Sudden cardiac death and implantable cardioverter defibrillators: two modern epidemics?

Demosthenes G. Katritsis1,2* and Mark E. Josephson3

1Athens Euroclinic, 9 Athanassiadou Street, Athens 11521, Greece; 2St Thomas’s Hospital, London, UK; and 3Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Received 19 October 2011; accepted after revision 30 December 2011; online publish-ahead-of-print 2 February 2012

Critical analysis of the existing evidence indicates that:

1. In patients with documented sustained ventricular arrhythmias and/or cardiac arrest, implantable cardioverter defibrillators (ICDs) confer a survival benefit. In several clinical settings this is rather transient, and might be lost when modern medical therapy including β-blockers is implemented.

2. In patients without sustained ventricular arrhythmias or cardiac arrest, ICDs confer a significant survival benefit only in high-risk patients with ischaemic cardiomyopathy and left ventricular ejection fraction of ≤35% due to a remote myocardial infarction.

3. Left ventricular ejection fraction alone is rather unlikely to be sufficient for effective sudden cardiac death risk prediction, due to low sensitivity and specificity.

4. The benefits of ICDs in the elderly as well as in women are not established.

5. With current prices, ICDs are probably cost-effective only when used in high-risk patients without associated comorbidities that limit the life expectancy to <10 years.

Recommendations by current guidelines may result in unnecessary overuse of ICD.

Keywords

Sudden cardiac death • Implantable cardioverter defibrillators • Primary prevention • Secondary prevention • Arrhythmic death

Sudden cardiac death: the problem

Sudden cardiac death (SCD) is usually defined as death of cardiac origin occurring within 1 h from the onset of symptoms. Its incidence approximates 300–350 000 in the USA (0.1–0.2% of the population annually) and annually increases as a function of advancing age, being 100-fold less in adolescents and adults <30 years (0.001%) of age than it is in adults >35 years of age.1 A similar incidence occurs probably in Europe.2,3 Approximately 50% of all cardiac deaths are sudden and this proportion remains the same despite the overall decrease in cardiovascular mortality the last decades. The proportion of all natural deaths due to SCD is 13%, whereas if a 24 h from onset of symptoms definition is used, it becomes 18.5%.3

Ventricular tachycardia (VT) or fibrillation was thought to be the most common cause of out-of-hospital cardiac arrest, accounting for approximately three-quarters of cases, the rest 25% caused by bradyarrhythmias or asystole.4–6 More recent studies suggest that the incidence of ventricular fibrillation (VF) or VT as the first recorded rhythm in out-of-hospital cardiac arrest has declined to perhaps even <30% in the past several decades.7–9 The risk of SCD in myocardial infarction (MI) survivors has also declined significantly over the past 30 years, presumably due to early reperfusion and optimal medical therapy practices.10 Recurrent ischaemia may not be significantly associated with SCD, whereas heart failure due to MI markedly increases the risk of SCD.10 Interestingly, acute ischaemia is an established cause of VF and polymorphic VT,11 whereas cardiac death in patients with nonischaemic dilated cardiomyopathy and functional class IV heart failure is more frequent.
due to bradyarrhythmia or electromechanical dissociation than due to ventricular tachyarrhythmias.12

Patients presenting with VF or sustained monomorphic VT are at a considerable risk of recurrence. Studies of out-of-hospital cardiac arrest survivors as well as of patients with sustained VT have shown that the actuarial incidence of sudden death at 2 years following the presenting arrhythmia varies from 15 to 30%. Up to 74% of patients with out-of-hospital cardiac arrest have VF recurrence during prehospital care and the time in VF is associated with worse outcome.13 Surprisingly, however, long-term survival among patients who have undergone rapid defibrillation after out-of-hospital cardiac arrest is similar to that among age-, sex-, and disease-matched patients who did not have out-of-hospital cardiac arrest, although only 40% of those survivors had received an implantable cardioverter defibrillator (ICD) after cardiac arrest.14

Thus, SCD represents a current epidemic that is not exclusively due to ventricular tachyarrhythmias. These observations may have important implications when considering both secondary and primary SCD prevention by implantable ICDs.

