Circulation

ORIGINAL RESEARCH ARTICLE

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

Editorial, see p 1374

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BACKGROUND: Left ventricular (LV) scar on late gadolinium enhancement (LGE) cardiac magnetic resonance has been correlated with life-threatening arrhythmic events in patients with apparently idiopathic ventricular arrhythmias (VAs). We investigated the prognostic significance of a specific LV-LGE phenotype characterized by a ringlike pattern of fibrosis.

METHODS: A total of 686 patients with apparently idiopathic nonsustained VA underwent contrast-enhanced cardiac magnetic resonance. A ringlike pattern of LV scar was defined as LV subepicardial/midmyocardial LGE involving at least 3 contiguous segments in the same short-axis slice. The end point of the study was time to the composite outcome of all-cause death, resuscitated cardiac arrest because of ventricular fibrillation or hemodynamically unstable ventricular tachycardia and appropriate implantable cardioverter defibrillator therapy.

RESULTS: A total of 28 patients (4%) had a ringlike pattern of scar (group A), 78 (11%) had a non-ringlike pattern (group B), and 580 (85%) had normal cardiac magnetic resonance with no LGE (group C). Group A patients were younger compared with groups B and C (median age, 40 vs 52 vs 45 years; $P<0.01$), more frequently men (96% vs 82% vs 55%; $P<0.01$), with a higher prevalence of family history of sudden cardiac death or cardiomyopathy (39% vs 14% vs 6%; $P<0.01$) and more frequent history of unexplained syncope (18% vs 9% vs 3%; $P<0.01$). All patients in group A showed VA with a right bundle-branch block morphology versus 69% in group B and 21% in group C ($P<0.01$). Multifocal VAs were observed in 46% of group A patients compared with 26% of group B and 4% of group C ($P<0.01$). After a median follow-up of 61 months (range, 34–84 months), the composite outcome occurred in 14 patients (50.0%) in group A versus 15 (19.0%) in group B and 2 (0.3%) in group C ($P<0.01$). After multivariable adjustment, the presence of LGE with ringlike pattern remained independently associated with increased risk of the composite end point (hazard ratio, 68.98 [95% CI, 14.67–324.39], $P<0.01$).

CONCLUSIONS: In patients with apparently idiopathic nonsustained VA, nonischemic LV scar with a ringlike pattern is associated with malignant arrhythmic events.

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The full author list is available on page 1371.

Key Words: arrhythmias ■ cardiac gadolinium ■ magnetic resonance angiography ■ prognosis

Sources of Funding, see page 1371

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Clinical Perspective

What Is New?

- In patients presenting with nonsustained ventricular arrhythmias and normal ECG and echocardiographic findings, the presence of late gadolinium enhancement (LGE) on cardiac magnetic resonance is associated with increased risk of major arrhythmic events over follow-up.
- The extent of the increase in risk is not homogenous across all the spectrum of patients with a positive LGE finding.
- The presence of a specific midmyocardial/subepicardial ringlike LGE pattern is associated with a particularly high risk of malignant arrhythmic events, which is independent of the total LGE burden and presence of other additional risk factors.

What Are the Clinical Implications?

- Cardiac magnetic resonance should be considered in the diagnostic workup of patients with apparently idiopathic nonsustained ventricular arrhythmias to detect concealed cardiomyopathic substrates and improve risk stratification.
- Identification of LGE with ringlike pattern in these patients deserves proper clinical attention, close follow-up, and careful evaluation for primary prevention implantable cardioverter-defibrillator implantation.

The presence of myocardial fibrosis detected by late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) has been demonstrated to have negative prognostic implications in several heart diseases including ischemic heart disease, nonischemic cardiomyopathy, hypertrophic cardiomyopathy, and myocarditis.[1–4] A growing body of evidence has also associated the presence of LGE with an increased risk of life-threatening arrhythmic events in patients presenting with ventricular arrhythmias (VAs) even in the presence of otherwise negative routine diagnostic workup including 12-leads ECG and transthoracic echocardiography.[5–7] However, risk stratification of patients with VA and normal ventricular function remains challenging. Previous CMR studies have documented LGE in up to 70% of patients with apparently idiopathic VA, and although these patients appear to have a higher risk of arrhythmic events over follow-up, the degree of increased risk is highly variable between different published series. This makes the presence of LGE at CMR a stand-alone risk stratification criterion impractical for clinical decision making, particularly with respect to the selection of patients for prophylactic implantable cardioverter-defibrillator (ICD) implantation.[5 7 8] In this context, additional studies focused on the identification of patients with apparently idiopathic VA who have a particularly high risk of malignant arrhythmic events during follow-up are needed. Although the presence or absence of LGE (as opposed to its extent) has been thought to be the primary predictor of cardiovascular adverse events in nonischemic cardiomyopathy, most of the previous studies have produced conflicting results.[2 9 10] Therefore, using the unique cohort of patients in the international idiopathic VA CMR registry, the present study investigated whether specific LGE phenotypes are more prone to arrhythmogenesis and can identify patients with apparently idiopathic nonsustained VA at particularly high risk of sudden cardiac death (SCD).

METHODS

Study Population

The data supporting the study findings will be made available on reasonable request. This is a retrospective multicenter observational study focused on patients with nonsustained VA of apparent idiopathic nature according to a routine diagnostic workup including physical examination, 12-lead ECG, transthoracic echocardiography, and noninvasive or invasive ischemic evaluation who also underwent additional contrast-enhanced CMR evaluation. Patients were selected from an ongoing international idiopathic VA CMR registry that includes patients with both nonsustained and sustained VA from 7 institutions across the United States, Europe, and Japan. No prespecified criteria were used to select patients for CMR and, for the purpose of this study, we included only patients with apparently idiopathic nonsustained VA. In particular, all patients had ECG documentation of nonsustained VA, including frequent premature ventricular contractions ([PVCs] ≥1000/24 hours) or episodes of nonsustained ventricular tachycardia (NSVT). Baseline ECGs were reviewed at each center by a single experienced cardiologist (≥5 years of clinical experience) who was blinded to clinical and outcome data. Absence of significant coronary artery disease was demonstrated by a maximal exercise stress test, functional imaging, computed tomography coronary angiography, or invasive coronary angiography. Patients with any abnormal baseline ECG findings (ie, sinus QRS with depolarization/repolarization abnormalities), abnormal transthoracic echocardiography findings (ie, dimension and function—global and regional—of the left ventricular [LV] and right ventricular [RV] chambers), positive ischemic evaluation, and other systemic diseases that may be associated with LGE were excluded. In addition, patients with documented sustained VA (ventricular tachycardia [VT] or ventricular fibrillation [VF], N=54 in the registry) were excluded.

A total of 699 patients from the registry between January 2002 and December 2018 met the inclusion criteria for the study. Of these, 13 (all with no evidence of LGE) were lost at follow-up and excluded from the analysis. Therefore, the final study cohort consisted of 686 patients, of whom 518 from a previous study who underwent extended follow-up for the purpose of the present investigation.[11] A deidentified database of patients with full DICOM (Digital Imaging and Communications in Medicine) data sets from the participating centers was used for data collection and analysis. Institutional review board approval was obtained at each center, and

written informed consent was obtained for anonymized medical information to be included in a research registry. A detailed description of the study protocol is presented in Table I in the Data Supplement.

Cardiac Magnetic Resonance

All participants underwent CMR with 1.5-T scanners. The CMR acquisition protocol and analysis are described in detail in Table I in the Data Supplement. All CMR studies were analyzed offline using a dedicated software (Circle CVI-42, Circle Cardiovascular Imaging, Calgary, Alberta, Canada). Images were evaluated by 2 independent expert investigators with >15 years (G.N.) and >5 years (D.M.) of experience in CMR imaging blinded to clinical data. Any discrepancies between the investigators were then adjudicated by revision and consensus between the two of them. Visual assessment for the presence and distribution of LGE areas for each LV myocardial segment was performed using a standard 17-segment cardiac model. Dichotomous presence or absence of RV LGE was also determined. Quantification of LGE extent was performed in the short-axis slices by manually drawing endocardial and epicardial borders and selecting a region of interest in the remote healthy myocardium. Mean signal intensity and SD of the region of interest were then measured, and enhanced myocardium was defined as myocardium with a signal intensity ≥5 SDs above the mean of the region of interest.[12] The extent of LGE was expressed as a percentage of the LV mass. LGE pattern was defined as ringlike if there were at least 3 contiguous segments with subepicardial/midmyocardial LGE in the same short-axis slice.[13] On the basis of the presence and distribution of LGE, patients were divided into 3 groups: group A characterized by the presence of LV LGE with a ringlike pattern, group B characterized by the presence of LV LGE with no ringlike pattern, and group C with no evidence of LGE (Figures 1 and 2).

Electrophysiological Study and Catheter Ablation

In patients who underwent catheter ablation (CA) of VA, the site of origin of the arrhythmia was determined based on detailed activation and pace mapping, as described previously.[14] Acute procedural success was defined as absence of spontaneous or inducible PVC with burst pacing from the RV apex or isoproterenol infusion for 30 minutes after radiofrequency ablation. Programmed electric stimulation (PES) with up to triple extrastimuli from 2 ventricular sites with at least 2 drive cycle lengths was performed in selected patients at the discretion of the attending electrophysiologist but was typically driven by the evidence of structural abnormalities on preprocedural CMR by a previous history of unexplained syncope or family history of SCD. PES was considered positive if monomorphic sustained VT was induced, whereas polymorphic VT or VF was not considered specific. The decision to implant an ICD was at the discretion of the attending electrophysiologist and the referring physician based on clinical, imaging, and electrophysiological study findings.

Outcomes

The end point of the study was time to the composite outcome of (1) death from any cause, (2) resuscitated cardiac arrest because of VF or hemodynamically unstable VT, and (3) appropriate implantable cardioverter-defibrillator (ICD) therapy.

