studies and expert consensus reached at the Heart Failure Association (HFA) online Workshop, held on 18 March 2021.

## Dilated cardiomyopathy

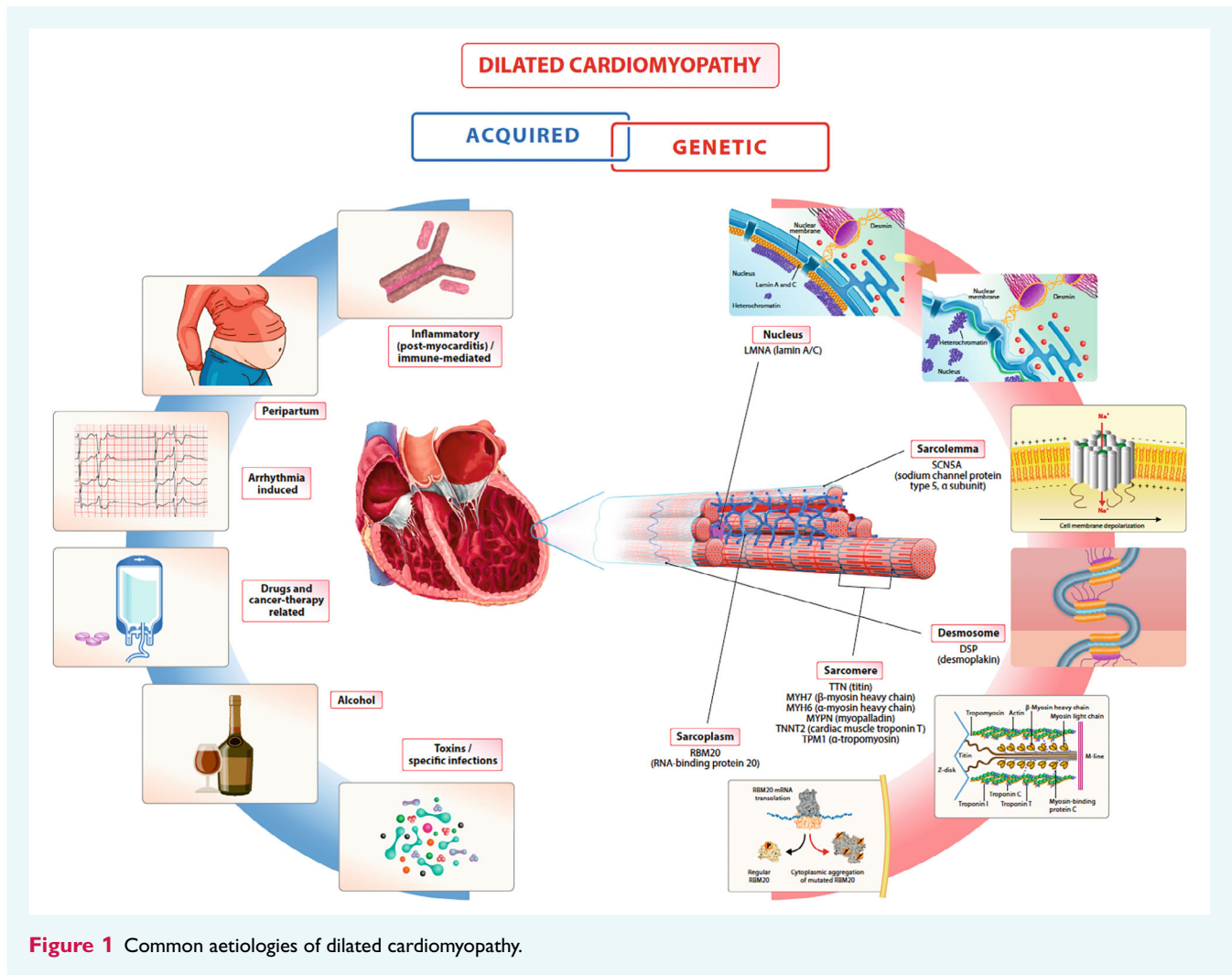
Dilated cardiomyopathy (DCM) is defined by left ventricular (LV) or biventricular dilatation with systolic dysfunction, not explained by abnormal loading conditions and/or significant coronary artery disease.<sup>1,2</sup> It is one of the major causes of HF with reduced ejection

fraction (HFrEF) and is associated with an increased risk of SCD. Current treatment mainly relies on standard, guideline-directed pharmacological and device therapies for HFrEF. Nevertheless, a significant proportion of patients face the risk of progressive HF and premature mortality.<sup>3</sup> Therefore, optimal management of DCM should focus on the integration of standard and specific, aetiology-based therapies (whenever available). The role of standard pharmacological and device therapies in DCM has been extensively covered elsewhere.<sup>2</sup> Furthermore, better understanding of the pathophysiological mechanisms has sparked an interest in novel treatments, as recently discussed by the HFA.<sup>4</sup> The present document reviews therapeutic strategies targeting specific aetiologies and/or perpetuating mechanisms, that may be of added value in optimizing patient care in DCM.

## Treatment perspectives of the genetic background, disease modifiers and phenotype expression

Dilated cardiomyopathy can be sporadic or familial (genetic), the latter accounting for 30–50% of all cases.<sup>1,5</sup> DCM can also be caused or aggravated by environmental factors (e.g. infections, exposure to toxins, chemotherapeutic agents, radiation, etc.), immune-mediated processes, cardiac arrhythmias, and metabolic or endocrine abnormalities (e.g. diabetes, endocrine disorders, nutritive deficiencies, etc.) (Figure 1).

The most frequent 'causative' mutations include truncating titin (TTN) variants, followed by mutations in other sarcomere proteins (troponin, beta-myosin heavy chain or alpha-myosin heavy chain), nuclear envelope protein – lamin A/C (LMNA), filamin (FLN), as well as ribonucleic acid binding motif 20 (RBM20), phospholamban (PLN) and several other genes<sup>6–8</sup> (Figure 1). Genotype–phenotype associations vary depending on the gene pathogenicity, penetrance and environmental interactions. A meta-analysis of more than 8000 patients with available genotype–phenotype data indicated a high prevalence of advanced HF, conduction abnormalities and ventricular arrhythmias in carriers of LMNA, PLN and RBM20 mutations.<sup>9,10</sup> Conversely, TTN mutations have less arrhythmogenic propensity and often underly apparently acquired forms of



**Figure 1** Common aetiologies of dilated cardiomyopathy.

DCM, occurring in the presence of a second hit such as cancer treatment or alcohol abuse.<sup>9,10</sup> Typical genotype–phenotype associations are presented in *Figure 2*.

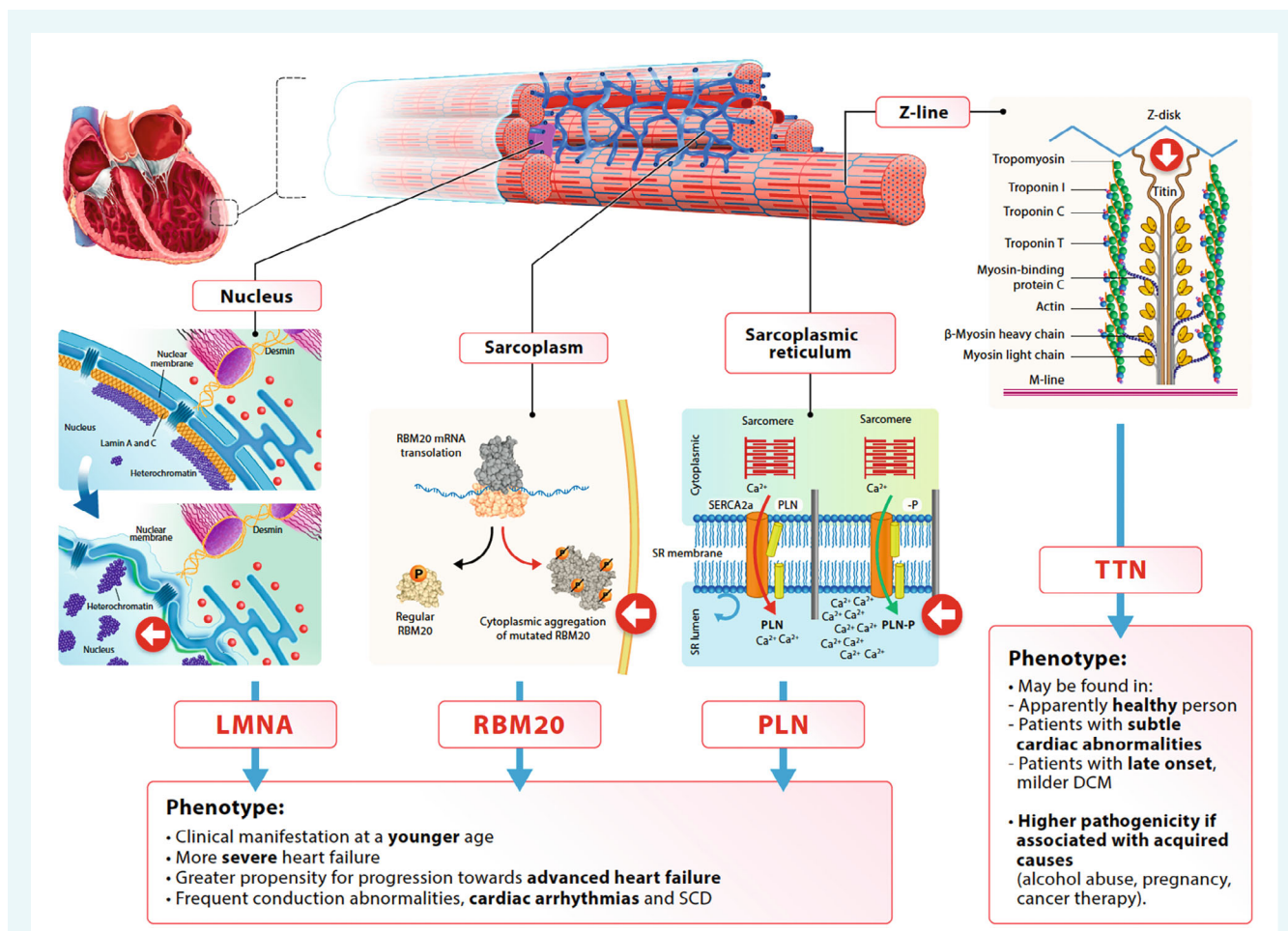
The interaction between genetic and acquired causes has significant prognostic implications. Patients with multiple causative factors, especially those with specific genetic background, tend to have more severe and progressive cardiomyopathy, greater risk of SCD and often respond less favourably to standard treatment.<sup>11,12</sup> A lower capacity for LV reverse remodelling (LVRR) has been demonstrated in carriers of PLN and RBM20 mutations, and to a lesser extent, in those with LMNA mutations.<sup>9,12</sup> Carriers of TTN mutations may have a greater potential for LVRR with the appropriate treatment, however, this may not always be the case.<sup>12,13</sup> Despite the undisputed significance of genetic characterization, high costs and low availability impose major limitations to its widespread utilization. A novel risk score (Madrid Genotype Score) has been developed to facilitate selection of patients for genetic testing. Based on readily available predictors (i.e. family history of DCM, absence of hypertension, skeletal muscle disease, absence of left bundle branch block, and low QRS voltage in peripheral electrocardiographic leads), the score has demonstrated good performance

in identification of patients with high probability of genetic DCM.<sup>14</sup> Some of those patients might benefit from an earlier implantable cardioverter-defibrillator (ICD) implantation due to the inherited higher risk for SCD.

