

**Development and Validation of a New Risk Prediction Score for Life-Threatening Ventricular Tachyarrhythmias in Laminopathies**

**Running Title:** *Wahbi et al.; Risk Prediction Score for VTA in LMNA Mutations*

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## Abstract

**Background:** An accurate estimation of the risk of life-threatening (LT) ventricular tachyarrhythmia (VTA) in patients with LMNA mutations is crucial to select candidates for implantable cardioverter defibrillator (ICD) implantation.

**Methods:** We included 839 adult patients with LMNA mutations, including 660 from a French nationwide registry in the development sample, and 179 from other countries, referred to 5 tertiary centers for cardiomyopathies, in the validation sample. LTVTA was defined as a) sudden cardiac death or b) ICD-treated or hemodynamically unstable VTA. The prognostic model was derived using Fine-Gray's regression model. The net reclassification was compared with current clinical practice guidelines. The results are presented as means (standard deviation) or medians [interquartile range].

**Results:** We included 444 patients 40.6 (14.1) years of age in the derivation sample and 145 patients 38.2 (15.0) years in the validation sample, of whom 86 (19.3%) and 34 (23.4%) suffered LTVTA over 3.6 [1.0-7.2] and 5.1 [2.0-9.3] years of follow-up, respectively. Predictors of LTVTA in the derivation sample were: male sex, non-missense LMNA mutation, 1st degree and higher atrioventricular block, non-sustained ventricular tachycardia, and left ventricular ejection fraction. In the derivation sample, C-index (95% CI) of the model was 0.776 (0.711-0.842) and calibration slope 0.827. In the external validation sample, the C-index was 0.800 (0.642-0.959) and calibration slope 1.082 (95% CI, 0.643-1.522). A 5-year estimated risk threshold  $\geq 7\%$  predicted 96.2% of LTVTA and net reclassified 28.8% of patients with LTVTA compared with the guidelines-based approach.

**Conclusions:** Compared to the current standard of care, this risk prediction model for LTVTA in laminopathies facilitated significantly the choice of ICD candidates.

**Clinical Trial Registration:** URL: <https://www.clinicaltrials.gov>. Unique Identifier: NCT03058185.

**Key Words:** sudden death; ventricular tachyarrhythmia; laminopathy; LMNA; implantable cardiac defibrillator

## Clinical Perspective

### What is new?

- We developed a new score to estimate the 5-year risk of life threatening ventricular tachyarrhythmias in patients with *LMNA* mutations.
- Compared to the current standard of care, the proposed risk prediction model offers more accurate prediction of life threatening ventricular tachyarrhythmias and correctly reclassifies a significant proportion of patients.
- This score can be derived from readily collected clinical and genetic parameters and estimated using an online calculator (<https://lmna-risk-vta.fr/>)

### What are the clinical implications?

- This prediction score offers an incremental clinical benefit in the prevention of sudden cardiac death and unnecessary defibrillator implantations.
- Future prospective studies should focus on the estimation of the clinical benefit conferred by the use of this score in terms of sudden death prevention.

## Introduction

Laminopathies are caused by mutations in *LMNA*, the gene encoding the A-type lamins, components of the nuclear envelope expressed in various tissues, including cardiac and skeletal muscles.<sup>1</sup> Arrhythmogenic dilated cardiomyopathy (DCM) is the most frequent clinical manifestation of laminopathies, alone<sup>2</sup> or in combination with Emery-Dreifuss<sup>3</sup> or limb girdle muscular dystrophy, lipodystrophic syndromes<sup>4</sup> or peripheral neuropathy.

