Timing of cardioverter-defibrillator implantation in patients with cardiac laminopathies—External validation of the *LMNA*-risk ventricular tachyarrhythmia calculator

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BACKGROUND *LMNA* genotype-positive patients have high risk of experiencing life-threatening ventricular tachyarrhythmias (VTAs). The *LMNA*-risk VTA calculator published in 2019 has not been externally validated.

OBJECTIVE The purpose of this study was to validate the *LMNA*-risk VTA calculator.

METHODS We included *LMNA* genotype-positive patients without previous VTAs from 2 large Scandinavian centers. Patients underwent electrocardiography, 24-hour Holter monitoring, and echocardiographic examinations at baseline and repeatedly during follow-up. Validation of the *LMNA*-risk VTA calculator was performed using Harrell's C-statistic derived from multivariable Cox regression analysis.

RESULTS We included 118 patients (age 37 years [IQR 27–49 years]; 39 [33%] probands; 65 [55%] women; 100 [85%] with non-missense *LMNA* variants). Twenty-three patients (19%) experienced VTA during 6.1 years (interquartile range 3.0–9.1 years) follow-up, resulting in 3.0% (95% confidence interval 2.0%–4.5%) yearly incidence rate. Atrioventricular block and reduced left ventricular ejection fraction were independent predictors of VTAs, while nonsustained ventricular tachycardia, male sex, and non-missense *LMNA* variants were not. The *LMNA*-risk VTA calculator showed 83% sensitivity and 26% specificity for identifying patients with VTAs during the coming 5 years, and a Harrell's C-statistic of 0.85, when applying ≥7% predicted 5-year VTA risk as threshold. The sensitivity increased to 100% when reevaluating risk at the time of last consultation before VTA. The calculator overestimated arrhythmic risk in patients with mild and moderate phenotype, particularly in men.

CONCLUSION Validation of the *LMNA*-risk VTA calculator showed high sensitivity for subsequent VTAs, but overestimated arrhythmic risk when using ≥7% predicted 5-year risk as threshold. Frequent reevaluation of risk was necessary to maintain the sensitivity of the model.

KEYWORDS *LMNA* cardiomyopathy; *LMNA*-risk VTA calculator; Lamin A/C; Laminopathy; Ventricular tachyarrhythmia; Primary preventive ICD

(Heart Rhythm 2023;20:423–429)

Funding Sources: This work was supported by Precision Health Care Center for optimized cardiac care (ProCardio) supported by the Norwegian Research Council (grant number #309762), European Research Area Network on Cardiovascular Diseases (EMPATHY project, NFR grant number #298736), the Innovation Fund Denmark (PM Heart), NordForsk, the Independent Research Fund Denmark (grant 0134-00363B, to Dr Christensen), and the Novo Nordisk Foundation, Denmark (NNF20OC0065799, to Dr Christensen). Disclosures: The authors have no conflicts of interest to disclose. **Address reprint requests and correspondence:** Dr Kristina H. Haugaa, Department of Cardiology, Oslo University Hospital, Rikshospitalet, 0372 Oslo, Norway. E-mail address: kristina.haugaa@medisin.uio.no.

https://doi.org/10.1016/j.hrthm.2022.11.024

Introduction

Cardiac laminopathies are highly malignant forms of familial dilated cardiomyopathy (DCM), caused by deleterious variants in the *LMNA* gene.[1–3] In DCM probands genetically tested for familial DCM in Norway and Denmark, 3% and 2%, respectively, carry pathogenic or likely pathogenic genetic variants in *LMNA*.[4,5]

A large proportion of *LMNA* genotype-positive patients receive a primary prevention implantable cardioverter-defibrillator (ICD) to protect against life-threatening ventricular tachyarrhythmias (VTAs) and sudden death.[6] Several previous studies have reported predictors of VTAs in *LMNA* genotype-positive patients[7–9] including nonsustained ventricular tachycardia (NSVT), atrioventricular (AV) block, left ventricular ejection fraction (LVEF) <45%, male sex, and non-missense *LMNA* variants. A risk calculator for predicting VTA in laminopathies was introduced in 2019,[10] which includes all the aforementioned predictors, and LVEF as a continuous variable. We aimed to perform an external validation of the *LMNA*-risk VTA calculator in a multicenter Norwegian-Danish cohort of *LMNA* genotype-positive patients.

