Towards a better risk stratification for sudden cardiac death in patients with structural heart disease

K. Kraaier, P.M.J. Verhorst, P.F.H.M. van Dessel, A.A.M. Wilde, M.F. Scholten

With the introduction of the implantable cardioverter defibrillator (ICD), patients can be protected against sudden cardiac death (SCD) due to ventricular arrhythmia (VA). Guidelines have been drawn up for selecting patients for primary and secondary prophylaxis. However, most ICD recipients today who receive an ICD for primary prevention will not experience a life-threatening VA requiring antitachypacing or shock therapy. Better risk stratification is desirable with efficacy, costs and complication rate in mind. An overview is presented of widely accepted and potentially valuable risk markers and the role they may play in better identifying candidates for ICD therapy. (*Neth Heart J* 2009;17:101-6.)

Keywords: sudden cardiac death, risk stratification, implantable cardioverter defibrillator

Sudden cardiac death (SCD) is the most common single cause of death in developed countries. Yearly, worldwide, more than three million people will die due to SCD, the majority because of ventricular arrhythmia (VA).^{1,2} With the introduction of the implantable cardioverter defibrillator (ICD), it is possible to protect patients who are at risk for life-threatening VA and subsequent SCD.³⁻⁸ In this setting, a low left ventricular ejection fraction (LVEF) is considered to be the most important risk factor. However, additional

risk markers are needed to further stratify since most ICD recipients do not experience a life-threatening VA. In this article an overview is presented of potential risk markers and the possible future role they may play in selecting patients for ICD therapy.

Left ventricular ejection fraction

LVEF measured at rest has an important impact on long-term prognosis; with a decrease in LVEF, the frequency of SCD increases.⁹ Compared with conventional pharmacological treatment (usually with amiodarone), ICD implantation improved survival in patients with a prior myocardial infarction and an LVEF <30%³ and in patients with all-cause cardiomyopathy in combination with mild to moderate heart failure (NYHA class II or III) and an LVEF <35%.⁵ These results form the basis of the current ACC/AHA/ESC guidelines for the management of patients with VA and prevention of SCD.¹⁰

In these guidelines, the use of echocardiography is advised to measure LVEF.¹⁰ Two-dimensional echocardiography is the most widely used method to assess LVEF. This technique allows real-time imaging of the function and anatomy of the heart, is readily available, inexpensive and non-invasive. Important limitations are its operator dependency, acoustic window dependency, moderate reproducibility and accuracy.¹¹⁻¹⁴ When accurate assessment by echocardiography is not feasible, other imaging modalities can be used.¹⁰

Other available techniques to calculate LVEF are cardiac magnetic resonance imaging (CMR), radionuclide ventriculography (RV) or computed tomography (CT). CMR is one of the most accurate imaging methods available.^{15,16} CMR is very useful in patients with cardiomyopathy, because no geometric assumption of the shape of the left ventricle is used.^{12,17} Compared with 2D-echocardiography, its reproducibility and accuracy of LVEF calculation is very high, both in normal and dilated hearts.^{12,14,15} RV for calculation of LVEF has been used for more than 25 years. Advantages of RV include high reproducibility and low inter- and intra-observer variability.^{18,19} In 95% of the cases, results of repeated quantitative radionuclide assessment of LVEF can be expected to

K. Kraaier
P.M.J. Verhorst
P.F.H.M. van Dessel
M.F. Scholten

Department of Cardiology, Medical Spectrum Twente, Enschede, the Netherlands

A.A.M. Wilde
Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Correspondence to: M.F. Scholten
Department of Cardiology, Medical Spectrum Twente,
PO Box 50 000, 7500 Enschede, the Netherlands
E-mail: marcoen.scholten@ziekenhuis-mst.nl

be within a 2% and 4% range. Calculating LVEF using the CT is a fast procedure, LVEF can be assessed in less than ten minutes.²⁰ This technique is useful in both normal and abnormal hearts.^{20,21} Its reproducibility and accuracy is comparable with the accuracy of CMR.^{20,22,23} However, CT is limited by radiation exposure and the use of iodinated contrast material with adjuvant risks.²⁰

A problem with all the primary prevention studies is the fact that the technique used to assess LVEF differs^{3,5} or is not described at all.⁶ Research has shown that the LVEF measured by different techniques may not be equal.¹² It is therefore of utmost importance that agreement is reached about which technique should be used to assess LVEF.

