Risk stratification for any disease is, in many ways, medicine’s attempt to predict the future. The challenges in risk stratification for sudden death, however, may be unparalleled in medicine. Although the many types of sudden death all present with similar phenotypes, risk stratification efforts generally center on the prediction of death resulting from either ischemic or arrhythmic events. The focus of this article is on current and future approaches to risk stratification for sudden death caused by ventricular tachyarrhythmias in patients with left ventricular dysfunction (referred to here as sudden cardiac death [SCD]). Recent advances that limit myocardial injury and remodeling that leads to left ventricular dysfunction continue to favorably affect SCD rates. However, the prevalence of SCD and the low survival rate once it occurs remain major public health concerns and underscore the importance of risk stratification and preemptive intervention.

The Moving Target of SCD
For many other disease processes for which risk factors are established or sought, investigators have successfully relied on objective criteria to define the end point of interest such as myocardial infarction (MI). For SCD, we have often depended on clinical trials that assessed arrhythmic death or surrogate markers such as appropriate implantable cardioverter-defibrillator (ICD) therapy or total mortality. Many of these end points, however, may not accurately assess the occurrence of fatal ventricular tachyarrhythmias that are otherwise amenable to defibrillation. Our ability to correctly distinguish cause of death on clinical grounds is marginal at best, with data suggesting that at least in patients with ischemic heart disease, we may be wrong nearly half the time. For example, in a substudy of the Valsartan in Acute Myocardial Infarction (VALIANT) trial, autopsies were performed on post-MI patients whose deaths were considered sudden on clinical grounds. Of these, 49% were due to nonarrhythmic causes led by recurrent MI and cardiac rupture.  Likewise, the use of ICD therapies as an end point may overestimate the incidence of life-threatening arrhythmias by 2-fold. These inherent difficulties in adjudicating the cause of a sudden death serve as a major challenge to our attempts to link any specific risk factor with arrhythmic death because a risk factor for SCD may predict arrhythmic SCD, nonarrhythmic SCD, or both.

Another challenge in predicting SCD is the changing nature of the underlying disease process itself. The commonly proposed mechanism of SCD involves the development of ventricular tachycardia (VT), which degenerates into ventricular fibrillation (VF), or primary VF; these ultimately lead to asystole and death. Studies of out-of-hospital cardiac arrest have shown that up to 40% of the initial arrhythmias are either VT or VF. Although current emergency medical services assess about 250,000 out-of-hospital cardiac arrests in the United States each year, the rate of SCD has actually decreased by 49% over the last 5 decades. The decline in rate is paralleled by a shift in cause of death. In Seattle, the adjusted annual incidence of cardiac arrest with VF as the first identified rhythm decreased by ~56% from 1980 to 2000. Previous estimates of the proportion of SCD resulting from a specific arrhythmia were limited to hospitalized patients under cardiac surveillance, the rare outpatient being monitored at the time of an event, or recordings taken from emergency medical services. All these sources are limited by potential biases in selection and delays in rhythm assessment, but recent technological advances have allowed additional insights. In a study using implantable cardiac monitors placed in patients with recent MI and depressed ejection fraction (EF), high-degree atrioventricular block occurred 3 times more often than sustained VT or VF and served as the most powerful predictor of cardiac death. The nature of these changes is undoubtedly a marker of successful therapies such as thrombolysis and primary angioplasty for the treatment of acute MI and primary and secondary preventive strategies for heart failure and ventricular tachyarrhythmias. Regardless, it is clear that the “moving target” of sudden death and its changing causes will affect strategies for risk stratification.

General Concepts of Risk Stratification
Risk factors for SCD can be divided into either epidemiological markers of risk that may not necessarily be pathophysi-
ologically linked to SCD or, alternatively, those that are integral to the development of fatal ventricular tachyarrhythmias. Both types of factors may be helpful in the process of risk stratification, although only identification of the latter group may yield potential new targets for treatment. To date, risk stratification has focused on either noninvasive techniques that could be applied to a large “at-risk” population or electrophysiological testing, which, because of its invasive nature, has been used in a more limited manner.

