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Risk stratification in phospholamban p.(Arg14del) cardiomyopathy

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Heart Rhythm, 2026

CHAPTER 6

Impact of Extended Rhythm Monitoring on Arrhythmic Risk Estimates in Pospholamban Cardiomyopathy

Short report

Phospholamban (PLN) p.(Arg14del)-positive individuals are at increased risk of life-threatening ventricular arrhythmias (VA). In 2022, a risk calculator was introduced to identify individuals at high risk and guide decisions regarding implantable cardioverter-defibrillator (ICD) insertion.[1] A strong predictor in this model is the 24-hour premature ventricular contraction (PVC) count, expressed on a logarithmic scale. Although fluctuations in PVC burden have been described in a large US population,[2] their potential impact on the PLN p.(Arg14del) risk estimate remains unknown, particularly given the nonlinear transformation. We assessed variability in PVC counts using long-term continuous ambulatory rhythm monitoring in PLN p.(Arg14del)-positive individuals. We quantified intra-individual 24-hour PVC count variability and the corresponding variation in PLN p.(Arg14del) risk estimate.

This study was approved by the institutional ethics committee. Participants ≥18 years of age were prospectively enrolled at Amsterdam UMC, and Zio Patch devices (iRhythm Technologies) were applied between July and September 2025. The intended monitoring duration was 14 days. After completion of monitoring, devices were returned to iRhythm Technologies for ECG analysis and review.[3] The 24- and 48-hour PVC counts were derived from full-day recordings only. The corresponding five-year malignant VA risk estimates were compared with the 5% and 10% risk thresholds for recommending ICD insertion (Class IIb and IIa recommendations, respectively in the original publication). The 10% threshold (Class IIa recommendation) may better balance arrhythmic risk against the potential complications of ICD implantation and the overestimation of 'true' sudden-death risk from inclusion of surrogate end points.[4] Clinical data required for calculating the PLN p.(Arg14del) risk estimates (left ventricular ejection fraction [LVEF], presence of low-voltage ECG, and number of T-wave inversions in precordial and inferior leads) were obtained from electronic medical records at the time of the outpatient clinic visit. All statistical analyses were performed using RStudio (version 4.3.3, R Foundation for Statistical Computing).

Twenty-five PLN p.(Arg14del)-positive individuals were included, median age 37 years (interquartile range [IQR] 33-46), including 13 (52%) females and one (4%) proband. None of the participants had a history of myocardial infarction, sustained VAs or ICD implantation. The mean LVEF was 46% ±4.9. One participant had a history of non-sustained ventricular tachycardia (NSVT) and was receiving sotalol. The median full-day monitoring period was 12 days (IQR 8-13). The median intra-individual difference in 24-hour PVC count was 119 (IQR 8-193), and 1.1% for the PLN risk estimates (IQR 0.4-2.3). The mean absolute difference in PLN risk estimates between the full monitoring period and the first 48-hour and first 24-hour monitoring were 0.4% (range 0-1.8), and 0.4% (range 0-2.1), respectively. Figure 1 illustrates the intra-individual variability in daily PVC counts (A) and its effect on PLN risk estimates (B). Notably, ICD decision-guidance was unchanged when applying the 5% and 10% risk thresholds (regardless of monitoring duration), when based on mean risk estimates across all monitoring periods. However, in five of 25 participants (20%), individual daily risk estimates crossed

the 5% or 10% threshold on subsequent monitoring days. Individuals with a mean five-year risk estimate ≥10% exhibited a more advanced clinical phenotype than those with a risk estimate <10%, characterized by older age (median 64 [IQR 41–64] vs 37 [IQR 23–44] years), lower LVEF (48% [IQR 48–54] vs 58% [IQR 55–59]), and a higher prevalence of low-voltage ECG (60% vs 15%) and late gadolinium enhancement on cardiac magnetic resonance imaging (75% vs 22%). In the overall cohort, six patients (24%) exhibited non-sustained ventricular tachycardia, with a median time to first detection 5.5 days (IQR 3-10).

