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Risk stratification in phospholamban p.(Arg14del) cardiomyopathy

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Under review

CHAPTER 9

A Novel Approach to Identify Candidates for Future Advanced Therapies in Inherited Heart Disease

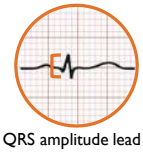
Graphical abstract

A Novel Approach to Identify Candidates for Future Advanced Therapies in Inherited Heart Disease

Baseline risk factor

New York Heart Association functional class ≥ II

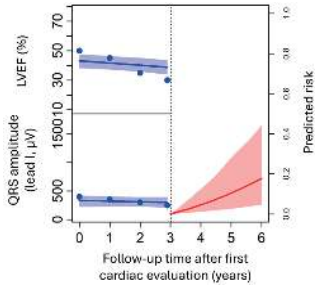
Dynamic risk factors



QRS amplitude lead I (μV)

Left ventricular ejection fraction (%)

Example: Individual risk prediction
Heart Failure Outcomes *



** Heart failure hospitalization, ventricular assist device implantation, heart transplantation or heart failure-related death.*

Key messages

- This study introduces a novel approach to identify potential candidates for future advanced therapies using a dynamic risk prediction model for heart failure outcomes.
- The model integrates baseline data (NYHA functional class ≥II) with longitudinal measures (LVEF (%) and QRS amplitudes in lead I), allowing risk estimates to be updated at each follow-up visit.
- Predictive performance was strong over a ten-year horizon, with a mean time-dependent AUC of 0.89 and a calibration slope of 1.01.

Abstract

Background and Aims

New therapies are rapidly developing for inherited cardiomyopathies, but accurate risk prediction is essential to identify those who will benefit most. This study presents a dynamic risk prediction model to identify potential candidates for future advanced therapies, offering a more personalized approach to patient selection compared to standard cross-sectional baseline models.

Methods and Results

This multicenter longitudinal cohort study was conducted in the Netherlands using data from the PLN/ACM Registry. The primary outcome was a composite of heart failure hospitalization, left or biventricular assist device (LVAD or BiVAD) implantation, heart transplantation, or heart failure-related death.

The study cohort included 330 PLN p.(Arg14del)-positive individuals, followed for a median of 7.1 years (IQR 3.6-11.6). Median age at inclusion was 42 years (IQR 30-55) and 149 (45%) were male. Heart failure outcomes occurred in 35 individuals (11%) during a median follow-up of 9.4 years (IQR 4.1-13.8). A dynamic risk model was developed using repeated electrocardiograms and echocardiograms including three variables: NYHA functional class ≥ II, LVEF on echocardiography, and QRS amplitude in lead I. Discriminative performance was strong, with a three-year time-dependent AUC ranging from 0.79 to 0.96 over a ten-year horizon (mean, 0.89; 95% CI, 0.79-0.97). Using this model, a hypothetical low number needed to treat of four may be achievable while minimizing the risk of missing high-risk patients.

Conclusion

This approach using a dynamic risk prediction model provides individualized risk estimates for heart failure outcomes and may inform timely intervention with future advanced therapy. Introduction

Introduction

Advances in therapy (such as genetic therapies) offer promising new therapeutic prospects for individuals with inherited heart diseases. However, their high costs and limited availability create an urgent need for well-defined patient selection methods to move toward clinical application in those who will benefit most.[1,2] Timely identification of high-risk individuals remains challenging because individual disease trajectories vary significantly. Most existing patient selection methods rely on static risk prediction models derived from cross-sectional data and are therefore based on a single time point. This approach assumes that risk remains stable over time, however, diseases, including inherited cardiomyopathies, progress and this requires updated risk assessments to account for temporal changes.[3-5] In this study, we aimed to develop an approach to identify potential candidates for future advanced therapies based on a dynamic risk prediction model that incorporates longitudinal data to enable personalized risk assessments.

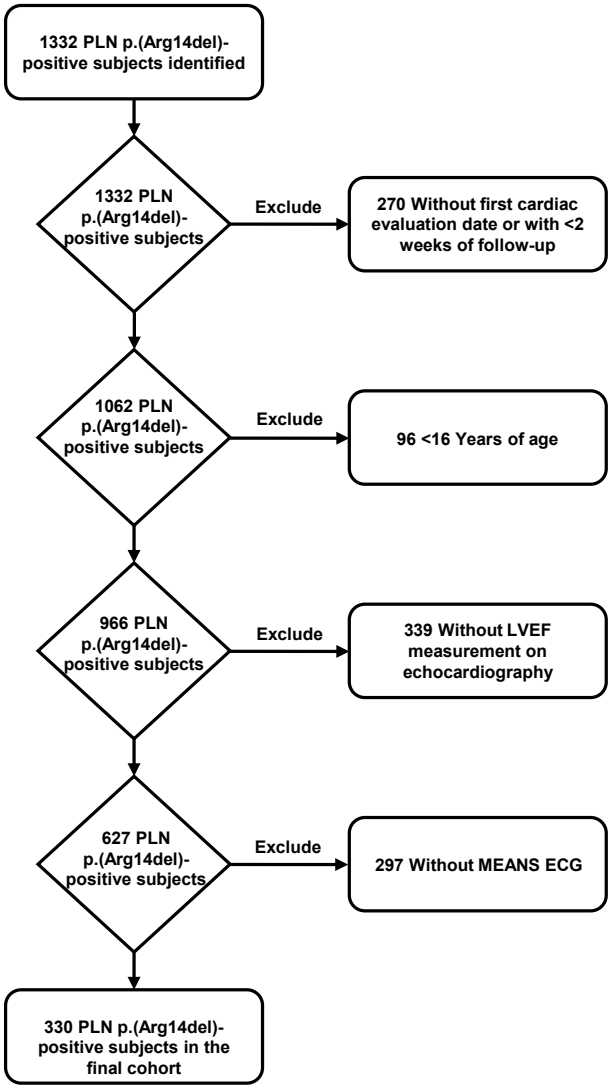
We developed the dynamic risk model in a cohort from the PLN/ACM registry, a multicenter, longitudinal study including individuals with the pathogenic phospholamban (PLN) p.(Arg14del) variant.[6] These individuals are at high risk of severe heart failure, yet expression of the variant is highly variable, ranging from young individuals with severe heart failure to older individuals without any disease features.[7,8] Current heart failure treatment is limited to standard therapies and heart transplantation, which do not halt disease progression and merely alleviate symptoms.[9,10] Thus, PLN p.(Arg14del)-positive individuals at high risk for heart failure outcomes represent an important population in whom dynamic prediction models can identify potential candidates for future advanced therapies.

Methods

Study Population and Design

Data were obtained from PLN p.(Arg14del)-positive individuals who were included in the PLN/ACM Registry (Netherlands Trial Registry project 70976) from 2009 through January 2025.[6] This was a multicenter, longitudinal cohort study. All individuals underwent genetic testing either for diagnostic purposes or through cascade genetic testing following genetic counseling. For the present study, only participants aged 16 years or older at time of their first cardiac evaluation were included. None had a history of heart failure-related events. For statistical modeling, participants were required to have undergone at least one echocardiogram and one electrocardiogram. A detailed overview of patient selection is provided in Figure 1. Many individuals who were excluded due to missing baseline date or insufficient follow-up time had only undergone genetic testing at the participating university hospitals. Additional exclusions due to missing imaging data were likely attributable to the retrospective nature of the study. This study was approved by the institutional review boards of the authors' institutions and conducted in accordance with the principles of the Declaration of Helsinki.

Figure 1. Patient selection.
Flowchart summarizing the selection process of PLN p.(Arg14del)-positive individuals. Subjects were excluded if they did not have a baseline date (defined as the date of first cardiac evaluation), had insufficient follow-up time (<2 weeks), or were under the age of 16 at baseline. None of the participants had prior heart failure-related events or myocardial infarction, such individuals had already been excluded based on follow-up criteria (minimum of two weeks follow-up). The final cohort for statistical modelling included all individuals with at least one LVEF measurement (%) on echocardiography and one QRS amplitude measurement (μV).



