Risk Stratification of Sudden Cardiac Death: The Evidence Reviewed

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Abbreviations

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<tr>
<th>ARVD</th>
<th>Arrhythmogenic right ventricular dysplasia</th>
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<tr>
<td>EPS</td>
<td>Ventricular tachycardias</td>
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<tr>
<td>HCM</td>
<td>Hypertrophic cardiomyopathy</td>
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<tr>
<td>ICD</td>
<td>Implantable cardioverter defibrillator</td>
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<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
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<td>NSVT</td>
<td>Non sustained ventricular tachycardia</td>
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<td>NYHA</td>
<td>New York Heart Association</td>
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<td>SAECG</td>
<td>Signal averaged electrocardiography</td>
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<td>SCD</td>
<td>Sudden cardiac death</td>
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<td>TWA</td>
<td>T wave alternans</td>
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<td>VT</td>
<td>Ventricular tachycardias</td>
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Abstract

In this review the evidence supporting methods used to risk stratify patients at risk for sudden cardiac death is explored and discussed.

Introduction

The annual incidence for sudden cardiac death (SCD) is estimated to be 0.36 to 1.28 per 1000 inhabitants. (1) 80% victims of SCD do not survive hospital discharge. Fortunately, the implantable cardioverter defibrillator (ICDs) is a very effective therapy in improving survival in patients at risk of SCD either as primary (2) or secondary prevention. (3) The use of ICD for primary prevention has been shown to reduce RRR and ARR of death compared to medical therapy (28% and 3%, respectively). (4, 5) The survival benefits are almost similar to secondary prevention resulting in an average of 35% RRR and 7.5% ARR of death. (4, 5) Although, most SCD victims have underlying structural heart disease (e.g. coronary heart
disease) there remains a significant portion of SCD patients have no previously recognised heart disease. (6)

The inappropriate use of ICDs can put patients at unnecessary risks of complications such as infection, life-time of generator changes, procedural risks and inappropriate shocks. (7) Therefore it is important to accurately risk stratify patients at risk of sudden cardiac death so that high risk patients gets an ICD and those patients deemed low risk do not. In order risk stratify effectively we first must understand the pathophysiology of SCD. 75-80% of patients with sudden cardiovascular collapse are often due to ventricular tachycardias (VT) that deteriorates to ventricular fibrillation (VF). (4) There is often the presence of an abnormal myocardial substrate and a transient triggering factor that initiates the tachyarrhythmia. Zarebra proposed the presence of three factors in the initiation of tachyarrhythmias: a) myocardial substrate, b) autonomic nervous system (ANS), and repolarisation abnormalities. (8) Thus, most risk stratification methods often test the presence of these factors. (See Fig 1)

Fig1. Diagram showing the interplay between the three main parameters: myocardial substrate, autonomic nervous system and repolarisation abnormalities. HCM-hypertrophic cardiomyopathy. ARVD- arrhythmogenic right ventricular dysplasia. (9)

**Left Ventricular Ejection Fraction (LVEF)**

Primary and secondary prevention ICD trials has demonstrated that LVEF to be the most important risk factor for SCD. (3, 10) Significant mortality benefits were gained by patients with LVEF ≤30% but no significant benefit in patients with LVEF>30%. (10) However, in the Maastricht circulatory arrest registry, 56.5 % of SCD victims had LVEF>30% and 20% had LVEF>50%. In addition, most SCD (66%) occurs at >2 years post myocardial infarction (MI) and 4.3 years from first heart failure presentation. (11) Thus the prognostic power of LVEF depends on other variables e.g. functional class, heart failure, NSVT and age etc.
Cardiac Magnetic Resonance Imaging (MRI) – Myocardial Fibrosis

MRI can be used to assess infarct mass and surface area which has been shown to predict inducibility of VT. (12) In addition, the presence of midwall fibrosis in patients with dilated cardiomyopathy was associated with a five-fold increase for SCD or VT. (13)

