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New prediction models for primary prevention ICD efficacy

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Aims This study was performed to develop and externally validate prediction models for appropriate implantable cardioverter-defibrillator (ICD) shock and mortality to identify subgroups with insufficient benefit from ICD implantation.

Methods and results We recruited patients scheduled for primary prevention ICD implantation and reduced left ventricular function. Bootstrapping-based Cox proportional hazards and Fine and Gray competing risk models with likely candidate predictors were developed for all-cause mortality and appropriate ICD shock, respectively. Between 2014 and 2018, we included 1441 consecutive patients in the development and 1450 patients in the validation cohort. During a median follow-up of 2.4 (IQR 2.1–2.8) years, 109 (7.6%) patients received appropriate ICD shock and 193 (13.4%) died in the development cohort. During a median follow-up of 2.7 (IQR 2.0–3.4) years, 105 (7.2%) received appropriate ICD shock and 223 (15.4%) died in the validation cohort. Selected predictors of appropriate ICD shock were gender, NSVT, ACE/ARB use, atrial fibrillation history, Aldosterone-antagonist use, Digoxin use, eGFR, (N)OAC use, and peripheral vascular disease. Selected predictors of all-cause mortality were age, diuretic use, sodium, NT-pro-BNP, and ACE/ARB use. C-statistic was 0.61 and 0.60 at respectively internal and external validation for appropriate ICD shock and 0.74 at both internal and external validation for mortality.

Conclusion Although this cohort study was specifically designed to develop prediction models, risk stratification still remains challenging and no large group with insufficient benefit of ICD implantation was found. However, the prediction models have some clinical utility as we present several scenarios where ICD implantation might be postponed.

Keywords Implantable cardioverter-defibrillator • Primary prevention • Risk factors • Mortality • Sudden cardiac death • Prediction models

What's new?

- Cumulative event rates of mortality and appropriate implantable cardioverter-defibrillator (ICD) shock are still significant despite the medical advancements in recent years.
- Appropriate ICD shock rates were similar in the ≤25% left ventricular ejection fraction (LVEF) vs. >25% LVEF group and non-ischaemic vs. ischaemic cardiomyopathy group.
- Appropriate ICD shock remains more difficult to predict than mortality, novel predictors are needed to increase the accuracy of the model.
- The presented prediction models have some clinical utility as we present several scenarios where ICD implantation might be postponed. However, risk stratification still remains challenging as no large group with insufficient benefit of ICD implantation was found.

Introduction

Clinical benefit and cost-effectiveness of implantable cardioverter-defibrillator (ICD therapy) in patients who meet current primary prevention international guideline criteria[1] are increasingly debated. Treatment of heart failure and myocardial infarction has dramatically improved since the early 21st century primary prevention randomized controlled trials[2,3] have been conducted, raising doubt about the generalization to current practice. Several studies have shown a decline in appropriate ICD therapy during the last decade, with rates of incident appropriate ICD shock of 1–3.6% per year.[4] Hence, many ICD recipients do not benefit from ICD therapy while remaining at risk for device-related complications and inappropriate therapy.[5] The results of a recent primary prevention RCT in patients with non-ischaemic cardiomyopathy led to even more debate, as ICD treatment did not lead to a statistically significant reduction in mortality.[6] Currently, only NYHA class and ejection fraction (LVEF) are routinely used as selection criteria to determine eligibility for a primary prevention ICD, which are contested to be sufficiently accurate. There is a strong need for improvement in patient selection for primary prevention ICD therapy.[7]

The Dutch outcome in ICD therapy (DO-IT) study aims to develop and externally validate models for the prediction of appropriate ICD shock and mortality during a 2-year follow-up period, with the use of routinely available clinical variables. In daily practice, these models may help identify patients who are more or less likely to benefit from ICD implantation for primary prevention of sudden cardiac death (SCD).

Methods

Study design

Within a nationwide multicentre observational prospective cohort study, we developed and internally validated prediction models for appropriate ICD shock and mortality and performed external validation of these models using a European cohort of primary prevention ICD carriers. Reporting was done according to the TRIPOD statement.[8]

Study population

Development cohort

Patients scheduled for ICD implantation, including cardiac resynchronization devices with defibrillator (CRT-D), for primary prevention of SCD with reduced LVEF in a setting of structural heart disease from all 28

ICD-implanting Dutch hospitals were included. The DO-IT had a target enrolment of 1500 patients with an approximate 5% annual mortality and appropriate ICD therapy rate to provide sufficient power for an adequate prediction model. The trial design has been published.[9] Inclusion criteria were based on current guidelines for primary prevention ICD implantation.[1]

Validation cohort

Implantable cardioverter-defibrillator recipients of the EU-CERT-ICD study were included, with the exclusion of patients of one overlapping DO-IT centre. The EU-CERT-ICD study was a prospective non-randomized, controlled cohort study performed in 44 centres in 15 European countries. First results were previously published.[10] Patients aged 18 years or older, who met the criteria for primary prevention according to current guidelines were included. Of note, patients who were candidates for cardiac resynchronization therapy were excluded. Both studies conform to the Helsinki declaration and were approved by local ethics review boards.

Study outcomes

Primary outcomes were time to death and time to first appropriate ICD shock where death was considered a competing event. Appropriate ICD shock was defined as ICD shock for ventricular fibrillation or ventricular tachycardia. For both cohorts, a blinded critical events committee (CEC) used prespecified criteria to adjudicate the primary outcomes. Secondary endpoints of the DO-IT registry were appropriate ICD therapy, consisting of shock + antitachycardia pacing (ATP), inappropriate ICD shock, and ICD-related complications. See Supplementary material online for criteria and outcome definitions.