Clinical Data Collection

All clinical data available from the first contact with a cardiologist or clinical geneticist up to the most recent follow-up visit were extracted from electronic health records. Data included the reason for presentation (i.e., through family screening or symptoms), New York Heart Association functional class ≥II derived from clinical reports, family history, medication use at baseline, laboratory findings, 12-lead electrocardiography, 24-hour Holter monitoring, exercise stress testing, transthoracic echocardiography, and cardiac magnetic resonance (CMR) imaging.

In addition, ECGs were analyzed using the Modular ECG Analysis System (MEANS), a validated automated analysis program, to quantify the QRS amplitudes in all individual leads.[11] All marker settings were manually inspected and adjusted when necessary. About 2% of the ECGs could not be analyzed by MEANS due to low signal quality and were excluded. This data collection ended in March 2021, therefore, all imaging data were censored two weeks after the last QRS amplitude measurement to avoid information bias in prediction modeling.

Primary outcome

The primary outcome was a composite of heart failure hospitalization, left or biventricular assist device (LVAD or BiVAD) implantation, heart transplantation, or heart failure-related death.

Statistical Analysis

Statistical analyses were performed in R Studio (version 4.4.3) using the *rms, survival, riskRegression, mice, lcmm,* and *JMBayes2* packages. Baseline characteristics were presented as mean (SD) for normally distributed continuous variables, median (interquartile range [IQR]) for nonnormally distributed continuous variables, and counts (percentages) for categorical variables. The number of observations for demographic, ECG, and imaging variables is reported per variable (Table 1). Baseline data were defined as those obtained within one year before or after first clinical evaluation. Kaplan-Meier methods were used to estimate the cumulative incidence of heart failure outcomes over time (Figure 2).

Variable selection

All analyses that were performed for predictor/model selection are described in detail in the supplementary material (Supplementary Table 1-4, Supplementary Figure 1). Variable selection for risk prediction was primarily guided by findings from a previous study that applied least absolute shrinkage and selection operator (LASSO) Cox regression, a penalized regression method used to identify the most relevant predictors for heart failure outcomes.[12] That analysis identified three main predictors: left ventricular ejection fraction (LVEF) on echocardiography or cardiac MRI, low-voltage ECG (yes/no), and NYHA functional class ≥II (yes/no).

In this study, the binary predictor low-voltage ECG was replaced with a continuous measurement of the QRS amplitude in lead I, enabling more accurate and individualized risk prediction. The QRS amplitude from each individual lead was tested separately in dynamic models, in addition to LVEF and NYHA functional class ≥ II. These analyses demonstrated that lead I had the highest predictive value (Supplementary Table 5). Additionally, LVEF (%) was measured using echocardiography or CMR imaging for baseline analyses, whereas only echocardiographic measurements were used for dynamic modeling.

Model Development and Validation

First, a multivariable Cox regression model was constructed to assess baseline predictors of the three-year risk of heart failure outcomes and to allow comparison with the dynamic model. Second, a dynamic risk prediction model was developed to estimate the risk of heart failure outcomes, consisting of a survival submodel for time-to-event data and longitudinal submodels for repeated measurements of time-varying covariates. Model performance was evaluated by discriminative ability using the area under the receiver operating characteristic curve (AUC) and the time-dependent AUC (tdAUC) at 0-3 and 3-6 years, and by visual inspection of cumulative incidence stratified into three predicted risk tertiles. Calibration was assessed using the mean calibration slope and calibration plots for three-year predictions (baseline) and for three-year predictions over a ten-year horizon (dynamic). Performance was internally validated with 1,000 bootstrap resamples.

Missing data

Multiple imputation (20 datasets) was used to handle missing data before baseline Cox regression analyses. Results of the baseline Cox regression model with and without imputation are provided in Supplementary Table 6. Missing data were assumed missing at random.

Results

Baseline characteristics for the overall cohort and stratified by heart failure outcomes are presented in Table 1. The cohort included 330 PLN p.(Arg14del)-positive individuals, followed for a median of 7.1 years (IQR 3.6-11.6). The median age at time of inclusion was 42 years (IQR 30-55) overall, 41 years (IQR 29–54) in patients without heart failure outcomes, and 51 years (IQR 41–56) in those with outcomes (p = .023). Most participants were identified through genetic cascade screening (68%), whereas among those who developed heart failure outcomes, the majority presented with symptoms (51%; p < .001). Compared with participants without outcomes, those with heart failure outcomes more frequently had a NYHA functional class ≥ II (31% vs 4%; p < .001), had more major ventricular arrhythmias (17% vs 5%; p = .023), had more often low-voltage ECG (63% vs 17%; p < .001), had a lower left ventricular ejection fraction (median, 37% (IQR 33–43) vs 55% (IQR 50–60); p < .001), and more often LGE on CMR (88% vs 29%; p = .002).

Table 1. Baseline characteristics.

	All (n = 330)	Without heart failure outcomes (n = 295)	With heart failure outcomes (n = 35)	*P*-value
Age at first evaluation,y	42 (30-55) (n = 330)	41 (29-54) (n = 295)	49 (41-56) (n = 35)	0.023
Sex, male	149 (45) (n = 330)	137 (46) (n = 295)	12 (34) (n = 35)	0.235
Caucasian ethnicity	313 (100) (n = 313)	282 (100) (n = 282)	31 (100) (n = 31)	/
Proband	88 (27) (n = 324)	56 (19) (n = 292)	20 (63) (n = 32)	<0.001
History				
Type of presentation				<0.001
--Symptomatic and alive	69 (21) (n = 330)	51 (17) (n = 295)	18 (51) (n = 35)	
-Resuscitated SCD (witness collapse and revival with CPR)	9 (3) (n = 330)	5 (2) (n = 295)	4 (11) (n = 35)	
-Abnormal test result	28 (9) (n = 330)	22 (8) (n = 295)	6 (17) (n = 35)	
-Family history	224 (68) (n = 330)	217 (74) (n = 295)	7 (20) (n = 35)	
Cardiac syncope <6 months before presentation	19 (6) (n = 330)	6 (2) (n = 295)	2 (6) (n = 35)	0.449
NYHA functional class ≥II	22 (7) (n = 330)	11 (4) (n = 295)	11 (31) (n = 35)	<0.001
First degree family member with heart failure	54 (16) (n = 330)	46 (16) (n = 295)	8 (23) (n = 35)	0.392
ECG/continuous rhythm monitoring				
Major ventricular arrhythmia[a]	22 (7) (n = 330)	16 (5) (n = 295)	6 (17) (n = 35)	0.023
NSVT[b]	68 (21) (n = 330)	54 (18) (n = 295)	14 (40) (n = 35)	0.005
Atrial fibrillation/flutter	11 (3) (n = 330)	11 (4) (n = 295)	0 (0) (n = 35)	0.507
24-Hour PVC count	146 (6-932) (n = 186)	108 (6-845) (n = 179)	1371 (1145-2194) (n = 7)	0.003
Low-voltage ECG[c]	52 (20) (n = 259)	40 (17) (n = 240)	12 (63) (n = 19)	<0.001
TWI in ≥3 precordial leads	48 (20) (n = 238)	39 (18) (n = 220)	9 (50) (n = 18)	0.003
TWI in ≥2 inferior leads	26 (11) (n = 238)	22 (10) (n = 220)	4 (22) (n = 18)	0.228
Imaging				
LVEF[d]	54 (48-60) (n = 279)	55 (50-60) (n = 254)	37 (33-43) (n = 25)	<0.001
RVEF[d]	56 (48-60) (n = 264)	56 (48-60) (n = 243)	60 (50-60) (n = 21)	0.325
LV dilatation[e]	27 (11) (n = 241)	19 (9) (n = 224)	8 (47) (n = 17)	<0.001

Tricuspid valve insufficiency[f]	0 (100) (n = 200)	0 (0) (n = 188)	0 (100) (n = 12)	/
Mitral valve insufficiency[g]	14 (7) (n = 211)	9 (5) (n = 198)	5 (39) (n = 13)	<0.001
LGE on CMR	47 (32) (n = 148)	40 (29) (n = 140)	7 (88) (n = 8)	0.002

Values are presented as percentages or median (interquartile range).
[a] Major ventricular arrhythmia is defined as sustained ventricular arrhythmia, ventricular fibrillation, appropriate ICD intervention, and (aborted) SCD.
[b] NSVT is defined as 3 or more consecutive premature ventricular contractions with a rate >100 bpm., lasting <30 seconds.
[c] Low-voltage ECG is defined as peak-to-peak QRS-amplitude of <0.5 mV in the limb leads and/or <1 mV in the precordial leads.
[d] Left- and right ventricular ejection fraction (%) measured with echocardiography and CMR.
[e] Left ventricular dilatation is a binary variable, measured with echocardiography and CMR.
[f] Tricuspid valve insufficiency is defined as moderate or greater echocardiography.
[g] Mitral valve insufficiency is defined as moderate or greater on echocardiography.

