Survival After Implantable Cardioverter-Defibrillator Implantation in the Elderly

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Background—The benefit of implantable cardioverter-defibrillators (ICDs) among elderly patients is controversial and may be attenuated by nonarrhythmic death. We examined the impact of age on device-delivered therapies and outcomes after primary or secondary prevention ICD.

Methods and Results—In a prospective, inclusive registry of 5399 ICD recipients in Ontario, Canada (February 2007 to September 2010), device-delivered therapies and complications were determined at routine clinic visits. Among primary prevention ICD recipients aged 18 to 49 (n=317), 50 to 59 (n=769), 60 to 69 (n=1336), 70 to 79 (n=1242), and ≥80 (n=275) years, mortality increased with age, as follows: 2.1, 3.0, 5.4, 6.9, and 10.2 deaths per 100 person-years, respectively (P<0.001). Secondary prevention ICD recipients aged 18 to 49 (n=114), 50 to 59 (n=244), 60 to 69 (n=481), 70 to 79 (n=462), and ≥80 (n=159) years also exhibited increasing mortality, as follows: 2.2, 3.8, 6.1, 8.7, and 15.5 deaths per 100 person-years, respectively (P<0.001). However, rates of appropriate shock were similar across age groups: from 6.7 (18–49 years) to 4.2 (≥80 years) per 100 person-years after primary prevention ICDs (P=0.139) and from 11.4 (18–49 years) to 11.9 (≥80 years) per 100 person-years after secondary prevention ICDs (P=0.993). Covariate-adjusted competing risk analysis demonstrated higher risk of death (P_{trend}<0.001 for both primary and secondary prevention) but no significant decline in appropriate shocks with older age after primary (P=0.130) or secondary (P=0.810) prevention ICD implantation.

Conclusions—Whereas elderly patients exhibited increased mortality after ICD implantation, rates of appropriate device shocks were similar across age groups. Decisions regarding ICD candidacy should not be based on age alone but should consider factors that predispose to mortality despite defibrillator implantation. **(*Circulation*. 2013;127:2383-2392.)**

Key Words: aged ■ defibrillators, implantabale ■ prognosis ■ prospective studies ■ registries

Implantable cardioverter-defibrillators (ICDs) used in appropriately selected patients at high risk of sudden cardiac death are associated with reduction in arrhythmic death.[1] Recommendations for ICDs are based on large randomized, controlled trials, which often enroll highly selected patients who are often young with few comorbidities. In contrast, the average patient with heart failure and severe left ventricular systolic dysfunction is aged >65 years with multiple comorbidities. With the aging population, the number of elderly patients being considered for ICD implantation is increasing, and an estimated 28% of those deemed potentially eligible by conventional criteria are octogenarians.[2] However, with advancing age and comorbidity burden, the relative contribution of nonarrhythmic causes of death may increase,[3,4] potentially attenuating the benefits of ICD therapy. Current guidelines do not specifically address the appropriateness or prognosis of ICD implantation with advanced age.[1,5,6]

Clinical Perspective on p 2392

Randomized trials can underrepresent elderly patients, while population-based registries may illuminate the impact and outcomes of ICDs implanted in this group. The Ontario ICD Database is a large, population-based, prospective registry of ICD recipients referred for primary or secondary prevention defibrillator implantation. Using this registry, we examined all-cause mortality, appropriate and inappropriate defibrillator shocks, hospitalization, and early complications in elderly ICD

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recipients. We also investigated clinical factors associated with mortality to provide guidance when considering candidates for ICD implantation in older age strata.

Methods

The Ontario ICD Database

The design and methodology of the Ontario ICD Database have been described previously.[7] The Ontario ICD Database prospectively collected information on patient characteristics, device indication, and implant-related data from all 10 adult defibrillator implantation centers in the province. Data were collected by cardiac electrophysiologists and trained research coordinators at ICD implantation centers, who entered real-time data into a secure, firewall- and password-protected Web-based registry. Clinical and device-related events occurring during follow-up were captured during defibrillator clinic visits at either the implanting hospital or peripheral device clinics.[7] The Ontario ICD Database used continuous data quality assessments via automated logic and range checks including dates of all events, notification of uncoded data elements, and random site audits performed in 5% of patients, ensuring κ statistic or crude agreement rates ≥0.7.

Patients

We examined patients undergoing de novo ICD implantation for primary or secondary prevention between February 2007 and September 2010. Patient data were collected at initial evaluation, at the time of ICD implantation, and at each device clinic follow-up. Data collection was mandated by the Ontario Ministry of Health and Long-term Care, and therefore we captured data on all patients undergoing defibrillator implantation at a province-wide level. Under Ontario health information privacy legislation, data were acquired on all registry patients without informed consent, and therefore participation bias was precluded. We compared patients in the following age categories: 18 to 49 (reference category), 50 to 59, 60 to 69, 70 to 79, and ≥80 years. In descriptive analyses, those aged 18 to 59 years were grouped together because of small cell sizes in the <50-years age category. In this analysis, we excluded patients who were cardiac transplantation candidates and those with congenital heart disease, hypertrophic cardiomyopathy, infiltrative diseases, Brugada syndrome, arrhythmogenic right ventricular dysplasia, congenital long-QT syndrome, or other inherited arrhythmia syndromes.

Administrative Data Sources

Using the patient's unique, encrypted health card number, we linked the following data sources to the clinical data in the Ontario ICD Database. The Canadian Institute for Health Information Discharge Abstract Database was used to identify hospitalizations, and the Registered Persons Database was used to determine occurrence of death. Cardiac admissions were identified by *International Classification of Diseases, Tenth Revision* (Canada) codes I11, I20–I25, I30–I39, I41–I52, I01–I02, I05–I09, I95, I97, and R57.0. Cardiovascular hospitalizations included all cardiac admission codes, including *International Classification of Diseases, Tenth Revision* (Canada) codes I60–I69, I10, I12, I13, I15, I26–I28, I57, I70–I74, I77–I82, G45, G46, R02, and R55. All other hospitalizations were designated as noncardiovascular.

Outcomes

The primary outcomes were (1) total mortality and (2) appropriate ICD shock for electrical therapy of ventricular tachyarrhythmia. Additional secondary outcomes included (1) appropriate therapy with either shock or antitachycardia pacing, (2) inappropriate shocks, (3) device-related complications within 45 days of implantation, and (4) hospitalizations. ICD therapies were classified as appropriate or inappropriate by the on-site treating physician and were reviewed by an external panel of 3 cardiac electrophysiologists, demonstrating excellent agreement for appropriate shock (κ statistic=0.928) and therapy (κ statistic=0.901) with crude agreement rates >99% for both outcomes.[8] To explore conditions that contributed to mortality, we identified all hospitalizations that occurred within 30 days before death and determined the primary reason for the hospital admission. Hospitalizations leading to death were categorized as cardiovascular (subcategory cardiac) or noncardiovascular. Complications were defined as major or minor on the basis of previously described consensus definitions.[9–11] In general, major complications required hospitalization, lead or device revision, or substantive parenteral therapy.

