Ventricular arrhythmia management in patients with genetic cardiomyopathies

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Genetic cardiomyopathies are associated with increased risk for cardiac arrhythmias and sudden cardiac death. The management of ventricular arrhythmias (VAs) in patients with these conditions can be nuanced due to particular disease-based considerations, yet data specifically addressing management in these patients are limited. Here we describe the current evidence-based approach to the management of ventricular rhythm disorders in patients with genetic forms of cardiomyopathy, namely, hypertrophic cardiomyopathy, arrhythmogenic cardiomyopathy, left ventricular noncompaction, and Brugada syndrome, including recommendations from consensus guideline statements when available.

KEYWORDS Arrhythmia; Cardiomyopathy; Catheter ablation; Implantable cardioverter-defibrillator; Sudden cardiac death

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Introduction

Genetic cardiomyopathies are associated with increased risks for cardiac arrhythmias and sudden cardiac death (SCD). The management of VAs in patients with these conditions can be nuanced due to particular disease-based considerations, yet data specifically addressing management in these patients are limited. Here we describe the current evidence-based approach to the management of ventricular rhythm disorders in patients with genetic forms of cardiomyopathy, including recommendations from consensus guideline statements when available.[1–5]

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is an inherited cardiac condition affecting 1 in 500 people.[6] SCD, the most feared complication of the disease, has an annual rate up to 1%.[7] Many factors contribute to the substrate that predisposes to malignant VAs. Abnormal cellular substrate, fibrosis, and structural abnormalities such as apical aneurysms can serve as a focus for reentry, coronary microvascular dysfunction can lead to ischemia, and dynamic changes in hemodynamics may contribute to arrhythmia propensity.[8]

Risk stratification for SCD

Phenotypic heterogenicity makes prediction of SCD risk challenging. Multiple risk factors have been implicated, including family history of SCD, unexplained syncope, maximal wall thickness >30 mm, apical aneurysm, and reduced left ventricular (LV) ejection fraction (LVEF). The presence of one of these risk factors makes implantable cardioverter-defibrillator (ICD) implantation reasonable (Class 2a) as per recent American Heart Association (AHA)/American College of Cardiology (ACC) HCM guidelines, with isolated nonsustained ventricular tachycardia (VT) in adults without these risk factors prompting consideration of an ICD (Class 2b) and Class 2a indication for implantation in children.[4] The 2014 European Guidelines recommend use of a risk prediction tool to estimate the absolute risk of a VA or SCD to facilitate risk stratification primary prevention ICD decision-making.[9]

Cardiac magnetic resonance (CMR) imaging is recommended for HCM patients in whom the decision to proceed with an ICD remains uncertain.[4] Magnetic resonance imaging may provide greater precision for assessment of maximum LV wall thickness and distribution, ejection fraction,[10–13] and LV apical aneurysm, and enable quantification of myocardial fibrosis with late gadolinium enhancement (LGE).[14–16] Assessment for myocardial disarray using diffusion tensor CMR holds promising predictive value.[17] CMR can differentiate HCM from infiltrative cardiomyopathies, athletic remodeling and hypertension, and inherited cardiomyopathies, all of which confer alternate arrhythmic risk.[18]

Extensive LGE represents a marker for increased arrhythmic risk that is not included in the latest European Society of Cardiology (ESC) risk stratification schema.[9,19] Some imaging studies suggest that the presence of extensive LGE comprising ≥15% of LV mass carries about a 2-fold increase in SCD risk,[20] with absence/minimal LGE associated with lower risk for SCD.[20,21]

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KEY FINDINGS

- Limited data exist addressing ventricular arrhythmia management in patients with specific genetic cardiomyopathies.
- We describe current management standards spanning patient selection for primary prevention implantable cardioverter-defibrillators, device programming considerations, and ventricular arrhythmia management, and cite existing consensus guideline recommendations when available.
- Further large-scale studies are required to truly individualize risk assessment and guide future ventricular arrhythmia management in patients with genetic cardiomyopathies.

Multiple SCD prediction models exist with the ESC HCM risk tool recommended by ESC guidelines to calculate 5-year SCD risk.[9] Recently 3 large studies[22–24] assessed the sensitivity and positive predictive value of the score, with the largest systemic review of the score in 9651 patients demonstrating sensitivity ranging between 41% and 71%, with possible variable power for risk assessment in different regions.[22] The ESC score was based on all HCM morphological subtypes, not specifically accounting for subtypes such as apical variant, with associated apical aneurysm conferring increased SCD risk. One retrospective study of 1940 HCM patients found a 3-fold increase in combined HCM-related death or HCM-related aborted death in aneurysmal compared to nonaneurysmal patients.[25] Therefore, the score may be miscalibrated to actual risk in some HCM subsets, although it does recommend considering associated adverse markers such as apical aneurysm when considering ICD.

The role of genotyping for risk stratification remains uncertain. Several studies report worse outcomes and higher incidence of SCD, atrial fibrillation (AF), and VAs with sarcomeric variant-positive HCM individuals compared to those who are negative.[26] However, significant variability in risk is seen with variants of the same gene, thus limiting its application in isolation for SCD prediction.

Ultimately, an individualized approach to risk assessment incorporating CMR, genotyping, and serum biomarkers as is being assessed in the Hypertrophic Cardiomyopathy Registry[27] in conjunction with assessment of traditional and emerging novel risk factors may prove the way forward in risk assessment.

