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Sudden Cardiac Death Prediction and Prevention Report From a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop

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Despite the significant decline in coronary artery disease (CAD) mortality in the second half of the 20th century,[1] sudden cardiac death (SCD) continues to claim 250 000 to 300 000 US lives annually.[2] In North America and Europe the annual incidence of SCD ranges between 50 to 100 per 100 000 in the general population.[3–6] Because of the absence of emergency medical response systems in most world regions, worldwide estimates are currently not available.[7] However, even in the presence of advanced first responder systems for

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resuscitation of out-of-hospital cardiac arrest, the overall survival rate in a recent North American analysis was 4.6%.[8] SCD can manifest as ventricular tachycardia (VT), ventricular fibrillation (VF), pulseless electric activity (PEA), or asystole. In a significant proportion of patients, SCD can present without warning or a recognized triggering mechanism. The mean age of those affected is in the mid 60s, and at least 40% of patients will suffer SCD before the age of 65.[4] Consequently, enhancement of methodologies for prediction and prevention of SCD acquires a unique and critical importance for management of this significant public health issue.

Prediction and prevention of SCD is an area of active investigation, but considerable challenges persist that limit the efficacy and cost-effectiveness of available methodologies.[7,9,10] It was recognized early on that optimization of SCD risk stratification will require integration of multi-disciplinary efforts at the bench and bedside, with studies in the general population.[11–13] This integration has yet to be effectively accomplished. There is also increasing awareness that more investigation needs to be directed toward identification of early predictors of SCD.[14] Significant advancements have occurred for risk prediction in the inherited channelopathies[15–17] and other inherited conditions that predispose to SCD, such as hypertrophic cardiomyopathy,[18] but there is much to be accomplished in this regard for the more common complex phenotypes, such as SCD, among patients with CAD. Many cardiovascular treatments (eg, lipid lowering and antihypertensive agents, antiischemic interventions, and heart failure therapies) prevent or delay the progression of the cardiovascular diseases that are the most frequent cause of SCD. However, the current workshop focused specifically on risk prediction for arrhythmic death in cardiac populations rather than on the broader topics of prediction and prevention of cardiac diseases in general.

Unfortunately, specific pharmacological therapies directed at the electrophysiological substrate and mechanisms that cause arrhythmias have proven disappointing when applied to high or moderate risk patients without prior documented clinical arrhythmias. The implantable cardioverter-defibrillator (ICD) in combination with heart failure drug therapy remains the mainstay of SCD prevention[19,20] but is likely to benefit only the small population at high risk who can be identified before an SCD event.[5,21]

On September 29 to 30, 2009, a working group of experts was jointly convened by the National Heart, Lung and Blood Institute and the Heart Rhythm Society to address and recommend research directions and strategies in prediction and prevention of SCD, for consideration by the National Heart, Lung, and Blood Institute and the greater research community. The panel was asked to consider the 3 broad areas of bench, clinical and population sciences. After deliberation on available information as well as critical needs for SCD prediction and prevention, the group came to a consensus, identifying investigational gaps and developing research recommendations in the 6 high-priority areas discussed below. The 6 recommendations are summarized in the Table, and detailed background information on each of the 6 recommendations is provided in this document. The Workshop's Executive Summary can be found at http://www.nhlbi.nih.gov/meetings/workshops/.

Recommendation 1: Facilitate Study of Well-Phenotyped SCD and Control Populations, Including Understudied Subgroups

Background

Like most complex traits, there are aspects of the SCD phenotype that present unique challenges and these, in turn, dictate the investigative approach. Because of the sudden, unexpected, and dynamic nature of the event, the vast majority of sudden cardiac arrests occur in the community and at least 90% to 95% of these individuals do not survive despite

resuscitation attempts performed in the field by emergency medical response systems.[7,8] In 40% to 50% of cases, SCD is unheralded by symptoms and in 30% to 40% can be unwitnessed.[5,7] It stands to reason that the ascertainment of the phenotype of individuals at risk of SCD must occur in the community, as opposed to the hospital and healthcare system. Therefore population-based approaches must be used.[7] In fact, there is now clear evidence that retrospective death-certificate methods of ascertainment are inaccurate, with unacceptably low positive predictive values for determination of the SCD phenotype when compared to prospective approaches.[4,22] Information on the burden of SCD is available for only selected world regions, limited largely to North America and Europe, with virtually no information available on SCD epidemiology in the vast majority of the world.[7] There is also a paucity of data on the epidemiology, risk factors, prognosis, and temporal trends for SCD in nonwhite ethnic and racial groups.

