Journal of the American College of Cardiology Vol. 49, No. 23, 2007

Published by Elsevier Inc.
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.02.058

Effect of Cardiac and Noncardiac Conditions on Survival After Defibrillator Implantation

Douglas S. Lee, MD, PHD,*†# Jack V. Tu, MD, PHD,*‡# Peter C. Austin, PHD,*#
Paul Dorian, MD, MSC,§# Raymond Yee, MD,‖ Alice Chong, BSC,* David A. Alter, MD, PHD,*‡#
Andreas Laupacis, MD, MSC*§#

Toronto and London, Canada

Objectives We sought to examine outcomes in recipients of implantable cardioverter-defibrillators (ICDs) and the effect of age, gender, and comorbidities on survival.

Background Age, gender, and comorbidities may significantly affect outcomes in ICD recipients.

Methods We examined factors associated with mortality in 2,467 ICD recipients in Ontario, Canada, using a province-wide database. Comorbidities were identified retrospectively by examining all diagnosis codes within the 3 years before implant.

Results Mean ages at ICD implant were 63.2 ± 12.5 years (1,944 men) and 59.8 ± 15.9 years (523 women). Mortality rates at one and 2 years were 7.8% and 14.0%. Older age at implant increased the risk of death with hazard ratios (HR) of 2.05 (95% confidence interval [CI] 1.70 to 2.47) and 3.00 (95% CI 2.43 to 3.71) for those 65 to 74 years and ≥75 years, respectively (both $p < 0.001$), but gender was not a predictor of death. Common noncardiac conditions associated with death included peripheral vascular disease (adjusted HR 1.50, 95% CI 1.18 to 1.91), pulmonary disease (adjusted HR 1.35, 95% CI 1.10 to 1.66), and renal disease (adjusted HR 1.57, 95% CI 1.25 to 1.99). Many ICD recipients had prior heart failure (46.2%) with an increased HR of 2.33 for death (95% CI 1.96 to 2.76; $p < 0.001$). Greater comorbidity burden conferred increased risk, with HRs adjusted for age, gender, and heart failure of 1.72 (95% CI 1.44 to 2.05), 2.79 (95% CI 2.15 to 3.62), and 2.98 (95% CI 1.74 to 5.10) for those with 1, 2, and 3 or more noncardiac comorbidities, respectively (all $p < 0.001$).

Conclusions Age, noncardiac comorbidities, and prior heart failure influence survival outcomes in ICD recipients. These factors should be considered in the care of ICD recipients. (J Am Coll Cardiol 2007;49:2408–15) © 2007 by the American College of Cardiology Foundation

The implantable cardioverter-defibrillator (ICD) has been demonstrated to be highly efficacious in randomized controlled trials of patients at risk of ventricular tachyarrhythmias by providing rapid identification and treatment of potentially lethal rhythm disturbances. The devices are appealing because they provide early defibrillation for life-threatening ventricular tachyarrhythmias, resulting in long-term survival that is associated with preserved quality of life (1). Landmark randomized controlled trials of ICDs have demonstrated reductions in arrhythmic death and all-cause mortality in patients receiving ICD therapy (2–5).

See page 2416

Interventions that have been shown to reduce mortality in randomized controlled trials have often had attenuated benefits in population-based studies because of the differences between community-based patients and the often highly selected individuals enrolled in randomized trials. For example, studies of community-based patients with heart failure (HF) and myocardial infarction have reported disparities in patient characteristics and mortality (6). These disparities have been attributed partly to differences in age and comorbidity burden, which may contribute to a greater risk of competing events that may reduce overall effectiveness of treatments in unselected patients (7).

From the *Institute for Clinical Evaluative Sciences, †University Health Network, ‡Sunnybrook and Women's Health Sciences Centre, and the §Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Canada; ‖London Health Sciences Centre, London, Canada; and the #University of Toronto, Toronto, Canada.
Supported by a grant from the Ontario Ministry of Health and Long-Term Care, a Canadian Institutes of Health Research (CIHR) Team Grant in Cardiovascular Outcomes Research, clinician-scientist (to Dr. Lee) and new investigator (to Dr. Austin) awards from the CIHR, career investigator awards from the Heart and Stroke Foundation of Ontario (to Drs. Tu and Alter), and a Canada research chair in health services research (to Dr. Tu).

Manuscript received November 9, 2006; revised manuscript received January 26, 2007, accepted February 27, 2007.

In response to the widening indications for ICDs, there have been calls for better stratification methods to identify risk groups that would most benefit, or that would be unlikely to benefit, from the device (8–11). Analysis of comorbidities may help identify subsets that are most likely to benefit from the ICD. Information about survival after ICD insertion in real-world samples, and the impact of age, gender, and comorbidities on outcomes, has not been previously assessed. In the present study, we hypothesized that HF and noncardiac conditions would be associated with higher mortality rates and could potentially aid in identifying those who would benefit less from ICD insertion.

