A though it is difficult to determine the precise number, the range for the number of sudden cardiac deaths (SCDs) per year in the United States alone has been reported from 184,000 to 462,000,1 with estimates that 50% to 70% are due to tachyarrhythmic mechanisms. Regardless of where within this range the true number lies, this represents a large epidemiological problem that warrants serious attention and attempts to identify solutions. There are many obstacles to achieving this laudable goal. First and foremost, although the vast majority of SCD victims have underlying structural heart disease (in particular, coronary artery disease), a significant percentage of SCD victims have previously unrecognized cardiac disease; on autopsy, advanced coronary artery disease with or without evidence of unstable plaques and acute or healed myocardial infarctions (often clinically silent) are commonly detected.2,3 The American Heart Association estimates that 195,000 first silent myocardial infarctions occur per year.4 Strategies to reduce SCD among individuals without known cardiac disease must therefore focus on better screening and identification of risk factors for coronary disease, with either known risk factors or heretofore unknown or unidentified risk factors. In patients with known cardiac disease, there may be diverse pathogeneses for sudden death, including primary ventricular tachyarrhythmias and acute myocardial ischemia/infarction, among others. Although therapies exist for treatment of life-threatening ventricular tachyarrhythmias and prevention of myocardial infarction/ coronary artery plaque rupture, significant challenges exist in identifying the individual patient within population subgroups who is at substantial personal risk of these events, and in whom the most intensive therapies could and should be applied. Although the incidence of out-of-hospital cardiac arrest due to ventricular tachycardia/fibrillation appears to be declining over time,4 this pathogenesis for SCD still occurs commonly. This article will therefore focus on the challenges and roadblocks that are present in the identification of patients at high risk for SCD due to ventricular tachyarrhythmias (referred to simply as SCD in the remainder of the article).

Much effort has been focused on the problem of risk stratification for SCD over a period of decades. In contrast to the era when risk stratification was first attempted, at the present time, the availability of therapies that have been shown to reduce SCD in various at-risk groups, including medications such as β-blockers, angiotensin-converting enzyme inhibitors, statins, and aldosterone blockers and devices such as the implantable cardioverter-defibrillator (ICD), makes risk stratification for SCD a very relevant exercise. Because of the isolated effects of the ICD on sudden arrhythmic death resulting from ventricular tachyarrhythmias, clinical trials related to the ICD have provided important information on the utility of various risk stratification approaches for the prevention of SCD. The concepts formed in the development of this information and its incorporation into risk stratification guidelines should be transferable to other therapies, both current and future.

The high prevalence of coronary artery disease, with its attendant risks for SCD, makes it a very important disease process to study, and potentially a great source of information regarding risk stratification. Thus, it will serve as the focus of this report. However, many of the fundamental benefits and limitations of risk stratification may be relevant to other cardiac diseases. For example, it seems likely that the pathophysiology of arrhythmias in congestive heart failure may share common elements regardless of whether the heart failure resulted from coronary heart disease or nonischemic cardiomyopathy.

Multiple invasive and noninvasive tests have been evaluated, but currently no optimal strategy for risk stratification exists. An ideal risk stratification strategy would identify
those patients who will experience SCD due to a reversible ventricular tachyarythmia within some specified time period (ie, 2 to 5 years) and exclude those who will not experience SCD. The current widely used strategy of stratifying risk on the basis of ejection fraction falls far short of these goals.\(^1\)\(^2\) The majority of patients who will experience SCD do not have a low ejection fraction,\(^6\)\(^\text{62}\) and many patients with a low ejection fraction may nevertheless be at low risk for SCD.\(^8\)\(^9\) Given the importance to public health, the increasing importance of appropriate deployment of precious resources such as ICDs in a contracting economic environment, and the continuing challenges of risk stratification despite the plethora of research time, effort, and resources expended on risk stratification, it is appropriate to chart a course that will most efficiently identify better strategies for risk stratification for SCD. In October 2005, the first of several annual meetings of experts in the areas of cardiovascular disease, cardiac electrophysiology, health policy, and outcomes research, as well as representatives 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), was held to identify approaches that will address the current limitations of risk stratification for SCD (a full list of attendees appears in Acknowledgments). The first step in charting a course for the future is to assess the roadblocks or limitations of the past approaches. Many issues related to risk stratification form significant challenges that must be considered. These include heuristic, statistical, and financial issues.

