

Prognostic Role of CMR in Patients Presenting With Ventricular Arrhythmias

Dana K. Dawson, DM, DPHIL,* Karin Hawlisch, MD,† Gordon Prescott, PhD,*
Isabelle Roussin, MD,† Elisa Di Pietro, MD,† Monica Deac, MD,† Joyce Wong, MD,†
Michael P. Frenneaux, MD,* Dudley J. Pennell, MD,† Sanjay K. Prasad, MD†
Aberdeen and London, United Kingdom

OBJECTIVES The goal of this study was to explore whether fibrosis detected by late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) is an independent predictor of hard cardiovascular events in patients presenting with ventricular arrhythmia.

BACKGROUND In patients at risk of sudden cardiac death, risk stratification for device therapy remains challenging.

METHODS A total of 373 consecutive patients with sustained ventricular tachycardia (VT) (n = 204) or nonsustained ventricular tachycardia (NSVT) (n = 169) underwent LGE-CMR. The group was prospectively followed up for a median of 2.6 years (range 11 months to 11 years). The predetermined endpoint was a composite of cardiac death/arrest, new episode of sustained VT, or appropriate implantable cardioverter-defibrillator discharge.

RESULTS Mean left ventricular (LV) ejection fraction (EF) was $60 \pm 13\%$. The presence of fibrosis was a strong and independent predictor of the primary outcome for the whole group (hazard ratio [HR]: 3.3, 95% confidence interval [CI]: 1.8 to 5.8, $p < 0.001$). In the sustained VT subset, both LV fibrosis and severely impaired systolic function (LVEF $<35\%$) were significant independent predictors in the multivariate model (HR: 3.0, 95% CI: 1.4 to 6.2, $p = 0.001$; and HR: 2.5, 95% CI: 1.1 to 6.2, $p = 0.038$, respectively). In the NSVT subset, the presence of fibrosis was the only independent predictor of the endpoint (HR: 4.2, 95% CI: 1.7 to 10.1, $p = 0.006$).

CONCLUSIONS LGE-CMR-detected fibrosis is an independent predictor of adverse outcomes in patients with ventricular arrhythmia and may have an important role in risk stratification. (The Prognostic Significance of Fibrosis Detection in Ischemic and Non-Ischemic Cardiomyopathy; NCT00930735) (J Am Coll Cardiol Img 2013;6:335–44) © 2013 by the American College of Cardiology Foundation

From the *Cardiovascular Medicine Research Unit, School of Medicine and Dentistry, University of Aberdeen, Aberdeen, United Kingdom; and the †Royal Brompton Hospital NHS Trust, National Heart and Lung Institute, Imperial College, London, United Kingdom. This study was supported by the UK NIHR Cardiovascular Biomedical Research Unit of Royal Brompton & Harefield NHS Foundation Trust and Imperial College. Dr. Dawson was the recipient of the van Geest Advanced Imaging Fellowship. Dr. Frenneaux has been a paid speaker for the Menarini Group. Dr. Pennell is a consultant for Siemens, and a shareholder in and Director of Cardiovascular Imaging Solutions Ltd. Dr. Prasad has received honoraria for talks from Bayer Schering. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received May 15, 2012; revised manuscript received August 17, 2012, accepted September 5, 2012.

In patients presenting with ventricular arrhythmia, accurate determination of the etiology and risk stratification remains challenging. These patients may be at risk of further ventricular arrhythmic events, and some have an increased risk of sudden cardiac death (SCD). Although device therapy has a major protective benefit, patient selection remains difficult.

See page 345

Current guidelines recommend device therapy in preference to antiarrhythmic medication in patients who are survivors of cardiac arrest or sustained ventricular tachycardia (VT) (secondary prevention), or in those with significantly reduced left ventricular (LV) ejection fraction (EF) (primary prevention) (1). The majority of randomized controlled studies that explored either the secondary (2–4) or primary (5) prevention benefit of automated implantable cardioverter-defibrillator (AICD) either enrolled only patients with reduced LVEF or showed a predominant benefit in those with reduced EF (6). Consequently, the device therapy guidelines target predominantly those with reduced EF. However, subsequent post hoc data analysis from the AVID (Antiarrhythmics Versus Implantable Defibrillators) randomized controlled trial (4) showed that patients with a clearly defined lower risk profile are not likely to benefit from secondary prevention AICD (7). Coupled with reports from the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) cohort that a significant proportion of patients implanted for primary prevention never use their device (5), the fact that defibrillator therapy remains very expensive, has certain restrictive lifestyle implications, and carries risks of complications, it would be beneficial if refinements of the current criteria could be added, on the basis of stronger indices of prediction for those patients who are at risk of further life-threatening ventricular arrhythmias.

