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**RESEARCH ARTICLE**

# Age-related penetrance of phospholamban p.Arg14del cardiomyopathy

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**Aims** Previous studies have shown that carriers of the pathogenic p.Arg14del variant in phospholamban (*PLN*) have an increased risk of mortality, heart failure and malignant ventricular arrhythmias. However, there are sparse data on the penetrance of cardiac features in these mutation carriers, and the optimal starting age and intervals of clinical follow-up remain to be defined.

**Methods and results** We collected clinical data from *PLN* p.(Arg14del) carriers. Cardiac penetrance was defined as the presence of a major event or risk factor. A major event consisted of malignant ventricular arrhythmias or symptomatic heart failure. Risk factors were low-voltage electrocardiogram, repolarization abnormalities, frequent premature complexes, left ventricular ejection fraction <45% or cardiac fibrosis on magnetic resonance imaging. Kaplan–Meier analysis with and without left truncation was used to assess penetrance. We identified 868 p.(Arg14del) carriers, with a median age of 43 (interquartile range [IQR] 29–55) years at first cardiac evaluation. Median follow-up was 5.3 (IQR 2.2–8.5) years and 207 (23.8%) carriers had a major event, at a mean age of 51 (± 15) years. Penetrance was age-related, with new cardiac phenotypes emerging from adolescence to senior age. At age 70, penetrance of a major event was 43% to 70%, penetrance of a risk factor was 84% to 100% depending on which Kaplan–Meier method was used.

**Conclusions** Penetrance of a major cardiac event is high in *PLN* p.(Arg14del) carriers, with a penetrance up to 70% at age 70. Penetrance of a cardiac risk factor is nearly complete at older age. Furthermore, cardiac phenotypes can emerge from adolescence to senior age. Life-long cardiac follow-up is needed, starting from adolescence.

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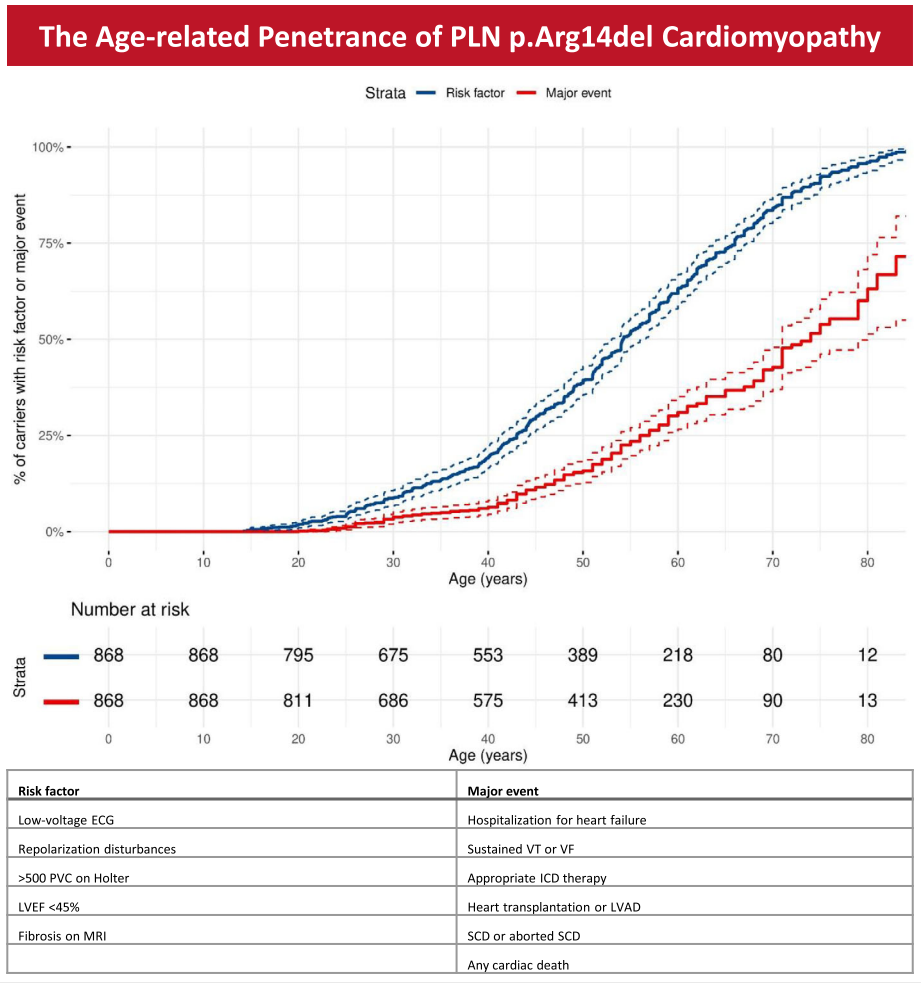
## Graphical Abstract