Predictors

We considered several routinely collected candidate predictors for all-cause mortality and appropriate ICD shock based on literature.[11] Candidate predictors from various domains were included like demographics (age and sex), ventricular arrhythmic history (NSVT), cardiomyopathy aetiology (ischaemic vs. non-ischaemic), heart failure characteristics (NYHA class, previous heart failure hospitalizations <1 year of baseline) pre-existing pacemaker system, previous cardiac surgery, atrial fibrillation, risk factors for coronary artery disease (smoking and positive family history of SCD), and comorbidity's (peripheral vascular disease, COPD, diabetes mellitus, and chronic kidney disease). The use of cardiac medications and results of different investigations (laboratory, echocardiographic, ECG parameters) were also included. Definitions of predictor variables are provided in the Supplementary material online, *Table S1*.

Data collection

The E-CRFs were used in compliance with good clinical practice. Hospitals collected data, with monitoring of the data by the trial coordinating centre in correspondence with the pre-specified monitorplan. All patients were followed up every 3–6 months, with a minimum of 2 years after inclusion of the last patient. The date of the last ICD interrogation was used for the ICD endpoint as the right censoring time. Information on mortality was retrieved from hospital records, contact with relatives, general practitioners, and local authorities.

Statistical analysis

Analyses were performed using Rstudio version 1.1.453 (Boston, MA, USA). Continuous variables are given as median (IQR) or mean (SD) where appropriate and categorical variables as frequencies. Values of the development set were compared to the validation set using Fisher exact and independent *t*-test or Wilcoxon rank-sum, as appropriate. Follow-up duration was defined as the time from ICD implantation to either endpoint or most recent follow-up visit. For appropriate ICD shock, the probability of experiencing the event of interest or competing event was estimated with the cumulative incidence function, based on the Fine and Gray proportional subdistribution hazards method. All-cause mortality was estimated using the Kaplan–Meier (KM) method. Mortality and appropriate ICD shock incidence was presented with Fine and Gray cumulative incidence curves which were subsequently stratified by LVEF and cardiomyopathy type subgroups. Separate models were derived for both primary outcomes, independent model selection was done for each endpoint based on one common pool of predictors. For all-cause death, a Cox proportional hazards model was used, as its aim was to identify patients at risk of death despite ICD implantation. For appropriate shock, we used a Fine and Gray proportional subdistribution hazards model with death as a competing event. Further details on model development and validation can be found in the Supplementary material online.

Missing data

Missing values for candidate predictors were handled with multiple imputation (R package MICE). The imputation model included all candidate predictors and outcomes (time to event). The resulting 10 complete datasets were separately analysed and the results combined with Rubin's rules to produce overall estimates and confidence intervals.

Model presentation

We used the linear predictor (sumproducts of individual predictor values and associated coefficients) of an individual patient to estimate the risk of either event during a 2-year timespan. For clinical use, an online risk calculator will be available at https://do-it-study.shinyapps.io/DO-IT-calculator/ .

Clinical utility

Potential scenario's with different thresholds of 2 years appropriate ICD shock risk to determine ICD implantation were explored. For each threshold, the numbers of false positive (ICD, no event), false negatives (no ICD, event), true positives (ICD, event), and true negatives (no ICD, no event) were calculated, which can be seen as the clinical implication of using the model at that threshold.

Results

Study cohort

Between September 2014 and May 2016, of 1640 patients deemed eligible we included 1443 in the development cohort (*Figure 1*). Two patients were lost to follow-up for the ICD endpoint before their first outpatient follow-up visit. The majority of the cohort, 1362 patients (95%), had over 2 year follow-up data available. Between May 2014 and September 2018, 2327 participants were recruited for the EU-CERT-ICD study. Excluding the non-ICD group and overlapping hospital, the validation cohort consists of 1450 ICD carriers. See *Table 1* for baseline characteristics of both cohorts.

Outcomes

In the development cohort, 193 patients (13.4%) died during a median follow-up of 2.4 years (2.1–2.8, crude rate: 5.6 per 100 patient-years). In 131 (68%) patients the cause of death was cardiovascular, including 82 due to heart failure, 20 were considered cardiac (lack of

