The effect of duration of follow-up and presence of competing risk on lifespan-gain from implantable cardioverter defibrillator therapy: who benefits the most?

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Background

In at-risk patients with left ventricular dysfunction, implantable cardioverter defibrillators (ICDs) prolong life. Implantable cardioverter defibrillators are increasingly implanted for primary prevention and therefore into lower risk patients. Trial data have demonstrated the benefit of these devices but does not provide an estimate of potential lifespan-gain over longer time periods, e.g. a patient’s lifespan.

Methods

Using data from landmark ICD trials, lifespan-gain was plotted against baseline annual mortality in the individual trials. Lifespan-gain was then extrapolated to a time-horizon of 20 years while adjusting for increasing ‘competing’ risk from ageing and non-sudden cardiac death (pump failure).

Results

At 3 years, directly observed lifespan-gain was strongly dependent on baseline event rate (r = 0.94, P < 0.001). However, projecting beyond the duration of the trial, lifespan-gain increases rapidly and non-linearly with time. At 3 years, it averages 1.7 months, but by 10 years up to 9-fold more. Lifespan-gain over time horizons >20 years were greatest in lower risk patients (∼5 life-years for 5% baseline mortality, ∼2 life-years for 15% baseline mortality). Increased competing risks significantly reduce lifespan-gain from ICD implantation.

Conclusion

While high-risk patients may show the greatest short-term gain, the dramatic growth of lifespan-gain over time means that it is the lower risk patients, e.g. primary prevention ICD implantation, who gain the most life-years over their lifetime. Benefit is underestimated when only trial data are assessed as trials can only maintain randomization over limited periods. Lifespan-gain may be further increased through advances in ICD device programming.

Keywords

ICD • Implantable cardioverter defibrillator • Lifespan • Mortality • Heart failure • Sudden death

Introduction

Implantable cardioverter defibrillators (ICDs) reduce the risk of sudden arrhythmic death in clinical trials of patients with chronic heart failure who have,1 or have not2,3 already experienced a life-threatening arrhythmia. Despite this, many patients who meet the guidelines for implantation do not receive an ICD,4,5 and conversely ICD implantation often falls outside evidence-based recommendations.6–8 Early studies of ICDs focused on patients at high risk of sudden cardiac death with a high event rate, so that relatively short follow-up could demonstrate a significant mortality effect. However, >70% of ICDs are now implanted for primary prevention and these patients are often at the lower end of the risk spectrum.

High-risk patients obtain the clearest early benefit, but as many patients with heart failure die for reasons other than arrhythmia, e.g. non-cardiac comorbidities, the average lifespan-gain may not...
be large. Conversely, lower risk patients may have a low rate of non-arrrhythmic death and therefore much longer exposure to the risk of arrhythmia, albeit at a lower annual rate, and so the extent of survival benefit may not be obvious during the relatively short time-horizon of most trials. It is therefore important to consider lifespan-gain from ICD implantation across the spectrum of risk and for longer duration of follow-up than assessed through trials.

Trials have focussed on recruiting patients with dominant cardiac disease and excluded patients with severe co-morbidities. However, in clinical practice, patients with advanced heart failure often suffer from multiple co-morbidities and are at increased risk of non-sudden cardiac death (pump failure) which may discourage ICD implantation.

Lifespan-gain from ICD implantation was assessed using data from the landmark trials. As these necessarily had relatively short durations of follow-up, we modelled survival in the post-trial period using a Gompertz–Makeham model. We assessed (i) the effect of baseline mortality, (ii) the interplay of sudden and non-sudden cardiac death, and (iii) competing risk from non-cardiac causes on the lifespan-gain from ICD implantation.

Methods

Identification of studies

A PubMed search using the keywords implantable cardioverter defibrillator, ICD, randomized controlled trial (RCT), survival and mortality was used to identify RCTs comparing ICD implantation with a no-ICD arm, and that reported survival in the form of a Kaplan–Meier curve for at least 6 months. Both primary and secondary prevention studies were included.

