A Novel Risk Model for Predicting Potentially Life-threatening Arrhythmias in Non-ischemic Dilated Cardiomyopathy (DCM-SVA risk)

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Abstract

Background: Non-ischemic dilated cardiomyopathy (DCM) can be complicated by sustained ventricular arrhythmias (SVA) and sudden cardiac death (SCD). By now, left-ventricular ejection fraction (LV-EF) is the main guideline criterion for primary prophylactic ICD implantation, potentially leading either to overtreatment or failed detection of patients at risk without severely impaired LV-EF. The aim of the European multi-center study DETECTIN-HF was to establish a clinical risk calculator for individualized risk stratification of DCM patients.

Methods: 1,401 patients (68% male, mean age of 50.5±14.4 years at first visit) from four European countries were included. The outcome was the occurrence of first potentially life-threatening ventricular arrhythmia. The model was developed using Cox proportional hazards model, and internally validated using cross validation. The model included six independent and easily accessible clinical parameters sex, history of non-sustained ventricular tachycardia, history of syncope, family history of cardiomyopathy, QRS duration, and LV-EF. The model was also expanded to account for presence of LGE as the seventh parameter for cases with available cMRI and scar information.

Results: During 7,907 patient years, 194 (13.8%) patients experienced an arrhythmic event. The calibration slope of the developed model was 0.99 (95% CI 0.92-1.06) and the C-index was 0.72 (95% CI 0.70-0.73). Compared to current guidelines, the model was able to protect the same number of patients (5-year risk ≥8.5%) with 12.1% fewer ICD implantations.

Conclusions: This DCM-SVA risk model could improve decision making in primary prevention of SCD in non-ischemic DCM using easily accessible clinical information and will likely reduce overtreatment.

Key words: dilated cardiomyopathy, sustained ventricular arrhythmia, risk calculator

Introduction

Besides progressive heart failure, non-ischemic dilated cardiomyopathy (DCM) patients are at increased risk for developing sustained ventricular arrhythmias (SVAs) and sudden cardiac death (SCD) and may benefit from primary preventive implantable cardioverter-defibrillator (ICD) implantation (1,2). While left ventricular ejection fraction (LV-EF) has been prospectively validated in ICD implantation guidelines (3,4), the clinical value of other risk factors and cut-off free estimates has not been shown convincingly. The importance of new approaches is, however, imminent: The contemporary Danish-Trial failed to show survival benefit in DCM patients after primary preventive ICD implantation, which questioned the usefulness of LV-EF as sole risk marker in non-ischemic etiologies (5). In sub-group analysis, it became evident that the concurrent mortality risk from heart failure and the stage of the disease is important. In a recent position statement by the European Society of Cardiology, the continuum of DCM phenotypes is appreciated by introducing the concept of dynamic disease expression, highlighting that arrhythmogenic stages can precede ventricular dysfunction and dilatation (6). Nearly one third of DCM patients, for example, develop ventricular arrhythmias without having severely reduced LV-EF (<35%) and hence are not fulfilling guideline criteria for primary prevention (7).

Several clinical and molecular factors for risk prediction in DCM have already been suggested (8-10). Furthermore, a systematic review and meta-analysis of 55 studies was conducted within the European Network DETECTIN-HF in search for independent and robust risk factors (1). For hypertrophic cardiomyopathy (HCM), the European Society of Cardiology (ESC) introduced successfully a cut-off-free, multivariable risk model for predicting life-threatening arrhythmias (11) and 6 years after its introduction several studies have validated its clinical applicability (12,13). However, in case of DCM there is lack of a suitable risk calculator

that allows easy integration of the individual factors and that is validated in a sufficiently large cohort. Hence, in daily practice, LV-EF remains the main determinant in decision making for ICD implantation in these patients.

To aggregate commonly available clinical risk factors and aggregate their individual weight to predict ventricular arrhythmia, we aimed to develop a risk calculator for clinical decision making. We restricted the model to broadly available clinical parameters. Our multi-stage model is, however, able to integrate further information such as presence of CMR-derived late gadolinium enhancement (LGE) if available.

Materials and Methods

Study design

The demographic and clinical data used for this study was retrieved from local registries (retrospective). For follow-up, patients were investigated at the recruiting center during their routine clinical visit or were contacted by phone during this study. The study was handled in accordance with the Declaration of Helsinki. The ethics committee and institutional review boards of all four centers approved the inclusion and study of biomaterials and collected clinical data and all patients had given informed written consent. After data harmonization and cleaning, a model based on previously identified and selected variables was developed using the Cox proportional hazards model. An internal validation was performed using cross validation.