Abbreviations and Acronyms

CI = confidence interval
HF = heart failure
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
ICD-9 = International Classification of Diseases, version 9
ICD-10 = International Classification of Diseases, version 10
VF = ventricular fibrillation
VT = ventricular tachycardia

Methods

Study sample. We identified patients who underwent ICD implantation in Ontario, Canada, from April 1, 1997, to March 31, 2003, using the Canadian Institute for Health Information (CIHI) discharge abstract and same-day surgery databases. The CIHI database contains information on all hospital separations and cardiac procedures, and the same-day surgery database contains data on procedures performed on outpatients. Patients undergoing implantation of the ICD and dates of implantation were identified using Canadian Classification of Procedures code 49.74, and International Classification of Diseases, version 10 (ICD-10), codes 1HZ53GRFS and 1HZ53LAFS. These codes are used by Ontario hospitals where electrophysiology services are provided and ICDs are implanted.

To identify first ICD implants, we excluded those who had a prior procedure within 10 years before the index implantation date. We also excluded patients who were <18 years or >105 years of age at the time of ICD implant, nonresidents, and those with an invalid health card number. Survival information was obtained up to the last follow-up date, March 31, 2005, from the Registered Persons Database of vital statistics. We compared the survival of ICD recipients with control subjects selected from the Registered Persons Database, who were alive in the year that the matched ICD patient underwent device implantation. In addition, control subjects were matched according to age (±2 years), prior arrhythmia (e.g., ventricular tachycardia [VT], cardiac arrest, ventricular fibrillation [VF], or none), prior HF, and number of significant comorbidities identified on the basis of the multivariable regression analysis to optimally match ICD recipients with control device nonrecipients.

Comorbidities. Comorbidities present before ICD insertion were identified from the secondary diagnosis fields of the CIHI database, and were classified into the categories of the Deyo-Charlson comorbidity classification system (12). Specific diagnoses were identified according to the International Classification of Diseases coding system, version 9 (ICD-9) (13) or version 10 (14) using previously published methods (15). We identified prior arrhythmia history by the diagnosis of cardiac arrest (ICD-9 code 427.5, ICD-10 code I46), VF (ICD-9 code 427.4, ICD-10 code I490), and VT (ICD-9 code 427.1, ICD-10 code I472). Patients with prior myocardial infarction were identified by ICD-9 codes 410 and 412 or ICD-10 codes I21, I22, and I25.2, and those with HF were identified by ICD-9 code 428 or ICD-10 code I50. Those with ischemic heart disease were identified by ICD-9 codes 411 to 414, or ICD-10 codes I20, I22, I24, and I25.

To enhance sensitivity for the presence of all chronic comorbid conditions and arrhythmia, we examined all secondary diagnosis data during the ICD implant admission, and all primary and secondary diagnoses from hospitalization data occurring 3 years before the date of ICD implant. Analysis of comorbidities was performed by modeling each group of cardiac and noncardiac conditions as independent model covariates.

Statistical analysis. We examined the frequency of cardiac conditions and noncardiac comorbidities in ICD recipients and unadjusted 1- and 2-year mortality rates. The mortality effects of gender and age were modeled by grouping age into the following categories: 18 to 64 years, 65 to 74 years, and ≥75 years. Variables associated with mortality after ICD insertion were evaluated using Cox proportional hazards regression analysis. Initially, we examined the effects of age, gender, the contribution of prior cardiac arrhythmia, and the Deyo-Charlson comorbidity score, followed by univariate Cox analysis of the mortality effects of individual comorbidities. In the latter analysis, comorbidities were categorized according to the moieties of the Deyo-Charlson classification, a widely adopted comorbidity index applicable to administrative databases (12). Multivariable analysis was performed to identify comorbidities significantly associated with mortality using backward elimination, retaining covariates significant at a $p < 0.05$ level. We assessed the effect of age continuously after adjustment for gender and all significant comorbidities on multivariable analysis using a cubic spline analysis with a Cox regression model (16). We modeled age as splines with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles and tested the null hypothesis of a linear relationship between the hazard for age and death relative to ICD recipients at the median age.

Cox proportional hazards regression analysis was performed to determine if survival was improved in ICD recipients compared with control subjects after adjusting for age, gender, prior VT, VF, or cardiac arrest, prior HF, and all noncardiac comorbidities that were significant predictors of mortality in multivariable analysis, adjusted for matching. Separate Cox regression models were also examined for patients with VT, VF, or cardiac arrest to determine if the effect of ICD insertion differed in these arrhythmia sub-

groups. Survival in ICD recipients was plotted using the Kaplan-Meier method, and adjusted survival curves were plotted for comparison of ICD recipients and matched controls.