Device indications and considerations

Current indications for primary prevention ICD implantation are highlighted earlier per AHA/ACC 2020 guidelines and European guidelines, with a shared decision-making model. Secondary prevention ICD are indicated following aborted SCD or sustained VT with high likelihood of subsequent lethal arrhythmia.[28,29] A 2012 meta-analysis demonstrated appropriate ICD intervention occurred at 3.3% per year, with annualized inappropriate ICD intervention and ICD-related complication rates of 4.8% and 3.4%, respectively.[30] Therefore, accurate estimation of risk of VAs and SCD for guiding ICD implantation is critical.

The increased propensity for AF and the consequences of onset make detection and early management paramount. Current guidelines recommend single-chamber transvenous or subcutaneous ICD if no atrial arrhythmia is present and pacing is unlikely to reduce long-term complications,[31–33] as well as single-coil rather than dual-coil ICD leads.[30] Defibrillation threshold testing in which right-sided implant is performed or massive hypertrophy is present should be considered. Indications for cardiac resynchronization therapy in patients with HCM do not differ from those of standard heart failure population guidelines.[34]

Dual-chamber pacing might benefit a subset of older patients with LV outflow tract obstruction. Atrioventricular sequential pacing has been examined in small randomized crossover trials,[35–37] with subgroup analysis in those >65 years suggesting possible benefit.[37] Pacing parameters are recommended to be optimized to achieve maximum preexcitation of the right ventricular (RV) apex with minimal compromise of LV filling, typically achieved with a resting sensed atrioventricular interval of 100 ± 30 ms,[38] and to program dynamic paced atrioventricular interval with programmed upper rate limit over fastest sinus rate achieved in exercise to enable complete ventricular capture during exercise.[39]

Optimum device settings

T-wave oversensing can be seen in HCM secondary to higher baseline electrical amplitude reflecting underlying hypertrophy. There are programming methods to minimize the risk of inappropriate shock, including reprogramming ventricular sensitivity, adjusting sensing bandwidth, and altering the sensing bipole.[40,41] AHA/ACC guidelines recommend programming antitachycardia pacing (ATP) to minimize risk of shocks considering higher frequency of monomorphic VT and ventricular flutter. A retrospective study of 71 patients with HCM and ICDs receiving appropriate therapy demonstrated 74 events were ventricular fibrillation, 18 ventricular flutter, and 57 monomorphic VT, with ATP successful in 74% of cases.[4,42]

Rhythm control

ICD shock prevention is important to improve quality of life and outcomes.[4] Beta-blockade initiation is a preliminary step with progression to antiarrhythmic drug (AAD) therapy if VA persists. AADs are limited in light of LV hypertrophy and myocardial disarray. Amiodarone carries a Class 1b recommendation in recent guidelines when symptomatic VA or recurrent ICD shocks occur despite beta-blockade, with mexiletine, sotalol, and dofetilide carrying Class 1c recommendations guided by severity of HCM, age, comorbidities, and patient preferences.[4] No large randomized controlled trial data exist supporting AADs for VA suppression, although amiodarone was associated with a lower incidence of nonsustained ventricular tachycardia (NSVT) in a small observational study.[43] However, there is suboptimal efficacy for SCD prevention, with 20% of patients in 1 retrospective series dying while taking amiodarone.[44] If VAs persist on maximally tolerated AADs, catheter ablation is feasible and can be useful to reduce arrhythmic burden.[45,46] Often epicardial or intramural substrate modification is required due to scar distribution in these areas.[47,48] Cardiac sympathectomy has also been described with reasonable outcomes and represents an option in refractory cases.[49,50]

Arrhythmogenic right ventricular cardiomyopathy/arrhythmogenic left ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy with prevalence between 1:1000 to 1:2000. Diagnosis is based on the 2010 Task Force Criteria encompassing familial and genetic factors, electrocardiographic (ECG) abnormalities, arrhythmias, and structural/functional ventricular alterations.[51] Although ARVC typically is a disease with manifestations in the RV, it is recognized that many patients with ARVC develop LV involvement.[52] LV predominant (usually in conjunction with RV involvement) structural abnormalities and early arrhythmia have been reported in conjunction with both desmosomal[53,54] and nondesmosomal arrhythmia-associated variants (eg, lamin A/C,[55] phospholamban,[56] filamin-C[57]). Therefore, “arrhythmogenic left ventricular cardiomyopathy” has been classified as a distinct entity, albeit with variable degree of overlap with ARVC, in the most recent Heart Rhythm Society (HRS) consensus guidelines[4] under the umbrella of arrhythmogenic cardiomyopathy (ACM). This section will focus on desmin pathogenic variants.

Desmosomal or intercalated disc–associated mutations lead to desmosomal and gap junction remodeling, increased fibrogenesis and adipogenesis, with progressive myocardial atrophy, fibrofatty replacement extending from epicardium to endocardium resulting in wall thinning, aneurysmal change, and ultimately ventricular dysfunction.[58,59] Histologically, in conjunction with survival of interspersed myocytes, this heterogenicity predisposes to reentry and VAs.