## Novel aspects of aetiology-based treatments for dilated cardiomyopathy

### Genetic causes

Current knowledge allows for therapies that can ameliorate clinical consequences of causative gene mutations in some patients with DCM. For example, LMNA mutations are known to predispose to malignant ventricular arrhythmias and SCD, regardless of LV (dys)function.<sup>6</sup> Therefore, in carriers of LMNA mutations, risk assessment for primary ICD implantation should include calculation of the absolute 5-year risk of malignant arrhythmias using a validated, disease-specific score (<https://lmna-risk-vta.fr>).<sup>15</sup> The score is derived from readily available predictors, including male sex, non-missense LMNA mutations, first-degree or higher atrioventricular block, the presence of non-sustained



**Figure 2** Genotype–phenotype associations of several genetic variants in dilated cardiomyopathy (DCM). LMNA, lamin A/C mutations: abnormalities within different cellular signalling pathways; frequency: 5%; association with skeletal muscle dystrophy, atrial fibrillation, conduction abnormalities and ventricular arrhythmias. RBM20, ribonucleic acid binding motif 20 mutations: perturbation in post-transcriptional pre-mRNA processing; frequency: 2%; association with conduction abnormalities, ventricular arrhythmias, and early progressive cardiomyopathy. PLN, phospholamban mutations: cellular  $\text{Ca}^{2+}$  dysregulation, contractile and metabolic dysfunction; frequency: 2%; association with low voltage electrocardiogram and ventricular arrhythmias. TTN, titin truncating mutations: increased non-sense mRNA decay, activation of the mammalian target of rapamycin (mTOR) complex signalling pathway, mitochondrial dysfunction, increased interstitial fibrosis; frequency: ~25%; variable genotype–phenotype associations. SCD, sudden cardiac death; SERCA2a, sarcoplasmic/endoplasmic reticulum  $\text{Ca}^{2+}$  ATPase 2a; SR, sarcoplasmic reticulum. Modified from references<sup>9,236–238</sup>

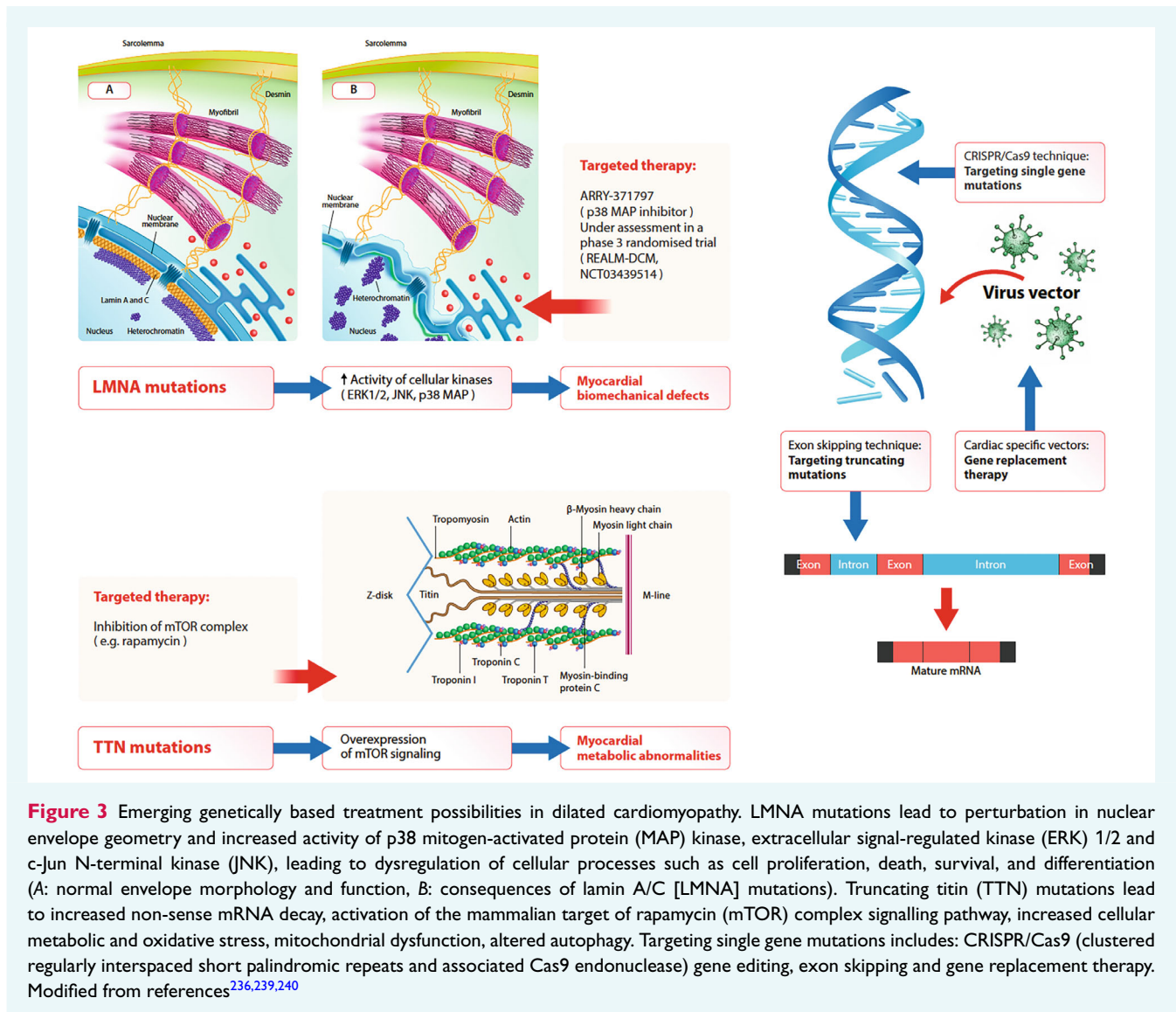
ventricular tachycardia (VT) and LV ejection fraction (LVEF) <45%. Its use can improve identification of high-risk patients that derive the greatest benefit from primary ICD implantation.<sup>15</sup> In other cases, the knowledge of a genetic substrate associated with the progressive cardiomyopathy (e.g. PLN and RBM20 mutations) may identify individuals requiring more intensive follow-up, and timely provision of advanced HF therapies, if necessary. Although data from specialized centres suggest improvement in outcomes with the meticulous management, this approach deserves further prospective evaluation in every-day clinical practice.

Genetic mutations result in distinct changes in the cellular signal transduction pathways, which may be the targets of future therapeutic interventions. Several promising strategies currently under assessment are presented in Figure 3.

### Targeting acquired causes

#### Immune-mediated/inflammatory mechanisms

Myocarditis can occur due to viral infection (e.g. coxsackievirus B, human herpes virus 6, cytomegalovirus, influenza, parvovirus B19, SARS-CoV-2, etc.), exposure to vaccines (e.g. mRNA COVID-19, smallpox, influenza vaccine, etc.), drugs (e.g. immune checkpoint inhibitors, clozapine, etc.), in patients with systemic immune-mediated disorders (e.g. systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, vasculitis, etc.), and due to non-viral infections (e.g. Lyme disease, trichinellosis).<sup>16–18</sup> It can be complicated by acute HF, conduction abnormalities, cardiac rhythm disorders and, in most severe cases, by haemodynamic instability and cardiogenic shock (fulminant myocarditis). Pathogenic gene variants commonly associated with cardiomyopathies



(desmoplakin and TTN) have been described in 8% of patients with myocarditis from a population-based cohort and associated with worse prognosis compared to individuals with myocarditis but without gene mutations.<sup>19</sup> Endomyocardial biopsy should be considered in patients with (suspected) myocarditis complicated by cardiogenic shock or acute HF and severe LV systolic dysfunction, with or without malignant ventricular arrhythmias and/or conduction abnormalities, to establish the histological diagnosis pertinent to treatment.<sup>20,21</sup> The European Society of Cardiology (ESC) guidelines advise against the routine use of immunosuppressive therapy in patients with myocarditis, without clinical or biopsy-based evidence of immune-mediated disease.<sup>1</sup> However, observational data suggest that in patients with giant-cell myocarditis, eosinophilic myocarditis, immune checkpoint inhibitor-induced myocarditis, vasculitis, sarcoidosis and other immune-mediated disorders, immunosuppressive therapy (high-dose methylprednisolone 500–1000 mg i.v. for 3 days in most reports, or combined immunosuppressive regimens) can be beneficial.<sup>22–25</sup> An ongoing

placebo-controlled randomized trial is assessing the effect of pulsed dose methylprednisolone on top of standard treatment on clinical outcomes in patients with myocarditis complicated by acute HF and LV systolic dysfunction (MYTHS, NCT05150704). Despite lack of evidence from randomized trials in the setting of acute myocarditis, the ESC guidelines recommend the use of standard HFREF therapies in patients with LV systolic dysfunction for the duration of at least 6 months after the acute phase, with subsequent echocardiographic re-evaluation.<sup>1</sup> Due to the risk of SCD or silent disease progression after the acute phase, exercise should be avoided for 3–6 months, until LV systolic function, serum troponin and inflammatory biomarker levels have normalized.<sup>26</sup> In addition, there should be no evidence of ongoing inflammation or myocardial fibrosis on cardiac magnetic resonance (CMR), and clinically relevant arrhythmias (e.g. frequent or complex repetitive forms of ventricular or supraventricular arrhythmias) should be absent on 24-h ambulatory electrocardiogram monitoring and exercise test.<sup>26</sup>

In some patients, there is evidence of persistent post-myocarditis inflammation (i.e. chronic myocarditis) in endomyocardial biopsy specimens and the development of DCM, which often remains unresponsive to conventional HF treatment. In a randomized trial in patients with LVEF <45% and a histopathological evidence of inflammation, immunosuppressive therapy with prednisone combined with either cyclosporine or azathioprine failed to show improvement in outcomes compared to conventional therapy.<sup>27</sup> A subsequent randomized study of 84 patients with biopsy proven, virus negative inflammatory DCM demonstrated that 3 months of prednisone and azathioprine treatment versus placebo resulted in a sustained improvement in LV systolic function, albeit without improvement in survival (perhaps due to the small sample size).<sup>28</sup> Another study of 85 patients demonstrated a significant LVRR within 6 months of prednisone and azathioprine treatment compared with placebo, without major adverse effects.<sup>29</sup> The 20-year follow up of this study group showed a late, but long-lasting beneficial effect with a significant reduction in cardiovascular mortality or requirement for heart transplantation in the treatment arm.<sup>30</sup> This agrees with a more recent propensity score-matched retrospective analysis of immunosuppressive therapy versus standard care, which confirmed potential benefits for LVRR and 1-year transplantation-free survival with immunosuppressive therapy in 180 patients with biopsy proven, immunohistology positive and virus negative severe cardiac inflammation.<sup>31</sup> Smaller trials in selected patients with HF, biopsy proven chronic inflammation and low copy numbers of parvovirus B19 showed a benefit from an immunosuppressive therapy without viral aggravation.<sup>32</sup> Furthermore, a randomized trial of 143 patients with endomyocardial biopsy proven viral persistence (enterovirus, adenovirus, and/or parvovirus B19) showed that immunomodulation with interferon-beta in addition to standard HF therapy was safe and effective in clearing/reducing viral load and improving functional capacity.<sup>33</sup> Thus, in selected patients with DCM and biopsy proven evidence of inflammation based on modern immunohistological and molecular techniques, immunomodulatory therapy may be an option, especially in patients with worsening or refractory HF despite standard treatment.<sup>20</sup> This opinion is based on the results of observational and small randomized studies of selected patients and definitive recommendations await larger prospective assessment.

Likewise, removal of cardiotoxic autoantibodies with immunoadsorption, in patients without evidence of cardiac inflammation, and their replacement with polyclonal immunoglobulin G showed some promising results.<sup>34,35</sup> Despite these positive findings, supporting evidence for these therapies in DCM, without inflammation, is limited and their clinical application awaits confirmation from larger randomized outcome trials.

