Sudden cardiac death (SCD) is a leading cause of mortality in industrialized countries, and ventricular fibrillation and sustained ventricular tachycardia are the major causes of SCD. Although there are now effective devices and medications that can prevent such serious arrhythmias, it is crucial to have methods of identifying patients at risk. Numerous studies suggest that most patients dying of SCD have coronary artery disease or cardiomyopathy. Functional or electrophysiological measurements are effective in risk stratification. Left ventricular ejection fraction measured by echocardiography or cardiac imaging techniques is the gold standard to detect high-risk patients. Noninvasive techniques and measurements, such as T-wave alternans, signal-averaged electrocardiography, nonsustained ventricular tachycardia, heart rate variability, and heart rate turbulence, have been proposed as useful tools in identifying patients at risk for SCD. This article reviews the epidemiology, mechanisms, substrates, and current status of risk stratification of SCD. (Circ J 2007; Suppl A: A-106–A-114)

Key Words: Practice guidelines; Risk stratification; Sudden cardiac death; Ventricular arrhythmia

Epidemiology of SCD

SCD is defined as death from cardiovascular causes in patients with or without known preexisting heart disease, for whom the mode and time of death were unexpected. The generally accepted temporal definition of SCD allows a period of up to 1 h between the onset of an abrupt change in clinical status and loss of consciousness, but there is great variability in the incidence of SCD among previous reports based, in part, on the inclusion criteria used in individual studies. Estimates of SCD range from less than 200,000 to more than 450,000 cases annually in the United States, giving rise to an overall incidence of 1.2 per 1,000 people (0.12%). In general, event rates in Europe are considered to be similar to those in the United States.

In Japan, information available is still limited; the most reliable data have been provided by the Fire and Disaster Management Agency in 2005 and by the Emergency Inspection Committee of the Emergency Service Foundation, Tokyo in 2001 (both reports are written in Japanese). The incidence of sudden death estimated by the emergency medical service staff was approximately 89,000 annually nationwide (83,353 in the report from the Emergency Inspection Committee and 94,920 in the report from the Fire and Disaster Management Agency). Of these, cardiogenic cause (ie, SCD) was estimated to contribute approximately 53,000 cases annually, because 60% of total SCD cases in Japan are considered to have a cardiogenic cause. The overall incidence of SCD in Japan is approximately 0.7 per 1,000 people (0.07%) annually. Thus the rate of SCD in Japan is less than that in the United States (approximately 0.6-fold).

Mechanism of SCD

SCD is caused by fatal ventricular arrhythmias (VF, VT, and torsade de pointes (TdP)) in patients with or without known structural heart disease. Causes for SCD may include cardiac dysfunction, a genetic basis, or electrophysiological abnormalities (Fig 1). In addition, autonomic nerve imbalance (low parasympathetic activity and high sympathetic activity) and presence of triggers are associated with ventricular arrhythmias and SCD. Such modulation may affect an electrophysiological and genetic substrate. General risk factors in each disorder are also important. Although the fundamental mechanisms responsible for SCD vary among patients, VF precipitated by sustained VT is considered a
common cause of cardiac arrest leading to SCD. Rapid sustained VT converts easily to VF, particularly in patients with markedly impaired left ventricular function. Previous studies in the United States suggest that 75–80% of SCDs occur via this mechanism and 15–20% are attributable to bradyarrhythmias, including atrioventricular block and sinus arrest.6,7 Similarly, approximately 70% of SCD cases in Japan may be the result of ventricular tachyarrhythmias (reference in Japanese).

**Substrates of SCD**

The incidence of SCD increases in the presence of structural heart disease. The most common etiology in developed countries is coronary artery disease (CAD). In Japan, approximately 50–60% of cases of SCD occur in patients with underlying acute or chronic CAD and approximately 30–35% in patients with cardiomyopathies, such as dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM). These estimates are from an epidemiological study of the inhabitants of Hisayama-cho (references in Japanese). In North America and Western Europe, the incidence of CAD (75–80% of all SCDs) is higher than that in Japan. DCM is the second most common etiology and accounts for approximately 10–15% of all SCDs. A high incidence of SCD on the basis of cardiomyopathies in Japan might be related to different lifestyle, food and heredity.