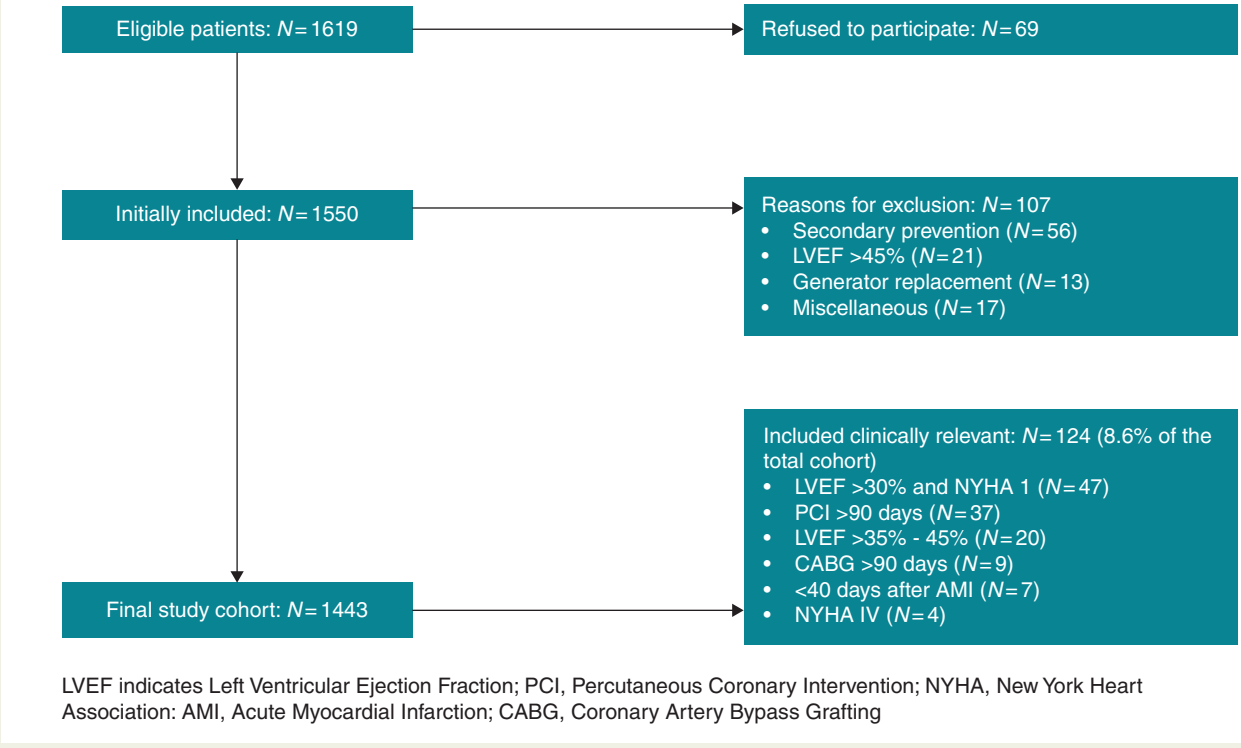

Figure 1 Flowchart of the participants of the development (DO-IT) cohort.

information regarding death circumstances), 15 SCD, and 14 miscellaneous (e.g. cerebrovascular accident, procedure-related, endocarditis). The KM estimate of all-cause mortality at 2 years was 9.1%. During a median follow-up of 2.3 years (2.0–2.7), an appropriate ICD shock was given in 109 (7.6%) patients with a crude rate of 3.3 per 100 patient-years. The Fine and Gray cumulative incidence estimate for appropriate ICD shock at 2 years was 5.9% (*Figure 2*). When stratified by subgroups of LVEF and cardiomyopathy type a significant difference was seen for mortality but not for ICD shock (*Figure 3*). The 2-year Fine and Gray mortality estimate was 9.3% in the LVEF ≤25% group compared to 6.4% in the LVEF >25% group (*P*-value 0.03), and 9.0% in the ischaemic cardiomyopathy (ICM) group compared to 5.9% in the non-ischaemic cardiomyopathy (NICM) group (*P*-value 0.005).

For the secondary outcomes, appropriate ICD therapy was given in 165 (11.4%) patients with a crude rate of 5.2 per 100 patient-years, where the first appropriate therapy was ATP only in 64 (39%) patients and ICD shock with or without ATP in 101 patients (61%). The Fine and Gray cumulative incidence estimate for appropriate ICD therapy at 2 years was 9.2%. 66 patients (4.6%) received inappropriate shocks and 230 complications occurred in 195 patients (13.5%). In 113 patients (7.8%), 128 complications were classified as major. Almost half (47%) of the major complications occurred within 30 days after implantation.

In the validation cohort, 223 (15.4%) participants died during a median follow-up of 2.7 years (2.1–3.4; crude rate: 5.7 per 100 patient-years). The KM estimate of 2-year mortality was 10.4%. For ICD shock, 105 (7.2%) participants received at least one appropriate ICD shock during a median follow-up of 2.6 years (2.0–3.3), with a crude rate of 2.8 per 100 patient-years. The Fine and Gray 2 year estimate of the proportion of participants with appropriate ICD shock was 5.3%.

Model development and validation

Two models were derived for both primary outcomes. Univariable hazard ratios of candidate predictors can be found in the Supplementary material online, *Table S2*. Selected predictors and their multivariable hazard ratios are shown in *Table 2*. We used log transformation for NT-pro-BNP as the log-linear relationship performed better. For the secondary outcome appropriate ICD therapy a third model was derived, further described in the Supplementary material online. The universal shrinkage factor for the mortality model was 0.82, and 0.60 for the ICD shock model. Risk formulas to calculate 2 year event risks can be found in Supplementary material online, *Table S3*. The development cohort showed an optimism corrected C-statistic of the mortality model of 0.74 (95% CI 0.70–0.78) and for appropriate ICD shock 0.61 (95% CI 0.56–0.66). At external validation, C-statistic was 0.74 (95% CI 0.70–0.78) for the mortality model and 0.60 (95% CI 0.53–0.67) for the ICD shock model. Internal and external validated calibration of both models are shown in Supplementary material online, *Figures S1* and *S2*.