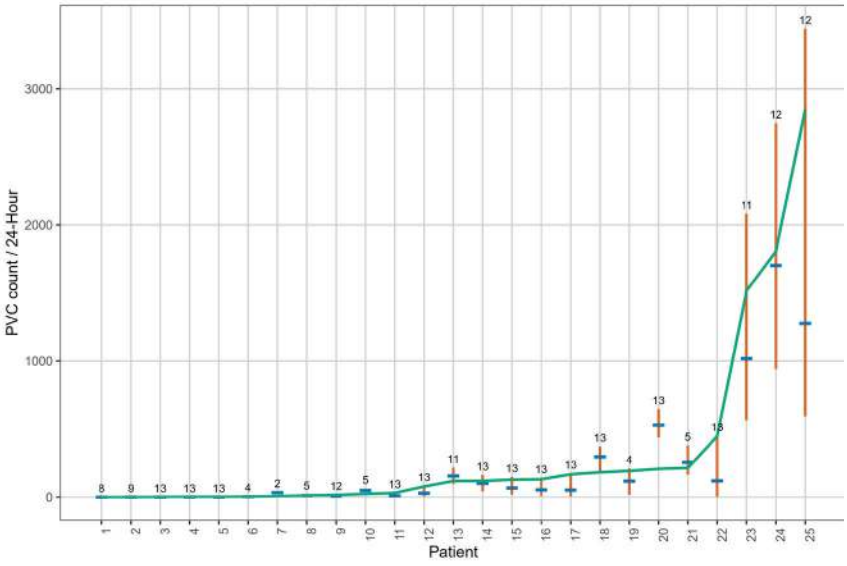
This study assessed the impact of day-to-day variability in 24-hour PVC counts on PLN p.(Arg14del) risk estimates. Although intra-individual PVC variability was substantial, the corresponding change in calculated risk was minimal. Mean risk estimates were essentially identical when calculated using the first 24-hour and 48-hour monitoring periods as compared with full monitoring. The limited effect of PVC fluctuations likely results from the logarithmic transformation of PVC burden in the risk model. Variability was greatest in individuals with higher PVC counts, but in these patients the logarithmic scale limited changes in estimated risk.

Our results align with studies in arrhythmogenic right ventricular cardiomyopathy (ARVC), showing significant day-to-day variability.[5] Although the impact on the ARVC risk model thresholds was not previously evaluated, similar findings would be expected given the same logarithmic PVC predictor. Whether incorporating long-term monitoring, including fluctuations, can further improve the accuracy of the PLN risk model requires a sufficiently powered prospective study to recalibrate the model. In clinical practice, extended monitoring may be considered in selected individuals with borderline estimates - particularly those with additional clinical risk markers - in whom small changes (1-2%), or very low 24-hour PVC counts (due to logarithmic scaling), could influence ICD decision-making.

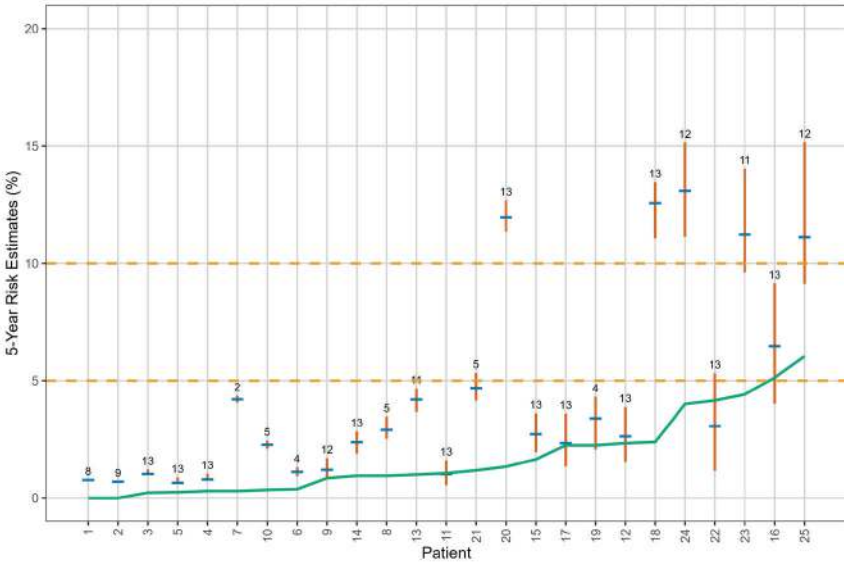
In conclusion, 24-hour PVC counts fluctuate considerably during long-term monitoring, but their effect on PLN p.(Arg14del) risk estimates is limited and does not significantly influence ICD implantation guidance.

Figure 1. Day-to-day variability in 24-hour PVC counts and the corresponding impact on PLN p.(Arg14del) risk estimates.
The x-axis shows individual patients; the y-axis shows 24-hour PVC counts (A) or five-year PLN p.(Arg14del) risk estimates (B). The red bars represent the range of measurements per patient, blue stripes the mean value, and the upper numbers above the bars the number of full monitoring days. The green line represents the absolute intra-individual variability and the orange dashed lines the 5% and 10% thresholds. In panel A, patients are ordered by variability in 24-hour PVC counts; in panel B, by variability in PLN risk estimates.

A.



B.



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