Sudden cardiac death (SCD) remains a high priority public health problem necessitating a multi-pronged approach for treatment and prevention. Tachyarrhythmic sudden cardiac death (SCD-VT/VF); ie, death attributable to potentially reversible ventricular tachyarrhythmias [ventricular tachycardia (VT) or fibrillation (VF)], is a major cause of SCD. Accurate assessment of risk for SCD-VT/VF is of critical importance to assist clinical decision-making regarding prescription of preventive therapies that reduce mortality. These therapeutic decisions include adherence to standard medical therapies, often in conjunction with tailored medications, implantable devices, catheter ablation, or heretofore untested treatments, such as spinal cord stimulation.¹ In cases in which the therapy is invasive or carries its own risk, such as these later interventions, each should be based on reliable demonstration of added benefit to the patient.

Pre-emptive risk stratification for SCD-VT/VF has substantial implications to public health for the following reasons: (1) Heart disease remains the number 1 cause of death in the United States, with >600,000 deaths attributable to heart disease annually reported by the National Center for Health Statistics (http://www.cdc.gov/nchs/fastats/deaths.htm); (2) Approximately half of these deaths are estimated to be sudden; (3) Approximately 50% of all SCDs are the first recognized cardiac event; and (4) Only a minority of those who suffer out-of-hospital cardiac arrest will ultimately survive. Although the incidence of VF as a cause of out-of-hospital cardiac arrest is declining, it remains a leading cause.² The introduction of the implantable cardioverter-defibrillator (ICD)—an effective, but costly therapy—has had meaningful, but limited, population impact on SCD;² thus, there are opportunities for new approaches (Figure) to address SCD. In particular, improved risk stratification techniques that identify individuals at high risk for SCD-VT/VF could have substantial impact,³ saving lives while stewarding medical resources for cases in which they are most effective. Since 2005, annual meetings of experts in the area of cardiovascular disease, cardiac electrophysiology, health policy, and outcomes research, and from government and industry (Boston Scientific Inc, Medtronic Inc, and St. Jude Medical Inc, who provided unrestricted educational grants that were used to support the meetings) have been convened for the purpose of identifying approaches that will address the current limitations of risk stratification for SCD-VT/VF (a list of participants is available in the online-only Data Supplement). This group recently described the heuristic, statistical, and financial issues that have served as obstacles to the field of risk stratification for SCD-VT/VF.⁴ The current state of risk stratification is well summarized in a September 13, 2008 New York Times article titled “A Lifesaver, but the Risks Give Pause: Second Thoughts About Defibrillators,” in which the following was noted: “Simply put, there is no adequate tool or test to predict which of the heart patients who might seem good candidates to get the expensive devices are the ones most likely to need their life-saving shock.” Furthermore, a National Heart, Lung, and Blood Institute and Heart Rhythm Society workshop⁵ highlighted the knowledge gaps in SCD prediction and prevention with general tactical recommendations on how to address these gaps. The present report describes new approaches that are needed to provide the basis for better risk stratification. A broad array of domains needs to be considered, including basic epidemiological approaches to modeling...
risk, identifying candidate risk markers that merit further evaluation in risk assessment algorithms, ethical and regulatory considerations, and funding and policy issues.

Where Do We Start?
An American Heart Association Scientific Statement addressed the process of risk stratification and incorporation of novel markers. The Table summarizes the phases of evaluation of a novel risk marker. Phase 3 addresses the incremental value of a novel marker when added to established, standard risk markers, or an existing risk score. It is reasonable to query what the established, standard risk markers are for SCD-VT/VF.

It is instructive to consider the example of coronary heart disease (CHD) risk estimation. CHD risk estimation relies on multivariable equations that weigh the influence of established risk factors and risk markers, such as age, sex, blood pressure, blood lipid levels, presence of diabetes mellitus, and cigarette smoking. The most widely used risk equations, from the Framingham Heart Study, form the basis of the Adult Treatment Panel - III risk assessment and treatment algorithm. In this algorithm, 10-year risk for hard CHD events (defined as nonfatal myocardial infarction or death attributable to CHD) is estimated using a Framingham model for individuals without history of CHD. Thresholds are then imposed on the risk estimate to guide clinical decision-making. Those with diabetes mellitus or a 10-year risk estimate >20% are recommended for lipid-lowering drug therapy. Those with a 10-year risk <10% are recommended for lifestyle modification, as needed. The group at intermediate 10-year risk (10% to 20%) can be treated at the discretion of the physician and patient, or further testing can be done to further stratify and characterize risk in a Bayesian fashion. The ability of new markers to add prognostic utility and contribute to risk stratification can then be assessed by a number of metrics, such as the change in the area under the receiver operating characteristic (ROC) curve and net reclassification.