Clinical utility

We explored scenarios where clinicians would postpone ICD implantation for 2 years when predicted ICD shock risk was under a

Table 1 Baseline characteristics of DO-IT patients and ICD patients from EU-CERT-ICD

Category	Variable	DO-IT (*n* = 1443), *N* (%) or mean/median (SD/IQR)	EU-CERT-ICD (*n* = 1450), *N* (%) or mean/median (SD/IQR)	*P*-value
Demographic	Gender (male)	1044 (72)	1196 (83)	<0.001
	Age	65.9 (10.2)	61.9 (11.5)	<0.001
	BMI	27.3 (4.7) (*n* = 1430)	27.7 (5.1) (*n* = 1444)	0.028
Cardiomyopathy characteristics	NYHA functional class	(*n* = 1433)		<0.001 (I or II vs. III or IV)
	I	207 (14)		
	II	905 (63)	Class I or II 886 (61)	
	III or IV	321 (23)	564 (39)	
	Ischaemic cardiomyopathy	882 (61)	1002 (69)	<0.001
	LVEF	26.1 (6.2) (*n* = 1437)	27.5 (5.6)	<0.001
	RV function (normal)	867 (71) (*n* = 1219)		
	HF hospitalization <1 year	303 (21) (*n* = 1431)		
	NSVT[a]	170 (12) (*n* = 1393)	36 (2.5)	<0.001
Co-morbidity	Vascular disease (CVA/TIA/peripheral)	291 (22) (*n* = 1319)	263 (18)	0.01
	Atrial fibrillation	438 (31) (*n* = 1419)	359 (25)	<0.001
	COPD	211 (15) (*n* = 1423)	168 (12)	0.01
	Hypertension	618 (44) (*n* = 1400)	938 (65)	<0.001
	Diabetes mellitus	386 (27) (*n* = 1436)	445 (31)	0.03
	Hypercholesterolaemia	594 (43) (*n* = 1380)		
Risk factor	Familial SCD	176 (15) (*n* = 1152)		
	Smoking	846 (68) (*n* = 1218)	949 (65)	0.03
Medication	Beta-blocker	1232 (85)	1380 (95)	<0.001
	Diuretic	1032 (72)	1106 (76)	0.004
	Aldosterone antagonist	667 (46)	1148 (79)	<0.001
	ACEi or ARB	1288 (89) (*n* = 1441)	1354 (93)	<0.001
	Oral anticoagulant	684 (47)	460 (32)	<0.001
	Digoxin	143 (10)	98 (6.7)	0.002
	Statin	976 (68)	1085 (75)	<0.001
ECG parameters	Heart rate	71.5 (14.5) (*n* = 1431)	71.4 (13)	0.85
	QRS duration	(*n* = 1359)	(*n* = 1444)	<0.001
	<120 ms	614 (45)	1109 (77)	
	120–150 ms	333 (25)	316 (22)	
	>150 ms	412 (23)	25 (2)	
	QTc bazett	465.1 (47.9)	438.8 (39.0)	<0.001

Continued

Table 1 *Continued*

Category	Variable	DO-IT (*n* = 1443), *N* (%) or mean/median (SD/IQR)	EU-CERT-ICD (*n* = 1450), *N* (%) or mean/median (SD/IQR)	*P*-value
		(*n* = 1429)		
Laboratory results	eGFR (mL/min)	61.3 (18.6)	72.2 (22.8)	<0.001
		(*n* = 1408)	(*n* = 1433)	
	Sodium (mmol/L)	139.4 (3.0)	139.2 (3.2)	0.09
		(*n* = 1401)	(*n* = 1429)	
	Potassium (mmol/L)	4.4 (0.4)		
		(*n* = 1398)		
	Haemoglobin (mmol/L)	8.6 (1.0)		
		(*n* = 1364)		
	NT-pro-BNP (pmol/L), median (IQR)	160 (65–373)	191 (77.5–452.4)	0.003
		(*n* = 595)	(*n* = 1043)	
Device characteristics	Previous pacemaker	76 (5)		
	Device type			<0.001
	Single chamber	480 (33)	1131 (78)	
	Dual chamber	231 (16)	293 (20)	
	CRT-D	623 (43)	0 (0)	
	SQ-ICD	109 (8)	24 (2)	
	Lowest ICD therapy zone			
	<180 b.p.m.	34 (2)		
	180–200 b.p.m.	1102 (76)		
	200–230 b.p.m.	305 (21)	Mandatory lowest ICD therapy settings >200 b.p.m.	
	>230 b.p.m.	3 (0)		

[a]DO-IT and EU-CERT-ICD use different definitions of NSVT, DO-IT: any history of NSVT is used and EU-CERT-ICD: NSVT at pre-implantation 24 h rhythm monitoring.
CRT-D, cardiac resynchronization devices with defibrillator; ICD, implantable cardioverter-defibrillator; SQ-ICD, subcutaneous implantable cardioverter-defibrillator; BMI, body mass index; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; RV function, right ventricular function; HF, heart failure; NSVT, non-sustained ventricular tachycardia; CVA, cerebrovascular accident; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; SCD, sudden cardiac death; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; SD, standard deviation; IQR, interquartile range.

risk threshold. *Figure 4* demonstrates the effects of using a specific risk threshold: i.e. using a hypothetical cut-off of 2.5% to defer ICD implantation in those with lower predicted risk results in 4 ICD implantations incorrectly withheld, and 376 correctly withheld in the DO-IT cohort. This corresponds to a number needed to treat (NNT) of 95 to protect one patient who would have received an ICD shock in 2 years. At external validation the 2.5% cut-off would result in 2 ICD's incorrectly withheld and 112 correctly withheld, corresponding to an NNT of 57.

Discussion

Main findings

Cumulative event rates of mortality and appropriate ICD shock are still significant despite the medical advancements in recent years. However, in the DO-IT cohort, most patients did not receive an appropriate ICD shock over the relatively short period of 2.3 years. Risk stratification before implantation remains an important objective to prevent unnecessary ICD implantations. Stratification based on LVEF category and cardiomyopathy type did not show a significant difference in ICD shock rate, thus other predictors have to be considered. This study developed and externally validated separate risk models for mortality and appropriate ICD shock with routinely available parameters. The model for mortality had a higher ability to distinguish patients at risk than the model for appropriate ICD shock. Predicted and observed risks were concordant for the mortality model, but less so for the ICD shock model. However, a subgroup with a low risk of receiving an ICD shock could be identified, explored in the clinical utility scenarios, which remained concordant at external validation.

