Circulation Research

COMPENDIUM ON CARDIOPULMONARY DISEASE AND EXERCISE: MOLECULAR TO CLINICAL MECHANISMS

Exercise in Inherited Cardiomyopathies: Optimizing the Dose-Response Curve

Eleanor E. Rye, Amy M. Mitchell, Celine F. Santiago, Andre La Gerche, Diane Fatkin

ABSTRACT: Exercise is generally considered beneficial for cardiovascular health, but for patients with inherited cardiomyopathies, exercise can be a source of anxiety due to concerns about arrhythmia risk and disease progression. In the general population, exercise avoidance can impact cardiometabolic health and diminished fitness is a risk factor for heart failure. At the other extreme, sustained high levels of exercise in competitive endurance athletes have been associated with an increased risk of some arrhythmias. Defining optimal threshold levels for exercise participation is not straightforward and one-size-fits-all recommendations are unlikely to be successful. In the context of inherited cardiomyopathies, the impact of exercise on myocardial function and arrhythmias depends on factors such as exercise frequency, intensity, and duration, as well as the type of cardiomyopathy, underlying genotype, and other unique intrinsic traits in each individual. This review outlines current knowledge with respect to the impact of exercise in hypertrophic, arrhythmogenic, and dilated cardiomyopathies based on studies in human cohorts and animal models. Several disease-specific and genotype-specific risk factors are highlighted, although our understanding of these factors remains incomplete. Importantly, although exercise activities remain restricted for those with high-risk features, emerging evidence suggests that moderate-to-high levels of exercise may be safe and beneficial for many patients. Harnessing the cardioprotective power of exercise holds enormous promise for expanding personalized strategies for cardiomyopathy treatment and prevention.

Key Words: arrhythmias, cardiac ■ cardiomyopathies ■ exercise ■ heart failure ■ risk factors

Inherited cardiomyopathies are a group of primary myocardial disorders associated with an increased risk of cardiac arrhythmias, heart failure (HF), stroke, and sudden cardiac death (SCD). These disorders are classified by their phenotypic features, with the most common types being hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and arrhythmogenic cardiomyopathy (ACM). Substantial progress has been made in elucidating the genetic underpinnings of inherited cardiomyopathies and genetic testing to identify causative rare variants is now routinely performed. Increasingly, however, there is recognition that additional patient-related and exogenous factors influence disease manifestation in genotype-positive individuals.

Regular physical activity is generally considered beneficial for cardiovascular health with favorable effects on blood pressure, body weight, lipid profiles, insulin sensitivity, endothelial function, adverse events related to coronary artery disease, and longevity.[1] Current American Heart Association guidelines recommend that adults undertake at least 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic exercise per week.[2] For families with inherited cardiomyopathies, the safety of exercise participation is a frequent dilemma with a relative paucity of guiding evidence. Concerns that exercise might accelerate cardiac dysfunction or trigger arrhythmias have led to physician hesitancy and patient reluctance to engage in physical activity. Consequently, many individuals opt for a sedentary lifestyle that in itself can be disease-promoting. In recent years, there has been a shift in thinking and greater appreciation of the value of exercise; however, the subject remains controversial.

Correspondence to: Diane Fatkin, MD, Victor Chang Cardiac Research Institute, 405 Liverpool St, Darlinghurst, New South Wales 2010, Australia. Email d.fatkin@victorchang.edu.au

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCRESAHA.125.326396.
For Sources of Funding and Disclosures, see page 329.

Circulation Research is available at www.ahajournals.org/journal/res

Nonstandard Abbreviations and Acronyms

ACM	arrhythmogenic cardiomyopathy
CREBH	cAMP-responsive element-binding protein H
DCM	dilated cardiomyopathy
ERK	extracellular signal–regulated kinase
G+P–	genotype-positive, phenotype-negative
HCM	hypertrophic cardiomyopathy
HF	heart failure
ICD	implantable cardioverter defibrillator
IGF-1	insulin-like growth factor 1
LINC	linker-of-nucleoskeletonand-cytoskeleton
LV	left ventricle
LVEF	left ventricular ejection fraction
LVOTO	left ventricular outflow tract obstruction
MACE	major adverse cardiac events
MAPK	mitogen-activated protein kinase
MET	metabolic equivalent
mTOR	mammalian target of rapamycin
NFAT	nuclear factor of activated T cell
NYHA	New York Heart Association
PDGF	platelet-derived growth factor
PEVK	proline-glutamatevaline-lysine
PGC-1α	peroxisome proliferator-activated receptor-gamma coactivator
PPARγ	peroxisome proliferator-activated receptor gamma
PI3K	phosphoinositide 3-kinase
RV	right ventricle
SCD	sudden cardiac death
TGF	transforming growth factor
***TTN*tv**	truncating variants in the *TTN* gene
VA	ventricular arrhythmia
VO_2peak	peak oxygen uptake
Wnt	wingless-related integration site
YAP	Yes-associated protein

Exercise dose per se is not the only consideration, with several factors contributing to the myocardial exercise response. In the context of inherited cardiomyopathies, this includes clinical determinants of cardiac size and function such as an individual's age and sex, cardiomyopathy type, genotype, phenotype, comorbidities, and lifestyle. In this review, we will outline current perspectives on the role of exercise in inherited cardiomyopathies and the aspiration toward personally tailored exercise prescriptions.

QUANTIFYING EXERCISE EXPOSURE

Individual exercise burden is determined by the frequency, intensity, time, and type of physical activity performed over time. Physical activities can be broadly categorized according to the type of hemodynamic stress imposed on the cardiovascular system. Classification exists on a continuum of relative intensity of the required static component (defined by the percentage of maximal voluntary skeletal muscle contraction) and dynamic component (defined by the percentage of peak oxygen uptake [VO_2peak]). High-dynamic activities involve repetitive isotonic skeletal muscle contraction that necessitates an increase in cardiac output, respiratory rate, and oxygen uptake. The intensity of high-dynamic activities similarly exists on a spectrum ranging from low to vigorous. Intensity can be expressed in absolute terms using standardized metrics such as the metabolic equivalents (METs), defining the metabolic cost of an activity as a multiple of resting energy expenditure. However, this does not account for the variability in individual cardiorespiratory fitness. Alternatively, exercise intensity can be expressed relative to individual capacity, represented as a percentage of VO_2peak, maximal heart rate, heart rate reserve, or the subjective rate of perceived exertion. The extremes of exercise participation are readily recognized, ranging from individuals with sedentary lifestyles (typically engaged in activities equal to 1.0–1.5 METs) to elite competitive athletes (engaged in activities up to 25 METs). Care is needed when interpreting the literature on the risks versus benefits of exercise in inherited cardiomyopathies, as criteria used to define exercise levels and experimental protocols have varied widely.

EFFECTS OF EXERCISE IN THE NORMAL HEART

The body responds to exercise with a tightly coordinated suite of physiological adaptations that act to meet elevated oxygen and metabolic demands.[3] During acute bouts of exercise, there is increased ventilation, withdrawal of the parasympathetic nervous system, and activation of the sympathetic nervous system which, in combination, increases heart rate and ventricular contraction. Cardiac output increases, resulting in elevated blood pressure and flow throughout the enclosed systemic vascular network. Vasodilation and changes in vascular resistance help to redistribute blood to exercising skeletal muscle. Over time, sustained exercise training results in structural and functional changes in both heart and skeletal muscle. Cardiac changes include slower resting heart rate, reduced ventricular stiffness, chamber dilatation, increased stroke volume, and physiological hypertrophy.[3] These features are predominantly seen with endurance rather than static forms of exercise and vary with the type and magnitude of the hemodynamic load. Exercise-induced cardiac remodeling has been mainly studied in elite endurance athletes (athlete's heart). Similar, albeit less marked, remodeling has been seen in sedentary middle-aged subjects after 12 to

24 months of exercise training.[4] Skeletal muscle adaptations include increases in mitochondrial function and oxidative capacity that enhance aerobic muscle contraction.[5]

At the cellular level, exercise training results in increased cardiomyocyte mitochondrial biogenesis associated with activation of AMP-activated protein kinase and production of PGC-1α (peroxisome proliferator-activated receptor-gamma coactivator).[3] Enhanced mitochondrial function has a key role in maintaining fatty acid oxidation rather than glucose utilization as the predominant energy source and protects against oxidative stress. In addition, exercise has anti-inflammatory actions and attenuates ischemia-induced apoptosis and autophagy.[5] Circulating myokines released from skeletal muscle further contribute to cardioprotective effects.[5] Transcriptional responses to exercise training have been studied in murine models, with differential expression of genes involved in fatty acid and glucose metabolism, contractile function, extracellular matrix remodeling, cell cycle regulation, protein ubiquitination, and proteasome activity. The PI3K/Akt (phosphoinositide 3-kinase/protein kinase B), mTOR (mammalian target of rapamycin), IGF-1 (insulin-like growth factor 1), and ERK5 (extracellular signal–regulated kinase) 5 signaling pathways have been implicated in exercise-induced physiological hypertrophy.

Although the effects of exercise in the normal heart are well described, relatively less is known about how these responses might differ in inherited heart disorders where the myocardial substrate is fundamentally abnormal. Genotype-specific differences in susceptibility to mechanical and metabolic stress, as well as patient-specific clinical risk factors and phenotype severity, could influence the tipping point between benefit versus harm. These issues will be discussed in subsequent sections of this review.

HYPERTROPHIC CARDIOMYOPATHY

HCM is characterized by left ventricular (LV) hypertrophy that arises in the absence of significant increases in afterload due to conditions, such as hypertension or aortic valve stenosis. The hallmark histological features of HCM include cardiomyocyte hypertrophy, myofibril disarray, and interstitial fibrosis. It is the most common genetic cardiomyopathy, occurring in 1:200 to 1:500 people. Phenotypic manifestations exist on a spectrum of severity of myocardial hypertrophy, fibrosis, diastolic dysfunction, normal or supranormal systolic function, LV outflow tract obstruction (LVOTO), and arrhythmia propensity. This disorder is clinically important due to its high prevalence and significant complications of SCD and HF.

HCM is caused by variants in genes that encode cardiac sarcomere-related proteins, with genetic testing yielding a positive result in 30% to 40% of sporadic cases and >60% of those with familial disease.[6] Recent gene curation has identified 14 genes with definitive or strong evidence for pathogenicity, encoding proteins in the thick filament (*MYBPC3*, *MYH7*, *MYL2*, *MYL3*), thin filament (*TNNT2*, *TNNI3*, *TNNC1*, *TPM1*, *ACTC1, FHOD3*), Z-disk (*ACTN2*, *CSRP3*), M-band (*ALPK3*), and sarcoplasmic reticulum (*PLN*).[7] Four additional genes classified as having moderate evidence encode proteins involved in functions of the M-band (*TRIM63*), sarcoplasmic reticulum (*JPH2*), intermediate filaments (*KLHL24*), and mitochondria (*MT-TI*). Variants in *MYH7* (β-myosin heavy chain) and *MYBPC3* (cardiac myosin binding protein C) account for 70% to 80% of genotype-positive cases.[6] Substantial progress has been made in elucidating the molecular basis of HCM, particularly for *MYH7* variants. During diastole, nonmutated sarcomeres enter a super-relaxed state where myosin heads adopt an interacting-heads motif.[8] *MYH7* variants disrupt interacting-heads motif formation, shifting myosin molecules into a weakly actin-bound state, that is, the disordered relaxed state.[9] When in the disordered relaxed state, myosin and actin can bind and generate force leading to increased contractility and impaired myocardial relaxation.[9] The disordered relaxed state consumes 5-fold greater ATP than the super-relaxed state, increasing myocardial ATP utilization.[8] Increased myocardial energy requirements and altered calcium (Ca^{2+}) sensitivity trigger a cascade of downstream signaling pathways that promote hypertrophy and fibrosis. Another key feature of HCM is microvascular dysfunction, the causes of which remain elusive.

Exercise intolerance and functional disability are important sequelae of HCM. Aerobic capacity, quantified by VO_2peak, is significantly reduced in patients with HCM.[10] Many experience debilitating exertional symptoms including dyspnea, chest pain, and syncope. The causes of exercise intolerance are multifactorial and interrelated, primarily stemming from cardiac limitation. Patients with HCM fail to appropriately augment cardiac output to meet metabolic demand, largely due to increased ventricular stiffness and impaired filling. Chamber stiffness is affected by both fiber stiffness and cavity geometry; increases in intrinsic fiber stiffness resulting from altered cross-bridging and fibrosis are further exacerbated by the increased chamber stiffness inherent in small cavity size.[11] At higher heart rates, impaired LV filling undermines the ability to augment stroke volume leading to insufficient cardiac output and increased anaerobic metabolism, which contributes to fatigue and exertional symptoms. Furthermore, LVOTO has heterogenous impacts on exercise capacity and exertional symptoms with the magnitude of gradient correlating poorly with functional limitation.[10,12–16] In patients with latent LVOTO, diastolic dysfunction remains a key driver of exercise limitation.[16] However in some patients with significant resting obstruction, there is impaired systolic augmentation in response to exercise that further reduces exercise capacity.[10] Exercise intolerance and functional disability contribute significantly to HCM-related morbidity and are strongly correlated with lower quality of life.[17] This underscores the importance of targeting physical capacity as a key therapeutic strategy in

HCM management. Studies exploring the impact of exercise in HCM are summarized in Table S1.

Acute Risks During Exercise in Patients with HCM

HCM is a widely publicized cause of SCD in athletes, leading to concerns about the safety of exercise participation (Figure 1). Physiological perturbations during exercise contributing to acute arrhythmic risk in the context of an abnormal myocardium include increased catecholamine release, sympathetic-vagal imbalance, and electrolyte imbalance. In addition, increased myocardial energetic demands inherent in HCM may cause energy depletion during mechanical stress sufficient to impair Ca^{2+} reuptake and raise cytosolic Ca^{2+} concentrations, potentially promoting sustained arrhythmias.[18] HCM-related microvascular dysfunction may promote myocardial hypoperfusion and ischemia during exertion.[19–21] Although most adverse events in HCM occur at rest, adjustments for relative time exposure suggest that there is an increased risk during exercise. One population-based study quantified the absolute risk of SCD during exercise as low (0.064 per 1000 HCM person-years), although this was 10× higher than in the general population. Due to advances in prophylactic intervention, SCD in patients with HCM is now rare (0.32%/y) and death due to HF or other cardiac causes is relatively more common.[22] Indeed, the majority of patients will survive to later age, experiencing morbidity related to exercise intolerance and unrelated conditions.