Other diseases predisposing to SCD include heritable abnormalities,8 which are the major substrate of SCD in younger patients. If both parents died from SCD, the relative risk for any offspring is 9.49 There also exist a group of inherited abnormalities, such as the long QT syndrome (LQTS) and the Brugada syndrome (BS), that can precipitate SCD without overt structural changes in the heart. Underlying heart disease of patients who underwent an ICD implantation in Japan are much different from those in the United States. In Japan, 35% of cases had cardiomyopathies (DCM: 16%, HCM: 12%), 34% had CAD, and 19% had idiopathic VF. In the United States, most cases (81%) had CAD and 10% had DCM and other diseases were rare.

These data are posted on web sites of the Japanese Circulation Society.

**General Risk Factors for SCD**

General risk factors for SCD are summarized in Table 1. The incidence of SCD increases with age, in parallel with an increase in the incidence of total death.10 Patients with a past history of syncope have a high incidence of SCD. There is a relationship between alcohol ingestion and arrhythmias. A number of studies claim a J-shaped relationship, with the risk lowest in individuals with low alcohol intake compared with those who rarely or never consume alcohol and those with a high alcohol intake.11

Classic predictors for CAD, such as smoking, obesity, hypertension, diabetes, hyperlipidemia, are associated with ventricular arrhythmias and SCD. The Framingham Study demonstrated that cigarette smokers have a 2- to 3-fold increase in SCD risk.12 The high risk for SCD is particularly evident in the severely obese individuals; 40–60-fold higher than in the age-matched general population.13 Diabetes is a major risk factor for premature and accelerated atherosclerosis, causing an increased incidence of myocardial infarction (MI), stroke, and death compared with age- and gender-matched populations without diabetes.14 High total and low-density lipoprotein-cholesterol levels have been shown to increase the rate of SCD.15 Appropriate lipid management strategies with the use of statins reduce the risk of SCD by preventing recurrent CAD.16 Regarding hypertension, systolic blood pressure and myocardial dysfunction have been suggested as the important determinants of complex arrhythmias.17

Changes in extracellular potassium (hypokalemia) and magnesium concentrations (hypomagnesemia) are associated with life-threatening ventricular arrhythmias, particularly TdP.18 Cardiovascular causes account for at least 40% of deaths in patients with end-stage renal failure and 20% of these are sudden. Arrhythmias often occur during hemodialysis sessions and for at least 4 to 5 h afterward. Endocrine disorders can induce ventricular arrhythmias by excessive or insufficient hormone activity on myocardial receptors (eg, pheochromocytoma, hypothyroidism). Severe hypoglycemia is associated with ventricular repolarization abnormalities, prolongation of the QT interval, and ventricular arrhythmias.
The incidence of SCD is increased in patients with seizure disorders, schizophrenia, and anorexia nervosa. Although most pregnancies are benign in industrialized countries, new-onset ventricular arrhythmias are of concern in women of higher age (>40 years). Although the presence of structural heart disease should be sought in these women, VT often occurs in the absence of overt structural heart disease and may be related to elevated catecholamines.

High drug concentrations because of overdose or drug interactions increase the risk of drug-induced arrhythmias. Antiarrhythmic drugs, such as sodium channel blocker-related toxicity, are the most common precipitants and their adverse effects were best demonstrated in the CAST study. Marked QT prolongation, often accompanied by TdP, occurs in 1–10% of patients receiving QT-prolonging antiarrhythmic drugs, and digitalis toxicity has a well-known association with malignant arrhythmias.

Techniques and Measurements for Risk Stratification

This section reviews the major techniques and measurements listed in the recent practice guidelines for identifying patients at risk for SCD (Table 2).