Prior studies

The observed appropriate shock rate is lower than in prior landmark studies, but similar to more contemporary cohorts (Supplementary material online, *Table S4*). The selected predictors for the mortality model overlap with previously observed prognostic factors for death in heart failure patients, with comparable C-statistics, 0.74 in the DO-IT model vs. 0.73 in the Seattle heart failure model.[12] However, no direct comparison could be made as the Seattle heart failure model used predictors which were not available in the DO-IT dataset. Predicting appropriate ICD shock seems less accurate than mortality with routine clinical parameters, similar to prior competing risk studies of appropriate ICD therapy.[13,14] The main selected predictors for appropriate ICD shock in the setting of competing mortality risks

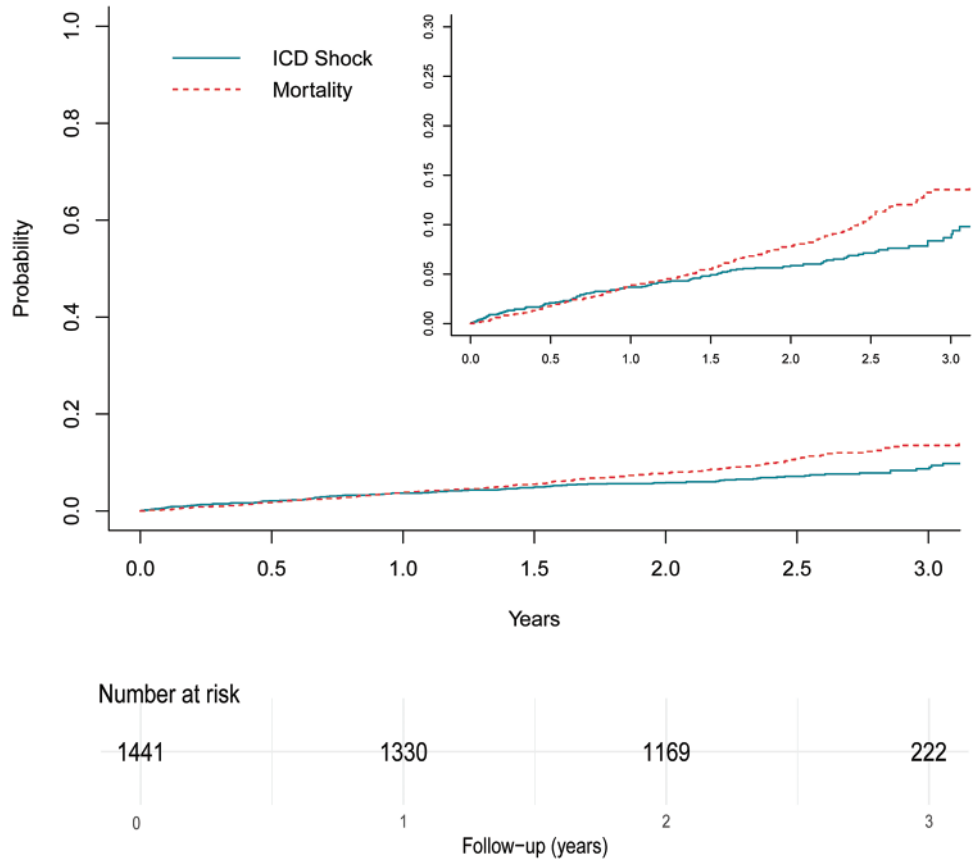

Figure 2 Cumulative incidence curves of appropriate ICD shock and mortality plotted with the Fine and Gray competing risk method. Follow-up duration is shown on the x-axis, and probability of either event on the y-axis. The upper right part of the figure contains the cumulative incidence curves with a probability range from 0 to 0.3. ICD, implantable cardioverter-defibrillator.

have been described previously as risk factors for ICD shock, such as AF history, digoxin, NSVT, and gender.[15] Not all univariable significant predictors were selected, for example, kidney function, possibly due to significant collinearity with other predictors. Moreover, LVEF, an established predictor of both outcomes, was not selected. This may be due to the used inclusion criteria based on low LVEF, where all patients already had the risk factor and further lowering might have marginal additional effects.

Clinical utility

The greatest clinical utility of this study lies in the quantification of mortality and arrhythmic 2-year risk (demonstrated in *Figure 5*) which aids risk stratification for primary prevention patients. The online risk stratification calculator can be found at https://do-it-study.shinyapps.io/DO-IT-calculator/ . The European guideline committee for hypertrophic cardiomyopathy is considered a yearly risk <1% of SCD acceptable to defer from ICD implantation.[16] Several studies pose that appropriate ICD shock is not a perfect surrogate for SCD, and only a fraction of delivered appropriate ICD shocks would actually have prevented SCD.[17,18] For example, if only up to 50% of appropriate ICD shocks may prevent SCD, this would correspond to a 2-year appropriate ICD shock risk threshold of 4%. Besides ICD shock, it is likely that a fraction of ATP only treatment prevented SCD in this study, and adds to the benefit from ICD implantation. However, it is currently unclear what fraction of ATP only therapy would prevent a SCD. Thus, our study does not aim to provide a definitive ICD implantation cut-off, as multiple risk thresholds may be appropriate and the preferred threshold could be different for individual patients. For the decision of implanting an ICD, other factors need to be weighted by the clinician, the patient, and health policymakers. These include factors such as ICD-related complications and inappropriate ICD shock and costs. In addition, all-cause mortality risk should be considered, as patients with a life expectancy <1 year should not receive an ICD in accordance with international guidelines.[1] Moreover there may be a ratio of SCD vs. non-SCD risk where ICD implantation is not beneficial. Several studies in primary prevention patients showed that patients at high risk of non-sudden death had no benefit of ICD implantation.[19,20] Levy *et al.*[20] proposed that a proportion of >31% SCD risk of the total mortality risk is needed to benefit from ICD implantation.

