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Predicting long-term survival after *de novo* cardioverter-defibrillator implantation for primary prevention: A population based study

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ABSTRACT

Background: Implantable cardioverter-defibrillators (ICDs) reduce the risk of sudden cardiac death in patients with left ventricular dysfunction. While short-term mortality benefit of ICD insertion has been established in landmark randomized controlled trials, little is known about the long-term outcomes of patients with ICDs in clinical practice. In this paper, we describe the long-term survival of patients following *de novo* ICD implantation for primary prevention in clinical practice and determine the factors which help predict survival after ICD implant.

Methods: Retrospective population-based study of all patients receiving a *de novo* ICD for primary prevention in Ontario, Canada from 2007 to 2011 using the Ontario ICD Database housed within ICES. Simple random selection was used to split the population into a derivation and internal validation cohort in a ratio of 2:1. Cox proportional hazards regression was used to determine predictors of interest and predict 10-year survival, model performance was assessed using calibration and validation.

Results: In the derivation cohort (n = 3399), mean age was 65.3 years (standard deviation [SD] = 11.0), 664 patients were female (19.5 %) and 2344 patients (69.0 %) had ischemic cardiomyopathy. Ten year survival was 45.7 % (95 % confidence interval [CI] 44.0 %–47.4 %). The final prediction model included age, sex, disease factors (ischemic vs nonischemic cardiomyopathy, left ventricular ejection fraction) and patient factors (symptoms, comorbidities), and biomarkers at the time of ICD assessment. This model had good discrimination and calibration in derivation (0.79, 95 % CI 0.77, 0.81) and validation samples (0.78, 95 % CI 0.76, 0.79).

Conclusions: A combination of demographic and clinical factors determined at baseline can be used to predict 10-year survival in patients with implantable cardioverter-defibrillators with good

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accuracy. Our findings help to identify individuals at risk of long-term mortality and may be useful in targeting future prevention strategies to enhance longevity in this high-risk population.

1. Introduction

Implantable cardioverter defibrillators (ICDs) are recommended to reduce the risk of sudden cardiac death (SCD) for patients at risk [1–3]. This includes patients with prior symptomatic arrhythmias for secondary prevention, but also patients with left ventricular dysfunction at high risk of SCD without prior cardiac events for primary prevention. Initial landmark randomized controlled trials demonstrated a reduction in arrhythmic death and all-cause mortality in patients at risk with reduced left ventricular ejection fraction [4–9]. Subsequent studies have found that the addition of cardiac resynchronization therapy (CRT) further improves outcomes in symptomatic heart failure patients with a low ejection fraction and QRS prolongation [10]. Current guidelines recommend the use of ICDs in patients with persistent LV dysfunction (LVEF $\leq$30 %) after 3 months of optimal medical therapy for NICM and 3 months after revascularization or 40 days after MI for ICM [1–3].

However, ICD recipients in clinical practice are often older with a greater burden of cardiac and non-cardiac comorbidities [11,12]. These patients are often at a higher risk of complications after ICD implant as well as mortality from competing noncardiac comorbidities. The care of ICD recipients continues to carry significant personal, clinical, and economic burden.

Previous observational studies have found death rates ranging from 12 to 19 % at 3 years and 25–36 % at 5 years after ICD implant [13–15]. However, population-level assessment of predictors of long-term outcomes remains limited and few studies report outcomes at 10-years post ICD insertion. Understanding the predictors of long-term outcome in patients after ICD implantation can inform shared decision making between patients and clinicians when deciding whether ICD therapy is appropriate. The aim of this study was to describe the 10-year survival and determine the predictors of survival for adult patients receiving ICD therapy for primary prevention in Ontario, Canada using population-based data.

2. Methods

2.1. Patient sample

This study included patients undergoing *de novo* ICD implantation for primary prevention who were registered in the Ontario ICD Database [16] between February 2007 and March 2011. In brief, the Ontario ICD database was a prospective registry mandated by the Ontario Ministry of Health and Long-Term Care of all patients (age$\geq$18 years) undergoing evaluation for defibrillator implantation in Ontario, Canada. Patient data were collected at initial evaluation, time of defibrillator implant and device-clinic follow-up. The Ontario ICD database was linked to other databases housed within ICES (formerly Institute for Clinical Evaluative Sciences). These datasets were linked using unique encoded identifiers and analyzed at ICES. As a prescribed entity under the Ontario health information privacy legislation housed within ICES (section 45 of Ontario's Personal Health Information Privacy Act), patient data were collected without consent thus minimizing participation bias [17]. The use of these data was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board. However, we obtained additional ethics approval from Queen's University.

2.2. Data sources

Data from the Ontario ICD database were collected by the local electrophysiologist and trained research coordinator and entered into a secure, firewall- and password-protected web-based registry at ICES. Data on patient characteristics, defibrillator indication, left ventricular ejection fraction, comorbidities, medications, and biomarkers were collected. Data quality was assessed using (1) regular review to ensure accuracy of coded data, (2) automated notification of uncoded data, (3) logic check of key data elements, and (4) random site audits of data reliability [16].

2.3. Outcomes

The primary outcome of all-cause mortality was identified using the Registered Persons Database at ICES. Vital status was available for all study patients. Patients were censored alive at 10-years follow-up and if Ontario Health Insurance Plan eligibility expired prior to the end of the follow-up period (n = 1445).

