Primary prevention of sudden cardiac death using implantable cardioverter defibrillators

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Despite substantial advances in prevention and medical treatment of cardiovascular diseases, sudden cardiac death (SCD) remains a leading cause of death in industrialized countries. Implantable cardioverter defibrillator (ICD) has been demonstrated to be an attractive option for primary prevention of SCD in high-risk patients. This review discusses the progress in the risk stratification for selecting high-risk patients, highlights the clinical trials of primary prevention for SCD, outlines the efficacy of combined use of cardiac resynchronization therapy with ICD, and analyses the cost-effectiveness issue of this device.

KEYWORDS

Sudden cardiac death; Implantable cardioverter defibrillator; Primary prevention

Introduction

Despite substantial advances in prevention and medical treatment of cardiovascular disease, sudden cardiac death (SCD) remains the leading cause of death in industrialized countries. In the USA, SCD claims ~400,000–450,000 lives per year.1,2 A series of clinical trials have demonstrated that anti-arrhythmic drugs, in addition to β-blockers, have no definitive survival benefit on patients with high risk of SCD.3,4 Conversely, based on the results of randomized clinical trials in patients with aborted sudden death and ventricular tachycardia with syncope,5–7 implantable cardioverter defibrillator (ICD) is now generally recommended as the prime therapy for the secondary prevention of SCD. However, because only a small percentage of patients who suffer a cardiac arrest survive to benefit from the ICD therapy as secondary prevention, prophylactic use of ICD for primary prevention of SCD becomes an attractive option for high-risk patients. In this review, we summarize the discussion of data on the primary prevention of SCD using ICD.

Risk stratification for implantable cardioverter defibrillator therapy

As the incidence of SCD in unselected adult population is only 2 per 1000 persons per year, screening of unselected patients is impracticable.8 As a result, efforts in risk stratification for SCD have primarily focused on patients with known structural heart disease, especially a history of myocardial infarction (MI) and/or congestive heart failure (CHF).

Currently, left ventricular ejection fraction (LVEF) is the primary factor used to select patients for ICD therapy. Other diagnostic factors, including signal-averaged electrocardiogram (SAECG), baseline ventricular arrhythmia, T-wave alternans, autonomic nerves function, and electrophysiological (EP) testing, may also improve the patients’ selection for ICD therapy.

Non-invasive evaluation for sudden cardiac death

Cardiovascular function

Left ventricular ejection fraction is the most consistent and powerful predictor of all-cause and cardiac mortality in patients with ischaemic and non-ischaemic heart diseases.9,10 In most of the ICD trials for primary prevention of SCD, an entry criterion of an LVEF <30–35% selected a high-risk group who might benefit from the intervention.3,11,12 Despite high power to predict death from cardiac causes, LVEF has relatively low specificity as a predictor of death from arrhythmia. In previous trials, two-thirds or more of the patients who received ICD did not develop tachyarrhythmia that required ICD intervention during the follow-up period of the trials.12

The New York Heart Association (NYHA) functional class reflects the degree of functional impairment in patients with CHF. Despite its obvious subjective and imprecise nature, this simple bedside assessment remains a potent risk-stratification tool for SCD. The degree of NYHA class is not linearly related with the prevalence of fatal arrhythmias, as patients with NYHA classes II and III symptoms are much more likely to die of arrhythmia than patients with NYHA class IV symptoms.13 In view of this limitation of the NYHA functional class, a new measurement of death mode...
in heart failure (HF) patients, the Seattle Heart Failure Model (SHFM), has been established. The study indicated that the SHFM discriminated between the HF severity and related risk more finely than does the NYHA class. However, further investigation is warranted to determine whether the SHFM predicts responses to or cost-effectiveness of the ICD therapy in HF patients.

**Ventricular arrhythmias**

Ventricular arrhythmias include a series of modalities ranging from premature ventricular complexes (PVCs) and non-sustained ventricular tachycardia (NSVT) in normal subjects to SCF due to ventricular tachyarrhythmias in patients with and without structural heart disease. The predictive value of single and repetitive PVCs has not been consistently demonstrated in subjects without structural heart disease. The majority of studies indicated that PVCs did not increase the risk prediction of initiation of fatal arrhythmia, whereas other studies suggested a small increase in risk. In contrast to PVCs and monomorphic NSVT, polymorphic ventricular tachyarrhythmia in the absence of structural heart disease has a risk indication.