We performed additional analyses to better characterize the effects of HF by examining those with a recent (occurring within 6 months before ICD implant) or earlier (occurring >6 months before ICD implant) event, adjusting for age and other significant noncardiac comorbidities. Events in the analysis included admissions for HF as the primary diagnosis or developed as an in-hospital complication. The effect of number of events on mortality was determined by categorizing patients into those with 1, 2, or ≥3 HF events in the 3 years before ICD insertion. All patients had at least 2 years of follow-up and were censored at this time unless death occurred during the follow-up period. The proportional hazards assumption was tested for all Cox analyses. Analyses were performed using SAS version 8.2 (SAS Institute, Cary, North Carolina).

Results

Patient characteristics and crude mortality rates. A total of 2,467 patients underwent first ICD implantation during the study period, providing 4,551 person-years of follow-up. Follow-up for mortality was determined until March 31, 2005. The majority of individuals were aged <65 years with a mean age of 62.5 ± 13.4 years. Most ICD recipients were men (1,944, 79%), who were collectively older at ICD implant than women (63.2 ± 12.5 years vs. 59.8 ± 15.9 years, respectively). Common noncardiac conditions included diabetes and peripheral or cerebral vascular, respiratory, and renal disease (Table 1). There were small numbers of patients with dementia (n = 9), rheumatologic disease (n = 24), hemi/paraplegia (n = 14), mild liver disease (n = 5), moderate/severe liver disease (n = 8), and metastatic cancer (n = 8) in all age categories combined (Table 1). The median Deyo-Charlson score was 1 (25th and 75th percentile scores: 1, 3). The prevalence of prior arrhythmia history was 83%. With older age, the prevalence of noncardiac comorbidities (peripheral vascular disease, chronic obstructive pulmonary disease, renal disease) increased (all p trend ≤0.001). The overall crude mortality rates were 7.8% at 1 year (192 deaths) and 14.0% at 2 years (346 deaths).

Effect of age and gender on mortality risk. On univariate analysis, hazard ratios (HRs) for all-cause mortality were 2.33 (95% confidence interval [CI] 1.93 to 2.81) and 3.36 (95% CI 2.73 to 4.15) in those aged 65 to 74 years and ≥75 years relative to those 18 to 64 years, respectively (both p < 0.001). The risk in men was increased relative to women with an HR of 1.25 (95% CI 1.02 to 1.53). The univariate HRs for mortality in those of older age and male gender were attenuated when age, gender, and Deyo-Charlson comorbidity score were included concomitantly in a multivariable model. The adjusted HRs for the older age groups 65 to 74 years and ≥75 years were 2.05 (95% CI 1.70 to 2.47) and 3.00 (95% CI 2.43 to 3.71), respectively (both p < 0.001), and male gender was no longer a significant predictor of mortality (HR 1.15, 95% CI 0.93 to 1.41).

Impact of comorbidities on mortality. The univariate and multivariable analyses for all-cause mortality according to type of comorbidity (in contrast to aggregate scores) are presented in Table 2. Common comorbidities that were more likely to be associated with adverse outcome in multivariable analysis included HF, peripheral/cerebral vas-

Table 1 Demographic Characteristics of ICD Recipients by Age Group

	Age 18–64 yrs (n = 1,180)	Age 65–74 yrs (n = 862)	Age ≥75 yrs (n = 425)	p Trend
Male gender, n (%)	899 (76.2)	723 (83.9)	322 (75.8)	0.24
Cardiac comorbidities, n (%)				
Myocardial infarction	454 (38.5)	394 (45.7)	184 (43.3)	0.01
Ischemic heart disease	700 (59.3)	710 (82.4)	330 (77.6)	<0.001
Heart failure	501 (42.5)	429 (49.8)	210 (49.4)	0.002
Arrhythmic conditions, n (%)				
Cardiac arrest	278 (23.6)	212 (24.6)	82 (19.3)	0.18
Ventricular fibrillation	314 (26.6)	184 (21.3)	80 (18.8)	<0.001
Ventricular tachycardia	764 (64.7)	625 (72.5)	278 (65.4)	0.16
Any arrhythmic condition	975 (82.6)	746 (86.5)	330 (77.6)	0.21
Noncardiac comorbidities, n (%)				
Peripheral vascular disease	69 (5.8)	90 (10.4)	41 (9.6)	0.001
Cerebrovascular disease	76 (6.4)	76 (8.8)	33 (7.8)	0.16
Chronic obstructive pulmonary disease	123 (10.4)	115 (13.3)	76 (17.9)	<0.001
Peptic ulcer disease	8 (0.7)	9 (1.0)	10 (2.4)	0.008
Renal disease	68 (5.8)	77 (8.9)	61 (14.4)	<0.001
Diabetes	215 (18.2)	184 (21.3)	83 (19.5)	0.29
Diabetes with complications	34 (2.9)	39 (4.5)	8 (1.9)	0.86
Nonmetastatic cancer	21 (1.8)	37 (4.3)	15 (3.5)	0.009

ICD = implantable cardioverter-defibrillator.

