MDPI

Review

Management Strategies in Arrhythmogenic Cardiomyopathy across the Spectrum of Ventricular Involvement

Yash Maniar [ID], Nisha A. Gilotra and Paul J. Scheel III *[ID]

Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA; ymaniar1@jh.edu (Y.M.)
* Correspondence: pscheel6@jhmi.edu; Tel.: +1-410-502-3592; Fax: +1-410-376-2149

Abstract: Improved disease recognition through family screening and increased life expectancy with appropriate sudden cardiac death prevention has increased the burden of heart failure in arrhythmogenic cardiomyopathy (ACM). Heart failure management guidelines are well established but primarily focus on left ventricle function. A significant proportion of patients with ACM have predominant or isolated right ventricle (RV) dysfunction. Management of RV dysfunction in ACM lacks evidence but requires special considerations across the spectrum of heart failure regarding the initial diagnosis, subsequent management, monitoring for progression, and end-stage disease management. In this review, we discuss the unique aspects of heart failure management in ACM with a special focus on RV dysfunction.

Keywords: arrhythmogenic cardiomyopathy; heart failure; arrhythmogenic right ventricular cardiomyopathy; guideline-directed medical therapy

1. Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) was initially described in the 1980s as a hereditary disorder with unique electrophysical properties and fibro-fatty replacement of the right ventricle (RV) [1–3]. Gene variants mostly in the cardiac desmosome were subsequently implicated [4,5]. Increasing recognition of left ventricle (LV) involvement led to redefinition as "biventricular" ARVC and arrhythmogenic left ventricular cardiomyopathy (ALVC) [6–8]. As a spectrum of ventricular involvement was established, these conditions are now described more broadly as arrhythmogenic cardiomyopathy (ACM). However, management and treatment continue to depend on ventricular morphologic phenotypes.

Arrhythmias and sudden cardiac death (SCD) are the hallmark features of ACM but heart failure prevalence is increasing and often under-appreciated [9–11]. Increased disease recognition, cascade family screening, and arrhythmic risk stratification have reduced the rate of SCD through appropriate use of implantable cardiac defibrillators (ICDs) and anti-arrhythmic drugs [12–14]. With subsequent increased survival, a subset of patients may develop progressive heart failure. Heart failure management guidelines are well established but dictated by LV function [15,16]. Predominant RV involvement in a large proportion of ACM patients leads to unique heart failure considerations in their care. In this review, we discuss different aspects of heart failure management in ACM, focusing on the unique considerations of significant RV involvement.

2. Epidemiology and Pathophysiology

Most estimates of prevalence for ACM are based on more narrowly defined ARVC and thought to be about 1:2000 to 1:5000 [17,18], likely an underestimate, with refined terminology and improved recognition. The diagnosis is based on the 2010 revised Task Force Criteria, which leverage distinct RV changes seen on testing in addition to other

factors [6,19]. These criteria are less sensitive for non-RV predominant forms. The proportion of patients who will develop heart failure is also unknown but one large cohort study demonstrated 142 of 289 (49%) of patients with ARVC had evidence of heart failure [9].

The diagnosis for all forms is supported by and sometimes predicated on identification of a pathogenic genetic variant but roughly 1/3 of patients meeting ARVC diagnostic criteria are gene-elusive [20], which may extrapolate to LV-dominant phenotypes. Most genetic variants in ACM occur in genes encoding proteins in the cardiac desmosome: plakophilin-2 (*PKP2*, the most common in ACM), plakoglobin (*JUP*, inheritance typically recessive), desmoplakin (*DSP*), desmoglein-2 (*DSG2*), desmocollin-2 (*DSC2*) [21,22]. Variants lead to altered cellular adhesion and signaling through multiple complex mechanisms outside the scope of this review [22]. Several non-desmosomal genes, including desmin (*DES*), integrin-linked kinase (*ILK*), LEM domain containing protein-2 (*LEMD2*), and phospholamban (*PLN*), among others, have also been identified in ACM [22]. The genotype influences phenotype variations. Wooly hair and palmoplantar keratoderma along with ACM are seen with variants in *JUP* (Naxos disease) and recessive forms of *DSP* cardiomyopathy (Carvajal syndrome) [23,24]. *PKP2* variants are associated with more arrhythmias and classical RV-dominant ACM while desmoplakin (*DSP*) and desmoglein-2 (*DSG2*) pathogenic variants are associated with more heart failure [21,25–27]. *DSP* pathogenic variants are also associated with an acute myocarditis-like presentation in ACM [28,29]. Non-desmosomal variants, like *DES*, have a wider spectrum of phenotypes including non-ACM cardiomyopathies and are therefore more often identified in LV-dominant forms [22]. Multi-variant patients have an earlier onset of disease for both arrhythmias and heart failure [21]. Conversely, gene-elusive patients seem to have less risk of arrhythmias but a less clear impact on heart failure. Genetic variant significance is based on systematic methodology applied across the genome but these can be difficult to apply to cardiac genetics specifically and should be carried out based on the clinical context in conjunction with expert cardiac genetic counseling [30–32]. Variants of unknown significance (VUS), not benign/likely benign or pathogenic/likely pathogenic, are often identified but with time can be reclassified based on familial clustering or identification in other individuals, necessitating periodic variant updating [33,34].

Fibrofatty replacement of the myocardium is the hallmark pathologic finding in ACM as shown in Figure 1. Mechanisms leading to fibrofatty replacement are outside the scope of this review but are actively under investigation and include altered inflammatory signaling due to intrinsic and extrinsic factors [35,36]. This replacement with non-contractile tissue impairs force generation, lessening cardiac reserve and ultimately resting cardiac output, cardinal features of heart failure. Even in patients with RV-dominant forms of ACM, fibrofatty replacement can be seen in the LV and is associated with more arrhythmias and heart failure [1]. A ventricular arrhythmia and SCD are the prototypical presentations of ACM with heart failure often manifesting many years later, sometimes after years of arrhythmia quiescence [9,37,38]. A subset of patients present with heart failure, even advanced disease, without arrhythmias playing a significant role [9]. Finally, some patients will be identified as gene-variant carriers through cascade screening and either be diagnosed with asymptomatic disease or monitored for progression to disease.
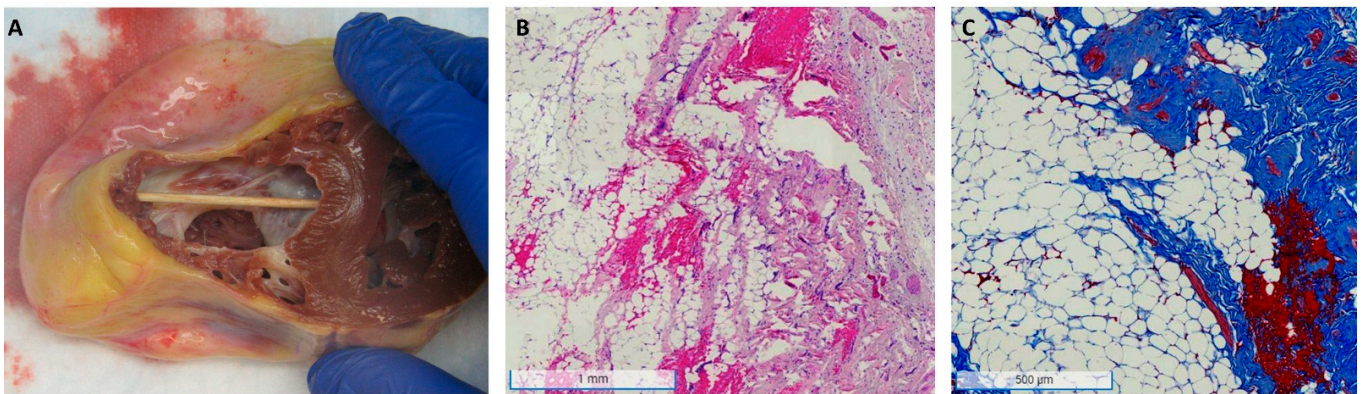
Figure 1. Representative heart explant pathology in arrhythmogenic cardiomyopathy (ACM). (**A**): Gross pathology focusing on the right ventricle demonstrating significant dilation and wall thinning with fatty replacement. (**B**): Hematoxylin and eosin (H&E) stain of right ventricle myocardium at 2×x magnification showing significant fibrofatty replacement surrounding residual cardiomyocytes. (**C**): Masson trichrome stain of the right ventricle at 4×x magnification showing increased fibrosis along with fatty infiltration.

