Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: February 29, 2024

Citation: Dodoo, S., N., et al., 2024. Novel Therapeutic strategies in the Management of Cardiomyopathies. Medical Research Archives, [online] 12(2). https://doi.org/10.18103/mra.v12i2.5081

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DOI: https://doi.org/10.18103/mra.v12i2.5081

ISSN: 2375-1924

RESEARCH ARTICLE

Novel Therapeutic strategies in the Management of Cardiomyopathies.

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ABSTRACT

Cardiomyopathies are a heterogeneous group of disorders that consist of primary dysfunction in cardiac contractility, myocardial relaxation, restrictive ventricular filling, and cardiac rhythm anomalies. This review discusses a limited number of cardiomyopathic disorders and the treatment modalities used to manage them.

Studies in elucidating pathophysiological mechanisms that underlie the development of these cardiomyopathies are leading to the development of novel therapeutic strategies. While some modalities have found expression in current practice recommendation guidelines, others are on the horizon.

While treatment strategies of cardiomyopathies are too large to discuss comprehensively in a single review, we present the current therapeutic landscape for cardiomyopathies. We also provide an update on the preclinical treatment options.

Introduction

Cardiomyopathies consist of a heterogeneous group of primary myocardial disorders with varied etiologies and pathophysiology, resulting in several clinical manifestations. Cardiomyopathies are significant causes of cardiovascular death and adverse outcomes[1]. Recent decades have witnessed notable strides in enhancing our current paradigm in the genetic bases and the underlying pathophysiological mechanisms critical in management approaches and effective risk stratification of cardiomyopathy. These advances have paved the way for the research and development of tailored therapeutic strategies focused on standard care and the prevention of sudden cardiac death. The focus of this review is to summarize contemporary and novel therapeutic strategies in the care of patients with dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, and arrhythmogenic cardiomyopathy.

Dilated Cardiomyopathy

Dilated Cardiomyopathy (DCM) is defined by progressive dilation and global contractile dysfunction of the left and right ventricle in the absence of coronary heart disease, primary valvular heart disease, or long-standing hypertension[1]. Commonly, however, patients with prior coronary artery disease with consequent left ventricular dilation and reduced ejection fraction are described as ischemic cardiomyopathy, while those with myocardial infarction/ ischemia are termed nonischemic cardiomyopathy. Due to the heterogeneous etiologies, managing DCM remains challenging for healthcare professionals, coupled with persisting uncertainties regarding its etiology and pathophysiology[2,3]. It is one of the leading causes of heart failure with reduced ejection fraction (HFrEF), often associated with sudden cardiac disease (SCD)[2]. Current management strategies have optimized guideline-directed medical and device therapies as American and European practice guideline documents recommended. Despite adherence to these strategies, a significant proportion of DCM patients succumb to progressive heart failure and premature death. Addressing these gaps in management assumes paramount importance in effectively treating the condition, facilitating prognostic stratification, and enabling the implementation of personalized therapeutic interventions.

Etiological Classification and Perspectives

The current European Society guidelines categorize DCM as either familial (genetic) or sporadic, with the former comprising about 30-50% of all cases[1]. Several risks and environmental factors have been suggested as precipitants of the sporadic form of DCM, including infections, alcohol, anticancer therapies, inflammatory/immune-mediated, peripartum, cardiac arrhythmias, substance abuse, nutritional deficiencies, and endocrine dysfunction (Figure 1).

The familial form of DCM is often denoted by the occurrence of otherwise unexplained DCM in two or more first-degree relatives, often with an autosomal dominance pattern of inheritance[5]. There are about 30 genes encoding for structural and nuclear proteins of cardiomyocytes implicated in DCM. Titin (TTN), beta and alpha myosin heavy chain

(MYH7, MYH6), and troponin T (TNNT2) mutations in the genes encoding for sarcomere proteins have been implicated. Other mutations include lamin A/C (LMNA), filamin(FLN), and ribonucleic acid binding motif 20 (RBM20) genes, phospholamban (PLN) encoding for nuclear envelope proteins[6,7] (Figure 2).

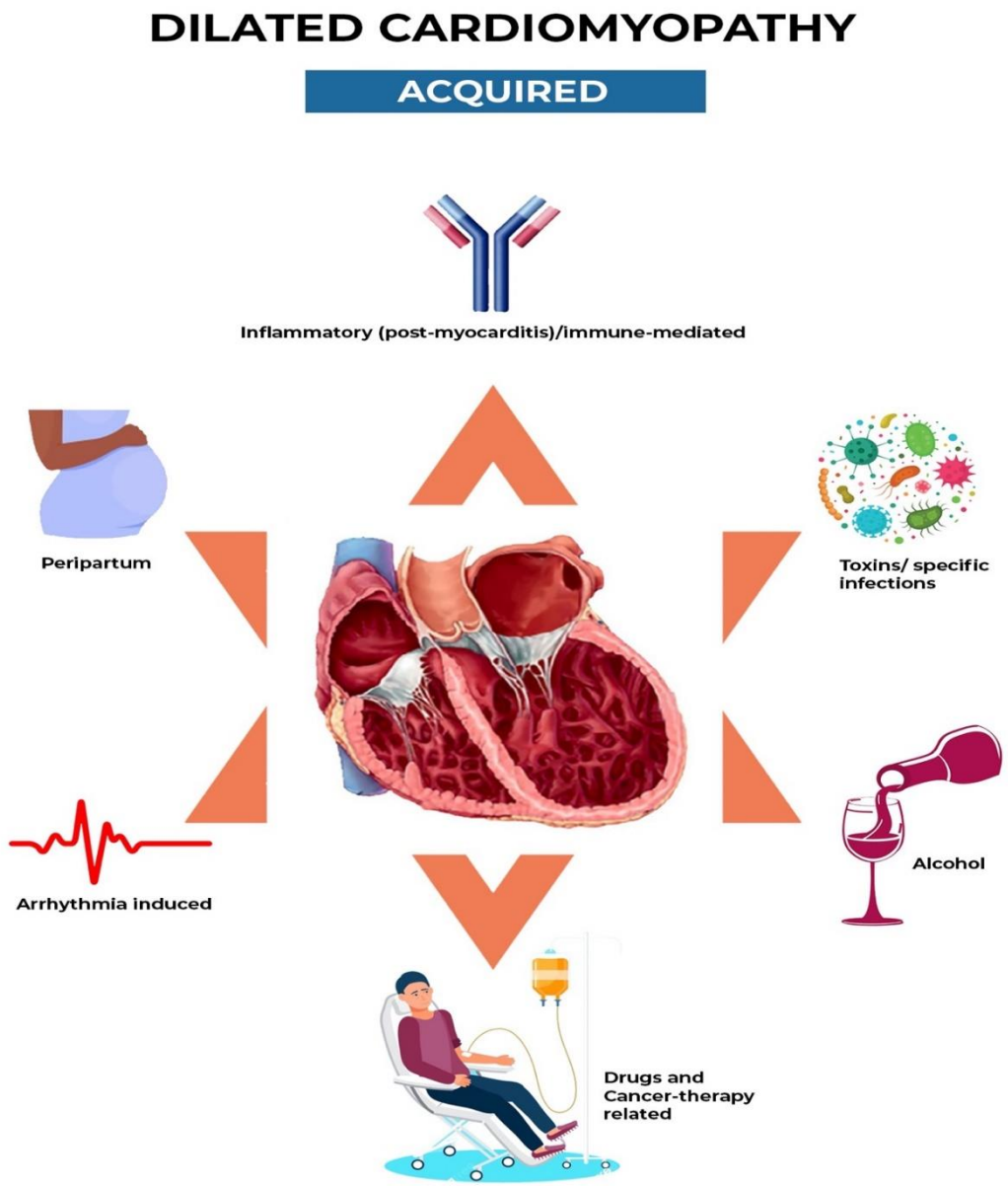

Figure 1 Some causes of acquired dilated cardiomyopathy.