A well-established mechanism for arrhythmia is the presence of myocardial fibrosis that predisposes to re-entrant circuits (8,9). Late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) is able to detect in vivo replacement fibrosis (10,11). CMR has emerged as an important pre-

dictor of cardiovascular mortality and morbidity in patients with both ischemic (12–14) and nonischemic cardiomyopathy (14–21). Several studies showed that the presence, amount of scar, and scar heterogeneity all appear to be important for both inducible and spontaneous ventricular tachycardia (VT) (22–26).

However, if myocardial fibrosis is to be a strong predictor of malignant ventricular arrhythmia and not a simple bystander at the end stage of disease processes, its predictive value should extend to all patients with myocardial fibrosis, independent of their LVEF, whereas the absence of fibrosis should indicate a population with a better outcome.

We sought to test this hypothesis by analyzing the prognostic value of myocardial fibrosis in a consecutive cohort of all-comers with documented ventricular arrhythmias, with a known or suspected *structural* cause for arrhythmia, who were referred for CMR.

METHODS

Study patients. Consecutive patients with a recent diagnosis of nonsustained VT (NSVT) or sustained VT referred for CMR to the Royal Brompton Hospital between 1999 and 2009 were prospectively enrolled for follow-up of cardiac events. Reasons for referral were further diagnostic evaluation: assessment of cardiac structure and function, known or suspected cardiomyopathy or nonacute ischemic heart disease, assessment of anomalous coronary origin, or valvular heart disease. Cases of congenital VT (catecholaminergic, Brugada, or idiopathic QT syndromes, diagnosed on the basis of the family history, electrocardiogram [ECG], and where available, genetic testing for known genes at the time of referral) were not included in this analysis. The study was approved by the institutional ethics committee, and the subjects gave full informed consent.

Cardiac magnetic resonance. A 1.5-T Siemens scanner (Siemens, Munich, Germany) was used. After localizer scans, cine images were acquired in 3 long axes, followed by a full short-axis cine stack in all patients and a LGE study. Gadolinium DTPA (Gadovist, Bayer, Berlin, Germany) was administered as a hand-injected bolus of 0.1 mmol/kg followed by a saline flush. LGE images were acquired in each corresponding long- and short-axis cine view using a 2-dimensional segmented turbo fast low-angle shot inversion recovery sequence. The inversion time was adjusted to optimize myocardial nulling. The LGE images were repeated after swapping the phase-encoding direction, and

ABBREVIATIONS AND ACRONYMS

ACE	= angiotensin-converting enzyme
AICD	= automated implantable cardioverter-defibrillator
CAD	= coronary artery disease
CI	= confidence interval
CMR	= cardiac magnetic resonance
ECG	= electrocardiogram
EF	= ejection fraction
EP	= electrophysiology
HF	= heart failure
HR	= hazard ratio
IQR	= interquartile range
LGE	= late gadolinium enhancement
LV	= left ventricle/ventricular
LVEF	= left ventricular ejection fraction
NSVT	= nonsustained ventricular tachycardia
RV	= right ventricle/ventricular
SCD	= sudden cardiac death
VF	= ventricular fibrillation
VT	= ventricular tachycardia

all areas of observed enhancement were cross-cut to exclude artifact.

Image analysis. Ventricular function and volumes were analyzed with dedicated software (CMRtools, Cardiovascular Imaging Solutions, London, United Kingdom) as previously described (27). All volume and mass measurements were indexed to body surface area (27). The entire short-axis LGE stack of images was analyzed quantitatively for fibrosis extent by 2 independent readers with customized software (MRI-MASS, Medis, Leiden, the Netherlands). The endocardial and epicardial borders were traced for each short-axis slice. A region of interest averaging 50 mm² was defined within the normal remote myocardium in an area with uniform myocardial suppression free of artifacts. A multipass region-growing algorithm was used to identify the fibrotic boundaries on the basis of the “full width half maximum” technique; fibrosis was expressed as present or absent, and its extent was quantified as a percentage of total LV mass (20).