In contrast, there is no widely accepted baseline model of individual risk estimation for SCD-VT/VF despite the wealth of data relating specific risk factors to SCD-VT/VF. However, recent retrospective analyses of patient populations selected to be at high risk for SCD-VT/VF have identified the potential role of easily obtainable clinical risk factors to provide important risk assessment for SCD-VT/VF. Prospective testing of these strategies is needed to enable broad implementation.

The most desirable model would address risk for SCD in a general, initially healthy population sample. This would be an important first step in determining whether, and how well, new risk assessment biomarkers or imaging modalities can refine risk assessment efforts for the large sample of asymptomatic individuals with a high ischemic burden or myocardial scar, but relatively preserved contractile function, who nevertheless account for the vast majority of SCDs. Practically, finding a cost-effective non invasive test that can be implemented in this healthier population is difficult because of the large numbers of patients needed to be screened and the low event rate.

Concerted efforts to establish baseline risk models to address these various situations is critical to advance this field. The approach to developing these models is governed by several important considerations. One way to initiate this process is by identifying community-based cohort studies that have collected similar clinical information and have carefully characterized SCD. There are several databases that meet this criterion, including the Cardiovascular Health Study (CHS), Atherosclerosis Risk in Communities (ARIC) Study, and the Framingham Heart Study (FHS). However, because SCD is relatively rare in the general population (60–90/100,000) even a cohort as large as 10,000 may not accrue numbers of cases sufficient for analysis even over a 10-year time period.

Table. Phases of Evaluation of a Novel Risk Marker

1. Proof of concept—Do novel marker levels differ between subjects with and without outcome?
2. Prospective validation—Does the novel marker predict development of future outcomes in a prospective cohort or nested case–cohort study?
3. Incremental value—Does the novel marker add predictive information to established, standard risk markers?
4. Clinical utility—Does the novel risk marker change predicted risk sufficiently to change recommended therapy?
5. Clinical outcomes—Does use of the novel risk marker improve clinical outcomes, especially when tested in a randomized clinical trial?
6. Cost-effectiveness—Does use of the marker improve clinical outcomes sufficiently to justify the additional costs of testing and treatment?

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Figure. Among the causes of sudden cardiac death (SCD), 2 major categories are ventricular tachycardia and fibrillation (VT/VF) and pulseless electric activity (PEA) or asystole. Within each category, there are opportunities for improved prevention (the middle slices) and improved response (the top 2 slices). In some cases (the bottom 2 slices), SCD is a terminal event for which no preventive or response measures could be effective, termed Zone of futility. The sizes of the slices are meant to be relative, not absolute; for example, more PEA/asystole events are likely terminal than VT/VF, and there may be greater opportunity for prevention of VT/VF than PEA/asystole. Risk stratification features prominently in the global approach to reduce SCD. Adapted from Ilkhanoff and Goldberger with permission of the publisher.
In addition, methods of retrospective identification of SCD cases, especially using death certificate data, have low accuracy (positive predictive value 19%). Accurate determination of SCD cases requires a planned, prospective approach. Keeping these issues in mind, prospective case-control approaches to SCD have been designed that provide sufficient numbers for analysis and have been conducted feasibly in the general population. For example, a study conducted among the residents of the Portland, Oregon metro area with a population of ≈1 million (The Oregon Sudden Unexpected Death Study) has ascertained >3000 SCD cases since February 2002 with comparisons with matched controls from the same geographic area. This approach focuses on the actual population at risk, because the vast majority of SCD cases occur in the community, and not in an institutionalized setting; and in ≈50% of cases, SCD is the first manifestation of heart disease. In turn, these community-based approaches have significant limitations related to missing data (because all SCD cases do not undergo previous or uniform health care evaluations) and the need for validating findings in other communities. Therefore, a more efficient approach may be to build these models using either cohort or population-based approaches and validate one against the other. After identifying a basic set of covariates that can be used to provide optimal risk stratification within one or more of these databases, further testing to determine whether the risk stratification model discriminates risk and is well calibrated to other populations would be necessary to establish its validity. Novel clinical, genetic, and plasma biomarkers have been identified separately from both kinds of studies, but testing across these populations is pending. Once a baseline model is in place, new risk markers could be tested as either replacements for currently included covariates or as additions to the model.