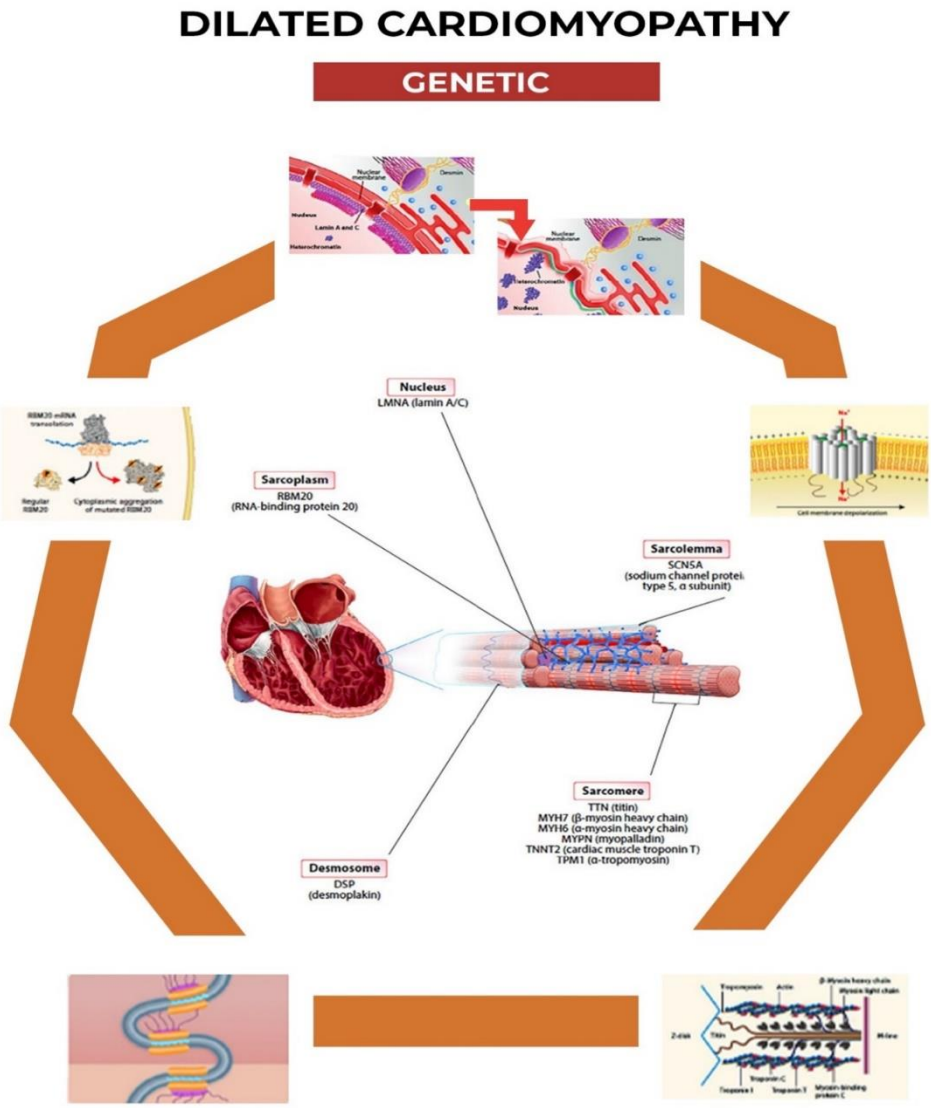

Figure 2 Common mutations underlying familial (genetic) Cardiomyopathy.

Contemporary Treatment Strategies:

Contemporary strategies for dilated cardiomyopathy are aimed at achieving reverse remodeling of left ventricular, recognizing DCM as a dynamic disease process rather than a discrete entity[1,2,4]. Guideline-directed medical therapy (GDMT) forms the cornerstone of preventing disease progression, encompassing the use of quadruple therapy, including angiotensin receptor neprilysin inhibitor(ARNI) or angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARB), heart failure specific beta-blockers, sodium-glucose cotransporter[2] inhibitors (sGLT2i) and mineralocorticoid receptor antagonists. It is imperative to acknowledge that discontinuing

these medications can reverse their beneficial effects[8]. Additionally, the implementation of interventions such as the implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) has demonstrated efficacy in reducing the incidence of sudden cardiac death and overall mortality, particularly in patients with significantly low ejection fraction (EF)[2]. Furthermore, administering iron transfusions to manage anemia has shown notable benefits in these patients[9]. The primary objective of the management approach is the early identification of underlying causes, comprehensive risk assessment, and the implementation of tailored, individualized management and surveillance for these patients.

Novel therapeutic approaches for dilated familial cardiomyopathy:

OPPORTUNITIES AND FUTURE DIRECTIONS
Recent successes in managing DCM include left ventricular reverse remodeling (LVRR), with studies indicating up to 21-37% recovery in cardiac function within the first six months of optimal treatment[10,11] and nearly complete recovery after 24 months[12]. CRT has gained favor due to its ability to induce LVRR by reducing microvascular resistance and enhancing coronary blood flow[13]. The combination of Valsartan and Sacubitril has shown promise in reducing mortality and hospitalization rates in patients with DCM and reduced HF by over 20%[14]. However, it is crucial to note that despite these therapeutic interventions, patients with DCM may experience worsening left ventricular function or arrhythmic events in the long term, emphasizing the necessity for individualized management and surveillance. DCM resulting from LMNA variants is associated with an adverse prognosis, necessitating more frequent surveillance and a lower threshold for primary prevention with ICD implantation[15]. Genetic testing is recommended for clinically unaffected relatives of individuals with genetically diagnosed DCM and P/LP variants, a process known as cascade/ predictive/pre-symptomatic testing[15]. Validated risk score developed for risk stratification and assessment of carriers of LMNA mutations have been developed and have found utility in the care of patients with dilated cardiomyopathy[16], predicting the absolute 5-year risk of malignant ventricular arrhythmias. It was derived from patient-level predictors including male gender, non-missense LMNA mutation, history of non-sustained ventricular tachycardia (NSVT), first-degree and high-grade atrioventricular block, and left ventricular dysfunction with ejection fraction <45%. This predictive score has improved the identification of high-risk LMNA cardiomyopathy patients who may benefit from primary ICD implantation[16].

The application of genomic profiling may improve the care of those with progressive familial cardiomyopathy, including patients with PLN and RBM20 mutations. This would allow for more intensive follow-up and prompt institution of advanced therapies, including durable mechanical circulatory support and heart transplantation.

Several genetic-guided therapies are under investigation, including clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease (CRISPR/Cas9)

gene editing, exon skipping, and gene replacement therapies[17,18,19]. Elucidation of the signal transduction pathways of the LMNA mutation leads to disturbances in the morphology of the nuclear envelope, including the deleterious effects of p38 mitogen-activated protein (MAP) kinase, extracellular signal-regulated kinase (ERK) 1 and 2, and c-Jun N-terminal kinase (JNK) and consequent adverse effects on cell proliferation, apoptosis, and differentiation, may offer opportunities for the application of CRISPR/Cas9 technology in the hope of finding a cure for Lamin A/C cardiomyopathy[17]. Investigations exploring the complex signaling pathways of truncating titin (TTN) mutations with increased non-sense mRNA decay, activation of the mammalian target of rapamycin (mTOR), increased oxidative stress, mitochondrial dysfunction, and defective autophagy may provide insights for the discovery of advanced therapies in the future[17,19].