*LMNA* mutations are one of the most important causes of inherited adult-onset DCM, accounting for 5 to 10% of cases,<sup>5</sup> and are associated with a comparatively high risk of sudden cardiac death (SCD) from ventricular tachyarrhythmias (VTA).<sup>6,7</sup> The largest published study identified four independent factors of risk of life-threatening (LT) VTA in patients with *LMNA* mutations: male sex, non-missense mutations, non-sustained ventricular tachycardia (NSVT) and a left ventricular ejection fraction (LVEF) <45%.<sup>7</sup> Based on these observations, the guidelines of the American College of Cardiology/American Heart Association/Heart Rhythm Society<sup>8</sup> and European Society of Cardiology<sup>9</sup> for the prevention of SCD recommended implantable cardioverter-defibrillator (ICD) therapy in patients with *LMNA* mutations and  $\geq 2$  of these risk factors. However, this is a crude estimate of the relative risk of SCD, failing to account for the different effect sizes of individual risk factors. The aim of this study was to develop and validate a prediction model to estimate the absolute 5-year risk of LTVTA in patients with *LMNA* mutations and compare its contribution with current clinical practice guidelines.

## Methods

The data, analytic methods, and study materials will not be made publicly available to other

researchers for purposes of reproducing the results or replicating the procedure because consent to participate in this study did not include public dissemination of patient data.

### **Derivation and validation samples**

We created our derivation sample from the French nationwide Registry on laminopathies (ClinicalTrials.gov - no NCT01136330), which included retrospectively all the French adult and pediatric patients diagnosed with pathogenic *LMNA* mutations since January 2000, when this gene testing became routinely available. The identification of all mutation carriers, including probands and symptomatic or asymptomatic relatives, was made possible by an analysis of records of the three French genetic departments offering *LMNA* gene testing, at Pitié-Salpêtrière and Saint Antoine hospitals in Paris and La Timone hospital in Marseille. The pathogenicity of all *LMNA* variants was determined using the criteria presented in the supplemental material.

Our validation sample was created by consecutive patients diagnosed with *LMNA* mutations, consecutively referred between January 2000 and June 2017 to the tertiary cardiology centers of Saint Bartholomew's Hospital in London, UK, Brigham and Women's Hospital in Boston, Massachusetts, USA, University Hospital in Bern, Switzerland, the University Medical Centre in Leiden, the Netherlands and the Royal Melbourne Hospital and University of Melbourne, in Australia, all specialized in the management of cardiomyopathies. Data from these samples have been partially analyzed in two prior studies.<sup>7,10</sup>

This study complies with the ethical principles formulated in the declaration of Helsinki, was approved by the ethics committees at Cochin (CPP Ile de France VI, France) and Brigham and Women's Hospital (USA), which granted waiver of participant consent. The ethics committee at Barts Hospital (UK) was informed, though did not request formal approval under the local research governance arrangements.

### **Study population**

From the derivation and validation samples, we extracted genetic and clinical information from the first documented visit to a cardiologist, which was the starting point of the time-to-event analysis, and all subsequent major cardiovascular events. We included patients who, between January 2000 and June 2017, were  $\geq 16$  years of age at first cardiac evaluation. Patients presenting with a personal history of LTVTA at or before the initial evaluation, a congenital or childhood-onset laminopathy, e.g. progeria, Werner syndrome or congenital muscular dystrophy,<sup>11</sup> a pathogenic mutation in a cardiomyopathy-related gene besides the *LMNA* mutation, or missing clinical data, were excluded from this analysis.

### **Study outcome**

The primary endpoint of this study was time to fatal or near fatal VTA, defined as 1) SCD,<sup>12</sup> 2) appropriate ICD therapy, defined as a shock or antitachycardia pacing to terminate a VTA, or 3) other manifestations of hemodynamically unstable VTA. All suspected cases of LTVTA along with all causes of death were reviewed and adjudicated by RBY and KW (France), KW and TG (UK), and SK and NL (other countries). Death was classified as sudden if it occurred unexpectedly a) within 1 h of onset of cardiac manifestations, in absence of prior hemodynamic deterioration, b) during sleep, or c) within 24 h after the patient was last seen alive and apparently stable clinically.<sup>12</sup>

