Original Article

Survival Benefit of the Primary Prevention Implantable Cardioverter-Defibrillator Among Older Patients

Does Age Matter? An Analysis of Pooled Data From 5 Clinical Trials

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Background—The impact of patient age on the risks of death or rehospitalization after primary prevention implantable cardioverter-defibrillator (ICD) placement is uncertain.

Methods and Results—Data from 5 major ICD trials were merged: the Multicenter Automatic Defibrillator Implantation Trial I (MADIT-I), the Multicenter UnSustained Tachycardia Trial (MUSTT), the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II), the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation Trial (DEFINITE), and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). Median age at enrollment was 62 (interquartile range 53–70) years. Compared with their younger counterparts, older patients had a greater burden of comorbid illness. In unadjusted exploratory analyses, ICD recipients were less likely to die than nonrecipients in all age groups: among patients aged <55 years: hazard ratio 0.48, 95% posterior credible interval 0.33 to 0.69; among patients aged 55 to 64 years: hazard ratio 0.69, 95% posterior credible interval 0.53 to 0.90; among patients aged 65 to 74 years: hazard ratio 0.67, 95% posterior credible interval, 0.53 to 0.85; and among patients aged ≥75 years: hazard ratio 0.54, 95% posterior credible interval 0.37 to 0.78. Sample sizes were limited among patients aged ≥75 years. In adjusted Bayesian–Weibull modeling, point estimates indicate ICD efficacy persists but is attenuated with increasing age. There was evidence of an interaction between age and ICD treatment on survival (two-sided posterior tail probability of no interaction <0.01). Using an adjusted Bayesian logistic regression model, there was no evidence of an interaction between age and ICD treatment on rehospitalization (two-sided posterior tail probability of no interaction 0.44).

Conclusions—In this analysis, the survival benefit of the ICD exists but is attenuated with increasing age. The latter finding may be because of the higher burden of comorbid illness, competing causes of death, or limited sample size of older patients. There was no evidence that age modifies the association between ICD treatment and rehospitalization. **(*Circ Cardiovasc Qual Outcomes*. 2015;8:179-186. DOI: 10.1161/CIRCOUTCOMES.114.001306.)**

Key Words: aging ■ defibrillators, implantable ■ meta-analysis

Clinical trials have demonstrated the efficacy of the implantable cardioverter-defibrillator (ICD) in reducing the risk of sudden cardiac death.[1–5] Consequently, ICD placement has become widespread, particularly among older patients. Greater than 40% of new ICDs are placed among patients aged ≥70 years and >10% among patients aged ≥80 years.[6] As the population ages,[7] the number of ICDs placed in older patients is expected to grow. Uncertainty about ICD efficacy among older patients exists[8]; however, they were underrepresented in individual clinical trials. This dearth of data is problematic. On the one hand, undergoing a potentially hazardous and expensive procedure without realizing a clinical benefit is objectionable. On the other hand, withholding an effective therapy is also undesirable. The impact of age on the likelihood of rehospitalization after ICD placement is similarly incompletely understood.

Pooling of clinical trial data permits more efficient appraisal of treatment effects among subgroups by increasing sample sizes. Given the small number of patients in subgroups of interest in individual trials, a consortium consisting of the investigators of 9 major ICD trials was created. Restricted to patients enrolled in primary prevention ICD trials, the current analysis examined whether age modifies the relationship between ICD treatment and mortality or rehospitalizations.

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WHAT IS KNOWN

- Placement of implantable cardioverter-defibrillators among older patients is common, yet such patients were underrepresented in the clinical trials establishing device efficacy.

WHAT THE STUDY ADDS

- In this analysis of pooled data from 5 major implantable cardioverter-defibrillator trials, the survival benefit of implantable cardioverter-defibrillator therapy persisted across the age spectrum but was attenuated with advancing age.
- There was no evidence that age influenced the likelihood of rehospitalization after implantable cardioverter-defibrillator placement.
- The current analysis suggests age per se is not a strict contraindication to placement of an implantable cardioverter-defibrillator, but rather patients and physicians should take into account a number of other factors such as patient preference, procedural risk, and comorbidity burden.

