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RESEARCH ARTICL

One-year mortality after implantable cardioverter-defibrillator placement within the Veterans Affairs Health System

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Aims Implantable cardioverter-defibrillator (ICD) therapy reduces mortality in patients with heart failure and current guidelines advise implantation of ICDs in patients with a life expectancy of >1 year. We examined trends in all-cause mortality in patients who underwent primary or secondary prevention ICD placement in the Veterans Affairs (VA) Health System.

Methods and results US veterans receiving a new ICD placement for primary or secondary prevention of sudden cardiac death between January 2007 and January 2015, who had heart failure with reduced ejection fraction (HFrEF) were included in the analysis. We assessed all-cause mortality 1 year post-ICD implantation. ICD implantation and HFrEF diagnosis were established with associated ICD-9 codes. The VA death registry was utilized to identify mortality rates following ICD placement. Results were subsequently age-stratified. There were 17 901 veterans with HFrEF with ICD placement nationwide. There was no statistically significant difference in 1-year mortality from 2007 (13.1%) to 2014 (13.4%, $P > 0.05$). There was a significant increase in 1-year mortality in patients in the oldest age quartile (81.6 years, 32.3% mortality) compared to the youngest quartile (55.5 years, 7% mortality). The finding of diverging clinical outcomes extended to the 30-day but also 8-year mark.

Conclusions Our data suggest there is a high 1-year mortality in aging HFrEF patients undergoing primary and secondary prevention ICD placement. This highlights the importance of developing better predictive models for mortality in our ICD eligible patient population.

Keywords Implantable cardioverter-defibrillator • Comorbidities • Outcomes

Introduction

Heart failure (HF) affects over 6.5 million Americans and over 15 million Europeans and is predicted to continue to increase in prevalence in the upcoming years.[1,2] Survival after the onset of HF has improved in recent years likely secondary to advancement in medical therapies along with prevention of sudden cardiac death (SCD) with implantable cardioverter-defibrillators (ICD).[1] It has been over 20 years since Moss and colleagues provided evidence to support the use of primary prevention ICD in high-risk patients with prior myocardial infarction in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-I).[3] Patients exhibited a survival benefit from ICD placement as compared to medical therapy alone. Survival benefit was also found in patients with HF with reduced ejection fraction (HFrEF) in MADIT-II and the SCD in Heart Failure Trial (SCD-HeFT).[4,5] Thus, ICD placement

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for both primary and secondary prevention is well-established and commonly performed, however continues to remain costly. Given the continuing increased focus on cost conscious care, it is important to isolate which patients are at highest risk for SCD and would derive the most benefit from ICD therapy. Current guidelines provide a class I recommendation for primary prevention ICD placement in patients with ischaemic heart disease with left ventricular ejection fraction (LVEF) ≤35% with New York Heart Association (NYHA) class II or III symptoms, or those with LVEF ≤30% with NYHA class I symptoms who have been medically optimized if their life expectancy is over 1 year.[6,7] A similar class I recommendation exists for ICD placement in patients with non-ischaemic cardiomyopathy, however at a slightly higher LVEF cutoff of ≤30% if they have NYHA class II or III symptoms.[6,7] Although there are risk scores that attempt to assess whether patient comorbidities should preclude them from ICD placement, these scores such as PACE (peripheral arterial disease, age, creatinine, ejection fraction) have been developed using observational studies and do not have enough evidence to be used in routine practice or direct current guidelines.[8] We evaluated the incidence and the 1-year mortality rate following ICD implant for primary or secondary prevention in a US Veterans Affairs (VA) Health System population. Trends in 1-year mortality and burden of comorbidities from 2007 to 2015 were compared. Furthermore, we sought to explore the relationship between comorbidity burden and age with 1-year outcomes, in an attempt to guide future decision-making.