Study population and participating centers

The study cohort originated from specialized cardiomyopathy centers across Europe: (i) Institute for Cardiomyopathies (ICH), Heidelberg, Germany (iia) Department of Cardiology, Division Heart & Lungs, University Medical Center Utrecht, the Netherlands (UNRAVEL) (iib) Netherlands Heart Institute, Utrecht, the Netherlands (iii) Unit for Screening Studies in Inherited Cardiovascular Diseases, National Institute of Cardiology, Warsaw, Poland (OBP-NIKARD) and (iv) Referral Center for hereditary heart disease, Pitié Salpêtrière Hospital & Sorbonne University, Paris, France (CEREFCOEUR). Patients were all evaluated and followed-up if they (i) were diagnosed with definite non-ischemic DCM and (ii) had not experienced sustained ventricular arrhythmia or aborted SCD before the first visit. Patients with assured diagnosis of cardiac sarcoidosis or fulminant myocarditis were excluded. Only patients ≥18 and <80 years at first visit were included in the model generation. Since we aim to introduce a model that is

applicable at first clinical visit, we took the age at first visit as inclusion age. Only few patients were diagnosed with DCM in childhood and enrolled after the age of >18 years (n=6, 0.5%).

Study outcomes

The study outcome was sustained ventricular arrhythmia (SVA) following first visit and included a composite of occurrence of SCD, aborted cardiac arrest (SCA), hemodynamically relevant ventricular tachycardia (VT), which had to be defibrillated internally or externally, and potentially life-threatening arrhythmia, terminated by adequate anti-tachycardia pacing (ATP). The endpoint for a patient was reached in case of the first event. ICD implantation during follow-up, heart transplantation (HTX), implantation of ventricular assist devices (VAD), and all-cause mortality were also reported.

Selection of predictors and sample size

Clinical variables were pre-selected based on the results of a systematic literature review and meta-analysis (1,8-10,14-21), clinical expertise, as well as their availability in clinical practice. The following variables were selected: gender, age at first visit, history for syncope, non-sustained ventricular tachycardia (nsVTs) in patients' history or in Holter performed till 14 days after first visit, family history for cardiomyopathy (CMP), family history for SCD, native QRS duration (QRS duration without pacing), as well as LV-EF and LVEDD in echocardiography. An additional model was built by adding LGE presence as a marker for myocardial scar.

To ensure model's accuracy and precision, a minimum number of 10 events per variable (EPV) are recommended (22). In our study cohort 194 first events were observed, which would allow estimation of 19 variables.

Data collection and statistical analysis

Patients were followed-up prospectively every 6-12 months or earlier if clinical symptoms worsened. Patients' medical records were extracted from the hospital information systems and study databases and critically reviewed by two experienced cardiologists/residents from each center (E.K and F.S from Germany, A.S and F.A from the Netherlands, P.C and Z.B from Poland, and P.C. and P.S from France). Data are available upon request and approval by the data access committee of the *Detectin-HF* consortium for external analyses. More information about data proposal requests may be found on *www.Detectin-HF.eu*.

All analyses were performed in Python 3.7. Statistical tests utilized the Scipy 1.4.1 package. Categorical variables were checked for significance with χ^2-tests and continuous variables with t-tests. For developing the Cox regression model Lifelines 0.24.5 was used. The follow-up duration was calculated from the date of first visit to the date of last visit at center or date of reaching an endpoint. In case of missing data points, Multiple Imputation by Chained Equations (MICE) was used for imputation. Patients with more than two missing variables were excluded from model development. The scikit-learn 0.22.1 implementation of MICE was used for the data imputation. The imputation model included all pre-selected predictors and the outcome variable. Overall, 30 datasets were imputed for different random states of the imputer. The imputed datasets were combined according to Rubin's rules (23).

Model development and validation

Multivariable cox regression was used for the model development. To eliminate problems associated with predictor selection, a significance level of 0.15 was defined. The final risk model was then built with the help of backward elimination. In order to make efficient use of the data, we used the entire cohort to build the risk model.

10-fold cross validation was used to internally validate the model. Furthermore, the cross validation was looped for ten times with different data splits to increase the accuracy of the performance estimation. The degree of agreement between the observed and predicted 5-year risk for SVA was estimated by the average calibration slope, with a value close to 1 showing good overall agreement (24). A calibration plot was also created to graphically evaluate the agreement between predicted and observed outcome. C index and D statistic were used as indicators of how well the model discriminates between high and low risk patients, with a value of 0.5 for C-index indicating no discrimination and 1 for perfect discrimination and increasing values for D-statistic meaning better discriminatory ability of the model.

