Heart disease is the leading cause of death in the US with 700,000 deaths annually, of which 460,000 are attributable to sudden cardiac death (SCD). SCD is usually attributed to ventricular fibrillation (VF). Despite recent reductions in cardiac mortality from other causes, the incidence of SCD remains high with minimal decline in the last decade. The large majority of patients who suffer life-threatening ventricular arrhythmias have advanced left ventricular (LV) systolic dysfunction. Coronary artery disease is the most common predisposing condition in developed countries, accounting for up to 75% to 80% of all cases. Non-ischemic cardiomyopathy and other cardiomyopathic disorders account for 10% to 15% of cases. Inflammatory disorders (i.e. myocarditis), structural heart disease (i.e. valvular or congenital heart disease), and infiltrative disorders (i.e. sarcoidosis) account for about 3% to 5% of cases. There are also comparatively rare but important heritable disorders that can cause SCD in the absence of structural abnormalities of the left ventricle. These include the long QT syndrome (LQTS), Brugada syndrome, and arrhythmogenic right ventricular dysplasia (ARVD), which account for approximately 1% to 2% of cases.

Identifying Patients at Risk for SCD

Genetic Markers of SCD

Genetically inherited disorders should be considered when evaluating patients with syncope or unexplained loss of consciousness and family history of SCD. These patients are often relatively young and have no overt evidence of structural heart disease. For example, the LQTS is a monogenetic disorder associated with prolonged ventricular repolarization, malignant ventricular arrhythmias, typically torsades de pointes, and SCD. In this subset of patients, genetic screening is currently available to identify patients at risk for SCD. Linkage analysis in the early 1990s heralded the identification of several mutations responsible for LQTS phenotypes. LQT1 is due to a mutation in KCNH2, the alpha subunit of the potassium channel, and responsible for cardiac slowly activated delayed rectifying potassium current (Iks). LQT2 is associated with mutation in the human ether-a-go-go gene (HERG), the protein responsible for rapidly activated delayed rectifying potassium current (Ik). LQT5 and LQT6 are due to mutation in KCNE1, the beta subunit of Iks, and KCNE2, the beta subunit of Ik respectively. Mutation in SCN5A, the alpha subunit of the cardiac sodium channel, is responsible for LQT3 and LQT4 is due to mutation in ankyrin B, a cytoskeletal protein that anchors ion channels to cell membrane. Brugada syndrome is characterized by electro-cardiogram (ECG) features of ST elevation in right precordial leads with right bundle branch pattern, and is caused by mutation in SCN5A. More recently, mutation in genes encoding the ryanodine receptor, or calcineurin, was identified as the cause of catecholaminergic polymorphic ventricular tachycardia.

Although these monogenic disorders would appear to be straightforward causes of SCD (i.e. besides carrying a mutated ion channel the patient is otherwise normal), they have revealed a great deal about the complexities and challenges associated with predicting a particular clinical phenotype from a patient’s genotype. Identification of abnormal genotype may not be sufficient to identify patients at risk for SCD. For example, significant proportions of genetically documented LQTS patients, referred to as ‘silent gene carriers’, never develop symptoms. This phenomenon of variable penetrance is widespread in inheritable disorders and thought to be due to environmental factors and genetic polymorphisms that co-exist in patients with abnormal genotypes.

Inherited cardiomyopathic disorders can also cause SCD in young individuals and, particularly, athletes. Hypertrophic cardiomyopathy, a rare form of cardiomyopathy, is familial in over 90% of cases, with over 200 mutations reported in genes encoding for beta-actin, actin, myosin, myosin binding protein C, and actin. Dilated cardiomyopathy (DCM), also referred to as non-ischemic cardiomyopathy, a more commonly observed form of primary myocardial disease and LV dilatation, is associated with inherited mutations in cytoskeletal proteins (desmin, titin, D-sarcoglan, metavinculin) and sarcomere proteins (troponin I, troponin T). Genetic testing, although not frequently
used in patients with DCM, may become a useful tool when more data is available. ARVD is a rare disorder characterized by fibro-fatty infiltration of the right ventricle and malignant ventricular arrhythmias. ARVD has been associated with inherited mutations in desmoplakin, plakophilin-2, plakoglobin, and ryanodine receptor. To date, the clinical utility of genetic screening for these disorders is not known. Therefore, diagnosis and therapy is typically guided by the pattern and severity of the clinical presentation. The signal averaged ECG has known utility in detecting RV conduction abnormality associated with ARVD.

