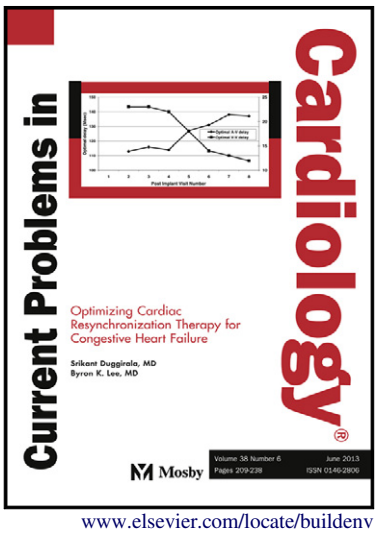

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Dr. Vikas Kuriachan joined the Cardiology / Cardiac Electrophysiology group at the Libin Cardiovascular Institute of Alberta and the University of Calgary in July 2010 after completing a year of complex ablation training at Brigham and Women's Hospital / Harvard Medical School. He is the Program Director for the Cardiac Electrophysiology training program. He is a Fellow of the Royal College of Physicians and Surgeons of Canada and Heart Rhythm Society. His clinical interests include ablation, in particular VT ablation, along with cardiac rhythm management device implantation and complex lead extraction.

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Dr. Sumner has been a Clinical Assistant Professor of Medicine in the Department of Cardiac Sciences at the Libin Cardiovascular Institute of Alberta, University of Calgary since 2008. He completed his medical training at Queen's University in Kingston (Ontario, Canada) and practiced as a rural family physician for seven years prior to embarking on clinical training in cardiology, echocardiography, and cardiac electrophysiology at Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire and McMaster University in Hamilton, Ontario. Dr. Sumner's main clinical and research interests are in cardiac

resynchronization therapy patient selection, cardiac device implantation, and cardiac device programming.

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Dr. Mitchell is a Professor in the Department of Cardiac Sciences in the Libin Cardiovascular Institute of Alberta at the University of Calgary. He obtained his training in clinical cardiology at Dalhousie University (Halifax, Nova Scotia) and his training in cardiac electrophysiology Stanford University. He was the Inaugural Head of the Department of Cardiac Sciences and the Inaugural Director of the Libin Cardiovascular Institute of Alberta. Dr. Mitchell's clinical practice and research interests are in the clinical science of tachyarrhythmias – their mechanisms, their investigation, and their management. His preferred tool in this science is the randomized clinical trial.

Abstract:

Sudden death accounts for 300,000-400,000 deaths annually in the United States. Most sudden deaths are cardiac and most sudden cardiac deaths are related to arrhythmias secondary to structural heart disease or primary electrical abnormalities of the heart. The most common structural disease leading to sudden death is ischemic heart disease. Non-ischemic cardiomyopathy and other structural abnormalities such as arrhythmogenic ventricular dysplasia and hypertrophic cardiomyopathy may also be causative. Patients without structural disease have a primary electrical abnormality, such as long QT syndrome or Brugada syndrome. Severe left ventricular systolic dysfunction is the main marker for sudden death in patients with ischemic or non-ischemic cardiomyopathy. In other conditions, other markers for structural heart disease and electrical abnormalities need to be considered. β-blocker therapy is associated with a reduction in sudden cardiac death across a broad range of disorders. Nevertheless, the Implantable Cardioverter Defibrillator remains the most effective treatment strategy in selected patients.

Abbreviations

ACE-I – Angiotensin Converting Enzyme Inhibitor

AF – Atrial Fibrillation

ARB – Angiotensin Receptor Blocker

ARVC – Arrhythmogenic Right Ventricular Cardiomyopathy

BrP – Brugada ECG Pattern

BrS – Brugada Syndrome

CAD – Coronary Artery Disease

CHD - Congenital Heart Disease

CHF – Congestive Heart Failure

cMRI – Cardiac Magnetic Resonance Imaging

CPVT – Catecholaminergic Polymorphic Ventricular Tachycardia

EAD – Early After Depolarization

ECG – Electrocardiogram

HCM – Hypertrophic Cardiomyopathy

ICD - Implantable Cardioverter Defibrillator

LVEF – Left Ventricular Ejection Fraction

LQTS – Long QT Interval Syndrome

MVP – Mitral Valve Prolapse

SCA – Sudden Cardiac Arrest

SCD - Sudden Cardiac Death

SQTS – Short QT Interval Syndrome

VF - Ventricular Fibrillation

VT - Ventricular Tachycardia

VHD – Valvular Heart Disease

A) INTRODUCTION

Sudden cardiac death (SCD) is defined as unexpected, non-traumatic death occurring within one hour of the onset of new or worsening symptoms (witnessed arrest) or, if unwitnessed, within 24 hours of last being seen alive(1). SCD has a multitude of potential aetiologies but is most commonly associated with ischemic heart disease. SCD may be preceded by symptoms such as chest pain, dyspnea, palpitations, presyncope, and syncope but many individuals have no symptoms prior to the event. By definition, a patient with SCD does not survive. When the patient survives, the event is termed aborted SCD or sudden cardiac arrest (SCA). The immediate cause of SCD in most instances is a ventricular arrhythmia: either ventricular fibrillation (VF) or ventricular tachycardia (VT). However, in a significant minority of cases, asystole or pulseless electrical activity is the initial documented rhythm.

The leading etiologies of sudden death are listed in Table 1. Broad categories of SCD include those related to ischemic heart disease, non-ischemic heart disease, primary electrical disease, and non-cardiac disease.

B) EPIDEMIOLOGY AND RISK FACTORS

SCD is common with an annual incidence of 60 per 100,000 in the United States(2). Accordingly, approximately 300,000-400,000 sudden cardiac deaths occur in the United States each year. The incidence is higher in men (76 per 100,000) than in women (45 per 100,000). Using death certificate data, it is estimated that SCD accounts for up to 15% of all deaths in western nations. However, death certificate data may overestimate the incidence. Extrapolated data from the Oregon Sudden Unexpected Death Study (SUDS) suggests that SCD accounts for approximately 5.6% of all deaths in the United States(2).

SCD incidence increases with age. The incidence of SCD in younger populations (<30 years) is 100-fold lower than that in older individuals(1). Women are relatively protected from SCD until the menopausal years when incidence increases to approach that of men. However, even in younger women, conventional CAD risk factors are predictive of SCD events. Genetic factors play a role in SCD at multiple steps in the pathophysiologic pathway. Mutations and polymorphisms modulate the risk of SCD associated with both CAD and non-CAD etiologies(1). In addition, at least two studies have described a familial propensity for SCD being the initial presentation of CAD. Some studies have demonstrated an increased risk of SCD in

African Americans compared to whites while Hispanic individuals may be at lower risk(1).

SCD is a leading cause of death. In men, SCD incidence exceeds other causes of death including individual cancers (lung, prostate, and colorectal), accidents, chronic respiratory diseases, diabetes, and cerebrovascular disease(2). In women, SCD incidence is similar to those of lung cancer and cerebrovascular disease and is higher than those of other causes of death including breast cancer, colorectal cancer, Alzheimer's disease, and accidents(2). When expressed as years of potential life lost (YPLL), the impact of SCD is impressive.

Nearly 50% of people with SCD had no known previously diagnosed heart disorder. In this population, risk stratification is particularly challenging(3). Furthermore, 40% of SCD occurs in individuals with known heart disease but with a left ventricular ejection fraction (LVEF) greater than 40%. Our ability to predict SCD in this population is also limited. The remaining (approximately 10%) incidence of SCD affects individuals with known structural heart disease and LVEF less than 40%(3). Accordingly, current risk stratification tools and therapies such as implantable cardioverter defibrillators (ICDs) have had a modest impact on the overall problem of SCD. Genetic-based arrhythmic conditions account for only 2% of all SCD. Thus, because the majority of SCD occurs in individuals without known heart disease, efforts to prevent SCD should be directed towards the identification and modification of conventional risk factors.

The risk factors for SCD are similar to those of ischemic heart disease and include smoking, hypertension, dyslipidemia, and diabetes. In the Framingham population, smoking conferred a 2-3 fold increased risk of SCD(1). Furthermore, in one study continued smoking after aborted SCD was associated with a recurrent cardiac arrest rate of 27% over 3 years compared to 19% in those who stopped smoking. Obesity also confers an increased risk of SCD in those with CAD(3). There is conflicting data with respect to sedentary lifestyle as a risk factor for SCD. The risk of SCD is increased (approximately 17 fold) during vigorous physical activity especially in those who are generally sedentary (approximately 74 fold). However, the absolute risk of SCD during a single episode of vigorous exercise is very low (1 per 1.51 million episodes of exercise) (4). Furthermore, regular participation in physical exercise attenuates the overall risk of SCD both during exercise and at rest. Psychosocial stressors also increase risk of SCD. Major disasters such as earthquake and war increase the incidence of SCD in affected populations(5). Heavy alcohol consumption (6 or more drinks per day) and binge drinking increase the risk of SCD while moderate alcohol consumption (one to two drinks per day) may

decrease the risk(6). In contrast, caffeine intake has not been shown to be a risk factor for SCD. Higher levels of long chain n-3 polyunsaturated fatty acids (eicosapentaenoic acid and docosahexaenoic acid; "fish oil") measured in plasma and in red cell membranes are associated with a lower risk for SCD(7). Higher serum C-reactive protein (CRP), a marker of generalized inflammation, has been shown to be levels are associated with increased risk of SCD(8). In 97 cases of SCD among apparently healthy men in the Physicians Health Study, CRP serum levels in the highest quartile were associated with a 2.78 fold increased risk compared to men in the lowest quartile. Prospective studies are required to evaluate the impact of modification of these risk factors on the incidence of SCD.

C) NONCARDIAC CAUSES OF SUDDEN DEATH

Most studies have evaluated causes of death using medical records and death certificates. A small population study in Japan in which 78% of the subjects had an autopsy suggested that the major causes of sudden death were heart disease (49%), stroke (33%), and aortic aneurysm/dissection (12%)(9).

a) Neurologic Disorders

Central nervous system disorders that can directly (or indirectly via cardiac interaction) result in sudden death include epilepsy, ischemic stroke, intracranial bleeding, and traumatic head injury(10).

Uncontrolled epilepsy may lead to Sudden Unexplained Death of Epilepsy (SUDEP). Among patients with epilepsy, the incidence of SUDEP is 6/1000 patient-years(11). SUDEP is usually triggered by a generalized tonic-clonic seizure. It is believed that rare channelopathies may predispose to both epilepsy and SCD. Apnea, bradycardia, and asystole have also been implicated as has the use of certain anti-seizure medications. Finally, associated stress-induced cardiomyopathy (Takutsubo) may also play a role(10).

Cerebral catastrophes such as stroke and major intracranial bleeding/injury can cause ECG changes and autonomic imbalance. It is possible that associated arrhythmias (severe bradycardia or VT/VFs) may cause sudden death. Patients with these neurologic disorders may also be predisposed to SCD due to underlying cardiovascular disease and an inflammatory state(10).

Preventative treatments include good control of seizure disorders and measures to reduce the incidence of stroke and cerebral injuries including blood pressure control and appropriate anticoagulation for patients with atrial fibrillation (AF). Cardiac monitoring after

cerebral catastrophes is important for recognition of cardiac arrhythmias.

b) Acute Aortic Syndromes

Acute aortic syndromes include entities that disrupt aortic integrity with complications ranging from aortic rupture to organ ischemia and death. These syndromes include aortic dissection, aneurysm expansion, trauma, penetrating ulcer, and intramural hematoma(12).

Patient risk factors include age and hypertension. Loss of tensile strength due to Marfan's syndrome, Ehlers-Danlos syndrome, familial thoracic aortic aneurysm disease, and the aortopathy associated with congenital bicuspid aortic valve also increase risk. Cocaine use is a risk factor due to increases in blood pressure and heart rate.

Treatment imperatives include rapid diagnosis, control of blood pressure and shear stress with β-blockers and vasodilators, and early surgical intervention(12).

c) Electrolyte, Metabolic, and Endocrine Derangements

Life-threatening arrhythmias may result from electrolyte imbalances (especially hypokalemia and hypomagnesemia), metabolic derangements (including acid-base disorders), and severe endocrine disorders (especially hypothyroidism, hyperthyroidism, hypercatecholaminergic states). Treatments are focused on the underlying disorder and acute correction of electrolyte, metabolic, and endocrine imbalances. Arrhythmias can also accompany eating disorders and the aggressive treatments intended to correct the metabolic consequences. Weight reduction in obesity and refeeding in anorexia should be controlled with attention to electrolyte fluctuations(1).

One major patient group prone to metabolic and electrolyte derangements are those on dialysis. Dialysis patients have a high mortality rate and up to 43% of their deaths are cardiac, with most being due to cardiac arrest(13). Risk factors for SCD in dialysis patients include electrolyte shifts, hyper- and hypovolemia, left ventricular hypertrophy, systolic and diastolic heart failure, CAD (CAD), hyperphosphatemia, sympathetic overactivity and autonomic dysfunction.

Prevention of SCD in dialysis patients is challenging. During dialysis, care is taken to minimize electrolyte shifts. Traditional medical therapies for CAD, such as statins have lesser benefits in dialysis patients suggesting that the role of coronary plaques in SCD maybe less important in dialysis patients(14). β-blockers decrease

ischemia but also have antiarrhythmic and sympathoinhibitory effects and decrease sudden deaths and increase survival of cardiac arrest in diabetic patients on dialysis. Survival benefits from angiotensin converting enzyme inhibitor (ACE-I) and angiotensin receptor blocker(ARB)treatments have also been demonstrated(14).

ICDs play a major role in the prevention of SCD in many predisposed patient populations. Many of the major trials demonstrating the benefits of ICDs excluded patients with end-stage renal disease. To date, no randomized trials of ICD use have been performed in patients with end-stage renal disease. Nevertheless, patients with end-stage renal disease are considered for an ICD if expected to survive more than a year with good functional status especially in patients who have survived aborted SCD(15). The comorbidities in this population generate competing non-arrhythmic causes of death and lead to higher ICD complication rates thereby limiting the benefits of ICD therapy. Although the benefits have been difficult to document, dialysis staff should have basic life-support training and an external cardiac defibrillator should be on-site.

d) Medications

Many drugs can cause proarrhythmia that may lead to syncope and sudden death. The most common mechanism of this proarrhythmia is suppression of the rapid component of the delayed rectifier potassium current (I_{Kr}) resulting in prolongation of the QT interval and torsades de pointes VT(16). Risk factors for this form of proarrhythmia include other factors that prolong the QT interval including hypokalemia, hypomagnesaemia, bundle branch block, bradycardia, CHF, inherited long QT abnormalities, and female sex. Accordingly, patients with a QTc greater than 460 msec should be exposed to additional QT prolonging drugs with great caution.

The non-cardiovascular drugs associated with this form of proarrhythmia include certain antibiotics, psychotropic medications, and diuretics (by magnesium and potassium depletion) (16). A web-based listing of potential culprit medications is available at www.torsades.org.

Cardiovascular drugs may also be proarrhythmic. Vaughn Williams Class III antiarrhythmic drugs (amiodarone, dronedarone, dofetilide, ibutilide,and sotalol) are potassium channel blockers that prolong QT and may produce torsades de pointes VT. Such agents are administered with close monitoring of QT intervals, maintenance of normal potassium and magnesium levels, and assurance of normal renal function for those

agents that are so excreted (dofetilide, sotalol) (16). Vaughn Williams Class Ia antiarrhythmic agents (disopyramide, procainamide, quinidine) are also potassium channel blockers that prolong QT and may produce torsades de pointes VT. In addition, these drugs and other Class I agents (lidocaine, mexiletine, propafenone, flecainide) are sodium channel blockers that may prolong QRS duration. Class I antiarrhythmic agents have been associated with SCD particularly in patients with underlying structural heart disease and myocardial fibrosis(17). Accordingly, Class I agents are used mainly in patients with no structural heart disease. Vaughn Williams Class II antiarrhythmic agents (β-blockers) and Class IV agents (non-dihydropyridine calcium channel blockers) may result in sinus and/or AV nodal suppression bradycardia especially if used in high doses in combination.