**Dichotomization of Risk and Risk Stratification**

Risk is a challenging concept for both physicians and patients. On a practical level, physicians incorporate risk stratification into their practice by implementing therapies based on the categorization of high or low risk. Thus, an ICD is currently recommended for primary prevention in patients considered to be at high risk for SCD.\(^10\) Because indications for therapy, as in an ICD prescription, are dichotomous, the underlying risk is often perceived to be dichotomous as well. However, in complex disease states, such as coronary atherosclerosis, the biological and statistical basis for risk estimation exceeds the limits of a dichotomous function, especially of a single risk stratification variable.\(^11\) Even in circumstances in which risk may logically be considered dichotomous, as in hereditary disorders that appear to be monogenic, the notion that those carrying the genetic variant are uniformly at risk is often an oversimplification. Variable expression, environmental interactions, and modifier genes impede dichotomizing risk in that carriers of the same genetic variant do not necessarily experience the same adverse outcomes, as observed in related carriers with long-QT syndrome or Brugada syndrome. Similarly, SCD (as well as coronary artery disease) is multifactorial, and is associated with a continuous risk function, as demonstrated in an analysis of the Multicenter Unsustained Tachycardia Trial (MUSTT) population.\(^9\) Although practice guidelines and reimbursement decisions tend to dichotomize patients into low- and high-risk groups to implement therapies such as the ICD, this is an artificial separation. The risk profile of patients with a left ventricular ejection fraction of 34% (below the threshold of 35% for ICD implantation) is not likely to be substantially different from the risk profile of patients whose ejection fraction is somewhat higher than this threshold. Thus, if a continuous risk function can be generated for a population, then the appropriate level of risk that justifies an intervention can be set on the basis of risk/benefit and cost/benefit considerations.

**Competing Risks**

Another issue, which is less well understood and/or appreciated, is the presence of competing risks for nonsudden death that can modify the relationship between arrhythmia risk and mortality. This concept can best be understood in the context of risk estimation by noting that many risk factors for SCD are also significantly associated with death due to other cardiovascular causes (and even noncardiovascular causes).\(^12\) This was nicely demonstrated in an analysis from the MUSTT,\(^9\) in which a scoring system was generated for total mortality and arrhythmic death. Most of the factors, such as ejection fraction, history of heart failure, intraventricular conduction defect, and inducible ventricular tachycardia, were significant contributors to both risk scores. Other post hoc analyses of data from randomized clinical trials using clinical factors/risk scores have demonstrated differential ICD benefits on the basis of risk profile;\(^8\)\(^13\)\(^14\); on the basis of clinical criteria, high-risk groups are identifiable in whom there may not be a survival benefit of the ICD, presumably because of competing risks of death from other causes. Current risk stratification strategies (which typically rely on standard Cox models) do not account for competing risks, which limits some of their discrimination and calibration utilities. Furthermore, the current focus on risk prediction for the short term (ie, the next 5 years) limits the identification of individuals who are at risk in the longer term or who have a life expectancy longer than 10 years. To appropriately select the optimal therapeutic strategy for a patient, physicians require tools that allow them to go beyond prognosticating all-cause mortality and identify various sources of life-threatening risk confronting a patient, with the associated absolute risk level for each source. With this information, physicians can determine whether the patient is more likely to succumb to SCD than other causes.

