How To Better Identify Patients That Do Not Benefit From Prophylactic ICD Therapy?

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Abstract

The implantable cardioverter defibrillator (ICD) has been demonstrated to improve survival by reducing sudden cardiac death (SCD) in patients with a low left ventricular ejection fraction (LVEF). Randomised trial data suggest that this mortality reduction is not constant among those implanted with a device, and has raised the significance of non-sudden cardiac death (non-SCD) as an important mode of death predicting limited benefit from ICD therapy. In this review article we explore the role of non-SCD and the risk prediction models that may aid identification of low LVEF patients unlikely to gain significant benefit from ICD therapy.

Introduction

Implantable cardioverter-defibrillator (ICD) therapy is the most effective treatment to prevent sudden cardiac death (SCD). Multiple prospective randomised controlled trials (RCTs) have demonstrated that ICD therapy improves survival in appropriately selected patients. The current basis for ICD implantation for primary prevention of sudden cardiac death (SCD) is centred mainly on left ventricular ejection fraction (LVEF), in that a low LVEF confers a higher risk of SCD. However recent data have suggested that ICD therapy may not reduce mortality in patients at high risk of non-SCD irrespective of their SCD risk.[1,2] In the low-LVEF population there appears to be significant heterogeneity in non-SCD risk, such that many patients have too high a risk of non-SCD to derive benefit from ICD therapy.[3-5] The identification of patients deemed to be "too high risk" for prophylactic ICD therapy is important to ensure that patient selection for device therapy is appropriate; particularly given its associated morbidity and cost implications.

In this review article we explore the different mechanisms of death in the low LVEF population, and evaluate the available methods of identifying low LVEF patients that are most likely to benefit from prophylactic ICD therapy.

Mode Of Death In The Low Left Ventricular Ejection Fraction Population

Significant heterogeneity in mode of death exists in the low LVEF population. Some patients die suddenly due to a ventricular arrhythmia, termed SCD, whereas others die from non-sudden modes of death such as progressive failure of cardiac function (pump failure).

With increasing heart failure severity the relative proportion of deaths due to SCD decreases and non-sudden modes predominate.[6] This has been well demonstrated by Mozaffarian et al. They used the Seattle Heart failure Model (SHFM) to assess mode of death in 10,538 ambulatory patients with NYHA functional class II to IV and applied a series of commonly observed clinical variables (e.g. age, gender, NYHA class, LVEF, medications, blood laboratory values) to ascertain a score for the prediction of mortality. Patients were grouped according to a SHFM score of zero to four. Those with a SHFM score of one compared with a score of zero had a 50% higher risk of sudden death, a 3-fold higher risk with a score of two, and almost a 7-fold increased risk with a score of three or four (P<0.001 for all comparisons) (Figure 1). However, the proportion of deaths caused by SCD versus pump-failure death decreased from a ratio of 7:1 with a SHFM score of 0 to a ratio of 1:2 with a SHFM score of 4 (P trend <0.001).[6]

Risk Of Non-Sudden Cardiac Death And Benefit From Implantable Cardioverter Defibrillator Therapy

ICD therapy significantly improves survival in the low LVEF patient population by the successful termination of ventricular arrhythmias that underlie preventable SCD. However it has no impact on the risk of non-SCD. On the basis of results from multiple large RCTs ICDs are targeted at patients at highest risk of SCD. However its clinical effectiveness is critically dependent not only on the risk of SCD but also on the risk of non-SCD.[1]

The relationship between risk of non-SCD and benefit from ICD therapy in the low-LVEF population has been investigated in analyses from RCTs.

Using a simplified version of the SHFM, the SCD-HeFT[1] investigators created a risk prediction model to divide 2487 patients into five groups of increasing predicted baseline all-cause mortality

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risk. Although in the overall study cohort ICD therapy significantly reduced mortality, patients in the highest risk quintile of predicted mortality were not shown to benefit from a device (relative risk (RR) for all-cause mortality 0.98, P=0.89). Post-hoc analysis suggested a threshold of benefit may be present based on an annual mortality risk of 20-25%, with patients at greater annualised risk than this unlikely to benefit from an ICD.