NYHA class

The New York Heart Association (NYHA) functional class reflects functional impairment in patients with chronic heart failure. In most studies,³⁻⁷ the percentage of class I and IV patients is very low. In a large meta-analysis, using results of large primary prevention trials, ICD implantation was beneficial in patients both in NYHA class II and III.²⁴ These considerations were taken into account in the US guidelines.¹⁰ In patients with prior myocardial infarction (MI) (>40 days) and LVEF <30-40%, there is a Class I (Level of evidence A) indication for ICD implantation if the patient is in NYHA functional class II or III. In NYHA class I, implantation is considered reasonable with a Class IIa (Level of Evidence B) indication. In patients with non-ischaemic dilated cardiomyopathy and an LVEF <30-35%, there is a Class I indication (level of evidence B) when in NYHA class II or III, and Class IIb indication (level of evidence C) for patients in NYHA class I. In the European guidelines, NYHA classification is not incorporated.

Cardiac MRI

Besides the fact that cardiac MRI (CMR) is an accurate technique to measure LVEF, it is also able to identify areas of scar or fibrosis (figure 1), which are possible substrates for re-entry VA. It can be observed in patients with a prior myocardial infarction, but also in a large percentage of patients with non-ischaemic cardiomyopathy.²⁵⁻²⁷ Prior research revealed that scar mass and surface were significantly larger in patients with inducible monomorphic VT than in those without inducible VT.^{28,29} This was found both in patients with ischaemic and non-ischaemic cardiomyopathy. In a clinical setting, patients with hypertrophic cardiomyopathy were investigated. A significantly higher occurrence of delayed enhancement (DE) was found in patients with non-sustained VT (nsVT), compared with patients without nsVT.³⁰⁻³² The amount of scar, however, did not influence outcome.^{31,32} Wu et al. studied the value of DE in predicting hospitalisation for heart failure, appropriate ICD therapy or SCD in a group of 65 patients with non-ischaemic CMP who received an ICD following current guidelines.³³ DE

Figure 1. Magnetic resonance image. A) Measurement of LVEF in a patient with prior myocardial infarction. Short-axis slices end-diastolic and end-systolic (frame). B) Example of contrast-enhanced MRI. Short-axis view shows a large hyperenhanced area (arrows).

was associated with a higher risk of the endpoints, but the absence of scar did not predict a follow-up free of VA. In the group with DE, four (15%) patients experienced appropriate ICD therapy, compared with three (9%) in the group without DE.

Another possible point of interest is the infarct heterogeneity. In scar tissue, areas with enhancement of a lower intensity can be found. In a study by Schmidt

et al., heterogeneity at the infarct periphery was strongly associated with inducibility for monomorphic VT in patients with left ventricular dysfunction.³⁴

The role of CMR in risk stratification is promising; however more research is needed to evaluate the ability to predict clinically important VA in ischaemic and non-ischaemic cardiomyopathy.

Serum markers

C-reactive protein (CRP) is an acute phase protein produced by the liver. Raised CRP concentrations have been shown to be related with myocardial infarction, stroke, peripheral arterial disease and SCD.³⁵ In a population of patients with reduced left ventricular function following myocardial infarction a CRP concentration >3 mg/l was significantly associated with the occurrence of VA.³⁶ The negative predictive value was 89%. Limitations of this study were its retrospective design, the one-time measurement of CRP and the small sample size. Results of a large prospective study with serial CRP measurements will be published soon.³⁷ Troponin (cTnI) is a cardiac specific marker of myocardial damage. Detectable cTnI levels are associated with a high mortality in patients with reduced left ventricular function.³⁸ In patients with chronic heart failure, serum cTnI is closely related to increased occurrence of VA on Holter monitoring.³⁹ No data about cTnI in relation to ICD therapy have been reported yet. Another potential serum marker is pro-brain natriuretic peptide (pro-BNP), which is released from the ventricles in response to increased intraventricular pressure or myocardial stretch. Several studies have already shown that pro-BNP can be used as a predictor of SCD in patients with heart failure.⁴⁰⁻⁴³

The role of these markers in risk stratification for ICD implantation certainly needs further research.