Premature ventricular complexes and NSVT in patients with established heart disease are generally viewed as a risk marker of SCD, although its magnitude varies with the nature and extent of the underlying diseases. In patients with MI, frequency and repetitiveness of PVCs, accompanied by a depressed LV EF (≤30%), predicted a high risk of SCD in a long-term follow-up (after 6 months). However, further analysis of MACAS showed that the length but not the rate of NSVT on 24 h ambulatory ECG was a predictor of major arrhythmic events in patients with idiopathic dilated cardiomyopathy (DCM). Patients with 3–4 beat runs of NSVT have a similar arrhythmia-free survival as patients without NSVT on baseline 24 h ambulatory ECG, but the incidence of major arrhythmic events during follow-up increased to 10% per year in patients with ≥10 beat runs of NSVT (P < 0.05).

**Electrocardiographic evaluation for sudden cardiac death**

**Standard electrocardiography**

Standard resting 12-lead ECG is a fundamental and primary measure of evaluation of ventricular arrhythmias. Electrocardiography is useful not only in the identification of underlying structural heart diseases (such as ventricular hypertrophy, ischaemic heart disease) but also in the identification of congenital abnormalities (e.g. long-QT syndrome, short-QT syndrome, and Brugada syndrome) and electrolyte disturbances. In parameters of ECG, prolonged QRS duration (usually >120 ms) and repolarization abnormalities are independent predictors of SCD. Both a prolonged corrected QT (QTC) interval (>420 ms, especially in patients with long-QT syndrome) and a familial short-QTc interval (generally <300 ms) indicate an increased risk of SCD. However, in a general population, a short-QT interval does not appear to indicate an increased risk for all-cause or cardiovascular mortality.

**QT dispersion, QT variability, and QT dynamics**

The prognostic value of QT dispersion and QT variability remains controversial. Although a few studies reported no relationship between QT dispersion or QT variability and patient outcomes, further analysis of the Multicenter Automatic Defibrillator Implantation Trial (MADIT II) indicated that QT dispersion and increased QT variability were associated with a high risk of ventricular tachycardia and ventricular fibrillation. QT dynamics, a measurement of QT/RR slopes with a computerized Holter system, has been shown to be associated with an increased risk of SCD in patients with DCM, ischaemic cardiomyopathy, and CHF. However, similar to other risk-stratification tests, QT dispersion, QT variability, or QT dynamics has not been clinically useful, currently.

**Microvolt T-wave alternans**

Microvolt T-wave alternans (MTWA), a measurement of repolarization abnormality in the ventricles, is defined as alternating T-wave amplitude and morphology from beat to beat and can be detected with carefully computerized signal processing techniques. This repolarization abnormality can be associated with re-entrant ventricular arrhythmias. A series of studies have demonstrated that MTWA has a very high negative predictive value for predicting ventricular arrhythmias, regardless of the aetiology (ischaemic or non-ischaemic heart disease) and the severity of left ventricular (LV) dysfunction. One prospective study, the Alternans Before Cardioverter Defibrillator (ABCD) trial, suggested that the positive and negative predictive values of the MTWA test were similar to those of EP testing at 1 year. Moreover, MTWA and EP testing have a synergistic value, such that the event rate is highest in those with two abnormal tests, extremely low in patients with two normal tests, and intermediate in patients with discordant test results.

However, a recent study (MASTER-I) showed that MTWA testing did not predict life-threatening ventricular tachyarrhythmic events (assessed by ICD shocks) in 575 post-MI patients with LV EF ≤30%, although it does appear to have predictive value in terms of all-cause mortality. Therefore, the results of current studies with regard to MTWA testing should not be overinterpreted. More studies are necessary to better define the predictive ability of MTWA testing.

**Signal-averaged electrocardiogram**

The SAECG detects evidence of slowed or delayed conduction which are low-amplitude, high-frequency electrical signals in the terminal portions of the QRS complex referred as ‘late potentials’, and the substrate for re-entry ventricular arrhythmia. Studies have shown that an abnormal SAECG was associated with a great increase of arrhythmia events in a post-MI setting. In the MUSTT (Multicenter UnSustained Tachycardia Trial) study, SAECG is a strong predictor of arrhythmic death and total mortality. The main role of SAECG is its excellent negative predictive value in patients with MI, whereas its positive value is relatively low (<30%), which limits its usefulness as a guide in preventive therapy. Moreover, in patients who received revascularization and aggressive reperfusion, the predictive value of SAECG is reduced. In another population with non-ischaemic cardiomyopathy (NICM), the available data of SAECG are conflicting. The MACAS trial shows that the abnormal SAECG was not helpful for arrhythmic risk prediction.