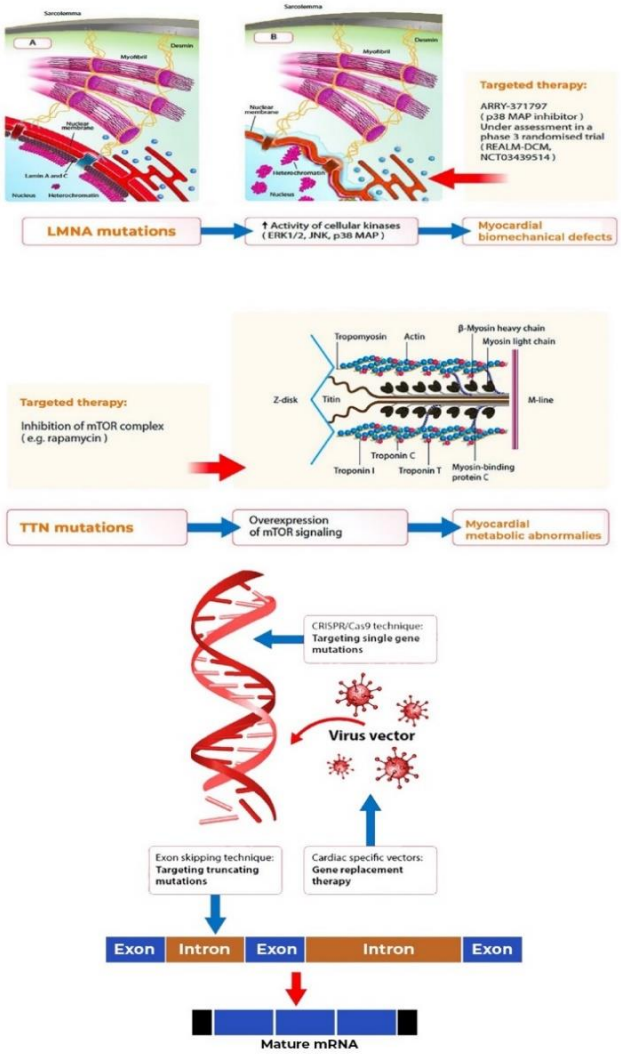

Figure 3 Genomic basis of Dilated Cardiomyopathy with the potential therapeutic targets. Abbreviations, LMNA lamin A/C, MAP mitogen-activated protein, ERK extracellular signal-regulated kinase (ERK), JNK c-Jun N-terminal kinase, TTN truncating titin, mTOR mammalian target of rapamycin, CRISPR/Cas9 clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease.

Exploring targeted therapies for acquired dilated cardiomyopathy

IMMUNE-MEDIATED CARDIOMYOPATHY/MYOCARDITIS

Dilated cardiomyopathy can occur following viral infection (e.g., Parvovirus B19, coxsackie B virus, HIV, SARS-CoV-2, etc.), exposure to drugs(immune checkpoint inhibitors, dobutamine, clozapine, allopurinol, etc.), rheumatologic disorders (systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, etc.), Vaccines(e.g., Influenza, smallpox, etc) and other infections (Lyme disease, trichinellosis)[20,21]. Inflammatory mechanisms with immune-mediated pathways are the underlying pathophysiology of this type of dilated cardiomyopathy and myocarditis. Clinical presentation is variable, including subclinical left ventricular dysfunction, acute myocarditis, conduction disturbances, arrhythmias, and more fulminant myocarditis with hemodynamic instability and cardiogenic shock.

A recent population-based study revealed that about 8% of patients with myocarditis have associated pathogenic mutations, including desmoplakin and TTN. It found that compared to those without gene mutation, these cohorts had worse clinical outcomes[22]. Endomyocardial biopsy may be considered in selected cases with fulminant myocarditis, with electrical and hemodynamic instability, especially those with cardiogenic shock, acute heart failure with severe LV dysfunction with ventricular tachycardia/ fibrillation or conduction abnormalities to help establish the histologic diagnosis and guide therapy[23]. Even though the European Society of Cardiology (ESC) guidelines discourage the routine use of immunosuppressive therapies in patients with myocarditis without clinical or histologic evidence of immune-mediated mechanisms, some anecdotal evidence of the clinical benefits of the use of immunosuppressive therapy, including a short course (3 days) high dose methylprednisolone 500mg to 1gm IV in patients with giant-cell myocarditis, eosinophilic myocarditis, immune checkpoint inhibitor- mediated myocarditis, have been reported[24,25,26,27].

Practice guidelines from the HFSA and ESC recommend quadruple foundational therapies, including angiotensin receptor neprilysin inhibitor(ARNI) or angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARB), heart failure specific beta-blockers, sodium-glucose cotransporter 2 inhibitors (sGLT2i) and mineralocorticoid receptor antagonists for at least six months and an echocardiographic assessment of left ventricular function[28,29]. Furthermore, exercise should be avoided for 3-6 months until recovery of left ventricular function and normalization of inflammatory markers and troponin because of the risk of sudden cardiac death (SCD). Before resumption of exercise, there should be no evidence of inflammation or scars on cardiac magnetic resonance (CMR) imaging or clinically significant cardiac rhythm disturbances on Holter monitoring and exercise tolerance testing[28].

PERIPARTUM CARDIOMYOPATHY

Peripartum Cardiomyopathy (PPCM), a subtype of DCM, is characterized by signs of heart failure and left ventricular ejection function (LVEF) <45% during the last month of pregnancy or within Six months of delivery in women without previous heart disease[30].

It has been suggested that about 15-20% of patients with PPCM have genetic mutations, including TTN, beta myosin heavy chain, myosin-binding protein C, or LMNA[31,32,33]. These gene mutations portend a poor prognosis, so genetic testing is recommended in patients with PPCM, especially those with a family history of cardiomyopathy[31]. Risk factors for the development of PPCM include multiparity, previous pre-eclampsia, advanced maternal age, and African American race. Anti-androgenic factors and oxidative stress late in pregnancy are prevailing pathophysiologic paradigms[31]. Left ventricular ejection fraction <30% and left ventricular end-diastolic dimension (LVEDD) >60mm predict a worse prognosis[35]. About 50-70% of PPCM patients will recover to normal left ventricular function with standard guideline direct medical treatment. However, pregnancy and breastfeeding complicate the administration of some of these therapies[34]. ACEI/ARB/ARNI is contraindicated in pregnancy. Hence, hydralazine with nitrate is a reasonable option. Additionally, ACEI use is reasonable while breastfeeding. Heart failure-specific beta-blockers are reasonable during pregnancy and breastfeeding[34].

N terminal prolactin has been implicated in initiating a pathophysiologic cascade of events, including the activation of cathepsin D. This ubiquitous lysosomal enzyme subsequently cleaves serum prolactin into its antiangiogenic and proapoptotic 16-kDa form. This is associated with endothelial inflammation, impaired cardiomyocyte metabolism, and reduced myocardial contraction[35].

Accordingly, small studies have suggested that bromocriptine, a dopamine agonist, and prolactin inhibitor, may increase the likelihood of left ventricular function recovery[36]. There is, however, no universal consensus on the clinical utility of bromocriptine in PPCM owing to its lactation suppressive effects in the postpartum period and its association with increased cardiovascular disease and stroke[37,38,39]. Randomized clinical trials (REBIRTH, NCT05180773; and BRO-HF, NCT02590601) currently assess bromocriptine's efficacy and safety in PPCM.

CANCER THERAPY-RELATED CARDIOMYOPATHY

Cancer therapy-related cardiomyopathy (CTRC) refers to the development of abnormalities in cardiac structure and function, with or without signs and symptoms of heart failure, during or after treatment with anticancer therapeutic agents[40].

The cardiotoxicity effect of anthracyclines has the most robust clinical data and is used as a prototype for other anticancer therapeutic agents[41,42,43]. Cancer therapies and their effects on cardiac structure and function are shown in Table 1.

