Role of the implantable defibrillator among elderly patients with a history of life-threatening ventricular arrhythmias

Jeffrey S. Healey1*, Al P. Hallstrom2, Karl-Heinz Kuck3, Girish Nair1, Eleanor P. Schron4, Robin S. Roberts5, Carlos A. Morillo1, and Stuart J. Connolly1

1 Population Health Research Institute, Hamilton Health Sciences—General Site, McMaster University, 237 Barton St. E amilton, Ontario, Hamilton, Canada L8L 2X2; 2 Department of Biostatistics, University of Washington, Seattle, Washington, USA; 3 Allgemeines Krankenhaus, St. Georg, Hamburg, Germany; 4 National Heart, Lung and Blood Institute, Bethesda, Maryland, USA; and 5 Henderson Research Group, McMaster University, Hamilton, Canada

Received 6 July 2006; revised 11 October 2006; accepted 24 November 2006; online publish-ahead-of-print 5 February 2007

See page 1665 for the editorial comment on this article (doi:10.1093/eurheartj/ehl549)

KEYWORDS
Implantable defibrillator; Ventricular tachycardia; Cardiac arrest; Mortality; Elderly

Aims The implantable defibrillator (ICD) reduces arrhythmic and all-cause mortality in patients with a history of life-threatening ventricular arrhythmias. However, its effectiveness in elderly patients is uncertain, given their competing risk of non-arrhythmic death.

Methods and results Individual patient data from all three secondary prevention trials comparing the ICD to amiodarone were pooled. Patients were divided into two groups based on age <75 and ≥75 years. Patient characteristics were reported and the effect of the ICD on all-cause mortality and arrhythmic death was determined for each group. The effect of age on these outcomes was determined by evaluating the interaction term (age-treatment). A total of 1866 patients were included in this analysis. Their mean age was 63.7 ± 10.4 years (intra-quartile range 58–71 years). There were 252 patients ≥75 years old (13.5% of total). Patients ≥75 years old had a similar left ventricular (LV) ejection fraction (EF) (32.6 ± 13.7 vs. 33.8 ± 14.9%, P = 0.20) and baseline prevalence of NYHA class 3 or 4 heart (12.3 vs. 11.8%, P = 0.79) failure as younger patients, but were less likely to have ventricular fibrillation as their presenting arrhythmia (39 vs. 53%, P = 0.0001). Over a mean follow-up of 2.3 years, older patients were more likely to die of non-arrhythmic death (8.74% per year vs. 3.96% per year, P = 0.001) and arrhythmic death (6.73% per year vs. 3.84% per year, P = 0.03). The ICD significantly reduced all-cause and arrhythmic death in patients <75 years old (all-cause death HR = 0.69, 95% CI: 0.56–0.85, P < 0.0001; arrhythmic death HR = 0.44, 95% CI: 0.32–0.62, P < 0.0001), but not in patients ≥75 years old (all-cause death HR = 1.06, 95% CI: 0.69–1.64, P = 0.79; arrhythmic death HR = 0.90, 95% CI: 0.42–1.95, P = 0.79). The interaction between age ≥75 and ICD use was of borderline significance in each case (P = 0.09 and P = 0.11, respectively).

Conclusion Elderly patients with a history of life-threatening ventricular arrhythmias have a high incidence of non-arrhythmic death. In these patients, the ICD may not afford the same survival advantage over amiodarone that is seen in younger patients. ICD therapy should not be withheld based on age alone; however, physicians should carefully consider the risk of non-arrhythmic death among elderly patients when selecting the appropriate therapy for an individual.

© The European Society of Cardiology 2007. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org

Introduction

Three randomized trials have compared the implantable defibrillator (ICD) to anti-arrhythmic medication for the treatment of patients with life-threatening ventricular arrhythmias.1–3 Together, they demonstrate a 28% reduction in all-cause mortality among patients receiving an ICD, when compared with amiodarone (95% CI: 0.60–0.87, P = 0.0006), which is primarily due to a 50% reduction in arrhythmic death (95% CI: 0.37–0.67, P < 0.0001).4 However, this benefit was not observed in all patient sub-groups. A pooled analysis of all three trials did not find a survival benefit from the ICD in patients with a left ventricular (LV) EF of >35%.4 Given the cost5 and potential complications1 of these devices, it is desirable to identify patients who are most likely to benefit.

