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*

Karim Wahbi, et al.

The full author list is available on pages 14-16.

Address for Correspondence:
Karim Wahbi, MD, PhD
Cardiology Department, Cochin Hospital
27 rue du Faubourg Saint Jacques
75679 PARIS Cedex 14, France
Tel: +33 1 58 41 16 53
Fax: +33 1 58 41 16 05
Email: karim.wahbi@aphp.fr

1

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 ≥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.[1] Arrhythmogenic dilated cardiomyopathy (DCM) is the most frequent clinical manifestation of laminopathies, alone[2] or in combination with Emery-Dreifuss[3] or limb girdle muscular dystrophy, lipodystrophic syndromes[4] or peripheral neuropathy.

   LMNA mutations are one of the most important causes of inherited adult-onset DCM, accounting for 5 to 10% of cases,[5] and are associated with a comparatively high risk of sudden cardiac death (SCD) from ventricular tachyarrhythmias (VTA).[6,7] 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%.[7] Based on these observations, the guidelines of the American College of Cardiology/American Heart Association/Heart Rhythm Society[8] and European Society of Cardiology[9] for the prevention of SCD recommended implantable cardioverter-defibrillator (ICD) therapy in patients with *LMNA* mutations and ≥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.[7,10]

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 ≥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,[11] 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,[12] 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.[12]

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.[13,14] 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

≥3 consecutive ventricular complexes at a rate ≥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.[9] We also selected age and two common disease manifestations: 1) atrial arrhythmias,

defined as a personal history of atrial fibrillation, flutter, or tachycardia lasting ≥30 sec, and 2)

atrioventricular (AV) block, analyzed as a semi-quantitative variable classified as a) absent, b) 1st

degree (≥0.20 sec PR interval), or 3) high degree (type II 2nd degree or 3rd 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.[15] 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.[16] 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.[17] 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.[18] A backward selection strategy based on Akaike information criterion was applied to the pooled model.[19] 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.[20] 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,[21] 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 ≤1 and 1 if ≥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 ([correct–incorrect

reclassifications]/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.[22] 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%), 1st 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 (1st 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$^{exp\ (prognostic\ index)}$

Where the prognostic index = 0.51573542*male + 0.85513823*1st 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 ≥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 ≥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,

11

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,[8,9] 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.[23,24]

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 careers. 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 LTVTA

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 LTVTA 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.[25] The latest randomized trial of ICD therapy in

optimally treated DCM, which stratified the patients on the basis of a LVEF ≤35% alone,

observed no significant effect on total mortality,[25] while >70% of patients who die suddenly have

a >35% LVEF.[26] Given the considerable progress in the understanding of the genetic[6] and

inflammatory[27] causes of DCM,[28] 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.[28] 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 LTVTA, which, compared with the current standard of care, facilitates the decision to implant an ICD as a primary prevention of SCD.

Authors

Karim Wahbi, MD, PhD[1]; Rabah Ben Yaou, MD[3,4]; Estelle Gandjbakhch, MD, PhD[5-7];

Frédéric Anselme, MD, PhD[8]; Thomas Gossios, MD[9]; Neal K. Lakdawala, MD, PhD[10];

Caroline Stalens, PhD[2,11]; Frédéric Sacher, MD, PhD[12]; Dominique Babuty, MD, PhD[13];

Jean-Noel Trochu, MD, PhD[14]; Ghassan Moubarak, MD[15]; Kostantinos Savvatis, MD, PhD[9,16];

Raphaël Porcher, PhD[17]; Pascal Laforêt, MD, PhD[18]; Abdallah Fayssoil, MD, PhD[3,18];

Eloi Marijon, MD, PhD[2,19]; Tanya Stojkovic, MD[3]; Anthony Béhin, MD[3];

Sarah Leonard-Louis, MD[3]; Guilhem Sole, MD[20]; Fabien Labombarda, MD, PhD[21];

14

Pascale Richard, MD[22]; Corinne Metay, MD[22]; Susana Quijano-Roy, MD, PhD[23];

Ivana Dabaj, MD[23]; Didier Klug, MD, PhD[24]; Marie-Christine Vantyghem, MD, PhD[25];