Extraction of data

For each trial, a calibrated enlargement of the published Kaplan–Meier survival curve was used to extract hazard ratios at 3 monthly intervals for each trial arm. The cumulative area between the Kaplan–Meier curves (lifespan gained per ICD implanted) was then calculated at a series of time points for each trial (Figure 1). Different trials had different lengths of follow-up; therefore, to allow comparison of survival benefit between trials, only data up to 3 years follow-up was used. Trial data giving a hazard ratio for sudden cardiac death were first tested for heterogeneity using Cochran’s Q and the I² statistic. A Mantel–Haenszel fixed effects model was used for meta-analysis where there was no significant heterogeneity.

Assessment of lifespan-gain from defibrillator implantation in the post-trial period

We considered mortality to be partitioned into cardiac and non-cardiac (competing) risk. Non-cardiac risk progressively increases with ageing, which was modelled using a Gompertz–Makeham function. We considered competing risk to increase over the lifespan of the patient by a factor of 1.1 with every year of ageing, as is typical. Lifespan-gain was calculated with increasing time-window of analysis.

Cardiac mortality was partitioned into two components: sudden cardiac death and non-sudden cardiac death (e.g. death from progressive pump failure). The relative proportion of these two modes of death changes with increased baseline mortality. This was incorporated into our model using data from the Seattle Heart Failure Model (SHFM) cohort which demonstrated a progressive decrease in sudden cardiac death (90% at 5% baseline mortality to 75% at 10% baseline mortality) with a corresponding increase in non-sudden cardiac death with increased baseline mortality. The proportion of deaths that were non-cardiac was ≏15%.

The SCD-HeFT trial showed differing ICD efficacy for sudden death prevention dependent on baseline mortality; hazard ratio of 0.27 in patients with a 5% baseline mortality, 0.42 in for 10% baseline mortality, and 0.58 for 15% baseline mortality. We first modelled the effect of ICD implantation assuming a constant hazard ratio based on a weighted mean from trial data, for (i) ICD implantation using the pacing settings of included trials and (ii) ICD implantation with device programming to minimize bradycardic pacing. Second, we used sub-group data from the SCD-HeFT trial, using a baseline risk-adjusted ICD hazard ratio to model the effect of differing efficacies of ICD therapy dependent on baseline mortality.

Effect of competing risk on lifespan-gain from implantable cardioverter defibrillator implantation within the landmark trials and beyond

We assessed the effect of an ICD on sub-groups of patients with different baseline cardiac and non-cardiac mortalities within the landmark trials. We then estimated lifespan-gain per patient and per device in the post-trial period and considered the effect of competing risk from non-sudden cardiac death.