Outcomes

The combined end point of heart failure outcomes occurred in 35 individuals (11%) during a median follow-up of 9.4 years (IQR 4.7-13.8), corresponding to an annual event rate of 1.3%. First events included 26 heart failure hospitalizations (74%), three LVAD or BiVAD implantations (9%), four heart transplantations (11%), and two heart failure-related deaths (6%). By the end of follow-up, a total of eight individuals had received an LVAD or BiVAD, of whom four subsequently underwent a heart transplantation and three died. In addition, a total of seven individuals underwent heart transplantation (including those with prior LVAD/BiVAD support), of whom one died of unknown causes. Overall, 18 deaths occurred: 12 had died from heart failure, three from sudden cardiac death, and three from unknown causes. Figure 2 displays the cumulative incidence of events over follow-up.

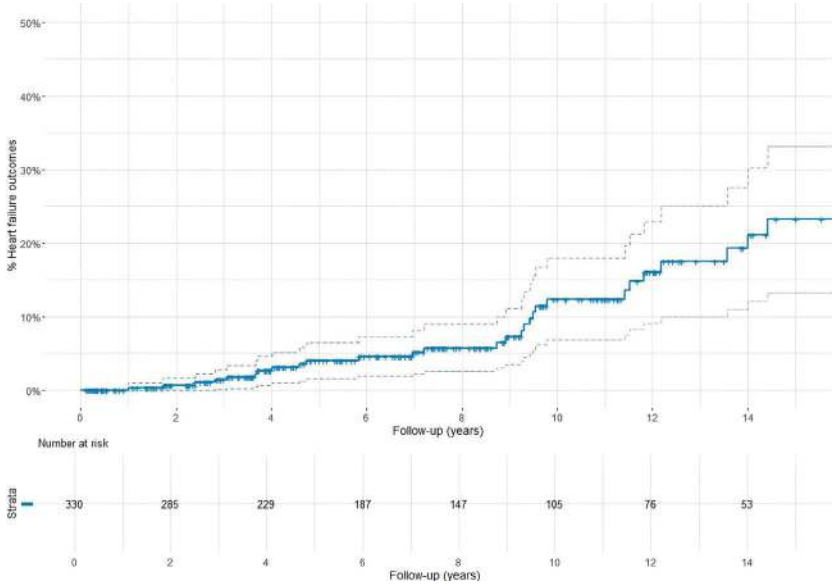
Model Development and Validation

Model Details and Discrimination

The baseline multivariable Cox regression model included LVEF, QRS amplitude in lead I, and NYHA functional class of II or higher. The detailed formula is provided in Supplementary Table 6. The model had an AUC of 0.96 (95% CI 0.94-0.99).

The dynamic model is presented in the Graphical Abstract and in Supplementary Table 7. This model had a three-year tdAUC ranging from 0.79 to 0.96 over a 10-years horizon, with a mean tdAUC of 0.89 (95% CI 0.79-0.97). A detailed visualization of the tdAUC over time is provided in Supplementary Figure 2. Since the tdAUC reflects model discrimination within specific time intervals and depends on the number of observed events, it is not directly comparable to the AUC from the baseline Cox regression model.

Figure 2. Cumulative incidence plot.
Kaplan-Meier analysis showing the cumulative incidence of PLN p.(Arg14del)-positive individuals with heart failure outcomes (%) (y-axis) and follow-up duration from first cardiac evaluation in years (x-axis).

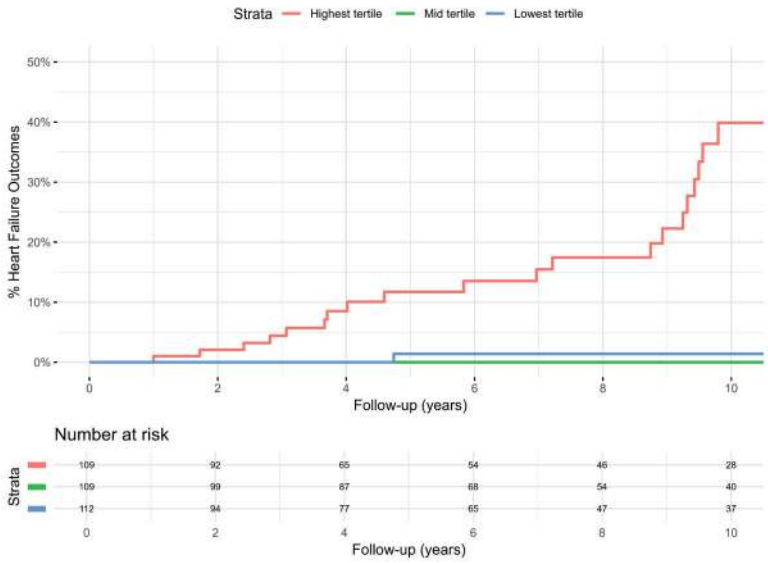


To improve comparability between models, a cumulative incidence plot was generated based on the three-year predicted risk of heart failure outcomes from the baseline model (Figure 3A). For the dynamic model, cumulative incidence plots were constructed for two time intervals (0-3 years and 3-6 years), illustrating individualized risk predictions (Figure 3B and 3C). Discrimination in risk groups was similar for both models, with almost all events classified as high risk. Misclassification occurred in two patients: one developed heart failure with preserved ejection fraction in the setting of multiple comorbidities (pulmonary hypertension and possible alcohol-induced cardiomyopathy), and the other had no LVEF measurements available during the prediction window. The first LVEF measurement, obtained five years after baseline, showed severe dysfunction (28%), which after reassessment would have classified this patient as high risk.

A considerable proportion of patients changed risk group between the 0-3 and 3-6 year intervals based on the dynamic predictions. Among 82 subjects with risk estimations for both intervals, 27 (33%) changed risk group over time. In the high-risk group, nine of 26 (35%) moved to a lower risk group. In the intermediate-risk group, two of 28 (7%) moved to the high-risk group and eight (29%) to the low-risk group. In the low-risk group, eight of 28 (29%) moved to a higher risk group.

Figure 3. Cumulative incidence of heart failure outcomes stratified by predicted risk tertiles. Cumulative incidence plots stratified by predicted risk tertiles. The x-axis presents the follow-up time (in years) after first cardiac evaluation; the y-axis presents the cumulative incidence of heart failure outcomes (%). (A) Shows stratification based on three-year risk estimates from the baseline Cox regression model. (B) Shows stratification using the three-year dynamic risk estimates from the dynamic model at time baseline and (C) at three years. The numbers included in these analyses differ, as the dynamic models were not imputed and relied on data availability at that specific time point. Therefore, (B) incorporates only 99 study participants with baseline data, the participant with an event after ~five years after first cardiac evaluation was not included in this analysis due to missing data.

A.



