Predictors of early mortality in implantable cardioverter-defibrillator recipients

Kenneth M. Stein1*, Suneet Mittal2, F. Roosevelt Gilliam3, David M. Gilligan4, Qian Zhong5, Stacia Merkel Kraus6, and Timothy E. Meyer7

1Maurice and Corinne Greenberg Division of Cardiology, Department of Medicine, Weill Medical College of Cornell University, 520 East 70th Street, Starr-4, New York, NY 10021, USA; 2St Luke’s-Roosevelt Hospital Center, New York, NY, USA; 3Cardiology Associates of NE Arkansas, Jonesboro, AR, USA; 4Virginia Cardiovascular Specialists, Richmond, VA, USA; 5University of California, Los Angeles, Los Angeles, CA, USA; 6The Integra Group, Brooklyn Park, MN, USA; and 7Boston Scientific, St Paul, MN, USA

Received 7 November 2008; accepted after revision 9 February 2009; online publish-ahead-of-print 11 March 2009

Aims

Multiple trials have shown that implantable cardioverter defibrillators (ICDs) prolong survival in secondary and primary prevention populations. Nevertheless, in spite of the efficacy of these devices in terminating life-threatening arrhythmias, total mortality remains high.

Methods and results

We evaluated 1703 patients (mean age: 67 ± 12 years, 82% male) with conventional ICD indications, who were enrolled and followed between 2001 and 2004 at 128 US centres. Patients were followed for up to a year, and vital status was obtained for 1655 patients (97%, median follow-up: 377 days). There were 183 deaths within 1 year of ICD implantation (1-year mortality rate: 16%). Predictors of mortality included a history of atrial fibrillation (AF, \( P < 0.0001 \)), diabetes (\( P = 0.0001 \)), failure to use cholesterol-lowering medications (\( P < 0.001 \)), use of digitalis and derivatives (\( P < 0.0001 \)), use of diuretics (\( P < 0.0001 \)), low body mass index (BMI, \( P < 0.0001 \)), increasing age (\( P < 0.0001 \)), low left ventricular ejection fraction (\( P < 0.0001 \)), low activity hours (\( P < 0.0001 \)), elevated resting heart rate (\( P = 0.014 \)), low mean arterial pressure (MAP, \( P = 0.007 \)), and poor functional status (New York Heart Association class, \( P < 0.0001 \)). In multivariate modelling, AF (\( P \leq 0.001 \)), diabetes (\( P = 0.004 \)), BMI (\( P = 0.001 \)), MAP (\( P = 0.040 \)), and functional class (\( P = 0.006 \)) predicted mortality.

Conclusion

In this population undergoing ICD implantation, poor functional status, low MAP, diabetes, low BMI, and AF were strongly associated with death within a year.

Keywords

Implantable cardioverter defibrillators (ICDs) • Mortality • Risk stratification

Introduction

Multiple clinical trials have shown that automatic implantable cardioverter defibrillators (ICDs) reduce mortality in both secondary1–3 and primary4,5 prevention populations. Nevertheless, even with the use of ICDs, total mortality was high in these trials, primarily due to non-arrhythmic causes of death in this population. Improved understanding of the risk factors for mortality despite ICD implantation would be beneficial: it is possible that identifying high-risk patients would enable physicians to better target interventions that would enhance survival. It is also possible that some populations are at such high risk of non-arrhythmic death that ICD implantation is futile. To better understand the predictors of mortality following ICD implantation, we analysed 1-year mortality in patients enrolled in the Synergistic Effects of Risk Factors for Sudden Cardiac Death (SERF) Study: a large-scale, multi-centre, prospective study examining the effect of several risk factors commonly observed in ICD patients on mortality and spontaneous arrhythmias after device implantation for standard clinical indications. We are only reporting on the predictors of mortality following ICD implantation in this manuscript.

