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Early identification of risk factors for sudden cardiac death

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Abstract

Sudden cardiac death (SCD) is a global health issue. The unexpected nature of this devastating condition compounds the urgency of discovering methods for early detection of risk, which will lead to more effective prevention. However, the complex and dynamic nature of SCD continues to present a considerable challenge for the early identification of risk factors. Measurement of the left ventricular ejection fraction (LVEF) is currently the only major risk factor used for stratification in clinical practice. Severely decreased LVEF is likely to manifest late in the natural history of SCD, however, and may only affect a small subgroup of patients who will suffer SCD. A growing body of literature describes novel risk markers and predictors of SCD, such as high-risk phenotypes, genetic variants and biomarkers. This Review will discuss the potential utility of these markers as early identifiers of risk, and suggests a framework for the conduct of future studies for the discovery, validation and deployment of novel SCD risk factors.

Introduction

Sudden cardiac death (SCD) remains a substantial, worldwide health issue. On a yearly basis, this condition results in 200,000–250,000 deaths in the US.1 At the present time an accurate assessment of the global burden of SCD is not available, but a crude estimate would be in the range of 4–5 million.1 SCD is an inevitable outcome for most victims of sudden cardiac arrest, which is defined as a sudden and unexpected pulseless condition of cardiac etiology. It is important to make a clear distinction between SCD and acute myocardial infarction (AMI) or heart attack. SCD is the manifestation of a fatal heart rhythm disorder such as ventricular tachycardia, ventricular fibrillation or a severe bradyarrhythmia, while AMI occurs due to an occlusion of a coronary artery resulting in an imbalance of blood flow demand and supply to the myocardium. However, a subgroup of patients who suffer SCD will initially present with AMI. SCD usually occurs within minutes of symptoms such as chest pain, dyspnea or palpitations; this outcome can in part be attributed to the fact that emergency medical response systems that provide advanced cardiac life support are available only in a minority of the world regions, concentrated largely in developed countries. However, even in North America where first responder systems are available and there have been extensive improvements in resuscitation methodology and deployment, average survival from sudden cardiac arrest remains below 5%.2 The discovery of effective prevention modalities, therefore, is of great importance. Additional features of SCD make early detection of risk factors critical. By definition, the sudden and unexpected nature of SCD prevents timely access to potentially life-saving interventions, such as thrombolytic therapy or percutaneous transluminal coronary angioplasty for acute coronary syndromes.1, 3 Furthermore, while there is usually an underlying substrate that puts individuals at risk,

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this may not be uncovered in advance. In fact, 40–50% of all SCD cases will have a cardiac arrest with no prior symptoms or warnings.[1, 3] As a result, SCD risk stratification is an area of active investigation and this Review describes several potential risk markers that have been identified and novel testing strategies that are in development.

Current status of SCD risk prediction

The risk of SCD increases with advancing age, peaking in the 75–84 year age group.[1, 3] The etiology of this condition is multi-factorial,[4] but most SCD cases (≥80%) have associated coronary artery disease (CAD). Other associated conditions include dilated or hypertrophic cardiomyopathy (10–15% cases) and a smaller subgroup (5–10%) have primary genetic or congenital disorders, such as long QT syndrome, Brugada syndrome, congenital structural heart disease or sudden unexplained death (sudden death with structurally normal heart but no identifiable genetic etiology).[1, 5] For the relatively rare primary genetic syndromes such as long QT syndrome and hypertrophic cardiomyopathy patients qualify as high-risk based on a combination of familial and individual clinical history, as well as the identification of specific genetic mutations that are associated with higher risk.[6, 7] However for the most common cases such as patients with CAD that constitute the vast majority, there are no established risk factors that can be used to identify a high-risk patient early in the natural history of the condition.[1] At present, severe left ventricular (LV) systolic dysfunction, measured by the LV ejection fraction (LVEF), is the only clinical variable utilized for SCD risk stratification in clinical practice.[1] Patients who have an LVEF <30–35% are considered to be high-risk, and qualify as candidates for primary prevention using an implantable defibrillator.[8, 9] Community-based studies clearly indicate, however, that the LVEF alone is insufficient for effective SCD risk stratification. It was hypothesized early on, that the minority of patients who suffer SCD may not have severe LV dysfunction.10 This was later proven by community-based studies that showed less than one-third of all SCD cases will have severely decreased LVEF that meets criteria for high risk of SCD (Figure 1).[11–13] Furthermore, only a small proportion of patients who qualify for defibrillator implantation based on severely decreased LVEF will suffer ventricular arrhythmia resulting in SCD (2–5% per year over a 3–5-year follow-up).[8, 9] Despite the shortcomings of the LVEF, numerous risk stratification test modalities have been evaluated over the past three decades and none has been found to be superior to this parameter.14 These include low long-term heart rate variability, a measure that correlates with overall mortality but is unlikely to be specific for risk of SCD.[14–16]; abnormal signal-averaged ECG, a modality that appears to be associated with SCD but a potential utility for prediction of risk has not been demonstrated;[17, 18]; and abnormal T-wave alternans for which results are mixed and more evidence is needed before this technique is employed widely for SCD risk stratification.[19–21] Finally, although a small subgroup of patients have asymptomatic severe LV systolic dysfunction, most patients have their LVEF evaluated only if they manifest with symptoms and this risk factor is identifiable late in the natural history of SCD.