Acute exercise can temporarily exacerbate symptoms in patients with HCM, including exertional syncope related to LVOTO, arrhythmia, or inappropriate systolic blood pressure response.[13,23] The mechanisms underlying the latter are poorly understood but may include excessive vasodilation due to overstimulation of mechanoreceptors associated with LVOTO-related increased LV afterload. Only one interventional trial has reported an episode of exercise-induced syncope.[24] Trials that excluded patients with a history of exertional syncope or

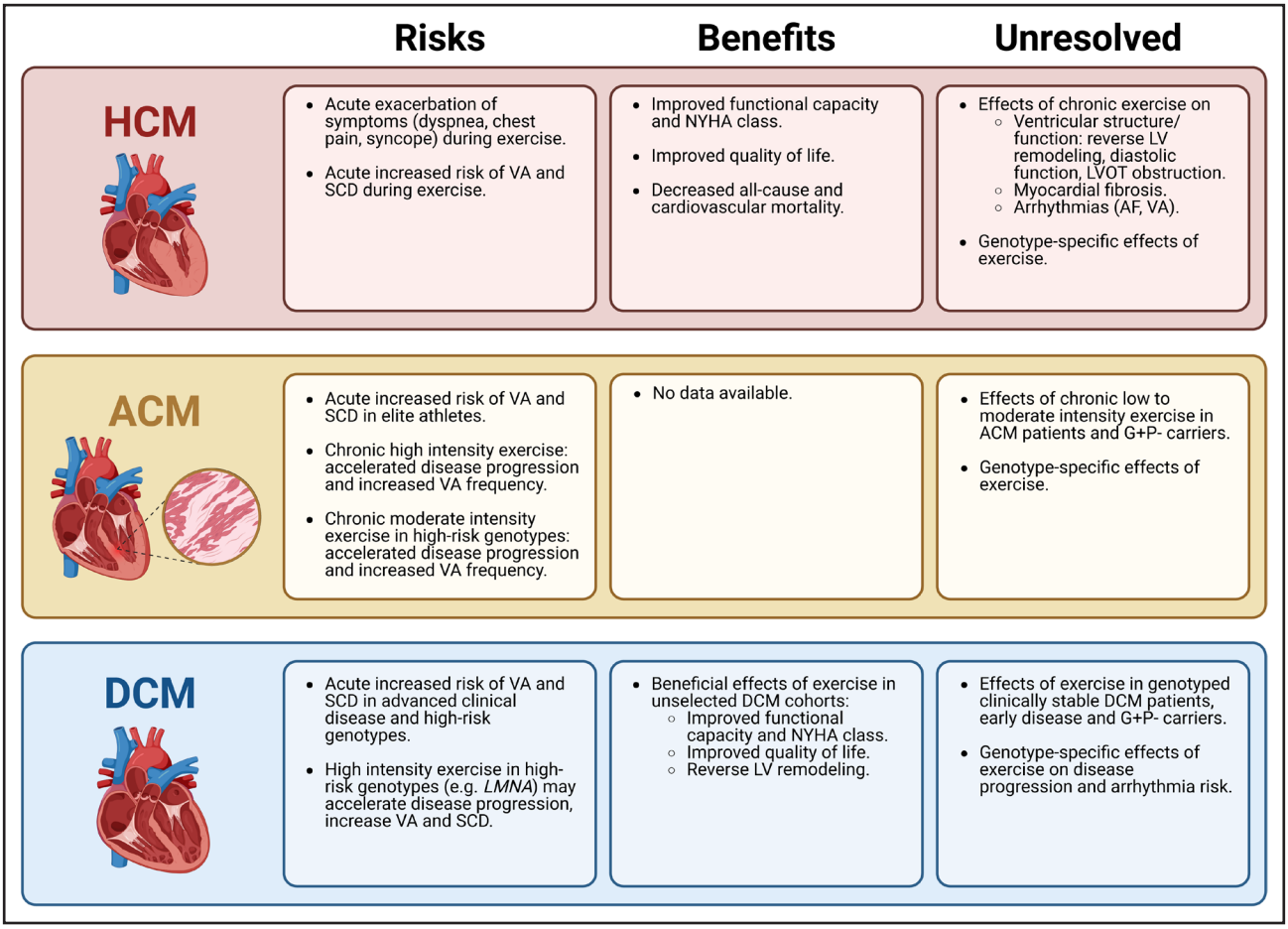

Figure 1. Risks, benefits, and unresolved questions for exercise effects in inherited cardiomyopathies.
Key points from published studies are summarized here (Tables S1 through S3 for full description of studies). ACM indicates arrhythmogenic cardiomyopathy; AF, atrial fibrillation; DCM, dilated cardiomyopathy; G+P–, genotype-positive phenotype-negative; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; SCD, sudden cardiac death; and VA, ventricular arrhythmias.

hypotension have reported no instances of syncope during supervised exercise training.

Is Exercise Training Harmful in Patients with HCM?

There is speculation that sustained mechanical, metabolic, or ischemic stress due to exercise training might also be proarrhythmic or exacerbate disease progression. Recent evidence suggests that the risk of major adverse cardiac events (MACE) with exercise training in HCM is low. Several interventional trials of moderate-to-vigorous exercise training reported no MACE over periods of up to 19 months.[25–30] In a study of 188 *MYBPC3* variant-positive individuals (55% affected), there was an increased risk of malignant ventricular arrhythmia (VA) in those engaged in high-dynamic activities (>22 MET-h/wk, adjusted hazard ratio of 3.26 compared with 7.5 MET-h/wk), but no association between overall activity level and MACE.[31] These observations suggested that high-dynamic activities like running and soccer might pose greater risk. In contrast, a study of athletes with mild HCM observed no serious arrhythmias or death over an average 4.5 years follow-up.[32] Some of these differences between studies may be attributable to the inclusion of low-risk phenotypes. It should be noted that due to the rarity of MACE, most studies are relatively underpowered for safety outcomes.

Data from interventional studies suggest that moderate- and high-intensity aerobic exercise training does not adversely impact LV hypertrophy, severity of LVOTO, levels of HF biomarkers, or nonfatal sustained arrhythmias.[24–28] Although these trials may not be long enough to capture potential complications, observational studies have also provided reassurance of long-term safety. One study found no association between lifetime vigorous activity and either increased LV hypertrophy or VA burden,[33] while another showed no correlation between early life vigorous exercise and arrhythmia risk.[34] In addition, patients with HCM classified as active or sedentary based on self-reported lifetime physical activity had no differences in New York Heart Association (NYHA) functional classification, symptom severity, nonsustained ventricular tachycardia burden, or implantable cardioverter defibrillator (ICD) implantation.[35] A prospective study of patients with *MYBPC3* variants similarly found no increased risk of HF across activity quartiles.[31] Although Aengevaeren et al[36] reported no difference in LV hypertrophy between the most sedentary and most active tertiles, they observed a higher burden of nonsustained ventricular tachycardia in the most active tertile. Notably the most active group had a greater prevalence of a family history of SCD, potentially indicative of a more severe familial disease.[36] Athletes with HCM were found to have lower maximal LV wall thickness and reduced LVOTO when compared with nonathletic patients with HCM, though this may reflect selection bias.[37] A long-term follow-up study of athletes found no difference in the incidence of new symptoms or arrhythmias between those who continued exercising and those who detrained postdiagnosis.[38]

The impact of chronic exercise on myocardial fibrosis remains uncertain. To date, no prospective interventional trials have assessed myocardial fibrosis before and after exercise training. Some retrospective observational studies have found no association between lifetime accumulation of physical activity, including vigorous or competitive exercise, and increased fibrosis burden,[33–35,37] whereas others have reported positive correlations between exercise volumes and fibrosis.[35,36] Elevated T2 mapping on cardiac magnetic resonance imaging has been linked to postexercise troponin elevation, suggesting patients with active disease or myocardial edema may be more susceptible to myocardial injury and fibrosis.[39]

Benefits of Exercise Training in Patients with HCM

There is emerging evidence that the benefits of chronic exercise outweigh the acute risks of single exercise bouts for most patients with HCM (Figure 1). Epidemiological data have shown progressive declines in all-cause and cardiovascular mortality across increasing tertiles of physical activity engagement in patients with HCM.[40] Supervised exercise interventions can lead to modest but clinically significant improvements in VO_2peak (1–2 mL/kg per minute) across various HCM populations, including those with obstructive and nonobstructive disease.[24–26,29,30] Nonrandomized cardiac rehabilitation programs have also conferred meaningful performance gains in maximal exercise testing among functionally impaired patients with HCM.[27,28] Exercise capacity is a significant prognostic marker in HCM, with VO_2peak increments of 1 mL/kg per minute associated with a 21% attenuation in mortality and heart transplant risk.[41] Some interventions employing cardiopulmonary exercise testing have reported improvements in ventilatory thresholds[24] and ventilatory efficiency (VE/VCO_2 [minute ventilation divided by expired carbon dioxide] slope),[29,30] both of which are robust prognostic indicators in HCM.[41] In healthy adults, improvements in aerobic capacity due to exercise result from enhancements in both cardiac and peripheral adaptations although the cardiovascular responses to exercise in patients with HCM remain incompletely understood. Most interventional trials did not show overt changes in cardiac morphology or cardiac functional indices, suggesting that improvements in VO_2peak may primarily result from peripheral adaptations in oxygen utilization rather than direct cardiac remodeling.[24–26] An exception to this was a study where improvements in exercise capacity were paralleled by improved cardiac output and pulmonary wedge pressures in nonobstructive patients with HCM.[30]

Several studies have shown that exercise can improve NYHA classification and quality of life. In symptomatic and functionally limited patients with HCM, Klempfner et al[28] found that 50% of patients improved their NYHA class after a cardiac rehabilitation program with no instances of progression. A combined exercise and dietary intervention in obese patients with HCM showed that 30% improved their NYHA class, although 3 patients developed systolic dysfunction.[29] Other observational studies showed no difference in NYHA class between active and sedentary patients with HCM.[35,36] Similarly, although some exercise interventions improved quality of life measures,[25,27,30] others did not show significant benefit.[24,26]

The impact of exercise training on LV wall thickness is variable. One study showed a reduction in interventricular septal diameter after 5 months of moderate- or high-intensity exercise,[26] whereas another reported no change.[27] Observational studies in more active patients with HCM have noted potential improvements in LV chamber stiffness, indicated by larger LV volumes and superior diastolic function.[33,37] Exercise interventions have not consistently replicated these findings. The only study to report increased LV volumes did so in response to high-intensity interval training and only one metric of diastolic function was improved.[26] This suggests that current exercise protocols may not provide a sufficient stimulus for cardiac remodeling, or that larger ventricular volumes in active individuals result from selection bias rather than direct training effects.

Insights from Animal Studies of HCM

Murine studies suggest that the intensity and timing of exercise intervention are important determinants of efficacy.[42] There is some evidence that exercise may worsen disease progression under certain conditions. For example, mice with *MYL3* variants demonstrated increased heart size, reactivation of the fetal gene program, increased collagen deposition, and attenuated Ca^{2+} sensitivity when subjected to an intense exercise regime, including twice daily exposures to exercise,[43] whereas transgenic mice overexpressing *TNNI3* showed no physiological adaptation to exercise training.[44]

In transgenic mice expressing a mutant myosin heavy chain, exercise initiated before phenotype onset afforded the greatest benefit, preventing hypertrophic progression, myocardial disarray, and fibrosis formation. This was associated with the downregulation of hypertrophic signaling via the calcineurin-NFAT (nuclear factor of activated T cell) pathway and a lack of induction of markers of pathological hypertrophy including *MYH7* and *NPPA* expression.[45] In contrast, initiation of exercise subsequent to phenotype onset failed to reverse hypertrophy or rescue derangement of myocyte architecture and fibrosis, and *NPPA* expression was only attenuated.[46] Exercise reversed proapoptotic signaling by restoring reduced CREBH (cAMP-responsive element-binding protein H) activity, and apoptotic activity to wild-type levels. In a murine model of the human *MYH7* p.R403Q variant, early exercise intervention failed to improve LV morphology (including septal thickness), stroke volume, diastolic function, or myocardial fibrosis but did result in increased exercise capacity, smaller left atrial size and reduced expression of extracellular matrix genes.[47] A further murine model harboring a *MYL2* p.E22K mutation found that exercise training improved transcriptional profiles associated with hypertrophic and fibrotic signaling.[48] Importantly, not all components of these pathways were impacted by exercise which may explain why habitual exercise does not consistently correlate with fibrosis severity in human studies.

Extrapolations from a murine model of HF with preserved ejection fraction may provide further insights. In these mice, exercise altered titin phosphorylation, which is predicted to increase myocardial compliance and improve diastolic function.[49] In addition, exercise upregulated proteins involved in Ca^{2+} handling, potentially reducing Ca^{2+}-dependent pathological signaling. It is unclear if these mechanisms would similarly affect patients with HCM with sarcomere mutations.

Variables: Exercise Intensity, Genotype, Disease Trajectory, and Patient Capacity

How much exercise is too much for patients with HCM? New evidence suggests that progressively increasing exercise intensity up to 85% of heart rate reserve or 95% maximal heart rate is well tolerated,[24,26,28] whereas vigorous exercise was shown to be equivalent to nonvigorous activity with respect to MACE.[50] Conclusions about exercise effects are confounded by a lack of standardization for exercise dose. For example, in the latter study, the threshold for classification as a vigorous exerciser was remarkably low, with just one hour of vigorous activity in the previous year meeting the criteria. Although METs were used to quantify intensity, this is a generalized measure and may not accurately reflect individual physiological responses. For a severely limited patient with HCM, even daily activities could qualify as vigorous exercise. Another analysis using similar definitions found vigorous exercise was not associated with increased arrhythmia or fibrosis and could result in superior diastolic function (although causation cannot be inferred due to study design).[33] A potential for vigorous exercise to elicit superior adaptions over moderate-intensity training was tested in a randomized control trial.[26] They found a trend towards greater VO_2peak improvement that did not reach significance potentially due to the heterogeneous and modest magnitude of response. Studies of athletes with HCM have found no increased incidence of new symptoms, arrhythmias, or MACE-free survival in athletes who continued to participate in competitive exercise.[38]

Although genetic heterogeneity of HCM complicates risk assessment, limited available data do not support genotype-specific exercise restrictions. Genotype was not correlated with adverse outcomes in a large multicenter prospective cohort,[50] nor with SCD during vigorous activity.[51] In addition, genotype did not significantly influence exercise response in an intervention trial.[25] However, certain genotypes may theoretically pose greater risks. *MYH7* variants impose a higher energy cost of contraction compared with *MYBPC3* variants,[52] potentially increasing susceptibility to exercise-induced energetic depletion and associated detriment (arrhythmogenesis and hypokinesis). Moreover, isogenic induced pluripotent stem cell models of thick filament mutations suggest that energetic stress may trigger increased cytotoxic activity.[53] Larger gene-specific cohort studies are needed before genotype-based exercise recommendations can be made.

Concerns that exercise in genotype-positive phenotype-negative (G+P—) individuals could enhance disease penetrance are not validated by current observational data.[31,36] In fact, greater exercise volume accumulated during youth correlated with better diastolic function in middle-aged patients with HCM, irrespective of hypertrophy severity.[34] This is reflected in current clinical guidelines, which no longer recommend strenuous exercise restrictions in G+P— subjects.

Exercise interventions have been conducted primarily in lower-risk patients with HCM leading to guideline changes that no longer restrict strenuous activity in these individuals.[54] Studies incorporating higher-risk patients, including those with ICDs or a history of sudden cardiac arrest found moderate-intensity exercise was not associated with increased nonfatal arrhythmias or MACE.[25,29] The presence of LVOTO did not result in adverse events or influence the ability to derive benefit from exercise.[25–27,29] Patients with severe LVOTO gradients, high fibrosis burden, extreme LV hypertrophy, or prior exertional syncope remain in higher-risk groups requiring careful assessment (Figure 1).