**Dynamic Risk Profiling**

Although many clinical trials, by design, execution, and analysis, have treated risk characteristics as static variables, many risk functions are likely dynamic.\(^15\) The quantitative and qualitative durability of a risk marker, such as ejection fraction, measured at different times after a myocardial infarction remains only partially defined, as does the implication of repeated measures over time. For example, risk of sudden death after a myocardial infarction declines with time from the infarction. In the Valsartan in Acute Myocardial Infarction (VALIANT) study, the monthly risk of SCD declined from 1.4% the first month to 0.14% after 2 years.\(^16\) The timing of risk assessment could therefore be an important variable. Indeed, the Risk Estimation Following Infarction—Noninvasive Evaluation (REFINE) study\(^17\) demonstrated that
Risk stratification testing 2 to 4 weeks after a myocardial infarction did not predict risk of serious events after a myocardial infarction, whereas testing 10 to 14 weeks after myocardial infarction did. A similar result was found in the Cardiac Arrhythmias and Risk Stratification After Myocardial Infarction (CARISMA) study. Moreover, a lack of favorable remodeling in autonomic tone in the initial 3 months after myocardial infarction was demonstrated to be a strong, consistent risk factor for sudden death in a combined analysis of the CARISMA and REFINE studies.

In addition, temporal variations in risk occur as functions of time of day,20–22 day of the week,20–22 and season of the year.20,21,23,24 Risk of sudden death is also known to be dramatically increased during exertion,25,26 but it is unknown whether it is better to assess risk under these conditions versus at rest. Finally, the frequency with which risk should be assessed is unknown because the duration of the predictive value of a test is rarely studied. These are all important variables that must be considered for incorporation into the framework of risk assessment.

Risk Subjectivity

Previous studies have indicated that subjective estimation of cardiovascular disease risk by physicians in the absence of scientifically based risk estimation equations is inaccurate, with both systematic underestimation and overestimation observed.27,28 As challenging as these concepts may be for caregivers to incorporate into their clinical approach to SCD prevention, it is even more of an issue for patients. Furthermore, patients have difficulty understanding and perceiving differences in both relative and absolute risk estimates.29 This is even more challenging when the topic is the risks for a frightening terminal event such as SCD.

Improving Risk Stratification

Given the desirability of accurate risk stratification and the long history of research in this area, it is important to understand why the field is not further advanced. It is important to acknowledge that risk stratification is difficult. The goal of a clinical risk evaluation is to be able to predict whether an otherwise stable patient will suffer a fatal ventricular tachyarrhythmia. Because this process is multifactorial and is not yet completely understood, this represents a huge challenge.

One possibility for the lack of sufficient progress in this area is that better risk stratification for SCD is unachievable. SCD, even when limited to ventricular tachyarrhythmias, can be the end result of a variety of different pathophysiological events, such as an acute ischemic event caused by plaque rupture or a sudden change in repolarization caused by electrolyte shifts or autonomic inputs; the presence or absence of substrate for scar-related ventricular tachycardia may also interact with these acute factors, resulting in either stable monomorphic ventricular tachycardia or ventricular fibrillation. Because each of these upstream events may be associated with different risk factors, it can be challenging to identify single risk factors for the end event. Because of the multifactorial nature of the problem and the unpredictability of its occurrence, it is possible that the clinician may never have enough information to better stratify risk than is currently available. Fortunately, compelling data exist that show that better risk stratification can be achieved. In a post hoc report from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II),8 5 easily identifiable clinical factors (New York Heart Association class >II, atrial fibrillation, QRS duration >120 ms, age >70 years, blood urea nitrogen >26 mg/dL) were each identified to be associated with a modestly increased mortality risk. The absence of all of these factors, which was noted in almost one third of the population, identified a group with very low mortality risk; no ICD benefit could be detected in this group. This provides sobering support for the concept that there might be an easily identifiable subpopulation of patients who currently receive ICDs who will not benefit because their risk for SCD is too low, even though left ventricular ejection fraction is markedly reduced. Although it will be challenging to define and establish this population, this represents an opportunity to better apply risk stratification techniques into the clinical decision-making paradigm.

