

Ring-like pattern, genetica e rischio aritmico

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SEDE DEI LAVORI

A. Roma Lifestyle Hotel
Via Giorgio Zoega 59, Roma



PROGRAMMA

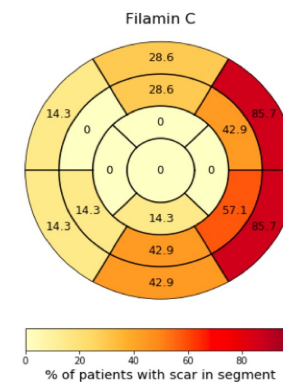
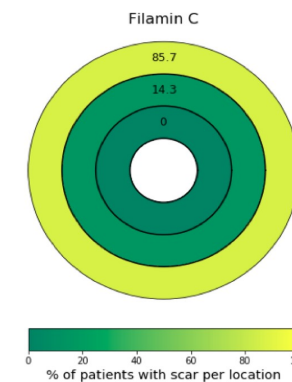
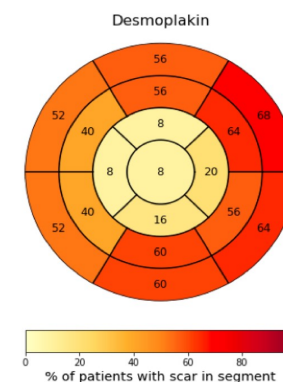
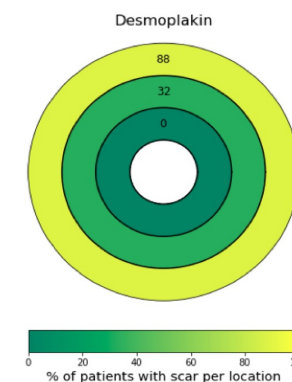
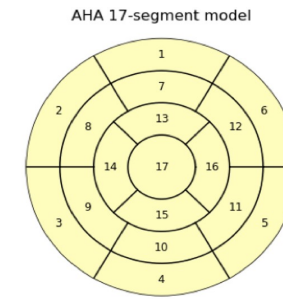
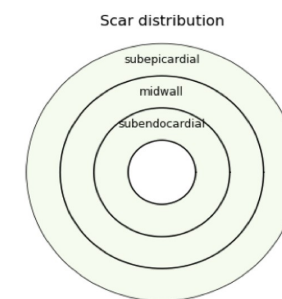
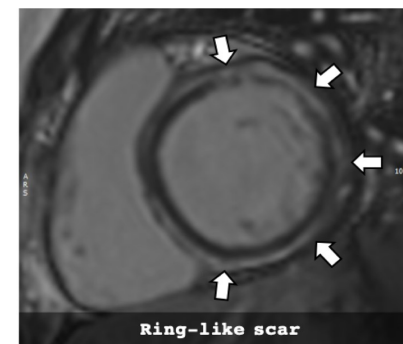
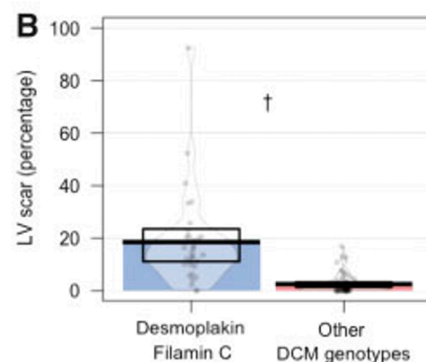
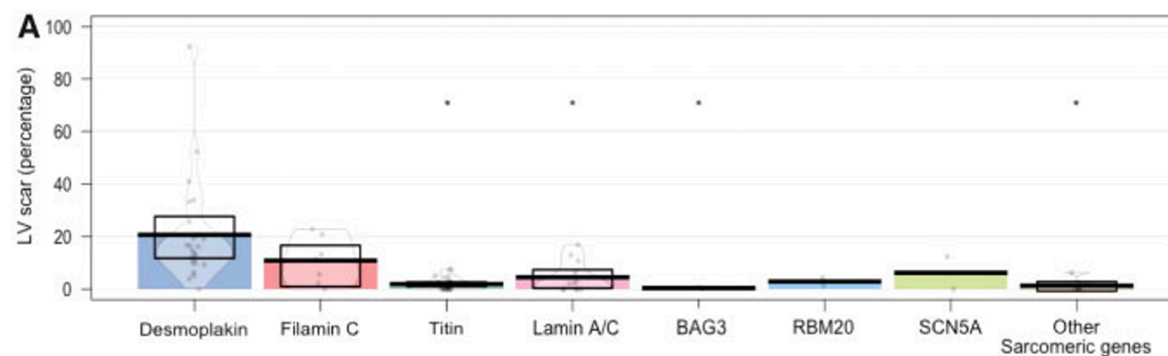
The ring-like scar

Dilated cardiomyopathy and arrhythmogenic left ventricular cardiomyopathy: a comprehensive genotype-imaging phenotype study

João B. Augusto^{1,2}, Rocio Eiros³, Eleni Nakou¹, Sara Moura-Ferreira⁴, Thomas A. Treibel^{1,2}, Gabriella Captur^{1,2,5}, Mohammed M. Akhtar^{1,2}, Alexandros Protonotarios¹, Thomas D. Gossios¹, Konstantinos Savvatis^{1,2}, Petros Syrris², Saidi Mohiddin^{1,6}, James C. Moon^{1,2,5}, Perry M. Elliott^{1,2}, and Luis R. Lopes^{1,2*}

Ring-like LV scar definition

Subepicardial and/or midmyocardial LV LGE involving at least 3 contiguous segments in the same short-axis slice.



The ring-like scar

Risk Stratification of Patients With Apparently Idiopathic Premature Ventricular Contractions

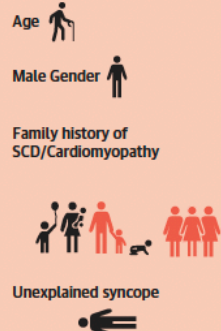
A Multicenter International CMR Registry

Daniele Muser, MD,^{a,b,c} Pasquale Santangeli, MD, PhD,^{a,c} Simon A. Castro, MD,^a Ruben Casado Arroyo, MD, PhD,^c Shingo Maeda, MD,^a Daniel A. Benhayon, MD,^c Ioan Liuba, MD,^d Jackson J. Liang, DO,^a Mouhannad M. Sadek, MD,^c Anwar Chahal, MD,^a Silvia Magnani, MD,^b Maurizio Pieroni, MD,^d Elena Santarossa, MD,^b

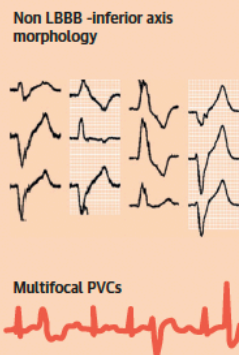
Apparently Idiopathic PVCs Risk Stratification

518 subjects, frequent PVCs (> 1,000/24h)
Normal ECG and normal Echo

Clinical Characteristics



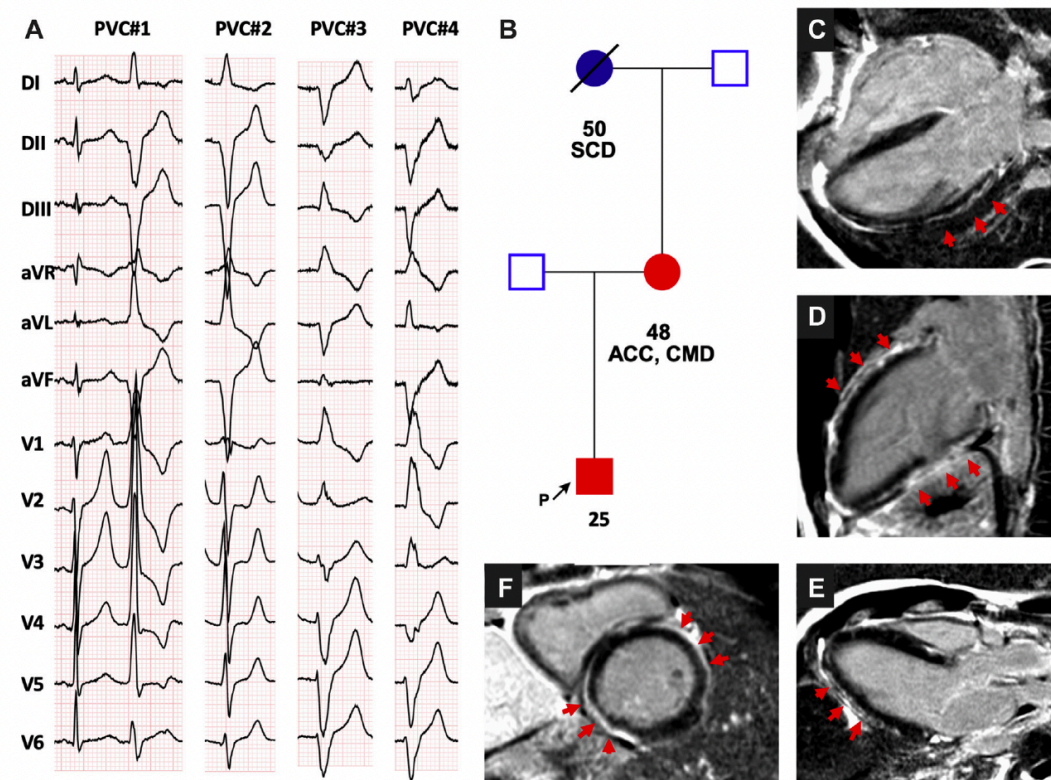
PVC Morphology



16% CMR Abnormalities



FIGURE 7 A 25-Year-Old Man Presenting With Frequent Multifocal PVCs



(A) A 25-year-old man presenting with frequent multifocal PVCs. (B) His grandmother died of SCD at the age 50 years, whereas his mother experience resuscitated cardiac arrest at the age 48 years and was subsequently diagnosed with mildly dilated left ventricular cardiomyopathy. (C to F) CMR of the proband showed subepicardial late gadolinium enhancement involving the left ventricular wall with a ring-like pattern (arrows). He died during follow-up of SCD during physical activity. Abbreviations as in Figures 2 and 5.

The ring-like scar

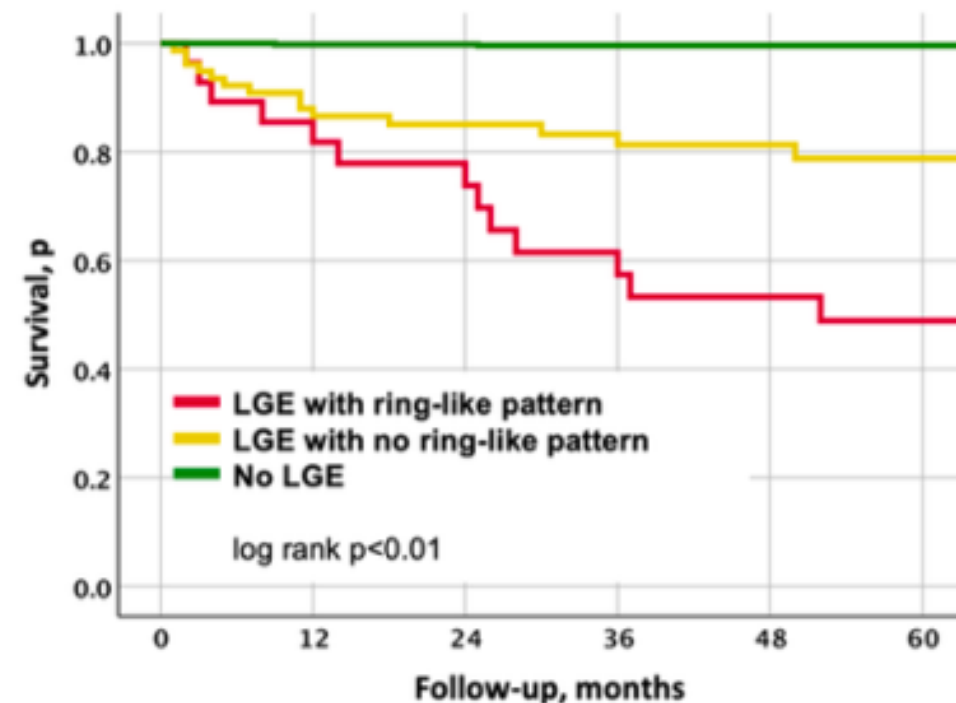
Circulation

ORIGINAL RESEARCH ARTICLE

Prognostic Value of Nonischemic Ringlike Left Ventricular Scar in Patients With Apparently Idiopathic Nonsustained Ventricular Arrhythmias

686 patients with apparently idiopathic non-sustained VA submitted to contrast-enhanced CMR.