3. Heart Failure Diagnosis and Assessment

Heart failure is broadly defined as a clinical syndrome with characteristic signs or symptoms caused by a structural and/or functional cardiac abnormality, corroborated by laboratory, imaging, or hemodynamic abnormalities [39]. Heart failure in ACM often manifests as a predominant right-sided heart failure syndrome, though biventricular and LV syndromes are also seen. Left- and right-sided heart failure share many signs and symptoms: lower extremity swelling, unintentional weight gain, jugular venous distension with hepatojugular reflex, exertional dyspnea, and fatigue. Conversely, orthopnea and paroxysmal nocturnal dyspnea (PND) typically indicate LV failure along with exam findings of pulmonary rales and a displaced point of maximal impulse (PMI) as shown in Figure 2. RV failure may have a palpable RV heave, hepatomegaly due to congestion, or a tricuspid regurgitation murmur along with a pulsatile liver. RV failure may have more predominant abdominal distension, anorexia or early satiety from gut edema, or scrotal swelling. In one study of heart failure specifically in ARVC where nearly 50% of patients had clinical heart failure, dyspnea on exertion, fatigue, and abdominal swelling were the highest frequency symptoms [9].

Not all ACM patients will develop heart failure but gene carriers and affected patients should be regularly assessed for the more subtle signs of RV dysfunction as outlined in Figure 3. Symptom identification is further complicated by recommendations for exercise restriction to prevent or slow progression in a population of patients that were disproportionately very physically active prior to the diagnosis [40]. Substantial exercise restriction limits symptom opportunity and residual conditioning, especially in younger patients, and may compensate for progressive cardiac dysfunction. Therefore, patients may remain asymptomatic until a significant portion of their cardiac reserve is lost and thereby present at a later stage of disease. Serial assessments of cardiac structure and function, as discussed later, aid in identification of progression. Progressive morphologic changes or any symptoms or subtle signs of heart failure warrant referral to a heart failure specialist for evaluation.
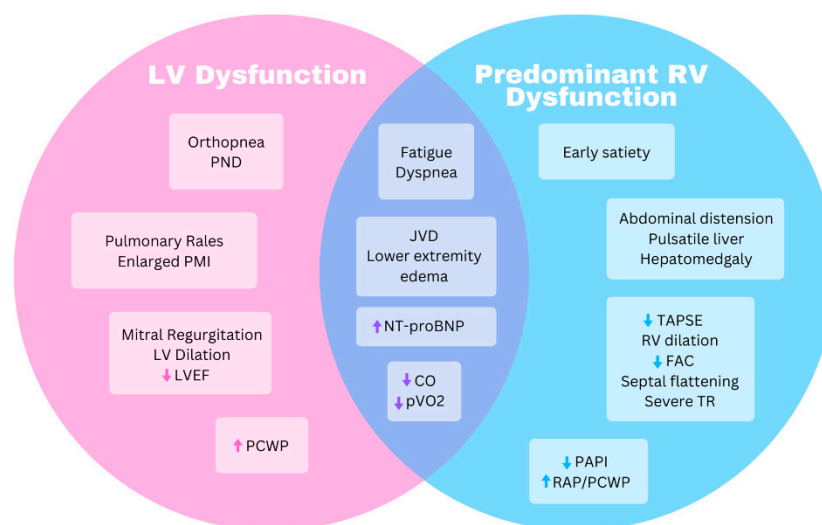
Figure 2. Venn diagram highlighting similarities and differences for symptoms and objective data between predominant right ventricle and left ventricle dysfunction. CO, cardiac output; FAC, fractional area change; JVD, jugular venous distension; LV, left ventricle; LVEF, left ventricle ejection fraction; NT-proBNP, N-terminal prohormone brain natriuretic peptide; PAPI, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; PND, paroxysmal nocturnal dyspnea; PMI, point of maximal impulse; pVO$_2$, peak oxygen uptake; RAP, right atrial pressure; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.
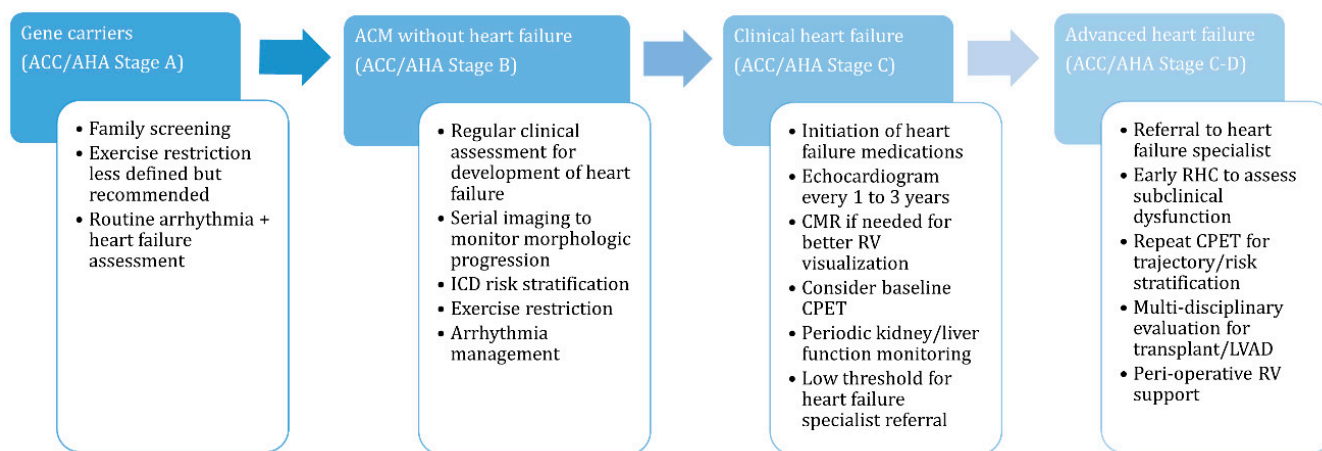

Figure 3. Heart failure management considerations across the arrhythmogenic cardiomyopathy disease spectrum. ACM, arrhythmogenic cardiomyopathy; CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise test; ICD, implantable cardioverter defibrillator; LVAD, left ventricular assist device; RHC, right heart catheterization; RV, right ventricle.

Laboratory tests supplement a heart failure diagnosis in ACM and novel markers may assist risk stratification. N-terminal pro-brain natriuretic peptide (NT-proBNP) correlates with RV dysfunction and RV dilation on cardiac magnetic resonance imaging (CMR) as well as with clinical outcomes including heart transplant and death [41,42]. Increased testosterone in males and decreased estradiol in females were associated with adverse cardiovascular outcomes in ACM in one study, offering a possible explanation for observed sex differences [43]. Serum inflammatory markers such as complement system components have been associated with structural changes and heart failure severity in ACM [44,45]. Many other novel serologic biomarkers including soluble ST2 protein, galectin-3, and extracellular matrix metalloproteinases 2 and 9 are under investigation, but to date have

limited clinical availability and according to a 2023 study, provide less prognostic value than NT-proBNP [41].