Table 2 Univariate and Multivariable Predictors of Death in ICD Recipients

	Univariate Hazard Ratio (95% CI)	p Value	Final Multivariable Hazard Ratio (95% CI)*	p Value
Age 18–64 yrs	Referent		Referent	
Age 65–74 yrs	2.33 (1.93–2.81)	<0.001	2.08 (1.73–2.51)	<0.001
Age ≥75 yrs	3.36 (2.73–4.15)	<0.001	3.10 (2.50–3.83)	<0.001
Male	1.25 (1.02–1.53)	0.03	n/a	
Myocardial infarction	1.29 (1.10–1.51)	0.001	n/a	
Heart failure	2.69 (2.28–3.17)	<0.001	2.33 (1.96–2.76)	<0.001
Peripheral vascular disease	1.93 (1.53–2.44)	<0.001	1.50 (1.18–1.91)	<0.001
Cerebrovascular disease	1.65 (1.29–2.11)	<0.001	n/a	
Chronic pulmonary disease	1.85 (1.51–2.26)	<0.001	1.35 (1.10–1.66)	0.004
Dementia	2.00 (0.75–5.34)	0.17	n/a	
Renal disease	2.74 (2.21–3.40)	<0.001	1.57 (1.25–1.99)	<0.001
Rheumatologic disease	1.73 (0.92–3.22)	0.09	1.89 (1.01–3.53)	0.046
Diabetes	1.45 (1.21–1.75)	<0.001	n/a	
Microvascular complications of diabetes	3.09 (2.28–4.18)	<0.001	2.33 (1.69–3.21)	<0.001
Peptic ulcer disease	2.31 (1.34–4.01)	0.003	n/a	
Mild liver disease	2.37 (0.76–7.38)	0.14	n/a	
Moderate/severe liver disease	2.45 (0.92–6.56)	0.07	n/a	
Cancer	2.06 (1.44–2.93)†	<0.001	1.81 (1.29–2.54)‡	<0.001
Metastatic cancer	3.29 (1.23–8.78)	0.02	n/a	
Hemi/paraplegia	1.60 (0.66–3.86)	0.29	n/a	
Cardiac arrest	0.96 (0.80–1.16)	0.68	n/a	
Ventricular fibrillation	0.78 (0.64–0.94)	0.009	n/a	
Paroxysmal VT	1.12 (0.94–1.33)	0.20	n/a	

*Covariates with hazard ratio (HR) and p values shown were included in the final multivariable model. †HR and p value for nonmetastatic cancer. ‡HR and p value for metastatic and nonmetastatic cancer.

CI = confidence interval; ICD = implantable cardioverter-defibrillator; n/a = variable did not meet criteria for inclusion in the multivariable model; VT = ventricular tachycardia.

cular disease, chronic pulmonary disease, complicated or uncomplicated diabetes, and renal insufficiency. Among the mortality predictors in the final multivariable model (Table 2), HF was a common cardiac condition, occurring in nearly one-half of all ICD recipients, and was associated with a greater than 2-fold increase in death among ICD recipients. The continuous effect of age on the hazard of death adjusted for gender and all significant comorbidities on multivariate analysis (from Table 2) using cubic spline analysis is shown in Figure 1. The hazard of death increased nonlinearly, particularly after age 70 years (test for nonlinearity: chi-square = 15.6; p = 0.001).

Survival curves are shown in Figure 2 for ICD recipients according to HF and comorbidity status. Compared with ICD recipients without HF or comorbidities, those with prior HF were at increased risk of death (log rank p < 0.001). The worst survival outcome was observed in ICD recipients with both HF and at least 1 additional model comorbidity (log rank p < 0.001). The number of additional noncardiac comorbidities (significant on multivariable analysis) was also associated with mortality. Relative to those without noncardiac comorbidities, the HRs for death adjusted for age, gender, and prior HF were 1.72 (95% CI 1.44 to 2.05; p < 0.001), 2.79 (95% CI 2.15 to 3.62; p < 0.001), and 2.98 (95% CI 1.74 to 5.10; p < 0.001) for those with 1, 2, and ≥3 noncardiac comorbidities, respectively. Unadjusted mortality rates for patients substratified by age, HF status, and number of comorbidities are presented in Table 3.