On the other end of the spectrum, it is also important to consider the challenge of applying risk stratification techniques to the broad population currently considered to be at low risk for SCD to identify subgroups of patients at sufficiently high risk to warrant therapy. An example of such an approach is the theoretical 3-step tiered risk stratification strategy, in which Bailey et al30 stratified patients who had a myocardial infarction (no a priori ejection fraction criteria) into low-risk (2.9% 2-year risk of a major arrhythmic event) and high-risk (41.4% 2-year risk of a major arrhythmic event) subgroups; only 8.2% could not be stratified into 1 of these groups (they had an intermediate risk of 8.9%). Given the plethora of techniques and approaches that exist for risk stratification, coordinated, thoughtful efforts are necessary to develop an efficient and effective risk stratification strategy in this group. Although several studies have shown the incremental benefit of predicting SCD through the combined use of multiple noninvasive risk tools, there are no prospective randomized clinical trial data to support the notion that strategies incorporating multiple tests can be used to efficiently guide ICD therapy.

Statistical Issues

Another possibility contributing to the current limitations of risk stratification is that the available techniques or approaches are not adequate. Indeed, it is noteworthy that a single ideal technique has not emerged. The reasons underlying the difficulty in identifying a single ideal technique can be appreciated from consideration of the statistical basis of risk stratification. Whether a particular test constitutes identification of a risk factor within a population is often relayed by the odds ratio or relative risk of sudden death among those with a positive versus negative test result. The identification of such risk factors can be helpful in understanding mechanisms, identifying new targets for therapy, and initiating therapies to prevent the outcome of interest. However, the ability of available tests to predict sudden death on an individual basis is limited. In general, odds ratios >15 to 20 are required to meaningfully affect prediction for an individu-
Such high odds ratios do not generally exist for individual dichotomous predictors of SCD or for individual continuous covariates that differ between groups of affected and unaffected individuals, even by large amounts. The science of risk stratification is well developed for cardiovascular disease, and many important lessons can be applied to risk prediction for SCD.

The best way to assess the utility of a risk marker or a risk score is to consider a number of parameters that describe different properties and to examine the overall pattern of performance. Some metrics that should be considered include sensitivity, specificity, area under the receiver operating characteristic (ROC) curve or C statistic, informativeness criteria, clinical likelihood ratios, model calibration, and reclassification. Although derived to describe the performance of diagnostic tests, ROC curves and the area under the ROC curve (AUC) (or C statistic) provide important information regarding the discrimination ability of a risk estimator. Specifically, these metrics describe how well a given test can discriminate between future cases and noncases. An AUC of 50% describes a test with no ability to discriminate cases from noncases, whereas a test with an AUC of 100% has perfect discrimination ability. It is generally accepted that AUCs of 0.80 denote excellent discrimination. When performance of cardiovascular disease risk estimation has been evaluated, the AUC has been the most widely cited metric. Only recently have other metrics been reported routinely; this should be viewed as a step forward in assessing risk estimators. 

Pepe et al have elegantly described the characteristics of the AUC in simulated settings that mimic clinical risk estimation. For example, they showed that for a risk marker that differs between cases and noncases by 2 SDs (a large difference for most risk markers), an odds ratio of 11 is required to achieve an AUC of 0.80. No currently known cardiovascular disease risk factors (other than possibly age) tend to differ commonly by such an extent between cases and noncases, and no single risk marker has such a high odds ratio. However, the combination of multiple moderately strong, independent risk factors or markers (such as age, sex, blood pressure and lipid levels, diabetes mellitus, and smoking) in risk scores can achieve this degree of separation and high combined odds ratios. Hence, the combination of risk factors used in the Framingham Risk Score for estimation of coronary heart disease risk typically achieves AUCs of 0.75 to 0.80 in most published studies.