**Integrating Current Tests**

There are many risk markers or risk stratification techniques that have undergone thorough phase 1 and phase 2 evaluations (Table). In general, these techniques evaluate cardiac anatomy/structure, electric properties—depolarization and repolarization—autonomic effects, and other clinical factors. Interestingly, within many of these categories there are a plethora of tests that have been shown to be associated with increased risk. For example, repolarization measures that have been used include the QT interval, QT variability, T wave alternans, QT/RR slope, and QRS-T angle, among others. Depolarization measures include QRS duration and fragmentation. Measures of autonomic function that have been studied include a number of heart rate variability parameters, baroreflex sensitivity, heart rate turbulence, heart rate recovery, among others. Given the multifactorial etiology of SCD-VT/VF, it is important to consider risk factors and risk markers that represent abnormalities across the spectrum of potential mechanisms implicated in the pathogenesis of ventricular tachyarrhythmias. However, an approach needs to be developed to identify the key parameter(s) within each physiological framework. This could be challenging because of the strong correlation among parameters that address the same physiology, inconsistent methodology, and lack of uniform data collection. Although developing consensus medical expert opinion will be invaluable for this endeavor, the basis for choosing an optimal set of parameters should be empirically based and should follow the guidelines set out in the American Heart Association Scientific Statement. It is unlikely that this can be done efficiently from existing databases because of methodologic and content differences. Therefore, prospective data collection will be required that can implement uniform criteria for measurement of candidate risk markers, as was done in the Multicenter ICD Risk Stratification Study (M2Risk). This study evaluated 484 postinfarction patients who were receiving primary prevention ICDs and among a cadre of autonomic, depolarization, and repolarization parameters found only the total QRS root mean square voltage (not a previously considered standard parameter for risk stratification) to predict VT/VF events.

Several reports suggest that no single test alone is likely to provide adequate risk stratification. The utility of combining tests or performing risk stratification in a sequential manner has been demonstrated. Based on the findings of the Risk Estimation Following Infarction, Noninvasive Evaluation (REFINE) study, the REFINE-ICD trial is evaluating the efficacy of the ICD to reduce mortality in postinfarction patients with ejection fraction of 36% to 49% and abnormal T wave alternans and heart rate turbulence. The ideal combination of parameters, as well as time(s) for evaluation, need to be determined.

**New Approaches to Risk Stratification**

In addition to careful evaluation of the utility of existing risk markers in the broader scheme of risk stratification, there are some promising new approaches that merit mention, as they may provide incrementally useful risk stratification. Phase 1 and 2 data (Table) are accumulating to support the potential role and contribution of these new modalities.

**Imaging Scar and Myocardial Sympathetic Innervation**

Although cardiac imaging to measure the left ventricular ejection fraction forms the current basis for utilization of ICDs for primary prevention of SCD-VT/VF, there are some new imaging approaches that may provide useful incremental information. Contrast-enhanced cardiac magnetic resonance has emerged as an important imaging modality capable of defining the extent and morphology of scar resulting from myocardial infarction. Animal studies of infarct models suggest that the amount of scar is larger in those who have inducible VT and that identification of particularly arrhythmogenic scars may be feasible. The Defibrillators to Reduce Risk by MRI Evaluation (DETERMINE) trial was designed to evaluate the efficacy of the ICD in patients with previous myocardial infarction and an infarct mass >10% of the left ventricular mass by cardiac magnetic resonance who were not candidates for an ICD by the current ejection fraction criteria. The trial was stopped because of poor enrollment. At this point, the accumulated studies in humans relating infarct characteristics determined by contrast enhanced cardiac magnetic resonance to inducible VT and arrhythmic outcomes provide
solid support to pursue further evaluation of this technique for risk stratification.