* Corresponding author. Tel: +1 212 746 2158, Fax: +1 212 746 6951, Email: kstein@mail.med.cornell.edu

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2009. For permissions please email: journals.permissions@oxfordjournals.org

The online version of this article has been published under an open access model. Users are entitled to use, reproduce, disseminate, or display the open access version of this article for non-commercial purposes provided that the original authorship is properly and fully attributed; the Journal, Learned Society and Oxford University Press are attributed as the original place of publication with correct citation details given; if an article is subsequently reproduced or disseminated not in its entirety but only in part or as a derivative work this must be clearly indicated. For commercial re-use, please contact journals.permissions@oxfordjournals.org.
Methods

The SERF Registry prospectively acquired data on 1703 patients undergoing initial ICD implantation for conventional indications at 128 US centers between the years 2001 and 2004. The patients received either a Guidant VENTAK® PRIZM™, VENTAK® PRIZM™ HE, or VENTAK® PRIZM™ 2 ICD (Guidant Corp., St Paul, MN, USA). Device programming was left to the discretion of the implanting physician. Patients were followed up to 1 year with scheduled device interrogations at 6-month intervals. One-year follow-up was actually 390

| Table 1 Baseline demographics and patient history of SERF study participants |
|-----------------------------|-------------------|-------------------|-------------------|-------------------|
| **Baseline demographics/history** | **Overall (n = 1655)** | **Survivors (n = 1472)** | **Non-survivors (n = 183)** | **χ²** |
| **Risk factor** | **n (%)** | **n (%)** | **n (%)** | **P-value** |
| **Age** | 66.81 ± 11.69 | 66.26 ± 11.74 | 71.23 ± 10.28 | <0.0001 |
| Age < 65 | 643 (39%) | 603 (41%) | 40 (22%) | |
| 65 ≤ age < 80 | 818 (49%) | 702 (48%) | 116 (63%) | |
| 80 ≤ age | 184 (11%) | 157 (11%) | 27 (15%) | |
| Unknown | 10 (<1%) | 10 (<1%) | 0 (0%) | |
| **Gender** | 0.383 | |
| Female | 296 (18%) | 259 (18%) | 37 (20%) | |
| Male | 1359 (82%) | 1213 (82%) | 146 (80%) | |
| **NYHA** | <0.0001 | |
| I | 310 (19%) | 296 (20%) | 14 (8%) | |
| II | 685 (41%) | 616 (42%) | 69 (38%) | |
| III | 399 (24%) | 329 (22%) | 70 (38%) | |
| IV | 37 (2%) | 24 (2%) | 13 (7%) | |
| Unknown | 224 (14%) | 207 (14%) | 17 (9%) | |
| **BMI** | <0.0001 | |
| BMI < 22 | 164 (10%) | 127 (9%) | 37 (20%) | |
| 22 ≤ BMI < 25 | 269 (16%) | 227 (15%) | 42 (23%) | |
| 25 ≤ BMI < 30 | 634 (38%) | 579 (39%) | 55 (30%) | |
| 30 ≤ BMI | 564 (34%) | 519 (35%) | 45 (25%) | |
| Unknown | 24 (1%) | 24 (1%) | 20 (1%) | |
| Rest HR < 80 | 1261 (76%) | 1136 (77%) | 125 (68%) | 0.021 |
| 80 ≤ rest HR | 375 (23%) | 322 (22%) | 53 (29%) | |
| Unknown | 19 (1%) | 19 (1%) | 14 (1%) | |
| **MAP** | 0.011 | |
| MAP ≤ 90 | 896 (54%) | 780 (53%) | 116 (63%) | |
| 90 < MAP | 737 (45%) | 671 (46%) | 66 (36%) | |
| Unknown | 22 (1%) | 21 (1%) | 1 (<1%) | |
| **LVEF** | 31.72 ± 12.38 | 32.16 ± 12.40 | 28.17 ± 11.72 | <0.0001 |
| LVEF < 20 | 172 (10%) | 137 (9%) | 35 (19%) | |
| 20 ≤ LVEF < 30 | 504 (30%) | 445 (30%) | 59 (32%) | |
| 30 ≤ LVEF < 40 | 545 (33%) | 489 (33%) | 56 (31%) | |
| 40 ≤ LVEF | 393 (24%) | 365 (25%) | 28 (15%) | |
| Unknown | 41 (2%) | 36 (2%) | 5 (3%) | |
| **Syncope** | 0.734 | |
| Prior MI | 203 (68%) | 192 (67%) | 11 (6%) | |
| Spontaneous non-sustained VT | 1120 (68%) | 987 (67%) | 133 (73%) | 0.132 |
| Atrial fibrillation | 433 (26%) | 358 (24%) | 75 (41%) | <0.0001 |
| Hypertension | 962 (58%) | 861 (58%) | 101 (55%) | 0.715 |
| Currently smoking | 394 (24%) | 353 (24%) | 41 (22%) | 0.643 |
| Diabetes | 508 (31%) | 429 (29%) | 79 (43%) | <0.0001 |
days (median: 377 days), as the clinical trial 12-month visit window consisted of 360 ± 30 days and will be referred to as such throughout this manuscript. In addition, vital status at 1 year was based on the device tracking of the manufacturer. This was confirmed when possible (1655/1703 cases) by case report forms and/or by regular query of the US National Death Index.