Age-related penetrance of phospholamban (*PLN*) p.Arg14del cardiomyopathy. ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PVC, premature ventricular contraction; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

**Keywords** Cardiomyopathy • Phospholamban • Heart failure

# Introduction

The pathogenic variant c.40_42del; p.(Arg14del) in the gene encoding phospholamban (*PLN*) is a known cause of dilated cardiomyopathy (DCM) and arrhythmogenic cardiomyopathy (ACM), including its subtype arrhythmogenic right ventricular cardiomyopathy (ARVC).[1,2] The PLN protein is a partner of the sarcoplasmic reticulum $Ca^{++}$-ATPase (SERCA) pump, which is vital for calcium regulation in cardiomyocytes. However, the mechanism underlying pathogenicity of the *PLN* p.(Arg14del) variant is still largely unknown, but aggregates of PLN protein can be found in carriers of this variant and are associated with disease severity.[3] Carriers of the *PLN* p.(Arg14del) variant have an increased risk of mortality, heart failure and malignant ventricular arrhythmias (VA).[4,5] Clinical manifestations are a low-voltage electrocardiogram (ECG), repolarization abnormalities, mechanical dispersion, inferolateral fibrosis and development of ACM/DCM.[6–8] Strikingly, cardiac manifestations of *PLN* p.(Arg14del) carriers vary, some display heart failure and ventricular dysfunction, while other carriers display VA. Moreover, penetrance is age-related with some carriers experiencing no symptoms at senescence while others develop a severe phenotype in adolescence. Thus, other factors, genetic and environmental, are assumed to play a role in progression of the phenotype. Of note, in patients carrying a pathogenic lamin

A/C (*LMNA*) variant, penetrance is age-related and this guides clinical recommendations.[9] However, up until now, there are sparse data of the age-related cardiac penetrance in *PLN* p.(Arg14del) carriers, and the optimal starting age and intervals of clinical follow-up remain to be defined. We aim to describe the age-related penetrance of a cardiac phenotype in *PLN* p.(Arg14del) pathogenic variant carriers. With this information, clinical management and counselling of carriers can be improved.

# Methods

## Study population

Data were collected from *PLN* c.40_42del; p.(Arg14del) carriers, identified between 2009 and 2021 in three Dutch university hospitals and one Spanish university hospital. Genetic analysis of the *PLN* gene was performed in a clinical setting in index patients with clinical signs of DCM/ACM and without apparent other causes of cardiomyopathy. Cascade genetic screening was routinely offered to relatives of index patients, regardless of their phenotype. Clinical evaluations were performed as part of standard clinical care and we collected clinical data from the first cardiac evaluation and follow-up visits. The majority of data was collected retrospectively, for which no standardized diagnostic and therapeutic protocols were used. We excluded patients without ECG or left ventricular ejection fraction (LVEF) measurements, as cardiac penetrance cannot be adequately measured without those parameters, but with an exception for carriers who presented with cardiac death. Design of the registry and collected parameters have been published earlier.[10] The study conformed to the principles of the Helsinki Declaration.

## Clinical definitions and outcomes

Dilated cardiomyopathy diagnosis was based on decreased LVEF and increased left ventricular end-diastolic dimension >112% of predicted for age and body surface area, and a reduced left ventricular function (LVEF <45% and/or fractional shortening <25%) on echocardiography or cardiac magnetic resonance imaging (MRI) with LVEF <45% and left ventricular end-diastolic volume >2 standard deviations above reference value.,[11,12] ARVC was diagnosed based on the 2010 modified task force criteria,[13] and was expert validated (Anneline te Riele). The presence of *PLN* p.(Arg14del) was not assigned a major criterion for ARVC diagnosis. Patients were assigned either a DCM diagnosis or an ARVC diagnosis. In case both criteria were met, the diagnosis first established was assigned as the primary diagnosis.

