Sudden cardiac death (SCD) remains a daunting problem. It is a major public health issue for several reasons: from its prevalence (20% of total mortality in the industrialized world) to the devastating psycho-social impact on society and on the families of victims often still in their prime, and it represents a challenge for medicine, and especially for cardiology. This text summarizes the discussions and opinions of a group of investigators with a long-standing interest in this field. We addressed the occurrence of SCD in individuals apparently healthy, in patients with heart disease and mild or severe cardiac dysfunction, and in those with genetically based arrhythmic diseases. Recognizing the need for more accurate registries of the global and regional distribution of SCD in these different categories, we focused on the assessment of risk for SCD in these four groups, looking at the significance of alterations in cardiac function, of signs of electrical instability identified by ECG abnormalities or by autonomic tests, and of the progressive impact of genetic screening. Special attention was given to the identification of areas of research more or less likely to provide useful information, and thereby more or less suitable for the investment of time and of research funds.

Keywords
- Sudden cardiac death
- Risk stratification
- Electrical instability
- Autonomic nervous system
- Cardiac function
- Genetics

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**Translational Perspective**

Sudden cardiac death (SCD) continues to be a major public health challenge, representing close to one-fifth of all mortality in industrialized countries and making about half of its victims among people not previously diagnosed with heart disease. Currently, applied techniques of risk assessment identify only a very small portion of all future cardiac arrests with sufficient specificity to justify defibrillator therapy and even in this small subgroup medical and economic reasons call for improving the positive predictive value of our methods. Better information about the incidence of SCD in different populations is urgently needed. Cardiovascular risk scores must be applied routinely in middle-aged persons and research is necessary to determine which further tests are effective in people without cardiovascular symptoms when risk scores remain high despite treatment. Integrated models for SCD risk must be developed and tested that combine various risk markers as identified for instance in the ECG, in autonomic tests, in cardiac function tests and in genetic profiles, where progress is rapid.

**Introduction**

Death from cardiac disease has been diminishing in the industrialized world during the last two decades. Nevertheless, ~20% of all deaths still occur suddenly and unexpectedly, mostly often caused by ventricular fibrillation (VF) or asystole. However, precise figures are lacking for many regions of the world. It is estimated that sudden cardiac death (SCD) claims ~10 times as many lives as do traffic accidents in the EU and USA combined, emphasizing the importance of this societal challenge and of efforts to improve SCD risk stratification.

Sudden cardiac death occurs in different population groups: (i) a large subset without a prior diagnosis of heart disease; (ii) patients with a history of heart disease with no or mild cardiac dysfunction; (iii) patients with a history of heart disease and severe cardiac dysfunction; and (iv) those diagnosed with a defined genetically based cause for a life-threatening cardiac arrhythmia (Table 1). The majority of SCD victims is not known to have had heart disease, or have heart disease with a normal or mildly impaired cardiac function (left ventricular ejection fraction, LVEF >40%). Our ability to recognize their risk before the event is severely limited. This raises the question whether our methods for prediction of SCD can be improved now and in the future, in order to develop appropriate preventive measures for this large number of potential victims.

In the following sections, we will consider how the risk of SCD can be assessed in those without a history of cardiac disease, how signs of electrical instability on the ECG may predict SCD, how results of autonomic nervous system (ANS) tests may be used, how pump function influences SCD risk and how genetic screening may help predict SCD.

**No previous history of cardiac disease**

Between 45 and 50% of SCD victims are not previously diagnosed with heart disease. Most have coronary artery disease (CAD), while younger age cardiomyopathies and ion-channelopathies play a major role in cardiac arrest and SCD. The risk of developing a CAD substrate, or expression of a coronary event, can be assessed by using risk scores (such as Framingham, or SCORE) based on age, gender, smoking, blood pressure, total and LDL cholesterol, body mass index, and diabetes. Some risk scores have added other lipid measurements, socio-economic factors or a family history of heart disease. It should be appreciated that the relation between levels of LDL cholesterol or blood pressure and subsequent cardiac events varies across countries. Therefore, SCORE provides different tables for high- and low-risk countries in Europe.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The different groups that contribute to the total number of sudden cardiac deaths and our current ability to identify possible candidates before the event</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of all SCD</td>
<td>Predictability</td>
</tr>
<tr>
<td>Not diagnosed with heart disease</td>
<td>45</td>
</tr>
<tr>
<td>History of heart disease: LVEF &gt;40%</td>
<td>40</td>
</tr>
<tr>
<td>History of heart disease: LVEF &lt;40%</td>
<td>13</td>
</tr>
<tr>
<td>Genetically based arrhythmic disease</td>
<td>2</td>
</tr>
</tbody>
</table>

SCD, sudden cardiac death; LVEF, left ventricular ejection fraction.

decision which risk calculator should be used has an important impact on risk categorization and absolute risk estimation, with broad implications for guidelines recommending therapies. Moreover, as time passes, it is likely that country-specific risk patterns may change, in parallel with emerging socio-economic and healthcare patterns.