#### *Peripartum cardiomyopathy*

Peripartum cardiomyopathy (PPCM) is defined as HFrEF (LVEF <45%) occurring within the last month before or 6 months after delivery in women without previous heart disease.<sup>36,37</sup> Observational data suggest that 15–20% of patients with PPCM have a genetic basis (most frequently, causative genes for DCM such as TTN, beta-myosin heavy chain, myosin-binding protein C or

LMNA), which may impart the more severe clinical course and worse prognosis.<sup>37–39</sup> Therefore, genetic testing is recommended in patients with PPCM, particularly in cases of familial history of cardiomyopathy.<sup>1,37</sup> Patients often display severe HF and a markedly reduced LVEF <35% with right ventricular (RV) involvement.<sup>40</sup> The potential for myocardial recovery is high in PPCM, and patients benefit from standard HF treatments that should be applied in guideline-recommended dosages. This treatment should be continued at least 12–24 months after improvement in LV function and be tapered only gradually, as relapses have been observed.<sup>37</sup> In many patients, substantial LVRR ensues during 6–12 months, but can be observed also after several years.<sup>36</sup> However, some PPCM patients suffer from severe acute HF or even cardiogenic shock.<sup>36,41</sup> While treatment with catecholamines (e.g. dobutamine) appears to be associated with worse outcomes,<sup>42</sup> levosimendan or milrinone can be used as an alternative, although, in a small randomized study, levosimendan was not associated with improved outcomes,<sup>43</sup> and a study comparing levosimendan and milrinone showed comparable haemodynamic improvement.<sup>44</sup> An early use of temporary mechanical circulatory support (MCS) in haemodynamically compromised patients with PPCM to unload the left ventricle, seems to promote recovery,<sup>45</sup> and may be considered with a lower threshold to avoid catecholamine toxicity.<sup>37</sup> Heart transplantation or implantation of a durable MCS may be rarely needed.<sup>46</sup>

Based on pathophysiological studies and a small clinical trial (without a placebo arm) demonstrating high rate of full LV recovery,<sup>47,48</sup> blocking prolactin with the dopamine D2 receptor agonist bromocriptine has emerged as a potential targeted therapy for PPCM. Current ESC guidelines state that bromocriptine may be used for the treatment of PPCM.<sup>1,49</sup> Bromocriptine (2.5 mg once daily for 1 week) is advised in uncomplicated cases, whereas prolonged treatment (2.5 mg twice daily for 2 weeks, then 2.5 mg once daily for 6 weeks) may be the choice in more severe cases, particularly if complicated by RV dysfunction and/or cardiogenic shock.<sup>37,50</sup> Due to a higher risk of thromboembolic events during bromocriptine treatment, it should be combined with anticoagulation at least in prophylactic dosages.<sup>37</sup> Anticoagulant therapy (e.g. unfractionated or low molecular weight heparin) should be provided while the patient receives bromocriptine and/or in patients with severely depressed LVEF ≤35%.<sup>41</sup> Bromocriptine also causes cessation of lactation, which may be necessary for the safe initiation of guideline-directed medical therapy (GDMT) and other therapies after delivery. There is no universal consensus on whether bromocriptine should be used in PPCM and there is significant international variability in its use, awaiting the results of outcome trials. Currently ongoing randomized clinical trials (REBIRTH, NCT05180773; and BRO-HF, NCT02590601) will further address efficacy and safety of bromocriptine in PPCM.

The decision about ICD implantation should balance the increased risk of SCD due to severely reduced LVEF, and the high propensity for LV recovery in patients with PPCM. Early implantation of an ICD in newly diagnosed patients is not appropriate, but in patients without recovery despite 3–6 months (up to 12 months) on optimal HF therapy, a conventional recommendation for the primary ICD implantation should be applied. In the first month after diagnosis and until the definitive decision about

**Table 1** Definition and classification of cancer therapy-related cardiac dysfunction according to the 2022 European Society of Cardiology guidelines on cardio-oncology<sup>52</sup>

	Mild	Moderate	Severe	Very severe
Asymptomatic CTRCD	LVEF $\geq$ 50% AND New relative decline in GLS by >15% from baseline AND/OR New rise in cardiac biomarkers	New LVEF reduction by $\geq$ 10% to an LVEF of 40–49% OR New LVEF reduction by <10 percentage points to an LVEF of 40–49% AND Either new relative decline in GLS by >15% from baseline OR new rise in cardiac biomarkers	New LVEF reduction to <40%	–
Symptomatic CTRCD	Mild HF symptoms, no intensification of therapy required	Need for outpatient intensification of diuretic and HF therapy	HF hospitalization	Requiring inotropic support, mechanical circulatory support or consideration for transplantation

CTRCD, cancer therapy-related cardiac dysfunction; GLS, global longitudinal strain; HF, heart failure; LVEF, left ventricular ejection fraction.

ICD implantation can be made, wearable cardioverter-defibrillator can be used instead.<sup>41</sup> Patients with a previously diagnosed PPCM should receive counselling about the long-term prognosis and the risk of subsequent pregnancies. Based on the available data, women with recovered systolic function (LVEF  $\geq$ 50%) have a lower risk of complications during a subsequent pregnancy, but there remains a higher risk of recurrent HF.<sup>51</sup> In women with persistent myocardial dysfunction (LVEF <50%), there is a high risk of recurrent HF, further deterioration of cardiac function, and increased mortality, as well as adverse foetal outcomes (pre-term-delivery, stillbirth).<sup>51</sup> Current ESC guidelines advise against subsequent pregnancy in women with persistent LV dysfunction, and all women with a history of PPCM who decide on subsequent pregnancy should be monitored by a multidisciplinary team throughout pregnancy and for at least 1 year postpartum.<sup>49</sup>

#### Cancer therapy-related cardiomyopathy

Cancer therapy-related cardiomyopathy is defined as the development of cardiac dysfunction, with or without HF, during the course or after treatment with anticancer therapies; a detailed consensus definition is provided in Table 1.<sup>52</sup>

Anthracyclines-induced cardiotoxicity has long been the prototype for cancer therapy-related cardiomyopathy, but many other agents have also been associated with cardiac dysfunction, including chemotherapy, targeted agents and immunotherapy (Table 2).<sup>53</sup> Additional genetic/acquired factors may perpetuate the development of cardiomyopathy.<sup>54</sup>

An early detection and treatment of cancer therapy-related cardiomyopathy is crucial for patient outcomes, as it may prevent further deterioration of LV function.<sup>55</sup> Therefore, regular monitoring of cardiac function with echocardiography and cardiac biomarkers, during and after systemic anti-cancer treatment should be applied to patients with an increased risk of cardiotoxicity, as

defined by baseline cardiovascular risk evaluation.<sup>56–58</sup> In addition, development of symptoms suggestive of HF should prompt further cardiovascular assessment; differential diagnosis includes other causes of heart disease and cancer progression that may mimic cardiac symptoms.

The development of cancer therapy-related cardiac dysfunction should prompt consideration of suspension of anticancer therapy and initiation of GDMT for HF, depending on the type of the offending anticancer agent, and the severity of cardiac dysfunction.<sup>1,52</sup> As outlined in the 2022 ESC guidelines on cardio-oncology, in patients who develop severe or moderate symptomatic or asymptomatic cancer therapy-related cardiac dysfunction during anthracycline treatment, oncological treatment should be interrupted, whereas in patients with symptomatic mild cancer therapy-related cardiac dysfunction, multidisciplinary team should decide whether to continue oncological treatment.<sup>52</sup> Oncological treatment should be continued under close surveillance in patients with mild asymptomatic cardiac dysfunction during anthracycline therapy.<sup>52</sup> In individuals receiving human epidermal receptor 2-targeted therapy (e.g. trastuzumab) who develop severe/moderate symptomatic or severe asymptomatic cardiac dysfunction, it is indicated to interrupt oncological treatment.<sup>52</sup> Multidisciplinary team decision is needed in patients with symptomatic mild cardiac dysfunction and in those with asymptomatic moderate dysfunction, whereas oncological therapy can be continued in patients with mild asymptomatic cardiac dysfunction, under close monitoring.<sup>52</sup> In patients receiving immune checkpoint inhibitors, myocarditis is a rare (1% of treated patients), but potentially fatal manifestation of cardiotoxicity.<sup>59</sup> It usually develops within the first 12 weeks of treatment (up to 20 weeks) and can take the form of fulminant myocarditis.<sup>52</sup> In patients with myocarditis, immune checkpoint inhibitor therapy should be discontinued regardless of clinical severity, and high doses of methylprednisolone (500–1000 mg i.v. once daily) should be given as soon as possible and continued for

**Table 2** Anticancer agents associated with cardiac dysfunction and heart failure

Drug class	Drug names	Main indications
Anthracyclines	Doxorubicin, epirubicin, daunorubicin, idarubicin	Breast cancer, lymphoma, acute, leukaemia, sarcoma
Alkylating agents	Cyclophosphamide, ifosfamide, melphalan	Breast cancer, lung cancer, ovarian cancer, sarcomas, leukaemia, lymphomas, multiple myeloma
HER2-targeted therapies	Trastuzumab, pertuzumab, trastuzumab emtansine (T-DM1), lapatinib, neratinib, tucatinib	HER2+ breast cancer HER2+ gastric cancer
VEGF inhibitors	TKIs: sunitinib, pazopanib, sorafenib, axitinib, tivozanib, cabozantinib, regorafenib, lenvatinib, vandetinib Antibodies: bevacizumab, ramucirumab	VEGF TKIs: renal cancer, hepatocellular cancer, thyroid cancer, colon cancer, sarcoma, GIST Antibodies: breast cancer, ovarian cancer, gastric cancer, gastro-oesophageal cancer, colon cancer
Multi-targeted kinase inhibitors	First generation: imatinib Second generation: nilotinib, dasatinib, bosutinib Third generation: ponatinib	Chronic myeloid leukaemia
Proteasome inhibitors	Carfilzomib, bortezomib, ixazomib	Multiple myeloma
Immunomodulatory drugs	Lenalidomide, pomalidomide	Multiple myeloma
Combination RAF and MEK inhibitors	Dabrafenib + trametinib, vemurafenib + cobimetinib, encorafenib + binimetinib	RAF-mutant melanoma
Immune checkpoint inhibitors	Anti-programmed cell death 1 inhibitors: nivolumab, pembrolizumab Anti-cytotoxic T-lymphocyte-associated Protein 4 inhibitor: ipilimumab Anti-programmed death-ligand 1 inhibitor: avelumab, atezolizumab, durvalumab	Melanoma (metastatic and adjuvant) Metastatic renal cancer, non-small cell lung cancer, small cell lung cancer, refractory Hodgkin's lymphoma, metastatic triple negative breast cancer, metastatic urothelial cancer, liver cancer, MMR-deficient cancer
EGFR inhibitors	Osimertinib	EGFR-mutant non-small cell lung cancer

EGFR, epidermal growth factor receptor; GIST, gastrointestinal stromal tumors; HER2, human epidermal growth factor receptor 2; MEK, mitogen-activated extracellular signal-regulated kinase; MMR, mismatch repair; RAF, serine/threonine protein kinase RAF family; T-DM1, ado-trastuzumab emtansine; TKI, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor.