**Secondary sudden cardiac death prevention implantable cardioverter defibrillator trials**

The first trial to investigate the use of ICD as first choice treatment in survivors of cardiac arrest compared with antiarrhythmic drugs was the Dutch study.15 In a relatively small population of 60 patients, a strategy of ICD implantation as first-line treatment was shown to be preferable to medical therapy, conferring a significant reduction of a combined endpoint of main outcome events, including death, recurrent cardiac arrest, and cardiac transplantation. Three subsequent randomized clinical trials have evaluated the effect of ICD on overall mortality (Table 1). The Antiarrhythmic versus Implantable Defibrillator (AVID) trial was the largest and best-designed secondary prevention trial, and the only one to demonstrate statistically significant total mortality reduction with ICD therapy (39 ± 20% at 1 year).16 The AVID trial enrolled 1016 patients with VF or symptomatic sustained VT, i.e. VT with syncope or associated with left ventricular ejection fraction (LVEF) of ≤0.40 and symptoms of haemodynamic compromise. After an interim analysis, the trial was prematurely terminated due to a 9% absolute increase in death in the antiarrhythmic group (mainly amiodarone) (24.0 vs. 15.8%, P = 0.02), over a mean follow-up of 18 ± 12 months. Nevertheless, the magnitude of the benefit from ICD may have been influenced by the imbalance in β-blocker use between the two arms (38.1% in the ICD arm vs. 11.0% in the antiarrhythmic arm at 12 months of follow-up), lower incidence of congestive heart failure in the ICD group, and higher incidence of New York Heart Association (NYHA) functional class III heart failure in the antiarrhythmic group.17 Furthermore, early termination may have created bias in favour of reporting a larger treatment effect for ICD.

Similar to the AVID trial, the Canadian Implantable Defibrillator Study (CIDS) randomized patients with prior cardiac arrest, VF, symptomatic VT, or unmonitored syncope with inducible sustained VT to amiodarone or ICD.18 The Canadian Implantable Defibrillator Study recorded a 20% relative risk reduction in all-cause mortality and a 33% reduction in arrhythmic deaths; however, this reduction was not statistically significant. Similar to AVID trial patients in the ICD arm may have benefited from the more frequent use of β-blockers, even though the difference in β-blocker use was less pronounced than in the AVID trial.

A comparison between the survival benefit from ICDs and several antiarrhythmic agents (namely amiodarone, metoprolol, and propafenone) was undertaken by the Cardiac Arrest Study Hamburg (CASH) investigators in survivors of cardiac arrest secondary to documented sustained ventricular arrhythmias.19 Results from CASH showed a significant reduction in sudden death, but a non-significant reduction in all-cause mortality, in

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Inclusion criteria</th>
<th>Therapy</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVID</td>
<td>1016</td>
<td>VF or symptomatic sustained VT</td>
<td>ICD vs. antiarrhythmic</td>
<td>0.62a</td>
<td>0.43–0.82</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>CASH</td>
<td>288</td>
<td>Cardiac arrest survivors</td>
<td>ICD vs. antiarrhythmic</td>
<td>0.77b</td>
<td>0.42–1.11</td>
<td>0.081d</td>
</tr>
<tr>
<td>CIDS</td>
<td>659</td>
<td>Cardiac arrest, VF or symptomatic VT</td>
<td>ICD vs. amiodarone</td>
<td>0.82c</td>
<td>0.60–1.10</td>
<td>NS</td>
</tr>
<tr>
<td>DEBUT</td>
<td>86</td>
<td>Cardiac arrest survivors</td>
<td>ICD vs. β-blocker</td>
<td>NA</td>
<td>NA</td>
<td>0.02</td>
</tr>
<tr>
<td>DUTCH</td>
<td>60</td>
<td>Prior MI, cardiac arrest survivors</td>
<td>ICD as first choice vs.</td>
<td>0.27a</td>
<td>0.09–0.85</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*aOverall mortality.
*bSudden death.
*cUpper bound of 97.5% confidence interval.
*dOne-tailed.
*eDeath, recurrent cardiac arrest, cardiac transplantation. CI, confidence interval; NA, not available; NS, non-significant (P > 0.05).
the ICD group. The evidence from CASH is not conclusive due to several methodological issues. The study had a long recruitment time spanning from 1987, well before the endocardial lead era, to 1996, which may have allowed the influence of secular trends, such as changes in natural history driven by changes in ICD and conventional therapy. In fact, 56% of patients in the ICD arm received an epicardial system with a perioperative mortality of 5.4%. Furthermore, the mortality in the amiodarone/metoprolol group was much lower than anticipated during the study design, thus rendering CASH underpowered to detect a lack of difference in survival between the two groups.