Clinical Follow-Up

Patients were routinely evaluated at 3- to 6-month intervals after CMR by clinic visits, ambulatory Holter monitoring, and telephone calls to confirm the absence of arrhythmias symptoms. Medical records were reviewed to determine the occurrence of hospital admission attributable to cardiovascular causes and implantation of an ICD. Vital status and date of death were determined by querying the respective national death indices. The cause of death was confirmed from a combination of medical records, death certification, and postmortem results. ICD interrogations were reviewed to assess ICD therapies among patients who underwent ICD implantation; ICD shocks or antitachycardia overdrive pacing were considered appropriate if triggered by VF or sustained VT.

Statistical Analysis

Continuous variables were expressed as median (25th to 75th percentile) and compared using the Kruskal–Wallis rank test. Categorical data were expressed as counts and percentages and compared using the χ^2 test. The Spearman correlation coefficient was used to test correlation between continuous variables. Survival curves were generated by the Kaplan–Meier method and compared by the log-rank test. Univariable and multivariable Cox proportional hazards analyses were used to test the association between the time to outcome event and baseline covariates. Event times were measured from the date of CMR study. All potential confounders (including age, gender, family history of SCD/cardiomyopathy, history of unexplained syncope, PVC burden, multifocal VA, VA with a non-left bundle branch block inferior axis morphology, LV end-diastolic volume indexed [EDVi], LV ejection fraction [LVEF], presence, pattern and extent of LGE, and CA) were initially entered into the multivariable model on the basis of known clinical relevance; then we performed a model reduction by excluding variables with a *P* value >0.20 based on the log-likelihood test. The proportional hazards assumption was assessed globally and for all variables using the Schoenfeld residuals test. As part of an exploratory analysis to further improve risk stratification of patients with ringlike and non-ringlike LGE pattern, the prevalence of additional risk factors (including family history of cardiomyopathy/SCD, history of syncope, multifocal PVC, and induction of sustained VT at PES) in the ringlike and non-ringlike groups was compared between patients who experienced outcome events and those who remained free from events at follow-up. Two-tailed tests were considered statistically significant at the 0.05 level. *P* values were adjusted for multiple comparisons using the Benjamini and Hochberg method.[15] All the analyses were performed using IBM SPSS version 25.0 software (IBM Corp, Armonk, NY).

RESULTS

Study Population

Clinical characteristics of the study sample according to the presence and distribution of LGE are presented in Table 1. A total of 106 patients (15%) had evidence

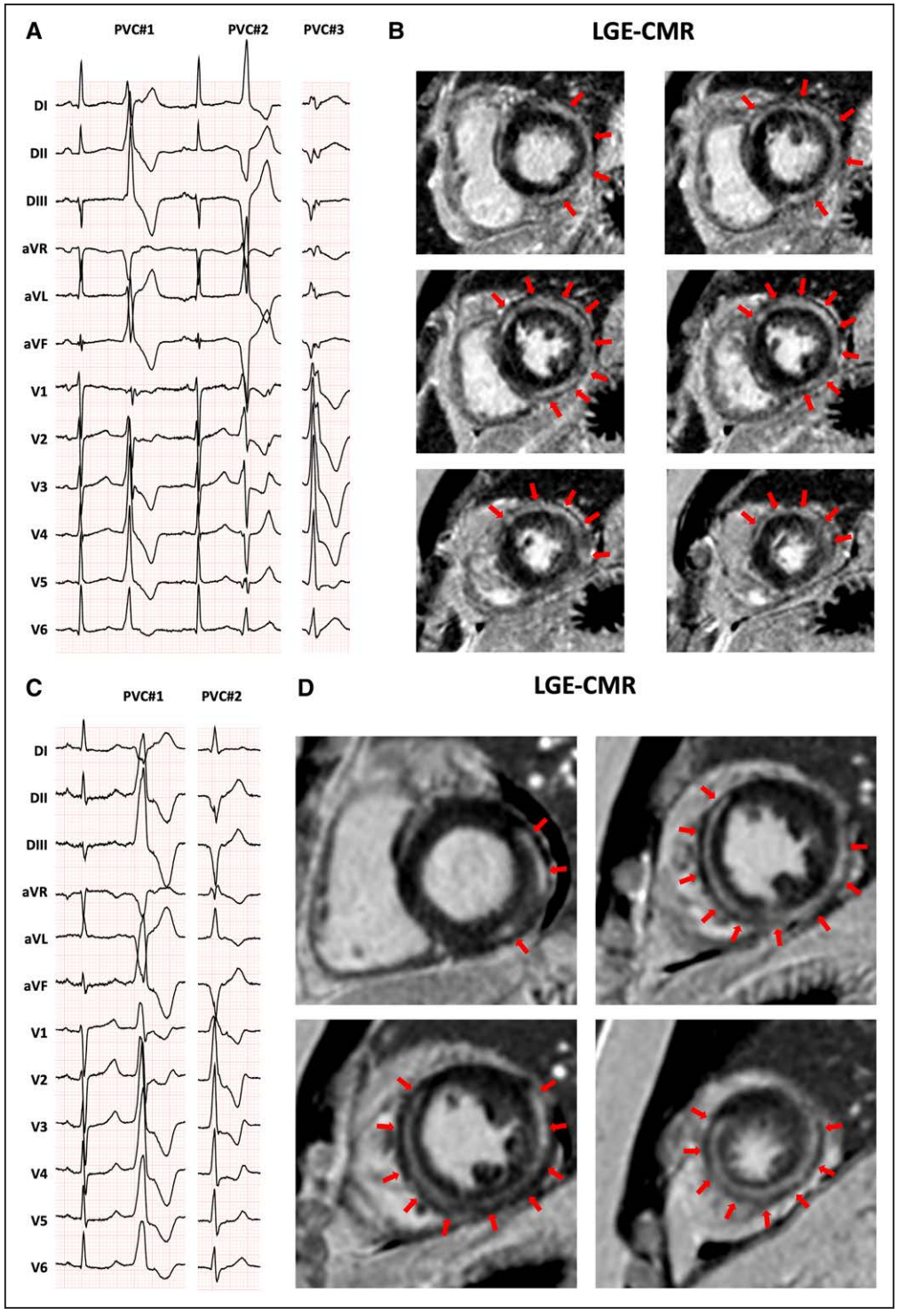

Figure 1. Ring-like left ventricular scar.
A 31-year-old man with family history of sudden cardiac death presenting with palpitations related to multifocal PVC (**A**) and evidence on LGE-CMR of subepicardial fibrosis with a ringlike pattern involving the LV free wall (**B**). A 54-year-old man presenting with palpitations related to multifocal PVC (**C**) and evidence on LGE-CMR of midmyocardial fibrosis with a ringlike pattern involving the septum and LV inferior and lateral walls (**D**). LGE-CMR indicates late gadolinium enhancement cardiac magnetic resonance; LV, left ventricular; and PVC, premature ventricular contraction.

of LV-LGE, with 28 patients (4%) displaying a ringlike pattern (group A) and 78 (11%) a non-ringlike pattern of scar (group B). The remaining 580 cases (85%) had normal CMR scans with no LGE (group C). Compared with groups B and C, group A patients were younger, more frequently men, more frequently had a family history of SCD/cardiomyopathy, and more frequently had a history of unexplained syncope. Overall, 25 patients had a family history of cardiomyopathy. Of these, 21 (68%) had a family history of dilated cardiomyopathy, 2

