Sudden Cardiac Death

Sudden Death From Genetic and Acquired Cardiomyopathies

Srijita Sen-Chowdhry, MBBS, MD (Cantab), FESC; William J. McKenna, MD, DSc, FESC

From the Inherited Cardiovascular Disease Group, University College London, The Heart Hospital, London, United Kingdom (S.S.C., W.J.M.); and Department of Epidemiology, Imperial College, St. Mary’s Campus, London, United Kingdom (S.S.C.).

Correspondence to William J. McKenna, MD, DSc, FESC, Inherited Cardiovascular Disease Group, University College London, The Heart Hospital, 16-18 Westmoreland Street, London W1G 8PH, United Kingdom. E-mail william.mckenna@uclh.nhs.uk

From the Inherited Cardiovascular Disease Group, University College London, The Heart Hospital, London, United Kingdom (S.S.C., W.J.M.); and Department of Epidemiology, Imperial College, St. Mary’s Campus, London, United Kingdom (S.S.C.).

Correspondence to William J. McKenna, MD, DSc, FESC, Inherited Cardiovascular Disease Group, University College London, The Heart Hospital, 16-18 Westmoreland Street, London W1G 8PH, United Kingdom. E-mail william.mckenna@uclh.nhs.uk

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1563

From the Aphorisms of Hippocrates to the sports fields of the twenty-first century, by both the lay public and the medical community, the cardiomyopathies have been recognized as causes of sudden cardiac death (SCD). Prevention of SCD in the cardiomyopathies is a 2-fold challenge. First, and central to clinical practice, is the need for reliable prognostication in individuals with established disease, and effective therapies to prevent or terminate events in those at risk. The second is the need for public health measures to preempt individuals with undiagnosed, asymptomatic disease from presenting with SCD: a not uncommon phenomenon in the cardiomyopathies. This review seeks to address the demographics and burden of SCD due to cardiomyopathy, its underlying mechanisms and determinants, and current approaches to risk prediction and management. Both genetic and acquired cardiomyopathies are discussed, with the former encompassing hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC), all of which demonstrate Mendelian inheritance. By expert consensus, the umbrella term “cardiomyopathy” is not applicable to myocardial dysfunction secondary to ischemic heart disease, valvular dysfunction, or congenital anomalies. Heart muscle disorders resulting from systemic, metabolic, or other identifiable causes are included if arrhythmia and SCD are prominent components of the phenotype.1

Burden of SCD From Cardiomyopathy

The cardiomyopathies differ in the relative contribution of SCD to overall mortality, with ARVC ranking the highest, followed by HCM and then DCM, in which heart failure is the leading cause of death (Figure).2–7 In evaluating the burden of SCD related to cardiomyopathy, 3 distinct questions need to be addressed. First, what is the annual incidence of SCD among individuals with an established diagnosis of cardiomyopathy? Second, to what extent do cardiomyopathies account for SCD from undiagnosed cardiovascular disease—unexpected SCD—in the general population? A third and more involved issue is whether current medical interventions have reduced the rate of SCD due to cardiomyopathy in patient cohorts and the general population.

Hypertrophic Cardiomyopathy

Annual SCD rates due to specific cardiomyopathies are readily gleaned from existing data. Although earlier series often overestimated mortality because of referral center bias, inclusion of affected relatives identified by prospective familial assessment has led to a more representative picture of the disease in many present-day studies.

Historical trends in reported survival rates have been evaluated in HCM. Among 956 patients with HCM followed up for an average of 69 months at a single center, the composite rate of SCD, implantable cardioverter-defibrillator (ICD) discharge, and resuscitated cardiac arrest was 1.02% per year (95% confidence interval [CI], 0.76–1.26). This was comparable to other contemporaneous studies and lower than previously published SCD rates. In contrast to older study samples, recent cohorts had fewer patients who underwent septal myotomy-myectomy or had severe functional limitation (New York Heart Association [NYHA] class III/IV).2 Taken together, these findings are consistent with the premise that referral center bias is less prominent in HCM than it has been in the past.

Arrhythmogenic Cardiomyopathy

Chronological trends in SCD rates are more difficult to evaluate in ARVC. The majority of existing follow-up series, both historical and contemporary, comprise a preponderance of index cases, in whom symptomatic ventricular tachycardia is often the mode of presentation. Earlier studies from the pre-ICD era found an annual incidence of SCD of 1 to 1.5% in ostensibly high-risk cohorts.8–12 Paradoxically, in more recent follow-up studies of ICD recipients, the annual rate of intervention for ventricular fibrillation/flutter is as high as 5% to 8%.13,14 The basis of this discrepancy is unresolved, although subject to speculation. First and foremost, ICD shocks may not be a reliable surrogate for SCD in the cardiomyopathies, a problem that is compounded when investigators report composite appropriate discharge rates without a breakdown for ventricular tachycardia versus ventricular fibrillation.15 If we assume instead that all appropriate ICD interventions are instances of averted SCD, it raises a more worrisome possibility: some element of ICD therapy, be it implantation of a lead in the diseased right ventricle or...
prolonged right ventricular pacing in patients on negatively chronotropic drugs, may be triggering arrhythmic events. The more optimistic explanation invokes timely diagnosis of individuals who, in a previous era, might have presented with SCD; with an ICD in situ, their propensity toward malignant arrhythmia manifests with multiple appropriate shocks. Growing awareness of ARVC among physicians, advances in imaging technology, and widespread use of validated diag-

Figure. (Top) The cumulative survival (%) free of cardiac death or transplantation by years of follow-up in hypertrophic cardiomyopathy (n=956 including 237 relatives), arrhythmogenic right ventricular cardiomyopathy (n=96 including 26 relatives), and dilated cardiomyopathy (101 index cases). The less favorable outcomes in the dilated cardiomyopathy cohort may be related in part to the case mix. (Bottom) The relative contribution of sudden cardiac death to overall mortality in 254 individuals with hypertrophic cardiomyopathy and 82 with dilated cardiomyopathy in the pre-ICD era. The data on arrhythmogenic cardiomyopathy are from the Newfoundland founder population, who have higher mortality rates than other cohorts, but demonstrate the typical natural history of the disease: early arrhythmic complications and mortality from sudden cardiac death, with subsequent development of heart failure in survivors. The proportion of deaths that are arrhythmic rather than related to heart failure should therefore be typical for arrhythmogenic cardiomyopathy (references 2–7). HCM indicates hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; ACM, arrhythmogenic cardiomyopathy; ARVC, arrhythmogenic right ventricular cardiomyopathy; ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death.
nostic criteria are all potential contributors to early detection. In contrast, increased interest in prospective evaluation of relatives is unlikely to be a factor, because most of the patients in the ICD follow-up studies of the past decade were identified from symptomatic profiling.

One of the few long-term follow-up studies to focus on familial ARVC reported an annual SCD rate of 0.08% in 151 affected relatives over ≈8.5 years. Although this would appear to be reassuringly low, subsequent reports have been more concerning: despite being relatively rare, SCD may occur in relatives at any age, in the presence of relatively mild disease, and in the absence of conventional risk factors.

