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

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 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 (1) sudden cardiac death or (2) implantable cardioverter defibrillator–treated or hemodynamically unstable VTA. The prognostic model was derived using the Fine-Gray regression model. The net reclassification was compared with current clinical practice guidelines. The results are presented as means (SD) 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%) experienced 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, nonmissense LMNA mutation, first degree and higher atrioventricular block, nonsustained ventricular tachycardia, and left ventricular ejection fraction (https://lmna-risk-vta.fr). In the derivation sample, C-index (95% CI) of the model was 0.776 (0.711–0.842), and the calibration slope 0.827. In the external validation sample, the C-index was 0.800 (0.642–0.959), and the calibration slope was 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 in comparison with the guidelines-based approach.

CONCLUSIONS: In comparison with the current standard of care, this risk prediction model for LTVTA in laminopathies significantly facilitated the choice of candidates for implantable cardioverter defibrillators.

**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.
- In comparison with 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.

**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 3 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 online-only Data Supplement.

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, United Kingdom; Brigham and Women’s Hospital in Boston, Massachusetts; 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 cardiomyopathy. Data from these samples have been partially analyzed in 2 previous studies.

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 (United States), which granted waiver of participant consent. The ethics committee at Barts Hospital (United Kingdom) was informed, although it 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 LVTA at or before the initial evaluation, a congenital or childhood-onset laminopathy, eg, progeria, Werner syndrome or congenital muscular dystrophy, 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 end point of this study was time to fatal or near-fatal VTA, defined as (1) SCD, 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 R.B.Y. and K.W. (France), T.G. (United Kingdom), and S.K. and N.L. (other countries). Death was classified as sudden if it occurred unexpectedly (1) within 1 hour of onset of cardiac manifestations, in the absence of previous hemodynamic deterioration, (2) during sleep, or (3) within 24 hours 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 to obtain a number of events per variable of 10.13,14 The 4 risk factors for LTVTA used in the current professional practice guidelines were considered candidate predictors, including (1) male sex; (2) nonsustained ventricular tachycardia, including insertions, deletions, truncating mutations, or mutations affecting splicing; (3) nonsustained ventricular tachycardia, defined as ≥3 consecutive ventricular complexes at a rate ≥120 bpm on 24-hour 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 2 common disease manifestations: (1) atrial arrhythmias, defined as a personal history of atrial fibrillation, flutter, or tachycardia lasting ≥30 s, and (2) atrioventricular (AV) block, analyzed as a semiquantitative variable classified as (a) absent, (b) first degree (≥0.20 s PR interval), or (c) high degree (type II second degree or third degree) AV block. We did not consider other potential predictors such as family history of SCD because of 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 SD or median and interquartile ranges, 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 data sets were generated for the derivation sample. Estimates were pooled using Rubin rules.16 Mean and variance of the imputation 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 2-way interactions were tested.

To gauge the model discrimination, we calculated the concordance (C-) index as the area under the time-dependent receiver operating characteristic 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 data sets. The optimism is the decrease in model performance between the bootstrap and the original samples, which can adjust the developed model for overfitting. 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 data set and then applying the shrinkage factor. Estimates, hazard ratios, and 95% CIs were calculated.

We validated our model in an external independent derivation sample,21 in which missing values were imputed and 25 imputed data sets 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 data sets in both study samples, we calculated the sensitivity, specificity, and positive and negative predictive values of the guidelines-based and prediction score models at 5 years. We performed comparison tests between the 2 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 in comparison with the guidelines-based approach used as a categorized score, and ascertained the net reclassification improvement calculated as (correct–incorrect reclassifications)/total number of patients) in patients with and without LTVTA, but not in both together, because the prognostic weight of misclassifying patients was far higher for patients with than for those without events.

In all analyses, the tests were 2-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 were referred after family screening. At baseline, 54 patients were pacemaker recipients and 52 were ICD recipients. ICDs were implanted for: (1) the presence of ≥2 of the 2 risk factors for LTVTA used in the current professional practice guidelines in 35 patients, (2) high-degree AV block with previous identification of LMNA mutation in 4 patients, (3) left ventricular dysfunction with an ejection fraction <30% in 3 patients, and (4) miscellaneous other indications in 10 patients. ICDs were programmed at the discretion of the implanting physician. ECG showed sinus rhythm in 336 patients (79.8%), supraventricular arrhythmias in 70 patients (16.6%), complete AV block in 2 patients (0.5%), junctional rhythm in 1 patient (0.2%), supra-ventricular and ventricular pacing in 12 patients (2.9%), first-degree AV block in 127 patients (34.2), and complete left and right bundle-branch blocks in 20 patients (4.6%) and 26 patients (6.0%), respectively. Over a median (interquartile range) 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.