Philippe Chevalier, MD, PhD[26]; Pierre Ambrosi, MD, PhD[27]; Emmanuelle Salort, MD[28];

Nicolas Sadoul, MD[29]; Xavier Waintraub, MD[7]; Khadija Chikhaoui, BS[3];

Philippe Mabo, MD, PhD[30]; Nicolas Combes, MD[31]; Philippe Maury, MD, PhD[32];

Jean-Marc Sellal, MD[33]; Usha B. Tedrow, MD, PhD[34]; Jonathan M. Kalman, MD, PhD[35];

Jitendra Vohra, MD, PhD[35]; Alexander F.A. Androulakis, MD, PhD[36];

Katja Zeppenfeld, MD, PhD[36]; Tina Thompson, MD, PhD[37]; Christine Barnerias, MD[38];

Henri-Marc Bécane, MD[3]; Eric Bieth, MD[39]; Franck Boccara, MD, PhD[40];

Damien Bonnet, MD, PhD[41]; Françoise Bouhour, MD[42]; Stéphane Boulé, MD[43];

Anne-Claire Brehin, MD[44]; Françoise Chapon, MD, PhD[45]; Pascal Cintas, MD[46];

Jean-Marie Cuisset, MD, PhD[47]; Jean-Marc Davy, MD, PhD[48];

Annachiara De Sandre-Giovannoli, MD[49]; Florence Demurger, MD[50];

Isabelle Desguerre, MD, PhD[38]; Klaus Dieterich, MD[51]; Julien Durigneux, MD[52];

Andoni Echaniz-Laguna, MD, PhD[53]; Romain Eschalier, MD, PhD[54]; Ana Ferreiro, MD, PhD[55];

Xavier Ferrer, MD[20]; Christine Francannet, MD[56]; Mélanie Fradin, MD[50];

Bénédicte Gaborit, MD[57]; Arnaud Gay, MD[58]; Albert Hagège, MD, PhD[59];

Arnaud Isapof, MD[60]; Isabelle Jeru, MD[61-63]; Raul Juntas Morales, MD[64];

Emmanuelle Lagrue, MD, PhD[65]; Nicolas Lamblin, MD[66]; Olivier Lascols, MD[61-63];

Vincent Laugel, MD, PhD[67]; Arnaud Lazarus, MD[68]; France Leturcq, MD[69];

Nicolas Levy, MD, PhD[49]; Armelle Magot, MD[70]; Véronique Manel, MD[71];

Raphaël Martins, MD, PhD[30]; Michèle Mayer, MD[60]; Sandra Mercier, MD[72];

Christophe Meune, MD, PhD[73]; Maud Michaud, MD[74]; Marie-Christine Minot-Myhié, MD[75];

Antoine Muchir, PhD[76]; Aleksandra Nadaj-Pakleza, MD[77]; Yann Péréon, MD, PhD[70];

Philippe Petiot, MD[42]; Florence Petit, MD[78]; Julien Praline, MD[79]; Anne Rollin, MD[80];

Pascal Sabouraud, MD[81]; Catherine Sarret, MD[82]; Stéphane Schaeffer, MD[45];

Frederic Taithe, MD[83]; Céline Tard, MD[84]; Vincent Tiffreau, MD, PhD[85];

Annick Toutain, MD[86]; Camille Vatier, MD[61-63,87]; Ulrike Walther-Louvier, MD[88];

Bruno Eymard, MD, PhD[3]; Philippe Charron, MD, PhD[5-7*];

Corinne Vigouroux, MD, PhD[61-63,87*]; Gisèle Bonne, PhD[4*]; Saurabh Kumar, MD, PhD[89*];

Perry Elliott, MD, PhD[9,90*]; Denis Duboc, MD, PhD[1,2*]

Acknowledgments

Source of Funding

Disclosures

The authors have no potential conflict of interest to disclose.