Results

Identification of studies

Thirteen RCTs met the inclusion criteria with data published in the form of Kaplan–Meier curves, giving a total population of 8910 patients and 2194 deaths during follow-up. Analysis of Kaplan–Meier curves allowed extraction of hazard ratios for the ICD and medical therapy groups at multiple time points. From the published data, we derived the annualized mortality in the no-ICD arm and the hazard ratio achieved by ICD implantation (Table 1).
**Table I  Details of included studies**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Treatment groups</th>
<th>Inclusion criteria</th>
<th>Number of patients enrolled</th>
<th>Number of deaths</th>
<th>Mean follow-up period (years)</th>
<th>Annual mortality in group randomized to receive no ICD (%)</th>
<th>Calculated hazard ratio for all-cause mortality from published data</th>
<th>Calculated hazard ratio for cardiac mortality from published data</th>
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<tbody>
<tr>
<td>Secondary prevention</td>
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<td></td>
<td></td>
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<tr>
<td>Wever et al.</td>
<td>RCT</td>
<td>ICD vs. AAD</td>
<td>Survivors of cardiac arrest following an old MI. Mean EF 30%</td>
<td>60</td>
<td>15</td>
<td>2.25</td>
<td>14.0</td>
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<td></td>
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<td>AVID</td>
<td>RCT</td>
<td>ICD vs. AAD</td>
<td>Patients resuscitated from VF or symptomatic sustained VT and EF &lt; 40%</td>
<td>1013</td>
<td>202</td>
<td>3</td>
<td>12.0</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>CIDS</td>
<td>RCT</td>
<td>ICD vs. amiodarone</td>
<td>Survivors of sudden death post-MI: patients resuscitated from VF or VT or with unmonitored syncope. Mean EF 33%</td>
<td>659</td>
<td>181</td>
<td>5</td>
<td>9.0</td>
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<tr>
<td>CASH</td>
<td>RCT</td>
<td>ICD vs. AAD</td>
<td>Patients resuscitated from cardiac arrest due to ventricular arrhythmia. Mean EF 45%</td>
<td>288</td>
<td>120</td>
<td>4.75</td>
<td>9.8</td>
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<tr>
<td>Primary prevention</td>
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<tr>
<td>MADIT</td>
<td>RCT</td>
<td>ICD vs. AAD/standard therapy</td>
<td>Previous MI, documented non-sustained VT and non-suppressible VT on EP study. Mean EF 26%</td>
<td>196</td>
<td>54</td>
<td>2.25</td>
<td>14.7</td>
<td>0.37 0.43</td>
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<td>MADIT II</td>
<td>RCT</td>
<td>ICD vs. standard therapy</td>
<td>Previous MI and EF &lt; 30%</td>
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<td>202</td>
<td>5.25</td>
<td>10.3</td>
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<td>DINAMIT</td>
<td>RCT</td>
<td>ICD vs. AAD</td>
<td>6–40 days post-MI. EF &lt; 35% and impaired autonomic function</td>
<td>674</td>
<td>120</td>
<td>4</td>
<td>5.8</td>
<td>1.04 0.43</td>
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<td>SCD HeFT</td>
<td>RCT</td>
<td>ICD vs. placebo</td>
<td>Heart failure NYHA II or III with EF ≤ 35%</td>
<td>2521</td>
<td>666</td>
<td>3.8</td>
<td>8.0</td>
<td>0.72 0.40</td>
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<td>AMIOVIRT</td>
<td>RCT</td>
<td>ICD vs. amiodarone</td>
<td>Non-ischaemic DCM, EF ≤ 35%, and asymptomatic NSVT</td>
<td>103</td>
<td>13</td>
<td>3</td>
<td>6.0</td>
<td>0.88</td>
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<tr>
<td>CAT</td>
<td>RCT</td>
<td>ICD vs. standard therapy</td>
<td>Recent onset DCM (&lt;9 months after diagnosis), EF ≤ 30%</td>
<td>104</td>
<td>30</td>
<td>5.5</td>
<td>6.0</td>
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<td>DEFINITE</td>
<td>RCT</td>
<td>ICD vs. standard therapy</td>
<td>Non-ischaemic dilated cardiomyopathy, EF &lt; 36% and premature ventricular complexes or NSVT</td>
<td>458</td>
<td>68</td>
<td>2.4</td>
<td>8.3</td>
<td>0.68 0.21</td>
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Lifespan-gain during the landmark trials
Across the 13 studies, there was a close relationship between baseline mortality and lifespan-gain from ICDs at 3 years (Figure 2) with trials that had a higher baseline annual mortality rate demonstrating greater lifespan-gain. The relationship was similar within the primary ($r = 0.94, P < 0.001$) and secondary ($r = 0.93, P = 0.07$) prevention trials, suggesting a consistent relationship between baseline mortality and lifespan-gain within the trial populations studied. The average weighted lifespan-gain at 3-year follow-up was 1.5 months for primary prevention trials and 2.2 months for secondary prevention trials. Over all trials, it was 1.7 months.

Lifespan-gain in the post-trial period: calculation using a fixed implantable cardioverter defibrillator hazard ratio
Using the Gompertz–Makeham formulation, we calculated lifespan-gain in the post-trial period for time horizons up to 40 years. We modelled survival using a fixed hazard ratio for ICDs on sudden death derived from five trials (SCD HeFT, MADIT, DEFINITE, IRIS, and DINAMIT). Cochran’s $Q$ was 1.38 ($P = 0.84$) and $I^2$ was 0.2%; therefore, a fixed effects model was used to produce a pooled estimate, with a weighted mean of 0.41 (95% confidence intervals, CI 0.33–0.52). The model showed close agreement with the MADIT II extended follow-up data (Figure 3).