**Autonomic function evaluation for sudden cardiac death**

Heart rate variability (HRV), baroreflex sensitivity, heart rate turbulence (HRT), and deceleration capacity of heart rate (HR-DC) reflect the function of the autonomic nerve system,
which may have a role in the genesis of fatal ventricular arrhythmias. Many studies have suggested that an impaired HRV, baroreflex sensitivity, and HRT were associated with an increased total and cardiac mortality in survivors of acute myocardial infarction (AMI), but these measurements did not appear to be a potent predictor of SCD.

One prospective study also suggested that HRV and baroreflex sensitivity had limited predictive power in identifying patients at risk of SCD after AMI in the β-blocking era. The investigators inferred that the optimal compliance to β-blockers, which might have a major influence on the prediction and epidemiological pattern of SCD, could explain the outcomes. In patients with NICM, the predictive value of HRV and baroreflex sensitivity remains to be determined. The MACAS study showed that HRV and low baroreflex sensitivity were not significant predictors of SCD.

Heart rate turbulence quantifies the physiological short-term fluctuation of sinus rhythm cycle lengths following singular ventricular premature complex. Several studies, including MPIP, EMIAT, and ATRAMI, have shown that the absence of HRT was an useful predictor of all-cause mortality in post-MI patients, but there is less evidence for sudden death or arrhythmic events.

The ISAR-HRT trial is the first prospective study to validate HRT in 1455 patients. In this trial, HRT was confirmed to be a potent risk-stratification tool, and it outperformed LV function in the reperfusion era. However, other studies, including the MADIT II and MACAS trials, found that HRT was not a significant predictor of all-cause mortality or major arrhythmic events.

Deceleration capacity of heart rate is a new Holter-based measure of cardiac autonomic modulation that quantifies deceleration-related HRV, and HR-DC was assessed in a cohort study which enrolled 1455 post-infarction patients from Munich, 656 patients from London, and 600 patients in Oulu. During a median follow-up of 24 months, an impaired HR-DC was a powerful predictor of all-cause mortality. It was more accurate than LVEF and the conventional measures of HRV. However, this study did not analyse the sudden death endpoint due to low incidence of arrhythmia death in the individual cohorts.

Serum markers

Several studies have shown that brain natriuretic peptide (BNP) might be useful in predicting who is at risk for SCD. One study that enrolled 521 survivors of AMI found BNP was a potent predictor of SCD even after adjusting for other clinical variables, including ejection fraction. Another recent study of 121 ICD recipients with MI showed that an increased BNP and C-reactive protein were associated with a higher VT incidence. An elevated pre-implantation BNP level may also predict future appropriate ICD therapies in patients with ischaemic and non-ischaemic cardiomyopathies, but C-reactive protein was not predictive of ICD therapies when compared with BNP.

Although present evidence shows a correlation between BNP and arrhythmic events, BNP is primarily a marker of progressive CHF, which itself may lead to an increased risk of arrhythmic events. Therefore, the role of BNP as a risk stratifier should not be over-estimated at present, and more studies are needed to validate the findings.

Invasive evaluation of sudden cardiac death

The predictive value of EP testing varies fundamentally with the kind and severity of the underlying heart diseases.

As to patients with ischaemic heart disease, the inducibility of sustained ventricular tachyarrhythmias during EP testing is a well-established marker of an increased risk of ventricular tachyarrhythmia. However, the limitation of this measure is a relatively high number of false-negative results. Non-inducibility of VT may not imply a lack of risk of recurrent lethal ventricular arrhythmia. Moreover, in patients with non-ischaemic heart disease, the value of electrophysiological studies remains controversial.

In conclusion, currently available data do not support routine use of any risk-stratification techniques for selection of patients for ICD therapy. More specific means and risk modelling are still needed to identify those patients who will benefit from an ICD.

Primary prevention of sudden cardiac death with implantable cardioverter defibrillator

Primary prevention in ischaemic cardiomyopathy with implantable cardioverter defibrillator

The effectiveness of ICD for the primary prevention of SCD has been validated by a series of randomized, controlled trials among patients with impaired LV systolic function due to underlying ischaemic cardiomyopathy. A summary of these trials is presented in Table 1.

The first MADIT I trial randomized subjects with prior MI, spontaneous NSVT, LVEF ≤35%, and inducible VT refractory to intravenous procainamide administration into either the ICD group or the conventional therapy group. MADIT I was prematurely aborted after enrolling only 196 patients when preliminary analysis revealed a significant benefit of ICD therapy in reduction of overall mortality by 54%.

The MUSTT trial enrolled a patient population similar to that in MADIT I. The original hypothesis of MUSTT was that EP-guided anti-arrhythmic therapy, either pharmacological or ICD therapy, could reduce arrhythmic and total mortality when compared with no anti-arrhythmic therapy in high-risk patients. At 5 years, there were absolute reductions in total mortality of 31% in the patients receiving ICD therapy when compared with those receiving pharmacological therapy and of 24% when compared with those receiving no therapy.