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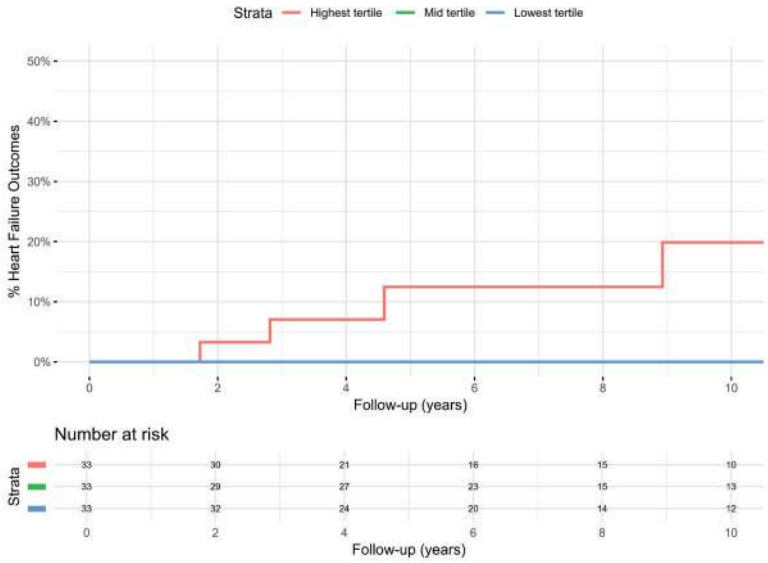

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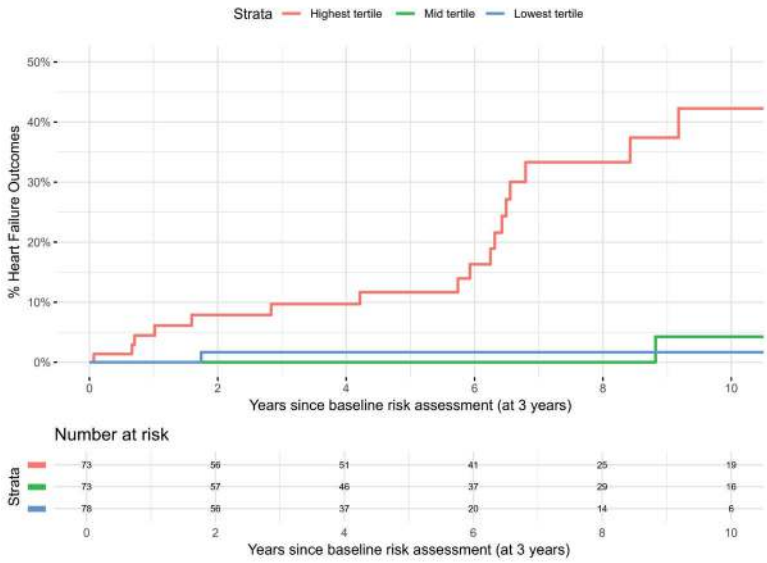


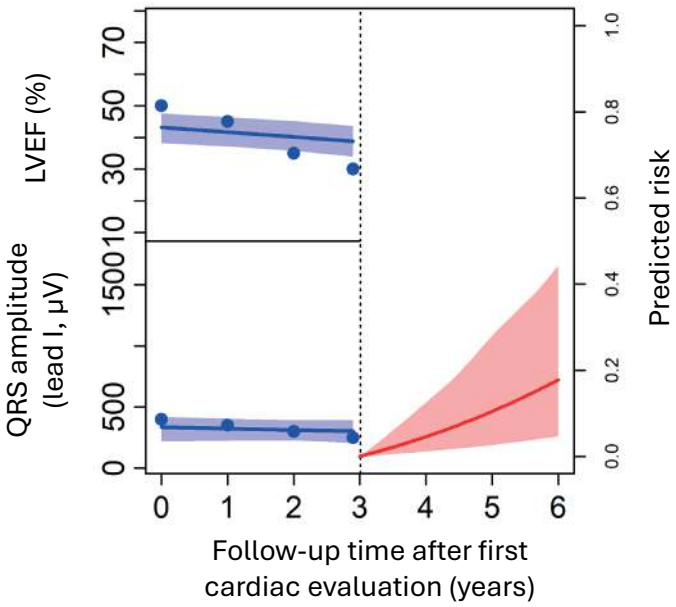
Model Calibration

Calibration curves for both models are shown in Supplementary Figure 3. The baseline Cox regression model calibration for three-year risk of heart failure outcomes had an average calibration slope of 0.69 (95% CI 0.60-0.78) across 20 imputed datasets, after bootstrapping and pooling with Rubin's rules. This suggests an overestimation of the true risk of heart failure outcomes. The dynamic model calibration for three-year risk of had an average calibration slope of 1.01 (95% CI 0.93-1.08) over a ten-year follow-up period using three-year time intervals, indication almost perfect calibration. However, this value represents an average across the entire ten-year period. Calibration varied by time point, reflecting the number of events in each interval.

Clinical Utility

Risk thresholds were explored for both models (Supplementary Figure 4). Interpretation is limited by the small number of events within the three-year prediction horizon. In the dynamic model, predictions were calculated separately for 0-3 and 3-6 years. In the 3-6 year interval, a 5% risk threshold corresponded to a hypothetical number needed to treat (NNT) of four. Figure 4 illustrated an example of a three-year risk prediction using the dynamic model at the 3-6 year interval. Predicted risk estimates increased over time in line with clinical deterioration, demonstrating that the model captures individual disease trajectories.

Figure 4. Example of heart failure outcome risk prediction using the dynamic model for the 3-6 year interval.
This figure illustrates an individualized prediction of the three-year risk of heart failure outcomes, made after a three-year follow-up period. The x-axis shows the follow-up time (in years) after first cardiac evaluation. The upper left y-axis depicts the LVEF (%), the lower left y-axis shows the QRS amplitude in lead I (μV), and the right y-axis displays the predicted three-year risk. Blue lines represent the longitudinal estimates from the submodels, with shaded areas indicating 95% confidence intervals. Blue dots are the observed values. The red line represents the predicted three-year risk over the 3-6 year time interval, with the shaded area indicating the 95% confidence interval.



Discussion

Main findings

This study introduces a novel approach to identify potential candidates for future advanced therapies based on a dynamic risk prediction model for heart failure outcomes. The model was derived from data of PLN p.(Arg14del)-positive individuals, an important cohort in which emerging treatments, such as genetic therapies, represent a promising and highly awaited approach once proven safe.[13] It integrates baseline data (NYHA functional class ≥ II (yes/no)) with longitudinal data (trajectories of LVEF (%) on echocardiography and QRS amplitude in lead I (μV)), allowing risk estimates to be updated at any follow-up visit. The model demonstrated strong performance over a ten-year horizon (mean tdAUC, 0.89) and was internally validated. Importantly, it relies on routinely obtained clinical parameters and is accessible as an online risk calculator.

Comparison with prior studies

To our knowledge, no validated patient selection methods exist for advanced therapies in inherited cardiomyopathies, such as genetic therapies, yet. Most risk prediction models in inherited heart disease focus on guiding implantable cardiac defibrillation (ICD) implantation to prevent sudden cardiac death (4). Only one published model predicts heart failure outcomes: a baseline Cox regression model developed for patients with arrhythmogenic right ventricular cardiomyopathy (ARVC).[14] This model incorporates LVEF, serum creatinine levels, tricuspid regurgitation, and atrial fibrillation. Comparison with our baseline risk model was not possible because serum creatinine and tricuspid regurgitation were not analyzed in our cohort. In a more general heart failure population, the application of dynamic models for all-cause mortality or cardiovascular mortality has been more extensively studied. A recent review summarized studies using joint modeling for risk prediction, however, these models were most often applied to assess the association of biomarkers with event risk rather than to support patient selection for therapy.[15] In other medical domains, such as oncology, dynamic risk prediction modeling has been used in patient with colorectal liver metastases after resection to predict progression-free and overall survival using longitudinal laboratory markers.[16] In this study, multiple risk models were compared, and the model incorporating repeated measurements performed best, reinforcing the value of dynamic prediction approaches.

Clinical implications

Timely and accurate identification of patients at risk for heart failure outcomes is essential to identify potential candidates for future advanced therapy. A dynamic risk prediction modeling approach appears most suitable. Our model, which updates risk estimates over time, showed that one-third of patients were reclassified after a three-year follow-up period, both to lower and higher risk groups. This shift likely reflects measurement variability and disease progression, and underscores the value of an individualized approach based on repeated measurements. Additionally, calibration was substantially better in the dynamic model compared with the static model (calibration slope, 1.01 vs 0.69), indicating excellent agreement between predicted and observed risks. Using this model, a hypothetical NNT of four might be achieved (5% threshold for three-year risk after three-year follow-up), representing a highly efficient threshold. Prospectively, however, applying a 5% risk threshold yields an NNT of 20. Therefore, when considering a threshold for advanced therapy, a 20% risk threshold might be more appropriate, corresponding to an NNT of four.