Echocardiography is often the first-line imaging test in heart failure, as it can provide a rapid, noninvasive appraisal of both right and left ventricular structure and function. RV regional akinesis or dyskinesis, an aneurysm of the RV free wall, and RV outflow tract dilation are all structural changes included in diagnostic criteria for ARVC [19]. Right atrial size and degree of tricuspid regurgitation along with RV functional measurements including fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE), peak systolic excursion velocity (S′), RV early diastolic myocardial velocity (e′), and an RV strain analysis can be assessed and are often abnormal in RV-predominant ACM (Figure 2) [46]. The degree of RV dysfunction on an echocardiogram correlates with the likelihood of clinical heart failure in ACM patients [9], and FAC and TAPSE in particular have been shown to predict adverse outcomes [47,48]. Additionally, septal flattening can suggest RV pressure and/or volume overload, and the inferior vena cava (IVC) diameter and respiratory variation assess volume status.

LV dilation and dysfunction are also easily assessed on echocardiography and may be the primary abnormality in some patients with ACM. LV dysfunction is well recognized as a poor prognostic factor in ARVC [7,49] and an LV ejection fraction (LVEF) < 50% in conjunction with RV dysfunction correlates with an increased risk of death or heart transplant [47]. Echocardiography also provides an easily accessible method for serial assessment to monitor progression of both LV and RV morphologic changes, which may precede worsening heart failure symptoms [50,51]. Repeat echocardiography is recommended every 1 to 3 years to monitor these changes (Figure 3) [6]. The main limitation of echocardiography in general is variable image quality but in ACM, this is further compounded by the geometric layout of the RV often hampering an echocardiographic analysis.

Cardiac magnetic resonance (CMR) imaging overcomes image quality and RV visualization limitations in ACM and also characterizes the myocardial tissue identifying fatty replacement and fibrosis [50]. Current diagnostic criteria do not include CMR tissue characterization but do have CMR-specific RV morphologic parameters that can satisfy major and minor criteria [19]. In ACM, patients with heart failure have a lower RV stroke volume index and RV cardiac index on CMR compared to those without heart failure [9]. In the setting of primarily LV dysfunction, late gadolinium enhancement (LGE) patterns can help identify potential etiologies including ACM. In patients presenting with acute myocarditis, a ring-like and septal LGE pattern was more common in patients later found to have a pathogenic or likely pathogenic variant in a desmosomal gene, most commonly *DSP* [29]. CMR is impractical for frequent serial assessment but occasional repeat assessment, especially in those with poor echocardiogram quality, can identify progression of both RV and LV morphologic changes as well as the degree of fibrosis [50,51].

Right heart catheterization (RHC) is the clinical gold standard for diagnosing RV failure and assessing severity. RHC also assesses for alternative causes of RV failure like pulmonary hypertension and LV failure if diagnostic uncertainty exists. Additionally, a simultaneous endomyocardial biopsy for a histopathologic analysis can be performed and is included in the diagnostic criteria for ARVC but is not routinely performed. RV failure in the setting of ACM classically manifests as elevated right atrial pressure (RAP) with normal pulmonary artery pressures and pulmonary capillary wedge pressure (PCWP). If there is LV involvement, PCWP may be elevated and additional parameters such as the RAP-to-PCWP ratio or pulmonary artery pulsatility index (PAPI) help identify the degree of primary RV dysfunction [52]. During the RHC, an estimate of cardiac output (CO) can be obtained using thermodilution or the indirect Fick equation. Thermodilution is the preferred method as it does not rely on assumptions like the indirect Fick method even in the setting of significant tricuspid regurgitation often seen in RV-predominant ACM [52]. Importantly, the measured CO using either method is only at rest and does not assess the ability of the heart to adequately increase CO with activity. RHC should be considered in patients with progressive heart failure symptoms or those with laboratory (rising creatinine

or abnormal liver parameters) or imaging abnormalities suggesting more severe heart failure than manifested by symptoms (Figure 3).

Cardiopulmonary exercise testing (CPET) has a well-validated role in assessment of heart failure severity [53], which can likely be extrapolated to heart failure in ACM. Peak oxygen uptake (pVO$_2$) quantifies exercise capacity and is used as a marker of heart failure severity with pVO$_2$ < 14 cc/kg/min indicating a poor prognosis [54]. Measurement of pVO$_2$ requires attaining maximal effort measured objectively with the respiratory exchange ratio (RER) but attaining this in ACM is often limited by anti-arrhythmic blunting of the heart rate or exercise hesitancy. Several effort-independent markers of cardiac function like inefficient ventilatory efficiency (minute ventilation to carbon dioxide (Ve/VCO$_2$) slope >34) and the presence of exercise oscillatory ventilation correlate with adverse outcomes in heart failure [53,55] and potentially ACM [56]. CPET in ACM appears to be safe based on a 2020 retrospective study of patients with ARVC undergoing CPET demonstrating no ventricular arrhythmias or other adverse events during or immediately after CPET [56]. Interval CPET testing provides information on the trajectory and need for advanced heart failure referral [53].

4. Heart Failure Management

4.1. Medical Management

Medical management of heart failure aims to stop or slow progression and manage fluid balance to alleviate symptoms as outlined in Figure 4. ACM patients with LV dysfunction should be treated with guideline-directed medical therapy (GDMT) per consensus recommendations [15,16]. These include a β-blocker (βB), mineralocorticoid receptor antagonist (MRA), sodium/glucose cotransporter-2 inhibitor (SGTL2i), and angiotensin receptor/neprilysin inhibitor (ARNI). Second-line for patients who cannot tolerate ARNI therapy is an angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor block (ARB) therapy. Similar evidence to guide management of patients with isolated or predominant RV dysfunction is lacking and mostly extrapolated from studies of LV dysfunction and smaller studies [12].

ACEi or ARB therapy was associated with slower reductions in TAPSE, RV dilation, and ventricular arrhythmias in one retrospective study [57]. Preemptive initiation of ACEi in mouse models of ARVC type 5 (an aggressive autosomal dominant form) led to reductions in myocardial fibrosis and mortality along with less severe reduction in LV dysfunction [58]. Initiation of ACEi or ARB should be considered in patients with symptomatic RV dysfunction, recognizing the subtle symptoms of heart failure in ACM and the benefit of early initiation, which may aid myocardial remodeling. ARNI therapy is an alternative but may be limited by hypotension and currently no clear evidence exists to recommend this preferentially over ACEi/ARB unless LV dysfunction is present. MRA similarly should be considered in symptomatic RV dysfunction due to beneficial remodeling effects seen in LV dysfunction.

SGTL2i therapy is the newest addition to heart failure GDMT and its benefits can likely be extrapolated to RV dysfunction. An added benefit of SGLT2i is the diuretic effect which can help reduce RV preload. In a plakophilin-deficient ACM mouse model, RV preload reduction with diuretics and isosorbide dinitrate prevented RV dilation [59], and use of isosorbide dinitrate (ISDN) can be considered in patients with symptomatic RV dysfunction [12]. Diuretic therapy, typically with furosemide or torsemide, is the primary method of preload reduction and should be used for ACM patients with evidence of volume overload. In general, there is no difference in outcomes between furosemide or torsemide [60]. However, torsemide has increased bioavailability and absorption is less affected by intestinal edema, which is a predominant manifestation of RV failure. Therefore, torsemide can be considered as an alternative to furosemide for initial therapy and should be utilized in the setting of ineffective preload management with furosemide. Adequate preload reduction needs to be balanced against the preload dependence of a failing RV.