Methods

The analysis included US veterans with a diagnosis of HFrEF and a new implantation of primary or secondary prevention ICD. Patients treated nationwide in the VA Health System from January 2007 to January 2015 were included. The VA Health System is a national, integrated health system, which provides close follow-up and a reliable ascertainment of clinical outcomes. The data source was the VA's Corporate Data Warehouse (CDW) through the VA Informatics and Computing Infrastructure (VINCI). Data were linked to VA electronic healthcare records and VA's death registry. The institutional review board of the Indianapolis, Indiana, VA approved the study. Diagnosis of HFrEF and ICD implantation were established through International Classification of Diseases, Ninth Revision (ICD-9-CM) codes. ICD-9 code (428.2)[9] and concomitant use of beta-blockers (metoprolol succinate and carvedilol) were required for HFrEF diagnosis. Metoprolol succinate and carvedilol are restricted to HF patients at the VA. By only including patients on these medical therapies the selection of HFrEF patients is expected to improve specificity.

We described the baseline characteristics including the Charlson Comorbidity Index where high values equal high comorbid indices. The index is a scoring system that prospectively evaluates comorbidities and how they contribute to mortality in longitudinal trials.[10] The Charlson Comorbidity Index accounts for 16 commonly encountered medical comorbidities and assigns point values to each comorbidity based on the respective mortality contribution.[10,11] The patient cohort was also stratified by age quartiles. Baseline characteristics and all-cause mortality were compared across age groups. Trend analysis was performed for the comorbidity index. Date of death was determined from the VA Vital Status File. Survival curves were plotted for 1-year mortality after device implantation. A Cox proportional hazard model analysis was performed adjusting for covariates for the overall sample. We controlled for age, gender, comorbidities, and medications in our multivariable modelling as these variables are possible confounders to our outcome variables of interest and were previously found to be associated with clinical outcomes.[12] We also performed proportionality tests to see if the models have a non-zero slope. Robust standard errors are used in the analysis. All tests were 2-tailed with $\alpha = 0.05$ and performed using STATA 15.1 (Stata Corp., College Station, TX, USA).

Results

Implantable cardioverter-defibrillator and 1-year mortality

From an initial cohort of 500 000 veterans in the US VA Health System, we identified 17 901 veterans with HFrEF and a new ICD implantation for primary or secondary prevention of SCD between January 2007 and January 2015 (*Figure 1*, online supplementary *Table S1*). Our patient population had a mean age of 66 years and was predominately male (98.8%) (*Table 1*). The most common medical comorbidities included coronary artery disease (mean 81%), which remained stable throughout the follow-up period (online supplementary *Table S2*). Other comorbidities included atrial fibrillation (mean 43%), chronic kidney disease (mean 42%), chronic obstructive pulmonary disease (mean 36%), hypertension (mean 72%), peripheral arterial disease (mean 27%), diabetes (mean 56%), and smoking (mean 29%). The patients were medically optimized with a large majority treated with loop diuretics (mean 85%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (mean 97%) and statins (mean 93%). Changes in medication during the observation period show an increased use of calcium channel blockers and a decreased use of aldosterone receptor blockers and oral anticoagulants (online supplementary *Table S3*). The average Charlson Comorbidity Index over the 8 years was 3.0, with a statistically significant decrease from 2007 to 2014 from 3.1 to 2.8 ($P < 0.001$) (*Figure 2*, online supplementary *Table S4*). Over the observation time period, age remained more or less stable with an annual increase in age of 1.004 (95% confidence interval 1.003–1.005). The number of patients with coronary artery disease ranged around 80% throughout the follow-up period.

Median follow-up time was 2.14 years (interquartile range 0.81–3.96) with a median time to death after ICD placement of 1.99 years (interquartile range 0.79–3.72). The average 1-year all-cause mortality after ICD implantation was 13% (2329 patients). There was no statistically significant difference in 1-year mortality rates from 2007 to 2014 ($P > 0.05$) despite the decreasing Charlson Comorbidity Index from 2007–2014 (*Figure 3*). The association of 1-year mortality post-ICD implantation and Charlson Comorbidity Index is presented in *Figure 4*.