2.4. Predictor variables

Patient factors including age, sex, comorbidities, medications, and biomarkers were determined from the Ontario ICD database at the time of ICD implant assessment. Relevant comorbidities include prior PCI or CABG, prior MI, atrial fibrillation, diabetes, hypertension, peripheral vascular disease, stroke or TIA, dialysis-dependent chronic kidney disease (CKD), and chronic obstructive pulmonary disease (COPD). Relevant medications included angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), beta-blockers, furosemide, aspirin, clopidogrel, oral anticoagulation, digoxin, amiodarone, and other class II

antiarrhythmic medications. Relevant biomarkers include QRS duration, estimated glomerular filtration rate (eGFR), hemoglobin, and sodium. Overall comorbidity burden was determined using The Johns Hopkins ACG® System Version 9.0. Patient frailty was estimated using the Hospital Frailty Risk Score [18], which used a weighted combination of 109 ICD-9 and/or ICD-10 diagnostic codes recorded in the preceding 2 years.

Device factors including device type, right ventricular (RV) lead fixation method and device manufacturer were determined using the Ontario ICD database. Provider factors including physician procedure volume in the preceding fiscal year, cardiologist vs. non-cardiologist, Canadian medical graduate status, and years since medical school graduation were determined using the ICES physician database (IPDB).

Surrogate measures of patient socioeconomic status were determined using the Ontario Marginalization Index and neighborhood income quintile, as previously described for other population-level studies [19]. Geographical distance from patient's resident to ICD implantation center was calculated using the automated geographic coding based on Statistics Canada's postal code conversion files using each person's residence postal code [19].

2.5. Statistical analysis

Baseline characteristics of the study population were examined using descriptive statistics. Derivation and internal validation cohorts were created using a random 2:1 split of the sample [20]. Potential predictors were included in a multivariable Cox regression model using a backwards variable elimination with retention of variables based on clinical and statistical significance with a generous cut-off of p-value <0.2. All multivariable models included age, sex, and disease etiology because of the potential of these variables to account for survival after ICD implant. Predictors were then categorized into groups (device factors, comorbidities, provider factors etc.) and added in a stepwise fashion into the prediction model.

Continuous variables were examined using cubic spline analysis to determine the strength and shape of association with death. Variables at risk of non-linearity were categorized using clinical significance and thresholds identified using cubic spline. Variables with a large amount of missing data (>10 %) were excluded from the regression model (physician implant volume, left ventricular end diastolic dimension LVEDD), but were included in a sensitivity analysis after single imputation of missing variables. Addition of device factors, provider factors, non-clinical surrogates of patient comorbidity and frailty burden, interactions between sex and clinically relevant predictor variables, and allowing maximum follow-up were also included in the sensitivity analyses.

Model fit was assessed for each model using the Akaike information criterion, calibration, and discrimination indices. Cox proportional hazard assumptions were met in the final model. Discrimination was determined with the construction of a receiver operator characteristic curve using bootstrapping of 100 replicate samples with replacement and calculation of the area under the curve (AUC). Calibration was visually examined with a plot of the observed proportions of death for 10 artificially conducted predicted risk groups

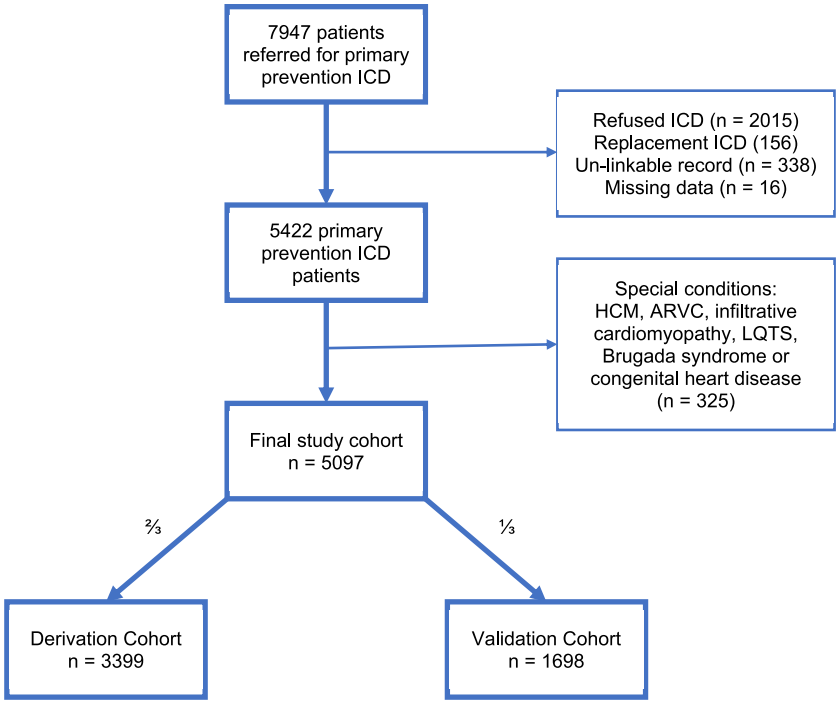


Fig. 1. Patient flow diagram
Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; HCM, hypertrophic cardiomyopathy, LQTS, long QT syndrome; ICD, implantable cardioverter defibrillator.