Electrocardiographic abnormalities were assigned when there were repolarization abnormalities (fulfilling the minor or major criteria as described in the modified ARVC 2010 task force criteria), or low-voltage ECG, defined as QRS peak-to-peak amplitude in leads I, II, and III <0.5 mV or amplitude in all precordial leads <1.0 mV. Twenty-four hour premature ventricular contraction (PVC) count was measured using ambulant ECG monitoring. The presence of fibrosis was evaluated by MRI with late gadolinium enhancement (LGE) and defined as any LGE mentioned in the report, which was adjudicated based on the clinical MRI report. LVEF was measured by echocardiography (modified Simpson) or MRI, for the LVEF <45% criterium either modality could be used, whichever was performed first. Right ventricular dysfunction was defined as either tricuspid annular plane systolic excursion <15 mm on echocardiography or right ventricular ejection fraction (RVEF) <45% on MRI. VA were classified as non-sustained ventricular tachycardia (VT) (≥3 consecutive ventricular complexes with a rate of >100 per minute and a duration of <30 s), or sustained VT (ventricular tachycardia with a rate of >100 per minute with a duration of >30 s). Appropriate implantable cardioverter-defibrillator (ICD) intervention was classified as ICD therapy (anti-tachycardia pacing or shock) for ventricular fibrillation (VF) or VT. Aborted sudden cardiac death (SCD) was defined as basic life support for cardiac arrest with return of stable circulation. SCD was defined as death (with or without documented VF) within 1 h of acute symptoms or an unexplained death with no antecedent history of worsening symptoms.

**Table 1 Cardiac penetrance definition**

| Risk factor | Major event |
|---|---|
| Low-voltage ECG[4,5] | Hospitalization for heart failure |
| Repolarization disturbances[4,5,14] | Sustained VT or VF |
| >500 PVC on Holter[4,5,14] | Appropriate ICD therapy |
| LVEF <45%[4,6] | Heart transplantation or LVAD |
| Fibrosis on MRI[7] | SCD or aborted SCD |
| | Any cardiac death |

ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device;LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PVC, premature ventricular contraction; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

Malignant VA was defined as a combined outcome of sustained VT/VF, appropriate ICD therapy and (aborted) SCD. Heart failure was defined as hospitalization for heart failure, implantation of a left ventricular assist device, heart transplantation or death due to heart failure. We divided penetrance in two categories: the penetrance of a risk factor or a major cardiac event (*Table 1*).[4–7,14] Relevant risk factors were based on previous studies.[4,5] Similarly, we categorized major events as arrhythmic or heart failure events (online supplementary *Table Appendix Appendix S1*).

## Statistical analysis

We selected carriers only if ECG and echocardiography or cardiac MRI were available to ensure adequate assessment of cardiac penetrance. For the baseline table, when measurements at first presentation were missing, measurements within 1 year after initial presentation were also considered baseline if not all diagnostic tests were completed at baseline. Continuous variables are expressed as mean ± standard deviation if normally distributed and medians ± interquartile ranges (IQR) are used if the data were skewed. Categorical variables are reported as percentages of complete cohort. A *p*-value of <0.05 is denoted as significant. Kaplan–Meier analysis was evaluated using two methods: (1) by presenting the time between birth and last follow-up; and (2) by presenting time since clinical presentation and last follow-up using left truncation. The former approach may lead to an overestimation of survival probability by having delayed entry of participants in the dataset[15] which is explained by the fact that patients have to be alive at first clinical contact, and some patients with a lethal phenotype at early age cannot be part of the dataset. Furthermore, the *PLN* gene became part of routine genetic testing since 2008, which could also have led to not including all relevant patients, for example if there was no DNA available of a deceased person.

Therefore, we performed additional analyses with left truncation using only data collected between first clinical contact and last follow-up for construction of age-related penetrance curves. Both methods will be presented since both are not ideal. However, if results point in the same direction, we assume our results are robust. Additionally, we performed a Kaplan–Meier analysis using time between first clinical contact and last follow-up while excluding carriers that already reached an outcome at baseline. For the risk factor outcome, follow-up started 1 year after clinical presentation to allow for all diagnostic tests to be finished prior to start of follow-up. Additionally, we evaluated predictors for risk factors and either heart failure or malignant VA event. We used a logistic regression model to study the association between predictor and outcome. Predictors were considered as the most abnormal value during follow-up.

SPSS version 26.0.0.0 (IBM Corp., Armonk, NY, USA), R version 4.1.0 and RStudio version 1.4.1717 (RStudio, Boston, MA, USA) with packages survival, survminer, rms, haven and ggplot2 were used for analysis.

# Results

We collected data from 868 *PLN* p.(Arg14del) carriers (*Figure 1*) with a median age of 43 years (IQR 29–55) and median LVEF of 54% (IQR 48–60%) at first cardiac evaluation. Of the 868 carriers, 200 (23%) were index patients and 668 were family members (77%) and 478 (55%) were female. Carrier characteristics at first cardiological visit are displayed in *Table 2*. Baseline characteristics, stratified by sex, heart failure event and malignant VA event can be found in online supplementary *Tables S3–S5* respectively.