Initiation and continuation of these medications should be accompanied by reassessment and monitoring of symptoms along with periodic evaluation of kidney and liver function.
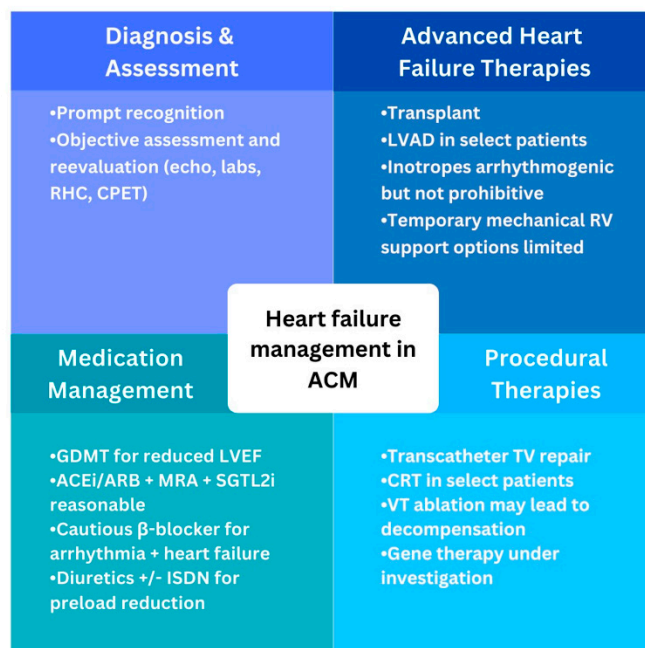

Figure 4. Global overview of heart failure management in arrhythmogenic cardiomyopathy. ACEi, angiotensin converting enzyme inhibitor; ACM, arrhythmogenic cardiomyopathy; ARB, angiotensin receptor blocker; CPET, cardiopulmonary exercise test; CRT, cardiac rexynchronization therapy; GDMT, guideline-directed medical therapy; ISDN, isosorbide dinitrate; LVAD, left ventricular assist device; LVEF, left ventricle ejection fraction; MRA, mineralocorticoid receptor antagonist; RV, right ventricle; SGLT2i, sodium/glucose cotransporter-2 inhibitor; TV, tricuspid valve; VT, ventricular tachycardia.

In ACM, β-blockers serve a dual purpose with their anti-arrhythmic properties and a theoretical heart failure benefit. Selection of appropriate anti-arrhythmic therapy in ACM is discussed elsewhere [12,14]. Similar to ACEi/ARB and MRA therapy, βB therapy should be considered in symptomatic RV dysfunction due to known benefits of myocardial remodeling seen in LV dysfunction. However, βBs have negative inotropy, which may be more detrimental in significant RV dysfunction compared to LV dysfunction. Beta-blockers should be started at low doses and up-titrated slowly with close monitoring for worsening symptoms. Safety of starting heart-failure-directed βB will also be influenced by medications used for arrhythmias like sotalol, flecainide, and amiodarone, which may already be slowing the heart rate significantly. Sotalol also has βB properties and combination with a heart failure βB (metoprolol, carvedilol, bisoprolol) must be carried out cautiously. As RV dysfunction progresses, the negative inotropic effects of βB may become more harmful, and down titration or discontinuation in conjunction with arrhythmia management should be considered as symptoms may improve with this intervention. However, even if symptoms improve, the need to decrease the dose is a sign of advancing heart failure and the need for further therapies needs to be considered.

4.2. Procedural Therapies

Invasive procedures for management of heart failure are potentially available when medical therapy is inadequate (Figure 4). Chronic resynchronization therapy (CRT) benefits symptomatic patients with heart failure, reduced LVEF, and a widened QRS complex [15,16] and these apply to ACM patients meeting the same criteria. The benefit of CRT or other pacemaker-related therapy in isolated RV dysfunction has not been demonstrated. Utility and selection of patients for ventricular tachycardia (VT) ablation are discussed elsewhere [12,14],

and data are lacking for heart-failure-related outcomes. However, the risk of hemodynamic decompensation during VT ablation due to repeated arrhythmias, fluid loading, and extended anesthesia needs to be balanced against the benefit and probability of success.

Progressive RV dilation can eventually lead to significant secondary tricuspid regurgitation (TR), which further exacerbates RV dysfunction. Transcatheter tricuspid valve repair for patients with severe symptomatic TR was recently shown to be safe and improve quality of life but did not affect mortality [61]. It is unclear how effective this therapy would be in predominant-RV-affected ACM but may be an option for patients with significant symptoms and appropriate anatomy without other options for heart failure relief. Remote pulmonary artery pressure monitoring using an implantable sensor prevents heart failure hospitalizations [62] and could be an attractive option for assessment and trajectory monitoring of subtle heart failure symptoms in RV-predominant ACM. However, it is unclear how effective they would be as many of these patients have normal pulmonary artery pressures, a rise in which is the primary parameter being measured with these devices.

4.3. Advanced Heart Failure Surgical Therapies

Patients with ACM may progress to develop or even present with advanced or end-stage heart failure. Evidence of advanced heart failure is similar across the LV and RV functional spectrum and includes the need for inotrope therapy, persistent symptoms and/or elevated biomarkers, worsening renal or liver function, repeat hospitalizations for heart failure, an increasing diuretic requirement, and low blood pressure [63]. While typically considered a sign of advanced heart failure, a recurrent ventricular arrhythmia is less applicable in ACM where arrhythmias are inherent to the condition and often occur independent of heart failure [37,38]. Similarly, inability to up-titrate GDMT or having to decrease GDMT is another sign of advanced heart failure that may be less applicable in ACM with significant RV dysfunction and must be considered in the context of RV physiology.

Cardiac transplantation is the definitive therapy for ACM, both for arrhythmia and heart failure clinical phenotypes. Transplants for ACM have increased over the last decade due to improved pre-transplant diagnoses and survival from SCD prevention [64]. A refractory ventricular arrhythmia is an indication for a transplant, but most ACM patients are transplanted because of end-stage heart failure [38,65]. Evaluation for transplant involves extensive multidisciplinary evaluation and diagnostic testing to ensure benefits outweigh risks of transplantation and the potential clinical course thereafter. Significant renal dysfunction, whether due to long-standing heart failure or other causes, may require evaluation for dual heart–kidney transplant. More unique to RV-predominant ACM is the potential for advanced liver disease due to long-standing congestion with case reports of dual heart–liver transplants in ACM [66]

Once waitlisted for a transplant, multiple patient factors including waitlist status, blood type, sex, size, and geography impact wait time and donor organ availability. In the interim, end-organ perfusion needs to be maintained despite poor cardiac function and may require additional inotropic and/or mechanical circulatory support. These modalities require special consideration in ACM [38]. Inotropes can be arrhythmogenic, worsening the predisposition to ventricular arrhythmias inherent in ACM. This should not preclude their use especially if arrhythmias are a remote issue, but initiation requires careful monitoring of arrhythmia burden. Most commonly used mechanical cardiac support devices are designed for isolated LV support; thus, they are ineffective for predominant-RV dysfunction. Percutaneous RV support options include Protek Duo® (LivaNova, London, UK) and Impella RP® (Abiomed, Danvers, MA, USA) but their use in ACM is often complicated by positioning challenges in a severely dilated RV. An extracorporeal membrane oxygenator (ECMO) provides full cardiac support but carries significant morbidity, including vascular and thrombotic complications. Decisions about transplant timing and peri-operative support require multi-disciplinary discussion and both medical and surgical expertise managing this complex physiology [38].