Table 1
Baseline characteristics of patients undergoing ICD implantation for primary prevention from the Ontario ICD Registry.
Abbreviations: ACEI = angiotensin converting enzyme inhibitor; ACG = Adjusted Clinical Group; ARB = angiotensin receptor blocker; BUN = blood urea nitrogen; CABG = coronary artery bypass graft; CCS = Canadian Cardiovascular Society; CRT-D = cardiac resynchronization therapy - defibrillator; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEDD = left ventricular end diastolic diamension; LVESD = left ventricular end systolic dimension; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; ICD = implantable cardioverter defibrillator; PCI = percutaneous coronary intervention; RV = right ventricle; std = standard deviation.

	Characteristic	Derivation cohort n = 3399	Validation Cohort n = 1698
Demographic	Age, mean (std)	65.28 (11.00)	65.55 (10.86)
	Female Sex	664 (19.54 %)	346 (20.4 %)
	Summary Score Median, mean (std)	3.10 (0.77)	3.13 (0.77)
	Neighborhood income quintile 1-2	1336 (39.30 %)	699 (41.17 %)
	Neighborhood income quintile 3-5	2053 (60.40 %)	992 (58.42 %)
	Rural	483 (14.21 %)	235 (13.84 %)
	Distance from residence to ICD center in km, mean (std)	76.49 (151.68)	69.50 (121.58)
	Hospital Frailty Risk Score, mean (std)	1.55 (2.93)	1.54 (3.00)
	John Hopkins ACG, mean (std)	8.90 (3.37)	8.87 (3.44)
Primary Disease Indication	Nonischemic cardiomyopathy	1023 (30.10 %)	504 (29.68 %)
	Ischemic cardiomyopathy	2344 (68.96 %)	1178 (69.38 %)
	Other cardiac disease	32 (0.94 %)	16 (0.94 %)
Cardiac History	LVEF≤20 %	760 (23.11 %)	341 (20.74 %)
	LVEF (20–30 %]	1878 (57.12 %)	953 (57.97 %)
	LVEF (30–35 %]	402 (12.23 %)	216 (13.14 %)
	LVEF >35 %	248 (7.54 %)	134 (8.15 %)
	Prior myocardial infarction	2002 (58.90 %)	983 (57.89 %)
	Prior PCI or CABG	1698 (49.96 %)	818 (48.17 %)
	NYHA HF class I-II	2139 (62.93 %)	1108 (65.25 %)
	NYHA HF class III-IV	1260 (37.07 %)	590 (34.74 %)
	CCS Angina class 0-II *	2551 (75.05 %)	1322 (77.86 %)
	CCS Angina class III-IV *	95 (2.79 %)	42 (2.47 %)
	Atrial fibrillation	1017 (29.92 %)	493 (29.03 %)
	LVEDD in mm, mean (std)	62.37 (10.32)	62.71 (9.47)
	LVESD in mm, mean (std)	52.04 (14.15)	52.46 (15.30)
	Urgency - in hospital (vs. out of hospital)	575 (16.92 %)	252 (14.8 %)
Non-Cardiac History	Hypertension	1991 (58.58 %)	966 (56.89 %)
	Cerebrovascular disease/transient ischemic attack	434 (12.77 %)	236 (13.90 %)
	Peripheral vascular disease	358 (10.53 %)	181 (10.66 %)
	Chronic obstructive pulmonary disease	556 (16.36 %)	308 (18.14 %)
	Diabetes	1298 (38.19 %)	621 (36.57 %)
	Dialysis	36 (1.06 %)	16 (0.94 %)
	Current smoker *	498 (14.65 %)	246 (14.49 %)
	Ever smoker	1981 (58.28 %)	976 (57.48 %)
Medications	Beta blockers	2974 (87.50 %)	1507 (88.75 %)
	ACEI	2531 (74.46 %)	1249 (73.56 %)
	ARB	622 (18.30 %)	299 (17.61 %)
	ACEI or ARB	3051 (89.76 %)	1504 (88.57 %)
	Amiodarone	318 (9.36 %)	174 (10.25 %)
	Other class III antiarrhythmic	12 (0.35 %)	<6
	Digoxin	862 (25.36 %)	401 (23.62 %)
	Oral anticoagulation	1081 (31.80 %)	566 (33.33 %)
	Aspirin	2097 (61.69 %)	994 (58.54 %)
	Clopidogrel	620 (18.24 %)	309 (18.20 %)
	Loop diuretic	2204 (64.84 %)	1101 (64.84 %)
Biomarkers	Sodium, mean (std)	138.42 (3.59)	138.64 (3.36)
	Creatinine, mean (std)	110.84 (59.92)	108.75 (54.93)
	BUN, mean (std)	9.37 (8.96)	9.43 (9.50)
	eGFR, mean (std)	68.82 (29.97)	68.97 (32.42)
	Hemoglobin, mean (std)	135.18 (16.98)	134.77 (17.20)
	QRS_Manual, mean (std)	130.29 (35.40)	129.09 (35.81)
	QRS_Computer, mean (std)	134.32 (35.06)	133.65 (36.04)
Device Type	Single chamber	1442 (42.42 %)	712 (41.93 %)
	Dual chamber	782 (23.01 %)	398 (23.44 %)
	CRT-D	1173 (34.51 %)	587 (34.57 %)
Manufacturer	Medtronic	1659 (48.81 %)	856 (50.41 %)
	St. Jude Medical	997 (29.33 %)	489 (28.80 %)
	Boston Scientific	665 (19.56 %)	306 (18.02 %
	Sorin	69 (2.03 %)	46 (2.71 %)
	Biotronik	9 (0.26 %)	<6
Lead Characteristics	Dual coil RV lead	2971 (87.43 %)	1477 (86.98 %)
	Single coil RV lead	423 (12.45 %)	216 (12.72 %)
	Active RV fixation	3192 (93.94 %)	1594 (93.88 %)