Exercise echocardiography and cardiopulmonary exercise can be valuable tools in guiding physical activity recommendations in individual patients.[55] Clinical exercise testing can identify patients for whom exercise may pose greater risks, such as those exhibiting ischemic changes, exercise-induced arrhythmia, or inappropriate blood pressure responses. These findings can inform shared decision-making around physical activity levels and guide risk mitigation strategies, including the need for supervised exercise interventions. Exercise echocardiography is particularly useful for detecting latent LVOTO under physiologically relevant conditions and offers insights into mechanisms of functional limitation, whereas cardiopulmonary exercise testing provides objective measures of functional capacity. Given the challenges of achieving true maximal effort in clinical populations, submaximal indices derived from cardiopulmonary exercise testing, such as ventilatory efficiency and anaerobic thresholds, offer unique insights for prognostication, tailoring exercise intensity, and evaluating the functional impact of therapeutic interventions in HCM.

Exercise and HCM: Current Status

The theoretical risk that exercise may promote pathological manifestations and enhance disease severity in HCM is now contested by evidence from human studies and murine models. Although acute exercise may transiently exacerbate symptoms and increase the risk of malignant VA or SCD, the latter events are rare. Emerging data from high-quality interventional trials confirms the safety and benefits of supervised exercise interventions for most patients with HCM. Accordingly, contemporary American and European clinical guidelines endorse low-to-moderate-intensity exercise to improve cardiorespiratory fitness, functionality, and subjective well-being (Figure 2).[1,56] Available evidence provides reassurance that vigorous and competitive exercise does not reduce MACE-free survival in lower-risk individuals, leading to guideline updates that do not recommend blanket restriction of vigorous activity and competitive sport in patients with HCM (class III evidence).[56] A universally safe upper threshold of activity in all patients with HCM is unlikely to exist given the stochastic nature of events, and exercise recommendations should ideally be individualized. There are many unresolved questions, including the long-term effects of exercise on phenotypic features and in different genotype groups (Figure 1).

ARRHYTHMOGENIC CARDIOMYOPATHY

ACM encompasses a phenotypic spectrum characterized by VA, an increased risk of SCD, and variably progressive structural and functional ventricular changes.[57] Historically considered a disease of the right ventricle (RV), more widespread use of cardiac magnetic resonance has challenged this assumption, with recognition of biventricular and LV-dominant subtypes. Although overall disease prevalence is low (1:2500 to 1:5000), ACM is an important cause of SCD in young adults and athletes.[58] Disease penetrance is higher in males, with phenotype onset typically between the second and fourth decades. Electrical abnormalities and arrhythmias often precede gross structural changes, and many patients are only diagnosed after a life-threatening event or familial cascade screening.[58] Arrhythmic events are often triggered by exercise or adrenergic stress, leading to the establishment of preparticipation screening in young athletes in several countries in an attempt to reduce mortality and increase disease detection.

Desmosomal gene mutations have been causally linked to ACM, with genetic testing identifying pathogenic variants in 50% to 70% of probands.[59] These

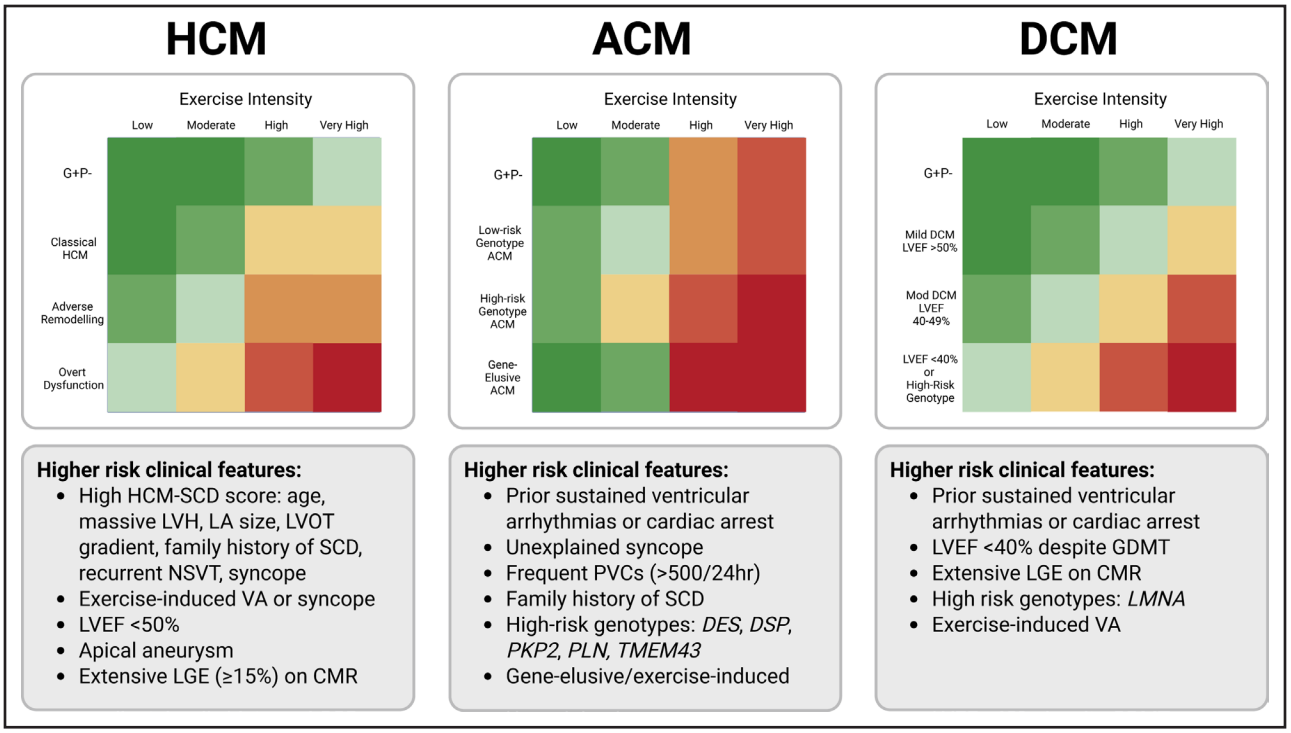

Figure 2. Impact of exercise intensity and myocardial substrate on risk of adverse outcomes.
Heat maps representing graded risk (green=low, red=high) of exercise in inherited cardiomyopathies based upon current guideline recommendations, with additional genotype-specific recommendations from relevant studies (Tables S1 through S3). Individualized exercise prescription is recommended as risk-benefit thresholds will vary between patients and over an individual's lifetime. Patients with higher-risk clinical features or poor baseline physical fitness may require more conservative exercise recommendations. With expert assessment and regular reassessment, most patients can enjoy the benefits of regular exercise. ACM indicates arrhythmogenic cardiomyopathy; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; G+P–, genotype-positive phenotype-negative; GDMT, guideline-directed medical therapy; HCM, hypertrophic cardiomyopathy; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricular; LVEF: LV ejection fraction, LVH, LV hypertrophy; LVOT, LV outflow tract; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular contraction; SCD, sudden cardiac death; and VA, ventricular arrhythmias.

genes encode desmosomal or intercalated disc proteins that provide crucial mechanical and electrometabolic coupling between cardiomyocytes, including *PKP2*, *JUP*, *DSP*, *DSC2*, and *DSG2*. Inheritance is typically autosomal dominant with reduced penetrance and variable expressivity. Heterozygous truncating *PKP2* variants are the most commonly identified cause of classical RV-dominant ACM, with RV dilation and high rates of VA. Truncating *DSP* variants are increasingly recognized in association with LV-dominant ACM, with a distinct ring-like pattern of late gadolinium enhancement on cardiac magnetic resonance, recurrent episodes of inflammatory myocarditis, and higher rates of HF when compared with *PKP2* mutation carriers.[60] With the broadening of ACM to include LV-dominant and biventricular phenotypes, variants in numerous nondesmosomal genes have additionally been identified. Gene recuration has demonstrated that only 3 genes currently have sufficient evidence for pathogenicity: *TMEM43*, *PLN*, and *DES*.[61] Nondesmosomal variants are found in only 2% to 3% of patients and are associated with highly penetrant and arrhythmogenic forms of ACM with greater LV involvement and rates of SCD as high as 50% in *TMEM43* variant-positive males.[62] In vitro studies indicate that nondesmosomal gene variants also result in reduced or dysfunctional desmosomal proteins, suggesting shared mechanistic pathways.[48,63] A minority of patients with ACM (1%–16%) carry multiple variants. These patients typically demonstrate more severe phenotypes with earlier disease onset and worse clinical outcomes.[60]

In at least 30% of patients with a clinical diagnosis of ACM, an underlying genetic variant is unable to be identified.[59] These gene-elusive patients present at an earlier age, are less likely to have a family history of ACM and typically perform greater volumes of high-intensity or endurance exercise when compared with carriers of desmosomal variants.[64] ACM in gene-elusive patients could result from unidentified single rare variants, polygenic influences, or epigenetic factors.[65] Rather than having a primary genetic cardiomyopathy, it has been proposed that at least some of these individuals might have a form of ACM that is induced by high-intensity endurance exercise. This theory reconciles the high rates of ACM seen among athletes and the relatively benign course of desmosomal variant carriers in general population cohorts. The concept of exercise-induced ACM is further supported by

studies in wild-type mice where high-intensity endurance exercise led to an ACM-like phenotype.[66]

Adverse Effects of High-Exercise Burden in ACM

Exercise has a well-documented association with the development of clinical disease and adverse outcomes in ACM. Studies investigating exercise effects are summarized in Table S2. In particular, high-intensity exercise has been associated with earlier phenotype onset,[67] increased VA,[68–74] greater degrees of ventricular remodeling, and HF (Figure 1).[67,69,75–77] Although the majority of individuals will restrict exercise after an ACM diagnosis, those who continue high or very high-intensity exercise are at increased risk of life-threatening VA.[78,79] Consequently, despite a lack of prospective or randomized clinical data, current clinical practice guidelines strongly advise individuals with overt ACM to avoid participation in high-intensity exercise or competitive sports (Figure 2).[57]

These recommendations extend to G+P− individuals in whom high-intensity exercise has been associated with an increased likelihood of meeting ACM diagnostic criteria[65,71] and the development of VA or HF.[71,80] In studies of ACM mutation carriers, individuals who undertook endurance exercise developed symptomatic disease a decade earlier than their sedentary counterparts, and were more likely to experience adverse events.[67,68] Observational studies of G+P− athletes have also shown that ongoing high-intensity sports participation is associated with more rapid phenotype development, HF, and increased arrhythmia burden.[81]

Genotype Differences in Exercise Risk in ACM

Current data suggest that exercise risk in ACM varies with different genotypes.[81] Desmosomal gene variants, particularly *PKP2*, are associated with increased arrhythmias, earlier disease penetrance due to accelerated structural defects, and impaired exercise-induced trophic remodeling.[67,81,82] Median exercise exposure before ACM diagnosis can be relatively modest in *PKP2* carriers (14.5 MET-h/wk) with greater rates of LV impairment. Exercise restriction after ACM diagnosis reduced the risk of future arrhythmic events[67] but did not lead to improvement in LV function.[83] Similarly, *DSP* variant-positive individuals have elevated rates of inflammatory myocarditis episodes, LV impairment, and arrhythmias among patients with a previous history of moderate- to vigorous-intensity exercise.[83,84]

There is limited information on exercise risk in nondesmosomal ACM. *TMEM43* variant-positive individuals seem to be a particularly vulnerable group, with a prospective study of 80 patients demonstrating a high prevalence of LV involvement and arrhythmias. Exercise exposure ≥9.0 MET-h/d before ICD insertion was associated with an adjusted 9.1-fold increased risk of appropriate ICD discharge.[85] In contrast, *PLN* variants were not associated with increased disease penetrance or structural progression with high-intensity exercise.[86] However, other studies of *PLN* variant-positive individuals have revealed that most episodes of VA and SCD occur during exercise,[87] underscoring the need for caution. Perhaps mirroring the role of exercise in disease pathogenesis, gene-elusive or patients with exercise-induced ACM receive relatively greater protection from high-intensity exercise restriction compared with patients with an identifiable mutation.[88]

Are Low or Moderate Exercise Levels Safe in ACM?

Although high-intensity exercise is known to be harmful in patients with ACM, there are limited data on the effects of lower exercise levels. Ruiz-Salas et al[89] examined a high-risk cohort of patients with definitive ACM who had undergone ICD implantation. They noted earlier onset arrhythmic events in individuals who undertook high- and moderate-intensity activity, compared with low-intensity activity suggesting a possible dose-dependent relationship between disease penetrance and exercise intensity. Building on this finding, Lie and colleagues explored the relationship between exercise intensity, exercise duration, and adverse events in a cohort of patients with ACM and G+ relatives.[69] They found that high-intensity exercise (>6 METs) remained a strong and independent predictor of VA after adjustment for exercise duration (odds ratio, 3.8 [95% CI, 1.3–11.0]; $P<0.001$). Longer-duration and low-intensity exercise were not associated with adverse outcomes suggesting that this may be a safe alternative to complete exercise restriction.

Given heterogeneous definitions of exercise and the lack of standardized activity assessment between studies, it is difficult to conclude whether there is a specific threshold of exercise exposure that could be considered safe in patients with ACM. Randomized studies are unlikely to be forthcoming given ethical concerns and as such, cautious inferences may need to be drawn from observational studies assessing the impact of low-to-moderate-intensity exercise. Such studies have generally been reassuring, demonstrating similar risk profiles between patients who undertook low-to-moderate-intensity exercise, and their sedentary counterparts.[90] Bosman et al[70] demonstrated that although exercise dose (METs×duration) was associated with VA during follow-up, no significant increase in risk was seen at exercise doses of 15 to 30 MET-h/wk, grossly equivalent to 150 minutes of low-to-moderate-intensity (3–6 MET) exercise. Similarly, 2 *PKP2*-predominant cohorts demonstrated that restriction of exercise to below the American Heart Association recommendations for minimum activity (650 MET-h/y) was not associated with harm. Below a <650 MET-h/y threshold, only 5%

of patients developed ACM, compared with 50% of patients exercising above this threshold.[91] G+P— individuals who exercised at or below 650 MET-h/y had favorable outcomes with lower rates of ACM diagnosis and no episodes of sustained VA.[71] In higher-risk and nondesmosomal cohorts, participation in recreational activities did not increase the risk of VA postcatheter ablation[92] nor accelerate symptom onset or increase the risk of arrhythmias or death.[68] These findings suggest that not all exercise is equal and that most patients with ACM may be able to enjoy the benefits of recreational exercise without excessive risk. Moving toward greater precision, a recent study by Ramos-Maqueda et al[93] utilized accelerometer-measured physical activity and 30-day Holter monitoring to assess the relationship between physical activity and rapid rate VA. In this LV-dominant, nondesmosomal cohort, physical activity of light- and moderate-intensity (average activity 290 min/d, including 21 min/d moderate-intensity exercise) was not associated with VA.

Exercise and ACM Pathophysiology

A mechanistic understanding of why exercise might accelerate ACM is incomplete. For desmosomal gene variants, initial hypotheses proposed that fragile or dysfunctional intercalated disc proteins were relatively more susceptible to acute increases in mechanical stress during exercise, resulting in increased cardiomyocyte apoptosis[94,95] and subsequent myocardial fibro-fatty replacement.[59] Because the RV is exposed to relatively greater wall stress during exercise, hemodynamic differences were thought to explain why the RV was preferentially prone to exercise-induced effects.