Effect of prior arrhythmia and ICD insertion. In contrast to the mortality associations with HF and the noncardiac conditions described in the preceding, prior cardiac arrhythmia was not associated with survival in ICD recipients. Specifically, the presence of prior cardiac arrest, VF, or VT was not predictive of mortality after multivariable adjustment. The HRs adjusted for age, gender, HF, prior myo-

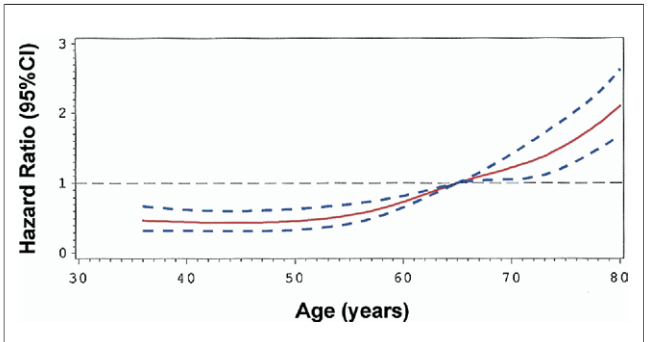

Figure 1 Effect of Age on Death

Cubic spline analysis demonstrating nonlinear effect of age on death using Cox regression adjusted for gender and significant model comorbidities. Hazard ratios by age **(solid red line)** are relative to those with median age; 95% confidence intervals (CI) are also shown **(dotted blue lines)**.

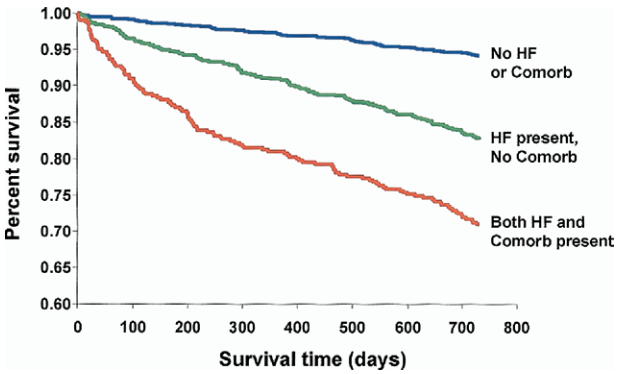

Figure 2 **Survival After ICD Insertion by HF and Comorbidity Status**

Kaplan-Meier survival plots for implantable cardioverter-defibrillator (ICD) recipients with or without heart failure (HF) and/or model comorbidities (Comorb). The presence of prior heart failure or model comorbidity (e.g., peripheral vascular disease, chronic pulmonary disease, renal disease, rheumatologic disease, microvascular complications of diabetes, or cancer) significantly worsened survival compared with patients who were free of these conditions (log rank $p < 0.001$).

cardial infarction, and significant noncardiac comorbidities in ICD recipients were 0.98 (95% CI 0.79 to 1.20) for those with prior occurrence of cardiac arrest, 0.86 (95% CI 0.69 to 1.07) for those with VF, and 0.97 (95% CI 0.82 to 1.16) for those with VT. The presence of these arrhythmic conditions in combination was also not associated with mortality on univariate (HR 0.93, 95% CI 0.76 to 1.15) or multivariable (HR 0.89, 95% CI 0.72 to 1.10) analyses.

Control subjects with the same arrhythmia history matched for age, prior HF, and comorbidities could be identified for 82.7% (n = 2,040 pairs) of ICD recipients. The ICD recipients had greater frequency of prior MI (39.7% vs. 34.6%), peripheral vascular disease (7.5% vs. 5.7%), and renal disease (7.3% vs. 5.3%) than control subjects. Control subjects had more chronic obstructive pulmonary disease (13.8% vs. 11.4%) and prior coronary revascularization (22.2% vs. 16.9%) and were younger (mean age 62.7 ± 13.1 years vs. 63.1 ± 13.1 years) than ICD recipients. In multivariable Cox proportional hazards regression analysis of all ICD recipients and control subjects, no significant effect of ICDs on survival was detected, but there was a beneficial trend with an adjusted HR of 0.86 (95% CI 0.72 to 1.02; p = 0.09) among device recipients. Figure 3 shows adjusted survival curves for ICD recipients and control subjects with prior VT (n = 1,307 pairs). In those with prior VT, the ICD was associated with a significant increase in survival, with an adjusted HR of 0.80 (95% CI 0.65 to 0.99; p = 0.043). The absolute increase in mortality in the control group at 2 years was 2% in those with prior VT or cardiac arrest and 1% overall. There was no significant interaction of ICD recipient status with age and comorbidities after adjustment for multiple tests.