Although none of the ICD trials excluded elderly patients,1–3 elderly patients were poorly represented in these trials, which all had a mean age of participants of <70 years.1–3 Therefore, the overall results of these trials may not be applicable to an
elderly population. The ICD reduces only arrhythmic death, thus its ability to reduce all-cause mortality depends on a relatively high frequency of arrhythmic death in the population treated. It also depends on a relatively low rate of non-arrhythmic death. The ratio of sudden death to all-cause death has been shown to fall steadily from 0.51 before age 50 to 0.26 after age 80,6 in patients with heart failure or following myocardial infarction. Thus, one would expect that elderly survivors of cardiac arrest may benefit less from the ICD than younger patients. This analysis was conducted to determine the effect of age on the benefits of the ICD in survivors of cardiac arrest.

Methods

The methods used to collect and combine the patient-level data from the three secondary prevention defibrillator trials1–3 have been previously described in detail.4 Patient-level data from the Anti-Arrhythmics vs. Implantable Defibrillators (AVID),2 Cardiac Arrest Study—Hamburg (CASH)3, and Canadian Implantable Defibrillator Study (CIDS)1 trials, for patients randomized to either an ICD or amiodarone, were collated into a master database, using pre-defined operational definitions for patient characteristics and outcomes.4 Using the pooled dataset, age ≥75 years was prospectively defined as representing elderly, prior to any age-specific data analyses. Patient characteristics were described for these two age groups, and survival curves constructed for all-cause mortality and arrhythmic death. Categorical variables were compared using Fisher’s exact test. The effect of the ICD on all-cause and arrhythmic mortality was expressed using the hazard ratio. Heterogeneity between trials for these outcomes was evaluated using the chi-squared test. The influence of age ≥75 on the size of the ICD treatment effect was evaluated using Cox proportional hazard modelling by determining the significance of the interaction term, when added to a model including both treatment allocation and age group and including data on both age groups. The suitability of the Cox model was assessed graphically and all analyses were stratified by the study of origin. Sensitivity analyses were conducted using different age cut-offs to define the elderly and the effect of age as a continuous variable was also evaluated. Throughout, a two-sided P-value of <0.05 was considered statistically significant; however, P-values were not adjusted for multiple comparisons.

Results

This analysis included a total of 1866 patients, who were randomized to receive an ICD or amiodarone. The mean age was 63.7 ± 10.4 years (intra-quartile range 58–71). There were 252 patients (13.5% of total) ≥75 years old. The AVID trial had a higher percentage of patients ≥75 years old than either the CIDS or CASH trials (18.1 vs. 9.4 vs. 3.1%, P = 0.0001). There were no significant differences in L V ejection fraction (EF), heart failure severity, history of myocardial infarction, or prior coronary bypass between the two age groups (Table 1). However, older patients were more likely to present with syncopal ventricular tachycardia and less likely to present with ventricular fibrillation (Figure 1A).

In patients <75 years old, the ICD significantly reduced both all-cause (HR = 0.69, 95% CI: 0.56–0.85, P < 0.0001) and arrhythmic death (HR = 0.44, 95% CI: 0.32–0.62, P < 0.0001) (Figure 1A and C). Neither benefit was clearly observed in the group of patients ≥75 years old (HR = 1.06, 95% CI: 0.69–1.64, P = 0.79, and HR = 0.90, 95% CI: 0.42–1.95, P = 0.79, respectively) (Figure 1B and D). Cox proportional hazard modelling demonstrated a borderline-significant interaction between age ≥75, and the effect of the ICD on both all-cause (P for interaction = 0.09) and arrhythmic death (P for interaction = 0.11). There was no significant heterogeneity between the individual trials for either all-cause mortality (P = 0.31) or arrhythmic death (P = 0.17).