The goal of such evaluation over the recent past has been to select appropriate patients for ICD implantation. However, efforts at risk stratification should be viewed more broadly for several reasons. Fundamentally, we know that the greatest absolute number of SCDs will arise in patients without known traditional risk factors for SCD or with SCD as the first manifestation of heart disease. Additionally, although the cost and invasive nature of the ICD are important factors in establishing a threshold for preventive intervention, the future will no doubt bring other treatment options that may be even more effective, less invasive, and maybe even less expensive than current technology. Therefore, risk stratification should be viewed beyond the context of distilling out the highest-risk individuals for ICD implantation and more as a basis for research into mechanisms and innovative preventive strategies.

Given the multifactorial nature of SCD, it is important to include risk factors that explore abnormalities across the spectrum of potential variables implicated in the pathogenesis of ventricular tachyarrhythmias. Because it is generally accepted that SCD requires the alignment of an acute trigger superimposed on a vulnerable substrate, stratification techniques have focused on uncovering abnormalities in myocardial substrate and electric instability with less emphasis on the seemingly unpredictable, and therefore difficult-to-study, acute triggering events. In general, these have included assessment of substrate (ie, EF), tests of autonomic function (ie, heart rate variability, baroreflex sensitivity, heart rate turbulence), repolarization abnormalities (ie, QT interval, T-wave alternans, QT variability), and depolarization abnormalities (ie, QRS duration, signal-averaged ECG). The utility of these individual markers has recently been reviewed, but only EF is considered to have enough supporting data to be recommended for use in routine clinical risk stratification (the Table). This fact appears logical because the prototypical factor underlying risk for SCD in patients after MI is the presence of scar tissue, which serves as the substrate for reentry. Because the extent of scar has been known for decades to be related to inducible VT and because EF has also been demonstrated over as long a period to be an easily determined marker of prognosis after MI, it is understandable that EF has been the most-studied marker of risk for SCD. Although EF is certainly related to infarct size, the strength of the relationship is poor and could be part of the explanation of the modest performance of EF alone as a predictor of SCD. The matter is made more complex by the knowledge that scar alone only partially explains the pathogenesis of malignant arrhythmias in patients with left ventricular dysfunction. Cardiac remodeling, defined clinically in relation to the changes in ventricular size, shape, and function that occur after myocardial injury, pressure, or volume overload, is determined at the tissue level through altered genome expression and molecular, cellular, and interstitial changes throughout the heart. Alterations in cardiac ion channels and sympathetic innervation are part of the remodeling process and play a crucial role in the changes in excitability and repolarization that promote arrhythmogenesis. For example, heart failure– and infarction-induced reductions in repolarizing K+ currents and increases in depolarizing Na+ plateau currents impair repolarization, prolong the action potential duration, and promote the formation of arrhythmogenic early afterdepolarizations. Triggered activity resulting from delayed afterdepolarizations may ensue as a result of spontaneous diastolic Ca2+ release caused by ion transport remodeling. Reentry circuits can form from the combined result of early and delayed afterdepolarization, heterogeneities in refactoriness owing to spatial variations in action potential duration, and slowed conduction caused by reduced connexin expression and phosphorylation, along with reductions in depolarizing Na+ currents. On a neuronal level, sympathetic nerve fibers distributed in perivascular areas and between myocytes may become injured during infarction or through systemic disease processes, resulting in wallerian degeneration of the distal stumps. Reexpression of neurotrophic factor genes from around the site of injury may then trigger proximal regeneration in the axonal sprouts, possibly in an attempt to reestablish neuronal control of contractile function. The precise mechanisms by which denervated regions predispose to arrhythmogenesis are speculative. However, denervation supersensitivity has been proposed as a possible explanation whereby myocardial tissue deprived of sympathetic innervation responds to sympathetic nerve stimulation or norepinephrine infusion with an exaggerated shortening of the effective refractory period, setting the stage for ventricular tachyarrhythmias. Additionally, alterations in the cardiac efferent sympathetic nervous system are an important determinant of coronary blood flow during increased sympathetic stimulation and could contribute to both arrhythmogenesis and the progression of heart failure in individuals with cardiac autonomic dysfunction.

An additional consideration is that some risk markers may be common to many types of structural heart disease and others may be unique to particular cardiac disorders. For example, in patients with hypertrophic cardiomyopathy, extreme left ventricular hypertrophy and abnormal blood pressure response to exercise are among the major risk factors for sudden death, whereas in the long-QT syndrome, sex, genetic locus, and QT interval serve as markers for future arrhythmic events. It is therefore necessary to consider risk stratification in relation to the underlying pathophysiology for arrhythmogenesis in each type of heart disease.