Systematic clinical evaluation of families has also highlighted variations in the accepted natural history of ARVC. In the classic pattern of disease expression, regional right ventricular abnormalities progress to global dysfunction, followed by left ventricular involvement and eventual biventricular pump failure. Two additional subtypes are now recognized: biventricular and left dominant, both characterized by the presence of early left ventricular involvement, which either parallels or exceeds the degree of right ventricular dysfunction. The broader term arrhythmogenic cardiomyopathy (ACM) has been proposed to encompass all 3 subtypes. The cardinal and unifying feature of ACM, and the principal means of distinction from DCM, is a propensity toward ventricular arrhythmia that is out of proportion to the degree of morphological and histological dysfunction.

### Dilated Cardiomyopathy

SCD accounts for at least 30% of the overall mortality in DCM, occurring in 8% to 10% of NYHA functional class I and 20% of class II–IV patients. Annual mortality rates also increase from 12% to 15% in class I–II to 60% in class IV. Nevertheless, between 50% and 60% of deaths in class I and II cases are sudden, in contrast to only 20% to 30% of the deaths in class IV patients, most of whom succumb to progressive congestive heart failure. Coupled with the higher prevalence of NYHA class I to class II cases in unselected DCM cohorts, this leads to an apparent paradox: most instances of SCD occur in individuals whose heart failure is well controlled, despite moderate to severely impaired left ventricular dysfunction.

The entity of DCM with conduction defects is characterized not only by bradyarrhythmia, but also by ventricular tachyarrhythmia and SCD, which may precede the onset of ventricular impairment. With the exception of this subgroup, arrhythmic events in DCM almost always arise in cases with left ventricular systolic dysfunction, representing another key difference from ACM, in which ventricular tachyarrhythmia may occur in the setting of preserved ventricular function. In further contrast to ACM, ventricular arrhythmia and SCD are seldom the first clinical manifestations of DCM. The natural history of DCM is characterized by presentation with heart failure, followed by either functional improvement—in which case death, if it occurs, is most likely to be arrhythmic—or progression to end stage, at which transplantation or death from heart failure are more likely outcomes. Left-dominant arrhythmogenic cardiomyopathy is often misdiagnosed as DCM; features suggestive of the former include arrhythmic presentation, minimal or absent heart failure symptoms, and a burden of arrhythmia exceeding the degree of left ventricular dysfunction.

### Muscular Dystrophies

Muscular dystrophies are a heterogeneous group of heritable disorders characterized by varying degrees of skeletal muscle weakness, wasting, and/or myocardial involvement. The following clinical-genetic classification has been proposed: dystrophinopathies (Duchenne and Becker muscular dystrophies, X-linked dilated cardiomyopathy); Emery-Dreifuss muscular dystrophy (X-linked and autosomal dominant); limb-girdle muscular dystrophies (autosomal dominant and recessive forms); myotonic dystrophy (types 1 and 2); and congenital muscular dystrophies including distal and myofibrillar myopathies. Of these, SCD is most prominent as a cause of mortality in Emery-Dreifuss muscular dystrophy (both types), limb-girdle muscular dystrophy type 1B, and myotonic dystrophy (particularly type 1), which are discussed in subsequent sections.

In both Duchenne and Becker muscular dystrophies, the cardiac involvement takes the form of DCM, sometimes preceded by localized hypertrophy. Age-related expression is observed, with signs of cardiac disease apparent in almost all Duchenne cases by 18 years, and 82% of Becker cases >40 years; up to 45% of female carriers also demonstrate cardiovascular abnormalities. As in DCM, ventricular dysfunction is a predictor of mortality but may stabilize or improve on angiotensin-converting enzyme inhibitors, and SCD may occur in the setting of deteriorating myocardial function, although heart failure predominates as a cause of cardiovascular death. Because skeletal muscle weakness is more slowly progressive, and respiratory insufficiency occurs later in the disease course, cardiovascular complications take on greater importance in Becker than in Duchenne muscular dystrophy, accounting for 50% versus 10% to 20% of the mortality, respectively. With the introduction of home nocturnal ventilation, and more successful management of both respiratory dysfunction and congestive heart failure, prevention of SCD is anticipated to become a more central goal for both Becker and Duchenne patients in the future.

### Acquired Cardiomyopathies

Cardiac involvement is common in primary (AL), senile systemic, and certain hereditary forms of amyloidosis, and less prevalent in secondary (AA) amyloidosis, but nonetheless a marker of adverse outcome when present. Among 232 patients with cardiac AL amyloidosis, the median duration (95% CI) of survival following diagnosis was 1.08 (0.83–1.25) years, with SCD accounting for 34% of the mortality. SCD is also a recognized outcome of cardiac senile amyloidosis, although scant data exist on its incidence, and heart failure predominates as a cause of death.

The prevalence of cardiac involvement in sarcoidosis is estimated at 39% by prospective clinical evaluation and 58% on postmortem series. Macroscopic findings may, however, be absent in some cases, leading to underestimation of the frequency of cardiac disease by both noninvasive imaging and gross anatomic examination. Lymphocytic foci, fibrosis,
and granulation tissue are often the most common histological findings, necessitating a rigorous search for microscopic nonnecrotizing granulomata to avoid missing the diagnosis of cardiac sarcoidosis on autopsy. Sarcoid granulomata show a predilection for the following sites: the left ventricular free wall (96%), interventricular septum (73%), right ventricle (46%), right atrium (11%), and left atrium (7%). SCF ranks as the second most common cause of mortality in sarcoidosis and accounts for at least a third of deaths in cases with cardiac involvement, although its true incidence is not known.30

Unexpected SCD

A separate issue is the extent to which the cardiomyopathies account for unexpected SCD. In the population as a whole, ischemic heart disease, whether known or undiagnosed, is the most common cause of SCD.31 The prevalence of ischemic heart disease increases with age; SCD in the young can therefore be considered a paradigm for nonischemic SCD. Furthermore, because a diagnosis of significant cardiovascular disease generally leads to disqualification from organized sports, nontraumatic fatalities in young athletes may be considered a surrogate for unexpected SCD from nonischemic causes. The profile of sports-related deaths may, however, be influenced by the degree to which different disease substrates confer instability to adrenergic stimulation.

In most studies of athletes, HCM (often amalgamated with unexplained left ventricular hypertrophy) is a leading cause of SCD. Notwithstanding potential flaws in the paradigm, this suggests that HCM is a major contributor to unexpected nonischemic SCD.32,33 In an Italian series, by contrast, ARVC was the most common cause of nonischemic SCD in the general population aged ≤35 years.34 The burden of SCD from ARVC was underscored by a postmortem series of 1930 cases of unexpected SCD between the ages of 1 and 65 years, in which ARVC was the cause in 200 (10.4%).35 Inclusion of nonclassic subtypes of ACM might increase this frequency still further. DCM is a rare cause of unexpected SCD, because heart failure is the first manifestation of the disease in the majority of patients; indeed, presentation with SCD and the presence of left ventricular dilation, wall thinning, and fibrosis on autopsy should raise suspicion of left-dominant arrhythmogenic cardiomyopathy.19 There are documented cases of both cardiac amyloidosis and sarcoidosis presenting with SCD, but the overall contribution of acquired cardiomyopathies to unexpected SCD in the general population remains limited.