Statistical Analysis

Data are presented as mean±SD for continuous variables or proportions for dichotomous variables. Comparisons were performed across age groups with the use of global tests of significance, such as ANOVA for continuous covariates and the χ^2 statistic for categorical variables. Rates of appropriate ICD shock, appropriate device-delivered

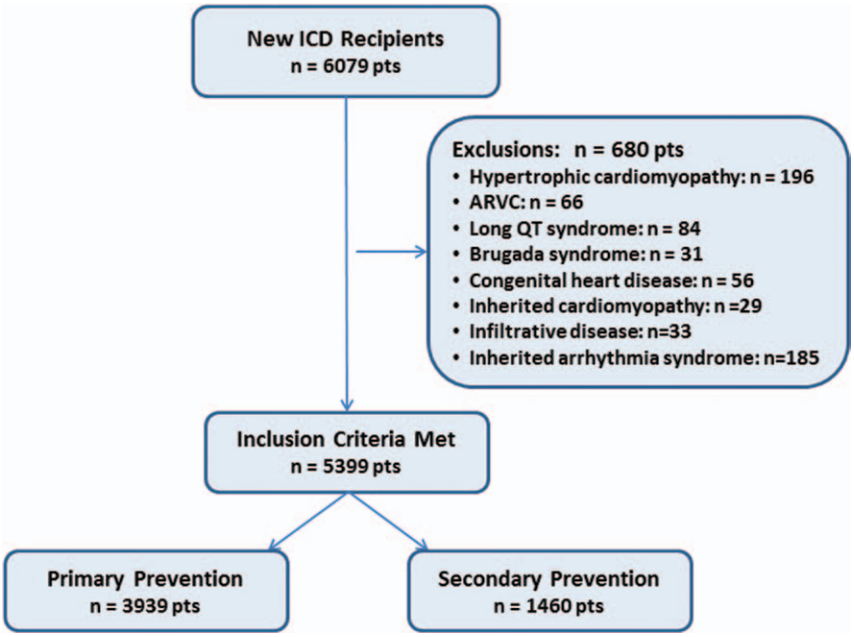

Figure 1. Patient flow diagram. ARVC indicates arrhythmogenic right ventricular cardiomyopathy; and ICD, implantable cardioverter-defibrillator.

Table 1. Baseline Characteristics

	Primary Prevention					Secondary Prevention				
Age group, y	18–59	60–69	70–79	≥80	*P* Value	18–59	60–69	70–79	≥80	*P* Value
Total n	1086	1336	1242	275		358	481	462	159	
Demographic data										
Age, mean (SD), y	51.6 (7.0)	64.5 (2.8)	74.1 (2.8)	82.3 (2.3)	<0.001	51.3 (6.9)	64.6 (2.8)	74.8 (2.8)	82.6 (2.6)	<0.001
Male, n (%)	857 (78.9)	1068 (79.9)	1014 (81.6)	219 (79.6)	0.413	288 (80.4)	409 (85.0)	391 (84.6)	125 (78.6)	0.106
Ischemic cardiomyopathy, n (%)	633 (58.3)	960 (71.9)	959 (77.2)	220 (80.0)	<0.001	256 (71.5)	393 (81.7)	398 (86.1)	143 (89.9)	<0.001
NYHA HF class, n (%)										
I	284 (26.2)	297 (22.2)	275 (22.1)	54 (19.6)	0.011	200 (55.9)	259 (53.8)	200 (43.3)	63 (39.6)	<0.001
II	440 (40.5)	573 (42.9)	481 (38.7)	111 (40.4)		107 (29.9)	140 (29.1)	187 (40.5)	69 (43.4)	
III–IV	362 (33.3)	466 (34.9)	486 (39.1)	110 (40.0)		51 (14.2)	82 (17.0)	75 (16.2)	27 (17.0)	
Syncope, n (%)	105 (9.7)	123 (9.2)	158 (12.7)	51 (18.5)	<0.001	200 (55.9)	270 (56.1)	258 (55.8)	81 (50.9)	0.694
Atrial fibrillation, n (%)	178 (16.4)	382 (28.6)	470 (37.8)	121 (44.0)	<0.001	68 (19.0)	136 (28.3)	179 (38.7)	75 (47.2)	<0.001
Diabetes mellitus, n (%)	346 (31.9)	578 (43.3)	464 (37.4)	73 (26.5)	<0.001	95 (26.5)	161 (33.5)	144 (31.2)	47 (29.6)	0.187
Hypertension, n (%)	498 (45.9)	781 (58.5)	763 (61.4)	180 (65.5)	<0.001	185 (51.7)	276 (57.4)	316 (68.4)	117 (73.6)	<0.001
Stroke or TIA, n (%)	105 (9.7)	175 (13.1)	187 (15.1)	46 (16.7)	<0.001	24 (6.7)	55 (11.4)	82 (17.7)	28 (17.6)	<0.001
PVD, n (%)	81 (7.5)	137 (10.3)	160 (12.9)	36 (13.1)	<0.001	30 (8.4)	48 (10.0)	75 (16.2)	18 (11.3)	0.002
Chronic lung disease, n (%)	142 (13.1)	268 (20.1)	228 (18.4)	35 (12.7)	<0.001	41 (11.5)	83 (17.3)	80 (17.3)	26 (16.4)	0.082
Current smoker, n (%)	250 (23.0)	198 (14.8)	89 (7.2)	10 (3.6)	<0.001	102 (28.5)	82 (17.0)	46 (10.0)	9 (5.7)	<0.001
Clinical information										
Systolic BP, mean (SD), mm Hg	116.6 (18.6)	121.1 (19.3)	124.6 (20.7)	127.3 (20.9)	<0.001	118.3 (18.3)	124.7 (21.1)	126.3 (20.8)	128.3 (19.8)	<0.001
Hemoglobin, mean (SD), g/L	140.0 (16.4)	135.1 (17.0)	132.2 (16.6)	130.0 (16.9)	<0.001	128.9 (19.8)	126.2 (19.7)	124.1 (18.8)	121.0 (17.4)	<0.001
Creatinine, mean (SD), µmol/L	96.6 (49.1)	110.4 (65.1)	120.6 (63.5)	129.9 (82.0)	<0.001	98.2 (56.1)	110.9 (79.4)	118.1 (61.6)	117.0 (39.2)	<0.001
Creatinine, mean (SD), mg/dL	1.09 (0.56)	1.25 (0.74)	1.36 (0.72)	1.47 (0.93)		1.11 (0.63)	1.25 (0.90)	1.34 (0.70)	1.32 (0.44)	
QRS duration, mean (SD), ms	125.4 (34.8)	132.9 (34.8)	141.0 (35.6)	141.3 (33.6)	<0.001	118.8 (30.0)	124.9 (31.0)	127.6 (37.8)	129.8 (33.4)	<0.001
LA size, mean (SD), mm	45.5 (9.0)	45.4 (9.3)	46.8 (9.6)	45.6 (9.3)	0.004	41.7 (8.7)	43.3 (9.0)	44.7 (8.4)	44.7 (7.5)	<0.001
LVEF, n (%)*										
≤20	254 (23.4)	295 (22.1)	223 (18.0)	58 (21.1)	0.022	51 (14.2)	49 (10.2)	47 (10.2)	9 (5.7)	0.120
21–30	600 (55.2)	751 (56.2)	706 (56.8)	128 (46.5)		73 (20.4)	118 (24.5)	106 (22.9)	34 (21.4)	
≥31	194 (17.9)	240 (18.0)	229 (18.4)	61 (22.2)		150 (41.9)	203 (42.2)	213 (46.1)	69 (43.4)	

BP indicates blood pressure; HF, heart failure; LA, left atrium; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PVD, peripheral vascular disease; and TIA, transient ischemic attack.