Cardiac Function and Imaging

Echocardiography is the technique that is most commonly used to evaluate cardiac function. The combination of echocardiography with exercise or pharmacological stress testing is applicable to a selected group of patients who have myocardial ischemia and resting ECG abnormalities. Cardiac magnetic resonance imaging (MRI), computed tomography (CT), or radionuclide techniques can be useful in patients with ventricular arrhythmias when echocardiography does not provide accurate assessment of left and right ventricular function and/or evaluation of structural changes. Advances in cardiac MRI include excellent image resolution with accurate quantification of chamber volumes, left ventricular mass and function; right ventricular size and function, including the detection of fatty infiltration; and cardiac CT has advanced greatly, with segmental images of the coronary arteries from which the extent of calcification can be quantified. Coronary angiography and left ventriculography can also be useful in diagnosing CAD and abnormalities of left ventricular function and wall motion.

LVEF

The LVEF is now the gold standard for identifying high-risk patients for SCD. Recommendations for prophylactic ICD implantation in published guidelines are based mostly on LVEF, which can be measured by echocardiography, cardiac MRI, radionuclide angiography, or left ventriculography. Many studies have reported that a reduced LVEF is significantly associated with serious ventricular arrhythmias, SCD, and mortality. Most studies have defined reduced LVEF as ≤35% or ≤40%; however, in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II trial for prophylactic implantation of an ICD in post-MI patients, LVEF was defined as ≤30%, and the recent ACC/AHA and ESC Practice Guidelines for the prevention of SCD made recommendations on the basis of data derived from that trial.

New York Heart Association (NYHA) Functional Class

NYHA functional class has been used for risk stratification of patients who may have future arrhythmic events or SCD, particularly patients with congestive heart failure. The consensus is that patients in NYHA functional class II–IV should receive optimal medical therapy and implantation of ICD should be taken into consideration if medical therapy for ventricular arrhythmias is ineffective.

B-Type Natriuretic Peptide (BNP)

BNP is a neurohormone synthesized predominantly in the ventricular myocardium. The baseline level of plasma BNP on admission independently predicts mortality after acute MI. The prognostic value of BNP is increased when combined with other neurohormones, such as the N-terminal fragment of its prohormone and troponin. The most appropriate cut-off value of BNP is supposed to be 200 pg/ml.

Resting Electrocardiography

A standard resting 12-lead ECG is indicated in all patients at risk for SCD to identify various underlying pathological conditions (eg, congenital abnormalities, electrolyte imbalance, ventricular hypertrophy, ischemic heart disease, and cardiomyopathy). A prolonged QRS duration (>130 ms) and T-wave abnormalities are both independent predictors of SCD. Although a prolonged corrected QT (QTc) interval >440 ms predicts SCD, a short QTc interval is also associated with increased risk.

Exercise or Pharmacological Stress Testing

Exercise testing is commonly used to evaluate the pa-


Risk Stratification for SCD

tients with CAD and/or adrenergic-dependent arrhythmias. Pharmacological testing is used as an alternative in aged persons or those who have a physical inability or more severe symptoms. These tests can also be used in conjunction with an imaging modality (echocardiography or single-photon emission computed tomography) to detect silent ischemia. In patients with CAD or cardiomyopathies, frequent premature ventricular contractions (PVCs) during or after exercise testing are associated with a greater risk for serious cardiovascular events, but not specifically for SCD.42,48

Ambulatory Electrocardiography

Continuous or intermittent ambulatory ECG recordings are helpful in diagnosing arrhythmias and their correlation with subjective symptoms. The recordings are also useful for detecting changes in ST-segment, QT-interval and T-wave morphology. A 24-h Holter recording is appropriate when the arrhythmia is known or suspected to occur at least once a day. For sporadic episodes producing palpitations, dizziness, or syncope, conventional event recorders are more appropriate because they can record over extended periods of time.39 Implantable recorders have been shown to be useful for documenting sporadic arrhythmia events,9 but are not used in Japan. Frequent PVCs (≥10 beats/h) and nonsustained VT (NSVT) defined as consecutive PVCs ≥3 have been shown to predict high-risk patients, but NSVT is more powerful than PVCs for risk stratification.40,41