**Model Development and Internal Validation**

The model selection procedure retained male sex, non-missense LMNA mutation, AV block (first degree and higher), nonsustained ventricular tachycardia, and LVEF, when based on Rubin rules for pooling the model results across imputed data sets. All 2-way 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:

\[
1 - 0.8884505^{\text{male}} \times (\text{prognostic index})
\]

Where the prognostic index = 0.51573542 × male + 0.85513823 × first-degree AV block + 1.05127326 × higher AV block + 0.76692653 × nonsustained ventricular tachycardia + 0.56318475 × nonmissense 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 (15.1) 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 factor threshold, as

---

**Table 1. Characteristics of the Derivation and External Validation Samples**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Derivation Sample Data (n=444)</th>
<th>Validation Sample Data (n=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Original</td>
<td>Missing (n)</td>
</tr>
<tr>
<td>Age at baseline, y</td>
<td>40.6 (14.1)</td>
<td>0</td>
</tr>
<tr>
<td>Men</td>
<td>194 (43.7)</td>
<td>0</td>
</tr>
<tr>
<td>Nonmissense LMNA mutation</td>
<td>127 (28.6)</td>
<td>0</td>
</tr>
<tr>
<td>AV block</td>
<td>141 (31.8)</td>
<td>0</td>
</tr>
<tr>
<td>Atrial arrhythmia</td>
<td>60 (13.7)</td>
<td>0</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>56.3 (13.2)</td>
<td>52</td>
</tr>
</tbody>
</table>

Values are means±SD or numbers (%) of observations.

---

**Table 2. Associations Between Predictors and Survival in the Derivation Sample**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Model</th>
<th>P Value</th>
<th>Final</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline, y</td>
<td>0.99 (0.97–1.01)</td>
<td>0.200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.80 (1.1–2.95)</td>
<td>0.029</td>
<td>1.67 (1.1–2.55)</td>
<td>0.017</td>
</tr>
<tr>
<td>Nonmissense LMNA mutation</td>
<td>1.78 (1.12–2.85)</td>
<td>0.043</td>
<td>1.76 (1.16–2.65)</td>
<td>0.007</td>
</tr>
<tr>
<td>AV block</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First degree*</td>
<td>2.74 (1.34–5.61)</td>
<td>0.002</td>
<td>2.35 (1.34–4.12)</td>
<td>0.003</td>
</tr>
<tr>
<td>&gt;First degree†</td>
<td>3.51 (1.5–8.19)</td>
<td>0.001</td>
<td>2.86 (1.54–5.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial arrhythmia</td>
<td>1.19 (0.71–1.99)</td>
<td>0.524</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsustained VT</td>
<td>2.25 (1.34–3.79)</td>
<td>0.002</td>
<td>2.15 (1.36–3.41)</td>
<td>0.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>0.98 (0.96–1.00)</td>
<td>&lt;0.001</td>
<td>0.98 (0.97–1)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Values are hazard ratios (95% CIs). The hazard ratios were pooled over the 25 imputed data sets. Hazards ratios in the final model are shrunk by the calibration slope (0.894). AV indicates atrioventricular; and VT, ventricular tachycardia.

*First degree only vs no AV block.
†All degrees vs no AV block.
recommended in the guidelines-based approach. Of the 225 patients with a complete data set 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.

In comparison with the guidelines-based approach, threshold scores between 7% and 10% would have net reclassified and potentially prevented the SCD of 11 to 15 patients (event net reclassification improvement, 21.2%–28.8%), and unnecessary ICD implantations in 24 to 50 patients without LTVTA (nonevent net reclassification improvement, 13.9%–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 pri-

---

**Table 3. Simulated Impact of Applying a 5-Year Life-Threatening VTA Risk Model or Guidelines-Based Approach to Implant an ICD**