Additional HF analyses. Relative to those without HF, ICD recipients with a recent episode of clinical HF were at greater risk of death. Patients with a recent episode of HF (≤6 months before ICD implant) had an HR for mortality of 2.98 (95% CI 2.41 to 3.69), whereas those with an event >6 months before ICD insertion had an HR for mortality of 2.06 (95% CI 1.71 to 2.48; both $p < 0.001$), after adjustment for age and the noncardiac comorbidities significant in multivariable analysis (Table 2). Increased number of prior clinical HF episodes was also associated with greater

Table 3 **Comparative Mortality Rates by Patients' Risk Characteristics**

Age (yrs)	Recent HF Within 6 Months Before ICD (Yes/No)	Number of Noncardiac Comorbidities*	n (% of Overall Sample)	1-Year Mortality (%)	2-Year Mortality (%)
≤59	No	0	593 (24.0)	1.7	3.9
	No	1	107 (4.3)	8.4	14.0
	No	≥2	23 (0.9)	17.4	30.4
≤59	Yes	0	76 (3.1)	5.3	9.2
	Yes	1	30 (1.2)	13.3	13.3
	Yes	≥2	8 (0.32)	12.5	25.0
60–69	No	0	446 (18.1)	6.1	11.2
	No	1	149 (6.0)	8.7	16.8
	No	≥2	33 (1.3)	21.2	27.3
60–69	Yes	0	73 (3.0)	12.3	20.6
	Yes	1	39 (1.6)	15.4	28.2
	Yes	≥2	19 (0.8)	15.8	26.3
≥70	No	0	494 (20.0)	5.9	11.1
	No	1	187 (7.6)	10.2	21.9
	No	≥2	52 (2.1)	17.3	34.6
≥70	Yes	0	71 (2.9)	15.5	33.8
	Yes	1	40 (1.6)	35.0	45.0
	Yes	≥2	27 (1.1)	48.2	63.0

*Noncardiac comorbidities include peripheral vascular disease, chronic pulmonary disease, renal disease, rheumatologic disease, microvascular complications of diabetes, and metastatic or nonmetastatic cancer.
ICD = implantable cardioverter-defibrillator.

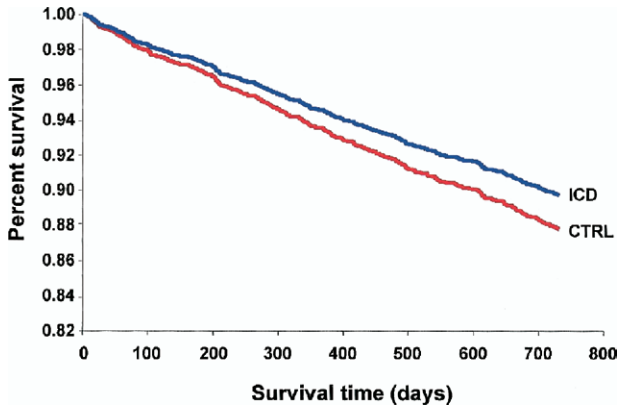

Figure 3 **Adjusted Survival Plots**

Comparison of implantable cardioverter-defibrillator (ICD) recipients and matched control subjects (CTRL) with prior ventricular tachycardia up to 2 years after device implantation.

risk of death after ICD insertion. Compared to those without HF in the previous 3 years, those with 1, 2, and ≥3 episodes had age- and comorbidity-adjusted HRs for all-cause death of 1.93 (95% CI 1.59 to 2.34), 2.44 (95% CI 1.79 to 3.32), and 3.67 (95% CI 2.61 to 5.16), respectively (all $p < 0.001$). The risk of death after ICD implant was comparable for HF patients with or without prior myocardial infarction, with HRs of 2.42 and 2.14, respectively (both $p < 0.001$).

Discussion

Thus far, the major sources of data for decisions related to ICDs are from randomized controlled trials. However, randomized trial enrollees and patients in the community often differ substantially, in part owing to older age and greater comorbidity burden in the latter. In the present study, we found that noncardiac comorbidities were frequently present in ICD recipients in a population-based setting. The effect of age on mortality was nonlinear throughout the range of patient ages, and the association increased in a curvilinear manner in ICD recipients who were older than 70 years. Comorbidities were significantly associated with mortality after device implantation, but after adjustment for age there was no significant gender difference in survival. The only cardiac condition that had a significant effect on mortality after ICD implant was HF. Among the noncardiac comorbidities, renal failure, chronic pulmonary disease, peripheral vascular disease, and diabetes with microvascular complications were of particular importance. Finally, the ICD was associated with a trend toward increased survival overall and significantly improved survival in those with prior VT, compared with control subjects without ICDs, in analyses adjusted for age and all comorbidity predictors of mortality.

Few studies have examined the effect of multiple comorbidity burden on outcomes after ICD implant. In patients who were on dialysis, survival after ICD implant was low, with death occurring in nearly half of device recipients by 2 years (17). In the Coronary Artery Bypass Graft Patch trial, diabetes was not associated with increased mortality after ICD implant (18). In the present study, consistent results were observed with increased mortality in those with renal failure and no effect of uncomplicated diabetes. However, we found increased mortality in those with microvascular diabetic complications, which may indicate more severe or uncontrolled disease. In addition, we found that a number of other noncardiac conditions were also associated with adverse outcomes after device implantation.