Model

The following equation calculates the risk of SVA at 5 years for each individual:

$P(\text{VA at time t}) = 1 - S0(t)^{\exp(LP)}$

S0(t): the average survival probability at time t, LP: prognostic index which is the sum of the products of the predictors and their associated coefficients for each given patient.

Secondary model development and further validation

For further validation, patients of 3 centers were used for model development and the ones from the remaining center were used for validation. This was performed 4 times so that each center was used once for validation. C index, D-statistic and calibration slope were calculated for each model to evaluate the homogeneity between centers.

For sensitivity analysis penalized Cox regression was used. Four different models were trained to estimate the center effect. Models were built with and without the information about the center. Furthermore, these two scenarios were evaluated on the subset of patients with

complete information and additionally the imputed dataset. To eliminate overestimation of risk by including ATPs as event, a further sensitivity analysis was performed excluding ATP events. Additionally, a sensitivity analysis was performed to investigate the model performance in patients without CRT.

To assess any potential superiority of our developed risk model, we compared its performance with current stratification strategies. According to most recent ESC guidelines, ICD implantation is indicated for LV-EF ≤35% + NYHA II/III or for asymptomatic patients with LV-EF ≤30% (25).

Results

Baseline clinical characteristics of study population

Our study population included 1,401 patients (7,907 patient years) with non-ischemic dilated cardiomyopathy. **Table 1** lists baseline clinical, electrocardiographic and echocardiographic characteristics of the study cohort. Sixty-eight percent of the patients were male with a mean age of 50.5±14.4 years at first visit. An unexplained and/or cardiac syncope before first visit was reported in 6.6% of the patients. 25.2% had positive family history for CMP, and 6.7% had positive family history for SCD. 27.5% were asymptomatic (NYHA I) at time of first visit, 66.8% reported obvious dyspnoea on exertion (NYHA II or III) and 5.7% were symptomatic at rest (NYHA IV). 27.3% had history of atrial fibrillation and the mean native QRS duration was 116±29ms. Mean left ventricular ejection fraction measured using echocardiography was 31.1±12.3%. Altogether around two-thirds had an LV-EF ≤35%. Mean left ventricular end-diastolic diameter (LVEDD) was 61.4±10.1mm. Mean atrial size was increased with 43.4±8.1mm, measured in parasternal long axis view (PLAX). Definitions of the pre-selected variables and their codings are summarized in **Table 2**. Altogether, 1,056 patients had complete data for the 9 pre-selected model parameters and 1,119 for the final model with 6 parameters. None of these 6 parameters correlated significantly with each other **(Figure 1A)**. Missing data occurred for 345 of the 9 predictors and for 282 of the 6 predictors of the final model.

The ICDs were programmed in each center based on its standard clinical practice routine including one VF zone and one or two VT zones with ATP that could be followed by 1 or 2 ICD shocks.

Outcomes (SVA/SVA equivalent events during follow-up)

The minimum follow-up time was one month. During a follow-up period of 57.0 months [IQR 24.7; 93.0 months], 194 (13.8%) patients reached the endpoint of first SVA/equivalent. **Figure 1B** shows Kaplan Meier survival plots of the study population. The study outcome consisted of 7 (0.5%) SCD, 28 (2.0%) aborted cardiac arrest, 96 (6.8%) hemodynamically relevant ventricular tachycardias that had to be defibrillated internally or externally, and 63 (4.5%) potentially life-threatening arrhythmia, which were terminated by adequate ATPs. The mean cycle length of VT at ATP response was available in 35 cases (320±28ms) and the mean cycle length at ICD shock in 32 cases (274±81ms). At last follow-up, 169 (12.1%) patients had died, 62 (4.6%) had undergone HTX, 35 (2.6%) had received VADs, and 587 (44.9%) had received ICD/CRT-D. 246 (17.6%) patients received at some point a CRT-P/CRT-D. There were altogether 6 patients with pediatric-onset DCM (0.4%), from whom only one had an event. Clinical characteristics of patients with and without the endpoint SVA are shown in **Table 1**.

Model development and validation

Table 3 shows the exploratory univariable analyses with estimates of the hazard ratios and their corresponding confidence intervals. Only sex, history of nsVT and syncope, family history of cardiomyopathy, as well as QRS duration (ms), and LV-EF (%) were significantly associated with outcome at the preselected significance level and were included in the multivariable analyses to build the final model. The risk of SVA in 5 years for an individual with DCM was finally calculated using following equation: $P(\text{VA at 5 years}) = 1 - 0.89163736^{\exp(LP)}$, where LP = Sex * 0.31 + History for nsVT * 0.86 + History for Syncope * 0.60 + Family history for CMP * 0.44 + QRS * 0.006 + LV-EF * -0.04.