Realities of Risk Assessment

The complexities of the issue are not limited to its pathophysiology. The field of risk stratification has been marked over the last 2 decades by techniques “du jour,” which have made sense physiologically, have proved useful in retrospective analysis and small prospective evaluations, but have often failed to provide suitable positive predictive value in large-
The inability of the majority of noninvasive risk stratification markers to reliably predict SCD either by themselves or in combination should come as little surprise. First, many of the risk factors identified as markers for SCD are also predictors of non-SCD. Second, advances in the treatment of MI and heart failure have resulted in fewer patients with low EF and improved survival from both pump failure and arrhythmias. Third, the aging population with its attendant burden of comorbidities brings with it increasing risk of death from nonarrhythmic causes, further blunting the predictive value of any SCD predictor. Fourth, our predilection for viewing these measures as static entities to be assessed at a single time point fails to consider the fact that remodeling, whether anatomic, ionic, or electric, is a dynamic process that may evolve over an extended period. Further, the presence of ventricular arrhythmias (VPBs, NSVT) on Holter monitoring is a well-demonstrated risk factor for SCD. In some populations, the presence of NSVT has been effectively used to select high-risk patients for application of therapy to prevent sudden arrhythmic death; this may also have limited sensitivity. Another potential problem is that abnormal T-wave alternans is a risk factor for SCD, although it may be more predictive with it increasing risk of death from nonarrhythmic causes, further blunting the predictive value of any SCD predictor. Fourth, our predilection for viewing these measures as static entities to be assessed at a single time point fails to consider the fact that remodeling, whether anatomic, ionic, or electric, is a dynamic process that may evolve over an extended period from a single insult or may occur in fits and starts as a result of repeated insults, some of which may be subclinical or vary with time of day, day of the week, or season. Finally, and perhaps most important, the hazard ratios associated with most risk stratification tools are modest at best. Taken together, the chances that any single technique measured at one point in time would prove robust are unfavorable.

In addition to the aforementioned challenges, risk stratification may also suffer from a too healthy/too sick principle. Currently, risk stratification is viewed as a dichotomous analysis tool in which treatment with an ICD is or is not recommended on the basis of published guidelines derived from clinical trial data. However, clinical practice often presents us with patients who fall outside the inclusion criteria for those clinical trials but are indicated for device implantation on the basis of guidelines. Yet, this same clinical trial data support the notion that not all patients with low EF are at equal risk. For example, from a retrospective analysis of the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II study, we know that patients with low EF but without other clinical “high-risk” factors (New York Heart

Table. Continued

| Technique | Conclusion |
|-----------|------------|
| Heart rate recovery and recovery ventricular ectopy | Limited data show that low heart rate recovery and ventricular ectopy during recovery are risk factors for SCD |
| T-wave alternans | A moderate amount of prospective data suggest that abnormal T-wave alternans is a risk factor for SCD |
| BRS | A moderate amount of data suggest that low BRS is a risk factor for SCD |

LVEF indicates left ventricular ejection fraction; SCD, sudden cardiac death; SAECG, signal-averaged ECG; HRV, heart rate variability; NSVT, nonsustained ventricular tachycardia; VPB, ventricular premature beat; NYHA, New York Heart Association; and BRS, baroreceptor sensitivity. Reprinted from Goldberger et al.12
Association functional class >II, age >70 years, blood urea nitrogen >26 mg/dL, QRS duration >0.12 second, and atrial fibrillation) have a very low mortality from arrhythmic events. On the other end of the spectrum are patients with low EF and high competing risks from other causes. These patients may derive no benefit from any intervention designed to terminate or prevent VT/VF, not because they are at low risk of arrhythmic events but because the attributable risk of death from this one cause is relatively low. This observation appears to be the case in special situations such as dialysis patients with low EF, in whom the risk of arrhythmic death is high but the mortality from competing risks is even greater, therefore leading to a situation in which interventions such as ICDs may have little or no impact or may actually reduce survival given the higher complication rates seen in this population.