In contrast to previous trials, MADIT II used broader entry criteria to identify patients who were at risk of SCD. This trial randomized 1232 patients with a prior MI and LVEF ≤30% to either the ICD group or the conventional therapy group. Electrophysiological testing for risk stratification was not required. During an average follow-up of 20 months, the ICD therapy resulted in a 31% reduction in the risk of all-cause mortality and a 67% reduction in SCD. However, one retrospective analysis of MADIT II indicated that although ICD use improved survival, it was associated with an increased risk of subsequent HF events. Right ventricular pacing with a dual-chamber ICD and myocardial damage induced by defibrillator shocks might have contributed to the HF risk among ICD-treated patients. Further therapeutic modalities, including cardiac resynchronization therapy and optimization of adjunctive medical therapy, may be needed to reduce HF progression in ICD-treated patients.
The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) published in 2005 is another milestone of a series of ICD trials. This trial randomized 2521 patients with an LVEF ≤ 35%, and NYHA class II (70%) or III (30%) HF symptoms, to receive an ICD, amiodarone, or conventional treatment. Over a median follow-up of 45.5 months, ICD therapy reduced the overall mortality by 23% over placebo, but amiodarone therapy had no survival benefit in such patients. The results were consistent regardless of the HF aetiology, but the benefit was limited to patients in NYHA class II.

However, not all studies have shown clinical benefits with the ICD therapy. The Coronary Artery Bypass Graft patch (CABG-patch) trial randomly assigned 900 patients with CHD, LVEF ≤ 36%, and an abnormal SAECG, to either treatment with ICD plus CABG (446 patients) or CABG only (454 patients). After an average follow-up of 32 months, there was no reduction in total mortality with the ICD therapy. The results were likely due to the reduced risk for SCD after revascularization by coronary artery bypass graft surgery, which might have protected against arrhythmias.

Another trial, Defibrillator IN Acute Myocardial Infarction Trial (DINAMIT), randomized 674 patients with a recent MI (6–40 days after MI), LVEF ≤ 35%, and impaired cardiac autonomic function to either the ICD or the non-ICD group. During a mean follow-up of 30 months, ICD therapy showed no benefit in overall mortality when compared with the non-ICD group. These results suggested that prophylactic implantation of defibrillator within the first month after MI remains of unproven benefit.

Primary prevention of sudden cardiac death in non-ischaemic cardiomyopathy

The role of ICD therapy for primary prevention of sudden death in patients with NICM has remained controversial. The Cardiomyopathy Trial (CAT) randomly allocated 104 patients with a recent onset of DCM (>9 months) and an LVEF ≤ 30% to either the implantation of ICD or control. After a mean follow-up of 5.5 years, there was no significant difference in cumulative survival between the two groups (P = 0.554). Similarly, the Amiodarone versus Implantable Cardioverter Defibrillator Trial (AMIOVIRT) showed no improvement in survival or arrhythmia-free survival with ICD treatment when compared with amiodarone therapy in 103 patients with non-ischaemic DCM, LVEF ≤ 35%, and asymptomatic NSVT. In these two trials, no survival benefit was reported in patients with prophylactic ICD therapy. However, some investigators indicated that two limitations may have attenuated the efficacy of ICD in those trials. The major limitation is the limited sample size of 104 patients in CAT and 103 patients in AMIOVIRT. Another limitation is the lack of a run-in phase on optimal medical therapy (OPT), which may considerably improve LV function. Therefore, LV function should be re-evaluated 3–4 months after the initiation of OPT before prophylactic ICD therapy is considered (Table 2).

However, several recent trials suggested a beneficial role for ICD in such population. The Defibrillators in Non-ischaemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial randomized 458 patients with NICM, LVEF < 35%, and frequent PVCs or NSVT to receive the best medical therapy with or without a single-chamber ICD. Throughout a mean follow-up of 29 months, there was a significant 80%
The combined use of cardiac resynchronization therapy and implantable cardioverter defibrillator

Progressive pump failure and ventricular tachyarrhythmias are the two most common causes of death in patients with chronic heart failure, despite OPT. On the one hand, studies have suggested that the risk of mortality of progressive HF can be reduced by CRT and SCD by ICD. On the other hand, for patients with a high risk of SCD, most of them have HF. Therefore, theoretically, the combined use of CRT and ICD, namely CRT-D, should be the optimal therapy for the selected patients.