Follow-up data. Events data were collected in all cases by communication with the patient via a mailed questionnaire and by examination of the primary care physician’s records as well as examination of the referring hospital records. Mortality data were cross-checked with the Office of National Statistics. Only new events after enrolment were considered in the analysis. Patients were censored after reaching the composite endpoint, which was a combination of dysrhythmic cardiac death, cardiac arrest, new episode of sustained VT or ventricular fibrillation (VF), or appropriate AICD discharge, as defined by a change in the configuration of the stored ECG (28). Patients who underwent electrophysiology (EP) ablation for VT were censored at the time of EP ablation, as this intervention skews the natural course of an arrhythmic history.

Statistical analysis. All statistical analyses were performed in SPSS version 18 (SPSS, Armonk, New York). Results are presented as mean ± SD or n (%) for continuous and categorical variables, respectively. Comparisons between groups were made with the independent Student *t* test of chi-square cross-tabulations for continuous and categorical data, respectively. Kaplan-Meier survival curves were used to test the significance of each independent variable as a predictor of the endpoint as a comparator between groups. All demographic, clinical, and scan variables that were significant univariate predictors (with a *p* value <0.05) were subsequently entered in a multivariate model. Each Cox proportional hazards model was constructed using

with a forward conditional stepwise procedure. The selected multivariate model was refitted without using a stepwise procedure to avoid problems of missing data in unselected variables. The assumption of proportional hazards was checked using graphical methods (29). The predictions from some simple models were compared using the net reclassification index (30).

RESULTS

Baseline characteristics. Between 1999 and 2009, a total of 373 patients were recruited. The baseline characteristics of the cohort are summarized in Table 1. They were followed up for a median of 2.6 years (range 11 months to 11 years, interquartile range [IQR]: 1.1 to 3.6 years). Replacement fibrosis was detected in 122 (33%) of patients on the LGE study, 55 of whom received an AICD. The group with fibrosis was older by 8 years than the no-fibrosis group and similar in ethnic origin. Fibrosis was present in 38% of VT patients and 27% of NSVT patients (*p* = 0.030). Coronary artery disease (CAD) (as diagnosed by coronary angiography), heart failure (HF), and diabetes were significantly higher in the fibrosis group (*p* < 0.01). Fibrosis was also more frequent in men versus women (42% vs. 17%, *p* < 0.001). The fibrosis group was more likely to be receiving angiotensin-converting enzyme (ACE) inhibitors or beta-blockers compared with the no-fibrosis group (*p* < 0.001 for each medication). The resting ECG was abnormal in 134 patients (T-wave inversion, ST/T-wave changes, voltage criteria of LV hypertrophy, left or right bundle branch block, atrial fibrillation, multiple ventricular ectopic beats, first-degree atrioventricular block). After clinical evaluation (which included access to the CMR report), 116 patients with LVEF >35% were implanted with an AICD.

CMR characteristics are presented in Table 2. The mean LVEF of the entire study population was 60 ± 13%. For the entire cohort (both NSVT and VT groups), patients with fibrosis had significantly increased LV volumes and mass (both before and after they were normalized to body surface area, sex, and decile of age, *p* < 0.001), reduced LVEF (*p* < 0.001), increased right ventricular (RV) volumes (*p* < 0.05), and reduced RVEF (*p* = 0.004). Fibrosis was located subepicardially (*n* = 2), mid-wall (*n* = 69), subendocardially (*n* = 18), transmurally (*n* = 23), or diffusely (*n* = 10) in the total 122 patients who demonstrated late enhancement.

Table 1. Baseline Characteristics of the 373 Patients Enrolled

	LGE Fibrosis (–) (n = 251)	LGE Fibrosis (+) (n = 122)	Total (N = 373)	p Value
Age at recruitment, yrs	48 ± 15	57 ± 15		<0.001
Male	139	99	238	<0.001
Ethnicity				0.952
Caucasian	136	64	200	
African-Caribbean/Asian	10	5	15	
Unknown/other	105	53	158	
Presentation				0.030
NSVT	124	45	169	
VT	127	77	204	
Medication				
Aspirin	52	53	105	<0.001
Beta-blocker	118	83	201	<0.001
ACE inhibitor	56	65	121	<0.001
Furosemide	8	23	31	<0.001
Statin	51	56	107	<0.001
Past medical history				
Hypertension	47	34	81	0.023
Hypercholesterolemia	50	37	87	0.011
Diabetes	11	17	28	0.001
Heart failure	8	14	22	0.001
Coronary artery disease	5	24	29	<0.001
Stroke	4	3	7	0.429