*LVEF with nonmissing values shown.

therapies, and inappropriate shocks were determined as rates per 100 person-years of follow-up with censoring at death.

We used regression methods described by Harrell,[12] in which potentially clinically important predictors of outcome with $P<0.25$ were considered for entry into a Fine and Gray competing risk time-to-event model. Covariates were retained in the final nonparsimonious multivariable model if the P value was <0.20 for competing risk of either death or appropriate ICD shock. All models were adjusted for sex irrespective of its nominal statistical significance. Potential variables considered in multivariable competing risks analysis of mortality versus appropriate ICD shock included New York Heart Association class, left ventricular ejection fraction (LVEF), QRS duration, cardiac resynchronization therapy, type of cardiomyopathy, family history of sudden cardiac death, syncope, atrial fibrillation, diabetes mellitus, hypertension, transient ischemic attack or stroke, peripheral vascular disease, dialysis, chronic obstructive pulmonary disease, active cancer, blood pressure, serum sodium, hemoglobin, blood urea nitrogen, glomerular filtration rate estimated with Modification of Diet in Renal Disease equation,[13] and medications (selected definitions are shown in the Appendix in the online-only Data Supplement).[14] Predictors of total death for use in noncompeting time-to-event analyses were identified by multiple Cox regression, retaining covariates with $P<0.05$. In the absence of an outcome event, time-to-event analyses were censored on the last follow-up date of December 15, 2011. Cumulative incidence curves were constructed separately for primary and secondary prevention cohorts. All tests of significance were 2-tailed, with $P<0.05$ considered statistically significant. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC) and with R for Fine and Gray competing risks analysis.

Results

Study Population

Among 6079 patients who underwent de novo ICD implantation, 5399 met study inclusion criteria. Indications for ICD implantation were primary (n=3939) and secondary (n=1460) prevention (Figure 1), with mean ages at implantation of 65.2±10.7 and 66.5±11.2 years, respectively (80.9% men). Elderly patients aged 70 to 79 and ≥80 years accounted for 31.6% and 8.0% of all ICD implantations, respectively. Among those referred for a device, ICD implantation rates were 81.3% (18–49 years), 80.6% (50–59 years), 81.9% (60–69 years), 81.5% (70–79 years), and 72.3% (≥80 years) overall

Table 2. Device Type and Medications Among Implantable Cardioverter-Defibrillator Recipients

	Primary Prevention					Secondary Prevention				
Age group, y	18–59	60–69	70–79	≥80	*P* Value	18–59	60–69	70–79	≥80	*P* Value
Total n	1086	1336	1242	275		358	481	462	159	
Device type, n (%)										
CRT-D	309 (28.5)	423 (31.7)	476 (38.3)	93 (33.8)	<0.001	33 (9.2)	52 (10.8)	46 (10.0)	10 (6.3)	0.552
Dual chamber	248 (22.8)	334 (25.0)	277 (22.3)	66 (24.0)		148 (41.3)	202 (42.0)	207 (44.8)	76 (47.8)	
Single chamber	529 (48.7)	579 (43.3)	489 (39.4)	116 (42.2)		177 (49.4)	227 (47.2)	209 (45.2)	73 (45.9)	
Medications, n (%)										
β-Blockers	991 (91.3)	1181 (88.4)	1062 (85.5)	226 (82.2)	<0.001	322 (89.9)	422 (87.7)	396 (85.7)	136 (85.5)	0.279
ACEI or ARB	992 (91.3)	1215 (90.9)	1111 (89.5)	230 (83.6)	0.001	296 (82.7)	395 (82.1)	369 (79.9)	124 (78.0)	0.499
Spironolactone	384 (35.4)	459 (34.4)	346 (27.9)	70 (25.5)	<0.001	68 (19.0)	83 (17.3)	73 (15.8)	23 (14.5)	0.527
Loop diuretics	660 (60.8)	880 (65.9)	851 (68.5)	197 (71.6)	<0.001	118 (33.0)	196 (40.7)	215 (46.5)	89 (56.0)	<0.001
Oral anticoagulant	292 (26.9)	441 (33.0)	445 (35.8)	98 (35.6)	<0.001	56 (15.6)	93 (19.3)	120 (26.0)	46 (28.9)	<0.001
Amiodarone	86 (7.9)	132 (9.9)	154 (12.4)	34 (12.4)	0.003	108 (30.2)	172 (35.8)	215 (46.5)	67 (42.1)	<0.001
Aspirin	642 (59.1)	829 (62.1)	744 (59.9)	168 (61.1)	0.486	252 (70.4)	359 (74.6)	338 (73.2)	115 (72.3)	0.590
Clopidogrel	224 (20.6)	245 (18.3)	205 (16.5)	52 (18.9)	0.086	120 (33.5)	149 (31.0)	129 (27.9)	49 (30.8)	0.387

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and CRT-D, cardiac resynchronization therapy defibrillator.

(*P*=0.008), with significantly higher rates of refusal among octogenarians (Table I in the online-only Data Supplement). Median follow-up was 670 days (25th, 75th percentiles: 376, 1007). Baseline characteristics are shown in Tables 1 and 2. LVEF ≤35% was present among 93.0% of primary and 59.3% of secondary prevention patients. Ischemic heart disease accounted for 70.4% of primary and 81.5% of secondary prevention patients, increasing in prevalence with age. Elderly patients were more likely to exhibit atrial fibrillation, hypertension, previous stroke, reduced kidney function, and wider QRS duration, but LVEF and left atrial dimension were similar across age groups. Most patients were in receipt of high rates of evidence-based cardiovascular medications.

Device-Related Outcomes

There were 373, 744, and 164 primary prevention patients who received an appropriate shock, appropriate therapy, and inappropriate therapy, whereas 284, 498, and 77 secondary prevention patients received these types of therapies, respectively (Table 3). Rates of appropriate shock were nonsignificantly lower with older age, as follows: 6.7 (18–49 years), 5.2 (50–59 years), 5.0 (60–69 years), 5.1 (70–79 years), and 4.2 (≥80 years) events per 100 person-years for primary prevention (*P*=0.139). Similar rates of appropriate shocks were observed among secondary prevention ICD recipients, as follows: 11.4 (18–49 years), 10.3 (50–59 years), 13.9 (60–69 years), 11.2 (70–79 years), and 11.9 (≥80 years) events per 100 person-years (*P*=0.993).

Appropriate ICD therapy was successful in terminating the arrhythmia in 97% of primary and 96% of secondary prevention patients. Inappropriate shock rates were <3.5% overall but tended to be slightly higher in younger primary prevention patients (Table 3). Early major 45-day complication rates were similar between age strata (Table 3).