Noninvasive Electrophysiological Techniques

Recent practice guidelines for risk stratification of SCD in both Western countries1 and Japan2 recommend noninvasive electrophysiological techniques such as TWA, signal-averaged electrocardiography (SAECG), heart rate variability (HRV), baroreflex receptor sensitivity (BRS), and heart rate turbulence (HRT), as well as an EPS, to improve the diagnosis and risk stratification of patients with ventricular arrhythmias. In the United States, TWA and SAECG have been approved by the Food and Drug Administration and HRV and BRS show considerable promise. Unfortunately, none of these modalities has been approved by the Ministry of Health, Labour and Welfare in Japan.

TWA  TWA, which is a fluctuation in the amplitude or morphology of the T wave, which alternates every other beat during assessment by exercise testing or atrial pacing, has been shown to be an effective tool for identifying high-risk patients after MI2 and in the presence of ischemic or nonischemic cardiomyopathy.43–45 TWA has a very high negative predictive accuracy for ventricular arrhythmias and SCD. Both positive and indeterminate results of TWA are considered to be abnormal for risk stratification in patients with reduced cardiac function (LVEF ≤30%).44–46 For risk stratification in patients with LVEF ≥40%, a positive TWA is a useful predictor.47 Combined assessment with other ECG modalities increases the power of TWA in predicting ventricular arrhythmias and SCD.48 The recent ACC/AHA/ESC Practice Guidelines1 for risk stratification of SCD granted only TWA a IIa rating, a higher weight of evidence/opinion for assessment of risk compared with other noninvasive electrophysiological techniques. Other modalities were given IIb or lesser ratings.

SAECG  SAECG improves the signal-to-noise ratio of a surface ECG, enabling the identification of low-amplitude signals at the end of the QRS complex, referred to as late potentials (LPs). LPs indicate regions of abnormal myocardium demonstrating slow conduction and as such are a substrate for reentrant excitations. Numerous previous studies have demonstrated that the presence of LPs increases the risk of arrhythmic events in patients after MI, with a high negative predictive value.49 However, contemporary widespread use of revascularization therapy has caused a noticeable reduction in its predictive power, probably through modification of the arrhythmogenic substrates. Therefore, LPs alone may not be useful for the identification of patients at risk of ventricular arrhythmias after MI.

HRV  HRV is the beat-to-beat variation in cardiac cycle length resulting from autonomic influences on the sinus node. Reduced HRV reflects autonomic dysfunction and predicts enhanced cardiac mortality. Among HRV parameters, the standard deviation of normal-to-normal RR intervals (SDNN) is the most useful in risk stratification for SCD. Reduced SDNN has been shown to independently predict risk of SCD and total mortality after MI both with and without impaired left ventricular function.50–53 Small observational studies proposed the usefulness of HRV for risk stratification of patients with nonischemic cardiomyopathy, but larger and more extensive studies are required to substantiate the proposal.

BRS  BRS is a quantitative assessment of autonomic nerve function (primarily vagal reflex) in response to acute stimulation. Depressed BRS identifies a subgroup at high risk for arrhythmic events after MI. The predictive value of BRS is increased when combined with an EPS44 or TWA53 in the post-MI setting. Additional prospective studies are needed to clarify the role of BRS in other clinical settings.

HRT  HRT has been shown to be useful in predicting arrhythmic events and SCD. HRT can be quantified by 2 variables: turbulence onset, which describes an early acceleration phase, and turbulence slope, a late deceleration phase of the heart rate after a single PVC. Absence of these phenomena indicates a significantly higher risk for SCD. The prognostic significance of HRT has been demonstrated in patients with prior MI and DCM.56,57