Patients of either sex who were older than 18 years of age were eligible for the study if they had a signed informed consent on file at the implanting centre prior to ICD implant and had experienced at least one or more of the following situations: survival of at least one episode of cardiac arrest (manifested by the loss of consciousness) due to ventricular tachyarrhythmia, recurrent, poorly tolerated sustained ventricular tachycardia (VT), prior myocardial infarction (MI), left ventricular ejection fraction (LVEF) of ≤35%, and (prior to publication of MADIT-II) a documented episode of non-sustained VT, with an inducible ventricular tachyarrhythmia.

Patients were excluded from consideration for enrolment if one or more of the following conditions were present: a unipolar pacemaker, ventricular tachyarrhythmias that potentially had a reversible cause, such as digitalis intoxication, electrolyte imbalance, hypoxia, or sepsis, or whose ventricular tachyarrhythmias had a transient cause, such as acute MI, electrocution, or drowning, receiving ICD replacements, life expectancy of less than 2 years due to other medical conditions, expectation of a heart transplant during the period of the study (~3–4 years), likely to receive a mechanical tricuspid valve during the course of the study, participation in other clinical investigations, women who are pregnant, and inability or refusal to complete the follow-up schedule at the study centre in which the patient was enrolled.

Patient demographics, aetiology of ventricular function, revascularization and arrhythmia history, medications, patient determined hours per week active, and clinical co-morbidities were assessed prior to device implantation. Data collected at the follow-up visits included medication changes, patient determined hours per week active, and clinical co-morbidities.

Continuous variables were grouped into clinically meaningful groups, and all grouped variables were summarized using frequencies and percentages. Baseline demographics, patient history, medications, and lab values were compared between survivors and non-survivors using χ² tests. Proportional hazards models were used to determine significant predictors of 1-year mortality. All significant univariate predictors were included in the multivariate proportional hazards model. One-year mortality was estimated using Kaplan–Meier methods. Analyses were performed using SAS V9.1, and P-values < 0.05 were considered significant.

**Table 2** Baseline medication/lab values of SERF study participants

| Medications/lab values                  | Overall (n = 1655) | Survivors (n = 1472) | Non-survivors (n = 183) | χ² | P-value |
|-----------------------------------------|--------------------|----------------------|-------------------------|----|---------|
| Risk factor                             | n (%)              | n (%)                | n (%)                   |    |         |
| Beta-blockers                           | 1122 (68%)         | 1007 (68%)           | 115 (63%)               | 0.128 |        |
| Cholesterol-lowering medications       | 894 (54%)          | 815 (55%)            | 79 (43%)                | 0.002 |        |
| Digitalis and derivatives               | 505 (31%)          | 428 (29%)            | 77 (42%)                | <0.001 |        |
| Anticoagulant                           | 756 (46%)          | 666 (45%)            | 90 (49%)                | 0.313 |        |
| Diuretic                                | 885 (53%)          | 752 (51%)            | 133 (73%)               | <0.0001 |        |
| Anti-arrhythmic medications            | 759 (46%)          | 675 (46%)            | 84 (46%)                | 0.991 |        |
| Hours/week physically active            |                    |                      |                         | 0.0001 |        |
| Act Hrs ≤ 5                            | 386 (23%)          | 325 (22%)            | 61 (33%)                |      |         |
| 5 < Act Hrs ≤ 15                       | 353 (21%)          | 308 (21%)            | 45 (25%)                |      |         |
| 15 < Act Hrs ≤ 35                      | 359 (22%)          | 324 (22%)            | 35 (19%)                |      |         |
| 35 < Act Hrs                           | 343 (21%)          | 324 (22%)            | 19 (10%)                |      |         |
| Unknown                                 | 214 (13%)          | 191 (13%)            | 23 (13%)                |      |         |
| LDL                                     |                    |                      |                         | 0.740 |        |
| LDL ≤ 130                               | 673 (41%)          | 615 (42%)            | 58 (32%)                |      |         |
| 130 < LDL                               | 115 (7%)           | 104 (7%)             | 11 (6%)                 |      |         |
| Unknown                                 | 867 (52%)          | 753 (51%)            | 114 (62%)               |      |         |
| HDL                                     |                    |                      |                         | 0.135 |        |
| HDL ≤ 40                                | 476 (29%)          | 427 (29%)            | 49 (27%)                |      |         |
| 40 < HDL                                | 332 (20%)          | 308 (21%)            | 24 (13%)                |      |         |
| Unknown                                 | 847 (51%)          | 737 (50%)            | 110 (60%)               |      |         |
(n = 1655). Overall medications and lab values are summarized in Table 2, as well as for survivors and non-survivors. Incomplete data exist for some variables in the tables such as lipid levels.