Phenotypes associated with SCD risk

Phenotypic traits other than severe LV systolic dysfunction have been associated with SCD, but are not currently utilized for assessment of risk. The Framingham Heart Study reported an association between LV hypertrophy as measured by a critical increase in echocardiographic LV mass and SCD, independent of risk factors for CAD. [22] The Rotterdam study reported that prolonged QTc interval was independently associated with SCD in a cohort of unrelated individuals; [23] this relationship was confirmed in the general population from the Oregon-Sudden Unexpected Death Study.[3, 13, 24–31] The latter study found a more than fivefold increased SCD risk among individuals with CAD who had idiopathic prolongation of the QTc interval in the absence of diabetes or QT-prolonging

drugs. [26] There are other electrocardiographic findings that have been associated with increased SCD risk. Among patients who suffer SCD in the setting of AMI, the subgroup with right coronary or left circumflex coronary artery involvement may be distinguished by a longer QRS interval when compared to cases of uncomplicated AMI.32 A fragmented morphology of the QRS complex, a high risk predictor in conditions such as arrhythmogenic right ventricular dysplasia has also been shown to predict risk of overall mortality and SCD among patients with CAD.33 Specific alterations in heart rate may also indicate elevated risk of SCD. Four cohort studies have reported an association between increased resting heart rate and future risk of SCD.34–[37] Furthermore, even small increases in heart rate (mean heart rate increase 8.9 ± 10.8 beats per minute) owing to mild mental stress, predicted long-term risk of SCD in the Paris Prospective Study.[38] Diverse conditions with a broad spectrum of effects, such as diabetes39–41 and low socioeconomic status, 30 have also been independently associated with increased SCD risk. The Oregon Sudden Unexpected Death Study has recently drawn attention to the fact that risk factors for SCD in the general population are likely to be gender-specific.[28] Women have a significantly lower prevalence of phenotypic traits that confer risk than men, with half the likelihood of severe LV dysfunction (odds ratio [OR] 0.51, 95% CI 0.31–0.84) and a threefold lower prevalence of established CAD (OR 0.34, 95% CI 0.20–0.60).[20]

Genetic Contribution to SCD

Four studies have been published in the past decade that provide clear evidence of an independent genetic contribution to SCD. A study of men and women who had been attended by paramedics following primary cardiac arrest was carried out between 1988 and 1994. 42, [43] A detailed history of SCD in first-degree relatives was obtained from the spouses of 235 cases and 374 control subjects. The risk of SCD was significantly higher in cases with a parental history of SCD that occurred under the age of 65, compared with controls (OR 2.7, 95% CI 1.3–5.4) after adjustment for parental history of myocardial infarction (MI) and other risk factors. The Paris Prospective Study was performed in a cohort of 7,746 asymptomatic middle-aged males (43–52 years) followed for a mean of 23 years.[44] The occurrence of SCD in a parent resulted in a 1.8-fold increase in SCD susceptibility after controlling for CAD risk factors as well as AMI. In a small number of cases in the Paris Prospective Study where there was a history of both maternal and paternal SCD (n = 19), the offspring had a ninefold increased risk of SCD. Two studies reported familial aggregation of SCD among patients who presented with symptomatic CAD. The first study compared cases with ST-elevation MI and ventricular fibrillation with controls who had ST-elevation MI, but no ventricular fibrillation. 45 Cases with ST-elevation MI and ventricular fibrillation were significantly more likely to have a family history of SCD than controls (OR 2.7, 95% CI 1.8–4.0). The Finnish Genetic Study of Arrhythmic Events carried out detailed postmortem examinations of out-of-hospital SCD cases. [46] A total of 138 SCD cases who had an acute ischemic event on autopsy were compared with 254 patients who had a nonfatal AMI (without a history of ventricular arrhythmias) as well as with a normal control group (n = 470). The Finnish study reported that a history of SCD was significantly more likely in the SCD group compared with the nonfatal AMI group (OR 1.6, 95% CI 1.2–2.2) or normal controls (OR 2.2, 95% CI 1.6–3.0). A strong family history (SCD in ≥2 first-degree relatives) was even more common among SCD cases compared with AMI survivors (OR 3.3, 95% CI 1.4–7.8) or controls (OR 11.3, 95% CI 4.0–31.8). These four studies conducted in diverse populations using varying methodology make a convincing case for familial aggregation of SCD cases owing to genetic transmission of susceptibility to SCD. Furthermore, this susceptibility seems to be independent of acute CAD manifestations, such as acute coronary syndromes and AMI.

Challenges of early SCD risk prediction

No symptoms have been identified as specific for SCD in those patients who do develop symptoms before the event. Patients can experience diverse symptoms such as palpitations, chest discomfort, dyspnoea, pre-syncope or syncope; or SCD can manifest in the complete absence of warning symptoms. There is also a considerable overlap between the risk factors for related conditions, such as acute coronary syndrome and congestive heart failure, which makes it difficult to identify patients who are likely to suffer from SCD. Superimposed on fundamental high-risk substrates such as CAD and congestive heart failure are a mosaic of conditions that function as risk markers and intermediate risk phenotypes (Figure 2). For example, diabetes doubles the risk of SCD, 40, 44 and the QT interval measured by the 12-lead electrocardiogram (ECG) is associated with up to six-fold increased risk in patients with CAD who have QT prolongation of unknown etiology. 26 Even for complex SCD phenotypes, there seems to be a considerable genetic contribution that is independent of CAD or other associated events, such as AMI. 47, 48 The challenges of early risk stratification in SCD are compounded by the generally accepted paradigm of requiring both a substrate and a trigger for occurrence of the final dynamic event.4 A large body of literature provides evidence for environmental influences on SCD, ranging from low socioeconomic status being an important determinant of risk, to psychological stress being a likely trigger of this dynamic event.[1, 30] Since a large proportion of patients who suffer SCD will be asymptomatic until the fatal event and the etiology of SCD is multifactorial,[49] it is logical that any identified risk factors could either consist of several related factors, or abnormal results from the tests that are employed to determine risk.