Durable left ventricular assist device (LVAD) therapy is a more readily available alternative to a transplant in advanced heart failure. In carefully selected patients with LV-predominant ACM, LVAD may be a viable option. However, use is limited in patients with significant RV disease as post-operative RV failure is a significant complication. Another consideration is the potential for increased ventricular arrhythmias post-LVAD caused by scarring around the LVAD cannula site or LV remodeling resulting in cannula myocardial irritation.

4.4. Emerging Therapies

Current management of ACM only targets disease manifestations (arrhythmia and heart failure) but pre-clinical work is ongoing to target disease mechanisms for treatment [35]. Investigators developed cell culture and small animal (mouse, zebrafish) models of ACM and targeted either cellular/inflammatory signaling pathways or gene expression [35]. Inhibition of nuclear factor of kappa-B (NFκB) and glycogen synthase kinase-3β (GSK3β) in two different animal models (*DSG2, JUP*) improved/preserved cardiac function and decreased myocardial fibrosis, respectively [67,68]. Similarly, small-molecule targeting of peroxisome proliferator activated receptor alpha/gamma (PPARα/γ) reduced cardiac fibrosis in mice and maintained regular electrical activity and calcium handling in human-induced pluripotent stem cells [69,70]. Off-target effects limit direct application clinically but improved understanding facilitates further discovery of potential therapeutics. Alternatively, advances in gene editing technology may allow for direct targeting of gene variants. Current techniques rely on introduction of genetic material into cells via viral vectors to incorporate into genomes and more recently genome editing with discoveries like CRISPR-Cas9. Correction of *DSG2*-deficient cardiomyocytes from stem cells via virally introduced normal *DSG2* has been demonstrated [71]. Implementation of genome-editing technology is actively being investigated in many genetic cardiomyopathies including ACM [72].

5. Conclusions

Heart failure prevalence in ACM is increasing and often manifests as predominant-RV dysfunction. This creates unique challenges in diagnosing, risk stratifying, and managing heart failure in ACM. Practitioners caring for these patients need to assess the need for modifications to standard heart failure therapy and determine when such therapy is ineffective. For those patients with progressive heart failure, advanced therapy options exist but evaluation and peri-operative management also require unique considerations. With a full understanding of these unique considerations across the spectrum of heart failure in ACM, practitioners should be able to adequately care for these patients. Additionally, care of these patients in structured multi-disciplinary clinics incorporating electrophysiologists, heart failure cardiologists, genetic counselors, and even translational researchers may improve longitudinal patient care and facilitate implementation of more data-driven management recommendations.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

ACEi	angiotensin converting enzyme inhibitor
ACM	arrhythmogenic cardiomyopathy
ALVC	arrhythmogenic left ventricular cardiomyopathy
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
ARVC	arrhythmogenic right ventricular cardiomyopathy
βB	beta-blocker
CMR	cardiac magnetic resonance
CO	cardiac output
CPET	cardiopulmonary exercise test
CRT	cardiac resynchronization therapy
DSG2	desmoglein-2
DSP	desmoplakin
ECMO	extracorporeal membrane oxygenator
FAC	fractional area change
GDMT	guideline-directed medical therapy
ICD	implantable cardioverter defibrillator
ISDN	isosorbide dinitrate
IVC	inferior vena cava
LGE	late gadolinium enhancement
LV	left ventricle
LVAD	left ventricular assist device
LVEF	left ventricle ejection fraction
MRA	mineralocorticoid receptor antagonist
NT-proBNP	N-terminal prohormone brain natriuretic peptide
PAPI	pulmonary artery pulsatility index
PCWP	pulmonary capillary wedge pressure
PKP2	plakophilin-2
PMI	point of maximal impulse
PND	paroxysmal nocturnal dyspnea
pVO_2	peak oxygen uptake
RAP	right atrial pressure
RER	respiratory exchange ratio
RHC	right heart catheterization
RV	right ventricle
SCD	sudden cardiac death
SGTL2i	sodium/glucose cotransporter-2 inhibitor
TAPSE	tricuspid annular plane systolic excursion
TR	tricuspid regurgitation
Ve/VCO_2	ventilation to carbon dioxide production ratio

References

1. Corrado, D.; Basso, C.; Thiene, G.; McKenna, W.J.; Davies, M.J.; Fontaliran, F.; Nava, A.; Silvestri, F.; Blomstrom-Lundqvist, C.; Wlodarska, E.K.; et al. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: A multicenter study. *J. Am. Coll. Cardiol.* **1997**, *30*, 1512–1520. [CrossRef]
2. Marcus, F.I.; Fontaine, G.H.; Guiraudon, G.; Frank, R.; Laurenceau, J.L.; Malergue, C. Right ventricular dysplasia: A report of 24 adult cases. In *Myocarditis Cardiomyopathy*; Springer: Berlin/Heidelberg, Germany, 1983; pp. 81–93. [CrossRef]
3. Thiene, G.; Nava, A.; Corrado, D.; Rossi, L.; Pennelli, N. Right ventricular cardiomyopathy and sudden death in young people. *N. Engl. J. Med.* **1982**, *65*, 384–398. [CrossRef]
4. Gandjbakhch, E.; Redheuil, A.; Pousset, F.; Charron, P.; Frank, R. Clinical diagnosis, imaging, and genetics of arrhythmogenic right ventricular cardiomyopathy/dysplasia. *J. Am. Coll. Cardiol.* **2018**, *72*, 784–804. [CrossRef] [PubMed]
5. James, C.A.; Syrris, P.; van Tintelen, J.P.; Calkins, H. The role of genetics in cardiovascular disease: Arrhythmogenic cardiomyopathy. *Eur. Heart J.* **2020**, *41*, 1393–1400. [CrossRef] [PubMed]

6. Corrado, D.; Van Tintelen, P.J.; McKenna, W.J.; Hauer, R.N.W.; Anastastakis, A.; Asimaki, A.; Basso, C.; Bauce, B.; Brunckhorst, C.; Bucciarelli-Ducci, C.; et al. International Experts. Arrhythmogenic right ventricular cardiomyopathy: Evaluation of the current diagnostic criteria and differential diagnosis. *Eur. Heart J.* **2020**, *41*, 1414–1429. [CrossRef] [PubMed]

7. Groeneweg, J.A.; van der Zwaag, P.A.; Jongbloed, J.D.; Cox, M.G.; Vreeker, A.; de Boer, R.A.; van der Heijden, J.F.; van Veen, T.A.; McKenna, W.J.; van Tintelen, J.P.; et al. Left-dominant arrhythmogenic cardiomyopathy in a large family: Associated desmosomal or nondesmosomal genotype? *Heart Rhythm.* **2013**, *10*, 548–559. [CrossRef] [PubMed]

8. Saguner, A.M. Arrhythmogenic ventricular cardiomyopathy: A paradigm shift from right to biventricular disease. *World J. Cardiol.* **2014**, *6*, 154–174. [CrossRef] [PubMed]

9. Gilotra, N.A.; Bhonsale, A.; James, C.A.; Te Riele, A.S.J.; Murray, B.; Tichnell, C.; Sawant, A.; Ong, C.S.; Judge, D.P.; Russell, S.D.; et al. Heart failure is common and under-recognized in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circ. Heart Fail.* **2017**, *10*, e003819. [CrossRef] [PubMed]

10. Kimura, Y.; Noda, T.; Matsuyama, T.-A.; Otsuka, Y.; Kamakura, T.; Wada, M.; Ishibashi, K.; Inoue, Y.; Miyamoto, K.; Okamura, H.; et al. Heart failure in patients with arrhythmogenic right ventricular cardiomyopathy: What are the risk factors? *Int. J. Cardiol.* **2017**, *241*, 288–294. [CrossRef]