### **Candidate predictor variables**

To ensure an accurate estimation of regression coefficients and associated quantities, we selected only 8 variables in our prediction model in order to obtain a number of events per variable of 10.<sup>13,14</sup> The four risk factors for LTVTA used in the current professional practice guidelines were considered candidate predictors, including 1) male sex; 2) non-missense mutations, including

insertions, deletions, truncating mutations or mutations affecting splicing; 3) NSVT, defined as  $\geq 3$  consecutive ventricular complexes at a rate  $\geq 120$  bpm on 24-h ambulatory electrocardiographic monitoring, and 4) LVEF as a continuous variable measured by echocardiography using visual estimation or quantitative methods at the discretion of the physician.<sup>9</sup> We also selected age and two common disease manifestations: 1) atrial arrhythmias, defined as a personal history of atrial fibrillation, flutter, or tachycardia lasting  $\geq 30$  sec, and 2) atrioventricular (AV) block, analyzed as a semi-quantitative variable classified as a) absent, b) 1<sup>st</sup> degree ( $\geq 0.20$  sec PR interval), or 3) high degree (type II 2<sup>nd</sup> degree or 3<sup>rd</sup> degree) AV block. We did not consider other potential predictors such as family history of SCD due to missing data for a high proportion of patients and not at random or heart failure functional class because of redundant prognostic information contributed by other variables.

### **Statistical analysis**

Quantitative variables are expressed as mean and standard deviation (SD) or median and interquartile ranges (IQR), as appropriate, and categorical variables are expressed as counts and percentages. Missing data were assumed to be missing at random, and their values were imputed with multiple imputations by chained equations.<sup>15</sup> All predictors used in the model development and the estimate of the cumulative hazard function were considered in the imputation model. A total of 25 imputed datasets was generated for the derivation sample. Estimates were pooled using Rubin's rules.<sup>16</sup> Mean and variance of the imputations streams were plotted to examine the convergence of the MICE algorithm.

A multiple variable Fine-Gray regression model, including all candidate predictor variables, was used to develop our risk prediction model.<sup>17</sup> Patients who died without experiencing an event were treated as a competing risk. The assumptions of the Fine-Gray model

were verified with respect to the proportionality of hazard ratio, linear functional form, and link function.<sup>18</sup> A backward selection strategy based on Akaike information criterion was applied to the pooled model.<sup>19</sup> All two-ways interactions were tested.

To gauge the model discrimination, we calculated the concordance (C-) index as the area under the time-dependent Receiver Operating Characteristic (ROC) curve in the derivation cohort. Internal bootstrap validation (100 bootstrap samples) was used to provide optimism-corrected estimates.<sup>20</sup> It was applied to each of the 25 imputed datasets. The optimism is the decrease in model performance between the bootstrap and the original samples, which can adjust the developed model for over-fitting. The corrected calibration slope was used as a shrinkage factor for the regression coefficients and the C-index corrected for overoptimism was estimated. We determined calibration slope by calculating the mean of the calibration slopes for the final model on each imputed dataset and then applying the shrinkage factor. Estimates, hazard ratios (HR) and 95% confidence intervals (CI) were calculated.

We validated our model in an external independent derivation sample,<sup>21</sup> in which missing values were imputed and 25 imputed datasets were generated. In a first step, we estimated the regression coefficient of the prognostic index (known as the calibration slope) in the validation sample, the prognostic index being calculated by applying the regression coefficients from the derivation sample. In a second step, we computed the discrimination of the score in the validation sample by the C-index.

To calculate the C-index and calibration slope of the guidelines-based approach, we constructed a risk score with a value of 0 if  $\leq 1$  and 1 if  $\geq 2$  risk factors are present, that was fitted as a continuous variable using the entire data. In patients with complete datasets in both study samples, we calculated the sensitivity, specificity, positive and negative predictive values of the

guidelines-based and prediction score models at 5 years. We performed comparison tests between the two cohorts for all covariates and found no significant difference. We also verified, for several risk score thresholds of our model, the reclassification of patients into high- or low-risk categories compared to the guidelines-based approach used as a categorized score, and ascertained the net reclassification improvement (NRI) calculated as  $([\text{correct} - \text{incorrect reclassifications}] / \text{total number of patients})$  in patients with and without LTVTA, but not in both together, as the prognostic weight of misclassifying patients was far higher for patients with than for those without events.