Methods

Data Sources and Study Selection

Patient-level data previously collected during 9 primary and secondary prevention trials were merged. The deidentified data set was granted exempt status by the Duke Institutional Review Board. Primary prevention clinical trials randomizing patients to an ICD or usual care were included in this analysis: the Multicenter Automatic Defibrillator Implantation Trial I (MADIT-I),[1] the Multicenter UnSustained Tachycardia Trial (MUSTT),[2] MADIT-II,[3] the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation Trial (DEFINITE),[4] and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)[5] (Table 1). Although patients were not randomized to ICD or usual care in MUSTT, the trial was nevertheless included because the observed treatment effect of electrophysiologically guided antiarrhythmic therapy was because of better outcomes among ICD recipients rather than antiarrhythmic drug recipients.[9] For the purposes of the present analysis, MUSTT ICD recipients received active intervention and nonrecipients usual care. The Antiarrhythmics versus Implantable Defibrillators trial[10] and the Cardiac Arrest Study Hamburg trial[11] were excluded given their focus on secondary prevention, and the amiodarone arms of SCD-HeFT[5] or MUSTT were excluded on the basis of amiodarone's potentially confounding effect. The Coronary Artery Bypass Graft trial[12] and Defibrillator in Acute Myocardial Infarction Trial[13] were also excluded based on the potential benefit of surgical revascularization on ventricular arrhythmia and the exclusion of patients with a recent myocardial infarction in current professional guidelines,[14] respectively. Within the included trials, individual patient inclusion criteria were heart failure (New York Heart Association class I-III), a left ventricular ejection fraction of ≤ 35%, and the availability of important covariates. Accordingly, patients without heart failure symptoms or with New York Heart Association Class IV symptoms (53 from MADIT-II), a left ventricular ejection fraction of >35% (2 from MADIT-I, 77 from MUSTT, and 3 from SCD-HeFT) or with time from myocardial infarction to randomization <40 days (16 from MADIT-I, 12 from MADIT-II, 89 from MUSTT, and 2 from SCD-HeFT), as well as those missing values for variables that define the inclusion criteria (87 from MADIT II, 248 from MUSTT, and 49 from SCD-HeFT) were excluded from this study.

Statistical Analysis

The primary end point was all-cause mortality. The secondary end point was rehospitalization for any reason. For descriptive analyses, the following age categories were chosen to balance interest with adequate sample sizes: <55, 55 to 64, 65 to 74, and ≥75years. Patients aged ≥65 years were considered "older," but younger categories were included to better understand trends. Baseline characteristics were summarized as percentages for categorical variables and medians with 25th and 75th percentiles for continuous variables. The association of age group with each characteristic was assessed using the χ^2 and equality of median tests as appropriate. Given the multilevel resolution of the data, that is, with patients within trials, we also assessed the association of age group with each characteristic using generalized linear mixed models with random effects for trials. This allowed us to borrow information across trials while also accounting for possible correlated observations within the same trial. Baseline data according to age were also stratified by trial and by sex.

Time zero was the day of randomization in both study arms. The absolute number of each end point was stratified according to age group and sex as well as the presence or absence of an ICD. Kaplan–Meier curves showing the survival of ICD recipients relative to nonrecipients were generated. Differences in the log-hazard ratios were assessed with a stratified Cox proportional hazards model allowing for separate baseline hazard functions for each trial. Cause-of-death data were not examined because of the degree of missingness.

Using Cox proportional hazards models, we examined factors associated with death in univariate fashion. In adjusted analyses,

Table 1. Primary Prevention ICD Trial Characteristics

Clinical Trial	Participating Countries	Year of Main Publication	Eligible Age Range at Entry, y	Eligible Left Ventricular Ejection Fraction, %	Cardiomyopathy	Factorial Comparison	No. of Participants	Mean Follow-Up, y
MADIT-I[1]	US, Italy, Germany	1996	25–80	≤35	Ischemic	ICD vs conventional medical therapy	95 vs 101	2.40 vs 2.07
MUSTT[2]	US, Canada	1999	<80	≤40	Ischemic	ICD or antiarrhythmic drugs vs placebo	167 vs 537	3.55 vs 3.16
MADIT-II[3]	US, the Netherlands, Germany, Israel	2002	>21	≤30	Ischemic	ICD vs conventional medical therapy	742 vs 490	1.71 vs 1.64
DEFINITE[4]	US	2004	21–80	<36	Nonischemic	ICD vs conventional medical therapy	229 vs 229	2.55 vs 3.40
SCD-HeFT[5]	US, Canada	2005	>18	≤35	Ischemic or nonischemic	ICD vs placebo vs amiodarone	829 vs 1692	3.40 vs 3.33