The PLN p.(Arg14del) cohort is an important cohort to develop new approaches that may inform patient selection for future advanced therapies. The age-related penetrance of heart failure outcomes in this patient population exceeds 25% by the age of 70 years, and standard heart failure therapies, including eplerenone, have not been proven effective to alter disease course.[8-10] Therefore, new and advanced therapies might offer great potential in this high-risk population. Current perspectives on patient selection

for genetic therapies are focused on young patients with lethal cardiomyopathy and limited or ineffective treatment options.[2] PLN p.(Arg14del)-positive individuals clearly fit this profile.

Limitations

The main limitation of this study is the presence of missing data, which is inherent to its observational design. Missingness was most pronounced for medication variables and laboratory findings, which were therefore excluded in this study. Furthermore, data collected for ECG MEANS analyses ended earlier, leading to censoring of imaging data two weeks after the last available QRS amplitude measurement. This may have limited the model's ability to capture late changes in disease trajectory. Nevertheless, this is unlikely to affect its clinical utility, as the model's aim is to identify individuals in an early stage of disease to enable timely intervention with gene therapy. A second limitation is the relatively low number of events, which may have caused overfitting. Although, the model was internally validated, further validation steps are required to confirm its generalizability, including validation in larger or independent external cohorts. At present, no sufficiently large external dataset is available. A third limitation concerns the occurrence of major ventricular arrhythmia and sudden cardiac death in this patient population. Competing risk was not incorporated in this model to avoid additional complexity, particularly given the limited number of events. For risk estimation of major ventricular arrhythmia, the previously published PLN risk score provides an adequate tool.[17]

Conclusion

This study introduces a method, based on a dynamic risk prediction model, to help identify candidates for future advanced therapies. The model improved risk stratification for heart failure outcomes and may provide personalized risk estimates to guide timely intervention.

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Supplementary material

Clinical definitions

» Major ventricular arrhythmia (major VA) is defined as sustained ventricular arrhythmia, ventricular fibrillation, appropriate implantable cardiac defibrillator (ICD) intervention, and (aborted) sudden cardiac death (SCD).

» Non-sustained ventricular arrhythmia (NSVT) is defined as three or more consecutive premature ventricular contractions with a rate >100 bpm., lasting <30 seconds.

» Low-voltage electrocardiogram (ECG) is defined as peak-to-peak QRS amplitude of <0.5 mV in the limb leads.

» Left ventricular (LV) dilatation is a binary variable, measured with echocardiography and cardiac magnetic resonance (CMR) imaging.

» Tricuspid valve insufficiency is defined as moderate or greater echocardiography.

» Mitral valve insufficiency is defined as moderate or greater on echocardiography.

Evaluating the dynamic predictive performance of individual variables on LVEF trajectories

Method

In our previously published analyses, we identified three variables with the strongest predictive performance for heart failure outcomes: left ventricular ejection fraction (LVEF), low-voltage ECG, and New York Heart Association (NYHA) functional class of II or higher.[1] These predictors were assessed at baseline using LASSO regression. To evaluate the predictive performance of these baseline variables on dynamic LVEF trajectories, we conducted latent class mixed models (LCMM). Additional ECG MEANS variables were explored but are not all reported in these Supplements. Analyses included all participants with more than one LVEF measurement (n = 627). Baseline characteristics of this cohort are presented in Supplementary Table 1. Individual LVEF trajectories were stratified by the occurrence of heart failure outcomes (Supplementary Figure 1A). Using LCMM, two latent classes of LVEF trajectory classes were identified (Supplementary Figure 1B). Each variable was then included as a fixed effect in separate LCMMs to assess its association with membership in the latent Class 1 (Supplementary Table 2). These models were estimated both in the original dataset and across 20 imputed datasets in which the baseline predictors were imputed. The estimates from the imputed datasets were pooled using Rubin's rules. Predictors that were significantly associated with class membership in the LCMM analyses were subsequently assessed and ranked based on their predictive performance, using the Akaike Information Criterion (AIC) values (Supplementary Table 3).

Results

The results of the LCMMs are presented in Supplementary Table 2. The variables significantly associated with LVEF latent class membership were: age at baseline, major VA, NSVT, PQ interval duration, amount of T-wave inversion, low-voltage ECG, QRS amplitude in lead I, 24-hour PVC count on Holter monitoring, and RVEF. QRS amplitude in lead I was missing for 63% and was largely imputed. To account for this, the binary low-voltage variable was included as well. All subjects with cardiac syncope <6 months before baseline (n = 17), NYHA functional class of II or higher (n = 15), LV dilatation at baseline (n = 52), and nearly all subjects with low-voltage ECG at baseline (n = 43 out of 44), were assigned to Class 2. As a result, the regression coefficient for these variables were often not estimable or highly inflated across the imputed datasets. For low-voltage ECG, 16 out of 20 datasets conversed, however, for LV dilatation only two out of 20 converged. Consequently, cardiac syncope < 6 months before baseline and NYHA functional class of II or higher were excluded from further analysis due to the low prevalence. Low-voltage ECG was excluded because it was replaced by continuous QRS amplitude measurements. In contrast, LV dilatation was retained in the joint models due to its known strong association with heart failure outcomes. The remaining significant variables were then assessed for their predictive value using the mean AIC across all imputed datasets. This resulted in the following ranking, from

lowest (strongest predictors) to highest AIC (weakest predictor): 24-hour PVC count on Holter monitoring, amount of T-wave inversion, age at baseline, QRS amplitude in lead I, major VA, PQ interval duration, NSVT, and lastly RVEF.

Supplementary Table 1. Baseline characteristics of PLN p.(Arg14del) individuals included in the LCMM analyses.

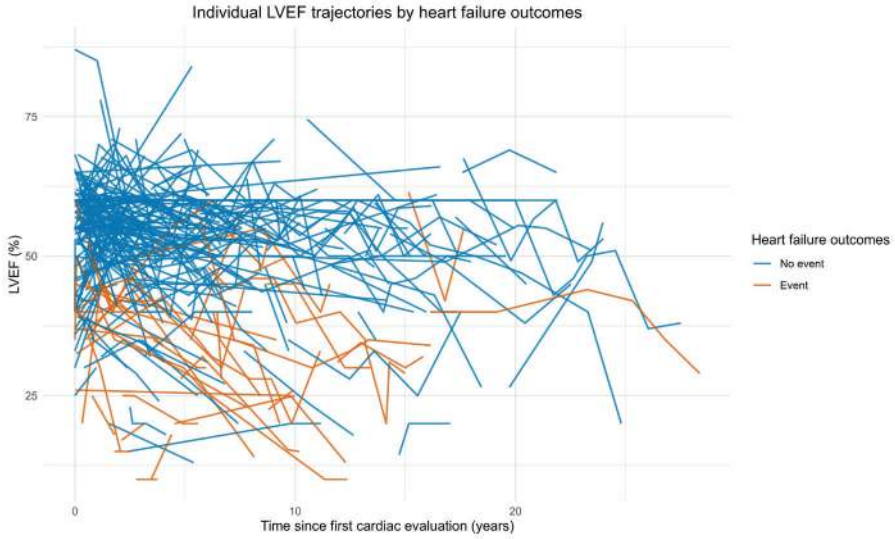
PLN p.(Arg14del)-positive individuals (n = number of observations)	**All (N = 301)**	**Latent Class 1**	**Latent Class 2**
Demographics			
Age at first evaluation, y	42 (31 – 53) (n = 301)	37 (26-49) (n = 199)	51 (42-60) (n = 102)
Sex, male	119 (39.5) (n = 301)	77 (39) (n = 200)	42 (42) (n = 101)
History			
Cardiac syncope <6 months before first cardiac evaluation	6 (2) (n = 301)	0 (0) (n = 201)	6 (6) (n = 106)
NYHA functional class ≥ II	15 (5) (n = 301)	0 (0) (n = 218)	15 (19) (n = 83)
First degree family member with heart failure	51 (17) (n = 301)	32 (16) (n = 200)	19 (19) (n = 101)
ECG/continuous rhythm monitoring			
Major ventricular arrhythmia	23 (8) (n = 301)	5 (3) (n = 200)	18 (18) (n = 101)
NSVT	54 (18) (n = 301)	21 (11) (n = 196)	33 (31) (n = 105)
Atrial fibrillation/flutter	9 (3) (n = 301)	5 (3) (n = 202)	4 (4) (n = 99)
24-Hour PVC count	5 (2-7) (n = 166)	3 (0-5) (n = 113)	7 (6-8) (n = 53)
Low-voltage ECG	44 (19) (n = 238)	1 (1) (n = 151)	43 (49) (n = 87)
TWI	0 (0-2) (n = 233)	0 (0-1) (n = 143)	2.5 (0-5) (n = 90)
Imaging			
LVEF (%)	55 (46-60) (n = 301)	59 (55-60) (n = 200)	40 (33-46) (n = 101)
RVEF (%)	69 (50-60) (n = 237)	60 (51-60) (n = 154)	60 (46-60) (n = 83)
Left ventricular dilatation	52 (22) (n = 238)	0 (0) (n = 152)	52 (60) (n = 86)