The results of multivariable analysis identified a number of variables associated with either an increased or decreased risk of 1-year all-cause mortality (*Table 2*) and 8-year all-cause mortality (*Table 3*). The mortality risk was significantly increased in the presence of certain comorbid states such as coronary artery disease, chronic kidney disease, chronic obstructive pulmonary

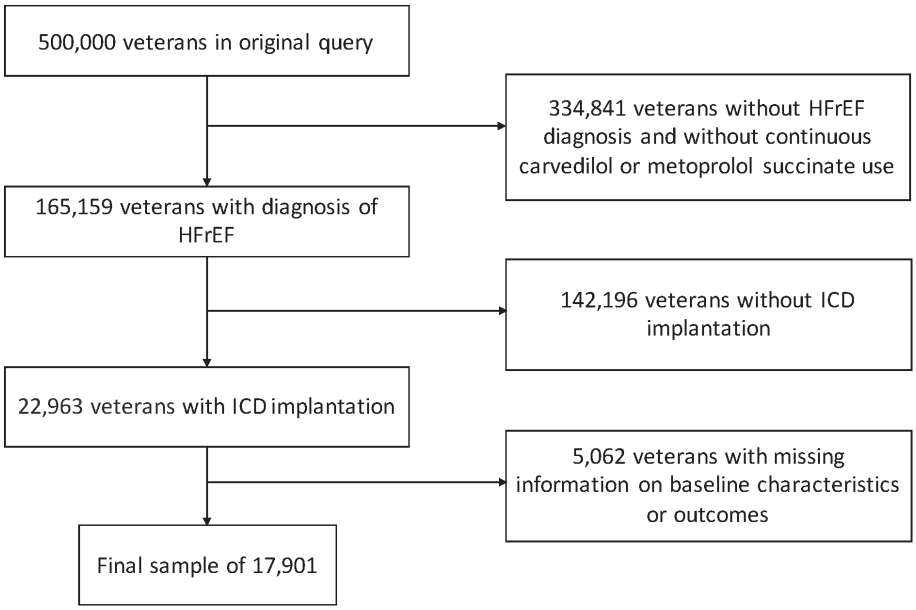

Figure 1 CONSORT diagram. HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator.

disease, cirrhosis, end-stage renal disease, and diabetes along with several other factors. Prior stroke history had no statistically significant association with all-cause mortality. Hypertension, obstructive sleep apnoea and the use of certain medications such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers were associated with a lower risk of mortality over 8 years.

Age-stratified analysis

Baseline characteristics stratified by age quartiles are presented in online supplementary *Table S5*. In quartile 1 ($n = 4478$) the mean age was: 53.8 years, quartile 2 ($n = 4472$): 61.9 years, quartile 3 ($n = 4476$): 68.2 years, and quartile 4 ($n = 4475$): 79.2 years. Patients in the higher quartiles had a higher burden of comorbid diseases [Charlson Comorbidity Index: Q1 (mean: 2.75), Q4 (mean: 3.07)] compared to those in lower quartiles. There was a significant increase in 1-year mortality with higher age range as shown on a continuous scale or divided by quartiles of patients (*Figures 5* and *6*). Over 1-year follow-up, there was a 93% survival in the youngest quartile of patients compared to a 67.7% survival in the oldest quartile. Complimentary peri-procedural mortality, defined by 30-day post-ICD all-cause mortality, is displayed in *Figure 6A*. The peri-procedural mortality shows a comparable age-related risk difference ($P < 0.001$).

Discussion

In a large contemporary cohort of VA patients with HFrEF undergoing new ICD implantation, the 1-year mortality was high. We found no significant difference in 1-year mortality despite a decreasing burden of comorbidities over the same time frame. An age-stratified analysis revealed significant increases in mortality with higher age quartiles. Thus, a very high 1-year mortality in the higher age groups (e.g. 32% mortality at 1 year post-ICD in the highest age quartile) is a key driver of mortality.

With an increase in HFrEF prevalence among the aging population there is an increased number of patients who might benefit from primary prevention ICD implantation. ICD implantations are associated with a marked financial cost and small but non-trivial peri-procedural risks. Further, surveys show that age is another significant concern that dissuades many physicians from referring their patients for evaluation.[13] American College of Cardiology/American Heart Association/Heart Rhythm Society and European Society of Cardiology guideline recommendations do not currently have an age limitation.[6,7] The guidelines instead have a survival recommendation for primary prevention ICDs that they only be implanted if the estimated meaningful survival is >1 year.[6,7]