**Follow-up**

A total of 183 deaths occurred within 1 year of ICD implantation, resulting in an overall 1-year mortality rate of 16%. Among those patients in whom the cause of death was known, 17% were judged to have died from progressive heart failure. However, the cause of death was known in only 67% of patients. No difference in survival existed between primary and secondary prevention patients (P = 0.86). As shown in Table 3, a history of atrial fibrillation (AF, P < 0.0001), diabetes (P = 0.0001), the failure to use cholesterol-lowering medications (P < 0.001), use of digitalis and derivatives (P < 0.0001), use of diuretic medications (P < 0.0001), low body mass index (BMI, P < 0.0001), increasing age (P < 0.0001), low LVEF (P < 0.0001), low activity hours per week (P < 0.0001), elevated resting heart rate (P = 0.01), low mean arterial pressure (MAP, P = 0.007), and poor functional status as assessed by New York Heart Association (NYHA) class (P < 0.0001) all had a statistically significant association with 1-year mortality in univariate analyses. Risk factors not significantly associated with mortality included history of syncope, MI, spontaneous non-sustained VT, hypertension, smoking, beta-blocker use, anticoagulant use, anti-arrhythmic use, lipid levels, and gender.

In a multivariate model, evaluating all significant univariate predictors of mortality in the overall population such as AF (P < 0.001), diabetes (P = 0.004), BMI (P = 0.001), low MAP (P = 0.040), and poor NYHA functional class (P = 0.006) significantly predicted 1-year mortality. In the multivariate model, risk increased with increasing symptoms of CHF (increasing NYHA functional class). Risk was also increased for those with low or ‘normal’ BMI compared with those who were nominally ‘overweight’ or obese. Individuals with a BMI between 25 and 30 or ≥30 had significantly lower risks of death compared with those with a BMI <22. No difference in mortality existed between those with a BMI <22 and those with a BMI of 22–25, despite a trend towards reduced mortality in the 22–25 BMI group. Other subgroups in which risk was increased were patients classified as NYHA class III compared with I, class IV compared with I, patients