SCD is generally defined as a sudden and unexpected pulseless event, but noncardiac conditions need to be excluded before the occurrence of a primary cardiac event can be confirmed.[7,23] Because of these complexities, multiple definitions have been employed. Studies assessing risk predictors of SCD have been performed in community-based cohorts[24,25] and there is increasing recognition that prospective studies of SCD in the general population are also feasible.[4,5,21,26–28] These studies have shown that definitions can be standardized and systematic circumstantial and clinical evidence can be obtained and utilized to maximize the accuracy of identifying the SCD phenotype.

Building on the available literature[4,7,24,25,29,30] and incorporating definitions that have been employed previously, this working group has developed a unified definition for SCD that can be used to ascertain the SCD phenotype in community-based cohort studies as well as investigations conducted in the general population. A case of *established SCD* is an unexpected death without obvious extracardiac cause, occurring with a rapid witnessed collapse, or if unwitnessed, occurring within 1 hour after the onset of symptoms. A *probable SCD* is an unexpected death without obvious extracardiac cause that occurred within the previous 24 hours. In any situation, the death should not occur in the setting of a prior terminal condition, such as a malignancy that is not in remission or end-stage chronic obstructive lung disease. The term “sudden cardiac arrest” should be used to describe SCD cases in which specific resuscitation records are available or the individual has survived the cardiac arrest event.

There is also strong evidence from studies in North America and Europe that there are significantly altered trends in the presenting arrhythmia observed by first responders among SCD cases.[31,32] The prevalence of SCD cases presenting with VF is decreasing with a corresponding increase in the proportion of cases presenting with PEA. Given the extremes of resuscitation outcome based on presenting arrhythmia (>25% survival for VF and <2% for PEA[4]), it is important to improve our understanding of the determinants of these altered trends. Because population-based investigative approaches for SCD are pivotal for understanding the phenotype, there is a need for greater numbers of subjects that are available for investigation. An annual incidence of SCD in the range of 60 to 90/100 000 individuals[4,5,7] necessitates the establishment of large community-based studies that ideally connect with other similar efforts, forming consortia that can share data, analyses and resources for common objectives such as refining methods to predict SCD.

Knowledge Gaps

- For the vast majority of world regions, there is virtually no available information on epidemiology of SCD.

- There is a critical need for large population-based studies that include women and understudied minorities in different regions of the US,
- There is a lack of infrastructure to facilitate collaborative links between different population-based studies.
- There is a need to improve our understanding of altered trends in the arrhythmias precipitating SCD (ie, significant changes in the prevalence of VF and PEA).

Specific Recommendations

- Facilitate the initiation and maintenance of large population-based studies of SCD to improve understanding of SCD mechanisms across gender and all racial/ethnic groups.
- Provide the infrastructure to connect individual population-based studies as consortia that can collaborate for a common set of objectives.
- Perform studies that will further the understanding of presenting arrhythmias (ie, VF, PEA, asystole, and the mechanistic differences between these conditions).

Recommendation 2: Develop and Validate a SCD Risk Score Utilizing Phenotypic, Biological, and Noninvasive Markers

Background

Numerous invasive and noninvasive techniques have been developed over the years to identify patients at risk for SCD.[33–35] Currently, assessment of left ventricular (LV) ejection fraction is commonly used to guide primary prevention of SCD,[20] but there is considerable interest in using markers that reflect arrhythmia substrates more directly, and therefore enrich the prediction of SCD events. Invasive electrophysiological testing using programmed cardiac stimulation adds considerable specificity to identification of patient populations with ischemic heart disease who are at risk for SCD.[36] and who, therefore, may benefit from ICD therapy.[37,38] However, there remain concerns as to whether electrophysiological testing possesses sufficient sensitivity to reliably exclude SCD risk in patients with a negative test.[39]

In contrast to invasive electrophysiological testing, noninvasive tests for predicting SCD are clearly more attractive in a clinical strategy for widespread screening. Numerous markers derived mainly from surface ECG have been correlated with SCD, cardiac, and total mortality over the past 3 decades. These can be classified as (1) indices of abnormal autonomic modulation of cardiovascular function such as heart rate variability,[40] heart rate turbulence,[41] heart rate recovery from exercise,[42] and baroreflex sensitivity[43]; (2) indices of abnormal impulse conduction such as signal averaged ECG[44] and QRS fractionation[45]; and (3) indices of abnormal repolarization such as microvolt T wave alternans,[46] QT interval dynamicity,[47,48] and various measures of T wave morphology and dispersion. Most of the autonomic markers have been correlated with total rather than arrhythmic mortality. Although extensive comparative data are not available, when examined in the same population with other risk markers T wave alternans appear to predict SCD-related events with greatest negative predictive value[49–51], suggesting that a patient with systolic dysfunction and a negative T wave alternans test may be at comparatively low risk for events. However, other recently published data from 2 large clinical trials of the prophylactic ICD indicate that the use of T wave alternans is likely to be limited by low predictive ability, higher number of indeterminate tests, and concern about incremental value over known risk factors.[52,53] Taken together, the available experience suggests that multiple risk markers used in combination may provide a more robust prediction of events,