As an example, to achieve an incremental improvement in AUC from the current 0.80 to 0.90 (near-perfect discrimination of cases from noncases) would require a risk marker that differs by 2 SDs between affected and unaffected individuals, and has an independent odds ratio for disease on the order of 3.5 (ie, an odds ratio of 3.5 even after adjustment for established risk factors). No currently available markers demonstrate such a strong degree of association with cardiovascular disease, given moderate to high correlations with 1 or more existing cardiovascular disease risk factors. When these concepts are extrapolated to SCD, it is no surprise that single risk factors do not provide adequate discrimination. Efforts to assess how well current paradigms predict risk of SCD with the use of ROC analysis will help to establish the baseline predictive accuracy of these paradigms. The value of adding risk predictors should then be assessed by how much the AUC increases. For example, combined assessment of repolarization alternans, heart rate turbulence, and myocardial scar (ejection fraction <50%) better predicted adverse outcomes in REFINE (combined AUC 0.74) than assessment of ejection fraction (AUC 0.62), repolarization alternans (AUC 0.62), or heart rate turbulence (AUC 0.66) individually. Defining this structure is essential to developing a mechanism able to incorporate and/or test the value of emerging genomic and proteomic markers.

What Information Do Implantable Cardioverter-Defibrillator Clinical Trials Provide Regarding Risk Stratification?

Currently, the single most widely used criterion or risk stratification tool for implantation of an ICD is a depressed left ventricular ejection fraction, typically ≥30% to 35%. This is based on multiple multicenter studies that have shown that the strategy of ICD intervention in patients with depressed left ventricular ejection fractions (often with another criterion) generally results in improved survival. This finding represents both an important verification that risk stratification can result in important clinical benefits and a challenge to identify whether this criterion results in optimal use or application of the ICD as therapy for prevention of SCD. Several recent reports have demonstrated that within this population of patients with a depressed left ventricular ejection fraction, a low-risk group can be identified who may not benefit from an ICD intervention. Thus, ICD use targeting all of those with left ventricular ejection fraction ≥35% may not select only those at high risk. To improve risk stratification, it is imperative that this be recognized, so that further efforts at risk stratification within this population can be pursued. A simple example will illustrate the problem. If penicillin had been utilized as a potential treatment for pharyngitis before throat cultures were available (for risk stratification to identify only those cases with streptococcal pharyngitis), a clinical trial evaluating whether penicillin would prevent acute rheumatic fever in patients with pharyngitis would likely be positive, and would lead the investigators to conclude that all patients with pharyngitis should be treated with penicillin. However, although this approach is effective, it is not the optimal approach to treating pharyngitis. The optimal approach involves the use of a throat culture to identify those at risk for development of acute rheumatic fever, in whom treatment should then be administered. However, if penicillin had already been shown to prevent
acute rheumatic fever in all patients with pharyngitis, a clinical trial showing the absence of benefit of treatment in those patients with pharyngitis and negative throat cultures might be necessary to implement this change in clinical practice. Similarly, a noninferiority or equivalence trial would be required to establish that a particular subgroup of patients with depressed left ventricular ejection fraction do not benefit from an ICD and to change current guidelines.

Stakeholders’ Varying Views on Risk Stratification

These issues are further complicated by the varied viewpoints of the many stakeholders interested in the issue of risk stratification. These include patients, clinicians, investigators, industry, government and other payors, and funding agencies. One may anticipate that each one of these groups has its own specific agenda related to risk stratification. For example, individual investigators often develop a strong interest in a particular technique and design their research efforts around the specific technique rather than the broader question of how well the technique fits into the larger framework of risk stratification. Payors are focused on data-driven use of devices, but not necessarily the research questions related to risk stratification. It is noteworthy that Medicare has recently instituted a mandatory ICD registry, although its potential to improve our understanding of optimal risk stratification is unclear. Industry might be expected to support strategies that increase use of ICDs. Finally, national healthcare systems may identify different thresholds of risk for treatment.