Limitations and future directions

Our findings are based on a nationwide (DO-IT) and European (EU-CERT-ICD) prospective registry and are limited by the observational nature of the studies. In the DO-IT study, extensive efforts were made to collect ICD read-outs of all ICD therapies CEC evaluation. However, in 15% of therapies, only documentation and

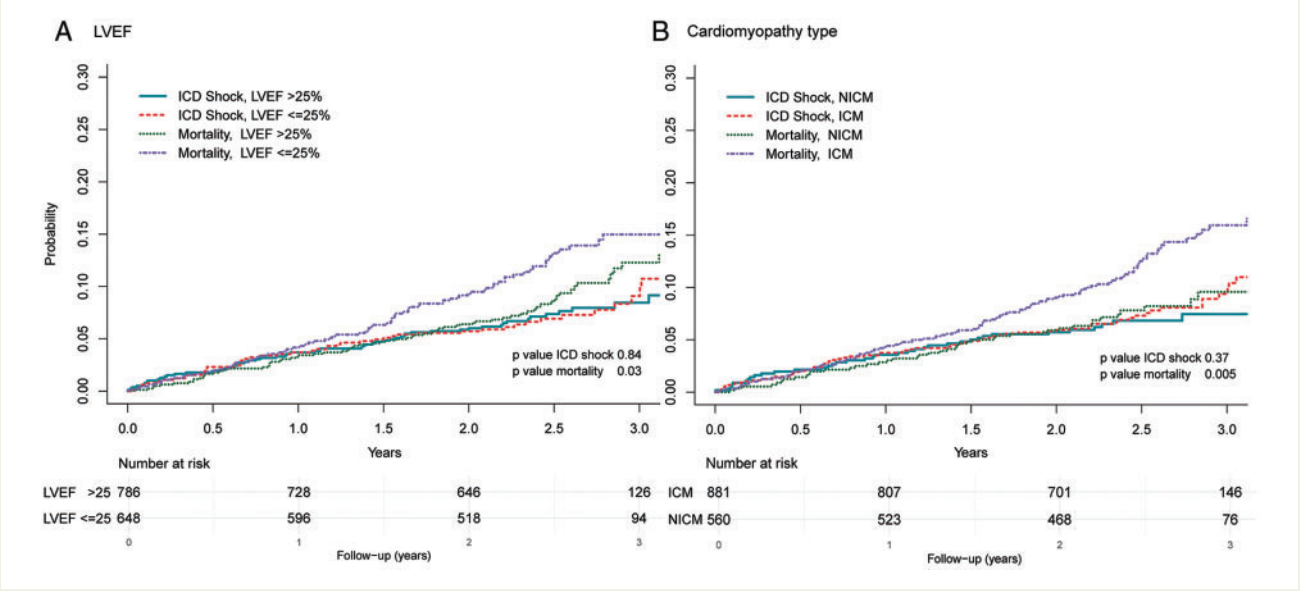

Figure 3 Cumulative incidence curves of appropriate ICD shock and mortality plotted with the Fine and Gray competing risk method stratified by LVEF and cardiomyopathy subgroups. Follow-up duration is shown on the x-axis, and probability of either event on the y-axis with a probability range of 0–0.3 shown. ICD, implantable cardioverter-defibrillator; ICM, ischaemic cardiomyopathy; LVEF, left ventricular ejection fraction; NICM, non-ischaemic cardiomyopathy.

Table 2 Multivariable hazard ratios (HR) of selected predictors with 95% confidence intervals and *P*-value

	HR mortality	HR appropriate ICD shock[a]
Age (per 1 year increase)	1.05 (95% CI 1.04–1.07, *P*-value <0.001)	Not selected
Diuretic use	2.93 (95% CI 1.80–4.73, *P*-value <0.001)	Not selected
Sodium (per 1 mmol/L increase)	0.90 (95% CI 0.86–0.94, *P*-value <0.001)	Not selected
NT-pro-BNP (per 1 log pmol/L increase)	1.54 (95% CI 1.33–1.78, *P*-value <0.001)	Not selected
ACEi or ARB use	0.47 (95% CI 0.32–0.68 *P*-value <0.001)	0.51 (95% CI 0.30–0.85, *P*-value 0.01)
Male sex	Not selected	4.76 (95% CI 2.31–9.81, *P*-value <0.001)
NSVT	Not selected	2.46 (95% CI 1.59–3.79, *P*-value <0.001)
AF history	Not selected	2.24 (95% CI 1.35–3.70, *P*-value <0.001)
Aldosterone antagonist use	Not selected	1.59 (95% CI 1.09–2.33, *P*-value 0.02)
Digoxin use	Not selected	1.56 (95% CI 0.91–2.69, *P*-value 0.11)
eGFR (per 1 mL/min/1.73 m^2 increase)	Not selected	1.01 (95% CI 1.00–1,02, *P*-value 0.09)
(N)OAC use	Not selected	0.58 (95% CI 0.35–0.94, *P*-value 0.03)
Peripheral vascular disease (incl CVA)	Not selected	0.70 (95% CI 0.41–1.20, *P*-value 0.20)