Affiliations

[1]APHP, Cochin Hospital, Cardiology Department, FILNEMUS, Centre de Référence de Pathologie Neuromusculaire Nord/Est/Ile de France, Paris-Descartes, Sorbonne Paris Cité University, 75006 Paris, France; [2]INSERM Unit 970, Paris Cardiovascular Research Centre (PARCC), Paris, France; [3]APHP, Centre de référence de pathologie neuromusculaire Paris-Est, FILNEMUS, Myology Institute, Neurology Department, Pitié-Salpêtrière University Hospital, Paris, France; [4]Sorbonne Universités, INSERM UMRS 974, CNRS, UMR-7215, Center for Research in Myology, Institut de Myologie, Pitié-Salpêtrière University Hospital, Paris, France; [5]Sorbonne Universités, UPMC Univ Paris 06, INSERM 1166, Institute of Cardiometabolism and Nutrition (ICAN), Paris, France; [6]Centre de Référence des Maladies Cardiaques Héréditaires, Paris, France[#]; [7]APHP, Pitié-Salpêtrière University Hospital, Institute of Cardiology, Paris, France; [8]Cardiology department, University Hospital of Rouen, Rouen, France; [9]Inherited Cardiovascular Diseases Unit, University College London & St. Bartholomew's Hospital, EC1A 7BE London, United Kingdom[#]; [10]Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Boston, MA; [11]Medical Affairs Department, AFM-Telethon, Evry, France; [12]Centre de reference des maladies rythmiques héréditaires, Bordeaux University Hospital (CHU), IHU Liryc, Electrophysiology and Heart Modeling Institute, fondation Bordeaux Université, Univ. Bordeaux, INSERM U1045, Bordeaux, France;[13]Université François Rabelais, Cardiology Department, CHU Tours, France;[14]INSERM, UMR1087, Université de Nantes, L'Institut du Thorax, CHU de Nantes, CIC, Centre de référence pour la prise en charge

des maladies rythmiques héréditaires de Nantes, Nantes, France[#]; [15]Department of Electrophysiology and Pacing, InParys Clinical Research Group, Clinique Ambroise Paré, Neuilly-sur-Seine, France; [16]William Harvey Research Institute, Queen Mary University London, EC1M 6BQ, London, United Kingdom; [17]APHP, Hôtel-Dieu Hospital, Centre d'Epidémiologie Clinique, INSERM U1153, Université Paris Descartes - Sorbonne Paris Cité, Paris, France; [18]APHP, Hôpital Raymond Poincaré, Centre de Référence des maladies neuromusculaires Nord-Est-Île de France, Garches, France;[19]Hôpital Européen Georges Pompidou, Département de Cardiologie, Unité de Rythmologie, Paris, France;[20]Centre de référence des maladies neuromusculaires AOC, Hôpital Pellegrin, CHU Bordeaux, Bordeaux, France; [21]Cardiology Department, University Hospital of Caen, Caen, France; [22]APHP, UF Cardiogénétique et Myogénétique, Centre de Génétique, GH Pitié Salpêtrière, Paris, France; [23]APHP, Centre de référence des maladies neuromusculaires Nord/Est/Ile de France, Service de Neurologie, Réanimation et Rééducation Pediatriques, Hôpital Raymond Poincaré, Garches, France; UMR 1179 INSERM, Université Versailles Saint-Quentin–en-Yvelines, Montigny-le-Bretonneux, France; [24]Cardiologie A, University Hospital, Lille, France; [25]CHU Lille, Endocrinology, Diabetology and Metabolism, Univ Lille, Inserm, UMR 1190 -Translational research in diabetes; EGID European Genomic Institute for Diabetes F-59000, Lille, France; [26]Service de Cardiologie, Hôpital Est, Lyon, France[#]; [27]Department of Cardiology, La Timone Hospital, Aix-Marseille Université, Marseille, France; [28]APHM, Centre de référence des maladies neuromusculaires PACA-Réunion-Rhône Alpes, Hôpital Timone; Aix Marseille Université, Inserm UMR_S 910, GMGF, Marseille, France; [29]Department of Cardiology, Institut Lorrain du Coeur et des Vaisseaux, CHU Nancy-Brabois, Vandoeuvre les Nancy Cedex, France;