The comorbidity index decrease, although statistically significant, may not be clinically significant. It is important however as it shows comorbidities have either remained stable or decreased despite a persistently high 1-year mortality rate. Although current guidelines recommend primary prevention ICD placement in HFrEF patients with a meaningful survival of >1 year without a consideration of age, our data suggest that age is an important prognostic factor regardless of expected survival time. Our patients were divided into four quartiles and mortality was assessed at 1 year and for the full duration of follow-up. Patients in the oldest age quartile had a marked increase in 1-year mortality compared to the other three quartiles. This is interesting as prior studies have shown that elderly patients with significant comorbidities with primary prevention ICD have a lower risk of mortality than those without ICDs.[14] In patients with non-ischaemic systolic HF it has

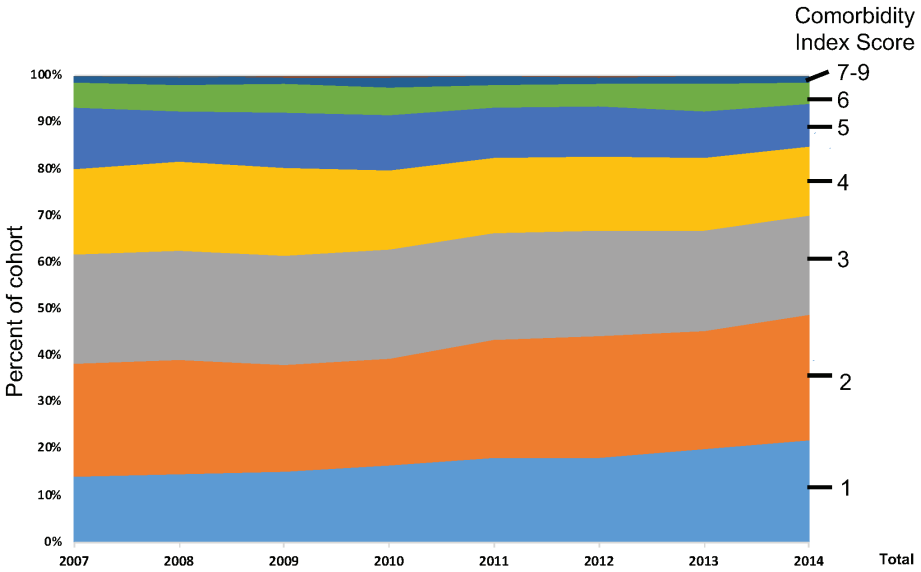

Figure 2 Trend in comorbidity index from 2007 to 2014.

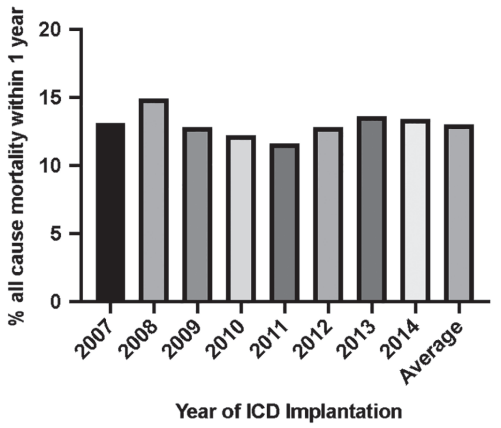

Figure 3 Incidence rates of 1-year all-cause death during follow-up. ICD, implantable cardioverter-defibrillator.

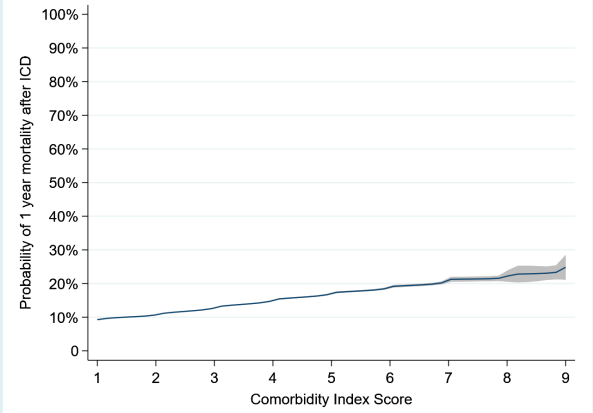

Figure 4 Charlson Comorbidity Index and 1-year mortality post-implantable cardioverter-defibrillator (ICD) implantation. The probability of 1-year mortality by comorbidity index score was obtained using a probit model after adjusting for age and gender. Grey bar indicates 95% confidence interval.