(*continued on next page*)

Table 1 (*continued*)

	Characteristic	Derivation cohort n = 3399	Validation Cohort n = 1698
	Passive fixation	202 (5.94 %)	100 (5.89 %)
Institution	Hamilton	599 (17.62 %)	287 (16.9 %)
	London	502 (14.77 %)	233 (13.72 %)
	Greater Toronto Area	2040 (49.07 %)	824 (48.53 %)
	Kingston	258 (7.59 %)	157 (9.25 %)
	Ottawa	372 (10.94 %)	197 (11.6 %)
Provider Characteristics	Canadian Medical Graduate	2196 (68.71 %)	1084 (67.58 %)
	Main specialty of Cardiology	2827 (88.43 %)	1417 (88.34 %)
	Volume of ICD inserted in last fiscal year, mean (std)	124.15 (120.69)	123.32 (120.79)
	Years since medical school graduation, mean (std)	19.32 (7.94)	19.06 (7.70)

of equal size using a previously described SAS macro [21].

3. Results

3.1. Patient characteristics

Among 7947 patients referred for *de novo* primary prevention ICD insertion, 2015 refused the device and 156 were replacement procedures. Patients were excluded if they were un-linkable to administrative databases or had specialized indications for ICDs including hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, Brugada syndrome, long QT syndrome or congenital heart disease (n = 679). The final cohort contained 5097 patients, which was split into a derivation (n = 3399) and validation cohort (n = 1698) using random selection at a ratio of 2:1. The patient flow diagram is shown in Fig. 1.

The final derivation cohort was comprised of 2735 men (80.5 %), mean age was 65.28 years (SD 11.0 years), and primary disease indication was ischemic cardiomyopathy in 2344 (69.0 %) patients. Devices implanted included 1442 (42.4 %) single chamber, 782 (23.0 %) dual chamber, and 1173 (34.5 %) cardiac resynchronization therapy defibrillator devices. Demographic and clinical characteristics of these patients are reported in Table 1.

3.2. Outcome events

Patients were followed for 10-years after device implant, during which time 1832 deaths occurred in the derivation cohort. Cumulative death rate was 5.5 % (n = 186), 16.4 % (n = 555), 28.1 % (n = 952), 44.7 % (n = 1510) and 54.3 % (n = 1846) at 1-, 3- 5-, 8-, and 10-years respectively. Mortality data were available for all patients. A Kaplan Meier survival curve is shown in Fig. 2.

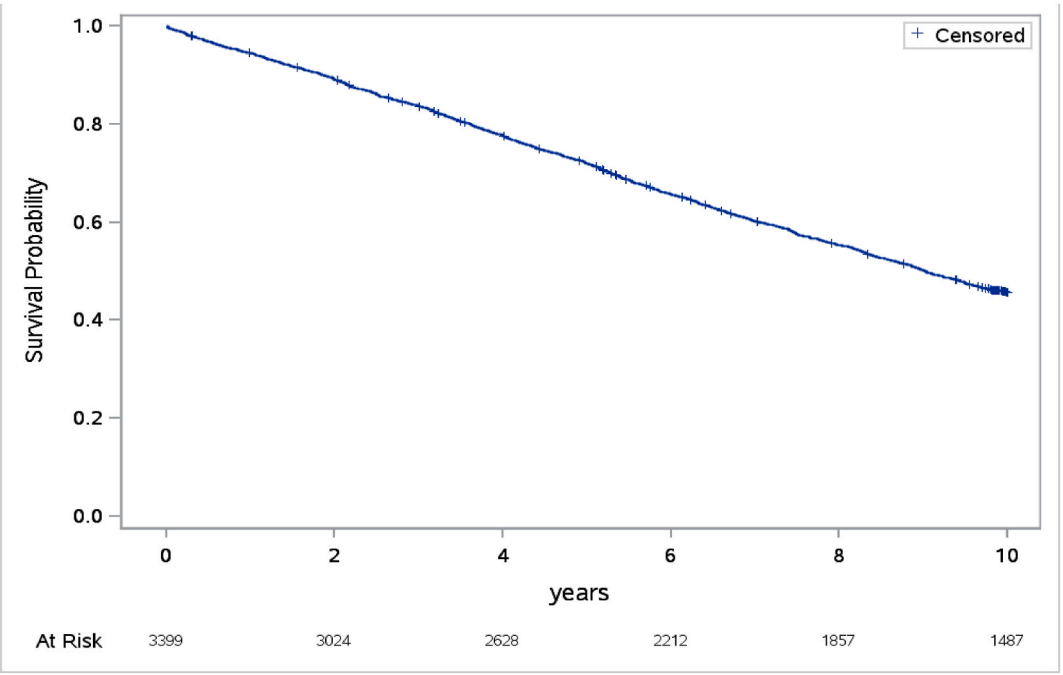


Fig. 2. Survival after ICD insertion for primary prevention.