ACM animal models have demonstrated ultrastructural abnormalities of desmosomes and intercalated discs.[96–98] However, arrhythmogenicity can precede identifiable histological changes.[99] This has been attributed to loss of desmosomal integrity due to gap junction remodeling,[100] reduced connexin 43 expression,[101–103] cardiac sodium channel dysfunction,[104] and abnormal intracellular Ca^{2+} handling.[105] Recent studies have demonstrated alterations in connexin 43 expression levels in forced versus voluntary exercise models of ACM. Interestingly, connexin 43 expression was shown to be increased by low-to-moderate-intensity exercise[106] but reduced by high-intensity and endurance exercise.[107] Overall, these alterations result in dysregulated Ca^{2+} handling with increased spontaneous Ca^{2+} release and susceptibility to VA with triggered activity,[108] such as adrenergic stimulation during intense exercise. In several murine models, treatment with preload-reducing therapies restored connexin 43 phosphorylation levels[109,110] and prevented exercise-induced cardiac dysfunction emphasizing the relationship between hemodynamic stress and arrhythmogenicity in ACM.

Several downstream pathways are perturbed in ACM hearts. Under normal conditions, exercise results in increased activity of the Wnt (wingless-related integration site)/β-catenin and Hippo/YAP (Yes-associated protein) pathways and PPARγ (peroxisome proliferator-activated receptor gamma).[111,112] These responses are important for cellular repair, cardiomyocyte hypertrophy, and autophagy. Desmosomal dysfunction results in increased nuclear translocation of plakoglobin and competitive suppression of the Wnt/β-catenin pathway.[113] Concurrent inhibition of the Wnt/β-catenin pathway and activation of Hippo/YAP and TGF (transforming growth factor) β is proposed to drive myofibroblast differentiation and fibro-fatty myocardial replacement.[114,115] Experimental studies support a profibrotic role of increased TGFβ signaling in both *JUP* knockout[116] and *PKP2* knockdown mice.[117] *TMEM43* murine models also demonstrate reduced PPARγ activity with disturbed fatty acid/lipid utilization, adipocyte infiltration, and exercise intolerance.[118] Interestingly, treatment of *DSP*-deficient zebrafish with a Wnt/β-catenin agonist prevented the developed of an ACM phenotype[119] and inhibition of glycogen synthase kinase-3β, a downstream regulator of the Wnt/β-catenin pathway, reversed abnormal remodeling and prevented cardiac dysfunction in murine *DSG2* and *TMEM43* models.[120,121] Endurance exercise is known to increase testosterone levels, and males are disproportionately probands, with earlier disease onset and more severe arrhythmic burden.[60] In vitro models of *PKP2*-deficient cardiomyocytes demonstrate accelerated lipogenesis and apoptosis in response to testosterone.[122] These data suggest that increased androgen levels may contribute to exercise-induced disease progression in ACM.

Changes in transcriptional profiles have been found in animal ACM models.[123] In wild-type mice, exercise was associated with downregulation of genes related to intercalated disc function, scaffolding proteins, and ion channel function, together with upregulation of genes involved in cellular respiration and mitochondrial metabolism. Induction of *PKP2* deficiency resulted in further downregulation of desmosomal genes and increased apoptosis pathways suggestive of an abnormal cellular response to exercise and impaired desmosomal reserve.[82,95] Exercise-induced transcriptional changes can vary between genotypes.[124] When compared with wild-type controls, differentially expressed genes in *DSP*-deficient mice predicted increased activation of inflammation and epithelial-mesenchymal transition and suppression of oxidative phosphorylation pathways. Exercise restored normal gene transcript levels in *DSP*-deficient mutants, with an overall reduction in cardiomyocyte apoptosis and preserved contractile function. Notably, exercise in this study was voluntary and at much lower levels when compared with murine studies showing the deleterious effects of endurance exercise.

Exercise and ACM: Current Status

ACM-associated genetic variants affect the structure and function of cardiomyocyte desmosomes and intercalated discs, enhancing susceptibility to environmental stresses imposed during exercise. Bringing clinical and animal data together, there is a clear message that high-intensity, endurance aerobic exercise is harmful in ACM. Current guidelines recommend avoidance of moderate-to-high-intensity exercise in patients with ACM and avoidance of high-intensity exercise in G+P— individuals (Figure 2).[1] Although no studies have directly shown disease- or genotype-specific benefits of exercise in ACM (Figure 1), observational data suggest that low-to-moderate-intensity exercise (<650 MET-h/y) is likely safe for most affected patients and G+P— relatives (Figure 2). There are many unresolved unanswered questions, including the long-term effects of low-to-moderate-intensity exercise in ACM, and how sex and genotype influence exercise risk assessment (Figure 1).

DILATED CARDIOMYOPATHY

DCM is a myocardial disorder characterized by LV dilatation and systolic dysfunction (LV ejection fraction [LVEF]<50%) that is unexplained solely by abnormal loading conditions or coronary artery disease.[1] Prevalence estimates range from 1:250 to 1:2500 people. There are numerous causes of DCM that can be genetic or acquired. Genetic testing identifies rare disease-causing variants in 30% to 40% of DCM cases.[1] Distinguishing between genetic and acquired causes of DCM is not always straightforward and multiple risk factors may coexist in individual cases.

Although numerous DCM-associated genes have been reported in the literature, <20 of these have robust evidence of pathogenicity.[125] These core genes encode proteins with pleiotropic roles in cardiomyocyte biology, including the structure and function of the sarcomere (*MYH7, TNNC1, TTNT2, TTN*), cytoskeleton (*DES, FLNC*), and nucleus (*LMNA, RBM20*), as well as ion channel function (*PLN, SCN5A*) and protein homeostasis (*BAG3*). Single-cell sequencing has shown that there is some convergence of transcriptional pathways due to end-stage HF in hearts from patients with different genetic causes of DCM; however, 20% to 40% of differentially expressed genes are genotype-specific and associated with distinctive cell states.[126] Given this heterogeneity of myocardial substrates, it seems likely that there might be varying tolerance to exercise. For example, genetic defects that impair the structural stability of cardiomyocytes might be less resistant to increased mechanical stress when compared with genes with non-structural functions.

Regular physical activity has been shown to improve functional capacity and quality of life in clinically stable patients with DCM (Figure 1).[127] In a meta-analysis of 18 studies, moderate-intensity continuous exercise was also found to improve LVEF, with the greatest benefits seen after long-term (>6 months) training.[128] Exercise data to date have mainly been gathered from nonselected DCM cohorts; few studies have specifically evaluated exercise effects on disease progression and arrhythmia risk in the subset of patients with genetic DCM. It is noteworthy that abnormal responses to exercise testing have been proposed as a marker of early disease.[129–132] Studies of exercise in DCM are summarized in Table S3.[133] Many of these have focused on 2 of the most clinically important DCM genes, *LMNA* and *TTN*.

Exercise and *LMNA* Variants

The *LMNA* gene encodes the intermediate filament proteins, lamins A and C (lamin A/C), which are key components of the nuclear lamina, a dense fibrillar network that lines the inner nuclear envelope. Lamin A/C is required for coupling the nuclear envelope to the cytoskeleton through interactions with the LINC (linker-of-nucleoskeleton-and-cytoskeleton) complex, desmin, and actin.[134] These connections regulate 3-dimensional tension within cardiomyocytes and provide a structural scaffolding that links the nucleus to intracellular elements and the extracellular matrix. Lamin A/C is also a major determinant of mechanical properties of the nucleus and transcriptional regulation. Loss of lamin A/C results in a range of defects including impaired sensing and responding to mechanical stress, mis-localization of cytoskeletal proteins (eg, desmin intermediate filaments, actin, microtubules, connexins 40/43), impaired nuclear-cytoplasmic transport, altered cellular signaling (mitogen-activated protein kinase [MAPK], ERK, Jun-N-terminal kinase, Akt/mTOR, Wnt/β-catenin, TGFβ, Hippo/YAP, and platelet-derived growth factor [PDGF] pathways), oxidative stress, premature senescence, apoptosis, and impaired protein turnover.[135]

LMNA variants have been associated with a suite of cardiac, skeletal muscle, adipose tissue, and neurological disorders, collectively termed laminopathies. The cardiac-predominant phenotype typically presents with conduction abnormalities and atrial arrhythmias from the second to third decades with the subsequent development of DCM. *LMNA* variants are one of the clinically significant causes of familial DCM and often have a progressive downhill course with high rates of malignant VA and HF.[136] Consequently, *LMNA* was the first DCM disease to be incorporated into clinical decision-making algorithms for ICD implantation and early consideration of heart transplantation is recommended.[137] Various potential therapies targeting downstream signaling pathways have been evaluated in murine and zebrafish models.[138,139] One of the most promising of these, a selective p38a MAPK inhibitor, ARRY-371797, progressed to phase 2 and 3 clinical trials.[140] Despite an absence of safety

concerns, the phase 3 trial of ARRY-371797, REALM-DCM (https://www.clinicaltrials.gov; Unique identifier: NCT03439514), was prematurely terminated due to lack of efficacy.[140] To date, effective disease-modifying therapies for *LMNA*-related DCM are lacking.

Exercise participation in patients with *LMNA* variants has generally been discouraged, due to concerns about accelerated disease progression and heightened arrhythmic risk. These recommendations are based mainly on longitudinal retrospective observational data in cohorts of genotyped patients with DCM and their relatives. In a study of 164 G+ individuals (64% affected), a self-reported history of highly dynamic competitive sports for periods of 10 years or more was found to be an independent predictor of MACE including HF and SCD.[136] Another study of 69 *LMNA* variant-positive probands and relatives (48% with DCM) evaluated self-reported exercise patterns from the age of seven years until genetic diagnosis.[141] All subjects undertook recreational activities only and none were elite athletes. Active individuals, defined by cumulative lifetime exercise greater than the median (ie, 4160 hours), had larger cardiac dimensions than expected for the level of exercise, and were more likely to have DCM, ICD implantation, and atrial fibrillation, compared with nonactive individuals. There was a significant inverse relationship between lifetime exercise exposure and LVEF.

Murine studies have enabled different threshold levels of exercise to be more closely evaluated. In male heterozygous *Lmna*-deficient (*Lmna*$^{+/-}$) mice subjected to a 6-week period of moderate treadmill exercise training (17 m/min, 40 minutes, 5 d/wk), LV size, and contraction were relatively more preserved when compared with nonexercised mice.

These benefits were not seen in *Lmna*$^{+/-}$ mice that underwent intermittent high-intensity exercise training (22 m/min, 40 minutes, 2 d/wk).[142] In contrast, cardiac function was significantly worse in heterozygous *Lmna*^{delK32} mice after 5 weeks of strenuous treadmill exercise (21 m/min, 45 minutes, 5 d/wk).[143] The effects of endurance swimming exercise (90 min/d, 5 d/wk) were evaluated in mice carrying the human *LMNA* p.R225X variant (*Lmna*$^{R225/WT}$). After 18 weeks, LVEF was markedly depressed in nonexercised *Lmna*$^{R225/WT}$ mice but was similar to the wild type in the exercised *Lmna*$^{R225/WT}$ mice.[144] Collectively, current data suggest that higher intensity and longer duration of exercise have cumulative wear-and-tear effects that accelerate *LMNA*-associated cardiac dysfunction. However, murine findings suggest that delineation of cardioprotective levels of exercise might be achievable.

Exercise and Truncating *TTN* Variants

The *TTN* gene encodes the giant sarcomeric protein, titin. Closely integrated with thick and thin filaments, titin constitutes a third filament network that contributes to sarcomere structure and function in cardiac and skeletal muscle. The titin A-band, comprised of super repeats of immunoglobulin-like and fibronectin-type 3 domains, runs along the outer surface of the thick filament backbone where it interacts with myosin. A-band titin is relatively inextensible and is a determinant of thick filament length.[145] The titin I-band, containing a series of extensible elements including PEVK (proline-glutamate-valine-lysine)-repeats and immunoglobulin-like domains, contributes to the elasticity and passive muscle properties. Posttranslational modifications and changes in the ratio of the various titin isoforms provide further dynamic regulation of myocardial passive stiffness.[146] It has been proposed that titin has a fundamental role in the Frank-Starling mechanism whereby increases in LV filling volume lead to increased contraction. This is thought to result from I-band mediated passive force that increases thick filament strain and the number of myosin heads interacting with actin.[145] The proximal and distal ends of titin are tethered to the Z-disk and M-band regions, respectively, where they interact with multiple structural and signaling proteins. These regions, together with key nodes along the titin protein, such as the cardiac-specific N2B unique sequence, PEVK, and thymidine kinase domains, are important for sensing and responding to mechanical stress.[147]

Truncating variants in the *TTN* gene (*TTN*tv) are the most frequent genetic cause of DCM, being present in 10% to 20% of sporadic cases and up to 25% of families.[148] The cardiac phenotype associated with *TTN*tv is predominantly characterized by DCM, although cardiac arrhythmias are not uncommon. Atrial fibrillation is seen in approximately one-third of patients with DCM and may precede DCM onset. Although nonsustained ventricular tachycardia occurs in ≥50% cases, malignant VA is mostly seen in patients with severe impairment of systolic function. The age of onset of DCM can be variable, ranging from early adolescence to late adult life. Clinical risk factors such as alcohol excess, pregnancy, or anthracycline chemotherapy, can result in earlier disease onset. Overall, the clinical course in *TTN*tv-related DCM is usually less severe than that associated with *LMNA* mutations. Of note, patients with *TTN*tv-related DCM often respond well to HF therapies, displaying LV reverse remodeling.

Whether exercise has detrimental or beneficial effects in *TTN*tv-related DCM is unclear. Studies in zebrafish models have shown that *TTN*tv are associated with blunted inotropic responses to adrenergic stimulation and hemodynamic load.[149] These observations provide evidence of mechanical insufficiency and identify factors that could impact negatively on exercise performance. In a recent study, exercise histories were obtained from 117 patients with *TTN*tv-related DCM and G+ relatives.[150] Individuals who engaged in vigorous activity for >4 h/wk

for a minimum of 6 years had similar arrhythmia prevalence and LVEF when compared with those with lower activity levels. The effects of vigorous exercise training versus usual care were further evaluated in a group of 13 patients with *TTN*tv-related DCM.[151] The 8-week bicycle training protocol (30 minutes, 3/wk, 70% heart rate reserve) was well tolerated with no adverse events. Several favorable end points were achieved, including increases in VO_2peak, resting cardiac output, total blood volume, total hemoglobin mass, and LVEF. This study was limited by the small sample size and relatively short follow-up period. Nevertheless, the data suggest that exercise could be a useful nonpharmacological method for LV reverse remodeling.

Exercise and DCM: Current Status

Current exercise guidelines for DCM vary with the presence/absence of symptoms and severity of LV dysfunction (Figure 2). For most patients with mild or moderate DCM, exercise is regarded as beneficial. High or very high-intensity exercise is not recommended in patients with severe DCM or those with high-risk clinical features including extensive myocardial fibrosis, past history of malignant VA, or high-risk genotypes. These guidelines have mainly been extrapolated from studies in unselected DCM cohorts with limited evidence for exercise effects in genetic DCM.