Methods

Study design and population

We performed an external validation cohort study, including consecutive *LMNA* genotype-positive patients at Oslo University Hospital, Rikshospitalet, Norway, from 2003 to 2020, and at the Heart Centre, Rigshospitalet, Copenhagen, Denmark, from 1987 to 2021. Inclusion criteria were the same as in the *LMNA*-risk VTA calculator study[10]: ≥16 years of age, no previous VTAs, no congenital or childhood onset laminopathy, and no other cardiomyopathy-related genetic variants. The interval of follow-up examinations was individualized and usually included yearly follow-ups.

Proband status was defined as the first affected individual in a family who sought medical attention because of symptoms of cardiac laminopathy, where genetic testing confirmed a pathogenic *LMNA* genotype. Genotype-positive family members were identified by cascade genetic screening. The pathogenicity of the genetic variant was evaluated according to the guidelines from the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.[11] Patients with pathogenic or likely pathogenic genetic variants were considered genotype positive. Genetic variants were classified as missense or non-missense (nonsense, frameshift, splice site, and large deletions). The study complied with the Declaration of Helsinki and was approved by the local medical ethics committees. All patients gave written informed consent.

Electrocardiogram

Twelve-lead electrocardiogram was obtained at the time of first consultation and at subsequent follow-up visits. We recorded rhythm, PR interval, and grade of AV block (PR interval >200 ms or higher degree). Twenty-four–hour Holter monitoring was performed on clinical indication and included yearly registrations in patients without cardiac device.

Ventricular arrhythmias

We defined life-threatening VTAs according to the LMNA-risk VTA calculator criteria, including sudden cardiac death, aborted cardiac arrest, appropriate therapy from a primary preventive ICD, or other manifestations of hemodynamically unstable VTAs.[10] *Appropriate ICD therapy* was defined as antitachycardia pacing or shock therapy for documented ventricular tachycardia (VT) or ventricular fibrillation. *NSVT*, defined as ≥3 consecutive ventricular beats ≥120 beats/min lasting <30 seconds,[10] and atrial fibrillation were recorded from the electrocardiogram, in-hospital telemetry, Holter monitoring, and ICD recordings. Outcome was adjudicated for all patients in February 2022.

Echocardiography

All participants underwent a transthoracic echocardiographic examination at study baseline (in Norwegian and Danish cohort using Vivid 7, E9, or E95, GE Healthcare, Horten, Norway; offline data analysis, EchoPac, GE Healthcare, and in Danish cohort also using iE33 or Epic 5, Philips Ultrasound, Bothell, WA; offline analysis IntelliSpace Cardiovascular v.4.1 Software, Philips Ultrasound). Left ventricular end-diastolic diameter was measured by 2-dimensional imaging. Left ventricular dilatation was defined as end-diastolic diameter ≥60 mm in men and ≥54 mm in women.[12] LVEF was calculated using the modified Simpson biplane method. Left atrial (LA) volume was calculated using the biplane area length method. *LA dilatation* was defined as LA volume index >34 mL/m^2.[12]

Statistics

Descriptive data are expressed as mean ± SD, frequency (percentage), or median with interquartile range (IQR). Continuous variables were compared using the Student *t* test or Mann-Whitney *U* test, as appropriate. Baseline predictors of first time VTAs were assessed by Cox regression analyses, with multivariable analyses including parameters from the *LMNA*-risk VTA calculator (sex, genetic variant, AV block, NSVT, and LVEF).