which is not surprising when one considers the complexity and diversity of electro-anatomic substrates that underlie SCD. To date, no randomized clinical trials have been conducted that demonstrate benefit of non-invasive risk stratification in reducing SCD events. That being said, there are extensive observational data suggesting that various ECG risk markers used alone or in combination can be useful in identifying subsets of patients who are more or less likely to benefit from ICD therapy to prevent SCD. It is important to emphasize that few studies have attempted to account for dynamic time-varying changes in SCD risk but rather tend to measure a risk marker at only 1 point in time to predict SCD risks indefinitely. Although premature ventricular beat frequency measured by ambulatory Holter monitoring has been associated with enhanced risk for SCD,[54] ectopic beats are so highly variable from day to day that it cannot be used as a reliable method for tracking SCD risk. Clearly, any viable strategy for predicting and preventing SCD will require tools for serial assessment of risk markers over time.

The aforementioned risk stratification and prevention efforts have been directed toward high risk subsets of patients with LV systolic dysfunction.[55] However, the overwhelming majority of SCDs occurs in the general population,[4,30,56] and approximately 55% of men and at least 68% of women have no clinically recognized heart disease prior to SCD[5,24,28,30] A community-based study has recently drawn attention to the phenomenon of gender-specific risk factors.[57] Women have a significantly lower prevalence of phenotypic traits that increase SCD risk, with half the likelihood of severe LV dysfunction (odds ratio 0.51, 95% confidence interval 0.31 to 0.84) and a 3-fold lower prevalence of established CAD (odds ratio 0.34, 95% confidence interval 0.20 to 0.60) compared to men. Although CAD continues to be observed in the majority of SCDs at autopsy,[58] many individuals are not diagnosed with CAD prior to death.[28,58] Even for those in whom CAD is recognized, there is only 1 major established clinical risk predictor: severe LV systolic dysfunction defined as a substantial decrease in the LV ejection fraction.[7] Therefore, patients with LV ejection fraction of less than 30% to 35% are deemed to be high risk and qualify as candidates for primary prevention using the ICD.[9] Recent studies confirm that ejection fraction alone is unlikely to be sufficient for effective SCD risk prediction, because it lacks both sensitivity and specificity. In the community, less than a third of all SCD cases have severely decreased LV ejection fraction that would have qualified them as candidates for an ICD.[21] Conversely, even among patients who do qualify for ICD implantation based on the ejection fraction criterion, only a small minority (2% to 5% per year), will suffer a ventricular arrhythmia resulting in SCD[19,20,59] Furthermore, for most patients, the ejection fraction is a risk factor that is identified relatively late in the natural history of this particular high-risk phenotype[14] and is of no utility for those in whom SCD is the initial manifestation of cardiovascular disease. To maximize effectiveness of prevention, risk factors need to be identified and utilized early in the natural history of specific high risk conditions.[14]

In the past decade, other clinical risk markers have been identified, but none of these are currently used for risk stratification.[25,28,60–63] These include LV hypertrophy,[62] QTc prolongation,[28,63] diabetes mellitus,[25,60–63] and elevated resting heart rate.[64] Serum biomarkers have also been identified that are associated with risk of SCD in cohorts and community-based studies.[65–68] In a significant proportion of patients, SCD is likely to be triggered by plaque rupture and acute myocardial infarction. There are significant ongoing efforts to identify biomarkers as well as imaging techniques that pinpoint key events related to inflammation and vulnerable plaque pathways.[69–71] The challenge is in identifying the specific patient who will suffer SCD with plaque rupture and acute myocardial infarction.

Upon the publication of 4 studies that provide strong evidence for independent genetic contributions to risk of SCD,[25,26,72,73] the identification of variants that confer genetic susceptibility has become an area of active investigation. Candidate-gene based association

studies have identified some candidates for SCD risk,[74–83] and genome-wide association studies (GWAS) are ongoing. The latter can be divided into 2 categories. The first are GWAS that have identified determinants of intermediate-risk traits for SCD such as the QT interval.[80,84,85] These have been followed by evaluation of specific significant variants in populations with SCD.[86,87] In this fashion, variants in NOS1AP have been identified as modest predictors of risk (odds ratios ≈1.3). The second GWAS approach investigates SCD risk directly in the general population using a case-control approach. These latter GWAS, which are unbiased by previous hypotheses relative to candidate genes and pathways, have the power to illuminate novel biological pathways involved in the genesis of lethal ventricular arrhythmias, which could ultimately lead to new therapeutic approaches for SCD prevention. An initial GWAS from the Oregon Sudden Unexpected Death Study has identified a novel genetic locus (glypican 5) that is protective against SCD, a finding that has been replicated in the ARIC and CHS cohorts.[88] Other investigators studied individuals with and without VF in the first 90 minutes of a first myocardial infarction (MI), and have identified a risk locus at chromosome 21q21.[89] These studies underscore the importance of conducting GWAS in significantly larger numbers of cases and controls.