Variables are presented as percentages or median (interquartile range).

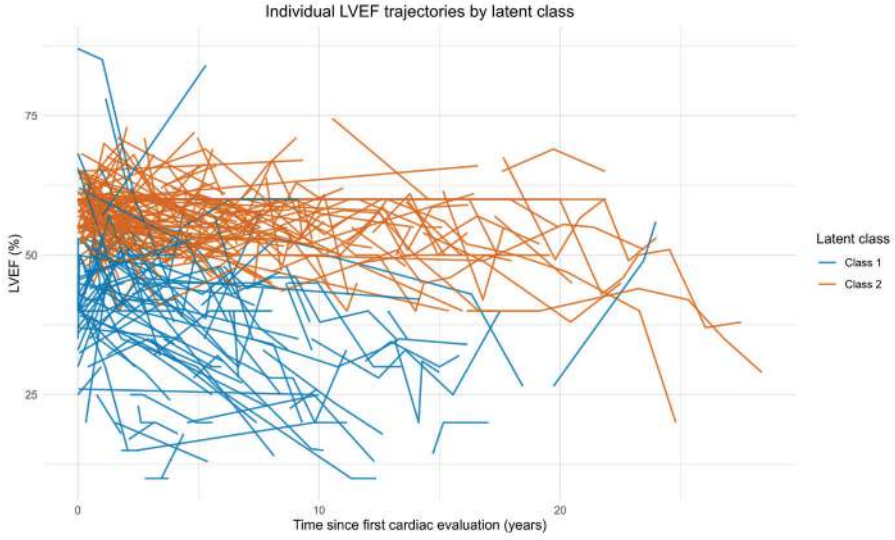
Supplementary Figure 1. Individual left ventricular ejection fraction trajectories by event and latent class.

Latent growth class analyses showing the individual left ventricular ejection fraction (LVEF) trajectories per individual. On the y-axis is the LVEF (%) displayed, and on the x-axis the time since first cardiac evaluation. The trajectories are stratified by heart failure outcomes (A) or latent growth class (B).

A.



B.



Supplementary Table 2. Latent Class Mixed Modelling.

	Original dataset				Imputed data: 20 datasets, results were pooled using Rubin's rules			
Predictor (assessed at baseline)	**Number of patients included**	**Coeff.**	**SE**	***P*-value**	**Number of patients included**	**Coeff.**	**SE**	***P*-value**
Age at baseline, y	301	-0,056	0,013	<0,001	/	/	/	/
Sex, male	301	-0,001	0,057	0,992	/	/	/	/
Cardiac syncope in the last six months	301	-3,277	2,383	0,169	/	/	/	/
NYHA functional class ≥ II	301	-22,332	1655,814	0,989	/	/	/	/
Family history of heart failure	301	-0,280	0,408	0,500	/	/	/	/
Major VA	301	-2,254	0,830	0,007	/	/	/	/
NSVT	301	-1,357	0,448	0,428	/	/	/	/
Atrial fibrillation/ flutter	301	-0,654	0,826	0,428	/	/	/	/
QRS duration (ms)	231	-0,013	0,009	0,173	301	-0,012	0,009	0,200
PQ duration (ms)	217	-0,022	0,009	0,017	301	-0,023	0,009	0,008
QT duration (ms)	222	-0,002	0,005	0,656	301	-0,003	0,004	0,440
TWI (n)	233	-0,523	0,129	<0,001	301	-0,568	0,138	<0,001
Low-voltage ECG	238	-3,274	1,108	0,003	301	-3,492	1,341	0,009
QRS amplitude, lead I (μV)	111	0,004	0,002	0,017	301	0,002	0,002	0,204
24h PVC count (log)	166	-0,426	0,098	<0,001	301	-0,416	0,109	<0,001
RVEF (%)	237	0,048	0,020	0,019	301	0,055	0,021	0,010
LV dilatation on echo-cardiography/ or CMR	238	-6,062	7,595	0,425	301	-5,097	2,790	0,068

Supplementary Table 3. Evaluation of the predictive value per predictor across 20 imputed datasets, using Akaike Information Criteria (AIC) values.

Imputation	24 h PVC count (log)	TWI (n)	Age at baseline (years)	QRS amplitude lead II (μV)	Major VA	PQ interval duration (ms)	NSVT	RVEF (%)
1	6568.9	6579,4	6595,1	6614,4	6605,8	6609,7	6608,2	6610,3
2	6564,6	6571,8	6595,1	6618,9	6605,8	6607,1	6608,2	6604,5
3	6560,9	6582,4	6595,1	6616,4	6605,8	6604,3	6608,2	6601,2
4	6554,0	6569,7	6595,1	6593,7	6605,8	6608,5	6608,2	6609,7
5	6562,3	6567,3	6595,1	6593,2	6605,8	6611,6	6608,2	6610,4
6	6570,2	6573,8	6595,1	6611,5	6605,8	6606,5	6608,2	6613,1
7	6565,2	6591,5	6595,1	6588,5	6605,8	6611,5	6608,2	6611,8
8	6543,8	6578,6	6595,1	6586,7	6605,8	6613,3	6608,2	6606,1
9	6554,4	6572,9	6595,1	6594,3	6605,8	6611,1	6608,2	6607,2
10	6562,0	6571,1	6595,1	6613,3	6605,8	6609,1	6608,2	6610,8
11	6551,9	6587,8	6595,1	6617,3	6605,8	6607,4	6608,2	6611,3
12	6538,9	6578,9	6595,1	6591,5	6605,8	6609,9	6608,2	6611,4
13	6551,8	6572,5	6595,1	6608,9	6605,8	6608,9	6608,2	6613,6
14	6562,5	6580,2	6595,1	6618,8	6605,8	6600,0	6608,2	6609,9
15	6578,3	6577,1	6595,1	6617,3	6605,8	6606,9	6608,2	6603,2
16	6570,5	6571,8	6595,1	6598,5	6605,8	6605,3	6608,2	6607,6
17	6570,3	6566,6	6595,1	6614,4	6605,8	6607,5	6608,2	6604,1
18	6559,5	6582,8	6595,1	6597,4	6605,8	6602,3	6608,2	6610,2
19	6540,5	6574,2	6595,1	6584,3	6605,8	6602,7	6608,2	6599,6
20	6530,9	6575,0	6595,1	6616,6	6605,8	6604,8	6608,2	6611,9
Mean AIC	6557,9	6576,0	6595,1	6604,8	6605,8	6607,4	6608,2	6608,4
Ranking low to high AIC	1	2	3	4	5	6	7	8

Supplementary Table 4. Joint models for predicting heart failure outcomes, using different sets.