Mortality

During 7688 person-years of follow-up, there were 415 deaths among primary prevention ICD recipients. Among secondary prevention patients, there were 194 deaths during 2761 person-years of follow-up. Deaths increased with older age after both primary and secondary prevention implantations; however, the incremental mortality effect was more pronounced in the secondary prevention group (Table 4; both *P*<0.001). Cardiovascular and noncardiovascular hospitalizations that ended in death increased with age (Table 4). Older age was a significant predictor of death in multivariable analysis of primary and secondary prevention ICDs (Table II in the online-only Data Supplement).

Competing Risk Analysis

Cumulative incidence plots of appropriate shock competing with death for primary and secondary prevention demonstrated higher risks of death among older ICD recipients but lesser separation of appropriate shocks according to age group (Figures 2 and 3 and Table III in the online-only Data Supplement). Competing risk analyses of death competing with occurrence of appropriate shocks examining the impact of age are shown in Table 5 (full models are shown in Tables IV and V in the online-only Data Supplement). The adjusted hazard ratio for appropriate shock competing with death decreased nonsignificantly, with no significant trend for older age groups among primary (*P*=0.130) and secondary (*P*=0.810) prevention ICD recipients. The hazard ratio for death increased with older age category (*P*<0.001), with significant increases beginning in the 60- to 69-year age group for primary prevention ICD recipients and ≥80-year age group for secondary prevention ICD recipients.

Factors Affecting Mortality

Primary prevention ICD recipients aged ≥60 years and secondary prevention ICD patients aged ≥80 years experienced increased mortality risk on multivariable analysis (Table 5). Parsimonious multivariable predictors of death are shown in Table II in the online-only Data Supplement. Multivariable

Table 3. Device-Related Outcomes

Outcome	18–49 y	50–59 y	60–69 y	70–79 y	≥80 y	*P* Value
Primary prevention	317	769	1336	1242	275	
Device therapies, n (rate per 100 person-years)						
Appropriate shock	39 (6.7)	78 (5.2)	121 (5.0)	116 (5.1)	19 (4.2)	0.139
Appropriate therapy	68 (12.7)	150 (10.8)	252 (11.1)	228 (10.7)	46 (11.1)	0.386
Inappropriate shock	24 (4.1)	39 (2.5)	51 (2.0)	39 (1.7)	11 (2.4)	0.003
Complications, n (rate per 100 patients)*						
Complication (major or minor) within 45 d	22 (7.4)	43 (5.9)	86 (6.8)	90 (8.0)	18 (7.1)	0.419
Major complication within 45 d	12 (4.0)	23 (3.1)	48 (3.7)	51 (4.3)	11 (4.2)	0.344
Secondary prevention	114	244	481	462	159	
Device therapies, n (rate per 100 person-years)						
Appropriate shock	22 (11.4)	44 (10.3)	106 (13.9)	86 (11.2)	26 (11.9)	0.993
Appropriate therapy	38 (24.7)	70 (18.1)	175 (26.8)	156 (23.6)	59 (34.0)	0.059
Inappropriate shock	8 (3.6)	14 (2.9)	29 (3.4)	15 (1.7)	11 (4.6)	0.488
Complications, n (rate per 100 patients)*						
Complication (major or minor) within 45 d	8 (7.5)	14 (6.1)	32 (7.1)	33 (7.6)	15 (10.7)	0.283
Major complication within 45 d	SC† (4.6)	9 (3.9)	24 (5.3)	23 (5.2)	7 (4.8)	0.704

*Complication rates are per 100 patients followed for 45 days.
†SC indicates that small cell sizes cannot be reported.

predictors of mortality common to both groups included New York Heart Association class, peripheral vascular disease, and use of loop diuretics. Syncope, reduced glomerular filtration rate, and left atrial size were predictors of mortality in primary prevention patients. There was no significant interaction between age and cardiac resynchronization therapy versus non–cardiac resynchronization therapy device type in multivariable-adjusted models for death among primary ($P_{interaction}$=0.149) and secondary ($P_{interaction}$=0.520) prevention defibrillator recipients.

Death after appropriate shock was highest among elderly primary and secondary prevention patients (Figures 4 and 5). After an appropriate shock, the adjusted hazard ratios for death per decade were 1.28 (95% confidence interval,

Table 4. Total Mortality and Prefatal Hospitalizations

Outcome	18–49 y	50–59 y	60–69 y	70–79 y	≥80 y	*P* Value
Primary prevention	317	769	1336	1242	275	
Mortality, n (rate per 100 person-years)						
Death after ICD implantation	13 (2.1)	47 (3.0)	140 (5.4)	167 (6.9)	48 (10.2)	<0.001
Death after successful appropriate shock	SC* (7.4)	SC* (4.9)	22 (15.0)	21 (14.8)	SC* (22.6)	0.014
Prefatal hospitalizations, n (rate per 100 person-years)						
Cardiac hospitalization	91 (17.4)	181 (13.2)	324 (14.5)	344 (17.0)	83 (21.1)	0.035
Cardiac hospitalization leading to death	8 (1.3)	13 (0.8)	42 (1.6)	37 (1.5)	17 (3.6)	0.005
Cardiovascular hospitalization	92 (17.8)	197 (14.6)	345 (15.6)	373 (18.7)	95 (25.1)	0.003
Cardiovascular hospitalization leading to death	8 (1.3)	15 (0.9)	45 (1.7)	42 (1.7)	18 (3.8)	0.002
Noncardiovascular hospitalization leading to death	SC* (0.2)	SC* (0.3)	19 (0.7)	41 (1.7)	11 (2.3)	<0.001
Secondary prevention	114	244	481	462	159	
Mortality, n (rate per 100 person-years)						
Death after ICD implantation	SC* (2.2)	19 (3.8)	54 (6.1)	78 (8.7)	38 (15.5)	<0.001
Death after successful appropriate shock	0 (0.0)	0 (0.0)	9 (6.8)	19 (16.7)	6 (21.0)	<0.001
Prefatal hospitalizations, n (rate per 100 person-years)						
Cardiac hospitalization	28 (14.6)	68 (16.7)	129 (17.3)	147 (20.8)	51 (26.0)	0.013
Cardiac hospitalization leading to death	SC* (1.3)	7 (1.4)	13 (1.5)	15 (1.7)	9 (3.6)	0.115
Cardiovascular hospitalization	30 (15.7)	72 (18.1)	142 (19.3)	162 (23.4)	58 (30.2)	0.003
Cardiovascular hospitalization leading to death	SC* (1.3)	8 (1.6)	16 (1.8)	18 (2.0)	11 (4.4)	0.046
Noncardiovascular hospitalization leading to dveath	0 (0)	SC* (1.0)	12 (1.3)	26 (2.9)	10 (4.0)	<0.001

ICD indicates implantable cardioverter-defibrillator.
*SC indicates that small cell values are not shown.