Median follow-up was 5.3 years (IQR 2.2–8.5 years) and 207 (23.8%) carriers had a major event, at a mean age of 51 (± 15) years. At last follow-up, 151 (17.4%) had experienced a first malignant VA event, with 20 carriers experiencing aborted SCD (including three with ICD implantation before aborted SCD) and 23 carriers with SCD, while 203 (23.4%) had a heart failure event. Further cardiac outcomes are displayed in *Table 3*. At last follow-up, 242 (28%) carriers had received an ICD for primary or secondary prevention. Furthermore, at last follow-up, left or right ventricular dysfunction was present in 40% (294/739) of carriers, of which 50% had both left and right (biventricular) ventricular involvement.

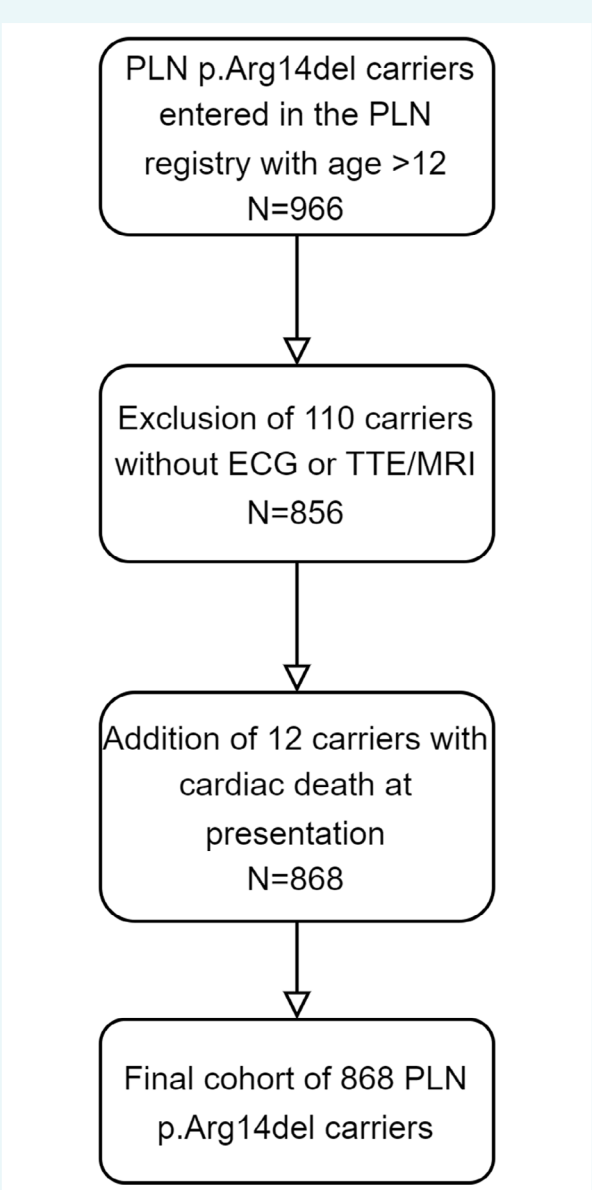



**Figure 1** Flowchart of the study participants. ECG, electrocardiogram; MRI, magnetic resonance imaging; PLN, phospholamban; TTE, transthoracic echocardiography.

## Age-related penetrance

Age-related penetrance of a cardiac risk factor and major event is shown in *Figure 2*. At age 70, 43% (95% CI 37–48%) of carriers had experienced a major event (heart failure or malignant VA). Furthermore, 84% (95% CI 80–86%) developed a risk factor at age 70. When limiting the analysis to the period an individual was under follow-up (i.e. left censoring with delayed entry), prevalence of a major cardiac event was 70% (95% CI 61–77%) at age 70, (online supplementary *Figure Appendix S1A*). Likewise, penetrance of any risk factor is already nearly complete at the age of 50 years, with 97% (95% CI 94–100%) of carriers displaying them (online supplementary *Figure Appendix S1B*). *Figure 3* depicts age-related penetrance of either malignant VA or heart failure events. Malignant VA were more prevalent at a younger age, preceding heart failure events by approximately 10 years. When stratifying by index patient versus family member, index patients more often had a major event ($p < 0.0001$) (*Figure 4*). Moreover, a severe phenotype was more prevalent in men versus women (*Figure 4*).

## Cardiac penetrance during follow-up

As shown in online supplementary *Figure S2A*, approximately 24% (95% CI 18–29%) of the cohort without baseline major event developed a first major event within 10 years after first presentation, translating in a relatively stable annual increase of ~2.4%. For carriers without any risk factor at baseline, risk of developing a risk factor was 60% (95% CI 53–67%) within 10 years (online supplementary *Figure S2B*).