3–5 days since its early institution can improve outcomes.<sup>52,60</sup> If the treatment results in clinical improvement and fall in troponin levels, a switch to oral corticosteroid therapy is recommended with subsequent tapering. If there is a lack of improvement, second-line immunosuppression should be considered although there is currently a paucity of data on the optimal choice (e.g. mycophenolate mofetil, anti-thymocyte globulin, abatacept, or alemtuzumab).<sup>61–63</sup> Patients who develop fulminant myocarditis require admission to intensive care units equipped for the treatment of cardiogenic shock, alongside the provision of corticosteroid therapy. Besides myocarditis, immune checkpoint inhibitor-related cardiotoxicity can manifest as takotsubo syndrome, (late) non-inflammatory HF, vasculitis, and acute coronary syndrome.<sup>52,64</sup>

Individuals who develop moderate/severe cancer therapy-related cardiac dysfunction with or without manifest HF, should be treated with standard HF therapies. The detection of mild asymptomatic cancer therapy-related myocardial dysfunction, including a >12–15% decline in LV global longitudinal strain or a rise in natriuretic peptides, may also be treated with neurohormonal inhibitors.<sup>65,66</sup> A large observational study showed that in patients with anthracycline-related decline in LVEF of at least 10% to a value below 50% (with or without HF) treatment

with a combination of enalapril and carvedilol/bisoprolol was followed by LVEF improvement in 82% of patients and a complete recovery of LVEF in 11%.<sup>67</sup> Furthermore, sacubitril/valsartan and sodium–glucose cotransporter 2 inhibitors have been associated with improvement in cancer therapy-related cardiomyopathy in pre-clinical or small clinical studies,<sup>68,69</sup> and some data suggest that standard doses of sacubitril/valsartan can be well tolerated in patients with long-standing cancer-therapy related HFREF, leading to the improvement in LV systolic function.<sup>70</sup>

The decision regarding the potential re-initiation of anticancer regimen or its replacement by another regimen depends on the severity of myocardial dysfunction, the stage and prognosis of malignancy and the expected benefits from anticancer agents. The decision should be reached by multidisciplinary team, weighing benefits and risks. Cancer therapy may be continued under close monitoring, although evidence from clinical trials remains limited.<sup>65,66</sup>

#### Other drug-related cardiomyopathies

Several cases of cardiotoxicity, characterized by conduction abnormalities and HF (due to DCM or restrictive cardiomyopathy [RCM]), have been reported following the use of chloroquine or hydroxychloroquine (for the treatment of malaria

or rheumatological disorders).<sup>71,72</sup> The mechanisms responsible for cardiotoxicity remain poorly understood, but some data point to lysosomal dysfunction.<sup>73</sup> Antipsychotic drugs, phenothiazines (chlorpromazine, promethazine)<sup>74</sup> and clozapine have also been implicated in the development of myocarditis and/or DCM.<sup>75</sup> In addition, lithium, an antidepressant medication, has been linked to the occurrence of sinus node dysfunction and DCM.<sup>76</sup> Monitoring of cardiac toxicity by electrocardiography (ST-segment changes, conduction abnormalities, QTc prolongation, etc.), plasma troponin and natriuretic peptide levels and echocardiography (if needed) can be employed for early detection of cardiotoxicity, followed by secession of the offending drug and institution of cardiovascular therapies.<sup>73</sup> Other medications potentially involved in DCM development have been extensively reviewed elsewhere.<sup>73</sup>

#### *Arrhythmia-induced cardiomyopathy*

Arrhythmia-induced cardiomyopathy is defined as a potentially reversible condition in which myocardial dysfunction leading to HF is induced by atrial or ventricular arrhythmias. Different types of arrhythmias can lead to the development of this type of cardiomyopathy, but the most frequent culprits include persistent atrial tachyarrhythmias (i.e. rapid rate atrial fibrillation [AF]) and frequent premature ventricular complexes (PVCs).<sup>77</sup> The diagnosis of arrhythmia-induced cardiomyopathy requires the presence of persistent/repetitive arrhythmia in a patient with otherwise unexplained DCM.<sup>77</sup> In an observational study of patients referred for ablation of frequent idiopathic PVCs, a count of >10% of PVCs on 24-h electrocardiogram monitoring was associated with the development of cardiomyopathy, but a PVC burden of >24% was shown to best separate patients with and without cardiomyopathy (sensitivity 79%, specificity 78%, area under the curve 0.89).<sup>78</sup> However, it may be difficult to distinguish true arrhythmia-induced cardiomyopathy from other genetic (LMNA, PLN, RBM20 mutations, etc.) or non-genetic causes of DCM in which arrhythmias are a part of the clinical presentation. Since the hallmark of arrhythmia-induced cardiomyopathy is substantial/complete recovery in LV function following resolution of arrhythmia in addition to HF therapy, a lack of a significant improvement should indicate other aetiologies of DCM.<sup>79</sup>

The treatment of arrhythmia-induced cardiomyopathy should aim at amelioration or suppression of the culprit arrhythmia by pharmacological treatment or catheter ablation in addition to GDMT for HF. In patients with AF, rhythm control may be more favourable than rate control in improving LV systolic function and the quality of life.<sup>80</sup> Furthermore, recent clinical trial data favour catheter ablation for rhythm control, given the greater success in sinus rhythm maintenance compared with antiarrhythmic drugs.<sup>81,82</sup> Although not specifically focused on patients with DCM, a small, randomized study of symptomatic patients with LVEF <35% and AF demonstrated improved outcomes with catheter ablation compared with medical treatment,<sup>82</sup> indicating that this may be the preferred treatment option in selected patients. In patients with cardiomyopathy induced by ventricular ectopy, catheter ablation was also shown to be beneficial for LVRR and improvement in functional status.<sup>83</sup> Patients with improved arrhythmia-induced cardiomyopathy require long-term follow-up and continuation of

medical therapy, since there is a risk of HF relapse with the recurrence of the arrhythmia.<sup>84,85</sup>

#### *Alcohol, toxins, infections and nutrient deficiencies*

Alcohol-induced cardiomyopathy is caused by chronic excessive alcohol consumption. There is no pre-defined cut-off amount of alcohol abuse that leads to DCM development. A recent analysis of individual-participant level data from 19 high-income countries suggested that for each 100 g per week of alcohol consumption there was a roughly linear association with a higher risk of developing HF, without a clear risk threshold.<sup>86</sup> In addition to the direct toxic effect on the myocardium, individual (genetic) predisposition, age, sex, nutritional deficiencies and exposure to other risk factors appear to have a significant role.<sup>87</sup> The mainstay treatment of alcohol-induced cardiomyopathy is complete abstinence in addition to medical treatment of HF and substitution of thiamine deficiency if present. This can lead to LVRR and functional improvement or at least slowed progression of myocardial dysfunction.<sup>88</sup> Otherwise, 5-year mortality rates can reach 40–50% in patients with continued alcohol abuse.<sup>89</sup>

Exposure to illicit drugs (e.g. cocaine and methamphetamines) can cause myocardial dysfunction by direct toxic effects, by provoking coronary vasospasm and by increasing sympathetic stimulation via reduced reuptake of catecholamines.<sup>90</sup> Recognition of an offending agent is crucial for the management since complete abstinence often provides clinical improvement.<sup>91</sup> Little is known about other treatment options for HF beyond drug abstinence. Since beta-blockade can expose patients to unopposed alpha-adrenergic effects, there have been some concerns about their use in cocaine/methamphetamine users, however, carvedilol (an alpha- and beta-blocker) could be regarded as safe, particularly if abstinence is achieved.<sup>90</sup>

In patients with human immunodeficiency virus (HIV) infection, the advent of antiretroviral therapy has significantly reduced the incidence of HIV-associated cardiomyopathy, which previously occurred in ~40% of individuals with advanced disease.<sup>92</sup> However, newer data suggest that ~8.3% of patients on antiretroviral therapy develop systolic dysfunction,<sup>93</sup> and the presence of DCM or overt HF portends a higher risk of mortality, including SCD.<sup>94</sup> The pathogenesis of HIV-associated cardiomyopathy is complex, including direct myocardial infection, autoimmunity, opportunistic infections, exposure to other toxins (alcohol, illicit drugs), nutritional deficiencies, and toxicity from antiretroviral medications.<sup>95</sup> Assessment of coronary artery disease is also indicated because of its known association with antiretroviral therapy.<sup>92,96</sup> The treatment of HIV-associated cardiomyopathy is currently driven by consensus, relying on observational data and extrapolation from clinical trials of non-HIV patients, and supports provision of guideline-directed medical and device therapies, whilst maintaining antiretroviral therapy to prevent worsening HIV infection.<sup>92</sup> Given the paucity of supportive data, the safety and efficacy of this approach remain to be established. Despite concerns that immunosuppression following heart transplantation may worsen HIV infection, growing body of data suggests no post-transplant deterioration in HIV status,<sup>97</sup> suggesting that heart transplantation could be an option in selected patients with advanced HF.<sup>98</sup> There are also data supporting the use

of LV assist devices in patients with HIV-associated cardiomyopathy,<sup>99</sup> which warrant confirmation from larger studies.

Chagas disease is an important cause of DCM in Central and South America and an emerging health problem in non-endemic countries due to immigration.<sup>100</sup> Chagas cardiomyopathy, the most severe manifestation of the disease, develops in ~20–40% of patients, usually years after the initial infection.<sup>101</sup> Its pathophysiology is multifactorial, including an interaction between the parasite persistence, immune mechanisms, and microvascular dysfunction, resulting in myocardial inflammation, necrosis and fibrosis.<sup>102</sup> The clinical manifestations include HF, conduction abnormalities (e.g. right bundle branch block, atrioventricular block), atrial and ventricular arrhythmias, segmental LV wall motion abnormalities, formation of LV aneurysms (typically with apical localization), thromboembolic complications and increased risk of SCD.<sup>103</sup> Antiparasitic treatment (benznidazole and nifurtimox) can be curative in the acute phase (in ~60–90% of patients), however in patients with established DCM, a clinical trial with benznidazole failed to demonstrate a significant improvement in cardiovascular outcomes over the 5-year follow-up.<sup>104</sup> Current expert recommendations advise provision of HF therapies, anticoagulation (in patients with AF, LV thrombus, or LV aneurysm with recent thrombus), and pacemaker or ICD implantation in accordance with current guidelines.<sup>103</sup> Heart transplantation can be an option in patients with advanced HF; however, surveillance of Chagas disease reactivation following transplantation, and prompt institution of antiparasitic treatment may be needed to prevent adverse outcomes.<sup>105</sup> An ongoing clinical trial is assessing the efficacy of ICD versus amiodarone for the prevention of all-cause mortality in patients with Chagas cardiomyopathy and non-sustained VT (CHAGASICS, NCT01722942). There is also a focus of exploring therapeutic possibilities of immunomodulation in Chagas cardiomyopathy.<sup>106</sup>

Persistent myocarditis in Lyme disease has been reported as a rare cause of DCM.<sup>107</sup> Antibiotic treatment in addition to standard HF therapy has been successful in improving LV function.<sup>108</sup>

Chronic micronutrient deficits in thiamine, niacin, vitamin D, selenium, copper, taurine, carnitine, and coenzyme Q10 caused by poor dietary intake, drug interactions, and several inherited or acquired disorders, have been associated with alterations in myocardial energy production, calcium handling and antioxidant defence mechanisms, which can play a contributory role in cardiomyopathy development (usually DCM or hypertrophic cardiomyopathy [HCM]).<sup>109–113</sup> In cases of confirmed deficits, nutrient supplementation can be used, but further research is needed to better understand its therapeutic value.