Further supporting evidence has come from an analysis of the 1,232 patients enrolled in MADIT-II. Goldenberg et al. described a U-shaped distribution for mortality benefit from ICD therapy compared to medical therapy alone. These patients were risk scored based on a scoring system comprising New York Heart Association (NYHA) functional class >II, atrial fibrillation (AF), QRS >120 ms, age >70 years, and blood urea nitrogen (BUN) ≥ 26 mg/dl (and <50 mg/dl). Patients were grouped based on their risk score ranging between 0 and ≥3 and a very high risk (VHR) group. Data revealed that in patients who were at very high risk or very low risk of all-cause mortality, ICD therapy conferred no significant mortality benefit at 2-years compared to medical therapy alone. Significant mortality benefit was noted in the intermediate risk group. Patients in the VHR group had a 50% 2-year mortality with or without an ICD, with the predominant mode of death being non-arrhythmic in nature.[2]

Additional evidence of the complex relationship between SCD and non-SCD in the LVEF population comes from data from the Immediate Risk-Stratification Improves Survival (IRIS)[7] trial and the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT).[8] Patients immediately post-infarct with a reduced LVEF were randomised to ICD therapy or conventional medical therapy alone. ICD therapy reduced SCD across both trials but with a commensurate increase in non-SCD resulting in no survival benefit overall. This further supports the concept that patients at high risk of non-SCD are unlikely to benefit from ICD therapy irrespective of their SCD risk.

Can Implantable Cardioverter Defibrillator Therapy Increase Risk Of Non-Sudden Cardiac Death?

An additional issue is the complex relationship between the therapies that ICDs deliver and non-SCD, especially death from pump failure. The two main therapies that ICDs deliver are pacing support and device therapy aimed at terminating ventricular arrhythmias (anti-tachycardia pacing [ATP] and shocks). Both therapies have been associated with worsening cardiac function and excess non-SCD mortality.

Results from the DAVID trial, as well as other studies, have clearly demonstrated that a high burden of right ventricular pacing can result in a deterioration of LVEF, with a consequent increase in the incidence heart failure and an adverse prognosis.[9] This problem can be at least in part addressed by judicious pacing mode selection and the more liberal use of CRT in selected patients.

A more contentious area is the association of shock therapy and mortality. Previous studies using data from both randomised trials (SCD-HeFT and MADIT II) and 'real world' cohorts have consistently demonstrated an association between appropriate and inappropriate shocks and increased mortality.[10, 11, 12] However, a recent prospective cohort study of over 7000 patients enrolled in the LATITUDE remote monitoring system found an adverse prognosis associated with appropriate shocks, as well as inappropriate

shocks for atrial fibrillation, but no significant difference in survival after inappropriate shocks for sinus tachycardia or noise/artifact/oversensing.[13] This raises the possibility that ICD shocks are a marker of a higher risk patient group, rather than causally related to adverse outcomes.

However, irrespective of the exact relationship between shocks and adverse outcomes, there is good evidence to suggest that unnecessary and inappropriate ICD therapy should be avoided by optimizing device programming.[14]

Risk Stratification Of Sudden Cardiac Death

One of the central issues underlying why patients with left ventricular dysfunction being considered for prophylactic ICD therapy are often at high risk of non-SCD, is the lack of specificity of the currently available risk stratification tests for SCD, versus other modes of death. Although patients with a low-LVEF, the most commonly used risk stratifier, have an increased risk of SCD compared with those with a higher LVEF, they have a similarly increased risk of non-SCD.

These issues are not limited to LVEF estimation alone but are a general limitation of the available risk stratification tools. This was well illustrated in an analysis from the Multicenter Unsustained Tachycardia Trial (MUSTT), in which scoring systems were generated to predict SCD and total mortality. Many of the factors, such as reduced LVEF, the presence of left-bundle branch block, a history of heart failure and inducible ventricular tachycardia at electrophysiological study, contributed to both scoring systems. Therefore most currently available SCD risk stratification tools used to select patients for ICD therapy are markers of non-SCD as well as SCD.