As outlined earlier, for a significant proportion of SCD cases the final event is the first outward manifestation of disease (ie, there have been no premonitory warning symptoms or signs that would prompt medical attention). Even when symptoms are reported prior to SCD, these have not been found to be specific for the phenotype. Given the complexity of the SCD phenotype and overlap with conditions such as CAD, congestive heart failure, and diabetes mellitus, it is likely that any prediction of risk will involve a combination of risk factors and/or tests as opposed to a single marker or test. The generally accepted paradigm of requiring both substrates and triggers for genesis of ventricular arrhythmia[90] lends additional complexity to SCD risk prediction. Further, recent studies have implicated a wide range of environmental influences, such as socioeconomic status, psychosocial factors, and even particulate matter, as possibly playing roles in SCD.[7,91,92]

One approach to identifying risk has been to study device therapies as end points in ICD cohorts. Although these are likely to contribute useful information, it is important to recognize that the nature of this study design and population are likely to limit any useful findings to the optimal selection of ICD candidates relatively late in the natural history of LV dysfunction. These studies will not contribute importantly to detection of risk factors early in the disease process.[14]

Knowledge Gaps

- Current methods of clinical risk prediction are inadequate and there is increasing recognition that employment of the LV ejection fraction as a risk predictor is effective in only a small subgroup of patients.
- Other risk markers have been discovered, but individually these markers appear to have only modest effects. Examples include LV hypertrophy, prolonged QT interval, fragmented QRS complex, diabetes mellitus, elevated resting heart rate, specific serum biomarkers, and novel genetic variants.
- There is a conspicuous lack of studies that combine panels of SCD risk markers to assess additive or synergistic effects on risk.
- There is a need for early detection of risk factors for SCD.

Specific Recommendations 2

- Facilitate studies that will discover novel risk markers for SCD. There is a role for 2 distinct categories of studies:

  - Optimization of risk prediction late in the natural history of SCD for improved efficiency of the ICD using large cohort studies of patients with heart failure and an ICD.
  - Discovery of novel risk predictors early in the natural history of conditions predisposing to SCD from large population-based studies that perform comprehensive evaluations among all subjects who suffer SCD.
- Facilitate studies that combine novel risk markers and testing to create risk scores for prediction of SCD.

Recommendation 3: Develop Novel Risk Stratification Strategies to Improve Outcomes in Select Populations at Risk of SCD, Including Patients With ICD Indications Based on Current Guidelines and Other Patients at Risk Such as Those With CAD and LV Ejection Fraction >35%; Early Phase Postacute MI; Heart Failure With Preserved Systolic Function; and/or LV Hypertrophy

Background

Numerous trials of empirical antiarrhythmic drug therapies have been conducted in patients with recent or remote MI and LV dysfunction as well as nonischemic cardiomyopathies, with disappointing results.[93,94] In such studies, an antiarrhythmic drug is often considered to be of value if it does not increase overall mortality. Over the last 25 years, clinical studies have shown that ICD therapy in high risk populations can reduce total, cardiac, and to a very high degree, arrhythmic mortality.[95] However, there are numerous well recognized limitations to ICD therapy. These include the cost of the devices, complications related both to the implantation procedure and to subsequent device function, device malfunction, and limited efficacy despite normal device function in the presence of significant concomitant disease.[96,97] Evidence-based guidelines for ICD therapy derived from these studies have been published and recently updated.[98,99] Current criteria are based largely on history of arrhythmia (resuscitated cardiac arrest, sustained ventricular tachycardia, syncope with induced VT, LV dysfunction, and heart failure functional class. Guideline recommendations for less common conditions such as inherited ion channelopathies or many cardiomyopathies are usually based on consensus opinion, because clinical trial data are not available.[98,99]

In real world practice where ICD recipients are often older and have more comorbidities than the average clinical trial enrollee, the ratio of nonsudden to sudden deaths among ICD recipients may even be higher.[100] Numerous tests have been proposed to improve the prediction of SCD as opposed to total mortality.[46,101,102] These include programmed electric stimulation, various tests of autonomic nervous system function, standard ECG findings such as QT variability or dispersion, microvolt T wave alternans, and others. Recent data suggest that because of the complexities of the substrates underlying SCD, multiple risk factors used in combination are likely to provide better prediction of SCD risk than any individual risk marker.[51,103]