Although there have been some recent advances in understanding the genetic basis for coronary vascular disease, the genetic basis for susceptibility to SCD in patients with coronary disease remains elusive. Recent epidemiological studies have demonstrated an interesting clustering of SCD in families where parents or siblings experience SCD. In the Paris Prospective Study I, the relative risk for SCD was 2.54 with maternal history of SCD, 1.82 with paternal history of SCD, and 9.4 if SCD was present in both parents. In the Seattle Kings County study, incidence of SCD was 50% higher if first degree relatives had SCD or myocardial infarction (MI). Although a few genetic polymorphisms based on limited genetic screening that confer increased susceptibility to SCD are currently known, a more comprehensive screening for candidate genes is necessary to identify the genetic basis for susceptibility to SCD in patients with coronary disease.

### Clinical Indices of SCD Risk

The risk of SCD is closely related to clinical severity of LV dysfunction as measured by LV ejection fraction (EF), and degree of functional impairment (e.g. New York Heart Association (NYHA) class). Numerous studies have demonstrated that when EF falls below 0.35, risk of death due to SCD increases substantially. One of the limitations of risk stratification for SCD based on EF or NYHA class is that the most advanced stages of heart failure are also associated with greatest mortality from progressive heart failure. Under these circumstances, therapy directed at preventing SCD (e.g. implantable cardioverter defibrillators (ICDs)), will not necessarily be helpful. This fact has led to exclusion of such patients in many recent trials aimed at establishing efficacy ICD therapy as primary prevention of SCD. Elevated plasma levels of brain natriuretic peptide, C-reactive protein and troponin T are currently available laboratory indices that are independent predictors of increased mortality in patients with ischemic cardiomyopathy, but have no known role for evaluating risk of SCD.

### Electrocardiographic Indices of SCD Risk

With recent advances in digital processing techniques it is now possible to extract information from the electrocardiogram (ECG) that is not visible on the surface. Several non-invasive electrocardiographic indices are currently available to assess arrhythmia susceptibility in patients at risk for SCD. Signal-averaged ECG (SAECG) is high-resolution ECG that is able to measure low amplitude electrocardiographic potentials in the depolarization phase of the ventricle that are not visible on the surface ECG. These low-amplitude ECG potentials, referred to as late potentials, originate from delayed depolarization within the region of a myocardial infarct (MI). Several clinical trials have used SAECG to assess risk for arrhythmic events after MI; the positive predictive value is approximately 20% and negative predictive value is 97%. However, SAECG failed to predict mortality in a major clinical trial with 1,800 patients followed for 34 months after MI. Furthermore, high-risk patients with non-ischemic cardiomyopathy for SCD cannot be identified using SAECG. At present, the SAECG has limited utility. A major limitation of SAECG is that it cannot be used in patients with bundle branch ECG pattern or atrial fibrillation (AF), which is present in a large number of patients with significant LV dysfunction. Various non-invasive indices of sympathovagal tone have also been used to risk-stratify patients. For example, heart rate variability (HRV) and baroreflex sensitivity were used in the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) trial, where 1,071 post-MI patients were followed for 21 months. Diminished HRV was associated with a 3.4-fold increase in relative risk for events in the whole study group; however, the relative risk for patients with EF<0.35 was only 1.3. There are several important limitations to clinical assessment of autonomic activity. HRV is highly dependent on the ambient conditions under which the measurement is being made, which greatly limits reproducibility in individual patients. Unlike SAECG, there are no randomized trials that have used HRV to guide therapy. There is also...
uncertainty as to the best method to assess HRV. More recently, computerized analysis of beat-to-beat fluctuation in the amplitude of the T wave (i.e. microvolt T wave alternans (TWA)) has been used to assess risk of SCD. TWA is not only a marker for SCD, but has been linked to the mechanism of ventricular arrhythmias that may trigger SCD. To date, numerous independent clinical trials have reaffirmed TWA as a marker for SCD, with positive and negative predictive values in the order of 35% and 95%, respectively. It is important to emphasize that the successful measurement of TWA requires carefully graded heart rate during exercise, so it is not possible to reliably detect TWA with Holter monitoring or during AF. The high negative predictive value of TWA is particularly important in light of recent primary prevention trials that have suggested that large numbers of patients with EF less than 0.35 benefit from ICD therapy; i.e. the question is not “who needs an ICD?”, but rather “who does not?” Bloomfield et al. investigated the prognostic value of the TWA test in 177 patients with EF<0.40, coronary disease, and no prior ventricular arrhythmias (i.e. MADIT II Trial criteria). Patients with a negative TWA test had significantly lower 20-month mortality (3.8%) than patients with a positive TWA test (17.8%). This was also found to be true in a recent study that examined TWA in 282 patients with dilated cardiomyopathy and EF<0.40. Over a 16-month follow-up period, patients with a normal TWA test were found to have significantly lower mortality (0%) than patients with a positive test (8.6%). These data suggest that TWA is an attractive clinical tool for risk-identifying patients who are unlikely to benefit from therapy. Approximately a third of patients who qualify for primary prevention of SCD will have negative TWA tests and, consequently, very low absolute likelihood of events, and corresponding low likelihood to benefit from therapy.