Incidence rates for VTAs was calculated using patient-years at risk with 95% confidence interval (CI). Each patient's predicted 5-year risk of experiencing VTAs was calculated using the online *LMNA*-risk VTA calculator tool (https://lmna-risk-vta.fr/). Predicted 5-year risk ≥7% was used as cutoff for classifying patients as high risk, as previously suggested.[10] Performance of the *LMNA*-risk VTA calculator was evaluated using Harrell's C-statistic derived from multivariable Cox regression analysis. The sensitivity, specificity, positive predictive value, and negative predictive value of the model was calculated with 95% CI by using ≥7% predicted 5-year risk as cutoff for ICD implantation.[10] Five-year VTA incidence was illustrated by Kaplan-Meier

failure estimates, grouped by different *LMNA*-risk VTA calculator scores. Akaike information criterion and Bayesian information criterion (BIC) were used as estimators of prediction error. Alternative prediction models with BIC reduction >2 was considered a significant improvement. *P* values were 2-sided and values <.05 considered significant (STATA version 16.1, StataCorp LLC, College Station, TX).

Results

Study population

We included 118 *LMNA* genotype-positive patients without previous VTAs (age 37 years [IQR 27–49 years]; 39 [33%] probands; 65 [55%] women; 100 [85%] with non-missense *LMNA* variants) (Table 1; Online Supplemental Table 1). Twenty-three patients (19%) experienced VTAs during 6.1 years (IQR 3.0–9.1 years) of follow-up, resulting in a 3.0% (95% CI 2.0%–4.5%) yearly incidence rate, similar to the reported incidence rates from the original risk calculator and validation cohorts (3.9% [95% CI 3.0%–4.7%] and 3.7% [95% CI 2.4%–4.9%], respectively). The median time between each examination was 1.0 years (IQR 0.4–1.4 years). Sixteen patients (70%) received appropriate ICD therapy (8 antitachycardia pacing, 5 shock therapy, 3 both), 4 (17%) experienced hemodynamically unstable VT, and 3 (13%) were resuscitated from cardiac arrest. Eleven VTAs were monomorphic, 7 were polymorphic (including 3 cardiac arrests), and 5 were undetermined. The median cycle length was 290 ms (IQR 256–300 ms), excluding the 3 patients with aborted cardiac arrest. Age at the time of first VTA was 49 years (IQR 40–56 years), with the youngest patient aged 25 years, and time from study inclusion to VTA was 4.5 years (IQR 1.6–8.7 years). Eight patients (7%) were censored because of cardiac transplantation, and 7 (6%) died of end-stage heart failure. No patient died of sudden arrhythmic death. A total of 114 patients (97%) had complete data at baseline.

Twenty-seven patients (23%) received a primary preventive ICD after first consultation, while 67 patients (57%) had received a primary preventive ICD by last follow-up. Of these, 16 patients (24%) received appropriate therapy and 1 (1%) experienced hemodynamically unstable VT in the monitoring zone. Six patients did not have an ICD implanted at the time of first VTA. Three of these patients experienced aborted cardiac arrest and 3 experienced hemodynamically unstable VT requiring cardioversion.

Predictors of life-threatening arrhythmias

Among the 5 parameters (NSVT, AV block, LVEF, non-missense genetic variants, and male sex) included in the *LMNA*-risk VTA calculator,[10] only AV block and reduced LVEF were independent predictors of first time VTAs (Table 2).

Five-year VTA incidence

Twelve patients (10%) had experienced VTAs by 5 years of follow-up. At baseline, 89 patients (75%) were classified as high risk (≥7% predicted 5-year risk of VTAs). Of these, 10 patients (11%) had experienced VTAs by 5 years of follow-up while 79 had not. Of the 79 patients classified as high risk who did not experience VTAs during the coming 5 years, 24 (30%) were classified as high risk on the basis of being men with a non-missense variant without other established risk factors. The *LMNA*-risk VTA calculator classified 30 patients as low risk at baseline, of whom 2 experienced VTAs within 5 years (after 2.1 and 4.0 years). However, reassessing risk in these 2 patients at the time of last clinical examination before VTA correctly classified both patients as high risk.