In the future, improved SCD risk stratification using tools with a higher specificity for SCD (versus non-SCD) and less emphasis on LVEF assessment may be more effective in identifying patients who are most likely to benefit from ICD therapy.

Current Guidelines

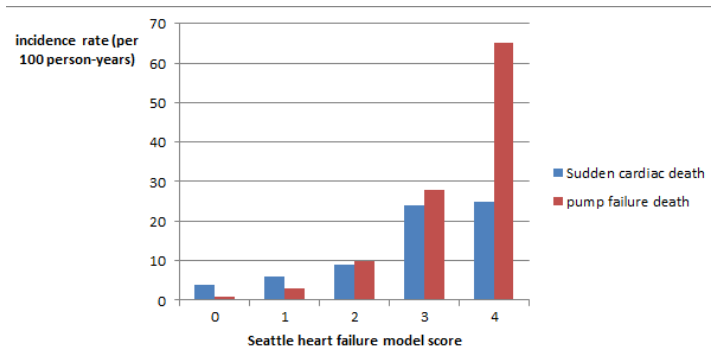Although it is clear that some low-LVEF patients at high risk

Figure 1: Relationship between mode of death and all-cause mortality with increasing Seattle heart failure model score.[6] Data were taken from 10538 patients with heart failure enrolled in to six randomised controlled trials or heart failure registries. The rate of SCD and pump failure death (per 100 patient-years) are presented for groups of patients in accordance with their SHFM score. As the SHFM score increases, the risk of both SCD and pump failure death increase. Patients with a lower overall risk of mortality (SHFM score 0-1), who reflect the majority of patients in the analysis have a higher incidence of SCD than pump failure death. The opposite can be observed in patients with the highest overall mortality groups (SHFM score 3-4). Numbers of patients (n) in each group are given.

of non-SCD may not gain significant benefit from ICD therapy, it is not clear how best to accurately and reproducibly identify these patients prior to device implantation. The current guidance is limited to suggesting that ICD therapy is not indicated in patients with advanced heart failure, defined as New York Heart Association (NYHA) functional class IV, or in patients who do not have a reasonable expectation of survival with an acceptable functional status for at least a year.[16]

Unfortunately there is no provision of how best to risk stratify patients in accordance with this guidance, making clinical interpretation difficult. Furthermore NHYA class is a relatively inaccurate prognostic variable, whose classification can sometimes be subjective.

A variety of alternative strategies to identify low LVEF patients with an elevated risk of non-SCD have been proposed. These include the use of individual clinical characteristics or risk markers such as advanced age and renal dysfunction, the presence of cardiac and non-cardiac comorbidities, and the use of more complex risk scores. These different approaches reflect the fact that in the low LVEF population the main contributor to non-SCD is pump failure, though non-cardiac mortality may also play an important role in patients with significant comorbidities.

Age As A Predictor

Recommendation for ICD therapy is based on large RCTs that often enrol young patients who are relatively free of comorbidity. This is particularly the case in primary prevention studies. By contrast, the average patient with heart failure encountered in clinical practice is >65 years old and has multiple comorbidities. Several studies have evaluated whether advancing age alone is a predictor of those unlikely to gain significant benefit from ICD therapy.

Previous randomised studies have reported conflicting results in terms of mortality benefit from ICD therapy in advancing age groups. In a MADIT II sub-study, 204 patients with ischaemic cardiomyopathy over the age of 75 years were shown to trend towards a benefit from ICD therapy (hazard ratio, 0.56; 95% confidence interval, 0.29–1.08; P=0.08).[16] This small mortality benefit was also seen in a substudy of the SCD-HeFT patients over the age of 65 years.[17] Santangeli et al.[18] conducted a meta-analysis of RCTs of prophylactic ICD and demonstrated less survival benefit in elderly patients as compared with young patients. Using the age cut-off of 60 or 65 years to define elderly, 5783 patients from five studies were analysed. ICD therapy revealed a smaller survival benefit in older (hazard ratio 0.75, 95% CI 0.61-0.91, P=0.004) than younger patients (hazard ratio 0.65, 95% CI 0.50-0.83, P<0.001).