DEFINITE indicates defibrillators in nonischemic cardiomyopathy treatment evaluation trial; ICD, implantable cardioverter-defibrillator; MADIT-I, multicenter automatic defibrillator implantation trial I; MADIT-II, multicenter automatic defibrillator implantation trial II; MUSTT, multicenter unsustained tachycardia trial; and SCD-HeFT, sudden cardiac death in heart failure trial.

Table 2. Baseline Characteristics According to Age at Enrollment*

	Age at Enrollment				
Characteristic	<55 y (n=1010)	55–64 y (n=1055)	65–74 y (n=1075)	≥75 y (n=390)	*P* value†
Randomized to ICD, %	52.2	50.1	51.6	58	0.127
Age, median interquartile range (IQR)	48 (43–52)	60 (57–62)	69 (67–72)	78 (76–80)	
Male, %	78.1	81.5	80.7	81	0.733
Race					<0.001
White	73.1	81.0	81.4	91.0	
Black	20.8	14.4	13.3	5.4	
Other	6.1	4.6	5.3	4.0	
Left ventricular ejection fraction, median (IQR)	23 (18–28)	25 (20–30)	25 (20–30)	25 (20–29)	0.004
New York Heart Association Class					0.034
I	13.6	19.1	20.2	24.4	
II	60.5	55.8	52.5	43.9	
III	25.9	25.1	27.4	31.8	
Medical history, %					
Atrial fibrillation	6.6	8.1	14.7	20.9	<0.001
Coronary artery bypass grafting	26.9	41.1	48.5	54.8	<0.001
Diabetes mellitus	23.3	34.2	33.4	23.8	<0.001
Hypercholesterolemia	65.5	46.9	42.9	9.1	0.013
Hypertension	47.0	53.8	58.0	55.0	<0.001
Ischemic heart disease	45.6	64.6	72.9	76.4	<0.001
Myocardial infarction	44.1	62.1	69.8	73.1	<0.001
Peripheral vascular disease	2.8	6.2	9.0	7.0	0.458
Percutaneous coronary intervention	25.2	30.3	32.5	31.6	0.498
Pulmonary disease	12.8	19.4	23.7	20.3	<0.001
Smoking	81.1	83.6	75.9	74.5	<0.001
Medication, %					
Angiotensin-converting enzyme inhibitor	91.2	86.5	81.6	76.4	<0.001
β-blocker	74.5	66.3	59.0	55.4	<0.001
Diuretic	79.6	79.1	79.2	78.2	0.100
Antiarrhythmic	1.8	4.0	4.3	3.1	0.200
Laboratory data					
Serum creatinine, median (IQR)	1.0 (0.9–1.2)	1.1 (1.0–1.3)	1.2 (1.1–1.4)	1.3 (1.1–1.6)	<0.001
Left bundle-branch block, %	16.4	18.0	22.0	24.1	<0.001
QRS duration, median (IQR)	104 (92–120)	110 (95–140)	114 (96–144)	120 (100–160)	<0.001
Included patients, n					
MADIT-I	33	58	74	14	
MUSTT	24	57	76	25	
MADIT-II	192	321	402	174	
DEFINITE	181	120	114	43	
SCD-HeFT	580	499	409	134	

DEFINITE indicates defibrillators in nonischemic cardiomyopathy treatment evaluation trial; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; MADIT-I, multicenter automatic defibrillator implantation trial I; MADIT-II, multicenter automatic defibrillator implantation trial II; MUSTT, multicenter unsustained tachycardia trial; and SCD-HeFT, sudden cardiac death in heart failure trial.