Demographics of SCD From Cardiomyopathy

Existing studies have provided insight, albeit incomplete, into the profile of SCD due to HCM and ARVC. The demographics and circumstances of SCD in DCM, the muscular dystrophies, and the acquired cardiomyopathies await systematic evaluation.

Hypertrophic Cardiomyopathy

A 1982 study examined the profile of 78 patients with HCM who experienced SCD or arrest, of whom 49 (63%) were males and 29 (37%) were females. The age range was 2 months to 58 years with a median of 19 years; of note, 67 patients (89%) were younger than 40 years. Six out of 75 cases (8%) experienced premonitory symptoms, including fatigue, chest pain, and syncope in the moments to hours preceding death, but the majority did not. At the time of the cardiac event, 4 of 75 subjects (5.3%) were asleep; 42 (56%) were engaged in sedentary activities or mild exertion (eg, sitting, walking, shopping) and 29 (39%) were engaged in strenuous activities such as running, jogging, or horse riding.36 Circadian variability in the timing of events was investigated in a subsequent study of 94 patients with HCM who died suddenly. SCD was found to occur in a bimodal pattern, with the first peak in midmorning between 7 AM and 1 PM, and the second peak in the early evening between 8 PM and 10 PM.37 Although the demographics of SCD in HCM remain incomplete, the following profile has emerged from these and other studies: events are most frequent in adolescents and young adults, but may occur at any age; sex is not a major determinant of the risk of SCD; and although HCM is the leading cause of SCD among athletes, most events are not exertion related.

Arrhythmogenic Cardiomyopathy

In 31% to 50% of index cases with ACM, the diagnosis is established on postmortem following SCD. In a US study, 8 (25%) of the 31 deceased index cases had experienced palpitation, presyncope, or syncope before death; but the prevalence of premonitory symptoms in a large series of SCD patients, with its implications for preemptive intervention, awaits evaluation.16,38 One of the largest series to date evaluated the profile of 200 SCD patients with postmortem evidence of ARVC. There were 108 men and 92 women, a nonsignificant difference, although other studies have suggested that men may be at increased risk of arrhythmic events. The mean age at death was 34 years, range 5 to 65 years, with 30% of patients dying in the fourth decade of life. As in hypertrophic cardiomyopathy, however, advancing age did not appear to guarantee protection from arrhythmic events. The circumstances of death were as follows: during daily activities at home or work in 150 (76%); perioperatively in 19 (9.5%), including induction of anesthesia, during surgery, and up to 2 hours afterward; and after a “stressful event” in 22 (11%), including minor road traffic accidents, falls without injury, police arrests, medical visits, childbirth (2 [1%]), hospitalization for drug overdose with suicidal intent, and influenza convalescence; and during exercise in 7 (3.5%), including jogging, tennis, boxing, and soccer.35 Although only a minority of the deaths occurred during strenuous activity, a 21-year prospective study of SCD patients in the Veneto region of Italy revealed that the relative risk of SCD from ARVC was 5.4-fold higher in athletes than in nonathletes.34

Mechanisms of SCD From Cardiomyopathy

SCD in the cardiomyopathies is thought to be the result of a vulnerable substrate coupled with specific intrinsic or extraneous triggers. The nature of the substrate and triggers may vary not only by underlying disease state, but also by clinicopathological stage, genetic determinants, and environmental factors.
Hypertrophic Cardiomyopathy

Analysis of stored intracardiac electrograms suggests that the majority of appropriate ICD discharges in HCM are a response to ventricular fibrillation (VF), although this does not exclude the possibility of SCD from bradyarrhythmia, the presence of which would be obscured on device interrogation owing to backup pacing.39 Myocyte disarray and fibrosis are purported to serve as the histopathologic substrate. Putative precipitants of SCD include diastolic (or systolic) dysfunction, myocardial ischemia, left ventricular outflow tract obstruction, abnormal vascular responses, conduction system disease, paroxysmal atrial fibrillation, supraventricular tachycardia with or without accessory pathway conduction, and nonsustained ventricular tachycardia (VT). Interplay between substrate and triggers is undoubtedly complex.40

In a postmortem series of 75 hearts from patients with HCM, myocyte disarray showed positive correlation with the number of relatives experiencing SCD before 40 years of age, and with the clinical ischemia score (0–3, based on the presence of typical angina, >2 mm ST-segment depression on exercise, and perfusion defects on thallium scanning). The extent of myocyte disarray was greater among cases with a flat or depressed blood pressure response to exercise, indicating vascular instability, and among those who died before 21 years of age. In contrast, myocardial fibrosis was greater in patients who died of heart failure and in patients with nonsustained ventricular tachycardia or a high-risk fractionation study.41 It is noteworthy that each of the risk predictors so far identified in HCM (Table) either indicate the presence of substrate or correspond to one of the triggers.40

Arrhythogenic Cardiomyopathy

In ACM, the nature of the molecular-histological substrate varies with disease progression, but the end result at each state is thought to be heterogeneity of conduction in the ventricles.42 The disease is most well recognized in its overt stage, in which myocyte loss has been repaired by fibrosis and/or adiposis. Macro-reentrant circuits may arise in the surviving myocardium surrounding fibrofatty islands, leading to sustained ventricular tachycardia that is inducible on programmed ventricular stimulation and demonstrates entrainment.43 The stability of reentry in this setting may explain why sustained ventricular tachycardia without hemodynamic compromise is a poor predictor of SCD in ACM.13 Of course, a number of factors, both intrinsic (such as new inflammation) and extrinsic (such as adrenergic stimulation) may destabilize scar-related reentry, precipitating SCD.

Arrhythmogenesis in the histopathologically apparent form of ACM is therefore relatively well understood. What is more novel and more challenging is the accumulating evidence that ventricular arrhythmia and even SCD may precede the development of the characteristic myocyte loss with fibrofatty replacement. That ACM has a concealed phase, in which subtle or absent morphological abnormalities belie the arrhythmic risk, has long been known, but has generally been ascribed to the presence of microscopic histopathology.

Overturning this tenet is the case of a girl homozygous for the Naxos mutation, 2157del2 in the plakoglobin gene (JUP), which encodes a component of desmosomes, the specialized intercellular junctions of cardiac and epithelial tissue.44 As is typical for Naxos syndrome, the cutaneous phenotype (palmo-plantar keratoderma and woolly hair) was evident from early childhood. Cardiac evaluation at the age of 5 revealed