In all analyses, the tests were two-sided and the level of significance was set at 0.05. Statistical analyses were performed using the R statistical software, version 3.4.3.<sup>22</sup> We used the *survival*, *cmprsk* and *riskRegression* packages for survival analyses, *crskdiag* to test the Fine-Gray model assumptions, *rms*, *pec*, *riskRegression* and *crrstep* for model building and internal and external validation, and *mice* for multiple imputations.

## Results

### Characteristics of the derivation sample

Among the 660 patients presenting with pathogenic *LMNA* mutations between January 2000 and June 2017, 444 with adult-onset laminopathies [mean (SD) age 40.6 years (14.1); 250 women (56.3%)] met the study inclusion criteria (Figure 1). Their characteristics at the time of initial referral to a cardiologist are presented in Table 1. A total of 284 patients (64%) had complete data. Of these 444 patients, 207 (46.6%) were probands and 237 (53.3%) relatives referred after family screening. At baseline, 54 patients were pacemaker and 52 were ICD recipients. ICDs were implanted for: 1) presence of two or more of the four risk factors for LTVTA used in the

current professional practice guidelines in 35 patients, 2) high degree AV block with prior identification of *LMNA* mutation in 4, 3) left ventricular dysfunction with an ejection fraction below 30% in 3, and 4) miscellaneous other indications in 10. ICDs were programmed at the discretion of the implanting physician. ECG showed sinus rhythm in 336 patients (79.8%), supraventricular arrhythmias in 70 (16.6%), complete AV block in 2 (0.5%), junctional rhythm in 1 (0.2%), supraventricular and/or ventricular pacing in 12 (2.9%), 1<sup>st</sup> degree AV block in 127 (34.2), complete left and right bundle branch blocks in 20 (4.6%) and 26 (6.0%), respectively. Over a median (IQR) follow-up of 3.6 years (1.0-7.2), 86 patients (19.3%) developed LTVTA, at a mean age of 46.7 (13.7) years, representing a 3.9% annual incidence (95% CI 3.03-4.69). LTVTA consisted of 31 appropriate ICD therapies (36%), 14 SCD (16%), and 41 (47%) other tachyarrhythmic events. All patients with ICD therapies had VTA with a ventricular rate of 165 bpm or more.

### **Model development and internal validation**

The model selection procedure retained male sex, non-missense *LMNA* mutation, AV block (1<sup>st</sup> degree and higher), NSVT, and LVEF, when based on Rubin's rules for pooling the model results across imputed datasets. All two-ways interactions have been tested and no interaction appeared to be significant. The regression coefficients for the full multiple variable and the retained models are presented in Table 2. The 5-year risk of LTVTA for individual patients with *LMNA* mutations was:

$$1 - 0.8884505^{\exp(\text{prognostic index})}$$

Where the prognostic index = 0.51573542\*male + 0.85513823\*1<sup>st</sup> degree AV block + 1.05127326\*higher AV block + 0.76692653\*NSVT + 0.56318475\*non-missense mutation - 0.01949484\*LVEF (%) and where 0.8884505 is the baseline 5-year survival estimate.

The model was well calibrated with a fit between predicted and observed outcomes that was the best in risk categories between 2.1 and 12.3% (Figure 2), a calibration slope of 0.827 and a calibration in-the-large of 5.9. Optimism-corrected C-index was 0.776 (95% CI, 0.711-0.842).

### **External validation**

Among the 179 patients in the validation sample, 145 [70 women (48.2%)] met the study inclusion criteria, whose mean age was 38.2 (15.0) years (Figure 1). Their characteristics at initial referral are presented in Table 1. A total of 156 patients (87%) had complete data. Of these 145 patients, 53 (36.5%) were probands and 92 (63.4%) were relatives. Over a median follow-up of 5.1 years (2.0-9.3), 34 patients (23.4%) developed LTVTA, at a mean age of 50.5 (12.8) years, representing a 3.7% annual incidence (95% CI 2.42-4.93). The model was well calibrated with a calibration slope of 1.082 (95% CI, 0.643-1.522) and discriminating, with a C-index of 0.800 (95% CI, 0.642-0.959).

