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Predictors of early mortality in implantable cardioverter-defibrillator recipients

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Aims Multiple trials have shown that implantable cardioverter defibrillators (ICDs) prolong survival in secondary and primary prevention populations. However, 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 secondary[1–3] and primary[4,5] 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.

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Table 1 Baseline demographics and patient history of SERF study participants

Baseline demographics/history				
Risk factor	**Overall (n = 1655) n (%)**	**Survivors (n = 1472) n (%)**	**Non-survivors (n = 183) n (%)**	**χ^2 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%)	
Resting heart rate				0.021
Rest HR ≤80	1261 (76%)	1136 (77%)	125 (68%)	
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	571 (35%)	506 (34%)	65 (36%)	0.734
Prior MI	1195 (72%)	1066 (72%)	129 (70%)	0.564
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

Methods

The SERF Registry prospectively acquired data on 1703 patients undergoing initial ICD implantation for conventional indications at 128 US centres between the years 2001and 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

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 χ^2 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.

Results

Demographics

We evaluated 1703 patients (mean age: 67 ± 12 years, 82% male, LVEF: 32 ± 12%) with conventional ICD indications. Patients were followed for up to a year, and vital status was obtained for 1655 patients (97%, median follow-up: 377 days). Slightly more than half of the population (52%) underwent ICD implant for secondary prevention [VT/ventricular fibrillation (VF)/cardiac arrest], whereas the remainder were implanted for primary prophylaxis (largely a MADIT-1 indication, representing 41% of the implant population). Baseline demographics and patient history are summarized in *Table 1* for all patients where 1-year mortality status was available

Table 2 Baseline medication/lab values of SERF study participants

Medications/lab values				
Risk factor	**Overall (*n* = 1655)** *n* (%)	**Survivors (*n* = 1472)** *n* (%)	**Non-survivors (*n* = 183)** *n* (%)	χ^2 ***P*-value**
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	<0.001
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			<0.0001			0.001
22 ≤ BMI < 25 vs. BMI < 22	0.69	0.44, 1.07	ns	0.71	0.42	ns
25 ≤ BMI < 30 vs. BMI < 22	0.36	0.24, 0.54	0.0001	0.45	0.28	0.001
30 ≤ BMI vs. BMI < 22	0.33	0.22, 0.51	0.0001	0.40	0.24	<0.001
Age			<0.0001			ns
65 ≤ age < 80 vs. age < 65	2.21	1.54, 3.16	<0.0001	1.57	1.04	0.034
80 ≤ age vs. age < 65	2.39	1.46, 3.89	<0.001	1.56	0.87	ns
LVEF			<0.0001			ns
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			<0.0001			ns
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			<0.0001			0.006
II vs. I	2.26	1.27, 4.01	0.006	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%,[1] CIDS: 9%,[2] and CASH: 8%[3]). Similarly, mortality was higher than observed in primary prevention trials (MADIT-II: 9%[4] and SCD-HeFT: 7%[5]). 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[5]) or due to 'recruitment' bias.[6] It may also reflect the possibility that participation in clinical trials may, in and of itself, lead to improved outcomes ('participation effect').[7] 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.[8] 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.[9] Moreover, data from a small retrospective study of patients undergoing implantation due to a history of VT or VF by Schernthaner *et al.*[10] 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.[11,12] The increased mortality is likely multifactorial, and that increases in heart failure, stroke, and drug toxicity may play a role.[13] Similarly, the relationship between mortality and functional status among patients with congestive heart failure is well recognized.[14,15] 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.[16–24] 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.[25] 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.[26] Interestingly, clinical criteria commonly used to establish CHF have not been validated in obese individuals, in whom dyspnoea, oedema, and basilar pulmonary crepitations may not necessarily reflect the presence of true CHF,[27–29] 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[30] 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.[31] 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.[32] 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.[33] Although low arterial pressure may limit the use of beta-blockers, no difference in beta-blockade was evident between survivors and non-survivors.[33] Importantly, one possible explanation for the observation that lower BMI individuals had a poorer prognosis than overweight or obese patients in this study may be that the higher blood pressure in these groups allows them to better tolerate adequate doses of optimal pharmacological treatment.[10]

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.[34] 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.[35] 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.[34] 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 a sicker population. These results therefore may not apply to a patient 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.[36] However, QRS duration was not shown to be a predictor of mortality in patients with ICDs in a previous paper.[10] 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).

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