Sudden cardiac death (SCD) remains a public health problem of immense magnitude, afflicting an estimated 300,000 persons per year in the US. Out-of-hospital arrest has an extremely poor prognosis, thus prevention is critical. Certain risk factors for atherosclerosis are particularly associated with SCD, especially smoking, and smoking cessation is a critical element of prevention. Other cardiac findings such as left ventricular hypertrophy atrial fibrillation have also been associated with SCD. Most patients have a symptomatic prodrome and patients should be educated to heed this warning. Electrocardiogram (ECG) findings at screening are generally non-specific; nevertheless, an elongated QTc interval and signs of left ventricular hypertrophy are markers associated with SCD. There is a genetic component to SCD that is under intense study; patients tend to have a family history of sudden death. Monogenic disorders such as long QT predispose patients to SCD during AMI. Genome-wide association studies have implicated several sites as being associated with SCD in the general population; a single allele linked to SCN5A is found in African-Americans. Treatment with statins is beneficial; other treatments have yet to be proven in primary prevention. Automatic external defibrillators in public sites used promptly by minimally trained personal can be life-saving. Risk stratification is dynamic and should be periodically reassessed.

Keywords
Sudden cardiac death, myocardial infarction, risk stratification, genetics, automatic external defibrillator

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Pathogenesis
Pathological studies have identified two dominant forms of coronary occlusion in SCD. Most cases result from an atherosclerotic plaque rupture of a thin fibrous cap with secondary thrombosis. Other cases are caused by plaque erosion without disruption of the fibrous cap. Plaque erosion is mostly seen in pre-menopausal women who are smokers and is not associated with cholesterol levels. The majority of cases of SCD are the result of ventricular tachyarrhythmias degenerating to ventricular fibrillation (VF). Acute thrombotic occlusion will cause adenosine triphosphate (ATP) depletion with the subsequent opening of potassium ATP (KATP) channels and heterogeneity in action potential duration and propagation, especially around the border zone of the infarct area, paving the way for re-entry circuits. Transmural dispersion of repolarization may be exacerbated by limited repolarization reserve in patients with mutations in genes for ion channels, explaining the increased risk of SCD in AMI for subjects with elongated QT intervals.

Therefore, risk reduction of SCD should target the instigating plaque, the mechanisms for development of ventricular arrhythmias and prompt defibrillation of lethal arrhythmias.
Clinical Epidemiology
Epidemiological studies and autopsies of victims of SCD in AMI indicate that several coronary disease risk factor profiles may predispose subjects to sudden death. Gender differences are particularly marked, with a male predominance to SCD, MI, and SD during MI. In contrast, most SCD in women is non-coronary.8 Age is an important consideration, with the incidence of SCD of an acute coronary occlusion increasing beyond the age of 40. In younger age groups cocaine abuse should be considered. Cigarette smoking is a provoker of acute thrombosis9 and coronary spasm10 and has been found to be an SCD risk factor in multiple studies.8,8-13 Smoking cessation rapidly reduces SCD risk even in secondary prevention.2,13 Promotion of smoking cessation is a critical element of risk reduction. Hypercholesterolemia, an insidious risk factor, is less prone to provoking VF, possibly due to myocardial preconditioning.11,14 A history of atrial fibrillation is associated in two studies with SCD.15,16

Prodomal Symptoms
Although the final event may be defined as sudden, many SCD victims have had unheeded symptoms well prior to their demise. Up to 50% suffer from prior angina in the preceding year11,14 and most have sentinel symptoms such as angina, dyspnea, and nausea. In one series, half of the victims had ingested pain killers less than 12 hours prior to death.2 Thus, education of the general population to act on these symptoms, particularly in high-risk groups, may enable patients and family members to take critical preventive measures.

The Electrocardiogram in Risk Stratification
The 12-lead electrocardiogram (ECG) provides important risk stratification for SCD; in non-ischemia-related sudden death disorders, such as long QT, Brugada, and arrhythmogenic right ventricular dysplasia, the ECG is central to the diagnosis. In general, the 12-lead ECG lacks markers that are sufficiently sensitive and specific for risk stratification in ischemic heart disease.17 ECG signs of left ventricular hypertrophy should be assessed.11 A corrected QT interval (QTc interval) longer than 440ms has a relative risk (RR) of two for SCD.18 During the course of infarction, the sum of ST elevation predicts a poor outcome.14

Several studies have found occlusion of the right coronary artery to be more prone to arrhythmia than occlusion of the arteries of the left system, but this finding is inconsistent.15,16 Multiple studies have found collateral flow to be protective, thus revascularization to restore coronary flow should be a preventive strategy even if a ruptured plaque would occlude a different artery.

Pharmacological Interventions
Several studies indicate that statin treatment reduces the incidence of SCD and appropriate implantable cardioverter-defibrillator (ICD) therapies in patients with ischemic heart disease.20 Although beta-blockers and angiotensin-converting enzyme (ACE) inhibitors have been proven to reduce mortality in patients post MI or with heart failure, their role in primary prevention of SCD in AMI remains unclear.

Genetic Factors
In theory, genetic studies have great potential as screening tools. It has long been appreciated that a family history of SCD is a predictor of SCD in offspring and siblings. The Paris Prospective study found an RR of 1.8 of SCD for patients with one parent who had suffered SCD, and an RR of 9.4 if both parents were afflicted.21 In the Arrhythmia genetics in the Netherlands (AGNES) trial, Dekker et al. found that the presence of one first-degree relative with SCD incurred an RR of 2.72 for SCD.15 Certain monogenic disorders are known to place patients at a particularly high risk for sudden death at presentation of an AMI. Patients with long QT syndrome suffering from an AMI may develop refractory torsades des pointes resulting from further elongation of the QT segment22,23 (see Figure 1).

Multiple studies have implicated mutations causing even modest increases in the QT interval with SCD. In one specific ethnic group, African-Americans, a common polymorphism in SCN5A, Y1102, increases the susceptibility to SCD with an RR of eight.24 Recent genome-wide association studies have implicated several alleles as
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being linked to sudden death in AMI. The first, found at chromosome 21q21, is at a site in proximity to a viral receptor gene known to participate in the pathogenesis of myocarditis.22 Another study found a different polymorphism in proximity to the SCN10A gene, a gene that modifies the PR interval.23 Despite the statistical significance of these findings, the absolute risk remains small, precluding use of routine genomic sequencing for risk stratification today.

Use of Automatic External Defibrillators

The use of automatic external defibrillators (AEDs) in public places has been shown to double the survival rate of out-of-hospital SCD.24 Training of laymen in basic life support and deployment of AEDs in public places will increase survival in cases of SCD with an initial rhythm of ventricular fibrillation to 56%.25 These studies indicate that in order to be beneficial, defibrillation should be deployed within three minutes of a witnessed arrest. Timely intervention is dependent on the immediate availability of an AED and minimally trained personnel capable of operating it. When lacking such preconditions, such as in home-based AEDs, no survival benefit is realized.

In conclusion, no single risk factor today has sufficient strength to justify an intervention alone. Several risk scoring algorithms have been suggested based on the assessment of multiple factors; none have been validated prospectively. Patients at high risk should be considered for risk factor modification and medical therapy and, and possibly revascularization. This assessment is dynamic and should be reassessed periodically.