EPS  An EPS consists of intracardiac recording during electrical stimulation at baseline and with drugs. This test has been used to assess the inducibility of VT, efficacy of antiarrhythmic drugs, arrhythmias causing loss of consciousness, indication for ICD, and risk of SCD.58–60 The yield of an EPS varies fundamentally with the stimulation protocol (number or prematurity of extrastimuli) and the site of stimulation. For the induction of sustained VT, 8 basic stimuli (at 2 basic cycle lengths between 400 ms and 600 ms) followed by 1–3 extrastimuli are applied, usually to the right ventricular apex. The stimulation is often repeated at the right ventricular outflow tract and the left ventricle, or during the infusion of isoproterenol. The value of the EPS as a risk stratification maker is established in various clinical settings,61–64 particularly post MI. A long interval between MI onset and an EPS is associated with a high VT inducibility.64 A high inducibility of sustained VT generally suggests a poor prognosis, whereas the prognostic value of VF inducibility is controversial.65

Genetic Analysis

In patients affected by LQTS, genetic analysis is very important for identifying the mutation carriers within an affected family in terms of risk stratification.66 Genetic analysis may help identify silent carriers of mutations re-
Risk Stratification in Individual Cardiac Disorders

The clinical usefulness of major measurements in each cardiac disorder is summarized in Table 3. This section focuses on risk stratification strategies for patients with prior MI, DCM, HCM, LQTS, and BS.

Prior MI
All patients with CAD are at risk for SCD. The conventional risk factors for CAD are useful for stratification of population risk, but their value is limited for risk stratification of individual patients. Most SCD occurs in patients with severe left ventricular dysfunction (LVEF ≤ 30%). In contrast, patients with preserved left ventricular function (LVEF >40%), are at low risk for SCD and prophylactic therapy is not indicated. Coronary revascularization during the acute phase of MI reduces the risk of SCD. Multiple factors, in addition to reduced LVEF, have been demonstrated to contribute to the risk for SCD after MI (eg, subjective symptoms [NYHA II–IV], TWA, NSVT, SAECG and VT inducibility by EPS). Evaluation of these factors should be done at least 3 weeks after the onset of acute MI or revascularization procedures. Noninvasive ECG measurements should be performed before an EPS. Our risk stratification strategy for post-MI patients based on clinical evidence is shown in Fig 2.

Table 3 Clinical Usefulness of Major invasive and Noninvasive Measurements in Each Cardiac Disorder

<table>
<thead>
<tr>
<th>LVEF</th>
<th>NSVT</th>
<th>SAECG</th>
<th>TWA</th>
<th>QTI</th>
<th>HRV</th>
<th>EPS</th>
<th>GA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior myocardial infarction</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>X</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Nonischemic dilated cardiomyopathy</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>X</td>
</tr>
<tr>
<td>Long QT syndrome</td>
<td>×</td>
<td>?</td>
<td>×</td>
<td>?</td>
<td>?</td>
<td>×</td>
<td>○</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>×</td>
<td>?</td>
<td>×</td>
<td>?</td>
<td>?</td>
<td>×</td>
<td>○</td>
</tr>
<tr>
<td>Idiopathic ventricular tachycardia</td>
<td>×</td>
<td>?</td>
<td>×</td>
<td>?</td>
<td>?</td>
<td>×</td>
<td>○</td>
</tr>
<tr>
<td>Syncope</td>
<td>×</td>
<td>?</td>
<td>×</td>
<td>?</td>
<td>?</td>
<td>×</td>
<td>○</td>
</tr>
</tbody>
</table>

○, There is evidence and/or general agreement that a given measurement is beneficial and useful; ○, weight of evidence and/or opinion is in favor of benefit and usefulness, but it is still conflicting; ? , evidence is a few and opposite opinion exists; ×, there is evidence and/or general agreement that a given measurement is not beneficial and useful; ?, there is no evidence or unknown.

LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; SAECG, signal-averaged electrocardiography; TWA, T-wave alternans; QTI, QT interval; HRV, heart rate variability; EPS, electrophysiological study; GA, genetic analysis.
**Idiopathic DCM**

Risk stratification of DCM patients is more difficult than for post-MI patients because the mode of SCD varies in DCM patients. Sustained VT and/or VF is the most common mechanism of SCD, but other causes such as electromechanical dissociation and bradycardia account for approximately 50% of SCDs in DCM patients.69 Factors that reflect the severity of disease, such as LVEF, NYHA functional class, BNP, and end-diastolic volume, are associated with SCD,70,71 but even a low LVEF (≤20%) does not have a high positive predictive value for SCD.72 Although ventricular arrhythmias (PVC and NSVT) are often present, these do not have a good correlation with SCD. TWA has been suggested to predict SCD in patients with DCM,44 but the clinical evidence is insufficient. The EPS plays a minor role in the evaluation and management of VT, because of the low inducibility and low reproducibility of the EPS.73 Genetic information is not currently useful for risk stratification.