#### *Takotsubo syndrome/cardiomyopathy*

Takotsubo syndrome (also called stress-induced cardiomyopathy) is characterized by an acute, transient LV systolic dysfunction with distinct circumferential wall motion abnormalities (apical localization in ~80%) exceeding the territory of a single coronary artery.<sup>114</sup> It is a notable example of a reversible LV systolic dysfunction which often resolves within a few weeks.<sup>115</sup> Complications, including acute HF, cardiogenic shock, LV outflow tract (LVOT) obstruction, acute mitral regurgitation, QT interval prolongation, arrhythmias, ventricular thrombi and cardiac arrest, occur in ~20%

of patients. In-hospital mortality (~4%) is mostly driven by underlying disorders and the occurrence of complications, and patients who survive the acute phase experience complete recovery of LV function and wall motion abnormalities usually within weeks.<sup>116</sup>

The management of patients with takotsubo syndrome is based on observational data since no prospective clinical trials have been reported yet. Acute phase management involves the treatment of complications and underlying disorders. According to an earlier international expert consensus document, acute HF should be treated with diuretics, whilst catecholaminergic agents should be avoided as they may be associated with excess mortality.<sup>117,118</sup> If inotropic support is needed, levosimendan may be an option.<sup>119</sup> In patients with LVOT obstruction, inotropes or vasodilators should be avoided and diuretics cautiously used, to prevent an increase in pressure gradient and haemodynamic deterioration.<sup>117</sup> There is some experience with the use of short-acting beta-blockers to alleviate pressure gradient in LVOT obstruction.<sup>120</sup> In case of haemodynamic deterioration, short-term MCS with micro-axial pumps or other devices has been described.<sup>121,122</sup> Anticoagulation should be instituted in patients with AF or ventricular thrombus.<sup>117</sup> QT interval prolonging medications should be avoided, whilst beta-blockers could be used instead to treat arrhythmias.<sup>117</sup> Long-term management is focused on the treatment of HF until the recovery of LV function and prevention of recurrences; however, high-quality evidence is lacking. A retrospective analysis suggested that post-discharge treatment with angiotensin-converting enzyme inhibitors (ACEI) or AT<sub>1</sub> receptor blockers (ARB) can improve 1-year survival, whereas beta-blockers provided no survival advantage.<sup>116</sup> By contrast, another retrospective cohort study suggested no survival benefit with post-discharge ACEI/ARB treatment, whilst beta-blockers conferred lower risk of death/recurrence.<sup>123</sup>

## Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is characterized 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, unexplained by abnormal loading conditions.<sup>124,125</sup> In most patients, HCM is caused by genetic mutations in the sarcomere genes (e.g. beta-myosin heavy chain, myosin-binding protein C, cardiac troponins, alpha cardiac actin, myosin light chain). Pathogenic variants in beta-myosin heavy chain and myosin binding protein C are the most common causative mutations, responsible for ~40–50% of all cases of HCM.<sup>126</sup> Genotype–phenotype associations in HCM are not thoroughly characterized and depend on variability in gene penetrance and expressivity, and modification by environmental factors.<sup>127</sup> The presence of beta-myosin heavy chain mutation was associated with earlier disease onset in a paediatric population,<sup>128</sup> and several studies suggested a higher risk of all-cause mortality, development of HF, AF and SCD in pathogenic gene carriers, highlighting the significance of genetic testing.<sup>129,130</sup> Most patients have asymmetric septal hypertrophy and LVOT obstruction (40–70%), defined as intracavitary gradient  $>30$  mmHg at rest or during exercise. LVOT obstruction is

the major cause of symptoms and progression towards HF and poor outcomes, whilst patients with non-obstructive HCM and preserved LV function have the more benign clinical course.<sup>125,131</sup> Symptoms are usually caused by diastolic dysfunction and/or dynamic LVOT obstruction, however, the disease can progress towards LV systolic dysfunction which portends poor prognosis.<sup>132</sup> Patients with HCM also have an increased risk of AF and thromboembolism, ventricular arrhythmias and SCD. The treatment focuses on the relief of symptoms with medical therapy and/or septal reduction therapies, prevention of SCD, stroke prevention and treatment of AF.

## Traditional medical therapy

Medical therapy is the mainstay treatment of symptomatic patients (New York Heart Association [NYHA] class  $\geq$ II) with LVOT obstruction.<sup>124,133</sup> It is directed towards improving symptoms of dynamic LVOT obstruction and does not influence the natural course of HCM. The first-line medical therapy includes non-vasodilating beta-blockers, which could be combined with low-dose diuretics to relieve congestion. If beta-blockers are ineffective, or not tolerated, non-dihydropyridine calcium channel blockers (verapamil or diltiazem) could be used, or disopyramide could be added.<sup>134</sup> A discontinuation of drugs that may aggravate LVOT obstruction including vasodilators, positive inotropic agents, and high-dose diuretics, is advised. The same principles apply to patients with midventricular obstruction, and for symptomatic patients with non-obstructive HCM and preserved LV systolic function.<sup>133,135</sup> In asymptomatic patients with non-obstructive HCM, the benefit of beta-blockers or non-dihydropyridine calcium channel blockers has not confirmed.<sup>124,133</sup>

## Therapy of heart failure and left ventricular systolic dysfunction

In a large cohort of patients from high-volume specialized centres, LV systolic dysfunction (i.e. LVEF  $<$ 50%) occurred in  $\sim$ 8% of patients with HCM over a 15-year follow-up and was associated with adverse outcomes (death/heart transplantation/assist device implantation occurred in 35% or patients with LV systolic dysfunction after a median time of 8.4 years).<sup>132</sup> In a recent, phase 2, placebo-controlled trial of young patients (mean age 23 years) with sarcomeric HCM, but without significant LV hypertrophy or symptoms, early institution of valsartan compared to placebo was associated with an improvement in a composite score reflecting cardiac structure and function over 2 years (i.e. LV wall thickness, mass, and volumes; left atrial volume; tissue Doppler diastolic and systolic velocities; and serum levels of troponin and natriuretic peptides).<sup>136</sup> These results suggest a possibility to modify disease progression in early-stage HCM and prevent further development of complications, such as HF.

In patients who develop LV systolic dysfunction, guideline-directed medical and device therapies for HFrEF should be introduced and negative inotropic agents (e.g. verapamil, disopyramide) should be discontinued. It is prudent to perform diagnostic assessment of the potential contributors to the development

of HF, such as significant valvular or coronary heart disease. A minority of patients may progress towards advanced HF, in whom heart transplantation or durable MCS should be considered in accordance with current guideline recommendations. According to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), only a minority of patients with HCM receive durable MCS, and most of them exhibit transition towards the features of the dilated phenotype.<sup>137</sup> The prognosis after assist device implantation is comparable to patients with DCM except for individuals with very small LV cavities who have inferior survival.<sup>137</sup>

## Septal reduction therapy

Septal reduction therapy, performed in specialized centres, is indicated in patients with LVOT obstruction and severe symptoms refractory to medical therapy.<sup>124,133</sup> There are two modes of septal reduction therapy: surgical myectomy and alcohol septal ablation. Surgical myectomy, performed in experienced centres, is considered the gold standard for the resolution of LVOT obstruction.<sup>138</sup> There are numerous variants of the original technique, and the intervention should be tailored to the individual patient and performed by an operator with specific expertise.<sup>139</sup> It is the preferred option in individuals with associated conditions requiring surgical treatment. Alcohol septal ablation is indicated in patients in whom surgical myectomy is contraindicated or associated with unacceptably high risk due to serious comorbidities or advanced age.<sup>133</sup> Long-term mortality rates, including (aborted) SCD, are similarly low after myectomy and alcohol septal ablation ( $\sim$ 1.5% per year).<sup>140</sup> However, patients treated with alcohol septal ablation have a higher rate of permanent pacemaker implantation (10% vs. 4.4%) and higher need for reintervention (7.7% vs. 1.5%) compared to those treated with myectomy.<sup>140</sup>

## Novel pharmacological treatment options for left ventricular outflow tract obstruction

Mavacamten is a first-in-class allosteric myosin inhibitor which selectively reduces myocardial contractility by increasing the proportion on myosin heads in the super relaxed state, which is abnormally low in sarcomeric HCM.<sup>141</sup> In the PIONEER-HCM phase 2 study, mavacamten was shown to reduce LVOT obstruction and improve exercise capacity and symptoms in patients with obstructive HCM.<sup>142</sup> Further evidence was derived from the EXPLORER-HCM, a multicentre, phase 3, double-blind study in which the efficacy and safety of mavacamten was assessed in 251 adult patients with symptomatic obstructive HCM (NYHA class II–III,  $>$ 90% on background treatment with beta-blockers or non-dihydropyridine calcium channel blockers).<sup>143</sup> Patients were randomized to receive oral mavacamten or placebo for 30 weeks. The primary endpoint, defined as either (i) an increase in peak oxygen consumption  $\geq$ 1.5 ml/kg/min and reduction of at least one NYHA class compared to baseline; or (ii) an improvement in peak oxygen consumption  $\geq$ 3.0 ml/kg/min with no worsening of

NYHA class, was achieved in 37% of patients in the mavacamten arm compared to 17% in the placebo arm (difference +19.4%,  $p=0.0005$ ). There was a consistent benefit of mavacamten versus placebo across all secondary endpoints, including peak oxygen consumption (+1.4 ml/kg/min,  $p=0.0006$ ), NYHA class ( $\geq 1$  class improvement in 65% vs. 31%), relief of post-exercise LV outflow gradient ( $-36$  mmHg,  $p<0.0001$ ) and symptomatic status and quality of life. Overall, mavacamten was well tolerated, with a safety profile comparable to placebo. A transient decrease in LVEF to  $<50\%$ , observed in seven patients (6%), resolved following treatment discontinuation. Patients on mavacamten showed a promising reduction in LV mass, left atrial volume index, and LV filling pressures,<sup>144</sup> which paralleled a favourable reduction in natriuretic peptide levels.<sup>143</sup> Finally, a recent interim analysis based on the EXPLORER-HCM long-term extension study showed sustained benefit and safety of mavacamten beyond 1 year.<sup>145</sup> The results of the EXPLORER-HCM trial are supported by the VALOR-HCM phase 3 study, which demonstrated that treatment with mavacamten compared with placebo for 16 weeks, significantly improved symptoms and reduced eligibility for septal reduction therapy (17.9% vs. 76.8%,  $p<0.0001$ ) among symptomatic patients with obstructive HCM who were considered for septal reduction.<sup>146</sup>

EXPLORER-HCM and VALOR-HCM are landmark studies opening the field of obstructive HCM to the possibility of a disease-specific treatment targeting the core mechanisms of the disease. The optimal positioning of mavacamten in the obstructive HCM treatment algorithm is yet unresolved. Due to the high starting price and caution required with the first-in-class negative inotrope, the drug will plausibly be indicated in patients with obstructive HCM who fail to respond to traditional drug regimens but are not immediate candidates or are not motivated for surgical or interventional options.<sup>147</sup> Further studies are needed to assess the long-term efficacy, tolerability and economic sustainability of mavacamten in obstructive HCM, as well as its potential impact on long-term outcomes.

## Prevention of sudden cardiac death

The rate of SCD in adult patients with HCM ranges from 0.5% to 2% per year and the ESC guidelines for the management of HCM recommend the use of a validated, disease-specific prediction tool (HCM Risk-SCD: <https://doc2do.com/hcm/webHCM.html>) to calculate a 5-year risk estimate for SCD and assess the indication for primary ICD implantation (Table 3).<sup>124</sup> A recent HFA position paper indicates that additional risk makers such as extensive myocardial fibrosis (as assessed by late gadolinium enhancement [LGE] on cardiac magnetic CMR imaging), LV apical aneurysms or deteriorating LVEF may be helpful in borderline or uncertain cases.<sup>2</sup> This is supported by the 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD.<sup>148</sup> In patients  $<16$  years of age, use of the HCM Risk-Kids model is advised.<sup>149</sup>

The 2020 American Heart Association/American College of Cardiology (AHA/ACC) guidelines on the management of HCM recommend non-invasive assessment of individual patient risk of

SCD and assessment of the indication for primary ICD implantation (Table 3).<sup>133</sup> In addition to clinical assessment, it is suggested to use CMR imaging to assess maximum LV wall thickness, LVEF, LV apical aneurysms, and the extent of myocardial fibrosis (by LGE on CMR).