[30]Univ Rennes, CHU Rennes, Inserm, LTSI - UMR 1099, Rennes, France; [31]Département de Rythmologie, Clinique Pasteur, Toulouse, France; [32]University Hospital Rangueil, Cardiology department; Unité Inserm U1048, Toulouse, France; [33]Département de Cardiologie, Centre Hospitalier Universitaire de Nancy; INSERM-IADI U1254, Vandœuvre lès-Nancy, France; [34]Cardiovascular Division, Brigham and Women's Hospital, Boston, MA; [35]Department of Cardiology, Division of Medicine, The Royal Melbourne Hospital and University of Melbourne, Melbourne, Victoria, Australia; [36]Department of Cardiology, Leiden University Medical Centre, Leiden, the Netherlands; [37]Department of Genetic Medicine, The Royal Melbourne Hospital and University of Melbourne, Melbourne, Victoria, Australia; [38]AP-HP, Centre de référence des maladies neuromusculaires Nord/Est/Ile de France, service de neurologie pédiatrique, Hôpital Necker, GH Necker-Enfants malades, Paris, France; [39]Service de Génétique Médicale, Hôpital Purpan, CHU Toulouse, Toulouse, France; [40]AP-HP, Hôpitaux de l'Est Parisien, Cardiology Unit, Hôpital Saint-Antoine; Sorbonne Universités, INSERM, UMR_S 938, Paris, France; [41]AP-HP, Unité Médico-Chirurgicale de Cardiologie Congénitale et Pédiatrique, Centre de référence des Malformations Cardiaques Congénitales Complexes-M3C, Hôpital Necker Enfants Malades, Université Paris Descartes, Sorbonne Paris-Cité, Paris, France; [42]Hospices Civils de Lyon, Centre de référence des maladies neuromusculaires PACA-Réunion-Rhône Alpes, Service d'ENMG, Hôpital Neurologique Pierre Wertheimer, Lyon-Bron, France; [43]Hôpital privé Le Bois, Service de Cardiologie, Lille, France; [44]Unité de Génétique Clinique, CHU Rouen, Rouen, France; [45]Centre de Référence des maladies neuromusculaires Nord/Est/Ile de France, Service de neurologie, CHU Caen; INSERM U1075, Université de Normandie, Caen, France; [46]Centre de référence des maladies neuromusculaires AOC, Département de Neurologie, Hôpital Purpan, CHU Toulouse, Toulouse, France; [47]Centre de Référence des maladies neuromusculaires

Nord/Est/Ile de France, Service de Neuropédiatrie, Hôpital Roger Salengro, CHRU Lille, Lille, France; [48]Service de Cardiologie, CHU Montpellier, Montpellier, France; [49]Aix Marseille University, INSERM, GMGF; Department of Medical Genetics, Childrens' Hospital La Timone, Marseille, France; [50]Centre de Référence Maladies Rares CLAD-Ouest, Service de Génétique Clinique, CHU Rennes, Hôpital Sud, Rennes, France; [51]Unité de Génétique Clinique, Hôpital Couple Enfant, CHU Grenoble; INSERM U1216, Grenoble Institut des Neurosciences Cellular Myology and Pathologies; Grenoble, France; [52]Centre de référence des maladies neuromusculaires AOC, Service de Neuropédiatrie, CHU Angers, Angers, France;

[53]Département de Neurologie, Hôpitaux Universitaires de Strasbourg, Strasbourg, France;

[54]Service de cardiologie, CHU Clermont-Ferrand; CNRS équipe thérapies guidées par l'image, Institut-Pascal, Clermont-Ferrand, France; [55]Basic and Translational Myology laboratory, UMR8251, Université Paris Diderot/CNRS, Paris, France; [56]Génétique médicale, CHU Estaing, Clermond-Ferrand, France; [57]APHM, pole ENDO, Hôpital la conception; INSERM, INRA, C2VN, Aix Marseille univ, Marseille, France; [58]Cardio-Thoracic Surgery Unit and Pathology Department, Rouen University Hospital, Rouen, France; [59]Department of Cardiology, Assistance Publique-Hôpitaux de Paris and INSERM U970, Hôpital Européen Georges Pompidou, Paris, France; Faculté de Médecine, Université Paris Descartes, Sorbonne Paris Cité, Paris, France; [60]Centre de Référence des maladies neuromusculaires Nord/Est/Ile de France, Service de neuropédiatrie, Hôpital Trousseau, Paris, France; [61]APHP, Pitié-Salpêtrière University Hospital, Department of Genetics, Paris, France; [62]Sorbonne University, Inserm U938, Saint-Antoine Research Centre, Institute of Cardiometabolism and Nutrition, Paris, France; [63]APHP, Saint-Antoine University Hospital, Department of Molecular Biology and Genetics, Paris, France;