been shown that with increasing age there is decreased survival benefit for ICDs in primary prevention in the DANISH study.[15] In a recent survey study of family practitioners, internal medicine physicians and cardiologists, over a quarter of physicians did not refer patients for a primary prevention ICD because of age alone, and less than a quarter of those surveyed considered patient prognosis before the referral.[13] Evaluating prognosis and estimating meaningful quality of life is inherently difficult in an aging population with multiple complex medical comorbidities. The 1-year mortality in our mixed population of primary and secondary prevention was high at 13% despite a declining Charlson Comorbidity Index. Stein and colleagues showed a similarly high 1-year mortality of 16% in mainly secondary prevention ICD placement.[16] The 1-year mortalities in both our study and Stein's study are substantially higher than what was reported in past randomized controlled trials (RCTs) for both primary and secondary prevention, which ranged from 7–9% and 8–11%, respectively.[4,5,16–19] The majority of our patients received ICD implantation for primary prevention given their associated HFrEF diagnosis without known cardiac arrest. The MADIT-II trial had a similar age distribution to our study with a mean age of 64 ± 10 years.[4] The SCD-HeFT trial recruited a slightly younger cohort with a mean age of 60 years, which may partially account for the reduced 1-year mortality of 7% in SCD-HeFT compared to 9% in MADIT-II.[4,5] MADIT-II had the

Table 1 Baseline characteristics ($n = 17\,901$)

	Mean	Standard deviation
Demographics		
Age (years)	65.8	10.2
Female sex (%)	1.2	0.1
Comorbidities (%)		
Atrial fibrillation	43.1	0.5
Coronary artery disease	81.1	0.4
Chronic kidney disease	42.5	0.5
End-stage renal disease	5.1	0.2
Chronic obstructive pulmonary disease	36.3	0.5
Stoke	12.1	0.3
Cirrhosis	2.5	0.2
Deep venous thrombosis	6.2	0.2
Pulmonary embolism	2.8	0.2
Hypertension	72.4	0.4
Obstructive sleep apnoea	19.5	0.4
Peripheral arterial disease	26.9	0.4
Diabetes	55.8	0.5
Smoking	28.8	0.5
Medications (%)		
Loop diuretics	84.8	0.4
Mineralocorticoid receptor antagonist	53.0	0.5
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	96.7	0.2
Calcium channel blocker	30.6	0.5
Digoxin	40.1	0.5
Nitrates	39.8	0.5
Hydralazine	17.5	0.4
Aspirin	64.8	0.5
Clopidogrel, ticagrelor or prasugrel	49.0	0.5
Statin	93.5	0.2

most similar mean age distribution of patients to our data set and yet with a mean ejection fraction of 23% only had a 9% 1-year mortality compared to 13% in our analysis.[4] It is important to note, however, that although the mean age was similar in MADIT-II to our study, we had a significant proportion of patients that were greater than 80 years in the oldest quartile while MADIT-II had a more narrow range of ages.[4] The patients in our study from a VA clinical setting may be both older and sicker than those in other randomized trials. There is an ongoing clinical trial within the VA Office of Research and Development which is examining the safety and efficacy of primary prevention ICD placement in patients ≥70 years; efficacy endpoints include all-cause mortality, SCD, and quality of life (NCT02121158). This trial and hopefully other future trials will further inform the risk–benefit ratio of primary prevention ICDs in the elderly.

