Is there benefit in implanting defibrillators in patients with severe heart failure?

Tushar V Salukhe, Natalia I Briceno, Emily A Ferenczi, et al.

*Heart* 2010 96: 599-603
doi: 10.1136/hrt.2009.179515

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ABSTRACT

Background It is current practice to withhold implantable cardioverter defibrillators (ICD) from patients with severe heart failure because their deaths are judged as non-sudden and therefore assumed not to be preventable by ICD. If this was true, there should be a trend towards reduced preventability of deaths in the severe heart failure subgroups within existing randomised control ICD trials. We tested the prevailing assumption that patients with most severe heart failure would not benefit from ICD implantation.

Methods Six trials were identified enrolling 7873 patients, with 2734 patients randomly assigned to receive an ICD. Reduction in mortality in the ICD arm varied between 5.6% and 31%. All six trials provided data separated into higher and lower ejection fraction subgroups. Five trials provided data separated into higher and lower New York Heart Association (NYHA) class patient subgroups.

Results For patients subcategorised by NYHA class, there was a non-significant difference in z-score (p=0.922) between patients with mild to moderate and severe heart failure. Similarly, subgrouping by left ventricular ejection fraction (LVEF) revealed no significant difference between z-scores (p=0.170). Both observations suggest no attenuation of benefit of ICD implantation in patients with higher NYHA class or lower LVEF.

Conclusion There is no evidence within the existing trial populations of a tendency for the relative risk reduction to be smaller in patients with severe heart failure. The prevailing assumption that severe heart failure patients are less likely to benefit from ICD therapy must be questioned.

METHODS


Inclusion criteria All trials had to be RCT comparing ICD with other medical therapy. Second, all trials had to present outcome data subcategorised by either NYHA class or left ventricular ejection fraction (LVEF) or both. Important and landmark trials that did not present subcategorised data were excluded. Trials that used combined devices (cardiac resynchronisation therapy with ICD) were also excluded.

Statistical analysis For each subgroup (mild to moderate and severe) of heart failure and left ventricular impairment in each trial, we calculated, from the hazard ratio (HR; and its confidence interval) of the defibrillator arm, the logarithm of the HR and its standard error (SE). From this we calculated D (the difference between the estimates of the logarithm of HR of the mild to moderate and severe subgroups), and its SE (the square root of the sum of the squares of SE of the logarithm of HR of the mild to moderate and severe subgroups). We then calculated for each study the z-score for the difference in benefit between the two subgroups, by D/SE. This z-score represents the degree to which the severe heart failure subgroup experienced a greater mortality reduction than the mild to moderate heart failure subgroup. If there was no difference between the effects it would be expected to have a mean of 0 and a standard deviation of 1.
Heart failure and cardiomyopathy

Figure 1  Expected trend in relative risk reduction from implantable cardioverter defibrillator (ICD) implantation within ICD trial subpopulations of heart failure patients if the prevailing belief that severe heart failure patients would not benefit from ICD implantation is true.

RESULTS
Characteristics of included trials
Seven publications7–13 from six RCT7 8 10–15 were identified: five stratified the data into NYHA classes and LVEF8 10–15 and one stratified the data only by LVEF. All six trials compared ICD therapy with either conventional or anti-arrhythmic drug therapy and all showed a reduction or a trend to reduction in mortality in patients receiving the ICD (table 1).

HR for mild to moderate versus severe heart failure or left ventricular dysfunction patients in individual trials
Figures 2 and 3 show the HR for mild to moderate patients (higher LVEF and lower NYHA class) and severe (lower LVEF and higher NYHA class) patients who had ICD implanted in the landmark RCT identified in this study. HR with confidence intervals are presented in table 2.

All six trials showed data for effectiveness of defibrillator implantation for LVEF subgroups (figure 2). In five of the six individual trials, patients with a lower LVEF showed a trend to greater mortality reduction than patients with a higher LVEF.