**HCM**

Most individuals with HCM are asymptomatic and the first manifestation is SCD74,75 The risk of SCD has been shown to relate directly to a left ventricular wall thickness >20 mm, with mortality reaching almost 40% at a wall thickness ≥30 mm.76 Extreme septal hypertrophy is also associated with SCD.76 A history of SCD in 1 or more family members is supposed to increase the risk for SCD in other members.77,78 Ventricular arrhythmias (PVC and NSVT) are often present, these do not have a good correlation with SCD. TWA has been suggested to predict SCD in patients with DCM,44 but the clinical evidence is insufficient. The EPS plays a minor role in the evaluation and management of VT, because of the low inducibility and low reproducibility of the EPS.73 Genetic information is not currently useful for risk stratification.

**LQTS**

In LQTS, SCD is often elicited by stress or emotion, but in some cases may also occur at rest or during sleep.82 Documentation of the arrhythmia [TdP] responsible for the cardiac event is uncommon and SCD could be the first clinical manifestation. A QTc >500 ms is the strongest risk predictor for SCD in LQT1 and LQT2 patients.83,84 LQT3 males represent a group at higher risk, irrespective of QT interval duration.85 The EPS has not proved useful in LQTS.85 In LQT2 patients, a HERG channel mutation at the pore region is associated with a higher risk of cardiac events compared with mutation at other regions.87

**BS**

In BS, SCD is caused by rapid polymorphic VT or VF, which frequently occurs at rest or during sleep. Cardiac events occur predominantly in males in the 3rd or 4th decades of life. Patients with a history of syncope have a higher risk of cardiac arrest than patients without syncope.86 ST-segment elevation can occur spontaneously or be exposed by administration of sodium-channel blockers, such as pilsicainide or ajmaline.89 Patients with spontaneous ST-segment elevation have a worse prognosis than individuals in whom the typical ECG is observed only after pharmacological challenge.90 Recently, the full stomach test (ie, ECG recording after a large meal) has been demonstrated as a novel diagnostic technique for identifying patients at risk of the syndrome.91 Among the ECG parameters, LPs detected by SAECG has been proposed as a risk stratification marker for the syndrome.92,93 The role of the EPS for risk stratification in this syndrome remains controver-
Conclusions
In recent years, we have had available numerous risk stratification markers, which have been discussed in this review. Unfortunately, the positive predictive value of these markers for SCD is not high (<20% even for some new markers). Combined analysis of multiple risk markers is a promising strategy to increase predictive value. An alternative strategy is to find a single marker with an extremely high (almost 100%) negative predictive value to identify the low-risk population. If a noninvasive marker determines that a patient is in the low-risk group, further invasive examinations may not be necessary. We anticipate that the present evidence-based recommendations concerning risk stratification for SCD will require revision in the light of future findings.

Acknowledgments
This review was supported in part by a Grant-in-Aid (18300157) for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan, a grant from the Fellows' Association of Medical Research and Technology of Japan, a grant from the Fukuda Memorial Foundation for Medical Research (Dr Ikeda), and a grant from the Japanese Society of Internal Medicine (Dr Ikeda).

References
natural peptide (BNP) and the aminoterminal fragment of ProBNP (N-terminal fragment of BNP) as prognostic indicators in a 6-year follow-up of a primary care population. *Int J Cardiol* 2005; 100: 125–133.


55. Maron BJ, Bonow RO, Cannon RO 3rd, Leon MB, Epstein SE. Hypertrophic cardiomyopathy: Interrelations of clinical manifesta-