Five-year survival free from VTAs was high in patients classified as low risk by the *LMNA*-risk VTA calculator, with 2 patients with VTAs during a total of 133 patient-years (Figure 1, left panel). In the 12 patients who had experienced VTAs by 5 years of follow-up (10%), the median *LMNA*-risk VTA calculator score was as high as 47.7% (IQR 12.6%–64.7%) at baseline. In patients with risk score <25%, 5-year survival free from VTAs was also good, with 4 patients with VTAs during a total of 368 patient-years (Figure 1, right panel). In patients with risk score ≥25%, there were 8 patients with VTAs during 102 patient-years, while in patients with risk score ≥40%, there were as much as 6 patients with VTAs during 46 patient-years (Online Supplemental Figure 1). Comparison of predicted and observed 5-year VTA incidence showed overprediction of VTAs in patients with *LMNA*-risk VTA calculator score <25% (Table 3).

Of the 4 patients with *LMNA*-risk VTA calculator score <25% at baseline who experienced VTAs within 5 years, 2 patients showed evident disease progression during follow-up and had a risk score >25% at the time of last consultation

Table 1 Baseline characteristics of *LMNA* genotype-positive patients without previous VTAs, 444 patients from the original *LMNA*-risk VTA calculator study and 118 patients from this external validation study

Characteristic	*LMNA*-VTA calculator cohort	External validation cohort
Age (y)	40.6 ± 14.1	37.6 ± 14.6
Proband	207 (47)	39 (33)
Female	250 (56)	65 (55)
Non-missense genetic variant	127 (29)	100 (85)
AV block		
Grade I	127 (34)	24 (21)
Grades II and III	67 (18)	30 (27)
Atrial arrhythmia	141 (32)	45 (38)
NSVT	60 (17)	36 (31)
LVEF (%)	56 ± 13	52 ± 12
LVEF <45%		24 (20)
LV dilatation		29 (26)
LA dilatation		55 (56)
Muscular dystrophy		14 (12)

Values are presented as mean ± SD or n (%).

AV = atrioventricular; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; VTAs = ventricular tachyarrhythmias.

Table 2 Baseline predictors of experiencing first-time VTAs (n = 23) during 6.1 y of follow-up in 118 *LMNA* genotype-positive patients without VTA at study inclusion

Predictor	Univariable HR (95% CI)	*P*	Multivariable HR (95% CI)	*P*
Age	1.04 (1.01–1.07)	.01		
Proband	3.39 (1.46–7.88)	.01		
Female	0.48 (0.21–1.10)	.08	0.50 (0.19–1.36)	.17
Non-missense genetic variant	1.56 (0.46–5.28)	.47	1.30 (0.32–5.31)	.72
NSVT	2.11 (0.92–4.82)	.08	0.84 (0.29–2.42)	.74
Syncope	0.64 (0.19–2.14)	.46		
Atrial fibrillation/flutter	3.33 (1.41–7.86)	.01		
AV block				
Grade I	1.80 (0.54–6.00)	.34	1.86 (0.51–6.76)	.35
Grades II and III	2.90 (1.12–7.54)	.03	2.93 (1.03–8.34)	.04
NYHA functional class ≥II	3.06 (1.34–7.01)	.01		
LVEF <45%	7.87 (3.45–17.98)	<.001		
LVEF	0.95 (0.93–0.98)	<.001	0.94 (0.91–0.97)	<.001
LV dilatation	2.97 (1.28–6.86)	.01		
LA dilatation	1.57 (0.59–4.18)	.37		

AV = atrioventricular; CI = confidence interval; HR = hazard ratio; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; NSVT = nonsustained ventricular tachycardia; VTAs = ventricular tachyarrhythmias.

before VTA (increased score from 6.2% to 65.1% after 2.1 years and from 11.6% to 26.1% after 4.5 years, respectively). Two patients did not have risk score >25% at the time of VTA. One patient had baseline score 13.5% and did not undergo reevaluation of risk during 1.7 years of follow-up before VTA, and 1 patient showed mild disease progression with baseline score 4.4%, which progressed to 12.9% after 4.0 years of follow-up.

Performance of the *LMNA*-risk VTA calculator

The *LMNA*-risk VTA calculator showed lower sensitivity, lower specificity, lower positive predictive value, lower negative predictive value, and higher proportion of ICD recipients in this validation cohort than in the original risk calculator cohort (Figure 2), with the exception of patients with risk score ≥25% (Online Supplemental Table 2). In this external validation cohort, the *LMNA*-risk VTA calculator provided a 5-year sensitivity and specificity of 83% (95% CI 52%–98%) and 26% (95% CI 18%–35%), respectively, when applying the suggested ≥7% predicted 5-year risk as cutoff. The 5-year positive predictive value was 11% (95% CI 6%–20%) and the negative predictive value was 93% (95% CI 78%–99%).