Survival free from the composite endpoint according to presence and phenotype of LGE



Number at risk

—	28	22	18	14	12	10
—	78	61	54	42	32	28
—	580	542	506	430	368	307

The ring-like scar

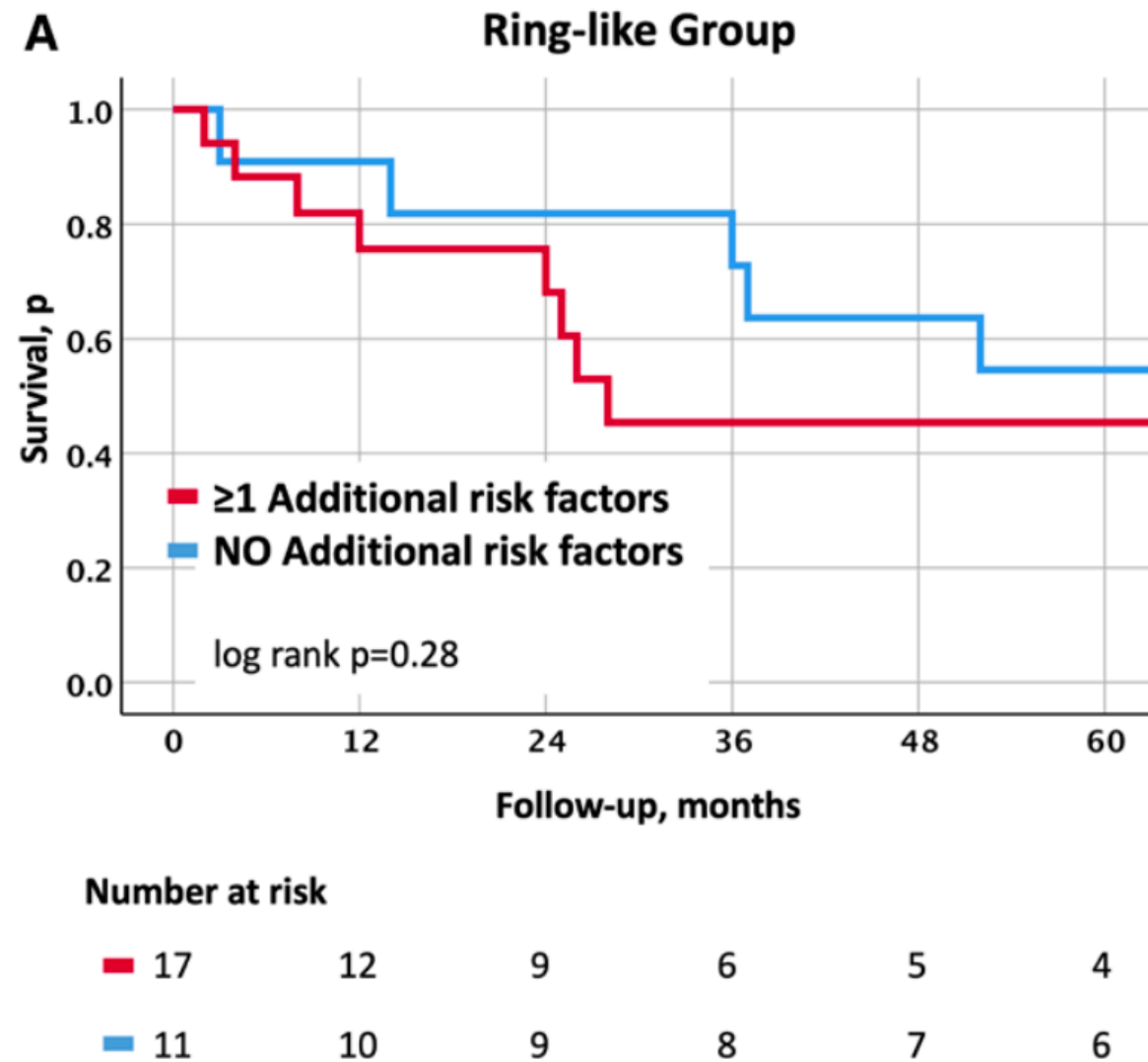
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ORIGINAL RESEARCH ARTICLE

Prognostic Value of Nonischemic Ringlike Left Ventricular Scar in Patients With Apparently Idiopathic Nonsustained Ventricular Arrhythmias

686 patients with apparently idiopathic non-sustained VA submitted to contrast-enhanced CMR.

Muser D. *et al*, Circulation 2021



Additional risk factors: family history SCD/cardiomyopathy, history of syncope, multifocal PVC, and sustained VT induction at programmed stimulation

RL scar in Left-dominant arrhythmogenic cardiomyopathy

Integrated role of cardiac magnetic resonance and genetics in predicting left ventricular reverse remodelling in dilated and non-dilated cardiomyopathy

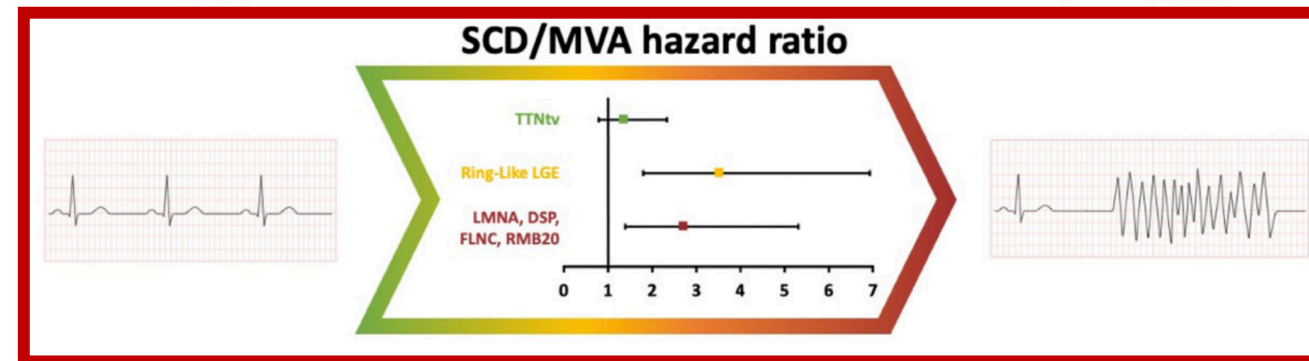
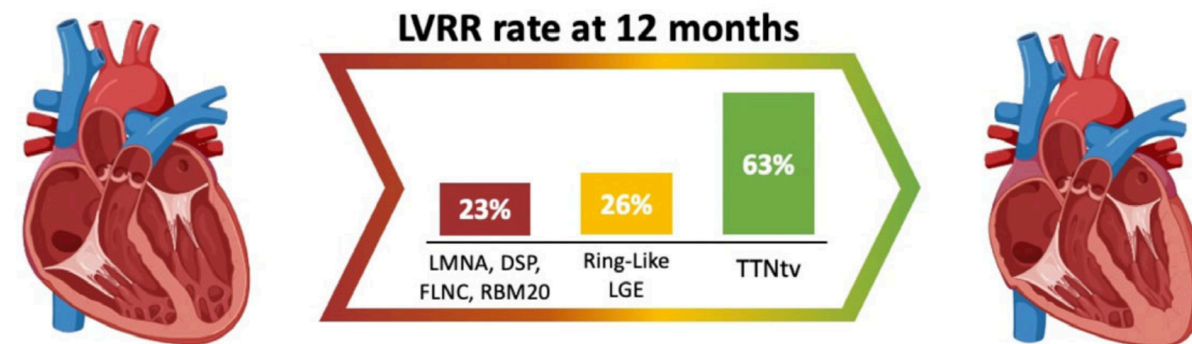
Martina Setti^{1,2,3†}, Manuela Iseppi^{1,2,4†}, Job A.J. Verdonchot^{2,5,6}, Jacopo G. Rizzi^{1,2}, Alessia Paldino^{1,2}, Carola Pio Loco Detto Gava^{1,2}, Giulia Barbatì⁷, Matteo Dal Ferro^{1,2}, Max F.G.H.M. Venner^{2,5}, Anne G. Raafs^{2,5,8}, Marta Gigli^{1,2}, Davide Stolfo^{1,2,9,10}, Antonio De Luca^{1,2}, Giulia De Angelis^{1,2,10}, Teresa M. Capovilla^{1,2}, Sharon Graw¹¹, Flavio L. Ribichini³, Matthew Taylor¹¹, Luisa Mestroni¹¹, Stephane R.B. Heymans^{2,5,12}, Gianfranco Sinagra^{1,2‡}, and Marco Merlo^{1,2*‡}

Ring-like LGE

- Lower probability of LV reverse remodeling
- Higher arrhythmic risk
- Associated with MVA/SCD irrespective of DCM/NDLVC phenotype

Arrhythmic risk factors:

Ring-like LGE **HR 3.52** (High-risk genotype HR 2.71)



RL scar in Left-dominant arrhythmogenic cardiomyopathy

Clinical Characteristics and Outcomes of Patients With Biventricular and Left-Dominant Arrhythmogenic Cardiomyopathy With Ring-like Late Gadolinium Enhancement Pattern

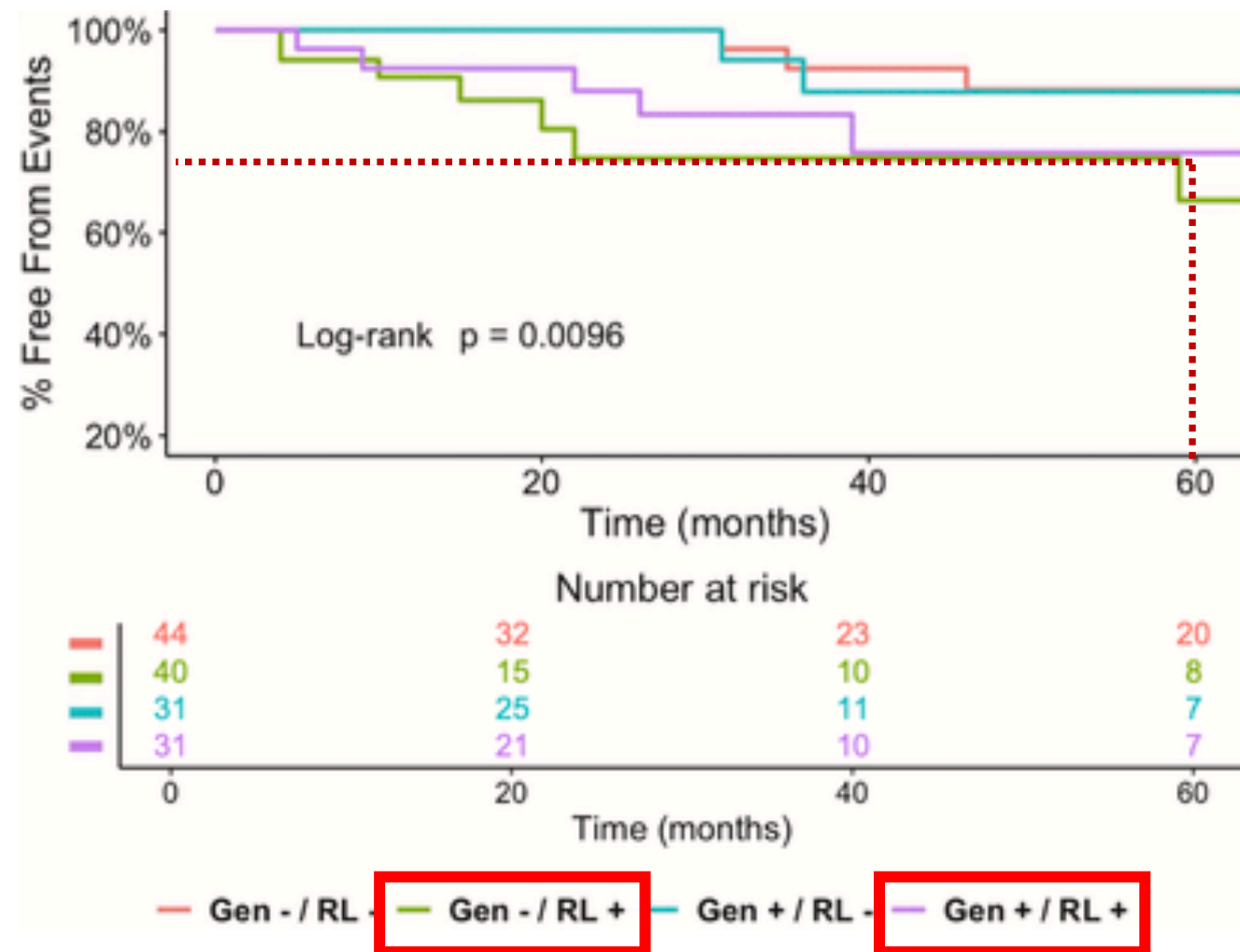
Nicolò Martini, MD,^{a,b} Raimondo Pittorru, MD,^{a,b} Rudi Celeghin, MD, PhD,^c Giovanni Civieri, MD,^{a,b} Maria Bueno Marinas, MD, PhD,^c Monica De Gaspari, MD,^{a,c} Annagrazia Cecere, MD,^{a,d} Ilaria Rigato, MD, PhD,^d Giorgio De Conti, MD,^e Simone Corradin, MD,^e Giulia Lorenzoni, PhD,^a Manuel De Lazzari, MD, PhD,^d Barbara Bauce, MD PhD,^{a,d} Alessandro Zorzi, MD, PhD,^{a,d} Dario Gregori, MD, PhD,^a Cristina Basso, MD, PhD,^{a,c} Domenico Corrado, MD, PhD,^{a,d} Federico Migliore, MD, PhD,^{a,d} Kalliopi Pilichou, MD, PhD,^{a,c} Alberto Cipriani, MD,^{a,d,*} Martina Perazzolo Marra, MD, PhD^{a,d,*}