Advances in early SCD risk detection

As with other disease conditions, the overall approach to early identification of risk predictors for SCD is driven by the complexity of the phenotype. Some risk predictors, such as genetic susceptibility, will apply to all patients who will suffer SCD, albeit to a varying degree in different subgroups and age categories. Other risk predictors, such as serum markers or ECG may be applicable to specific subgroups. Similarly, the nature of noninvasive tests that will be adopted in the future may also limit their use to specific SCD subgroups. For example, patients who are in an early stage of a cardiomyopathy may benefit from myocardial imaging whereas patients with subclinical atherosclerosis should be stratified by imaging directed at identifying vulnerable plaques in the coronary circulation. An important distinction also needs to be made between risk factors and testing in an individual, versus factors and testing that may be utilized in the general population. Selected individuals, for example those exhibiting specific symptoms such as chest pain, or sub-phenotypes such as LV hypertrophy, may benefit from a particular test or risk factor, whereas applying these to the general population may be inefficient because of low specificity. Unless methods for early detection of SCD risk factors meet stringent criteria for both efficacy and cost-effectiveness, it will not be feasible to deploy them as screening tools in the general population.

Measuring genetic susceptibility

Up until the past decade, our limited knowledge of genetic susceptibility for SCD has been drawn from largely monogenic familial syndromes that cause increased risk of sudden death. In subjects with the long QT syndrome (LQTS), prolongation of the QT interval and susceptibility to torsades de pointes arrhythmia and SCD[50, 51] (Figure 3) are attributed to cardiac ion channel dysfunction.52, 53 In the majority of cases, cellular repolarization is prolonged either by decreased outward potassium current IKs (LQT1, LQT5) or IKr (LQT2, LQT6), or by increased activity of mutant inward sodium current (LQT3).[54, 55] At the present time, mutations causing LQTS have been described in at least 12 distinct genes.56

Brugada syndrome is associated with ECG findings of right ventricular conduction delay and ST elevation in the right precordial leads along with an increased risk of SCD (Figure 4).[57–59] Most frequently, this condition is caused by mutations in SCN5A that result in a gain of sodium current. The same gene is implicated in LQTS 3 but the phenotype is reversed and mutations result in a gain of sodium current. Less frequently, Brugada syndrome results from mutations in GPD1L or SCN1B also through a decrease in sodium current, or from mutations in CACNA1C and CACNB2b that result in loss of function of the L-type calcium channel. Catecholaminergic polymorphic ventricular tachycardia, a condition characterized by exercise-induced syncope and SCD, has been associated with mutations in RYR2 (the cardiac ryanodine receptor gene). Even with multiple genes characterized, risk stratification in LQTS is based largely on the clinical phenotype including age, gender, history of symptoms (aborted cardiac arrest or syncope), and extent of QT interval prolongation. However, there is growing evidence that the nature of the LQTS genotype may also influence risk. Patients who have mutations in two LQTS genes usually manifest with a more severe clinical phenotype and a recent study reported that non-LQTS genes can function as genetic modifiers of SCD risk in LQTS patients.[60] In the post-genomic era, however, genetic studies are being conducted among unrelated individuals and two distinct approaches are rapidly contributing knowledge regarding genetic variants associated with SCD.26,28 The candidate gene approach examines association of SCA risk with common variations in genes selected from established molecular pathways leading to ventricular arrhythmogenesis.47 The technique utilizes linkage disequilibrium in the genome to evaluate genotype-phenotype associations. Therefore, all known common variants in the gene can be efficiently evaluated using a limited set of genetic markers. However, the inherent shortcoming of this approach is that genetic variants are uncovered only from the candidate genes that are tested, with no consideration given to the remainder of the genome. Studies using this approach have contributed and evaluated multiple and diverse genetic variants that either confer risk or protection from SCD, but many were not reproducible in separate populations.[29–34] By contrast, genome-wide association studies (GWAS) examine and compare the genetic sequence of individuals to identify regions of common variants (Figure 5). Since a survey is conducted of the entire genome, GWAS are unbiased, with a potentially higher yield than the candidate gene approach.[26] An early proof of concept was provided by a GWAS conducted to identify genetic variants that determine duration of the QT interval measured from the 12-lead ECG. Novel variants in the gene encoding the carboxyl-terminal PDZ ligand of neuronal nitric oxide synthase protein (*NOS1AP*) were identified[35] and replicated in multiple studies.[29,36–40] Furthermore, variants in this gene also have a modest but notable effect on risk of SCD—an effect that has now been observed in at least two separate populations.[61, 62] Interestingly, variants in *NOS1AP* have also been reported as modifiers of SCD risk in patients with familial long QT syndrome.[60] An initial GWAS of SCD using a population-based case-control approach has recently been published from the Oregon Sudden Unexpected Death Study and replicated in the combined Atherosclerosis Research in Communities and Cardiovascular Health Study cohort.[63] This GWAS identified a single nucleotide polymorphism in the gene *GPC5* that codes for glypican-5, the minor allele of which confers protection against risk of SCD (Figure 6).[63] The glypican family contains six members (GPC1 to GPC6) all of which are heparan sulfate preoteoglycans expressed in large quantities on cell surfaces as well as extracellular matrix in the cardiovascular system.[64] Since these genes regulate vasculogenesis following ischemic injury, as well as interactions of cells with adhesive proteins and blood vessels65 it is postulated that the protective effect of the GPC-5 SNP may be mediated by yet unknown actions on the vulnerable plaque or thrombosis cascade. Defects in GPC5 have yet not been associated with disease, but mutations in GPC3 and GPC4 cause the Simpson-Golabi-Behmel syndrome a condition accompanied by increased risk of arrhythmias and SCD.66, 67 Autosomal recessive omodysplasia, characterized by severe short stature and congenital heart defects, is caused by homozygosity for null