11. Kimura, Y.; Noda, T.; Otsuka, Y.; Wada, M.; Nakajima, I.; Ishibashi, K.; Miyamoto, K.; Okamura, H.; Aiba, T.; Kamakura, S.; et al. Potentially lethal ventricular arrhythmias and heart failure in arrhythmogenic Right Ventricular cardiomyopathy. *JACC Clin. Electrophysiol.* **2016**, *2*, 546–555. [CrossRef]

12. Towbin, J.A.; McKenna, W.J.; Abrams, D.J.; Ackerman, M.J.; Calkins, H.; Darrieux, F.C.; Daubert, J.P.; de Chillou, C.; DePasquale, E.C.; Desai, M.Y.; et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm.* **2019**, *16*, e301–e372. [CrossRef]

13. Castrichini, M.; Eldemire, R.; Groves, D.W.; Taylor, M.R.; Miyamoto, S.; Mestroni, L. Clinical and genetic features of arrhythmogenic cardiomyopathy: Diagnosis, management and the heart failure perspective. *Prog. Pediatr. Cardiol.* **2021**, *63*, 101459. [CrossRef]

14. Gaine, S.P.; Calkins, H. Antiarrhythmic drug therapy in arrhythmogenic right ventricular cardiomyopathy. *Biomedicines* **2023**, *11*, 1213. [CrossRef] [PubMed]

15. Heidenreich, P.A.; Bozkurt, B.; Aguilar, D.; Allen, L.A.; Byun, J.J.; Colvin, M.M.; Deswal, A.; Drazner, M.H.; Dunlay, S.M.; Evers, L.R.; et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the american college of cardiology/american heart association joint committee on clinical practice guidelines. *J. Am. Coll. Cardiol.* **2022**, *79*, e263–e421. [CrossRef] [PubMed]

16. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O.; et al. 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **2023**, *44*, 3627–3639. [CrossRef]

17. Calkins, H. Arrhythmogenic right ventricular dysplasia/cardiomyopathy—Three decades of progress. *Circ. J.* **2015**, *79*, 901–913. [CrossRef] [PubMed]

18. Corrado, D.; Thiene, G. Arrhythmogenic right ventricular cardiomyopathy/dysplasia: Clinical impact of molecular genetic studies. *Circulation* **2006**, *113*, 1634–1637. [CrossRef] [PubMed]

19. Marcus, F.I.; McKenna, W.J.; Sherrill, D.; Basso, C.; Bauce, B.; Bluemke, D.A.; Calkins, H.; Corrado, D.; Cox, M.G.; Daubert, J.P.; et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circulation* **2010**, *121*, 1533–1541. [CrossRef] [PubMed]

20. Groeneweg, J.A.; Bhonsale, A.; James, C.A.; Te Riele, A.S.; Dooijes, D.; Tichnell, C.; Murray, B.; Wiesfeld, A.C.; Sawant, A.C.; Kassamali, B.; et al. Clinical presentation, long-term follow-up, and outcomes of 1001 arrhythmogenic right ventricular dysplasia/cardiomyopathy patients and family members. *Circ. Cardiovasc. Genet.* **2015**, *8*, 437–446. [CrossRef]

21. Bhonsale, A.; Groeneweg, J.A.; James, C.A.; Dooijes, D.; Tichnell, C.; Jongbloed, J.D.H.; Murray, B.; Te Riele, A.S.J.M.; Van Den Berg, M.P.; Bikker, H.; et al. Impact of genotype on clinical course in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated mutation carriers. *Eur. Heart J.* **2015**, *36*, 847–855. [CrossRef]

22. Gerull, B.; Brodehl, A. Insights into genetics and pathophysiology of arrhythmogenic cardiomyopathy. *Curr. Heart Fail. Rep.* **2021**, *18*, 378–390. [CrossRef] [PubMed]

23. McKoy, G.; Protonotarios, N.; Crosby, A.; Tsatsopoulou, A.; Anastasakis, A.; Coonar, A.; Norman, M.; Baboonian, C.; Jeffery, S.; McKenna, W.J. Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (naxos disease). *Lancet* **2000**, *355*, 2119–2124. [CrossRef]

24. Nehme, N.; El Malti, R.; Roux-Buisson, N.; Caignault, J.-R.; Bouvagnet, P. Evidence for genetic heterogeneity in carvajal syndrome. *Cell Tissue Res.* **2012**, *348*, 261–264. [CrossRef] [PubMed]

25. Castelletti, S.; Vischer, A.S.; Syrris, P.; Crotti, L.; Spazzolini, C.; Ghidoni, A.; Parati, G.; Jenkins, S.; Kotta, M.-C.; McKenna, W.J.; et al. Desmoplakin missense and non-missense mutations in arrhythmogenic right ventricular cardiomyopathy: Genotype-phenotype correlation. *Int. J. Cardiol.* **2017**, *249*, 268–273. [CrossRef]

26. Hermida, A.; Fressart, V.; Hidden-Lucet, F.; Donal, E.; Probst, V.; Deharo, J.C.; Chevalier, P.; Klug, D.; Mansencal, N.; Delacretaz, E.; et al. High risk of heart failure associated with desmoglein-2 mutations compared to plakophilin-2 mutations in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Eur. J. Heart Fail.* **2019**, *21*, 792–800. [CrossRef] [PubMed]

27. Protonotarios, A.; Bariani, R.; Cappelletto, C.; Pavlou, M.; García-García, A.; Cipriani, A.; Protonotarios, I.; Rivas, A.; Wittenberg, R.; Graziosi, M.; et al. Importance of genotype for risk stratification in arrhythmogenic right ventricular cardiomyopathy using the 2019 ARVC risk calculator by guest on 12 August 2023. *Eur. Heart J.* **2022**, *43*, 3053. [CrossRef] [PubMed]

28. Smith, E.D.; Lakdawala, N.K.; Papoutsidakis, N.; Aubert, G.; Mazzanti, A.; McCanta, A.C.; Agarwal, P.P.; Arscott, P.; Dellefave-Castillo, L.M.; Vorovich, E.E.; et al. Desmoplakin cardiomyopathy, a fibrotic and inflammatory form of cardiomyopathy distinct from typical dilated or arrhythmogenic right ventricular cardiomyopathy. *Circulation* **2020**, *141*, 1872–1884. [CrossRef]

29. Ammirati, E.; Raimondi, F.; Piriou, N.; Infirri, L.S.; Mohiddin, S.A.; Mazzanti, A.; Shenoy, C.; Cavallari, U.A.; Imazio, M.; Aquaro, G.D.; et al. Acute myocarditis associated with desmosomal gene variants. *JACC Heart Fail.* **2022**, *10*, 714–727. [CrossRef]

30. Kelly, M.A.; Caleshu, C.; Morales, A.; Buchan, J.; Wolf, Z.; Harrison, S.M.; Cook, S.; Dillon, M.W.; Garcia, J.; Haverfield, E.; et al. Adaptation and validation of the ACMG/AMP variant classification framework for MYH7-associated inherited cardiomyopathies: Recommendations by ClinGen's inherited cardiomyopathy expert panel. *Anesth. Analg.* **2018**, *20*, 351–359. [CrossRef]

31. Richards, S.; Aziz, N.; Bale, S.; Bick, D.; Das, S.; Gastier-Foster, J.; Grody, W.W.; Hegde, M.; Lyon, E.; Spector, E.; et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Anesth. Analg.* **2015**, *17*, 405–424. [CrossRef]

32. Wilde, A.A.M.; Semsarian, C.; Márquez, M.F.; Shamloo, A.S.; Ackerman, M.J.; Ashley, E.A.; Eduardo, B.S.; Barajas-Martinez, H.; Behr, E.R.; Bezzina, C.R.; et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases. *J. Arrhythmia* **2022**, *38*, 491–553. [CrossRef] [PubMed]