| Table 3 Univariate and multivariate predictors of death in the SERF study |
|---|---|---|---|---|---|---|
| Risk factor | Univariate model | Multivariate model |
| | Hazard ratio | 95% CI | P-value | Hazard ratio | 95% CI | P-value |
| Atrial fibrillation | 2.00 | 1.49, 2.69 | <0.0001 | 1.89 | 1.33 | <0.0001 |
| Diabetes | 1.78 | 1.33, 2.39 | 0.0001 | 1.68 | 1.18 | 0.004 |
| Cholesterol-lowering medications | 0.58 | 0.44, 0.78 | <0.001 | 0.74 | 0.52 | ns |
| Digitalis and derivatives | 1.83 | 1.37, 2.46 | <0.0001 | 1.11 | 0.76 | ns |
| Diuretic | 2.52 | 1.82, 3.49 | <0.0001 | 1.26 | 0.84 | ns |
| BMI 22 ≤ BMI < 25 vs. BMI < 22 | 0.69 | 0.44, 1.07 | ns | 0.71 | 0.42 | ns |
| BMI 25 ≤ BMI < 30 vs. BMI < 22 | 0.36 | 0.24, 0.54 | 0.0001 | 0.45 | 0.28 | 0.001 |
| BMI 30 ≤ BMI vs. BMI < 22 | 0.33 | 0.22, 0.51 | 0.0001 | 0.40 | 0.24 | <0.001 |
| Age 65 ≤ age < 80 vs. age < 65 | 2.21 | 1.54, 3.16 | <0.0001 | 1.57 | 1.04 | 0.034 |
| Age 80 ≤ age vs. age < 65 | 2.39 | 1.46, 3.89 | <0.001 | 1.56 | 0.87 | ns |
| LVEF | | | | | | |
| 20 ≤ LVEF < 30 vs. LVEF < 20 | 0.55 | 0.36, 0.84 | 0.005 | 0.62 | 0.38 | ns |
| 30 ≤ LVEF < 40 vs. LVEF < 20 | 0.46 | 0.30, 0.71 | <0.001 | 0.60 | 0.36 | ns |
| 40 ≤ LVEF vs. LVEF < 20 | 0.33 | 0.20, 0.55 | <0.0001 | 0.59 | 0.32 | ns |
| Hours/week physically active | | | | | | |
| 5 < Act Hrs ≤ 15 vs. Act Hrs ≤ 5 | 0.73 | 0.50, 1.07 | ns | 0.96 | 0.62 | ns |
| 15 < Act Hrs ≤ 35 vs. Act Hrs ≤ 5 | 0.54 | 0.36, 0.82 | 0.004 | 0.70 | 0.44 | ns |
| 35 < Act Hrs vs. Act Hrs ≤ 5 | 0.28 | 0.17, 0.47 | <0.0001 | 0.49 | 0.27 | 0.015 |
| Resting heart rate | | | | | | |
| Rest HR ≤ 80 vs. 80 < rest HR | 0.67 | 0.49, 0.92 | 0.014 | 0.78 | 0.54, 1.13 | ns |
| MAP | | | | | | |
| MAP ≤ 90 vs. 90 < MAP | 1.52 | 1.12, 2.05 | 0.007 | 1.46 | 1.02, 2.10 | 0.040 |
| NYHA | | | | | | |
| II vs. I | 2.26 | 1.27, 4.01 | <0.0001 | 1.50 | 0.79 | ns |
| III vs. I | 4.26 | 2.40, 7.57 | <0.0001 | 2.25 | 1.16 | 0.017 |
| IV vs. I | 12.00 | 5.64, 25.56 | <0.0001 | 3.94 | 1.61 | 0.003 |
between the ages of 65–80 years compared with those <65 years, and patients physically active ≤5 h/week compared with those physically active >35 h/week.

Discussion

The principal finding of this study is that in a broad population undergoing ICD implantation for routine clinical indications (VT/VF 52%, MADIT-I 41%, MADIT-II 7%), mortality is relatively high in the first year after the procedure. A history of AF, diabetes mellitus, low MAP, low BMI, and poor NYHA functional status are independent predictors of death within a year after ICD implantation.

The observed 1-year mortality rate of 16% in the present study is substantially higher than that observed in secondary prevention trials (AVID: 11%, CIDS: 9%, and CASH: 8%). Similarly, mortality was higher than observed in primary prevention trials (MADIT-II: 9% and SCD-HeFT: 7%). Importantly, compared with these studies, the patients in the SERF study seemed to be on average older, on medications such as anti-arrhythmics and anticoagulant therapy, and a larger percentage with a history of AF, VT, and/or syncope. It is very likely that this may represent the decision in general practice to implant ICDs in ‘sicker’ patients who would not have been enrolled in clinical trials either due to explicit exclusion criteria (e.g. exclusion of class IV patients in SCD-HeFT) or due to ‘recruitment’ bias. It may also reflect the possibility that participation in clinical trials may, and in of itself, lead to improved outcomes (‘participation effect’). These differences highlight the difficulty in extrapolating the results of randomized clinical trials of ICDs into general clinical practice.