mutations in GPC6.[68] Even though this SNP did not reach genome-wide significance defined by $p<5\times10^{-8}$ (*GPC5* SNP $p<8.2\times10^{-5}$), the finding was successfully reproduced in a separate community-based cohort.[63] Clearly, additional GWAS conducted on larger numbers of SCD cases are warranted. Given the complexity of the phenotype and the fact that GWAS identify common variants, this type of analysis is likely to provide a panel of genetic variants that will be used to assess SCD risk. However, before these methodologies become used in clinical practice, the panels as well as the technologies will require validation and replication in multiple populations to minimize the potential confounding effects of false positive results. There is also significant room for an ongoing discussion on the broader implications of genetic screening. In the immediate future, it is likely that that the technology for generation of personal genomic information will outpace the understanding of the functional significance of genetic variants that are discovered.[69] To maximize the clinical utility of SCD genomic screening for prevention, the functional evaluation of novel genetic variants must proceed at a matched pace. For example, premature clinical utilization of genomic information predicting susceptibility to SCD could lead to inappropriate use of preventive modalities such as the implantable defibrillator, representing unjustified use of health care resources. Conversely, careful ongoing evaluation of the predictive ability and cost-benefit balance of newly developed tests that effectively utilize genotype-phenotype correlations could significantly enhance the process of SCD risk stratification.[69] These developments need to proceed in concert with a societal dialogue that equips individuals with the information they need to balance risk of disease vs. the intervention, testing in family members and economic implications, particularly if such tests will be sold directly to consumers.[69]

Other biomarkers

Several cohort studies have reported risk markers of SCD in the blood. The Physicians' Health Study identified C-reactive protein levels as a potential risk marker in men, where men in the highest quartile of C-reactive protein levels had significantly greater risk of SCD than men in the lowest quartile (OR 2.78, 95% CI 1.35–5.72).[70] The Nurses' Health Study, however, reported N-terminal pro b-type natriuretic peptide (NT-proBNP) levels as a risk marker in women. Rates of SCD were twofold higher in the highest quartile than in the lowest quartile (RR 2.37, $P = 0.05$) when adjusted for CAD risk factors and biomarkers.[71] Further work is needed before these biomarkers can be employed for early detection of SCD risk.[72] Prospective cohort studies have also identified some markers of membrane stability, such as nonesterified fatty acids, n-3 fatty acids, and *trans* fatty acids that are associated with SCD risk.[70, 73] Two additional population-based studies reported consistent associations between *trans* fatty acid levels and SCD.74, [75] Both found significantly increased risk associated with the trans isomer of linoleic acid (trans-18:2) (OR 2.34, 95% CI 1.27 to 4.31), and decreased risk with the trans isomer of oleic acid (trans-18:1) (OR 0.18, 95% CI 0.06–0.54).[75,] 76 Cause and effect has yet not been proven for the association between elevated levels of specific fatty acids and increased SCD risk. However it has been hypothesized that free fatty acids are likely to alter the configuration of the cell membrane lipid bilayer, resulting in deleterious effects on the function of cardiac ion channels.77 A small study of 32 healthy human subjects reported that increase in serum FFA correlated with prolonged QTc interval as well as independently increased levels of serum epinephrine, both of which have potential arrhythmogenic effects.78

Imaging to detect risk of SCD

For an imaging technique to successfully provide assessment of SCD risk, the technique would need to capture the pathophysiology of a mechanistic pathway leading to ventricular arrhythmia (molecular imaging), and the measurements would need to be quantifiable and reproducible. Abnormal remodeling of the myocardial interstitium, with excessive and

abnormal deposition of collagen is an established determinant of ventricular arrhythmogenesis.79 Therefore, techniques that detect diffuse fibrosis are likely to play a role in SCD risk assessment. Early studies with conventional Gadolinium-based contrast agents have focused on quantifying the extent of infarct border-zone80 or intermediate ("gray") zones in other SCD high-risk conditions.81 However, there are early attempts at imaging diffuse fibrosis using this methodology as well.82 Three are early reports of successful imaging directed at other targets of potential interest. Cardiomyocyte apoptosis has been imaged with MRI using an annexin-labeled magneto-fluorescent nanoparticle 83. Abnormalities of autonomic tone have long been associated with increased risk of SCD84 and there are imaging techniques that can evaluate both sympathetic and parasympathetic nerve activity in the heart. Specific cardiac sympathetic nerve activity can be assessed in vivo by ^{123}I-metaiodobenzyl-guanidine (MIBG) scintigraphy and increased MIBG washout represents increased sympathetic nerve activity. In a study of 106 patients with mild to moderate congestive heart failure followed for 65 ± 31 months, those with abnormal MIBG washout rate (>27%) had a significantly higher risk of SCD compared with those who had a normal washout rate (adjusted hazard ratio 4.79, 95% CI 1.55–14.76).[85] These findings were observed in patients with and without severe LV dysfunction as measured by LVEF<35% (Figure 7). In humans, the cardiac parasympathetic system can be imaged in vivo using positron emission tomography (PET) and the specific muscarinic antagonist [^{11}C]methylquinuclidinyl benzilate ([^{11}C]MQNB). A recent small study of 20 patients reported that following a myocardial infarction, this technique can identify regional differences in muscarinic receptor density within myocardium, which could indicate regional differences in parasympathetic innervation [86]. In the future, such techniques could be of potential utility for SCD risk stratification and merit evaluations in larger numbers of patients.

The future of early SCD risk prediction

The complex nature of the SCD phenotype demands an integrated and inter-disciplinary approach for identification of early risk predictors.[1, 87–89] Findings from population-based analyses, implantable defibrillator populations, prospective human studies of high risk phenotypes and mechanistic evaluations in the animal laboratory as well as the bench will need to be effectively amalgamated for the highest yield.[1, 90] It is likely that the ongoing identification of potential genetic, clinical, molecular and imaging risk predictors will lead to a panel of markers that will be more effective in predicting risk than any individual marker. Discovery of such novel risk markers will require investment in population-based studies of SCD with validation of an 'early detection SCD risk score (EDRS)' in multiple populations. Given the annual incidence of SCD in the general population (60 in 100,000), future deployment of a SCD EDRS will need to be focused and cost-effective. Rather than generalized screening of the population, it will be more feasible to focus on patients who present for clinical attention or are recognized to have risk factors or a diagnosis made of an SCD substrate. For example, in the future, patients with an established diagnosis of CAD could undergo screening with an SCD EDRS (Figure 8). Some studies that aim to identify and validate SCD risk markers are being conducted in patients with implantable defibrillators; it should, however, be recognized that these studies serve the separate purpose of optimizing the candidate for the implantable defibrillator and are unlikely to be acceptable surrogate populations for defining early detection of SCD risk.