Lifespan-gain increases with increased duration of follow-up. Compared with RCT data limited to 3-year follow-up duration, lifespan-gain was 2–3 times greater at 5-year follow-up and 6- to 9-fold greater at 10-year follow-up.

The impact of time-horizon of analysis on lifespan-gain from ICD implantation was heavily dependent on baseline risk profile (Figure 4). Over follow-up times of <10 years, the higher risk population (15% annual mortality) had greater lifespan-gain than lower risk patients (5% annual mortality). However, when lifespan-gain was calculated over longer durations, such as the lifespan of the patient, the lower risk patients had the greatest lifespan-gain per patient (Figure 4).

Analysis per device, as is commonly performed in economic cost-effectiveness analysis, demonstrated the converse: patients with the highest cardiac risk had the greatest lifespan-gain per device reflecting the much shorter time-frame over which this is assessed (5 years, the average battery life of the device).

Lifespan-gain from implantable cardioverter defibrillator therapy in trials minimising right ventricular pacing
Of the five trials (SCD HeFT, MADIT, DEFINITE, IRIS, and DINAMIT) that provided a pooled estimate for the hazard ratio for sudden cardiac death, three (SCD HeFT, DEFINITE, and DINAMIT) used single chamber devices with a low rate (35–40 beats/min) for brady-cardiac pacing to minimize right ventricular (RV) pacing. Of the other two trials, MADIT did not include details of pacing settings used during the study and IRIS used a single chamber ICD in 81% of patients and a Fidelis lead in 21% of patients with a backup pacing rate of 40 beats/min. The pooled estimate of the hazard ratio for these three trials was 0.39 (95% CI 0.28–0.54).
Lifespan-gain at each time point in the RV pacing model was slightly greater owing to the lower hazard ratio. For example, for an annual mortality of 10%, the lifespan-gain was 0.38 years at 5-year follow-up and 2.42 years at 20-year follow-up using the minimal RV pacing model and 0.37 years at 5 years and 2.32 years at 20 years for the standard model. In addition, the minimal RV pacing model showed the same patterns as the original model; lifespan-gain over the lifespan of the patient was greatest in the lower risk patients.

**Figure 2** Impact of baseline mortality on lifespan-gain from implantable cardioverter defibrillator implantation. In both primary and secondary prevention, trials with a higher baseline annual mortality rate demonstrated more lifespan gained per implantable cardioverter defibrillator implanted than those with lower annual mortality rates over 3-year follow-up. The size of the trial population is represented by the area of the marker. Primary prevention trials are shown with filled circles (top panel); secondary prevention trials with open circles (bottom panel).
Lifespan-gain in the post-trial period: calculation using a baseline risk-adjusted implantable cardioverter defibrillator hazard ratio

Using the data from SCD-HeFT, we refined our Gompertz–Makeham formulation using a baseline risk-adjusted ICD hazard ratio (Figure 5). This showed greater lifespan-gain in the 5% baseline risk population with an attenuated benefit in the 15% baseline mortality population compared with the fixed hazard ratio model. This model incorporated the effects of minimal RV pacing as the SCD-HeFT protocol used a single chamber device with a backup rate of 34 beats/min.

Impact of competing risk on lifespan-gain from implantable cardioverter defibrillator implantation within the landmark trials and in the post-trial period

Two RCTs presented sub-group analyses (MADIT-II and SCD-HeFT, Table 2) that compared efficacy in patients with high competing risk (including older age and renal impairment) vs. patients with lower competing risk. In both trials, these high competing risk sub-groups showed no benefit from ICD implantation.

In the post-trial period, the same pattern is shown: lifespan-gain from ICD implantation is attenuated with increasing competing risk (Figure 6). For example, for a patient with 5% annual mortality using a fixed hazard ratio of 0.4, if 15% of the cardiac risk is non-sudden, the lifespan-gain at 10 years is 0.84 life-years and at 20 years is 2.4 life-years. However, if 50% of the risk is non-cardiac, the lifespan-gain is reduced, with 0.5 life-years at 10-year follow-up and 1.3 life-years at 20-year follow-up.