*Data are presented as % unless otherwise indicated and are based on patients with available data.

†Tests do not treat age as an ordered categorical variable.

Bayesian–Weibull survival regression modeling[15,16] was used to combine trial data and address missingness. Specifically, a model including continuously valued age and ICD therapy, as well as their interaction, was fitted. Additional covariates were selected on the basis of clinical relevance among those available across trials and included sex, race, left ventricular ejection fraction, New York Heart Association class, indicator of QRS duration ≥120 ms, indicator of ischemic disease (prior coronary artery bypass grafting, prior myocardial infarction, or history of ischemic heart disease), and the use of angiotensin-converting enzyme inhibitors, β-blockers, and history of

Table 3. Outcomes According to Age at Enrollment*

	<55 y						55–64 y					
	Usual care			ICD			Usual care			ICD		
	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women
Event	(n=483)	(n=374)	(n=109)	(n=527)	(n=415)	(n=112)	(n=527)	(n=433)	(n=94)	(n=528)	(n=427)	(n=101)
Death	17.4 (84)	17.4 (65)	17.4 (19)	8.2 (43)	8.4 (35)	7.1 (8)	26.4 (139)	27.9 (121)	19.2 (18)	18.4 (97)	18.7 (80)	16.8 (17)
≥1 rehospitalization	54.4 (200)	53.4 (150)	57.5 (50)	66.2 (272)	64.6 (210)	72.1 (62)	59.9 (240)	58.3 (193)	67.1 (47)	69.7 (294)	68.6 (231)	74.1 (63)

(*Continued*)

diabetes mellitus. Within our Bayesian–Weibull survival model, we performed multiple imputations to address missingness of QRS duration or history of diabetes mellitus. The imputations were performed for each trial based on the empirical distribution of the variable of interest. To account for the possible heterogeneity in treatment effect or in the underlying risk of death from all causes between patients in the different trials, trial-specific treatment effects and parameters defining trial-specific baseline hazard functions were considered random effects. The significance of the interaction value was evaluated with the two-sided tailed posterior probability for a null interaction as a Bayesian analogue to the frequentist *P* value. For additional details, see the Data Supplement Statistical Appendix. We also fitted similar unadjusted models, that is, that do not include additional covariates beyond age and treatment for comparison. The interaction of age with ICD treatment on the secondary end point of rehospitalization was assessed in an analogous fashion in a Bayesian logistic regression model[17] without or with the same adjustment variables with patients from MUSTT and DEFINITE removed given nonavailability of the secondary outcome. In sensitivity analyses, we fitted a quadratic model on age with an interaction with ICD treatment on the end points of death and rehospitalization and assessed the interaction. Additional details about our models are provided in the Data Supplement Statistical Appendix. Analyses were performed with R version 3.1.0 and WinBugs version 1.4.3.[18]

Results

Baseline Characteristics

The final study population consisted of 3530 patients from 5 clinical trials. The median age in the overall sample was 62 (interquartile range, 53–70) years. The number of patients aged ≥75 years was 390 (11.0%). Some differences in baseline characteristics according to age group were present at baseline (Table 2). Compared with their younger counterparts,