On-line access has made these risk scores readily accessible for physician and layman. Primary prevention of cardiovascular disease using validated risk scores is possible, although questions remain about the appropriate intensity of intervention in relation to the level of risk. The parameters used in the current risk scores are derived from population studies and have limited power for individual risk stratification, with possible exceptions in the highest risk subgroups such as diabetics who smoke and have high blood pressure and LDL cholesterol levels (although having diabetes already puts patients in the high or very high-risk category). Also, these risk markers do not specifically predict SCD, but rather combined cardiac events (Framingham) or cardiovascular mortality (SCORE).

At present risk scores can be used to identify subjects who are most likely to achieve a statistical benefit from preventive medical therapy and to motivate individuals to reduce correctable risk factors. This emphasizes the need for public education initiatives creating awareness of easily accessible risk assessment models on the Internet. As a general approach a risk score should be routinely performed around the age of 40 years in males and in post-menopausal women, by a first line healthcare professional. Repeat risk assessments are appropriate depending on the presence and severity of risk markers.
The incremental value of a family history of heart disease or SCD and biochemical and genetic markers reflecting atherosclerosis, coagulation, endothelial function, inflammation, oxidative stress, renal function, neuro-humoral status, and cardiac pump function to predict cardiovascular events, particularly SCD, needs to be evaluated as a function of age, gender and ethnic background. Risk assessment should be dynamic, repeated over time. The risk level at which more advanced diagnostic methods should be performed in the person without a history of heart disease needs to be better defined in the context of clinical and economic efficacy.

**Electrical instability and sudden cardiac death**

A plethora of studies has examined the value of different ECG-derived risk parameters, both in the general population and in patients with different cardiac diseases. Their practical value is sometimes unclear because of small sample size or limited follow-up duration, and studies determining which parameter combinations provide strong risk predictors are lacking. Table 2 lists their availability in the 12 lead ECG or Holter recording, and their reported value in people without diagnosed heart disease or in the presence of heart disease with either a preserved or diminished LVEF. When the absolute risk is low, the predictive value of a single test will also be low, although relative risks up to three have been reported for some parameters. Identification of the optimal combination of ECG risk markers remains a challenge, realizing that some give information about an arrhythmia substrate, and others about possible arrhythmia triggers, neural influences, and genetic background.

Among a population without clinical evidence of cardiovascular disease sinus rate at rest, during and after exercise or during mental stress, have been helpful in recognizing SCD risk over a long follow-up period. Risk was markedly elevated (Hazard Ratio between 2 and 6) with a high resting heart rate (>75 b.p.m.), a limited heart rate increase during exercise (<89 b.p.m.), or a sluggish heart rate recovery (<25 b.p.m.). This was interpreted as an impaired ability to increase not only vagal but also sympathetic activity to appropriate levels.

The usefulness of corrected QT interval (QTc) has been evaluated in prospective cohort studies and in subjects >55 years of age a prolonged QTc (>450 ms in men and >470 ms in women) was associated with a three-fold increased risk of SCD. A prolonged Tpeak–Tend interval measured in lead V5 seems independently associated with SCD, even when the QTc is normal. In a study of 10,864 middle-aged subjects from Finland, prevalence and prognostic significance of early repolarization in the inferior/lateral leads of the 12-lead ECG over a mean follow-up of 30 years was determined.

When stratified according to the degree of J-point elevation (>0.2 mV) in inferior and/or lateral leads, there was a three-fold higher risk for both death from cardiac causes and from arrhythmias. In the same database, T-wave inversions, wide QRS-T angle, and prolonged QRS duration due to either left bundle branch block (LBBB) or intraventricular conduction delay but not right bundle branch block, predicted SCD. In similar studies of general population samples essentially the same ECG variables predicted all-cause mortality and also SCD, yet none of them usefully predicts individual risk.