These data are, however, consistent with data from a previous retrospective study of patients undergoing ICD implantation (mainly for a secondary prevention indication) at a single centre. As in our patients, advancing age, the presence of AF, and poor NYHA functional class were predictors of early mortality, despite ICD implantation. Baseline renal insufficiency was also shown to be a potent predictor of outcome. However, we do not have data regarding renal function available to analyse in the current population as the relationship between renal insufficiency and mortality was not known at the time this study was designed. The data are also consistent with those from a large registry of ICD recipients in Ontario, Canada, in which advancing age, congestive heart failure, and diabetes were all associated with an adverse outcome. Moreover, data from a small retrospective study of patients undergoing implantation due to a history of VT or VF by Schernthaner et al. confirm the associations between mortality and low BMI, poor functional class, and AF following ICD implant reported in our study.

The adverse prognosis associated with AF in patients with structural heart disease is well recognized. The increased mortality is likely multifactorial, and that increases in heart failure, stroke, and drug toxicity may play a role. Similarly, the relationship between mortality and functional status among patients with congestive heart failure is well recognized. The relationship between BMI and non-arrhythmic mortality in congestive heart failure is less intuitive. Indeed, it seems paradoxical that overweight or ‘obese’ patients have better survival than do patients who are ‘underweight’ or normal. This ‘obesity paradox’, also referred to as the ‘reverse epidemiology’ of CHF, is due to the association of increasing levels of obesity, cholesterol, and blood pressure with better outcomes in CHF. The ‘obesity paradox’ concept is clinically relevant because obese patients with established CHF may be advised not to lose weight, however the obesity itself may have detrimental health effects. Interestingly, clinical criteria commonly used to establish CHF have not been validated in obese individuals, in whom dyspnea, oedema, and basilar pulmonary crepitations may not necessarily reflect the presence of true CHF, possibly explaining the better survival in higher BMI patients, as they may, in fact, have been healthier. However, whether the paradox actually exists or if in fact a U-shaped HF survival curve similar to that established from the NHANES I, II, and III data sets is apparent when accounting for more severely obese individuals is unknown. Our data in newly implanted ICD patients indicate that the obesity paradox does exist in this patient population and that obesity is associated with better survival.

Evidence suggests that diabetic patients derive a similar benefit from ICD therapy compared with non-diabetic patients. However, diabetic patients treated conventionally (without ICDs) tend to be much sicker and have a much higher mortality rate than non-diabetics treated conventionally, presumably due to more co-morbidities. Thus, it is not surprising that diabetes is associated with an increased mortality in this patient population. The presence of low systemic arterial pressure has been shown to be associated with a poor prognosis in patients with CHF. Reduction in non-arrhythmic mortality in ICD recipients would better able to target interventions that would enhance survival. It is also worth noting those variables that were not associated with mortality. There may be a perception that the elderly and those with the most severe left ventricular dysfunction are at particularly high risk of non-arrhythmic mortality after ICD implantation. Perhaps, as a result, elderly cardiac arrest survivors are less likely to be treated with ICD therapy than younger patients, independent of co-morbidities. In the present population, both age and LVEF were univariate predictors of risk. However, in multivariate modelling, neither variables predicted outcome independent of confounding factors. This supports data from clinical trials, showing that elderly patients derive the same benefit from prophylactic ICD implantation as younger patients. Likewise, there was no difference in outcomes according to whether the ICD was implanted for a primary or secondary prevention indication.

Better understanding of the factors associated with mortality, despite ICD implantation, is important in several respects. First, by better identifying high-risk patients, physicians might be better able to target interventions that would enhance survival. Reduction in non-arrhythmic mortality in ICD recipients would improve the survival advantage associated with ICD implantation and may improve the cost-effectiveness of device therapy. It is also possible that some populations exist at such high risk of non-arrhythmic death and that ICD implantation is futile. For example, although prospective validation is required, the multivariate
analysis suggests that patients with the combination of poor functional status, low MAP, diabetes, low BMI, and AF are at such high risk of non-arrhythmic mortality that prophylactic ICD implantation ought not to be considered. In addition, understanding which patients are at low risk of non-arrhythmic mortality may provide further impetus for ICD implantation in these patients when indicated for primary prevention. Patients with only one or two of the above risk factors still have reasonable survival, and the mere presence of one or two of these risk factors ought not to be considered a contraindication to device implantation.