### **Comparison of the new prediction model with the guidelines-based approach**

The calibration and discrimination properties of the guidelines-based approach were lower than those of our prognostic model, with calibration slope and C-index of 1.316 (95% CI, 0.886-1.745) and 0.696 (95% CI, 0.622-0.770), respectively.

Tables 3 and 4 show the LTVTA prediction performance and the *simulated* clinical implications of selecting patients for ICD therapy, using 1) different 5-year risk score thresholds estimated by our prediction model or 2) a  $\geq 2$  conventional risk factors threshold, as recommended in the guidelines-based approach. Of the 225 patients with a complete dataset included in this analysis, 52 (23.1%) had  $\geq 1$  LTVTA over the 5-year follow-up. Based on the professional practice guidelines, 86 patients (38.2%) would have received an ICD, with 67.3,

70.1, 40.2, and 87.8%, sensitivity, specificity, positive and negative values, respectively, to predict LTVTA.

Compared to the guidelines-based approach, threshold scores between 1 and 15% were more sensitive (Table 3) and net reclassified between 9.6 and 32.7% of events, which represents the proportions of patients potentially saved from SCD (Table 4). Within this range, a threshold between 7 and 10% may be considered optimal, as it would have prompted the implantation of an ICD in 120 to 150 patients (53.3 to 66.7%), of whom 34.0 to 37.3% would have suffered a LTVTA, corresponding to a) 1 patient potentially saved from SCD for every 2.5 to 3 implants over 5 years, and b) the accurate identification of 84.6 to 96.2% of patients with LTVTA.

Compared to the guidelines-based approach, a threshold between 7 and 10% would have net reclassified and potentially prevented the SCD of 11 to 15 patients (event NRI = 21.2 to 28.8%), and unnecessary ICD implantations in 24 to 50 patients without LTVTA (non-event NRI of 13.9 to 28.9%), corresponding to 2.7 to 3.2 supplemental ICD implantations to prevent 1 SCD.

## **Discussion**

We have developed a model to predict the risk of LTVTA in patients with DCM caused by *LMNA* mutations, which can assist patients and physicians in the making of shared decisions regarding the implantation of ICD for the primary prevention of SCD. Compared with the current standard of care,<sup>8,9</sup> the proposed risk prediction model offers an incremental clinical benefit in the prevention of SCD, or the unnecessary implantation of ICD, or both, by offering more accurate discrimination and calibration and, most importantly, by correctly reclassifying a significant proportion of patients. This greater accuracy in the prediction of LTVTA is most

likely attributable to the calculation of an absolute instead of a relative risk, as well as to the incremental prognostic information conferred by the inclusion of LVEF as a continuous variable and AV block as a supplemental independent predictor. From a broader perspective, there is a general consensus that the prognostic information contributed by risk prediction scores is greater than one might expect solely by a count of risk factors, and the  $>0.75$  C-index in our derivation and external validation samples, is generally considered to indicate a reliable discrimination.<sup>23,24</sup> Also, we observed similar or even greater accuracy of our score in the validation sample compared to the derivation sample despite different patient characteristics including different proportions of probands and non-missense mutations carriers. These differences can be related to sampling variation and/or real different prevalence of mutation types in different populations. This observation strengthens our results as it shows that our model can be applied in different settings or in populations with different structures. It is noteworthy that the risk of LVTVA should be reappraised during patient follow-up, as it is likely to increase over a lifetime with the growing prevalence of the various predictors of this score in a majority of patients.