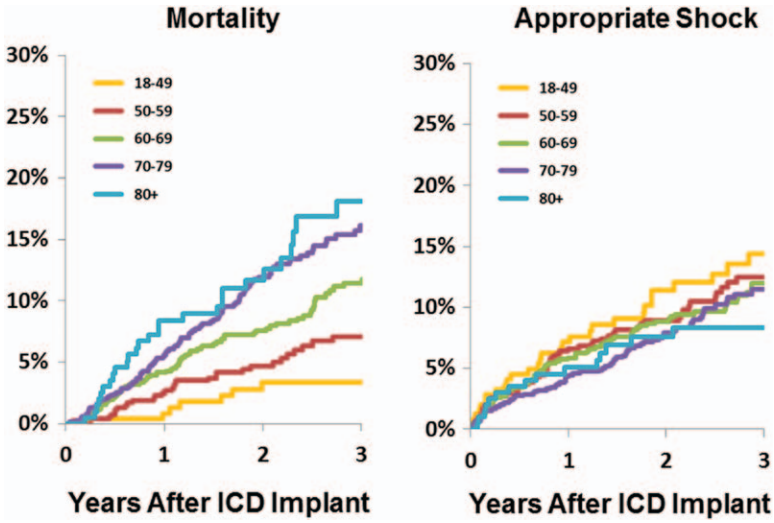

Figure 2. Cumulative incidence of death and appropriate shock in competing risk analysis after primary prevention implantable cardioverter-defibrillator (ICD) implantation.

1.14–1.44; *P*=0.001) for primary and 1.34 (95% confidence interval, 1.13–1.59; *P*<0.001) for secondary prevention after parsimonious covariable adjustment (see Table II in the online-only Data Supplement for model covariates).

Discussion

It has been postulated that elderly patients with left ventricular systolic dysfunction or prior ventricular arrhythmias may not derive the same benefit from ICD implantation as younger patients.[15,16] Information on the utilization and effectiveness of ICD implantation in the elderly for prevention of sudden arrhythmic death is increasingly important with the aging population. In this population-based registry, we found that elderly patients undergoing primary or secondary prevention ICD implantation experienced rates of appropriate and inappropriate shock similar to those of their younger counterparts. Although 45-day complications were not increased, deaths increased significantly with older recipient age.

Previous randomized studies have reported divergent results on the benefit of ICDs in the elderly. In a Multicenter Automatic Defibrillator Implantation trial II (MADIT-II) substudy evaluating 204 elderly patients (aged >75 years) with ischemic cardiomyopathy, there was a nonsignificant trend toward benefit with ICD therapy (hazard ratio, 0.56; 95% confidence interval, 0.29–1.08; *P*=0.08).[17] Subgroup analysis of patients aged >65 years in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) and Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) studies also showed little mortality benefit.[18,19] A meta-analysis of secondary prevention trials (Cardiac Arrest Study Hamburg [CASH], Antiarrhythmics Versus Implantable Defibrillators [AVID], Canadian Implantable Defibrillator Study [CIDS]) showed that patients aged >75 years did not derive all-cause mortality benefit with a hazard ratio of 1.06 (95% confidence interval, 0.69–1.64; *P*=0.79).[15] However, these randomized trials enrolled selected patient subsets and were not drawn from population-based cohorts. The underrepresentation of elderly patients in randomized trials, varying thresholds for defining advanced age, and inconsistent results necessitated an in-depth examination of a large population registry with outcomes reported to guide clinical decisions.

Our study extends the existing literature by providing further insights on the outcomes of elderly ICD recipients. A retrospective review of new ICD implantations between 1997 and 2003 with the use of a large administrative

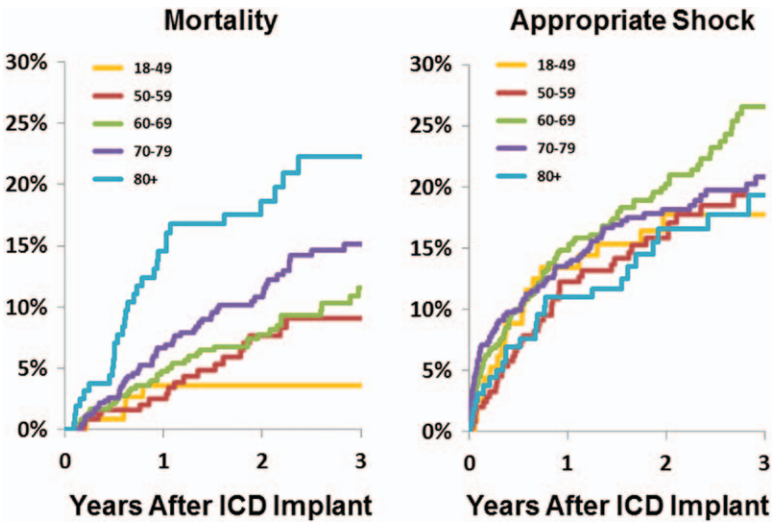

Figure 3. Cumulative incidence of death and appropriate shock in competing risk analysis after secondary prevention implantable cardioverter-defibrillator (ICD) implantation.

Table 5. Effect of Age on Mortality and Appropriate Shocks in Competing Risk Analysis

	Hazard Ratio	95% CI	P_{trend} Value
Competing risk analysis: primary prevention*			
Death			
Age 18–49 y	Reference	Reference	
Age 50–59 y	1.56	0.71–3.39	
Age 60–69 y	2.10	1.01–4.39	<0.001
Age 70–79 y	2.42	1.16–5.06	
Age ≥80 y	3.01	1.36–6.68	
Appropriate shock			
Age 18–49 y	Reference	Reference	
Age 50–59 y	0.83	0.54–1.29	
Age 60–69 y	0.77	0.50–1.18	0.130
Age 70–79 y	0.68	0.44–1.07	
Age ≥80 y	0.71	0.38–1.34	
Competing risk analysis: secondary prevention†			
Death			
Age 18–49 y	Reference	Reference	
Age 50–59 y	1.41	0.51–3.89	
Age 60–69 y	1.56	0.59–4.08	<0.001
Age 70–79 y	1.88	0.72–4.93	
Age ≥80 y	3.61	1.35–9.67	
Appropriate shock			
Age 18–49 y	Reference	Reference	
Age 50–59 y	0.91	0.55–1.50	
Age 60–69 y	1.15	0.73–1.82	0.810
Age 70–79 y	0.89	0.55–1.45	
Age ≥80 y	0.79	0.43–1.44	

*Primary prevention models adjusted for sex and other significant covariates: New York Heart Association class, ischemic vs nonischemic disease, syncope, peripheral vascular disease, chronic lung disease, current smoking, glomerular filtration rate, QRS duration, left atrial size, angiotensin-converting enzyme inhibitor or receptor blocker, and loop diuretic use.