In patients with cardiovascular disease but preserved LV function, several ECG parameters predict the occurrence of cardiac death. This patient group is of particular importance as it generates ~30–40% of all SCDs. In particular, heart rate turbulence (HRT) and deceleration capacity were shown to select patients with preserved LV function who have similarly high risk of SCD as those with depressed LV function. In the combined Finnish and German database of survivors of acute myocardial infarction (AMI), non-sustained ventricular tachycardia (VT) and several measures of heart rate variability predicted SCD among those with preserved left ventricular function. However, none of these variables was associated specifically with the occurrence of SCD since they were stronger predictors of non-SCD. Similarly, microvolt T-wave alternans (MTWA) carries prognostic value in patients with preserved LV function, but results cannot be obtained in a large group that does not show the required heart rate increase or is in atrial fibrillation. Based on these and similar studies, the REFINE-implantable cardioverter-defibrillator (ICD) trial is currently randomizing infarct survivors with a LVEF between 36 and 49%, reduced HRT and positive MTWA to standard therapy or the ICD.

In patients with cardiovascular disease and impaired LV function parameters such as QRS duration, particularly in the presence of LBBB, HRT, baroreflex sensitivity (BRS), or T-wave alternans are independently associated with increased risk for SCD. The latter may have a particularly high negative predictive value potentially useful in selecting patients unlikely to benefit from device therapy.

There are limitations of current ECG-derived risk predictors. For instance, some of the more promising methodologies such as HRT or MTWA assessment cannot be applied to patients in atrial fibrillation (which by itself is a risk predictor for SCD). The REFINE and CARISMA trials have demonstrated that risk stratification in patients after an acute ischaemic event should be done 6–8 weeks later as tests performed earlier lack strong predictive power, likely due to the fact that there is remodelling of the arrhythmogenic substrate during the early weeks after myocardial infarction. However, this may not apply to autonomic parameters, as demonstrated by the validity of risk stratification performed by BRS assessed 2–3 weeks post-MI in ATRAMI and by similarly early assessment of HRT and deceleration capacity. Finally, there is a lack of dynamic risk assessment studies over time. At present, it remains largely unknown for which time interval a given risk assessment will optimally predict individual risk for SCD.

In patients with genetically based causes for lethal arrhythmias, the evidence that ECG parameters are helpful in risk stratification is clear; particularly for the long QT syndrome (LQTS), and partially for the Brugada syndrome. This is well established for the magnitude of QT interval prolongation, whereas the evidence of a risk predictive role for heart rate is more recent and limited to specific genetic subgroups.
To prospectively determine the best risk score using ECG parameters, listed in Table 2 for the four groups from Table 1, remains a challenge. It seems that static, ECG-based parameters as well as dynamic metrics of RR interval patterns, and of ventricular repolarization can be useful for risk stratification in all groups. Further research is needed into the dynamic behaviour of parameters and into the predictive power of parameter combinations.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>ECG-derived risk stratifiers reported to have prognostic value in different clinical settings</th>
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<tbody>
<tr>
<td></td>
<td>No HD diagnosis</td>
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<tr>
<td>Sinus rhythm</td>
<td>Resting rate, profile during exercise tolerance test</td>
</tr>
<tr>
<td></td>
<td>Heart rate variability</td>
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<tr>
<td></td>
<td>Heart rate turbulence</td>
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<tr>
<td></td>
<td>Deceleration capacity</td>
</tr>
<tr>
<td>Intra-atrial conduction delay</td>
<td>+</td>
</tr>
<tr>
<td>Atrial dilatation</td>
<td>+</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>+</td>
</tr>
<tr>
<td>AV conduction</td>
<td>Site of AV block</td>
</tr>
<tr>
<td>Presence of accessory AV pathways</td>
<td>+</td>
</tr>
<tr>
<td>QRS</td>
<td>Width &gt;100 ms</td>
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<tr>
<td></td>
<td>Left bundle branch block</td>
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<tr>
<td></td>
<td>Notching, fractionation</td>
</tr>
<tr>
<td></td>
<td>Number and location of Q waves</td>
</tr>
<tr>
<td></td>
<td>Reduced voltage (limb leads)</td>
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<tr>
<td></td>
<td>Signal-averaged ECG</td>
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<tr>
<td></td>
<td>Left ventricular hypertrophy</td>
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<td></td>
<td>Mean QRS—T angle</td>
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<tr>
<td>QT interval</td>
<td>Duration</td>
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<td></td>
<td>Dispersion</td>
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<td></td>
<td>Dynamicity</td>
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<tr>
<td>ST segment</td>
<td>Elevation/depression</td>
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<tr>
<td></td>
<td>Early repolarization (infero-lateral leads)</td>
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<tr>
<td>T-wave</td>
<td>Axis</td>
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<tr>
<td></td>
<td>Negativity</td>
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<td></td>
<td>T-wave alternans</td>
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<tr>
<td></td>
<td>T&lt;sub&gt;peak&lt;/sub&gt;—T&lt;sub&gt;min&lt;/sub&gt; interval in V5</td>
</tr>
<tr>
<td></td>
<td>T amplitude V1 and aVR</td>
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<tr>
<td>Ventricular ectopy</td>
<td>Width and site of origin</td>
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<tr>
<td></td>
<td>VPB coupling interval</td>
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<tr>
<td></td>
<td>Frequent VPBs</td>
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<td></td>
<td>Increase during exercise</td>
</tr>
<tr>
<td></td>
<td>Non-sustained VT</td>
</tr>
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<td></td>
<td>Sustained VT</td>
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</table>