**Table 2 Patient characteristics at first clinical presentation of all 868 *PLN* p.(Arg14del) carriers, measurements taken until 1 year after baseline**

| Variable | |
|---|---|
| Total | 868 |
| Follow-up (years) | 5.3 [2.2–8.5] |
| Demographics | |
| Age at presentation (years) | 43 [29–55] |
| Male sex | 390 (45) |
| Caucasian ethnicity | 868 (100) |
| Index patient | 200 (23) |
| History | |
| First-degree family member with malignant VA | 126 (15) |
| Reason for presentation: Family screening (number shown) vs. symptomatic or abnormal test result | 586 (68) |
| Heart failure (including NYHA class >I) | 80 (9.2) |
| Malignant VA event | 63 (7.3) |
| ECG/continuous rhythm monitoring | |
| Low-voltage ECG ($n = 686$) | 116 (16.9) |
| TWI in ≥3 precordial leads ($n = 618$) | 102 (16.5) |
| TWI in ≥2 inferior leads ($n = 618$) | 64 (10.4) |
| NSVT | 88 (10.1) |
| 24 h PVC count >500 ($n = 441$) | 144 (32.6) |
| Imaging | |
| LVEF <45% ($n = 701$) | 132 (18.8) |
| RV dysfunction ($n = 680$) | 79 (11.6) |

Values are given as *n* (%), or median [interquartile range].
ECG, electrocardiogram; IQR, interquartile range; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; PVC, premature ventricular contraction; RV, right ventricular; TWI, T-wave inversion; VA, ventricular arrhythmia.

**Table 3 Cardiac outcomes at last follow-up of the 868 *PLN* p.(Arg14del) carriers**

| | |
|---|---|
| Phenotype | |
| No risk factor or major event | 276 (31.8) |
| Risk factor | 575 (66.2) |
| Major event (heart failure or sustained arrhythmic event) | 207 (23.8) |
| Both risk factor and major event | 190 (21.9) |
| Arrhythmic event[a] | 151 (17.4) |
| SCD | 23 (2.6) |
| Aborted SCD | 20 (2.3) |
| Sustained ventricular tachycardia | 59 (6.8) |
| Appropriate ICD therapy | 49 (5.6) |
| Heart failure event | 122 (14) |
| Heart failure hospitalization | 117 (13.7) |
| Heart transplant or LVAD | 52 (6.1) |
| Heart failure death | 54 (6.2) |
| Both heart failure and malignant VA event | 94 (10.8) |
| Diagnosis | |
| Dilated cardiomyopathy | 183 (21.1) |
| ARVC TFC+ | 82 (9.4) |
| ICD | 242 (27.9) |
| Atrial arrhythmia (flutter or fibrillation) | 90 (10.4) |
| Low-voltage ECG | 305 (35.1) |
| Repolarization abnormality | 308 (35.5) |
| >500 PVC Holter | 294 (33.9) |
| NSVT | 251 (28.9) |
| Fibrosis on MRI | 193 (22.2) |
| LVEF <45% | 276 (31.8) |
| RVEF <45% or TAPSE <15 mm | 203/740 (27.4) |

Values are given as *n* (%).
ARVC, arrhythmogenic right ventricular cardiomyopathy; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular contraction; RVEF, right ventricular ejection fraction; SCD, sudden cardiac death; TAPSE, tricuspid annular plane systolic excursion; TFC+, 2010 task force criteria; VA, ventricular arrhythmia.
[a]First arrhythmic event is shown.

## Predictors of risk factor and events

Age at first presentation is significantly associated with the presence of a risk factor, as demonstrated in *Table 4*. Several significant associations with heart failure were identified, with LVEF <45% emerging as the strongest predictor, yielding a multivariable odds ratio of 41 (19.7–99) (*Table 4*). Finally, for malignant VA, all evaluated predictors were significantly associated with the outcome (*Table 4*).

# Discussion

## Main findings

This study assessed the *PLN* p.(Arg14del) cardiomyopathy and its age- and sex-related penetrance in a large cohort, consisting of both index patients and family members. Cardiac phenotypes may develop from adolescence to advanced age (*Graphical Abstract*). Major cardiac events have a penetrance of 43–70% at age 70, while cardiac risk factors have a penetrance of 84–100% at this age. Importantly, also carriers without apparent risk factors or event at baseline were at significant risk of developing these during follow-up. We consider our results robust, as both Kaplan–Meier analysis variants estimating considerable age-related penetrance. Our findings have consequences for the care of *PLN* p.(Arg14del) variant carriers. First, life-long clinical follow-up of carriers of *PLN* p.(Arg14del) is warranted. Second, the high annual incidence of new cardiac phenotypes plea for at least yearly follow-up where an estimation of the 5-year malignant VA risk to guide timing of primary prophylactic ICD implantation should be performed.[5] Third, carriers of *PLN* p.(Arg14del) must be counselled on the clinical course and expression of their disease. Finally, if an untested family member or potential *PLN* variant carrier is clinically completely unaffected at old age (≥70 years), it is unlikely for that individual to have the p.(Arg14del) pathogenic variant.