Our results have several important limitations. During the era in which patients were enrolled into this study, electrophysiological testing was routinely used for risk stratification prior to prophylactic ICD implantation. Thus, the majority of ‘primary prevention’ patients underwent implantation according to a ‘MADIT-I’ indication and not a ‘MADIT-II’ indication. Importantly, 93% of the patients studied thus had arrhythmic histories that may indicate aicker population. These results therefore may not apply to a population selected for ICD implantation using more liberal criteria. Another important limitation is that QRS duration was not collected in this study, and the QRS duration has been shown to be predictive of VT/VF in a predominantly secondary prevention trial. However, QRS duration was not shown to be a predictor of mortality in patients with ICDs in a previous paper.

Limited data are available regarding specific causes of death in this population as roughly one-third of the deaths were of unknown causes. However,~17% of deaths were due to pump failure.

Conflict of interest: K.M.S.: Speaking honoraria (Boston Scientific, Medtronic, St.Jude Medical), Advisory Boards (Boston Scientific, Medtronic); S.M.: Consultant (Biotronik, Lifewatch), Fellowship support (Boston Scientific, Medtronic), Speaking honoraria (Boston Scientific, Medtronic, St. Jude Medical); F.R.G.: Consultant (Boston Scientific), Speaking honoraria (Boston Scientific, Medtronic, St. Jude Medical, Phillips Medical), Advisory boards (Boston Scientific), Research funding (Boston Scientific); D.M.G.: Speaking honoraria (Boston Scientific, Medtronic); Q.Z.: Paid intern (Boston Scientific); S.M.K.: Consultant (Boston Scientific); T.E.M.: Employee (Boston Scientific).

Funding
This study was supported in full by Boston Scientific Corporation. Funding to pay the Open Access publication charges for this article was provided by Boston Scientific Corporation.