Although many recreational drugs may result in SCD the one most implicated is cocaine. Studies in Europe report that 1-4% of young adults have used cocaine in the past year(18). Cocaine is an indirect sympathomimetic agent and may increase blood pressure, heart rate, increase ventricular contractility, and lower VT threshold placing users at risk for myocardial infarction, major hemorrhages, and arrhythmias. Up to 9% of young adults with sudden cardiac death were recent cocaine users(18).

Clearly, the best prevention of sudden death related to drug effects is to limit the use of implicated agents and to carefully monitor their effects when they are used, particularly when therapy is first prescribed and shortly after dosage increments.

e) Other causes of non-cardiac sudden death

Other causes of non-cardiac sudden death are extremely rare and include pulmonary hemorrhage, pulmonary embolism, chronic obstructive pulmonary disease, asthma, rupture of esophageal varices, and rupture of ectopic pregnancy. Prevention of sudden death from these causes mainly involves diagnosis and treatment of the underlying disorder.

D) CARDIAC CAUSES OF SUDDEN DEATH

a) Arrhythmic Causes Due to Primary Electrical Abnormalities

i) Tachycardias

1) Wolff-Parkinson-White Pattern and Syndrome

In 1930, Drs. Wolff, Parkinson, and White described group of patients with palpitations and an ECG abnormality in the absence of structural heart disease now recognized to be ventricular

preexcitation associated with an atrioventricular reentrant supraventricular tachycardia(19). Ventricular preexcitation reflects the presence of an accessory connection between atrial and ventricular myocardium. If ventricular preexcitation is associated with symptoms such as palpitations, presyncope, or syncope then the condition is termed Wolff-Parkinson-White (WPW) syndrome. In the absence of associated symptoms or documented tachydysrhythmia, the ECG abnormality is termed WPW pattern or asymptomatic WPW.

The incidence of the WPW pattern in the population is 1-3/1000. Approximately 65% of adolescents and 40% of individuals over 30 years of age with the WPW pattern are asymptomatic(20). The mechanism of SCD in WPW is rapid conduction of atrial flutter or atrial fibrillation over the accessory connection that precipitates VF. Most episodes of SCD in the setting of WPW occur in children or adolescents and in those with symptoms. However, SCD may be the initial presentation. The risk of SCD in one prospective study of asymptomatic adults with a WPW-pattern ECG followed for 38 months was 4.5 per 1000 patient years. Another study suggested that the 10 year risk of developing AF is 15% but the risk of SCD only 1%(20).

High-risk features for SCD in patients with a WPW-pattern include age <30, male gender, history of AF, prior syncope, associated congenital or other heart disease, and familial WPW(20). Nevertheless, none of these findings are particularly sensitive or specific. Additional risk stratification is based on the electrophysiologic properties of the accessory connection. Data from survivors of WPW-associated SCA, properties of the AP that suggest high-risk include antegrade conduction with a shortest preexcited R-R interval in AF less than 220-250 msec(20). The sensitivity of the cutoff of less than 220 msec is 88-100% for predicting the risk of WPW-associated VF in adults. However, because the incidence of SCD in WPW is very low, the positive predictive value is only 19-38%. Similar data are provided by measurement of the antegrade refractory period of the accessory connection or the maximal atrial pacing rate with continuous preexcitation during programmed atrial stimulation at an electrophysiology study using transvenous catheters or a transesophageal pacing catheter(20).

Non-invasive risk stratification uses Holter monitoring or exercise testing to observe disappearance of ventricular preexcitation at physiologic heart rates(20). If there is clear evidence of intermittent loss of preexcitation the risk of SCD is likely low. It may be challenging to identify loss of preexcitation with increasing heart rates as elevated sympathetic tone may increases the speed of AV nodal conduction such that preexcitation is masked. Accordingly, only

the abrupt loss of preexcitation that was clear on the previous heart beat is accepted as a marker of low risk. The identification of multiple accessory pathways on non-invasive evaluation by virtue of ventricular preexcitation with multiple morphologies is a marker of higher risk that warrants further invasive evaluation(20).

If an accessory connection has high risk features or if the patient is symptomatic with atrioventricular reciprocating tachycardia, transcatheter ablation of the accessory connection is considered. The success rate for catheter ablation in this setting is greater than 95% with a low complication rate estimated at 1-3%. A proposed algorithm for the approach to SCD risk stratification is presented in Figure 1(20).

2) Long QT Syndrome

The congenital Long QT syndromes (LQTS) are genetically-determined channelopathies that result in prolongation of myocardial action potential duration. This is manifest on an ECG as a prolonged QT interval. The QT interval varies inversely with heart rate and therefore measurement of the QT interval is corrected (QTc) for heart rate using various formulae. Bazett's formula produces a corrected QT interval by dividing the measured QT interval by the square root of the corresponding R-R interval(in seconds). In adolescence, the normal QTc range (370-440 msec) is the same in males and females. In adulthood, the upper limit of normal for the QTc is 450 msec in men and 470 msec in women(21).

Epidemiology

LQTS may be congenital or acquired. The acquired form, induced by drugs, electrolyte, or metabolic disturbances is discussed above. It was once believed that a genetic abnormality is required to be susceptible to the acquired form of LQTS. However, such a genetic abnormality has only been identified in less than 10% of cases of acquired LQTS(22). In either congenital or acquired LQTS abnormal prolongation of repolarization can precipitate, through early afterdepolarizations (EADs), a specific type of polymorphic VT known as torsades de pointes ("twisting of the points") (Figure 2). (23) Although torsades de pointes is often self-terminating it may also precipitate VF and SCD.

Congenital LQTS leads to approximately 3000-4000 SCDs in childhood in the United States(24). The incidence of congenital LQTS in the general population is estimated at 1 in 2500. However, the incidence may be significantly underestimated in that many genotypes have a low penetrance and may not manifest overt QT prolongation(24). Most

individuals with congenital LQTS present in childhood. One registry identified the mean age of presentation as 6.8 years; another, which enrolled predominantly adults, reported a mean age at diagnosis of 21 years(25).

Genetics

To date, 12 gene mutations have been identified that lead to the LQTS (Table 2) (26). Approximately 70% of individuals with a LQTS will have an identifiable mutation on genetic testing with the majority of mutations encoding different components of the potassium channel.

The three most common LQTS are LQT-1 (KCNQ1), LQT-2 (KCNH2), and LQT-3 (SCN5A) (26). LQTS-affected individuals may present with palpitations, presyncope, or syncope but a high proportion are asymptomatic. LQT-1 (KCNQ1) is responsible for 30-35% of all LQTS cases. Individuals with LQT-1 may present with symptoms that are precipitated by exercise or other high adrenergic states. There may be a predilection for swimming as a precipitating event. LQT-2 (KCNH2)is responsible for 25-30% of genotyped individuals with LQTS. They typically have symptoms precipitated by emotional stress or sudden noise. A loud alarm clock is a commonly cited example of a precipitating event in LQT-2. In contrast, individuals with a LQT-3 (SCN5A) genotype, which represents 7-10% of genotyped LQTS patients, have symptoms that are typically occur at rest or while sleeping. Cardiac arrest or SCD incidence is highest in LQT-2 (0.6%/year) and LQT-3-affected individuals (0.56%/year) and is lowest in those with a LQT-1 genotype (0.3%/year) (23).

Two clinical phenotypes of congenital LQTS have been described. The Romano-Ward syndrome is transmitted as an autosomal dominant trait and may have any of the known genetic substrates. The Jervell and Lange-Neilsen syndrome is transmitted as an autosomal recessive trait and is associated with both sensorineural deafness and LQTS. This phenotype has only been described with mutations in KCNQ1 (LQT1) and KCNE1 (LQT5) and has a higher risk natural history(23).

Risk factors for SCD

Analysis of the natural history over 28 years of follow-up of 647 individuals with LQT-1, LQT-2, or LQT-3 showed that cardiac events (defined as syncope, cardiac arrest, or sudden death prior to age 40 years) varied as a function of both genotypes and magnitude of QTc(26). Cumulative event rates were highest in LQT-2 and LQT-3 genotypes at 46% and 42%, respectively. LQT-1 genotypes had the lowest event rate at 30%. In addition, those individuals with a QTc of >500msec in the LQT-1 and LQT-2 genotypes had higher event rates, a

finding not observed in LQT-3 genotypes. Finally, the risk of cardiac events was higher for females in LQT-2 and for males in LQT-3. No significant gender effect was seen in LQT-1(26).

Diagnosis:

The primary diagnostic criterion is a QTc interval above the normal limits defined above. To improve the sensitivity of this measure in patients with concealed LQTS, QTc may be measured standing, during exercise, and following an epinephrine challenge(23). It is important to recognize that the response of patients with LQTS to provocation testing has significant overlap with that of normal individuals. All individuals diagnosed with LQTS should be referred to a center with expertise in family screening, genetic testing and counselling.

Treatment:

The cornerstone of treatment for patients with symptomatic LQTS is β-blockade. The β-blockers that have been best studied for LQTS are nadolol and propranolol although others have been used. A recent database analysis of the efficacy of β-blocker therapy in LQT1 and LQT2 revealed that nadolol was superior to metoprolol, atenolol, and propranolol in LQT2 patients and of similar efficacy in LQT1 with respect to prevention of cardiac events(27). The importance of 24-hour therapeutic medication levels may influence the choice of individual β-blockers. β-blockers are most effective in LQT-1 and LQT-2. The mechanism of benefit is believed to be a reduction of sympathetic tone that limits prolongation of the QT interval both at rest and with activity(27).

Another effective anti-adrenergic therapy is left cardiac sympathetic denervation. This therapy is especially useful when β-blockers are contraindicated or when symptoms have occurred while on adequate β-blocker therapy. It has also been used in infants who have extremely prolonged QT intervals and are at high risk of SCD(23).

Implantable Cardioverter Defibrillator therapy has a limited role in LQTS. Recently, based on the findings in a European LQTS/ICD registry, the indications for ICD therapy have been refined to include: cardiac arrest while on therapy; cardiac arrest while not on therapy (exception: LQT-1); syncope on β-blockers when left cardiac sympathetic denervation is unavailable or declined by the patient; compound heterozygous/homozygous patients with syncope on β-blockers; and, primary prevention in unique phenotypes with extreme QT prolongation and other high risk features(28).

Lifestyle modifications are important for prevention of cardiac events. LQTS patients must be counselled to avoid drugs that prolong the QT interval and to maintain normal magnesium and potassium levels especially during illnesses when electrolyte loss may occur. Sporting activities should be restricted to low intensity, non-competitive sports although this recommendation has been challenged by the identification of only 2 events in 650 athlete-years of follow-up; both events occurring in the same individual when non-adherent to β-blocker therapy(23). Genotype-positive patients with normal QT intervals may participate in competitive sports with the exception of LQT-1 patients with respect to competitive swimming(23).

3) Brugada Syndrome

Brugada syndrome (BrS) is an autosomal dominant genetic cardiac disorder with variable penetrance that manifests with characteristic resting ECG abnormalities associated with VT/VF, SCA, and SCD. The ECG patterns, which predominantly affect the right precordial leads, have been recently classified into two characteristic types: Type I and Type II (Figure 3) (29). The Type I pattern, also termed "coved" type, shows ST segment elevation ≥2mm followed by an upward convexity and abrupt descent to an inverted T wave. The Type II pattern, also termed "saddleback" type, has a lesser degree of ST segment elevation and resolves into an upright or biphasic T wave. When the ECG abnormalities occur in the absence of VT/VF or potential symptoms thereof, the findings are termed Brugada pattern (BrP). Another syndrome, termed Sudden Unexpected Nocturnal Death Syndrome (SUNDS) has been described in Southeast Asians and is believed to have a similar pathophysiology(30).

Epidemiology

The prevalence of BrP on the 12 lead ECG varies with the population studied being most prevalent in Asian populations. In Japan, the BrP is estimated to occur in 0.7-1.0% of the population with 0.12-0.16% having the Type I BrP(31). In population samples from the United States, the prevalence varied widely from 0.012-0.4%(32). The prevalence of BrP in patients who present with unexplained VF is up to 24%. Men are approximately nine times more frequently affected than females. Most commonly, BrS presents in adulthood but childhood presentations have been reported(33).

Genetics/Pathophysiology/Mechanism of SCD

An abnormality of the alpha subunit of the SCN5A sodium channel gene is identified in 18-30% of individuals with BrS that causes a loss of function shortening the action potential duration in affected

myocytes(30). The action potential duration is further shortened by the transient outward I_{to} current resulting in marked heterogeneity of action potential durations both across layers of myocardial cells and within the ventricular epicardium. This electrical substrate predisposes to VT/VF(34). Similar phenotypes have been observed with mutations at other genetic loci including the cardiac L-type ion channel, a locus on chromosome 3p22-25, and in KCNE3 and KCNE2, which leads to a gain of function in the transient outward I_{to} current(35). In addition, other SCN5A mutations have been associated with BrS often in association with other clinical abnormalites including isolated AV conduction defects, congenital LQTS-3, congenital sick sinus syndrome, and familial dilated cardiomyopathy with conduction defects and a susceptibility to AF(35).

Clinical Features and Treatment

BrP is diagnosed by the characteristic ECG features in the absence of symptoms while BrS is defined by the presence of the ECG abnormality associated with unexplained syncope, documented VT/VF (most commonly VF) (30). SCA is the initial presentation in up to one third of patients. Patients may also present with palpitations related to the AF associated with BrS in 10-20% of cases. Nocturnal agonal respirations may be observed and are associated with VT/VF. Events in BrS characteristically occur at night or during periods of rest. BrS-related arrhythmias only rarely occur in association with exercise.

Diagnostic sensitivity for the ECG diagnosis of BrS may be enhanced with the administration of sodium channel blocking agents such as flecainide (2mg/kg over 10 minutes IV or 400 mg po), procainamide (10 mg/kg over 10 minutes IV), ajmaline (1 mg/kg over 5 minutes IV), or pilsicainide (1 mg/kg over 10 minutes IV) (36). Such testing may be used, for example, to elicit a definitive Type I ECG BrP in asymptomatic individuals with a family history of premature SCD and a Type II BrP ECG or in patients with unexplained SCA. Up to 2% of patients undergoing such a drug challenge may have sustained VT/VF that require defibrillation.

The value of electrophysiologic testing for asymptomatic individuals with the BrP (either type I or type II) is controversial. One study of 547 asymptomatic patients with a Type I BrP ECG showed that inducibility of VT/VF was predictive of future arrhythmic events(37). In contrast, in another multinational European registry, inducible VT/VF did not predict future events and the cardiac event rate in asymptomatic Type I BrP patient was only 0.4-0.8% per year(38). Accordingly, many experts recommend a conservative approach

for asymptomatic patients with the BrP rather than recommending invasive electrophysiologic testing for risk stratification.

Treatment

A history of SCA in BrS confers an 11-fold risk of future VT/VF events over long-term follow-up while a history of unexplained syncope confers a 3.4-fold risk when compared to individuals with BrP alone(30). Accordingly, ICD implantation is recommended for secondary prevention of SCD in BrS. Individuals who then have recurrent appropriate ICD shocks are candidates for antiarrhythmic therapy. The most effective agents in this setting are quinidine and amiodarone. Quinidine is believed to exert a specific antiarrhythmic effect in BrS by inhibition of I_{to} current thereby prolonging the action potential and reducing electrical heterogeneity. Amiodarone similarly acts favourably in BrS by prolonging action potential duration(30).

A list of drugs which may precipitate VT/VF in BrS patients appears at www.brugadadrugs.org.