†Secondary prevention models adjusted for sex and other significant covariates: New York Heart Association class, ischemic vs nonischemic disease, syncope, diabetes mellitus, hypertension, stroke or transient ischemic attack, peripheral vascular disease, chronic lung disease, hemoglobin, glomerular filtration rate, QRS duration, left ventricular ejection fraction, angiotensin-converting enzyme inhibitor or receptor blocker, and loop diuretic use.

database showed that age >75 years, recent-onset heart failure, and noncardiac comorbidities were independent predictors of death.[3] However, this study did not distinguish primary and secondary prevention indications and lacked important clinical information, including laboratory values, LVEF, and New York Heart Association class. Tsai et al[20] examined a large population of primary prevention ischemic cardiomyopathy patients from the National Cardiovascular Data ICD Registry and found that age was only a weak predictor of nonarrhythmic death after covariate adjustment, but only in-hospital outcomes were reported. Epstein et al[21] evaluated outcomes from the Advancements in ICD Therapy Registry and found that noncardiac death was more frequent but the sudden cardiac death rate was similar among elderly patients. Chan et al[22] compared a prospective cohort of 123 ICD recipients aged >75 years with 146 patients without the device and showed a significant reduction in mortality. Koplan et al[23] demonstrated shorter median survival among octogenarian ICD recipients at 4.2 years compared with 7 years in patients aged 60 to 70 years. However, these prior studies did not stratify by prophylactic indication, nor did they systematically examine prognosis after device implantation or appropriate ICD shock. In addition, data on ICD therapies, cause of death, and complication rates were not explored. Prior observational studies have also evaluated small samples at single centers and lacked sufficient clinical data to control for confounders.[24,25]

The current report is novel because the data were collected in a prospective fashion with detailed longitudinal follow-up. Outcomes were determined bimodally with the use of a combination of both clinical assessments and passive follow-up through well-established administrative databases. We therefore comprehensively captured important outcomes, including death, hospitalization, appropriate ICD therapy, and complications. The registry was mandated by the single payer of healthcare services in Ontario, and participation from all ICD implantation centers was required. Thus, we were able to study all patients in a robust multicenter fashion irrespective of age and comorbidities. To our knowledge, this is one of the largest prospective and longitudinal registries of ICD implantation in a contemporary cohort of elderly patients.

All-cause annualized mortality rate was 5.4% in the primary prevention cohort, which is similar to that reported in SCD-HeFT but lower than the 7.5% to 8.5% rate reported in other primary prevention trials.[18,26,27] The annual mortality rate of 7% for the secondary prevention group was lower than previously reported randomized trial data.[28,29] Improved treatment of heart failure and coronary disease in the last decade along with better patient selection may account for the lower observed mortality rate. Elderly patients demonstrated a higher rate of all-cause death, particularly in the secondary prevention cohort. The appropriate shock rate of 5% for primary prevention was similar to the rate reported in the literature, but the secondary prevention shock rate of 12% was lower than that reported previously.[29,30] This may be explained by a trend toward more thoughtful programming and concomitant use of antiarrhythmic medication to avert unnecessary shocks. After we accounted for clinical differences and comorbidities, the rate of appropriate shock was not different for elderly patients, suggesting that they derive benefit in reduction of arrhythmic death similar to that in younger patients. The effect of an appropriate shock on prognosis in elderly patients has not been systematically examined previously. In our study, appropriate shocks were successful in terminating acute malignant arrhythmia in virtually all patients, and almost all elderly patients survived >30 days after the shock. This refutes the argument that elderly patients are more susceptible to unsuccessful shocks or electromechanical dissociation after ICD shock, coined previously as *cardiac annihilation*.[31]

The annualized inappropriate shock rate of ≈1.5% to 3.5% per year in our study was similar to a rate of 18% at 5 years reported in a recent study,[32] although prior estimates up to 24% over 3 years have been demonstrated.[33] This is likely related to better rhythm discrimination algorithms, more aggressive

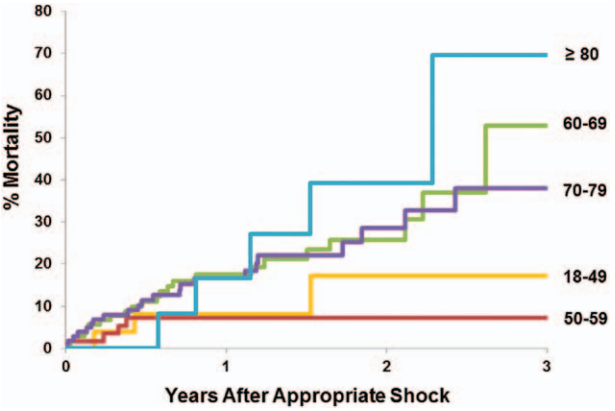

Figure 4. Death after the first appropriate implantable cardioverter-defibrillator shock (primary prevention).

use of antitachycardia pacing, and elimination of unnecessary therapy zones in primary prevention devices. Misdiagnosis of supraventricular tachycardia has accounted for the vast majority of inappropriate ICD shocks in previous studies.[32–34] The higher incidence of atrial fibrillation in our elderly population did not result in a greater number of inappropriate ICD shocks compared with younger patients. Indeed, there were more inappropriate shocks in younger patients, likely as a result of sinus tachycardia. This verifies a report by van Rees et al[32] that determined that age <70 years was a multivariate predictor of inappropriate shock. The impact of inappropriate therapy on mortality was not evaluated and warrants further investigation. Early complications were not increased in elderly patients and were consistent with those found in a prior report.[11]

The findings from this study suggest that ICD implantation in the elderly requires individualized consideration. Age was an independent predictor of death in our contemporary cohort of ICD recipients; however, other factors that also confer increased mortality risk may also be associated with older age. Lee et al[11] used administrative data to show that survival after ICD implantation was inversely related to an increasing number of comorbidities. The MADIT-II Investigators suggested that ICD efficacy for primary prevention in ischemic cardiomyopathy is U-shaped, with attenuated benefit in the lowest- and highest-risk subgroups.[35] Age >70 years was considered a risk factor in this model, suggesting that all elderly patients are classified as at least intermediate risk. Buxton et al[36] performed a similar risk stratification using the Multicenter Unsustained Tachycardia Trial (MUSTT) data set and found that New York Heart Association class, conduction disturbance, history of heart failure, LVEF, atrial fibrillation, and age were predictors of mortality. We found differential impacts of age in primary and secondary prevention groups, which may reflect differences in risk factor profile and the clinically distinct nature of patients based on device indication.

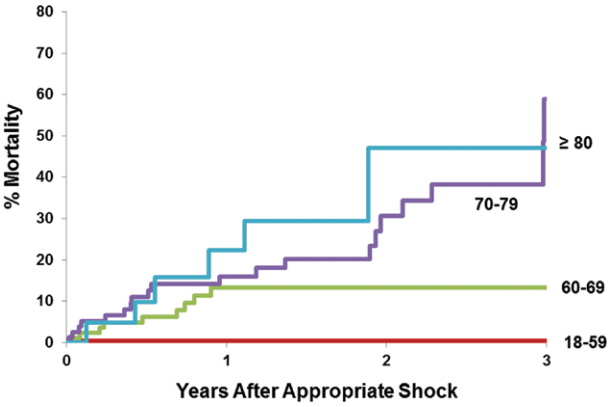

Figure 5. Death after the first appropriate implantable cardioverter-defibrillator shock (secondary prevention).