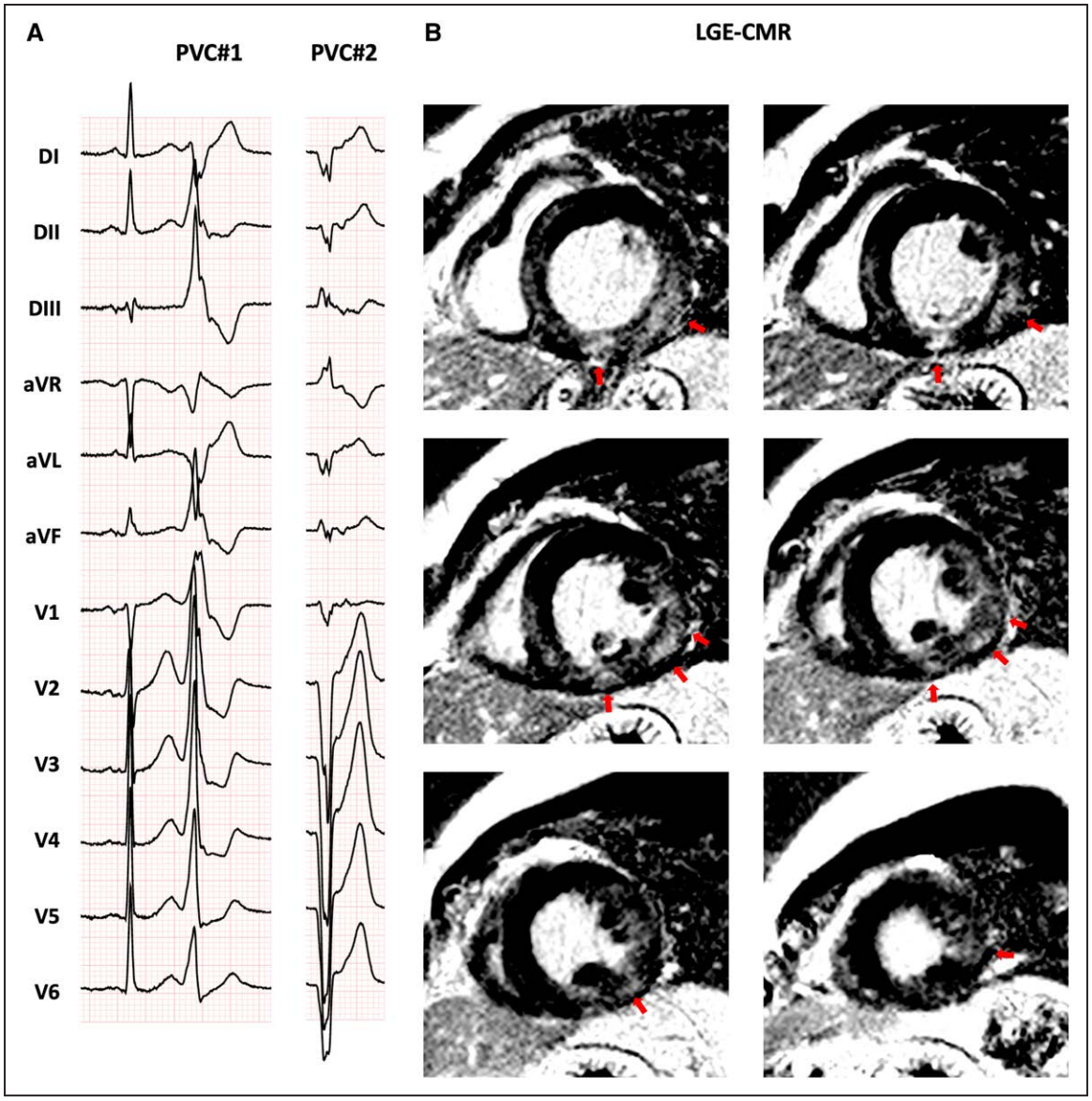

Figure 2. Non-ringlike left ventricular scar.
A 40-year-old man presenting with frequent PVC of 2 different morphologies (**A**) and evidence on LGE-CMR of patchy areas of midmyocardial scar (non-ringlike pattern) involving the inferolateral LV wall (**B**). LGE-CMR indicates late gadolinium enhancement cardiac magnetic resonance; LV, left ventricular; and PVC, premature ventricular contraction.

(8%) of LV noncompaction, and 2 (8%) of arrhythmogenic RV cardiomyopathy. None of the affected family members underwent genetic testing, which precluded a further characterization of specific causes. Treatment with at least 1 antiarrhythmic drug or β-blockers was attempted in 497 patients (72%). There was no significant difference in the use of β-blockers or antiarrhythmic drug therapy across the 3 patient groups, with the exception of class III agents, which were more frequently used among group A patients. All patients in group A presented with VA having a right bundle-branch block morphology compared with 33 patients (42%) in group B and 48 (8%) in group C ($P<0.01$). The prevalence of multifocal PVC was significantly higher among group A patients (13, 46%) compared with groups B (20, 26%) and C (22, 4%; $P<0.01$). A total of 593 12-lead ECGs (86%) of the VA were available for digital measurement. The median QRS duration was 151 ms (136–169 ms) with no significant difference among the 3 groups (group A: 158 ms [141–178 ms] vs group B: 151 ms [134–165 ms] vs group C: 151 ms [136–169 ms]; $P=0.27$). Fragmentation in ≥1 lead (defined as a deflection of ≥0.5 mV on the QRS that did not cross baseline)[16] was observed in 105 cases (18%), of whom there were 9 (32%) in group A versus 15 (20%) in group B versus 81 (17%) in group C ($P=0.10$).

None of the patients had a definite diagnosis of arrhythmogenic RV cardiomyopathy according to the 2010 task force recommendations.[17] A single patient in group C met criteria for a borderline diagnosis of

Table 1. Baseline Clinical Characteristics and Imaging Findings According to the Distribution of LGE

Variable	Group A: ventricular arrhythmia and ringlike LGE (N=28)	Group B: ventricular arrhythmia and non-ringlike LGE (N=78)	Group C: ventricular arrhythmia and no LGE (N=580)	*P* value
Age, years	40 (34–53)	52 (43–64)	45 (29–55)	<0.01
Male sex, n (%)	27 (96)	64 (82)	317 (55)	<0.01
Family history of sudden cardiac death, n (%)	7 (25)	8 (10)	28 (5)	<0.01
Family history of cardiomyopathy, n (%)	10 (36)	5 (6)	10 (2)	<0.01
History of unexplained syncope, n (%)	5 (18)	7 (9)	15 (3)	<0.01
Symptoms, n (%)				0.26
Asymptomatic	6 (21)	7 (9)	97 (17)	
Chest pain	2 (7)	0	13 (2)	
Palpitations	16 (57)	63 (81)	418 (72)	
Dizziness	2 (7)	5 (6)	34 (6)	
Fatigue	2 (7)	5 (6)	34 (6)	
Type of ventricular arrhythmias				
Frequent premature ventricular contraction (≥1000/24 h), n (%)	27 (96)	76 (97)	568 (98)	0.88
Nonsustained ventricular tachycardia (≥4 consecutive beats), n (%)	5 (18)	11 (14)	56 (10)	0.26
Premature ventricular contraction burden, % of 24-h beats	17 (16–28)	17 (14–23)	17 (10–20)	0.20
Multifocal premature ventricular contraction, n (%)	13 (46)	20 (26)	22 (4)	<0.01
ECG morphology of the arrhythmia, n (%)				<0.01
Left bundle branch block: inferior axis	0	21 (27)	423 (73)	
Left bundle branch block: superior axis	0	3 (4)	34 (6)	
Right bundle branch block: inferior axis	3 (11)	21 (27)	75 (13)	
Right bundle branch block: superior axis	25 (89)	33 (42)	48 (8)	
Medical therapy				
β-Blockers, n (%)	18 (64)	37 (47)	279 (48)	0.28
Class I antiarrhythmic drugs, n (%)	3 (11)	23 (30)	161 (28)	0.20
Class III antiarrhythmic drugs, n (%)	15 (54)	37 (47)	169 (29)	<0.01
Catheter ablation, n (%)	12 (43)	34 (44)	261 (45)	0.95
Cardiac magnetic resonance findings				
Left ventricle				
End-diastolic volume index, mL/m^2	90 (75–98)	77 (69–90)	77 (68–86)	0.02
Ejection fraction, %	57 (55–62)	65 (58–70)	64 (59–69)	<0.01
Left ventricular ejection fraction between 50% and 55%, n (%)	4 (14)	6 (8)	27 (5)	0.08
Mass index, g/m^2	71 (66–80)	65 (57–70)	59 (51–67)	<0.01
Regional wall motion abnormalities, n (%)	15 (54)	12 (15)	0	<0.01
Intramyocardial fat signal, n (%)	7 (25)	9 (12)	0	<0.01
Segments with LGE, n	6 (5–8)	2 (1–3)	—	<0.01
Scar volume, left ventricular mass, %	7 (5–10)	3 (2–5)	—	<0.01
LGE pattern				
Subepicardial, n (%)	25 (89)	31 (40)	—	<0.01
Midwall, n (%)	15 (54)	36 (46)	—	0.65
Subendocardial/transmural, n (%)	0	16 (21)	—	<0.01
LGE location				
Septum, n (%)	17 (61)	27 (35)	—	0.03
Anterior wall, n (%)	10 (36)	11 (14)	—	0.02
Lateral wall, n (%)	25 (89)	42 (54)	—	<0.01

(*Continued*)

Table 1. Continued

Variable	Group A: ventricular arrhythmia and ringlike LGE (N=28)	Group B: ventricular arrhythmia and non-ringlike LGE (N=78)	Group C: ventricular arrhythmia and no LGE (N=580)	*P* value
Inferior wall, n (%)	23 (82)	20 (26)	—	<0.01
Right ventricle				
End-diastolic volume index, mL/m^2	78 (71–93)	81 (69–91)	81 (72–91)	0.83
Ejection fraction, %	62 (59–68)	61 (57–66)	61 (56–67)	0.86
Regional wall motion abnormalities, n (%)	1 (4)	5 (6)	32 (6)	0.86
Intramyocardial fat signal, n (%)	0	3 (4)	2 (0.3)	<0.01
LGE, n (%)	1 (4)	6 (8)	—	0.79

LGE indicates late gadolinium enhancement.

arrhythmogenic RV cardiomyopathy because of 1 major criterion (NSVT of left bundle branch block with superior axis) plus 1 minor criterion (evidence of regional RV wall motion abnormalities in association with an RV-EDVi ≥100 mL/m^2), and 6 patients (4 in group C and 2 in group B) met criteria for possible arrhythmogenic RV cardiomyopathy because of a single major criterion in 4 cases (NSVT of left bundle branch block with superior axis) and 2 minor criteria (NSVT of left bundle branch block and inferior axis or >500 PVC/24 hours plus RV abnormalities on CMR) in the remaining 2 cases (Tables II and III in the Data Supplement).

CMR Findings

Imaging results are summarized in Table 1. Overall, group A patients had a larger LV volume (median EDVi, 90 [75–98] vs 77 [69–90] vs 77 [68–86] mL/m^2; *P*<0.01) and lower LVEF (median LVEF, 57% [55%–62%] versus 65% [58%–70%] versus 64% [59%–69%]; *P*<0.01]. No significant differences were detected in RV volume and function among the 3 groups.