Discussion

Lifespan-gain from ICD implantations is underestimated when benefit is assessed only over short-time periods such as the duration of RCTs. Compared with lifespan-gain at 3 years (the duration of most RCTs), benefit is —two to three times greater at 5-year follow-up and 6- to 9-fold greater at 10-year follow-up.

The majority of ICDs are now implanted in lower risk patients, for primary prevention. Naive inspection of RCT results might suggest maximal benefit in high-risk patients, but this is because follow-up has to be relatively short. In contrast, taking a longer term view by the analysis processes described in this manuscript reveals that lower risk patients stand to gain the greatest lifespan. Increasing risk from non-cardiac disease causes attenuation in lifespan-gain in both the trial and post-trial period.

Modelling survival in the post-trial period

Survival modelling allows projection of lifespan-gain from an intervention over a much greater time-frame than is possible with a clinical trial. The model uses trial data to establish the hazard ratio associated with an intervention such as ICD implantation. The Gompertz–Makeham formulation adjusts for the effect of increasing age and comorbidities with time. As the patient becomes older, there is an increased probability of non-cardiac pathologies and the device therefore becomes less effective at reducing total mortality due to an increase in non-cardiac death.

Modelling allows assessment of lifespan-gain over follow-up periods of 20 years or more. It cannot replace real-life long-term follow-up data but has the advantage of being able to control for the effects of an intervention and confounding factors such as non-cardiac disease. It is also dependent on the trial data used to derive hazard ratios. While this means that the model is based on a strong body of evidence, the hazard ratio for ICD implantation will reflect disease management at the time.

Impact of follow-up duration on who gains most lifespan: modelling survival in the post-trial period

Lifespan-gain can be observed directly from trial data, but the short duration of most trials leads to gross underestimation of a patient’s total lifespan-gain. Survival modelling allows projection of lifespan-gain from an intervention over a much greater timeframe. It cannot replace real-life long-term follow-up data but has the advantage of being able to control for the effects of an intervention and confounding factors such as non-cardiac disease.

For short durations, such as the 3- to 5-year follow-up of many of the landmark ICD trials, patients with the greatest lifespan-gain are those at highest risk of having a defibrillator-preventable event. Lower risk populations obtain little benefit over short follow-up due to their low event rate. In these patients, it is only when follow-up continues for the lifetime of a patient that the true benefit from ICD implantation is observed.
implantation is revealed. Our analysis suggests in low-risk patients that lifespan-gain may be up to nine times greater after 10-year follow-up than after 3-year follow-up. Our results are consistent with previous economic analysis using data from SCD-HeFT, and MADIT II trials. This has large clinical implications as the majority of ICDs are now being implanted in the lower risk primary prevention populations.

Economic analyses are more dependent on a ‘per ICD’ metric for lifespan-gain, whereas the ‘per patient’ data are more relevant for day-to-day clinical practice. For lifetime analysis, lifespan-gain per device was greatest in the higher risk patients (due to the lower number of replacement devices required) whereas lifespan-gain per patient was greatest in the lower risk patients. We suggest that presentations of benefit, and analyses of cost effectiveness, should quote both values.

Figure 4 Effect of increasing mortality and time-horizon on lifespan-gain with fixed implantable cardioverter defibrillator hazard ratio. In all panels, low competing risks are assumed (15% of baseline mortality is non-cardiac) and the hazard ratio for sudden cardiac death is 0.41. In (A), the annual mortality without an implantable cardioverter defibrillator is 5%, in (B) 10%, and in (C) 15%. The lifespan gained per patient (grey line) in all cases is heavily dependent on length of follow-up. While lower risk patients gain less lifespan per patient when assessed at 5 or even 10 years (dotted lines) compared with higher risk populations, it is only over the lifespan of the patient that the full benefit of the device becomes apparent, with the greatest lifetime benefit in the lowest risk cohort. However, as lower risk patients live longer and therefore require a larger number of replacement devices (assuming they are replaced), the lifespan-gain per device is higher in the higher risk populations over all follow-up times.