Autonomic innervation of the heart plays a major role in the normal regulation of myocardial function, heart rate, and coronary blood flow. Patients with myocardial infarction as well as patients with heart failure exhibit well recognized abnormalities in autonomic tone. In chronic heart failure, abnormalities in cardiac autonomic control, characterized by sympathetic overactivity or parasympathetic withdrawal, appear to contribute to the progression of the disease and are associated with a worse prognosis. Myocardial infarction (even in the absence of heart failure) results in regional sympathetic denervation, in both the infarcted tissue, and in viable myocardium downstream from the infarct. Regional inhomogeneity in myocardial sympathetic innervation can also develop in viable dysfunctional or hibernating myocardium in the absence of infarction and is associated with a high incidence of VT/VF in preclinical studies. This can result in denervation hypersensitivity as well as spatial inhomogeneity in repolarization in the distal viable myocardium that may contribute to genesis of arrhythmias. In patients with heart failure increased central sympathetic tone, decreased myocardial catecholamine levels, desensitization of β-adrenergoreceptors, and elevation of plasma norepinephrine levels are well documented and may contribute to arrhythmogenesis.

Metaiodobenzylguanidine (MIBG) is a norepinephrine analog taken up by adrenergic neurons. When tagged with iodine-123, MIBG can be used to image adrenergic receptors in the heart with conventional planar or single photon emission computed tomography (SPECT) techniques. Patients with dilated cardiomyopathy have reduced MIBG uptake and an increased MIBG washout rate compared with healthy subjects. An abnormally low ratio of MIBG uptake in the heart to mediastinum (H/M ratio), or increased rate of washout of MIBG, have been shown to be independent predictors of death in several studies. In a small study of heart failure patients (ejection fraction <40%), MIBG washout rate and ejection fraction predicted arrhythmic death, pump failure death, and total cardiac mortality. A subsequent prospective observational study (ADMIRE-HF) involving 937 patients with New York Heart Association class II/III heart failure attributable to coronary disease or nonischemic cardiomyopathy demonstrated that an abnormally low H/M ratio predicted a composite end point of cardiovascular events, including heart failure progression, potentially life-threatening arrhythmias (sustained VT, resuscitated cardiac arrest or any appropriate ICD therapy), and cardiac death. Furthermore, a low MIBG H/M ratio was associated with the risk for composite arrhythmic events as defined above. This study did not find any benefit of assessing regional MIBG uptake abnormalities. Nevertheless, a recent study showed that the extent of the SPECT MIBG defect correlated with occurrence of ventricular tachyarrhythmias in patients with ICDs. The potential prognostic utility of MIBG after a recent myocardial infarction has also been demonstrated. In a study of 213 patients with acute ST elevation myocardial infarction, MIBG scans were evaluated 3 weeks after presentation. After a median follow-up of 982 days, MIBG abnormalities were an independent predictor of cardiac death.

Positron emission tomography (PET) can also evaluate myocardial sympathetic innervation as well as infarct size and viability. Several cyclotron generated norepinephrine analogs have been developed but the most extensively used for cardiac imaging has been 11C-meta-hydroxyephedrine (HED). PET is advantageous in comparison to SPECT MIBG in that it allows routine regional quantification of sympathetic innervation along with myocardial viability with less radiation exposure as compared to SPECT. The Prediction of Arrhythmic Events with Positron Emission Tomography Study (PAREPET) was a prospective observational study of 204 patients with ischemic cardiomyopathy eligible to receive a primary prevention ICD. Its primary end point was to determine the ability of HED defect volume to predict cause-specific mortality from SCD-VT/VF (ICD discharge for VT >240 bpm or arrhythmic death). Patients developing SCD-VT/VF had larger HED defects (33±10% versus 26±11% in survivors, P<0.001) with those in the highest tertile having a SCD-VT/VF event rate of 6.7%/yr versus 2.2%/yr in the mid and 1.2% in the lowest tertile. On multivariate analysis, HED defect volume remained 1 of 4 independent predictors of SCD-VT/VF, whereas ejection fraction and infarct volume were not. Although quantifying inhomogeneity in regional sympathetic innervation with PET appears promising, widespread application of 11C-generated radiopharmaceuticals is limited to clinical centers with an on-site cyclotron because of the short 20-minute half-life. Fortunately, longer half-life norepinephrine analogs labeled with 18-Fluorine could be synthesized centrally (like FDG for oncology imaging) and easily overcome this limitation if they are validated to provide similar predictive information.

The available data suggest that imaging infarct size and characteristics or assessing sympathetic innervation may potentially provide independent information that is useful for risk stratification in selected patient populations. Substantial further investigation is required to determine which techniques can be practically implemented and provide incremental information to other risk markers.

Genetics, Genomics, and Proteomics

Familial clustering of cardiac arrest and SCD as the initial clinical expression of coronary artery disease has been demonstrated in multiple studies, such as the Paris Prospective Study, an independent case–control study from Seattle, a Dutch study of VF arrest in the setting of acute myocardial infarction, and a study of SCD from Finland. These studies suggested that a family history of SCD as the initial manifestation of coronary heart disease is a predictor of SCD during acute coronary syndromes in subsequent generations, independent of traditional risk factors and family history of myocardial infarction.