Despite a decreasing Charlson Comorbidity Index along with advancement in ICD technology and procedural technique, patients have a consistently higher annual mortality than what was observed in both primary and secondary prevention RCTs. These observations bring to question whether the patient population sampled in the landmark ICD trials can be generalized to clinical practice. Our population has a very high rate of coronary artery disease (81%) and is therefore more generalizable to the average patient encountered with HFrEF than prior studies with non-ischaemic cardiomyopathy. Our study reflects the mortality likely seen in routine clinical practice and highlights the multiple medical comorbidities encountered in the VA population. Our population is more likely to reflect the treatment and adherence to HF medications of the general population as compared to healthier patients that have been medically optimized as a part of enrollment in prior RCTs. Interestingly, there has been one prior analysis comparing survival between patients receiving primary prevention ICD in RCTs (MADIT-II, SCD-HeFT) and those receiving an ICD in clinical practice and enrolled in a large national registry (National Cardiovascular Data Registry ICD Registry) which did not show any survival difference between groups.[20] It is surprising that we found trends towards worsening 1-year mortality despite mild improvement in comorbidity rates. One-year mortality rates in previous RCTs where patients are medically optimized during enrollment are high. Our findings of higher mortality rates despite a stable to decreasing comorbidity index may indicate that our population is sicker compared to those in RCTs. If we studied mortality in our population with no ICD, we likely would see an even higher mortality rate. With an already high mortality following ICD placement, optimizing patient selection is very important to attempt to isolate higher risk from lower risk patients. The significant difference in short and long-term mortality in patients at either extreme of the age quartiles highlights the importance of considering age as one component of the decision for ICD implantation in the future. Our analysis exhibited a high 1-year mortality, which shows the need for future large-scale studies to determine if ICD therapy is a cost-effective approach by preventing all-cause mortality and SCD in an aging population with an overall decreasing incidence of SCD.[21,22]

The presented data raise several areas of concern for clinical practice and guideline implementation. The first is that in our patient population there appears to be a high 1-year mortality following ICD placement. It is important to assess whether this increased mortality is more representative of real-world clinical practice compared to patients assessed in prior trials. If the 1-year mortality is as high as 13% then the risk–benefit ratio may need to be reassessed. Current guidelines do not consider a strict age cutoff for primary prevention device placement, although many physicians consider increasing age as a deterrent for referral for device placement. Our data support the conclusion that there is both a higher than anticipated 1-year mortality post-ICD placement, and there is an increased risk associated with increasing age alone despite only minor difference in comorbidity burden between the age quartiles.

Limitations

There are several limitations to our analysis; the most important is the inability to distinguish between primary prevention and secondary prevention indications for ICD placement. Although the majority of the HFrEF population had ICD placement for primary prevention, we cannot exclude that there may have been a disproportionate sampling of secondary prevention patients

Table 2 Cox proportional hazard model for predicting 1-year mortality[a]

Variable	Hazard ratio	95% confidence interval	*P*-value
Age	1.04	1.04–1.05	<0.001
Atrial fibrillation	1.10	0.99–1.23	0.078
Coronary artery disease	1.38	1.21–1.58	<0.001
Chronic kidney disease	1.18	1.08–1.30	<0.001
Chronic obstructive pulmonary disease	1.12	1.02–1.22	0.013
Cirrhosis	1.48	1.20–1.84	<0.001
End-stage renal disease	1.73	1.49–2.01	<0.001
Hypertension	0.86	0.78–0.95	0.002
Obstructive sleep apnoea	0.84	0.74–0.94	0.003
Peripheral arterial disease	1.13	1.03–1.24	0.009
Pulmonary embolism	1.40	1.12–1.74	0.003
Smoking	1.11	1.0–1.23	0.042
Diabetes	1.46	1.33–1.60	<0.001
Loop diuretic	1.31	1.14–1.51	<0.001
$P2Y_{12}$ inhibitor	0.92	0.85–1.01	0.07
Aldosterone antagonist	0.91	0.84–0.99	0.034
Anticoagulants	0.87	0.78–0.97	0.012
Angiotensin-converting enzyme inhibitor	0.70	0.58–0.84	<0.001
Calcium channel blocker	0.75	0.68–0.82	<0.001
Statin	0.57	0.49–0.66	<0.001
Digoxin	1.16	1.06–1.26	0.001

[a]Other variables that were non-significant were adjusted for included female gender, stroke, deep venous thrombosis, nitrate, hydralazine and aspirin use.