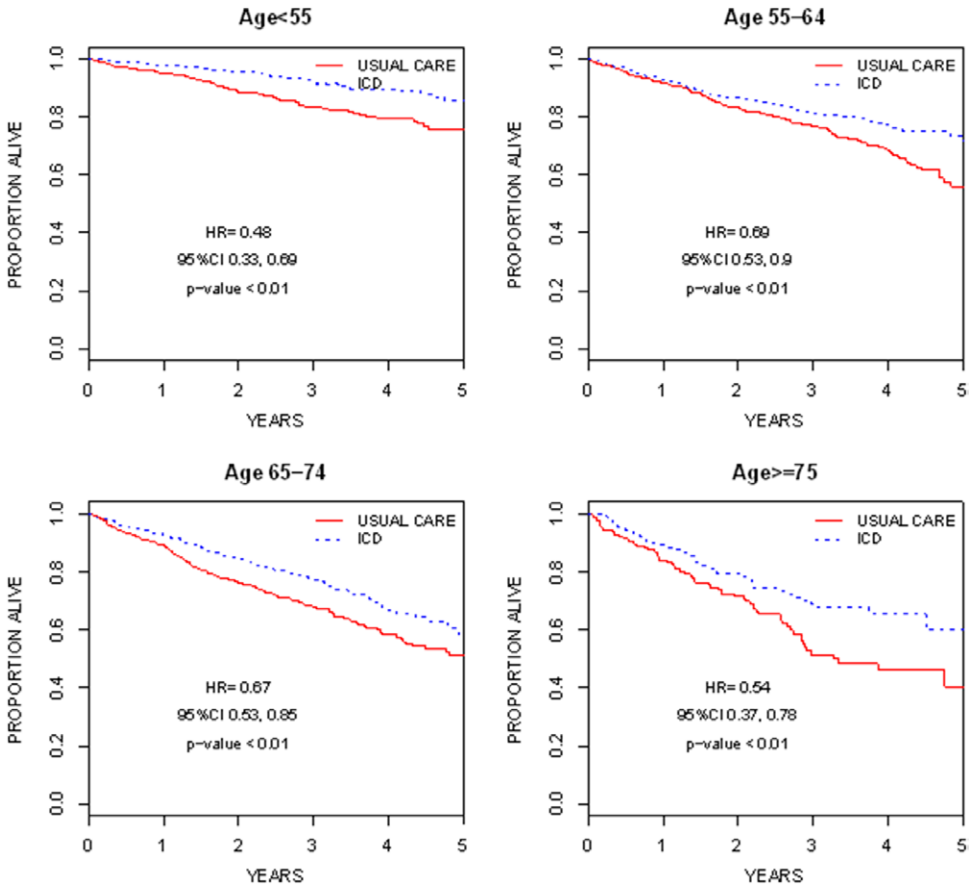

Figure 1. Unadjusted Kaplan–Meier survival curves by age groups. Hazard ratios (HRs), 95% confidence intervals (CIs) and *P* values are based on a stratified Cox regression model by trial.

Table 3. Outcomes According to Age at Enrollment, Continued*

65–74 y						>75 y					
Total	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women
(n=520)	(n=421)	(n=99)	(n=555)	(n=447)	(n=108)	(n=164)	(n=134)	(n=30)	(n=226)	(n=182)	(n=44)
33.5 (174)	35.9 (151)	23.2 (23)	22.9 (127)	20.8 (93)	31.5 (34)	40.2 (66)	44.0 (59)	23.3 (7)	24.8 (56)	26.4 (48)	18.2 (8)
62.3 (238)	60.1 (188)	72.5 (50)	76.1 (343)	75.7 (274)	77.5 (69)	72.1 (93)	74.8 (80)	59.1 (13)	75.6 (136)	76.7 (115)	70 (21)

ICD indicates implantable cardioverter-defibrillator.
*Data are presented as % (n).

older patients were more commonly white, more frequently had advanced heart failure symptoms, and were more likely to have several comorbidities, including atrial fibrillation, hypertension, peripheral vascular disease, and pulmonary disease. They were also more likely to have been revascularized either surgically or percutaneously. They more commonly had an elevated creatinine, a left bundle-branch block, and a widened QRS. Furthermore, they were less likely to be taking a β-blocker or an angiotensin-converting enzyme inhibitor. Differences were also observed when the baseline data were stratified by trial (Supplementary Table I) and by sex (Supplementary Table II).

Outcomes

After a median duration of follow-up of 2.6 years, 323 of 1836 (21.3%) ICD recipients and 463 of 1694 nonrecipients (30.6%) died. ICD recipients were less likely to die than nonrecipients in all age groups (Table 3). Death rates among women receiving usual care were comparable with those of men among patients aged <55 years and lower in older age groups. The reduction in death observed in ICD recipients was comparable between sexes among patients aged <55 years and lower in older age groups (Table 3). Kaplan–Meier estimates of death as a function of time and corresponding hazard ratios from the stratified Cox proportional hazards models showed a mortality benefit of ICD therapy in all age groups (Figure 1). In the total study cohort, 1045 (71.4%) ICD recipients and 771 (60.2%) nonrecipients were hospitalized one or more times. This trend was consistent across all age groups (Table 3).