Validation of the *LMNA*-risk VTA calculator provided a Harrell's C-statistic of 0.85. Removing patient sex and non-missense genetic variants from the model provided a C-statistic of 0.81 (Figure 3). Akaike information criterion remained unchanged and BIC was reduced (106–100) when removing patient sex and non-missense variants, indicating a superior prediction model. Removing these parameters from the model resulted in a sensitivity of 75% and a specificity of 48% as compared with 83% and 26% in the original *LMNA*-risk VTA calculator model (Figure 3).

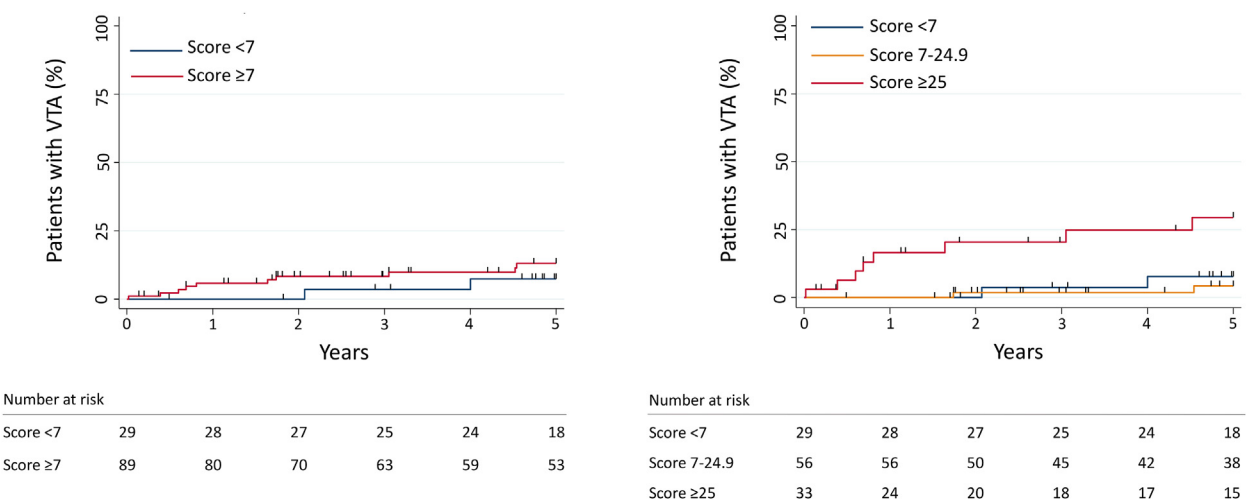

Figure 1 Cumulative 5-year incidence of first time VTAs in 118 *LMNA* genotype-positive patients, grouped by *LMNA*-risk VTA calculator score. VTAs = ventricular tachyarrhythmias.

Table 3 Comparison of predicted and observed 5-year VTA incidence, grouped by *LMNA*-risk VTA calculator score at baseline

Predicted score by the *LMNA*-risk VTA calculator	No. of patients	No. of patients with VTAs	Person-time at risk (y)	5-Y VTA incidence (%) (95% CI)
Score <7	29	2	128	7.8 (2.0–31.2)
Score 7–24.9	56	2	240	4.2 (1.0–16.6)
Score ≥25	33	8	102	39.2 (19.6–78.3)

CI = confidence interval; VTAs = ventricular tachyarrhythmias.

Discussion

Validation of the *LMNA*-risk VTA calculator showed that the model performed well in this external Norwegian-Danish cohort of *LMNA* genotype-positive patients. The sensitivity of the model to predict VTAs was high when applying the suggested threshold of ≥7% predicted 5-year risk. In contrast, the specificity was low and evidently lower than the reported specificity from the original study population.[10] Because of rapid disease progression in some patients, frequent reevaluation of patient risk was necessary to maintain the sensitivity of the model. Male sex and non-missense genetic variants did not predict VTAs in our cohort. Removing patient sex and genetic variant from the model increased the specificity and improved the model fit, but also gave a small reduction of sensitivity.