Available data suggest that the relative propensity for risk versus benefit in genetic DCM varies with exercise dose and the underlying genotype; however, further investigation is needed (Figure 1). High-risk genotypes are mainly considered with respect to arrhythmia propensity and include DCM genes, such as *LMNA*, and ACM genes that present with LV-dominant disease, such as *TMEM43*. Other highly arrhythmic DCM genes that could potentially be added to this list include *FLNC* (truncating variants), *RBM20*, and *SCN5A*. An equivalent list of genotypes that might be more vulnerable to exercise-induced disease progression has yet to be defined. Animal data suggest, however, that even in identified high-risk groups, such as *LMNA*-positive probands and relatives, beneficial levels of exercise may be found. Consideration of exercise factors, genetic factors, and patient factors is needed to optimize exercise recommendations in individual DCM cases.

The efficacy of personalized exercise prescription in patients with DCM is currently under investigation in the activeDCM trial, a prospective randomized intervention trial with a 12-month follow-up.[152] The study end points will be assessed in 3 risk groups, based on clinical and genetic risk characteristics. Studies such as activeDCM are critically needed and will provide a valuable evidence base for refinement of exercise guidelines. Whether exercise training can protect against DCM onset has yet to be investigated.

LIMITATIONS AND FUTURE DIRECTIONS

The current evidence base regarding exercise effects in inherited cardiomyopathies has several limitations. Exercise levels vary throughout an individual's lifetime and retrospective assessments are inherently prone to recall bias and regression to the mean. Definitions of exercise, inclusion of nonsports-related physical activity and study end points, are heterogeneous in clinical cohorts which limit comparison between registries. Few studies use objective measures of exercise intensity or duration, and prospective long-term or randomized data are lacking. The increased use of wearable activity monitors and uptake of exercise tracking applications provide new opportunities to gather exercise data with unprecedented detail and accuracy. The majority of clinical data comes from large established registries which introduces a degree of bias. Disproportionate representation of certain genotypes limits the ability to generalize findings to less common genotype groups. Registry cohorts also include a high proportion of probands, which may exaggerate risk when generalized to G+P— family members given that the majority of those detected via cascade screening have a relatively more benign clinical course compared with probands. Further, women are underrepresented in most registry cohorts and sex-sensitive analysis is difficult. Most genotype-specific data come from animal models; however, these often fail to recapitulate human disease phenotypes precisely, and translation of findings should be cautious.

A one-size-fits-all approach is unlikely to be universally successful and exercise recommendations should ideally be tailored to individual patient capacity and risk factors (Figure 3). We propose a model in which exercise dose is closely titrated to myocardial vulnerability, determined by underlying genetic defects, phenotypic features, disease stage, and patient factors such as age, sex, comorbidities, and drug therapies (Figure 3). Testing this model at scale is challenging and will require thoughtful design of clinical trials. Implementation of exercise as therapy will also require a better understanding of factors that influence patient compliance.

CONCLUSIONS

Exercise is a profound modifier of cardiac structure, function, and electrophysiology properties with the potential to significantly impact the clinical course of inherited cardiomyopathies. Depending upon the phenotype and genotype, exercise may ameliorate or accentuate pathology with the effect dependent upon exercise intensity and duration. Evolving evidence strongly argues against a one-size-fits-all approach to exercise but, rather, that every patient deserves a tailored exercise program and an understanding that evidence continues to evolve.

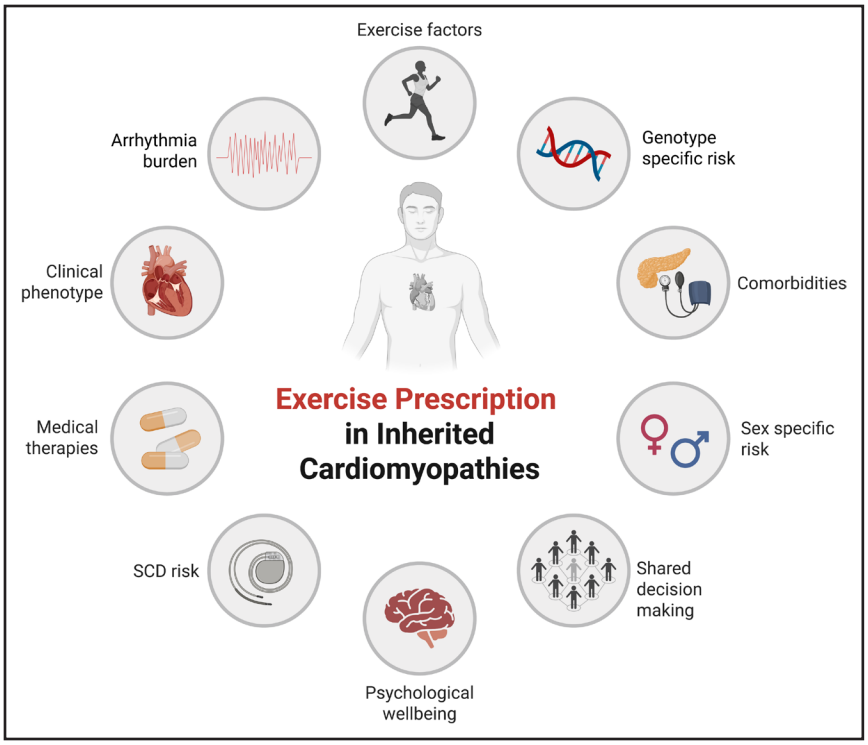

Figure 3. Factors to consider in an individualized exercise prescription. SCD indicates sudden cardiac death.

ARTICLE INFORMATION

Received March 29, 2025; revision received May 4, 2025; accepted May 15, 2025.

Affiliations

Victor Chang Cardiac Research Institute, Darlinghurst, New South Wales, Australia (E.R., A.L.G., D.F., C.F.S.); now with Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, United Kingdom (C.F.S.). School of Clinical Medicine, Faculty of Medicine and Health, UNSW Sydney, Kensington, New South Wales, Australia (E.R., D.F.). Cardiology Department, St Vincent's Hospital, Darlinghurst, New South Wales, Australia (E.R., D.F.). Heart Exercise and Research Trials (HEART) Lab, St Vincent's Institute of Medical Research, Fitzroy, Victoria, Australia (A.M., A.L.G.) Department of Medicine, University of Melbourne, Parkville, Victoria, Australia (A.M., A.L.G.). Cardiology Department, St Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia (A.L.G.).

Acknowledgments

Figures were generated using Biorender.

Sources of Funding

The authors acknowledge funding support from the National Health and Medical Research Council (E.E. Rye, A.M. Mitchell, A. La Gerche), National Heart Foundation of Australia (E.E. Rye), Australian Government Research Training Program (E.E. Rye), and New South Wales Health (D. Fatkin).

Disclosures

None.

REFERENCES

1. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, Basso C, Bezzina CR, Biagini E, Blom NA, de Boer RA, et al; ESC Scientific Document Group. 2023 ESC Guidelines for the management of cardiomyopathies: developed by the task force on the management of cardiomyopathies of the European Society of Cardiology (ESC). *Eur Heart J.* 2023;44:3503–3626. doi: 10.1093/eurheartj/ehad194
2. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, George SM, Olson RD. The physical activity guidelines for Americans. *JAMA.* 2018;320:2020–2028. doi: 10.1001/jama.2018.14854
3. Vega RB, Konhilas JP, Kelly DP, Leinwand LA. Molecular mechanisms underlying cardiac adaptation to exercise. *Cell Metab.* 2017;25:1012–1026. doi: 10.1016/j.cmet.2017.04.025
4. Howden EJ, Sarma S, Lawley JS, Opondo M, Cornwell W, Stoller D, Urey MA, Adams-Huet B, Levine BD. Reversing the cardiac effects of sedentary aging in middle age-a randomized controlled trial: implications for heart failure prevention. *Circulation.* 2018;137:1549–1560. doi: 10.1161/CIRCULATIONAHA.117.030617
5. Pinckard K, Baskin KK, Stanford KI. Effects of exercise to improve cardiovascular health. *Front Cardiovasc Med.* 2019;6:69. doi: 10.3389/fcvm.2019.00069
6. Topriceanu CC, Pereira AC, Moon JC, Captur G, Ho CY. Meta-analysis of penetrance and systematic review on transition to disease in genetic hypertrophic cardiomyopathy. *Circulation.* 2024;149:107–123. doi: 10.1161/CIRCULATIONAHA.123.065987
7. Hespe S, Waddell A, Asatryan B, Owens E, Thaxton C, Adduru ML, Anderson K, Brown EE, Hoffman-Andrews L, Jordan E, et al. Genes associated with hypertrophic cardiomyopathy: a reappraisal by the ClinGen Hereditary Cardiovascular Disease Gene Curation Expert Panel. *J Am Coll Cardiol.* 2025;85:727–740. doi: 10.1016/j.jacc.2024.12.010
8. Hooijman P, Stewart Melanie A, Cooke R. A new state of cardiac myosin with very slow ATP turnover: a potential cardioprotective mechanism in the heart. *Biophys J.* 2011;100:1969–1976. doi: 10.1016/j.bpj.2011.02.061
9. Alamo L, Ware JS, Pinto A, Gillilan RE, Seidman JG, Seidman CE, Padrón R. Effects of myosin variants on interacting-heads motif explain distinct hypertrophic and dilated cardiomyopathy phenotypes. *eLife.* 2017;6:e24634. doi: 10.7554/eLife.24634
10. Critoph CH, Patel V, Mist B, Elliott PM. Cardiac output response and peripheral oxygen extraction during exercise among symptomatic hypertrophic cardiomyopathy patients with and without left ventricular outflow tract obstruction. *Heart.* 2014;100:639–646. doi: 10.1136/heartjnl-2013-304914
11. La Gerche A, Howden EJ, Haykowsky MJ, Lewis GD, Levine BD, Kovacic JC. Heart failure with preserved ejection fraction as an exercise deficiency syndrome: JACC focus seminar 2/4. *J Am Coll Cardiol.* 2022;80:1177–1191. doi: 10.1016/j.jacc.2022.07.011
12. Le VV, Perez MV, Wheeler MT, Myers J, Schnittger I, Ashley EA. Mechanisms of exercise intolerance in patients with hypertrophic cardiomyopathy. *Am Heart J.* 2009;158:e27–e34. doi: 10.1016/j.ahj.2009.06.006
13. Shah JS, Esteban MT, Thaman R, Sharma R, Mist B, Pantazis A, Ward D, Kohli SK, Page SP, Demetrescu C, et al. Prevalence of exercise-induced left ventricular outflow tract obstruction in symptomatic patients with non-obstructive hypertrophic cardiomyopathy. *Heart.* 2008;94:1288–1294. doi: 10.1136/hrt.2007.126003