Cross validation revealed a calibration slope of 0.99 (95% CI 0.92-1.06). The good overall agreement between the predicted and observed 5-year risk is shown in **Figure 2**. The C-index of the model was 0.72 (95% CI 0.70-0.73). The D-statistic was 1.24 (95% CI 1.15-1.32). This suggests that the hazard of SVA as predicted by the model is 3.5 times higher in the high-risk group compared with the hazard in the low risk group.

Secondary model development with further validation and sensitivity analyses

The overall further validation C-index was 0.65 (95% CI 0.47-0.82) with a calibration slope of 0.87 (95% CI -0.42-2.15) **(Online Tables 1A-1D)**. For sensitivity analyses, we estimated the hazard ratios from the model by adjusting for study center effect. Those were similar to the initial model without attributing the individual center **(Online Table 2)**. The C-index for this model was 0.72 (95% CI 0.7-0.73). We repeated this process for patients with complete data, without and with the data label center. This also resulted in only small changes to the coefficients with a C-index of 0.72 (95% CI 0.71-0.74) and C-index of 0.72 (95% CI 0.71-0.74), respectively **(Online Table 3)**. A further sensitivity analysis was performed excluding patients with ATPs as event. This included 63 fewer patients. The coefficients did not significantly change and the model showed a C-index of 0.71 (95% CI 0.69-0.72), calibration slope of 0.98 (95% CI 0.89-1.07), and D-statistic of 1.26 (95% CI 1.15-1.37) **(Online Table 4)**. We also performed an additional sensitivity analysis to investigate our model performance in patients without CRT. This included 1,155 patients with 135 events. The C-index of the resulting model was 0.72 (95% CI 0.70-0.73) with calibration slope of 0.99 (95% CI 0.89-1.09) and D-Statistic of 1.25 (95% CI 1.14-1.37). This shows that our model performs very well in DCM patients, regardless of whether they carry a CRT or not **(Online Table 5)**.

Comparison with conventional risk factors

To underline the performance of the suggested model, **Figure 3** shows the impact of potential 5-year SVA risk thresholds for ICD implantation in our model vs. current stratification strategies (ICD implantation in DCM patients with LV-EF ≤35% + NYHA II/III or in asymptomatic patients with LV-EF ≤30%) (25). This analysis could be performed in 799 patients of our cohort, in whom 5-year follow-up information was available. 129 patients had an event. By applying the guideline criteria, 497 out of 799 patients (62.2%) would have been treated with an ICD and 106 patients with events would have been protected. To avoid under-treatment and provide the same level of protection, the developed model would indicate 437 device implantations (54.6%), thereby reducing the total number of ICD implants by 12.1% [(497–437)/497] (P=0.002). When implanting the same number of patients with ICDs as current guidelines (n=497) but use the new model for selection of patients, 109 patients with end-point SVA would have been protected. These analyses were repeated in patients with available 3-year follow-up and showed similar significant results **(Online Text)**. **Online Figure 1** shows number of events missed when applying our model vs. conventional risk factors. Choosing a threshold of 8.5% predicted 5-year risk would result in equal number of missed events using each method, while implanting 60 fewer ICDs when using our model.

Addition of LGE presence as marker for myocardial scar

We aimed to establish a broadly applicable risk score and show its superiority compared to traditional stratification. To address emerging or specialized diagnostic tools and their value to improve risk stratification, we tested our model performance after adding LGE presence as marker for myocardial scar. By doing so, hazard ratio confidence interval and p-value further improved (HR 2.00, 95% CI 1.22-3.27, P=0.01), suggesting that LGE is a useful additional

predictor and should be included in risk stratification once available (C-index=0.73; 95% CI 0.72-0.74 and D-statistic=1.33; 95% CI 1.23-1.43). **Online Table 6** shows model performance after adding presence of LGE to the initial model.

Discussion

The utility of ICDs in DCM patients has been controversially discussed. Whereas the DANISH trial showed no significant improvement in all-cause mortality after primary preventive ICD implantation in DCM patients in comparison to contemporary medical and cardiac resynchronization therapy (5), meta-analyses that were performed since then showed significant mortality reduction of up to 24% after primary prophylactic ICD implantation (2,26). Although the overall mortality was not reduced in DANISH trial, SCD was reduced by approx. 50% in the ICD group (5). It is therefore important to identify those patients at high risk for SVAs.