Family Screening:

Because of the autosomal dominant inheritance pattern, first-degree relatives of patients with BrS should be screened with a history and an ECG. No further follow-up is required in asymptomatic individuals with a normal ECG(30). When there is a history of syncope and a Type I BrP is present an ICD is indicated. When there is a history of syncope and the ECG is normal or equivocal, drug challenge testing should be performed followed by ICD implantation if a Type I BrP is elicited. Genetic testing of the proband will identify a known BrS mutation in only 15-30%. Nevertheless, is if a BrS mutation is identified, family screening is simplified(30).

4) Short QT Syndrome

The short QT syndrome (SQTS) is a very rare cardiac channelopathy first described in 2000 by Gussak and colleagues(39). Only approximately 100 cases of SQTS have been reported worldwide. SQTS manifests as a short ECG QT interval and is associated with AF and a predisposition to polymorphic VT and VF and, therefore, to SCD. The QT interval is considered short when the QTc is <330 msec. There are environmental and metabolic factors that may lead to a short QT interval including hyperkalemia, hypercalcemia, hyperthermia,acidosis, high catecholamine states, and the effects of drugs such as digitalis(40). Nevertheless, a short QT interval is rare. Although a study of 46,129 healthy American volunteers showed a prevalence of 2% when a short QT interval was defined as <360 msec, a Japanese cohort

of 114, 334 individuals suggested a prevalence of 0.4%(41, 42). In a Finnish cohort of 10,822 individuals only 0.4% had a QT interval <340 msec while 0.1% had a QT interval <320 msec(43). Multiple international cohorts report that an isolated short QT interval imparts only a low risk of SCD.

Genetics and Pathophysiology

Six genetic subtypes have been described. The genes identified code for components of either potassium or L-type calcium channels(40). The potassium channel mutations lead to a gain of function of the outward potassium channel current that leads to action potential shortening and increased dispersion of repolarization predisposing to both atrial fibrillation and VT/VFs. The calcium channel mutations lead to a loss of function of the affected ion channel has similar electrophysiologic effects.

Clinical Presentation/Diagnostic Criteria

Symptoms of SQTS include SCA (34%), palpitations (31%), syncope (24%) and AF (17%). Up to 38% of individuals are asymptomatic. Symptoms may develop in infancy in a small percentage of patients suggesting that SQTS may be a cause of Sudden Infant Death Syndrome. ECG features include an abnormally short QT interval (<360 msec; range 220-360 msec), absence of an ST segment, tall and peaked T waves in the precordial leads, poor rate adaptation of the QT interval, and prolonged T_{peak}-T_{end} interval and T_{peak}-T_{end}/QT ratio(40).

Diagnostic criteria for SQTS have been proposed (Table 3) (44).

Treatment

Patients who present with symptomatic VT/VF or SCA usually receive an ICD for secondary prevention of SCD. Individuals with an isolated short QT interval should be managed conservatively. Patients with a family history of unexplained SCD and a short QT interval and patients with unexplained syncope and a short QT interval should be considered for an ICD for the primary prevention of sudden death(45). Because large T waves are associated with SQTS, patients with ICDs in this condition have a high prevalence of T-wave oversensing which may lead to inappropriate shocks. Programming a decay delay function or lower ventricular lead sensitivity may alleviate this issue.

Individuals must be counselled regarding environmental and metabolic conditions known to further shorten QT interval (listed above). For patients who have appropriate shocks related to VT/VF, quinidine is

the first line antiarrhythmic drug treatment(45). Quinidine acts through its effect on multiple ion channels, including I_{to}, to increase action potential duration and reduces dispersion of repolarization. Disopyramide and amiodarone may act via a similar mechanism.

Family Screening:

Because of the rarity of SQTS, formal guidelines for family screening have not been developed. However, it is recommended that first-degree relatives of the proband undergo a history and ECG as an initial step. The SQTS diagnostic criteria score would then be applied to each relative to determine risk stratification and management(44).

5) Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare genetic condition characterized by exercise or emotional stress-induced polymorphic VT that occurs in the absence of structural heart disase or an abnormal QT interval(46). CPVT usually presents in childhood. Classically, the polymorphic VT of CPVT is bidirectional with alternating positive and negative QRS complexes as may also be seen with digitalis toxicity (Figure 4) (47, 48).

Genetics/Pathophysiology

Two different genetic substrates have been identified, one in the cardiac ryanodine receptor and also in its associated calsequestrin receptor. These entities control the release of calcium from the sarcoplasmic reticulum(46, 47). In CPVT, hyperadrenergic states produce excessive calcium release from the sarcoplasmic reticulum during diastole leading to early afterdepolarizations and PMVT.

Clinical Features/Diagnostic Testing

CPVT patients present with syncope, PMVT, or VF that is associated with exercise or emotional stress. Events associated with swimming have been described. The ECG at rest is normal. The PMVT may be of two types – bidirectional VT or polymorphic VT with a constantly changing QRS morphology. Electrophysiologic testing is not useful for diagnosis as CPVT is usually non-inducible(47).

Treatment

CPVT patients should not participate in competitive sports as an adrenergic surge is the trigger for polymorphic VT. Patients with stress-induced VT are treated with a β-blocker(49). β-blocker therapy is also recommended for asymptomatic CPVT patients diagnosed in childhood. In the largest reported series, 101 patients with CPVT were

followed for a mean of 7.9 years. β-blockers were prescribed to 81 patients (80%) at diagnosis. For those receiving β-blockers, the event rate (syncope, cardiac arrest, appropriate ICD shocks, or SCD) was 27% compared to 58% for those not receiving β-blockers(50). A meta-analysis of 403 CPVT patients of whom 88% were prescribed a β-blocker suggested an event rate (syncope, SCA, SCD) of 18.6% and 37.2% after 4 and 8 years follow-up, respectively.

For CPVT patients who have events on β-blockers therapy, the addition of verapamil therapy or flecainide therapy may be beneficial(51). Finally, small studies have suggested that left cardiac stellate denervation may provide a benefit when added to β-blocker therapy in this setting(52).

For CPVT patients who present with SCA, ICD implantation is indicated for secondary prevention of SCD(30). Counselling of the patient and family is required prior to ICD placement since even appropriate ICD shocks may lead to VT storm related to the associated adrenergic surge. In addition, since CPVT patients are usually young, life-long ICD therapy subjects the patient to multiple device procedures and their potential complications. ICDs have been shown to be effective in CPVT patients in small observational studies. In one such study, 24 CPVT patients who had an ICD implanted (mean age 13.7 years) were followed for a median of 3.3 years. Fourteen patients (58%) received a total of 140 shocks of which 54% were felt to be appropriate(53).

6) Early Repolarization Syndrome and Idiopathic VF

Early repolarization (ER) is defined as J-point elevation of ≥0.1mV in two contiguous ECG leads. ER is common in the general population with a prevalence ranging from 5-13% and has been considered to be a benign finding(54). More recently, ER has been associated with idiopathic VF(55). However, the incidence of idiopathic VF is very low: estimated at 10 per 100,000 population. Isolated ER on a 12-lead ECG increases the risk of SCD (HR 1.70; 95%CI 1.19-2.42) but the absolute risk is very low (70 per 100,000 person-years) (54). Nevertheless, in patients with idiopathic VF who are found to have diagnostic J waves, the VF is ascribed to the Early Repolarization Syndrome.

Genetics/Pathophysiology

The genetic basis of the ER syndrome has not been clearly elucidated. One mutation involving the KCNJ8 gene that results in a gain of function of the ATP-sensitive potassium channel, Kir6.1, has been implicated (56). Other mutations involve genes associated with loss of function of the L-type calcium channel current(57). One case of a

mutation in SCN5A leading to loss of function through reduction in sodium current density has been reported(58).

The basic mechanism of ER-related VF is still unknown but is believed related to an abnormal imbalance in ion channel currents responsible for the terminal portion of depolarization and the early portion of repolarization.

Diagnostic Criteria/Clinical Features

In the Heart Rhythm Society/European Heart Rhythm Society consensus statement on inherited primary arrhythmic syndromes, diagnostic criteria for both ER and ER syndrome have been proposed (Table 4) (30). No specific investigation or treatment is required for in patients with isolated ER on their ECG. ER syndrome patients rarely present with syncope and syncope is no more common in ER pattern patients than in the general population. ER syndrome is most commonly considered present in a survivor of SCA secondary to idiopathic VF in the presence of an ECG ER pattern and in the absence of structural heart disease or another cause for VF after a complete diagnostic evaluation. Because J-waves may be transient a complete review of all available ECGs is warranted, J-waves are often most evident just prior to VF onset, during bradycardia, and during other periods of high vagal tone. Arrhythmia events associated with ER syndrome typically occur at rest or during sleep(54).

Treatment

Because of the usual benign nature of the incidental finding of the ER pattern on an ECG, no treatment is required. For survivors of SCA in the setting of ER syndrome the rate of recurrence is high (22-37% at 2-4 years). Current consensus guidelines recommend ICD therapy for these patients(30).

When ER syndrome patients have acutely recurrent VF the treatment of choice is intravenous isoproterenol(59). In one study intravenous isoproterenol was effective for suppression of recurrent VF electrical storm in 7 out of 7 patients(60). For chronic therapy of recurrent VF in ER syndrome quinidine and other Vaughn Williams Class Ia drugs may be beneficial.

7) Commotio Cordis

Commotio cordis (Latin for "agitation of the heart") is defined as the relatively mild chest wall impact leading to VF and SCA. It is one of the more common causes of SCD in athletes(61). SCD following chest trauma has been described since the 1700s but the exact

incidence is unknown(62). A National Commotio Cordis Registry was established in the United States in the 1990s permitting data collection on over 200 confirmed cases(61). Commotio cordis occurs predominantly at young males (mean age 15 years; 75% male) with only 9% of cases occurring in people over 25 years old. Three quarters of the cases have occurred during a sporting event. Blunt projectiles (baseball, lacrosse ball, hockey puck) are most commonly involved but physical contact (football, hockey) has also been implicated. Outside the U.S., soccer may be the most common sport associated with commotio cordis(63). Although initially considered to carry a very high mortality rate, recent data suggests that survival of commotio cordis occurs in up to 58% of cases(63, 64). Improved survival may reflect early recognition of the event, activation of emergency medical services, effective early bystander CPR, and early defibrillation.

Mechanism of VF

The mechanism of VF induction during chest wall impact is influenced by several factors in experimental models. The most critical element is the timing of impact on the chest wall. Only direct impact during a 20-40 msec window on the upslope of the T wave leads to VF(65). In addition, only impact that occurs directly on the chest wall over the cardiac silhouette leads to VF. The projectile velocity is also important. As velocity increases to up to 40 miles per hour the incidence of VF increases. At impact velocities greater than 40 miles per hour the likelihood of VF decreases. Harder objects are more likely to cause VF. Flat objects have not been implicated in VF induction while smaller diameter spheres are more likely to induce VF. Following the critically-timed impact, there is activation of the ATP-sensitive potassium channel which leads to dispersion of ventricular repolarization and VF(66).

Prevention

Coaching and protective equipment are key aspects in prevention of commotio cordis. Athletes should be coached to turn away from oncoming projectiles to avoid chest wall contact. Softer balls may be used for young children(67). Chest wall protectors have not been demonstrated to provide significant protection from commotio cordis(68).

ii) Bradycardias

Bradyarrhythmias are usually due to sinus node dysfunction or atrioventricular (AV) block. Sinus node dysfunction or sick sinus syndrome encompasses persistent sinus bradycardia, sinus pauses, sinoatrial exit block, chronotropic incompetence, and tachycardia-

bradycardia syndrome(69). Sinus node dysfunction can present with fatigue, exertional intolerance, syncope, or other symptoms due to hypoperfusion. It is very rare for sinus node dysfunction to result in sudden death unless the bradycardia precipitates a long QT interval-related torsades de pointes VT in a susceptible individual. Sinus node dysfunction may be the initial manifestation of diffuse conduction system disease with an annual incidence of progression from sinus node dysfunction to complete AV block of 0.6%(70).

Patients with AV block may present with the same symptoms as mentioned for sinus node dysfunction. Mobitz Type II second degree block and acquired complete AV block have a poor prognosis with one year mortality rates of 30-50%(69).

When no reversible causes for a bradyarrhythmia can be identified, the only long-term treatment option is a permanent pacemaker. For those patients with irreversible LV dysfunction and CHF frequent RV pacing may lead to interventricular dys-synchrony and biventricular pacing may then be preferred(71). In addition, in patients with severe LV dysfunction that is not expected to improve the pacing platform may need to be an ICD.

b) Structural Heart Disease

i) Coronary Artery Disease and Ischemic Cardiomyopathy

Coronary artery disease (CAD) with its associated ischemic cardiomyopathy is a major cause of SCD. VF and polymorphic VT may be due to acute ischemia or infarction. In this setting, revascularization can decrease VT/VF and improve survival(1). β-blockers and correction of electrolytes may also reduce VT/VF in the context of an acute ischemia. VF that occurs during or within 48 hours of an acute coronary syndrome is associated with increased in-hospital mortality but not subsequent long-term mortality(1). Accordingly, acute phase polymorphic VT or VF are not indications for an ICD.

Mechanism of SCD

SCD remote from prior myocardial infarction is most often due to VT/VF from the myocardial scar with or without modulation by ongoing myocardial ischemic episodes. The scar can be an anatomic substrate initiating ventricular tachycardia that can degenerate into ventricular fibrillation and then asystole or pulseless electrical activity(1).

Prevention

Many studies have substantiated the beneficial effects of β-blockers for the prevention of VT/VF and SCD in patients with CAD, prior myocardial infarction, systolic LV dysfunction, and CHF(1). Other antiarrhythmic medications have not shown a clear benefit. Indeed, Vaughn Williams Class I antiarrhythmic agents increased mortality in post-MI patients in the Cardiac Arrhythmia Suppression Trials(17). Sotalol, a β-blocker with Class III antiarrhythmic activity has not been shown to prevent SCD but neither has it been shown to increase SCD. The latter observation is responsible, in part, for its preferential use for the prevention of recurrent VT/VF episodes in patients with ICDs(1). Amiodarone has been studied in post-MI populations and although there is a reduction in VT/VF and in SCD this did not translate into a clear reduction in all-cause mortality(72).

The renin-angiotensin-aldosterone system (RAAS) can exert adverse effects on the cardiovascular system through multiple mechanisms. Angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), and aldosterone antagonists are the main drugs that are used to modulate the RAAS system. ACE-I have been studied in patients at risk of cardiovascular disease as well as in patients with prior myocardial infarction and CHF(1). These studies have shown that ACE-I therapy is associated with a decrease is SCD and in all-cause mortality. ARBs have similar effects on mortality and should be used in this setting when ACE-I cannot be tolerated. Aldosterone antagonists have also been shown to reduce SCD and all-cause mortality in the post-MI population with CHF(1). Finally, HMG-CoA reductase inhibitors (statins) not only reduce lipid levels but also have pleomorphic effects that are associated with reductions in SCD and all-cause mortality(1).

In the 1990's, the ICD emerged as a viable alternative for the prevention of SCD. Randomized trials of ICD therapy were first accomplished in patients who had survived a cardiac arrest or had experienced life-threatening VT/VF (secondary prevention of SCD). These studies included the Antiarrhythmics Versus Implantable Defibrillators(AVID)Trial, the Canadian Implantable Defibrillator Study (CIDS), and the Cardiac Arrest Study Hamburg (CASH)(72). These studies randomized patients to treatment with either an antiarrhythmic drug (usually amiodarone, rarely sotalol or propafenone) or to implantation of an ICD. A meta-analysis of these studies found that

ICD therapy was associated with a reduction in arrhythmic death of 50% and an all-cause mortality reduction of 28%(72). ICD therapy benefits were independent of β-blockers use, structural heart disease, or surgical revascularization.