Values are mean ± SD or n. Where a characteristic is clearly binary (medication used or not, disease present or not), only the counts for 1 of the 2 categories is presented, and the p value is presented on the same row as the name of the characteristic. The p value represents comparisons between the LGE fibrosis negative (–) and LGE fibrosis positive (+) groups.
ACE = angiotensin-converting enzyme; LGE = late gadolinium enhancement; NSVT = nonsustained ventricular tachycardia; VT = ventricular tachycardia.

Patients with each of the 2 clinical presentations were also analyzed separately (Table 2). In the VT group, patients with fibrosis showed significant LV and RV remodeling compared with those without fibrosis. In the NSVT group, there was significant LV remodeling in those with fibrosis, but there were no differences in the RV volume parameters between groups. When fibrosis was present, the amount of fibrosis measured in the LV was comparable between the VT and NSVT subgroups.

Hard events. During follow-up, there were 6 non-cardiac deaths, and 15 patients underwent EP ablation, all for VT. Fifty-three patients (35 in the VT and 18 in the NSVT group) reached the composite endpoint (15 [28%] cardiac death, 1 [1.8%] cardiac arrest, 15 [28%] AICD discharge, 22 [41%] sustained VT); and 9 patients met the primary outcome on 2 occasions (but were censored at first event for analysis). Of the 53 reaching the primary outcome, 33 (62%) were in the fibrosis group. For the entire cohort, variables that were found to be significant univariate predictors of the primary outcome were a past medical history of CAD (log-rank chi-square test = 5.8, $p = 0.016$), an increased LV end-systolic volume (log-rank

chi-square test = 5.2, $p = 0.023$), and presence of LGE fibrosis (log-rank chi-square test = 22, $p < 0.001$). Reduced LVEF was a significant predictor of events in the univariate analysis, whether it was represented with a cutoff at LVEF <55% (log-rank chi-square test = 10, $p = 0.002$), or a cutoff at LVEF ≤35% (log-rank chi-square test = 6.1, $p = 0.014$), or as 3 categories (≤35, 36 to 54, ≥55, log-rank chi-square test = 11.3, $p = 0.004$) (Fig. 1A). Reduced RVEF was similarly associated with the events, but added nothing extra when fitted in the same model with LVEF. The most inclusive list of variables offered to the forward stepwise selection included past medical history of myocardial infarction, of CAD and of HF, family history of SCD, LV end-systolic volume category, presence of LGE fibrosis, and a representation of LVEF. In the multivariate model, the presence of fibrosis was the only independent predictor of the primary outcome (hazard ratio [HR]: 3.3, 95% confidence interval [CI]: 1.8 to 5.8, $p < 0.001$). LVEF <55% had an elevated HR, but was not significant at the 5% significance level for the primary outcome after adjusting for presence of fibrosis (HR: 1.4, 95% CI: 0.7 to 2.5, $p = 0.31$). No other representations of