Randomized trial data have been used to identify subgroups with greater potential benefit from the ICD. For example, investigators from CIDS (Canadian Implantable Defibrillator Study) reported that patients 70 years old or more were more likely to benefit from ICD therapy (19). However, we found that older ICD recipients were more likely to exhibit greater comorbidity burden and increased mortality risk despite ICD implantation. The effect of HF severity has been examined in the randomized trial setting, with divergent results. In the CIDS and DEFINITE (Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation) trials, patients with worse New York Heart Association (NYHA) functional class derived greater benefits from ICD therapy (19,20). In contrast, in the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), the survival benefit of ICDs was significant in NYHA functional class II HF, but there was no benefit in patients with NYHA functional class III HF (21). The present findings are aligned with the aforementioned observations from the SCD-HeFT, because increased risk of death was observed in ICD recipients with greater HF symptom burden as reflected by a recent event or greater frequency of HF hospitalization. We cannot exclude, however, that there may be identifiable subsets of HF patients who by virtue of their high baseline mortality risk may experience an absolute benefit from ICD therapy.

Unlike pharmacologic therapies that may have pleiotropic effects on noncardiac organ systems (e.g., angiotensin-converting enzyme inhibitors), the ICD has a purely cardiac mechanism of action specific to the treatment of life-threatening dysrhythmias (2). The observation that prior arrhythmia was not a significant predictor of mortality after ICD implant in part reflects the efficacy of the device in preventing arrhythmic death and the likelihood that in the "real world" ICD recipients are likely to die of competing comorbidities rather than arrhythmias. The present data demonstrated lower prevalence of noncardiac conditions than in population-based HF samples (22), suggesting that ICD recipients in Ontario during the study period were already selected to have a lower comorbidity burden. Other published studies support this assertion, with greater relative comorbidity burden demonstrated in ICD nonrecipients

(23,24). The underlying reasons for the selectiveness evident in decisions of candidacy for ICDs are likely multifactorial but may include empirical filtering in the decision-making process owing to finite quantities of ICDs available to implanting institutions or variations among referring physicians and electrophysiologists in their estimation of the ratio of risks of arrhythmic versus nonarrhythmic death (25).

The present study has important implications as health care systems attempt to translate the broadened indications for ICD insertion from randomized trials into clinical practice (5,21). First, although the ICD is effective in reducing arrhythmic death, competing noncardiac morbidities are associated with increased mortality in ICD recipients and may affect outcomes of these patients in the "real world" setting. Second, although older age has been suggested as a means of identifying those who would benefit from the ICD, it is also strongly associated with mortality after ICD implant. Therefore the decision to implant based on patient age could lead to greater comorbidity burden and lower impact of the ICD on all-cause mortality in the population. Finally, because clinical HF was an important determinant of outcome, examination of other factors associated with HF outcomes may also be worthy of further examination in future studies of risk stratification in ICD candidates. The implications of HF in ICD recipients are further magnified because the life-prolonging benefit of ICD therapy is associated with an increase in HF events over time (26). To the clinician contemplating ICD insertion for a given patient, age and the presence or absence of chronic diseases are largely unmodifiable. The present findings suggest, therefore, that it is both a personal and societal decision about how high the risk of death from competing causes should be before an ICD is no longer justified.

Study limitations. The present study was limited by the lack of clinical information on left ventricular function, inducibility and severity of ventricular tachyarrhythmias, and other clinical variables that may influence HF-specific outcomes. Determinations of cardiac conditions and comorbidities were based on administrative data sources which may be undercoded. However, prior analysis of administrative comorbidities suggests high degree of specificity compared with primary chart records (27). Similarly, further clinical characterization of comorbidities (e.g., subclassification of prior cardiac arrest due to bradyasystolic or tachyarrhythmic events) and modes or causes of death could not be performed. Unlike the control subjects in the present analyses, the follow-up of ICD recipients occurs on a regularly scheduled basis, and therefore differences in medical management between the 2 groups could have occurred over time. However, this would not have resulted in differential follow-up for mortality outcomes, because vital status information is obtained in both ICD recipients and control subjects in a similar manner. Finally, we did not examine continuous clinical data (e.g., laboratory test results) and varying levels of severity of comorbidities, because the majority of comorbidity data available in administrative databases are binary in nature (present or absent). Such data could potentially improve modeling of outcome events and predictive model performance.