Subsequently, randomized clinical trials also evaluated the ICD for prevention or SCD and all-cause mortality in patients who had not experienced VT/VF or SCA but who were deemed to be at risk for doing so (primary prevention of SCD)(Table 5). The Multicenter Automatic Defibrillator Implantation Trial (MADIT-I) randomized patients with CAD, nonsustained VT, LVEF <35%, and inducible VT that was not suppressible with procainamide to receive or not to receive an ICD in addition to standard medical therapy. ICD therapy was associated with a 54% relative reduction in all-cause mortality(73). The Multicenter Unsustained Tachycardia Trial(MUSTT)enrolled patients with prior MI, LVEF <40%, and spontaneous unsustained VT(74). Patients with inducible VT were randomly assigned to receive antiarrhythmic therapy or no antiarrhythmic therapy and those without inducible VT were followed in a registry. Patients in the antiarrhythmic therapy group underwent serial electropharmacologic testing and those who failed at least one antiarrhythmic drug could then receive an ICD. The five-year all-cause mortality rate was 24% for those who received an ICD, 55% for those treated with antiarrhythmic drugs, and 48% for those randomized to no antiarrhythmic therapy. The antiarrhythmic drugs used in MUSTT included Class I agents, sotalol, and amiodarone and although not statistically-significant, their use seemed to be be associated with a higher all-cause mortality(74).

The five-year all-cause mortality rates of patients with inducible VT and of patients without inducible VT were similar (48% and 44%, respectively) suggesting that patients without inducible VT may also benefit from a primary prevention ICD. Accordingly, the MADIT-II study randomized patients with prior MI and LVEF <30% regardless of inducibility status to receive or not to receive an ICD in addition to standard care(75). ICD therapy was associated with a 14.2% mortality rate compared to 19.8% in the standard care group after an average follow up of 20 months. In these patients, the mortality rate remained substantial for up to 15 years after MI. The Sudden Cardiac Death-CHF Trial (SCD-HeFT) included ischemic and non-ischemic cardiomyopathy patients with CHF and LVEF <35%(76). Patients were randomized to placebo, amiodarone, or ICD treatment groups. Patients randomized to receive an ICD had a 7% absolute reduction in the risk of mortality compared to placebo. Patients randomized to receive amiodarone had a similar mortality rate to those randomized to receive placebo.

Two major ICD trials did not show benefit from ICD therapy in patients with CAD. The Coronary Artery Bypass Graft Patch (CABG-Patch) Trial randomized patients undergoing CABG with LVEF <35% and abnormal signal-averaged ECG to receive or not to receive an ICD in addition to standard care(77). No mortality benefit was seen in the ICD group in the CABG-Patch Trial an observation that has been variable ascribed to the benefits of revascularization overall, to the use of a thoracotomy ICD system, and to the limited value of SAECG in selecting high-risk patients. The Defibrillators in Acute Myocardial Infarction Trial (DINAMIT) randomized patients with a recent MI (6 – 40 days), LVEF <35%, and impaired cardiac autonomic function (low heart rate variability or high 24-hour resting heart rate) to receive or to not receive an ICD in addition to standard care(78). No mortality benefit was seen in the ICD group an observation variable ascribed to competing modes of death due to CHF or recurrent ischemic events early after MI and to the inability of impaired heart rate variability to select patients at risk of SCD in comparison to patients at risk of pump failure death(78). Notably, these two negative ICD trials enrolled patients at an unstable point in the natural history of their CAD – at the point of CABG or just after an acute MI. These trials have affected ICD therapy guidelines. Accordingly, ICD therapy is not recommended either early after an MI or early after revascularization(79).

Thus, in patients with stable CAD, prior MI, reduced LVEF, and symptomatic CHF, ICD therapy is effective at both primary and secondary prevention of SCD. There is now also evidence that biventricular pacing /cardiac resynchronization therapy (CRT) provides a mortality benefit in appropriately selected patients(79).

ii) Non-Ischemic Cardiomyopathy

Non-ischemic cardiomyopathies (NICM) are a diverse group of cardiac conditions that represent both genetic and acquired disorders. By definition, the associated left ventricular systolic function is not the result of CAD, valvular, or hypertensive heart disease. Approximately 35% are familial in origin; the acquired forms secondary to infection, toxins, autoimmune, neuromuscular, and nutritional disorders(80). In up to 50% of cases, there is no identifiable etiology and is therefore termed idiopathic. NICM is much less common than ICM with an estimated annual incidence of 5-8 per 100,000 population. The overall prevalence of NICM is estimated at 36-40 per 100,000. In general, patients with NICM are younger, have a better overall prognosis, and benefit less from ICD therapy when compared to patients with ischemic cardiomyopathy(80).

Nevertheless, NICM is the second leading cause of LV systolic dysfunction and imparts a 12-20% mortality at 3 years(81). A meta-analysis of ICD trials in this setting showed that there was a 31% reduction in all-cause mortality with ICD therapy(82). This suggests that VT/VF represent a significant contributor to all-cause mortality in NICM.

Mechanism of SCD

In contrast to ischemic cardiomyopathy, the pathophysiology of arrhythmias that lead to SCD in NICM is less well understood. Arrhythmia mechanisms in this setting are multifactorial and include structural changes such as scar formation/fibrosis, ventricular dilatation, and electrophysiological changes that result in VT/VFs due to reentry, abnormal automaticity, and triggered activity(81). Similar to ischemic cardiomyopathy the substrate for monomorphic VT is likely scar that facilitates a reentry mechanism. Recent cardiac magnetic resonance imaging and electrophysiologic data has correlated the extent of myocardial fibrosis in NICM with adverse outcomes including appropriate ICD therapy(83).

Risk Stratification

Risk stratification for SCD in NICM is important to best define those likely to benefit from ICD therapy. Current clinical risk stratification tools including NYHA functional class and LVEF are insensitive and nonspecific. Accordingly, many NICM patients at high risk for SCD do not receive an ICD and conversely many patients selected for ICD therapy do not receive an appropriate ICD therapy in follow-up. A recent meta-analysis of 45 studies involving 6088 NICM patients (mean age 52.8 ± 14.5 years; mean LVEF 30.6±11.4%) evaluated risk predictors for SCD in NICM(81). Arrhythmic outcomes were evaluated over a mean follow-up period of 33.6±19.9 months. The most robust predictor of arrhythmic outcomes was the presence of a fragmented QRS complex (OR 6.73; 95% CI 3.85-11.76) followed by the presence of microvolt T wave alternans (OR 4.66; 95% CI 2.55-8.53). Other predictors had lower ORs including signal-averaged ECG, electrophysiological study, and non-sustained VT. Functional measures including LVEF and left ventricular end diastolic dimension were weaker predictors of arrhythmic outcomes (OR 2.87; 95% CI 2.09-3.95 and OR 3.47; 95% CI 1.90-6.35; respectively(81). Interestingly, measures of autonomic function including heart rate variability, heart rate turbulence, and baroreceptor sensitivity were not predictive of arrhythmic outcomes in this population(81).

Measures of myocardial fibrosis including cMRI-determined late gadolinium enhancement are also important prognostic determinants in NICM. A prospective study of 472 patients with NICM evaluated mid-wall fibrosis on cMRI as a predictor of all-cause mortality and a composite of SCD or SCA(84). Over a median follow-up of 5.3 years, mid-wall fibrosis was associated with an absolute increase in all-cause mortality by 16.2% compared to those without mid-wall fibrosis (HR 2.96; 95% CI 1.87-4.69). Mid-wall fibrosis was also associated with an increase in the absolute risk of the composite arrhythmia outcome by 22.6% (HR 5.24; 95% CI 3.15-8.72. These findings remained significant after adjustment for LVEF and other known prognostic factors(84). Similar findings have been observed in other studies.

Primary and secondary prevention of SCD

The only Vaughn Williams antiarrhythmic drug class shown to prevent SCD in NICM are β-blockers(85, 86). Nevertheless, in patients with LVEF ≤35% ICDs have been shown superior to optimal medical therapy(76).

Early, small clinical trials of ICD therapy for primary prevention of SCD in NICM did not show a benefit. The Cardiomyopathy Trial (CAT) randomized 104 patients with NICM and LVEF ≤30% to receive or not to receive an ICD in addition to standard care(87). There was no significant difference in all-cause mortality after 2 or 4 years of follow-up. The Amiodarone Versus Implantable Cardioverter-Defibrillator (AMIOVIRT) trial enrolled 103 patient with NICM, LVEF ≤35%, NYHA Class I-III symptoms, and nonsustained VT(88). Amiodarone therapy was compared to ICD therapy (individuals were often also amiodarone-treated). There was no difference in all-cause mortality on follow-up. In contrast, the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial enrolled 458 patients with NICM, LVEF ≤35%, and non-sustained VT to receive or not to receive an ICD in addition to standard care(89). DEFINITE reported a trend to reduction of all-cause mortality in the ICD group (7.9% versus 14.1%; HR 0.65; 95% CI 0.40-1.06). A DEFINITE subgroup analysis of NYHA Class III patients showed a significant benefit (HR 0.37; 95% CI0.15-0.9)) (89).

The largest trial of primary prevention ICD therapy in NICM was the Sudden Cardiac Death in Heart Failure (SCD-HeFT) trial that randomized 2521 patients (52% ICM 48% NICM) with a LVEF ≤35% and NYHA Class II-III CHF symptoms to receive placebo, amiodarone, or an ICD in addition to optimal CHF care(76). The principal finding was a significant reduction in all-cause mortality in the ICD arm versus placebo (HR 0.77; 95% CI 0.62-0.96). There was no difference between

amiodarone and placebo. Importantly, there were no differences in ICD mortality benefit between ICM and NICM patient populations. Interestingly, subgroup analysis of NYHA Class III patients showed no mortality benefit from ICD therapy (HR 1.16). The significance of this finding is not clear and is in contrast to the subgroup analysis in DEFINITE that showed benefit only in Class III patients. In SCD-HeFT, another subgroup analysis did not show a mortality benefit from ICD therapy in patients with LVEF >30%(76). The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial randomized 1520 patients in a with advanced heart failure and a QRS duration >120 msec to receive either medical therapy alone, medical therapy with a cardiac resynchronization therapy (CRT) pacemaker, or medical therapy with a CRT defibrillator(90). A total of 903 patients were randomized to the medical therapy versus the CRT defibrillator comparison and 397 patients (44%) in this comparison had NICM. CRT therapy with a defibrillator reduced all-cause mortality compared to optimal medical therapy in patients with NICM (HR 0.50; 95% CI 0.29-0.88; p=0.015).

Current guidelines for primary prevention of SCD in NICM patients recommend implantation of an ICD in patients with Class II-III heart failure symptoms and an LVEF ≤35% after optimal medical therapy for 6-9 months(91).

With respect to secondary prevention of SCD, patients with NICM and prior VT/VF are at high risk of recurrence and ICD therapy has been shown to reduce the risk SCD compared to amiodarone in this setting(72).

iii) Congenital Heart Disease

Congenital heart disease (CHD) occurs in 0.8% of live births and up to half of those may require surgical intervention(92). Advances in diagnostic imaging and in corrective surgical repairs have improved survival such that patients born with CHD commonly live to be adults. Nevertheless, SCD is still a problem in this population. The major cause of SCD in patients with CHD is VT/VF. For example, in repaired tetralogy of Fallot the prevalence of VT/VF is 3-14% and the incidence of SCD is 2-5% per decade. Bradycardias and atrial tachyarrhythmias are rare causes of SCD in patients with CHD(92, 93).

CHD patients at greatest risk for VT/VF include those that have had repairs involving ventriculotomy and/or a ventricular patch. The surgical scar may provide the substrate for macro-reentrant VT circuits(94). VT/VF may also occur in patients without discrete surgical scars due to ventricular systolic dysfunction or hypertrophy.

Nevertheless, it is not clear if LV systolic dysfunction predictors of SCD developed in patients with ICM or NICM are useful in identifying high-risk patients with CHD. Nevertheless, CHD patients with a systemic ventricular EF <35% and Class II-III heart failure symptoms are generally considered for a primary prevention ICD(93). Similarly, patients with syncope of unclear origin and systemic ventricular dysfunction or inducible VT/VF may also be considered for an ICD(93). In repaired tetralogy of Fallot patients, increased QRS duration, nonsustained VT, palliative shunt surgery, ventriculotomy incision, older age at surgery, and inducible VT/VF may all be risk factors for SCD(92, 93). ICD implantation in patients with CHD often presents technical challenges due to anatomical issues and non-traditional vascular access routes, epicardial systems, and subcutaneous ICD systems may need to be considered. Management of concomitant hemodynamic concerns also complicates ICD implantation procedures. Accordingly, such patients should have their ICDs implanted and managed in centers with experience in CHD.

In general, CHD patients presenting with symptomatic sustained VT/VF or SCA will benefit from an ICD (secondary prevention of SCD) and have been reported to have a high rate of appropriate shocks on follow-up(93). In a small subset of such patients, particularly those without significant hemodynamic concerns, who present with a single, stable, slow VT, catheter ablation may considered as primary therapy. However, the usual status of ablation in such patients is to reduce (rather than eliminate) the frequency of VT/VF in patients with an ICD(92).

As in other settings, optimal treatment of the underlying structural heart disease is a cornerstone in SCD prevention.

Patients with anomalous origin of the coronary arteries are found in approximately 1% of angiography studies. Mechanisms for SCD include acute ostial angulation, an abnormal slit-like opening, vasospasm, and mechanical compression of anomalous coronary arteries that cross between the aorta and pulmonary artery during exercise(95). Diagnosis of an anomalous coronary artery leads to consideration of surgical intervention especially in patients whose left coronary artery arises from the right coronary cusp as such patients are at higher risk of SCD. However, in asymptomatic patients with the right coronary artery arising from the left coronary cusp and no evidence of ischemia or arrhythmias with exercise, the risk of SCD appears to be low and prophylactic surgery is usually not recommended(95).

iii) Valvular Heart Disease and Sudden Cardiac Death

Patients with valvular heart disease (VHD) are at risk of both brady- and tachy-arrhythmias that may lead to SCD. Such patients should be managed according to the current clinical guidelines for both the valve lesion and arrhythmia propensity in question(1, 96).

The mechanism of SCD in VHD is similar to that of other cardiac diseases. Arrhythmias arise from secondary effects of VHD on the myocardium including chamber dilatation, hypertrophy, systolic dysfunction, and scarring. In addition, may VHD patients also have CAD(1). Most of the data regarding SCD in patients with VHD arises from knowledge about aortic valve disease. Although the overall risk of SCD is low, aortic stenosis carries one of the highest known risks of SCD of all valve lesions at 0.4% per year. In patients with aortic regurgitation, the SCD risk is less than 0.2% and is similar to that of patients with mitral valve disease 0.2%(1).

The association of myxomatous mitral valve prolapse (MVP) with SCD is controversial but is supported by observational data. A Mayo Clinic series evaluated 24 patients who survived unexplained out-of-hospital SCA(97). Detailed investigation identified MVP as the only potentially-causative abnormality in 42% of these patients. These patients were more likely to have T wave abnormalities and complex ventricular ectopy when compared to the other patients in the series without MVP. Over a mean follow-up of 1.8 years, 54% of the cohort had appropriate shocks for VT/VF. Only bileaflet MVP was associated with recurrent VT/VF in this cohort (OR 7.2; 95% CI 1.1-48; p=0.028) (97). The incidence of SCD in people with MVP without mitral regurgitation has been estimated at 1.9 per 10,000 patient-years. However, when significant mitral regurgitation is present, this risk is 50-100 times higher (0.9%-1.9% per year) (98, 99). Other reports that included MVP with a wide range of MR severity estimated the risk of SCD somewhat lower at 0.2%-0.4% per year. When MVP is associated with significant leaflet redundancy (leaflet thickness ≥5mm the SCD risk increases to 1.6% per year compared to 0.1% per year in those without redundant leaflets. The presence of a flail mitral leaflet is also associated with a higher risk of SCD. The sudden death rates in 348 patients with a flail mitral leaflet at 5 and 10 years were 8.6±2.0% and 18.8±4.0%, respectively(100). Despite these risk estimates, current guidelines do not recommend a specific risk-stratification protocol for patients with MVP.

v) Hypertrophic Cardiomyopathy and Sudden Cardiac Death

Hypertrophic Cardiomyopathy (HCM) is an autosomal-dominant genetic cardiac disease with variable penetrance and a prevalence of approximately 1/500 of the general population(101). Fourteen hundred

mutations in at least 11 genes that code for elements of the cardiac sarcomere contractile apparatus have been implicated. However, 70% of genotype positive individuals have mutations in either the β-myosin heavy chain or myosin-binding protein C(101). The vast majority of individuals with HCM are asymptomatic or have minimal symptoms and have a normal lifespan. However, a subset of individuals with HCM are highly symptomatic with dyspnea, palpitations, exercise intolerance, presyncope, and syncope. In some, important manifestations of their disease include sustained VT/VF and SCD(101). HCM has achieved a public profile because it is the most common cause of SCD in young individuals, particularly in young atheletes.