As is common in mono-genetic cohorts, index patients are more severely affected and have a higher risk of major events. This is at least partly explained for by ascertainment bias.[16]

Cardiac penetrance of heart failure and arrhythmic phenotypes differ, with arrhythmia events being more common at younger age

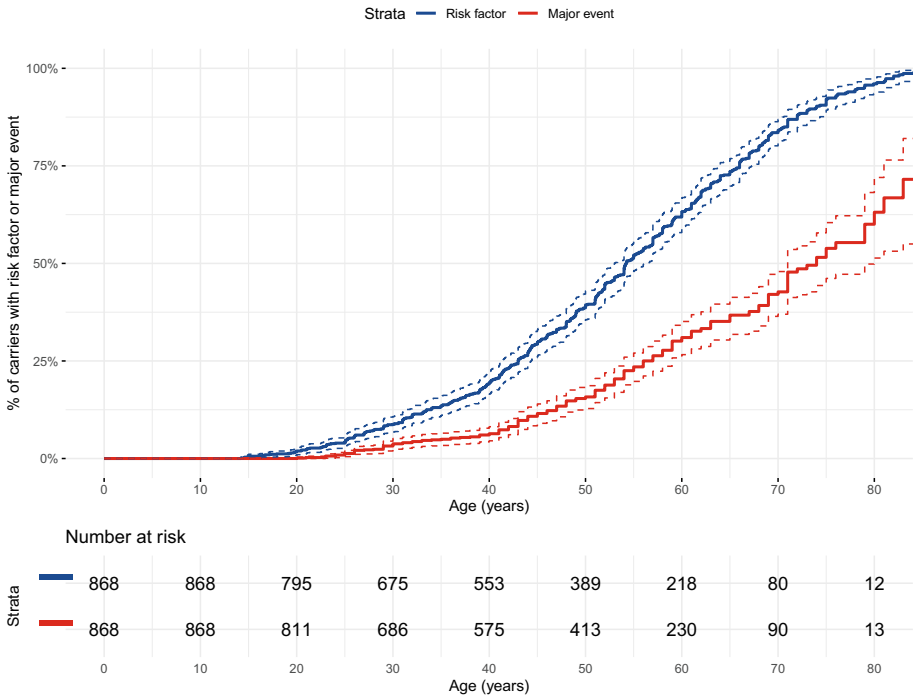



**Figure 2** Kaplan–Meier plot showing penetrance of a risk factor and major event with age as time scale.

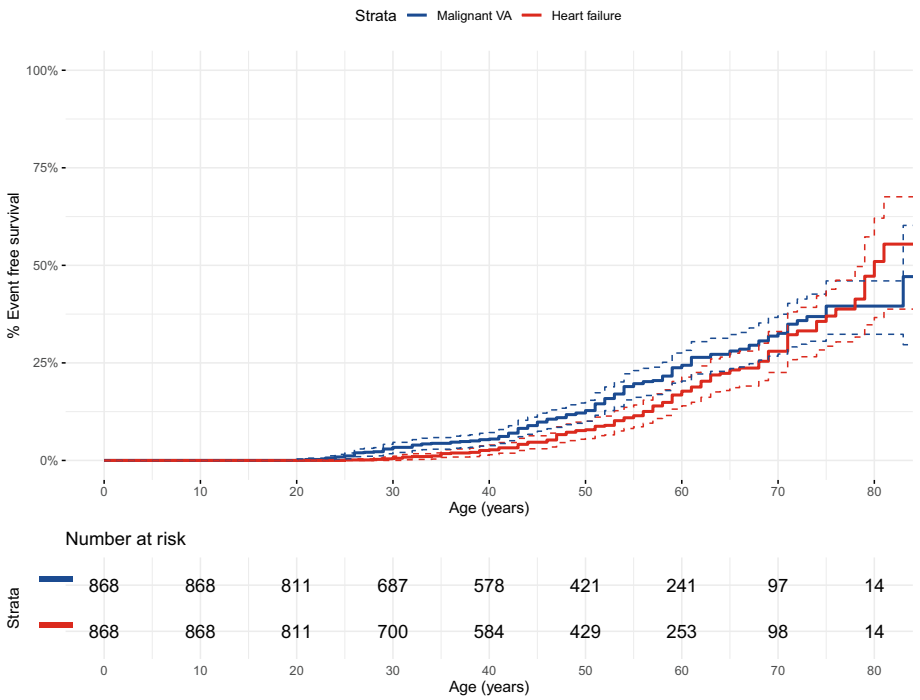



**Figure 3** Kaplan–Meier plot showing penetrance of malignant ventricular arrhythmia (VA) and heart failure with age as time scale.