Table 3 Cox proportional hazard model for predicting 8-year mortality[a]

Variable	Hazard ratio	95% confidence interval	*P*-value
Age	1.04	1.04–1.0	<0.001
Female sex	0.78	0.59–1.03	0.082
Atrial fibrillation	1.07	1.01–1.13	0.033
Coronary artery disease	1.23	1.15–1.3	<0.001
Chronic kidney disease	1.29	1.22–1.35	<0.001
Chronic obstructive pulmonary disease	1.19	1.13–1.25	<0.001
Cirrhosis	1.5	1.32–1.7	<0.001
Deep vein thrombosis	1.1	1.01–1.2	0.03
End-stage renal disease	1.62	1.47–1.78	<0.001
Hypertension	0.89	0.84–0.94	<0.001
Obstructive sleep apnoea	0.89	0.84–0.94	<0.001
Peripheral arterial disease	12	1.10–1.22	<0.001
Pulmonary embolism	1.2.	1.06–1.36	0.005
Smoking	1.14	1.08–1.21	<0.001
Diabetes	1.38	1.31–1.46	<0.001
Loop diuretic	1.38	1.28–1.5	<0.001
$P2Y_{12}$ inhibitor	0.96	0.91–1.01	0.097
Aldosterone antagonist	0.95	0.90–1.0	0.035
Anticoagulants	0.92	0.87–0.98	0.005
Angiotensin-converting enzyme inhibitor	0.76	0.661–0.86	<0.001
Calcium channel blocker	0.84	0. –0.89	<0.001
Statin	0.62	0.56–0.68	<0.001
Digoxin	1.16	1.11–1.22	<0.001
Hydralazine	1.1	1.03–1.7	0.004

[a]Other variables that were non-significant were adjusted for included stroke, nitrate and aspirin use.

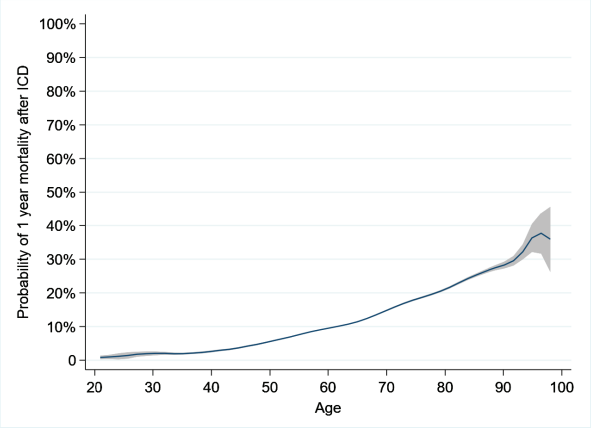

Figure 5 Age and 1-year mortality post-implantable cardioverter-defibrillator (ICD) implantation. The probability of 1-year mortality by age was obtained using a probit model after adjusting for gender, comorbidities, and medications. Grey bar indicates 95% confidence interval.

that could contribute to the increased 1-year mortality observed. Although our mortality percentage was higher than that observed in RCTs for both primary and secondary prevention, we cannot exclude the potential that our patients in the VA clinical setting may have been sicker than those enrolled in other randomized clinical trials.[4,5,16–19] The third limitation is the absence of echocardiographic ejection fraction data. Although we do not have mean ejection fraction recordings for our patients, we did utilize ICD-9-CM codes to identify patients with reduced LVEF. Medication history was also used to help identify patients with reduced LVEF since carvedilol and metoprolol succinate are restricted to HFrEF patients (LVEF ≤35%) with pharmacy review for medication approval in the VA system. The absence of data regarding NYHA functional status and left ventricular function is a limitation as these have been shown to be important predictors of survival post-ICD implantation. Another limitation was the inability to determine what proportion of our patients were on guideline-directed medical therapy prior to ICD placement. Non-adherence and lower rates of guideline-directed medical therapy in the general population could contribute to an increased mortality as compared to similar patients on optimal medical therapy in prior RCTs. Unlike mortality, other minor and major peri-procedural complications were not captured in our analysis. Finally, the VA system serves predominantly men, and female underrepresentation might preclude the extrapolation of the results to women.