[64]Centre de référence des maladies neuromusculaires AOC, Department of Neurology, CHU

Montpellier, Montpellier, France; [65]CHRU de Tours, Université François Rabelais de Tours, UMR INSERM U1253, Tours, FILNEMUS, French neuromuscular reference centers, France; [66]Univ. Lille, Inserm U1167, Institut Pasteur; CHRU de Lille, Department of cardiology, Lille, France; [67]Centre de Référence des maladies neuromusculaires Nord/Est/Ile de France, Service de neuropédiatrie, CHU Strasbourg, Hôpital Hautepierre, Hôpitaux Universitaires de Strasbourg, Strasbourg, France; [68]InParys Clinical Research Group, Clinique Ambroise Paré, Neuilly sur Seine, France; [69]Service de Génétique, Hopital Cochin, AP-HP, Paris, France; [70]Centre de Référence des Maladies Neuromusculaires AOC, Laboratoire des Explorations Fonctionnelles, CHU de Nantes, Nantes, France; [71]Centre de référence des maladies neuromusculaires PACA-Réunion-Rhône Alpes, Service Explorations Fonctionnelles Neurologiques, Hôpital Femme Mère Enfant, CHU Lyon, Lyon, France; [72]Service de génétique médicale, CHU Nantes, Nantes, France; [73]APHP, Department of Cardiology, Bobigny Hospital, Paris XIII University, INSERM UMR S-942, Paris, France; [74]Centre de Référence des maladies neuromusculaires Nord/Est/Ile de France, Service de Neurologie, CHU Nancy, Nancy, France; [75]Centre de référence des maladies neuromusculaires AOC, Service de Neurologie, Hôpital Pontchaillou, CHU Rennes, Rennes, France; [76]Centre de Recherche en Myologie, Sorbonne Universités, UPMC - Inserm UMRS 974, Institut de Myologie, Groupe Hospitalier Pitié-Salpêtrière, Paris, France; [77]Centre de référence des maladies neuromusculaires AOC, Service de Neurologie, CHU Angers, Angers, France; [78]Clinique de Génétique, Hôpital Jeanne de Flandre, CHRU Lille, Lille, France; [79]Centre de référence des maladies neuromusculaires AOC, Service de Neurologie et de Neurophysiologie Clinique CHRU Tours, Tours, France; [80]University Hospital Rangueil, Cardiology department, CHU Toulouse, Toulouse, France; [81]Service de Pédiatrie A, Neurologie pédiatrique, CHU Reims, Reims, France; [82]Centre de référence des maladies neuromusculaires PACA-Réunion-

Rhône Alpe, Service de Neuropédiatrie, CHU Estaing, Clermont-Ferrand, France; [83]Centre de référence des maladies neuromusculaires PACA-Réunion-Rhône Alpes, Service de Neurologie, Hôpital Gabriel Montpied, CHU Clermont-Ferrand, Clermont-Ferrand, France; [84]Service de Neurophysiologie Clinique, Hôpital Roger Salengro, CHRU Lille, Université de Lille 2; Département de Neurologie, Hôpital Roger Salengro, CHRU Lille, Lille, France; [85]Centre de référence des maladies neuromusculaires Nord/Est/Ile de France, Service de Médecine Physique et de Réadaptation, CHRU de Lille; URePSSS - EA 7369, équipe "Activité Physique, Muscle, Santé », Université de Lille 2, Lille, France; [86]Service de Génétique, CHU Tours; Inserm UMR 1253, iBrain, Université de Tours, Tours, France; [87]APHP, Saint-Antoine University Hospital, National Reference Center for Rare Diseases of Insulin Secretion and Insulin Sensitivity, Department of Endocrinology, Diabetology and Reproductive Endocrinology, Paris, France; [88]Centre de référence des maladies neuromusculaires PACA-Réunion-Rhône Alpes, Service de Neuropédiatrie, CHU Montpellier, Montpellier, France; [89]Department of Cardiology, Westmead Hospital, Westmead Applied Research Centre, University of Sydney Westmead, Australia; [90]University College London & St. Bartholomew's Hospital, London EC1A 7BE, United Kingdom[#]

*These authors contributed equally to this work

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)

References

1. Stuurman N, Heins S, Aebi U. Nuclear lamins: their structure, assembly, and interactions. J Struct Biol. 1998;122:42–66.