3.3. Multivariate regression models for the prediction of death

Multivariate predictors of time to death were modelled using a Cox regression model. After the initial backward selection, no socioeconomic or device factors remained significant. A simplified prediction model using only age, sex, and disease etiology had good calibration and moderate discrimination with an AUC of 0.70 (95 % CI 0.68–0.72) and 0.71 (0.68, 0.73) in the derivation and internal validation cohorts respectively. The stepwise addition of disease factors, medications, and biomarkers continued to improve model discrimination (Table 2). However, model calibration deteriorated after the addition of medications. Cubic spline testing using 5 knots suggested that the biomarkers sodium, renal function, hemoglobin, and QRS duration may not have a linear relationship with the outcome, so these variables were subsequently categorized using clinical significance and cubic spline thresholds. Categorized biomarkers improved model discrimination and calibration, with the calibration improving further with the removal of patient medications. The final model parameters are shown in Table 3 showing good discrimination with AUC 0.79 (0.77, 0.81) and 0.78 (0.76, 0.79) in derivation and internal validation cohorts respectively. This model also showed good calibration when assessed visually (Fig. 3). Increasing age, procedure urgency, symptoms assessed using NYHA HF scale, LVEF <20 %, comorbidities, hyponatremia, anemia, renal dysfunction, and prolonged QRS duration were associated with increased risk of death. Female sex and nonischemic cardiomyopathy were associated with decreased risk of death. Missing predictor data was relatively low at 7.9 % and 7.1 % in the derivation and validation cohorts respectively.

3.4. Sensitivity analyses

Several sensitivity analyses were performed to ensure that the best prediction model was chosen within data limitations. Sensitivity analyses investigated the effect of additional variables of unclear significance including device type, provider factors (provider main specialty, Canadian medical graduate status), implantation site, frailty score, and comorbidity burden using the Johns Hopkins ACG comorbidity index. Since left ventricular end diastolic dimension (LVEDD) and implanter volume may be important variables which had significant missing variables, they were included in a sensitivity analysis after using missing variable imputation. Sex-etiology interaction terms and allowing for maximal follow-up of up to 14 years without censoring were also studied. Sensitivity model performance was assessed in the derivation and internal validation cohorts, and discrimination and calibration are reported in Supplement S1 and S2 respectively. None of the sensitivity analyses showed improved performance when compared to the final base model.

4. Discussion

As ICD implant rates continue to rise and healthcare providers adopt the use of CRT devices [22,23], it can often be challenging to translate randomized controlled trial evidence to clinical practice. Follow-up of ICD recipients in clinical practice indicate that complications and morbidity after ICD implant remain high [24–26]. Since the average lifespan of ICD devices ranges from 5- to 10-years [27], it is crucial to have accurate long-term survival data in order to have well-informed patient-centered discussions when assessing patients for ICD therapy.

To our knowledge, our study is the first prognostic model using population-based data to predict 10-year survival using baseline patient and demographic predictors determined at the time of evaluation for ICD insertion. Since Ontario utilizes a universal single-payer healthcare system where all devices are paid for by the Ministry of Health and Long-term Care, and data was collected at ICES without requirement of informed consent, we were uniquely able to capture accurate long-term patient outcomes in clinical practice on a population-level.

Table 2
Model performance assessed using Akaike information criterion and area under the curve for the development of the base model.
Abbreviations: ECG = electrocardiogram, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association dyspnea scale.

Models	Predictors	Derivation Cohort IPCW AUC (95 % CI)	Validation Cohort IPCW AUC (95 % CI)
Model 1	Age, sex, etiology	0.70 (0.68, 0.72)	0.71 (0.68, 0.73)
Model 2	Age, sex, etiology, LVEF, NYHA	0.74 (0.72, 0.75)	0.73 (0.70, 0.75)
Model 3	Age, sex, etiology, LVEF, NYHA, comorbidities[a]	0.77 (0.75, 0.79)	0.76 (0.74, 0.78)
Model 4	Age, sex, etiology, LVEF, NYHA, comorbidities[a], medications[b]	0.78 (0.77, 0.80)	0.77 (0.75, 0.79)
Model 5	Age, sex, etiology, LVEF, NYHA, comorbidities[a], medications[b], biomarkers[c]	0.79 (0.78, 0.81)	0.78 (0.45, 1)
Model 6a	Age, sex, etiology, LVEF, NYHA, comorbidities[a], medications[b], categorized biomarkers[d]	0.80 (0.78, 0.81)	0.78 (0.76, 0.80)
Model 6b	Age, sex, etiology, LVEF, NYHA, comorbidities[a], categorized biomarkers[d]	0.79 (0.77, 0.81)	0.78 (0.76, 0.79)

[a] Comorbidities: diabetes, hypertension, cerebrovascular accident/transient ischemic attack, current smoker, peripheral vascular disease, chronic obstructive pulmonary disease, dialysis.
[b] Medications: loop diuretic, oral anticoagulant, digoxin, aspirin, clopidogrel.
[c] Biomarkers: sodium, hemoglobin, estimated glomerular filtration, QRS on ECG.
[d] Categories for biomarkers: Sodium:≤135 mmol/L, 136–140 mmol/L, >140 mmol/L; Hemoglobin:≤70 g/L, 71–120 g/L, 121–140 g/L, >140 g/L; eGFR:≤60 mL/min/1.73 m^2, >60 mL/min/1.73 m^2; QRS:≤120 ms, 121–160 ms, >160 ms

Table 3
Predictors of death after ICD implant for primary prevention
Abbreviations: CM = cardiomyopathy; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; eGFR = estimated glomerular filtration rate; HF = heart failure; NYHA = New York Heart Association; TIA = transient ischemic attack.