Table 2. CMR Characteristics of the 373 Patients Enrolled

	All Patients			VT Patients (n = 204)			NSVT Patients (n = 169)		
	LGE (-) (n = 251)	LGE (+) (n = 122)	p Value	LGE (-) (n = 127)	LGE (+) (n = 77)	p Value	LGE (-) (n = 124)	LGE (+) (n = 45)	p Value
LVEDV, ml	154 ± 43	213 ± 86	<0.001	153 ± 43	218 ± 86	<0.001	154 ± 43	205 ± 86	0.001
LVEDVi, ml/m ²	80 ± 19	107 ± 40	<0.001	80 ± 19	107 ± 40	<0.001	81 ± 20	105 ± 40	<0.001
LVESV, ml	56 ± 30	114 ± 79	<0.001	58 ± 29	117 ± 80	<0.001	54 ± 31	110 ± 78	<0.001
LVESVi, ml/m ²	29 ± 15	57 ± 38	<0.001	30 ± 15	58 ± 39	<0.001	28 ± 15	57 ± 39	<0.001
LVEF, %	65 ± 10	51 ± 16	<0.001	64 ± 10	51 ± 16	<0.001	66 ± 9	51 ± 18	<0.001
LVM, g	140 ± 43	178 ± 79	<0.001	142 ± 44	170 ± 78	0.006	137 ± 42	192 ± 81	<0.001
LVMi, g/m ²	73 ± 19	89 ± 36	<0.001	74 ± 18	83 ± 35	0.033	71 ± 19	98 ± 36	<0.001
RVEDV, ml	162 ± 47	182 ± 71	0.010	164 ± 50	191 ± 73	0.008	161 ± 43	166 ± 67	0.634
RVEDVi, ml/m ²	80 ± 28	75 ± 47	0.337	81 ± 29	79 ± 48	0.771	78 ± 28	69 ± 46	0.184
RVESV, ml	69 ± 31	90 ± 57	0.001	72 ± 35	97 ± 61	0.002	66 ± 26	77 ± 49	0.190
RVESVi, ml/m ²	34 ± 17	37 ± 31	0.248	35 ± 18	40 ± 33	0.226	32 ± 15	32 ± 28	0.982
RVEF, %	59 ± 9	53 ± 14	0.001	58 ± 10	52 ± 14	0.008	60 ± 8	56 ± 13	0.072
Fibrosis, absolute	0 (0)	16 (8-34)	n/a	0 (0)	16 (8-33)	n/a	0 (0)	16 (7-34)	n/a
Fibrosis, % of LVM	0 (0)	10 (5-23)	n/a	0 (0)	10 (6-23)	n/a	0 (0)	10 (4-20)	n/a

Values are mean ± SD or median (IQR). p Values represent comparisons between the LGE negative (-) and LGE positive (+) groups.
CMR = cardiac magnetic resonance; IQR = interquartile range; LVEDV = left ventricular end-diastolic volume; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVESVi = left ventricular end-systolic volume index; LVM = left ventricular mass; LVMi = left ventricular mass index; RVEDV = right ventricular end-diastolic volume; RVEDVi = right ventricular end-diastolic volume index; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; RVESVi = right ventricular end-systolic volume index; other abbreviations as in Table 1.

LVEF (cutoff at ≤35% or in 3 categories: LVEF ≤35, 36% to 54%, ≥55%) were significant after adjusting for fibrosis. Given the significance of the multivariate analysis of presence/absence of fibrosis for the combined outcome, data were also represented with a cutoff at the median value of 10% fibrosis: relative to having no fibrosis, having <10% fibrosis, or ≥10% fibrosis showed a comparable hazard of the composite endpoint (HR: 3.5, 95% CI: 1.8 to 6.7; and HR: 3.7, 95% CI: 1.9 to 7.3, respectively). Figure 1B shows the survival analysis of the patients with fibrosis compared with those without fibrosis, and Figure 1C shows the increase in absolute risk of reaching the composite endpoint for all patients with presence of fibrosis.

Subgroup analyses. In the sustained VT group, the univariate variables that significantly influenced survival were a past medical history of CAD (chi-square test = 10.2, p = 0.001) as well as presence of LV fibrosis (chi-square test = 12.1, p < 0.001). Reduced LVEF was a significant univariate predictor whether divided into 3 categories, that is, LVEF ≤35%, 36% to 54%, ≥55%, (chi-square test = 13.2, p = 0.001) (Fig. 2A) or using a cutoff at LVEF ≤35% (chi-square test = 12.9, p < 0.001), but not quite significant at the 5% level as a cutoff at LVEF <55%.

The most inclusive list of variables offered to the forward stepwise selection included past medical history of CAD and of HF, family history of SCD,

presence of LGE fibrosis, and a representation of LVEF. Both LV fibrosis and a severely impaired systolic function (LVEF ≤35%) appeared to be significant predictors in the multivariate model (HR: 3.0, 95% CI: 1.4 to 6.2, p = 0.001, and HR: 2.5, 95% CI: 1.1 to 6.2, p = 0.038, respectively). There was no evidence of an interaction between fibrosis and LVEF.