Over a mean follow-up of 2.3 ± 1.9 years, the incidence of death from heart failure or non-cardiac causes was significantly higher among patients ≥75 years old; however, the rate of arrhythmic death was similar between the two groups (Table 2). This gives a ratio of arrhythmic death to all-cause mortality that is lower in patients ≥75 years old (Table 2). Within the first year after randomization, these differences in cause-specific mortality were even more significant, as elderly patients were more likely to die of non-cardiac causes (4.4 vs. 1.2%, P = 0.001) and heart failure (9.1 vs. 4.3%, P = 0.002), but not arrhythmic death (6.0 vs. 4.9%, P = 0.44). Sensitivity analyses were conducted, to explore the effect of age on arrhythmic and all-cause mortality. As one lowers the age cut-off that defines elderly, a greater reduction in arrhythmic and all-cause mortality is seen with the ICD, in the older age group. There is a statistically significant improvement in survival with the ICD among the elderly age group using a cut-off of >70 years old for all-cause mortality and >72 years old for arrhythmic mortality. If one examines age as a continuous variable, age does not influence the effect of the ICD on all-cause mortality (P = 0.38) or arrhythmic death (P = 0.71).

Discussion

Based on the pooled results of all secondary prevention ICD trials, there is a suggestion that elderly patients may derive less benefit from an ICD than younger patients, although this effect is not nominally statistically significant. The biological plausibility of this observation is supported by the marked increased incidence of non-arrhythmic mortality among elderly patients, often occurring during the first year after their ventricular arrhythmia. The increase in non-arrhythmic death in the elderly is due to an increase in both non-cardiac and heart failure mortality, and is consistent with prior observational reports indicating a lower proportional risk of arrhythmic death among the elderly.6 In fact, the rate of non-cardiac mortality in this pooled analysis

---

**Table 1** Baseline characteristics in patients: age <75 years vs. ≥75 years

<table>
<thead>
<tr>
<th>Age &lt;75 years</th>
<th>Age ≥75 years</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 1614)</td>
<td>(n = 252)</td>
<td></td>
</tr>
<tr>
<td>LV EF</td>
<td>33.8 ± 14.9%</td>
<td>32.6 ± 13.7%</td>
</tr>
<tr>
<td>NYHA 3 or 4</td>
<td>190 (11.8%)</td>
<td>31 (12.3%)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>1114 (69%)</td>
<td>169 (67%)</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>129 (8%)</td>
<td>30 (12%)</td>
</tr>
<tr>
<td>Presenting arrhythmia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VT</td>
<td>855 (53%)</td>
<td>98 (39%)</td>
</tr>
<tr>
<td>VT with syncope</td>
<td>242 (15%)</td>
<td>58 (23%)</td>
</tr>
<tr>
<td>VT</td>
<td>436 (27%)</td>
<td>81 (32%)</td>
</tr>
<tr>
<td>Other</td>
<td>81 (5%)</td>
<td>19 (6%)</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association; MI, myocardial infarction; CABG, coronary artery bypass grafting; VF, ventricular fibrillation; VT, ventricular tachycardia.
almost certainly underestimates the true rate, as patients with serious non-cardiac conditions were excluded from participating in these trials.\(^1\)

Several cohort studies have previously examined outcomes in elderly ICD recipients. The first report examined 769 patients, including 74 patients \(\geq75\) years, who received an ICD between 1983 and 1995, a period spanning the introduction of trans-venous systems.\(^7\) The investigators found an increased 4 year mortality among elderly recipients (43 vs. 22\%, \(P = 0.0001\)), which was due to an increased rate of non-arrhythmic, cardiac death.\(^7\) Elderly patients had similar rates of appropriate shocks (42 vs. 43\% at 4 years) compared to younger patients; despite the fact that 43\% of elderly patients had an epicardial implant, only 1 elderly patient died within the peri-operative period. This latter observation is consistent with the observation that elderly recipients of pacemakers and ICDs have similar complication rates as younger patients,\(^8\) except perhaps a slightly increased risk of lead perforation.\(^9\) In a more recent cohort study, 102 patients \(\geq70\) years old, who received an ICD between 1999 and 2003, were compared to 273 younger patients.\(^10\) Over a mean follow-up of \(26.5 \pm 18.1\) months, the investigators found similar mortality between groups (12.7 vs. 12.5\%), and similar rates of appropriate shocks (44 vs. 40\%).\(^10\) The more favourable outcomes among elderly patients in this later report may, as the authors suggest,\(^10\) reflect advances in the medical therapy of heart failure or may simply result from the lower age cut-off used to define the elderly. Three additional cohort studies, which included nearly 200 patients over the age of 75, also suggest equivalent survival among elderly ICD recipients;\(^11-13\) however, each of these cohort studies is small and susceptible to selection bias, as only ‘healthier’ elderly patients may have received ICDs.