Conclusions

Although SCD risk prediction is an area of active research, identification of severe LV systolic dysfunction by measurement of the LVEF is the only major risk factor utilized in clinical practice. For most patients, this is unlikely to represent an early risk factor for SCD.

Therefore, there are currently no risk factors that are used in clinical practice for early identification of SCD risk. Community-based studies have confirmed that approximately 70–75% of all SCD cases have either normal or mild to moderately decreased LV systolic function prior to their fatal event. As a result there is a critical need for novel risk factors to be identified and utilized. Several additional clinical phenotypes have been associated with SCD risk and need to be further evaluated. There is a clear genetic contribution to SCD, even for the most common kind of SCD patient who has associated CAD. Much has been learned from the less common familial syndromes but more recently, genome wide association studies have begun to identify novel genetic variations associated with SCD. Serum biomarkers that predict SCD risk are being identified on an ongoing basis. The tools for molecular imaging of the coronary arteries and myocardium have undergone significant development and several will soon find application in enhancing SCD risk stratification. The ultimate goal of integrating novel markers into cost-effective risk panels for early detection of SCD risk has become an important and urgent priority. Effective early detection of SCD risk cannot currently be performed for most patients, but investigative approaches and the requisite technology are advancing at a pace that will make this a clinical reality in the near future.

Biography

Dr Chugh is the Pauline and Harold Price Professor, Associate Director of the Heart Institute and Director of Cardiac Electrophysiology at Cedars-Sinai Medical Center, Los Angeles, California, USA. His research focuses on enhancing prediction and prevention of sudden cardiac death, and he directs the Oregon Sudden Unexpected Death Study ongoing since 2002. He is currently a charter member of the Electrical Signaling, Ion Transport, and Arrhythmias Study Section, National Institutes of Health; chair of the Clinical and Research Training Committee of the Heart Rhythm Society; and chair of the Global Burden of Disease panel on arrhythmias and conduction system disorders.

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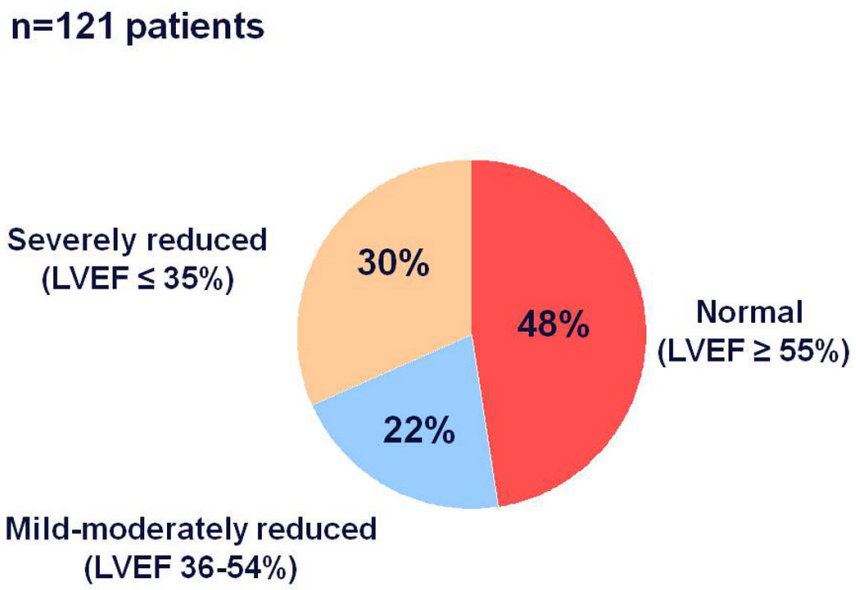

Figure 1. Contribution of severe LV systolic dysfunction to SCD in the general population
Findings from the Oregon Sudden Unexpected Death Study. Measured by LVEF≤35% and currently the risk predictor most widely used in clinical practice, severe LV dysfunction affects less than a third of all cases of sudden cardiac death in the general population. Abbreviations: SCD, sudden cardiac death; LVEF, left ventricular ejection fraction. **Figure modified by permission of Progress in Cardiovascular Diseases ©2008**.

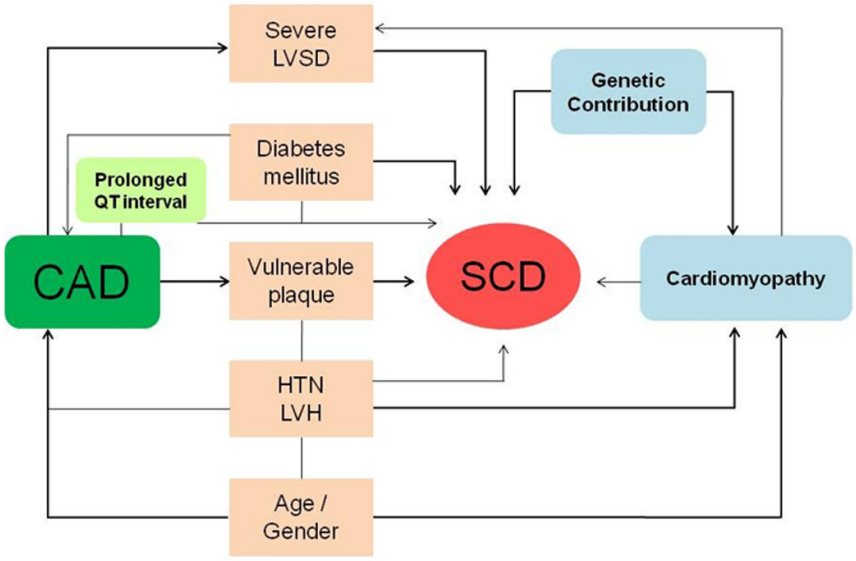

Figure 2. Risk factors associated with SCD in patients with coronary artery disease