TABLE 2 Variables Associated With the Primary Endpoint During Follow-Up in the Overall Patient Cohort

	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age	1.03 (1.01-1.05)	0.035		
Male sex	1.85 (0.69-4.97)	0.22		
MVA at diagnosis	8.18 (3.67-18.27)	<0.001		
Positive genetic testing	0.73 (0.31-1.72)	0.47		
PVB >500/24 h	2.19 (0.45-10.64)	0.33		
NSVT	3.48 (1.48-8.13)	0.004	2.62 (1.17-6.41)	0.033
LV EF <50%	0.83 (0.36-1.94)	0.67		
LV EDV >100 mL/m ²	1.59 (0.74-3.59)	0.27		
RV EF <50%	0.78 (0.32-1.86)	0.57		
RL-LGE	3.36 (1.43-7.88)	0.007	2.47 (1.10-6.02)	0.042

The variable PVB >500/24 h was available for 108 (74.0%) patients. All other variables were available in all patients.

Abbreviations as in Table 1.

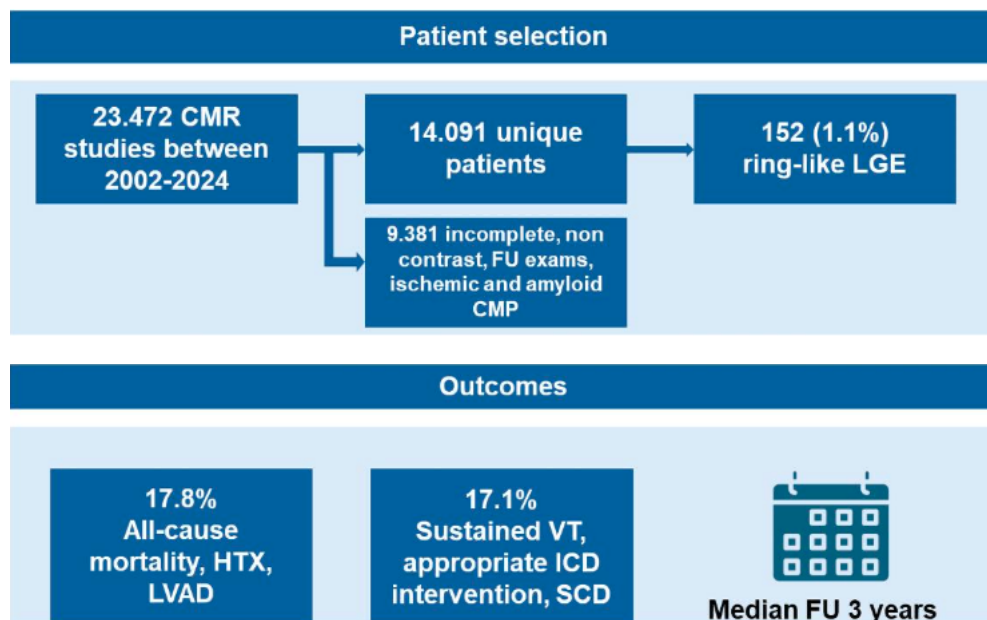


Studies focusing on RL scar patients

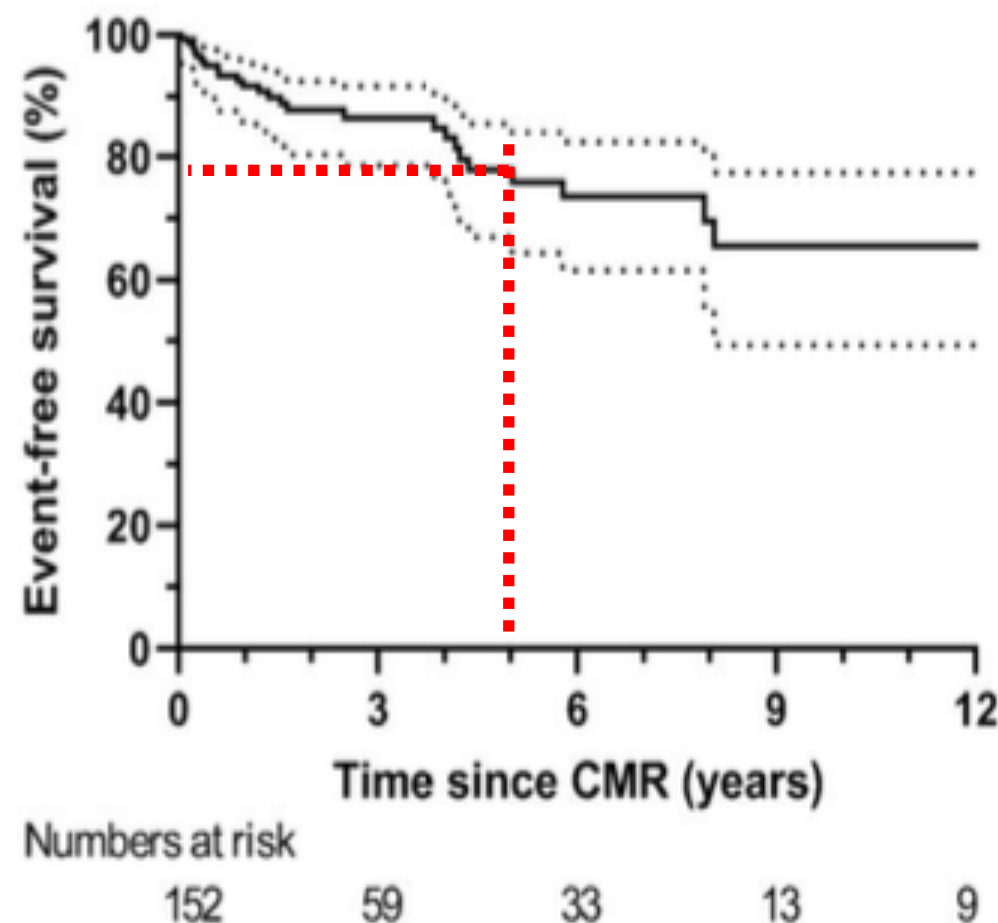
Ring-like scar genetic background and arrhythmic outcome

Cardiac diagnoses and long-term outcomes in ring-like late gadolinium enhancement evaluated by cardiac magnetic resonance

Domenico Filomena ^{1†}, Bert Vandenbergk^{2,3†}, Tom Dresselaers ^{4,5}, Rik Willems ^{2,3}, Pier Giorgio Masci⁶, Tomas Robyns ^{2,3‡}, and Jan Bogaert ^{4,5*‡}



Sustained VT, appropriate ICD interventions, or SCD



Ring-like scar genetic background and arrhythmic outcome

- Genetic testing identified likely pathogenic/pathogenic variants in 59 (58.4%) patients, affecting both desmosomal and non-desmosomal genes.
- Inflammatory CMP was diagnosed in 15.8%.
- Other rare aetiologies included genetic neuromuscular diseases and inborn errors of metabolism.
- Primary and secondary endpoints occurred in 17.8 and 17.1%, respectively, over a median follow-up of 3 years.

Ring-like scar genetic background and arrhythmic outcome

Table 3 Continued

	No SVT/shock/SCD <i>n</i> = 126	SVT/shock/SCD <i>n</i> = 26	<i>P</i> -value
.....			
TWI lateral, <i>n</i> (%)	55 (46.6)	16 (64.0)	0.114
Genetics			
Genetic available, <i>n</i> (%)	83 (65.9)	18 (69.2)	0.741
Any LP/P variant, <i>n</i> (%)	49 (59.0)	10 (55.6)	0.786
Desmosomal, <i>n</i> (%)	10 (12.0)	2 (11.1)	0.568
Non-desmosomal, <i>n</i> (%)	28 (33.7)	8 (44.4)	
Inborn error of metabolism, <i>n</i> (%)	4 (4.8)	0 (0.0)	
Neuromuscular, <i>n</i> (%)	7 (8.4)	0 (0.0)	
High-risk variant, <i>n</i> (%)	29 (46.0)	8 (50.0)	0.776

Ring-like scar genetic background and arrhythmic outcome

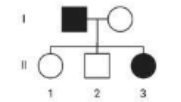
Arrhythmic risk stratification in patients with left ventricular ring-like scar

Vanda Parisi ^{1,2,3†}, Maddalena Graziosi ^{1,3†}, Luis R. Lopes ^{4,5}, Antonio De Luca ⁶, Ferdinando Pasquale ^{1,3}, Giacomo Tini ⁷, Mattia Targetti ⁸, Maria R. Cueto ^{4,9}, Ana R. Moura ^{4,10}, Raffaello Ditaranto ^{1,2,3}, Camilla Torlasco ¹¹, Nevio Taglieri ^{1,3}, Elena Nardi ², Luigi Lovato ¹², João B. Augusto ^{5,13,14}, Nazzareno Galiè ^{1,2,3}, Lia Crotti ^{3,11,15}, Alessio Gasperetti ¹⁶, Mauro Biffi ^{1,3}, Camillo Autore ⁷, Marco Merlo ⁶, Iacopo Olivetto ¹⁷, Gianfranco Sinagra ⁶, Perry M. Elliott ^{4,5‡}, and Elena Biagini ^{1,3*‡}

Multicentre cohort of 115 patients with LV ring-like scar *and* one among:



P/LP genetic variant
(73%)



Family history
of cardiomyopathy
(18%)