In patients with recurrent ICD activations due to sustained VT, antiarrhythmic drugs, individualized to patients' age, arrhythmic substrate and comorbidities, represent the first-choice treatment. Despite the unfavourable profile of (extra)cardiac side effects, amiodarone (combined with beta-blockers) seems to be the most effective.<sup>150</sup> Although limited, data on catheter ablation of ventricular arrhythmias suggest that this may be a viable alternative for patients with VT refractory to pharmacological treatment.<sup>151,152</sup>

## Management of atrial fibrillation

According to a systematic review of 7381 patients, the prevalence and annual incidence of AF in HCM were 22.4% and 3.7%, respectively, whilst a history of thromboembolic complications was present in 20.1%.<sup>153</sup> Current guidelines recommend lifelong use of oral anticoagulant medications (preferably with direct oral anticoagulants) for stroke prevention in patients with HCM and clinically documented AF regardless of the type (paroxysmal/persistent) or the the CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score.<sup>124,133,154</sup> Subclinical AF episodes detected by cardiac implantable electronic devices are frequent in patients with HCM (annual rate 7.5%), and some data suggest their association with adverse prognosis.<sup>17,155</sup> The AHA/ACC guidelines recommend that in patients with subclinical AF episodes, lasting  $>5$  min but  $<24$  h, anticoagulation may be considered.<sup>133,156</sup> With respect to the treatment of acute AF, rate control with beta-blockers or non-dihydropyridine calcium channel blockers could be the first-line option in haemodynamically stable patients, whereas immediate cardioversion may be necessary for haemodynamically compromised individuals. Long-term, however, rhythm control strategy is preferable for symptom control, and catheter ablation can be considered if antiarrhythmic drugs (e.g. amiodarone, sotalol) are ineffective or contraindicated. However, AF ablation seems to be less successful in patients with HCM compared to the general population, with a higher risk of relapse, and more frequent requirement for repeat procedures and postoperative need for antiarrhythmic drugs.<sup>157,158</sup> The more favourable outcome was observed in patients with less advanced arrhythmic substrate, including those with less dilated atria and recent-onset, paroxysmal AF.<sup>157</sup>

## Restrictive cardiomyopathy

Restrictive cardiomyopathy is defined by the presence of restrictive physiology (i.e. rapid rise in ventricular pressure with only small increases in filling volume) of one or both ventricles caused by increased ventricular wall stiffness.<sup>125</sup> RCM is characterized by a significant heterogeneity in the underlying aetiologies and phenotypic expression that imposes a challenge to the diagnosis and therapeutic approach. In some instances, restrictive phenotype may be pronounced only early in the disease course with

**Table 3 Sudden cardiac death risk assessment and guideline recommendations for primary implantable cardioverter-defibrillator implantation in hypertrophic cardiomyopathy**

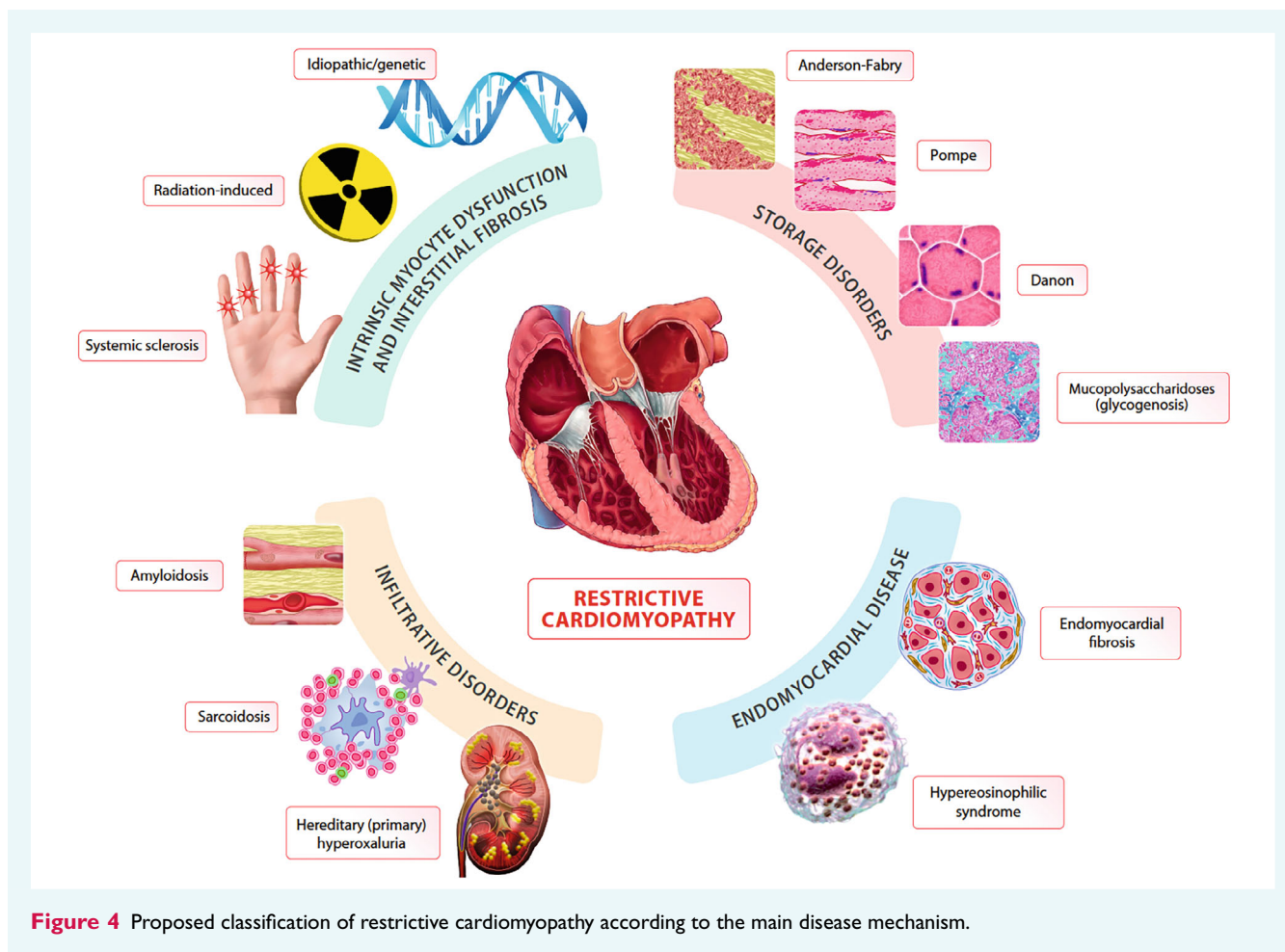
<p>2014 European Society of Cardiology guidelines for the management of hypertrophic cardiomyopathy</p> <p>Assessment of an estimated 5-year risk of SCD, based on HCM Risk-SCD score (components)</p> <ul style="list-style-type: none"> <li>• Age</li> <li>• Maximum LV wall thickness</li> <li>• Maximum LVOT gradient</li> <li>• LA diameter</li> <li>• Family history of SCD</li> <li>• Personal history of unexplained syncope</li> <li>• Presence of non-sustained ventricular tachycardia</li> </ul>	<p>Recommendations for ICD implantation</p> <p>ICD should be considered in patients with an estimated 5-year risk <math>\geq 6\%</math></p> <p>ICD may be considered in patients with an estimated 5-year risk <math>\geq 4\%</math> and <math>&lt; 6\%</math></p>
<p>2020 American Heart Association/American College of Cardiology guidelines for the management of hypertrophic cardiomyopathy</p> <p>Assessment of individual patient risk of SCD</p> <ul style="list-style-type: none"> <li>• Personal history of SCD/sustained ventricular arrhythmia</li> <li>• Family history of SCD</li> <li>• Maximum LV wall thickness</li> <li>• LV apical aneurysm</li> <li>• Presence of non-sustained ventricular tachycardia</li> </ul>	<p>Recommendations for ICD implantation</p> <p>ICD should be considered in adults with <math>\geq 1</math> major risk factors including</p> <ol style="list-style-type: none"> <li>(1) SCD in <math>\geq 1</math> first-degree or close relatives <math>\leq 50</math> years of age</li> <li>(2) LV hypertrophy <math>\geq 30</math> mm in any LV wall segment</li> <li>(3) <math>\geq 1</math> recent episodes of unexplained syncope</li> <li>(4) LV apical aneurysm</li> <li>(5) LV systolic dysfunction (LVEF <math>&lt; 50\%</math>)</li> </ol>
<p>2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD</p> <ul style="list-style-type: none"> <li>• Assessment of an estimated 5-year risk of SCD, based on HCM Risk-SCD score at baseline evaluation, and at 1–3-year intervals</li> <li>• Genetic testing</li> <li>• Cardiac magnetic resonance</li> <li>• Exercise stress test</li> </ul>	<p>ICD should be considered in patients aged <math>\geq 16</math> years with an estimated 5-year risk of SCD <math>\geq 6\%</math></p> <p>ICD should be considered in HCM patients aged <math>\geq 16</math> years and an intermediate 5-year risk of SCD <math>\geq 4\%</math> to <math>&lt; 6\%</math>, and with any of the following:</p> <ol style="list-style-type: none"> <li>(a) Significant LGE at CMR (usually <math>\geq 15\%</math> of LV mass)</li> <li>(b) LVEF <math>&lt; 50\%</math></li> <li>(c) Abnormal blood pressure response during exercise test</li> <li>(d) LV apical aneurysm</li> <li>(e) Presence of sarcomeric pathogenic mutation</li> </ol> <p>ICD implantation may be considered in HCM patients aged <math>\geq 16</math> years and an intermediate 5-year risk of SCD of <math>\geq 4\%</math> to <math>&lt; 6\%</math> as well as in patients with a low estimated 5-year risk of SCD (<math>&lt; 4\%</math>) and with any of the following:</p> <ol style="list-style-type: none"> <li>(a) Significant LGE at CMR (usually <math>\geq 15\%</math> of LV mass);</li> <li>(b) LVEF <math>&lt; 50\%</math></li> <li>(c) Abnormal blood pressure response during exercise test</li> <li>(d) LV apical aneurysm</li> <li>(e) Presence of sarcomeric pathogenic mutation</li> </ol>

CMR, cardiac magnetic resonance; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; SCD, sudden cardiac death.

later transformation into the DCM phenotype with reduced LVEF (e.g. iron overload and sarcoidosis). Also, a significant overlap may be found between the hypertrophic and restrictive phenotype (e.g. in patients with storage disorders). The disorders presenting as RCM can be classified according to the four main disease mechanisms also pertaining to the therapeutic approach: (1) intrinsic myocardial dysfunction or interstitial fibrosis, (2) interstitial infiltration, (3) cardiomyocyte accumulation of storage material, and (4) endomyocardial fibrosis (Figure 4). The treatment of patients with RCM should encompass general treatment of HF and prevention of complications, as well as targeted therapeutic options based on specific aetiologies.<sup>159</sup>

## General treatment principles in restrictive cardiomyopathy

Regardless of the aetiology, patients with RCM usually present with HF and are poorly responsive or intolerant to standard medications. The restrictive physiology in RCM mandates that the treatment of HF be modified compared to standard care. In patients with pronounced restrictive filling, heart rate lowering medications (e.g. beta-blockers) should be avoided or cautiously used due to the risk of haemodynamic deterioration.<sup>2</sup> Likewise, patients with RCM tend to have low-to-normal blood pressure and drugs acting on the renin–angiotensin–aldosterone system are



**Figure 4** Proposed classification of restrictive cardiomyopathy according to the main disease mechanism.

often poorly tolerated due to hypotension. Although loop diuretics are the mainstay therapy to relieve congestion, care should be taken to avoid over diuresis, because even mild hypovolaemia may lead to hypotension and hypoperfusion.<sup>2</sup>

Restrictive cardiomyopathy is frequently associated with cardiac arrhythmias, conduction abnormalities, and a greater risk of SCD. Both bradyarrhythmias and AF are poorly tolerated because of impaired ventricular filling due to low heart rate in the former and loss of atrial contribution in the latter. Therefore, pacemaker implantation is indicated in patients with significant conduction abnormalities, while sinus rhythm maintenance should be preferred over rate control in AF. In addition, patients with RCM are at increased risk of thromboembolic complications, and the use of oral anticoagulant medications (either vitamin K antagonists or direct oral anticoagulants) is indicated in patients with AF, cardiac thrombus, or a history of systemic embolization. Patients with cardiac amyloidosis and AF are at a particularly high risk of thromboembolism, and atrial thrombus formation has been documented even in patients with low CHA<sub>2</sub>DS<sub>2</sub>-VASc score.<sup>160,161</sup> Risk stratification and indications for ICD implantation in primary prevention in RCM are currently unresolved. Current guidelines suggest that ICD may be considered in patients with AL or transthyretin (ATTR) cardiac amyloidosis and haemodynamically not tolerated VT.<sup>148</sup>

## Aetiology-based, targeted therapeutic options

### Intrinsic myocyte dysfunction and interstitial fibrosis

Idiopathic RCM (including primary and genetic forms) is a rare group of disorders in which increased myocardial wall stiffness occurs because of myofilament oversensitivity to calcium, increased deposition of collagen type III, and intracellular aggregates of the mutant proteins (desmin or filamin C).<sup>162</sup> Most patients present with severe HF in childhood with frequently associated conduction abnormalities (particularly in patients with desminopathies) and myopathy of distal extremities.<sup>163</sup>

Radiation-associated RCM develops as a consequence of radiation exposure for the treatment of malignant disorders, usually with a latent period of 5 to 10 years.<sup>164</sup> It occurs as a consequence of radiation-induced inflammation, microvascular damage, and myocardial capillary rarefaction, which lead to ischaemia, necrosis and diffuse replacement fibrosis.<sup>165</sup>

Currently, there are no specific therapeutic options available for idiopathic RCM or radiation-associated RCM. The treatment should follow the general principles of HF management in RCM, and in selected patients with advanced HF, heart transplantation should be considered.