Parameter	Category	Parameter Estimate	Hazard Ratio	95 % CI	p-value
Sex	female	−0.20141	0.82	0.72, 0.93	0.0029
Age (years)	…	0.04129	1.04	1.04, 1.05	<.0001
Etiology (reference = ischemic CM)	Non-ischemic	−0.10944	0.90	0.79, 1.01	0.1571
	Other	−0.25612	0.77	0.42, 1.41	
Urgency (reference = ambulatory)	In hospital	0.12252	1.13	0.99, 1.28	0.0602
NYHA HF Scale (reference = I-II)	III-IV	0.38306	1.47	1.32, 1.63	<.0001
Left ventricular ejection fraction (reference = >35 %)	0–20 %	0.25348	1.29	1.05, 1.58	0.0001
	21–30 %	0.00722	1.01	0.83, 1.22	
	31–35 %	−0.05632	0.95	0.75, 1.18	
Diabetes	…	0.34677	1.41	1.28, 1.57	<.0001
Hypertension	…	−0.07502	0.93	0.84, 1.03	0.1568
CVA/TIA	…	0.19752	1.22	1.06, 1.40	0.0043
Current smoker	…	0.32417	1.38	1.20, 1.60	<.0001
Peripheral vascular disease	…	0.35176	1.42	1.23, 1.64	<.0001
COPD	…	0.36865	1.45	1.28, 1.63	<.0001
Dialysis	…	0.80191	2.23	1.51, 3.30	<.0001
Sodium (reference = 135–140 mmol/L)	≤135 mmol/L	0.30327	3.31	0.82, 13.40	<.0001
	>140 mmol/L	0.02762	1.32	1.16, 1.50	
Hemoglobin (reference = 120–140 g/L)	≤70 g/L	1.19812	0.82	0.73, 0.92	<.0001
	70–120 g/L	0.27725	1.35	1.19, 1.54	
	>140 g/L	−0.19455	1.03	0.91, 1.16	
eGFR	≤60 mL/min/1.73 m^2	0.46828	1.60	1.44, 1.78	<.0001
QRS (reference = <120 ms)	120–160 ms	0.12840	1.14	1.01, 1.28	0.0405
	>160 ms	−0.00661	0.99	0.87, 1.13	

4.1. Survival

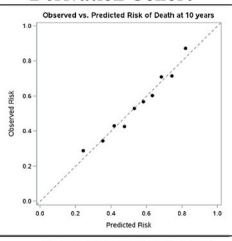
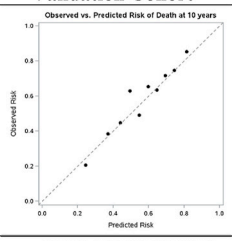
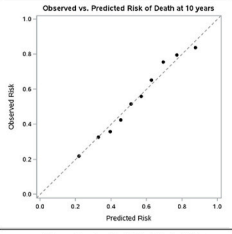
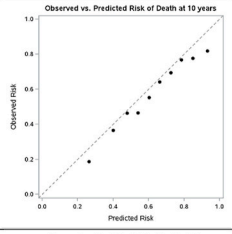
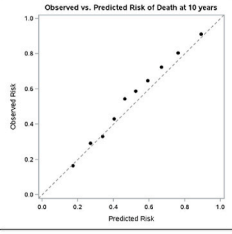
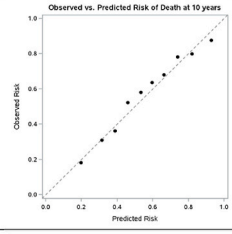
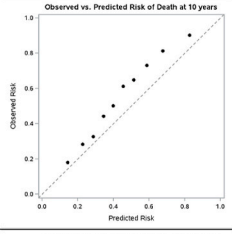
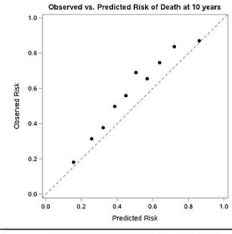
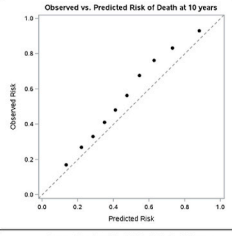
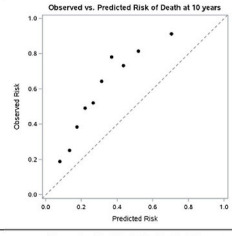
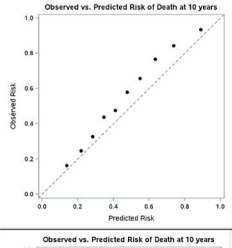
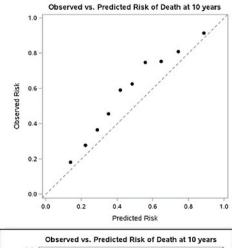
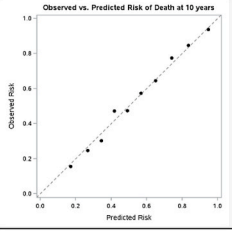
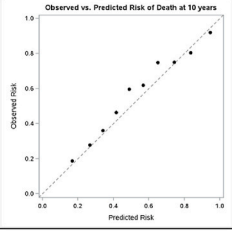
Only a few studies have reported long-term survival rates of patients after receiving ICD therapy for primary prevention. Follow-up of the MADIT II population found a median survival of 8 years, with cumulative probability of death of 40 % at 6 years [28] and 49 % at 8 years [29]. Long-term follow-up of the SCD-HeFT population found a 52.5 % death rate at 10-years [30]. Cumulative death rates in our study using the Ontario ICD database were similar to previous observational studies [14,15,31,32], with 1, 3, 5, 8, and 10-year cumulative death rates of 5.5 % (n = 186), 16.4 % (n = 555), 28.1 % (n = 952), 44.7 % (n = 1510), and 54.3 % (n = 1846) respectively. Survival at 1- and 3-years predicted using this model performed similarly in terms of discrimination and calibration to previously published models with AUC 0.73 (95 % CI 0.68, 0.79) and AUC 0.71 (95 % CI 0.67, 0.74) respectively in the internal validation cohort [33].