14. Re F, Zachara E, Avella A, Baratta P, Di Mauro M, Penco M, Musumeci F, Tondo C. Rest and latent obstruction in hypertrophic cardiomyopathy: impact on exercise tolerance. *J Cardiovasc Med (Hagerstown)*. 2013;14:372–379. doi: 10.2459/JCM.0b013e328355fb00
15. Erez Y, Ghantous E, Shetrit A, Zamanzadeh RS, Zahler D, Granot Y, Sapir OR, Laufer Perl M, Banai S, Topilsky Y, et al. Exercise limitation in hypertrophic cardiomyopathy: combined stress echocardiography and cardiopulmonary exercise test. *ESC Heart Fail*. 2024;11:2287–2294. doi: 10.1002/ehf2.14776
16. Cui H, Schaff HV, Olson TP, Geske JB, Dearani JA, Nishimura RA, Sun D, Ommen SR. Cardiopulmonary exercise test in patients with obstructive hypertrophic cardiomyopathy. *J Thorac Cardiovasc Surg*. 2024;167:701.e3–710.e3. doi: 10.1016/j.jtcvs.2022.05.025
17. Capota R, Militaru S, Ionescu AA, Rosca M, Baicus C, Popescu BA, Jurcut RJH. Quality of life status determinants in hypertrophic cardiomyopathy as evaluated by the Kansas City Cardiomyopathy Questionnaire. *Health Qual Life Outcomes*. 2020;18:1–8. doi: 10.1186/s12955-020-01604-9
18. Coleman JA, Ashkir Z, Raman B, Bueno-Orovio A. Mechanisms and prognostic impact of myocardial ischaemia in hypertrophic cardiomyopathy. *Int J Cardiovasc Imaging*. 2023;39:1979–1996. doi: 10.1007/s10554-023-02894-y
19. Cannon RO, Dilsizian V, O'Gara PT, Udelson JE, Schenke WH, Quyyumi A, Fananapazir L, Bonow RO. Myocardial metabolic, hemodynamic, and electrocardiographic significance of reversible thallium-201 abnormalities in hypertrophic cardiomyopathy. *Circulation*. 1991;83:1660–1667. doi: 10.1161/01.cir.83.5.1660
20. Pop GAM, Cramer E, Timmermans J, Bos H, Verheugt FWA. Troponin I release at rest and after exercise in patients with hypertrophic cardiomyopathy and the effect of betablockade. *Arch Cardiol Mex*. 2006;76:415–418.
21. Isobe S, Izawa H, Takeichi Y, Nonokawa M, Nanasato M, Ando A, Kato K, Ikeda M, Murohara T, Yokota M. Relationship between exercise-induced myocardial ischemia and reduced left ventricular distensibility in patients with nonobstructive hypertrophic cardiomyopathy. *J Nucl Med*. 2003;44:1717–1724.
22. Abdelfattah OM, Martinez M, Sayed A, ElRefaei M, Abushouk AI, Hassan A, Masri A, Winters SL, Kapadia SR, Maron MS. Temporal and global trends of the incidence of sudden cardiac death in hypertrophic cardiomyopathy. *JACC Clin Electrophysiol*. 2022;8:1417–1427. doi: 10.1016/j.jacep.2022.07.012
23. Mascia G, Crotti L, Groppelli A, Canepa M, Merlo AC, Benenati S, Di Donna P, Della Bona R, Soranna D, Zambon A, et al. Syncope in hypertrophic cardiomyopathy (part I): an updated systematic review and meta-analysis. *Int J Cardiol*. 2022;357:88–94. doi: 10.1016/j.ijcard.2022.03.028
24. Basu J, Nikoletou D, Miles C, MacLachlan H, Parry-Williams G, Tilby-Jones F, Bulleros P, Fanton Z, Baker C, Purcell S, et al. High intensity exercise programme in patients with hypertrophic cardiomyopathy: a randomized trial. *Eur Heart J*. 2025;46:1803–1815. doi: 10.1093/eurheartj/ehae919
25. Saberi S, Wheeler M, Bragg-Gresham J, Hornsby W, Agarwal PP, Attili A, Concannon M, Dries AM, Shmargad Y, Salisbury H, et al. Effect of moderate-intensity exercise training on peak oxygen consumption in patients with hypertrophic cardiomyopathy: a randomized clinical trial. *JAMA*. 2017;317:1349–1357. doi: 10.1001/jama.2017.2503
26. MacNamara JP, Dias KA, Hearon CM Jr, Ivey E, Delgado VA, Saland S, Samels M, Hieda M, Turer AT, Link MS, et al. Randomized controlled trial of moderate-and high-intensity exercise training in patients with hypertrophic cardiomyopathy: effects on fitness and cardiovascular response to exercise. *J Am Heart Assoc*. 2023;12:e031399. doi: 10.1161/JAHA.123.031399
27. Wasserstrum Y, Barbarova I, Lotan D, Kuperstein R, Shechter M, Freimark D, Segal G, Klempfner R, Arad M. Efficacy and safety of exercise rehabilitation in patients with hypertrophic cardiomyopathy. *J Cardiol*. 2019;74:466–472. doi: 10.1016/j.jjcc.2019.04.013
28. Klempfner R, Kamerman T, Schwammenthal E, Nahshon A, Hay I, Goldenberg I, Dov F, Arad M. Efficacy of exercise training in symptomatic patients with hypertrophic cardiomyopathy: results of a structured exercise training program in a cardiac rehabilitation center. *Eur J Prev Cardiol*. 2015;22:13–19. doi: 10.1177/2047487313501277
29. Limongelli G, Monda E, D'Aponte A, Caiazza M, Rubino M, Esposito A, Palmiero G, Moscarella E, Messina G, Calabro P, et al. Combined effect of mediterranean diet and aerobic exercise on weight loss and clinical status in obese symptomatic patients with hypertrophic cardiomyopathy. *Heart Fail Clin*. 2021;17:303–313. doi: 10.1016/j.hfc.2021.01.003
30. Gudmundsdottir HL, Axelsson Raja A, Rossing K, Rasmusen H, Snoer M, Andersen LJ, Gottlieb R, Christensen AH, Bundgaard H, Gustafsson F, et al. Exercise training in patients with hypertrophic cardiomyopathy without left ventricular outflow tract obstruction: a randomized clinical trial. *Circulation*. 2025;151:132–144. doi: 10.1161/CIRCULATIONAHA.124.070064
31. Hassanzada F, Jansen M, van Lint FHM, Bosman LP, Schmidt AF, Dooijes D, van de Sande D, Miah B, van der Crabben SN, Wilde AAM, et al. Recreational and occupational physical activity and risk of adverse events in truncating MYBPC3 founder variant carriers. *Circ Genom Precis Med*. 2024;17:e004561. doi: 10.1161/CIRCGEN.124.004561
32. Basu J, Finocchiaro G, Jayakumar S, Schönfeld J, MacLachlan H, Miles C, Parry-Williams G, Tome M, Papadakis M, Sharma S. Impact of exercise on outcomes and phenotypic expression in athletes with nonobstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2022;80:1498–1500. doi: 10.1016/j.jacc.2022.08.715
33. Dejgaard LA, Haland TF, Lie OH, Ribe M, Bjune T, Leren IS, Berge KE, Edvardsen T, Haugaa KH. Vigorous exercise in patients with hypertrophic cardiomyopathy. *Int J Cardiol*. 2018;250:157–163. doi: 10.1016/j.ijcard.2017.07.015
34. Andreassen K, Dejgaard LA, Lie O, Fink TS, Lunde IG, Edvardsen T, Haugaa KH, Stokke MK. Exercise training during childhood and adolescence is associated with favorable diastolic function in hypertrophic cardiomyopathy. *Int J Cardiol*. 2022;364:65–71. doi: 10.1016/j.ijcard.2022.06.042
35. Cavigli L, Ragazzoni GL, Vannuccini F, Targetti M, Mandoli GE, Senesi G, Pastore MC, Focardi M, Cameli M, Valente S, et al. Cardiopulmonary fitness and personalized exercise prescription in patients with hypertrophic cardiomyopathy. *J Am Heart Assoc*. 2024;13:e036593. doi: 10.1161/JAHA.124.036593
36. Aengevaeren VL, Gommans DF, Dieker HJ, Timmermans J, Verheugt FW, Bakker J, Hopman MT, De Boer MJ, Brouwer MA, Thompson PD, et al. Association between lifelong physical activity and disease characteristics in HCM. *Med Sci Sports Exerc*. 2019;51:1995–2002. doi: 10.1249/MSS.0000000000002015
37. Sheikh N, Papadakis M, Schnell F, Panoulas V, Malhotra A, Wilson M, Carré F, Sharma S. Clinical profile of athletes with hypertrophic cardiomyopathy. *Circ Cardiovasc Imaging*. 2015;8:e003454. doi: 10.1161/CIRCIMAGING.114.003454
38. Pelliccia A, Caselli S, Pelliccia M, Musumeci MB, Lemme E, Di Paolo FM, Maestrini V, Russo D, Limite L, Borrazzo C, et al. Clinical outcomes in adult athletes with hypertrophic cardiomyopathy: a 7-year follow-up study. *Br J Sports Med*. 2020;54:1008–1012. doi: 10.1136/bjsports-2019-100890
39. Cramer GE, Gommans DF, Dieker HJ, Michels M, Verheugt F, de Boer MJ, Bakker J, Fouraux MA, Timmermans J, Kofflard M, et al. Exercise and myocardial injury in hypertrophic cardiomyopathy. *Heart*. 2020;106:1169–1175. doi: 10.1136/heartjnl-2019-315818
40. Kwon S, Lee HJ, Han KD, Kim DH, Lee SP, Hwang IC, Yoon Y, Park JB, Lee H, Kwak S, et al. Association of physical activity with all-cause and cardiovascular mortality in 7666 adults with hypertrophic cardiomyopathy (HCM): more physical activity is better. *Br J Sports Med*. 2021;55:1034–1040. doi: 10.1136/bjsports-2020-101987
41. Coats CJ, Rantell K, Bartnik A, Patel A, Mist B, McKenna WJ, Elliott PM. Cardiopulmonary exercise testing and prognosis in hypertrophic cardiomyopathy. *Circ Heart Fail*. 2015;8:1022–1031. doi: 10.1161/CIRCHEARTFAILURE.114.002248
42. Najafi A, Schlossarek S, van Deel ED, van den Heuvel N, Güçlü A, Goebel M, Kuster DW, Carrier L, van der Velden J. Sexual dimorphic response to exercise in hypertrophic cardiomyopathy-associated MYBPC3-targeted knock-in mice. *Pflugers Arch*. 2015;467:1303–1317. doi: 10.1007/s00424-014-1570-7
43. Kazmierczak K, Yuan CC, Liang J, Huang W, Rojas AI, Szczesna-Cordary D. Remodeling of the heart in hypertrophy in animal models with myosin essential light chain mutations. *Front Physiol*. 2014;5:353. doi: 10.3389/fphys.2014.00353
44. Nguyen L, Chung J, Lam L, Tsoutsman T, Semsarian C. Abnormal cardiac response to exercise in a murine model of familial hypertrophic cardiomyopathy. *Int J Cardiol*. 2007;119:245–248. doi: 10.1016/j.ijcard.2006.09.001
45. Wang H, Lin Y, Zhang R, Chen Y, Ji W, Li S, Wang L, Tan R, Yuan J. Programmed exercise attenuates familial hypertrophic cardiomyopathy in transgenic E22K mice via inhibition of PKC-α/NFAT pathway. *Front Cardiovasc Med*. 2022;9:808163. doi: 10.3389/fcvm.2022.808163
46. Konhilas JP, Watson PA, Maass A, Boucek DM, Horn T, Stauffer BL, Luckey SW, Rosenberg P, Leinwand LA. Exercise can prevent and reverse the severity of hypertrophic cardiomyopathy. *Circ Res*. 2006;98:540–548. doi: 10.1161/01.RES.0000205766.97556.00
47. Andreassen K, Rixon C, Hansen MH, Hauge-Iversen IM, Zhang L, Sadredini M, Erusappan PM, Sjaastad I, Christensen G, Haugaa KH, et al. Beneficial effects of exercise initiated before development of hypertrophic

cardiomyopathy in genotype-positive mice. *Am J Physiol Heart Circ Physiol.* 2023;324:H881–H892. doi: 10.1152/ajpheart.00701.2022
48. Bermúdez-Jiménez FJ, Carriel V, Brodehl A, Alaminos M, Campos A, Schirmer I, Milting H, Abril B, Álvarez M, López-Fernández S, et al. Novel desmin mutation p.Glu401Asp impairs filament formation, disrupts cell membrane integrity, and causes severe arrhythmogenic left ventricular cardiomyopathy/dysplasia. *Circulation.* 2018;137:1595–1610. doi: 10.1161/CIRCULATIONAHA.117.028719
49. Slater RE, Strom JG, Granzier H. Effect of exercise on passive myocardial stiffness in mice with diastolic dysfunction. *J Mol Cell Cardiol.* 2017;108:24–33. doi: 10.1016/j.yjmcc.2017.04.006
50. Lampert R, Ackerman MJ, Marino BS, Burg M, Ainsworth B, Salberg L, Esteban MTT, Ho CY, Abraham R, Balaji S, et al. Vigorous exercise in patients with hypertrophic cardiomyopathy. *JAMA Cardiol.* 2023;8:595–605. doi: 10.1001/jamacardio.2023.1042
51. Lee HJ, Gwak SY, Kim K, Cho I, Shim CY, Ha JW, Hong GR. Factors associated with high-intensity physical activity and sudden cardiac death in hypertrophic cardiomyopathy. *Heart.* 2025;111:253–261. doi: 10.1136/heartjnl-2024-324928
52. Witjas-Paalberends ER, Güçlü A, Germans T, Knaapen P, Harms HJ, Vermeer AM, Christiaans I, Wilde AA, Dos Remedios C, Lammertsma AA, et al. Gene-specific increase in the energetic cost of contraction in hypertrophic cardiomyopathy caused by thick filament mutations. *Cardiovasc Res.* 2014;103:248–257. doi: 10.1093/cvr/cvu127
53. Cohn R, Thakar K, Lowe A, Ladha FA, Pettinato AM, Romano R, Meredith E, Chen YS, Atamanuk K, Huey BD, et al. A contraction stress model of hypertrophic cardiomyopathy due to sarcomere mutations. *Stem Cell Rep.* 2019;12:71–83. doi: 10.1016/j.stemcr.2018.11.015
54. Ommen SR, Ho CY, Asif IM, Balaji S, Burke MA, Day SM, Dearani JA, Epps KC, Evanovich L, Ferrari VA, et al; Writing Committee Members. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR guideline for the management of hypertrophic cardiomyopathy: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2024;83:2324–2405. doi: 10.1016/j.jacc.2024.02.014
55. Rowin EJ, Maron BJ, Olivotto I, Maron MS. Role of exercise testing in hypertrophic cardiomyopathy. *JACC Cardiovasc Imaging.* 2017;10:1374–1386. doi: 10.1016/j.jcmg.2017.07.016
56. Ommen SR, Ho CY, Asif IM, Balaji S, Burke MA, Day SM, Dearani JA, Epps KC, Evanovich L, Ferrari VA, et al; Peer Review Committee Members. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR Guideline for the management of hypertrophic cardiomyopathy: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation.* 2024;149:e1239–e1311. doi: 10.1161/CIR.0000000000001250
57. Heidbuchel H, Arbelo E, D'Ascenzi F, Borjesson M, Boveda S, Castelletti S, Miljoen H, Mont L, Niebauer J, Papadakis M, et al; EAPC/EHRA update of the Recommendations for participation in leisure-time physical activity and competitive sports in patients with arrhythmias and potentially arrhythmogenic conditions. Recommendations for participation in leisure-time physical activity and competitive sports of patients with arrhythmias and potentially arrhythmogenic conditions. Part 2: ventricular arrhythmias, channelopathies, and implantable defibrillators. *Europace.* 2021;23:147–148. doi: 10.1093/europace/euaa106
58. Corrado D, Link MS, Calkins H. Arrhythmogenic right ventricular cardiomyopathy. *N Engl J Med.* 2017;376:61–72. doi: 10.1056/NEJMra1509267
59. James CA, Syrris P, van Tintelen JP, Calkins H. The role of genetics in cardiovascular disease: arrhythmogenic cardiomyopathy. *Eur Heart J.* 2020;41:1393–1400. doi: 10.1093/eurheartj/ehaa141
60. Bhonsale A, Groeneweg JA, James CA, Dooijes D, Tichnell C, Jongbloed JDH, Murray B, te Riele ASJM, van den Berg MP, 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. doi: 10.1093/eurheartj/ehu509
61. James C, Jongbloed J, Hershberger R, Morales A, Judge D, Syrris P, Pilichou K, Domingo A, Murray B, Cadrin-Tourigny J, et al. International evidence based reappraisal of genes associated with arrhythmogenic right ventricular cardiomyopathy using the clinical genome resource framework. *Circ Genom Precis Med.* 2021;14:e003273. doi: 10.1161/CIRCGEN.120.003273
62. Hodgkinson KA, Connors SP, Merner N, Haywood A, Young TL, McKenna WJ, Gallagher B, Curtis F, Bassett AS, Parfrey PS. The natural history of a genetic subtype of arrhythmogenic right ventricular cardiomyopathy caused by a p.S358L mutation in TMEM43. *Clin Genet.* 2013;83:321–331. doi: 10.1111/j.1399-0004.2012.01919.x
63. van der Zwaag PA, van Rijsingen IA, Asimaki A, Jongbloed JD, van Veldhuisen DJ, Wiesfeld AC, Cox MG, van Lochem LT, de Boer RA, Hofstra RM, et al. Phospholamban R14del mutation in patients diagnosed with dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy: evidence supporting the concept of arrhythmogenic cardiomyopathy. *Eur J Heart Fail.* 2012;14:1199–1207. doi: 10.1093/eurjhf/hfs119
64. Sawant AC, Bhonsale A, te Riele AS, Tichnell C, Murray B, Russell SD, Tandri H, Tedford RJ, Judge DP, Calkins H, et al. Exercise has a disproportionate role in the pathogenesis of arrhythmogenic right ventricular dysplasia/cardiomyopathy in patients without desmosomal mutations. *J Am Heart Assoc.* 2014;3:e001471. doi: 10.1161/JAHA.114.001471
65. Paldino A, Rossi M, Dal Ferro M, Tavčar I, Behr E, Sharma S, Papadakis M, Sinagra G, Finocchiaro G. Sport and exercise in genotype positive (+) phenotype negative (–) individuals: current dilemmas and future perspectives. *Eur J Prev Cardiol.* 2023;30:871–883. doi: 10.1093/eurjpc/zwad079
66. Benito B, Gay-Jordi G, Serrano-Mollar A, Guasch E, Shi Y, Tardif JC, Brugada J, Nattel S, Mont L. Cardiac arrhythmogenic remodeling in a rat model of long-term intensive exercise training. *Circulation.* 2011;123:13–22. doi: 10.1161/CIRCULATIONAHA.110.938282
67. James CA, Bhonsale A, Tichnell C, Murray B, Russell SD, Tandri H, Tedford RJ, Judge DP, 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. doi: 10.1016/j.jacc.2013.06.033
68. Ruwald AC, Marcus F, Estes NA, Link M, McNitt S, Polonsky B, Calkins H, Towbin JA, Moss AJ, Zareba W. Association of competitive and recreational sport participation with cardiac events in patients with arrhythmogenic right ventricular cardiomyopathy: results from the North American multidisciplinary study of arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J.* 2015;36:1735–1743. doi: 10.1093/eurheartj/ehv110
69. Lie H, Dejgaard LA, Saberniak J, Rootwelt C, Stokke MK, Edvardsen T, Haugaa KH. Harmful effects of exercise intensity and exercise duration in patients with arrhythmogenic cardiomyopathy. *JACC Clin Electrophysiol.* 2018;4:744–753. doi: 10.1016/j.jacep.2018.01.010
70. Bosman LP, Wang W, Lie H, van Lint FHM, Rootwelt-Norberg C, Murray B, Tichnell C, Cadrin-Tourigny J, van Tintelen JP, Asselbergs FW, et al. Integrating exercise into personalized ventricular arrhythmia risk prediction in arrhythmogenic right ventricular cardiomyopathy. *Circ Arrhythm Electrophysiol.* 2022;15:e010221. doi: 10.1161/CIRCEP.121.010221
71. Sawant AC, Te Riele AS, Tichnell C, Murray B, Bhonsale A, Tandri H, Judge DP, Calkins H, James CA. Safety of American Heart Association-recommended minimum exercise for desmosomal mutation carriers. *Heart Rhythm.* 2016;13:199–207. doi: 10.1016/j.hrthm.2015.08.035
72. Costa S, Gasperetti A, Medeiros-Domingo A, Akdis D, Brunckhorst C, Saguner AM, Duru F. Familial arrhythmogenic cardiomyopathy: clinical determinants of phenotype discordance and the impact of endurance sports. *J Clin Med.* 2020;9:3781. doi: 10.3390/jcm9113781
73. Lie H, Rootwelt-Norberg C, Dejgaard LA, Leren IS, Stokke MK, Edvardsen T, Haugaa KH. Prediction of life-threatening ventricular arrhythmia in patients with arrhythmogenic cardiomyopathy: a primary prevention cohort study. *JACC Cardiovasc Imaging.* 2018;11:1377–1386. doi: 10.1016/j.jcmg.2018.05.017
74. Rootwelt-Norberg C, Lie H, Chivulescu M, Castrini AI, Sarvari SI, Lyseggen E, Almaas VM, Bogsrud MP, Edvardsen T, Haugaa KH. Sex differences in disease progression and arrhythmic risk in patients with arrhythmogenic cardiomyopathy. *Europace.* 2021;23:1084–1091. doi: 10.1093/europace/euab077
75. Costa S, Koch K, Gasperetti A, Akdis D, Brunckhorst C, Fu G, Tanner FC, Ruschitzka F, Duru F, Saguner AM. Changes in exercise capacity and ventricular function in arrhythmogenic right ventricular cardiomyopathy: the impact of sports restriction during follow-up. *J Clin Med.* 2022;11:1150. doi: 10.3390/jcm11051150
76. Saberniak J, Hasselberg NE, Borgquist R, Platonov PG, Sarvari SI, Smith HJ, Ribe M, Holst AG, Edvardsen T, Haugaa KH. Vigorous physical activity impairs myocardial function in patients with arrhythmogenic right ventricular cardiomyopathy and in mutation positive family members. *Eur J Heart Fail.* 2014;16:1337–1344. doi: 10.1002/ejhf.181
77. Akdis D, Saguner AM, Burri H, Medeiros-Domingo A, Matter CM, Ruschitzka F, Tanner FC, Brunckhorst C, Duru F. Clinical predictors of left ventricular involvement in arrhythmogenic right ventricular cardiomyopathy. *Am Heart J.* 2020;223:34–43. doi: 10.1016/j.ahj.2020.01.019
78. Vergara P, Pannone L, Calvo F, Falasconi G, Foppoli L, Cireddu M, D'Angelo G, Limite L, Boccellino A, Palmisano A, et al. Physical activity volume in patients with arrhythmogenic cardiomyopathy is associated with recurrence after ventricular tachycardia ablation. *J Interv Card Electrophysiol.* 2022;65:15–24. doi: 10.1007/s10840-021-01019-6