This schematic focuses on the subgroup of patients with CAD who suffer SCD; the complexity of the SCD phenotype presents considerable challenges for the discovery of risk factors early in the natural history of the condition. Abbreviations: CAD, coronary artery disease; HTN, hypertension; LVH, left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; SCD, sudden cardiac death.

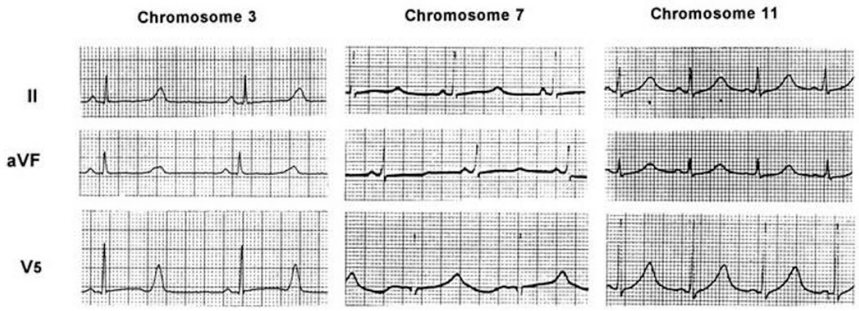

Figure 3. Electrocardiographic patterns in genetically distinct forms of the long QT syndrome

ECG recordings from leads II, aVF, and V5 in three patients from families with long QT syndrome linked to genetic markers on chromosomes 3, 7, and 11. Chromosome 3, 15-year-old boy (family 1) with a mutation in the cardiac sodium channel gene SCN5A; the QTc in lead II is 570 ms with late-onset T waves of normal duration and amplitude. Chromosome 7, 21-year-old woman (family 3); the QTc in lead II is 583 ms with low-amplitude T waves. Chromosome 11, 31-year-old woman (family 6); the QTc in lead II is 573 ms with early onset of broad-based T waves. Abbreviation: QTc, corrected QT interval.

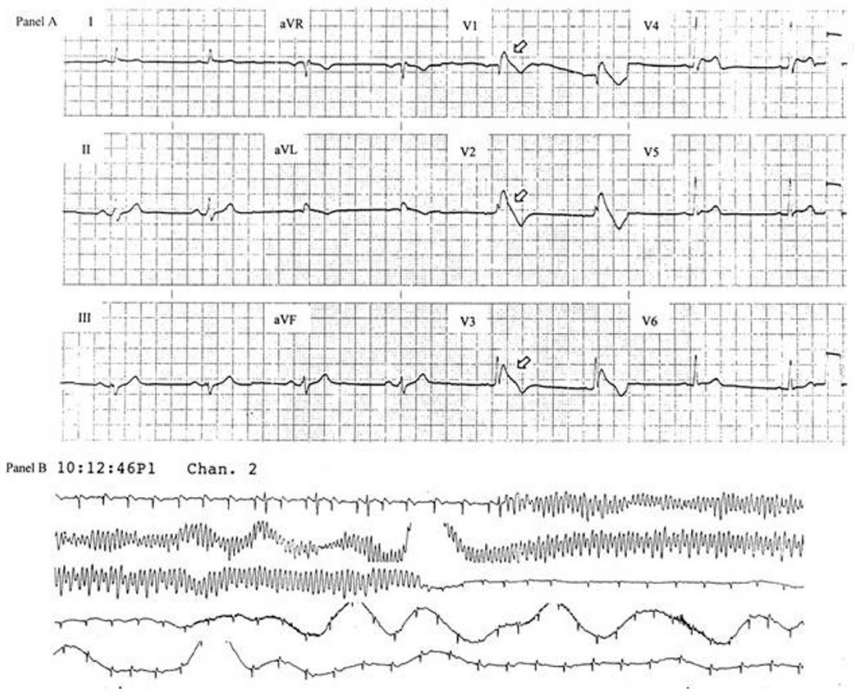

Figure 4. Electrocardiographic findings and manifestation of arrhythmia in the Brugada syndrome

(A) Twelve-lead electrocardiogram of a patient with the Brugada syndrome. The right precordial leads, V1 to V3, display a down-sloping ST segment elevation. QRS is normal but QT dispersion between V2 and V6 is larger than normal (120 ms). (B) Self-terminating polymorphic ventricular tachycardia (continuous recording) in a patient with the Brugada syndrome. Closely coupled premature ventricular contractions precede the onset of tachyarrhythmia. Note the disappearance of the repolarization abnormalities following the arrhythmia.