33. Campuzano, O.; Sarquella-Brugada, G.; Fernandez-Falgueras, A.; Coll, M.; Iglesias, A.; Ferrer-Costa, C.; Cesar, S.; Arbelo, E.; García-Álvarez, A.; Jordà, P.; et al. Reanalysis and reclassification of rare genetic variants associated with inherited arrhythmogenic syndromes. *EBioMedicine* **2020**, *54*, 102732. [CrossRef] [PubMed]

34. Barrios, E.M.; Brugada, G.S.; Gomez, J.C.; Diaz, S.C.; Ccasani, F.C.; Greco, A.; Fiol, V.; Cerralbo, P.; Terradellas, J.B.; Larrea, O.C. Update on rare variants in inherited arrhythmogenic syndromes: When to reclassify? *EP Eur.* **2023**, *25*. [CrossRef]

35. Engel, M.; Shiel, E.; Chelko, S.P. Basic and translational mechanisms in inflammatory arrhythmogenic cardiomyopathy. *Int. J. Cardiol.* **2023**, 131602. [CrossRef] [PubMed]

36. Boogerd, C.J.; Lacraz, G.P.A.; Vértesy, Á.; van Kampen, S.J.; Perini, I.; de Ruiter, H.; Versteeg, D.; Brodehl, A.; van der Kraak, P.; Giacca, M.; et al. Spatial transcriptomics unveils ZBTB11 as a regulator of cardiomyocyte degeneration in arrhythmogenic cardiomyopathy. *Cardiovasc. Res.* **2022**, *119*, 477–491. [CrossRef] [PubMed]

37. Dalal, D.; Nasir, K.; Bomma, C.; Prakasa, K.; Tandri, H.; Piccini, J.; Roguin, A.; Tichnell, C.; James, C.; Russell, S.D.; et al. Arrhythmogenic right ventricular dysplasia: A united states experience. *Circulation* **2005**, *112*, 3823–3832. [CrossRef]

38. Scheel, P.J.; Giuliano, K.; Tichnell, C.; James, C.; Murray, B.; Tandri, H.; Carter, D.; Fehr, T.; Umapathi, P.; Vaishnav, J.; et al. Heart transplantation strategies in arrhythmogenic right ventricular cardiomyopathy: A tertiary ARVC centre experience. *ESC Heart Fail.* **2021**, *9*, 1008–1017. [CrossRef]

39. Bozkurt, B.; Coats, A.J.; Tsutsui, H.; Abdelhamid, M.; Adamopoulos, S.; Albert, N.; Anker, S.D.; Atherton, J.; Böhm, M.; Butler, J.; et al. Universal definition and classification of heart failure. *J. Card. Fail.* **2021**, *27*, 387–413. [CrossRef]

40. James, C.A.; Bhonsale, A.; Tichnell, C.; Murray, B.; Russell, S.D.; Tandri, H.; Tedford, R.J.; Judge, D.P.; Calkins, H. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy–associated desmosomal mutation carriers. *J. Am. Coll. Cardiol.* **2013**, *62*, 1290–1297. [CrossRef]

41. Borowiec, K.; Woźniak, O.; Wróbel, A.; Śmigielski, W.; Skrzypczyńska-Banasik, U.; Kowalik, E.; Lutyńska, A.; Hoffman, P.; Biernacka, E.K. NT-proBNP is superior to novel plasma biomarkers for predicting adverse outcome in arrhythmogenic right ventricular cardiomyopathy. *Pol. Arch. Intern. Med.* **2023**, *133*, 16443. [CrossRef]

42. Cheng, H.; Lu, M.; Hou, C.; Chen, X.; Wang, J.; Yin, G.; Chu, J.; Zhang, S.; Prasad, S.K.; Pu, J.; et al. Relation between n-terminal pro-brain natriuretic peptide and cardiac remodeling and function assessed by cardiovascular magnetic resonance imaging in patients with arrhythmogenic right ventricular cardiomyopathy. *Am. J. Cardiol.* **2015**, *115*, 341–347. [CrossRef] [PubMed]

43. Akdis, D.; Saguner, A.M.; Shah, K.; Wei, C.; Medeiros-Domingo, A.; von Eckardstein, A.; Lüscher, T.F.; Brunckhorst, C.; Chen, H.V.; Duru, F. Sex hormones affect outcome in arrhythmogenic right ventricular cardiomyopathy/dysplasia: From a stem cell derived cardiomyocyte-based model to clinical biomarkers of disease outcome. *Eur. Heart J.* **2017**, *38*, 1498–1508. [CrossRef] [PubMed]

44. Chen, L.; Yang, F.; Chen, X.; Rao, M.; Zhang, N.-N.; Chen, K.; Deng, H.; Song, J.-P.; Hu, S.-S. Comprehensive myocardial proteogenomics profiling reveals C/EBPα as the key factor in the lipid storage of ARVC. *J. Proteome Res.* **2017**, *16*, 2863–2876. [CrossRef] [PubMed]

45. Ren, J.; Chen, L.; Chen, X.; Zhang, N.; Sun, X.; Song, J. Acylation-stimulating protein and heart failure progression in arrhythmogenic right ventricular cardiomyopathy. *ESC Heart Fail.* **2022**, *10*, 492–501. [CrossRef] [PubMed]

46. Qasem, M.; Utomi, V.; George, K.; Somauroo, J.; Zaidi, A.; Forsythe, L.; Bhattacharrya, S.; Lloyd, G.; Rana, B.; Ring, L.; et al. A meta-analysis for the echocardiographic assessment of right ventricular structure and function in ARVC: A study by the research and audit committee of the british society of echocardiography. *Echo Res. Pract.* **2016**, *3*, 95–104. [CrossRef] [PubMed]

47. Pinamonti, B.; Dragos, A.M.; Pyxaras, S.A.; Merlo, M.; Pivetta, A.; Barbati, G.; Di Lenarda, A.; Morgera, T.; Mestroni, L.; Sinagra, G. Prognostic predictors in arrhythmogenic right ventricular cardiomyopathy: Results from a 10-year registry. *Eur. Heart J.* **2011**, *32*, 1105–1113. [CrossRef] [PubMed]

48. Saguner, A.M.; Vecchiati, A.; Baldinger, S.H.; Rüeger, S.; Medeiros-Domingo, A.; Mueller-Burri, A.S.; Haegeli, L.M.; Biaggi, P.; Manka, R.; Lüscher, T.F.; et al. Different prognostic value of functional right ventricular parameters in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circ. Cardiovasc. Imaging* **2014**, *7*, 230–239. [CrossRef]

49. Lemola, K.; Brunckhorst, C.; Helfenstein, U.; Oechslin, E.; Jenni, R.; Duru, F. Predictors of adverse outcome in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy: Long term experience of a tertiary care centre. *Heart* **2005**, *91*, 1167–1172. [CrossRef]

50. Malik, N.; Mukherjee, M.; Wu, K.C.; Zimmerman, S.L.; Zhan, J.; Calkins, H.; James, C.A.; Gilotra, N.A.; Sheikh, F.H.; Tandri, H.; et al. Multimodality imaging in arrhythmogenic right ventricular cardiomyopathy. *Circ. Cardiovasc. Imaging* **2022**, *15*, 106–121. [CrossRef]

51. Mast, T.P.; James, C.A.; Calkins, H.; Teske, A.J.; Tichnell, C.; Murray, B.; Loh, P.; Russell, S.D.; Velthuis, B.K.; Judge, D.P.; et al. Evaluation of structural progression in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *JAMA Cardiol.* **2017**, *2*, 293–302. [CrossRef]

52. Hsu, S.; Fang, J.C.; Borlaug, B.A. Hemodynamics for the heart failure clinician: A state-of-the-art review. *J. Card. Fail.* **2021**, *28*, 133–148. [CrossRef]