With a similar cutoff at the median value of 10%, having <10% fibrosis, relative to having no fibrosis, increased the hazard of the composite endpoint (HR: 2.9, 95% CI: 1.2 to 6.9), and having ≥10% fibrosis similarly increased the risk (HR: 3.8, 95% CI: 1.7 to 8.2). Figure 2B shows the survival analysis of the VT patients with fibrosis compared with those without fibrosis. Figure 2C shows the increase in absolute risk of reaching the composite endpoint for the VT patients with presence of fibrosis.

In the NSVT group, the univariate variables that predicted the likelihood of reaching a primary outcome were the LV mass index (log-rank chi-square test = 4.6, p = 0.031), LVEF <55% (log-rank chi-square test = 7.2, p = 0.007), and the presence of LV fibrosis (log-rank chi-square test = 8.8, p = 0.003). (LVEF represented as 3 categories was also a significant predictor [log-rank chi-square test = 13.5, p = 0.001], but LVEF cutoff at 35% was not.) The most inclusive list of variables offered to the forward stepwise selection included past medical history of CAD and of HF, family history of SCD,

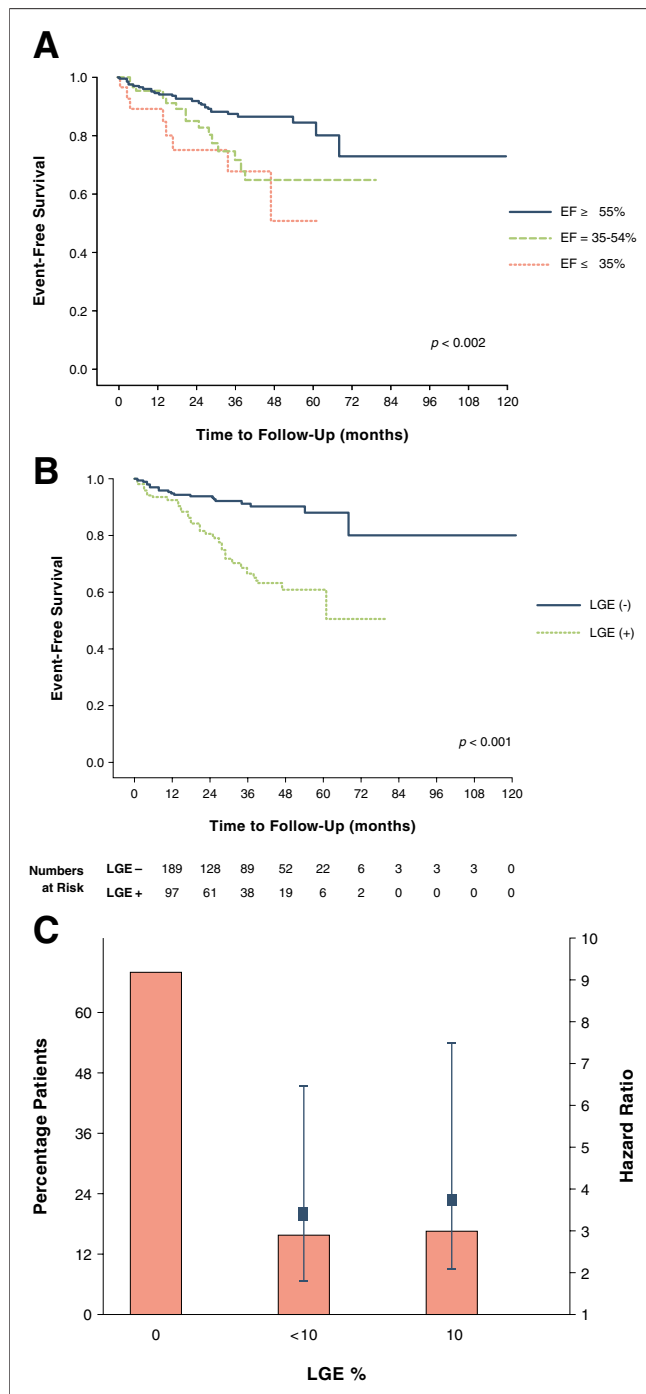


Figure 1. Entire Cohort: Survival Analysis by EF and LGE, and Proportional Hazards Relative to Extent of Fibrosis