Table 1 Common types of anticancer therapy, specific agents, indications and their cardiotoxic effects

Anticancer therapy	Specific agent	Common cancer indication	Cardiotoxicity (frequency)
Anthracycline	doxorubicin, daunorubicin, epirubicin	Breast, lung, bladder, gastric, prostate, leukemia, lymphoma	HF, LVD, arrhythmia
Alkylating agents	cyclophosphamide, ifosfamide, cisplatin, melphalan	Breast, lymphoma, myeloma, sarcoma, stem cell transplantation, lung, esophageal, head/neck, ovarian	HF, LVD, myopericarditis, arrhythmia VTE, HTN
Antimetabolite	fluorouracil, capecitabine	Colon, pancreatic, gastric, breast, head/neck	Coronary vasospasm, ischemia, arrhythmia Myocarditis
Antimicrotubule	docetaxel, paclitaxel, vinblastine	Breast, lung, prostate, gastric, head/neck.	HF, LVD, arrhythmia
Monoclonal antibody	rituximab, alemtuzumab	Lymphoma, leukemia	Infusion-related hypotension, HTN LVD, HF
HER2 antibody	trastuzumab, bevacizumab, pertuzumab	Breast, gastric, gastroesophageal, colorectal, GU	HF, LVD HTN, VTE
Small molecule tyrosine kinase inhibitors	dasatinib, sorafenib, sunitinib, nilotinib, ibrutinib, imatinib, erlotinib, etc.	Melanoma, leukemia, breast, renal, thyroid, lymphoma, colorectal, lung	HF, LVD AF, bleeding HTN
Immune checkpoint inhibitors	ipilimumab, nivolumab, pembrolizumab)	Melanoma, lung, kidney, bladder, head/neck, lymphoma	Myocarditis LVD, arrhythmia, pericarditis
Protease inhibitors	bortezomib, carfilzomib	Multiple myeloma	HF, LVD, VTE HTN
mTOR inhibitor	everolimus, temsirolimus	Breast, pancreas, renal	HTN
Immunomodulatory drugs	lenalidomide, thalidomide, pomalidomide	Multiple myeloma	VTE

Anticancer therapy	Specific agent	Common cancer indication	Cardiotoxicity (frequency)
Histone deacetylase inhibitors	vorinostat, belinostat	Lymphoma	QT prolongation VTE
Aromatase inhibitor	Anastrazole, letrozole, exemestane	Breast	VTE, HTN, HLD
LHRH antagonists	goserelin, leuprolide	Breast, endometrial, prostate	HF, LVD, ischemia, VTE, CVA, QTc prolongation
Antiandrogen	flutamide, bicalutamide, nilutamide	Prostate	HTN HF, LVD, VTE, arrhythmia
Chimeric antigen receptor T-cell therapy (CART)	Tisagenlecleucel, Tocilizumab, Axicabtagene ciloleucel	B-cell ALL, large B-cell lymphoma	Tachycardia, arrhythmia, hypotension, HTN, HF, capillary leak syndrome
Radiation therapy	N/A	Several indications	Valvular disease, macro- and microvascular coronary disease, LVD, HF, pericardial disease

AF, Atrial fibrillation; CVA, Cerebrovascular accident; HF, Heart failure; HTN, Hypertension; LVD, left ventricular dysfunction; VTE, venous thromboembolism. (Table adapted from doi:10.1016/j.annonc.2021.10.023)

Early detection, surveillance, and treatment of CTRC are essential as they have prognostic and survival value in cancer patients[41]. Surveillance and monitoring of cardiac function with cardiac biomarkers, echocardiography, and strain imaging before, during, and after anticancer therapy are critical for cardiovascular risk stratification[43,44,45].

According to the guidelines from American and European cardio-oncology societies, asymptomatic left ventricular dysfunction from anticancer therapy should initiate treatment with ACEI/ARB and beta-blocker therapy and prompt cardio-oncology evaluation. Additionally, if the LVEF is less than 40%, the anticancer therapy should be held with the potential to restart anticancer therapy with recovery of ejection fraction. If the LVEF is more than 40%, the continuation of non-anthracycline anticancer therapy with close surveillance with echocardiography, global longitudinal stress imaging, and cardiac biomarkers at intervals of every three weeks and every three months. If the LVEF is more than 40% on anthracycline anticancer therapy, then the anthracycline should be held, then close surveillance with echocardiography, global longitudinal stress imaging, and cardiac biomarkers at intervals of every three weeks and every three months. Consider resuming the anticancer therapy with recovery of left ventricular function[46].

For those with CTRC who are symptomatic with reduced left ventricular ejection fraction, anticancer therapy should be stopped with the initiation of guideline-directed therapy with ACEi/ARB and beta-blockers, with cardio-oncology evaluation in all cases. It may be reasonable to resume anticancer therapy if left ventricular function recovers. However, if the cancer patient continues to be symptomatic, it may be reasonable to discontinue anticancer therapy permanently[46].

Those who develop moderate to severe CTRC with or without clinical heart failure should be put on standard guideline direct medical therapies for the management of heart failure[46]. Neurohumoral inhibitor therapies have been explored in patients who are asymptomatic with mild CTRC myocardial dysfunction, including >12-15% decline in baseline global longitudinal strain or a rise of natriuretic peptide[47,48]. Furthermore, sGLT2 inhibitors with angiotensin receptor-neprilysin inhibitor agent use have been associated with improved clinical outcomes in small anecdotal studies, even though there are no recommendations for their use in current practice guidelines[49,50,51].

CTRC-myocarditis is a rare (1% of treated subjects) complication of patients receiving immune checkpoint inhibitors (ICI). However, it has a potentially fatal prognosis[52]. Manifestations of ICI myocarditis usually occur within the first 30 days of initiation of chemotherapy up to 20 weeks, often with fulminant presentations of about 50% mortality[53]. Clinical manifestations of ICI myocarditis include atrial arrhythmias, heart failure, advanced atrioventricular blocks, myocarditis, and cardiogenic shock. Urgent echocardiographic evaluation and electrocardiogram have utility in diagnosing ICI myocarditis. Cardiac biomarkers, including high-sensitivity troponin and Nt- Pro BNP, are essential for diagnostic and prognostic purposes. Current management strategies for ICI myocarditis include discontinuation of ICI therapy irrespective of clinical severity and prompt initiation of high-dose methylprednisolone with a tapering dose for about 4-6 weeks until clinical stabilization in the ICU setting[53].

Immune modulator therapies may be tried as options for those who do not respond to steroid therapy, however. However, limited data exist on the clinical benefits of these steroid-sparing therapies, including tacrolimus, infliximab, mycophenolate mofetil, rituximab, anti-thymocyte globulin, abatacept, or alemtuzumab[54,55,56].

Those who are refractory to these initial treatment options should be considered for advanced therapies, including heart transplantation, following a multi-specialty Collaborative team assessment[53].

ARRHYTHMIA-INDUCED CARDIOMYOPATHY

Arrhythmia-induced cardiomyopathy (AIC) is a retrospective diagnosis following the improvement of left ventricular dysfunction to normal function after the resolution of the cardiac arrhythmia. AIC is a potentially reversible, otherwise unexplained myocardial dysfunction deemed to be induced by persistent or repetitive cardiac arrhythmias[57]. The most frequent cardiac arrhythmias associated with AIC include Atrial fibrillation with rapid ventricular response and frequent premature ventricular complexes (PVC)[57].

In a small study of patients referred for PVC-related Ablation, a PVC burden of 10% or more was associated with myocardial dysfunction with PVC burden while a PVC burden of 24% or more best separated the patients with impaired as compared with preserved left ventricular function with a sensitivity of 79%, specificity of 78% and area under the curve of 0.89[58].

The therapeutic strategies to treat AIC have traditionally aimed at suppressing or aborting the culprit cardiac arrhythmia either using antiarrhythmic medications or catheter-based ablation while using standard treatment pillars as recommended by current practice guidelines[58]. Patients with heart failure with atrial fibrillation have derived more benefits in the recovery of left ventricular function when compared with rate control strategies[59].