Owing to the similarities in the studied patient populations and interventions evaluated, a pooled analysis of the previously mentioned trials was planned before their completion. In a follow-up period of 6 years, the prolongation of life in patients with ICD was 4.4 months and the advantages of ICD therapy seem to be present only in the first 3–4 years of follow-up. Furthermore, subgroup analysis revealed that in patients with an EF of >35% ICD therapy did not improve survival.

The skeptic, therefore, might interpret these results as suggesting that ICD confers a relatively small and rather transient survival benefit for secondary SCD prevention in patients with LVEF of 35–40%, and this might be lost when modern medical therapy including β-blockers is implemented.

**Primary sudden cardiac death prevention implantable cardioverter defibrillator trials**

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) and the Multicenter Unsustained Tachycardia Trial (MUSTT) targeted patients with ischaemi cardiomyopathy with reduced LVEF (≤40% in MUSTT and ≤35% in MADIT), a documented episode of asymptomatic non-sustained VT and inducible sustained VT during an electrophysiology study (EPS). These trials have demonstrated that prophylactic ICD therapy may improve survival in patients with increased risk of arrhythmic death (Table 2). In the MADIT, during a mean follow-up of 27 months, all-cause mortality was 15.8% in the ICD group, compared with 38.6% in the conventional therapy group, yielding a number needed to treat (NNT) of 4. The findings from the MADIT were corroborated by the larger MUSTT, in which 704 patients with coronary artery disease (CAD), LVEF of ≤0.40, asymptomatic non-sustained ventricular tachycardia, and a positive EPS were randomly assigned to antiarrhythmic treatment, with antiarrhythmic drugs or ICDs, or no antiarrhythmic treatment. As compared with the patients who received antiarrhythmic drugs, patients who received ICD had a significantly lower relative risk of arrhythmic events and of overall mortality. The results from the MADIT and MUSTT may not be directly applicable to current medical practice, as the low rates of medication administration are not in compliance with current treatment guidelines. For instance, in the MADIT only 8% of patients in the control group and 26% of patients in the ICD group were receiving β-blockers at 1 month of follow-up. Similarly, in the MUSTT only 29% of the electrophysiologically guided therapy group was on β-blockers. Data on patients who had no inducible arrhythmias, or had arrhythmias suppressible by procainamide, were not presented in the MADIT publication, and this, along with the disproportionate number of patients in the ICD arm who were receiving β-blockers, has drawn criticism of the MADIT findings.

Skepticism on the benefits of ICD therapy for primary prevention of sudden death was further compounded when the results of the Coronary Artery Bypass Graft Patch (CABG-Patch) Trial were reported shortly after the MADIT. In the CABG-Patch Trial, 900 patients with CAD, a reduced LVEF of ≤0.35, and abnormalities on signal-averaged ECGs, who were scheduled for elective CABG surgery were randomly assigned to prophylactic therapy with an ICD or to the control group. The study indicated no difference in mortality between the ICD and the control groups. All patients randomized in the CABG-Patch trial had successful revascularization surgery, which may have improved left ventricular function and reduced propensity to ventricular arrhythmias. These differences were reflected in overall mortality, which in the CABG-Patch trial was lower than in the MADIT or AVID.