Factors associated with death in univariate fashion are shown (Table 4). Fitting Weibull survival regression models that included continuously valued age, ICD therapy, and their interaction, without or with adjustment for baseline characteristics, we found that point estimates for ICD therapy efficacy compared with usual care were consistent with a survival benefit across the spectrum of age. However, the absence of a survival benefit could not be ruled out above the age of 70 years (Figure 2 for adjusted model; results for the unadjusted model are similar and thus omitted in the figure). Furthermore, the impact of ICD therapy on survival is attenuated with increasing age (two-sided posterior tail probability of no interaction is 0.02 in the unadjusted model and <0.01 in the adjusted model). By contrast, when examining rehospitalizations, there was no evidence of an interaction between age and ICD treatment (two-sided posterior tail probability of no interaction is 0.58 in the unadjusted model and 0.44 in the adjusted model). In sensitivity analyses, using a quadratic model on age, there was evidence of an interaction between age with ICD treatment on the end point of death but not on rehospitalization. The final model for the primary outcome of death inclusive of other adjustment covariates with and without the interaction term using the linear term for age is shown (Table 5).

Discussion

Our analysis has 3 main findings. First, after pooling data from 5 clinical trials and adjusting for patient demographics, medical comorbidities, and laboratory values, point estimates indicate that the survival benefit of ICD therapy persists across the age spectrum. Second, the survival advantage conferred by ICD therapy is attenuated with advancing age. However, the number of patients older than 75 years was modest, and this may have affected corresponding efficacy estimates and the observed attenuation of ICD survival benefit. Third, there is no evidence that age influences the odds of rehospitalization after ICD placement.

In a secondary evaluation of MADIT-II, the ICD was associated with a reduction in mortality among patients aged ≥75 years comparable to that of younger patients.[19] By contrast, two meta-analyses indicate that ICD survival benefit persists but becomes less striking with older age.[20,21] The latter two

Table 4. Factors Associated With Death in Univariate Analysis

Factor	Hazard Ratio (95% Confidence Interval)
ICD	0.64 (0.55–0.73)
Age, y	1.04 (1.03–1.04)
Male sex	1.22 (1.01–1.47)
Race	
Black	0.98 (0.69–1.37)
White	0.84 (0.62–1.13)
History of diabetes mellitus	1.67 (1.43–1.94)
History of coronary artery bypass grafting	1.29 (1.11–1.51)
Left ventricular ejection fraction	0.59 (0.46–0.77)
New York Heart Association Class	
II	1.12 (0.88–1.43)
III	2.39 (1.88–3.03)
QRS duration	1.36 (1.17–1.57)
Angiotensin-converting enzyme inhibitor use	1.29 (1.11–1.51)
β-blocker use	0.60 (0.52–0.70)

ICD indicates implantable cardioverter-defibrillator.

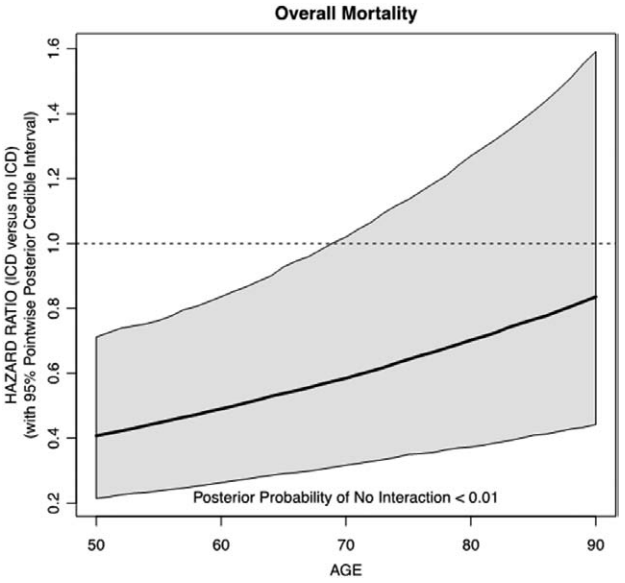

Figure 2. Adjusted hazard ratio of mortality according to age. ICD indicates implantable cardioverter-defibrillator.

studies were limited by the use of trial-level estimates of study outcomes. Patient-level analysis allows for adjustment for differences in comorbidities and medical therapies and continuous rather than categorical valuation of relevant covariates such as age. Although the former aspect is central to the assessment of the independent relationship of covariates with outcomes, the latter minimizes potential loss of information. These two study design features and assessment of the age-related risk of rehospitalization set the current analysis apart from those preceding it.