Despite these clinical and population-based suggestions of a genetic contribution to individual SCD risk, identification of markers with sufficient effect to be useful for individual risk prediction has remained a challenge. A number of genetic variants have been linked to rare, heritable arrhythmias and SCD not associated with coronary disease, and some (eg, ion channel variants associated with QT duration) were viewed as candidates of interest for familial patterns of SCD in coronary heart disease. Although these candidates have not
yet emerged as targets for risk prediction in SCD attributable to coronary heart disease, other common gene variants have been linked to SCD or to surrogate, mainly electrocardiographic risk factors, in apparently healthy populations. Alternative pathways that appear to modulate QT duration are among these, as are associations that do not necessarily involve QT control. Unbiased scans of the human genome have provided proof of concept and potentially important insights into novel mechanisms involved in the development of CAD and acute myocardial infarction, ECG surrogates, and SCD itself. The limitation to clinical applicability of these observations to date is the relatively small effect sizes of the associations identified. However, amplification of effect size by identification of enriched phenotype subgroups as well as from interactions between multiple genetic variants and clinical markers remains a realistic goal for the future, based on the hypothesis that altered gene and gene product expression—especially of genes that modify the substrate or act as triggers of malignant ventricular arrhythmias—is likely to be associated with SCD.

The foregoing has motivated studies based on the premise that new markers of risk are most likely to be mined from groups of genes and proteins that underlie the substrate (eg, structure and excitability genes and their neurohumoral modulators) and triggers (eg, inflammatory mediators, thrombosis modulators and genes governing substrate utilization). Changes in the expression of a number of structural and excitability genes are associated with an increased risk of SCD in patients with acquired heart disease and in structurally normal hearts. The altered expression of these genes creates a substrate for malignant ventricular arrhythmias.

The role of serial evaluation of protein biomarkers, whether of inflammation or myocardial injury, in risk prediction of SCD remains unexplored. A single elevated level of an inflammatory marker has been associated with an increased risk of cardiac arrhythmias and sudden death. It is unclear whether persistent abnormalities, progressively increasing levels of the biomarker, or the magnitude of the highest peak provides additional information regarding risk. In contrast, persistent elevations in markers of myocardial injury have been associated with more adverse outcomes and echocardiographic evidence of progression of LV dysfunction but not SCD.

Understanding the Pathophysiology of the Development of Risk for Sudden Cardiac Death

In patients with CAD, myocardial infarction serves as the focal point for the development of a substrate that mediates or allows for the development of ventricular tachyarrhythmias responsible for SCD-VT/VF. It is well known that the risk for SCD is highest immediately after the infarction and progressively declines in the ensuing months. Yet, 2 randomized clinical trials failed to demonstrate improved survival when an ICD was implanted within 30 to 40 days in postinfarction patients selected based on high-risk markers. These findings raise several important questions regarding the pathophysiology of SCD, which is not all attributable to reversible ventricular tachyarrhythmias. It should be noted that more marked progressive remodeling changes over the course of several years after the infarction has been noted in patients who will die versus those who will survive. The aforementioned REFINE ICD trial is evaluating the efficacy of ICD therapy in patients with better-preserved left ventricular systolic function beyond the early remodeling phase and will provide additional data in this patient population. Further research on the pathophysiologic basis of SCD and the development of the arrhythmic substrate that can lead to SCD is necessary to better develop appropriate risk stratification tools.

The Emerging Importance of Non-VF Sudden Cardiac Death

The last 3 decades have witnessed a significant change in the manifestation of out-of-hospital cardiac arrest. There has been a progressive decrease in the prevalence of sudden cardiac arrest presenting as ventricular fibrillation, and proportional increase in those presenting with non-VF rhythms (pulseless electric activity [PEA] and asystole). This altered trend in the epidemiology of SCD, which has been confirmed in separate North American and European studies has significant implications for prevention of SCD. Defibrillation is an effective therapy for VF, but there are no existing specific or effective treatments for PEA. Thus, survival from sudden cardiac arrest is a function of the presenting rhythm. The combination of rising prevalence and low survival rates in PEA cases increases the urgency of improving the understanding of PEA mechanisms and development of new therapies for prevention and management.