Validation of the *LMNA*-risk VTA calculator

Most *LMNA* genotype-positive patients who later experienced VTAs had a very high predicted 5-year arrhythmic risk with a median value of 48% at baseline. Importantly, the overall risk of developing VTAs was low in *LMNA* genotype-positive patients with mild cardiac phenotype, and risk was frequently overestimated by the risk calculator. In patients with predicted 5-year VTA risk <25%, only 5% of patients experienced VTA by 5 years of follow-up. Frequent reevaluation of risk improved the detection of the transformation to high-risk individuals. Importantly, only 2 patients had risk scores <25% at the time of last consultation before the event, and the lowest predicted risk score was 13%. These findings support recent guidelines[13] recommending primary preventive ICD implantation in *LMNA* patients only if 5-year estimated VTA risk is ≥10% and they have a cardiac phenotype including NSVT, LVEF <50%, or AV conduction delay.

The current management of *LMNA* patients include the implantation of a defibrillator when there is a need for a pacemaker or a cardiac resynchronization therapy device.[14] However, implantation of a primary prevention ICD in young *LMNA* patients without a need for pacing should be carefully considered.[15] Risk calculators for the prediction of VTAs has been introduced for many genetic cardiac diseases. The calculators have a tendency to favor ICD implantation, and concern has been raised that an excessive and inappropriate number of ICDs are being implanted in these patients.[16] We suggest that the *LMNA*-risk VTA calculator threshold of ≥7% may be a threshold set too low and, furthermore, that using a preset threshold value may not be the best approach for selecting patients for primary prevention ICD implantation.

Male sex and non-missense genetic variants

In our study, non-missense genetic variants and male sex were not predictors of VTAs. This is in contrast to several previous studies,[7,17] including the *LMNA*-risk VTA calculator study.[10] However, our study is in line with other recent studies, which have not been able to reproduce non-missense variants and male sex as predictors of VTAs.[18,19] This may be explained by a lower number of included patients than in the larger multicenter studies such as the *LMNA*-risk VTA calculator study. Furthermore, as many as 85% of our patients had

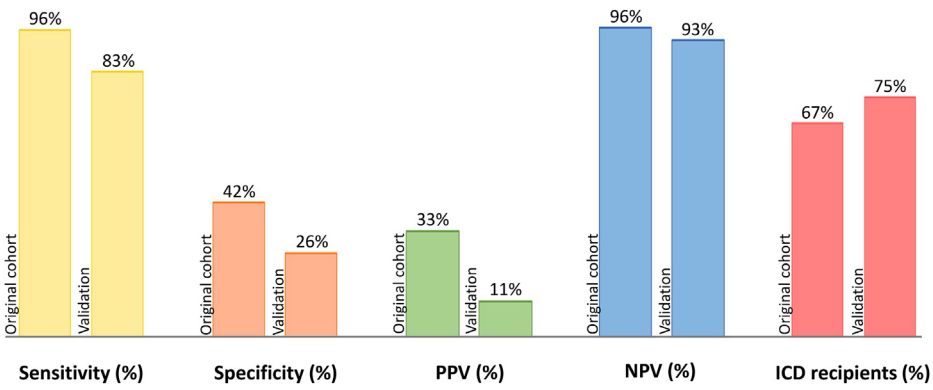

Figure 2 Sensitivity, specificity, PPV, and NPV for the prediction of VTAs in the original study cohort and the validation cohort when applying the *LMNA*-risk VTA calculator with ≥7% predicted 5-year risk as cutoff. ICD recipients refers to the percentage of patients qualifying for primary preventive ICD implantation at baseline according to the calculator. ICD = implantable cardioverter-defibrillator; NPV = negative predictive value; PPV = positive predictive value; VTAs = ventricular tachyarrhythmias.