Joint Model (S: Survival submodel, L: Longitudinal submodel)	**n / observations**	**Events (n)**	**Survival Submodel (P-value)**	**Longitudinal Submodel (P-value)**	**C-stat 0-3 n at risk SN SP**	**C-stat 3-6 n at risk SN SP**
S: NYHA functional class at first evaluation ≥ II (yes/no)	30	35	0,056	/	0,96 114	0,87 224
L: LVEF (%)	638		<0,001	<0,001	0,98 0,97	0,84 0,87
S: NYHA functional class at first evaluation ≥ II (yes/no)	330	35	0,022	/	0,97 114	0.88 224
L: LVEF (%)	638		0,016	0,128	0,98	0.85
L: Low-voltage ECG (yes)[a]	936		0,475	<0,001	0,97	0.84
S: NYHA functional class at first evaluation ≥ II (yes/no)	**330**	**35**	**0.056**	/	**0.96** **99**	**0.89** **224**
L: LVEF (%)	**638**		**<0.001**	**<0.001**	**0.98**	**0.84**
L: QRS amplitude lead I (μV)[a]	**1449**		**<0.001**	**<0.001**	**0.96**	**0.90**
S: Age at baseline (years)	330	35	0.224	/	0.96	0.89
S: NYHA functional class at first evaluation ≥ II (yes/no)	330		0.068	/	99 0.97	224 0.84
L: LVEF (%)	638		<0.001	<0.001	0.96	0.94
L: QRS amplitude lead I (μV)[a]	1449		<0.001	<0.001		
S: NYHA functional class at first evaluation ≥ II (yes/no)	330	35	0.058	/	0.96 101	0.88 228
L: LVEF (%)	638		<0.001	0.019	0.98	0.83
L: QRS amplitude lead I (μV)[a]	1449		0.021	<0.001	0.96	0.91
L: 24h PVC count (log)	534 (of 244 subjects)		0.053	<0.001		

S: NYHA functional class at first evaluation ≥ II (yes/no)	330	35	0.0449	/	0.97 115	0.89 231
L: LVEF (%)	638		<0.001	0.0247	0.98	0.84
L: QRS amplitude lead I (μV)[a]	1449		0.0013	<0.001	0.97	0.90
L: T-wave inversion (N)	891 (of 287 subjects)		0.9258	0.1873		
S: NYHA functional class at first evaluation ≥ II (yes/no)	330	35	0.0616	/	0.96 99	0.90 224
S: Major VA at baseline (yes/no)	330		0.9004	/	0.98	0.85
L: LVEF (%)	638		<0.001	<0.001	0.96	0.92
L: QRS amplitude lead I (μV)[a]	1449		0.0011	<0.001		
S: NYHA functional class at first evaluation ≥ II (yes/no)	330	35	0.0391	/	0.97 116	0.89 234
L: LVEF (%)	638		<0.001	0.0069	0.99	0.71
L: QRS amplitude lead I (μV)[a]	1449		0.0136	<0.001	0.98	0.99
L: 24h PVC count (log)	534(of 244 subjects)		0.0136	<0.001		
L: T-wave inversion (n)	891(of 287 subjects)		0.4476	0.2658		

In bold the final selected joint model.
[a] Variables were corrected for sex.

Evaluating the predictive performance of ECG leads using time-dependent AUCs derived from joint models

Method

The predictive value of each ECG leads was assessed using the time-dependent AUC (tdAUC) derived from a joint model. This joint model consisted of one survival submodel and two longitudinal submodels. The survival submodel included the presence of NYHA functional class of II or higher The first longitudinal submodel incorporated LVEF over time (%), while the second longitudinal submodel incorporated the QRS amplitude of the ECG lead. The tdAUC reflected the predictive performance of each ECG lead by capturing the longitudinal trajectory of its QRS amplitude in relation to heart failure outcomes.

Results

The ranking of the ECG leads by predictive performance based on tdAUC is shown in Supplementary Table 5. Lead I demonstrated the highest performance, although the difference between leads were minimal.

Supplementary Table 5. Ranking of ECG leads by predictive value of QRS amplitude.

Lead	tdAUC 3-6y
I	0.8882
V1	0.8862
aVR	0.8840
V5	0.8813
aVL	0.8799
III	0.8789
II	0.8772
aVF	0.8762
V6	0.8758
V4	0.8726
V2	0.8720
V3	0.8600

Supplementary Table 6. Baseline univariable and multivariable Cox regression analyses for heart failure outcomes (original data vs. multiple imputation data).

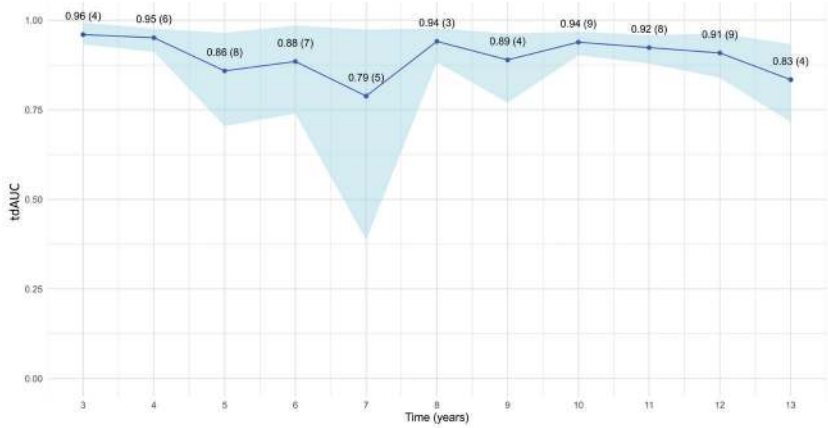
Variable	Univariable Cox regression analyses		Multivariable Cox regression analyses		Multivariable Cox regression analyses	
	Hazard ratio (95% CI)	**P-value**	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**
	Original data Univariable: NYHA ≥II (n = 330, Events = 15), LVEF (n = 210, Events =14), QRS amplitude lead I (n = 245, Events = 15) Multivariable: n = 188, Events = 10				**Imputed data** n = 330, Events =35 Number of imputed datasets = 20	
NYHA functional class ≥ II at first evaluation (yes/no)	8.29 (4.02-17.12)	<0.001	0.55 (0.08-3.80)	0.545	1.59 (0.53-4.81)	0. 423
LVEF, per 1% decrease	1.12 (1.08-1.16)	<0.001	1.14 (1.06-1.23)	<0.001	1.12 (1.08-1.16)	<0.001
QRS amplitude lead I, per 1μV decrease	1.006 (1.002-1.009)	0.002	1.01 (1.00-1.01)	0.042	1.00 (0.99-1.01)	0.254

Formula for the multivariable Cox regression model (using multiple imputation data): P(event at 3 years)=1−0.979exp(LP). With LP = -0.111*LVEF(%) – 0.002*QRS amplitude lead I (μV) – 0.463*NYHA functional class of II or higher.

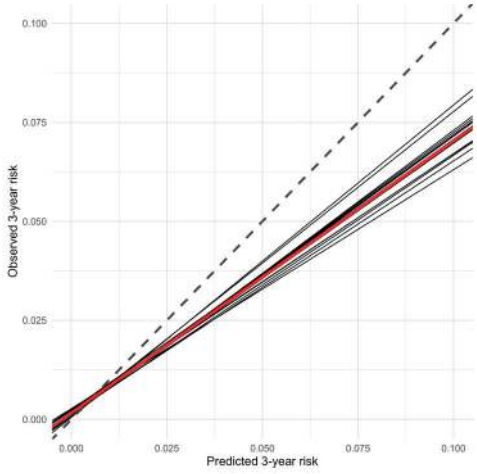
Supplementary Table 7. Dynamic prediction model for heart failure outcomes using joint modelling, final model.