Pathophysiology and Mechanisms of SCD

HCM is characterized by the presence of myocyte disarray, myocardial hypertrophy, and intramyocardial scar. These factors, in association with local myocardial ischemia and autonomic dysfunction contribute to the pathophysiology of VT/VF in HCM(102). Cardiac MRI in patients with HCM demonstrates the presence of fibrosis by late gadolinium enhancement and supports the presence of an arrhythmic substrate. In one study of 177 HCM patients both ventricular premature beats and non-sustained VT were significantly more common in patients with late gadolinium enhancement compared to those without that finding (89% vs. 72% for VPBs; 28% versus 4% for NSVT) suggesting that this tool may identify a HCM population at increased risk for VT/VF(103).

Prevalence of Ventricular Arrhythmias and SCD

Ventricular arrhythmias are frequent in patients with HCM (VPBs in >80% and NSVT in approximately 30%)(104). The presence of NSVT is associated with greater degrees of LVH and the presence of severe HF symptoms. The overall rate of SCD in all HCM patients is approximately 1% per year. NSVT in HCM is more common with increasing age and is a predictor of SCD risk especially in younger patients(104). One study of 531 HCM patients of mean age 39 years with a prevalence of Holter-documented NSVT of 19.6% was followed for 70 months(105). In patients under 30 years of age, the five-year probability of SCD was higher in patients with NSVT compared to those without(22.4% vs. 5.9%; p=0.003). No significant relationship between NSVT and SCD was evident in patients over 30 years of age. Documented sustained VT in the pre-ICD era was relatively rare. Although sustained VT is uncommonly demonstrated on diagnostic Holter monitoring, ICD monitoring has clearly shown VT/VF to be the mechanism of aborted SCD events. The overall rate of appropriate ICD discharge in HCM patients with an ICD is approximately 7% per year. In those

who had their ICD implanted for a prior SCA, the rate of appropriate discharge is approximately 11% per year while in primary prevention patients the corresponding rate is 5% per year(106).

Risk Stratification for SCD

The majority of individuals with HCM are at relatively low risk for SCD with an overall incidence of approximately 1% per year. The advent of the ICD and its success in aborting life-threatening VT/VF has increased the importance of identifying high-risk HCM individuals. Accordingly, patients diagnosed with HCM should undergo risk stratification for SCD to assess their candidacy for ICD therapy. Guidelines have summarized the known major risk factors for SCD (Table 6) (106).

As in other settings, the most potent risk factor for SCD in patients with HCM is prior sustained VT or cardiac arrest. A pre-ICD era study of 33 HCM patients who had survived a SCA event evaluated the risk of recurrent SCA after medical therapy and, in select cases, after septal myectomy(107). The survival rates free of either recurrent SCA or death at one, five, and ten years were 83%, 65%, and 53%, respectively. ICD-era studies of patients with prior SCA and ICDs estimate the risk of subsequent appropriate ICD therapy at approximately 10-11% per year. However, individual HCM patients may have decades-long arrhythmia-free intervals after surviving SCA(108). Such observations emphasize the unpredictability of the arrhythmic substrate in HCM.

A family history of SCD in a patient with HCM is a significant risk predictor especially if SCD events occur in multiple and/or younger family members(106). In patients with HCM, the prevalence of a family history of SCD in at least one first degree relative is approximately 25%.

Syncope not attributable to a neurocardiogenic mechanism is also a risk factor for SCD in patients with HCM(109). This risk factor is especially important if the syncope is recurrent or exercise-related(106).

As noted above, NSVT (defined as ≥3 beats at 120/minute) is associated with increased risk of SCD. This risk is especially important in younger patients and in those with symptomatic HCM(106).

An abnormal blood pressure response to exercise (failure to increase systolic blood pressure from baseline by at least 20 mmHg during peak

exercise or a decrease in systolic blood pressure by 20 mmHg or greater during exercise or recovery) has been identified, in some studies, as a predictor of SCD in HCM patients(110, 111). One prospective study of 161 consecutive patients with HCM identified 37% of cohort with an abnormal blood pressure response to exercise. During a mean follow-up of 44 months, SCD occurred in 15% of individuals with an abnormal blood pressure response compared to 3% in those with a normal blood pressure response ($p<0.009$). Another study suggested that an abnormal blood pressure response in patients ≤50 years old was associated with a 4.5 fold increased risk for cardiovascular mortality compared to those with a normal blood pressure response. In each of these studies, the positive predictive value for SCD was low (approximately 15%) while the negative predictive value was relatively high (approximately 95%)(110, 111). Accordingly, the finding of an abnormal blood pressure response to exercise requires integration with other known risk factors.

Massive left ventricular hypertrophy, defined as a wall thickness ≥30 mm, is another major risk marker for SCD in patients with HCM(112, 113). Massive LVH is present in approximately 10% of patients with HCM and is a stronger risk predictor in patients under 30 years of age. In one study of 480 consecutive patients with HCM, the actuarial probability of SCD in patients with LV wall thickness ≥30mm was close to 40% while the SCD risk was negligible risk in patients with LV wall thickness ≤19mm. It appears that the contribution of LV wall thickness to the risk of SCD is best in combination with other risk factors. It has been suggested that in patients <30 years of age the predominant risk of massive LVH is SCD while patients ≥60 years of age the LVH risk was related to progressive heart failure(114).

Other potential but less well-defined SCD risk factors in patients with HCM include younger age at diagnosis, the presence of a significant left ventricular outflow tract gradient, diastolic dysfunction, myocardial ischemia, late gadolinium enhancement on cMRI, and genotype(106).

The presence of multiple major risk factors as defined above has been shown to significantly escalate the risk of SCD in HCM(106).

Indications for ICD implantation/Prevention of SCD

Current guidelines for prevention of SCD in patients with HCM recommend placement of an ICD for secondary prevention of SCD in patients with prior sustained VT/VF or SCA and/or primary prevention of SCD in patients with one or more major risk factors for SCD (Table

6). An approach to the selection of HCM patients for ICD therapy is presented in Figure 5(106).

Registry data suggests that the annual rate of appropriate ICD therapy in HCM patients who received an ICD for a secondary prevention of SCD is approximately 10-11% while the corresponding rate for those who received an ICD for primary prevention of SCD is 4-5%(115).

At present, there is no evidence that therapy with β-blockers or antiarrhythmic drugs such as amiodarone are effective for prevention of SCD in high-risk patients with HCM(116). However, such therapy is often required in patients with frequently recurrent VT/VF leading to ICD therapy. There is some evidence that septal myectomy (but not septal ablation) performed to reduce symptomatic left ventricular outflow tract obstruction in patients with HCM also reduces the risk of SCD and appropriate ICD therapy(117). Physical activity restriction is an important component of SCD prevention in patients with HCM. All elite or competitive athletes with HCM, regardless of the presence of risk markers, should be counselled not to participate in competitive sporting activity except those of low intensity such as billiards, riflery, golf, and bowling(118). Recreational athletics should be limited to low to moderate intensity activities such as biking, doubles tennis, swimming laps, golf, and skating. These recommendations apply equally to those HCM patients with and without an ICD.

vi) Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is an inherited disorder that can cause heart failure, VT/VF, and SCD(119). It was initially referred to as Arrhythmogenic Right Ventricular Dysplasia but, due to the ambiguous nature of the word “dysplasia”, “cardiomyopathy” is now preferred. It has also been suggested that “right” be dropped as the left ventricle may also be involved but this has not yet been widely adopted(119). The prevalence of ARVC in the general population ranges from 1 in 2000 to 1 in 5000 with men being affected three times more often than women(120). ARVC is most commonly inherited as an autosomal dominant disorder with variable penetrance and expression. Loss of electrical coupling between cardiac myocytes results from dysfunctional desmosomes caused by defective cell adhesion proteins, such as plakoglobin, desmoplakin, plakophilin, and desmoglein(120). Rarely autosomal-recessive inheritance is seen, as in Naxos disease, which has associated wooly hair and palmoplantarar keratoderma due to a junctional plakoglobin mutation. The coupling disturbances can lead to death of myocytes and fibrofatty changes enabling a substrate for arrhythmias(119, 120).

Patients with ARVC may present with symptoms due to premature ventricular contraction or VT including palpitations, pre-syncope, syncope, or SCA(121). Others are asymptomatic but have had ventricular arrhythmias discovered incidentally. Since the arrhythmias originate from the right ventricle they usually have left bundle branch block morphology with a superior axis. Left bundle branch block morphology VTs with an inferior axis are more common in patients with idiopathic right ventricular outflow tract VT which has a good prognosis but is diagnosis of exclusion after structural heart disease has been ruled out. On occasion, the VT in ARVC can be very fast, 200 – 250bpm, without significant hemodynamic instability due to the function of a normal left ventricle.

Diagnosis

The diagnostic criteria for ARVC were initially developed in 1994 and were then modified in 2010 to increase their sensitivity and to incorporate new knowledge and technology(122). The modified criteria use the same approach as the 1994 criteria by incorporating structural, histological, electrocardiographic, arrhythmic, and genetic features of the disease (Table 7)(122). A definite diagnosis requires 2 major criteria, or 1 major and 2 minor criteria, or 4 minor criteria from different categories. A borderline diagnosis is made with 1 major and 1 minor criterion or 2 minor criteria from different categories. A possible diagnosis requires 1 major or 2 minor criteria from different categories. Although genotyping is a criterion, genetic screening is only suggested in patients that have more than one minor criterion or for mutation-specific testing in family members of an index patient who has an identified mutation(122, 123). Diagnosis from cardiac biopsy maybe limited by the lack of involvement of the interventricular septum that the transvenous bioptome usually targets. Other non-septal RV biopsy sites, guided by voltage mapping or imaging, maybe helpful but will increase the risk of perforation.

The differential diagnosis includes RVOT-VT which is usually benign, responds to β-blockers and calcium channel blockers, and may be cured with catheter ablation(124). Sarcoidosis can mimic ARVC and should be considered if there is no family history of ARVC, if concomitant conduction system disease is present, with early involvement of the septum, or with a known history of non-cardiac sarcoid. Patients with ARVC and involvement of both ventricles may be difficult to distinguish from patients with dilated cardiomyopathy(124).

Treatment

Treatment considerations include lifestyle modification, antiarrhythmic drug therapy, ICD treatment, arrhythmia substrate ablation, and cardiac transplantation(120). The main lifestyle modification is avoiding competitive and endurance athletics. For control of recurrent VT/VF, β-blockers, sotalol, and amiodarone may be considered. Amiodarone is usually avoided given the young age of many ARVC patients. When the patient has left ventricular systolic dysfunction, standard therapies for such should be initiated. Whether an ICD should be placed in all ARVC patients is controversial. ICDs should be considered in patients with SCA, unexplained syncope, young age, decreased LV systolic function, or markedly decreased RV systolic function. Many patients with ARVC tolerate their VT very well due to preserved LV function and reported ICD benefits may be overestimated(125). Shortcomings of ICD therapy that are of importance in patients with ARVC include the expected need for many system revisions given the young age of the ARVC population, lead perforations and poor RV pacing and sensing function given the RV abnormalities at the core of ARVC. ICDs should be programmed to deliver antitachycardia pacing therapies in even fast VT zones. Over 90% of the VTs in ARVC can be pace-terminated, perhaps due to the proximity of the RV pacing lead to the RV tachycardia(125). Catheter ablation may be a useful therapy to help control recurrent VT. Given the progressive nature of the underlying disease, ablation is unlikely to be curative over the long-term(120). In patients with uncontrollable VT/VF or unmanageable heart failure, cardiac transplantation should be considered.

E. SPECIAL POPULATIONS

a) Athletes

SCD in either recreational or competitive athletes is rare. For elite or competitive athletes the estimated risk of SCD is 1/50 000 to 1/300 000 individuals over a 10 to 20 year period(126, 127). For recreational athletes, the absolute risk of SCD during any single exercise session was estimated to be one death per 1.51 million sessions in the Physicians Health Study of 21,481 men followed for 12 years(4). In the Nurses' Health Study of 69,693 women, the estimated risk was lower with one death per 36.5 million hours of exertion(128). These low risks may be even lower if exercise is performed on a regular basis. The most common mechanism of SCD in athletes is related to sustained VT/VF. Only approximately 15% of SCDs in the athlete population are related to non-cardiovascular causes(129).

The etiology of SCD in athletes varies by age. In athletes under the age of 35 years, structural heart disease is present in most cases but its form varies between North American and European cohorts. A United States registry of 1435 young competitive athletes enrolled between 1980 and 2005 showed that HCM was the most common etiology of SCD and accounted for 36% of cases(129). In addition, 8% of SCD was attributed to indeterminate LVH possibly related to HCM. The second most common cause of SCD in this registry was coronary artery anomalies, which accounted for 17% of cases. Other, less common etiologies included myocarditis (6%), ARVC (4%) and mitral valve prolapse (4%)(129). In contrast, a study from the Veneto region of Italy evaluated 49 athletes <35 years of age who presented with SCD and found that ARVC was the most common etiology (22.4%) while attributing few SCDs to HCM (2%)(130). Other etiologies of SCD in this study included CAD (18.4%) and coronary artery anomalies (12.2%). Of note, the prevalence of ARVC in the Veneto region of Italy is known to be high. Another registry of 6 million military recruits (mean age 19 years) in the United States identified 108 non-traumatic sudden deaths related to exercise. Autopsies were performed in all cases. Of the 64 cases where structural heart disease was present, the most common etiology was coronary artery anomalies (33%). Other causes included myocarditis (20%), CAD (16%), and HCM (13%)(131). In athletes over the age of 35, the predominant etiology of SCD is CAD(132).

In the absence of structural heart disease the etiologies of SCD in athletes include congenital LQTS, BrS, CPVT, idiopathic VF and commotio cordis(129). In addition, there are case reports in young athletes that describe a possible association between performance enhancing androgen use and cardiac hypertrophy or myocarditis associated with SCD(133, 134). However, causality has not been firmly established in these cases. In addition cocaine use in athletes has been associated with SCD(18).

Because of relatively low yield, pre-participation cardiovascular screening of recreational or competitive athletes remains controversial. The American Heart Association has proposed a screening procedure for competitive athletes in the United States (Table 8)(132). This procedure involves a selective history and physical examination but does not incorporate a screening 12-lead ECG. When abnormalities are identified referral for further cardiovascular evaluation is suggested. In contrast, recommendations from both the European Society of Cardiology and the International Olympic Committee suggest a screening 12-lead ECG in addition to the history and physical examination(135). The rationale for including the ECG in the evaluation of competitive athletes is related to the observation that

95% of athletes with HCM will have significant abnormalities on their 12-lead ECG. In addition, the majority of athletes with ARVC will have ECG abnormalities. In contrast, the yield of history and physical examination alone to identify important cardiovascular conditions that may lead to SCD is estimated to be only 3%(132, 135).

b) Pregnancy

SCA during pregnancy or at the time of delivery is a devastating event with the potential loss of two lives. However, SCA in pregnancy is a rare event with an incidence in the range of 1 in 12000 to 1 in 2400(136, 137). Nevertheless, this incidence is greater than that in athletes. There are no large observational reports of SCA in pregnancy and much of the data in that regard comes from case reports and from small registry data. Furthermore, most of these data were derived from patients hospitalized for delivery; data regarding out-of-hospital SCA in pregnant patients is very sparse.