Effect of competing risks on lifespan-gain from implantable cardioverter defibrillator implantation

Lifespan-gain from ICD implantation is attenuated in the trial and the post-trial period by competing risks that are not accessible to ICD therapy. This was recognized in the formulation of ‘years needed to treat’, a measure that accounts for potential long-term benefits and costs of pharmacological therapy.

In real life, heart failure patients often have multiple comorbidities. Within SCD-HeFT and MADIT-II, older subpopulations with renal dysfunction and other non-cardiac comorbidities were identified who did not show survival benefit from ICD implantation (Table 2). Patients with heart failure requiring diuretics are more likely to die prior to the first appropriate ICD therapy and patients with
significant co-morbidities are known to have a higher proportion of non-sudden death. Our analysis indicates that device implantation confers little gain in lifespan within the trial and post-trial period when the patient is at high-risk of non-cardiac death.

**Mode of death and implantable cardioverter defibrillator effectiveness: can a high-risk patient ever benefit from implantable cardioverter defibrillator implantation?**

It is the interplay of cardiac sudden and non-sudden death, as well as competing risks, that determines whether a patient will ultimately benefit from ICD implantation. The proportion of sudden and non-sudden cardiac death varies depending on annual baseline mortality. Patients with high baseline mortality tend to have a much greater proportion of non-sudden cardiac death (50% at 25% annual mortality in the Seattle Heart Failure data compared with 10% at 5% annual mortality). In contrast, the efficacy of ICD therapy in reduction of sudden cardiac death is in the lower risk patient population. When a more realistic variable hazard ratio for ICD-efficacy was used, as seen from the SCD-HeFT data, this effect was even more dramatic. Use of scoring systems such as the Seattle Heart Failure score allows estimation of likely benefit from ICD implantation.

**Figure 5** Effect of increasing mortality on lifespan-gain with baseline risk-adjusted implantable cardioverter defibrillator hazard ratio. The same patient populations as Figure 4 are considered with a baseline risk-adjusted hazard ratio which accounts for varying implantable cardioverter defibrillator efficacy related to baseline annual mortality. In this model, the annual mortalities without an implantable cardioverter defibrillator are again (A) 5%, (B) 10%, and (C) 15% with the same proportions of sudden cardiac/non-sudden cardiac deaths and low competing risk. However, we adjust for the finding that implantable cardioverter defibrillators are more efficacious at prevention of sudden death in the lower mortality population, with an hazard ratio of 0.27 in the 5% population (A), 0.42 in the 10% population (B), and 0.58 in the 15% population (C). Adjustment for relative efficacy increases the lifespan-gain in the lowest risk population compared with the fixed hazard ratio model and demonstrates a greater benefit in this population compared with the higher risk populations.
Lifespan-gain may be larger in modern practice

There are multiple reasons why current-day ICD implantation may be able to deliver more benefit in lifespan than calculated using data from the original landmark trials:

(i) The hazard ratios used in our calculations are based on the best available evidence from RCTs. However, many of these trials are now over 10 years old, and therefore do not capture the effects of improved clinical practice that have since occurred, e.g. device insertion aimed at minimizing isolated RV pacing with implantation of fewer dual chamber ICDs and more CRT-D in eligible patients. By reducing the risk of death from pump failure, this may potentially increase the benefit from ICD implantation.

(ii) Modern refinements to ICD programming use anti-tachycardia pacing and defibrillation more frugally. Reducing episodes of therapy in this way has been shown to improve mortality.

(iii) No RCT to date has focused on patients with channelopathies, purely genetic arrhythmias, arrhythmogenic RV cardiomyopathy, or other congenital heart disease. These conditions, which can be diagnosed at a young age and are associated with little or no co-morbidities, will likely generate a long period of large hazard ratio reduction, permitting larger lifespan-gains than calculated here.