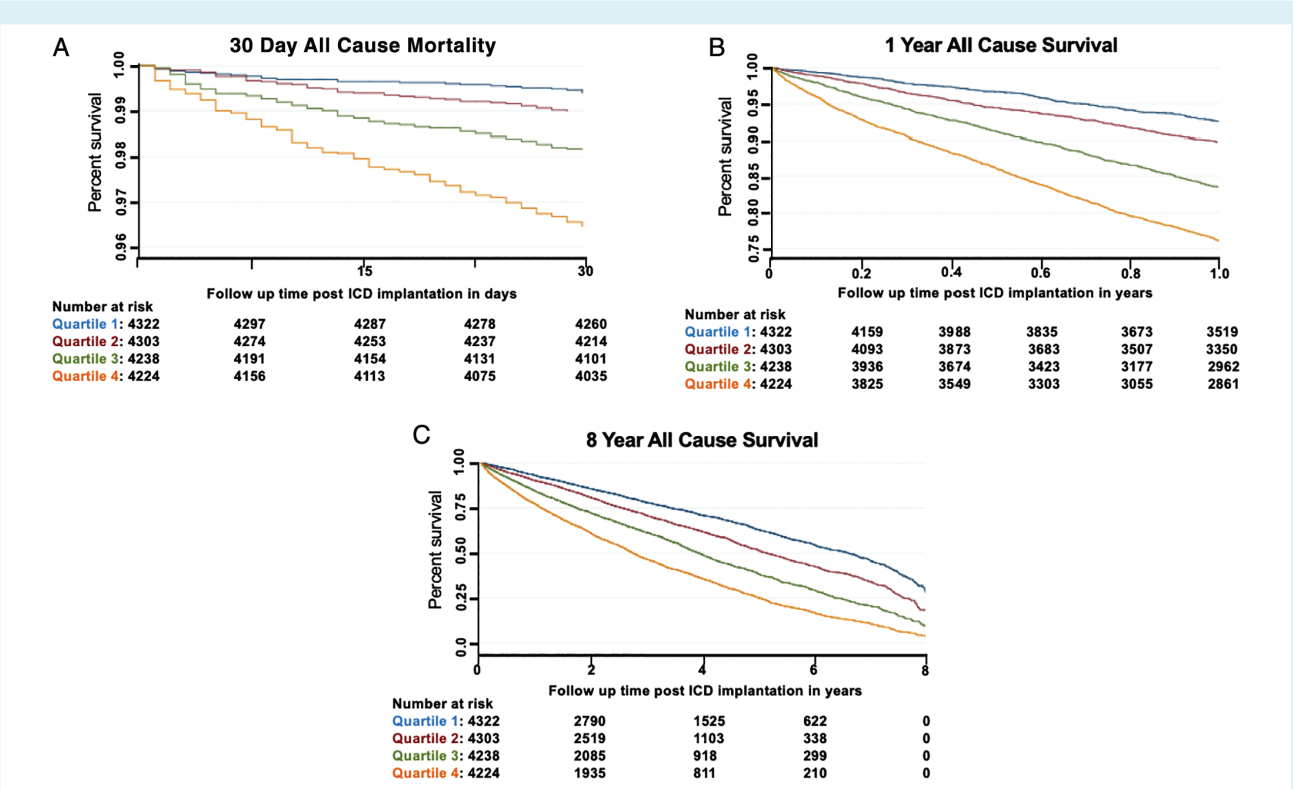

Figure 6 All-cause mortality following new implantable cardioverter-defibrillator (ICD) implantation at (*A*) 30 days, (*B*) 1 year and (*C*) 8 years. Quartile 1 mean age: 55.5 ± 5.6 years, quartile 2: 63.9 ± 1.5) years, quartile 3: 70.6 ± 2.7) years and quartile 4: 81.6 ± 4.2) years. For higher follow up years, the number at risk maybe smaller as there could be limited observations in our sample who received ICD in later years, but have not been followed until the entire study period.

Conclusions

Among patients in the integrated VA Health System with HFrEF undergoing ICD implantation, there was a higher 1-year mortality than shown in previous clinical trials despite a decreasing comorbidity index. Short-term and long-term mortality rates were higher in older patients. The mortality rates highlight the importance of developing better predictive models for mortality in the ICD eligible patient population.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Reason for patient exclusion.

Table S2. Prevalnce of coronary artery disease during the observation period.

Table S3. Change in background medication over the observation period.

Table S4. Incidence rate ratios of our Poisson regression analysis.

Table S5. Age-stratified baseline characteristics.

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