In two subsequent trials, LVEF was used as the sole identifier of high-risk patients for SCD. In the MADIT II, 1232 patients with CAD and an EF of ≤30% were randomized to either an ICD or conventional medical therapy. At 20 months of follow-up, patients in the ICD group had a 5.6% lower mortality rate compared with patients with conventional medical therapy. The relatively small absolute risk reduction means that the NNT to prevent one sudden death in this population was ~18. Furthermore, 30% of the patients who received an ICD had heart failure NYHA of 3 or 4 and 18% of the patients had bundle branch block; thus, results may not be applicable to asymptomatic patients with just an ICD of ≤30%. Interestingly, an analysis of the MADIT II results, with all the caveats that a subgroup analysis entails, has shown that patients who have recently had a MI (<18 months) do not benefit from an ICD, as opposed to those with old infarcts. In two randomized trials that have addressed the issue of early ICD implantation within 30 days after MI, ICD conferred no mortality benefit. This is surprising, as the risk of SCD after MI is the highest during the first 30 days after the event. Although the risk of SCD was reduced by ICD therapy, this effect was offset by an increase in the risk of non-SCD, and this certainly requires further investigation as far as the benefits of ICD are considered. Last, but not least, a study on 1126 patients from the Marshfield Epidemiologic Study Area (MESA), detected a prevalence of 1.95/1000 of MADIT II eligible patients. Sudden cardiac death rate in the MESA was considerably lower than in MADIT II control patients (2.6 vs. 12%, respectively). The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) randomized 2521 patients with an LVEF of ≤0.35 and stable CHF (NYHA class II or III) due to ischaemic or non-ischaemic causes, to ICD, amiodarone, or placebo. Over a median follow-up of 45.5 months, ICDs were associated with a 23% reduction of the relative risk of death as compared with placebo. Patients with non-ischaemic cardiomyopathy comprised 48% of the SCD-HeFT population: 394 patients in the placebo group and 398 patients in the ICD group. Compared with placebo, ICDs were associated with a non-significant reduction of overall mortality (hazard ratio: 0.73, 97.5% confidence interval: 0.40–1.30).
0.50–1.07; \( P = 0.06 \). Actually, no single trial has demonstrated a statistically significant mortality benefit from ICD therapy in patients with dilated cardiomyopathy.

The Cardiomyopathy Trial, which was prematurely terminated because of a lower-than-expected incidence of all-cause mortality, did not detect a significant difference in survival between the ICD and the control groups. In the Amiodarone versus Implantable Defibrillator trial, the survival rates were similar at 1 and 3 years between the two treatment groups of amiodarone and ICD. The study, however, was underpowered to detect a statistically significant difference and was stopped prematurely due to statistical futility in reaching the primary endpoint of reduced total mortality.

Using a sample size of 458 patients, the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial evaluated the prophylactic use of ICDs in patients with nonischemic cardiomyopathy, an LVEF of \( \leq 35\% \), NYHA class I–III, and the presence of ambient arrhythmias. At a mean follow-up of 29.0 ± 14.4 months, patients with ICD had a reduced risk of sudden arrhythmic death (hazard ratio: 0.20; \( P = 0.006 \)) as compared with patients receiving only standard medical treatment; however, no statistically significant benefit in overall survival was observed. 35

In the DEFINITE population the observed mortality rates were notably low (14.1\% in the control group vs. 7.2\% in the ICD group), which could be attributed to the high usage of \( \beta \)-blockers and angiotensin-converting enzyme inhibitors as background therapy.