The median extent of LGE was 42% to 7% of the LV (75% to 10% in group A versus 32% to 5% in group B; *P*<0.01). The overall distribution of LGE was different between groups A and B, with group A patients having a predominant lateral (89%) and inferior (82%) wall involvement (vs 54% and 26% in group B, respectively; *P*<0.01). Septal involvement was observed in 17 cases (61%) in group A versus 27 (35%) in group B (*P*<0.01). In the majority of group A patients, LGE distribution was subepicardial (extension through the outer one third of the LV myocardium of the free wall or outer one third to the right side of the septum: 25 cases, 89%) with extension to the midwall in 15 cases (54%) compared with 31 (40%) and 36 (46%) of the cases in group B (*P*<0.01 and *P*=0.61, respectively). None of the group A patients had evidence of subendocardial or transmural areas of LGE compared with 16 (21%) in group B (*P*<0.01; Figure 3). The extent of LGE showed a weak correlation with the LV EDVi (ρ=0.27; *P*<0.01) and the LVEF (ρ=–0.32; *P*<0.01), whereas no correlation was observed between PVC burden and LV EDVi (*P*=0.64), LVEF (*P*=0.89), or LGE extent (*P*=0.43). Overall, 53% of patients with evidence of LGE and 46% of those with a ringlike scar pattern had VA with no evidence of multifocal origin or QRS fragmentation. In particular, LGE was present in 33 (60%) of 55 patients with multifocal PVCs versus 73 (12%) of 631 patients without multifocal PVCs (*P*<0.01). The pattern of LGE was ringlike in 13 (39%) of the 33 patients with multifocal PVCs and LGE compared with 15 (21%) of 73 of those without multifocal PVCs and LGE (*P*=0.04). Among the 105 patients (23%) with PVC QRS fragmentation, LGE was present in 24 (23%) compared with 81 (17%) of 488 of those without fragmentation (*P*=0.13). The LGE pattern was ringlike in 9 (38%) of 24 cases with PVC QRS fragmentation and LGE versus 19 (24%) of 81 of those without QRS fragmentation and LGE (*P*=0.17).

Outcomes

After the CMR evaluation, 307 patients (45%) underwent CA (12 patients, 43% in group A; 34 patients, 44% in group B; and 261 patients, 45% in group C; *P*=0.95). Acute procedural success was achieved in 263 cases (86%) with no significant difference among the 3 groups (9 patients, 75% in group A; 26 patients, 77% in group B; and 228 patients, 87% in group C; *P*=0.33). PES was performed in 106 (35%) of 307 patients who underwent CA, and sustained monomorphic VT was inducible in 12 (11%) of 106 patients, of whom 9 (19%) of 48 of those had evidence of CMR abnormalities and 3 (5%) of 58 of those had normal CMR. Twenty patients (3%) underwent primary prevention ICD implantation (10 patients in group A, 11 in group B, and none in group C). The indication for ICD implantation was the presence of CMR myocardial abnormalities associated with either history of unexplained syncope/family history of SCD (16 patients) or induction of hemodynamically unstable sustained VT during PES (4 patients).

After a median follow-up of 61 months (34–84 months), 3 patients (0.4%) died, 19 (3.0%) had a

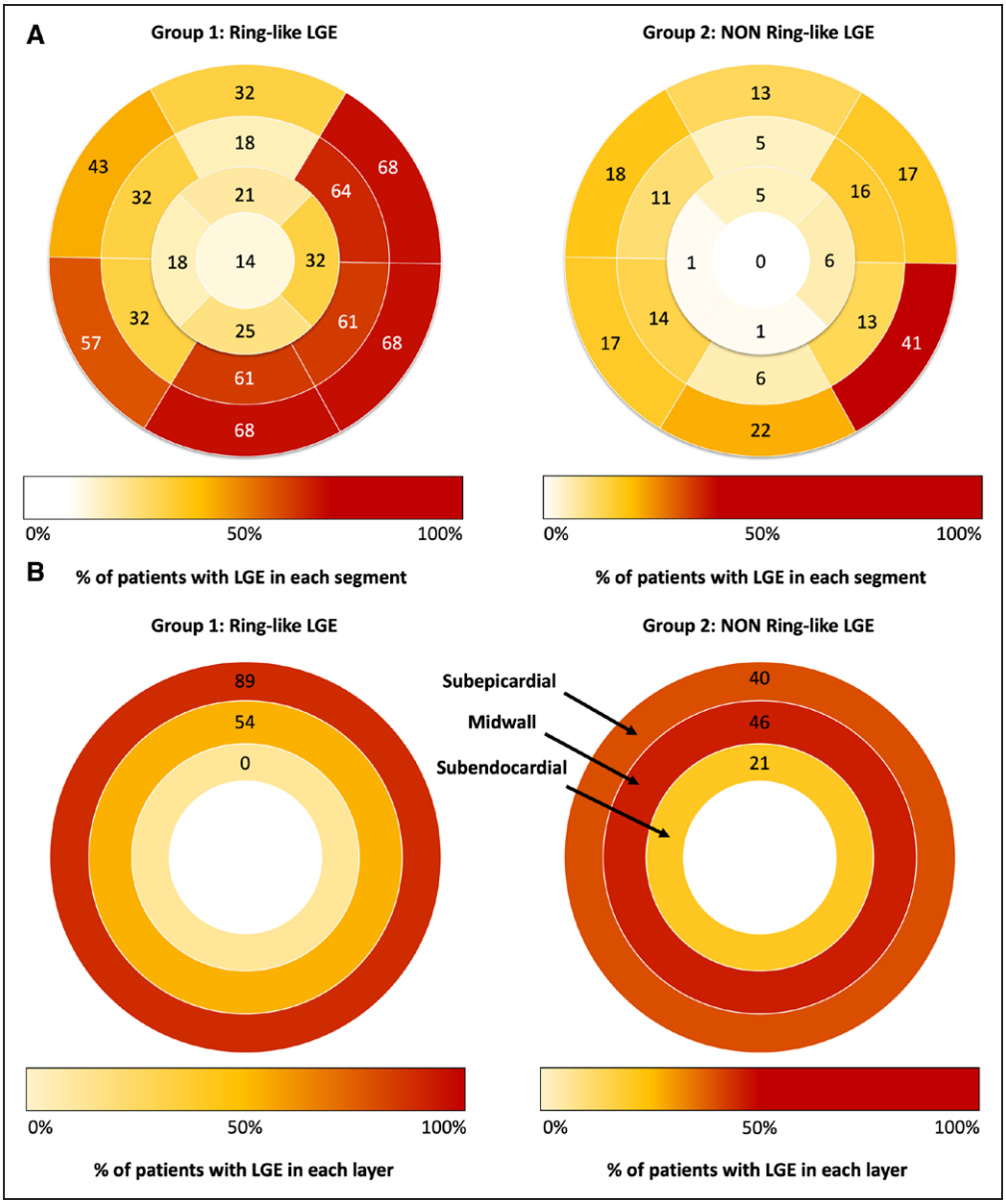

Figure 3. Distribution of left ventricular scar.
Distribution of LGE according to the 17-segment American Heart Association model (**A**) and myocardial layers (**B**; **outer circle**, subepicardial layer; **middle circle**, midwall; **inner circle**, subepicardial layer). LGE indicates late gadolinium enhancement.

resuscitated cardiac arrest, and 9 (1.0%) experienced appropriate ICD shocks for sustained monomorphic VT (5 patients, all with fast VT ≥250 beats per minute) or VF (4 patients; Table 2). All 3 patients who died had no ICD implanted and experienced witnessed SCD. Overall, the incidence of the composite outcome was significantly higher among patients with inducible sustained VT (6 patients, 50%) compared with those noninducible (9 patients, 10%; *P*<0.01; Figure I in the Data Supplement). All 6 patients with VT inducibility who experienced events at follow-up also had evidence of LGE on CMR. CA (hazard ratio [HR], 0.96 [95% CI, 0.47–1.94]; *P*=0.90) or acute ablation success (HR, 0.47 [95% CI, 0.15–1.46]; *P*=0.23) did not appear to affect the composite outcome during follow-up. Similarly, the use of β-blockers (HR, 1.95 [95% CI, 0.91–4.14]; *P*=0.18) or antiarrhythmic drug (HR, 2.64 [95% CI, 0.82–5.61]; *P*=0.15) had no significant interaction with the composite outcome at follow-up.

By Kaplan–Meier analysis, the risk of composite outcome was significantly higher in group A patients compared with group B and group C patients (log rank *P*<0.01; Figure 4). Moreover, the presence of ringlike scar was significantly associated with worse outcomes compared with other scar patterns (HR, 2.58 [95% CI, 1.24–5.34]; *P*=0.02) even after adjustment for LGE extent (HR, 2.39 [95% CI, 1.11–6.01]; *P*=0.03). In particular, Kaplan–Meier analysis of patients with ringlike LGE versus those with non-ringlike LGE, stratified by the highest tertile of LGE extent (≥5%), shows that the incidence of the composite end point was higher

Table 2. Long-Term Outcomes According to Presence and Distribution of LGE

Variable	Group A: ventricular arrhythmia and ringlike LGE (N=28)	Group B: ventricular arrhythmia and non-ringlike LGE (N=78)	Group C: ventricular arrhythmia and no LGE (N=580)	*P* value
Primary prevention implantable cardioverter-defibrillator implantation	10 (63)	11 (65)	0	<0.01
Clinical outcomes				
Death	3 (11)	0	0	<0.01
Resuscitated cardiac arrest	6 (21)	11 (14)	2 (0.3)	<0.01
Appropriate implantable cardioverter-defibrillator shock	5 (18)	4 (5)	0	<0.01
Composite outcome	14 (50)	15 (19)	2 (0.3)	<0.01

Values shown are n (%). LGE indicates late gadolinium enhancement.

for patients with ringlike LGE, irrespective of LGE extent (Figure 4). Furthermore, the ringlike pattern of LGE was associated with a significantly higher incidence of outcome events during follow-up also when compared with a similar extent of LGE in contiguous segments with a non-ringlike distribution (Figure II in the Data Supplement).

After multivariable adjustment, the presence of LGE with ringlike pattern remained independently associated with increased risk of the composite end point (HR, 68.98 [95% CI, 14.67–324.39]; *P*<0.01; Table 3).