Although the reasons for this paradigm shift are not entirely clear, it cannot be attributed to delays in response time for resuscitation, because these have decreased significantly in the same time period. Several studies have reported an association between black race and increased propensity to present with PEA. Other factors have been identified. Sex is a significant determinant, and women are more likely to manifest with PEA. Several studies have reported an association between black race and increased propensity to present with PEA. Recent analyses from the Oregon Sudden Unexpected Death Study have confirmed these earlier findings and also identified novel predictors of cardiac arrest presenting with PEA. A likely factor explaining the increased prevalence of PEA is that VF is more likely to occur among patients with coronary artery disease, but mortality from coronary disease has been cut by half over the last 60 years. A single study had analyzed the prescription medications among 179 cases of SCD and reported an association between β-blocker use and occurrence of PEA. However, a more recent comprehensive assessment of drugs involved in myocardial contractility in a population of >800 patients in the Oregon Sudden Unexpected Death Study could not confirm the relationship with β-blockers. In multivariate analyses, use of antipsychotic drugs was a significant and independent risk factor for PEA, possibly related to the established negative inotropic effects of this group of drugs. Based on suggestive findings that at least a subgroup of cardiac arrest patients presenting with PEA are going to be amenable to successful resuscitation, PEA mechanisms are currently the focus of intensive investigation with the goal of...
Addressing Ethical and Regulatory Concerns

Although several post hoc analyses of large scale randomized clinical trials have identified subpopulations of patients that may be at either too low or too high a risk for mortality/SCD to derive meaningful benefit from an ICD, advancing the field of risk stratification by demonstrating prospectively that these risk stratification schema can be applied clinically is challenging. Analysis of the well executed randomized clinical trials that support the current indications for ICD implantation after myocardial infarction strongly suggests that risk for SCD is not uniform across the study populations. While identifying, within a trial, subpopulations that may not benefit is possible, demonstrating this prospectively is challenging once guidelines are established around the population benefit of the intervention. Theoretically, a subgroup might be identified in whom, despite relatively high risk for arrhythmic death, there are such high competing risks of nonarrhythmic cardiac death or noncardiac death that addressing the arrhythmic risk proves futile. Assuming that risk stratification can be implemented in this heretofore identified high-risk population to identify either a low-risk subpopulation or a high-competing risk subpopulation that does not benefit from an ICD, to change guidelines to reflect this new information, randomized clinical trial data would be required. Although it would be important to have good justification for the choice of the criteria, the trial would involve not implanting an ICD in some patients who do meet guideline-based criteria.

Such a conundrum is a feature of all rigorous clinical trials. Ethical justification for performing such a clinical trial derives from the concept of clinical equipoise. Clinical equipoise indicates there is genuine uncertainty about the efficacy of an intervention over nontreatment or existing treatment. In this case, subgroup analyses of the ICD trials’ outcomes suggest that there are adequate data to support the notion that not implanting an ICD is equivalent to implanting an ICD in selected patients; yet, there is an accepted indication in these patient subgroups, and at this time clinicians have no way to evaluate or predict whether these patient subgroups will be helped by the intervention. A strong rationale for entertaining this question can be also be derived from examining the disparity between enrollment criteria and actually enrolled patients. Most trials have enrollment criteria that include a left ventricular ejection fraction in the 30% to 40% range in various studies, with 35% in most, despite actual enrollments skewed to much lower ranges and subgroup analyses questioning benefit in the higher ranges of qualifying ejection fractions. Furthermore, because there is some element of risk related to implanting an ICD, it is critical to ensure that its benefit outweighs the risk. Hence, although much is unknown about risk and ICDs, enough is surely now known about the inaccuracies of our current categorizations as well as the possibility that bias, social, and economic factors are affecting clinical choices. Thus, it might well be unethical not to go forward with an open label, fully consented clinical trial. Despite the ethical mandate to perform randomized clinical trials to address these questions, practical issues remain about physician acceptance, patient acceptance, and Institutional Review Board acceptance of this notion. It will be important to establish whether the post hoc analyses of current databases that demonstrate the utility of risk stratification provide strong enough evidence of the utility of a Risk Algorithm to justify a randomized clinical trial, or whether further prospective observational studies with ICD patients will need to be performed before randomizing patients into this type of trial. Alternatively, well-designed registry/observational studies with adequate clinical data and follow-up information may need to be accepted. For this field to advance, it will be essential to consider any clinical trial that addresses valid, unresolved scientific issues, without bias or perceptions that may arise from medical-legal or other societal concerns. The mandate to do so should be considered as significant as the need to develop and implement risk stratification algorithms in heretofore underserved patient groups (ie, those that currently account for the majority of SCDs).