53. Malhotra, R.; Bakken, K.; D'elia, E.; Lewis, G.D. Cardiopulmonary exercise testing in heart failure. *JACC Heart Fail.* **2016**, *4*, 607–616. [CrossRef]

54. Corrà, U.; Piepoli, M.F.; Adamopoulos, S.; Agostoni, P.; Coats, A.J.; Conraads, V.; Lambrinou, E.; Pieske, B.; Piotrowicz, E.; Schmid, J.-P.; et al. Cardiopulmonary exercise testing in systolic heart failure in 2014: The evolving prognostic role. *Eur. J. Heart Fail.* **2014**, *16*, 929–941. [CrossRef] [PubMed]

55. Guazzi, M.; Raimondo, R.; Vicenzi, M.; Arena, R.; Proserpio, C.; Braga, S.S.; Pedretti, R. Exercise oscillatory ventilation may predict sudden cardiac death in heart failure patients. *J. Am. Coll. Cardiol.* **2007**, *50*, 299–308. [CrossRef]

56. Scheel, P.J.; Florido, R.; Hsu, S.; Murray, B.; Tichnell, C.; James, C.; Judge, D.P.; Russell, S.D.; Tedford, R.J.; Calkins, H.; et al. Safety and utility of cardiopulmonary exercise testing in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *J. Card. Fail.* **2018**, *24*, S50–S51. [CrossRef]

57. Tu, B.; Wu, L.; Zheng, L.; Liu, S.; Sheng, L.; Liu, L.; Zhu, Z.; Yao, Y. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers: Anti-arrhythmic drug for arrhythmogenic right ventricular cardiomyopathy. *Front. Cardiovasc. Med.* **2021**, *8*, 769138. [CrossRef] [PubMed]

58. Domínguez, F.; Lalaguna, L.; López-Olañeta, M.; Villalba-Orero, M.; Padrón-Barthe, L.; Román, M.; Bello-Arroyo, E.; Briceño, A.; Gonzalez-Lopez, E.; Segovia-Cubero, J.; et al. Early preventive treatment with enalapril improves cardiac function and delays mortality in mice with arrhythmogenic right ventricular cardiomyopathy type 5. *Circ. Heart Fail.* **2021**, *14*, e007616. [CrossRef]

59. Fabritz, L.; Hoogendijk, M.G.; Scicluna, B.P.; van Amersfoorth, S.C.; Fortmueller, L.; Wolf, S.; Laakmann, S.; Kreienkamp, N.; Piccini, I.; Breithardt, G.; et al. Load-reducing therapy prevents development of arrhythmogenic right ventricular cardiomyopathy in plakoglobin-deficient mice. *J. Am. Coll. Cardiol.* **2011**, *57*, 740–750. [CrossRef]

60. Mentz, R.J.; Anstrom, K.J.; Eisenstein, E.L.; Sapp, S.; Greene, S.J.; Morgan, S.; Testani, J.M.; Harrington, A.H.; Sachdev, V.; Ketema, F.; et al. Effect of torsemide vs. furosemide after discharge on all-cause mortality in patients hospitalized with heart failure: The TRANSFORM-HF randomized clinical trial. *JAMA* **2023**, *329*, 214–223. [CrossRef]

61. Sorajja, P.; Whisenant, B.; Hamid, N.; Naik, H.; Makkar, R.; Tadros, P.; Price, M.J.; Singh, G.; Fam, N.; Kar, S.; et al. Transcatheter repair for patients with tricuspid regurgitation. *N. Engl. J. Med.* **2023**, *388*, 1833–1842. [CrossRef]

62. Abraham, W.T.; Stevenson, L.W.; Bourge, R.C.; Lindenfeld, J.A.; Bauman, J.G.; Adamson, P.B.; CHAMPION Trial Study Group. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: Complete follow-up results from the CHAMPION randomised trial. *Lancet* **2016**, *387*, 453–461. [CrossRef] [PubMed]

63. Baumwol, J. "I Need Help"—A mnemonic to aid timely referral in advanced heart failure. *J. Heart Lung Transplant.* **2017**, *36*, 593–594. [CrossRef] [PubMed]

64. Giuliano, K.; Scheel, P.; Etchill, E.; Fraser, C.D.; Suarez-Pierre, A.; Hsu, S.; Wittstein, I.S.; Kasper, E.K.; Florido, R.; Tandri, H.; et al. Heart transplantation outcomes in arrhythmogenic right ventricular cardiomyopathy: A contemporary national analysis. *ESC Heart Fail.* **2022**, *9*, 988–997. [CrossRef] [PubMed]

65. Tedford, R.J.; James, C.; Judge, D.P.; Tichnell, C.; Murray, B.; Bhonsale, A.; Philips, B.; Abraham, T.; Dalal, D.; Halushka, M.K.; et al. Cardiac transplantation in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J. Am. Coll. Cardiol.* **2012**, *59*, 289–290. [CrossRef] [PubMed]

66. Lewsey, S.C.; Sharma, K.; Kilic, A.; Halushka, M.K.; Vaishnav, J.; Wittstein, I.S.; Tandri, H.; Calkins, H.; James, C.A.; Gilotra, N.A. Dual-organ transplantation in a Woman with right ventricular failure secondary to arrhythmogenic Right Ventricular cardiomyopathy. *JACC Case Rep.* **2020**, *2*, 59–63. [CrossRef] [PubMed]

67. Chelko, S.P.; Asimaki, A.; Andersen, P.; Bedja, D.; Amat-Alarcon, N.; DeMazumder, D.; Jasti, R.; MacRae, C.A.; Leber, R.; Kleber, A.G.; et al. Central role for GSK3β in the pathogenesis of arrhythmogenic cardiomyopathy. *J. Clin. Investig.* **2016**, *1*, e85923. [CrossRef]

68. Chelko, S.; Asimaki, A.; Lowenthal, J.; Bueno-Beti, C.; Bedja, D.; Scalco, A.; Amat-Alarcon, N.; Andersen, P.; Judge, D.P.; Tung, L.; et al. Therapeutic modulation of the immune response in arrhythmogenic cardiomyopathy. *Circulation* **2019**, *140*, 1491–1505. [CrossRef]

69. Reisqs, J.; Moreau, A.; Charrabi, A.; Sleiman, Y.; Meli, A.C.; Millat, G.; Briand, V.; Beauverger, P.; Richard, S.; Chevalier, P. The PPARγ pathway determines electrophysiological remodelling and arrhythmia risks in DSC2 arrhythmogenic cardiomyopathy. *Clin. Transl. Med.* **2022**, *12*, e748. [CrossRef]
70. Qiu, Z.; Zhao, Y.; Tao, T.; Guo, W.; Liu, R.; Huang, J.; Xu, G. Activation of PPARα Ameliorates Cardiac Fibrosis in Dsg2-Deficient arrhythmogenic cardiomyopathy. *Cells* **2022**, *11*, 3184. [CrossRef]
71. Shiba, M.; Higo, S.; Kondo, T.; Li, J.; Liu, L.; Ikeda, Y.; Kohama, Y.; Kameda, S.; Tabata, T.; Inoue, H.; et al. Phenotypic recapitulation and correction of desmoglein-2-deficient cardiomyopathy using human-induced pluripotent stem cell-derived cardiomyocytes. *Hum. Mol. Genet.* **2021**, *30*, 1384–1397. [CrossRef]
72. Romeo, F.J.; Mavropoulos, S.A.; Ishikawa, K. Progress in clinical gene therapy for cardiac disorders. *Mol. Diagn. Ther.* **2023**, *27*, 179–191. [CrossRef] [PubMed]