Recently published studies have favored catheter-based ablation to medical therapies, with superior clinical benefits and functional capacity compared to antiarrhythmic medications[60,61]. Additionally, in small randomized clinical trials, catheter-based ablation is of clinical benefit with recovery of myocardial function and improved quality of life in patients with PVC-induced cardiomyopathy[62]. Long-term clinical follow-up is required for patients with AIC who recover left ventricular function following the resolution of cardiac arrhythmia, given a small but significant risk of relapse and recurrence of the cardiac arrhythmia[63].

ALCOHOL-INDUCED, TOXIN-, AND NUTRITIONAL DEFICIENCY- RELATED CARDIOMYOPATHY

Alcohol-induced cardiomyopathy is caused by the direct toxic effect of chronic excessive alcohol on cardiac myocytes, leading to an otherwise unexplained impaired cardiac function and dilated ventricles[64]. No threshold amount of alcohol consumption induces its cardiotoxic effects; however, a recent study of subject-level data from 19 high-income countries suggested that for each 100g per week of alcohol consumption, there is a partly linear association with a higher risk of development of heart failure[65] without a clear risk threshold. Dilated cardiomyopathy typically develops in the setting of 7-8 drinks of alcohol daily for more than five years 66. Risk factors that predispose subjects to alcohol-induced cardiotoxicity include age, sex, nutritional deficiencies (selenium, thiamine), and other traditional cardiovascular disease risk factors such as hypertension, hyperlipidemia, etc[67]. The primary treatment strategy for alcohol-induced cardiomyopathy is complete abstinence. Different strategies include standard guideline-directed medical therapies for heart failure and appropriate replacement of deficient nutrients. Complete absence of alcohol consumption has been associated with recovery of left ventricular function, quality of life, and functional capacity 68. Prognosis is poor in patients with alcohol-induced cardiomyopathy who continue to abuse alcohol, with a 5-year mortality rate of 40-50%[69]. Recreational drugs abuse, such as cocaine and amphetamine, have a direct toxic effect on the contractile apparatus of the cardiomyocytes, resulting in left ventricular dysfunction[70]. These illicit drugs are also stimulants that can cause coronary vasospasm and inhibit the reuptake of catecholamine, increasing the myocardial oxygen demand and leading to myocardial ischemia and subsequent ventricular

dysfunction[71]. Abstinence is the mainstay of treatment. Selective beta-adrenergic blockers have no role in the treatment of cocaine or amphetamine-induced cardiotoxicity, as their use leads to unopposed alpha-adrenergic effects; however, carvedilol, an alpha- and beta-adrenergic receptor blocker, may be safe, with illicit drug abstinence[71].

The prevalence of Human immunodeficiency virus (HIV) was previously about 40%, but this has precipitously decreased to about 8.3% with the advent of highly active antiretroviral therapy[72,73]. The association of overt heart failure and HIV portends the risk of sudden cardiac death[74]. The pathogenesis of HIV-associated cardiomyopathy is an interplay of several pathways, including direct cardiomyocyte infection, exposure to opportunistic infection, effects of immune reconstitution syndrome, and toxic effect of the highly active antiretroviral therapies such as Abacavir, lopinavir[75]. The standard guideline-directed medical therapies are employed in the management of HIV- HIV-associated cardiomyopathy while maintaining highly active antiretroviral therapies in HIV infection[72]. This current treatment paradigm is backed by expert consensus in the setting of paucity of randomized control trials[72]. Advanced therapies, including heart transplantation and durable assisted devices, have been utilized in refractory advanced heart failure in HIV infection patients[76,77].

In Central and South America, Chagas disease is an essential cause of DCM[78]. Chagas cardiomyopathy is a late manifestation of the disease in 20 to 40% of patients over the years[78]. The hallmarks of its pathogenesis include myocardial inflammation, necrosis, and fibrosis from direct parasitic infection of the cardiomyocytes, immune-mediated mechanisms, and microvascular dysfunction[79]. The clinical presentation of Chagas cardiomyopathy includes HF, conduction abnormalities, cardiac arrhythmias, regional wall motion abnormalities, apical LV aneurysm, thromboembolism, and increased risk of sudden cardiac death[80]. In the acute phase of Chagas disease, antiparasitic therapy is curative in about 60-90% of patients. However, the chronic phase with subsequent DCM does not respond to antiparasitic medications, including benznidazole and nifurtimox[81]. The primary treatment strategy of standard GDMT for HF is anticoagulation in patients with specific indications for anticoagulation and pacemaker/ ICD placement in consonance with practice guideline recommendations[80]. Advanced therapies, including heart transplantation, have been utilized in patients with refractory, advanced HF[80]. Recently, there has been a resurgence of the clinical utility of immune modulator therapies, including granulocyte colony-stimulating factor, pentoxifylline, and N, N-dimethylsphingosine[82].

DCM is a rare late manifestation of Lyme disease[83]. Standard GDMT with antibiotic therapy is the effective treatment strategy for Lyme-induced cardiomyopathy[84].

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic Cardiomyopathy (HCM) is a cardiac condition characterized by the thickening of the left ventricular (LV) wall to more than 15mm in any myocardial segment without any identifiable pathology accounting for this change. In cases where the wall thickness falls within the range of 13-14mm, additional investigations are necessary,

particularly in patients presenting risk factors such as positive family history, genetic predisposition, or abnormal findings on an electrocardiogram (ECG)[85]. Diagnosis of HCM in pediatric patients involves the identification of LV wall thickness that exceeds two standard deviations (SD) from the predicted mean (Z-score > 2)[86].

Managing HCM involves thoroughly evaluating left ventricular outflow tract obstruction (LVOTO), where blood flow from the left ventricle is impeded, leading to symptoms in affected patients. Despite the majority of HCM cases being asymptomatic, some patients may experience symptoms before the appearance of abnormal ECG or echocardiography findings.

Although research involving randomized trials for HCM treatment remains limited[87,88,89], the standard approach typically involves initiating empirical pharmacological therapy to alleviate symptoms and enhance functional capacity. In cases where patients present with symptoms associated with LVOTO, the primary goal of management is to alleviate symptoms using medications, surgical procedures, or alcohol septal ablation therapy 85. On the other hand, for symptomatic patients without LVOTO, the focus shifts to preventing and managing arrhythmias, reducing left ventricular filling pressure, and preventing or treating angina[85]. In cases where patients exhibit progressive left ventricular dysfunction that is unresponsive to medical interventions, cardiac transplantation is the ultimate form of management.

The quantification of LVOTO involves the measurement of the peak Doppler left ventricular outflow tract gradient, which is deemed significant if it exceeds 30mmHg, for values surpassing 50mmHg, invasive therapeutic interventions are recommended. Patients diagnosed with LVOTO are often advised to undertake weight loss measures in cases of overweight or obesity while simultaneously being cautioned against dehydration and excessive alcohol consumption[85]. Specific medications such as nitrates and phosphodiesterase type 5 inhibitors (vasodilators) are generally contraindicated due to their potential exacerbation of LVOTO[89]. The first-line treatment for these patients typically involves using non-vasodilating beta-blockers, administered up to the maximum tolerable dose[90]. When patients cannot tolerate or respond to beta-blockers, non-dihydropyridine beta-blockers such as verapamil or diltiazem may be considered alternatives[90,91,92]. However, the use of disopyramide, while potentially effective in abolishing basal left ventricular outflow pressure gradients, is associated with an increased risk of arrhythmias that are not linked to sudden cardiac death (SCD)[93,94]. It is imperative to closely monitor the QTc interval in patients taking disopyramide and avoid its use in individuals with glaucoma due to its potential anticholinergic effects. Additionally, its use in elderly patients should be approached cautiously due to the risk of urinary retention or hesitancy, dry eyes, dry mouth, and constipation[95,96,97]. Disopyramide may be combined with verapamil in some instances[93].