While there is no international consensus relative to the absolute risk of SCD that represents an indication for ICD therapy, this study suggests that a threshold between 7 and 10% at 5 years represents a satisfactory compromise between the identification of the maximum number of patients with LVTVA and the minimization of unnecessary ICD implantations. This approach compares favorably with current general guidance for non-ischemic DCM, which fails to account for individual patient characteristics.<sup>25</sup> The latest randomized trial of ICD therapy in optimally treated DCM, which stratified the patients on the basis of a LVEF  $\leq 35\%$  alone, observed no significant effect on total mortality,<sup>25</sup> while  $>70\%$  of patients who die suddenly have a  $>35\%$  LVEF.<sup>26</sup> Given the considerable progress in the understanding of the genetic<sup>6</sup> and

inflammatory<sup>27</sup> causes of DCM,<sup>28</sup> our study is evidence that models to predict SCD based on disease etiology are achievable and improve the management of patients.

### **Limitations of our study**

Our score, which has not been validated in patients <16 years of age or presenting with congenital or childhood-onset laminopathies, should not be applied in these patients.

Furthermore, the derivation and external validation of our score was based on the analysis of data collected retrospectively; a prospective study design is desirable since it would optimize the measurements of predictors and outcomes.<sup>28</sup> Finally, like most prior studies of SCD prediction in inherited cardiomyopathies, we included ICD therapy in our primary endpoint, despite our awareness that it is not invariably equivalent to SCD.

### **Conclusions**

We have developed and validated internally and externally, in patients with *LMNA* mutations, a model to predict the risk of LVTVA, which, compared with the current standard of care, facilitates the decision to implant an ICD as a primary prevention of SCD.

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### **Acknowledgments**

Rodolphe Ruffy, MD reviewed the manuscript for style and language.

### **Source of Funding**

This study was funded by grants from the AFM-Téléthon (French Alliance against Myopathies), which was not involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Some of this work was undertaken at University College London (United Kingdom) and St. Bartholomew's Hospital (London, United Kingdom), which received a portion of funding from the United Kingdom Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme.

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The authors have no potential conflict of interest to disclose.

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# These centers are members of the ERN GUARD-Heart (European Reference Network for rare, low prevalence and complex diseases of the heart, <http://guardheart.ern-net.eu>)

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**Table 1.** Characteristics of the derivation and external validation samples

	Derivation sample (n=444)			Validation sample (n=145)		
	Data			Data		
	Original	Missing (n)	Imputed	Original	Missing (n)	Imputed
Age at baseline, years	40.6 (14.1)	0	40.6 (14.1)	38.2 (15.1)	0	38.2 (15.1)
Men	194 (43.7)	0	194 (43.7)	75 (51.7)	0	75 (51.7)
Non-missense <i>LMNA</i> mutation	127 (28.6)	0	127 (28.6)	67 (46.2)	0	67 (46.2)
AV block						
1 <sup>st</sup> degree*	127 (34.2)	73	152 (34.2)	41 (32.3)	18	49 (33.8)
>1 <sup>st</sup> degree†	67 (18.1)	73	81 (18.2)	19 (15)	18	23 (15.9)
Atrial arrhythmia	141 (31.8)	0	141 (31.8)	55 (37.9)	0	55 (37.9)
Non-sustained VT	60 (17.4)	99	79 (17.8)	30 (20.7)	0	30 (20.7)
Left ventricular ejection fraction, %	56.3 (13.2)	52	56.5 (13.0)	55.8 (12.2)	7	55.6 (12.3)

Values are means  $\pm$  SD or numbers (%) of observations

Values are numbers of non-missing data in the original dataset, averaged over all complete imputed data datasets.

\*1<sup>st</sup> degree versus no AV block; † all degrees versus no AV block.