In the current study, we developed and internally validated a clinical risk calculator for estimating 5-year risk of sustained ventricular arrhythmia in patients with non-ischemic DCM. Altogether more than 1,400 patients from 4 European countries have been used for model development. High-quality retrospective clinical data and prospective follow-ups were available and the proportion of missing data was satisfactorily low. The clinical model predictors were selected relying on previous studies, systematic reviews, meta-analyses, and expert consensus. The model was designed to include only parameters that are broadly available in clinical routine worldwide. There was no exclusion of patients with comorbidities so that the model is applicable to the majority of adult DCM patients. The final model included 6 predictors including sex, history for nsVT, history for syncope, family history for cardiomyopathy, QRS duration, and LV-EF. The C-index of our developed model was 0.72 (95% CI 0.70-0.73), showing a good discrimination between patients with and those without SVA. The calibration analysis also showed a good agreement between predicted and observed SVA risk and sensitivity analyses showed no significant center bias.

By comparing the model performance with current stratification strategies, the improvement in risk stratification becomes evident. Applying our model would have resulted in

implanting 12.1% fewer ICDs, while protecting the same number of patients. Additionally, our cut-off-free model could be particularly helpful for decision making in patients who do not fulfil ICD criteria based on current guidelines, e.g. when having LV-EF of >35% in presence of several other risk factors. Besides the 6 clinical model parameters, imaging biomarkers such as presence of LGE have been found to have prognostic value in cardiomyopathy patients, but are not readily available in many primary or secondary centers (8). Adding LGE as a seventh parameter further improved the model (HR 2.00, 95% CI 1.22-3.27, P=0.01) and could be integrated in the risk calculator.

Carrying pathogenic variants in high-risk genes such as Lamin A/C (*LMNA)*, sodium channel protein type 5 subunit alpha *(SCN5A)*, RNA binding motif protein 20 *(RBM20)*, phospholamban (*PLN)*, or filamin-C *(FLNC)* have been repeatedly associated with higher rates of life-threatening arrhythmia (27-32). This information is, however, often not available due to missing consent and since current guidelines do not encourage genotyping in DCM patients. Genetic testing including *LMNA*, *SCN5A*, *RBM20*, and *PLN* were performed in 570 patients (40.7%) of our cohorts, from which 71 (12.5%) patients had at least one pathogenic or likely pathogenic variant in a high-risk gene. While this relatively low number is insufficient to reach statistical power in a generalized model, it still has considerable impact on individual patients and should not be neglected, but incorporated into each patient's management.

Potential limitations

A recruitment bias cannot be ruled out, since all participating centers are specialized for treating cardiomyopathies. In a comparable study on HCM, the applicability of our approach was underlined and results were validated in several succeeding studies (11). Generalizability, however, will depend on further studies applying our risk model and we are already planning a

validation study within the German DZHK TORCH-Plus registry. Including ATP as outcome might have resulted in an overestimation of risk as ATP stimulation depends upon ICD programming. However, most recorded VTs were fast paced and thus likely becoming hemodynamically relevant. These assumptions are also reflected in current expert consensus statements on implantable cardioverter-defibrillator programming (33). Importantly, sensitivity analysis excluding ATPs showed similar performance. Lastly, cardiac resynchronization was shown to positively impact on reverse remodeling of DCM and is able to reduce arrhythmia associated outcomes. Still, our model performs well regardless of whether patients were implanted with CRT-P/D or not.

Conclusions

By carefully developing and validating a novel risk stratification model, we aimed to improve decision making for primary preventive ICD implantation in DCM patients. Further DCM cohorts are needed to externally validate this model and further prospective studies are needed to evaluate its impact on mortality, avoidance of ICD complications and costs-effectiveness.

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Figure legends

Figure 1: Independence of the selected six model parameters and outcome of the study population. A) Shown are color coded correlation coefficients. None of the 6 model parameters were significantly correlated. B) Cumulative event-free survival of the entire cohort (SVA). Shaded area shows 95% confidence intervals.

Figure 2: Agreement between observed (y axis) and predicted (x axis) 5-year risk for the compound outcome measure. Kaplan–Meier estimates with 95% CI intervals for quintiles of predicted risk are shown by triangles. Number of patients with a predicted risk is shown as spike histogram on x axis.

Figure 3: Outcome depending on model-based ICD implantation thresholds. Bars show implications of ICD implantation in 0-97.5% of patients (based on the calculated risk), as well as in patients with LV-EF ≤35% + NYHA II/III or asymptomatic patients with LV-EF ≤30% (current ESC guideline). The black triangles represent number needed to treat (NNT, right y axis). The dotted line shows the reference NNT. Left y axis shows patient fraction. The percentages refer to the light red section (no ICD, event).