79. Mazzanti A, Ng K, Faragli A, Maragna R, Chiodaroli E, Orphanou N, Monteforte N, Memmi M, Gambelli P, Novelli V, et al. Arrhythmogenic right ventricular cardiomyopathy: clinical course and predictors of arrhythmic risk. *J Am Coll Cardiol*. 2016;68:2540–2550. doi: 10.1016/j.jacc.2016.09.951
80. Binzenhöfer L, Clauss S, Strauß K, Höpler J, Kraft M, Hoffmann S, Brunner S, Tomsits P, Schüttler D, Massberg S, et al. Lifetime cumulative activity burden is associated with symptomatic heart failure and arrhythmic risk in patients with arrhythmogenic right ventricular cardiomyopathy: a retrospective cohort study. *Europace*. 2024;26:euae236. doi: 10.1093/europace/euae236
81. Lampert R, Chung EH, Ackerman MJ, Arroyo AR, Darden D, Deo R, Dolan J, Etheridge SP, Gray BR, Harmon KG, et al. 2024 HRS expert consensus statement on arrhythmias in the athlete: evaluation, treatment, and return to play. *Heart Rhythm*. 2024;21:e151–e252. doi: 10.1016/j.hrthm.2024.05.018
82. Cerrone M, Marrón-Liñares GM, van Opbergen CJM, Costa S, Bourfiss M, Pérez-Hernández M, Schlamp F, Sanchis-Gomar F, Malkani K, Drenkova K, et al. Role of plakophilin-2 expression on exercise-related progression of arrhythmogenic right ventricular cardiomyopathy: a translational study. *Eur Heart J*. 2022;43:1251–1264. doi: 10.1093/eurheartj/ehab772
83. Lie H, Chivulescu M, Rootwelt-Norberg C, Ribe M, Bogsrud MP, Lyseggen E, Beitnes JO, Almaas V, Haugaa KH. Left ventricular dysfunction in arrhythmogenic cardiomyopathy: association with exercise exposure, genetic basis, and prognosis. *J Am Heart Assoc*. 2021;10:e018680. doi: 10.1161/JAHA.120.018680
84. Jacobsen AP, Chiampas K, Muller SA, Gasperetti A, Yanek LR, Carrick RT, Gordon C, Tichnell C, Murray B, Calkins H, et al. Endurance exercise promotes episodes of myocardial injury in individuals with a pathogenic desmoplakin (DSP) variant. *Heart Rhythm*. doi: 10.1016/j.hrthm.2024.12.035
85. Paulin FL, Hodgkinson KA, MacLaughlan S, Stuckless SN, Templeton C, Shah S, Bremner H, Roberts JD, Young TL, Parfrey PS, et al. Exercise and arrhythmic risk in TMEM43 p.S358L arrhythmogenic right ventricular cardiomyopathy. *Heart Rhythm*. 2020;17:1159–1166. doi: 10.1016/j.hrthm.2020.02.028
86. van Lint FHM, Hassanzada F, Verstraelen TE, Wang W, Bosman LP, van der Zwaag PA, Oomen T, Calkins H, Murray B, Tichnell C, et al. Exercise does not influence development of phenotype in PLN p.(Arg14del) cardiomyopathy. *Neth Heart J*. 2023;31:291–299. doi: 10.1007/s12471-023-01800-4
87. van Rijsingen IAW, van der Zwaag PA, Groeneweg JA, Nannenberg EA, Jongbloed JDH, Zwinderman AH, Pinto YM, dit Deprez RHL, Post JG, Tan HL, et al. Outcome in phospholamban R14del carriers. *Circ Cardiovasc Genet*. 2014;7:455–465. doi: 10.1161/CIRCGENETICS.113.000374
88. Wang W, Orgeron G, Tichnell C, Murray B, Crosson J, Monfredi O, Cadrin-Tourigny J, Tandri H, Calkins H, James CA. Impact of exercise restriction on arrhythmic risk among patients with arrhythmogenic right ventricular cardiomyopathy. *J Am Heart Assoc*. 2018;7:e008843. doi: 10.1161/JAHA.118.008843
89. Ruiz Salas A, Barrera Cordero A, Navarro-Arce I, Jiménez Navarro M, García Pinilla JM, Cabrera Bueno F, Abdeselam-Mohamed N, Morcillo-Hidalgo L, Gómez Doblas JJ, de Teresa E, et al. Impact of dynamic physical exercise on high-risk definite arrhythmogenic right ventricular cardiomyopathy. *J Cardiovasc Electrophysiol*. 2018;29:1523–1529. doi: 10.1111/jce.13704
90. Zorzi A, Cipriani A, Bariani R, Pilichou K, Corrado D, Bauce B. Role of exercise as a modulating factor in arrhythmogenic cardiomyopathy. *Curr Cardiol Rep*. 2021;23:57. doi: 10.1007/s11886-021-01489-0
91. Wang W, Tichnell C, Murray BA, Agafonova J, Cadrin-Tourigny J, Chelko S, Tandri H, Calkins H, James CA. Exercise restriction is protective for genotype-positive family members of arrhythmogenic right ventricular cardiomyopathy patients. *Europace*. 2020;22:1270–1278. doi: 10.1093/europace/euaa105
92. Müssigbrodt A, Czimbalmos C, Stauber A, Bertagnolli L, Bode K, Dagres N, Döring M, Richter S, Sommer P, Husser D, et al. Effect of exercise on outcome after ventricular tachycardia ablation in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Int J Sports Med*. 2019;40:657–662. doi: 10.1055/a-0962-1325
93. Ramos-Maqueda J, Migueles JH, Molina-Jiménez M, Ruiz-González D, Cabrera-Borrego E, Ruiz Salas A, Soriano-Maldonado A, Jimenez-Jaimez J. Lifestyle physical activity and rapid-rate non-sustained ventricular tachycardia in arrhythmogenic cardiomyopathy. *Heart*. 2023;109:992–999. doi: 10.1136/heartjnl-2022-321824
94. Chelko SP, Keceli G, Carpi A, Doti N, Agrimi J, Asimaki A, Beti CB, Miyamoto M, Amat-Codina N, Bedja D, et al. Exercise triggers CAPN1-mediated AIF truncation, inducing myocyte cell death in arrhythmogenic cardiomyopathy. *Sci Transl Med*. 2021;13:eabf0891. doi: 10.1126/scitranslmed.abf0891
95. Pérez-Hernández M, van Opbergen CJM, Bagwan N, Vissing CR, Marrón-Liñares GM, Zhang M, Torres Vega E, Sorrentino A, Drici L, Sulek K, et al. Loss of nuclear envelope integrity and increased oxidant production cause DNA damage in adult hearts deficient in PKP2: a molecular substrate of ARVC. *Circulation*. 2022;146:851–867. doi: 10.1161/CIRCULATIONAHA.122.060454
96. Lyon RC, Mezzano V, Wright AT, Pfeiffer E, Chuang J, Banares K, Castaneda A, Ouyang K, Cui L, Contu R, et al. Connexin defects underlie arrhythmogenic right ventricular cardiomyopathy in a novel mouse model. *Hum Mol Genet*. 2014;23:1134–1150. doi: 10.1093/hmg/ddt508
97. Moncayo-Arlandi J, Guasch E, Sanz-de la Garza M, Casado M, Garcia NA, Mont L, Sitges M, Knöll R, Buyandelger B, Campuzano O, et al. Molecular disturbance underlies to arrhythmogenic cardiomyopathy induced by transgene content, age and exercise in a truncated PKP2 mouse model. *Hum Mol Genet*. 2016;25:3676–3688. doi: 10.1093/hmg/ddw213
98. Hammer KP, Mustroph J, Stauber T, Birchmeier W, Wagner S, Maier LS. Beneficial effect of voluntary physical exercise in Plakophilin2 transgenic mice. *PLoS One*. 2021;16:e0252649. doi: 10.1371/journal.pone.0252649
99. Kirchhof P, Fabritz L, Zwiener M, Witt H, Schäfers M, Zellerhoff S, Paul M, Athai T, Hiller KH, Baba HA, et al. Age- and training-dependent development of arrhythmogenic right ventricular cardiomyopathy in heterozygous plakoglobin-deficient mice. *Circulation*. 2006;114:1799–1806. doi: 10.1161/CIRCULATIONAHA.106.624502
100. Kaplan SR, Gard JJ, Protonotarios N, Tsatsopoulou A, Spiliopoulou C, Anastasakis A, Squarcioni CP, McKenna WJ, Thiene G, Basso C, et al. Remodeling of myocyte gap junctions in arrhythmogenic right ventricular cardiomyopathy due to a deletion in plakoglobin (Naxos disease). *Heart Rhythm*. 2004;1:3–11. doi: 10.1016/j.hrthm.2004.01.001
101. Cruz FM, Sanz-Rosa D, Roche-Molina M, García-Prieto J, García-Ruiz JM, Pizarro G, Jiménez-Borreguero LJ, Torres M, Bernad A, Ruíz-Cabello J, et al. Exercise triggers ARVC phenotype in mice expressing a disease-causing mutated version of human plakophilin-2. *J Am Coll Cardiol*. 2015;65:1438–1450. doi: 10.1016/j.jacc.2015.01.045
102. van Opbergen CJM, Noorman M, Pfenniger A, Copier JS, Vermij SH, Li Z, van der Nagel R, Zhang M, de Bakker JMT, Glass AM, et al. Plakophilin-2 haploinsufficiency causes calcium handling deficits and modulates the cardiac response towards stress. *Int J Mol Sci*. 2019;20:4076. doi: 10.3390/ijms20174076
103. Martherus R, Jain R, Takagi K, Mendsaikhan U, Turdi S, Osinska H, James JF, Kramer K, Purevjav E, Towbin JA. Accelerated cardiac remodeling in desmoplakin transgenic mice in response to endurance exercise is associated with perturbed Wnt/β-catenin signaling. *Am J Physiol Heart Circ Physiol*. 2016;310:H174–H187. doi: 10.1152/ajpheart.00295.2015
104. Sato PY, Musa H, Coombs W, Guerrero-Serna G, Patiño GA, Taffet SM, Isom LL, Delmar M. Loss of plakophilin-2 expression leads to decreased sodium current and slower conduction velocity in cultured cardiac myocytes. *Circ Res*. 2009;105:523–526. doi: 10.1161/CIRCRESAHA.109.201418
105. Cerrone M, Montnach J, Lin X, Zhao YT, Zhang M, Agullo-Pascual E, Leo-Macias A, Alvarado FJ, Dolgalev I, Karathanos TV, et al. Plakophilin-2 is required for transcription of genes that control calcium cycling and cardiac rhythm. *Nat Commun*. 2017;8:106. doi: 10.1038/s41467-017-00127-0
106. Veeranki S, Givvimani S, Kundu S, Metreveli N, Pushpakumar S, Tyagi SC. Moderate intensity exercise prevents diabetic cardiomyopathy associated contractile dysfunction through restoration of mitochondrial function and connexin 43 levels in db/db mice. *J Mol Cell Cardiol*. 2016;92:163–173. doi: 10.1016/j.yjmcc.2016.01.023
107. Tiscornia GC, Moretta R, Argenziano MA, Amorena CE, Garcia Gras EA. Inhibition of connexin 43 in cardiac muscle during intense physical exercise. *Scand J Med Sci Sports*. 2014;24:336–344. doi: 10.1111/sms.12017
108. van Opbergen CJM, Bagwan N, Maurya SR, Kim JC, Smith AN, Blackwell DJ, Johnston JN, Knollmann BC, Cerrone M, Lundby A, et al. Exercise causes arrhythmogenic remodeling of intracellular calcium dynamics in plakophilin-2-deficient hearts. *Circulation*. 2022;145:1480–1496. doi: 10.1161/CIRCULATIONAHA.121.057757
109. Fabritz L, Fortmueller L, Gehmlich K, Kant S, Kemper M, Kucerova D, Syeda F, Faber C, Leube RE, Kirchhof P, et al. Endurance training provokes arrhythmogenic right ventricular cardiomyopathy phenotype in heterozygous desmoglein-2 mutants: alleviation by preload reduction. *Biomedicines*. 2024;12:985. doi: 10.3390/biomedicines12050985
110. Fabritz L, Hoogendijk MG, Scicluna BP, van Amersfoorth SC, 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. doi: 10.1016/j.jacc.2010.09.046