**Table 2.** Associations between predictors and survival in the derivation sample

	Model			
	Full multiple variable	<i>p</i>	Final	<i>p</i>
Age at baseline, years	0.99 (0.97-1.01)	0.200		
Men	1.80 (1.1-2.95)	0.029	1.67 (1.1-2.55)	0.017
Non-missense <i>LMNA</i> mutation	1.78 (1.12-2.85)	0.043	1.76 (1.16-2.65)	0.007
AV block				
1 <sup>st</sup> degree*	2.74 (1.34-5.61)	0.002	2.35 (1.34-4.12)	0.003
>1 <sup>st</sup> degree†	3.51 (1.5-8.19)	0.001	2.86 (1.54-5.31)	<0.001
Atrial arrhythmia	1.19 (0.71-1.99)	0.524		
Non-sustained VT	2.25 (1.34-3.79)	0.002	2.15 (1.36-3.41)	0.001
Left ventricular ejection fraction, %	0.98 (0.96-1.00)	<0.001	0.98 (0.97-1)	0.017

Values are hazard ratios (95% confidence intervals). The hazard ratios were pooled over the 25 imputed datasets. Hazards ratios in the final model are shrunk by the calibration slope (0.894).

\* 1<sup>st</sup> degree only versus no AV block; † all degrees versus no AV block.

**Table 3.** Simulated impact of applying a 5-year life-threatening VTA risk model or guidelines-based approach to implant an ICD

ICD recipients selection strategy	Threshold values	ICD recipients (%)	Performance to predict LTVTA			
			Sensitivity, %	Specificity, %	Positive predictive value, %	Negative predictive value, %
Guidelines-based	≥2 risk factors*	86 (38.2)	67.3	70.5	40.7	87.8
Prognostic model to estimate the 5-year risk of LTVTA	≥1%	225 (100)	100	0.0	23.1 [17.6-28.6]	NM
	≥2%	225 (100)	100	0.0	23.1 [17.6-28.6]	NM
	≥3%	214 (95.1)	100	6.4 [2.7-10.0]	24.3 [18.6-30.0]	100
	≥4%	185 (82.2)	98.1 [94.3-100]	22.5 [16.3-28.8]	27.6 [21.1-34.0]	97.5 [92.7-100]
	≥5%	179 (79.6)	98.1 [94.3-100]	26.0 [19.5-32.5]	28.5 [21.9-35.1]	97.8 [93.6-100]
	≥6%	166 (73.8)	96.2 [90.9-100]	32.9 [25.9-40.0]	30.1 [23.1-37.1]	96.6 [92.0-100]
	≥7%	151 (67.1)	96.2 [90.9-100]	41.6 [34.3-49.0]	33.1 [25.6-40.6]	97.3 [93.6-100]
	≥8%	137 (60.9)	90.4 [82.4-100]	48.0 [10.5-55.4]	34.3 [26.4-42.3]	94.3 [89.5-99.2]
	≥9%	130 (57.8)	88.5 [79.8-97.1]	51.4 [44.0-58.9]	35.4 [27.2-43.6]	93.7 [88.8-98.6]
	≥10%	121 (53.8)	88.5 [79.8-97.1]	56.6 [49.3-64.0]	38.0 [29.4-46.7]	94.2 [89.7-98.7]
	≥15%	90 (40)	76.9 [65.5-88.4]	71.1 [64.3-77.9]	44.4 [34.2-54.7]	91.1 [86.3-95.9]
	≥20%	67 (29.8)	65.4 [52.5-78.3]	80.9 [75.1-86.8]	50.7 [38.8-62.7]	88.6 [83.7-93.6]
≥25%	48 (21.3)	53.8 [40.3-67.4]	88.4 [83.7-93.2]	58.3 [44.4-72.3]	86.4 [81.4-91.5]	

The score were calculated in patients with complete datasets in the derivation and validation samples.

\*Conventional risk factors for LTVTA in the guidelines-based approach are: male sex, non-missense mutations, NSVT and left ventricular ejection fraction <45%.

LTVTA = life-threatening ventricular tachyarrhythmia; NM = not measured.