[a]Appropriate shock hazard ratios are based on the Fine and Gray competing risk proportional subdistribution hazards model.
ICD, implantable cardioverter-defibrillator; NSVT, non-sustained ventricular tachycardia; CVA, cerebrovascular accident; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; AF, atrial fibrillation.

interpretation of the local electrophysiologist/ICD technician was available, which were ultimately used. We compared CEC and local judgement in the 85% available ICD read-outs, showing total agreement between the observers in 94%, with a Cohen's kappa of 0.52. In the DO-IT cohort, a minority of patients did not conform to the ICD implantation guideline criteria. As a sensitivity analysis, no difference was found in ICD therapy rate between guideline and non-guideline patients, *P*-value 0.68 (Supplementary material online, *Figure S3*). There are differences between the DO-IT and EU-CERT-ICD cohort, and while many are statistically significant, their clinical relevance may be limited as reflected in the similar two-year risks of mortality and appropriate shock. A major difference between the DO-IT cohort and EU-CERT cohort is the absence of CRT-D devices in the latter, which could influence the external validation results. However, type of ICD, CRT-D vs. non-CRT-D, was tested as an interaction term in the models which proved to be non-significant (*P*-value 0.4). Type of ICD is also reflected in QRS duration at baseline, as most patients with long QRS duration are suitable for CRT, thus

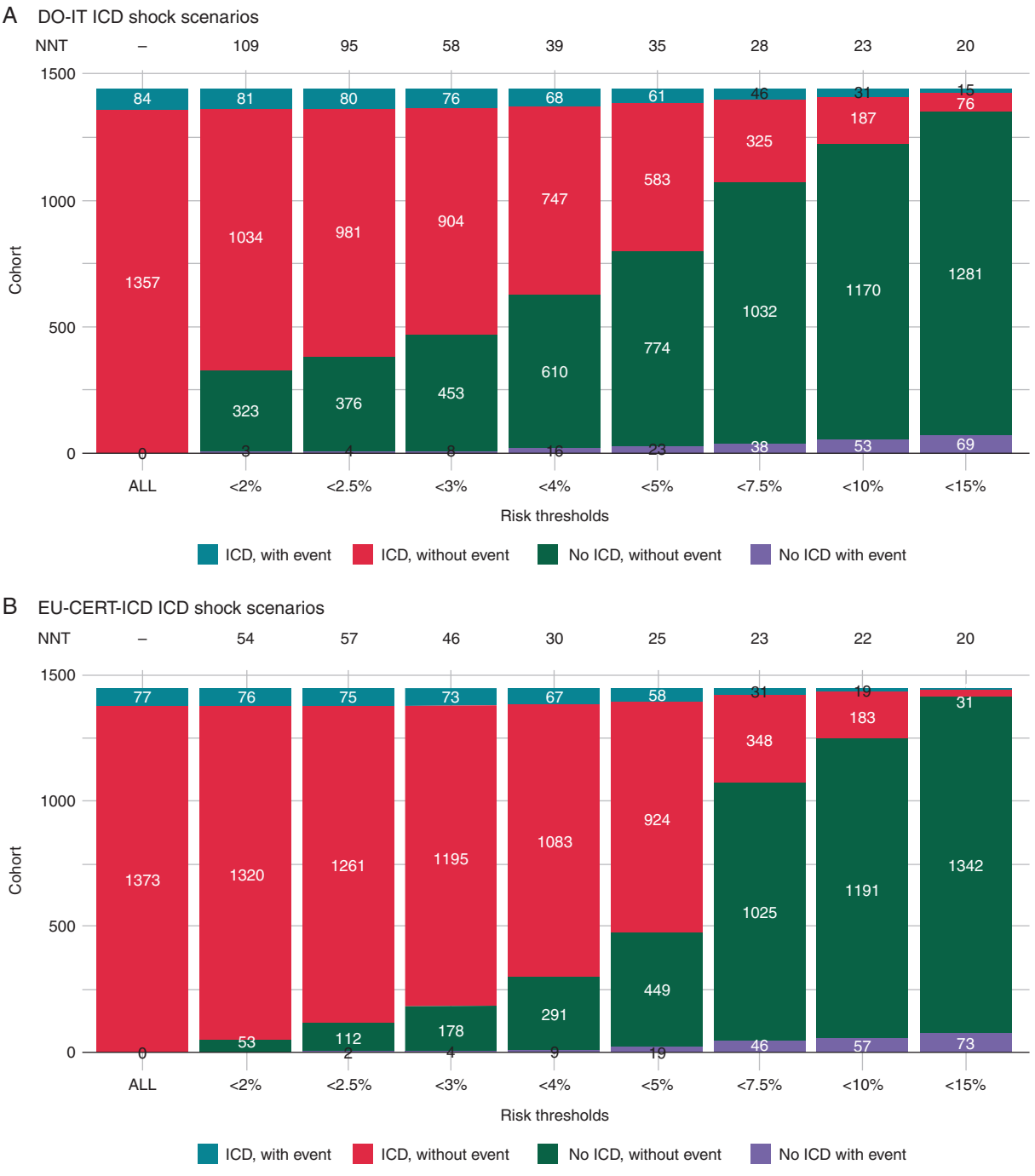

Figure 4 Scenario analysis with the ICD shock model in the DO-IT (*A*), and EU-CERT-ICD (*B*) cohort. The effects of applying the model to the DO-IT and EU-CERT population where patients with a lower predicted probability of ICD shock than the risk threshold would not be treated with an ICD are shown. Risk threshold is on the x-axis, the number of patients on the y-axis. Each bar represents the complete cohort, where the different colours represent the proportion of carriers experiencing the event (appropriate ICD shock) as well as the placement or non-placement of an ICD. Number needed to treat (NNT) refers to the number of patients needed to treat to protect one patient who would have received an ICD shock in 2 years for the group below the risk threshold. ICD, implantable cardioverter-defibrillator.