Risk stratification for SCD

Fifty percent of ARVC patients present with VA and 11% with cardiac arrest, with a median age at arrest of 25 years of age from 1 large cohort study.[60] ARVC may account for a substantial proportion of SCD.[61–63] The data determining risk factors in ARVC are predominantly retrospective and registry based in nature. Risk factors to be considered for primary prevention ICD as outlined by recent HRS consensus guidelines[4] include previous syncope suspected to be related to VAs, specific gene variant carrier status, LVEF, RV ejection fraction, and the presence of a certain number of major and/or minor criteria (Table 1).

Male sex confers higher arrhythmic risk likely reflecting testosterone/estrogen balance, with testosterone reported to promote apoptosis and lipogenesis.[64] Premature ventricular contraction (PVC) burden, NSVT, and an abnormal electrophysiological study (EPS) are barometers of electrical instability, with high burden of PVCs, NSVT, and positive programmed ventricular stimulation predicting appropriate ICD intervention.[65–67]

Genotype-positive patients may have a higher risk of SCD.[68,69] Variants within specific genes may confer a higher incidence of developing LV dysfunction, however, penetrance is widely variable.[70,71] Carriers of multiple pathogenic variants may have a more severe phenotype, with earlier disease and VA onset,[72,73] and higher likelihood of arrhythmia or SCD.[74,75]

The ARVCrisk.com risk score estimates absolute risk of sustained VAs based on several variables found to be associated with events in a multivariable analysis, including male sex, age, recent syncope, NSVT, 24-hour PVC count, number of leads with inverted T-wave inversion, and RV ejection fraction.[76,77] The risk function comprising these variables has been reported to exhibit moderate discrimination for sustained VAs, with a c-statistic of 0.77 and good calibration. External validation of the model is warranted.

CMR parameters such as fibrosis, fat infiltration, and LV involvement are not included in the ARVC risk score. The largest CMR study examined 140 definite ARVC patients, with isolated RV involvement in 41% and LV involvement in almost 50%,[78] consistent with previous data.[79] In a multivariable analysis, LV involvement, LV-dominant phenotype, and the 5-year ARVC risk score were independent predictors of major events, with no impact of RV LGE, fat infiltration, or wall-motion abnormality. A normal CMR conferred low arrhythmic risk. Interestingly, although the ARVC risk score accurately identified risk in those with a lone RV phenotype, it underestimated risk in those with LV predominant disease. Further data are required to estimate risk with LV predominant disease.

Device indications and considerations

Current indications for primary prevention ICD implantation are outlined in the 2019 HRS ACM consensus guidelines[4] and 2015 International Task Force Consensus Guidelines,[80] with a shared decision model recommended. Secondary prevention ICD carries a Class 1 indication in both guidelines following aborted SCD, with HRS ACM guidelines carrying a Class 2a indication for ICD if sustained VT is hemodynamically tolerated (Table 1).

HRS guidelines give Class 2a or 2b indications for ICD placement for primary prevention of SCD if a certain number of major and/or minor risk factors are present.[5] If LV systolic dysfunction with an ejection fraction ≤35% exists and the patient has New York Heart Association functional class II or III symptoms and a reasonable life expectancy, there is a Class 1 indication for ICD implantation; there is a Class 2a indication if the symptoms are class I.

Table 1 Summary of primary prevention recommendations

Pathology	Risk factors for SCD	Primary prevention ICD indication	Relevant guidelines
HCM	Family history SCD Unexplained syncope Maximal wall thickness >30 mm Apical aneurysm LVEF NSVT ESC risk score	ACC/AHA: Class 2a: 1 of family history SCD, unexplained syncope, maximal wall thickness >30 mm, apical aneurysm, LVEF Class 2b: Isolated NSVT ESC: Utilization of risk score	AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy 2020[4] ESC Guidelines on Diagnosis And Management of Hypertrophic Cardiomyopathy 2014[9]
ARVC/ALVC	Previous syncope suspected related to VA Specific gene positivity LVEF, RVEF, LV HRS major criteria; NSVT, inducible VT at EPS, LVEF ≤49% HRS minor criteria: male sex, PVC frequency, RV dysfunction, proband status, ≥2 desmosomal variants ITFC major risk factors: Syncope, NSVT, moderate dysfunction of RV, LV, or both ITFC minor risk factors: Male sex, young age, QRS fragmentation, extent of T-wave inversion, positive EPS, proband status, heart failure, RV or RA dilation, voltage map findings, precordial QRS amplitude ratio No. of leads with inverted T wave on basal ECG ARVCrisk.com score	HRS: Class 1: LVEF ≤35%, NYHA II–III, expected survival >1 yr Class 2a: Hemodynamically tolerated VT LVEF ≤35%, NYHA I, expected survival >1 yr 3 major, 2 major and 2 minor, 1 major and 4 minor criteria Class 2b: 2 major, 1 major and 2 minor, 4 minor criteria ITFC : Class 1 (>10% annual risk): Sustained VT Severe LV, RV, or biventricular dysfunction Class 2a (1%–10% annual risk): ≥1 major risk factors Class 2b (1%–10% annual risk): ≥1 minor risk factors	HRS ACM Consensus Guidelines 2019[5] ITFC Guidelines 2015[80]
LMNA/FLNC	LVEF <45% NSVT LGE Gene positivity, particularly truncated mutations Risk score LMNA	HRS: LMNA Class 2a: ≥2 of the following: LVEF <45%, NSVT, male sex If pacing need arises FLNC Class 2a: LVEF <45%	HRS ACM Consensus Guidelines 2019[5]
LVNC	NSVT associated with depressed LVEF LVEF RV volumes and fibrosis on CMRI Younger age at diagnosis Coexistence of certain phenotypes	HRS: Class 2a: NSVT associated with reduced LVEF Primary prevention indications follow general guidelines	HRS ACM Consensus Guidelines 2019[5] ACC/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities 2008[133]
Brugada syndrome	Spontaneous type 1 ECG pattern VA suspected syncope Positive EPS AF Male sex ECG parameters including fractionated QRS Brugada risk score	Both HRS/EHRA/APHRS and ESC guidelines Class 2a: Spontaneous type 1 ECG pattern who experienced a probable arrhythmia-related syncope	ESC 2013 VA Management and SCD Prevention Guidelines[2] HRS/EHRA/APHRS 2015 Primary Arrhythmia Guidelines[3]