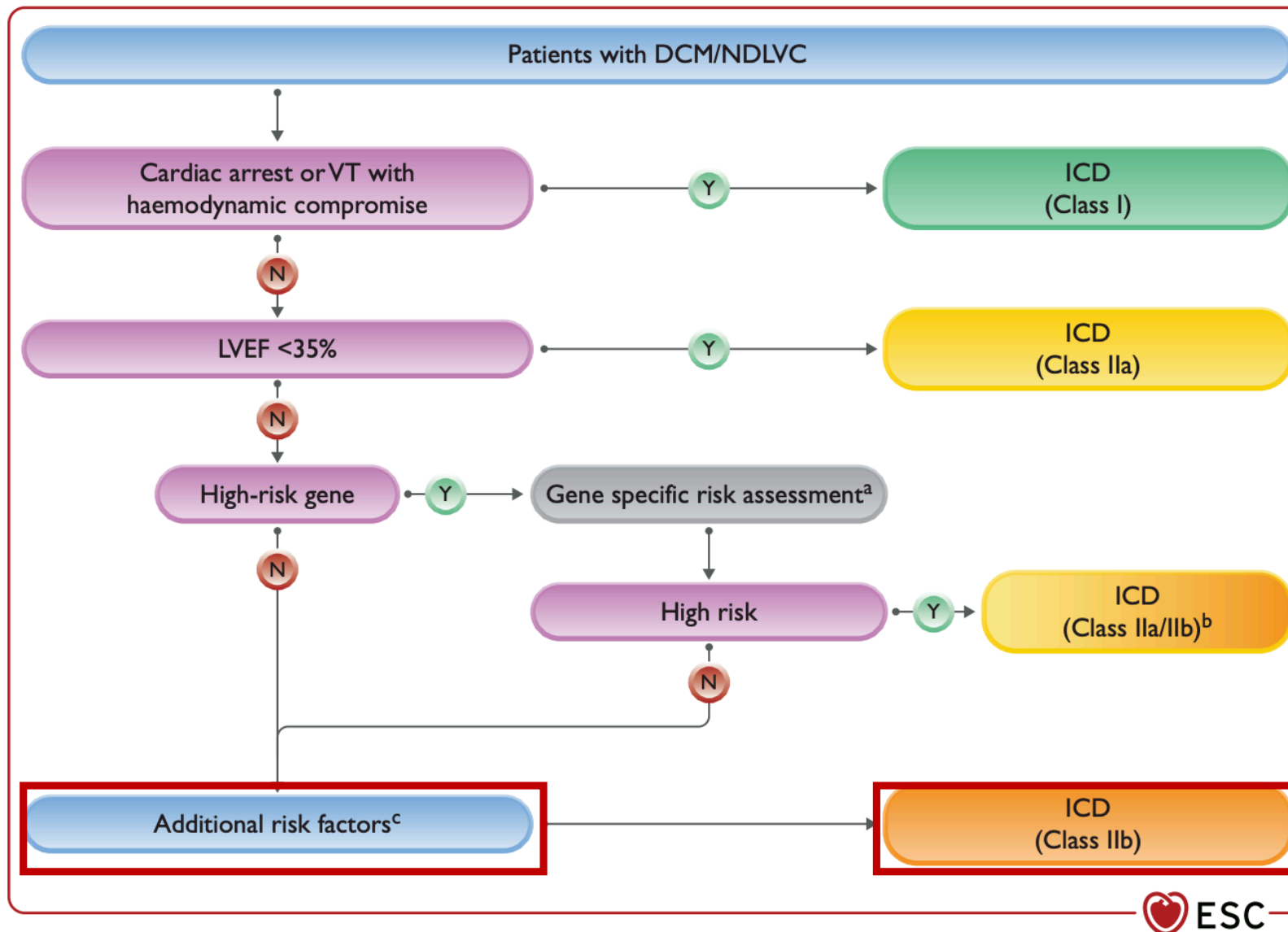
ACM diagnosis according to
2024 European Task Force ⁷
(9%)



19% LAEs (SCD, aborted SCD, SVT) after a median follow up of 4.6 years (3.8 events/100 patients/year)

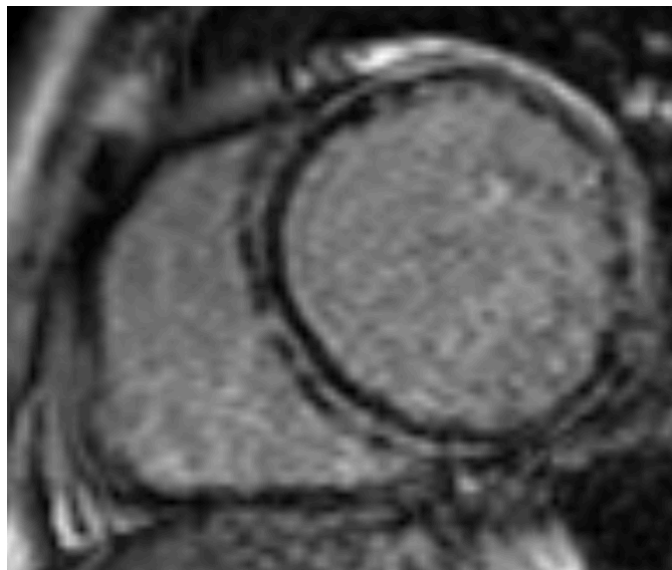
Table 2 Continued

	Univariate analysis HR (95% CI)	P-value
LGE total number of segments	0.946 (0.834–1.072)	0.388
P/LP genetic variant		
DSP P/LP variant ^a	0.286 (0.095–0.854)	0.025
FLNC P/LP variant	0.630 (0.193–2.051)	0.443
Other gene P/LP variant	1.703 (0.512–5.658)	0.385



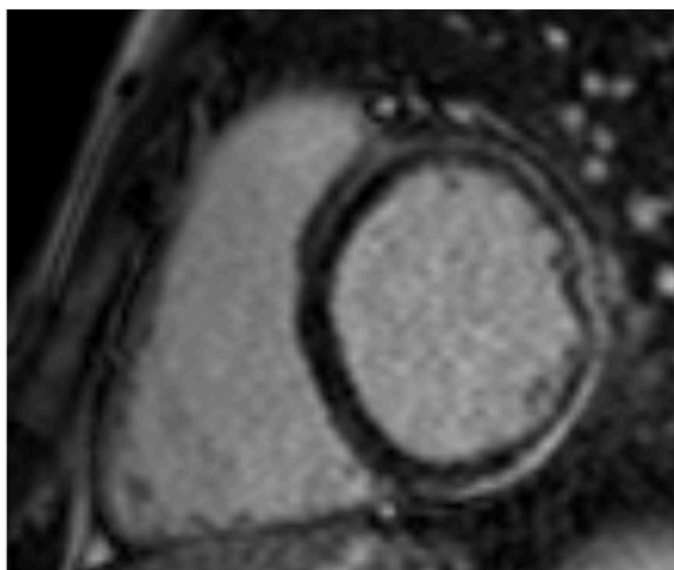
^c Additional risk factors include syncope, LGE presence on CMR.

Clinical management of patients with RL scar



Ring-like AND «high risk genes»

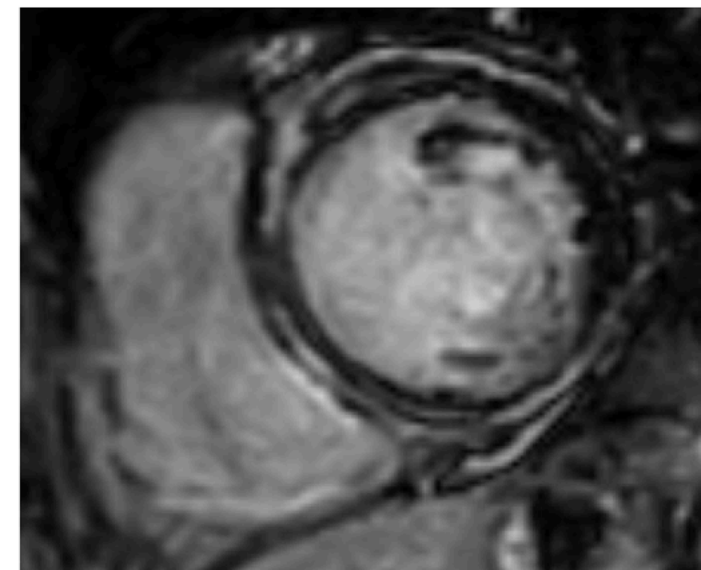
Ila



Non high-risk genes

IIb

?

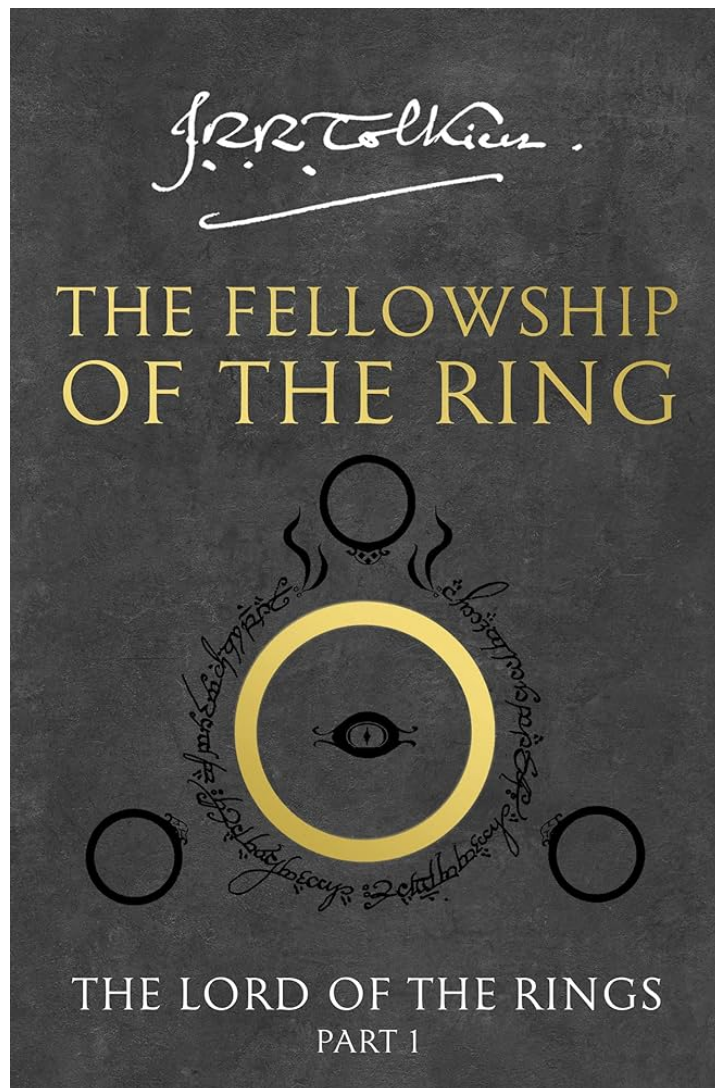


Ring-like geno -

IIb

??

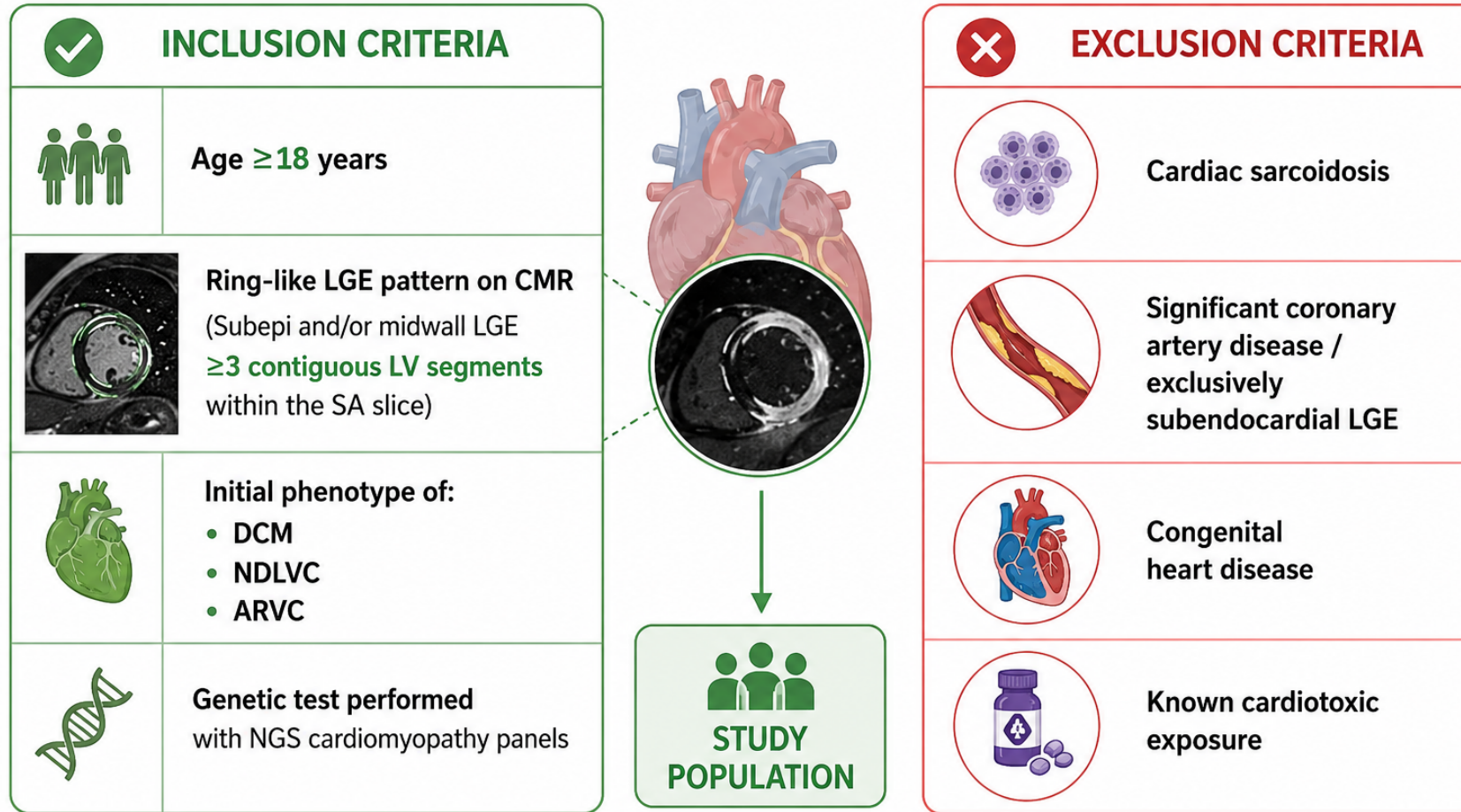
The Fellowship of the Ring



Long-term outcome and Arrhythmic Risk Stratification in Genotyped Patients with Left Ventricular Ring-Like Scar (Data from The Fellowship of the Ring Network)