Future success in risk stratification for SCD will be predicated on reframing the collective viewpoints, so that there is a common purpose among all stakeholders. A single vision that serves as the guiding principle for future endeavors will result in an important and necessary harmonization of efforts. Although this seems like a daunting task, there is a simply stated goal for risk stratification that could and should be adopted as this guiding principle. The goal of research in risk stratification is to identify the vast majority of patients at risk of SCD, while at the same time minimizing the number of patients who have been identified as high risk but will not experience SCD. A focus on achieving this goal will help to direct research efforts and policy decisions.

Financial Issues

Little debate surrounds the issue of risk stratification as it relates to the use of available medications that are effective in reducing SCD. In contrast, the invasive nature and significant expense and risk associated with an ICD have reserved its use for those at highest risk of sudden death. Because one of the stated goals of risk stratification is to identify all those who will experience arrhythmic sudden death so that this can be prevented by the ICD (or any future therapy that will be effective for this purpose), further efforts to stratify risk in patients with mild to moderately depressed left ventricular function are necessary. If the overall risk of SCD is currently <1% per year in this group, the screening and evaluation process will need to incorporate at least 10 to 20 times as many patients as studied in previous trials to try to identify the small (ie, 5% to 10%) subgroup of patients who have sufficient risk to justify an ICD. Typical recent ICD trials37,40 have included >1000 patients. To attain a group with similar risk that would be eligible for a randomized trial from within the group of patients with mild to moderately depressed left ventricular function would therefore require screening >10 000 to 20 000 patients. With clinical trial costs of >$10 000 per patient, this could represent a total cost of >$100 million (even a highly streamlined budget of $5000 per patient results in a minimum $50 million cost for a clinical trial). Furthermore, this does not include the cost of the devices and their implantation. Given the absence of a known, or even likely, risk stratification strategy that can magnify risk to a sufficient degree within this population, a significant financial barrier to performing such studies exists. Nonetheless, a randomized trial is the only reliable means to determine whether an ICD or another therapy will in fact predict the desired outcome (eg, a mortality reduction with ICD therapy).

Another stated goal of risk stratification is to identify those patients who currently meet criteria for an ICD but derive no benefit from its use. In the post hoc analysis from MADIT-II,4 this could include the very-low-risk group (none of the clinical risk factors; 2-year mortality ~8%) and the very-high-risk group (2-year mortality ~50%). To change clinical practice, a randomized clinical trial would be necessary to demonstrate the noninferiority of medical therapy alone (no ICD) in either of these subgroups. The critical issue with noninferiority trials is establishing the margin within which the test group mortality results are considered noninferior. The smaller the margin for acceptable noninferiority, the larger is the sample size needed to demonstrate noninferiority, as indicated in the Table. With the range of sample sizes shown in the Table and clinical trial costs of >$10 000 per patient, this could represent total costs of >$50 to 100 million.

Table. Projected Sample Size for a Noninferiority Trial Postulating That Survival With Medical Therapy Alone Is No Worse Than Survival With an Implantable Cardioverter-Defibrillator

<table>
<thead>
<tr>
<th>2-Year Mortality (ICD Patients), %</th>
<th>Margin of Noninferiority, %</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk group</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>1.6</td>
</tr>
<tr>
<td>Very-high-risk group</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>8</td>
</tr>
</tbody>
</table>