Genetics

The number of cardiac syndromes being linked with familial forms of SCD is increasing rapidly. Several genetic markers have already been identified in the channelopathies (long-QT syndrome, short-QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia) and arrhythmogenic cardiomyopathies (arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, familial dilated cardiomyopathy).⁴⁴⁻⁴⁷ In less rare diseases related to SCD, such as coronary artery disease, there are strong indications as well that there is a role for a genetic basis.

Family history appears to be a strong independent risk factor for SCD. In the Paris Prospective Study, relative risk of SCD associated with parental SCD was 1.8 (95% CI, 1.11 to 2.88).⁴⁸ Friedlander et al. observed an increased risk with an odds ratio of 2.7 in patients with a positive family history (95% CI 1.3 to 5.4).^{49,50} If both parents have a positive family history, the risk of SCD will increase even more; in the Paris Prospective Study, the relative risk was increased by a

factor 9.⁴⁸ Dekker et al. examined patients with acute ST-elevation MI (STEMI). In patients presenting with STEMI and VF, a family history of SCD was more common than among STEMI patients without VF. The odds ratio was 2.8 (95% CI 1.8 to 4.0).⁵¹ This suggests that at least some genetic factors may predispose to VA specifically rather than to ischaemic heart disease alone.⁵² A genetic marker in those patients has not been identified yet, and progress in this search is slow, probably due to the polygenic nature of SCD. The number of genes involved may be large, and the contribution of variations in each gene may be small.⁴⁵

In the past few years, a number of studies have investigated specific candidate genes. These candidate genes were related to ion channels and thrombosis and coagulation pathways. The most examined candidate gene for ion channels is the *SCN5A* gene. This gene is also linked to LQTS and Brugada syndrome. In case-control studies consisting of African Americans and Chinese Han, variations of this gene were associated with increased risk of VA.⁵³⁻⁵⁵ However, this risk is small, and most carriers will never experience VA. In a Caucasian population, no association was found.⁵⁶ Other candidate genes have been less well examined.⁵² Enhanced thrombosis can cause ischaemic events, which may play a role in the occurrence of VA. However, with candidate genes for platelet glycoproteins, no associations have been found yet.⁵²

The search for new candidate genes or new combinations of candidate genes continues, and if found, case-control testing is needed before they can play a role in risk stratification.

Markers of the autonomic nervous system

It is suggested that there is a role for the autonomic nervous system in the triggering or sustaining of malignant ventricular arrhythmias.⁵⁷ The predictive value of three indices of the autonomic nervous system were studied: heart rate turbulence (HRT), baroreflex sensitivity (BRS) and heart rate variability (HRV).

HRT is a characteristic pattern of early acceleration and subsequent deceleration of the sinus rhythm after a premature ventricular extra systole (VES). A possible explanation for this phenomenon is the baroreflex response, which responds to the change in arterial pressure which follows the VES.⁵⁸ Studies have shown that in high-risk patients, this pattern is absent.^{59,60} However, in a retrospective substudy analysis in 884 patients of the MADIT II population, HRT could not be used as a predictor for all-cause mortality.⁶¹ In patients with dilated or hypertrophic cardiomyopathy HRT does not seem to be predictive for VA or SCD.⁶²⁻⁶⁴

BRS can be evaluated by correlating blood pressure rise and subsequent R-R-interval lengthening in response to a bolus injection of phenylephrine.⁶⁵ In the ATRAMI study, depressed BRS was associated with an increased mortality.⁶⁶ For the risk of SCD and VA, a study showed a significant association with

depressed BRS in patients with prior myocardial infarction.⁶⁷ Studies using BRS for risk stratification in dilated cardiomyopathy revealed conflicting results.^{63,68}

HRV is defined as the standard deviation of all normal RR intervals on a 24-hour Holter. Already in 1987, it was shown that reduced HRV is a predictor of long-term survival after acute myocardial infarction.⁶⁹ However, subsequent research showed conflicting results.^{66,68,70-72}