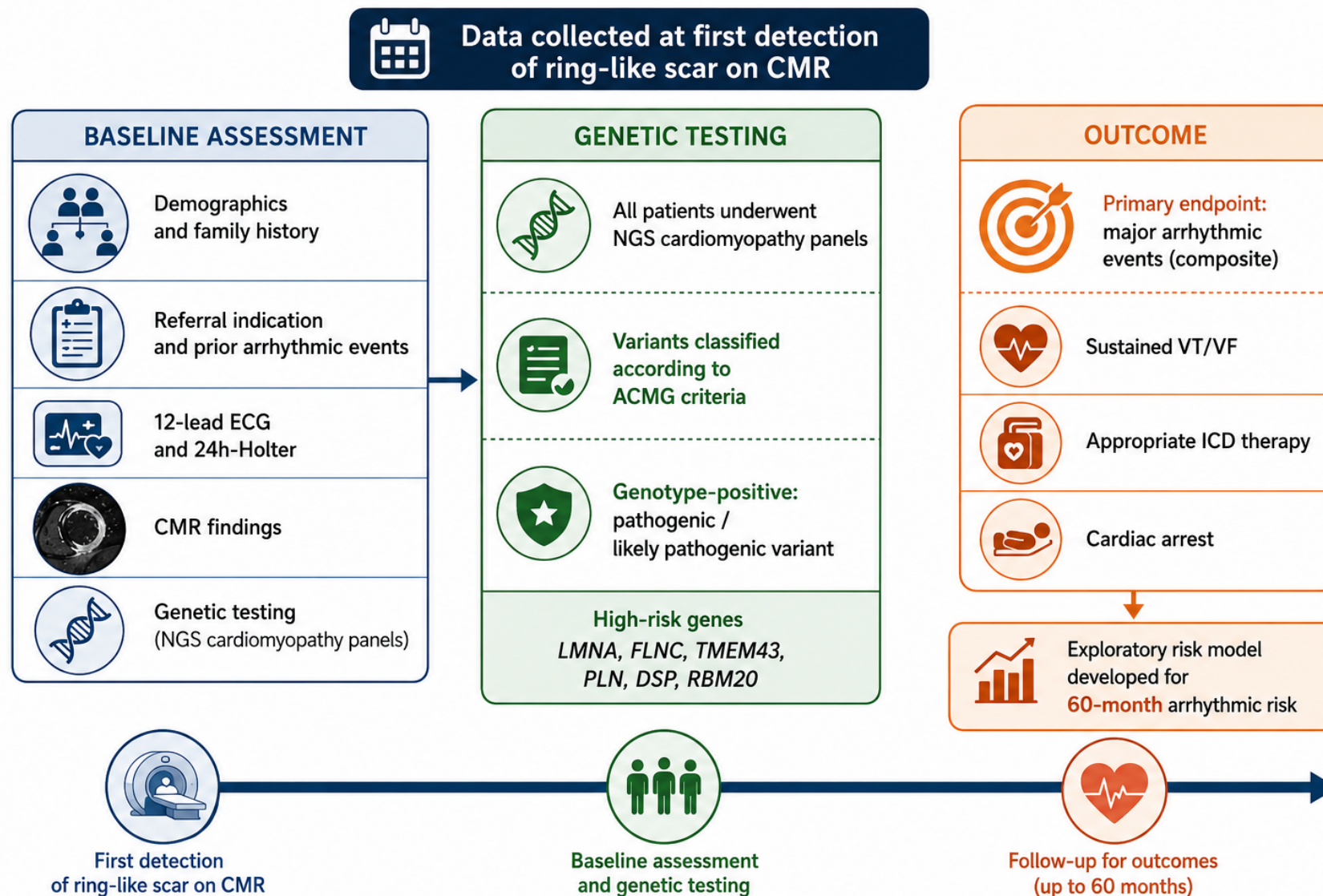
- Multicenter retrospective observational
- **16 European** tertiary referral centers for cardiomyopathies, advanced cardiac imaging, and/or cardiac electrophysiology (11 centers in Italy, 3 in Spain, 1 in the United Kingdom, 1 in Norway)
- **Aims:** to investigate the *clinical profile* and the *arrhythmic outcome* the prognostic implications of an RL pattern identified by CMR

Study Population



Patients must meet **ALL** inclusion criteria and **NONE** of the exclusion criteria to be eligible for the study.

Baseline assessment and outcomes



Genetic features

523 RL genotyped patients

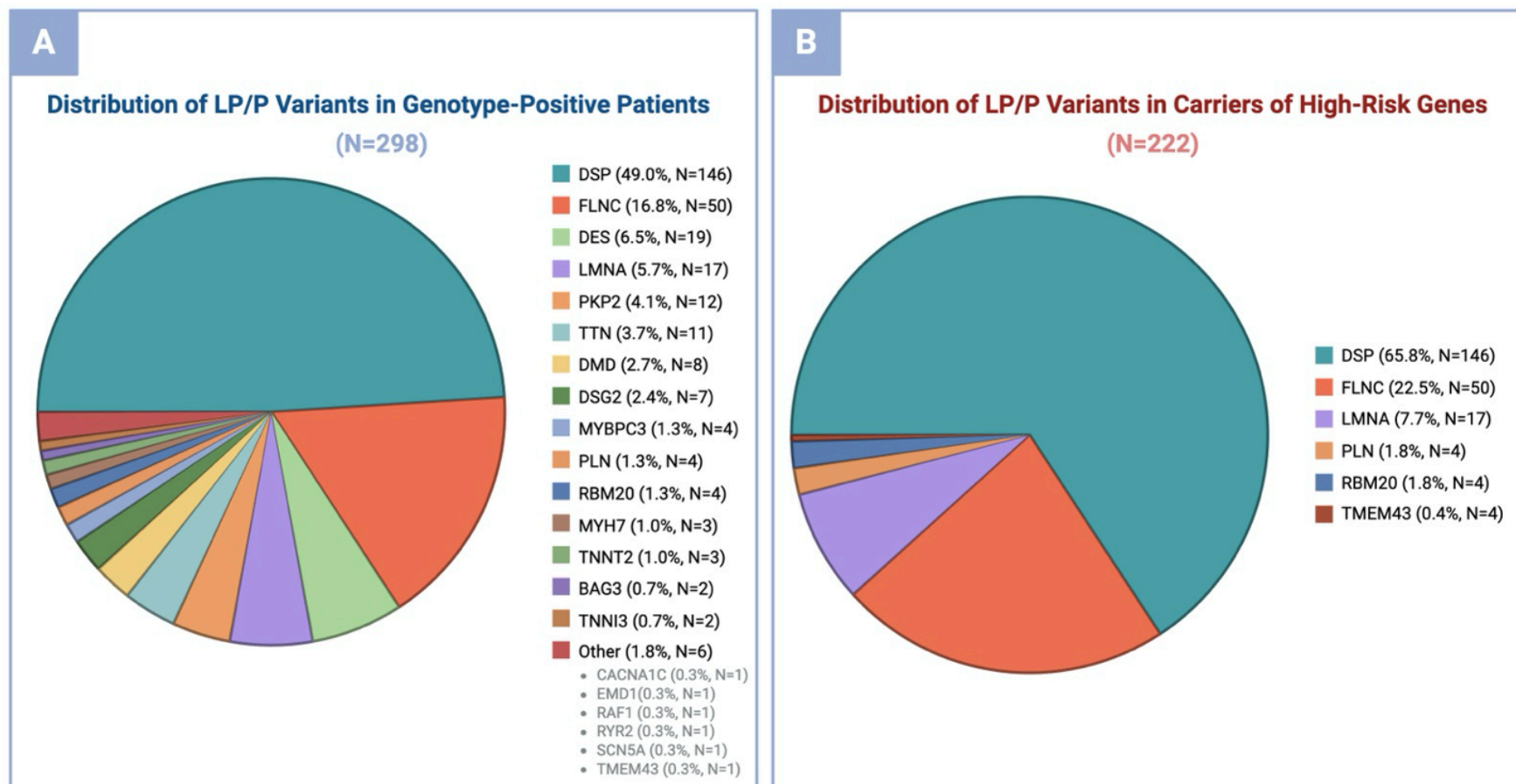
225 (43%)

RL geno-

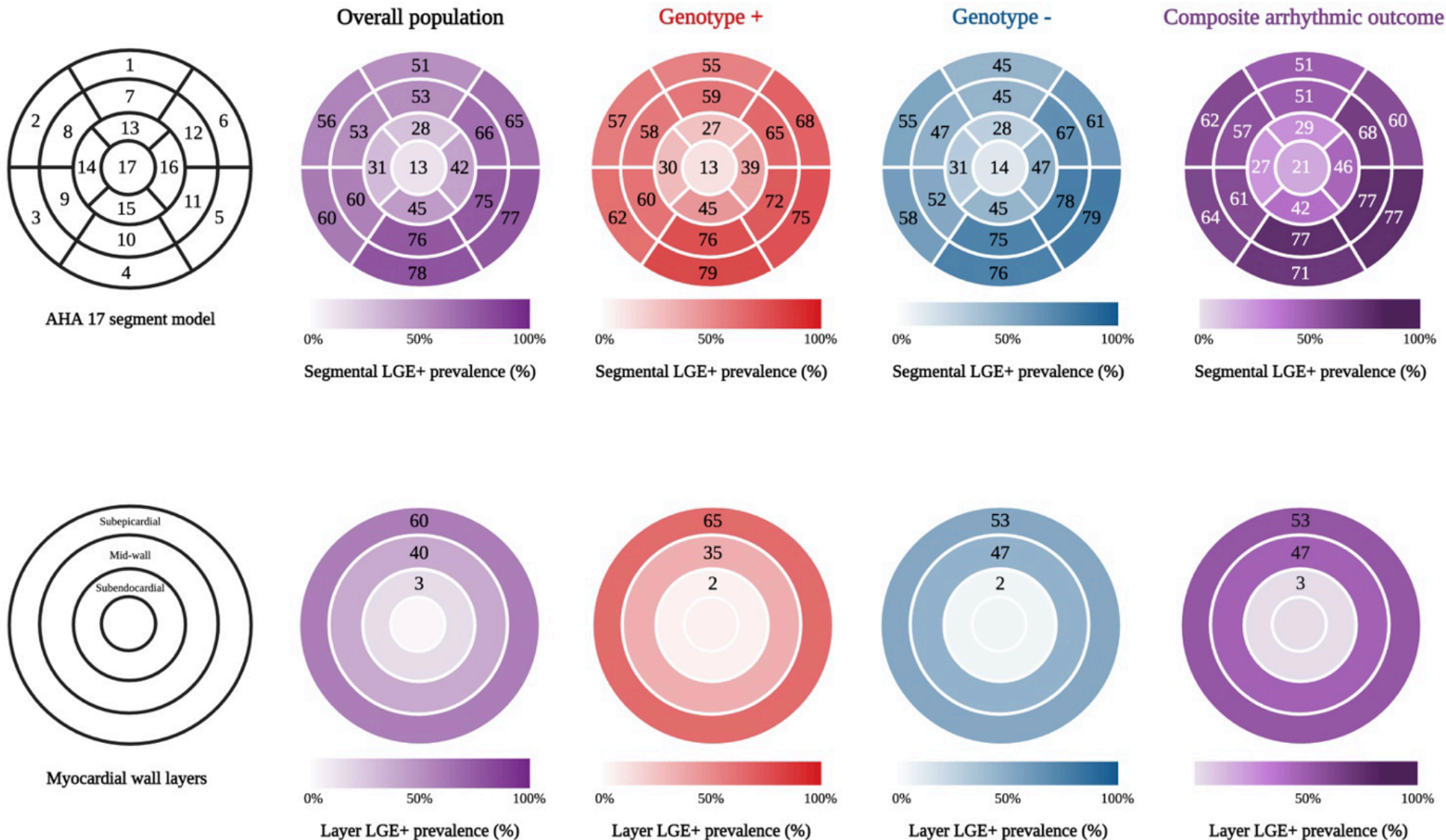
298

(57%)