The efficacy of CRT-D has been demonstrated by a series of randomized, controlled clinical trials. To date, COMPANION is the largest trial that tested the efficacy of CRT-D among patients with advanced HF and intraventricular conduction delays. This study showed that CRT alone could improve survival and reduce hospitalization when compared with OPT. Moreover, the addition of a defibrillator to CRT further increased the survival benefit, resulting in a substantial 36% risk reduction of death (P = 0.003). The efficacy of CRT-D in patients with NYHA class IV remains to be determined, as the implantation procedure may destabilize the HF, and thus cause prolonged hospitalization and increased mortality. However, a recently published study has demonstrated that both CRT and CRT-D improved time to all-cause mortality and hospitalizations in NYHA class IV patients, and only CRT-D prolonged the time to sudden death (P = 0.03). Thus, CRT-D should be considered in ambulatory NYHA class IV HF patients.

The high cost and sophisticated implantation techniques are the main causes that limit the use of CRT-D in suitable patients. The cost-effectiveness analyses, which were conducted in the CARE-HF and COMPANION trials showed that long-term treatment with CRT appeared to be cost-effective when compared with OPT. Furthermore, the clinical benefit of CRT-D could also be achieved at a reasonable cost, although to a lesser extent, when compared with CRT plus OPT.

The cost-effectiveness issue of implantable cardioverter defibrillator use

Extensive cost-effectiveness analyses have been done in two major prophylaxis trials of ICD. Extensive implantable cardioverter defibrillator was associated with an increased cost when compared with standard medical therapy. Using MADIT II data, a cost of $54,000 per quality-adjusted life-year (QALY) saved was calculated. This gave a range of $78,600 to $114,000 in a 12 year projection of cost-effectiveness ratio. In the SCD-HF trial, the calculated cost is about $41,530 per QALY saved and $38,389 per year of life saved based on a 10 year projected survival. However, data on the cost-effectiveness of ICD therapy in high-risk patients with inherited cardiac disorders or NICM are limited. One study in patients with long-QT syndrome and hypertrophic cardiomyopathy indicated that ICD therapy is cost-effective both in primary and secondary prevention of SCD.

As the ICD implantation technique becomes more straightforward and the devices are increasingly effective, the benefits of ICD are increasing. At the same time, device and procedure costs are coming down. Therefore, ICD will become more and more economically attractive in the future.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Control therapy</th>
<th>No. of patients</th>
<th>Population</th>
<th>Mean follow-up (Mo)</th>
<th>Mortality (%)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>CAT</td>
<td>Conventional</td>
<td>104</td>
<td>NYHA classes II/III, NIDCM; LVEF ≤ 30%; asymptomatic NSVT</td>
<td>66</td>
<td>31</td>
<td>26</td>
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<tr>
<td>AMIOVIRT</td>
<td>Amiodarone</td>
<td>103</td>
<td>NYHA classes I–III, NIDCM; LVEF ≤ 35%; asymptomatic NSVT</td>
<td>36</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>DEFINITE</td>
<td>Conventional</td>
<td>458</td>
<td>NIDCM; LVEF ≤ 36%; NSVT or PVCs</td>
<td>29</td>
<td>12</td>
<td>17</td>
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<tr>
<td>SCD-HeFT</td>
<td>Conventional</td>
<td>2521</td>
<td>NYHA classes II/III CHF (ischaemic and non-ischaemic); LVEF ≤ 35%</td>
<td>45.5a</td>
<td>29</td>
<td>22</td>
</tr>
</tbody>
</table>

CAT, Cardiomyopathy Trial; AMIOVIRT, Amiodarone vs. Implantable Defibrillator In Patients with Non-ischaemic Cardiomyopathy and Asymptomatic Non-sustained Ventricular Tachycardia; DEFINITE, Prophylactic Defibrillator Implantation in Patients with Non-ischaemic-Dilated Cardiomyopathy; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; CHF, congestive heart failure; ICD, Implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NIDCM, non-ischaemic dilated cardiomyopathy; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; and PVC, premature ventricular complex.

*Median follow-up.
Conclusion
Sudden cardiac death remains a major public health problem worldwide. At present, the approaches for identifying high-risk patients of SCD remain inadequate. Besides the prevention of structural heart disease and the use of antiarrhythmic agents for the prevention of SCD, multiple clinical trials have documented the significant survival benefit of ICD therapy in certain subsets of patients. Cardiac resynchronization therapy has also been shown to produce substantial symptomatic improvement and survival benefits in a subgroup of chronic HF patients. This therapy should be considered in selected HF patients undergoing ICD implantation who have evidence of ventricular dysynchrony.

Conflict of interest: none declared.

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