Prevalence of Additional Risk Factors According to LGE Pattern and Outcome Events

A total of 80 patients (12%) had at least 1 additional risk factor, which included family history SCD/cardiomyopathy, history of syncope, multifocal PVC, and sustained VT induction at PES. The prevalence of additional risk factors was not significantly different between patients with a ringlike LGE pattern who experienced outcome events over follow-up compared with those who remained free from events (64% vs 57%; *P*=1.00). In contrast, patients with non-ringlike LGE pattern who had events at follow-up also had a significantly higher prevalence of additional risk factors compared with those who remained free from events (67% vs 22%; *P*<0.01) as shown in Table IV in the Data Supplement and in Figure 5 by Kaplan–Meier analysis.

DISCUSSION

The present study investigated whether a specific CMR scar phenotype characterized by LV midmyocardial/subepicardial ringlike pattern of LGE is associated with risk of life-threatening arrhythmic events among patients presenting with apparently idiopathic nonsustained VA.

The main clinical messages arising from our study are as follows:

1. The absence of any LGE in patients with idiopathic VA is usually associated with a good long-term prognosis. These patients can be reassured that their risk of malignant arrhythmic events over follow-up is low.
2. The presence of LGE does increase the risk of major arrhythmic events over follow-up, in line with previous findings. However, the extent of the increase in risk is not homogenous across all of the spectrum of patients with a positive LGE finding.
3. The presence of a distinct ringlike LGE pattern is associated with a particularly high risk of malignant arrhythmic events, which is independent of the total LGE burden and presence of other additional risk factors. Identification of this specific LGE pattern in these patients deserves proper clinical attention, close follow-up, and careful evaluation for primary prevention ICD implantation.

The link between the presence of myocardial fibrosis detected by LGE-CMR and the risk of malignant arrhythmic events in patients presenting with VA has already been reported in previous studies.[5–7,11] However, risk stratification based only on the presence of LGE in patients with apparently idiopathic VA and normal ventricular function remains challenging, because previous CMR studies have reported LGE in up to 70% of these patients.[5,7,8] With such a high prevalence of positive LGE, this CMR criterion remains impractical for clinical decision making, particularly with respect to the selection of patients truly at high risk who may benefit from ICD implantation.

In this context, an evaluation of the pattern of distribution of LGE may offer additional valuable prognostic information beyond the mere presence and extent of LGE. In our study, the presence of LGE with a subepicardial/midmyocardial ringlike pattern was associated with an almost 3-fold increase in the risk compared to other types of scar distribution (Figure 4). These results are of important clinical value, because LGE distribution patterns can be readily determined by a qualitative

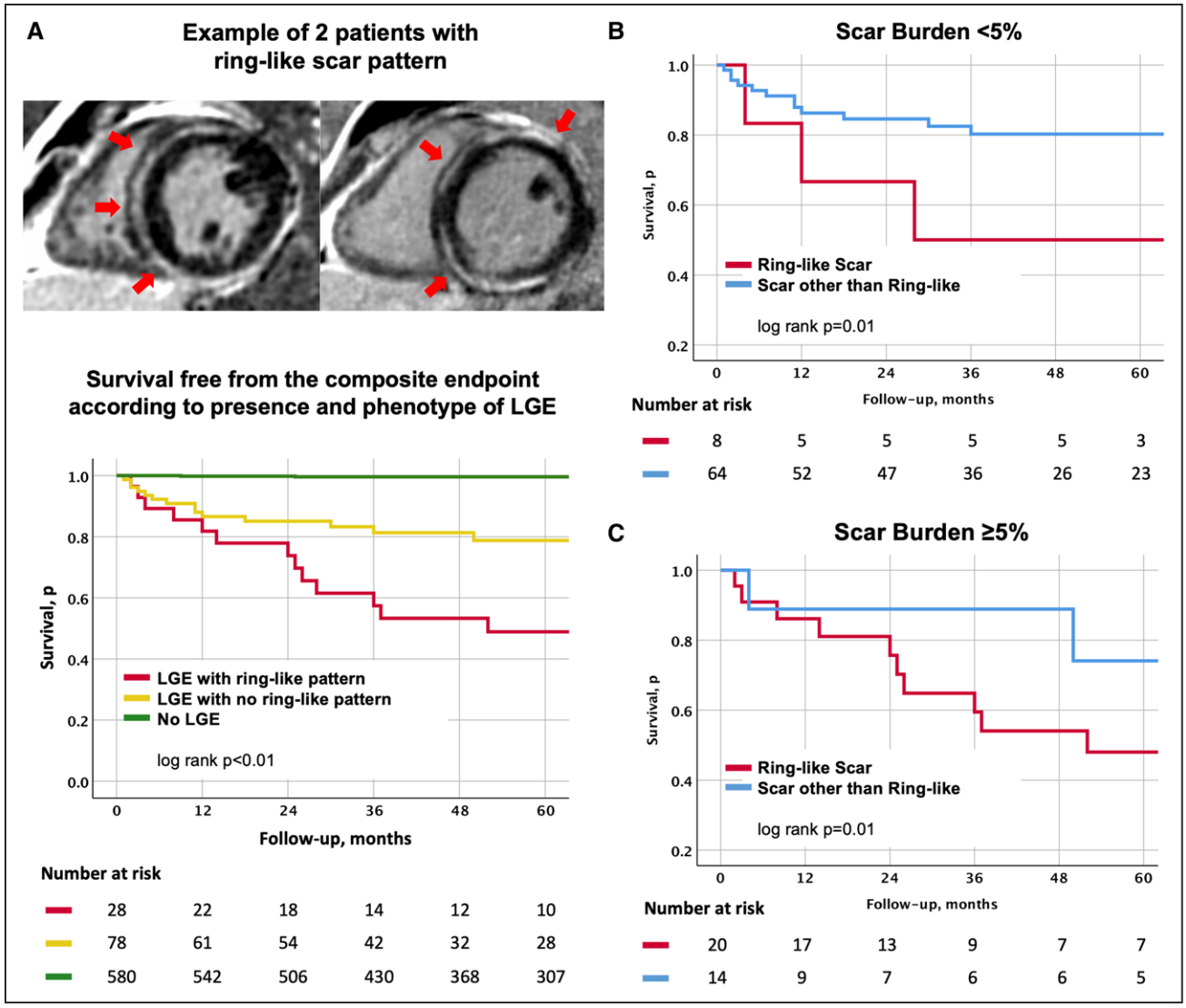

Figure 4. The effect of presence, extent, and pattern of left ventricular scar on long-term outcomes.
Kaplan–Meier survival curves showing survival free from the composite outcome according to LGE presence and pattern (**A**) and stratified by the highest tertile of LGE extent: >5% of LV mass (**B**) versus ≤5% of LV mass (**C**). LGE indicates late gadolinium enhancement; and LV, left ventricular.

assessment of CMR images and, most important, do not require quantitative analyses that may be cumbersome and time consuming.

Previous studies have correlated specific VA characteristics, such as presence of multifocal PVC and PVC-QRS fragmentation, with the presence of abnormalities found on CMR.[8,11,16,19,20] The aforementioned VA characteristics could be considered red flags to identify subjects that may present concealed cardiomyopathic substrates despite normal ECG and echo findings and prompt for a more comprehensive diagnostic workup including CMR, although the lack of these features does not necessarily rule out the presence of concealed structural abnormalities or a ringlike scar pattern. Indeed, 53% of patients with evidence of LGE and 46% of patients with a ringlike scar pattern in our study did not present multifocal PVCs or PVC-QRS fragmentation. Possible explanations include the fact that some PVC-QRS characteristics including likelihood of fragmentation are related to the specific arrhythmia site of origin. Indeed, QRS fragmentation is commonly observed for PVCs arising from the left ventricular outflow tract region (including aortic cusps and aorto-mitral continuity), the LV summit region, and the papillary muscles typically in the absence of detectable structural heart disease.[21–24] Similarly, a broader QRS duration, which may impact the likelihood of detecting fragmentation, may also be related to an epicardial focus.[25,26]

The presence of nonischemic LV scar with a subepicardial/midmyocardial layered distribution preferentially involving an LV-free wall has been associated previously with an increased risk of SCD[27] and a similar type of ringlike LGE distribution with genetically determined forms of left-dominant arrhythmogenic cardiomyopathy linked to mutations in the desmoplakin or filamin C genes.[13,28–30] It is conceivable that at least a subset

Table 3. Univariable and Multivariable Cox Proportional Hazards Analysis of Baseline Covariates in Relation to Outcome Events

	Univariable		Multivariable	
Variable	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age	1.00 (0.98–1.03)	0.74		
Male sex	3.70 (1.42–9.63)	<0.01		
Family history of sudden cardiac death, cardiomyopathy, or both	6.89 (3.30–14.39)	<0.01		
History of unexplained syncope	7.76 (3.34–18.02)	<0.01		
β-Blockers	1.95 (0.91–4.14)	0.18		
Antiarrhythmic drug therapy	2.64 (0.82–5.61)	0.15		
Premature ventricular contraction burden	0.99 (0.95–1.02)	0.54		
Multifocal premature ventricular contraction	15.70 (7.74–31.84)	<0.01	5.68 (2.45–13.15)	<0.01
Right bundle branch block: superior axis*	59.85 (14.13–253.35)	<0.01		
Right bundle branch block: inferior axis*	9.58 (1.76–52.32)	<0.01		
Left bundle branch block: superior axis*	5.68 (0.52–62.68)	0.22		
Non–left bundle branch block: inferior axis morphology	29.13 (6.95–122.08)	<0.01		
Left ventricular diastolic volume indexed	1.04 (1.02–1.07)	<0.01		
Left ventricular ejection fraction	0.95 (0.89–1.00)	0.09		
Ringlike late gadolinium enhancement pattern†	174.96 (39.73–770.42)	<0.01	68.98 (14.67–324.39)	<0.01
Non-ringlike late gadolinium enhancement†	67.89 (15.51–297.08)	<0.01	25.39 (5.33–120.93)	<0.01
Late gadolinium enhancement extent	1.27 (1.21–1.33)	<0.01		
Catheter ablation performed	0.96 (0.47–1.94)	0.90		
Acute ablation success	0.47 (0.15–1.46)	0.23		