Therapy for Patients at Risk for SCD

Pharmacological Therapy

The Cardiac Arrhythmia Suppression Trial (CAST) firmly established that the use of anti-arrhythmic drugs to suppress or treat ventricular arrhythmias is not only ineffective, but actually increases mortality due to pro-arrhythmic side effects. Despite optimism from earlier trials, amiodarone has failed to prevent SCD in several recent trials. Therefore, currently available anti-arrhythmic drugs have essentially no role in the primary prevention of SCD.

In contrast to anti-arrhythmic drugs directed at cardiac ion channels, pharmacological agents that modulate neurohormonal reflexes have proven effectiveness in preventing SCD. Beta-adrenergic blocking therapy is associated with a 37% reduction in arrhythmic mortality, and is effective in patients with both ischemic and non-ischemic cardiomyopathy. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB), by blocking the harmful effects of angiotensin II on the heart, promote ventricular remodeling, improve EF, and reduce SCD risk by 20% in patients with LV dysfunction. More recently, patients without LV dysfunction with ischemic heart disease had a similar mortality benefit after ACE-inhibitor therapy. Aldosterone antagonists, in recent clinical trials, were associated with an approximately 30% reduction in SCD, although the mechanism for improved survival remains poorly understood. High-dose 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA)- inhibitor therapy in patients with coronary disease has shown evidence of reducing overall mortality; however, its impact on SCD remains to be seen. Recent meta-analysis in patients who consumed dietary and non-diary supplements rich in n-3 polyunsaturated fatty acids was associated with 30% risk reduction for SCD.

Coronary Revascularization

Complete and definite coronary revascularization is of paramount importance in preventing SCD in patients with coronary artery disease. Residual and persistent ischemia is a common cause of increased mortality.

Primary Prevention with ICD Therapy

As many as half of SCDs occur without warning in patients with no previous signs of heart disease. Moreover, without prompt defibrillation, survival rates from out-of-hospital cardiac arrest are extremely poor. Therefore, primary prevention approaches are essential to meaningfully impact SCD from a public health perspective. MADIT I and MUSTT were the first randomized trials to establish the efficacy of ICD therapy in patients with no previous history of life-threatening arrhythmias. MADIT I evaluated patients with coronary disease, EF<0.35, non-sustained ventricular tachycardia (VT) on Holter, and sustained VT during EPS. ICD therapy reduced relative mortality risk by 54% compared with conventional therapy. The MUSTT trial found 76% relative risk reduction in mortality in patients who received ICD therapy. The MADIT II study randomized patients with prior MI, EF<0.30 to ICD therapy versus conventional medical therapy without prior risk stratification (i.e. no EPS). A 30% relative reduction in mortality was observed in patients who received ICD therapy, but absolute risk reduction was only 5.6%. Patients with non-ischemic cardiomyopathy were targeted in the recent Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), which randomized patients with both ischemic and non-ischemic cardiomyopathy in NYHA class II or III and EF<0.35 to ICD therapy, amiodarone therapy, or conventional
medical therapy. A modest 23% relative reduction in mortality was observed in patients who received ICD therapy but not amiodarone therapy; however, the absolute risk reduction was only 7%. Patients with NYHA class II HF with high incidence of SCD benefited the most from ICD therapy in the SCD-HeFT trial, highlighting the importance of early ICD therapy in the natural history of the disease in improving overall survival. Patients in the first few weeks after an MI are at increased risk for SCD. The role of ICD therapy in this population was addressed by the Defibrillators In Acute Myocardial Infarction Trial (DINAMIT), which studied patients within six to 40 days after an MI with EF<0.35 and depressed autonomic tone. Although there was a 58% reduction in arrhythmic mortality with ICD therapy, there was no improvement in overall mortality due to an increased number of non-arrhythmic deaths in patients who received ICDs. The DINAMIT trial suggested that risk stratification for primary prevention of SCD should be deferred beyond the early post-MI period. Despite clear advantages inherent to ICD therapy in improving survival from SCD, several caveats should be considered:

- If one were to follow the primary prevention criteria established in the MADIT II and SCD-HeFT trials, 13 to 17 ICDs would have to be implanted to prevent one SCD. This leaves a large number of patients with the burden of device therapy and no clear clinical benefit, and is associated with significant cost to the healthcare system.

- There is a 10% incidence of complications associated with ICD implantation (i.e. infections, lead failure, etc.), which must be carefully balanced against the benefits of therapy. The number of inappropriate shocks is estimated to be 12% to 35% in patients who receive ICD therapy, potentially causing significant emotional and physical trauma. Therefore, there must be continued development of means of identifying those patients most likely to benefit from this therapy.

Biventricular pacing, an adjunct therapy for patients with ventricular dysynchrony, improves HF symptoms by resynchronizing ventricular activation. Although there are some early reports of mortality benefit, the improvement above and beyond what is gained by ICD therapy remains unclear.

Automated External Defibrillators

Automated external defibrillators (AEDs) are external devices capable of identifying and treating life-threatening ventricular arrhythmias in the absence of trained medical personnel. Increasing public awareness of SCD has triggered lay person training in cardiopulmonary resuscitation and public availability of AEDs. Of the 460,000 annual SCD events, 75% occur at home and 25% occur in public places. Early defibrillation is the key to survival during an episode of VF. Defibrillation within the first minute is associated with 95% survival, within two to seven minutes is associated with 50% to 60% survival, and between eight to 15 minutes is associated with 5% survival. The average emergency medical service response time in the US is eight to 15 minutes, accounting for poor survival of VF in the community. Using the AED, lay personnel with no prior training can perform timely defibrillation, thereby improving the survival rate of VF in the community to 60%. Due to the fact that SCD occurs more frequently at home than in public places and more frequently in patients over 60, it is currently debated whether all patients over 60 should have an AED at home. Patients at high risk after MI or with cardiomyopathy who do not currently qualify for ICD therapy may benefit from home AEDs.

Future Directions

SCD is often the first devastating manifestation of cardiac disease, and often occurs in patients with no previous history of arrhythmias or heart disease. A recent autopsy study of 453 SCDs not related to acute ischemia found structurally normal hearts in more than half the patients. This highlights the importance of discovering reliable markers to identify patients at high risk for SCD. Current strategies to identify susceptibility to SCD are based on assessment of mechanical dysfunction (i.e. reduced EF), and, therefore, are not highly specific to identification of arrhythmia substrates. Therefore, non-invasive risk stratification tools are needed to allow more precise identification of high-risk subsets of patients. At the time of writing, the Alternans Before Cardioverter Defibrillator (ABCD) trial has just completed enrollment and, as the first trial using TWA to guide ICD therapy, may provide novel and much needed indications for ICD therapy. There is also active interest in developing genetic markers for SCD risk. Although recognized mutations causing SCD are rare, it is believed that single nucleotide polymorphisms (SNPs), or subtle alterations in genes encoding relevant proteins, may be relatively common predisposing factors that can be screened by genetic testing. This is an active area of investigation. ICD shocks, although extremely effective in terminating otherwise fatal arrhythmias, do not modify the natural history of SCD. Medical devices are needed that act to prevent or ameliorate progression of electrical instability in the heart, rather than simply responding to VF. One potentially exciting approach is the use of devices that influence arrhythmia substrates by modulating vagal innervation to the heart. Finally, with increasing understanding of the molecules responsible for causing SCD, there will be greater opportunities to use cell,
gene, and pharmacological therapies directed at novel targets. One recent example has been the use of innovative cell therapy strategies to engineer biological cardiac pacemakers.  

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Sudden Cardiac Death