Only by combining the available clinical data, meta-analyses have estimated a 27–31% risk reduction in all-cause mortality with ICD therapy relative to medical therapy in patients with cardiomyopathy regardless of its cause. 36,37 Assuming an annual mortality of \( \sim 7\% \) according to data from these studies, a 31\% relative risk reduction results in an absolute reduction of \( \sim 2\% \) in all-cause mortality. Accordingly, 25 patients with nonischaemic cardiomyopathy would need to be treated to prevent one death at 2 years. 37

### Table 2 Major implantable cardioverter defibrillator trials for primary prevention of sudden cardiac death

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Inclusion criteria</th>
<th>Therapy</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMIOVIRT</td>
<td>103</td>
<td>NYHA I–III, DCM, asymptomatic NSVT, LVEF ( \leq 0.35 )</td>
<td>ICD vs. amiodarone</td>
<td>0.87</td>
<td>0.31–2.42</td>
<td>NS</td>
</tr>
<tr>
<td>CABG-Patch</td>
<td>900</td>
<td>Scheduled for CABG, LVEF ( \leq 0.35 ), positive SAECG</td>
<td>ICD vs. standard medical therapy</td>
<td>1.07</td>
<td>0.81–1.42</td>
<td>NS</td>
</tr>
<tr>
<td>CAT</td>
<td>104</td>
<td>NYHA II or III, DCM ( \leq 9 ) months, LVEF ( \leq 0.30 )</td>
<td>ICD vs. standard medical therapy</td>
<td>0.83</td>
<td>0.45–1.82</td>
<td>NS</td>
</tr>
<tr>
<td>DEFINITE</td>
<td>458</td>
<td>DCM, LVEF ( \leq 0.35 ), PVCs, or NSVT</td>
<td>ICD vs. standard medical therapy</td>
<td>0.65</td>
<td>0.40–1.06</td>
<td>0.08</td>
</tr>
<tr>
<td>DINAMIT</td>
<td>674</td>
<td>Recent MI, LVEF ( \leq 0.35 ), impaired cardiac autonomic function</td>
<td>ICD vs. standard medical therapy</td>
<td>1.08</td>
<td>0.76–1.55</td>
<td>NS</td>
</tr>
<tr>
<td>IRIS</td>
<td>898</td>
<td>Recent MI, LVEF ( &lt;0.40 ), or NSVT</td>
<td>ICD vs. standard medical therapy</td>
<td>1.04</td>
<td>0.81–1.35</td>
<td>NS</td>
</tr>
<tr>
<td>MADIT</td>
<td>196</td>
<td>NYHA I–III, prior MI, LVEF ( \leq 0.35 ), and positive EPS</td>
<td>ICD vs. standard medical therapy</td>
<td>0.46</td>
<td>0.26–0.82</td>
<td>0.009</td>
</tr>
<tr>
<td>MADIT-II</td>
<td>1232</td>
<td>Prior MI, LVEF ( \leq 0.30 )</td>
<td>ICD vs. standard medical therapy</td>
<td>0.69</td>
<td>0.51–0.93</td>
<td>0.016</td>
</tr>
<tr>
<td>MUSTT</td>
<td>351</td>
<td>CAD, LVEF ( \leq 0.40 ), NSVT, and positive EPS</td>
<td>ICD vs. conventional antiarrhythmic therapy</td>
<td>0.40</td>
<td>0.27–0.59</td>
<td>( &lt;0.001 )</td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td>1676</td>
<td>NYHA II or III, LVEF ( \leq 0.35 ), ischaemic and nonischaemic cardiomyopathy</td>
<td>ICD plus standard medical therapy vs. placebo plus standard medical therapy</td>
<td>0.77</td>
<td>0.62–0.96</td>
<td>0.007</td>
</tr>
</tbody>
</table>