4.2. Predictors of survival

Increased age has been identified as a strong predictor of death after ICD in several observational trials [13,15,28,34,35], [[,15,28,34,35] as well as higher risk of complication after device insertion [36]. It is postulated that with advancing age, patients are at increasing risk of death by non-arrhythmic causes [37]. There may be decreased ICD benefit with increased age as evidenced in post-hoc analysis of the DANISH trial [38]. Interestingly, previous research from using the Ontario ICD database has shown that there is no significant decline in the rate of appropriate ICD shocks when using competing risk analysis [35]. However, the relative morbidity associated with sequelae of appropriate ICD therapy for older adults vs. younger adults is unknown. It is plausible that while older adults continue to receive appropriate shocks, they may have increased emergency department visits and longer hospitalizations which are subsequently translated to increased morbidity and mortality when compared to younger populations. Our analysis helps to further highlight that increasing age is a strong predictor of death even in a multivariate model controlling for several patient comorbidities and biomarkers up to 10-years after ICD implant.

Female patients were significantly under-represented in the initial landmark ICD trials, with most enrolling 75–90 % male patients [4–6]. While ICD therapy is assumed to be equally beneficial in women and men, recent studies have identified that women were less likely to receive appropriate ICD therapy via anti-tachycardia therapy or ICD shocks [39–41] and more likely to experience complications after device implantation [36,39,42]. However, women are more likely to benefit from CRT [43]. This may be due to less sudden death in women when adjusted for heart failure severity [44]. Our multi-center analysis showed higher survival rates in women with primary prevention ICD therapy when compared to men persisting up to 10-years after insertion, consistent with previous observational studies [26,40,42]. However, two meta-analyses of clinical trials did not find a significant reduction of sudden cardiac death in women implanted with ICD for primary prevention [45,46]. Further studies in women are required to better understand the benefit of ICD therapy in this population.

Similar predictors of death were identified by the BaSIS model, which weighed risk of appropriate shock against 1-year risk of death after ICD insertion using data from the Ontario ICD Database [47]. In both models, increasing age, ischemic cardiomyopathy, worse

Model[a]	Predictors[b]	Derivation Cohort[c]	Validation Cohort[d]
Model 1	Age, sex, etiology		
Model 2	Age, sex, etiology, LVEF, NYHA		
Model 3	Age, sex, etiology, LVEF, NYHA, comorbidities[1]		
Model 4	Age, sex, etiology, LVEF, NYHA, comorbidities[1], medications[2]		
Model 5	Age, sex, etiology, LVEF, NYHA, comorbidities[1], medications[2], biomarkers[3]		
Model 6	Age, sex, etiology, LVEF, NYHA, comorbidities[1], medications[2], categorized biomarkers[4]		
Model 7	Age, sex, etiology, LVEF, NYHA, comorbidities[1], categorized biomarkers[4]		

(caption on next page)

Fig. 3. Model calibration using observed vs predicted risk of death for the development of the base model. Model name, predictors included in each model, and corresponding derivation and validation calibration plots are indicated in columns a to d respectively. Diagonal dotted line indicates perfect calibration. Seven models were sequentially tested, Model 7 was identified as the final model with the best performance in calibration and discrimination. Abbreviations: ECG = electrocardiogram, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association dyspnea scale [1]Comorbidities: diabetes, hypertension, cerebrovascular accident/transient ischemic attack, current smoker, peripheral vascular disease, chronic obstructive pulmonary disease, dialysis [2]Medications: loop diuretic, oral anticoagulant, digoxin, aspirin, clopidogrel [3]Biomarkers: sodium, hemoglobin, estimated glomerular filtration, QRS on ECG [4]Categories for biomarkers: Sodium:≤135 mmol/L, 136–140 mmol/L, >140 mmol/L; Hemoglobin:≤70 g/L, 71–120 g/L, 121–140 g/L, >140 g/L; eGFR:≤60 mL/min/1.73 m^2, >60 mL/min/1.73 m^2; QRS:≤120 ms, 121–160 ms, >160 ms

heart failure symptoms, diabetes, smoking history, COPD, impaired renal function, hyponatremia, and anemia were identified as predictors of increased risk of death. Prior revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) was associated with improved survival at 1-year in the BaSIS model but were not significant predictors of outcomes in our model. Additionally, we found that diabetes, prior CVA/stroke, peripheral vascular disease, and dialysis were also associated with increased risk of death, with improved model performance when medications were excluded from the final prediction model. This is likely because any additional predictive power afforded with the addition of medications was counteracted by model over-fitting and collinearity between medications and other predictor variables (e.g. comorbidities).

4.3. Sensitivity analyses

Several additional models were constructed during sensitivity analyses and compared to the final model (Supplement S1-2). Previous literature suggests that increasing device complexity is associated with increased complications and short-term risk of death, with dual-chamber and CRT devices having more complications than single-chamber devices [15,36,48], [[,36,48] though it was not associated with death in our model. Addition of device type did not improve model performance.