Although positive results have been reported in selected populations (eg, programmed stimulation in post MI patients with intermediate LV ejection fraction values),[39,59] no single test strategy has proven to be sufficiently sensitive and specific to justify widespread adoption. New imaging techniques now exist for assessing a range of myocardial pathophysiological processes that may be implicated in the pathways that lead to SCD. Magnetic resonance based imaging can quantify cardiac structure and function and the

presence and extent of myocardial fibrosis and ischemia. New imaging tracers using positron emission tomography provide measures of cardiac sympathetic function. These sophisticated imaging techniques are promising but have not been tested to date in large studies.[104–109]

Analyses using combinations of new and old risk factors may be more valuable. For example, in a retrospective analysis of the MADIT-II data, Goldenberg et al[95] identified 5 variables that might predict benefit of ICD therapy benefit: New York Heart Association functional class, atrial fibrillation, QRS duration, age, and moderate renal dysfunction. Patients with 1, 2, and to a lesser degree 3 risk factors showed benefit whereas those with 0, >3, or severe renal dysfunction alone did not. Studies examining various combinations of risk factors might well improve the efficiency of ICD therapy in patients with current indications.

There are several populations known to be at substantial risk for SCD for whom effective management guidelines have not yet emerged. The early period after MI is associated with a very high mortality rate, but 2 studies, the DINAMIT[110] and IRIS[111] trials, failed to show benefit in total mortality after ICD implantation. It is noteworthy, however, that deaths classified as arrhythmic were reduced in patients randomized to ICD treatment in both studies. Although medical therapies directed at ischemia and heart failure have substantially improved outcomes in the early postinfarction period,[112] the ability to identify and treat those specifically at high risk for arrhythmia would be of importance. There are other populations that may not benefit because they are at low risk: for example, patients in the early period after coronary revascularization.[113]

Specific pharmacological or device-based antiarrhythmic therapy has not been well studied in other populations with moderate risk, including patients with genetic primary arrhythmia or cardiomyopathy disorders, those with known or probable ischemic heart disease, patients with heart failure with normal or only mildly impaired systolic function, and patients with LV hypertrophy without clinical heart failure. Although the individual annual SCD risk in these populations is relatively low, the number of events in some of these groups may be large. Current strategies to identify the subsets of patients with sufficient risk to justify intervention and prescribe appropriate therapy are very limited. Most therapeutic approaches have been directed at the underlying disease processes of the patients (eg, atherosclerosis, ischemia, and hypertension) rather than the arrhythmogenic potentials for SCD of these conditions. SCD risk detection strategies in these intermediate-risk but numerically substantial populations would need to be relatively simple and inexpensive to justify their widespread use. Even for the familial disorders, such as hypertrophic cardiomyopathy and the long QT syndrome that increase SCD risk, efforts continue to refine prediction of risk.[15–18]

Knowledge Gaps

- Current methods to differentiate patients at highest risk for arrhythmic death from all-cause death are insufficient and lack robustness in guiding the use of ICD therapy.
- Data on SCD risk are best developed in patients with moderate or severe LV dysfunction either after MI or with chronic ischemic or nonischemic cardiomyopathies. Although patients without severe systolic dysfunction are at lower individual risk, many sudden deaths occur in such patients. Strategies for effective risk stratification in these moderate risk populations should be investigated.

- The optimal approaches for combining potential risk factors to identify individuals at risk and to target risk factors for treatment have not been determined.
- The utility of interventions other than ICD therapy, including the wearable cardioverter-defibrillator and cardiac resynchronization without defibrillation capability in select populations needs to be better defined.
- The influence of comorbidities including advanced age, atrial arrhythmias, QRS duration or other ECG parameters, and renal or other organ dysfunction on the effectiveness and efficiency of ICD is not well understood.

Specific Recommendations 3

For patients with ICD indications based on current guidelines, research should assess new approaches that may provide incremental information on SCD risk beyond LV ejection fraction.

- For patient groups known to have high all-cause mortality, research that uses new approaches in assessing risk in SCD versus non-SCD should be encouraged. Approaches that involve a combination of risk factors (identified by novel biomarkers, genetic profiles, and new imaging methods of cardiac structure and physiology) should be evaluated in clinical studies.
- At the population level, simple and inexpensive tools should be developed to identify patients at elevated risk of SCD.