Non-sustained Ventricular Tachycardia and Ventricular Ectopy

The severity and complexity of ventricular arrhythmias worsen as LVEF deteriorates. Despite this there is a lack of correlation between SCD and symptoms of heart failure. For instance, more patients with NYHA class I-II die of SCD (60%) than patient with NYHA class III-IV (<30%). (14) This maybe because patients with NYHA class III-IV succumb to pump failure before they experience a life-threatening arrhythmic event. Nonetheless, primary prevention ICD trials (MUSTT, MADIT, DEFINITE) demonstrated patients with reduced LVEF and inducible VT at EPS benefited the most from ICD therapy. (5) In patients with LVEF >40% it remains unclear whether NSVT or frequent ventricular ectopy are markers of a poor prognosis.

QRS Duration

Data from primary prevention ICD trials indicates that an ICD confers greater survival benefit with a QRS≥120ms than QRS<120ms, although both groups had mortality benefit. (10) Other studies would suggest that QRS duration was not associated with mortality outcomes. (15) Therefore QRS duration is not a reliable risk marker for SCD.

T Wave Alternans

T wave alternans (TWA) is caused by variation in cardiac repolarisation on a beat-to-beat basis and is measured by assessing T wave morphology using specialised signal processing. A meta-analysis demonstrated TWA had a 19.3 % positive predictive valve (PPV) and a 97.2 % negative predictive for an arrhythmic event in patients with ischaemic and non-ischaemic cardiomyopathy. (16) Thus it appears to be quite useful in identifying low risk patients particularly those with ischaemic heart disease. However, the general consensus would suggest that there is currently insufficient evidence to use TWA as a tool to withhold ICD therapy in patients who are at risk of SCD. (17)

Electrophysiology Studies (EPS)

MADIT and MUSTT trials demonstrated patients with positive EPS, prior MI, LVEF≤40 and NSVT had mortality benefit from ICD therapy. (18, 19) In a sub-study of MUSTT patients, overall mortality was 48% at five years in patients with inducible tachyarrhythmias vs. 44% in patients with negative EPS. (20) MUSTT trial found the negative predicted value (NPV) of EPS for SCD is about 88%, which decreases over time as coronary artery disease (CAD) and LVEF worsens. In addition, other factors such as NYHA class, NSVT and age affects
the prognostic value of EPS. (21) More recently, MADIT II study found positive EPS was a good predictor for VT but not for VF. (22) In summary, EPS has limited prognostic information but can be useful in risk stratification in asymptomatic patients with NSVT, CAD and LVEF between 30-40%.

**Signal Averaged Electrocardiography (SAECG)**

SAECG assesses the terminal QRS complex for late potentials which are low amplitude, high frequency signal at the terminal portion of the ECG which represents delayed activation secondary to scar or fibrosis that may be substrates for VTs. (See Fig 2) The following are abnormal parameters: filtered QRS duration (QRSd) >120ms, the root mean square voltage of the terminal 40ms of the filtered QRS complex (RMS 40) <20µV and the duration of the low amplitude in the terminal QRS>38ms. (23) A normal SAECG is quite useful in identifying low risk patients. It has a negative predictive accuracy of 95-99% and a positive predictive accuracy of 14-29% for sustained VT or sudden death in a post MI population. (24) SAECG is useful for risk stratification in patients with IHD, heart failure and arrhythmogenic right ventricular tachycardia.

Fig 2: SAECG and late potentials. (9)
Conclusion

LVEF is the single most important marker for risk stratification as represented in all current guidelines for the use of ICD in both primary and secondary prevention. (25, 26) These guidelines help to identify high risk patient groups but this still represent only a minority of the overall SCD victims. Markers of abnormal myocardial substrate (LVEF, NSVT, QRS duration and frequent ventricular ectopy) and electrical instability (EPS, TWA and SAECG) can be useful in risk stratifying certain patient. The challenge for the future is to accurately identify patient with LVEF>35% who are at risk of SCD and form a greater proportion of the overall SCD population.

Reference List


10. Moss AJ. Should everyone with an ejection fraction less than or equal to 30% receive an implantable cardioverter-defibrillator? Everyone with an ejection fraction< or= 30%