Five trials presented results for the efficacy for NYHA subgroups (figure 3). In three out of the five (CASH, CIDS and DEFINITE), there was a trend to lower HR for death from ICD implantation in patients with higher NYHA classes, whereas in the remaining two trials (SCD-HeFT and MADIT II) the trend is in the opposite direction.

z-Scores for mild to moderate versus severe heart failure and left ventricular dysfunction
For patients categorised by NYHA class, there was a non-significant difference in z-score (p=0.922). Similarly, subgrouping by LVEF revealed no significant difference between z-scores (p=0.170). Both observations suggest no attenuation of benefit of ICD implantation in patients with higher NYHA class or lower LVEF.

DISCUSSION
In this study, we found there is no evidence within the existing trial populations of a tendency for the relative risk reduction of ICD implantation to be smaller in patients with severe heart failure or with lower LVEF.

Prevailing belief
It is widely believed that patients with severe heart failure are less likely to have their death prevented by defibrillator implantation. This belief arises from the observation that in severe heart failure, deaths are more often classified as non-sudden. However, there is a great potential for bias: a patient

Table 1  Description of trials included in this study

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Treatment groups</th>
<th>N</th>
<th>Mean follow-up period</th>
<th>Clinical setting</th>
<th>Reported outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCD-HeFT7</td>
<td>RCT</td>
<td>ICD versus amiodarone versus conventional therapy</td>
<td>2521</td>
<td>3.79 years</td>
<td>Patients with heart failure NYHA II or III and EF &lt;35%</td>
<td>7.2% Reduction in mortality in ICD arm (p=0.007). RRR from ICD 23%</td>
</tr>
<tr>
<td>MADIT II4 5</td>
<td>RCT</td>
<td>ICD versus conventional therapy</td>
<td>1232</td>
<td>1.67 years</td>
<td>Patients with recent MI (&lt;1 month) and EF &lt;30%</td>
<td>5.6% Reduction in mortality in ICD arm (p=0.007). RRR from ICD 31%</td>
</tr>
<tr>
<td>Multicenter Automated Defibrillator Implantation Trial II</td>
<td>RCT</td>
<td>ICD versus conventional therapy</td>
<td>1013</td>
<td>3 years</td>
<td>Survivors of VF/VT arrest and EF &lt;40%</td>
<td>31% Reduction in mortality in ICD arm (p=0.02). RRR from ICD 39.5%</td>
</tr>
<tr>
<td>AVID5</td>
<td>RCT</td>
<td>ICD versus antiarrhythmic drug therapy</td>
<td>1987</td>
<td>4.75 years</td>
<td>Survivors of VF/VT arrest</td>
<td>11.4% Reduction trend in mortality in ICD arm (p=NS). RRR from ICD 23%</td>
</tr>
<tr>
<td>CASH6</td>
<td>RCT</td>
<td>ICD versus antiarrhythmic drug therapy</td>
<td>659</td>
<td>5 years</td>
<td>Survivors of VF/VT arrest or unmonitored syncope</td>
<td>3.75% Reduction trend in mortality in ICD arm (p=NS). RRR from ICD 19.7%</td>
</tr>
<tr>
<td>Canadian Implantable Defibrillator Study</td>
<td>RCT</td>
<td>ICD versus amiodarone</td>
<td>458</td>
<td>2.42 years</td>
<td>Patients with dilated cardiomyopathy, EF &lt;36% and PVC or NSVT</td>
<td>6.2% Reduction trend in mortality in ICD arm (p=NS). RRR from ICD 35%</td>
</tr>
</tbody>
</table>

Trials that were not randomised or did not publish data in subgroups split by New York Heart Association (NYHA) class or ejection fraction (EF) were excluded.

ICD, implantable cardioverter defibrillator; MI, myocardial infarction; NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular ectopy; RCT, randomised controlled trial; RRR, relative risk reduction; VF, ventricular fibrillation; VT, ventricular tachycardia.
with NYHA class IV heart failure who dies is unlikely to be classified as a sudden death, unless a ventricular arrhythmia happens to have been monitored.

A variety of methods has been used to classify the mode of death as sudden or non-sudden, but all have the weakness that the presence of background symptoms will favour a classification of non-sudden death.14

Even with the unavoidable bias towards classifying more symptomatic patients’ deaths as non-sudden, the Seattle Heart Failure Model15 reported that the absolute rate of clinically sudden deaths increased with increasing heart failure severity. Because the numbers of deaths classified as non-sudden increased even faster with disease severity, the proportion classified as sudden fell with increasing disease severity.16 This means that if defibrillators were ineffective in preventing deaths that were to be pronounced non-sudden, then this ineffectiveness should manifest progressively as one moves across the spectrum from mild to severe heart failure. This was not observed in the present study.