(A) Kaplan-Meier estimated freedom from reaching the combined endpoint in all 373 patients (sustained and nonsustained ventricular tachycardia [VT]) according to the left ventricular ejection fraction (EF) represented by 3 categories. (B) Entire cohort: survival analysis by late gadolinium enhancement (LGE). Kaplan-Meier estimated freedom from reaching the combined endpoint in all 373 patients (sustained and nonsustained VT) according to presence or absence of fibrosis. (C) Entire cohort: proportional hazards relative to extent of fibrosis. Hazard ratios for reaching the composite endpoint for all 373 study patients grouped into 3 categories: no fibrosis, <10% fibrosis, or $\geq 10\%$ fibrosis.

ordered categories of LV mass index, presence of LGE fibrosis, and a representation of LVEF. Patients with NSVT and fibrosis were more likely to reach a primary outcome (HR: 4.2, 95% CI: 1.7 to 10.1, $p = 0.006$) compared with those without fibrosis, and this remained the only significant predictor in the multivariate model. Figure 3A shows the estimated survival analysis of the NSVT patients with fibrosis compared with those without fibrosis. Although there was an elevated HR for the percentage of fibrosis, it was not statistically significant (HR: 1.09, 95% CI: 0.91 to 1.29, $p = 0.331$). Relative to having no fibrosis, having <10% fibrosis significantly increased the hazard of the composite endpoint (HR: 5.9, 95% CI: 2 to 17.3), but having $\geq 10\%$ fibrosis did not (HR: 2.4, 95% CI: 0.7 to 8) (Fig. 3B).

The unadjusted and adjusted hazard ratios for all variables included in the Cox multivariate models are presented in Table 3.

A net reclassification index (30) was used to compare risk prediction between LGE (as 3 categories: normal [no scarring], less than median scarring [10%] among those with scarring, median or greater scarring among those with scarring) and LVEF (also as 3 ordered categories: normal [$\geq 55\%$], high abnormal [36% to 54%], and low abnormal [$\leq 35\%$]). Higher proportions were classified as high risk using LGE $\geq 10\%$ (34% of patients with the outcome and 14% without) than LVEF $\leq 35\%$ (15% and 6%, respectively). Overall, there was marginally better risk prediction of the composite endpoint on the basis of LGE than on LVEF, but this did not reach statistical significance ($p = 0.10$). Patients with VT showed the same modest improvement in prediction with LGE than LVEF ($p = 0.13$), and there was no difference for patients with NSVT ($p = 0.59$).

DISCUSSION

The main findings of this study are:

1. In patients presenting with ventricular arrhythmia (excluding those with arrhythmia of congenital or genetic etiology), the presence of myocardial fibrosis is an important independent predictor of the combined endpoint of cardiac death, cardiac arrest, new episode of sustained VT, VF, or appropriate AICD discharge.
2. In patients who presented with an episode of sustained VT, both the presence of fibrosis on CMR-LGE and a poor LVEF ($\leq 35\%$) were significant predictors of the combined endpoint. In this study, the assessment of fibrosis was not only an

independent predictor, but also a better predictor of the composite endpoint than LVEF.

3. In patients who presented with a previous episode of NSVT, the presence of fibrosis on CMR-LGE was the only independent predictor of the combined endpoint.

These findings suggest that assessment of myocardial fibrosis could be complementary to measurement of LVEF for risk stratification and could bring refinements to the current criteria for prescription of AICD as well as identify other high-risk groups that did not previously qualify.

A well-recognized mechanism for sudden cardiac death is the presence of fibrosis causing electrical instability in the LV myocardium through re-entrant arrhythmias (31). In EP studies, a key aim is to identify areas of fibrosis as a focus for ablation. The negative predictive value of a normal LGE-CMR has already been suggested in smaller studies, for example, absence of fibrosis in nonischemic cardiomyopathy identified a group at much lower risk (24). Conversely, the presence of fibrosis in hypertrophic cardiomyopathy (17,18,32), ischemic cardiomyopathy (22), or other nonischemic (21) cardiomyopathy identified those at higher risk. However, most of these studies followed up patients who already qualified for an AICD by the current criteria and therefore most had severely depressed EF (<35%).