Perhaps one of the most striking elements of all the risk stratification measures is found not in their positive predictive value but in their negative predictive value. Although this seems to be an appealing feature of a purported risk stratification technique, this observation is obviously due in large part to low event rates. In fact, the negative predictive value of these tests is only somewhat better than a coin toss. With low event rates and low hazard ratios, it seems that the most valuable clinical utility of many of the currently available risk stratification techniques could be in identifying individuals with multiple negative results who would then be at very low risk for sudden death. This would be analogous to the use of multiple positive results to enhance risk stratification for the identification of high-risk individuals.

### Current Approach

Scant attention is given to risk stratification for SCD in patients with left ventricular dysfunction in published guidelines. Instead, emphasis has been placed on the identification of knowledge gaps and on the delineation of indications for ICD implantation. For primary prevention of SCD in patients with ischemic and nonischemic cardiomyopathy, the Class I recommendations based on multiple randomized-controlled trials that demonstrate a consistent decrease in overall mortality include ICD implantation under the following circumstances: (1) patients with left ventricular EF (LVEF) ≤35% owing to prior MI who are at least 40 days after the MI and are in New York Heart Association functional class II or III; (2) patients with nonischemic dilated cardiomyopathy who have an LVEF ≤35% and are in New York Heart Association functional class II or III; (3) patients with left ventricular dysfunction resulting from prior MI who are at least 40 days after MI, have an LVEF ≤30%, and are in New York Heart Association functional class I; and (4) patients with nonsustained VT resulting from prior MI, LVEF ≤40%, and inducible VF or sustained VT at electrophysiological study. These recommendations contain implicit recognition of the LVEF and New York Heart Association class as indicated tools for risk stratification. In patients with borderline EF, monitoring for nonsustained VT or the use of additional noninvasive testing such as T-wave alternans testing, signal-averaged ECG, and heart rate turbulence may be useful. If the patient manifests multiple abnormal tests, electrophysiological testing may be considered to evaluate for inducible VT. The Figure depicts an algorithm that may assist in decision making in these borderline cases and outlines areas for future study.

At times, physicians may be confronted with incidental findings such as those that may occur when a patient is being monitored for another indication but is found to have nonsustained VT. In the setting of relatively preserved LV function, a conservative approach to dealing with this situation would be to assess for reversible causes such as myocardial ischemia and ensure good medical therapy, in particular beta-blocker therapy. Attempts to further assess risk could include other noninvasive tests such as T wave alternans and signal averaged electrocardiography or electrophysiological testing. Although these strategies are as yet untested, the importance of electrophysiologic testing in the prediction of future events in some settings is well-established. Careful and individualized choice of the diagnostic workup is essential in these cases.

### Future Directions

Additional risk stratification techniques have been evaluated that hold promise. For example, EF represents a global assessment of left ventricular systolic function but does not necessarily correlate with the anatomic substrate needed for reentry, ie, myocardial scar. Magnetic resonance imaging has proven useful in diagnosing arrhythmogenic right ventricular cardiomyopathy and delineating myocardial scar in patients with hypertrophic, ischemic, and nonischemic dilated cardiomyopathies, which is a potent risk factor for arrhythmic events and overall cardiovascular mortality. In addition, infarct morphology and tissue heterogeneity visualized on contrast-enhanced magnetic resonance imaging are strong predictors of inducibility on electrophysiological study and spontaneous ventricular arrhythmia in ICD recipients with prior MI and with nonischemic cardiomyopathy. An other interesting measure is cardiac 123-I metaiodobenzylguanidine imaging. Cardiac sympathetic denervation has long been known to play an important role in ventricular arrhythmogenesis. Although many techniques may indirectly measure cardiac sympathetic tone, 123-I metaiodobenzylguanidine provides a means of direct qualitative assessment and has been used in clinical studies to predict arrhythmic events. In studies of patients with left ventricular dysfunction and those with ICDs, sympathetic denervation as assessed through 123-I metaiodobenzylguanidine score was a strong and independent predictor of SCD and appropriate ICD therapy and outperformed other noninvasive markers.

Major obstacles exist in the field of risk stratification, but they are not insurmountable. Technological advances that allow us to measure vulnerable substrate directly, eg, scar on magnetic resonance imaging, as opposed to a global measure of ventricular function, eg, EF, may prove useful in large populations with even milder degrees of left ventricular dysfunction. Additionally, moving the focus beyond the evaluation of vulnerable myocardium and into the realm of common triggers such as vulnerable plaque may be important because a large number of SCDs occur in patients with only this latter risk factor. Serum markers and advances in
imaging may all prove useful in this arena. Family history of SCD has also been shown to be an important risk factor for SCD. Although genetic testing is valuable in several forms of channelopathies and cardiomyopathies, its role in predicting arrhythmic events in the general population is uncertain, but genetic testing may be particularly useful when applied to surviving family members of unexplained SCD victims. Finally, we must recognize that risk is not a static measure; repeated evaluation over time may be necessary as remodeling progresses and new insults occur. The time course of such reevaluation is, at present, unknown.