Tables

Table 1: Clinical characteristics of patients with and without the endpoint SCD

Variable	Overall	Patients with event	Patients with no event	*P*-Value
Demographics				
Number of patients, n	1401	194	1207	
Male sex, n (%)	954 (68.1%)	145 (74.7%)	809 (67.0%)	0.03*
Mean age at first visit, years ± SD	50.5 ± 14.4	50.9 ± 14.2	50.4 ± 14.4	0.69
Non-sustained VT before first visit, n (%)	228 (20.7%)	58 (46.4%)	170 (17.4%)	<0.0001*
History of unexplained and/or cardiac syncope, n (%)	92 (6.6%)	21 (10.8%)	71 (5.9%)	0.01*
Family history for CMP, n (%)	277 (25.2%)	36 (28.8%)	241 (24.7%)	0.32
Family history for SCD, n (%)	94 (6.7%)	16 (8.2%)	78 (6.5%)	0.36
NYHA class, n (%)				0.02*
I	380 (27.5%)	38 (19.9%)	342 (28.7%)	0.05
II	575 (41.6%)	82 (42.9%)	493 (41.4%)	
III	348 (25.2%)	56 (29.3%)	292 (24.5%)	
IV	79 (5.7%)	15 (7.9%)	634 (5.4%)	
Medication at first visit				
ACE inhibitor/AT1 antagonist	1056 (96.0%)	122 (97.6%)	934 (95.8%)	0.3
Aldosteron antagonist	538 (48.9%)	77 (61.6%)	461 (47.3%)	0.003*
Other diuretics	562 (51.1%)	75 (60.0%)	487 (49.9%)	0.03*
Beta blocker	992 (90.2%)	118 (94.4%)	874 (89.6%)	0.09
Medication at follow-up				
ACE inhibitor/AT1 antagonist	772 (82.1%)	96 (82.1%)	676 (82.1%)	1.0
Aldosteron antagonist	490 (52.1%)	86 (73.5%)	404 (49.1%)	<0.0001*
Other diuretics	455 (48.4%)	85 (72.6%)	370 (45.0%)	<0.0001*
Beta blocker	815 (86.7%)	109 (93.2%)	706 (85.8%)	0.03*
ECG				
History of atrial fibrillation, n (%)	381 (27.3%)	72 (37.5%)	309 (25.7%)	0.001*
Native QRS duration, mean ± SD	116.2 ± 29.2	122.5 ± 31.2	115.2 ± 28.7	0.002*
Holter	685	83	602	
nsVT on 24h holter, n (%)	245 (35.8%)	56 (67.5%)	189 (31.4%)	<0.0001*
Echocardiography				
LV-EF ≤ 35%, n (%)	794 (64.7%)	140 (81.9%)	654 (61.9%)	<0.0001*
LV-EF, mean ± SD (%)	31.1 ± 12.3	25.6 ± 10.6	32.0 ± 12.3	<0.0001*
LVEDD, mean (mm)	61.4 ± 10.1	65.6 ± 10.8	60.8 ± 9.8	<0.0001*
Left atrium size, mean (mm)	43.4 ± 8.1	45.8 ± 8.8	43.1 ± 7.9	0.0003*

Table 2: Definitions of the pre-selected variables and their codings

Predictor variable	Definition	Coding
Sex (male)	Patients‘ reported sex	Binary (male/female)
Age	Age at evaluation	Continuous, years
History for nsVT	3 or more consecutive ventricular beats with a rate of >100 beats per minute with the duration of less than 30 seconds without haemodynamic compromise	Binary (yes/no)
History for syncope	Transient loss of consciousness, unexplained or probably cardiac	Binary (yes/no)
Family history for CMP	At least one 1st and/or 2nd degree family member <65 years of age with proven DCM, HCM or ACM	Binary (yes/no)
Family history for SCD	At least one 1st degree family member with proven SCD or aborted SCD <50 years of age	Binary (yes/no)
QRS duration	Duration in ms	Continuous, ms
LV-EF	Determined by echocardiography	Continuous, %
LVEDD	Determined by echocardiography	Continuous, mm

Table 3: Univariable cox regression model

Predictor variable	Univariable model		Multivariable model	
	Hazard ratio (95% CI)	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**
Sex (male)	1.35 (0.96-1.88)	0.08	1.36 (0.98-1.89)	0.07
Age	1.00 (0.99-1.01)	0.47	Not included in the final model	
History for nsVT	2.30 (1.70-3.13)	<0.005	2.36 (1.74-3.19)	<0.005
History for syncope	1.83(1.16-2.90)	0.01	1.82 (1.15-2.87)	0.01
Family history for CMP	1.49 (1.06-2.11)	0.02	1.55 (1.11-2.18)	0.01
Family history for SCD	1.33 (0.78-2.26)	0.29	Not included in the final model	
QRS duration	1.01 (1.00-1.01)	0.04	1.01 (1.00-1.01)	0.01
LV-EF	0.96 (0.95-0.98)	<0.005	0.96 (0.94-0.97)	<0.005
LVEDD	1.01 (0.99-1.03)	0.31	Not included in the final model	