### Infiltrative disorders

The most important representative of the infiltrative type of RCM is cardiac amyloidosis. Over 95% of cases are caused by the deposition either of immunoglobulin light chains in plasma cell dyscrasias (AL amyloidosis), or transthyretin fibrils (ATTR amyloidosis).<sup>166,167</sup>

There are two subtypes of ATTR amyloidosis, namely, ATTR-m, which occurs due genetically mediated transthyretin tetramer instability (very infrequent in Europe), and ATTR-wt caused by age-related transthyretin overproduction (more prevalent). In addition to cardiac infiltration, myocardial damage in ATTR amyloidosis also occurs due to a direct toxic effect on cardiac cells. Cardiac amyloidosis is characterized by HF with preserved/mildly reduced ejection fraction and is frequently associated with AF, conduction abnormalities, intracardiac thrombus formation (particularly in AL cardiac amyloidosis), and, in some cases, with aortic stenosis. Patients with cardiac amyloidosis are often resistant to conventional HF treatment, however with a timely diagnosis, administration of targeted treatments in both types of cardiac amyloidosis can improve outcomes.

For patients with AL amyloidosis, a multidisciplinary collaboration between cardiologists and haematologists is required in delivering and monitoring available treatments, which include chemotherapy and/or administration of high-dose melphalan followed by autologous stem cell transplantation.<sup>167</sup>

For patients with ATTR amyloidosis, there are currently two targeted treatment strategies, which have been proven effective in phase 3 clinical trials: (1) stabilization of transthyretin precursor protein with the use of tafamidis, and (2) knocking down production of the precursor protein either through gene silencing techniques with small interfering RNAs (patisiran and vutrisiran), antisense oligonucleotides (inotersen, AKCEA-TTRLRx/ION682884)<sup>168,169</sup> or with targeted *in vivo* gene editing technique (NTLA-2001- CRISPR-Cas9 technology).<sup>170</sup> It is noteworthy that these treatments target the precursor protein and not the already formed and accumulated amyloid in the heart.

In the phase 3 ATTR-ACT randomized trial, treatment with tafamidis was associated with a 30% lower risk of all-cause mortality and cardiovascular hospitalizations and a lower rate of the decline in functional capacity and quality of life compared with placebo.<sup>171</sup> Long-term extension of the pivotal ATTR-ACT trial demonstrated that patients initially treated with tafamidis had substantially improved survival compared to those treated with placebo after a median follow-up of ~5 years.<sup>172</sup> Tafamidis is currently the only approved treatment for patients with NYHA class I to II and cardiac amyloidosis, either ATTR-wt, or ATTR-m without polyneuropathy.<sup>173–177</sup> The ESC guidelines suggest the use of tafamidis in patients with NYHA class I or II, without explicitly addressing the issue of patients with NYHA class III, who showed less convincing results in the ATTR-ACT trial in terms of hospitalizations.<sup>171,172</sup> In cases with a mixed neurological and cardiac phenotype, patisiran and inotersen can be considered.<sup>174</sup> Monitoring of therapy with these drugs still represents an area of uncertainty. In particular, there is a lack of validated criteria to identify responders and probable non-responders at an early stage, in time to be able to suspend useless treatments and eventually

switch to (or combine with) other drugs. Heart and liver transplantation can be considered in some patients with advanced cardiac amyloidosis of the ATTR-m type, without severe neuropathy.<sup>178</sup>

Cardiac sarcoidosis can also be the cause of RCM. Cardiac involvement occurs in at least 20% of patients with sarcoidosis,<sup>179</sup> but the prevalence may be underestimated because of a subclinical/silent course. Overt cardiac sarcoidosis is present in 2–5% of patients, including conduction abnormalities (right bundle branch block, high-degree atrioventricular block, His–Purkinje system conduction block), ventricular and supraventricular arrhythmias (predominantly AF), and the development of a cardiomyopathy.<sup>180</sup> The cardiomyopathy usually takes the RCM phenotype early in the disease course, with subsequent development of LV systolic dysfunction and the DCM phenotype.<sup>159</sup>

The treatment of cardiac sarcoidosis encompasses the treatment of inflammation and its consequences (e.g. conduction abnormalities and prevention of SCD).<sup>181</sup> The European Respiratory Society guidelines suggest the use of glucocorticoids (with or without other immunosuppressive agents) in patients with clinically evident cardiac sarcoidosis to improve the prognosis.<sup>182</sup> The recommendations are based mainly on retrospective observational studies, whilst the optimal duration of therapy, dosing and the selection of drug regimen remain to be determined.<sup>182</sup> However, the bulk of available data suggests beneficial effects of immunosuppression, primarily with glucocorticoids (i.e. resolution of the heart block and improvement in LVEF), albeit with a caveat of the long-term risk of toxicity.<sup>183–185</sup> The treatment with corticosteroids appears to be particularly effective if administered early, before the development of LV systolic dysfunction.<sup>183</sup> Whether the use of another immunosuppressant in addition to low-dose prednisone can be safe and effective is currently under prospective investigation (CHASM CS-RCT, NCT03593759).<sup>186</sup>

Cardiac sarcoidosis is associated with an increased risk of SCD, particularly among patients with overt HF.<sup>183,187</sup> Current ESC guidelines recommend primary ICD implantation in patients with LVEF  $\leq$ 35% and in those with LVEF >35% and significant LGE on CMR following resolution of inflammation, without specifying the extent of LGE that imposes a significant risk.<sup>148</sup> Primary ICD is also recommended in patients with LVEF 35–50% and positive programmed electrical stimulation.<sup>148</sup> Whether these approaches capture most patients at risk remains unclear, given that some data suggest that patients without guideline indications for an ICD may have a significant risk of SCD (i.e. 5% SCD incidence, over 5-year follow-up).<sup>188</sup>

### Accumulation of storage material within the cardiomyocytes

A particular form of RCM is caused by intracellular accumulation of metabolites causing myocardial damage. It is mainly caused by inborn errors of metabolism except for some types of iron overload. Typical examples of genetic disorders leading to myocardial storage include lysosomal storage diseases (Anderson–Fabry disease, mucopolysaccharidoses), and glycogen storage disorders (Danon disease, Pompe disease, Cori disease, PRKAG2 cardiomyopathy).<sup>189</sup> Cardiomyopathies caused by inborn errors of

metabolism often have an overlapping phenotype between HCM and RCM, although occasionally can present as DCM. Clinical manifestations also include electrophysiological changes (conduction abnormalities) and/or valvular involvement.

Targeted therapies have been developed for several inborn errors of metabolism. In patients with Anderson–Fabry disease, the deficiency of alfa-galactosidase A can be partly corrected by enzyme-replacement therapy, namely agalsidase alfa or beta, leading to improved prognosis. At the cardiac level, treatment is particularly effective if started before the development of irreversible fibrotic changes. As an alternative, the pharmacological chaperone migalastat has shown stabilization of the clinical course of the disease and reduction in cardiac mass in Anderson–Fabry patients. Such treatment is approved in patients with amenable mutations, in whom the synthesis of a functional but misfolded enzyme is preserved.<sup>190,191</sup> Novel enzyme replacements, substrate reduction therapies, and genetic treatments are being developed and tested in clinical trials.<sup>118,192,193</sup>

Similarly, cardiac improvements have been reported in infantile type of Pompe disease (a glycogen storage disorder caused by acid alpha glucosidase deficiency) with the use of enzyme replacement therapy with alglucosidase alfa, and several other options are currently under development.<sup>194,195</sup>

Mucopolysaccharidoses represent a group of lysosomal storage diseases caused by genetically mediated absence of functional enzymes that degrade glycosaminoglycans. Current therapeutic strategies differ according to the type of mucopolysaccharidoses and the mechanism of cardiac involvement, and include: enzyme replacement therapy (e.g. laronidase, idursulfase, elosulfase alfa, galsulfase, vestronidase alfa), valvular surgery, or hematopoietic stem cell transplantation.<sup>196</sup>

Iron overload cardiomyopathy can be caused by hereditary hemochromatosis or secondary due to iron overload caused by repeated blood transfusions in patients with ineffective erythropoiesis due to haemoglobinopathies (e.g. thalassaemia, sickle cell anaemia). In either case, the iron binding capacity of transferrin is exceeded, and deposition of iron occurs in various organs (e.g. liver, endocrine glands, skin, joints) including the heart, where it causes impaired cardiomyocyte function, conduction abnormalities, and a propensity for supraventricular (i.e. AF) and ventricular arrhythmias and SCD. Iron overload cardiomyopathy usually begins as the RCM type, which later evolves into the DCM phenotype. Serum ferritin levels >300 ng/ml in males or >200 ng/ml in females and transferrin saturation >45% should prompt further diagnostic assessment.<sup>197</sup> T2\*-weighted CMR can be used to quantify myocardial iron load, which inversely correlates with LVEF and predicts the development of HF.<sup>198</sup> Therapeutic phlebotomy is the mainstay treatment in non-anaemic and haemodynamically stable patients as it can prevent or reverse liver fibrosis, cardiac dysfunction and skin hyperpigmentation, whilst arthropathy and pancreatic endocrine dysfunction show variable response to this treatment.<sup>199</sup> It consists of removing 400–500 ml of whole blood (200–250 mg of iron) every 1–2 weeks (depending on patient tolerance), until the goal of serum ferritin of <50 ng/ml is achieved (haemoglobin should be kept >11 g/dl), and to maintain the serum ferritin level at 50–100 ng/ml thereafter by periodic phlebotomies (usually 3–4

times a year).<sup>199</sup> Iron chelation therapies (parenteral deferoxamine, and oral deferiprone and deferasirox) can be used as an adjunctive or alternative therapy for patients in whom phlebotomy is ineffective or contraindicated, such as those with severe HF or anaemia.<sup>199</sup>