ACC = American College of Cardiology; AF = atrial fibrillation; AHA = American Heart Association; ALVC = arrhythmogenic left ventricular cardiomyopathy; APHRS = Asian Pacific Heart Rhythm Society; ARVC = arrhythmogenic right ventricular cardiomyopathy; CMRI = cardiac magnetic resonance imaging; ECG = electrocardiogram; EHRA = European Heart Rhythm Association; EPS = electrophysiological study; ESC = European Society of Cardiology; FLNC = filamin C; HCM = hypertrophic cardiomyopathy; HRS = Heart Rhythm Society; ICD = implantable cardioverter-defibrillator; ITFC = International Task Force Consensus; LGE = late gadolinium enhancement; LMNA = lamin A; LVEF = left ventricular ejection fraction; LVNC = left ventricular noncompaction; NYHA = New York Heart Association; NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular contraction; RA = right atrium; RV = right ventricle; RVEF = right ventricular ejection fraction; SCD = sudden cardiac death; VA = ventricular arrhythmia; VT = ventricular tachycardia.

Task Force guidelines stratify patients into high-, intermediate-, and low-risk groups based on the presence of risk factors, with varying strength of ICD recommendation based on determined risk. Intermediate-risk patients deemed to have 1%–10% annual risk of major arrhythmic events have either a Class 2a or 2b indication for ICD implantation based on the presence of major or minor criteria. Low-risk patients having no risk factors and healthy gene carriers are given a Class 3 indication for ICD. Further modification to primary prevention ICD recommendations in future guidelines are anticipated as evidence emerges, with a need for prospective, randomized studies evaluating outcomes.

Optimum device settings

Inappropriate ICD interventions appear predominantly at younger age caused by sinus tachycardia or atrial arrhythmias.[81] Optimum programming to avoid inappropriate shocks is warranted, and although no pathology-specific guideline exists for device programming, a delayed therapy zone with more aggressive therapy at higher heart rates seems prudent to avoid inappropriate therapies with modification based on previous VA characteristics.[82]

Detection of atrial arrhythmia for management adjustment or detection discrimination, as well as ATP delivery, which is highly effective in terminating VT episodes in ARVC, may favor transvenous ICDs over subcutaneous ICDs for select patients. A study of 22 ARVC patients with ICD *in situ* with 950 ICD therapies over follow-up of approximately 9 years found 61.3% of VA episodes were treated with ATP, with about 95% of these therapies found to be appropriate.[83] Dual-chamber transvenous systems may aid discrimination of atrial arrhythmias but are associated with a higher incidence of complications, with Task Force guidelines recommending single-chamber devices.[80]

Rhythm control

Exercise modification is warranted for prevention of irreversible disease progression even in genotype-positive, phenotype-negative individuals. Recommendations include cessation of competitive and endurance sports.[84] Exercise increases RV systolic pressure, representing a common trigger for arrhythmia and SCD. Those individuals reducing exercise to the greatest degree have a 90% lower risk of developing VAs.[85] Limited walking, golfing, and weight-lifting are recommended over higher aerobic training.[5]

According to HRS guidelines, beta-blocker for sympathetic antagonization and prevention of ventricular remodeling is indicated as Class 2a in patients without an ICD. Amiodarone (Class 2b), sotalol (Class 2b), and flecainide (Class 2b where preserved biventricular function) may be considered to control arrhythmic symptoms or reduce ICD intervention.[5] Although most evidence does not demonstrate reduction in life-threatening VA events with these agents, sotalol in the earlier stages of disease may avoid long-term adverse effects of amiodarone, although data in this regard are lacking.[1,5]

2019 HRS Catheter Ablation of Ventricular Arrhythmia Guidelines provide a class 1 indication for ablation if recurrent sustained VT or frequent appropriate ICD interventions occur when AADs are ineffective or intolerable.[86] Preprocedural imaging should be considered to guide substrate modification and reduce procedural time. Consideration can be made for either computed tomography with detection of wall thickness and tissue heterogeneity, given reported sensitivity and specificity for low-voltage areas harboring late potentials[87] or CMR. The epicardial surface frequently is affected and often requires a combined endocardial and epicardial approach.[88–90] The pathology preferentially affects the right ventricular outflow tract (RVOT), basal inferior and anterior wall, and LV posterolateral wall. The RV apex does not seem to be involved in isolation. Substrate modification and targeting clinical VTs can lead to long-term success rates of 60%–80%.[88–90] Single and multiple procedure cumulative VT-free survival postablation was 49.8% and 69.6%, respectively, at 5 years in a study of 116 ARVC patients, with significant reduction in VT burden after final ablation compared to preablation (mean 0.7 vs 10.0 events per year; $P < .001$).[91] Ablation is aimed at improving quality of life rather than survival or prevention of disease progression.