The current analysis suggests that the survival benefit of ICD therapy exists but diminishes with increasing age. Analyses of ICD effectiveness yielded similar results. In the American Heart Association Get With the Guidelines-Heart Failure registry database linked with Medicare claims, receipt of ICD therapy was associated with a lower risk of mortality 3 years after implantation up to 84 years of age (among patients, 65–74 years: adjusted hazard ratio, 0.65; 95% CI, 0.47–0.89 and among patients, 75–84 years: hazard ratio, 0.80; 95% CI, 0.62–1.03).[22] In the Ontario ICD database, mortality also increased with age (2.1, 3.0, 5.4, 6.9, and 10.2 deaths per 100 person-years in ICD recipients aged 18–49, 50–59, 60–69, 70–79, and ≥80 years, respectively).[23] In an analysis of two European registries, the survival benefit of ICD therapy was considerably lower among ICD recipients aged ≥75 years compared with those aged <75 years, and their mortality rates were comparable with those of age-matched controls from the general population.[24] The decline in the survival benefit of ICD therapy observed in the current analysis is not only biologically plausible but also consistent with existing knowledge of sudden cardiac death. Its incidence rises with increasing age, but the competing risk of nonsudden death becomes proportionally higher.[25] The lower fraction of sudden deaths accompanying advancing age corresponds to a reduced number of opportunities for the ICD to improve patient survival. The greater burden of comorbid illness with advancing age observed in the current analysis may underlie the increase in nonsudden death. Advancing age was also accompanied by a reduction in receipt of evidence-based medications, including β-blockers and angiotensin-converting enzyme inhibitors. This has been observed previously[26] and represents a potential missed opportunity to improve patient outcomes.[27] Our multivariable analysis included the use of these medications, but residual confounding related to the quality of medical care otherwise received may persist and potentially impact the magnitude or directionality of the observed ICD treatment effect. The modest sample size of patients aged ≥75 years or

Table 5. Factors Associated With Death in Multivariable Analysis

	Multivariable Model Without Interaction Term	Multivariable Model With Interaction Term
Factor	Hazard Ratio (95% Posterior Credible Interval)	Hazard Ratio (95% Posterior Credible Interval)
Age, y	1.03 (1.02–1.04)	1.02 (1.01–1.03)
Male sex	1.23 (1.02–1.50)	1.21 (0.98–1.46)
Race		
White	0.71 (0.55–0.97)	0.69 (0.54–1.01)
Black	0.98 (0.73–1.37)	0.95 (0.70–1.40)
Left ventricular ejection fraction	0.62 (0.48–0.80)	0.62 (0.48–0.78)
New York Heart Association Class		
II vs I	1.05 (0.82–1.34)	1.07 (0.86–1.39)
III vs I	2.04 (1.67–2.62)	2.05 (1.67–2.71)
Ischemic disease	1.52 (1.25–1.92)	1.58 (1.28–1.97)
Diabetes mellitus	1.44 (1.23–1.67)	1.45 (1.22–1.68)
Medication		
β-Blocker	0.69 (0.60–0.81)	0.69 (0.59–0.79)
Angiotensin-converting enzyme inhibitor	0.92 (0.74–1.12)	0.93 (0.77–1.16)
QRS duration	1.20 (1.03–1.39)	1.21 (1.03–1.41)
ICD therapy		
DEFINITE	0.61 (0.39–0.96)	0.48 (0.30–0.79)
MADIT-I	0.48 (0.28–0.81)	0.37 (0.22–0.61)
MADIT-II	0.59 (0.45–0.78)	0.44 (0.31–0.59)
MUSTT	0.37 (0.20–0.64)	0.27 (0.14–0.49)
SCD-HeFT	0.73 (0.60–0.89)	0.58 (0.45–0.74)
Overall	0.54 (0.30–0.95)	0.41 (0.21–0.71)
Heterogeneity in treatment effect (standard deviation)	0.57 (0.38–1.04)	0.59 (0.38–0.99)
Age and ICD therapy interaction	-	1.02 (1.01–1.03)