The greatest impact on the largest number of SCD events requires a focus on patients barely on today's radar: those with milder forms of heart disease and those whose first manifestation of heart disease is SCD. Although genetic testing is valuable in several forms of channelopathies and cardiomyopathies, its role in predicting arrhythmic events in the general population is uncertain, but genetic testing may be particularly useful when applied to surviving family members of unexplained SCD victims. Finally, we must recognize that risk is not a static measure; repeated evaluation over time may be necessary as remodeling progresses and new insults occur. The time course of such reevaluation is, at present, unknown.

The greatest impact on the largest number of SCD events requires a focus on patients barely on today's radar: those with milder forms of heart disease and those whose first manifestation of heart disease is SCD. At present, much of the effort in risk stratification has focused on finding which patients with low EF are at highest risk of SCD and therefore most likely to benefit from ICD implantation (or vice versa, those at lowest risk) and which patients with known heart disease and more preserved EF are nevertheless at significant risk of SCD. With long-term follow-up results from the MADIT II trial demonstrating that we need to implant only 8 ICDs in post-MI patients with an EF ≤30% to save 1 life, it may be difficult to reduce this number substantially with currently available techniques. Clinical trials designed to evaluate risk stratification strategies in patients with more preserved EFs face significant challenges. One such trial, the Defibrillators to Reduce Risk by Magnetic Resonance Imaging Evaluation (DETERMINE) trial, which was to randomize patients with coronary artery disease, LVEF >35%, and scar burden >10% on cardiac magnetic resonance imaging to ICD or standard therapy, was recently discontinued because of poor enrollment rates. Further efforts at risk stratification may also force difficult ethical issues to light. Can we risk stratify patients who already meet implantation criteria and withhold therapy in what we may believe is a low-risk patient despite the low EF? Can we deny therapy to patients who have major competing risks of death from other causes such as those on dialysis or of very advanced age, even though treatment may impart at best a small survival advantage? Like predicting the future, risk stratification for sudden death is fraught with great challenges but has the potential for great rewards. Concerted efforts to improve our ability to reliably perform risk stratification for SCD based on cause are necessary to enhance public health and resource use.

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Figure. Global risk assessment algorithm for population screening for risk of sudden cardiac death (SCD). Flowchart depicting a potential global risk assessment algorithm for population screening for risk of SCD. Areas highlighted in blue represent potential evaluations for which there are no large-scale data to support a specific recommendation or in which development of new testing approaches is required. Although the risk of SCD diminishes as one proceeds from left to right, the actual number of SCDs in each of the groups may not be substantially different, highlighting the importance of addressing the areas in blue to materially affect the public health burden of SCD. The most established paradigm for risk stratification for SCD is in the leftmost branch in patients with left ventricular (LV) ejection fraction <35% to 40%, in whom an implantable cardioverter-defibrillator (ICD) may be considered after an appropriate clinical evaluation. But even within this group, there are opportunities to refine our approaches to risk stratification (blue box) to identify particularly low-risk subgroups that may not benefit from an ICD and particularly high-risk subgroups that have competing risks that mitigate potential benefit from an ICD. In patients with mild to moderate LV systolic dysfunction, overall risk of SCD is low, requiring the identification of other risk factors that will select for higher-risk subgroups. These may include clinical risk factors such as diabetes mellitus and renal disease and results of specialized testing, including tests of depolarization and repolarization abnormalities, autonomic dysfunction, inducibility of arrhythmias, and imaging. Many of these factors have already been shown to increase the risk for SCD, but their incorporation into a patient-based treatment algorithm is yet to be established. Novel genetic and biomarkers may also be incorporated to aid in risk stratification. Finally, in patients with normal LV function (without known channelopathies), given the very low risk in this population, effective risk stratification will require the development of novel markers that are powerful enough to select out the small subgroup that is at substantial risk for SCD.
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