The limitations of our study should be noted. All patients approved for ICD implantation in Ontario were assessed by board-certified electrophysiologists, who made decisions on the basis of conventional evidence-based indications. The generalizability of our findings to other jurisdictions with more liberal policies of ICD selection is unknown. Although we were unable to compare elderly ICD recipients with nonimplanted controls, our study suggests that the absolute benefit of implanted defibrillators will be diminished in the elderly unless those with fewer concomitant factors contributing to mortality can be selected. We were only able to indirectly determine the mode or cause of death by linkages with administrative hospitalization databases, but we anticipate that deaths were likely primarily nonarrhythmic because all patients were implanted with ICDs, which are highly effective in reducing death from arrhythmia. Finally, although our study is informative about the age-related risk profile of ICD recipients, it should only be used in conjunction with good clinical judgment when medical decisions are made.

Our study represents one of the largest age-stratified systematic evaluations of ICD implantation in primary and secondary prevention patients and explores the risk-benefit relationship in an increasingly important aging population. Although elderly patients with ICDs are at increased risk of death compared with their younger counterparts, the absolute mortality risk is modest when patients are carefully selected. Elderly individuals also received similar rates of appropriate shock without increased risk of adverse events. These results may serve as a guide for discussion when elderly ICD candidates are evaluated. Consideration of comorbidities and known predictors of mortality will help to identify patients who are most likely to derive relative benefit. In sum, older age does not diminish the likelihood of receiving appropriate device-delivered electrical therapies, but elderly patients should be evaluated carefully for comorbidities that may increase the relative risk of nonarrhythmic mortality.

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CLINICAL PERSPECTIVE

The benefit of implantable cardioverter-defibrillators (ICDs) among elderly patients is controversial and may be attenuated by nonarrhythmic death. An estimated 28% of those deemed potentially eligible for ICD implantation by conventional criteria are octogenarians. The Ontario ICD registry is a large, prospective, inclusive database designed to evaluate adjudicated clinical and device-related outcomes after ICD implantation. We examined 5399 primary and secondary prevention ICD recipients between February 2003 and September 2010 to determine the effect of age on mortality, hospitalization, device therapy, and complications. Among primary prevention ICD recipients aged 18 to 49, 50 to 59, 60 to 69, 70 to 79, and ≥80 years, mortality increased significantly with age, as follows: 2.1, 3.0, 5.4, 6.9, and 10.2 deaths per 100 person-years, respectively. Secondary prevention ICD recipients also demonstrated increasing mortality, as follows: 2.2, 3.8, 6.1, 8.7, and 15.5 deaths per 100 person-years. However, rates of appropriate shock were similar across age groups, with a mean of 5.1 and 12.0 events per 100 person-years for primary and secondary prevention cohorts, respectively. Competing risk analysis verified an increase in all-cause mortality but no significant decline in appropriate shocks with advanced age. Furthermore, inappropriate therapy and complications were similar regardless of age. These results suggest that decisions regarding ICD candidacy should not be based on age alone. Cardiovascular and noncardiovascular hospitalizations were elevated in the elderly, reflecting a greater impact of comorbidities. Consideration of prognostic factors that predict mortality in conjunction with individualized clinical judgment will help to identify older patients who are more likely to benefit from ICD implantation.

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SUPPLEMENTAL MATERIAL

Supplemental Appendix . Detailed definitions of clinical covariates

Peripheral vascular disease. Presence of one or more of the following: a) limb amputation for arterial vascular insufficiency, b) vascular surgery of aorta or peripheral artery excluding carotid arteries, c) angioplasty or percutaneous intervention of aorta or peripheral artery excluding carotid arteries, d) angiographically documented non-carotid peripheral artery stenosis >50%, e) noninvasive vascular test documenting aortic aneurysm or ankle-brachial index <70%, f) symptoms of intermittent claudication. Carotid disease and venous disease were not considered peripheral vascular disease.

Syncope. Sudden loss of consciousness with loss of postural tone (not related to anesthesia) with spontaneous recovery.

Supplemental Table 1. Rate of ICD implantation and non-implant reasons by age category

	18-49	50-59	60-69	70-79	≥ 80	p-value
Referred for ICD, N	1005	1635	2731	2507	711	
Implanted, n(%)	817 (81.3)	1317 (80.6)	2237 (81.9)	2043 (81.5)	514 (72.3)	0.008
Not implanted due to:						
(a) Did not meet criteria	93 (9.3)	154 (9.4)	214 (7.8)	173 (6.9)	69 (9.7)	0.069
(b) Patient refusal	56 (5.6)	90 (5.5)	137 (5.0)	144 (5.7)	76 (10.7)	0.002
(c) Deferred to optimize meds	25 (2.5)	42 (2.6)	73 (2.7)	74 (3.0)	15 (2.1)	0.793

Supplemental Table 2. Parsimonious Multivariate Cox Regression Analysis for Predictors of Total Mortality

PRIMARY PREVENTION			
	Hazards Ratio	**95% CI**	**p-value**
Age 18-49 years	reference	reference	reference
50-59 years	1.45	0.72 - 2.93	0.3027
60-69 years	2.21	1.15 - 4.27	0.0173
70-79 years	2.46	1.28 - 4.72	0.0072
≥ 80 years	2.99	1.46 - 6.10	0.0027
Male	1.18	0.88 - 1.58	0.2655
NYHA class			
I or II	reference	reference	reference
III or IV	1.59	1.26 - 2.00	<.001
Syncope	1.43	1.04 - 1.96	0.0273
Peripheral vascular disease	1.95	1.47 - 2.58	<.001
GFR >60 mL/min	reference	reference	reference
<30 mL/min	3.55	2.45 - 5.13	<.001
30-60 mL/min	2.04	1.57 - 2.63	<.001
Left atrial size <45 mm	reference	reference	reference
≥45 mm	1.30	1.02 - 1.66	0.0364
Prescribed ACEI or ARB	0.67	0.50 - 0.91	0.0106
Prescribed loop diuretics	1.55	1.15 - 2.09	0.0037
SECONDARY PREVENTION			
	Hazards Ratio	**95% CI**	**p-value**
Age 18-49 years	reference	reference	reference
50-59 years	1.48	0.55 - 3.97	0.437
60-69 years	2.10	0.84 - 5.28	0.114
70-79 years	2.85	1.15 - 7.07	0.024
≥ 80 years	4.80	1.88 - 12.27	0.011
Male	0.99	0.68 - 1.45	0.969
Ischemic vs. non-ischemic cardiomyopathy	1.73	1.08 - 2.77	0.023
NYHA class			
I or II	reference	reference	reference
III or IV	1.88	1.36 - 2.62	0.0002
Peripheral vascular disease	2.13	1.52 - 3.01	<.001
Chronic lung disease	1.86	1.29 - 3.01	0.0009
Prescribed loop diuretics	1.75	1.29 - 2.37	0.0003

Supplemental Table 3.