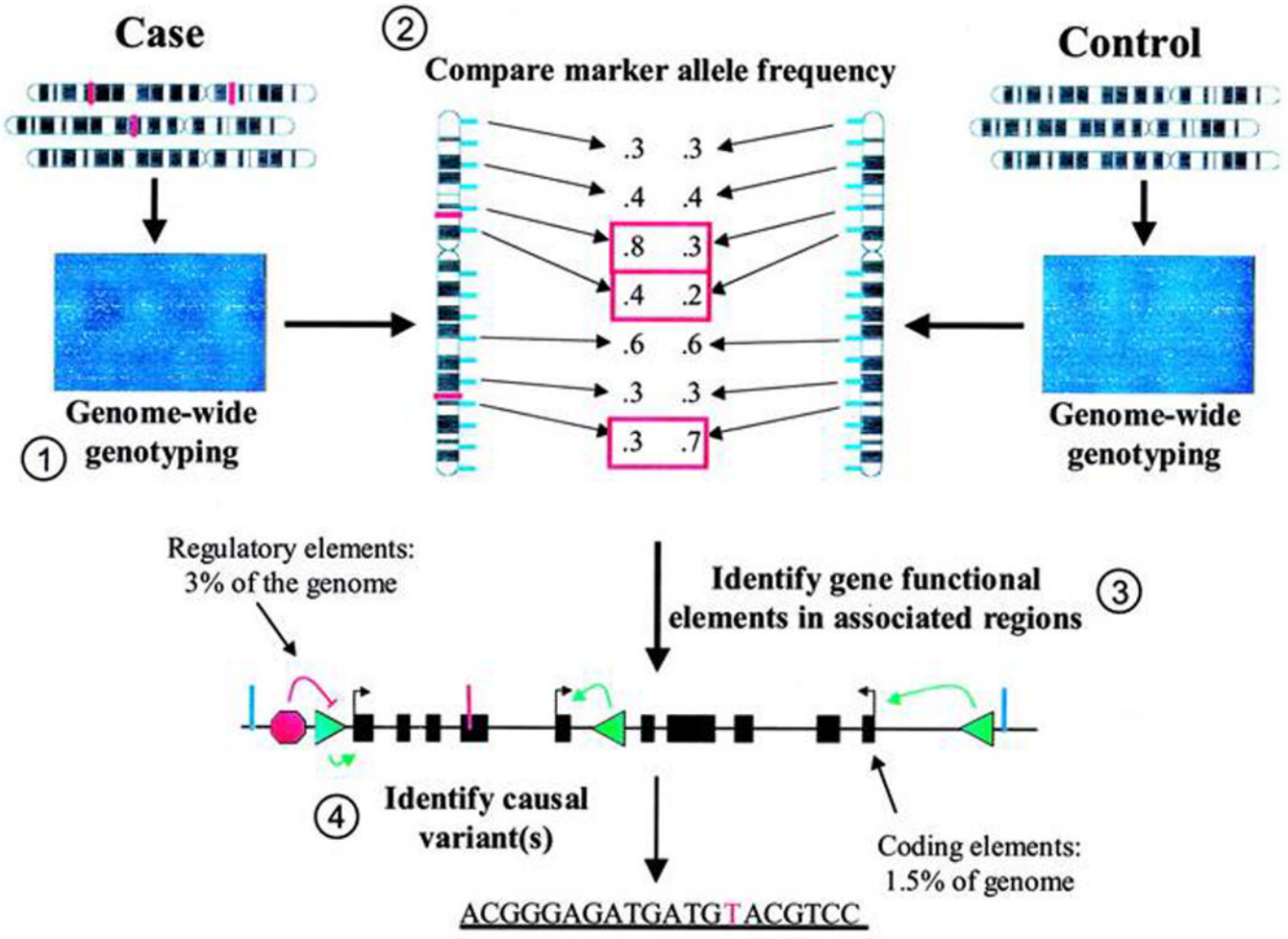

Figure 5. Schematic of genome-wide association study design

(1) Appropriately matched cases and controls are subjected to genome-wide SNP genotyping (shown here using Affymetrix chips), (2) SNP allele frequencies are compared to identify regions associated with disease, (3) disease-associated regions are scanned for known functional elements and cross-species comparisons can be used to identify unknown regulatory elements, and (4) direct sequencing of functional elements to identify causal variants. Abbreviation: SNP, single nucleotide polymorphism