Mavacamten, classified as a cardiac myosin ATPase inhibitor, has emerged as a potential therapeutic option in cases of refractory LVOTO. Its mechanism reduces actin-myosin

cross-bridge formation, decreasing contractility and LVOT gradient. Recent studies have shown promising results, with 27% of HCM patients with symptomatic LVOTO (NYHA II-II and EF>55%) treated with mavacamten experiencing a reduction in LVOT gradient to less than 30mmHg, resulting in an improvement in heart failure symptoms to NYHA Class I[96]. Mavacamten has demonstrated a favorable safety profile, with only a subset of patients developing systolic dysfunction, a reversible condition upon discontinuation of the medication[96]. Furthermore, mavacamten has the potential to induce positive cardiac remodeling, decreasing myocardial mass and LV thickness[98,99,100]. Another compound, Aficamten, also categorized as a cardiac myosin ATPase inhibitor, has been mentioned briefly in the literature; however, further research and studies on its clinical application are ongoing.

The utilization of diuretics in the management of symptomatic patients with LVOTO remains a contentious topic due to the associated risks of dehydration. Caution must be exercised when considering the use of diuretics in these cases.

Invasive management of LVOTO, also known as septal reduction therapy (SRT), is often recommended in symptomatic patients, while its benefits in asymptomatic patients are not well-established. Early intervention is deemed crucial, particularly in patients presenting even minimal symptoms but with significantly elevated LVOT gradient, as it has been shown to provide better therapeutic outcomes and prognostic value[101,102]. SRT is recommended for patients with severe LVOT gradient equal to or greater than 50mmHg, accompanied by severe symptoms (NYHA functional class III-IV) and cases of exertional or unexplained syncope despite receiving the maximum tolerated medical therapy[103]. The two primary modalities for SRT include ventricular septal myomectomy and alcohol septal ablation, each offering its own set of advantages and associated risks. Ventricular septal myomectomy is recognized as the most common surgical procedure for addressing LVOTO, with a success rate of over 90% in reducing LVOT gradient and over 80% in alleviating symptoms[104,105,106]. Improved outcomes are observed in male patients younger than 50 years, those without atrial fibrillation (AF), and individuals with a left atrial size less than 46mm[107]. Alcohol septal ablation, which has gained prominence in advanced medical centers, has also demonstrated similar benefits, albeit with a risk of non-fatal atrioventricular (AV) blocks in 7-20% of cases[106-115]. Attempts have been made to use coils in the context of SRT, albeit with relatively lesser beneficial outcomes[117,118]. Surgical myomectomy is preferred in cases where associated valvular dysfunctions are present, primarily due to the possibility of simultaneous valvular repair or replacement[119-125].

The management of heart failure in patients without LVOTO primarily revolves around reducing LV diastolic pressures and enhancing LV filling. This can be achieved by administering beta-blockers or non-dihydropyridine calcium channel blockers to lower the heart rate and the cautious use of loop diuretics to prevent hypovolemia. Beta-blockers and calcium channel blockers have effectively controlled angina, even without LVOTO. Nitrates and ranolazine may also be cautiously used in these patients[126,127].

While cardiac resynchronization therapy (CRT) is critical in managing dilated cardiomyopathy, its utility in managing HCM remains relatively restricted. Its application in HCM aligns with its use in other forms of cardiomyopathy.

ARRHYTHMOGENIC (RIGHT VENTRICULAR) CARDIOMYOPATHY

Contemporary Management of Arrhythmogenic Cardiomyopathy

Arrhythmogenic cardiomyopathy (ACM), previously known as arrhythmogenic right ventricular cardiomyopathy (ARVC), is a relatively rare but potentially life-threatening inherited cardiac disorder. ACM is characterized by progressive myocardial fibrofatty replacement and an increased risk of ventricular arrhythmias. Contemporary management strategies for ACM involve a multi-disciplinary team approach to diagnosis, risk stratification, and treatment. This article reviews the current state of ACM management, including diagnostic methods, risk assessment, and therapeutic interventions.

DIAGNOSTIC CONSIDERATIONS:

1. Clinical Evaluation

Diagnosing ACM typically begins with a comprehensive clinical evaluation. Symptoms such as palpitations, syncope, and sudden cardiac arrest may prompt further investigations. Clinical criteria, like the 2010 Task Force Criteria, have been widely used for diagnosis[128]. ARVC diagnosis involves assessing six domains. A confirmed diagnosis requires two primary criteria, one major and two minor or four minor criteria from different clinical factor groups. Due to the diverse nature of the diagnostic criteria, a collaborative effort among experts in electrophysiology, cardiac imaging, genetics, and cardiac pathology is crucial for accurate ARVC diagnosis.

2. Imaging

Advanced imaging techniques, including cardiac magnetic resonance imaging (CMR) and echocardiography, are pivotal in assessing myocardial structure and function. CMR can identify myocardial fibrofatty replacement, a hallmark of ACM[129].

3. Genetic Testing

ACM is frequently associated with genetic mutations. Genetic testing, often performed using next-generation sequencing, helps identify affected individuals and carriers, allowing for genetic counseling and family screening. In cases where the diagnosis is uncertain or falls into a borderline category, detecting a gene variant can significantly assist in confirming ARVC as the diagnosis rather than considering other potential conditions that may mimic its symptoms[130].

4. Risk Stratification

a. Arrhythmia Risk Assessment

When assessing arrhythmic risk, it is crucial to consider several key factors. These include electrical and hemodynamic instability, which encompasses the frequency of premature ventricular contractions and sustained ventricular arrhythmia, whether the individual is the proband, the extent of structural cardiac disease, episodes of cardiac syncope, being male, the presence of multiple mutations or a mutation in TMEM43, age $\geq$ 39 years, willingness to limit physical activity and discontinue participation in competitive or endurance exercise[131].

b. Risk Scoring Models

Various risk-scoring models have been proposed to predict sudden cardiac death in ARCM patients. These models incorporate clinical, genetic, and imaging data to provide a more accurate risk assessment[131].

5. Management Strategies

a. Lifestyle Modification

Maintaining a balanced exercise routine is essential for managing individuals with ARCM[132]. Studies conducted on patient cohorts emphasize the positive impact of limiting exercise activities in reducing ventricular arrhythmias (VAs) among ARCM patients[133,134]. Restricting exercise is critical in minimizing the risk of heart failure in ARVC patients[135]. Exercise levels >650 MET-hours per year accelerated the phenotypic expression of ARVC[134]. Participating in recreational sports or engaging in low-to-moderate intensity exercise might not have adverse effects, and individuals with ARVC/D should not be entirely denied the advantages of physical activity[136].

b. Medical Therapies

β-blockers, Sotolol, and amiodarone Have been used to manage ARCM. There are mixed results for the efficacy of different antiarrhythmic agents[137,138]. β-blockers continue to be widely used in clinical practice. It has been shown that the addition of flecainide in combination with sotalol or metoprolol may be an effective antiarrhythmic strategy for the control of ventricular arrhythmias in patients with ARCM refractory to single-agent therapy and catheter ablation[139].

Recent animal studies show that pharmacological substances designed to directly address the fundamental disease mechanisms in the different manifestations of ARCM are currently undergoing research. SB216763, a compound that inhibits GSK3β, a key controller of Wnt/β-catenin signaling, was identified through an unbiased chemical screening using a zebrafish model of ARVC. This compound has demonstrated a remarkable ability to significantly decrease arrhythmias, cardiac damage, and exercise-induced injuries in mouse models of ARVC[140,141].

c. Implantable cardiac Defibrillators

An implantable cardioverter defibrillator (ICD) is the only lifesaving treatment despite significant morbidity because of ICD-related complications, including inappropriate shocks. The International Task Force recommends ICD placement for patients who sustained VT (>100 beats/min for >30 seconds), severe RV or LV dysfunction, or a history of cardiac arrest[142]. Risk stratification score can be used in other patients with ARCM to consider ICD placement. The risk cutoffs for ICD placement are relatively lower in ARCM patients than in Hypertrophic cardiomyopathy patients, as the risk of VTs is higher in this subgroup of patients[142,143]. In patients with more than 15% risk of VA, ICD placement must be considered. A lower score may be considered in variables with a higher risk of VTs and SCD, like LV predominant and TMEM43 variants[144,145]. Transvenous ICD placement is preferred since anti-tachycardia pacing and shock can be delivered. Also, apical endocardial lead placement has been shown to reduce R wave sensing over time[146]. Subcutaneous ICD placement is becoming increasingly popular, has a comparable risk profile to transvenous ICDs, and is non-inferior[147].

d. Ablation procedure

Indications for ablation generally include partial response to pharmacological agents, repeated episodes of VT, or multiple shocks with ICD. The pathologic process of ARCM typically originates in the epicardium or subepicardial layers and progresses toward the endocardium. Epicardial and endocardial approaches are commonly used for ablation.