<table>
<thead>
<tr>
<th>ICD Recipients Selection Strategy</th>
<th>Threshold Values</th>
<th>ICD Recipients, n (%)</th>
<th>Performance to Predict LTVTA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sensitivity, %</td>
<td>Specificity, %</td>
</tr>
<tr>
<td>Guidelines-based</td>
<td>( \geq 2 ) risk factors*</td>
<td>86 (38.2)</td>
<td>67.3</td>
</tr>
<tr>
<td>Prognostic model to estimate the 5-y risk of LTVTA</td>
<td>( \geq 1% )</td>
<td>225 (100)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>( \geq 2% )</td>
<td>225 (100)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>( \geq 3% )</td>
<td>214 (95.1)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>( \geq 4% )</td>
<td>185 (82.2)</td>
<td>98.1 [94.3–100]</td>
</tr>
<tr>
<td></td>
<td>( \geq 5% )</td>
<td>179 (79.6)</td>
<td>98.1 [94.3–100]</td>
</tr>
<tr>
<td></td>
<td>( \geq 6% )</td>
<td>166 (73.8)</td>
<td>96.2 [90.9–100]</td>
</tr>
<tr>
<td></td>
<td>( \geq 7% )</td>
<td>151 (67.1)</td>
<td>96.2 [90.9–100]</td>
</tr>
<tr>
<td></td>
<td>( \geq 8% )</td>
<td>137 (60.9)</td>
<td>90.4 [82.4–100]</td>
</tr>
<tr>
<td></td>
<td>( \geq 9% )</td>
<td>130 (57.8)</td>
<td>88.5 [79.8–97.1]</td>
</tr>
<tr>
<td></td>
<td>( \geq 10% )</td>
<td>121 (53.8)</td>
<td>88.5 [79.8–97.1]</td>
</tr>
<tr>
<td></td>
<td>( \geq 15% )</td>
<td>90 (40)</td>
<td>76.9 [65.5–88.4]</td>
</tr>
<tr>
<td></td>
<td>( \geq 20% )</td>
<td>67 (29.8)</td>
<td>65.4 [52.5–78.3]</td>
</tr>
<tr>
<td></td>
<td>( \geq 25% )</td>
<td>48 (21.3)</td>
<td>53.8 [40.3–67.4]</td>
</tr>
</tbody>
</table>

The scores were calculated in patients with complete data sets in the derivation and validation samples. ICD indicates implantable cardioverter defibrillator; LTVTA, life-threatening ventricular tachyarrhythmia; and NM, not measured.

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

---

**Figure 2. Calibration by risk group in the derivation cohort.**

The vertical bars represent the observed (black) and model-based predicted (gray) probabilities of life-threatening ventricular tachyarrhythmia (LTVTA) at 5 years. Risk groups correspond to 5-year predicted probabilities of LTVTA divided into quartiles across the 25 imputed data sets. These groups were selected for the purposes of validation rather than for clinical decision making.
mary prevention of SCD. In comparison with the current standard of care,\textsuperscript{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 signifi-

<table>
<thead>
<tr>
<th>Table 4. Simulated Impact of Applying Different Thresholds of 5-Year LTVTA Risk Score to Implant an ICD on the Risk Reclassification in Comparison With the Guidelines-Based Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estimate of 5-y LTVTA Risk Threshold Used to Implant ICD</strong></td>
</tr>
<tr>
<td><strong>Guidelines-Based Approach</strong></td>
</tr>
<tr>
<td>≥1%</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>≥2%</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>≥3%</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>≥4%</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>≥5%</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>≥6%</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>≥7%</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>≥8%</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>≥9%</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>≥10%</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>≥15%</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>≥20%</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>≥25%</td>
</tr>
<tr>
<td>High risk</td>
</tr>
</tbody>
</table>

The scores were calculated in patients with complete data sets in the derivation and validation samples.

ICD indicates implantable cardioverter defibrillator; LTVTA, life-threatening ventricular tachyarrhythmia; and NRI, net reclassification improvement.
cant 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, and to the incremental prognostic information conferred by the inclusion of LVEF as a continuous variable and AV block as a supplemental independent predictor, as well. 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, in general, is considered to indicate a reliable discrimination.23,24 Also, we observed similar or even greater accuracy of our score in the validation sample in comparison to the derivation sample despite different patient characteristics including different proportions of probands and nonsissence mutations careers. These differences can be related to sampling variation and real different prevalence of mutation types in different populations. This observation strengthens our results because 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, because it is likely to increase over a lifetime with the growing prevalence of the various predictors of this score in a majority of patients.

Although 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 cardiomyopathies, which stratified the patients on the basis of a LVEF ≤35% alone, observed no significant effect on total mortality,25 whereas >70% of patients who die suddenly have a >35% LVEF.26 Given the considerable progress in the understanding of the genetic6 and inflammatory27 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, because it would optimize the measurements of predictors and outcomes.28 Finally, like most previous studies of SCD prediction in inherited cardiomyopathies, we included ICD therapy in our primary end point, 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.

ARTICLE INFORMATION

Received December 19, 2018; accepted April 24, 2019.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

The online-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.118.039410.