No HD DIAGN, no diagnosis of heart disease; LVEF, left ventricular ejection fraction; preLVEF, cardiac disease, preserved LVEF; redLVEF, cardiac disease, reduced LVEF; VPB, ventricular premature beat. The majority of these parameters has been shown to predict mortality, not specifically SCD.
Risk prediction based on autonomic abnormalities

The ANS helps maintain body homeostasis. Autonomic nervous system abnormalities may be caused directly by autoimmune diseases and metabolic neuropathies, such as diabetes mellitus. Autonomic nervous system imbalance may cause clinically relevant perturbations in cardiac physiology. In cardiac patients, the strength of the association between ANS abnormalities, poor outcome, and cause-specific mortality, namely SCD, likely depends upon the underlying cardiac condition and upon the presence of diabetes or renal insufficiency. Although obviously important, genetic predisposition to ANS abnormalities is still poorly understood. Experimental and clinical data show that enhanced parasympathetic influence on the heart is generally antiarrhythmic and antifibrillatory, while increased sympathetic influence is generally pro-arrhythmic. In particular, sympathetic dominance combined with other pro-arrhythmic processes such as myocardial ischaemia leads to increased probability of VF and thus SCD risk. Specific autonomic tests distinguishing the risk of arrhythmic vs. asystolic SCD are desirable but not developed.

Autonomic tests include recording and analysis of spontaneous RR intervals, simple or complex provocations such as the Valsalva manoeuvre, handgrip test, cold face test, carotid massage, neck suction, low body pressure test, and baroreflex testing. While exploring different reflexes, involving different aspects of autonomic modulation, all of them measure RR interval and blood pressure responses.

Clinical exploration of autonomic markers for SCD risk stratification has been largely obtained from studies involving autonomic modulation of RR interval changes following either provoked or spontaneously occurring blood pressure changes to assess baroreflex responsiveness, and has been fostered mainly by pioneering studies of BRS in a conscious post-MI canine model for SCD. A particularly powerful risk prediction for cardiac death and life-threatening arrhythmias in ischaemic heart disease and HF has been obtained with BRS and with tests separating the sympathetic and vagal control of sinus node activity, such as with HRT and deceleration capacity. Autonomic nervous system function can also be assessed from heart rate responses to exercise testing. Heart rate recovery after exercise has prognostic significance for both total and sudden cardiac mortality.

Validated models of spectral analysis of RR intervals permit assessing the strength of cardiac sympathetic and vagal modulations, especially when measuring responses to well-defined provocations. The environmental data stability and accuracy of the analyses, including rejection of ectopic beats, are essential in such studies. Despite the large number of existing ANS function tests, little comparative data exist regarding their predictive value. No guidance exists to which ANS test or combination of tests is most appropriate in different clinical conditions. Advanced age decreases but does not eliminate the value of ANS tests in predicting poor outcome, as shown with baroreflex testing in elderly post-MI patients. Autonomic nervous system tests are not influenced by usual clinical doses of beta-blockers, whereas sleep abnormalities affect autonomic testing based on full 24-h data.

A consensus exists that the risk prediction power of ANS tests increases when quantifying autonomic responses to specific provocations rather than studying unprovoked baseline ANS function. Not only the provocations underlying a test but also its environmental conditions must be standardized: while the predictive power of 24-h RR interval variability in hospitalized cardiac patients has been well documented, similar analysis of recordings in truly ambulating out-of-hospital patients is of little value because of the differences in environmental challenges to which the ANS responds. Short-duration tests should become the standard for ANS testing in cardiac patients for risk prediction. For studies of RR interval dynamicity, a combination of sufficiently long-resting period (e.g. 20–30 min) with a strictly standardized staged exercise test (including its recovery phase or tilting) might prove useful, as well as tilt or simple postural provocations.

Autonomic nervous system-based risk assessment has been attempted in patients without cardiovascular disease but its predictive value is likely too low to make such studies useful for first line SCD risk-screening.