Informed consent is the traditional mediator of research ethics. However, it is unclear whether patients can accurately perceive, internalize, and rationalize risk. Physicians are also poor at estimating individual risk without assistance, rendering both elements of informed consent problematic. Structuring a just and transparent informed consent discussion presents an ethical, medical, and legal challenge to physicians, investigators, the national field, and to the Institutional Review Boards who oversee such research. Educational efforts at all levels—patients, physicians, and regulatory bodies—are required to consider how clinical trials in situations of uncertain clinical practice will be normatively established so that they can have broad societal acceptance. Well designed trials with full informed consent will require education, moral courage, and altruism on the part of all stakeholders to ensure that clinical research can proceed.

Overcoming Financial Barriers

The financial barriers to performing studies focusing on risk stratification have been reviewed. As noted, a proper noninferiority trial to evaluate the ICD in a subgroup of the population with a currently approved indication for an ICD would need to be quite large. Although such a trial could be completely self-funded by redirecting the clinical costs of implanting an ICD in one-half of the population that would otherwise be accrued in practice (but not in the trial) to underwriting the costs of the trial, payors do not currently fund this kind of research. However, there is a logic supporting the notion of payor participation in research costs. It is undisputed that a component of payor costs for ICDs, prescribed on the basis of indications from ICD trials that were not designed to assess parameters that would determine individual benefit, are expended for patients who may not derive benefit. If payors undertook funding a large study to assess risk stratifiers, the results could benefit the patients who no longer are unnecessarily exposed to the risks of ICDs they do not need, and the payor would not fund the costs for the device and associated medical costs for such patients. The ability to identify lack of benefit in some currently-qualifying subgroups, would, in the long-term, accrue to the benefit of both payors and patients. Alternative randomized trial designs, including large simple
trials that utilize electronic medical records (EMRs) as the source data or cluster randomized trials, offer the potential to conduct broad scale trials in a more cost-efficient and less intrusive manner. These and other designs may provide solutions to conduct large randomized trials in the present economic climate. Moreover, given the costs of ICD therapy, studies designed to better select patients for these therapies should be desirable to healthcare payors in the United States and beyond.

From an epidemiological perspective, the greatest challenge is developing an effective risk stratification scheme for patients with more preserved left ventricular function (ie, those patients at risk for SCD who do not meet current criteria for an ICD). Community-based studies in the United States and Europe have found consistent evidence that the majority of SCD cases (at least 65%) have ejection fraction >35% with 50% having normal LV systolic function before their SCD event. The need to screen a large number of patients and an effective risk stratification approach to enrich the population risk require significant investment.

The primary value in stratification of patient populations based on risk and comparative effectiveness results lies in empowering patients and their physicians to select and receive treatment when likelihood of benefit is high and likelihood of harm is low and allowing them to avoid treatment when the likelihood of benefit is low or the likelihood of harm is high. Such personalization of treatments may lead to efficiency in economic terms where a proportion of the patient population automatically declines treatment even when such treatment is offered for free. Consequently, from an insurer’s (payor) perspective, stratification is extremely valuable because it can reduce utilization and expenditure without sacrificing, and probably enhancing, population-level benefits. However, payors may still not have the incentives to invest in risk stratification research unless they can document return on their investment. Furthermore, if such information were made public, then all competitor payors would act on it and translate the savings into competitive premiums, thereby mitigating returns on the original investments on stratification research by the payor funding the research.

In noncompetitive payor markets (eg, single payor systems), however, incentives to invest may be higher. Ironically, public payors, who perhaps stand to gain the most from stratification research, do not have adequate capacity, financially and legally, to make such investments. Decisions on investing public dollars on research rest with other institutes such as the National Institutes of Health and the Agency for Healthcare Research and Quality. Although both the public insurance programs and the public research enterprises in the United States fall under the purview of the Department of Health and Human Services, to what extent priorities for research investments are driven by the priorities of the public insurers remains uncertain. Developing a more direct and transparent link between them will certainly reinvigorate research on risk stratification and improve patient welfare.