2. Fatkin D, MacRae C, Sasaki T, Wolff MR, Porcu M, Frenneaux M, Atherton J, Vidaillet HJ Jr, Spudich S, De Girolami U, Seidman JG, Seidman C, Muntoni F, Müehle G, Johnson W,

McDonough B. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. N Engl J Med. 1999;341:1715-1724.

3. Bonne G, Di Barletta MR, Varnous S, Bécane HM, Hammouda EH, Merlini L, Muntoni F, Greenberg CR, Gary F, Urtizberea JA, Duboc D, Fardeau M, Toniolo D, Schwartz K. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. Nat Genet. 1999;21:285-288.

4. Vantyghem MC, Pigny P, Maurage CA, Rouaix-Emery N, Stojkovic T, Cuisset JM, Millaire A, Lascols O, Vermersch P, Wemeau JL, Capeau J, Vigouroux C. Patients with familial partial lipodystrophy of the Dunnigan type due to a LMNA R482W mutation show muscular and cardiac abnormalities. J Clin Endocrinol Metab. 2004;89:5337-5346.

5. Haas J, Frese KS, Peil B, Kloos W, Keller A, Nietsch R, Feng Z, Müller S, Kayvanpour E, Vogel B, Sedaghat-Hamedani F, Lim WK, Zhao X, Fradkin D, Köhler D, Fischer S, Franke J, Marquart S, Barb I, Li DT, Amr A, Ehlermann P, Mereles D, Weis T, Hassel S, Kremer A, King V, Wirsz E, Isnard R, Komajda M, Serio A, Grasso M, Syrris P, Wicks E, Plagnol V, Lopes L, Gadgaard T, Eiskjær H, Jørgensen M, Garcia-Giustiniani D, Ortiz-Genga M, Crespo-Leiro MG, Deprez RH, Christiaans I, van Rijsingen IA, Wilde AA, Waldenstrom A, Bolognesi M, Bellazzi R, Mörner S, Bermejo JL, Monserrat L, Villard E, Mogensen J, Pinto YM, Charron P, Elliott P, Arbustini E, Katus HA, Meder B. Atlas of the clinical genetics of human dilated cardiomyopathy. Eur Heart J. 2015;36:1123-1135a.

6. Meune C, Van Berlo JH, Anselme F, Bonne G, Pinto YM, Duboc D. Primary prevention of sudden death in patients with lamin A/C gene mutations. N Engl J Med. 2006;354:209-210.

7. van Rijsingen IA, Arbustini E, Elliott PM, Mogensen J, Hermans-van Ast JF, van der Kooi AJ, van Tintelen JP, van den Berg MP, Pilotto A, Pasotti M, Jenkins S, Rowland C, Aslam U, Wilde AA, Perrot A, Pankuweit S, Zwinderman AH, Charron P, Pinto YM. Risk factors for life-threatening ventricular arrhythmias in lamin a/c mutation carriers a European cohort study. J Am Coll Cardiol. 2012;59:493-500.

8. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, Gillis AM, Granger CB, Hammill SC, Hlatky MA, Joglar JA, Kay GN, Matlock DD, Myerburg RJ, Page RL. 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2018;72:1677-1749

9. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekvål TM, Spaulding C, Van Veldhuisen DJ; ESC Scientific Document Group. ESC Scientific Document Group. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Eur Heart J. 2015;36:2793-2867.

10. Kumar S, Baldinger SH, Gandjbakhch E, Maury P, Sellal JM, Androulakis AF, Waintraub X, Charron P, Rollin A, Richard P, Stevenson WG, Macintyre CJ, Ho CY, Thompson T, Vohra JK, Kalman JM, Zeppenfeld K, Sacher F, Tedrow UB, Lakdawala NK. Long-Term Arrhythmic and Nonarrhythmic Outcomes of Lamin A/C Mutation Carriers. J Am Coll Cardiol. 2016;68:2299-2307.