1Overall mortality.
2Death from arrhythmia.
3Group randomized to EPS-guided therapy with antiarrhythmic medications or ICDs (out of 704 patients in total).
4Cardiac arrest or death from arrhythmia.
5ICD and placebo arms only (excluding amiodarone arm).
6CI, confidence interval; DCM, dilated cardiomyopathy; NSVT, non-sustained ventricular tachycardia; NS, non-significant (\( P > 0.05 \)); SAECG, signal-averaged electrocardiogram; PVC, premature ventricular complex.
It should also be noted that the survival benefit gained with an ICD varied between studies. In the MADIT II and SCD-HeFT, which used only LVEF as an inclusion criterion, the NNT to prevent one death was 18 and 15, respectively. Conversely, in the MADIT and MUSTT, which enrolled theoretically higher-risk patients, the NNT was only 4 and 3, respectively. As ICDs are by design effective in preventing sudden arrhythmic death, their ability to prolong overall survival is associated with the selection of a patient population with sufficiently high incidence of lethal arrhythmias and a sufficiently low incidence of death from all other causes combined.

Thus, according to existing evidence, in the modern reperfusion and medical therapy era, a significant survival benefit has been demonstrated only in high-risk patients with ischaemic cardiomyopathy and with an LVEF of ≤35% usually due to a remote MI. In dilated cardiomyopathy, ICD may reduce the risk of SCD but total mortality is not significantly affected.

**Left ventricular ejection fraction as the sole criterion for implantable cardioverter defibrillator therapy**

Currently, assessment of left ventricular systolic function by LVEF is used to identify high-risk patients. Left ventricular ejection fraction is simple to evaluate, and has been a qualifying criterion of all the primary prevention trials. Concerns have been raised that LVEF is unlikely to be sufficient for effective SCD risk prediction, because it lacks both sensitivity and specificity. In the community, less than a third of all SCD cases have severely decreased LVEF (≤0.35) that would have qualified them as candidates for ICD therapy. Conversely, a recent analysis of data from the MUSTT has shown that patients whose only risk factor is LVEF of ≤30%, and would qualify for ICD therapy according to current guidelines, may have a predicted 2-year arrhythmic death risk of ≤5%. In patients with heart failure, the association of mortality with LVEF is not dichotomous, but rather increases in a near linear manner for an LVEF decrease from ≤45 to ≤15%.

Analysis of the MADIT II patients also indicates that the benefit of the ICD in the low EF population may not be uniform. Patients were classified according to a risk score model that consisted of five clinical factors [NYHA class ≥II, age >70 years, blood urea nitrogen (BUN) >26 mg/dl, QRS duration >0.12 s, and atrial fibrillation]. Crude mortality rates in the conventional group were 8 and 28% in patients with 0 and ≥1 risk factors, respectively, and 43% in very high-risk patients (defined by BUN ≥50 mg/dl and/or serum creatinine ≥2.5 mg/dl). Defibrillator therapy was associated with a 49% reduction in the risk of death (P < 0.001) among patients with ≥1 risk factors, whereas no ICD benefit was identified in patients with 0 risk factors and in very high-risk patients. Therefore, depending on the presence of other risk factors, patients with LVEF from 30 to 40% may have total mortality and sudden death risks that exceed those of some patients with LVEF of ≤30%.

**The impact of age in implantable cardioverter defibrillator therapy**

In the young population (<25–40 years), the most common diagnoses that increase risk for SCD are hypertrophic cardiomyopathy, coronary artery anomalies of wrong sinus origin, myocarditis, arrhythmogenic right ventricular cardiomyopathy, and genetic channelopathies. When findings suggest cardiomyopathy or genetic channelopathy evaluation of family members is necessary. In the event of unexplained sudden death, examination of relatives has a high diagnostic yield, and even a molecular autopsy may be considered as part of the community forensic investigation to enhance prevention for other family members. Young patients with documented aborted sudden death in the context of diagnosed genetic channelopathy or cardiomyopathy deserve an ICD.