DEFINITE indicates defibrillators in nonischemic cardiomyopathy treatment evaluation trial; ICD, implantable cardioverter-defibrillator; MADIT-I, multicenter automatic defibrillator implantation trial I; MADIT-II, multicenter automatic defibrillator implantation trial II; MUSTT, multicenter unsustained tachycardia trial; and SCD-HeFT, sudden cardiac death in heart failure trial.

residual confounding may also, in part, explain the observed attenuation in ICD survival benefit.

Previous studies examining the relationship between age and rehospitalization were sparse, conducted in single centers, and divergent. In a retrospective analysis of 65 consecutive patients undergoing ICD placement between 1991 and 1993, age was not associated with readmission.[28] In a similar analysis, age >60 years independently predicted rehospitalization for both cardiovascular and arrhythmic causes among 180 patients who underwent ICD placement in the late 1990s.[29] A trend between increasing age and rates of cardiovascular rehospitalization was also observed in the Ontario ICD database (17.4%, 13.2%, 14.5%, 17.0%, and 21.1% among patients aged 18–49, 50–59, 60–69, 70–79, and ≥80 years, respectively; P=0.035).[23] Differences in the clinical practices between trials and real-world settings may, in part, explain these discrepancies. Other potential explanations include modest sample sizes or residual confounding. An increased risk of rehospitalization among ICD recipients versus nonrecipients has been observed previously and may be because of shocks, shock-associated heart failure exacerbations, and postprocedural complications.[30,31]

Our data indicate that the survival benefit of ICDs is comparable between sexes among patients aged <55 years. It becomes less so with increasing age but nonetheless persists. Notably, the death rate among men was lower than that of women receiving usual care, and thus there may have been fewer opportunities for the ICD to alter the natural course of events by aborting sudden death.[32] Randomized or observational analyses with larger sample sizes and higher event rates allowing for adjustment are needed to further inform the ongoing debate about ICD utilization in women.

The current analysis suggests that age per se should not be a contraindication to ICD placement. Rather, clinical judgment should take into account other factors, including patient preference, periprocedural risk, and comorbidity burden.[33,34] However, randomized data of patients aged ≥75 years are limited, and more studies are needed. The absence of an association between age and the likelihood of rehospitalization in the clinical trial setting but not the real-world setting is likewise noteworthy and also deserves further study.

Limitations

The current analysis was retrospective; however, data were collected prospectively. Data were also derived from clinical trials, and thus the findings may not be generalizable to less monitored or controlled settings. Data are stratified by sex for descriptive purposes; the study sample size cannot afford testing interactions by sex in addition to by age. More studies on older patients in clinical and real-world settings are needed. Adjustment covariates were limited to those available in all included trials. Our study may be subject to residual or unmeasured confounding by relevant covariates such as frailty, atrial fibrillation, chronic kidney disease, or lung disease. In spite of pooling of data, subgroup sample sizes were modest, particularly among patients aged ≥75 years. The power of our study to detect small differences in ICD treatment effect was correspondingly limited, particularly among older age groups. Because the treatment benefit of ICD therapy likely increases with time after ICD placement and the follow-up of the current analysis was short compared with some,[35] our ability to discern a survival benefit of ICD therapy may have been correspondingly limited.

Conclusions

In this analysis of 3530 patients from 5 clinical trials, the survival benefit of ICD therapy is attenuated with increasing age and may be related to an accompanying increase in the burden of comorbid illness. The survival benefit nonetheless seems to persist. Randomized data of patients aged ≥75 years of age are sparse, and this may in part explain the observed attenuation in ICD survival benefit. More studies among older patients are needed. There was no evidence that age modifies the association between ICD treatment and rehospitalization.

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Disclosures

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