11. Heller F, Dabaj I, Mah JK, Bergounioux J, Essid A, Bönnemann CG, Rutkowski A, Bonne G, Quijano-Roy S, Wahbi K. Cardiac manifestations of congenital LMNA-related muscular

dystrophy in children: three case reports and recommendations for care. Cardiol Young. 2017;27:1076-1082.

12. Hinkle LE Jr., Thaler HT. Clinical classification of cardiac deaths. Circulation. 1982;65:457-464.

13. van Smeden M, de Groot JA, Moons KG, Collins GS, Altman DG, Eijkemans MJ, Reitsma JB. No rationale for 1 variable per 10 events criterion for binary logistic regression analysis. BMC Med Res Methodol. 2016;16:163.

14. Austin PC, Allignol A, Fine JP. The number of primary events per variable affects estimation of the subdistribution hazard competing risks model. J Clin Epidemiol. 2017;83:75-84.

15. White IR, Royston P, Wood, AM. Multiple imputation using chained equations: issues and guidance for practice. Stat Med. 2011;30:377-399.

16. Rubin, DB. Multiple Imputation for Nonresponse in Surveys. New York, NY: John Wiley and Sons, 2004.

17. Fine J, Gray RJ. A proportional hazards model for the sub-distribution of a competing risk. J Am Stat Assoc. 1999;94:496–509.

18. Li J, Scheike TH, Zhang MJ. Checking Fine and Gray subdistribution hazards model with cumulative sums of residuals. Lifetime Data Anal. 2015; 21:197-217.

19. Vergouwe, Y, Royston P, Moons KG, Altman DG. Development and validation of a prediction model with missing predictor data: a practical approach. J Clin Epidemiol. 2010;63:205-214.

20. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996;15:361-387.

21. Royston P, Altman DG. External validation of a Cox prognostic model: principles and methods. BMC Med Res Methodol. 2013;13:33.

22. Team, R Core. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, 2017. https://www.R-project.org/.

23. Hosmer DW, Lemeshow S. Assessing the fit of the model. In: Hosmer DW, Lemeshow S, eds. Applied Logistic Regression. 2nd ed. New York, NY: John Wiley & Sons; 2000:143-202.

24. D'Agostino RB, Nam B-H. Evaluation of the performance of survival analysis models: discrimination and calibration measures. In: Balakrishnan N, Rao CR, eds. Handbook of Statistics v23: Advances in Survival Analysis. Amsterdam, the Netherlands: Elsevier; 2004.

25. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjær H, Brandes A, Thøgersen AM, Gustafsson F, Egstrup K, Videbæk R, Hassager C, Svendsen JH, Høfsten DE, Torp-Pedersen C, Pehrson S; DANISH Investigators. DANISH Investigators. Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. N Engl J Med. 2016;375:1221-1230.

26. Stecker EC, Vickers C, Waltz J, Socoteanu C, John BT, Mariani R, McAnulty JH, Gunson K, Jui J, Chugh SS. Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: two-year findings from the Oregon Sudden Unexpected Death Study. J Am Coll Cardiol. 2006;47:1161–1166.

27. Heymans S, Eriksson U, Lehtonen J, Cooper LT Jr. The Quest for New Approaches in Myocarditis and Inflammatory Cardiomyopathy. J Am Coll Cardiol. 2016;68:2348-2364.

28. Alba AC, Agoritsas T, Walsh M, Hanna S, Iorio A, Devereaux PJ, McGinn T, Guyatt G. Discrimination and Calibration of Clinical Prediction Models: Users' Guides to the Medical Literature. JAMA. 2017;318:1377-1384.

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 *LMNA* mutation	127 (28.6)	0	127 (28.6)	67 (46.2)	0	67 (46.2)
AV block						
1st degree*	127 (34.2)	73	152 (34.2)	41 (32.3)	18	49 (33.8)
>1st 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 ± SD or numbers (%) of observations

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

*1st 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	*p*	**Final**	*p*
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 *LMNA* mutation	1.78 (1.12-2.85)	0.043	1.76 (1.16-2.65)	0.007
AV block				
1st degree*	2.74 (1.34-5.61)	0.002	2.35 (1.34-4.12)	0.003
>1st 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).

* 1st 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.

27

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.

29

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 before16 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