The predictive value of ANS testing in cardiac patients appears independent of ventricular function and can be thus used in patients with and without compromised LVEF. Tests involving RR interval measurements (either alone or in combination with blood pressure measurements), however, require normal sinus node function.

Indices of the QT interval variability and other ventricular repolarization markers may allow investigating ANS influence at the ventricular level and can be used to quantify autonomic function providing information probably complementary to that derived from heart rate variability. The measurement of QT variability, alone or simultaneously with RR variability, may improve risk stratification in patients with life-threatening arrhythmic diseases, specifically those with the LQTS.

Autonomic nervous system-based risk assessment in patients with genetically based cardiac diseases is in its infancy but preliminary encouraging data are being obtained. Hyperreactive ANS reflexes leading to very abrupt RR interval changes in either direction appear to pose an increased risk in those LQTS patients (LQT1) whose genetic mutations impair the _K_ _<sub>Na</sub> _current_ and who are thereby unable to appropriately adapt their QT interval to abrupt heart rate changes. This is an example of how ANS responses may dangerously interact with underlying genetic abnormalities.

Regional abnormalities in cardiac sympathetic innervation are associated with increased arrhythmic risk and they can be quantified by imaging techniques. Recently, the _I_ _123_ -I MIBG defect score was found to independently predict ventricular arrhythmias causing appropriate ICD shocks. The combination of traditional markers of ANS activity with imaging techniques quantifying the degree of sympathetic denervation at ventricular level appears promising.

**Autonomic nervous system markers contribute to SCD risk stratification.** Arrhythmic risk is enhanced whenever markers of vagal activity decrease or markers of sympathetic activity increase. Both RR and QT variability may provide useful and complementary information. Reflex autonomic responses are more informative than baseline measurements. The limited use of ANS tests is partially due to their complexity. Analyses derived from tests as simple as an exercise stress test are more likely to impact on clinical practice.
Role of cardiac function

Left ventricular function as reflected by ejection fraction, as well as functional capacity, expressed by a variety of parameters (NYHA class, maximum oxygen uptake, and exercise duration) are directly related to both total mortality and SCD in patients with heart disease. As such, LVEF has been used as a primary entry criterion for multiple clinical trials. In addition, NYHA functional class has been added to LVEF as an entry criterion in trials of SCD in patients with HF. Easy to measure, but with significant errors depending on the method used, LVEF now occupies a central position in guidelines for use of ICDs when recommended for primary prevention of SCD. The rationale is that LVEF significantly modifies the effects of all other variables that impact on both total mortality and SCD risk. However, there are multiple limitations to the use of LVEF as the sole determinant of high risk and, therefore, as indication for ICD: (i) the population with HF and reduced (<30 or 35%) LVEF (HFrLVEF) accounts for <20% of all SCDs; (ii) there is no evidence that LVEF bears a direct causal relation to arrhythmia mechanisms; (iii) LVEF exhibits considerable spontaneous variability in some individuals; (iv) measurement of LVEF in practice is often less than precise. Furthermore, recent data indicate that most of SCD victims did not have a previously documented depressed LVEF, and would have not been candidates for ICD therapy.

Among survivors of AMI whether in the pre- or post-reperfusion era, low LVEF (cutoffs 30–40%) has accounted for 22–72% of SCD cases. The relation between LVEF and mode of death (SCD vs. non-SCD) in patients with CAD shows no significant difference in per cent of SCD for any range of LVEF. Similar findings characterize patients with HF in the CHARM programme. Thus, LVEF lacks both sensitivity and specificity for prediction of SCD risk.

Multiple factors other than LVEF and NYHA class, and their interaction, may contribute useful information towards prediction of SCD risk. Another important caveat is that not all SCDs are due to arrhythmia. Non-arrhythmic causes are found by autopsy in 50–60% of SCD cases, in myocardial ischaemia-related SCD, and in the general population. Among survivors of AMI whether in the pre- or post-reperfusion era, low LVEF (cutoffs 30–40%) has accounted for 22–72% of SCD cases. The relation between LVEF and mode of death (SCD vs. non-SCD) in patients with CAD shows no significant difference in per cent of SDC for any range of LVEF. Similar findings characterize patients with HF in the CHARM programme. Thus, LVEF lacks both sensitivity and specificity for prediction of SCD risk.

Role of genetics

Genetic screening has the potential of contributing significantly to the identification of individuals at greater risk for SCD. A few concepts need clarification before examining its role in genetically based disorders, in myocardial ischaemia-related SCD, and in the general population.