### Table. Risk Predictors in Hypertrophic Cardiomyopathy and Pathogenic Basis

<table>
<thead>
<tr>
<th>Risk Predictor</th>
<th>Significance/Etiology</th>
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<tbody>
<tr>
<td>Prior cardiac arrest</td>
<td>Spontaneous sustained VT</td>
</tr>
<tr>
<td>Family history of 1 or more instances of SCD</td>
<td>LV apical aneurysm</td>
</tr>
<tr>
<td>Nonsustained VT (≥3 consecutive beats at ≥120 bpm)</td>
<td>Genetically determined high-risk substrate</td>
</tr>
<tr>
<td>Failure of systolic BP to rise by ≥20 mm Hg during maximal upright exercise testing</td>
<td>Indicator of arrhythmogenic substrate and potential trigger of ventricular fibrillation</td>
</tr>
<tr>
<td>Unexplained syncope</td>
<td>Paradoxical peripheral vasodilatation</td>
</tr>
<tr>
<td>Maximum LV wall thickness ≥30 mm</td>
<td>LV mechanoreceptor activation</td>
</tr>
<tr>
<td>Ancillary and putative risk factors</td>
<td>Abnormal vascular responses</td>
</tr>
<tr>
<td>Coexisting obstructive coronary artery disease</td>
<td>LV outflow tract obstruction</td>
</tr>
<tr>
<td>Resting LV outflow tract obstruction</td>
<td>Systolic anterior motion of the mitral valve</td>
</tr>
<tr>
<td>Microvascular ischemia</td>
<td>Capillary-mass mismatch</td>
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<tr>
<td>Diffuse late gadolinium enhancement on cardiovascular magnetic resonance</td>
<td>Extravascular compressive forces Reduced endocardial vasodilator response</td>
</tr>
<tr>
<td>Paced electrogram fractionation analysis</td>
<td>Myocyte disarray</td>
</tr>
<tr>
<td>Prior alcohol septal ablation</td>
<td>Potential for scar related arrhythmia</td>
</tr>
<tr>
<td>Burnt out disease*</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>High-risk mutation†</td>
<td>Genetically determined high-risk substrate</td>
</tr>
</tbody>
</table>

Prior cardiac arrest and spontaneous sustained VT are indications for ICD placement for secondary prevention. The decision to implant a prophylactic cardioverter-defibrillator is based on establishing a composite risk profile from primary and ancillary markers. VT indicates ventricular tachycardia; SCD, sudden cardiac death; BP, blood pressure; and LV, left ventricular.

*The burnt out phase of hypertrophic cardiomyopathy develops in 2% to 15% of patients each year and is characterized by wall thinning, cavity enlargement, and impaired systolic function, with an annual mortality rate of up to 11%.

†Despite early interest in benign versus malignant mutations, identifying a causal mutation has little impact on prognostication beyond that of the family history, which is itself a primary risk factor. A case can be made for mutation screening of troponin T and perhaps troponin I (see text). The role of genotyping in risk stratification is otherwise limited, although it has other clinical applications, such as enabling cascade screening of families.
frequent ventricular extrasystoles (14,451 isolated and 21 couplets in 24 hours), mainly of RV origin, and progressive depolarization abnormalities including right precordial QRS prolongation (from 80 to 110 ms) and epsilon waves. Echocardiography, however, was within normal limits. After her death from a hematologic malignancy at the age of 7, gross examination of her heart was unremarkable, as was in vivo cardiovascular magnetic resonance. More conspicuously, histological examination failed to identify any evidence of fibrofatty replacement of the myocardium, leukemic infiltrates, or degenerative features suggestive of chemotherapy-related injury.44

Establishing the likely cause of her high-burden ventricular ectopy and ECG changes required a step beyond standard histopathologic assessment. A combination of confocal immunohistochemistry, immunoblotting, and electron microscopy demonstrated smaller and fewer gap junctions and markedly reduced localization of the gap junction protein connxin-43 to intercalated disks. So-called gap junction remodeling, purported to result from impaired mechanical coupling of cells with genetically abnormal desmosomes, would lead to heterogeneity of conduction and provide a basis for the observed arrhythmia. Whether this mechanism is sufficient to cause malignant ventricular tachyarrhythmia and SCD in the early, prehistological stages of the disease remains unresolved. Similar abnormalities in gap junction structure and connxin-43 expression have since been identified in cases with other desmosomal gene mutations, including desmoplakin and plakophilin-2, but generally in the context of overt histopathology and arguably secondary to it. The original Naxos case is remarkable for the absence of histological abnormalities, which implies that gap junction dysfunction may be a direct consequence of the genetic defect.18,44

Myocyte necrosis, with or without accompanying inflammation, may promote arrhythmia throughout the disease course. In transgenic mice overexpressing the equivalent of the human desmoglein-2 mutation DSG2-N266S, myocyte necrosis was the first manifestation of the disease. Massive inflammatory infiltrates followed, with deposition of granulation and early loose connective tissue.45 Spontaneous ventricular arrhythmia and premature SCD were observed relatively early in the disease course, implicating necrosis and inflammation as likely substrates, in particular, because gap junction remodeling was not identified. In keeping with this premise is the case of a teenage boy harboring the DSP-S299R ARVC-related mutation. He was considered unaffected during clinical evaluation at the age of 13, but experienced SCD 2 years later. Examination of his heart revealed acute-subacute myocyte necrosis with polymorphous inflammatory infiltrates, loose fibrous and granulation tissue.17 In this case, the diagnosis was not in doubt because the histopathology could be interpreted in the context of the known disease-causing genotype; but, without genetic data, an early death from ACM might be misattributed to infective myocarditis if fibrofatty repair were nascent or absent.18

Extension of the disease process to a previously unaffected region of the myocardium is thought to occur in a stepwise rather than a constant fashion. These so-called “hot phases” may punctuate prolonged periods of disease quiescence and stability. Clinical manifestations may include new or worsening symptoms, ECG changes (dynamic or permanent), and/or increased burden or severity of arrhythmia. Structural and functional abnormalities may also advance, although their evolution is usually more gradual than the evolution of the electric features. Some cases are undoubtedly clinically silent, but, at the other extreme, a hot phase may result in an early, unheralded arrhythmic event or late-stage decompensation.19,46

The substrate for ventricular arrhythmia in 1 setting in ARVC remains unresolved. Ten-month-old heterozygous plakoglobin-deficient mice had increased right ventricular volumes, reduced right ventricular function, and spontaneous ventricular ectopy; endurance training accelerated phenotypic maturation.47 Affected hearts showed neither histopathologic abnormalities nor reduced connxin-43 expression to account for the increased burden of arrhythmia; mechanoelectric feedback is a speculative explanation.46,47

**Dilated Cardiomyopathy**

The histopathology of DCM is characterized by reduction in the number of contractile myocytes, hypertrophy, interstitial and perivascular fibrosis, and sometimes foci of myocyte necrosis and replacement fibrosis, all of which may contribute to the arrhythmic substrate. The mechanisms underlying arrhythmia in DCM are diverse. Mapping of explanted DCM hearts during VF revealed reentry initiated by epicardial breakthrough, followed by a line of conduction block parallel to the epicardial fiber orientation. Histological examination in areas with lines of block showed significantly increased fibrosis, purported to lead to continuous generation of reentry.48

Reentry is also the mechanism underlying sustained VT in DCM, which, like VF, is associated with increased myocardial fibrosis. Sustained VT is, however, rare enough in DCM to raise suspicion of sarcoidosis, Chagas disease, and left-dominant arrhythmogenic cardiomyopathy.19,49 The 1% to 2% of DCM cases with spontaneous sustained VT often have scar-related (62%) or bundle-branch (19%) reentry and inductive VT on programmed ventricular stimulation, in contrast to the far higher proportion (up to 35%) with nonsustained VT.49 Nonreentrant mechanisms such as focal automaticity are thought to contribute to spontaneous ventricular ectopy and nonsustained VT in DCM.50 Electrolyte disturbances and stretch-induced arrhythmia secondary to mechanical overload also may contribute to arrhythmogenesis in DCM. Asystolic arrest or pulseless electric activity may be more frequent in patients with NYHA class IV heart failure requiring treatment with intravenous inotropic drugs and high-dose loop diuretics.