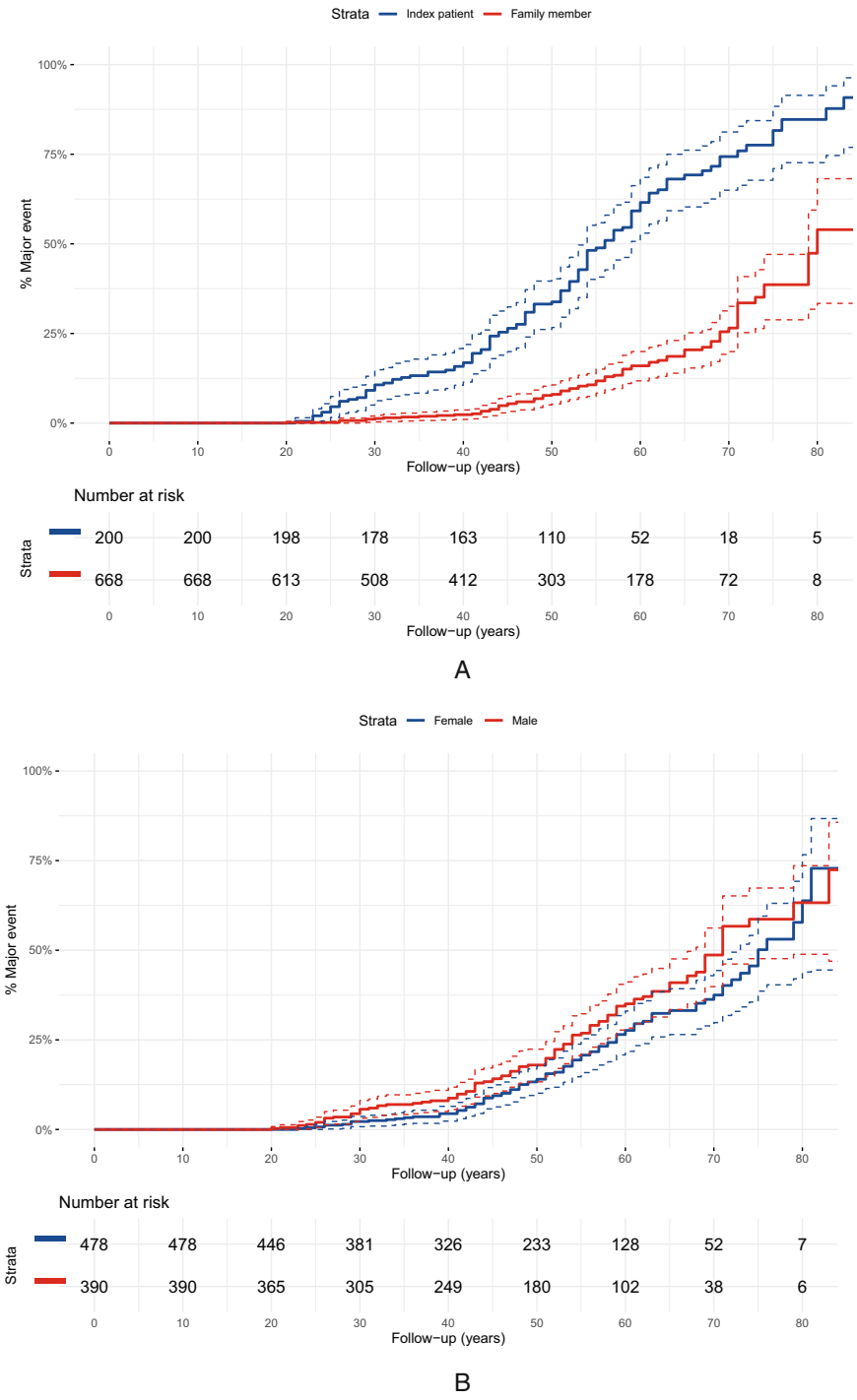



**Figure 4** (*A*) Kaplan–Meier plot showing penetrance of a major event stratified by index status with index carriers and family members and age as time scale. (*B*) Kaplan–Meier plot showing penetrance of a major event stratified by sex and age as time scale.

leading to heart failure events by approximately 10 years. However, there is also considerable overlap of phenotypes demonstrated in *Table 3*. This is partly explained by either entity possibly leading to the other, e.g. VA leading to heart failure. Furthermore, a strong correlation between LVEF and RVEF was found in a previous MRI study.[7] Further research is needed to elucidate why in some patients arrhythmic events occur and in other heart failure. Finally, this study might also provide insight in pathogenesis. The relatively steady annual increase of cardiac penetrance indicates that there is no 'plateau' phase of the disease. Furthermore, varying degrees of