Recommendation 4: Establish Strategies for SCD Prevention by Targeting Intermediate-Risk Phenotypes

Background

There are significant differences in prediction and prevention of SCD at the level of the individual versus the general population. A particular test or risk factor may enhance risk prediction in an individual, but may not be deployable as a screening tool in the general population because of low overall specificity and limited cost-effectiveness.[14] Similarly, only selected prevention modalities may be deployed in the general population. The ICD is clearly an effective prevention modality for the appropriately selected patient, but it has long been recognized that burgeoning healthcare costs are likely to limit its use in the community.[56] Novel and more cost-effective methods of SCD screening and prevention will need to be discovered. There are a number of intermediate-risk traits (for example, heart failure, CAD, and LV hypertrophy), that are already being targeted with consequent attenuation of SCD risk. Measures to prevent CAD will continue to have a significant and lasting effect on SCD prevention.[1] Similarly, drugs such as β-blockers and angiotensin-converting enzyme inhibitors contribute to prevention of SCD in the large number of patients with heart failure and LV systolic dysfunction.[114] It is also likely that prevention, reversal, and attenuation of LV hypertrophy have an impact on SCD prevention.[115] However there are other traits such as heart rate abnormalities,[64,116,117] prolonged QT interval,[28,63] and fragmented QRS[118] that contribute to an increasing list of clinical phenotypes associated with SCD risk. These could be targeted by focused investigation to explore potential beneficial effects on the burden of SCD in the community.

Knowledge Gaps

- Intermediate-risk phenotypes or endophenotypes of SCD remain to be discovered and validated as targets for risk stratification and ultimately SCD prevention.

Specific Recommendations 4

- Facilitate investigative approaches that target discovery of SCD intermediate-risk phenotypes.
- Facilitate investigative approaches that target modulation of SCD intermediate-risk phenotypes for prevention of SCD.

Recommendation 5: Develop High-Throughput Strategies to Efficiently Establish the Functional Relevance of Newly Discovered Genetic Information

Background

There has been an explosion in the discovery of genes contributing to normal and abnormal myocyte biology, and with that there has formed a new understanding of the functional relevance of this emerging genetic information. For example, disease genes responsible for monogenic syndromes associated with increased SCD risk have added importantly to our understanding of the broad problem of SCD susceptibility by identifying new biological interactions and pathways whose perturbation increases SCD risk. This paradigm has highlighted the role of genes encoding ion channel pore-forming (eg, SCN5A,[119] KCNQ1[120]) and accessory subunits (eg, CACNB2[121] and SCN4B[122]), as well as cytoskeletal (SNTA1[123] ANK2,[124] ANK3[125]) and trafficking (CAV3[126]) proteins. Common variants in these genes are now being studied as modulators of SCD-related phenotypes: KCNE1 D85N as a risk factor for drug-induced torsades or the congenital Long QT syndrome[127,128] and SCN5A S1103Y as a modulator of SCD and of Sudden Infant Death Syndrome risk in African Americans[129–131] are examples. Findings in mouse models of "monogenic" disease also have important implications for the broad problem of SCD. One example is the strain-dependence of electrophysiological phenotypes, reinforcing the idea that genetic background plays a crucial role in modulating clinical phenotypes.[132] Another is the striking contrast between near-normal electrophysiological properties of a mutant channel in heterologous expression and the obvious abnormal phenotype observed in patients[133] and in mice.[134] Similarly, cellular mechanisms supporting arrhythmias in the monogenic Timothy Syndrome gene (CACNA1C) require recruitment of signaling pathways that are not present in heterologous expression systems, suggesting that there will not be a 1-size-fits-all approach to successfully evaluate arrhythmia-causing disease genes.[135]

Unbiased strategies, exemplified by GWAS approaches, are identifying new genetic loci and, in some cases, pathways implicated in arrhythmic disease syndromes. Some of these GWAS "hits" are in genetic regions known to be important for normal electrogenesis, such as those encoding ion channels or intracellular calcium control mechanisms, whereas others are in regions not previously implicated in cardiac electrophysiology. The best-studied example to date is NOS1AP, which as described above is a regulator of the normal QT interval, and variants also seem to predict SCD in the community (ARIC, CHS).[87] These findings also reinforce previous observations suggesting that QT prolongation (eg, post-MI) is a marker for SCD[28,136] NOS1AP variants have been implicated as modulators of risk in the congenital long QT syndromes,[137] and have been associated with variability in calcium channel blocker-associated SCD.[138] The latter observations highlight the facts that (1) drug-induced arrhythmias may represent a useful model within which to explore SCD risk variation, and (2) SCD due to drug exposure may be more common than previously appreciated and may have a "non-QT" component. Another example is sequence variation in SCN10A, which encodes the $Na_v1.8$ sodium channel pore-forming subunit, which has recently been associated with cardiac conduction parameters, including QRS duration,[139,140] which is a predictor of SCD.[141] New pathways and mechanisms regulating cellular

electrophysiology have the potential to influence SCD susceptibility. Examples are stretch,[142] trafficking,[143,144] and intracellular signaling pathways.[145] Dysregulation of microRNA expression has also recently been implicated as a modulator of channel dysfunction that leads to SCD susceptibility.[146,147]

A range of methods, including heterologous expression in cells and genetically modified animal models, are available to study the function of protein-coding genes and to assess the consequences of missense and nonsense sequence variants. However, all of these approaches suffer from their relatively low throughput, particularly when detailed electrophysiological function is to be ascertained. Efficient strategies to determine how sequence variants in noncoding regions influence SCD predisposition are even more elusive. Novel approaches, such as screens using zebrafish[148,149] or *Drosophila*,[150] are an important advance. It is also conceivable that embryonic stem cell and induced pluripotent stem cell-derived cardiomyocytes may provide additional high-throughput assay systems[151,152] relevant to SCD prediction and prevention.