References
1. The Antiarrhythmics Versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997; 337:1576–83.
2. Connolly SJ, Gent M, Roberts RS, Dorian P, Roy D, Sheldon RS et al. Canadian Implantable Defibrillator Study (CIDS): a randomized trial of the implantable cardioverter-defibrillator against amiodarone. Circulation 2000;101:1297–302.
3. Kuck KH, Capponi A, Rebeiz E, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). Circulation 2000;102:748–54.
4. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS et al. The Multicenter Automatic Defibrillation Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial dysfunction and reduced ejection fraction. N Engl J Med 2002;346:877–83.
5. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R et al. for the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–37.
6. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. Lancet 2004;363:263–70.
7. Davis S, Wright PW, Schulman SF, Hill LD, Pinkman RD, Johnson LP et al. Participi-
ants in prospective, randomized clinical trials for resected non-small cell lung cancer have improved survival compared with nonparticipants in such trials. Cancer 1985;56:1710–8.
8. Parkash R, Stevenson WG, Epstein LM, Maisel WH. Predicting early mortality after implantable defibrillator implantation: a clinical risk score for optimal patient selection. Am Heart J 2006;151:397–403.
9. Lee DS, Tu V, Austin PC, Dorian P, Yee R, Chong A et al. Effect of cardiac and noncardiac conditions on survival after defibrillator implantation. J Am Coll Cardiol 2007;49:408–15.
10. Scherf MM, Marz M, Strohmer B. Lower body mass index and atrial fibrillation as independent predictors for mortality in patients with implantable cardioverter-defibrillator. Gastroenterology 2007;133:59–67.
11. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. N Engl J Med 1982;306:1018–22.
12. Benigni RJ, Wolf PA, D’Agostino RB, Silbershatz H, Kannel WB. Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946–52.
13. Bigger JT Jr. Epidemiological and mechanistic studies of atrial fibrillation as a basis for treatment strategies. Circulation 1998;98:943–5.
14. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG et al. American College of Cardiology: American Heart Association Task Force on Practice Guidelines. American College of Chest Physicians; International Society for Heart and Lung Transplantation; Heart Rhythm Society ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2005;46:1116–43.
15. Ahmed A. A propensity matched study of New York Heart association class and natural history end points in heart failure. Am J Cardiol 2007;99:549–53.
16. Mostard A, Cost B, Hoes AW, de Bruin MC, Deckers JW, Hofman A et al. The prognosis of heart failure in the general population: the Rotterdam Study. Eur Heart J 2002;23:1318–27.
17. Horwich TB, Fonarow GC, Hamilton MA, MacLelland WR, Woo MA, Tilisch JK. The relationship between obesity and mortality in patients with heart failure. J Am Coll Cardiol 2005;46:789–95.
18. Kenchaiah S, Pencock SJ, Wang D, Finn PV, Zornoff LM, Skali H et al., for the CHARM Investigators. Body mass index and prognosis in patients with chronic heart failure: insights from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM) Program. Circulation 2007;116:627–36.
19. Lissim LW, Gauri AJ, Froelicher VF, Ghayoumi A, Myers J, Giacommini J. The prog-
nostic value of body mass index and standard exercise testing in male veterans with congestive heart failure. J Card Fail 2002;8:206–15.
20. Davos CH, Doehner W, Rauchhaus M, Cicoira M, Francis DP, Coats AJS et al. Body mass and survival in patients with chronic heart failure without cachexia: the importance of obesity. J Card Fail 2003;9:29–35.
21. Lavi CJ, Osman AF, Milani RV, Mehra MR. Body composition and prognosis in chronic systolic heart failure: the obesity paradox. Am J Cardiol 2003;91:891–4.
22. Curtis JP, Selzer JG, Wang Y, Rathore SS, Jovin IS, Jadavji FB et al. The obesity paradox: body mass index and outcomes in patients with heart failure. Arch Intern Med 2005;165:55–61.
23. Gustafsson F, Kragelund CB, Torp-Pedersen C, Seibaek M, Burchardt H, Akkan D et al., DIAMOND Study Group. Effect of obesity and being overweight on long-term mortality in congestive heart failure: influence of left ventricular systolic function. Eur Heart J 2004;25:268–64.
24. Bozkurt B, Deswal A. Obesity as a prognostic factor in chronic symptomatic heart failure. Am J Cardiol 2005;95:1223–9.
25. Kalantar-Zadeh K, Block G, Horwich T, Fonarow GC. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. J Am Coll Cardiol 2004;43:1439–44.
26. Habbu A, Lakkis MN, Hisham D. The obesity paradox: fact or fiction? Am J Cardiol 2006;98:944–8.
27. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. JAMA 1989;261:884–8.
28. Sahebjami H, Gartside PS. Pulmonary function in obese subjects with a normal FEV1/FVC. Chest 1996;110:1425–9.
29. Caruana L, Petrie MC, Davie AP, McMurray JJV. Do patients with suspected heart failure and preserved left ventricular systolic function suffer from ‘diastolic heart failure’ or from misdiagnosis? A prospective descriptive study. BMJ 2000;321:215–8.
30. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. JAMA 2005;293:1861–7.
31. Wittenberg SM, Cook JR, Hall WJ, McNitt S, Zareba W, Moss AJ. Multicenter Automatic Defibrillator Implantation Trial. Comparison of efficacy of implanted cardioverter-defibrillator in patients with versus without diabetes mellitus. Am J Cardiol 2005;96:417–9.
32. Cowburn PJ, Cleland JG, Coats AJ, Komajda M. Risk stratification in chronic heart failure. Eur Heart J 1998;19:676–710.
33. Voigt A, Ezzeddine R, Barrington W, Obiaha-Ngwu O, Ganz L, London B et al. Utilization of implantable cardioverter-defibrillators in survivors of cardiac arrest in the United States from 1996 to 2001. J Am Coll Cardiol 2004;44:855–8.
34. Huang DT, Sesselberg HW, McNitt S, Noyes K, Andrews ML, Hall WJ et al., for the MADIT-II Research Group. Improved survival associated with prophylactic implantable defibrillators in elderly patients with prior myocardial infarction and depressed ventricular function: a MADIT-II substudy. J Cardiovasc Electrophysiol 2007;18:833–8.
35. Passman R, Kadish A. Sudden death prevention with implantable devices. Circulation 2007;115:561–71.
36. Klein G, Lissel C, Fuchs AC, Gardiwal A, Oswald H, Desousa M et al. Predictors of VT/VF-occurrence in ICD patients: results from the PROFIT-Study. Europace 2006;8:618–24.