111. Fujimaki S, Hidaka R, Asashima M, Takemasa T, Kuwabara T. Wnt protein-mediated satellite cell conversion in adult and aged mice following voluntary wheel running. *J Biol Chem*. 2014;289:7399–7412. doi: 10.1074/jbc.M113.539247
112. Thomas AW, Davies NA, Moir H, Watkeys L, Ruffino JS, Isa SA, Butcher LR, Hughes MG, Morris K, Webb R. Exercise-associated generation of PPARγ ligands activates PPARγ signaling events and upregulates genes related to lipid metabolism. *J Appl Physiol (1985)*. 2012;112:806–815. doi: 10.1152/japplphysiol.00864.2011
113. Garcia-Gras E, Lombardi R, Giocondo MJ, Willerson JT, Schneider MD, Khoury DS, Marian AJ. Suppression of canonical Wnt/beta-catenin signaling by nuclear plakoglobin recapitulates phenotype of arrhythmogenic right ventricular cardiomyopathy. *J Clin Invest*. 2006;116:2012–2021. doi: 10.1172/JCI27751
114. Chen SN, Gurha P, Lombardi R, Ruggiero A, Willerson JT, Marian AJ. The hippo pathway is activated and is a causal mechanism for adipogenesis in arrhythmogenic cardiomyopathy. *Circ Res*. 2014;114:454–468. doi: 10.1161/CIRCRESAHA.114.302810
115. Maione AS, Stadiotti I, Pilato CA, Perrucci GL, Saverio V, Catto V, Vettor G, Casella M, Guarino A, Polvani G, et al. Excess TGF-β1 drives cardiac mesenchymal stromal cells to a pro-fibrotic commitment in arrhythmogenic cardiomyopathy. *Int J Mol Sci*. 2021;22:2673. doi: 10.3390/ijms22052673
116. Li D, Liu Y, Maruyama M, Zhu W, Chen H, Zhang W, Reuter S, Lin SF, Haneline LS, Field LJ, et al. Restrictive loss of plakoglobin in cardiomyocytes leads to arrhythmogenic cardiomyopathy. *Hum Mol Genet*. 2011;20:4582–4596. doi: 10.1093/hmg/ddr392
117. Dubash AD, Kam CY, Aguado BA, Patel DM, Delmar M, Shea LD, Green KJ. Plakophilin-2 loss promotes TGF-β1/p38 MAPK-dependent fibrotic gene expression in cardiomyocytes. *J Cell Biol*. 2016;212:425–438. doi: 10.1083/jcb.201507018
118. Orgil BO, Munkhsaikhan U, Pierre JF, Li N, Xu F, Alberson NR, Johnson JN, Wetzel GT, Boukens BJD, Lu L, et al. The TMEM43 S358L mutation affects cardiac, small intestine, and metabolic homeostasis in a knock-in mouse model. *Am J Physiol Heart Circ Physiol*. 2023;324:H866–H880. doi: 10.1152/ajpheart.00712.2022
119. Celeghin R, Risato G, Beffagna G, Cason M, Bueno Marinas M, Della Barbera M, Facchinello N, Giuliodori A, Brañas Casas R, Caichiolo M, et al. A novel DSP zebrafish model reveals training- and drug-induced modulation of arrhythmogenic cardiomyopathy phenotypes. *Cell Death Discov*. 2023;9:441. doi: 10.1038/s41420-023-01741-2
120. Chelko SP, Asimaki A, Andersen P, Bedja D, Amat-Alarcon N, DeMazumder D, Jasti R, MacRae CA, Leber R, Kleber AG, et al. Central role for GSK3β in the pathogenesis of arrhythmogenic cardiomyopathy. *JCI Insight*. 2016;1:e85923. doi: 10.1172/jci.insight.85923
121. Padrón-Barthe L, Villalba-Orero M, Gómez-Salinero JM, Domínguez F, Román M, Larrasa-Alonso J, Ortiz-Sánchez P, Martínez F, López-Olañeta M, Bonzón-Kulichenko E, et al. Severe cardiac dysfunction and death caused by arrhythmogenic right ventricular cardiomyopathy type 5 are improved by inhibition of glycogen synthase kinase-3β. *Circulation*. 2019;140:1188–1204. doi: 10.1161/CIRCULATIONAHA.119.040366
122. Akdis D, Saguner AM, Shah K, Wei C, Medeiros-Domingo A, von Eckardstein A, Lüscher TF, Brunckhorst C, Chen HSV, 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. doi: 10.1093/eurheartj/ehx011
123. Munteanu S, Wagih Gomez J, Nicolas Rocamora EM, Gil Ortuno C, Bernabe Garcia A, Judez Serrano A, Martinez Perez C, Gimeno Blanes JR, Cayuela Fuentes ML, Sabater Molina M. Zebrafish dspb-/- mutant as model for arrhythmogenic cardiomyopathy—impact of physical activity. *Cardiovasc Res*. 2024;120(suppl1):i157. doi: 10.1093/cvr/cvae088.126
124. Cheedipudi SM, Hu J, Fan S, Yuan P, Karmouch J, Czernuszewicz G, Robertson MJ, Coarfa C, Hong K, Yao Y, et al. Exercise restores dysregulated gene expression in a mouse model of arrhythmogenic cardiomyopathy. *Cardiovasc Res*. 2020;116:1199–1213. doi: 10.1093/cvr/cvz199
125. Jordan E, Peterson L, Ai T, Asatryan B, Bronicki L, Brown E, Celeghin R, Edwards M, Fan J, Ingles J, et al. Evidence-based assessment of genes in dilated cardiomyopathy. *Circulation*. 2021;144:7–19. doi: 10.1161/CIRCULATIONAHA.120.053033
126. Reichart D, Lindberg EL, Maatz H, Miranda AMA, Viveiros A, Shvetsov N, Gärtner A, Nadelmann ER, Lee M, Kanemaru K, et al. Pathogenic variants damage cell composition and single cell transcription in cardiomyopathies. *Science*. 2022;377:eabo1984. doi: 10.1126/science.abo1984
127. Flynn KE, Piña IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ, Fine LJ, Howlett JG, Keteyian SJ, Kitzman DW, et al; HF-ACTION Investigators. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA*. 2009;301:1451–1459. doi: 10.1001/jama.2009.457
128. Tucker WJ, Beaudry RI, Liang Y, Clark AM, Tomczak CR, Nelson MD, Ellingsen O, Haykowsky MJ. Meta-analysis of exercise training on left ventricular ejection fraction in heart failure with reduced ejection fraction: a 10-year update. *Prog Cardiovasc Dis*. 2019;62:163–171. doi: 10.1016/j.pcad.2018.08.006
129. Mahon NG, Sharma S, Elliott PM, Baig MK, Norman MW, Barbeyto S, McKenna WJ. Abnormal cardiopulmonary exercise variables in asymptomatic relatives of patients with dilated cardiomyopathy who have left ventricular enlargement. *Heart*. 2000;83:511–517. doi: 10.1136/heart.83.5.511
130. Ollila L, Heliö T, Sovijärvi A, Jalanko M, Kaartinen M, Kuusisto J, Kärkkäinen S, Jurkko R, Reissell E, Palojoki E, et al. Increased ventilatory response to exercise in symptomatic and asymptomatic LMNA mutation carriers: a follow-up study. *Clin Physiol Funct Imaging*. 2017;37:8–16. doi: 10.1111/cpf.12260
131. Le TT, Bryant JA, Ang BWY, Pua CJ, Su B, Ho PY, Lim S, Huang W, Lee PT, Tang HC, et al. The application of exercise stress cardiovascular magnetic resonance in patients with suspected dilated cardiomyopathy. *J Cardiovasc Magn Reson*. 2020;22:10. doi: 10.1186/s12968-020-0598-4
132. Baig MK, Goldman JH, Caforio AL, Coonar AS, Keeling PJ, McKenna WJ. Familial dilated cardiomyopathy: cardiac abnormalities are common in asymptomatic relatives and may represent early disease. *J Am Coll Cardiol*. 1998;31:195–201. doi: 10.1016/s0735-1097(97)00433-6
133. Sugihara M, Odagiri F, Suzuki T, Murayama T, Nakazato Y, Unuma K, Yoshida K, Daida H, Sakurai T, Morimoto S, et al. Usefulness of running wheel for detection of congestive heart failure in dilated cardiomyopathy mouse model. *PLoS One*. 2013;8:e55514. doi: 10.1371/journal.pone.0055514
134. Nikolova V, Leimena C, McMahon AC, Tan JC, Chandar S, Jogia D, Kesteven SH, Michalicek J, Otway R, Verheyen F, et al. Defects in nuclear structure and function promote dilated cardiomyopathy in lamin A/C-deficient mice. *J Clin Invest*. 2004;113:357–369. doi: 10.1172/JCI19448
135. Veltrop RJA, Kukk MM, Topouzidou K, Didden L, Muchir A, van Steenbeek FG, Schurgers LJ, Harakalova M. From gene to mechanics: a comprehensive insight into the mechanobiology of LMNA mutations in cardiomyopathy. *Cell Commun Signal*. 2024;22:197. doi: 10.1186/s12964-024-01546-5
136. Pasotti M, Klersy C, Pilotto A, Marziliano N, Rapezzi C, Serio A, Mannarino S, Gambarin F, Favalli V, Grasso M, et al. Long-term outcome and risk stratification in dilated cardiolaminopathies. *J Am Coll Cardiol*. 2008;52:1250–1260. doi: 10.1016/j.jacc.2008.06.044
137. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, et al. 2017 AHA/ACC/HRS Guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2018;72:1677–1749. doi: 10.1016/j.jacc.2017.10.053
138. Wu W, Jin Q, Östlund C, Tanji K, Shin JY, Han J, Leu CS, Kushner J, Worman HJ. mTOR inhibition prolongs survival and has beneficial effects on heart function after onset of lamin A/C gene mutation cardiomyopathy in mice. *Circ Heart Fail*. 2024;17:e011110. doi: 10.1161/CIRCHEARTFAILURE.123.011110
139. Pan SW, Wang HD, Hsiao HY, Hsu PJ, Tseng YC, Liang WC, Jong YJ, Yuh CH. Creatine and L-carnitine attenuate muscular laminopathy in the LMNA mutation transgenic zebrafish. *Sci Rep*. 2024;14:12826. doi: 10.1038/s41598-024-63711-7
140. Garcia-Pavia P, Palomares JFR, Sinagra G, Barriales-Villa R, Lakdawala NK, Gottlieb RL, Goldberg RI, Elliott P, Lee P, Li H, et al; REALM-DCM Investigators. REALM-DCM: a phase 3, multinational, randomized, placebo-controlled trial of ARRY-371797 in patients with symptomatic LMNA-related dilated cardiomyopathy. *Circ Heart Fail*. 2024;17:e011548. doi: 10.1161/CIRCHEARTFAILURE.123.011548
141. Skjølsvik ET, Hasselberg NE, Dejgaard LA, Lie H, Andersen K, Holm T, Edvardsen T, Haugaa KH. Exercise is associated with impaired left ventricular systolic function in patients with lamin A/C genotype. *J Am Heart Assoc*. 2020;9:e012937. doi: 10.1161/JAHA.119.012937
142. Chandar S, Yeo LS, Leimena C, Tan JC, Xiao XH, Nikolova-Krstevski V, Yasuoka Y, Gardiner-Garden M, Wu J, Kesteven S, et al. Effects of mechanical stress and carvedilol in lamin A/C-deficient dilated cardiomyopathy. *Circ Res*. 2010;106:573–582. doi: 10.1161/CIRCRESAHA.109.204388

143. Cattin ME, Ferry A, Vignaud A, Mougenot N, Jacquet A, Wahbi K, Bertrand AT, Bonne G. Mutation in lamin A/C sensitizes the myocardium to exercise-induced mechanical stress but has no effect on skeletal muscles in mouse. *Neuromuscul Disord*. 2016;26:490–499. doi: 10.1016/j.nmd.2016.05.010
144. Cai ZJ, Lee YK, Lau YM, Ho JC, Lai WH, Wong NL, Huang D, Hai JJ, Ng KM, Tse HF, et al. Expression of Lmna-R225X nonsense mutation results in dilated cardiomyopathy and conduction disorders (DCM-CD) in mice: impact of exercise training. *Int J Cardiol*. 2020;298:85–92. doi: 10.1016/j.ijcard.2019.09.058
145. Granzier HL, Labeit S. Discovery of titin and its role in heart function and disease. *Circ Res*. 2025;136:135–157. doi: 10.1161/CIRCRESAHA.124.323051
146. Loescher CM, Hobbach AJ, Linke WA. Titin (TTN): from molecule to modifications, mechanics, and medical significance. *Cardiovasc Res*. 2022;118:2903–2918. doi: 10.1093/cvr/cvab328
147. Linke WA. Sense and stretchability: the role of titin and titin-associated proteins in myocardial stress-sensing and mechanical dysfunction. *Cardiovasc Res*. 2008;77:637–648. doi: 10.1016/j.cardiores.2007.03.029
148. Roberts AM, Ware JS, Herman DS, Schafer S, Baksi J, Bick AG, Buchan RJ, Walsh R, John S, Wilkinson S, et al. Integrated allelic, transcriptional, and phenomic dissection of the cardiac effects of titin truncations in health and disease. *Sci Transl Med*. 2015;7:270ra6. doi: 10.1126/scitranslmed.3010134
149. Huttner IG, Wang LW, Santiago CF, Horvat C, Johnson R, Cheng D, von Frieling-Salewsky M, Hillcoat K, Bemand TJ, Trivedi G, et al. A-band titin truncation in zebrafish causes dilated cardiomyopathy and hemodynamic stress intolerance. *Circ Genom Precis Med*. 2018;11:e002135. doi: 10.1161/CIRCGEN.118.002135
150. Savonitto G, Paldino A, Setti M, Berra A, Radesich C, Perotto M, Del Mestre E, Cittar M, Tavcar I, Ribichini FL, et al. Exercise intensity and cardiac disease development in carriers of titin variants. *Eur J Prev Cardiol*. doi: 10.1093/eurjpc/zwaf094
151. Flensted IF, Stemmerik MG, Skriver SV, Axelsen KH, Christensen AH, Lundby C, Bundgaard H, Vissing J, Vissing CR. Exercise training improves cardiovascular fitness in dilated cardiomyopathy caused by truncating titin variants. *Heart*. 2024;110:1416–1425. doi: 10.1136/heartjnl-2024-323995
152. Sedaghat-Hamedani F, Amr A, Betz T, Kayvanpour E, Reich C, Wettstein R, Heinze O, Mohr I, Krisam R, Sander A, et al. Personalized care in dilated cardiomyopathy: rationale and study design of the activeDCM trial. *ESC Heart Fail*. 2024;11:4400–4406. doi: 10.1002/ehf2.14970