Sympathectomy can be useful for refractory VAs despite antiarrhythmic therapy and/or catheter ablation, and as a bridge to cardiac transplantation.[92] Heart transplantation is recommended in Task Force guidelines as a final therapeutic option for recurrent episodes of VAs refractory to ablation in experienced centers and/or ICD therapy.

Other ACMs (specifically lamin A/filamin C cardiomyopathy)

Studies indicate a prevalence of pathogenic or likely pathogenic genetic variants in 20% of idiopathic cardiomyopathy patients and between 25% and 50% of familial idiopathic cardiomyopathy cases.[93,94] This next section will focus on ACM caused specifically by mutations in lamin A *(LMNA)* and filamin C *(FLNC)*.

LMNA-mediated ACM is characterized by AF and cardiac conduction disease early in the disease course, with cardiomyopathy and VA developing later.[95] In a familial cardiomyopathy cohort of patients referred for genetic testing, there was a 6.2% prevalence of *LMNA* mutation (n = 79) with high cardiac penetrance; 72% presented with or developed AV block, 42% had documented NSVT, and 18% had sustained VT during 4.4 ± 2.9 years of follow-up.[96]

FLNC-mediated ACM is characterized by high rates of VA and SCD, and milder and infrequent cardiac conduction abnormalities. A genetic evaluation of 28 affected families identified a characteristic phenotype in probands with an associated truncating mutation in 23 of 28, with the phenotype consisting of LV dilation (68%), systolic dysfunction (46%), myocardial fibrosis (67%), and frequent SCD (40 cases in 21/28 families).[97]

Risk stratification for SCD

Whereas LVEF is a strong marker of risk stratification in other cardiomyopathies, arrhythmogenesis appears at an earlier stage and thus identical LVEF cutoffs for primary prevention cannot be utilized. Recent data examining a cohort of patients with idiopathic cardiomyopathy undergoing VT ablation following monomorphic VT found that 49% of those with likely or known pathogenic variants had LVEF ≥35%.[98]

In a large European registry cohort of 269 patients with *LMNA* ACM, NSVT, LVEF <45%, male sex, and loss-of-function variants were associated with VAs, but only if ≥2 factors were present.[99] In a study of 28 families affected by *FLNC* truncating mutations, mean LVEF in those with SCD was 39.6% ± 12%.[97] These findings are supportive of HRS ACM guidelines supporting higher LVEF thresholds for primary prevention ICD implantation in *LMNA* and *FLNC* cardiomyopathies.[5]

The role of CMR in risk stratification is of ongoing interest. A recent study of 41 patients demonstrated a significant association of LGE at baseline with malignant VAs over 10 years, but no patients without LGE suffered malignant VAs during this time period.[100] Another recent study of 145 patients with *FLNC*-associated cardiomyopathy found SCD to be associated with the presence of LV fibrosis on CMR but not with severe systolic dysfunction.[101] Further data investigating the role of CMR in risk stratification are awaited.

Gene positivity for likely or pathogenic mutations seems to confer a worse outcome,[99,102] particularly for *LMNA* ACM.[103] As noted earlier, specific mutations (truncation rather than missense) may correlate with earlier manifestation of phenotype[99] and may influence risk stratification and management. Considering the adverse prognostic profile of gene positivity, identification of certain pathogenic mutations (eg, a truncating *LMNA* mutation) may help guide decision-making regarding primary ICD implantation or guide earlier screening for arrhythmia and heart transplantation referral.

A recent novel risk prediction score for malignant VA modeled on data from 839 patients with *LMNA* mutations demonstrated promise, with a c-index of 0.776 (95% confidence interval 0.711–0.842). The 5-year estimated risk threshold >7% predicted 96.7% of SCD events or unstable VAs requiring an ICD shock. Of note, predictors in this cohort of VAs were male sex, NSVT, LVEF as noted in the earlier described registry study,[99] nonmissense mutations, and first-degree or higher AV block.[104]

Device indications and considerations

Guidelines in the HRS 2019 Consensus Guidelines for *LMNA* and *FLNC* cardiomyopathy incorporate the decision-making process for primary prevention ICD implantation within that for evaluation of the ACM patient (Table 1). Secondary prevention recommendations are the same as those for ARVC.

In patients with a lamin A/C ACM and ≥2 of the following (LVEF <45%, NSVT, male sex), an ICD is reasonable (Class 2a). In patients with an *FLNC* mutation and LVEF <45%, an ICD is reasonable. Considering the prevalence of conduction disease with *LMNA* ACM, an ICD with pacing capabilities carries a Class 2a indication, favoring transvenous over subcutaneous system.[5] An atrial lead is reasonable in anticipation of possible sinus nodal dysfunction or high-grade atrioventricular block.