Expectant mother who are at risk for SCD include those that are older, and obese(138). The risk factors of older age and obesity suggest that the incidence of SCD in pregnancy will increase as the prevalence of characteristics is increasing in the pregnant population. Associated medical conditions that increase the risk of SCD in pregnancy include hypertension, malignancy, liver disease, systemic lupus erythmematous, pulmonary hypertension, and structural heart disease(CAD, valvular heart disease, CHD) (138).

The obstetrical risks include stillbirth, cesarean delivery, severe preeclampsia/eclampsia and placenta previa. The mnemonic "BEAUCHOPS" is suggested to help recall the etiologies of maternal SCA: **B**leeding/DIC, **E**mbolism (coronary, pulmonary, amniotic fluid), **A**nesthetic complications, **U**terine atony, **C**ardiac disease (ischemia/infarct, coronary/aortic dissection, cardiomyopathy), **H**ypertension/pre-eclampsia/eclampsia, **O**ther (standard ACLS differential diagnosis), **P**lacenta abruption, and **S**epsis(139). The most common causes are due to hemorrhage, heart failure, amniotic fluid embolus, and sepsis(139). In some cases the etiology of the SCA may never be truly determined. Given these etiologies, it is not surprising that the initial cardiac rhythm may not be VT/VF but rather more often is pulseless electrical activity or asystole(138).

The in-hospital SCA survival rate in this setting is better than in other settings leading to SCA with up to 60% maternal survival and 89% neonatal survival. Of course, survival rates depend on the etiology with aortic dissection/rupture and trauma having the worst prognosis. The maternal resuscitation protocol is similar to that of standard

adult resuscitation (including defibrillation energy and drug dosing) but there are differences due to the pulmonary physiology changes in pregnancy, aortocaval compression, and the need for multiple health care teams (including obstetrics and neonatology) (139). Left uterine displacement should be performed to help increase cardiac output during resuscitation. If spontaneous circulation is not established within four minutes of resuscitation, Caesarian section (definitive treatment for aortocaval compression) should be considered immediately. Upper airway changes, reduction in oxygen reserve, increased intra-pulmonary shunting, and lower esophageal dysfunction can add to the challenges of airway management. Specific guidelines by the American Heart Association (2010) as well as consensus statements by other organizations have been developed to address maternal resuscitation(138, 139).

As in many rare scenarios, establishing and maintaining coordination between multiple disciplines (using an "obstetrical code blue" instead of a regular "code blue"), having an organized and standardized approach, and regular simulations for the team help to achieve positive outcomes(139).

F. NEW DEFIBRILLATOR TECHNOLOGIES

Early ICDs required epicardial leads and patches that were at the time of a thoracotomy and impulse generators sufficiently large that they required placement in the abdomen. Later, fully-transvenous systems were developed with lead usually placed in the right ventricle apex and the impulse generator usually placed in a pre- or subpectoral left-sided pocket. Transvenous systems still present challenges secondary to lead fractures and insulation breaks, vascular access, and the risks of bacteremia. A subcutaneous (non-transvenous) ICD (S-ICD) has been recently developed that avoids some of the problems associated with transvenous lead systems(140). The S-ICD is placed in the left lateral position via a lateral submammary incision and the lead is tunneled to be positioned parasternally. Implant complications are minor and are usually due to wound infections that can be treated with antibiotics. The S-ICD has algorithms to discriminate SVT and VF, can deliver shocks with efficacies similar to those of conventional transvenous systems, but cannot provide chronic anti-bradycardia or acute anti-tachycardia pacing other than transthoracic pacing for 30 seconds after shock delivery if necessary). Ongoing challenges with the S-ICD include T wave oversensing and discrimination of AF with rapid ventricular rates from VT/VF in the VF zone(140). Nevertheless, studies have shown similar rates of inappropriate shocks comparing the S-ICD system and standard transvenous ICD systems. At present, the S-

ICD is an attractive option for patients in whom transvenous lead or septic complications are particularly likely to occur(140).

Some patients who are at risk for VT/VF may only need temporary protection from SCD because their risk is reversible or because they are still in the process of having their candidacy for an ICD assessed). Such patients include those early post-MI or CABG, those with as yet untreated CHF, those undergoing a work-up for other potentially reversible causes of SCD, and those waiting for ICD system infection to be cleared. To avoid having such patients remain in hospital or to accept a risk to stay at home, a wearable ICD has been developed. The LifeVest®(Zoll, Pittsburgh, PA, USA) consists of a vest with two defibrillation patch electrodes on the back, an elastic belt with a front defibrillation patch electrode, and four non-adhesive ECG electrodes connected to a monitoring unit capable of automatic synchronized cardioversion or unsynchronized defibrillation(141). The main limiting factor is that patients have to wear the garment continuously. In trials, patients only wear the vest 19-24 hours a day, and about 14% discontinued its use completely. Small studies with the wearable defibrillator have been conducted in immediately post-MI, after coronary revascularization, and in heart failure patient populations. These studies have reported spontaneous VT/VF events with successful resuscitation by the wearable defibrillator.

Automated External Defibrillators (AEDs) are now becoming common-place in public areas and have saved lives even when used by laypersons. The Home AED Trial(HAT) was a randomized, controlled trial to determine the advantages, disadvantages, and risks of home use of an AED(142). Patients with prior anterior MI who were not current candidates for an ICD and who had a live-in partner that could perform CPR, call for help, and use the AED were randomized to receive or not to receive a home AED in addition to partner training to call for help and to perform CPR. In HAT, the home AED was not demonstrated to reduce all-mortality. This unexpected result has been ascribed to a much lower mortality rate than expected with resultant loss of study power, to benefits of the training of partners in the control group to perform CPR, and to the observation that more than half the SCA in the study were unwitnessed(142). Accordingly, from a public policy perspective the home AED may be inefficient but there may be high-risk patients that are not candidates for an ICD for whom a home AED may be a reasonable strategy.

G. DRIVING IMPLICATIONS

With any illness that predisposes to a risk of sudden incapacitation, consideration must be given to the appropriateness of allowing that

individual to drive a motor vehicle. These considerations inevitably lead to conflict between the rights of the individual (being unable to drive may constitute a major hardship) and the rights of society (drivers who are suddenly incapacitated constitute a hazard).

This conflict was first addressed, in a quantitative sense, by Dr. James Brennan et al. in 1992(143). Reasoning that society had accepted risks of allowing an individual who after an acute MI who was NYHA Class I and had a negative exercise test at 7 METs to drive a heavy truck (since such individuals were extended this right) and recognizing that this individual had an annual risk of SCD of approximately 1%, there were (admittedly weak) data that allowed calculation of the risk of harm to others in this setting assuming the risk of sudden incapacitation behind the wheel is not higher than at other times. A risk of harm formula was developed that considered the driver's annual risk of sudden incapacitation, the time spent driving, the vehicle being driven, and the probability that sudden incapacitation would result in an accident causing death or serious injury to others(143). This exercise suggested that a driver with a risk of SCD of 1%/year who spent 25% of their time driving large trucks would pose a risk of causing death or serious injury to others of 0.00005 (1/20,000) each year. Applying the same standard to a driver of a car who spends 4% of their time driving results in accepting a similar risk of harm to others if the car driver's annual risk of sudden incapacitation is <22%. One of the advantages of the formula is that it permits estimation of the risks of driving in less common situations such as driving a small vehicle 25% of the time (acceptable if the driver's risk of sudden incapacitation is <4%/year) (143).

Application of these standards to the patients considered in this review would suggest that most should not drive large motor vehicles as an occupation but that most would be permitted to drive smaller motor vehicles on an as-needed basis at least in the absence of an episode of SCA in the previous 6 months(144).

It is important that medical practitioners note that their input into the driving privileges deliberation is only advisory. Transport regulators are responsible for issuing or withdrawing driving licenses. Nevertheless, medical practitioners are responsible for advising their patients of their fitness to drive and, in some jurisdictions, are responsible for informing driving regulators when their patient is not considered fit to drive. Medical practitioners must be aware of the regulations in their jurisdiction(144-146).

H. CLINICAL APPROACH TO THE INVESTIGATION OF SUDDEN CARDIAC ARREST

The approach to investigation of the survivor of SCA involves the following components:

1) assessment for reversible causes
2) assessment for structural heart disease
3) assessment for primary electrical disease when there is no significant structural heart disease
4) evaluation of family members if an inheritable syndrome is suspected or identified.

Table 9 lists some of the potentially reversible causes that are associated with SCA(147).

Assessment of the cardiac arrest survivor begins with a complete history and physical examination that includes evaluation of the presence of symptoms or signs suggestive of or a previous diagnosis of structural heart disease. The ingestion history and medication list (both prescribed and non-prescribed) should be appraised for the possibility of drug- or toxin–induced arrhythmias or electrolyte disturbances. A three-generation family history should include exploration for SCA (often called a massive heart attack by patients), syncope, neuromuscular disorders, unexplained drowning, sudden infant death, and sensorineural deafness(148). Laboratory testing should be performed immediately upon presentation to assess for electrolyte, acid-base, and metabolic abnormalities that may aid in diagnosis or require immediate treatment. However, the natural tendency to ascribe SCA to mild electrolyte abnormalities is to be avoided as such abnormalities may be the result of rather than the cause of the cardiac arrest(149).

Serial ECG evaluation should be performed to screen for myocardial ischemia or infarction, conduction abnormalities, and repolarization or depolarization abnormalities. Continuous ECG telemetry monitoring may identify non-sustained and sustained arrhythmias or reversible myocardial ischemia(148).

Invasive coronary angiography should be performed in most cardiac arrest survivors to seek CAD that may require intervention(150). When coronary spasm is suspected, provocative testing with either ergonovine or acetylcholine may be performed. Non-invasive computed tomography coronary angiography may also be of value to rule out the presence of CAD and coronary artery anomalies when coronary angiography is not to be performed.

Cardiac imaging is indicated to assess cardiac structure and function, to stratify risk in terms of adverse clinical outcomes, and to guide therapeutic intervention. Clinical experience and experimental data indicate that there is often significant myocardial stunning and global impairment of left ventricular function in the

first few days after a SCA event(151). Accordingly, in SCA survivors, formal assessment of left ventricular systolic function should be repeated no sooner than a week after the event.

2D echocardiography will identify many important etiologies of SCA including CAD (focal wall motion abnormalities), HCM (asymmetric left ventricular hypertrophy), ARVC (right ventricular wall motion abnormalities and aneurysms), aortic stenosis, and non-ischemic dilated cardiomyopathies (global left ventricular systolic dysfunction). Nevertheless, cMRI is now considered the gold standard for assessment of cardiac volumes and function(36). In addition to those conditions listed above, cMRI may be useful in the diagnosis of myocarditis , cardiac sarcoidosis, and cardiac amyloidosis. Furthermore, cMRI is more sensitive for the detection of right ventricular wall motion abnormalities of importance in the diagnosis of ARVC. Using the technique of late gadolinium enhancement, cMRI can also quantify the extent and distribution of myocardial scar. Finally, T2-weighted imaging, which identifies unbound myocardial water, characterizes myocardial edema associated with inflammatory conditions such as myocarditis, sarcoidosis, and acute ischemia(36).

Exercise testing may be performed to provide a functional assessment and to expose symptoms and signs of exercise-related myocardial ischemia, myocardial dysfunction, or arrhythmia(36). Exercise testing is of particular value in the diagnosis of catecholamine-dependent arrhythmias including CPVT and LQTS. A failure to increase systolic blood pressure by at least 20 mmHg with exercise identifies a potentially high-risk individual with HCM.

Approximately 5-10% of SCA survivors have neither structural heart disease nor a noncardiac etiology for their event. Such individuals are considered to have a primary electrical disorder. Pharmacological challenge testing with epinephrine and with a Class IC sodium channel blocker (procainamide, ajmaline, or flecainide) may unmask the otherwise subtle ECG abnormalities in conditions such as congenital LQTS, CPVT, and BrS syndrome(36).

When a graded epinephrine infusion elicits an absolute increase in the QT interval by at least 30 msec then congenital LQTS-1 should be strongly considered. When the same infusion elicits polymorphic VT or bidirectional VT, the diagnosis of CPVT is supported. Similarly, when a Class IC antiarrhythmic drug infusion elicits a Type I BrP ECG (≥2 mm J-point elevation and coved ST-T segment elevation in V1 and V2), a diagnosis of BrS is likely(36).

Transvenous catheter electrophysiologic studies (EPS) are not routinely performed in the assessment of SCA. In patients with structurally normal hearts, lack of inducibility of VT or VF does not predict a favourable outcome and an ICD would be indicated regardless of the results of testing(152). In patients with manifest WPW syndrome, EPS may identify an accessory connection with a very short refractory period. Ablation of the accessory connection would then be indicated(20).

When an inheritable condition such as congenital LQTS, BrS, CPVT, or ARVC is identified, the patient and immediate family members may benefit from the genetic testing. One study evaluated the yield of systematic advanced cardiac imaging and provocative testing in patients with unexplained SCA(153). In 63 patients, a diagnosis was obtained in 56%. Targeted genetic testing revealed causative mutations in 47% of those diagnosed. In addition, of 64 immediate family members screened, 24% were treated for a hitherto clinically silent condition.

I.RISK STRATIFICATION

As noted above, SCD accounts for the deaths of more than 350,000 individuals per year in North America and the majority occur in patients with CAD. Patients with prior MI are at higher risk and therefore have been the principal target of the risk stratification investigations(154). The most consistently identified predictor of SCD risk is lower LVEF(155). Nevertheless, this predictor is insensitive in that most patients experiencing SCD have an LVEF >30% and nonspecific in that <20% of patients who receive an ICD for primary prevention of SCD based upon a low LVEF receive an appropriate ICD therapy for VT/VF (of which fewer than half of these therapies were truly lifesaving) (154).

Many other potential predictors have been studied to enhance risk stratification. Catheter electrophysiologic studies have predictive capacity, particularly in the setting of CAD with previous MI and in ARVC but the sensitivities and specificities of this predictive capacity are strongly affected by the aggressiveness of stimulation protocol used (two to five extrastimuli) and definitions of a positive study (polymorphic VT, ventricular flutter, and VF are usually considered to be nonspecific responses) (1). In the MUSTT study, the follow-up all-cause mortality rate was very similar between the inducible and non-inducible group, questioning the value of invasive electrophysiologic studies in this setting(74). Heart rate variability and a high resting heart rate are considered to be markers of a higher risk of SCD were included as an enrollment criterion in

the DINAMIT study (that did not show a survival advantage with ICDs) (78). Similarly, the signal-averaged ECG, which identifies ventricular late potentials that represent slow conduction through scar was included as an enrollment criterion in the CABG-Patch study (that did not show a survival benefit with ICD therapy) (77). Accordingly, these potential predictors are not commonly used with the exception of the signal-averaged ECG in patients with ARVC. Microvolt T-wave alternans, due to alternating beat-to-beat T wave changes, is a measure of dispersion of repolarization linked to abnormal intracellular calcium handling. T wave alternans appears to be a possible marker of SCD risk but enough evidence does not exist to support its use to guide early ICD implantation(155). The Risk Estimation Following Infarction, Noninvasive Evaluation (REFINE)study showed that many risk stratification tests (T-wave alternans, heart rate variability, signal-averaged ECG, baroreceptor sensitivity) are not predictive of SCD when measured in the first 2-4 weeks after MI(156). More recently, cMRI and genetic testing have emerged as potential SCD risk stratifiers(155). cMRI can measure infarct size and define viable myocardium, infarct core, and per-infarct zone. In patients with inherited SCD syndromes, genetic testing is being evaluated for its role in risk stratification with the expectation of predictive value.