**Unwarranted assumption**

It should not be assumed that patients with severe heart failure and a non-documented arrhythmia at death should be classed as having a non-arhythmic death. These deaths may in fact have been caused by a preventable arrhythmia. It should also not be assumed that if a greater proportion of deaths is classified as ‘non-arhythmic’ in severe heart failure patients, this automatically implies that the sudden arrhythmic death rate (preventable by ICD) is lower than in mild to moderate heart failure patients.

There is evidence for a greater propensity to arrhythmia in patients with severe heart failure.7 17–19 Böcker et al.17 using hypothetical death rates, showed that patients with NYHA class III heart failure benefited from ICD implantation. The authors showed that the benefit accrued was initially higher in patients with worse heart failure, although the benefit would most likely be sustained in patients with mild or no functional impairment. In their study population, patients in NYHA class I had a 22.5% rate of tachyarrhythmias that would have been fatal had the ICD not intervened. The rates in NYHA classes II and III were 22.4% and 26.9%, respectively. In the MADIT II trial, sudden cardiac death was twice as frequent in patients with NYHA class III heart failure than NYHA class II heart failure.5 Trappe et al.19 found that patients in NYHA class II, II–III and III received a higher mean number of shocks than patients in NYHA class I, and patients with severe heart failure had a significantly shorter interval between ICD implantation and the first shock.

**Clinical implications**

We have found that within current landmark trial data, there is no compelling evidence to suggest that patients with severe heart failure (as classified by NYHA class) or severe left ventricular dysfunction (as classified by ejection fraction) benefit less from defibrillator implantation. It is therefore unwarranted to assume that patients with severe heart failure cannot benefit from defibrillator implantation.

We do not suggest that a lower ejection fraction equates to more severe heart failure or higher NYHA class. However, the overall trends for both ejection fraction and NYHA class across the trials suggests that benefit from ICD implantation is at least maintained as one approaches the sicker end of both left ventricular function and symptom status in heart failure. The trials included in our analysis were a mixture of primary and

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**Figure 2** Hazard ratios as a result of implantable cardioverter defibrillator (ICD) implantation in patients with higher and lower left ventricular ejection fraction (LVEF).

**Figure 3** Hazard ratios as a result of implantable cardioverter defibrillator (ICD) implantation in patients with lower and higher New York Heart Association (NYHA) class.
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Table 2  HR and calculated z-scores for mild to moderate versus severe heart failure patients with an ICD

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>RCT</th>
<th>Mild to moderate heart failure or LV dysfunction</th>
<th>Severe heart failure or LV dysfunction</th>
<th>z-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR2 (CI)</td>
<td>Log HR2</td>
<td>SE</td>
<td>D</td>
</tr>
<tr>
<td>EF</td>
<td>1.08 (0.57 to 2.07)</td>
<td>0.033</td>
<td>0.143</td>
<td>0.137</td>
</tr>
<tr>
<td>EF</td>
<td>MADIT II</td>
<td>0.75 (0.375 to 1.25)</td>
<td>-0.125</td>
<td>0.133</td>
</tr>
<tr>
<td>EF</td>
<td>CAS H</td>
<td>0.685 (0.307 to 1.53)</td>
<td>-0.164</td>
<td>0.178</td>
</tr>
<tr>
<td>EF</td>
<td>AVID</td>
<td>0.857 (0.457 to 1.6)</td>
<td>-0.067</td>
<td>0.139</td>
</tr>
<tr>
<td>EF</td>
<td>CIDS</td>
<td>1.092 (0.554 to 2.0)</td>
<td>0.038</td>
<td>0.142</td>
</tr>
<tr>
<td>EF</td>
<td>DEFINITE</td>
<td>0.5 (0.3 to 1.667)</td>
<td>-0.301</td>
<td>0.171</td>
</tr>
<tr>
<td>NYHA</td>
<td>SCD-HeFT</td>
<td>0.54 (0.4 to 0.74)</td>
<td>-0.268</td>
<td>0.068</td>
</tr>
<tr>
<td>NYHA</td>
<td>MADIT II</td>
<td>0.638 (0.488 to 0.925)</td>
<td>-0.195</td>
<td>0.071</td>
</tr>
<tr>
<td>NYHA</td>
<td>CAS H</td>
<td>0.593 (0.284 to 1.354)</td>
<td>-0.225</td>
<td>0.181</td>
</tr>
<tr>
<td>NYHA</td>
<td>CIDS</td>
<td>0.809 (0.585 to 1.123)</td>
<td>-0.093</td>
<td>0.072</td>
</tr>
<tr>
<td>NYHA</td>
<td>DEFINITE</td>
<td>1.033 (0.5 to 2.167)</td>
<td>0.014</td>
<td>0.162</td>
</tr>
</tbody>
</table>