RL geno+



LGE distribution according to genotype and outcome

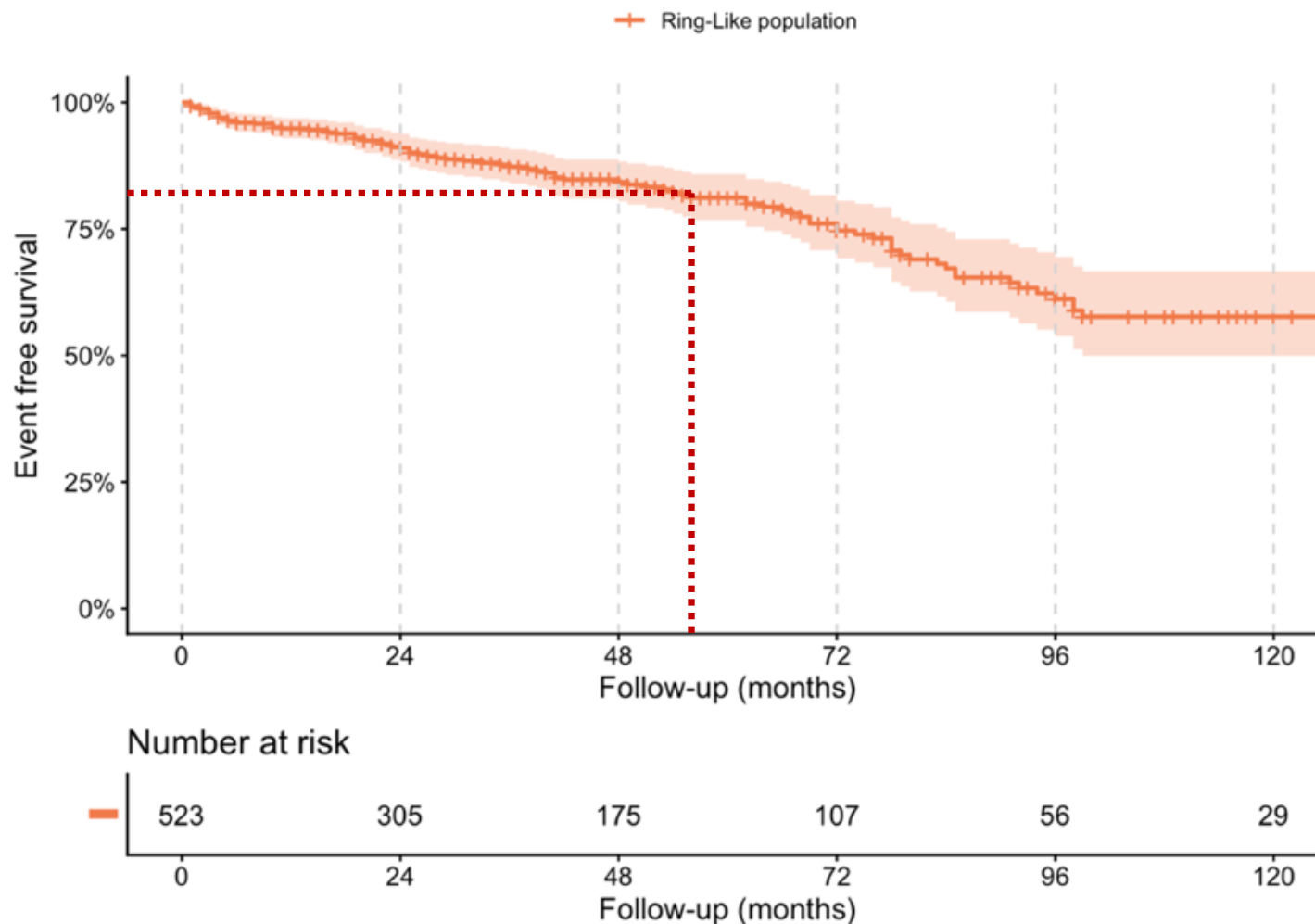


Arrhythmic outcome

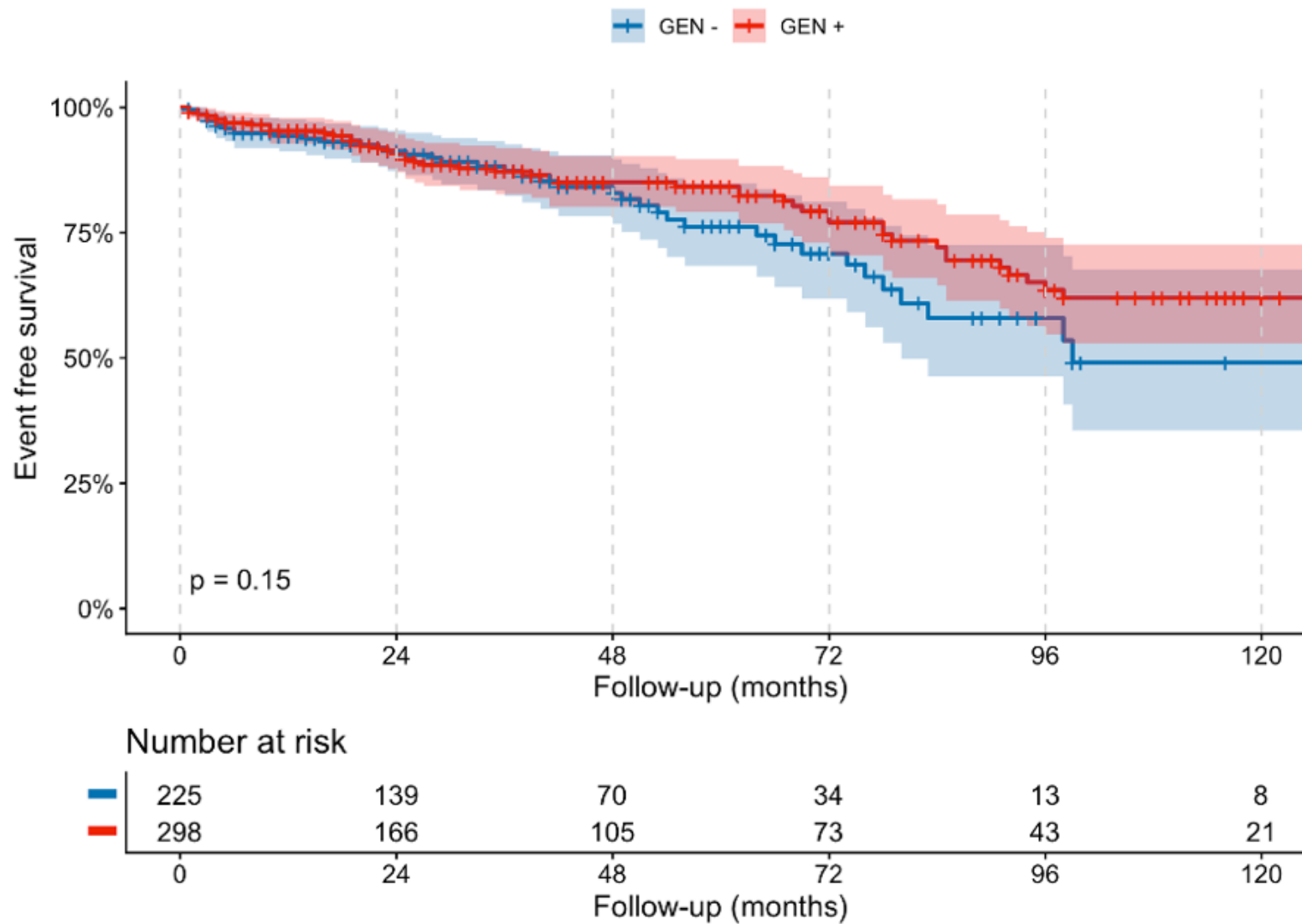
96/523 patients (18.4%)
experienced MAEs