Cohort studies have identified atrioventricular block as a univariate predictor for VAs in lamin A/C ACM,[96,105] with recent consensus guidelines suggesting consideration of ICD implantation (Class 2a) if the need for pacing arises.[5]

Optimum device settings

Recent data have demonstrated a high risk of recurrent VT in those undergoing ICD implantation for secondary prevention and less so for primary prevention with laminopathies.[106] ATP was highly effective at termination of VA (95% success rate) except when shorter cycle lengths were present (<250 ms), which was associated with a 40% ATP success rate.[106] Thus, transvenous ICD programmed with ATP to treat VT, with more aggressive therapy for faster VAs of shorter cycle length, seems to be beneficial.

Rhythm control

For VAs refractory to AADs in patients with a cardiomyopathy due to a *LMNA* genetic variant, catheter ablation can be performed. Outcomes after ablation remain poor, with acute success even following multiple procedures in a series of 25 patients with *LMNA* cardiomyopathy as low as 25%, with acute partial success (inducibility of nonclinical VT) of 50%.[107] Of note in this cohort, 36% presented with VT storm. High recurrence rates of 91% and 83% following single and multiple VA catheter ablation, respectively, have been reported in patients with *LMNA* cardiomyopathy.[55,108]

Myocardial fibrosis appears early,[109] and the location seems to be influenced by the presence of mutation as well as the specific mutation. In a study investigating the influence of pathogenic or likely pathogenic mutations on ablation outcomes in patients with dilated cardiomyopathy (DCM), among those with such mutations (38% DCM) 60% had a dominant basal anteroseptal scar, and 41% had a dominant inferolateral scar.[99] *LMNA*[98,108,111] appears to have a higher predilection for basal anteroseptal myocardium, with other mutations favoring the inferoseptal wall. Previous studies demonstrated worse catheter ablation outcomes for targeting anteroseptal compared to inferolateral scars,[110,111] possibly due to less fat over the inferolateral wall, epicardial accessibility, and challenging intramural substrate. Pathogenic mutation–positive patients had a worse prognosis, with decreased 24-month VT-free survival (16% vs 54%; P = .001) and higher cardiac mortality in those with likely or confirmed pathogenic mutations.[98]

Median time to transplantation, ventricular assist device, or death was found to be 18 months if high-burden VT was observed on ICD interrogation in patients with laminopathies; therefore, a high burden of VT should prompt referral to a heart failure specialist.[107]

LV noncompaction

Left ventricular noncompaction (LVNC) is a disorder characterized by excessive LV, RV, or biventricular trabeculation, defined by CMR criteria as a ratio of noncompacted to compacted ratio >2.3, occurring at a rate of approximately 1 in

7000.[112,113] Nine recognized phenotypes have been reported, ranging from a most benign form (normal LV size, thickness, systolic function, lack of arrhythmia) to more malignant forms, with arrhythmias observed in patients as young as infants.[114]

The etiology of arrhythmogenesis has been hypothesized to arise from inadequate perfusion to areas of noncompaction,[115] as well as from areas of fibrosis resulting in reentry around border zone of noncompaction and normal myocardium. Overlapping genetic channelopathies can lead to polymorphic VT and bradyarrhythmia, with upstream ionic channel mutations possibly implicated in overlapping phenotype.[116]

The prevalence of VAs varies substantially between different phenotypes, and large-scale registry data determining the prevalence of either are lacking. In an analysis of the NCDR® ICD registry, 661 patients with LVNC with device *in situ* were found in 67% cases to have a history of nonsustained VT, and 30% had a history of sustained VT or previous arrest.[117]

Risk stratification for SCD

Clear evidence-based guidance for risk stratification is lacking.[116,118] Change from one LVNC phenotype to another can occur, and knowledge of risk factors for change to a more malignant form of LVNC is lacking.[119,120]

Reduced LVEF has been associated with worse outcomes.[121,122] The ratio of noncompacted to compacted myocardium may correlate with adverse cardiac outcomes.[123,124] A study of about 100 patients identified lower LVEF, LGE, and noncompacted to total myocardium ratio as adverse prognostic markers.[124] Other recent studies implicate LVEF, RV volumes, and fibrosis on CMR as predictors of cardiac events.[125–128] However, a subset of patients with preserved systolic function without LGE present with adverse outcomes including SCD, and identifying risk factors to identify this vulnerable population is an area of future research.[119,129] HRS ACM consensus guidelines give imaging, including CMR, a Class 2b recommendation for risk stratification.

Genetic inheritance with sarcomeric gene variants is the most common etiology for LVNC.[130] Sarcomeric mutations are more common in adults and are associated with relatively low adverse risk, with rare X-linked and chromosome defects appearing more frequently among children associated with severe outcome.[130] Of note, sporadic LVNC is more common in the adult population, with recognized genetic mutations more prevalent in children.[131] Improving the accuracy of phenotypic diagnosis and genotype–phenotype correlation may improve patients at higher risk for SCD.

Coexistence with other cardiomyopathy phenotypes (eg, HCM, DCM) has been found to have an adverse prognostic effect in the pediatric population.[119,122] Younger age at diagnosis may carry an adverse prognosis,[119,120,123,131] with conflicting studies in this regard.[122,132] Nevertheless, LVNC disease is heterogeneous, with more guidelines and registries required to identify further risk stratification parameters in LVNC.