*In comparison with left bundle branch block: inferior axis.
†In comparison with absence of late gadolinium enhancement.

of our patients with ringlike LGE pattern indeed were affected by left-dominant arrhythmogenic cardiomyopathy presenting with apparently idiopathic VA. In this regard, it is important to emphasize that a family history of SCD was present in 25% of patients with ringlike scar, and 36% of cases had family members with nonischemic cardiomyopathy. Our findings may have significant implications for genetic screening of the proband and clinical/genetic screening of the family members of the proband.[13,28,29] These subjects should be evaluated for possible arrhythmia-related symptoms and screened for asymptomatic VA with ECG and/or more extended cardiac monitors, taking into consideration that the large majority of our patients had only minimal or no symptoms. If repetitive VAs are detected, CMR investigation should be considered to assess if a similar ringlike LGE pattern is present. Additional studies are needed to determine whether there may be a benefit of "cascade" CMR screening of family members of the proband regardless of the presence of VA. The lack of systematic genotype analysis for our patients and affected family members represents a limitation of our study as detailed in the Data Supplement. However, the clinical relevance of genetic testing specifically for risk stratification of SCD is still unclear, and more studies are needed to determine whether specific genetic mutations are conclusively associated with a more malignant arrhythmic prognosis. In fact, to date genetic testing is not recommended for SCD risk stratification in most cardiomyopathies with an arrhythmic phenotype because of the variable diagnostic yield, low penetrance of mutations, phenotypic heterogeneity even in subjects with the same mutation in the same family, relevance of environmental (ie, sport, overlapping pathologies, and other conventional risk factors) and genetic modifiers, and frequent detection by next-generation sequencing of new mutations classified as variants of unknown or uncertain significance with no immediate diagnostic or clinical implications. [31–39]

The LGE extent in our sample of patients with ringlike scar (median 7%) was lower compared with other reports (median, 19%–21%).[13,40] Previous studies have reported a significant correlation among LV dysfunction, LGE extent, and ECG abnormalities, potentially explaining the smaller degree of LGE extent in our population associated with no evidence of ECG abnormalities.[40] Furthermore, the lack of any significant ECG depolarization/repolarization abnormality has also been reported in a variable proportion of patients included in studies specifically focused on left-dominant forms of arrhythmogenic cardiomyopathy.[13,28,29,40]

It is interesting to note that a ringlike scar pattern remained associated with a substantially higher risk of outcome events independent of the total burden of LGE

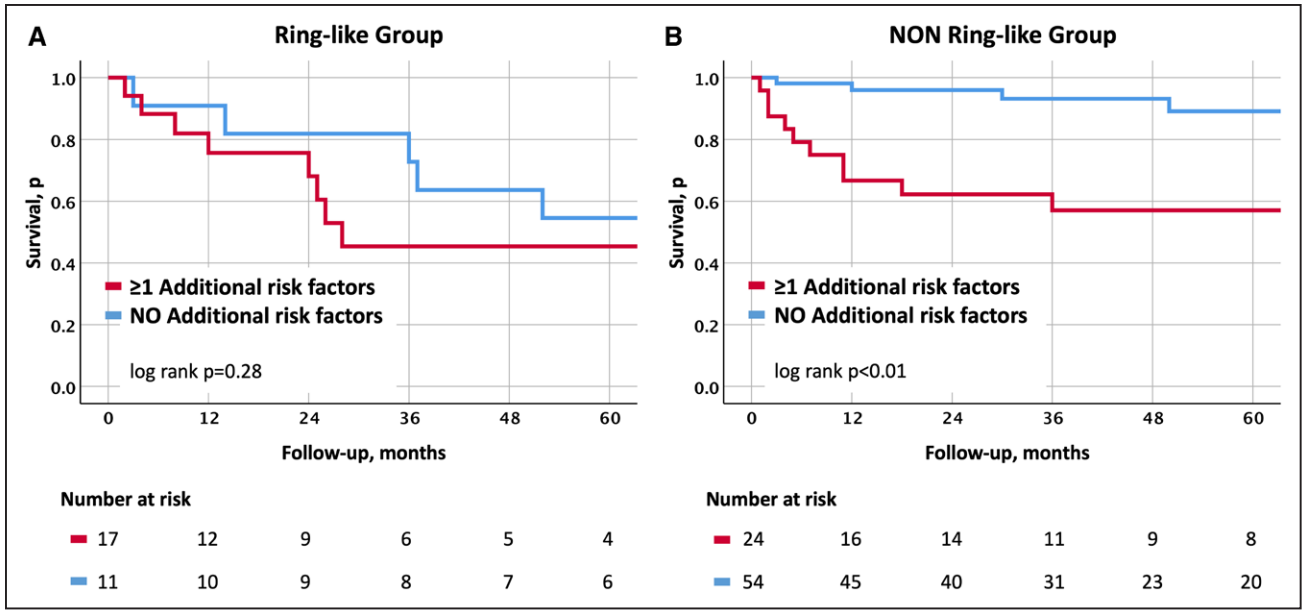

Figure 5. The effect of additional risk factors on long-term outcomes.
Survival free from the composite outcome according to the presence of additional risk factors in patients with ringlike (**A**) and non-ringlike LGE pattern (**B**). Additional risk factors: family history SCD/cardiomyopathy, history of syncope, multifocal PVC, and sustained VT induction at programmed stimulation (see also Table IV in the Supplement). LGE indicates late gadolinium enhancement; LV, left ventricular; SCD, sudden cardiac death; and VT, ventricular tachycardia.

(Figure 4) and also when compared to a similar extent of LGE in contiguous segments with a non-ringlike distribution. This is in line with previous reports showing that, in patients with idiopathic dilated cardiomyopathy, there is a nonlinear relationship between LGE extent and outcomes, with predictive models using LGE presence and location being superior to models based on LGE burden.[2,4,10] In particular, it has been shown that, in patients with dilated cardiomyopathy, concomitant LGE in the septum and free-wall (possibly reflecting a ringlike pattern at least in some cases) accounted for the greatest risk of SCD even when the absolute scar burden is small.[2] In addition, LGE was commonly observed in the absence of concomitant wall motion abnormalities or global LV dilation or dysfunction. In this regard, the peculiar nontransmural distribution sparing the inner layers of the LV wall may preserve myocardial contractility, thus explaining the absence of wall motion abnormalities and the underrecognition of the structural abnormalities detected at CMR by conventional transthoracic echocardiography.

Of note, the risk of outcome events associated with the presence of a ringlike LGE pattern appeared independent of the coexistence of additional arrhythmic risk factors, whereas patients with non-ringlike LGE may need to present additional risk factors to have truly increased arrhythmic risk (Figure 5). This finding may have important clinical implications for the selection of patients who may benefit from prophylactic ICD implantation and warrants further investigation. In this context, we found that inducibility of VT by PES at the time of the CA procedure correlated with major arrhythmic events during follow-up. In addition, among patients who underwent PES, 19% of those with evidence of LGE on CMR had inducible VT, and 67% of them experienced major arrhythmic events during follow-up confirming the value of PES in risk stratification of patients with nonsustained VA and evidence of scar on CMR.[8 41]

It is notable that neither CA nor acute ablation success appeared to influence outcomes during follow-up. It is important to point out that, in all of our cases, CA was performed because of symptomatic VA after a failed attempt at controlling symptoms with antiarrhythmic drug. As such, the main purpose of CA was to alleviate symptoms and improve quality of life and not specifically to prevent the occurrence of life-threatening arrhythmic events during follow-up. As such, although our analysis does not suggest a beneficial impact of CA on major arrhythmic outcomes over follow-up, further studies are needed to evaluate whether a more systematic adoption of CA in patients with LGE on CMR (both ringlike and non-ringlike) to target all spontaneous and inducible VA regardless of their association with symptoms and modify the abnormal arrhythmogenic substrate may be beneficial.

The findings from this study should mainly alert the practicing clinicians about specific patterns of LGE on CMR that are associated with a particularly high risk of malignant arrhythmic outcomes over follow-up. Although our results strongly suggest that patients with a ringlike scar pattern may derive benefit from prophylactic ICD implantation, we remain cautious to recommend this practice because we still believe that a properly designed prospective study specifically

evaluating the benefit and risks of ICD therapy in this group is needed.

Study Limitations

This observational study was conducted at tertiary referral centers for the diagnosis and management of VA and, as such, it is affected by an unavoidable degree of referral bias. Although the current standard at all the participating institutions, also in light of the results from this study, is to consider CMR evaluation for all patients referred for apparently idiopathic repetitive nonsustained VA to detect concealed cardiomyopathic substrates, this registry included data from a 16-year period and 7 different institutions. As expected in the context of a registry study of this kind, the criteria to proceed with CMR evaluation in patients with apparently idiopathic PVC/NSVT were not prespecified. This factor may have introduced a degree of selection bias that may have influenced the prevalence of CMR abnormalities. However, our patient population appears quite representative of an unselected cohort of "all comers" with apparently idiopathic VA, because the overall patient demographics (eg, mean age and proportion of males and females), as well as the regional distribution of VA in our study (70% arising from the outflow tract and 30% nonoutflow tract origin), are superimposable to what has been reported in other large series of patients with idiopathic VA.[42–44] Data regarding the number of patients evaluated for frequent PVC/NSVT during the same 16-year registry period but not referred for CMR were not collected, and the criteria to refer patients to CA, PES, and ICD implantation were not standardized. In this regard, the end point of appropriate ICD therapies can be influenced by the specific device programming, thus introducing some ascertainment bias. In addition, patients with an ICD are inherently followed more intensively from an arrhythmia standpoint. The small number of patients with ringlike scar, as well as the small number of outcome events, may have underpowered the multivariable analysis to appraise independent predictors of outcome events, thus affecting the HR estimates. Data on LV remodeling and scar progression by follow-up CMR were not systematically collected. Last, the lack of systematic genotype analysis or additional invasive characterization of the myocardial substrate with biopsy represent a limitation as further clarified in the Data Supplement. However, the primary objective of our study was to describe the particular clinical characteristics and evaluate the prognostic value of a specific pattern of LGE distribution in subjects with apparently idiopathic VA. As such, an additional characterization of the underlying myocardial substrate or genetic analysis, although of interest, was beyond the scope of our study and needs additional investigation.