A recent prospective analysis of a registry of 5399 patients, including 3939 primary prevention ICD implants, was undertaken by Yung et al.[19] The age of registry patients ranged 18 years to >80 years. Unsurprisingly mortality significantly increased with advancing age, however, the rate of appropriate shock was similar across all age ranges from 6.7 (18–49 years) to 4.2 (≥80 years) per 100 person-years (P=0.139). Despite this, death after an appropriate shock was highest among elderly patients [hazard ratios for death per decade were 1.28 (95% CI 1.14–1.44; P=0.001)].

Significant difficulty comes from interpreting data with regard to age as a predictor of benefit from ICD therapy due to the significant variation in the age cut-offs used. Many trials use the age of 60-65 years as a cut-off, while others use 75 years of age.

The Impact Of Renal Failure

Significant renal dysfunction (eGFR <60 ml/min/1.73m^2) is a major risk factor for sudden cardiac death and is present among approximately a third of heart failure patients.[20] Furthermore, cardiovascular disease is the leading cause of death in end stage renal failure (ESRF) patients, accounting for 43% of all-cause mortality, and approximately two thirds of cardiovascular deaths in ESRF are attributed to arrhythmia and SCD.[21] The relationship between renal dysfunction and benefit from ICD therapy is therefore an important area.

Several studies have demonstrated a relationship between renal dysfunction and mortality in ICD recipients. A large meta-analysis of 11 observations studies with 3010 patients covering both primary and secondary prevention concluded that chronic kidney disease (CKD) was associated with a significantly higher risk of mortality than patients without CKD (hazard ratio 3.44, P <0.001).[22] Furthermore, a gradient of risk has been identified with advancing renal dysfunction in that a 10 mL/min reduction in eGFR conferred a 48% increase in the risk of death (P <0.001).[23]

In a sub-study of MADIT II patients, Goldenberg et al.[24] retrospectively analysed the relationship between renal dysfunction and benefit from a device. For each 10 unit reduction in eGFR, the risk of all-cause mortality and SCD increased by 16% (P=0.005) and 17% (P=0.03). A survival benefit with ICD therapy was seen in patients with an eGFR ≥35 ml/min/1.73m2 (overall risk reduction for all-cause mortality 32%, P=0.01 and for SCD 66%, P <0.001). However in the 80 patients with an eGFR <35 ml/min/1.73m2, ICD therapy was not associated with improved survival (hazard ratio 1.09, P=0.84).

Other Comorbidities

The presence of multiple comorbidities in the ambulatory heart failure population has been independently associated with an increased risk of non-SCD.[25]

Lee et al.[26] investigated the impact of comorbidity on survival after ICD implantation. In a cohort of 2467 patients, relative to those without non-cardiac comorbidity, the hazard ratio for death adjusted for age, sex and prior heart failure were 1.72 (P< 0.001), 2.79 (P< 0.001) and 2.98 (P,0.001) for patients with one, two or three non-cardiac comorbidities. Peripheral and cerebral vascular disease, chronic pulmonary disease, diabetes and renal insufficiency were found to be the most common non-cardiac comorbidities associated with mortality.

Risk Prediction Models

It is clear that using a single clinical marker is insufficient to accurately predict an individual's mortality risk. For this reason a number of studies have evaluated the use of risk prediction models. These have been derived from both RCTs as well as "real world" cohorts.