Device indications and considerations

Recent HRS ACM consensus guidelines encompassing LVNC recommend ICD implantation in those with previous VAs associated with resuscitated sudden death or syncope for which survival is expected over a year (Class 1).[5]

With regard to primary prevention, adherence to the ACC/AHA guidelines on device-based therapies for cardiac rhythm abnormalities is recommended for primary and secondary prevention indications.[134] HRS guidelines advise ICD consideration (Class 2a) in those with LVNC and a history of NSVT associated with reduced ejection fraction.

Optimum device settings

The average age of patients receiving ICD therapy was 46 years in the NCDR® ICD registry[117]; therefore, optimum programming to avoid inappropriate shocks for sinus tachycardia and atrial arrhythmia is warranted (particularly with regard to the higher rates AF in LVNC). A delayed therapy zone with a more aggressive therapy zone at higher heart rates again seems prudent, with no specific programming guidelines for this cohort.[83] Specific device recommendations as to single or dual chamber are lacking, with consideration of the patient's age, atrial discrimination requirement, and possibility of developing conduction disease based on phenotype all considerations when selecting a device.

Rhythm control

Limited data exist regarding both medical and interventional therapy for VA. Sympathetic and neurohormonal antagonization with beta-blockers as an initial therapy is reasonable. AADs can be limited, with sotalol and class IC agents not advised in cases of significantly increased LV wall thickness. Concomitant cardiomyopathy and channelopathy can limit options, and tailoring AAD to phenotype is appropriate.

The role of ablation is not well established. In a series of 9 LVNC patients with VA on AADs undergoing ablation, the substrate typically involved midapical LV segments, with electroanatomical findings correlating with previously identified noncompaction on imaging, and focal PVC origin located in LV basoseptal regions and/or papillary muscles.[134] Another series of 42 patients demonstrated more heterogeneous culpable substrate reflecting the heterogenous associated pathologies included.[135] Outcomes of ablation seem variable and dependent on the substrate involved.[134,135] With refractory arrhythmia, as with end-stage heart failure, heart transplant plays a role.[136]

Brugada syndrome

Brugada syndrome (BrS) is a genetic cardiac condition which manifests with a characteristic ECG pattern ocurring in the right precordial leads. Recent advances in imaging and electroanatomical mapping suggest an increased structural component to what was previously thought to be an exclusively electrical disease. Prevalence varies but is highest in southeast Asian populations, reaching 0.5–1 per 1000.[137] Recent advances in cardiac imaging have demonstrated structural abnormalities,[138] with electroanatomical mapping demonstrating predominantly RVOT epicardial abnormal signals.[139] Given the preponderance of data indicating that structural anomalies may play a role, we have included a discussion of BrS here, although we acknowledge that the disease is heterogeneous and not all patients may have a structural basis for or contribution to the disease.

BrS is associated with SCD. Structural changes and electrical remodeling not limited to but predominantly in the epicardial RVOT area[140] play a key role in the pathogenesis of malignant VA events in some patients. Biopsy specimens from surgical ablation and autopsy studies demonstrate marked epicardial and interstitial myocardial fibrosis, correlating with low-voltage, prolonged, fractionated electrograms on EPS.[139] In addition, a recent autopsy study of 28 decedents demonstrated increased biventricular fibrosis irrespective of sampling location or myocardial layer, with a higher proportion of fibrosis in the epicardial RVOT.[141] VAs occur at a mean age 41 ± 15 years, with increased prevalence during rest or sleep.[142]

Risk stratification for SCD

Risk prediction to guide primary prevention ICD implantation in patients with BrS typically incorporates a history of syncope and the 12-lead ECG characteristics at rest. Other risk factors that have held interest include EPS, genetic testing, and signal-averaged ECG. Recent smaller studies have suggested current guideline-accepted clinical risk markers carry low predictive accuracy for SCD.[143]

Previous cardiac arrest and a spontaneous type 1 ECG pattern in patients who experienced a probable arrhythmia-related syncope both carry higher rates of cardiac adverse events. Annual rates of malignant VA were 7.7% in those with a history of cardiac arrest and 1.9% in those with a history of syncope from the FINGER Brugada Syndrome Registry, which studied approximately 1000 patients.[144]

Asymptomatic BrS individuals generally have low rates of adverse events,[145] but this risk is not negligible, with 12% experiencing appropriate ICD therapy at 10 years.[146] Identifying those in this group at risk for SCD, particularly in whom type 1 pattern exists, is an ongoing topic of research. Recently, a decision-analytic model identified that in certain asymptomatic BrS patients with type 1 pattern, ICD-based therapies are likely to be effective, particularly when BrS is diagnosed at a younger age.[147] Although the decision to implant an ICD should be dependent on the presence of certain characteristics, the strength of data supporting this for current patient factors remains limited. AF development and male sex seem to confer a worse outcome.[148,149] Results of genetic testing have not been found to influence risk assessment thus far. Twelve-lead parameters such as fragmented QRS and effective refractory period <200 ms on EPS have also been investigated as risk prognosticators.[150–152]

The role of EPS in risk stratification has been examined. A pooled analysis of studies including 1312 BrS patients without previous arrest demonstrated an association between inducibility of arrhythmias during programmed ventricular stimulation with future malignant VA events (a 2- to 3-fold increased risk), and association with inducibility with fewer extrastimuli. However, noninducibility did not guarantee low risk, especially when these patients had associated high-risk clinical features such as spontaneous type 1 pattern and a history of syncope.[153]