**Muscular Dystrophies**

SCD accounts for ≈40% the mortality in the natural history of X-linked Emery-Dreifuss muscular dystrophy and has also been reported in female carriers without skeletal muscle involvement.51 Findings on postmortem include fibrous and fibroadipose replacement of the myocardium, with a predilection for the atria, sometimes resulting in massive atrial dilation; diffuse and interstitial fibrosis in the ventricles,
particularly the right, is also observed.\textsuperscript{52,53} Causal mutations have been identified in emerin (EMD) and FH1L1, and elucidation of associated molecular pathways may eventually reveal novel arrhythmic mechanisms, as it has in ACM. Nevertheless, the histopathologic abnormalities are currently purported to underlie the clinical features, which may include low-amplitude P waves, prolonged PR interval, atrial fibrillation/flutter, junctional escape rhythm with atrial standstill, atrioventricular and bundle-branch block, varying degrees of ventricular dilation and dysfunction, and ventricular arrhythmia.\textsuperscript{22,52,54} The incidence of SCD appears lower following permanent pacemaker implantation, implicating bradyarrhythmia as one of the main causes. However, cases are emerging of appropriate ICD discharges and SCD despite pacing, suggesting that ventricular tachyarrhythmia is another contributing mechanism.\textsuperscript{22,53}

Autosomal-dominant Emery-Dreifuss muscular dystrophy appears similar to the X-linked variant at a histopathologic level, but it is associated with mutations in lamin A/C, as are limb girdle muscular dystrophy type 1B and the entity of DCM with conduction system disease.\textsuperscript{22,55,56} The cardiac profile of lamin A/C disease includes sinus and/or atrioventricular node dysfunction, which can manifest as sinus bradycardia, sinus node arrest with junctional rhythms, or atrioventricular block (often first-degree at the outset, progressing to higher grades). Conduction system involvement commonly precedes development of DCM and likely contributes to the high incidence of SCD, which is more frequent than death from heart failure (46% versus 12%, respectively). Permanent pacing fails to prevent many cases of SCD, however, pointing to ventricular tachyarrhythmia as the origin.\textsuperscript{22,56,57} As in DCM, individuals with advanced ventricular impairment and current or previous heart failure may experience SCD; but, as in ACM, SCD may be the first clinical manifestation of lamin A/C disease and occur in the setting of preserved ventricular function. The arrhythmogenic pathway awaits elucidation, although connexin-43 remodeling has been reported.\textsuperscript{58}

In myotonic dystrophy type 1, the repetitive trinucleotide (CTG) segment in the 3\textsuperscript{\textprime} untranslated region of the myotonic dystrophy protein kinase gene, which normally numbers 5 to 37, is expanded to hundreds or even thousands of copies. Anticipation is recognized, with earlier onset and more severe clinical manifestations in successive generations owing to further elongation of the unstable CTG segment. Histopathology reveals fibrosis, fatty infiltration, and atrophy of the sinus node, atrioventricular node, atrioventricular bundle, and/or bundle branches, the purported substrate for the conduction defects observed in \textapprox65% of affected adults.\textsuperscript{22,59} Clinical manifestations include atrioventricular block, complete/incomplete right/left bundle-branch block, and His-Purkinje conduction delay on electrophysiological studies; atrial arrhythmia is also observed.\textsuperscript{22,60,61} SCD accounts for \textapprox23% of the mortality in myotonic dystrophy type-1 and has historically been ascribed to conduction blocks. Reports of deaths despite pacemaker implantation, however, point to a potential role for ventricular tachyarrhythmia in SCD.\textsuperscript{62} Lending further strength to this view is increasing documentation of sustained monomorphic VT in patients with myotonic dystrophy, sometimes shortly before an event.\textsuperscript{63} Diffuse interstitial fibrosis may be observed in the myocardium, and mild to moderate ventricular dysfunction is well recognized, but congestive heart failure is relatively uncommon (2% to 7%) and VT typically arises from a bundle-branch reentry mechanism.\textsuperscript{22,64,65}

### Acquired Cardiomyopathies

Cardiac sarcoidosis is associated with both conduction system disease, including development of complete atrioventricular block, and ventricular tachyarrhythmia. In a 15-case series, the disease appeared to be in its active phase, as measured by gallium-67 citrate scintigraphy, in 80% of those presenting with new-onset complete atrioventricular block; atrioventricular conduction also improved in just \textgreater50% following corticosteroid therapy. In contrast, only 14% of cases presenting with sustained VT had positive gallium uptake, implying that ventricular tachyarrhythmia is not always linked with disease activity; in keeping with this, corticosteroid treatment did not alleviate ventricular arrhythmia.\textsuperscript{66} Sarcoidosis patients with spontaneous sustained VT commonly, but not always, have inducible VT on programmed electric stimulation, with demonstrable entrainment in some cases.\textsuperscript{67} Macereentropy cardia granulomata is therefore a plausible mechanism for ventricular tachyarrhythmia in many, but not all, instances.

Despite the burden of SCD in AL amyloidosis, relatively little is known about precipitating rhythms or underlying mechanisms. Among 4 cases with AL amyloidosis who had out-of-hospital cardiac arrests, the presenting rhythm was VF in 2 and pulseless electric activity in the others, the latter being less amenable to successful resuscitation or ICD therapy.\textsuperscript{58} Although there are anecdotal reports of cases with monomorphic VT and VF terminated by ICDs, the outcomes in a series of 19 patients with AL amyloidosis with prophylactic ICDs were less encouraging. All had a history of syncope and high-grade ventricular ectopic activity; but over a 2 year follow up period, only 2 had sustained ventricular tachyarrhythmia successfully treated by the ICD, whereas 7 died as a result of pulseless electric activity.\textsuperscript{69} Development of a reliable risk stratification model is therefore of paramount importance to facilitate identification of patients with AL amyloidosis who will benefit from ICDs. Bradyarrhythmia requiring ventricular pacing occurred only rarely in this series, but progressive distal conduction system disease with high-degree AV block is relatively common in senile amyloidosis.\textsuperscript{69} Cardiac resynchronization therapy may be preferable for patients requiring permanent pacing, because right ventricular pacing often decompensates existing ventricular dysfunction.

### Risk Stratification in Cardiomyopathy

#### Hypertrophic Cardiomyopathy

Prognostication algorithms are most well developed in HCM, with consensus recognition of principal and ancillary risk factors (Table 1).\textsuperscript{40,70,71} Previous cardiac arrest is an unequivocal indication for ICD placement, with an estimated appropriate discharge rate of 10.6% per year in secondary prevention cases.\textsuperscript{39} Debilitating heart failure symptoms appear
relatively uncommon in cardiac arrest survivors, underscoring the value of averting SCD in adding quality-adjusted life years. Sustained VT has a similar prognostic impact to SCD, although it is relatively uncommon in HCM and raises suspicion of a left ventricular apical aneurysm. The remaining principal predictors serve as the core of risk prediction for primary prevention and can be determined from evaluation with clinical and family history, 2-dimensional echocardiography, maximal upright exercise testing, and ambulatory ECG monitoring. Adherence to a noninvasive protocol facilitates reassessment on an annual basis and application to asymptomatic relatives without potential for iatrogenic complications.