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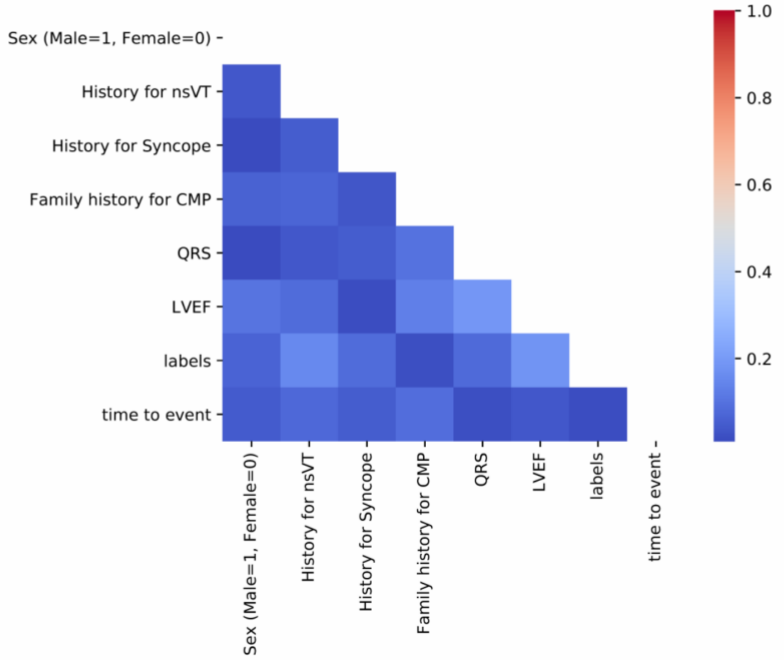
Figure 1

A


Sex (Male=1, Female=0)
History for nsVT
History for Syncope
Family history for CMP
QRS
LVEF
labels
time to event
1.0
0.8
0.6
0.4
0.2

B

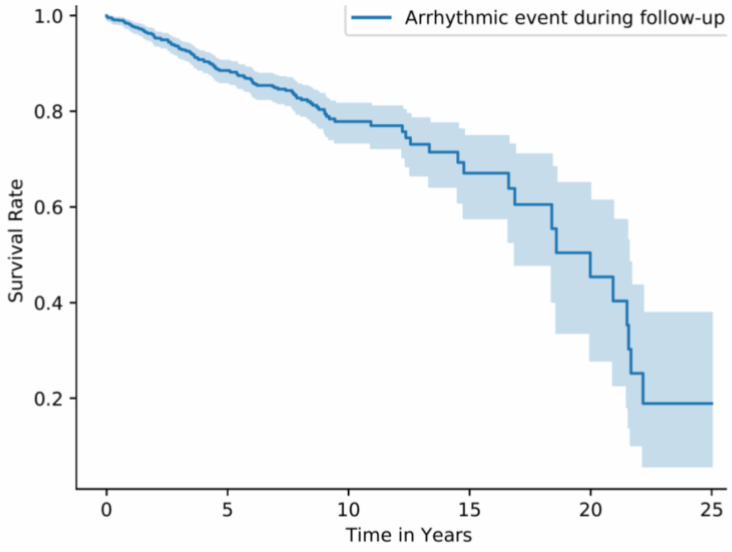

Arrhythmic event during follow-up
Survival Rate
1.0
0.8
0.6
0.4
0.2
0
5
10
15
20
25
Time in Years