Cumulative incidence of death at 1, 2, and 3 years

	Age Group (years)				
Time	18-49	50-59	60-69	70-79	80+
Primary prevention					
1 year	0.83%	2.46%	4.17%	5.55%	8.37%
2 years	3.40%	4.69%	7.57%	11.97%	11.72%
3 years	3.40%	7.11%	11.45%	16.14%	18.10%
Secondary prevention					
1 year	3.61%	2.50%	4.73%	6.67%	14.57%
2 years	3.61%	7.69%	7.76%	10.83%	18.59%
3 years	3.61%	9.08%	11.53%	15.11%	22.27%

Cumulative incidence of appropriate shock at 1, 2, and 3 years

	Age Group (years)				
Time	18-49	50-59	60-69	70-79	80+
Primary prevention					
1 year	7.15%	6.60%	5.85%	4.33%	5.08%
2 years	11.43%	8.92%	8.85%	7.89%	7.54%
3 years	14.40%	12.49%	11.94%	11.44%	8.30%
Secondary prevention					
1 year	13.44%	12.24%	14.87%	13.78%	11.00%
2 years	17.78%	15.85%	20.26%	18.18%	16.63%
3 years	17.78%	19.31%	26.57%	20.81%	19.33%

Supplemental Table 4. Nonparsimonious competing risk model for appropriate shock (competing with death) – Using R – Fine & Gray Model

SHOCK - PRIMARY PREVENTION			
	Hazards Ratio	**95% CI**	**p-Value**
Age 18-49 years	reference	reference	
50-59 years	0.83	0.54 -1.29	
60-69 years	0.77	0.50 – 1.18	0.130
70-79 years	0.68	0.44 – 1.07	
≥ 80 years	0.71	0.38 – 1.34	
Male	1.45	1.02 – 2.06	0.040
Ischemic vs. non-ischemic	0.81	0.62 – 1.05	0.120
NYHA class			
I or II	reference	reference	
III or IV	0.85	0.66 – 1.10	0.220
Syncope	1.45	1.03 – 2.04	0.031
Peripheral vascular disease	0.88	0.59 – 1.32	0.550
Chronic lung disease	1.09	0.77 – 1.55	0.640
Current smoker	1.57	1.14 – 2.16	0.006
GFR >60 mL/min	reference	reference	
<30 mL/min	1.13	0.64 – 2.00	0.240
30-60 mL/min	1.20	0.92 – 1.57	
QRS duration (per 10 msec)	0.97	0.96 – 0.99	0.008
Left atrial size <45 mm	reference	reference	
≥45 mm	1.48	1.14 – 1.93	0.004
Prescribed ACEI or ARB	0.88	0.61 – 1.29	0.520
Prescribed loop diuretics	1.15	0.88 – 1.50	0.310
SHOCK - SECONDARY PREVENTION			
	Hazards Ratio	**95% CI**	**p-Value**
Age 18-49 years	reference	reference	
50-59 years	0.91	0.55 – 1.50	
60-69 years	1.15	0.73 – 1.82	0.810
70-79 years	0.89	0.55 – 1.45	
≥ 80 years	0.79	0.43 – 1.44	
Male	1.37	0.95 – 1.97	0.092
Ischemic vs. non-ischemic	0.75	0.56 – 1.01	0.056
NYHA class			
I or II	reference	reference	
III or IV	1.06	0.76 – 1.49	0.720
Syncope	0.94	0.74 – 1.19	0.600
Diabetes	0.66	0.48 – 0.91	0.011
Hypertension	0.99	0.77 – 1.28	0.950
Stroke or TIA	1.15	0.68 – 1.96	0.600
Peripheral vascular disease	1.72	1.24 – 2.39	0.001
Chronic lung disease	1.69	1.22 – 2.35	0.002
Hemoglobin			
>120 g/L	reference	reference	
≤120 g/L	0.90	0.71 – 1.14	0.390

GFR >60 mL/min	reference	reference	
<30 mL/min	0.85	0.56 – 1.31	0.230
30-60 mL/min	1.34	1.06 – 1.71	
QRS duration (per 10 msec)	0.98	0.96 – 1.00	0.033
LVEF ≥31%	reference	reference	
≤20%	1.24	0.98 – 1.58	0.510
21-30%	0.87	0.70 – 1.08	
Prescribed ACEI or ARB	1.04	0.76 – 1.42	0.830
Prescribed loop diuretics	0.97	0.76 – 1.25	0.840

Supplemental Table 5. Nonparsimonious competing risk model for death (competing with appropriate shock) – Using R – Fine & Gray Model

DEATH - PRIMARY PREVENTION			
	Hazards Ratio	**95% CI**	**p-Value**
Age 18-49 years	reference	reference	
50-59 years	1.56	0.71 – 3.39	
60-69 years	2.10	1.01 – 4.39	<0.001
70-79 years	2.42	1.16 – 5.06	
≥ 80 years	3.01	1.36 – 6.68	
Male	1.09	0.79 – 1.50	0.610
Ischemic vs. non-ischemic	1.29	0.96 – 1.73	0.093
NYHA class			
I or II	reference	reference	
III or IV	1.72	1.33 – 2.22	<0.001
Syncope	1.36	0.96 – 1.93	0.082
Peripheral vascular disease	1.68	1.22 – 2.32	0.002
Chronic lung disease	1.29	0.93 – 1.79	0.130
Current smoker	1.26	0.85 – 1.87	0.250
GFR >60 mL/min	reference	reference	
<30 mL/min	3.76	2.50 – 5.65	<0.001
30-60 mL/min	2.07	1.56 – 2.76	
QRS duration (per 10 msec)	0.99	0.98 – 1.01	0.610
Left atrial size <45 mm	reference	reference	
≥45 mm	1.29	0.98 – 1.68	0.065
Prescribed ACEI or ARB	0.68	0.48 – 0.96	0.028
Prescribed loop diuretics	1.45	1.05 – 2.01	0.024
DEATH - SECONDARY PREVENTION			
	Hazards Ratio	**95% CI**	**p-Value**
Age 18-49 years	reference	reference	
50-59 years	1.41	0.51 – 3.89	
60-69 years	1.56	0.59 – 4.08	<0.001
70-79 years	1.88	0.72 – 4.93	
≥ 80 years	3.61	1.35 – 9.67	
Male	1.24	0.80 – 1.93	0.340
Ischemic vs. non-ischemic	1.83	1.01 – 3.32	0.045
NYHA class			
I or II	reference	reference	
III or IV	1.53	1.04 – 2.26	0.030
Syncope	1.27	0.92 – 1.76	0.150
Diabetes	1.36	0.96 – 1.92	0.082
Hypertension	0.79	0.55 – 1.12	0.180
Stroke or TIA	1.73	0.95 – 3.16	0.740
Peripheral vascular disease	1.86	1.25 – 2.75	0.002
Chronic lung disease	1.54	0.99 – 2.39	0.058
Hemoglobin			
>120 g/L	reference	reference	
≤120 g/L	1.38	1.00 – 1.90	0.053

GFR >60 mL/min	reference	reference	
<30 mL/min	1.46	0.81 – 2.62	0.180
30-60 mL/min	1.19	0.84 – 1.67	
QRS duration (per 10 msec)	1.01	0.99 – 1.04	0.200
LVEF ≥31%	reference	reference	
≤20%	1.14	0.79 – 1.64	0.041
21-30%	0.88	0.64 – 1.20	
Prescribed ACEI or ARB	0.73	0.50 – 1.05	0.092
Prescribed loop diuretics	1.62	1.13 – 2.31	0.008

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