Electrophysiological parameters

MTWA

Microvolt T-wave alternans (MTWA) is a heart rate-dependent measurement of subtle changes in the amplitude of the T wave which occur in every alternate beat. It is believed that this phenomenon reflects temporal heterogeneity or dispersion in ventricular repolarisation, which can lead to formation of re-entry circuits and cause VA.⁷³ An example of a positive MTWA test result is presented in figure 2. MTWA has been approved by the United States Food and Drug Administration (FDA) for non-invasively predicting the risk for life-threatening ventricular arrhythmia.⁷⁴ A large meta-analysis, consisting of 19 studies and involving 2608 patients, showed a negative predictive value (NPV) of 97.2% (95% CI 96.5 to 97.9) and a positive predictive value (PPV) of 19.3% (95% CI 17.7 to 21.0).⁷⁵ In this analysis, there was a wide diversity in the populations studied and the predictive value of MTWA varies, depending on which type of patients were studied. In most of the studies used in this meta-analysis,⁷⁵ patients with indeterminate tests were excluded. Contrary to the meta-analysis, in 2008 two large studies were presented with less promising results. Both in the MASTER and in a substudy of the SCD-HeFT, MTWA was found to predict difference in total mortality, but not in death caused by VA.^{76,77}

Signal averaged ECG

The signal averaged ECG (SAECG) can be used to detect low-amplitude signals in the terminal part of the QRS complex. These low-amplitude signals are known as late potentials and represent delayed activation of the ventricular myocardium triggering arrhythmia. Because results from previous studies are conflicting, the prognostic role of SAECG in predicting VA is doubtful.^{72,78-80}

Holter registration

Non-sustained ventricular tachycardia (nsVT) in patients with prior myocardial infarction and left ventricular dysfunction has been associated with a two-year mortality around 30%.³ Therefore in the MADIT I, nsVT was one of the inclusion criteria.³ Other Holter risk variables were evaluated in the FINGER study.⁸¹ In this study, only non-sustained VT (nsVT), defined as three or more consecutive ventricular beats with a duration of less than 30 seconds, was significantly

Figure 2. Example of a positive MTWA result. Top: heart rate profile (HR), ectopy (% bad beats), and noise (uV). Bottom: alternans magnitude in the precordial leads V1 to V6 demonstrates sustained alternans at 91 beats/min.

associated with SCD. In patients with non-ischaemic cardiomyopathy, no significant association between nsVT and SCD was found.⁷²

QT dispersion, QT variability and QT dynamicity

The QT interval represents ventricular repolarisation. Variability in the interval can represent heterogeneity of repolarisation, which might play a role in the initiation of re-entry tachycardia. In the MADIT II population, Haigney et al. and Atiga et al. showed that QT distortion and an increased QT variability were associated with a higher risk for SCD and VA, resulting in defibrillator therapy.^{82,83} However, in the MADIT II, the presence of low QT variability did not predict

event-free survival.⁸² Therefore risk stratification using these indices does not seem possible.

Electrophysiology study

For many years, an electrophysiology study (EPS) was obligate in SCD risk stratification. Several studies showed significantly higher prevalence of SCD in patients with prior infarction and inducible VA during EPS. However, in a substudy of the MADIT II, results were conflicting. In the MADIT II, 82% of the patients underwent EPS, and they were analysed in a substudy. Inducibility was associated with a higher prevalence of VT requiring ATP or shock therapy; however, non-inducible patients had a considerable VT event rate and even a higher VF event rate.⁸⁴ In the MUSTT trial, patients with inducible VT (without ICD implantation) had similar rates of VA and SCD compared with patients with non-inducible VT.⁶ As a risk stratifier, EPS has therefore limited value. Its predictive role in patients with non-ischaemic cardiomyopathy is limited as well.⁸⁵⁻⁸⁷

Psychological factors

There is evidence that psychological factors may play a role in the onset of VA or SCD.^{88,89} Both anxiety and depressive symptoms can be considered as risk factors in the occurrence of VA in patients with an ICD. This can probably be explained by the relationship between anxiety, increased sympathetic cardiac control, decreased parasympathetic control and occurrence of VA and SCD.^{90,91} The influence of personality on SCD and VA has been examined. Especially the type-D personality is increasingly considered as a risk factor.^{92,93} This type-D personality is characterised by the tendency to experience negative emotions and the tendency to inhibit these feelings in social interactions. Its relation with occurrence of VA has not been presented yet.

Discussion

Most ICD recipients who receive an ICD for primary prevention will not experience life-threatening VA. In a critical review, Tung et al. question if the guidelines are based on solid evidence.⁹⁴ They state that the effect of ICD is overestimated and discuss the discordance between evidence and guidelines.