Susceptibillity to life-threatening VT/VF generally requires a myocardial structural abnormality, impaired autonomic modulation, and a trigger(155). For many, one of these abnormalities alone may not provide sufficient information for risk stratification. The ongoing REFINE-ICD Trial(ClinicalTrials.gov NCT00673842) is enrolling post-MI patients with LVEFs of 36-49%, abnormal heart rate turbulence, and T-wave alternans to receive or not to receive an ICD. Programmed Ventricular Stimulation to Risk Stratify for Early Cardioverter-Defibrillator Implantation to Prevent Tachyarrhythmias following Acute Myocardial Infactions (Protect ICD Study - Australian New Zealand Clinical Trials 12614000042640) will evaluate EPS-guided ICD implantation in post-MI patients with LV dysfunction. A subgroup in PROTECT-ICD will also undergo cMRI to identify scar characteristics with inducibility and arrhythmia endpoints. The results of these studies and future research will further refine our ability to predict SCD risk.

J) CONCLUSION

As is evident from the foregoing, the past 35 years have seen remarkable advances in the identification of patients at risk for SCD and in the management of this risk. Nevertheless, although these advances have saved many lives and have been of

great importance to those whose lives have been saved, these advances have only just begun to impact the much greater global population problem of SCD. Much more needs to be done and will undoubtedly be done over both the short-term and the longer-term future.

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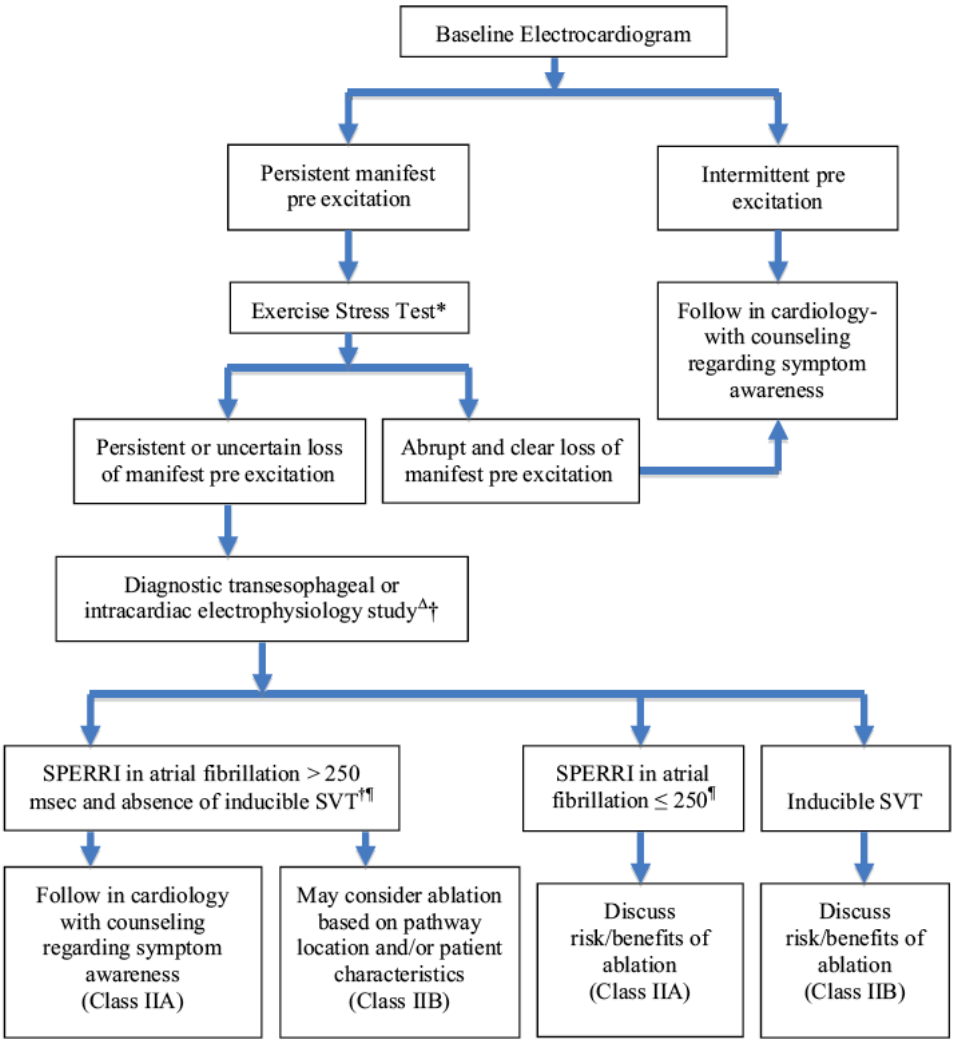
Figure 1. Approach to asymptomatic pre-excitation.

(Reproduced with permission from Cohen MI, Triedman JK, Cannon BC, et al. PACES/HRS expert consensus statement on the management of the asymptomatic young patient with a wolff-parkinson-white electrocardiographic pattern. *Heart Rhythm*. 2012;9:1006.)



* patients unable to perform an exercise stress test should undergo risk-stratification with an EP study
Δ prior to invasive testing, patients and the parents/guardians should be counseled to discuss the risks and benefits of proceeding with invasive studies, risks of observation only, and risks of medication strategy.
† patients participating at moderate-high level competitive sports should be counseled with regards to risk-benefit of ablation (Class IIA) and follow the 36th Bethesda Conference Guidelines[6]
¶ in the absence of inducible atrial fibrillation, the shortest pre-excited RR interval determined by rapid atrial pacing is a reasonable surrogate

Figure 2. Torsades de Pointes

Reproduced with permission from Chokr MO, Darrieux FC, Hardy CA, et al. Short-coupled variant of "torsades de pointes" and polymorphic ventricular tachycardia. *Arq Bras Cardiol*. 2014;102(6):e60-4.

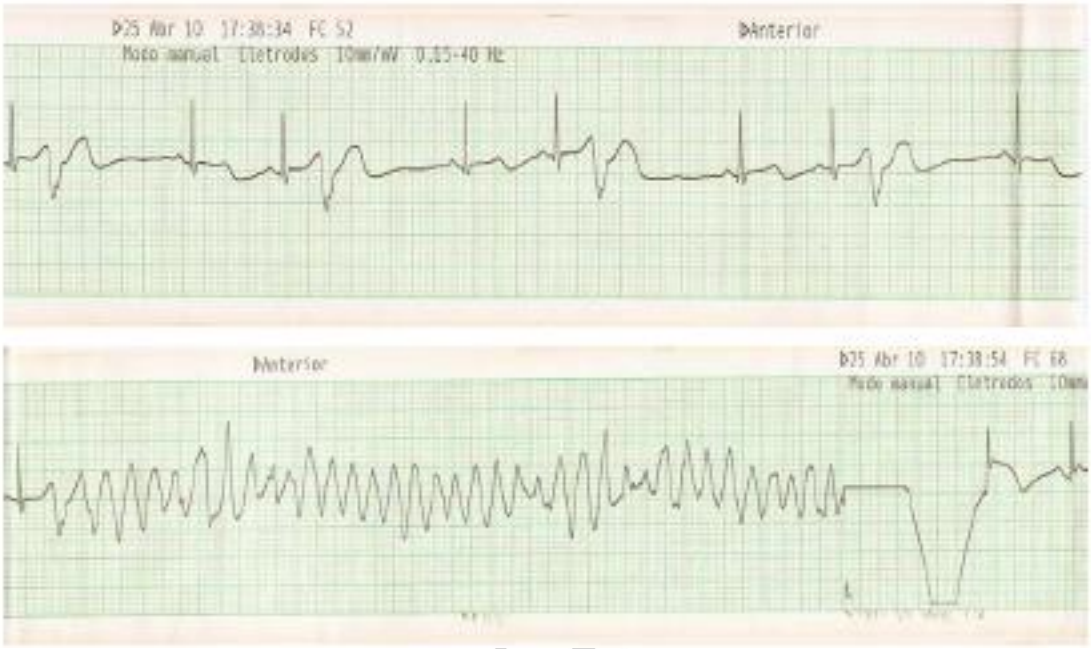


Figure 3. ECG patterns of Brugada Syndrome in V1 and V2

Reproduced with permission from Bayes de Luna A, Brugada J, Baranchuk A, et al. Current electrocardiographic criteria for diagnosis of brugada pattern: A consensus report. *J Electrocardiol*. 2012;45(5):433-442.

ECG patterns of BrS in V1-V2

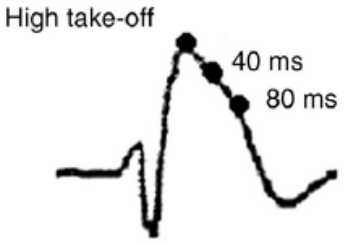
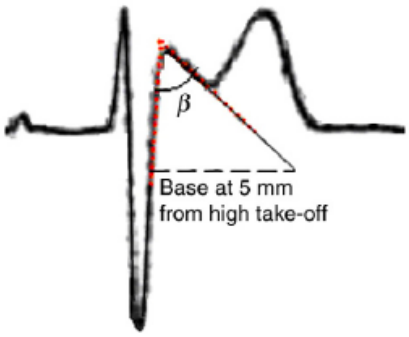
Type 1: coved pattern	Type 2: saddle-back pattern
	
This typical coved pattern present in V1-V2 the following: a. At the end of QRS, an ascending and quick slope with a high take-off ≥2mm followed by concave or rectilinear downsloping ST. There are few cases of coved pattern with a high take-off between 1 and 2 mm. b. There is no clear r' wave. c. The high take-off often does not correspond with the J point (Fig. 4 B). d. At 40 ms of high take-off, the decrease in amplitude of ST is ≤4mm.[28] In RBBB and athletes, it is much higher. e. ST at high take-off > ST at 40 ms > ST at 80 ms. f. ST is followed by negative and symmetric T wave g. The duration of QRS is longer than in RBBB, and there is a mismatch between V1 and V6 (see text).	This typical saddle-back pattern present in V1-V2 the following: a. High take-off of r' (that often does not coincide with J point) ≥2 mm. b. Descending arm of r' coincides with beginning of ST (often is not well seen). c. Minimum ST ascent ≥0.5 mm d. ST is followed by positive T wave in V2 (T peak > ST minimum > 0) and of variable morphology in V1. e. The characteristics of triangle formed by r' allow to define different criteria useful for diagnosis (see above and text). • β angle.[26] • Duration of the base of the triangle of r' at 5 mm from the high take-off greater than 3.5mm[31] f. The duration of QRS is longer in BrP type 2 than in other cases with r' in V1, and there is a mismatch between V1 and V6 (see text).

Figure 4. Bidirectional Ventricular Tachycardia

Reproduced with permission from Chapman M, Hargreaves M, Schneider H, Royle M.Bidirectional ventricular tachycardia associated with digoxin toxicity and with normal digoxin levels. Heart Rhythm 2014:11(7): 1222-1225

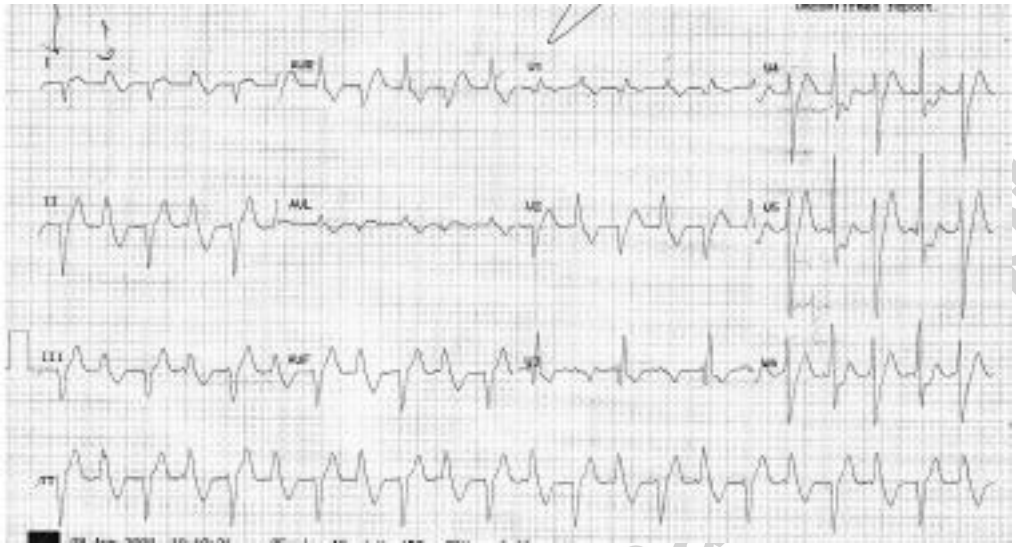
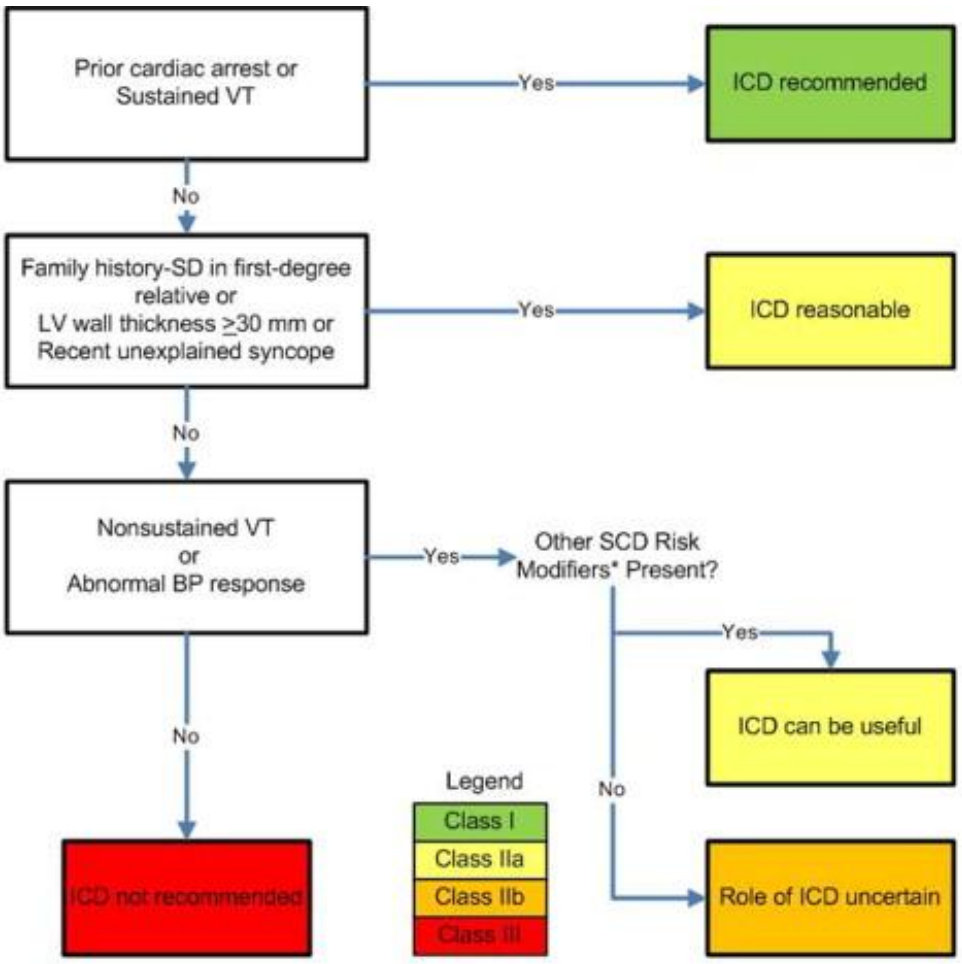


Figure 5. An approach to selection of hypertrophic cardiomyopathy patients for implantable defibrillator therapy.