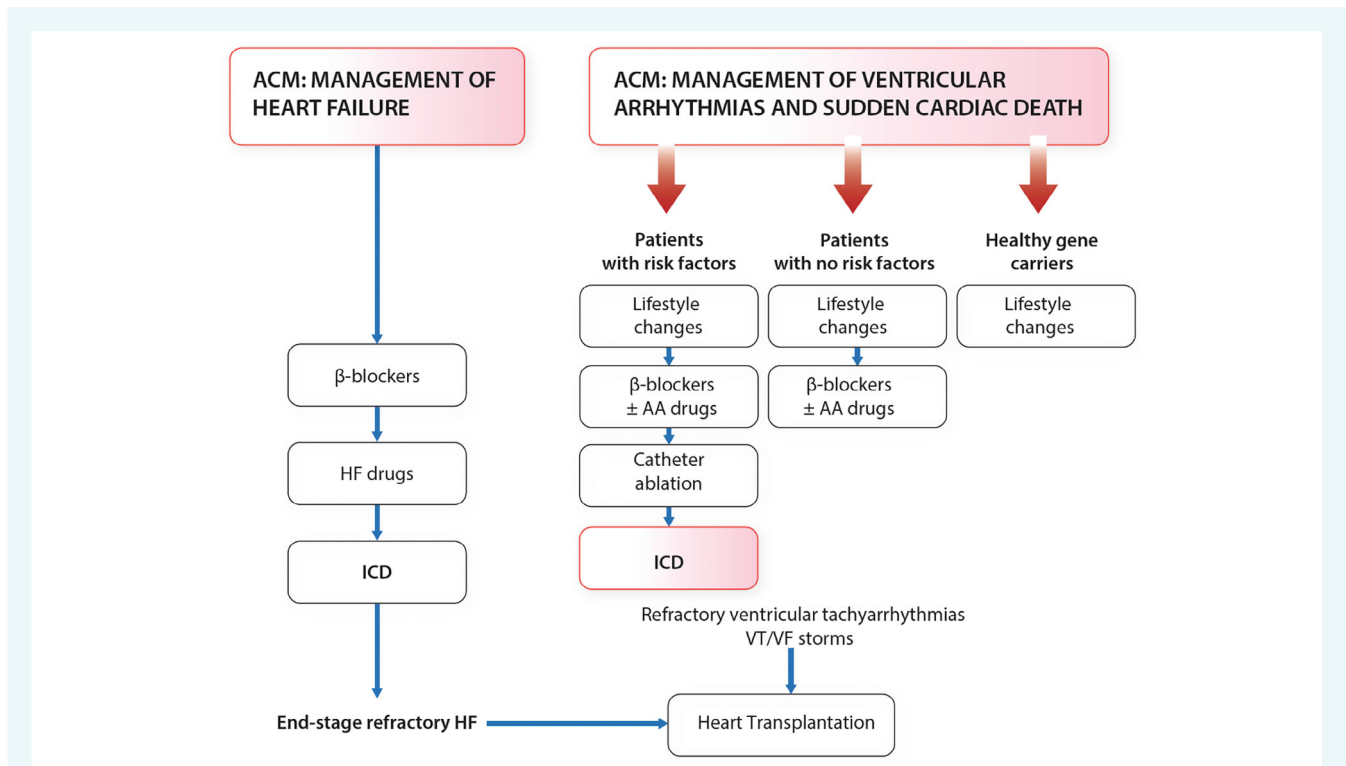
### Endomyocardial diseases

Restrictive cardiomyopathy in endomyocardial disorders (endomyocardial fibrosis and hypereosinophilic syndrome) is the result of the toxic damage of the endocardium produced by eosinophils. Endomyocardial fibrosis is most frequently encountered in sub-Saharan Africa, where it accounts for a substantial proportion (~20%) of all cases of HF, and it has been reported in some of the South American countries (Colombia, Brazil).<sup>100,200</sup> The natural course of endomyocardial fibrosis encompasses an active phase characterized by inflammation and eosinophilia that progresses to the chronic phase in which RCM develops.<sup>200</sup> In more than a half of patients, RCM involves both ventricles, while the rest is characterized by isolated right-sided or left-sided heart involvement. AF is present in >30% of patients, and thromboembolic complications are common.<sup>201</sup> Hypereosinophilic syndrome is a rare condition affecting young and middle-aged patients (20–50 years of age), caused by the release of highly active biological substances from eosinophils that damage the endocardium and myocardium. In the active phase of the hypereosinophilic syndrome, therapy with corticosteroids alone or in combination with hydroxyurea or interferon-1 was shown to produce improvement in cardiac function and symptoms.<sup>202</sup> Likewise, promising results were shown with imatinib.<sup>203</sup> Similar treatment options can be used in endomyocardial fibrosis, albeit without supporting evidence. In the chronic phase, cardiac surgery (endocardectomy with or without valve repair/replacement) can be considered in experienced centres,<sup>203</sup> whilst heart transplantation remains an option for patients with advanced HF.

## Arrhythmogenic (right ventricular) cardiomyopathy

Arrhythmogenic RV cardiomyopathy (ARVC) is a genetic heart muscle disease characterized by fibro-(fatty) myocardial replacement. This is the cause of structural and functional abnormalities and life-threatening ventricular arrhythmias responsible for SCD.<sup>204</sup> ARVC is the original phenotype characterized by predominant RV involvement; however, the increasing identification of biventricular and left-dominant (i.e. arrhythmogenic LV cardiomyopathy) forms has led to the use of the term arrhythmogenic cardiomyopathy.<sup>205–207</sup>

Arrhythmogenic RV cardiomyopathy is most frequently the consequence of genetic mutations in the genes encoding desmosomal proteins (plakophilin, desmoplakin, desmoglein, desmocollin and plakoglobin).<sup>208,209</sup> Desmosomal ARVC is characterized by impaired function of the desmosomes, with typical abnormalities in cell–cell adhesion, ‘slippage’ of the cardiomyocytes, and dysfunction of the intermediate filaments. This translates into cardiomyocyte loss, fibrofatty replacement and low-grade inflammation.<sup>204</sup>



**Figure 5** Pharmacologic and non-pharmacologic treatment of arrhythmogenic (right ventricular) cardiomyopathy. AA, antiarrhythmic; ACM, arrhythmogenic cardiomyopathy; HF, heart failure; ICD, implantable cardioverter-defibrillator; VF, ventricular fibrillation; VT, ventricular tachycardia.

Recently, several non-desmosomal mutations have been described in ARVC, for example mutations in transmembrane protein 43 (TMEM43), and PLN.<sup>209</sup> Interestingly, ARVC due to these mutations more often presents as biventricular cardiomyopathy, with severe structural heart disease and HF.<sup>204</sup> It has been demonstrated that myocardial fibrosis is more dominant in non-desmosomal ARVC.<sup>210</sup> Genetic testing can yield a positive result in up to 73% of probands and is one of the major criteria for the diagnosis.<sup>207,211</sup>

Individual risk assessment in patients with ARVC is based on the severity of ventricular arrhythmias and ventricular systolic dysfunction.<sup>212,213</sup> Patients with sustained VT or ventricular fibrillation have a high rate of recurrences. Unexplained syncope, non-sustained VT and dilation/dysfunction of the right ventricle, left ventricle, or both have been reported as major predictors of malignant arrhythmic events. Emerging risk predictors include moderate LV systolic dysfunction (LVEF <45%), the amount of myocardial fibrosis, and a series of scar-related electrical features such as T-wave inversion in the lateral leads, low QRS voltages and frequent/complex ventricular arrhythmias.<sup>214–216</sup>

Clinical management of ARVC involves the following: (1) prevention of SCD; (2) prevention of disease progression, and (3) treatment of HF which can occur over time (Figure 5).

Only the implantation of an ICD has been proven to successfully prevent SCD.<sup>204,205,212</sup> Data from observational studies have consistently shown that ICD therapy is effective and safe.<sup>217–219</sup> Risk assessment for ICD in primary prevention is challenging, given

the limited supporting evidence for risk factors for life-threatening ventricular arrhythmias. Unexplained (arrhythmic) syncope,<sup>218,220</sup> severe RV dysfunction (e.g. RV fractional area change <23%), male sex, T-wave inversion, QRS dispersion, non-sustained VT and LV dysfunction have been associated with an increased risk of life-threatening ventricular arrhythmias and SCD.<sup>221,222</sup> Risk assessment models have been proposed for predicting the risk of life-threatening ventricular arrhythmias (including SCD),<sup>223,224</sup> however their practical use requires further validation.<sup>225</sup> Recently, a risk prediction model to estimate the 5-year risk of incident ventricular arrhythmias in ARVC has been developed (ARVCrisk.com) and validated.<sup>224,226</sup> However, it seems to perform best in gene-positive ARVC (in particular, plakophilin mutations), suggesting that further refinement in the risk prediction tools is needed.<sup>227</sup> According to the 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD, indications for ICD implantation in secondary prevention in patients with ARVC, include ventricular fibrillation/haemodynamically not tolerated VT, and in primary prevention, arrhythmic syncope, significant RV dysfunction or moderate RV or LV dysfunction and either non-sustained VT or inducible sustained monomorphic VT.<sup>148</sup>

According to the same guidelines, beta-blockers may be considered in all patients with ARVC.<sup>148</sup> Avoidance of high-intensity sports activities is regarded important in the prevention of exercise-related malignant arrhythmias and disease progression.<sup>220</sup>

Antiarrhythmic drug therapy can ameliorate symptoms in patients with ventricular arrhythmias, although there is no proof that it protects against SCD.<sup>228</sup> Catheter ablation (often involving combined endocardial/epicardial ablation) is a viable option for patients with drug-resistant sustained monomorphic VT<sup>228</sup> (Figure 5). ICD implantation is the only treatment with a proven efficacy to prevent SCD.

Patients who developed HF should receive standard GDMT. In advanced stages of the disease, when advanced HF or refractory arrhythmias occur, heart transplantation should be considered.<sup>212</sup>

## Future directions

Several new and emerging therapeutic concepts, based on integration of traditional and aetiology-based treatment options, discussed in this review, offer the possibility for improved outcomes and better quality of life in specific aetiologies of cardiomyopathies. However, there is still much scope for future research. In genetic cardiomyopathies, expanding the knowledge on genotype–phenotype associations, maladaptive mechanisms (i.e. perturbations in contractile performance, neurohormonal regulation, cardiac metabolism and extracellular fibrosis) and extrinsic modulating factors can advance the ability to target key pathological pathways. In many of the acquired cardiomyopathies there is an unmet need to develop aetiology-based therapies, explore modulation of the perpetuating mechanisms (e.g. immunomodulation), and provide dedicated research into the efficacy and safety of the commonly applied standard treatments.

In DCM, several options are currently being investigated as therapeutic targets, such as danicamtiv, a novel cardiac myosin activator (NCT04572893) or several antifibrotic agents (e.g. antifibrotic microRNAs; HF-REVERT, NCT05350969). In HCM, the next-in-class myosin inhibitor, aficamten, is currently in phase 3 assessment in patients with obstructive HCM (SEQUOIA-HCM, NCT05186818). This agent has also shown promising results for functional and symptomatic improvement in a recent phase 2 trial of patients with non-obstructive HCM (REDWOOD-HCM, NCT04219826).<sup>229</sup> New strategies of management of ATTR amyloidosis focus on degradation/removal of amyloid fibrils,<sup>230</sup> and anti-seeding therapies (i.e. prevention of the formation of ‘amyloid seeds’ defined as small fibril fragments that induce aggregation, spread and deposition of amyloid fibrils).<sup>231</sup> One strategy of amyloid removal has already shown promising clinical results. In the phase 1 trial of the recombinant human antibody NI006 for the treatment of patients with ATTR cardiac amyloidosis and HF, the treatment with the antibody was safe and associated with evidence of ATTR removal from the heart.<sup>232</sup> In patients with the X-linked dominant cardioskeletal myopathy due to Danon disease (caused by LAMP2 mutation), a phase 1 trial of gene replacement therapy with an adeno-associated virus (AAV9:LAMP2B) demonstrated promising results in stabilization of serologic, echocardiographic and clinical parameters.<sup>233</sup> For patients with non-desmosomal ARVC (i.e. due to TMEM43 and PLN mutations), emerging treatment options explore inhibition of glycogen synthase kinase-3 $\beta$ , as well as gene editing and selective gene silencing for the improvement in cardiac

contractile and metabolic function and attenuation of cardiomyocyte death and fibro-fatty replacement.<sup>234,235</sup> These and other avenues of ongoing and future research are expected to further advance targeted treatments and hold the potential to improve patient management and outcomes in cardiomyopathies.

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