(iv) Modern ICDs have growing capacity for home monitoring, feeding back information on episodes of tachyarrhythmia, anti-tachycardia pacing episodes, impedance changes, amounts of pacing required, lead impedance changes, and device faults. This wealth of information may assist physicians to improve outcomes further.

It is therefore important to be cautious in interpreting our results. Exactly how much more beneficial current-day ICDs might be is difficult to state with confidence. We can estimate using, for example, the hazard ratio of MADIT-RIT (0.45; 95% CI, 0.24–0.85) for the frugal therapy compared with historically conventional therapy. If this tremendous step-change is applicable across all ICD recipients, lifespan gained could be almost twice as large as we have calculated.

Avoidance of RV pacing will contribute further, as demonstrated by the more efficacious hazard ratio from our analysis and as seen in the DAVID trial. While the exact effect of all these features combined cannot be stated exactly, we suggest a potential estimate of the overall hazard ratio for modern ICD strategies might be 0.45 × that seen in the landmark trials. This would mean an overall hazard ratio of 0.45 × 0.41 = 0.18 (Figure 7C).

Implications for heart failure management

While absolute survival benefit in lower risk populations is modest within the short time-frame of clinical trials, our results using a longer time-horizon suggest substantially greater benefit (Figures 4 and 5). This is concordant with the findings when the SHFM was applied to SCD-HeFT with an ∼4–5 years increase in estimated lifespan with an ICD in patients with an annual mortality of 5%. These results suggest that perhaps we should not delay consideration of ICD therapy in lower risk populations.

Improved heart failure therapy through widespread utilization of CRT, more finely tuned coronary interventions both in acute myocardial infarction and chronic ischaemic heart disease, and greater uptake of drugs including angiotensin-converting enzyme inhibitors, β-blockers and mineralocorticoid antagonists, may lead to progressive improvement in ventricular function so that a patient eligible for an ICD at the outset might not meet criteria for implantation at the end of battery life. Nevertheless, it should be remembered that the analysis must not stop at that time point, since that would be only be valid if all patients who had their lives saved by ICD therapy were to die on that day. In reality, the higher survival in those that had the ICD would continue after its battery life, as shown in

### Table 2  Characteristics of high-risk populations in MADIT-II and SCD-HeFT

<table>
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<th>Very high risk patients (n = 60)</th>
<th>Rest of patient population (n = 1172)</th>
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<td><strong>Sub-group analysis of MADIT II</strong></td>
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<tr>
<td>BUN (mg/dL)</td>
<td>58 (54, 66)</td>
<td>29 (15, 26)</td>
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<td>Creatinine (mg/dL)</td>
<td>2.3 (1.9, 2.6)</td>
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<td>Age</td>
<td>72 (66, 77.5)</td>
<td>65 (57, 72)</td>
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<td>Ejection fraction</td>
<td>20 (17, 25)</td>
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<td>Quintiles 1–4 (lower risk)</td>
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<td>Mean age</td>
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<td>% of patients on β-blockers</td>
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<td>% of patients on ACEi or ARBs</td>
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<tr>
<td>% ischaemic heart failure</td>
<td>46</td>
<td>75</td>
</tr>
<tr>
<td>Quintile 5 (highest risk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age</td>
<td>72 (66, 77.5)</td>
<td>65 (57, 72)</td>
</tr>
<tr>
<td>Mean EF</td>
<td>25 (17, 25)</td>
<td>25 (20, 28)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>2.3 (1.9, 2.6)</td>
<td>1.1 (0.96, 1.3)</td>
</tr>
<tr>
<td>% of patients on β-blockers</td>
<td>75</td>
<td>46</td>
</tr>
<tr>
<td>% of patients on ACEi or ARBs</td>
<td>98</td>
<td>89</td>
</tr>
<tr>
<td>% ischaemic heart failure</td>
<td>46</td>
<td>75</td>
</tr>
</tbody>
</table>
Thus again the lifespan-gain per ICD implanted may be larger than calculated here.