**Table 4.** Simulated impact of applying different thresholds of 5-year LTVTA risk score to implant an ICD, on the risk reclassification compared to the guidelines-based approach

Estimate of 5-year LTVTA risk threshold used to implant ICD		Patients with LTVTA (n=52)			Patients with no LTVTA (n=173)		
		Guidelines-based approach		Net reclassification (event NRI)	Guidelines-based approach		Net reclassification (nonevent NRI)
		Low risk	High risk		Low risk	High risk	
≥1%	Low risk	0	0	17 (32.7%)	0	0	-122 (-70.5%)
	High risk	17	35		122	51	
≥2%	Low risk	0	0	17 (32.7%)	0	0	-122 (-70.5%)
	High risk	17	35		122	51	
≥3%	Low risk	0	0	17 (32.7%)	11	0	-111 (-64.2%)
	High risk	17	35		111	51	
≥4%	Low risk	1	0	16 (30.8%)	39	0	-83 (-48%)
	High risk	16	35		83	51	
≥5%	Low risk	1	0	16 (30.8%)	45	0	-77 (-44.5%)
	High risk	16	35		77	51	
≥6%	Low risk	2	0	15 (28.8%)	57	0	-65 (-37.6%)
	High risk	15	35		65	51	
≥7%	Low risk	2	0	15 (28.8%)	72	0	-50 (-28.9%)
	High risk	15	35		50	51	
≥8%	Low risk	5	0	12 (23.1%)	82	1	-39 (-22.5%)
	High risk	12	35		40	50	
≥9%	Low risk	6	0	11 (21.2%)	87	2	-33 (-19.1%)
	High risk	11	35		35	49	
≥10%	Low risk	6	0	11 (21.2%)	91	7	-24 (-13.9%)
	High risk	11	35		31	44	
≥15%	Low risk	11	1	5 (9.6%)	108	15	1 (0.6%)
	High risk	6	34		14	36	
≥20%	Low risk	16	2	-1 (-1.9%)	120	20	18 (10.4%)
	High risk	1	33		2	31	
≥25%	Low risk	17	7	-7 (-13.5%)	122	31	31 (17.9%)
	High risk	0	28		0	20	

The score were calculated in patients with complete datasets in the derivation and validation samples.

NRI = net reclassification improvement; LTVTA = life-threatening ventricular tachyarrhythmia.

## Figure Legends

**Figure 1. Creation of the derivation and external validation samples**

**Figure 2. Calibration by risk group in the derivation cohort.** The vertical bars represent the observed (black) and model-based predicted (grey) probabilities of life-threatening ventricular tachyarrhythmias (LTVTA) at 5 years. Risk groups correspond to 5-year predicted probabilities of LTVTA divided into quartiles across the 25 imputed datasets. These groups were selected for the purposes of validation rather than clinical decision making.

## Derivation sample

French Nationwide Registry of Laminopathies

**660** Patients diagnosed with pathogenic *LMNA* mutations between January 2000 and June 2017 (France)

### 216 Excluded

- 23 First visit to cardiologist before January 2000
- 21 LTVTA prior to baseline
- 39 Age <16 years
- 38 Neuromuscular or systemic disease of onset before 16 years of age
- 3 Other cardiomyopathy gene mutations
- 92 Absence of clinical data

**444** Patients with adult-onset laminopathies

- 261 With cardiac involvement
- 75 LGMD 1B
- 65 EDMD
- 60 Asymptomatic
- 72 Lipodystrophy
- 26 Other muscular manifestations
- 7 Peripheral neuropathy
- 13 Other manifestations

## Validation sample

Multicenter Cohort with Patients Referred to 5 Tertiary Centers Specialized in the Management of Cardiomyopathies

**179** Patients diagnosed with pathogenic *LMNA* mutations between 2000 and June 2017 (London, UK; Boston, US; Bern, Switzerland; Leiden, Netherlands; Melbourne, Australia)

### 34 Excluded

- 7 First visit to cardiologist before January 2000
- 25 LTVTA prior to baseline
- 2 Absence of clinical data

**145** Patients with adult-onset laminopathies

- 129 With cardiac involvement
- 27 Asymptomatic
- 6 EDMD
- 6 LGMD 1B
- 2 Other muscular manifestations
- 1 Peripheral neuropathy
- 1 Lipodystrophy