**Table 4 Univariable and multivariable odds ratios for predictors of developing a risk factor, a heart failure event or a malignant ventricular arrhythmia event**

| Variable | Univariable | | Multivariable | |
|---|---|---|---|---|
| | Odds ratio (95% CI) | *p*-value | Odds ratio (95% CI) | *p*-value |
| **Predictors of developing a risk factor** | | | | |
| Age at first presentation (per 1-year increase) | 1.06 (1.05–1.07) | <0.001 | 1.06 (1.05–1.07) | <0.001 |
| Male sex | 0.89 (0.67–1.19) | 0.44 | 0.96 (0.70–1.33) | 0.82 |
| **Predictors of a heart failure event** | | | | |
| Age at first presentation (per 1-year increase) | 1.03 (1.01–1.04) | <0.001 | 1 (0.98–1.02) | 0.87 |
| Male sex | 0.83 (0.56–1.22) | 0.35 | 0.75 (0.46–1.23) | 0.26 |
| LVEF <45% | 46.6 (23.7–105.7) | <0.001 | 41 (19.7–99) | <0.001 |
| Abnormal repolarization criteria | 1.28 (0.86–1.90) | 0.22 | 0.48 (0.28–0.80) | 0.006 |
| Low-voltage ECG | 6.93 (4.50–10.96) | <0.001 | 2.74 (1.59–4.79) | <0.001 |
| >500 PVC/24 h | 1.64 (1.1–2.44) | 0.014 | 0.73 (0.44–1.21) | 0.22 |
| **Predictors of a malignant VA event** | | | | |
| Age at first presentation (per 1-year increase) | 1.01 (1.00–1.02) | 0.04 | 0.99 (0.97–1.00) | 0.04 |
| Male sex | 1.74 (1.22–2.48) | 0.002 | 1.96 (1.27–3.05) | 0.002 |
| LVEF <45% | 10.62 (7.04–16.40) | <0.001 | 6.55 (4.07–10.78) | <0.001 |
| Abnormal repolarization criteria | 3.78 (2.61–5.51) | <0.001 | 2.10 (1.35–3.29) | 0.001 |
| Low-voltage ECG | 6.09 (4.13–9.11) | <0.001 | 2.75 (1.71–4.46) | <0.001 |
| >500 PVC/24 h | 2.91 (2.02–4.20) | <0.001 | 1.64 (1.05–2.57) | 0.03 |

CI, confidence interval; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; PVC, premature ventricular contraction.

cardiomyocyte damage and/or fibrosis formation between carriers can explain the variable penetrance and might be a result of still unidentified additional modifying factors, including genetic and/or environmental factors. Identification of these disease modifiers is of high interest for future studies.

## Prior studies

Already in 2013 van der Zwaag *et al.*[17] showed that *PLN* p.(Arg14del) was a founder variant which originated over an estimated 575 years ago. Maintenance of the variant in the population, even though it can lead to severe cardiac events, already hinted at an age-related and incomplete penetrance, with limited or absent premature death before the reproductive age. Previous studies focusing on age-related penetrance in ARVC and *LMNA* cohorts have provided important data on disease progression and have influenced clinical practice guidelines.[1,9,15] Compared to these ARVC and *LMNA* cohorts, *PLN* p.(Arg14del) carriers show a lower prevalence of a severe cardiac phenotype.

## Limitations

Data were mainly collected retrospectively. Both index patients and relatives were included to reduce selection bias. However, we cannot rule out that in some families *PLN* presents more benign and therefore these families may remain completely undiscovered. Recent population studies corroborate this observation in for example desmosomal gene-related ARVC: individuals with ARVC-related- likely pathogenic/pathogenic variants only show signs to a lesser extent, if any.[18,19] Furthermore, we stratified additional analysis by index status as a sensitivity analysis to assess differences between index and family members. However, index patients are by definition more severely affected as they prompted genetic testing. Thus, population wise in this study might overestimate cardiac penetrance. Nevertheless, new carriers presenting in our clinics are likely to be discovered by the same method as this study, which makes the results of this study applicable to these new carriers. We presented two Kaplan–Meier analysis variants to describe age-related penetrance. Both methods are used in the literature to describe age-related penetrance in cardiogenetic disease with similar cohorts.[9,15]

# Conclusion

Penetrance of a major cardiac event is high in *PLN* p.(Arg14del) carriers and ranges between 43% and 70% at age 70. Penetrance of a cardiac risk factor is nearly complete at older age with a penetrance of 84% to 100% at age 70. Furthermore, cardiac phenotypes can emerge from adolescence to senior age. Life-long cardiac follow-up is needed, starting from adolescence.

# Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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