Authors

Karim Wahbi, MD, PhD; Rabah Ben Yaou, MD; Estelle Gandjbakhch, MD, PhD; Frédéric Anselme, MD, PhD; Thomas Gossios, MD; Neal K. Lakdawala, MD; Caroline Stalens, PhD; Frédéric Sacher, MD, PhD; Dominique Babet, MD, PhD; Jean-Noël Trochu, MD, PhD; Ghassan Moubarak, MD; Kostantinos Savvatis, MD, PhD; Raphaël Porcher, PhD; Pascal Laforté, MD, PhD; Abdallah Fayssoil, MD, PhD; Elii Marjion, MD; Tanya Stoikoivitch, MD; Anthony Béhin, MD; Sarah Leonard-Louis, MD; Guilhem Sole, MD; Fabien Labombarda, MD; Pascale Richard, MD; Corinne Metay, MD; Susana Quijano-Roy, MD, PhD; Ivana Dabaj, MD; Didier Klug, MD, PhD; Marie-Christine Vantyghem, MD, PhD; Philippe Chevalier, MD, PhD; Pierre Ambrosi, MD, PhD; Emmanuelle Salort, MD; Nicolas Sadoul, MD; Xavier Waintraub, MD; Khadija Chikhaoui, BS; Philippe Mabo, MD, PhD; Nicolas Combes, MD, PhD; Philippe Maury, MD, PhD; Jean-Marc Sellal, MD; Usha B. Pedrow, MD, PhD; Jonathan M. Kalman, MD, PhD; Jitendra Vohra, MD, PhD; Alexander F.A. Androulakis, MD, PhD; Katja Zeppenfeld, MD, PhD; Tina Thompson, MD, PhD; Christine Barnenas, MD; Henri-Marc Bécanne, MD; Eric Bieth, MD; Frank Boccara, MD, PhD; Damien Bonnet, MD, PhD; François Bouhour, MD; Stéphane Boulé, MD; Anne-Claire Brehin, MD; François Chapron, MD, PhD; Pascal Cintas, MD; Jean-Marie Cuisset, MD, PhD; Jean-Marc Davy, MD, PhD; Annachiara De Sandre-Giovannoli, MD; Florence Demurger, MD; Isabelle Desguerre, MD, PhD; Klaus Dieterich, MD; Julien Durigneux, MD; Andoni Echaniz-Laguna, MD, PhD; Romain Eschalier, MD, PhD; Ana Ferreiro, MD, PhD; Xavier Ferrer, MD; Christine Francannet, MD; Mélanie Fradin, MD; Bénédicte Gaborit, MD; Arnaud Gay, MD; Albert Hagège, MD, PhD; Arnaud Isapof, MD; Isabelle Jeru, MD; Raul Juntas Morales, MD; Emmanuelle Lagrue, MD, PhD; Nicolas Lambilin, MD; Olivier Lascols, MD; Vincent Laugel, MD, PhD; Arnaud Lazaur, MD; France Leturcq, MD; Nicolas Levy, MD, PhD; Armélie Magot, MD; Véronique Manel, MD; Raphaël Martins, MD, PhD; Michèle Mayer, MD; Sandra Mercier, MD; Christophe Meune, MD, PhD; Maud Michaud, MD; Marie-Christine Minot-Myhê, MD; Antoine Muchir, PhD; Aleksandra Nadaj-Pakleza, MD; Yann Péron, MD, PhD; Philippe Petitot, MD; Florent Petit, MD; Julien Praline, MD; Anne Rollin, MD; Pascal Sabouraud, MD; Catherine Sarret, MD; Stéphane Schaeffer, MD; Frederic Taite, MD; Célia Tard, MD; Vincent Tiffreau, MD, PhD; Annick Toutain, MD; Camille Vateir, MD; Ulrike Walther-Louvier, MD; Bruno Eymard, MD, PhD; Philippe Charron, MD, PhD; Corinne Vigouroux, MD, PhD; Gisèle Bonne, PhD; Saurabh Kumar, MD, PhD; Perry Elliott, MD, PhD; Denis Duboc, MD, PhD.

Correspondence

Karim Wahbi, MD, Cardiology Department, Cochin Hospital, 27 rue du Faubourg Saint Jacques, 75679 Paris Cedex 14, France. Email karim.wahbi@aphp.fr
Acknowledgments

R. Ruffy reviewed the manuscript for style and language.

Sources 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’s Department of Health’s National Institute for Health Research Biomedical Research Centres funding scheme.

Disclosures

None.

REFERENCES