Component	Variable	Estimate	95% CI	*P*-value	Interpretation
Longitudinal submodel LVEF	Intercept LVEF (%)	53.71	52.56 - 54.86	<0.001	Baseline value of LVEF
	Time effect LVEF (%)	-0.62	-0.83 - -0.42	<0.001	LVEF declines over time
Longitudinal submodel QRS amplitude	Intercept QRS amplitude lead I (μV)	410.25	381.65 – 438.35	<0.001	Baseline value QRS amplitude lead I
	Time effect QRS amplitude lead I (μV)	-8.67	-11.96 - -5.59	<0.001	QRS amplitude lead I declines over time
	Sex (male)	116.60	81.20 – 152.37	<0.001	Sex (male) is associated with a higher QRS amplitude in lead I
	Variable	**Hazard ratio**	**95% CI**	***P*-value**	**Interpretation**
Survival submodel	NYHA functional class of II or higher at first evaluation (yes)	3.17	0.97 – 9.64	0.058	NYHA functional class of II or higher at first evaluation is associated with a higher risk (nonsignificant)
	LVEF, per 1% decrease	1.16	1.10 – 1.22	<0.001	Lower LVEF is associated with a higher risk
	QRS amplitude lead I, per 1μV decrease	1.006	1.002-1.009	0.001	Lower QRS amplitude in lead I is associated with a higher risk

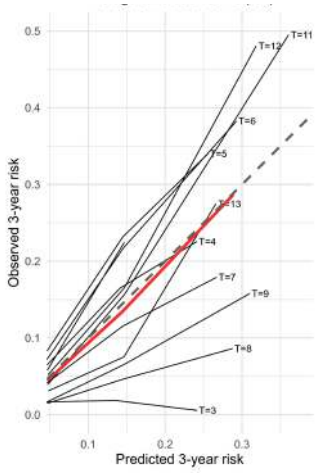
Supplementary Figure 2. Time-dependent AUC.
Time-dependent AUC (tdAUC) over three-years intervals (number of events per interval). On the y-axis is the tdAUC displayed, and on the x-axis the time since first cardiac evaluation (years). The shaded area indicates the 95% confidence interval.



Supplementary Figure 3. Calibration plots of predicted and observed three-year risk of heart failure outcomes.
Predicted 3-year risk of heart failure outcomes (x-axis) is plotted against observed risk (y-axis). Panel A displays the calibration of three-year predicted risk at baseline (timepoint 0), using a Cox regression model across 20 imputed datasets (black lines). The red curve represents the average calibration across these imputations. Panel B shows the calibration of dynamic three-year predicted risk over a ten-years horizon, starting at T=3 (i.e., the interval from 0 to 3 years). The calibration curves across time intervals are shown in black, the with average curve in red. In both panels, the dotted line represents perfect calibration.



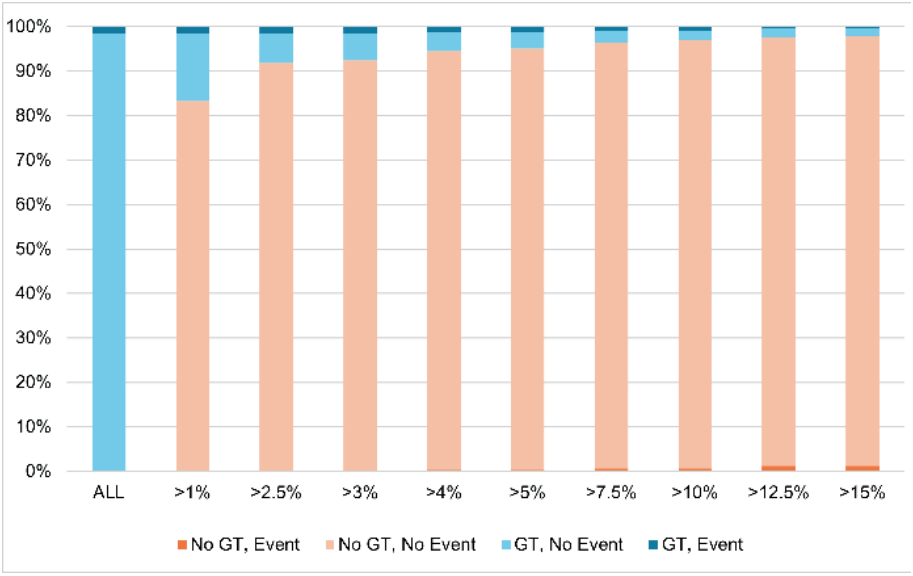
A.



B.

Supplementary Figure 4. Comparison of risk threshold between the Cox regression model (baseline) and joint model (dynamic) at multiple timepoints.
The clinical implications of different risk thresholds are visualized in bar graphs. Different risk thresholds result in different proportions of patients selected for future gene therapies, as well as different proportions of events that could potentially be prevented by such therapies. The baseline Cox regression model is displayed in panel A and includes 330 individuals with five events. The dynamic model with dynamic risk predictions at the 0-3 year time interval is shown in panel B and includes 99 individuals with two events, the 3-6 year time interval is visualized in panel C and includes 224 individuals with eight events.

A.



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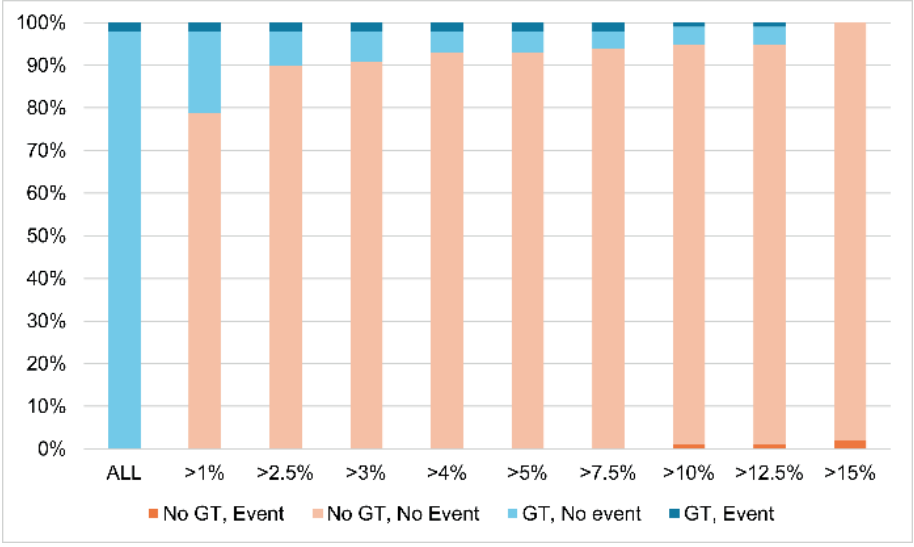
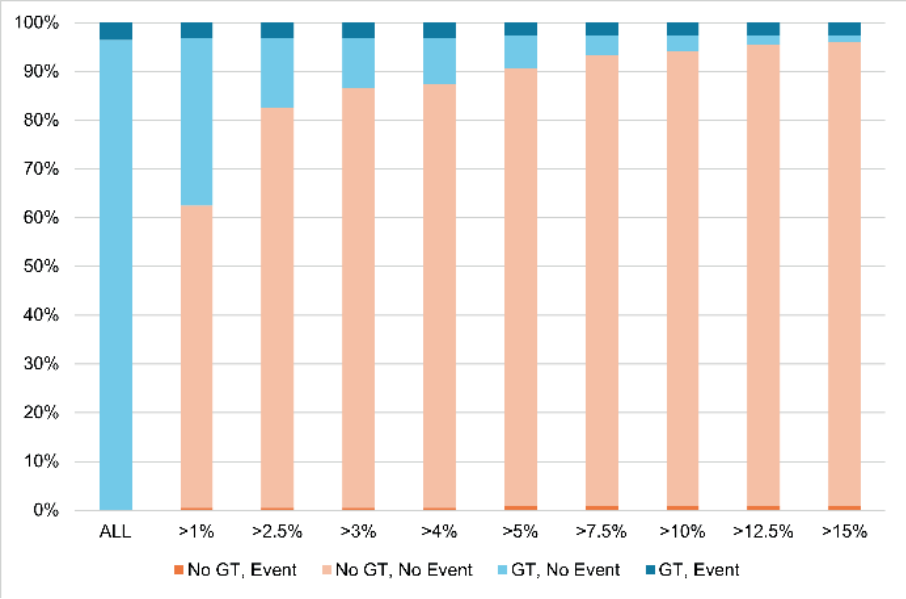


C.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References

1. van der Heide MYC, Verstraelen TE, de Brouwer R, et al. Identifying Predictors for Heart Failure Outcomes in Phospholamban p.(Arg14del)-Positive Individuals. JACC Heart Fail. Aug 8 2025;13(10):102558. doi:10.1016/j.jchf.2025.102558