Knowledge Gaps

- The functional relevance and mechanisms of action of sequence variants in genes associated with increased risk of SCD are largely unknown.
- Experimental strategies to evaluate the physiological relevance of individual genes/gene products, sequence variants in genes, and pathways are inefficient and may not provide relevant information for human disease susceptibility.

Specific Recommendations 5

- Establish high-throughput tools to determine functional relevance of newly discovered genetic information.
- Evaluate candidate genes in multiple systems.

Recommendation 6: Establish Multiscale Integrative Models, Including Molecular, Cellular, and Organ Level, Animal, and Computational, Relevant to Human Electrophysiology and Disease

Background

A fundamental tenet in the field is that SCD represents the interaction between triggers and a susceptible substrate. A corollary of this concept, yet unproven, is the notion that improved understanding of triggers and substrate, at varying levels of complexity ranging from molecular through the emerging field of systems biology, is likely to provide insight into SCD prediction and prevention.[153,154] For example, recent theoretical, experimental, and clinical data suggest that the Purkinje fiber network is an important arrhythmic trigger in disease states, including acquired and inherited syndromes.[155–158] Experimental data with potential relevance to arrhythmic behavior and SCD derives from multiple domains, including molecular structure and dynamics,[159,160] gene expression networks,[161] cellular,[162] organ-level[163–165] and whole organism[166] behavior. Multiscale models representing the different levels of structural and functional integration will be required to explore behavior from the molecule to the organ to the patient.[167] This involves bridging the spatial and temporal scales, from nanometer to meter, and from nanoseconds to minutes, hours or longer.[168] Such an endeavor will require developing new algorithms and approaches to achieve necessary levels of integration. Furthermore, to address the contribution of various factors to the origin and maintenance of arrhythmias, simulations will increasingly become multi-faceted, representing the consequences of factors such as soft tissue mechanics and

fluid dynamics on electrophysiological behaviors.[169,170] Finally, the relationship between structure and electric function at the various (molecular, cellular, tissue, organ) levels of complexity in the heart will have to be incorporated in a comprehensive manner in arrhythmia models and simulations.[171] Cardiac function at any level cannot be dissociated from the underlying structure. This relationship holds special prominence in the mechanisms of arrhythmogenesis in cardiac disease and needs to be reflected in the modeling efforts.[172]

Some of these modeling and simulation approaches are already under development, including (1) a canine epicardial action potential model that reproduces a wide range of experimentally observed rate-dependent behaviors such as adaptation, restitution, and accommodation[173]; (2) an updated mathematical model of CaMKII signaling in the canine epicardial infarct border zone,[174] which establishes abnormal CaMKII signaling as an important component of remodeling; (3) new models of the neonatal mouse ventricular myocyte,[175] rabbit ventricular myocyte,[176] and human atrial myocyte[177]; (4) a human Purkinje cell model[155]; (5) the first action potential model that integrates excitation-contraction coupling and mitochondrial bioenergetics[178] and the application of this model to examine the control and regulation of oxygen consumption[179]; (6) a mathematical model of Ca^{2+} spark triggering under voltage-clamp conditions that predicts changes in excitation-contraction coupling "gain" resulting from diverse experimental interventions[180]; and (7) a rabbit sino-atrial node model featuring coupled subsarcolemmal Ca^{2+} and sarcolemmal voltage clocks.[181]

Similarly, there is progress in understanding the dynamic mechanisms that underlie alternans, arrhythmogenesis, and the transition from VT to VF.[182,183] This new framework builds on the knowledge that alternans at the cellular level can be caused by dynamical instabilities arising from either membrane voltage (V_m) attributable to steep APD restitution and/or to calcium (Ca) cycling.[184,185] Emerging novel insights include mechanistic links between Ca sparks and whole-cell Ca alternans,[186] as well as the role of fibroblast-myocyte coupling in cardiac alternans.[187]

Progress in SCD prediction may also derive from a new class of integrative models that rely on reconstructions of cardiac structure from histology or structural imaging modalities. Examples include 3-dimensional reconstructions of sinoatrial and atrioventricular nodes,[188] as well as image-based reconstructions of the heart and remodeling associated with infarction or heart failure. These may serve to demonstrate the role of infarct scar morphology in VT and the emergence of 3-dimensional electromechanical delay in heart failure.[189]

The electrocardiographic imaging technique,[190] which represents an inverse problem where the epicardial potential is determined from body surface potentials and computed tomography, has made a major foray into clinical applications. In a series of studies, the investigators imaged noninvasively atrial repolarization, ventricular bigeminy, and ablation of accessory pathways.[191–194] One can easily imagine extension of this approach to use functional imaging to enhance prediction of those at risk of SCD.