5.2 events per 100 patient-years

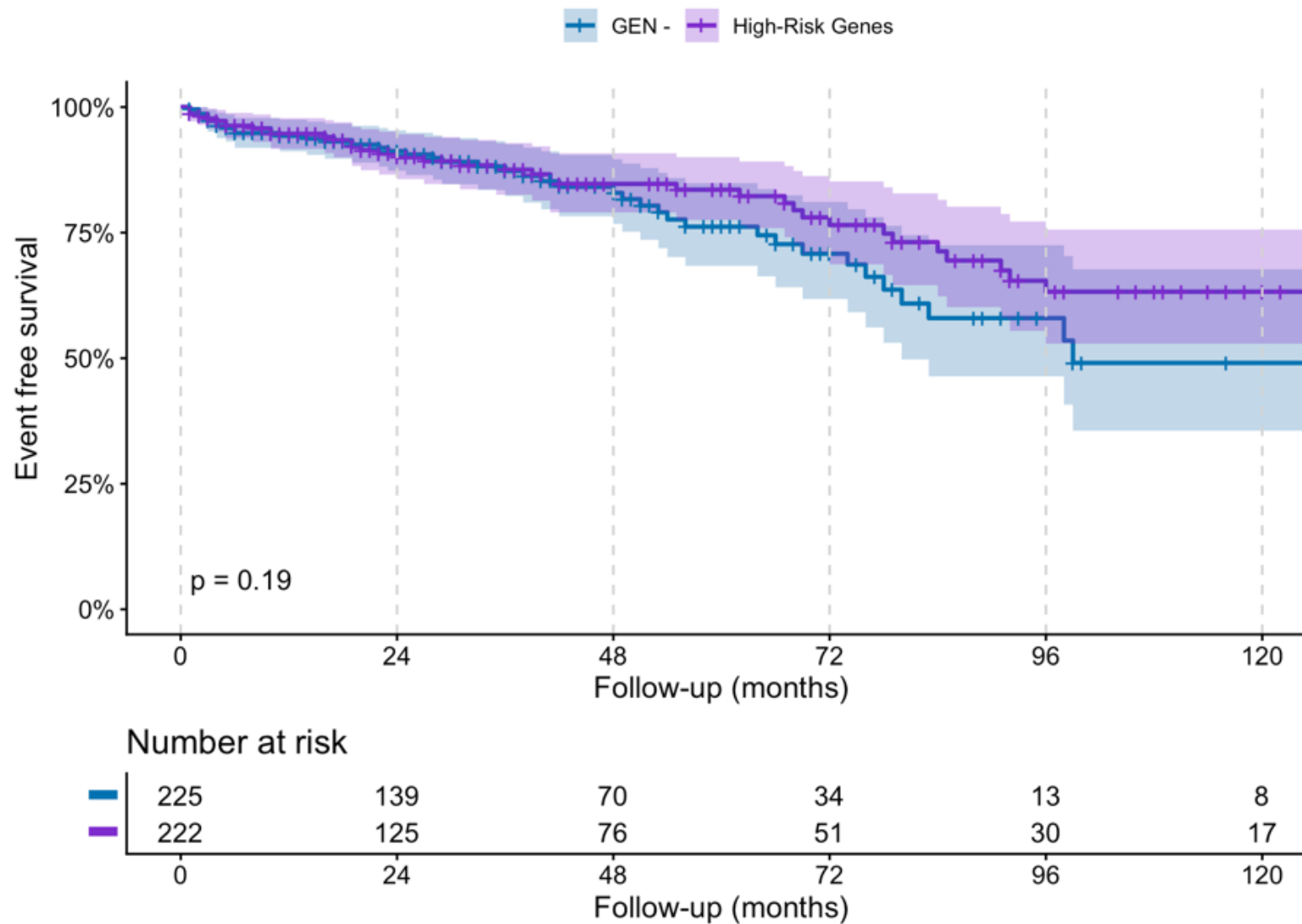
Median FU: 36 months



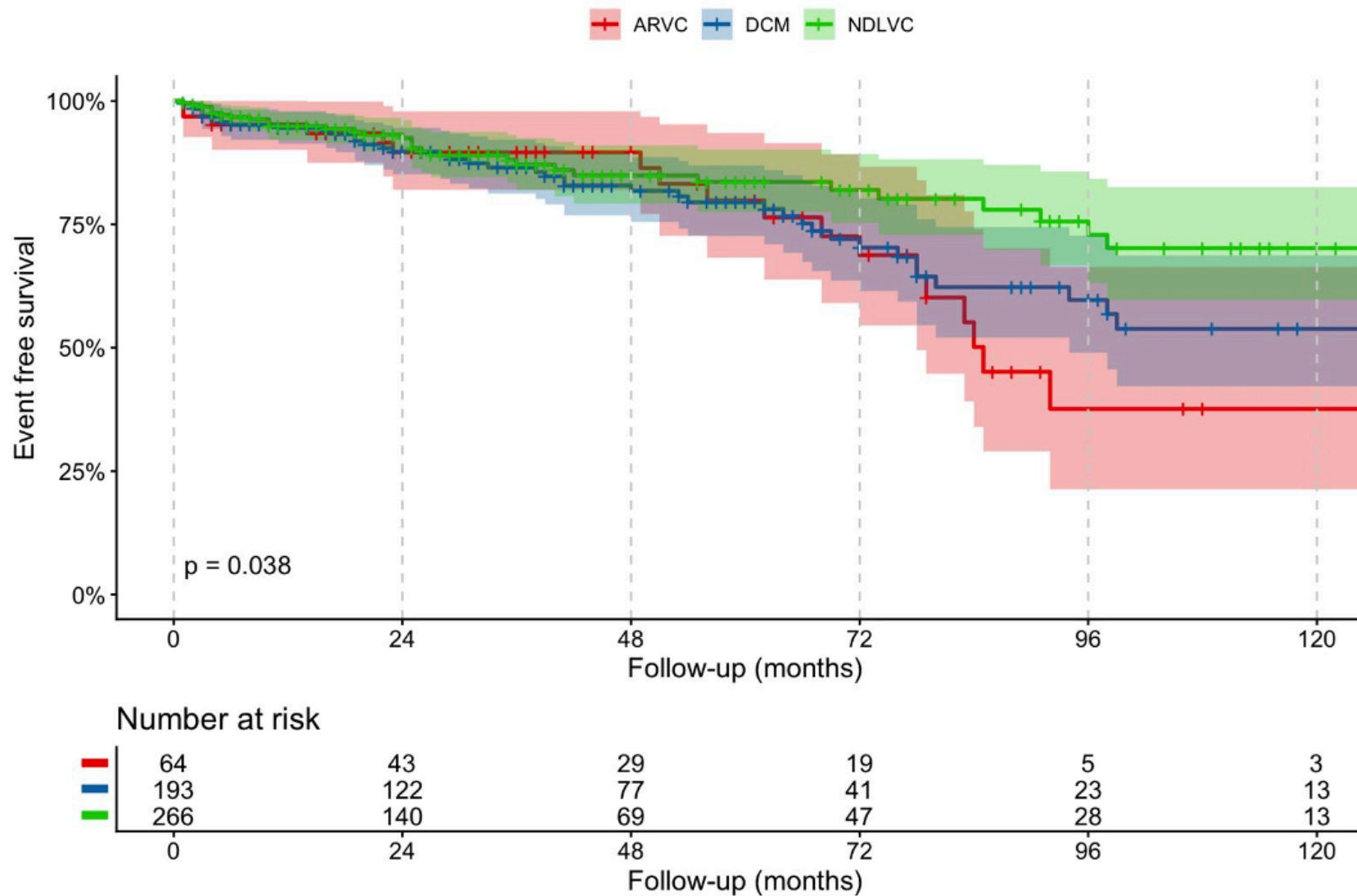
Arrhythmic outcome



Arrhythmic outcome



Arrhythmic outcome



Predictors of the arrhythmic outcome

Table 4. Multivariate Cox proportional hazards analysis for MAEs in the overall population.

Variable	N	Hazard Ratio (95% CI)	P-value
Male sex	467	1.44 (0.87-2.39)	0.160
Age at diagnosis	467	0.99 (0.97-1.01)	0.139
High Risk Genes	467	1.00 (0.62-1.61)	0.996
RAD	467	2.76 (1.45-5.28)	0.002
LVEF < 45 %	467	1.81 (1.11-2.96)	0.017
RVEF < 40%	467	2.23 (1.26-3.94)	0.006
Polymorphic PVCs	467	1.88 (1.17-3.04)	0.010
NSVT	467	1.72 (1.07-2.77)	0.024

CENTRAL ILLUSTRATION: Long-term outcome and Arrhythmic Risk Stratification in Genotyped Patients with Left Ventricular Ring-Like Scar

523 adult patients from
16 European tertiary
centers



CMR-defined LV ring-like scar +
comprehensive genetic testing



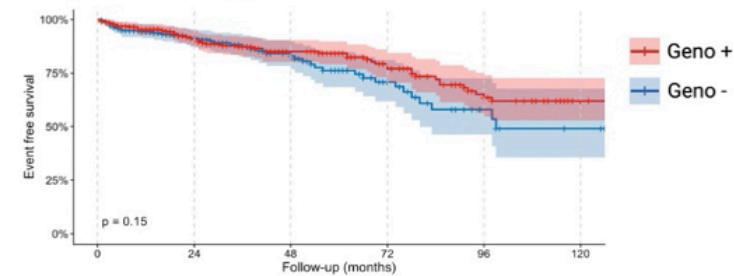
P/LP variants in 298 patients (57%) with ring-like scar
High-risk genes in 222/298 (74%)
Median follow-up 30 months

Ring-like scar identifies a high-risk arrhythmic substrate

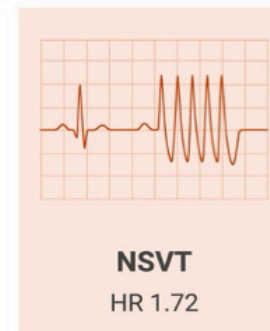
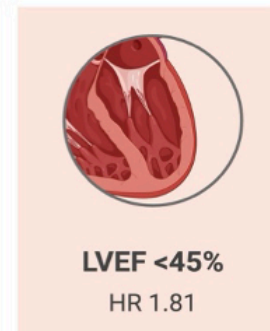
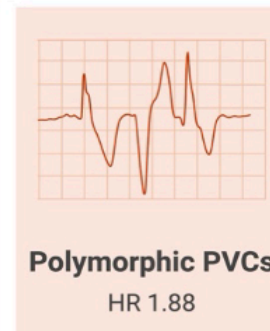
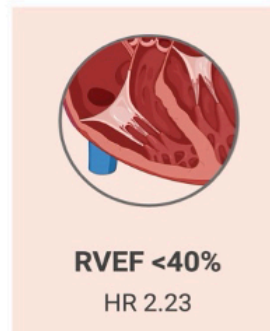
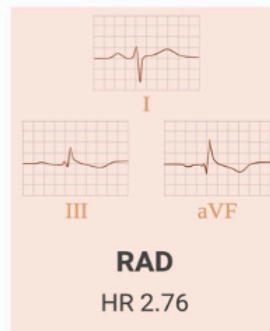
96/523 patients (18.4%)
experienced MAEs

5.2 events per 100 patient-years

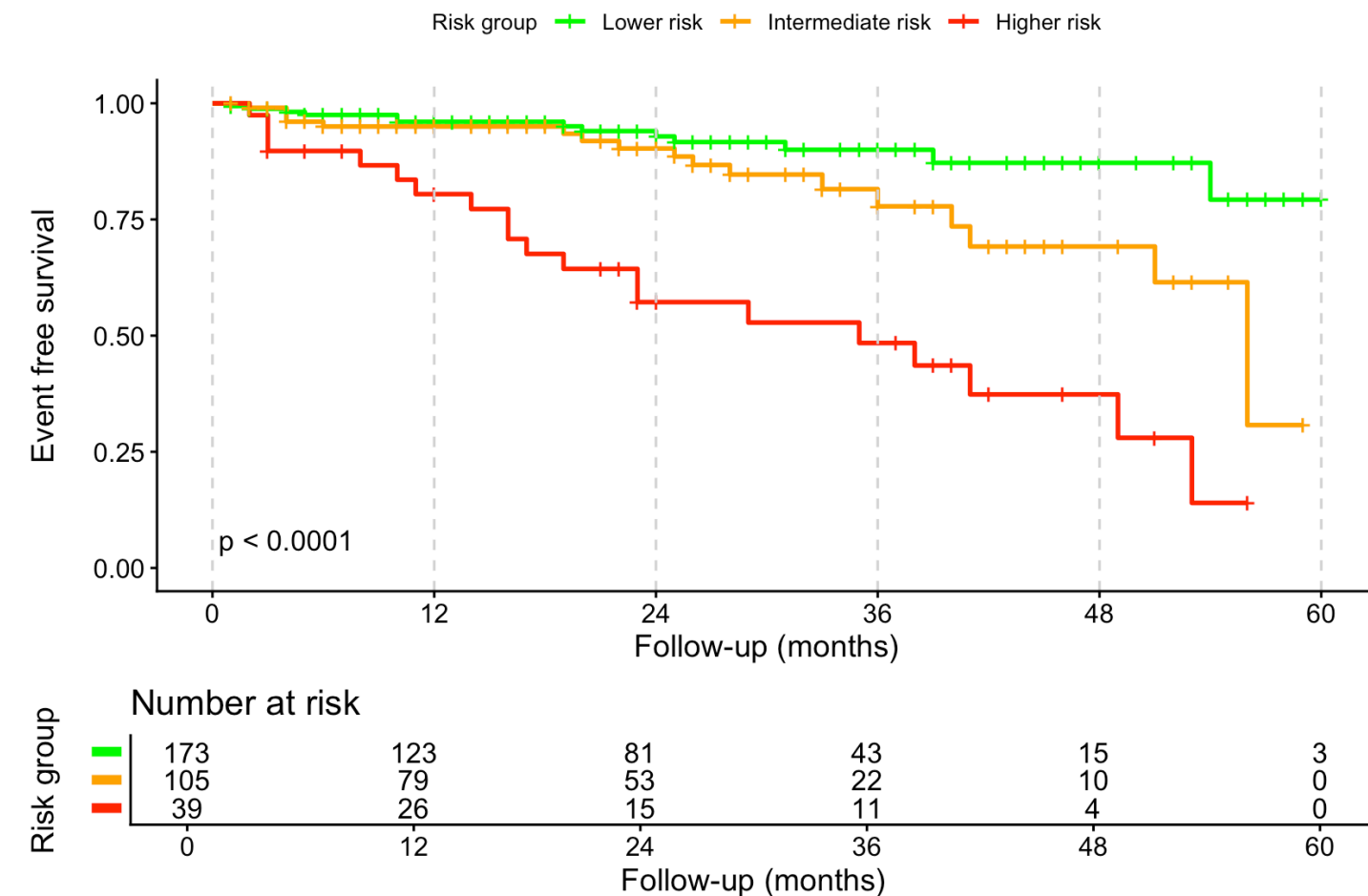
Genetic status was **not**
independently associated with MAEs



Independent predictors of MAEs



Another risk score?



Risk formula

$$\text{5-year MAE risk} = 1 - [S_o(60)]^{\exp(PI)}$$

$$S_o(60) = 0.856$$

Discrimination performance

Harrell C: **0.692**

Bootstrap-corrected C: **0.690**

95% CI: **0.601–0.780**

Table S13. Pairwise comparisons using Log-Rank test

	Lower	Intermediate
Intermediate	0.02883	-
Higher	<0.001	<0.001

Another risk score?