(Reproduced with permission from Gersh B et al. *J Am Coll Cardiol*. 2011;58(25):e212-60.



Regardless of the level of recommendation put forth in these guidelines, the decision for placement of an ICD must involve prudent application of individual clinical judgment, thorough discussions of the strength of evidence, the benefits, and the risks (including but not limited to inappropriate discharges, lead and procedural complications) to allow active participation of the fully informed patient in ultimate decision making.

Table 1 - Major Causes of Sudden Cardiac Death

Ischemic Heart Disease
Coronary artery disease with myocardial infarction or angina
Coronary artery embolism
Non-atherogenic coronary artery disease (arteritis, dissection, congenital coronary anomalies)
Coronary artery spasm
Non-Ischemic Heart Disease
Hypertrophic cardiomyopathy
Dilated cardiomyopathy
Valvular heart disease
Congenital heart disease
Arrhythmogenic right ventricular cardiomyopathy
Myocarditis
Cardiac tamponade
Acute myocardial rupture
Aortic dissection
No Structural Heart Disease
Idiopathic ventricular fibrillation/J wave syndrome
Brugada syndrome
Long QT syndrome with torsades de pointes
Preexcitation syndrome
High grade atrioventricular block with torsades de pointes
Familial sudden cardiac death

Commotio cordis
Non-Cardiac Disease
Pulmonary embolism
Intracranial hemorrhage
Drowning
Pickwickian syndrome
Drug overdose/toxicity
Central airway obstruction
Sudden infant death syndrome

Table 2. Long QT syndrome genotypes, mechanism of effect, and treatment strategies.

(Reproduced with permission from Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. *N Engl J Med*. 2003;348(19):1866-1874

Table Inherited LQTS

Locus	Name	Chromosomal Locus	Gene Symbol	Protein (Symbol)	Current	In Vitro Characterization	Gene-Specific Therapy*
LQT1		11p15.5	*KCNQ1*	I_{Ks} potassium channel α-subunit (KvLQT1)	↓ IKs	Dominant negative suppression, trafficking defect, abnormal gating, reduced response to β-AR signal	β-blockers,† potassium channel openers†
LQT2		7q35-q36	*KCNH2*	I_{Kr} potassium channel α-subunit (HERG)	↓ IKr	Dominant negative suppression, trafficking defect, abnormal gating	β-blockers,† potassium supplement,† potassium channel openers, fexofenadine and thapsigargin
LQT3		3p21	*SCN5A*	Cardiac sodium channel α-subunit (Nav 1.5)	↑ INa	Abnormal gating: sustained current, slower inactivation, faster recovery, increased window current	Sodium channel blockers (mexiletine)†
LQT4		4q25-q27	*ANK2*	Ankyrin B, (ANKB)	↓ Ncx1, Na/K ATPase, InsP3	Loss of expression and mislocalization	None proposed
LQT5		21q22.1-q22.2	*KCNE1*	I_{Ks} potassium channel β-subunit (MinK)	↓ IKs	Dominant negative suppression, abnormal gating, reduced response to β-AR signal	β-blockers, potassium supplement, potassium channel openers
LQT6		21q22.1-q22.2	*KCNE2*	I_{K} potassium channel beta subunit (MiRP)	↓ IKr	Reduced current density and abnormal channel gating	β-blockers, potassium supplement, potassium channel openers, fexofenadine and thapsigargin
LQT7/Andersen		17q23.1-q24.2	*KCNJ2*	I_{K1} potassium channel (Kir2.1)	↓ IK1	Dominant negative suppression, nonfunctional channels, trafficking defect, abnormal gating	None proposed
LQT8/Timothy		12p13.3	*CACNA1c*	Voltage-gated calcium channel, CaV1.2	↑ ICa	Loss of inactivation	Calcium channel blockers†
LQT9		3p25	*CAV3*	Caveolin-3	↑ INa	Increased late Ina	Sodium channel blockers (mexiletine)
LQT10		11q23	*SCN4B*	Cardiac sodium channel β-4 subunit	↑ INa	Increased late Ina	Sodium channel blockers (mexiletine)
LQT11		7q21–22	*mAKAP*	A-kinase anchoring proteins	↓ IKs	Reduced phosphorylation of the IKs channel	β-blockers
LQT12		20q11.2	*SNTA1*	Syntrophin	↑ INa	Increased late INa	Sodium channel blockers (mexiletine)

NCx indicates sodium calcium exchanger; Na/K ATPase, sodium potassium ATP pump; InsP3, inositol 3-phosphate receptor; β-AR, β-adrenergic receptor.
*Possible gene/mechanism-specific therapies are reported based on known pathophysiology.
†Experimentally or clinically tested therapies.

Table 3. Proposed Diagnostic Criteria for Short QT Syndrome

(Reproduced with permission from Gollob MH, Redpath CJ, Roberts JD. The short QT syndrome: Proposed diagnostic criteria. *J Am Coll Cardiol*. 2011;57(7):802-812.

	Points
QT_c, ms	
<370	1
<350	2
<330	3
Jpoint-Tpeak interval <120 ms	1
Clinical history*	
History of sudden cardiac arrest	2
Documented polymorphic VT or VF	2
Unexplained syncope	1
Atrial fibrillation	1
Family history*	
First- or second-degree relative with high-probability SQTS	2
First- or second-degree relative with autopsy-negative sudden cardiac death	1
Sudden infant death syndrome	1
Genotype*	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

High-probability SQTS: ≥4 points, intermediate-probability SQTS: 3 points, low-probability SQTS: ≤2 points. Electrocardiogram: must be recorded in the absence of modifiers known to shorten the QT. Jpoint-Tpeak interval must be measured in the precordial lead with the greatest amplitude T-wave. Clinical history: events must occur in the absence of an identifiable etiology, including structural heart disease. Points can only be received for 1 of cardiac arrest, documented polymorphic VT, or unexplained syncope. Family history: points can only be received once in this section. *A minimum of 1 point must be obtained in the electrocardiographic section in order to obtain additional points.

VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Table 1.

Table 4. Consensus Statement on Early Repolarization Syndrome Diagnosis

Reproduced with permission from Priori SG, Wilde AA, Horie M, et al. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm*. 2013;15(10):1389-1406.

Expert Consensus Statement on Diagnosis
1. ER syndrome is diagnosed in the presence of J-point elevation ≥ 1mm in ≥2 contiguous inferior and/or lateral leads of a standard 12 lead ECG in a patient resuscitated from otherwise unexplained VF/polymorphic VT
2. ER syndrome can be diagnosed in a SCD victim with a negative autopsy and medical chart review with a previous ECG demonstrating J-point elevation ≥1mm in ≥2 contiguous inferior and/or lateral leads of a standard 12 lead ECG.
3. ER pattern can be diagnosed in the presence of J-point elevation ≥1mm in ≥2 contiguous leads of a standard 12 lead ECG

Table 5 - Selected Trials of ICD therapy for Primary Prevention

Reproduced with permission from Klein MH, Gold MR. Use of traditional and biventricular implantable cardiac devices for primary and secondary prevention of sudden death. *Cardiol Clin*. 2008;26(3):419-31, vi-vii.

Selected clinical trials of implantable cardioverter defibrillator therapy for primary prevention of sudden cardiac death

Trial	Number of patients	Inclusion criteria	Mean follow-up (months)	Control therapy	Relative risk reduction (%)	Absolute risk reduction (%)	P value
MADIT-I [32]	196	Nonrecent MI (>3 wks) or CABG (>3 mos), EF ≤35%, spontaneous NSVT, and inducible VT	27	Medical therapy	54	22.8	0.009
MUSTT [34]	704	Nonrecent MI (≥4 days), EF ≤40%, spontaneous NSVT, and inducible VT	39	Medical therapy	51	23	<.001 (ICD versus medical therapy)
MADIT-II [40]	1232	EF ≤30%, remote MI (>1 mo)	20	Medical therapy	31	5.4	0.02
AMIOVIRT [51]	103	EF ≤35%, NICM, NSVT	24	Medical therapy	13	1.7	0.8
Cardiomyopathy Trial (CAT) [52]	104	NYHA II-III, EF ≤30%, NICM, recent-onset heart failure (≤9 mos)	23	Medical therapy	17	5.4	0.6
DEFINITE [53]	458	NICM, EF <35%, NSVT, or ≥10 PVCs/hr	29	Medical therapy	35	5.2	0.08
SCD-HeFT [54]	1676	NYHA II-III, nonrecent MI or revascularization (>30 days), nonrecent heart failure onset (>3 mos)	46	Placebo	23	6.8	<0.01

Abbreviations: CABG, coronary artery bypass graft surgery; EF, ejection fraction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NICM, nonischemic cardiomyopathy; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association functional class; PVC, premature ventricular complex; VT, ventricular tachycardia.

Table 6 – Risk factors for SCD in Hypertrophic Cardiomyopathy

(Reproduced with permission from Maron BJ, Maron M. Hypertrophic Cardiomyopathy. Lancet 2013;381:242-255)

***Panel 2:* Risk factors for sudden death**

Secondary prevention

- Cardiac arrest or sustained ventricular tachycardia

Conventional primary prevention risk markers

- Family history of sudden death due to hypertrophic cardiomyopathy
- Unexplained recent syncope
- Multiple repetitive non-sustained ventricular tachycardia (on ambulatory ECG)
- Hypotensive or attenuated blood pressure response to exercise
- Massive left-ventricular hypertrophy (thickness, ≥30 mm*)
- Extensive and diffuse late gadolinium enhancement

Potential high-risk subsets for primary prevention

- End-stage phase (ejection fraction <50%)
- Left-ventricular apical aneurysm and scarring

Potential arbitrators for primary prevention†

- Substantial left-ventricular outflow gradient at rest
- Alcohol septal ablation
- Multiple sarcomere mutations
- Modifiable
  - Intense competitive sports
  - Coronary artery disease

*Or the equivalent in children according to body size. †To arbitrate decision-making about implantable defibrillators in patients for whom risk level remains ambiguous after assessment by the conventional risk factor algorithm. ECG=electrocardiogram. Modified from reference 6, with permission of the American Heart Association.

Table 7 - Original and Revised Task Force Criteria for Arrhythmogenic Right Ventricular Cardiomyopathy

Reproduced with permission from Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: Proposed modification of the task force criteria. *Eur Heart J.* 2010;31(7):806-814.

Table I Comparison of original and revised task force criteria

Original task force criteria	Revised task force criteria
I. Global or regional dysfunction and structural alterations*	
Major	
	By 2D echo:
• Severe dilatation and reduction of RV ejection fraction with no (or only mild) LV impairment • Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging) • Severe segmental dilatation of the RV	• Regional RV akinesia, dyskinesia, or aneurysm • *and* 1 of the following (end diastole): — PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m^2) — PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m^2) — *or* fractional area change ≤33%
	By MRI:
	• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • *and* 1 of the following: — Ratio of RV end-diastolic volume to BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female) — *or* RV ejection fraction ≤40%
	By RV angiography:
	• Regional RV akinesia, dyskinesia, or aneurysm
Minor	
	By 2D echo:
• Mild global RV dilatation and/or ejection fraction reduction with normal LV • Mild segmental dilatation of the RV • Regional RV hypokinesia	• Regional RV akinesia or dyskinesia • *and* 1 of the following (end diastole): — PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m^2) — PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m^2) — *or* fractional area change >33% to ≤40%
	By MRI:
	• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction • *and* 1 of the following: — Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (female) — *or* RV ejection fraction >40% to ≤45%
II. Tissue characterization of wall	
Major	
• Fibrofatty replacement of myocardium on endomyocardial biopsy	• Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Minor	• Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
III. Repolarization abnormalities	
Major	• Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block QRS ≥120 ms)
Minor	
• Inverted T waves in right precordial leads (V_2 and V_3) (people age >12 years, in absence of right bundle-branch block)	• Inverted T waves in leads V_1 and V_2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V_4, V_5, or V_6 • Inverted T waves in leads V_1, V_2, V_3, and V_4 in individuals >14 years of age in the presence of complete right bundle-branch block

Continued

Table 1 *Continued*

Original task force criteria	Revised task force criteria
IV. Depolarization/conduction abnormalities	
Major	
• Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads (V_1 to V_3)	• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1 to V_3)
Minor	
• Late potentials (SAECG)	• Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG • Filtered QRS duration (fQRS) ≥114 ms • Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms • Root-mean-square voltage of terminal 40 ms ≤20 μV • Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V_1, V_2, or V_3, in the absence of complete right bundle-branch block
V. Arrhythmias	
Major	
	• Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)
Minor	
• Left bundle-branch block-type ventricular tachycardia (sustained and nonsustained) (ECG, Holter, exercise) • Frequent ventricular extrasystoles (>1000 per 24 hours) (Holter)	• Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis • > 500 ventricular extrasystoles per 24 hours (Holter)
VI. Family history	
Major	
• Familial disease confirmed at necropsy or surgery	• ARVC/D confirmed in a first-degree relative who meets current Task Force criteria • ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative • Identification of a pathogenic mutation[†] categorized as associated or probably associated with ARVC/D in the patient under evaluation
Minor	
• Family history of premature sudden death (<35 years of age) due to suspected ARVC/D • Familial history (clinical diagnosis based on present criteria)	• History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria • Premature sudden death (<35 years of age) due to suspected ARVC/D in a first-degree relative • ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative

PLAX indicates parasternal long-axis view; RVOT, RV outflow tract; BSA, body surface area; PSAX, parasternal short-axis view; aVF, augmented voltage unipolar left foot lead; and aVL, augmented voltage unipolar left arm lead.
Diagnostic terminology for original criteria: This diagnosis is fulfilled by the presence of 2 major, or 1 major plus 2 minor criteria or 4 minor criteria from different groups.
Diagnostic terminology for revised criteria: definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories; borderline: 1 major and 1 minor or 3 minor criteria from different categories; possible: 1 major or 2 minor criteria from different categories.
[*]Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria.
[†]A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large non-ARVC/D control population, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree.

Table 8 – Screening Recommendations for Athletes. With permission, from Maron BJ, Thompson PD, Ackerman MJ, et al. Recommendations and considerations related to preparticipation screening for cardiovascular screening in competitive athletes: 2007 update. A scientific statement from the american heart association council on nutrition, physical activity, and metabolism. Endorsed by the american college of cardiology. Circulation 2007;115: 1643.

TABLE. The 12-Element AHA Recommendations for Preparticipation Cardiovascular Screening of Competitive Athletes

Medical history*

Personal history

1. Exertional chest pain/discomfort
2. Unexplained syncope/near-syncope†
3. Excessive exertional and unexplained dyspnea/fatigue, associated with exercise
4. Prior recognition of a heart murmur
5. Elevated systemic blood pressure

Family history

6. Premature death (sudden and unexpected, or otherwise) before age 50 years due to heart disease, in ≥1 relative
7. Disability from heart disease in a close relative <50 years of age
8. Specific knowledge of certain cardiac conditions in family members: hypertrophic or dilated cardiomyopathy, long-QT syndrome or other ion channelopathies, Marfan syndrome, or clinically important arrhythmias

Physical examination

9. Heart murmur‡
10. Femoral pulses to exclude aortic coarctation
11. Physical stigmata of Marfan syndrome
12. Brachial artery blood pressure (sitting position)§

*Parental verification is recommended for high school and middle school athletes.

†Judged not to be neurocardiogenic (vasovagal); of particular concern when related to exertion.

‡Auscultation should be performed in both supine and standing positions (or with Valsalva maneuver), specifically to identify murmurs of dynamic left ventricular outflow tract obstruction.

§Preferably taken in both arms.[37]

Table 9. Reversible Causes of Sudden Cardiac Arrest:

Acidosis
Cardiac Tamponade
Hypothermia
Hypovolemia, Hemorrhage, Anemia
Hypoxia
Hypomagnesemia
Hyperkalemia and Hypokalemia
Myocardial Infarction
Poisoning
Pulmonary embolism
Tension Pneumothorax