Conclusions

In patients presenting with apparently idiopathic nonsustained VA based on routine diagnostic investigation, the presence of nonischemic LV LGE with a subepicardial/midmyocardial ringlike distribution identifies a subgroup at particularly high risk of malignant arrhythmic events during follow-up. Identification of this specific LGE pattern deserves proper clinical attention, close follow-up, and careful evaluation for primary prevention ICD implantation.

ARTICLE INFORMATION

Received April 12, 2020; accepted December 7, 2020.

The Data Supplement, podcast, and transcript are available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.119.047640.

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Sources of Funding

This study was supported by the Winkelman Family Fund in Cardiovascular Innovation and by the Richard T. and Angela Clark Innovation Fund in Cardiovascular Medicine.

Supplemental Materials

Assessment of arrhythmogenic right ventricular cardiomyopathy criteria according to the 2010 Task Force recommendations
Genetic testing
Prognostic impact of midmyocardial/subepicardial late gadolinium enhancement extent in contiguous segments
Data Supplement Tables I–IV
Data Supplement Figures I–II
References 45–48

REFERENCES

1. Disertori M, Rigoni M, Pace N, Casolo G, Masè M, Gonzini L, Lucci D, Nollo G, Ravelli F. Myocardial fibrosis assessment by LGE is a powerful predictor of ventricular tachyarrhythmias in ischemic and nonischemic LV dysfunction: a meta-analysis. *J Am Coll Cardiol. Cardiovasc Imaging*. 2016;9:1046–1055. doi: 10.1016/j.jcmg.2016.01.033
2. Halliday BP, Baksi AJ, Gulati A, Ali A, Newsome S, Izgi C, Arzanauskaite M, Lota A, Tayal U, Vassiliou VS, et al. Outcome in dilated cardiomyopathy related to the extent, location, and pattern of late gadolinium enhancement. *J Am Coll Cardiol. Cardiovasc Imaging*. 2019;12(8 pt 2):1645–1655. doi: 10.1016/j.jcmg.2018.07.015
3. Mentias A, Raeisi-Giglou P, Smedira NG, Feng K, Sato K, Wazni O, Kanj M, Flamm SD, Thamilarasan M, Popovic ZB, et al. Late gadolinium enhancement in patients with hypertrophic cardiomyopathy and preserved systolic function. *J Am Coll Cardiol*. 2018;72:857–870. doi: 10.1016/j.jacc.2018.05.060
4. Aquaro GD, Perfetti M, Camastra G, Monti L, Dellegrottaglie S, Moro C, Pepe A, Todiere G, Lanzillo C, Scatteia A, et al; Cardiac Magnetic Resonance Working Group of the Italian Society of Cardiology. Cardiac MR with late gadolinium enhancement in acute myocarditis with preserved systolic function: ITAMY study. *J Am Coll Cardiol*. 2017;70:1977–1987. doi: 10.1016/j.jacc.2017.08.044
5. Nucifora G, Muser D, Masci PG, Barison A, Rebellato L, Piccoli G, Daleffe E, Toniolo M, Zanuttini D, Facchin D, et al. Prevalence and prognostic value of concealed structural abnormalities in patients with apparently idiopathic ventricular arrhythmias of left versus right ventricular origin: a magnetic resonance imaging study. *Circ Arrhythm Electrophysiol*. 2014;7:456–462. doi: 10.1161/CIRCEP.113.001172
6. Dawson DK, Hawlisch K, Prescott G, Roussin I, Di Pietro E, Deac M, Wong J, Frenneaux MP, Pennell DJ, Prasad SK. Prognostic role of CMR in patients presenting with ventricular arrhythmias. *J Am Coll Cardiol. Cardiovasc Imaging*. 2013;6:335–344. doi: 10.1016/j.jcmg.2012.09.012
7. Aquaro GD, Pingitore A, Strata E, Di Bella G, Molinaro S, Lombardi M. Cardiac magnetic resonance predicts outcome in patients with premature ventricular complexes of left bundle branch block morphology. *J Am Coll Cardiol*. 2010;56:1235–1243. doi: 10.1016/j.jacc.2010.03.087
8. Yokokawa M, Siontis KC, Kim HM, Stojanovska J, Latchamsetty R, Crawford T, Jongnarangsin K, Ghanbari H, Cunnane R, Chugh A, et al. Value of cardiac magnetic resonance imaging and programmed ventricular stimulation in patients with frequent premature ventricular complexes undergoing radiofrequency ablation. *Heart Rhythm*. 2017;14:1695–1701. doi: 10.1016/j.hrthm.2017.06.040
9. Gulati A, Jabbour A, Ismail TF, Guha K, Khwaja J, Raza S, Morarji K, Brown TD, Ismail NA, Dweck MR, et al. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. *JAMA*. 2013;309:896–908. doi: 10.1001/jama.2013.1363
10. Halliday BP, Gulati A, Ali A, Guha K, Newsome S, Arzanauskaite M, Vassiliou VS, Lota A, Izgi C, Tayal U, et al. Association between midwall late gadolinium enhancement and sudden cardiac death in patients with dilated cardiomyopathy and mild and moderate left ventricular systolic dysfunction. *Circulation*. 2017;135:2106–2115. doi: 10.1161/CIRCULATIONAHA.116.026910
11. Muser D, Santangeli P, Castro SA, Casado Arroyo R, Maeda S, Benhayon DA, Liuba I, Liang JJ, Sadek MM, Chahal A, et al. Risk stratification of patients with apparently idiopathic premature ventricular contractions: a multicenter international CMR registry. *J Am Coll Cardiol. Clin Electrophysiol*. 2020;6:722–735. doi: 10.1016/j.jacep.2019.10.015
12. Bondarenko O, Beek AM, Hofman MB, Kühl HP, Twisk JW, van Dockum WG, Visser CA, van Rossum AC. Standardizing the definition of hyperenhancement in the quantitative assessment of infarct size and myocardial viability using delayed contrast-enhanced CMR. *J Cardiovasc Magn Reson*. 2005;7:481–485. doi: 10.1081/jcmr-200053623
13. Augusto JB, Eiros R, Nakou E, Moura-Ferreira S, Treibel TA, Captur G, Akhtar MM, Protonotarios A, Gossios TD, Savvatis K, et al. Dilated cardiomyopathy and arrhythmogenic left ventricular cardiomyopathy: a comprehensive genotype-imaging phenotype study. *Eur Heart J Cardiovasc Imaging*. 2020;21:326–336. doi: 10.1093/ehjci/jez188
14. Santangeli P, Marchlinski FE, Zado ES, Benhayon D, Hutchinson MD, Lin D, Frankel DS, Riley MP, Supple GE, Garcia FC, et al. Percutaneous epicardial ablation of ventricular arrhythmias arising from the left ventricular summit: outcomes and electrocardiogram correlates of success. *Circ Arrhythm Electrophysiol*. 2015;8:337–343. doi: 10.1161/CIRCEP.114.002377
15. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B Methodol*. 1995;57:289–300.
16. Hoffmayer KS, Machado ON, Marcus GM, Yang Y, Johnson CJ, Ermakov S, Vittinghoff E, Pandurangi U, Calkins H, Cannom D, et al. Electrocardiographic comparison of ventricular arrhythmias in patients with arrhythmogenic right ventricular cardiomyopathy and right ventricular outflow tract tachycardia. *J Am Coll Cardiol*. 2011;58:831–838. doi: 10.1016/j.jacc.2011.05.017
17. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, Calkins H, Corrado D, Cox MG, Daubert JP, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Circulation*. 2010;121:1533–1541. doi: 10.1161/CIRCULATIONAHA.108.840827
18. Neilan TG, Farhad H, Mayrhofer T, Shah RV, Dodson JA, Abbasi SA, Danik SB, Verdini DJ, Tokuda M, Tedrow UB, et al. Late gadolinium enhancement among survivors of sudden cardiac arrest. *J AM COLL CARDIOL. Cardiovasc Imaging*. 2015;8:414–423. doi: 10.1016/j.jcmg.2014.11.017
19. Oebel S, Dinov B, Arya A, Hilbert S, Sommer P, Bollmann A, Hindricks G, Paetsch I, Jahnke C. ECG morphology of premature ventricular contractions predicts the presence of myocardial fibrotic substrate on cardiac magnetic resonance imaging in patients undergoing ablation. *J Cardiovasc Electrophysiol*. 2017;28:1316–1323. doi: 10.1111/jce.13309
20. Ozawa K, Funabashi N, Takaoka H, Uehara M, Daimon M, Ueda M, Matsumoto K, Murakawa Y, Kobayashi Y. Various morphological types of fragmented ventricular premature beats on 12 lead Holter ECG had positive relationship with LV fibrotic volume on CMR in HCM subjects. *Int J Cardiol*. 2013;168:5015–5022. doi: 10.1016/j.ijcard.2013.07.155
21. Yoshida Y, Hirai M, Murakami Y, Kondo T, Inden Y, Akahoshi M, Tsuda M, Okamoto M, Yamada T, Tsuboi N, et al. Localization of precise origin of idiopathic ventricular tachycardia from the right ventricular outflow tract by a 12-lead ECG: a study of pace mapping using a multielectrode "basket" catheter. *Pacing Clin Electrophysiol*. 1999;22:1760–1768. doi: 10.1111/j.1540-8159.1999.tb00408.x
22. Tada H, Ito S, Naito S, Kurosaki K, Ueda M, Shinbo G, Hoshizaki H, Oshima S, Nogami A, Taniguchi K. Prevalence and electrocardiographic characteristics of idiopathic ventricular arrhythmia originating in the free wall of the right ventricular outflow tract. *Circ J*. 2004;68:909–914. doi: 10.1253/circj.68.909
23. Yamada T, Yoshida N, Murakami Y, Okada T, Muto M, Murohara T, McElderry HT, Kay GN. Electrocardiographic characteristics of ventricular arrhythmias originating from the junction of the left and right coronary sinuses of Valsalva in the aorta: the activation pattern as a rationale for the electrocardiographic characteristics. *Heart Rhythm*. 2008;5:184–192. doi: 10.1016/j.hrthm.2007.09.029
24. Bala R, Garcia FC, Hutchinson MD, Gerstenfeld EP, Dhruvakumar S, Dixit S, Cooper JM, Lin D, Harding J, Riley MP, et al. Electrocardiographic and electrophysiologic features of ventricular arrhythmias originating from the right/left coronary cusp commissure. *Heart Rhythm*. 2010;7:312–322. doi: 10.1016/j.hrthm.2009.11.017
25. Berruezo A, Mont L, Nava S, Chueca E, Bartholomay E, Brugada J. Electrocardiographic recognition of the epicardial origin of ventricular tachycardias. *Circulation*. 2004;109:1842–1847. doi: 10.1161/01.CIR.0000125525.04081.4B
26. Daniels DV, Lu YY, Morton JB, Santucci PA, Akar JG, Green A, Wilber DJ. Idiopathic epicardial left ventricular tachycardia originating remote from the sinus of Valsalva: electrophysiological characteristics, catheter ablation, and identification from the 12-lead electrocardiogram. *Circulation*. 2006;113:1659–1666. doi: 10.1161/CIRCULATIONAHA.105.611640
27. Zorzi A, Marra MP, Rigato I, Lazzari MD, Susana A, Niero A, Pilichou K, Migliore F, Rizzo S, Giorgi B, et al. Nonischemic left ventricular scar as a substrate of life-threatening ventricular arrhythmias and sudden cardiac death in competitive athletes. *Circ Arrhythm Electrophysiol*. 2016;9:e004229. doi: 10.1161/CIRCEP.116.004229
28. Ortiz-Genga MF, Cuenca S, Dal Ferro M, Zorio E, Salgado-Aranda R, Climent V, Padrón-Barthe L, Duro-Aguado I, Jiménez-Jáimez J, Hidalgo-Olivares VM, et al. Truncating FLNC mutations are associated with high-risk dilated and arrhythmogenic cardiomyopathies. *J Am Coll Cardiol*. 2016;68:2440–2451. doi: 10.1016/j.jacc.2016.09.927
29. Smith ED, Lakdawala NK, Papoutsidakis N, Aubert G, Mazzanti A, McCanta AC, Agarwal PP, Arscott P, Dellefave-Castillo LM, Vorovich EE, et al. Desmoplakin cardiomyopathy, a fibrotic and inflammatory form of cardiomyopathy distinct from typical dilated or arrhythmogenic right