We also assessed the effect of adding provider factors including Canadian Medical Graduate status, physician main specialty, and implantation center to the final model. While provider factors are not classically included in prognostic models, our goal was to assess if provider factors played a role in changing patient outcomes. We did not find that the addition of provider factors improved our predictive model.

Previous prognostic scores developed to predict outcomes after ICD insertion lack measurement of patient frailty, which can be an important decision factor for clinicians when discussing ICD therapy with patients. We attempted to address this with the inclusion of the Hospital Frailty Risk Score and the Johns Hopkins ACG comorbidity index, which identify patients at high risk of prolonged hospital admission and comorbidity burden respectively [18,49] using health services data. Addition of these surrogate measures of frailty did not affect model performance.

While missing predictor data was not a significant issue in our model, two potentially important predictors were excluded from the original model due to missing data. Enlarged left ventricular dimension [36] and low implanter volume [24] have previously been associated with increased risk of complications and subsequent mortality in previous research from the Ontario ICD database. Our analysis showed that after single imputation of missing variables, the addition of left ventricular end diastolic dimension and implanter volume in the last fiscal year did not improve model performance.

Previous observational studies have identified that women receiving ICD therapy are more likely to have NICM when compared to men. To further investigate whether sex may modify the ability of disease factors to predict long-term outcomes after ICD insertion, several interaction terms between sex and disease etiology, NYHA HF symptoms, and LVEF were explored. After initial multivariate analysis, only the sex and disease etiology interaction term remained significant ($p = 0.04$). Addition of the sex and disease etiology interaction term did not improve model performance.

Finally, allowing for maximal follow-up up to 14 years after ICD insertion also did not improve model performance.

4.4. Strengths and limitations

There are some notable limitations to our study. First, while the Ontario ICD database is broadly inclusive of patients receiving ICD therapy in Ontario, recipients must have an active Ontario Health Card. Generalization to military populations as well as populations outside of Ontario are unknown. Second, our model was not validated using an independent external database. While external validation is crucial prior to using prognostic models in clinical practice, our research helps to conceptualize the import predictors of long-term outcomes in patients receiving ICD therapy. There is a potential risk of misclassification and loss of information with the categorization of non-linear predictor variables (LVEF, serum hemoglobin, sodium, QRS interval). While polynomial transformations and cubic spline can be used to model non-linearity, the use of these methods would further complicate a clinical risk score meant to be used at the bedside. While we attempted to capture the most important baseline variables which may affect long-term outcomes, there may still be unmeasured confounders such as history of malignancy and chemotherapy. Finally, recent advances in goal-directed medical therapy (GDMT) for medical management of heart failure may modify the population of patients referred for primary prevention ICD. While we expect similar factors to be important in the prediction of long-term outcomes, our model would need to be re-validated in a long-term follow-up of contemporary heart failure patients. These limitations are outweighed by the unique strengths of this study, including the completeness of data on patient outcomes in long-term follow-up, the population level data collection with minimal risk of selection bias, and ability to predict 10-year outcomes using only baseline clinical information collected at time of

initial ICD assessment.

4.5. Clinical significance and future directions

We were able to identify a new prognostic model using baseline clinical predictors to predict long-term outcomes after ICD insertion for primary prevention. Using several additional sensitivity analyses, we were able to find the simplest model with the best statistical performance to identify important predictor variables (Table 3) using internal validation. Risk stratifying patients into those who are at high and low risk of early death can inform clinicians and patients in shared decision making in determining when ICD therapy is most appropriate.

There are several areas of additional research which can help identify the best care of patients with primary prevention ICD therapy beyond baseline patient characteristics. Competing risk of dying from non-arrhythmic causes, risk of device implantation related complications, and the impact of ICD shocks are important considerations when choosing patients for ICD insertion for primary prevention. These would be better studied using a competing risks prediction model with time-dependent predictors such as device infections, ICD shocks, and device revisions.

Finally, previous literature has identified that despite the mortality benefit obtained with ICD therapy for primary prevention, healthcare utilization in this patient population remains high. The ability to predict patterns of healthcare utilization at baseline as well as studies into costs of care of patients after ICD implant would be invaluable for health policy makers to optimally allocate healthcare resources. The Ontario ICD database would be uniquely able to study this relationship due to data linkage with other acute and ambulatory health-care resource utilization databases housed within ICES.

Conclusion

In this paper, we present a new prognostic model which accurately assesses prognosis up to 10-years after ICD insertion for primary prevention. The model uses baseline clinical predictors easily available to clinicians at the time of evaluation for ICD therapy and performed well with good discrimination and calibration in an internal validation cohort. Accurate personalized prediction of outcomes after ICD insertion can be used in shared decision making when counselling patients for ICD therapy.

Ethics statement

Approval was obtained from Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (HSREB). Department Code; SMED-249-21, TRAQ # 6034674.

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Data availability statement

The data associated with this study have not been deposited into a publicly available repository, as the data are confidential.

CRediT authorship contribution statement

Chang Nancy Wang: Writing - review & editing, Writing - original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Zihang Lu:** Writing - review & editing, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Christopher S. Simpson:** Visualization, Validation, Supervision, Conceptualization. **Douglas S. Lee:** Writing - review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Joan E. Tranmer:** Writing - review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Douglas Lee reports financial support was provided by Canadian Institutes of Health Research. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23355.

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