Figure 2

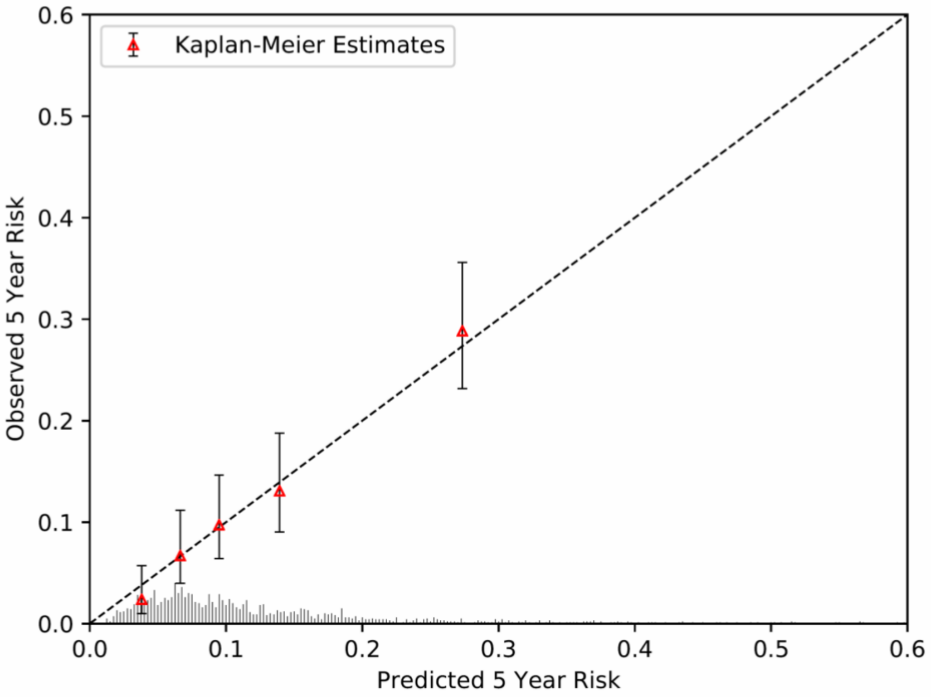
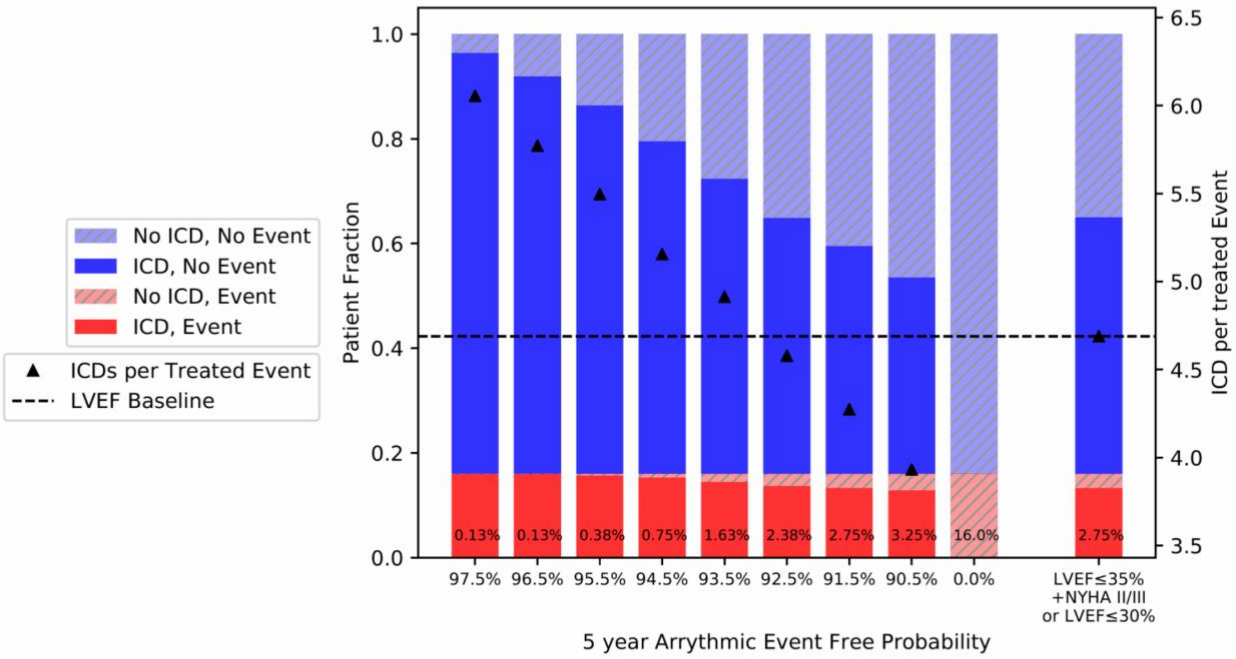

Kaplan-Meier Estimates
Observed 5 Year Risk
Predicted 5 Year Risk
0.0
0.1
0.2
0.3
0.4
0.5
0.6

Figure 3


No ICD, No Event
ICD, No Event
No ICD, Event
ICD, Event
ICDs per Treated Event
LVEF Baseline
Patient Fraction
ICD per treated Event
1.0
0.8
0.6
0.4
0.2
0.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
0.13%
0.13%
0.38%
0.75%
1.63%
2.38%
2.75%
3.25%
16.0%
2.75%
97.5%
96.5%
95.5%
94.5%
93.5%
92.5%
91.5%
90.5%
0.0%
LVEF≤35%
+NYHA II/III
or LVEF≤30%
5 year Arrythmic Event Free Probability