There are data to suggest that the mechanism of death is related to age in patients with prior MI or congestive heart failure, with the proportion of sudden death steadily decreasing with advancing age. As the survival benefit of ICD therapy is directly dependent on the effect of SCD, it is reasonable to expect that older patients would not gain the same benefit from prophylactic ICD therapy. Amendment of a recent meta-analysis of primary prevention trials in patients with severe left ventricular dysfunction showed that a smaller survival benefit was found in elderly patients that was not confirmed when MADIT II patients >70 years of age were excluded or when data from the DINAMIT and IRIS were included. Furthermore, in a pooled analysis of secondary prevention trials, ICD therapy was not associated with a reduction in all-cause and arrhythmic mortality, when patients >75 years of age were considered. Even though none of the primary or secondary prevention trials excluded elderly patients, elderly patients were underrepresented in these trials, which all had mean patients’ age of ≤65 years. This is in contrast to real-world practice, where ~69% of ICDs are implanted in patients >60 years of age, and >40% are implanted in patients with >70 years of age. In light of this evidence and given of the cost and the potential risks associated with ICD implantation, the benefits of ICD therapy in the elderly are not established. Current guidelines ignore this issue.

**Gender-specific differences in the survival benefit from implantable cardioverter defibrillators**

Subgroup analysis in several primary prevention trials revealed that the reduction of overall mortality achieved by ICD was more pronounced in male patients and it did not reach statistically significant levels in women. As women were underrepresented in these trials, comprising 15–30% of the study populations, these findings could be attributed to the lack of sufficient statistical power. To overcome this issue, several meta-analyses have assessed the effectiveness of ICDs for the primary prevention of sudden death in women, none of them showing a significant survival benefit from ICDs. Specifically, a lower rate of...
malignant arrhythmias was found in women, whereas overall mortality was similar in both sexes, thus suggesting significant differences in arrhythmic risk associated with severe left ventricular dysfunction. This finding is in line with previous observations supporting a lower risk of SCD in women, and lower propensity to ventricular tachyarrhythmias. Current guidelines ignore this issue.

Cost-effectiveness of implantable cardioverter defibrillators

As ICD implantation is associated with substantial up-front costs, the economic effects of ICD therapy need to be thoroughly evaluated. The cost-effectiveness of a particular treatment has been historically compared with the cost of renal dialysis, which approximated to $40 000 per patient per year in 2002. In the USA, treatments with incremental cost-effectiveness ratios (iCER calculated as the difference in discounted costs divided by the difference in discounted life expectancy) < $50 000 are usually considered acceptable, whereas those exceeding $100 000 are considered too expensive. A figure for Europe is difficult to ascertain, but the accepted limit is most probably €40 000 (€57 000). In the UK, the National Institute of Clinical Excellence is unlikely to reject a technology with an iCER per quality-adjusted life-year (QALY) < £15 000 ($24 000) and would require special reasons for supporting technologies with iCER > £30 000 ($48 000). In secondary prevention trials, the cost-effectiveness of ICD ranged from an iCER of $66 677 per life-year saved in the AVID trial to $213 514 in the CIDS. On the basis of lifetime projections, analysis of primary prevention trials in which a significant device-related mortality reduction has been observed, estimated that prophylactic ICD therapy was associated with iCERS per QALY ranging between $34 000 and $70 200. This analysis demonstrated that only as long as the mortality benefit associated with the prophylactic implantation of the ICD exceeds 7 years, the incremental cost of ICDs is < $100 000 per QALY gained. During the 3.5-year period of the MADIT II, the average survival gain for the defibrillator arm was 0.167 years per QALY gained. During the 3.5-year period of the MADIT II, the average survival gain for the defibrillator arm was 0.167 years per QALY gained. The existing evidence does not support recommendations for ICD therapy by current guidelines on several occasions. We may over treat certain patients in a way similar to that in unjustified coronary angioplasty in patients with stable, non-acute CAD. Implantable cardioverter-defibrillators are life-saving in high-risk populations that, however, cannot be defined simply by the LVEF. Serious comorbidities that limit the life expectancy of the patient, as well as gender and age should also be taken into account. The adoption of strict criteria for ICD implantation is a necessary step towards a rational use of our limited resources, particularly in an era of economic uncertainty and potentially anticipated financial crises.

Conflict of interest: none declared.

References