excluded from the EU-CERT-ICD cohort. Another difference was the definition of NSVT, where the DO-IT model uses any history of NSVT and the EU-CERT only had NSVT at baseline 24-h rhythm monitoring available, which explains the baseline difference. Finally, device programming was not uniform, with the DO-IT population generally having a slightly lower therapy cut-off rate and this might influence ICD therapy rate. Arrhythmia rate was available in 99/109 (92%) of ICD shocks. A minor fraction, 7/99 (7%) of ICD shocks in

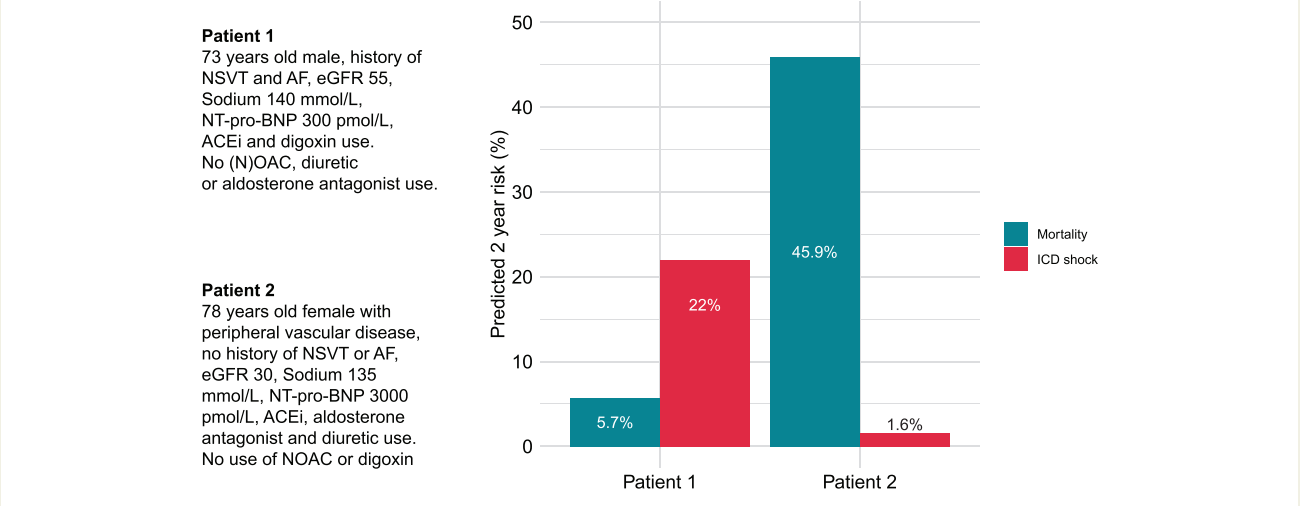

Figure 5 Example prediction of all-cause mortality and ICD shock in two patients. With the prediction models individual estimations of all-cause mortality and ICD shock risk can be made. In combination with an appropriate ICD shock risk threshold, these estimations can be used to guide ICD implantation for primary prevention of SCD. ICD, implantable cardioverter-defibrillator.

the DO-IT cohort was <200 beats per minute. However, the differences between the development and validation cohort can also be seen as a way to test the validity of the models outside the context of the development cohort, and when adequate, improve generalizability. Both models included medication use at baseline as predictor, though this may only be a marker for underlying disease state (e.g. heart failure severity) and a reflection of the state-of-the-art in clinical practice, and should not be interpreted as causal. Thus, the models should not be used to evaluate medication strategies. Removing medication as predictors would result in an undesirable decrease in the discriminative ability of both models. Internally validated C-statistic decreased from 0.74 to 0.72 and 0.61 to 0.56 for mortality and appropriate ICD shock respectively. We included only routine clinical parameters for the current prediction models reflective of current clinical practice. Unfortunately, few were electrophysiologically relevant as evidenced in the poor predictive performance of the ICD shock model. Future risk stratification is likely to be improved when adding more arrhythmic substrate and electrophysiological related parameters. Finally, all included patients were implanted with a defibrillator, gain or loss of life expectancy when using the models cannot be truly estimated with this study and will require a randomized controlled study.

Conclusion

We describe current outcomes of primary prevention ICD therapy in a contemporary nationwide cohort, with the ICD shock rate still being significant with a crude rate of 3.3%/year. To identify patients who insufficiently benefit from ICD therapy we developed new prediction models for risk of death and appropriate ICD shock. The performance of the mortality model was good at both internal and external validation, but the performance was poor for the appropriate ICD shock model. Although this cohort study was specifically designed to develop prediction models, risk stratification still remains challenging using current routinely collected parameters. As a large well-defined group with insufficient benefit of ICD therapy was not found. However, the prediction models have some clinical utility as we present several scenarios where ICD implantation might be postponed.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

The data underlying this article cannot be shared due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

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