In addition, public investment in such research would encourage, not stifle, private investments. Even though the already established results of randomized clinical trials establish the superiority of the ICD based on average effectiveness, the ICD has not completely or nearly completely penetrated the market. Perhaps there are concerns about costs and other aspects of ICD therapy that contribute toward this slow uptake. From the private manufacturer’s perspective, an argument can be made that there is an incentive to engage in risk stratification research to identify the subgroups who accrue better than average benefits from the device. One of the factors limiting clinical penetration based on the outcomes of the ICD trials is the uncertainty among physicians regarding the benefits based on the guidelines. Future definitive research that provides more specific individual indications, and larger absolute benefits, should quell these concerns and could lead to utilization that is both larger and more appropriate for the patients.

Identifying private manufacturers’ motives and partnering with them can provide an efficient mechanism to investing public dollars to generate nuanced information on risk and comparative effectiveness. To effectuate this process, contributions by conventional public sources for research funding must be complemented by payor- and industry-supported participation, all elements that stand to gain from a more comprehensive and rational approach to solving these utilization questions and delivering best medical care.

Public funding for research is also in a decline. The National Heart, Lung, and Blood Institute (NHLBI) has revised the process for funding large clinical trials (>500K in annual direct costs) in this tight fiscal environment. NHLBI has decided to use this as an impetus to develop new strategies for conduct of research, including clinical trials. The goal is to reduce costs, by streamlining procedures and collecting only the required data points needed to evaluate study treatment. Investigators are being asked to limit costly patient visits, take advantage of evolving ways to capture data, use ongoing projects or infrastructure/registries to conduct clinical trials or collect data, and devise new ways to interact with investigators and research subjects without adversely affecting patient safety. Optimal patient outcomes and cost containment will rest entirely on clear and well-supported clinical trials.

**Risk Stratification-Based Trials**

To date, the only reliable metric to predict benefit from an ICD is a severely depressed ejection fraction. Yet, as noted, the understanding of the pathophysiology of SCD-VT/VF would suggest that markers of autonomic tone, cardiac repolarization, and scarring may better discriminate patients at risk versus not at risk of SCD-VT/VF. However, the capacity to address this hypothesis is presently limited because of the challenges with conducting large-scale randomized trials. Nonetheless, efforts are needed to undertake risk stratification-based trials to better identify which patients do and do not need ICD therapy or other potential interventions that may be effective for prevention of SCD.

**Special Populations**

Certain populations of patients merit separate consideration from the perspective of risk stratification. For example, those with very high competing risks for mortality from other causes (eg, patients with end stage renal disease) may require a different approach to risk stratification. Similarly, diabetes
mellitus has a poorly-defined associated risk for SCD that may have different operative mechanisms than other cardiac diseases. It is known to alter the prognosis of patients with myocardial infarction and congestive heart failure and may interact differently with other risk stratification approaches or techniques. Identifying these unique populations for individualized study can only help our ability to improve risk stratification and better deliver on the promise of personalized medicine.

Conclusion

The path to improved risk stratification requires a concerted effort to address the issues outlined in this report. The basic steps involve the following:

1. Establishing baseline risk models composed of important, readily available clinical variables for common patient groups (general population, post-myocardial infarction patients, heart failure patients);
2. Generating a consensus list of currently available risk stratification techniques that should be assessed for improvement in the performance of the baseline model;
3. Thorough evaluation of the added prognostic utility of novel risk markers, including assessment of interactions, discrimination, calibration, model fit, and reclassification, when added to the adjusted model from step 2;
4. Evaluation of optimized risk stratification approaches in randomized clinical trials;
5. Using different randomized trial designs to more efficiently collect data;
6. Creation of a full and transparent process for promoting clinical trials that is well funded and socially supported by all stakeholders.

Additional efforts should be devoted to better understanding the pathophysiology of SCD which may help identify risk predictors and consideration of special populations that may have discrete risk stratification approaches. These approaches will require sustained and substantial effort and significant financial investment, and perhaps a change in the current financial structure and approach to funding trials in this field. Specifically, joint efforts among clinicians, patient advocacy groups, payors, industry, and government agencies using a coordinated, thoughtful approach will be required to address the challenges inherent in developing risk stratification for SCD. Ultimately, the costs of not addressing these issues—both in human lives and in the poor, ineffective deployment of resources—will far exceed the costs of obtaining the data to advance the field of risk stratification.

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Disclosures

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Appendix

Below is a partial list of participants in Path to Improved Risk Stratification meetings. We gratefully acknowledge all the input, interchange, insights, and collaboration of all the participants.

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