Genetic variants may be rare (<1 in 1000), common (>1 in 100), or of intermediate frequency. The greatest disease effect is caused by rare variants (mutations), whereas the common ones (single nucleotide polymorphisms, SNPs) have been associated with modest or minimal effects. Genetically based disorders—such as LQTS, Brugada syndrome, and catecholaminergic polymorphic VT—are due to disease-causing mutations, whereas in complex diseases (MI...
and CHF) an interaction likely takes place between the arrhythmogenic substrate (scar and dilated ventricles) and several SNPs, each contributing to a decrease or increase in cardiac electrical stability. These relatively common genetic variants capable of modifying the propensity to life-threatening arrhythmias are referred to as ‘modifier genes’. Their effects may help understanding why patients with the same disease and similar clinical parameters may either survive long term or die suddenly.

Genetic variants are not immutable. There is growing evidence, encompassed by epigenetics, that environmental factors (age, food, pollution, and radiation) may modify clinical expression of SNPs. A critical concept is that of the algebraic summation of different SNPs. Each SNP has, by definition, a small effect and is thus unlikely to play a major role by itself. The number of SNPs potentially interacting with either the disease-causing mutation or with the arrhythmogenic substrate is large, however, and a cumulative effect must be expected. Protective and arrhythmogenic SNPs may annul each other but if an individual inherits a series of SNPs acting predominantly in one direction, there may be an important effect on clinical outcome (Figure 1), and initial examples have been published.98 This cumulative effect, depending on which SNPs are inherited, represents the unpredictable play of chance. The progressive identification of SNPs acting on cardiac electrical stability will allow to significantly refine risk stratification by the use of ‘clusters of SNPs’. This should be an area of expanding research.

Two additional concepts are relevant. The probability of identifying modifier genes increases whenever the disease-causing mutation is the same in the population under study, as it happens in the so-called ‘founder populations’, because this approach corrects for the different effects produced by different individual mutations.99 Also, research in this field must deal with clean phenotypes. Regarding SCD, this requires that the population studied must be at risk of dying because of a primary lethal arrhythmia related to a single trigger (e.g. acute myocardial ischaemia) and not as a consequence of VF resulting from progressively worsening cardiac function.

Based upon this conceptual foundation, we can discuss where we stand and where we should go for a more fruitful approach to risk stratification for SCD.

Long QT syndrome, with 80 – 85% success in positive genotyping, is the best understood among the genetically based channelopathies and serves as an appropriate paradigm for SCD. Risk stratification in LQTS has progressively incorporated clinical parameters (e.g. previous occurrence of syncope, QTc >500 ms), specific genetic subgroups (LQT1 vs. LQT2 vs. LQT3), the mutation site (e.g. transmembrane vs. C-terminal), the type of mutation (missense vs. non-missense), the biophysical function (dominant negative vs.

![Figure 1](image-url) Illustration of the potential impact on outcome (survival vs. sudden death) of the interaction between two arrhythmogenic substrates (acute myocardial infarction or heart failure, and mutations causing arrhythmogenic diseases) and predominantly protecting or damaging clusters of common genetic variants (SNPs). As the cluster of SNPs of a given individual reflects the inheritance by the parents, this interaction is clearly governed by chance.
haploinsufficiency), and mutation-specific consequences. The focus is now on the interaction between the disease-causing mutations and the SNPs which have already been found to modify the arrhythmic risk. Most of them increase risk,\textsuperscript{101} and sometimes QT interval duration, but recently also ‘protective’ SNPs have been recognized.\textsuperscript{102,103} This is a critically important area of research because of its implications for individual risk prediction, both for the inherited channelopathies and SCD generally.

Although a strong genetic component exists in the risk for SCD, typically occurring in individuals over 40 years with cardiac ischaemia or infarction,\textsuperscript{104–108} the underlying genetic variation remains unknown. Key barriers to the identification of these genetic factors have been restricted sample sizes, heterogeneity of the associated cardiac substrate, and the difficulty of ascertaining adequate phenotype information after cardiac arrest.\textsuperscript{109} Especially heterogeneity of the substrate hampers successful gene finding in population sample studies as within every individual substrate the interplay of many different pro-arrhythmic factors involves too many potentially causative genes.\textsuperscript{110} By contrast, VF in the setting of a first AMI is most likely based on re-entry and as such has one underlying arrhythmic mechanism. To date, four genome-wide association studies (GWAS) on VF/SCD have been published\textsuperscript{111–114} and one of the two SNPs that were identified in GWAS studies comes from AGNES, a study in patients with and without VF in the setting of a first AMI.\textsuperscript{111} A stark contrast is represented by studies based on mixed phenotypes as in ICD patients using appropriate shocks as endpoint.\textsuperscript{115–117} Such patients are at risk of VF through many different mechanisms (pump failure in a scarred ventricle, different medications, electrolyte disorders, etc.) and the hope to identify single genetic variants predicting SCD in these populations is probably naive. Future research and funding should go for studies with a clean phenotype and a homogeneous underlying arrhythmia mechanism likely to provide the highest yield.