Femoral access with conscious sedation is commonly used for the Endocardial approach.

A pericardial access with general anesthesia is favored for the epicardial approach. A combination of endo-epicardial ablation has shown to be more successful than pure endocardial ablation[148]. Administering isoproterenol intraprocedural can be beneficial by induction of VT[149]. Radiofrequency ablation (RFA) resulted in favorable VT-free survival following a single intervention, but additional procedures were often necessary for longer-term prevention of VT recurrence[150].

e. Cardiac Sympathectomy

Bilateral cardiac sympathetic denervation (BCSD) has been demonstrated to decrease the occurrence of implantable cardioverter-defibrillator (ICD) shocks in patients with structural heart conditions and refractory ventricular tachycardia (VT)[151]. BCSD can be considered in patients with failed ablation procedures.

f. Cardiac Transplant

The primary indication for transplantation in these cases is advanced right ventricular (RV) dysfunction causing heart failure. However, it can also benefit individuals struggling with intractable ventricular arrhythmias (VAs)[152]. Encouragingly, individuals with ARCM undergoing transplantation seem to exhibit more comparable outcomes to non-ARCM patients and favorable outcomes when compared to those with ischemic or restrictive cardiomyopathies[153].

RESTRICTIVE CARDIOMYOPATHY

Novel therapeutic strategies for treating cardiac amyloidosis

Managing cardiac amyloidosis has been challenging as standard heart failure therapies, like beta blockers and mineralocorticoid receptor antagonists, lack definitive recommendations due to limited data and patient intolerance[154,155,156]. There are two main types of cardiac amyloidosis (CA), namely, transthyretin (ATTR) and light chain (AL) cardiac amyloidosis. AL amyloidosis is generally associated with cellular plasma disorders. Recent advancements in the treatment of cardiac amyloidosis, particularly transthyretin amyloidosis (ATTR), have significantly changed treatment strategies. These developments pivot around disease-modifying therapies targeting the underlying mechanisms of amyloid deposition in the heart[155].

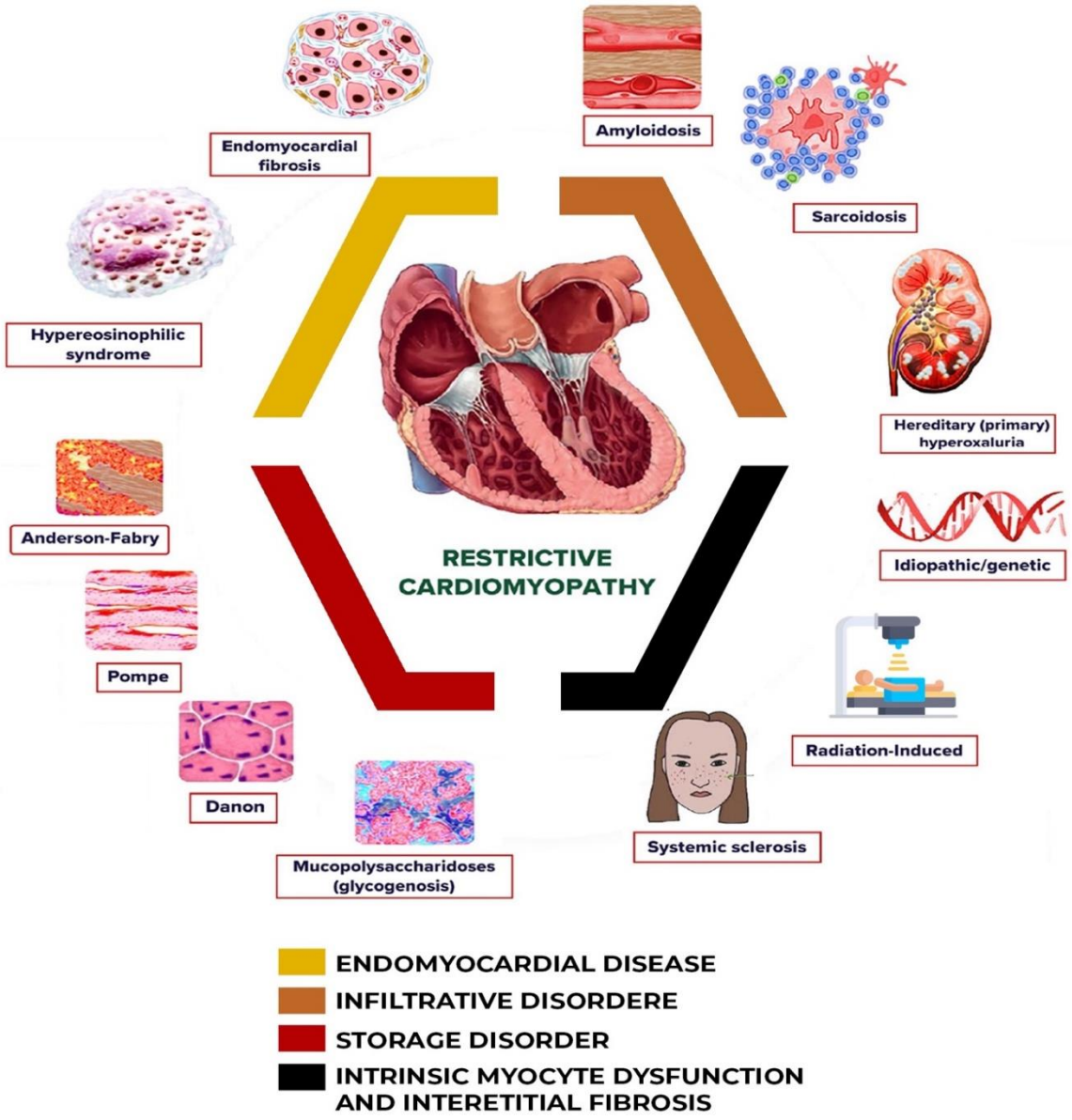

Figure 4 Categories and etiologies of restrictive cardiomyopathy

A. Transthyretin (TTR)-Stabilizers

Tafamidis, which inhibits transthyretin (TTR) tetramer cleavage, has demonstrated efficacy in reducing functional decline, cardiovascular-related hospitalizations, and mortality as demonstrated by the ATTR-ACT trial, a Phase 3 multicenter randomized study[157,158]. In a phase 3 randomized trial involving[130] patients

with transthyretin familial amyloid polyneuropathy (ATTR-FAP) variant experiencing symptomatic neuropathy, diflunisal, a nonsteroidal anti-inflammatory drug, was compared with placebo. Although diflunisal significantly limited the progression of neurological impairment, it did not show beneficial effects on improving cardiac status. Furthermore, the potential for severe adverse events due to inhibition of cyclooxygenase is a significant concern, leading to off-label use of diflunisal in treating ATTR-FAP[159,160].

Acoramidis (AG10) is a novel TTR stabilizing compound undergoing a phase 3 clinical trial. In vitro studies have demonstrated that ceramides exhibit stronger TTR tetrameric stability compared to tafamidis and diflunisal[161,162].