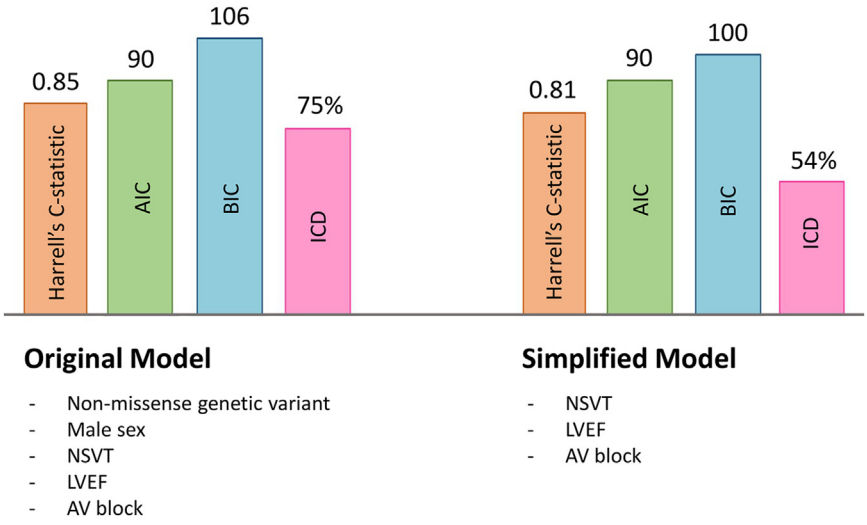

Figure 3 Validation of the *LMNA*-risk VTA calculator prediction model in 118 *LMNA* genotype-positive patients, and comparison to a simplified version of the model. Validation showed a slightly decreased C-statistic, unchanged AIC, and improved BIC when applying the simplified model. Lower number of patients qualifying for primary preventive ICD (≥7% predicted 5-year risk) when using the simplified model. AIC = Akaike information criterion; AV = atrioventricular; BIC = Bayesian information criterion; CI = confidence interval; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; VTA = ventricular tachyarrhythmia.

non-missense genetic variants, which is a higher proportion than that in many previous reports.[10,18,19] Hence, the patient population of this study and that of the *LMNA*-risk VTA calculator are not directly comparable.

Clinical implications

This study demonstrated that the *LMNA*-risk VTA calculator can provide valuable guidance in clinical practice when used frequently for reevaluation of patient risk. However, the previously proposed cutoff value of ≥7% predicted 5-year risk for primary prevention ICD may result in premature implantation of devices. In particular, male risk may be overestimated by the calculator, and classification of patients as high risk on the basis of male sex and non-missense genetic variants alone may not be applicable in all populations. We suggest that male sex and a non-missense variant alone should not lead to implantation of a primary prevention ICD. We highlight the importance of close follow-up in these patients, as risk prediction was most accurate when using the most recent patient data.

Limitations

This is a multicenter study including 2 large Scandinavian tertiary referral hospitals. We cannot exclude referral bias and the external validity to other regions is undetermined. The longitudinal study design with retrospective collection of prospective data has inherent limitations. The number of end points was limited, and the follow-up time varied between the study participants. End points were dominated by ICD therapies, and extrapolation to prevention of sudden cardiac death is uncertain. Patients with primary prevention ICD had continuous rhythm monitoring and therefore had a higher likelihood of detecting VT, both sustained and nonsustained. There is a need for larger multicenter studies to explore selection criteria for primary prevention ICD implantation in *LMNA* genotype-positive patients.

Conclusion

In this multicenter Norwegian-Danish cohort study including *LMNA* genotype-positive patients without VTAs at baseline, the yearly incidence rate for VTA was 3.0%. The *LMNA*-risk VTA calculator performed well, with high sensitivity (83%) for detecting forthcoming VTAs. However, the specificity was low (26%), and the calculator overestimated arrhythmic risk particularly in male patients. The proposed threshold of ≥7% predicted 5-year risk for experiencing VTAs seemed to be a threshold set too low for selection for primary prevention ICD implantation in this *LMNA* cohort. Frequent reevaluation of patient risk improved the ability to detect forthcoming VTAs, with no patient showing a predicted risk below 13% at the time of last consultation before VTA.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2022.11.024

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