A recent multicenter international cohort of 1110 patients with no history of cardiac arrest was examined, assessing 16 clinical or ECG markers for VA/SCD at follow-up and formulating a risk score. Syncope, spontaneous type 1 pattern, type 1 pattern in the peripheral leads, and early repolarization in the peripheral leads significantly carried the strongest association for this endpoint. Although this risk score did not incorporate programmed stimulation or genetic testing due to incomplete use in the cohort, the risk score model incorporating the 4 main factors had sensitivity of 71.2% and specificity of 80.2% in predicting 5-year risk of VA/SCD.[154] Other studies have looked at combined risk score analysis in smaller cohorts.[155,156]

It is evident that future efforts to improve risk stratification are warranted in patients without a Class 1 indication for ICD. With regard to risk stratification in asymptomatic BrS patients, data remain limited, with existing literature possibly overestimating the annual rate of SCD in this cohort. This limits the ability to interpret the evidence base and make decisions with regard to SCD prevention. Further research is warranted.

Device indications and considerations

ICD implantation currently is recommended as secondary prevention in BrS survivors of cardiac arrest, in those with previously documented spontaneous sustained VT even without syncope (Class 1 indication in both North American and European guidelines), and in patients with a spontaneous type 1 ECG pattern who experienced a probable arrhythmia-related syncope (Class 2a for both guidelines) (Table 1).[2,3] It is important to distinguish arrhythmia-sounding syncope from vagal syncope, which occurs more frequently in BrS.[157]

An evidence gap guiding the decision for AAD, ablation, and indeed device therapy exists for patients outside the sphere discussed. The subcutaneous ICD represents an attractive option, particularly in young patients, considering the potential for lifetime lead failure with transvenous leads.[146,147] However, it is worth noting the possibility of screening failure secondary to high T-wave voltages. A study of 61 BrS patients noted inappropriate morphology analysis of 18% compared with 5% in other channelopathies.[158] However, recent algorithm improvements likely have mitigated such limitations.[159]

Of note, VA inducibility during programmed ventricular stimulation carries a Class 2b indication for implantation, with a Class 3 recommendation in asymptomatic BrS with drug-induced type 1 ECG and on the basis of a family history of SCD alone.

Optimum device settings

The high prevalence of AF must be considered when programming therapy zones, with AF/atrial tachycardia a potential cause of inappropriate shocks.[160] Ten-year follow-up data have demonstrated inappropriate shock rates twice as high as appropriate (24% vs 12%).[146] Although there is no specific guideline recommendation for ICD programming, a single detection zone with a high VF cutoff rate as well as longer detection times can be considered.[145]

Rhythm control

Aggressive treatment of fever and nonconsumption of excessive alcohol and large meals are important to avoiding VA, as well as not taking medications that may induce ST-segment elevation in the right precordial leads (http://www.brugadadrugs.org). These are all Class 1 recommendations in ESC and HRS/European Heart Rhythm Association/Asian Pacific Heart Rhythm Society guidelines.[2,3]

From a pharmacologic standpoint, VA suppression has only been found to be efficacious with quinidine, with its strong I_{to} channel modulation.[160,161] Low-dose quinidine was found to reduce the risk of malignant VA in survivors of previous cardiac arrest,[161] with good tolerability (6% cessation rate due to side effects). Current guidelines recommend quinidine in patients during electrical storm or for those who refuse or do not qualify for an ICD.[2,3] Randomized data are lacking. The QUIDAM study (Hydroquinidine Versus Placebo in Patients With Brugada Syndrome) terminated early due to dropout and a paucity of endpoints,[162] with the largest nonrandomized data suggesting favorable outcomes utilizing an electrophysiology-guided therapy approach.[163]

Epicardial RVOT substrate modification has shown promising initial data, particularly in those having drug-refractory BrS with recurrent malignant VA.[140,141] Concomitant endocardial ablation or targeting of PVCs triggering VF also has been described.[164] Epicardial substrate modification seems to be more effective than an endocardial-only approach, with success rates in preventing malignant VA of 96.7%, 70.6%, and 80% with epicardial, endocardial, and triggering-PVC ablation approaches, respectively, over follow-up of 2.5 to 78 months.[165] Infusion of sodium channel blockers or warm saline can unveil local abnormal electrograms to target and confirm procedural success with their elimination postablation. Elimination of the BrS ECG pattern seems to be an endpoint conferring long-term success,[139,165,166] but noninducibility postablation is controversial as an endpoint.[165] The Ablation in Brugada Syndrome for the Prevention of VF (BRAVE) study (ClincialTrials.gov Identifier: NCT02704416) will further determine the role of ablation, with current guidelines recommending a Class 2a indication for those with a history of recurrent sustained VA or frequent appropriate ICD interventions.[86]

Conclusion

Rhythm management of genetic cardiomyopathies can be challenging. We describe the current standard for management of this diverse group of patients, and discuss VA management, ICD ,indications and considerations. A summary of current guidelines pertinent to each pathology, as well as risk factors identified pertaining to SCD, is outlined in Table 1. Further large-scale studies are required to truly individualize risk assessment, with machine learning analytics, genetic risk assessment with further phenotype–genotype correlation, and studies in underrepresented populations all playing important roles.

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