Levy et al. used a modified version of the SHFM to examine the relationship between baseline predicted overall mortality risk and benefit form ICD therapy in 2487 patients enrolled in SCD-HeFT. This risk prediction model was used to identify five equally sized groups of increasing predicted mortality risk. These patients were followed for a period of 4 years. Despite improved survival with ICD therapy in the overall cohort, patients in the highest risk quintile did not derive benefit. The absolute 4-year reductions in mortality with ICD therapy were 6.6%, 8.8%, 10.6%, 14.0%, and -4.9% across
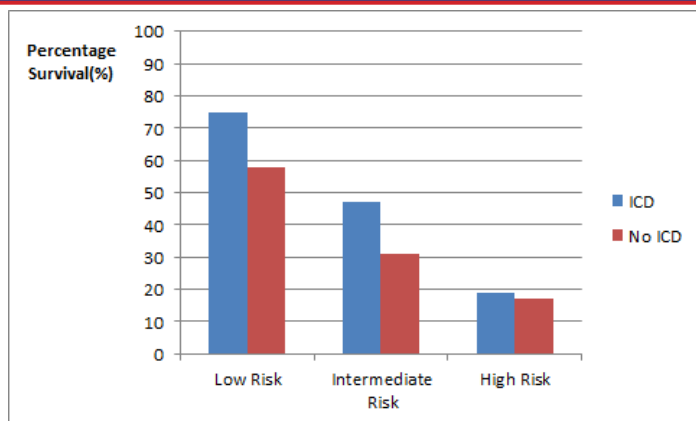
Figure 2: Relationship between predicted all-cause mortality risk and cumulative survival in patients treated with and without an ICD at 8 years of follow-up.[27] As the predicted all-cause mortality risk increases, there is a reduction in percentage survival. In the low and intermediate risk group there is a significant survival advantage in those treated with an ICD. In the high risk group however, no significant difference in 8 year survival was observed in those treated with an ICD compared to those without. Numbers of patients (n) in each group are given.

the five increasing risk quintiles, respectively. Furthermore, there was an increase in the percentage of patients receiving an appropriate ICD shock with increasing risk quintile (16% to 33% in lowest- to highest-risk quintile, respectively). However despite an elevated incidence of appropriate ICD shocks in the highest risk group, there was no benefit in terms of mortality reduction in these patients.

Barsheshet et al. explored the long term survival benefit of prophylactic ICD therapy in accordance with a risk stratification score in patients from MADIT II (Figure 2).[2,27] Risk scoring using 5 clinical parameters (age, NYHA class, BUN, QRS duration and atrial fibrillation) was utilised to divide 1992 patients in to low-risk (none of the five clinical risk factors), intermediate-risk (1 to 2 risk factors) and high-risk (≥3 risk factors). At 8 years follow up the cumulative probability of mortality across all study patients was 54%. Comparison of cumulative probability of mortality between those treated with an ICD versus those without an ICD was 50% and 64% respectively (P<0.001). In the low- and intermediate-risk groups the cumulative survival rate when comparing those treated with ICD therapy to those without ICD therapy, a significant benefit in the ICD therapy arm was noted (P=0.004 and P<0.001 respectively). Conversely, in the high-risk group no benefit from ICD therapy was observed (P=0.50).

More recently Kraaier et al. have produced a simple risk score for early mortality specifically in the prophylactic ICD patient population. With a primary end-point of all-cause mortality at 1 year, 861 patients undergoing prophylactic ICD therapy were risk scored based on age ≥75 years, LVEF ≤ 20%, history of AF, and estimated glomerular filtration rate (eGFR) ≤ 30 mL/min/1.73m². Low-, intermediate- and high-risk groups were identified based on having ≤1 risk factor, 2 risk factors or ≥2 risk factors, respectively. Predictions of 3.4%, 10.9% and 38.9% 1-year mortality were made in these respective risk stratified groups, and the risk score validated in 706 patients afterwards. One-year mortality was, respectively, 2.5%, 13.2% and 46.3% (all P <0.01). A trend towards early mortality was also found in patients with chronic obstructive pulmonary disease. Interestingly, in the high-risk group only two patients experienced

appropriate shock therapy, further emphasising that SCD related to arrhythmia may not be the predominant mode of death in the high-risk patient.[28]

Conclusion:

In the low LVEF population, benefit from prophylactic ICD therapy is critically dependent on not only the risk of SCD but also the risk of non-SCD. Patients whose risk of non-SCD is significantly elevated may not gain meaningful benefit from a prophylactic ICD despite a high SCD risk. Although a number of strategies have been proposed to identify potential ICD recipients at high non-SCD risk, the best approach remains unclear. In order to improve the clinical and cost-effectiveness of ICD therapy further research is needed to evaluate the optimal strategy to identify these high-risk patients.

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