Absence of all prognostic indicators affords strong, albeit not complete, reassurance. Among a cohort of 368 patients with HCM followed up for a mean of 3.6 years, there were only 4 instances of SCD in patients without any of the 5 principal risk factors. In each of these cases, one of the ancillary predictors could be implicated, including coexistent coronary artery disease in 2, resting left ventricular outflow tract obstruction in 1, and microvascular ischemia in the fourth case. In HCM, microvascular ischemia manifests clinically with exertional chest pain/dyspnea accompanied by deep ST depression on exercise testing or reversible defects on perfusion scanning, in the absence of underlying coronary artery disease; verapamil is the mainstay of treatment among patients without significant outflow gradients or systolic impairment; diltiazem is a possible alternative. Specific therapies are also indicated for the other ancillary predictors first line; left ventricular outflow tract obstruction, for example, is amenable to surgical myectomy or alcohol septal ablation if pharmacological treatment with β-blockers/disopyramide fails, although there may be a low threshold for intervention for significant coronary artery stenoses.

A number of specific therapies are also available for the principal risk factors. β-Blockers and amiodarone may suppress nonsustained ventricular tachycardia in some cases. Propranolol, clonidine, and paroxetine have been shown to reverse paradoxical vasodilation during lower body negative pressure in patients with an abnormal blood pressure response to exercise; paroxetine also improves the systolic blood pressure response to exercise and alleviates related symptoms. Whether such measures also reduce the overall risk of SCD is currently unresolved; although low-dose amiodarone was shown in earlier studies to confer a survival benefit in HCM, the ICD alone affords optimal protection against SCD. The principal adverse prognostic indicators are therefore evaluated chiefly as a guide to the need for an ICD.

Multiple risk factors would intuitively be expected to have a cumulative effect and early work was in keeping with this. Although a subsequent report of 506 HCM patients with ICDs found no association between the number of risk factors and the incidence of appropriate interventions, the study had limitations. Ambulatory ECG monitoring data were lacking in a significant proportion of cases, and the analysis omitted one of the principal predictors (an abnormal blood pressure response to exercise), as well as secondary indicators (eg, ischemia and left ventricular outflow tract obstruction). Nevertheless, the chief drawback of the current risk prediction algorithm is the consistent identification of a substantial subset of HCM cases (20% to 30%) with a single risk factor; the majority of these patients will enjoy favorable outcomes and should ideally be spared the potential hazards of long-term device therapy. Case-by-case tailoring of risk prediction is therefore imperative. Nonexertional syncope, for example, has limited predictive capacity for SCD in HCM because a number of nonarrhythmic causes, including vasovagal syndrome, may be responsible. Combine syncope with a family history of SCD, however, and the risk ratio increases to 5.3 (95% CI, 1.9–14.9). Similarly, an abnormal blood pressure response to exercise has, in isolation, a low positive predictive value (14%–15%) for SCD. Yet among individuals with troponin T mutations, in whom left ventricular hypertrophy may be subtle or absent and nonsustained VT is rare, abnormal exercise blood pressure may be the strongest predictor of SCD and an indication for ICD placement, because treatment failures with amiodarone are documented in this subgroup.

Risk prediction is also more challenging at the extremes of age. Most long-term follow-up studies have focused on the adult HCM population, and comparable data in children and older patients are limited. Three of the five principal risk predictors (nonsustained VT, abnormal blood pressure response to exercise, and marked left ventricular hypertrophy) have significantly higher predictive potential in young adult HCM patients than the >50 age group, and a family history of SCD is also considered less relevant with advancing years. Superficially, survival beyond middle age per se may seem to point to a benign prognosis, but a minority of older patients with HCM have delayed-onset disease, with a concomitant risk of events in later life. At present, the validity of the existing risk stratification algorithm in older patients remains unresolved. In children with HCM, the difficulties may be compounded by underlying metabolic syndromes such as Noonan, Costello, Beckwith-Wiedemann, and Fukuyama, although the majority (like adults) harbor sarcomeric mutations. Among a series of 80 Australian children with HCM who presented <11 years of age, freedom from death or transplantation was 83% (95% CI, 73–90) 5 years after presentation and 76% (95% CI, 62–86) 10 years after presentation. Cohort-specific risk predictors included concentric left ventricular hypertrophy, age at presentation <1 year, lower initial fractional shortening Z score, and increasing left ventricular posterior wall thickness relative to body surface area. Large-scale studies in the pediatric HCM population are needed to validate these findings and tailor prognostication in this age group.

The current approach to risk stratification in HCM is therefore effective but not infallible. Attempts are ongoing to refine the algorithm through integration of other risk markers. Primary mutation analysis has a limited role in prognostication, although there is a case for screening families for mutations in troponin T, owing to the peculiarities of the phenotype, and perhaps troponin I, which is associated with reduced penetrance and restrictive physiology.

An electrophysiological study may be indicated if there is a strong suspicion of an accessory pathway in association with
with HCM. Programmed electric stimulation, however, has been extensively investigated and confers no significant advantage over noninvasive risk stratification in HCM; the polymorphic ventricular tachycardia induced by aggressive electrophysiological protocols is nonspecific and of little prognostic value. In contrast, paced electrogram fractionation analysis was evaluated in a cohort of 179 patients with HCM and found to have a positive predictive value of 38% and a negative predictive value of 95% for arrhythmic events; the area under the receiver-operating characteristic curve was an impressive 0.88. Invasive tests are generally less appealing for asymptomatic relatives and less suitable for periodic reassessment, but paced electrogram fractionation analysis may be a useful adjunct to conventional risk stratification in borderline cases.

Accumulating evidence suggests that cardiovascular magnetic resonance with late gadolinium enhancement may be a valuable prognostic tool in HCM. A preliminary study showed that the extent of late gadolinium enhancement was greater in patients with 2 or more risk factors. Subsequent investigations have confirmed that late enhancement is an independent predictor of cardiovascular mortality in HCM. Standardization of image acquisition and analysis protocols and integration into the existing prognostication algorithm are awaited.

**Arrhythmogenic Cardiomyopathy**

The central goals in the management of ACM are prevention of SCD and alleviation of symptoms related to ventricular arrhythmia. An early study of antiarrhythmic therapy in ARVC found sotalol to be highly effective in suppressing both inducible and noninducible VT. In a more recent report, however, neither β-blockers nor sotalol appeared to be protective, despite the purported contribution of adrenergic stimulation to arrhythmia. In contrast, preliminary evidence suggested that amiodarone significantly lowered the risk of any clinically relevant ventricular arrhythmia (hazard ratio 0.25, 95% CI, 0.07–0.95, \( P = 0.041 \)). Although catheter ablation may be of value in the palliative treatment of drug-resistant VT, the progressive course of ACM precludes any curative role. The ICD affords optimal protection against SCD but is not hazard-free. Among 60 ARVC patients (aged 43 ±16 years) with ICDs followed up for 80 ±43 months, 37 (62%) experienced a total of 53 adverse events, of which 38 (72%) were classified as severe. Major complications included hemorrhage, device infection, pocket perforation, and lead malfunction. Survival free of any adverse event after discharge was 90%, 78%, 56%, and 42% after 1, 3, 5, and 7 years, respectively. The present knowledge gap regarding the consequences of extended device therapy is also of particular relevance in young patients in whom the aim is to achieve normal life expectancy, underscoring the importance of reliable prognostication.