Better risk stratification is desirable, with efficacy, complication rate and cost-effectiveness in mind. In this article, potential tools to better identify patients who will or will not benefit from ICD implantation are described.

In the current guidelines, a low LVEF is considered to be the most important risk factor. However, there are some problems using LVEF as a selection criterion. In the primary prevention trials, the entry criterion was an LVEF below 30-35%, but after analysis, the mean LVEF appeared to be much lower.^{3,5,6} Therefore, the value of 30-35% as cut-off value seems open for discussion. Another problem with LVEF is that values measured by different techniques are not comparable.¹²

Both calculated LVEF and cardiac volumes differ significantly between the various methods. This leads to important questions. How strict do we have to follow the guidelines and which method to assess LVEF is preferred, since the differences between the different methods have considerable impact on the choice of treatment? Further study to better specify cut-off values seems warranted and accurate estimation of LVEF is preferred. Therefore we advise the use of CMR; with this technique it is not only possible to calculate an accurate LVEF, but it is also possible to detect and analyse areas of scar in the myocardium, which may play an important role in the occurrence of VA.

In the US, NYHA functional class system is incorporated in the guidelines; however, there is no consistent method of NYHA class assessment and interobserver variability is high (concordance of only 54%).⁹⁵ Therefore, it is questionable if the NYHA functional class can be used to make important treatment decisions.

MTWA seems to be useful, especially to identify a subgroup of patients who will not benefit from ICD implantation, but this test also has its limitations. First of all, the test is not suitable for every patient. Patients with supraventricular or ventricular arrhythmia or inability to exercise can not be tested and 20 to 40% of the performed test results will be interpreted as indeterminate due to patient factors or technical factors.⁹⁶ Without changing the negative predictive power, it is possible to group indeterminate tests together with positive tests as non-negative. However, this lowers the positive predictive value.⁷⁵ Also little is known about reproducibility and value of MTWA testing over years. There are some small studies about immediate and long-term reproducibility, which suggest that in patients in a stable stage of their disease, time does not influence MTWA results.^{97,98} In patients with ischaemic heart disease, nsVT on Holter ECG is associated with higher risk for SCD. However, in the MADIT II and SCD-HeFT, reduction in mortality was also shown in patients in the absence of nsVT.^{5,8} In the Dutch guidelines, there is still a role for the absence or presence of nsVT. For patients with an ischaemic CMP and an LVEF between 30 and 40%, an ICD implantation is only recommended if nsVT is present.⁹⁹

The role of serum markers in risk stratification seems promising; however, further research is warranted. Psychological factors may play a role in the occurrence of SCD and VA, paying attention and interference with psychotherapy to these factors may be useful to reduce the number of shocks received. The role of the autonomic markers SAECG, Holter and EPS is doubtful, because results from previous studies are conflicting.

Family history is a strong independent risk factor for SCD. Therefore, genetic factors seem to play an important role in the occurrence of VA and SCD. In the channelopathies, causal genetic markers were

already identified; however, in the less rare cardiac disease, such as coronary heart disease, no causal or contributing gene variants have been found yet. It is likely that we have to consider the role of polymorphisms in further research.

It seems unlikely that one single test will predict VA. Therefore we will most likely have to develop clinical risk scores based on a combination of test results. Some simple clinical risk scores have already been developed. Goldenberg et al. developed a risk score in the MADIT II population.¹⁰⁰ The score comprised five clinical factors (NYHA functional class >II, age >70 years, blood urea nitrogen >26 mg/l, QRS conduction >0.12 sec and atrial fibrillation). Retrospectively, the benefit of ICD therapy was most prominent among patients with one or two risk factors. No evidence of an ICD effect was shown among patients with 0 risk factors, and in patients with ≥3 risk factors. Very high-risk patients were excluded (blood urea nitrogen >50 mg/l and/or serum creatinine ≥2.5 mg/dl, but also in this group, ICD therapy showed no benefit.

Conclusion

Despite the fact that ICDs are effective in preventing SCD, better risk stratification is needed. Several tests were evaluated for their role in risk stratification; however, no single test reliably predicts the risk of VA and SCD accurately enough to be applied in daily care. The search continues for the perfect combination of tests, which will eventually lead to an update of the guidelines. ■

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