ventricular cardiomyopathy. *Circulation*. 2020;141:1872–1884. doi: 10.1161/CIRCULATIONAHA.119.044934
30. Segura-Rodríguez D, Bermúdez-Jiménez FJ, Carriel V, López-Fernández S, González-Molina M, Oyonarte Ramírez JM, Fernández-Navarro L, García-Roa MD, Cabrerizo EM, Durand-Herrera D, et al. Myocardial fibrosis in arrhythmogenic cardiomyopathy: a genotype-phenotype correlation study. *Eur Heart J Cardiovasc Imaging*. 2020;21:378–386. doi: 10.1093/ehjci/jez277
31. Maron MS, Rowin EJ, Wessler BS, Mooney PJ, Fatima A, Patel P, Koethe BC, Romashko M, Link MS, Maron BJ. Enhanced American College of Cardiology/American Heart Association strategy for prevention of sudden cardiac death in high-risk patients with hypertrophic cardiomyopathy. *JAMA Cardiol*. 2019;4:644–657. doi: 10.1001/jamacardio.2019.1391
32. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Gimeno JR, Limongelli G, McKenna WJ, et al; Hypertrophic Cardiomyopathy Outcomes Investigators. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J*. 2014;35:2010–2020. doi: 10.1093/eurheartj/eht439
33. Cadrin-Tourigny J, Bosman LP, Nozza A, Wang W, Tadros R, Bhonsale A, Bourfiss M, Fortier A, Lie ØH, Saguner AM, et al. A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J*. 2019;40:1850–1858. doi: 10.1093/eurheartj/ehz103
34. Sieira J, Conte G, Ciconte G, Chierchia GB, Casado-Arroyo R, Baltogiannis G, Di Giovanni G, Saitoh Y, Juliá J, Mugnai G, et al. A score model to predict risk of events in patients with Brugada syndrome. *Eur Heart J*. 2017;38:1756–1763. doi: 10.1093/eurheartj/ehx119
35. Letsas KP, Bazoukis G, Efremidis M, Georgopoulos S, Korantzopoulos P, Fragakis N, Asvestas D, Vlachos K, Saplaouras A, Sakellaropoulou A, et al. Clinical characteristics and long-term clinical course of patients with Brugada syndrome without previous cardiac arrest: a multiparametric risk stratification approach. *Europace*. 2019;21:1911–1918. doi: 10.1093/europace/euz288
36. Cerrone M, Remme CA, Tadros R, Bezzina CR, Delmar M. Beyond the one gene-one disease paradigm: complex genetics and pleiotropy in inheritable cardiac disorders. *Circulation*. 2019;140:595–610. doi: 10.1161/CIRCULATIONAHA.118.035954
37. James CA, Syrris P, van Tintelen JP, Calkins H. The role of genetics in cardiovascular disease: arrhythmogenic cardiomyopathy. *Eur Heart J*. 2020;41:1393–1400. doi: 10.1093/eurheartj/ehaa141
38. Charron P, Arad M, Arbustini E, Basso C, Bilinska Z, Elliott P, Helio T, Keren A, McKenna WJ, Monserrat L, et al; European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J*. 2010;31:2715–2726. doi: 10.1093/eurheartj/ehq271
39. Walsh R, Lahrouchi N, Tadros R, Kyndt F, Glinge C, Postema PG, Amin AS, Nannenberg EA, Ware JS, Whiffin N, et al; Nantes Referral Center for inherited cardiac arrhythmia. Enhancing rare variant interpretation in inherited arrhythmias through quantitative analysis of consortium disease cohorts and population controls. *Genet Med*. 2021;23:47–58. doi: 10.1038/s41436-020-00946-5
40. Cipriani A, Bauce B, De Lazzari M, Rigato I, Bariani R, Meneghin S, Pilichou K, Motta R, Aliberti C, Thiene G, et al. Arrhythmogenic right ventricular cardiomyopathy: characterization of left ventricular phenotype and differential diagnosis with dilated cardiomyopathy. *J Am Heart Assoc*. 2020;9:e014628. doi: 10.1161/JAHA.119.014628
41. Ghannam M, Siontis KC, Kim MH, Cochet H, Jais P, Eng MJ, Attili A, Sharaf-Dabbagh G, Latchamsetty R, Jongnarangsin K, et al. Risk stratification in patients with frequent premature ventricular complexes in the absence of known heart disease. *Heart Rhythm*. 2020;17:423–430. doi: 10.1016/j.hrthm.2019.09.027
42. Kim RJ, Iwai S, Markowitz SM, Shah BK, Stein KM, Lerman BB. Clinical and electrophysiological spectrum of idiopathic ventricular outflow tract arrhythmias. *J Am Coll Cardiol*. 2007;49:2035–2043. doi: 10.1016/j.jacc.2007.01.085
43. Latchamsetty R, Yokokawa M, Morady F, Kim HM, Mathew S, Tilz R, Kuck KH, Nagashima K, Tedrow U, Stevenson WG, et al. Multicenter outcomes for catheter ablation of idiopathic premature ventricular complexes. *J Am Coll Cardiol. Clin Electrophysiol*. 2015;1:116–123. doi: 10.1016/j.jacep.2015.04.005
44. Fichtner S, Senges J, Hochadel M, Tilz R, Willems S, Eckardt L, Deneke T, Lewalter T, Dorwarth U, Reithmann C, et al; German Ablation Registry. Safety and efficacy in ablation of premature ventricular contraction: data from the German ablation registry. *Clin Res Cardiol*. 2017;106:49–57. doi: 10.1007/s00392-016-1022-9
45. Maceira AM, Prasad SK, Khan M, Pennell DJ. Normalized left ventricular systolic and diastolic function by steady state free precession cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2006;8:417–426. doi: 10.1080/10976640600572889
46. Maceira AM, Prasad SK, Khan M, Pennell DJ. Reference right ventricular systolic and diastolic function normalized to age, gender and body surface area from steady-state free precession cardiovascular magnetic resonance. *Eur Heart J*. 2006;27:2879–2888. doi: 10.1093/eurheartj/ehl336
47. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS; American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105:539–542. doi: 10.1161/hc0402.102975
48. Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. *Eur Heart J*. 2005;26:1461–1474. doi: 10.1093/eurheartj/ehi258