Retrospective analysis of ARVC patients with ICDs has elicited the following predictors of VF: previous cardiac arrest; VT with hemodynamic compromise; unexplained syncope; moderate to severe RV dilation; and LV involvement. The annual incidence of VF among individuals with unexplained syncope was 8%, approaching that in survivors of cardiac arrest or VT with hemodynamic compromise (10%); ICD placement for any of these indications may arguably be considered secondary prevention. In contrast, individuals receiving ICDs for hemodynamically stable VT had a significantly lower annual incidence of VF (1%). Younger age and male sex were independent risk factors for VF in some studies. It should be noted, however, that ACM shows age-related expression; survival beyond middle age cannot, therefore, be considered a guarantee of benign prognosis. The utility of programmed ventricular stimulation in prognostication is controversial; 1 study reported that VT induction during electrophysiological study was associated with increased risk for ICD intervention in ARVC patients, but others have found it of limited value, with a positive predictive value of 20% and negative predictive value of 74% in a recent study of patients without previous VF/VT. A family history of SCD does not appear to be an independent predictor of arrhythmic events in ACM.

Because existing studies have focused on advanced, “classic” disease, they leave open the challenge of risk stratification in patients with early and nonclassic subtypes, increasingly identified by familial assessment, genetic testing, and improved imaging. Although most affected relatives enjoy favorable outcomes, a minority experience events that elude prediction by conventional prognostic indicators. At present, timely recognition of hot phases depends on periodic reassessment and encouraging patients to remain vigilant for new or worsening symptoms, although care must be taken to avoid precipitating cardiac neurosis. Lifelong follow-up is recommended because hot phases have been documented from early adolescence to the eighth decade of life. Besides ECG changes and increased arrhythmic burden, the disease exacerbation may be accompanied by cardiac enzyme release, which, in the older patient, is particularly likely to be misattributed to myocardial infarction. Elevated troponin I levels have been documented in Boxer dogs with ARVC, and on a phasic basis in a 29-year-old man with ARVC and repeatedly normal coronary angiograms. Whether biomarkers may enable prediction of hot phases remains unresolved. Coupled with evidence of gap junction remodeling as a “concealed” arrhythmic mechanism, the erratic hot phase phenomenon shifts the emphasis away from conventional investigative modalities. Electroanatomic mapping has the potential to identify heterogeneous conduction from not only histopathologic substrate, but also gap junction remodeling and early necrotic/inflammatory changes. Molecular and genetic analysis might facilitate noninvasive prognostication in early disease.

That a family history of SCD is not a predictor of arrhythmic events in ARVC suggests that primary mutation analysis will be minimally contributory. The main exception is the Newfoundland founder population, in which the 5-year mortality among affected men is 28%, and screening for the causal mutation (TMEM43 1073C/T, S358L) pivotal to enabling timely diagnosis and ICD placement. Among other genotype-phenotype associations, left ventricular involvement appears more extensive in individuals with chain termination and/or desmoplakin mutations, but a direct impact on outcomes remains to be established. Emerging
Dilated Cardiomyopathy

With the exception of the subgroup with conduction system disease, DCM patients present with heart failure, and the initial goal of management is to stabilize them on the maximum tolerated doses of renin-angiotensin system antagonists (or hydralazine/nitrates in the setting of renal failure) and β-blockers. Evidence-based pharmacological therapy diminishes morbidity and mortality from heart failure, foretells and may even reverse left ventricular remodeling, and reduces the risk of SCD, particularly with the introduction of β-blockers.

Various studies have investigated the efficacy of amiodarone in further lowering the arrhythmic risk. The Amiodarone versus Implantable Defibrillator (AMIOVIRT) trial failed to demonstrate a statistically significant difference in 1- and 3-year survival rates between DCM patients on amiodarone therapy and those who received an ICD. A trend toward improved arrhythmia-free survival rates and cost of medical care was observed in the patients treated with amiodarone. All patients had left ventricular ejection fraction (LVEF) ≤0.35, documented nonsustained ventricular tachycardia, and NYHA functional Class I–III. In contrast were the results of the Sudden Cardiac Death in Heart Failure trial (SCD-HeFT), which compared placebo, amiodarone, and ICD insertion in >2500 patients with NYHA class II or III heart failure, and LVEF <35% despite optimal medical therapy. Approximately equal numbers of patients with ischemic heart failure and DCM were recruited. There was a 23% reduction in all-cause mortality at 5 years in the ICD group compared with placebo, but no effect was observed for amiodarone versus placebo. SCD-HeFT had a larger population size and longer duration of follow-up than AMIOVIRT, but was not restricted to DCM cases (although results did not vary between ischemic and nonischemic causes of heart failure). There may be a role for empirical use of amiodarone in DCM patients with relatively preserved left ventricular systolic function, but documented nonsustained VT despite adequate β-blockade. The ICD is, however, the initial goal of management for DCM patients at risk of SCD, particularly in the presence of significant left ventricular systolic dysfunction.

Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) was a randomized controlled trial of standard medical therapy versus standard medical therapy plus a single-chamber ICD in 458 patients with DCM, left ventricular ejection fraction ≤35%, and premature ventricular complexes or nonsustained ventricular tachycardia. After a mean follow-up of 2.4 years, there were 17 instances of SCD, of which 3 occurred in the ICD group and 14 in the standard-therapy group (hazard ratio, 0.2; 95% CI, 0.06–0.71, P = 0.006). There is little doubt as to the efficacy of the ICD in preventing SCD in DCM. Previous cardiac arrest, sustained ventricular tachycardia, and unexplained syncope are strong indications for an ICD; the similar incidence of VF in these subgroups suggests that both the latter scenarios should be considered equivalent to secondary prevention. The major challenge remains identification of individuals in whom the risk of complications is outweighed by the benefits of prophylactic ICD placement, with or without adjunctive cardiac resynchronization therapy (CRT). A retrospective study of 503 CRT recipients found greater survival benefit and improvement in left ventricular systolic function in DCM patients than in those with ischemic heart disease. CRT is recommended in DCM patients in sinus rhythm, with NYHA class III/IV heart failure, LVEF ≤35%, and QRS >120 ms and/or evidence of mechanical dyssynchrony. Furthermore, in the MADIT-CRT trial, DCM patients with NYHA class II symptoms, LVEF ≥30%, and QRS duration ≥130 ms who were implanted with a CRT-ICD had a significantly reduced risk of death or heart failure events in comparison with those receiving ICD therapy only. A 41% reduction in the risk of heart-failure events accounted for most of this benefit, which was apparent chiefly in the subgroup of patients with QRS ≥150 ms. Women also benefited significantly more than men from CRT-ICD therapy, a finding of particular note because pooled analysis of previous ICD trials had failed to show any reduction in all-cause mortality among women receiving ICDs for primary prevention of SCD.