Separate sample sizes are calculated for the low- and very-high-risk groups identified in the Multicenter Automatic Defibrillator Implantation Trial II with the indicated absolute noninferiority margins (mortality without implantable cardioverter-defibrillator [ICD] does not exceed the 2-year mortality for patients with medical therapy plus the noninferiority margin). For the low-risk group, the noninferiority margins of 1% and 1.6% would correspond to “acceptable” mortality increases of 12.5% and 20%, respectively. For the very-high-risk group, the noninferiority margins of 2%, 5%, and 8% would correspond to acceptable mortality increases of 4%, 10%, and 16%, respectively. Sample sizes are calculated for log-rank test with 1-tailed α of 0.05 and 85% power. Two-year exponential survival is assumed for both groups, and all patients are already accrued at the beginning of reference time. No crossover or dropout is figured into these calculations. PASS 2008 software, routine for noninferiority comparison of 2 survival curves, was used for these sample size calculations.
There are several implications of these underlying economic issues. As noted, currently multiple treatments reduce the incidence of SCD, with the ICD being the most specific therapy currently available. If an alternative therapy of equivalent efficacy and lower cost becomes available, the required selectivity of the risk stratification paradigms could change. The cost of the ICD and the inefficiency that exists in our current patient selection criteria serve as major drivers to improve the risk stratification paradigms. Finally, significant financial resources will be required to demonstrate that new paradigms can more efficiently select patients who will benefit from an ICD. It is important to consider the cost of performing well-designed studies that will improve risk stratification in the context of the future costs of continuing to implant ICDs with the currently demonstrated inefficient criteria. Because the costs of performing clinical trials and providing clinical ICDs are not borne by the same groups, this may hamper the financial component of the incentive to achieve better risk stratification, particularly among the group of patients who currently meet criteria for an ICD.

Importantce of Risk Stratification

Given the relatively poor performance of current risk stratification approaches for SCD and the aforementioned various challenges and limitations, it is reasonable to query whether further efforts should be devoted to this area. From a therapeutic perspective, there is great need for risk stratification for SCD. Although lifestyle modifications and medical therapies may reduce SCD, there remain patients on optimal therapy who experience SCD and in whom implanting a prophylactic ICD could be life saving. Furthermore, other therapies may be developed in the future that could benefit those patients at risk for SCD, but whose use would need to be appropriately limited to those at greatest risk. From a health economics perspective, it is becoming increasingly apparent that there are potentially both low- and high-risk subgroups within the population of patients who currently qualify for an ICD on the basis of accepted guidelines who do not benefit from this therapy. Whether the cost/benefit ratio of ICD use is favorable remains somewhat controversial, but data exist to support its cost-effectiveness over the long term as used within the current guidelines. However, it is clear that further efforts at refinement of these guidelines could dramatically improve the cost-effectiveness of this therapy. Identifying the low- and high-risk groups that do not benefit from the ICD because of either very low risk of sudden death or overwhelming competing risks and not using ICDs in these patients decreases the overall costs and increases effectiveness (because ICDs are used more effectively in the remainder of the population that derives benefit from the ICD). For example, ICD efficacy in selected high-risk populations, such as those with end-stage renal disease, has not been evaluated; it is therefore unknown whether the ICD provides clinical benefit and whether it is cost-effective in such populations.

From the public health perspective, our current approach to the use of ICDs does not identify most of the patients who will experience SCD. The number of SCDs per year has been reported to range from 184,000 to 462,000. Because the majority of these sudden deaths occur in individuals with left ventricular ejection fractions >35%, there is a tremendous opportunity for the development and application of risk stratification techniques within this population. If further significant inroads are expected in this public health problem, better means of identifying those at risk and those who could benefit from more intensive therapy are necessary. Finally, from the perspective of the patient, a clearer delineation of risk may lead to a more informed decision about therapeutic options.

Conclusion

Future strategies for risk stratification should address the general importance of SCD, the history of risk stratification research, and our current state of knowledge, basic issues regarding the concept of risk, varying stakeholder perspectives, and financial issues. Furthermore, as described above, the complexities related to risk stratification mandate close cooperation between clinicians and biostatisticians to enhance our statistical approach to risk stratification for sudden death. A more concerted effort to incorporate the realities of the clinical and statistical barriers to risk stratification into further research in this area is critical to achieve more clinically useful risk stratification. Forming a solid foundation for risk stratification with the currently available clinical information and statistical approaches is particularly important, as an era of new imaging techniques, proteomics, and genomic approaches is likely to emerge.

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