An alternative approach to unravel the genetic basis of SCD is to identify genetic variants associated with phenotypes that are considered as risk factors for SCD, i.e. ‘intermediate phenotypes’, such as heart rate, QRS width, and QT interval. Genome-wide association studies have identified numerous ‘hits’,\textsuperscript{110} but attempts to link them to SCD have so far not been successful.\textsuperscript{112,117,118} Genetic screening has a high potential to contribute to the identification of individuals at risk for SCD, as has already been proved for genetically based diseases. There is a strong rationale for expecting significant insights also for SCD in the general population but this will require studying homogeneous phenotypes. The use of novel technologies including next generation sequencing\textsuperscript{119} and the smart analysis of clusters of common genetic variants, as risk modifiers, hold significant promise.

**Conclusions and recommendations**

Both national and regional SCD registries are needed with data about medical history, gender, and race. They must allow the evaluation of the effects of different measures taken to reduce out of hospital cardiac arrest mortality to increase insight of their value.

For the population without a history of heart disease, more attention should be given to public education initiatives, addressing awareness of risk for development of coronary disease as a cause of early death, including SCD.

Primary healthcare providers should be strongly encouraged to apply risk scores routinely, both in men over 40 years of age and in women after the onset of menopause. There is also need for a comparison of the value of the different risk score methods. The estimated level of risk can be used in a dynamic way\textsuperscript{11} to determine whether and when advanced diagnostics are appropriate. The incremental value of bio- and genetic markers reflecting atherosclerosis, coagulation, inflammation, neuro-humoral status, and ventricular function requires evaluation in this population, in the context of clinical and cost efficiency.

Current guidelines recommend 12-lead ECG screening for certain high-risk occupations and for professional athletes, but not for all asymptomatic middle-aged subjects. Since many of ECG indexes have the potential to identify future arrhythmic death, the utility of routine screening of the 12-lead ECG should be explored from existing databases, especially considering value and cost of analysing a 12-lead ECG in addition to a standard risk score. The main rationale of this approach is the identification of subclinical cardiac disease, such as asymptomatic myocardial infarction, left ventricular hypertrophy, and fibrosis, which are common autopsy observations in victims of SCD even in the absence of previously diagnosed cardiac disease.

In patients with cardiac disease and preserved or reduced ventricular function, we need large registries and randomized trials to determine the value of ECG markers for risk assessment.

Autonomic balance affects the cardiac response to acute challenges such as ischaemia or tachyarrhythmia, thus importantly influencing outcome. The large number of proposed tests and the inability to standardize acquisition and analysis of parameters have contributed to preventing ANS-based tests becoming routinely used for the clinical assessment of SCD risk. This is unfortunate because some tests, especially those quantitating reflex responses, are of proven value. Future approaches should focus on well-standardized tests that are easily obtained and can be readily interpreted. Long-term ambulatory monitoring no longer represents a favoured approach for ANS assessment. Autonomic responses during exercise testing or other provocative manoeuvres under standardized circumstances will likely provide optimal information but this requires prospective evaluation.

Measurement of resting systolic function (LVEF) and assessment of clinical severity of HF (NYHA Class) are the only risk stratifiers currently in widespread use. While they are good predictors of total mortality, their sensitivity and specificity for prediction of SCD is not adequate. Current practice guidelines for implantation of ICDs for primary prevention of SCD, based on these parameters, have demonstrated their clinical and cost-effectiveness but they do not impact the majority of patients who will die suddenly as a first cardiac event or during the onset of AMI.\textsuperscript{74,120} Apart from LVEF and NYHA Class, many other factors are probably important for the SCD risk profile, such as age, gender, ethnicity, blood pressure and heart rate, ischaemic vs. non-ischaemic cause, diabetes, kidney function, as well as findings during cardiac imaging, electrical instability, ANS balance, biochemical markers, and the genetic profile. Whether the significance of these factors is affected by treatment and by time needs to be evaluated.

At present, there is scant information about SCD risk in patients with HFrEVEF. Newer functional markers of pump failure, such as BNP, show promise as indicators of SCD risk, but prospectively well-designed clinical trials evaluating their ability to guide ICD therapy are needed, before they can be recommended.
While individual risk markers often lack the power to influence clinical practice, it seems important to investigate integrated risk models, combining parameters that characterize properties of the arrhythmia substrate, the triggers and the ANS.