**Study limitations**

We utilized data from multiple landmark ICD trials which have varying inclusion criteria. Some of these trials, particularly those of secondary prevention, are now over 10 years old and the standard of optimal medical therapy and revascularization decisions in the control arm will therefore be different to contemporary management. This may mean that the hazard ratio for sudden death prevention from an ICD may differ if such trials were performed using contemporary management in the control arm, although there is no evidence to suggest an attenuation of benefit from ICD implantation in patients with milder heart failure.

Post-trial survival was assessed using a Gompertz–Makeham function. This has been well validated as a descriptor of long-term survival patterns but in our study only provides a projection of potential benefit rather than direct observation. Other models including the DEALE method may be employed but may overestimate mortality over longer time horizons.\(^{37}\) It is unlikely that long-term survival data from ICD trials can be totally relied up to provide an unbiased estimate of lifespan-gain from ICD implantation as patients will cross over from control to active arms following completion of the trial. This artificially attenuates benefit, through equalization of therapy. Therefore, methods such as those we present may be a useful alternative approach to assess lifetime benefit.

We assessed lifespan-gain but did not assess quality-adjusted life years (QALYs) or other measures of health related quality of life. As the patients with the most to gain from device implantation were those with milder disease who usually have a numerically higher quality of life using such scoring systems,\(^{38}\) it is likely that the gain in the lower risk population would exceed that in the higher risk population by even more in QALY terms than in plain lifespan terms.
It should not be forgotten that some ICDs or leads can suffer recalls, which contribute additional cost to the healthcare system and inconvenience and worry to the patient. Although rates of requiring replacement of device or lead are low (2–3% of all ICD implants), any formal cost-effectiveness analysis should address this element. Routine end-of-life replacement of the ICD generator is also not without risk, including infection or haematoma in the pocket, or trauma or displacement of the lead. While the balance of these complications is different between first and replacement devices, the total rates of device-related complications are similar between initial and follow-up device replacement. The impact of these complications on lifespan-gain should therefore be accounted for using the data derived from the landmark trials.

**Conclusions**

Lifespan-gain from ICD implantation is highly dependent on the duration of analysis. Short follow-up gives the impression that higher risk patients have the most to gain but extending analyses to cover the patient’s whole lifetime suggests that patients at lower risk, especially when that risk is mainly of sudden cardiac death, have the most to gain from ICD implantation. Modern improvements in device programming may further increase this benefit.

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**Conflict of interest:** J.G.F.C. has received modest consultancy fees and/or honoraria from St Jude, Medtronic and Biotronik within the last 5 years. D.P.F. has received modest consultancy fees and/or honoraria from Medtronic within the last 5 years. C.L. was principal investigator of REVERSE, a clinical trial involving the use of ICDs.
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Thrombus trapped in patent foramen ovale

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A 63-year-old man was hospitalized with 2 days of increasing dyspnoea and presyncope. He had developed confusion, dysarthria, and a left-sided facial droop that morning. Three weeks previously the patient had suffered a urinary tract infection and had taken prolonged bed rest. His only back-ground was hypertension. Clinical assessment revealed tachycardia, sinus tachycardia, and a mild left-sided motor deficit. Laboratory testing revealed elevated high-sensitivity troponin (5122 ng/L), positive D dimer and elevated urea (20 mmol/L), and creatinine (420 µmol/L). Transoesophageal echocardiography (TOE) illustrated a mobile mass crossing the interatrial septum and present in both atria and ventricles. Doppler ultrasound revealed a right lower limb deep vein thrombosis (DVT).

Brain magnetic resonance imaging demonstrated multiple small strokes. Thrombophilia screening was negative.

He was diagnosed with a thrombus straddling a patent foramen ovale (PFO) causing coronary, pulmonary, renal, and cerebral embolism. The patient was heparinized and surgical thrombectomy was arranged for the subsequent day. However, preoperative TOE showed the thrombus was no longer present. The patient was transitioned to warfarin therapy. His dyspnoea, neurological signs, and renal function gradually improved. He remains well 1 month after discharge and is due for percutaneous PFO closure as soon as possible.

Thrombosis can be attempted if in extremis.

Supplementary material is available at European Heart Journal online.

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CARDIOVASCULAR FLASHLIGHT

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