AVID, Anti-arrhythmics Versus Implantable Defibrillator; CASH, Cardiac Arrest Study Hamburg; CI, confidence interval; CIDS, Canadian Implantable Defibrillator Study; DEFINITE, Defibrillators in Non-Ischaemic Cardiomyopathy Treatment Evaluation; EF, ejection fraction; HR, heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LV, left ventricular; MADIT II, Multicenter Automated Defibrillator Implantation Trial II; NYHA, New York Heart Association; RCT, randomised controlled trial; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; SE, standard error.

Secondary prevention trials with a mixture of heart failure aetiologies. Interestingly, only the DEFINITE trial showed a reverse trend, with lower LVEF patients showing less mortality reduction. The DEFINITE trial enrolled the fewest patients and was not powered to detect subgroup trends. Unlike the other trials, DEFINITE enrolled patients with non-ischaemic cardiomyopathy exclusively. It is plausible that the myocardial substrate important for ventricular arrhythmia susceptibility in non-ischaemic patients is reflected less in LVEF compared with patients with ischaemic substrates—the predominant group in all the other trials.

Current guidelines in the USA and UK recommend that ICD should not be implanted in patients with NYHA class IV heart failure. While this stance may be financially justifiable in the absence of clinical trial data proving benefit in this group, the present study challenges the prevailing assumption that patients with severe heart failure will not benefit as much from an ICD. Our data highlight the need for future studies of the efficacy of ICD in patients with severe heart failure. This should include both RCT and studies looking specifically at the frequency of serious arrhythmias in patients in NYHA class IV heart failure.

In practice, as patients near the later stages of severe heart failure, the question of balance between quality and quantity of life afforded by an ICD comes to the fore. It is accepted that ICD can only prevent sudden arrhythmic death, and although it is arguable that almost all deaths are ultimately sudden, in the late stages of heart failure ICD therapy may only portend inevitable death from another cause within a shorter time frame. Clearly, this may not benefit the patient. The decision to turn off therapy or withhold ICD implantation is often a difficult one for the patient and the physician. Informed patient choice is paramount to counselling and the decision-making process. To this end, knowing the evidence base is critical. Much of this evidence already exists for patients of NYHA class I–III. Our study suggests that survival gain from ICD implantation may be at least maintained with higher NYHA class. We do not imply from our results that NYHA IV patients should automatically be considered for ICD implantation, but rather that this particular population should be similarly addressed through randomised controlled study.

Study limitations

This is a retrospective study of prospectively collected and published trial data. These landmark trials did not seek to enrol patients in NYHA class IV, and therefore we cannot determine for certain what the findings would be in that group. However, if that unstudied group of severe heart failure were to have no benefit, it would be expected that among the studied groups, the severe subgroups should show an attenuated benefit. This attenuation was not observed.

CONCLUSION

This study has shown that, within the groups studied, patients with severe heart failure benefit no less from ICD implantation than patients with mild to moderate heart failure. The assumption that the boundary of the studied groups is the boundary of the population who may benefit is therefore implausible, and as a result a large population of patients may be missing out on a potentially life-saving therapy. Further investigation is warranted into the true rate of fatal ventricular arrhythmia in NYHA IV patients, and their receptivity to benefit from defibrillator implantation, by prospective RCT.

Funding TVS is supported by the British Heart Foundation FS/09/018/26963.
Competing interests None.
Provenance and peer review Not commissioned; externally peer reviewed.

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