As in the other primary myocardial disorders, programmed ventricular stimulation is not useful in predicting SCD risk among DCM patients. The prospective observational Marburg Cardiomyopathy study (MACAS) sought to determine the clinical value of noninvasive prognostic indicators in a 343 patients with DCM. The exclusion criteria included a history of sustained VT or VF, unexplained syncope within the previous 12 months, and amiodarone therapy. Evaluation included echocardiography, signal-averaged ECG, ambulatory ECG monitoring, microvolt T-wave alternans, heart rate variability, baroreflex sensitivity, and QTc dispersion. After a mean follow-up period of 52 months, the only independent predictor of major arrhythmic events (sustained VT, VF, or SCD) was reduced LVEF. In addition, there was a tendency toward increased arrhythmic risk in patients with nonsustained ventricular tachycardia on Holter monitoring and those who were not on β-blocker therapy at enrolment. The combination of LVEF <30% and nonsustained VT was associated with an 8.2-fold risk of major arrhythmic events. A number of earlier and subsequent studies have, however, reported findings in favor of indicators including increased QRS duration, QT dynamicity, and particularly T-wave alternans (ALPHA - Prognostic Value of T-Wave Alternans in Patients with Heart Failure Due to Nonischemic Cardiomyopathy), with mixed results from markers of autonomic tone such as baroreceptor sensitivity testing, heart rate variability, and turbulence. Many studies are disadvantaged by underpowering, and the jury is still out on the utility of many of these putative predictors.
In current clinical practice, risk stratification of DCM is based primarily on left ventricular systolic dysfunction, with nonsustained VT as an auxiliary marker. Cardiovascular magnetic resonance may also be a useful adjunct; midwall late gadolinium enhancement appears to correspond to macroscopic midmyocardial fibrosis on postmortem examination and serves as a predictor of SCD/VT (hazard ratio, 5.2; \( P = 0.03 \)). This approach is ideally complemented by screening for mutations in the \( SCN5A \) gene, associated with conduction disturbances and ventricular arrhythmia; desmosomal genes, if there is suspicion of left-dominant arrhythmogenic cardiomyopathy; and, importantly, the \( LMNA \) gene, the phenotype of which includes conduction system disease, atrial fibrillation, and a high incidence of ventricular tachyarrhythmia and SCD. Monitoring and risk prediction in families with DCM and conduction defects is a distinct challenge discussed in further detail below.

Muscular Dystrophies

Because large-scale prospective follow-up studies and clinical trials are lacking in the muscular dystrophies, consensus guidelines capitalize on available evidence and encourage a pragmatic approach to cardiovascular care. In the dystrophinopathies, the emphasis is on serial evaluation with 12-lead ECG and echocardiography for timely identification of cardiac involvement; early initiation of angiotensin-converting enzyme inhibitors and addition of \( \beta \)-blockers to forestall progression of cardiomyopathy; and consideration of cardiac transplantation for end-stage heart failure if comorbidities allow (Becker patients and female carriers are more likely to be candidates). Few recommendations have been issued on prevention of SCD, although the option of ICD therapy may be discussed in individuals with severe left ventricular systolic dysfunction and/or nonsustained VT on ambulatory ECG monitoring, but otherwise good functional status.

In X-linked Emery-Dreifuss muscular dystrophy, 12-lead ECG and ambulatory ECG monitoring is worth repeating at least once a year, with 2D echocardiography on a less regular basis. Permanent pacing is recommended, even in asymptomatic patients, if there is evidence of sinus or atrioventricular node disease. Among individuals with permanent pacemakers, the incidence of SCD is low but not negligible; an ICD may be preferable to a pacemaker in the presence of significant ventricular dysfunction, but other risk markers await identification.

SCD despite permanent pacing is a still more pressing concern in autosomal dominant Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy 1B, and DCM with conduction system defects, 3 entities often considered under the umbrella term of “laminopathies” owing to their association with \( LMNA \) mutations. Cardiac assessment including 12-lead ECG, 2D echocardiography, and ambulatory ECG monitoring is recommended on a minimum annual basis. In a retrospective observational study of 94 \( LMNA \) mutation carriers from 27 families followed up for a median of 4.75 years, splice site defects and participation in highly dynamic competitive sports for \( \geq 10 \) years were predictors of SCD. Symptomatic ventricular arrhythmia, VT, and moderate to severe left ventricular systolic impairment are considered indications for an ICD. The weight of evidence also favors placement of an ICD rather than a pacemaker in individuals with symptomatic bradyarrhythmia or asymptomatic but significant conduction system defects. That ICD therapy is also associated with more complications underscores the importance of individualized decision making, with mutual specialist and patient participation, in these complex cases.

Periodic evaluation recommendations are similar in myotonic dystrophy. Electrophysiological studies may have a role in management of these patients; invasive measurement of the HV interval (infra-nodal conduction delay: HV >70 ms) may sway in favor of permanent pacing in borderline cases, and broad complex tachycardia or symptoms thereof warrant a high index of suspicion of bundle-branch reentrant tachycardia, which may be abolished by catheter ablation. Whether individuals with an indication for pacing should receive an ICD instead is currently unresolved; the length of the CTG repeat may influence the onset of cardiac complications in myotonic dystrophy, but a reliable risk stratification algorithm is awaited.

Acquired Cardiomyopathies

Early treatment with corticosteroids and, if required, additional immunosuppressive agents, improves outcome in cardiac sarcoidosis, underscoring the importance of timely diagnosis. Despite the availability of disease-modifying treatment, however, the risk of SCD may be significant. Cardiovascular magnetic resonance with late gadolinium enhancement appears more than twice as sensitive for detection of cardiac involvement in patients with sarcoidosis as existing consensus criteria and is associated with a 9-fold higher incidence of adverse events and 11.5-fold rate of cardiac death. Programmed ventricular stimulation may also be of use in risk stratification; in a recent series of 76 patients with cardiac sarcoidosis followed up for 5 years, the event rate (SCD or ICD intervention for VT) was 75% among the 8 cases with inducible VT, but only 1.5% in those with a negative stimulation study. Larger-scale studies are needed, but a combination of cardiovascular magnetic resonance and electrophysiological studies may facilitate identification of sarcoidosis patients who will benefit from ICD therapy.

Proposed predictors of SCD in cardiac amyloidosis include the presence of complex ventricular arrhythmia on ambulatory ECG monitoring, late potentials on signal-averaged ECG, and prolonged infra-His conduction times (which may predispose to complete atrioventricular block and bradyarrhythmia). Although management of cardiac complications in amyloidosis patients remains largely symptomatic and empirical, therapeutic options targeting the underlying systemic disorder are widening, providing grounds for cautious optimism.

Conclusion

In the past half-century, interrelation of clinical observations with underlying histopathology has provided fundamental insights into the pathogenesis of the cardiomyopathies and their association with sudden cardiac death. At the same time, large-scale intervention trials and follow-up studies have led
to disease-modifying pharmacological therapies and workable guidelines for identifying individuals who may benefit from implantable cardioverter-defibrillators: the ultimate, albeit not hazard-free, protection against SCD. Gene identification and early expression/functional studies have also provided a platform for in-depth investigation of the cellular and molecular mechanisms underlying arrhythmia in myocardial disease, which holds the eventual promise of targeted and potentially curative therapies.

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Srijita Sen-Chowdhry and William J. McKenna

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