The optimal treatment of elderly survivors of life-threatening ventricular arrhythmias must include careful consideration of their co-morbidities and the patients’ goals of therapy.\(^14,15\) For patients with co-morbidities, such as advanced heart failure, life-prolonging therapy with an ICD, may be less attractive than other therapies, such as cardiac resynchronization,\(^16\) that may also improve quality of life.\(^14\) Overall, in the present analysis, almost 20\% of elderly patients died within 1 year of their episode of life-threatening ventricular arrhythmia, and

### Table 2

<table>
<thead>
<tr>
<th>Mortality Rate (% per year)</th>
<th>Age (&lt;75) years</th>
<th>Age (\geq75) years</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmic death</td>
<td>3.84</td>
<td>6.73</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart failure death</td>
<td>3.96</td>
<td>8.74</td>
<td>0.001</td>
</tr>
<tr>
<td>Non-cardiac death</td>
<td>1.51</td>
<td>4.72</td>
<td>0.001</td>
</tr>
<tr>
<td>Non-arrhythmic death</td>
<td>5.47</td>
<td>13.46</td>
<td>0.001</td>
</tr>
<tr>
<td>All-cause death</td>
<td>9.31</td>
<td>20.19</td>
<td>0.001</td>
</tr>
<tr>
<td>Ratio of arrhythmic: all-cause death</td>
<td>0.41</td>
<td>0.33</td>
<td>(P)-value</td>
</tr>
</tbody>
</table>
three-quarters of these deaths were due to non-arrhythmic causes. Accordingly, particular attention needs to be given to the risk of non-arrhythmic death in the elderly when deciding on the optimal therapy for their arrhythmia.

Limitations of current analysis

The apparent reduction in the effectiveness of the ICD among elderly patients must be interpreted cautiously as there were only 252 elderly patients in this analysis, and thus limited statistical power to detect an interaction between age ≥75 years and the effectiveness of the ICD. As well, age ≥75 years was just one of many sub-groups analysed using this data-set, thus it should be appreciated that the results of this analysis are more susceptible to type-I error. Still, this analysis includes more elderly patients than the two large cohort studies combined,7,10 includes every elderly patient from all secondary prevention ICD trials, and is a randomized evaluation of the ICD in elderly patients. As a randomized controlled trial is the only proper way to address this question and further randomized trials in secondary prevention are unlikely, we are left to make important decisions based on this analysis and the results of cohort studies. Although the results of this analysis are not compelling enough to conclude that ICDs do not benefit elderly patients, they should be cause for caution. The excess of non-arrhythmic deaths among elderly patients in this study is clear, consistent with previous reports,6,7 and provides biological plausibility for a reduced effectiveness of ICDs in the elderly.7

The results of this analysis do not apply to the use of the ICD as primary prophylaxis against arrhythmic death. There is a greater opportunity for patient selection and referral bias in primary prevention, thus elderly patients referred for primary prophylaxis may be more likely to benefit from an ICD than elderly survivors of life-threatening ventricular arrhythmias.17 Indeed, patients from the MADIT-II trial, who where ≥75 years old (n = 204), experienced a 46% relative risk reduction in total mortality when randomized to receive an ICD (P = 0.04).18 However, sub-group analyses from the COMPANION19 and SCD-HeFT20 trials suggest a trend (statistically non-significant) towards a reduced benefit of the ICD in patients older than 65 years; perhaps a reflection of the increased prevalence of heart failure in these two trials. Progressive heart failure was the major cause of death among elderly patients in this analysis. ICDs that incorporate biventricular pacing reduce heart failure mortality16,19 in patients with severe LV dysfunction and a prolonged QRS duration, and the appropriate use of these devices could result in a more favourable impact on overall mortality in elderly patients.

Conclusions

Elderly patients with a history of life-threatening ventricular arrhythmias have a high incidence of non-arrhythmic death. In these patients, the ICD may not afford the same survival advantage over amiodarone that is seen in younger patients. ICD therapy should not be withheld based on age alone; however, physicians should carefully consider the risk of non-arrhythmic death among elderly patients when selecting the appropriate therapy for an individual.

Conflict of interest: J. S. H. is the recipient of a personnel grant from the Canadian Institutes of Health Research. The authors declare no conflicts.

References