Risk formula

5-year MAE risk = $1 - [S_o(60)]^{\exp(PI)}$

$S_o(60) = 0.856$

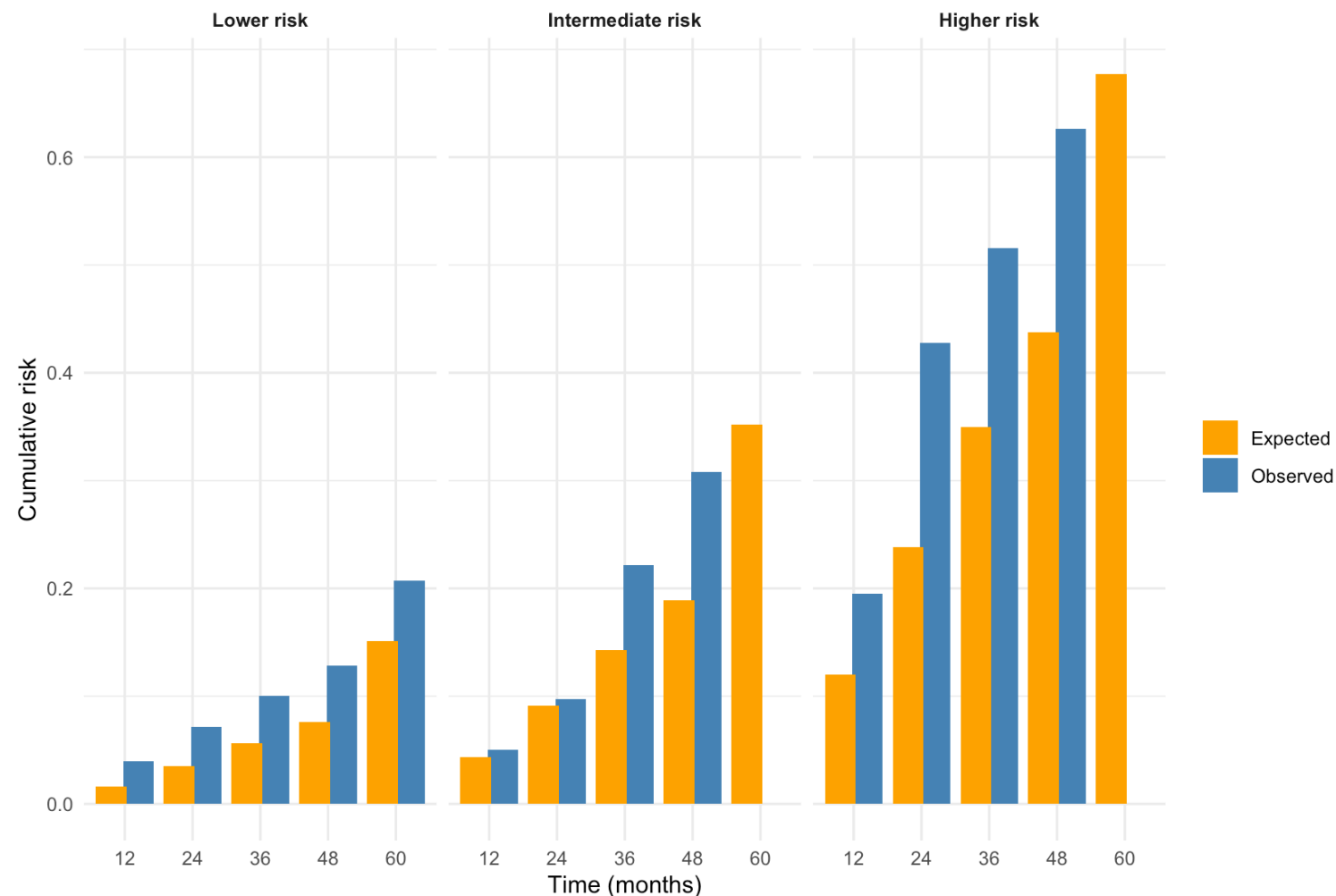
Performance

Harrell C: **0.692**

Bootstrap-corrected C: **0.690**

95% CI: **0.601–0.780**

Prediction performance: **good agreement
between predicted and observed risk**



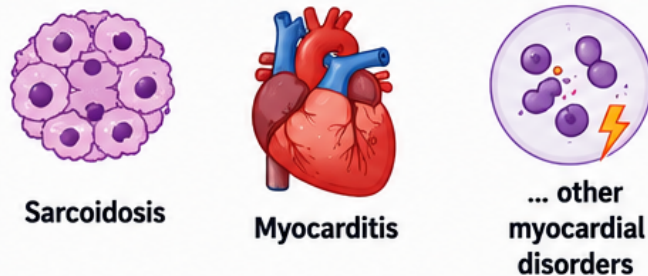
Origins and Arrhythmic Risk Progression of Left Ventricular Ring-Like Scars

1 ETIOLOGY: ORIGINS

GENETIC ETIOLOGIES



ACQUIRED MYOCARDIAL DISORDERS



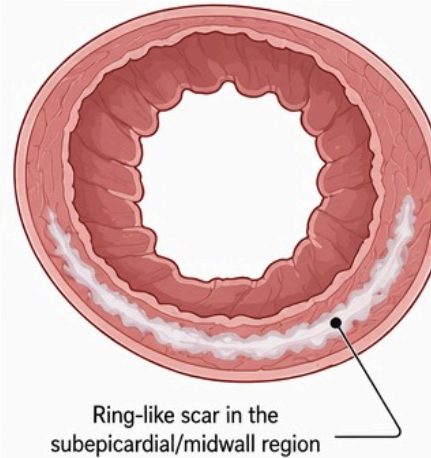
2 SCAR FORMATION / TRANSITION

Ongoing transition:
Scar development

Arrhythmic
risk (early):
Gene-related
risk



Arrhythmic
risk (early):
Disorder-
related risk



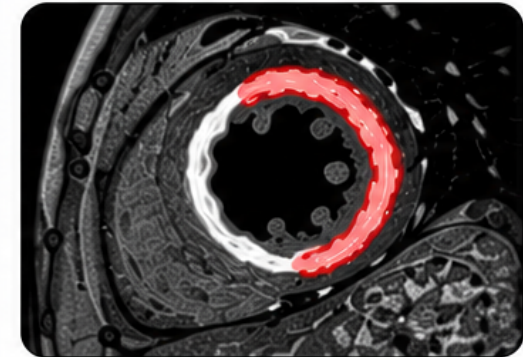
Ring-like scar in the
subepicardial/midwall region



Arrhythmic
risk (late):
Scar-related
risk

3 OVERT SCAR & IMAGING

CMR: Left ventricular
ring-like scar



Ring-like scar (highlighted)



At this stage,
arrhythmic risk is
predominantly
scar-related

PATHWAY OF ARRHYTHMIC RISK PROGRESSION

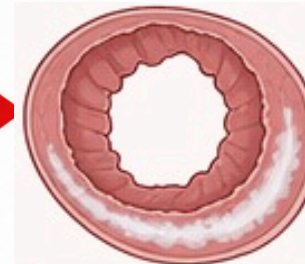
EARLY ARRHYTHMIC RISK (GENE/DISORDER-RELATED)



Risk driven by underlying genetic
variants or acquired myocardial
disorders (before overt scar is present)

PROGRESSION

As the scar becomes overt
(ring-like scar develops)



LATE ARRHYTHMIC RISK (SCAR-RELATED)



Risk shifts to being primarily
driven by the substrate (scar)







Risk formula

FLORIAN
CARDIO
MYPHOS

$$5\text{-year MAE risk} = 1 - [S_o(60)]^{\exp(PI)}$$

$$S_o(60) = \mathbf{0.856}$$

Risk stratification

Lower risk: <25%

Intermediate risk: 25–50%

Higher risk: >50%

Model results

Applied to **317** patients

50 arrhythmic events

Predicted risk range: **11.6% to >50%**

Risk distribution:

173 lower risk

105 intermediate risk

39 higher risk

Significant stepwise separation across strata:

log-rank P < 0.001

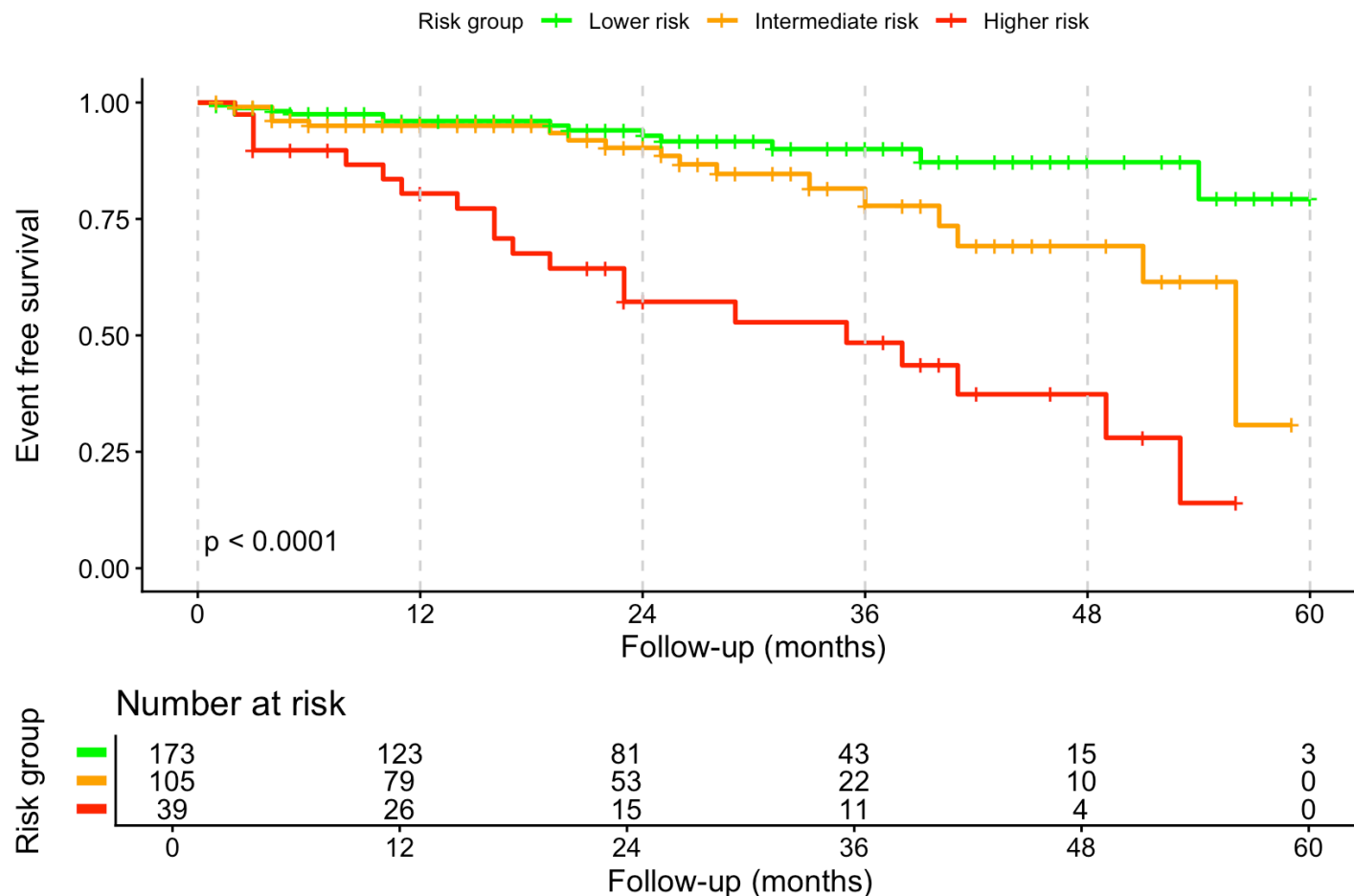
Garcia M. *et al*, under review



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Why did the score not perform so well?

Risk formula

5-year MAE risk = $1 - [S_o(60)]^{\exp(PI)}$

$$S_o(60) = 0.856$$

Performance

Harrell C: **0.692**

Bootstrap-corrected C: **0.690**

95% CI: **0.601–0.780**

Calibration: **good agreement between predicted and observed risk**

$$P(VA \text{ at 5 year}) = 1 - 0.965^{\exp(LP)}$$

$LP = 0.466(\text{centring constant}) - 0.0364 * LVEF + 0.0906 \times \text{amount of negative T waves} + 0.615 \times \text{low-voltage ECG (Yes)} + 0.309 \times \text{Log}(\text{amount of PVC/24 h})$

PLN

Myrthe Y.C. van der Heide *et al*, Europace 2024

$$5 \text{ year risk for LTVA} = 1 - (0.975)^{\exp(PI)} \quad (3)$$

DSP

Richard T. Carrick *et al*, EHJ 2023

$$5 - \text{year risk of MAE} = 1 - (0.99600731958437)^{\exp(PI)}$$

NDLVC

Peretto G *et al*, EHJ 2026