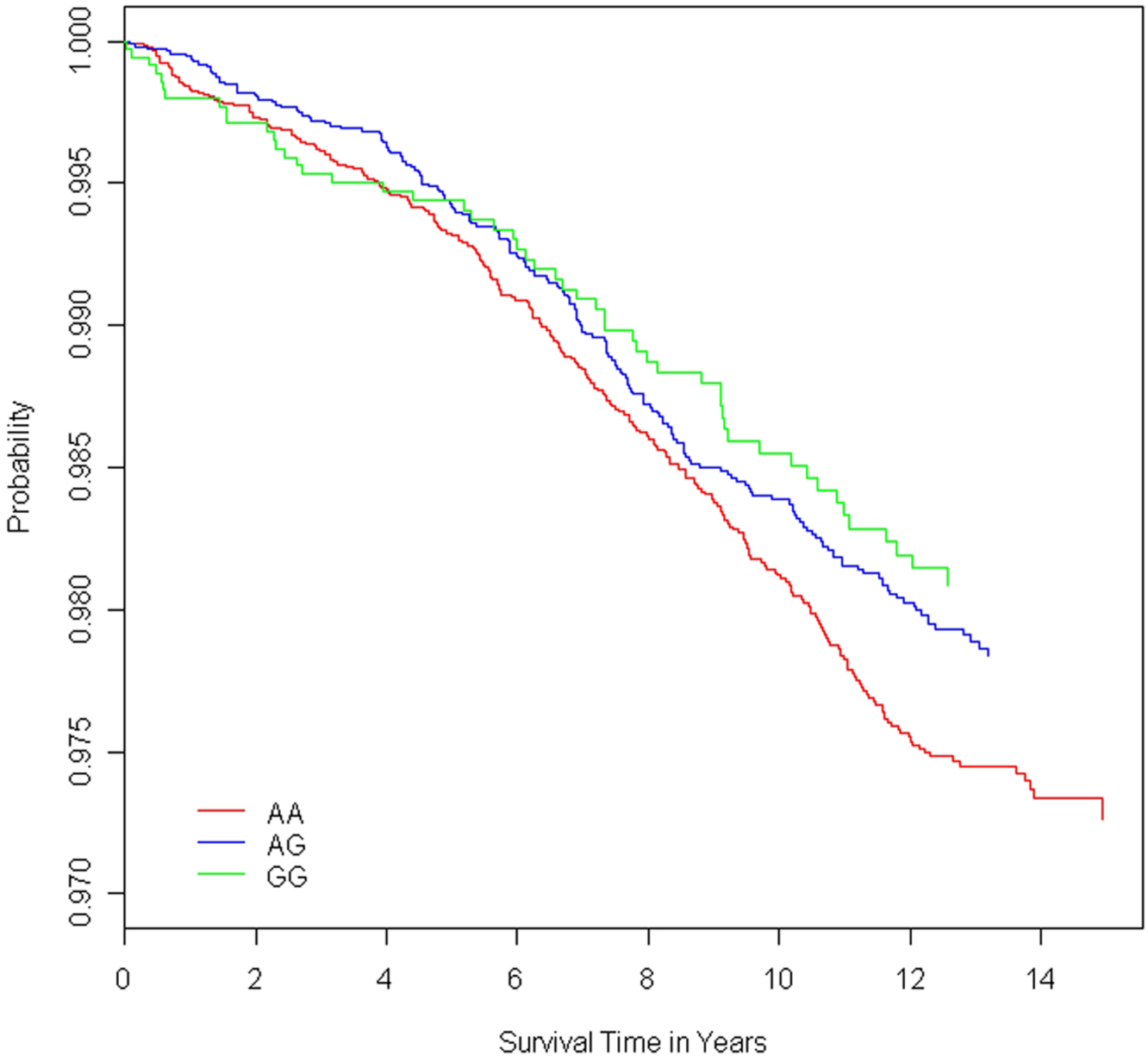

Figure 6. Survival curves (free of sudden cardiac death) stratified by the protective rs3864180 genotype

In the combined Atherosclerosis Research in Communities and Cardiovascular Health Study cohort, Cox proportional hazards model was adjusted for age, sex, and race/ethnicity. Individuals homozygous for the protective allele (GG) are shown in green, heterozygotes (AG) in blue, and homozygous for the risk allele (AA) are in red.

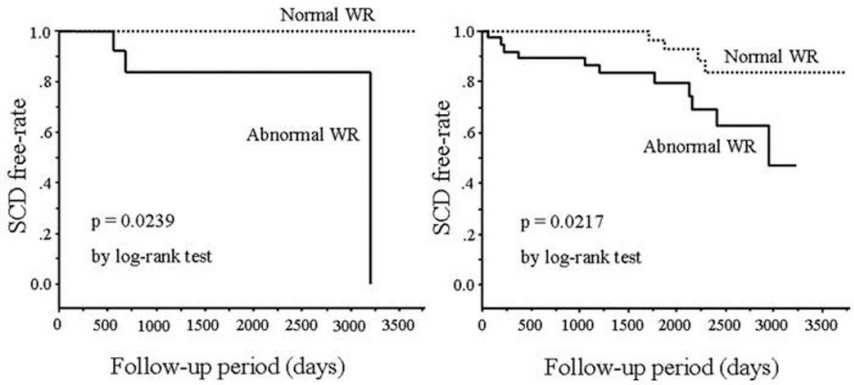

Figure 7. Kaplan-Meier SCD-Free Curves after Cardiac Metaiodobenzylguanidine Imaging
(Left) Left ventricular ejection fraction (LVEF) >35%. (Right) LVEF 35%. Abbreviation: WR, washout rate of cardiac metaiodobenzylguanidine.

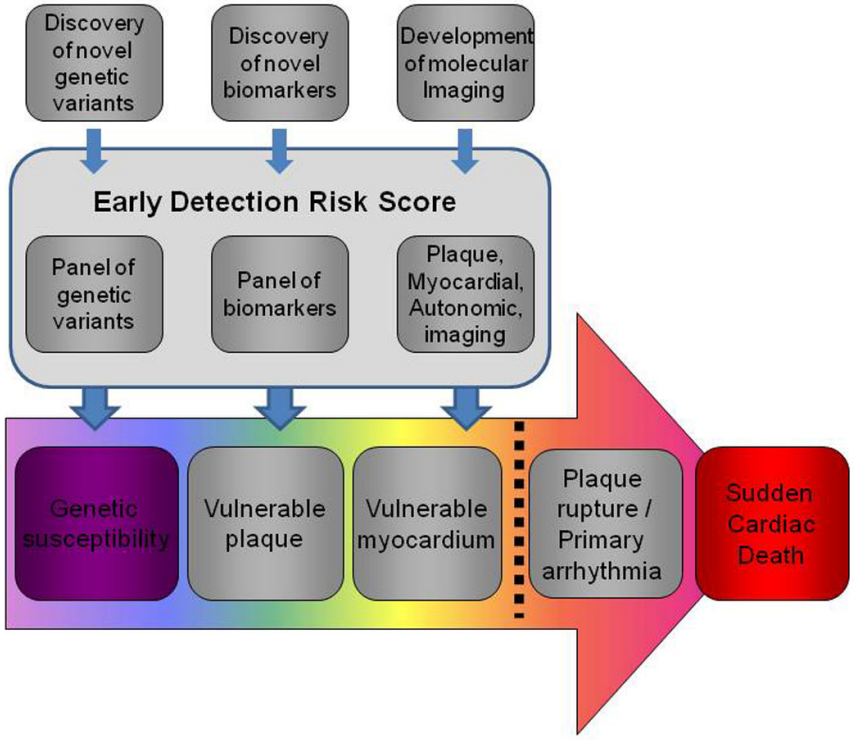

Figure 8. Development of an early detection risk score for SCD

The discovery of novel genetic variants and biomarkers, and the advancement of molecular imaging, will allow the development of an early detection risk score. The score will predict an individual's likelihood of suffering SCD. Abbreviation: SCD, sudden cardiac death.