The genetic variants, identified thus far either as modulators of ECG traits or of SCD, have proved useful for genetically based diseases such as LQTS, but are not ready to be used clinically for assessing genetic susceptibility to SCD in the general population. Yet, genetic factors can contribute significantly to this huge health problem. The areas where research should expand, for further refinement of risk stratification, include the use of clusters of relatively common or even rare genetic variants (SNPs) capable of increasing or decreasing the risk for SCD associated either to a disease-causing mutation or to an arrhythmogenic substrate.

Worldwide collaboration is needed in order to increase sample sizes and consequently statistical power for detecting more variants. Currently, the published efforts to gain statistical power have been at the expense of phenotypic homogeneity (unexplained SCD in the community or post-MI ICD patients). Instead, to further the field it will probably be ideal to use whole exome or whole genome sequencing in large cohorts with a clean phenotype associated with SCD, possibly through just one or two well-defined arrhythmogenic mechanisms.

When designing prognostic models for assessing SCD risk or clinical studies for demonstrating ICD benefit, it is important to consider that risk factors may change over time and that patients may be at a substantial risk of dying from other causes than the one intended to be treated. Modern statistical techniques such as time-dependent covariates in Cox proportional hazards models and cause-specific hazard (competing risks) modelling must be used to address such challenges in risk stratification.

Table 3 summarizes the currently recommended approach to SCD risk stratification as well as our suggestions for areas of research. We feel that better methods for identification of high SCD risk are especially needed following AMI, either by combining presently available risk markers or by developing new ones. Genetic studies already provided markers for arrhythmia risk but thus far only in small subgroups of the population.

It is obvious that we still have a lot to learn on how to make a dependable risk profile for individual patients. When realizing our current inability to identify most cardiac arrest victims before the event, we should also consider the development of better strategies to improve results of SCD resuscitation attempts. This will require public education and training, better emergency response systems, and probably the development of minimally invasive devices that upon detection of VF sound an audible alarm and provide the victim’s location to emergency services.

### Table 3  Our current approach to sudden cardiac death risk stratification and areas for research

<table>
<thead>
<tr>
<th>Based on what we know today</th>
<th>Assess CV-risk factors in men &gt;40 and women after menopause; correct risk factors. Give advice about lifestyle; when corrective measures remain insufficient, refer to cardiologist for additional testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of heart disease, no or mild dysfunction</td>
<td>Determine anatomic and functional cardiac status (Echo and LVEF); check ECG for abnormalities; exercise stress test; correct cardiac ischaemia and other risk factors.</td>
</tr>
<tr>
<td>History of heart disease, reduced LV function</td>
<td>Determine anatomic and functional cardiac status (Echo, LVEF, and MRI); check ECG for abnormalities; correct cardiac ischaemia, risk factors and HF; NTproBNP; determine indication for ICD and resynchronization; FOLLOW the GUIDELINES</td>
</tr>
<tr>
<td>Genetically based pro-arrhythmic disorders</td>
<td>Genetic work-up based upon phenotype; genetic evaluation of the family of the proband; FOLLOW the GUIDELINES</td>
</tr>
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<tr>
<th>What we recommend for research</th>
<th>Registries collecting ALL SCDs per year per region with data about medical history, gender, and race; value of ‘old’ risk markers in current reperfusion practice; long-term prospective studies of current and new risk markers; develop and implement systems to improve resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No diagnosis of cardiovascular disease</td>
<td>Study value of adding biomarkers and genetic markers to present risk scores</td>
</tr>
<tr>
<td>History of heart disease, no or mild dysfunction</td>
<td>Study value of adding biomarkers to present risk scores prospectively determine the best combination of ECG-derived risk stratifiers</td>
</tr>
<tr>
<td>History of heart disease, reduced LV function</td>
<td>Study value of adding biomarkers to present risk scores prospectively determine the best combination of ECG-derived risk stratifiers improve patient selection for ICD implant and cardiac resynchronization study value of MRI for arrhythmic risk stratification</td>
</tr>
<tr>
<td>Genetically based pro-arrhythmic disorders</td>
<td>Further define different phenotypes, improve risk stratification, knowledge of modifiers, and gene therapy</td>
</tr>
</tbody>
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will also continue to depend on the willingness of governments worldwide, through their funding agencies, as well as philanthropic foundations and interested corporate sectors, to accelerate a well-focused effort in this direction.

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Conflict of interest:

References