Conclusions

In this community-based examination of ICD recipients, we found that the presence of noncardiac comorbidities and prior clinical HF were significant predictors of death in ICD recipients. Increased age was associated with comorbidities, and ICD recipients in older age groups had worse survival than their younger counterparts. Our findings suggest that greater attention to noncardiac comorbidities and HF status may assist in the decision to implant an ICD, and may improve outcomes in ICD recipients. Further research is needed to better characterize HF and other comorbidities as potential determinants of outcome.

Reprint requests and correspondence: Dr. Douglas S. Lee, Institute for Clinical Evaluative Sciences, Room G-106, 2075 Bayview Avenue, Toronto, Ontario, Canada M4N 3M5. E-mail: dlee@ices.on.ca.

REFERENCES

1. Bunch TJ, White RD, Gersh BJ, et al. Long-term outcomes of out-of-hospital cardiac arrest after successful early defibrillation. N Engl J Med 2003;348:2626–33.
2. Lee DS, Green LD, Liu PP, et al. Effectiveness of implantable defibrillators for preventing arrhythmic events and death: a meta-analysis. J Am Coll Cardiol 2003;41:1573–82.
3. 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.
4. Connolly SJ, Gent M, Roberts RS, et al. Canadian Implantable Defibrillator Study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 2000;101:1297–302.
5. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–83.
6. Braunstein JB, Anderson GF, Gerstenblith G, et al. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. J Am Coll Cardiol 2003;42:1226–33.
7. Jong P, Vowinckel E, Liu PP, Gong Y, Tu JV. Prognosis and determinants of survival in patients newly hospitalized for heart failure: a population-based study. Arch Intern Med 2002;162:1689–94.
8. Gehi A, Haas D, Fuster V. Primary prophylaxis with the implantable cardioverter-defibrillator: the need for improved risk stratification. JAMA 2005;294:958–60.
9. McClellan MB, Tunis SR. Medicare coverage of ICDs. N Engl J Med 2005;352:222–4.
10. Stevenson LW. Implantable cardioverter-defibrillators for primary prevention of sudden death in heart failure: are there enough bangs for the bucks? Circulation 2006;114:101–3.
11. Toma M, McAlister FA, Ezekowitz J, et al. Proportion of patients followed in a specialized heart failure clinic needing an implantable

cardioverter defibrillator as determined by applying different trial eligibility criteria. Am J Cardiol 2006;97:882–5.
12. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613–9.
13. International Classification of Diseases, Ninth Revision, Clinical Modification. Washington, DC: Public Health Service, U.S. Department of Health and Human Services, 1988.
14. International Statistical Classification of Diseases and Related Health Problems, 10th revision. Geneva: World Health Organization, 1992.
15. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol 2004;57:1288–94.
16. Harrell FEJ. Regression modeling strategies. New York, NY: Springer-Verlag, 2001.
17. Herzog CA, Li S, Weinhandl ED, Strief JW, Collins AJ, Gilbertson DT. Survival of dialysis patients after cardiac arrest and the impact of implantable cardioverter defibrillators. Kidney Int 2005;68:818–25.
18. Whang W, Bigger JT Jr., for the CABG Patch Trial Investigators and Coordinators. Diabetes and outcomes of coronary artery bypass graft surgery in patients with severe left ventricular dysfunction: results from the CABG Patch trial database. J Am Coll Cardiol 2000;36:1166–72.
19. Sheldon R, Connolly S, Krahn A, Roberts R, Gent M, Gardner M. Identification of patients most likely to benefit from implantable cardioverter-defibrillator therapy: the Canadian Implantable Defibrillator Study. Circulation 2000;101:1660–4.
20. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004;350:2151–8.
21. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–37.
22. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA 2003;290:2581–7.
23. Chan PS, Hayward RA. Mortality reduction by implantable cardioverter-defibrillators in high-risk patients with heart failure, ischemic heart disease, and new-onset ventricular arrhythmia: an effectiveness study. J Am Coll Cardiol 2005;45:1474–81.
24. Curtis AB, Hallstrom AP, Klein RC, et al. Influence of patient characteristics in the selection of patients for defibrillator implantation (the AVID Registry). Antiarrhythmics Versus Implantable Defibrillators. Am J Cardiol 1997;79:1185–9.
25. Owens DK, Sanders GD, Heidenreich PA, McDonald KM, Hlatky MA. Effect of risk stratification on cost-effectiveness of the implantable cardioverter defibrillator. Am Heart J 2002;144:440–8.
26. Goldenberg I, Moss AJ, Hall WJ, et al. Causes and consequences of heart failure after prophylactic implantation of a defibrillator in the Multicenter Automatic Defibrillator Implantation Trial II. Circulation 2006;113:2810–7.
27. Lee DS, Donovan L, Austin PC, et al. Comparison of coding of heart failure and comorbidities in administrative and clinical data for use in outcomes research. Med Care 2005;43:182–8.