B.Transthyretin (TTR) Silencers

Gene-silencing medication, patisiran, a small interfering RNA (siRNA), and inotersen, an antisense oligonucleotide (ASO), inhibit hepatic TTR synthesis, thereby hindering amyloid fibril formation. Both patisiran and inotersen have been approved by the Food and Drug Administration (FDA) for treating the polyneuropathy of hereditary ATTR amyloidosis, regardless of cardiac phenotype[163,164]. Following evidence of some preliminary benefits on the cardiac phenotype, there has been growing interest in exploring patisiran's potential for managing ATTR cardiomyopathy (ATTR-CM)[165,166]. A novel siRNA, vutrisiran, and another ASO formulation, eplontersen, are undergoing phase III clinical trials in patients with ATTR-CM[161].

Currently undergoing a phase 1 trial, NTLA-2001 is a new CRISPR–Cas9–mediated in vivo gene-editing therapy that represents a promising strategy for obtaining a highly effective blockade of TTR gene expression[161,167].

C. Transthyretin (TTR) disrupters

ATTR degraders are drugs that may lead to disease regression by resorption of already deposited amyloid fibrils. A phase II study has a synergistic effect of combined administration of doxycycline and the antiapoptotic agent, tauroursodeoxycholic acid (TUDCA), in degrading non-fibrillar TTR deposits. However, extensive studies are needed to assess the effectiveness of this potential therapy[159,161].

While therapeutic options have increased, challenges remain in tolerability, cost barriers, and refining treatment strategies, which warrants ongoing research for more effective interventions and improved outcomes in this complex disease entity.

ORGAN TRANSPLANTATION IN CARDIAC AMYLOIDOSIS

Refractory cases necessitate advanced interventions such as transplantation (heart, liver, or combined heart-liver) or mechanical circulatory support. Sequential heart transplant (HT) followed by autologous stem cell transplant (ASCT) has been selectively used for patients with AL cardiac amyloidosis, where heart failure is the primary manifestation of amyloidosis. This approach has shown a 5-year survival rate of approximately 60% in limited studies[168-171].

For wild-type TTR amyloidosis (ATTRwt) patients, where cardiac manifestation typically remains isolated, heart transplantation emerges as a potential intervention. However, age considerations often limit the feasibility of

heart transplantation in this group[159,168]. The experience with heart transplantation in ATTRwt individuals is limited, necessitating a more refined approach to patient selection and timing for this intervention[172]. In variant-type TTR amyloidosis (ATTRv), where abnormal amyloid production occurs primarily in the liver, the management approach typically involves considering liver transplantation. However, combined heart-liver transplantation presents potential advantages over isolated heart or liver transplantation in halting disease progression due to the systemic nature of amyloidosis[159,168]. Further research into better patient selection criteria and improved transplant techniques are required to enhance clinical outcomes.

PACEMAKERS AND IMPLANTABLE CARDIAC DEFIBRILLATORS

For ATTR cardiac amyloidosis (ATTR-CA) patients with symptomatic atrioventricular block or bradycardia, cardiac pacing may be required. The indications follow current standard guidelines for pacemaker implantation. No guidelines exist for prophylactic pacemaker implantation in asymptomatic ATTR-CA patients[159,173]. The efficacy of Implantable Cardioverter Defibrillators (ICDs) in patients with cardiac amyloidosis remains controversial, and they have not shown any mortality benefit[159].

MECHANICAL CIRCULATORY SUPPORT

Barriers to the successful use of durable mechanical circulatory support devices in cardiac amyloidosis include the small left ventricular cavity and biventricular involvement, resulting in the risk of right ventricular failure when left ventricular assist devices (LVADs) are placed. However, mechanical circulatory support may be necessary, particularly in AL-amyloidosis while waiting for transplantation[156].

NOVEL THERAPEUTIC STRATEGIES FOR TREATING CARDIAC SARCOIDOSIS

Managing cardiac sarcoidosis (CS) poses significant diagnostic challenges due to the limitations of modalities like endomyocardial biopsy regarding sensitivity and specificity.

Additionally, there is no single reference standard to diagnose cardiac sarcoidosis. Currently used guidelines arise from three main sets of clinical criteria, namely, the Japanese Ministry of Health and Welfare (JMHW)[174], the Heart Rhythm Society (HRS)[175], and the World Association for Sarcoidosis and Other Granulomatous Disorders criteria (WASOG)[176,177], which mainly depend on expert opinions and lack robust validation through clinical trials[177]. However, with the increased utilization of advanced imaging modalities like cardiac magnetic resonance imaging (CMR) and 18–fluorodeoxyglucose–positron emission tomography (FDG-PET), the diagnosis of CS is witnessing a revolution. These newer techniques are proving invaluable as they reduce the reliance on histological confirmation, which poses a challenge due to the patchy involvement characteristic of CS[175,176,177]. The newer modalities offer more accurate diagnostic information and help evaluate treatment responses in CS patients[177]. Despite these advancements in diagnostic tools, there remains a notable lack of large-scale studies that could effectively guide treatment plans in CS. Immunosuppressive therapies, primarily corticosteroids, are the cornerstone of CS treatment[181-183]. However, comprehensive data regarding these therapies' optimal dosage and

duration is lacking. Current recommendations are predominantly based on limited observational studies[181]. Steroid-sparing agents, including methotrexate, azathioprine, leflunomide, mycophenolate mofetil, cyclophosphamide, and infliximab, have shown efficacy in systemic sarcoidosis. Their use, independently or in conjunction with corticosteroids, for managing CS remains controversial[184]. The new immunosuppressant agents like TNF-alpha inhibitors[185] and interleukin-1 blockers (anakinra)[186] hold promise in autoimmune diseases, but their application in CS requires careful consideration and further evidence of their efficacy and safety before integration into routine clinical practice. Other therapies include the insertion of a pacemaker (indications similar to non-CS patients) or implantable defibrillator in patients at high risk of sudden cardiac death. Heart transplantation (HT) is typically considered for advanced-stage cardiac sarcoidosis, refractory to medical therapy[187].

NOVEL THERAPEUTIC STRATEGIES FOR TREATING IDIOPATHIC RESTRICTIVE CARDIOMYOPATHY.

Idiopathic restrictive cardiomyopathy (RCM) is a genetic disease. In an observational study by Gallego-Delgado et al. involving 32 unrelated patients, identifiable disease-causing mutations were found in at least 60% of cases, suggesting the importance of genetic testing for patients with RCM for diagnostic purposes as well as the potential benefits it may offer to the family members of such patients 188. Further research must be conducted for tailored treatments based on individual genetic profiles.

No specific therapy exists for idiopathic RCM. The current treatment approach involves general heart failure management. As the disease progresses, left ventricular assist devices (LVADs) may be used as a bridge to heart transplantation[189].

However, emerging therapeutic options based on research models of idiopathic RCM suggest potential scopes for targeted treatments. These include targeting the translation of mutant proteins involved in idiopathic RCM using microRNAs (miRNAs) or long non-coding RNAs (lncRNAs), as proposed by Mosqueira et al., for the hypertrophic cardiomyopathy model[189,190].

Therapeutic strategies used in conditions like cardiac amyloidosis, like TTR stabilizers (tafamidis) or TTR disrupters (doxycycline and taurosodeoxycholic acid), might also hold potential for RCM[189]. Monoclonal antibodies targeting pathological deposits of proteins as proposed in the treatment of AL-amyloidosis in a study[191] and stimulating protein disposal mechanisms, like ubiquitinylation and activation of a microtubule-associated deacetylase, HDAC6 may also hold promise in the future, as potential therapeutic avenues for idiopathic RCM[189-191].

Conclusion

Continuous advancements in treatments for dilated cardiomyopathy provide a promising outlook for improving patient outcomes and their quality of life. Nevertheless, the intricacies and variations associated with this condition underscore the ongoing need for nuanced, personalized approaches to care and surveillance, ensuring that patients receive timely interventions and comprehensive support to manage their unique conditions effectively.

Conflict of Interest:

None

Acknowledgements

None

Funding:

None

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