Knowledge Gaps

- Strategies to integrate data across scales of increasing complexity, from molecule to cell, tissue, the whole heart, and ultimately the patient are lacking.
- Methods to extrapolate mechanisms from animal models of arrhythmogenesis to the human heart are incompletely developed.
- Patient-specific approaches to prediction and prevention of SCD are not well established.

- Accessible interfaces that allow utilization of computer models by nonexperts are needed.
- The theoretical and mechanistic bases of how complex systems undergo transitions from stable to unstable behavior are poorly understood.

Specific Recommendations 6

- Establish multiscale models to integrate behavior from the molecule to the organ and the patient.
- Enhance acceptance and utilization of such models to achieve improved mechanistic understanding of arrhythmogenesis as well as the effects and implications of new antiarrhythmia therapies.

Conclusion

The prediction and prevention of SCD remains an enormous challenge. Despite the accumulation of remarkable insight into the genetic basis and regulation of cardiac excitability, translation of this knowledge into novel strategies to identify the majority of individuals at risk of SCD is lacking, as it has targeted antiarrhythmic therapy. Translating new genetic information into improved understanding of physiology and disease represents a bottleneck to progress in mechanistic SCD research. Recent population, clinical, and basic science research studies, however, suggest there are real opportunities to improve our ability to identify individuals at moderate and high risk of SCD and to intervene to diminish such risk. Nonetheless, the complexity of the problem cannot be overstated and integrative strategies spanning a broad range of scales from molecular through organism and population studies, will be required to make progress in this area.

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Table

Summary of Specific Recommendation for the Prediction and Prevention of SCD

Recommendation 1: Facilitate study of well-phenotyped SCD and control populations, including under-studied subgroups.
Facilitate the initiation and maintenance of large population-based studies of SCD to improve understanding of SCD mechanisms across gender and all racial/ethnic groups.
Provide the infrastructure to connect individual population-based studies as consortia that can collaborate for a common set of objectives.
Perform studies that will further the understanding of presenting arrhythmias, i.e., VF, PEA, asystole and the mechanistic differences between these conditions.
Recommendation 2: Develop and validate a SCD risk score utilizing phenotypic, biological and non-invasive markers
Facilitate studies that will discover novel risk markers for SCD. There is a role for two distinct categories of studies:
Optimization of risk prediction late in the natural history of SCD for improved efficiency of the ICD using large cohort studies of patients with heart failure and an ICD.
Discovery of novel risk predictors early in the natural history of conditions predisposing to SCD from large population-based studies that perform comprehensive evaluations among all subjects who suffer SCD.
Facilitate studies that combine novel risk markers and testing to create risk scores for prediction of SCD.
Recommendation 3. Develop novel risk stratification strategies to improve outcomes in select populations at risk of SCD, including patients with ICD indications based on current guidelines and other patients at risk such as those with CAD and LV ejection fraction>35%; early phase post-acute MI; heart failure with preserved systolic function; and/or LV hypertrophy.
For patients with ICD indications based on current guidelines, research should assess new approaches that may provide incremental information regarding SCD risk beyond LV ejection fraction.
For patient groups known to have high all-cause mortality, research using new approaches in assessing the ratio in SCD vs non-SCD should be encouraged. Approaches that involve a combination of risk factors (identified by novel biomarkers, genetic profiles, and new imaging methods of cardiac structure and physiology), should be evaluated in clinical studies.
At a population level, simple and inexpensive tools should be developed to identify patients at elevated risk of SCD.
Recommendation 4: Establish strategies for SCD prevention by targeting intermediate risk phenotypes
Facilitate investigative approaches that target discovery of SCD intermediate risk phenotypes.
Facilitate investigative approaches that target modulation of SCD intermediate risk phenotypes for prevention of SCD.
Recommendation 5: Develop high throughput strategies to efficiently establish the functional relevance of newly discovered genetic information.
Establish high throughput tools to determine functional relevance of newly discovered genetic information.
Evaluate candidate genes in multiple systems.
Recommendation 6: Establish multiscale integrative models, including molecular, cellular, organ-level, animal and computational, relevant to human electrophysiology and disease.
Establish multiscale models to integrate behavior from the molecule to the organ and the patient.
Enhance acceptance and use of such models to achieve improved mechanistic understanding of arrhythmogenesis as well as the effects and implications of new antiarrhythmia therapies.