Implications for secondary prevention. Our current study was novel in enrolling all comers with VT and NSVT, so that we can adequately compare the individual impacts of LGE and LV remodeling with respect to their predictive values. Indeed, the mean EF of our study population was $60 \pm 13\%$. This is markedly different from the landmark studies on the basis of which AICD is recommended for secondary prevention by the current guidelines: in the AVID trial (4), the mean EF of patients was 32%; in CASH (Cardiac Arrest Study Hamburg) (2), the mean EF was 46%; and in CIDS (Canadian Implantable Defibrillator Study) (3), the mean EF was 33%. Our findings in the VT subgroup, which identified an EF $\leq 35\%$ and the presence of LV fibrosis as the only 2 important predictors of hard cardiovascular events after multivariate analysis, is in agreement with the earlier studies: a poor EF is a significant predictor of further ventricular arrhythmia. However, an important finding in this study is that the presence of LV fibrosis appears to be a stronger predictor of events, even in those with poor EF. The implication that in those with mild-to-moderate LV impairment or normal LVEF, the presence of fibrosis is in fact the

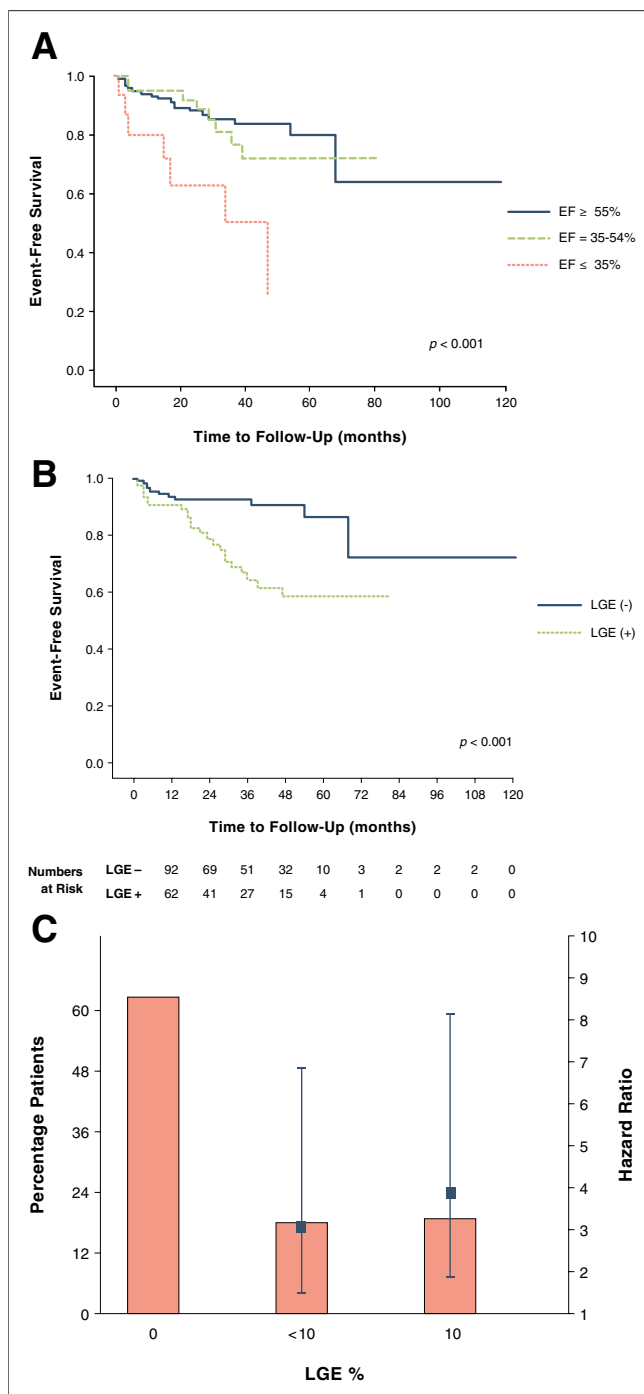


Figure 2. Sustained VT Group: Survival Analysis by EF and LGE, and Proportional Hazards Relative to Extent of Fibrosis

(A) Kaplan-Meier estimated freedom from reaching the combined endpoint in the 204 VT patients according to the left ventricular EF represented by 3 categories. (B) Sustained VT group: survival analysis by LGE. Kaplan-Meier estimated freedom from reaching the combined endpoint in the 204 patients with sustained VT according to presence or absence of fibrosis. (C) Sustained VT group: proportional hazards relative to extent of fibrosis. Hazard ratios for reaching the composite endpoint for the 204 sustained VT patients grouped into 3 categories: no fibrosis, <10% fibrosis, or $\geq 10\%$ fibrosis. Abbreviations as in Figure 1.

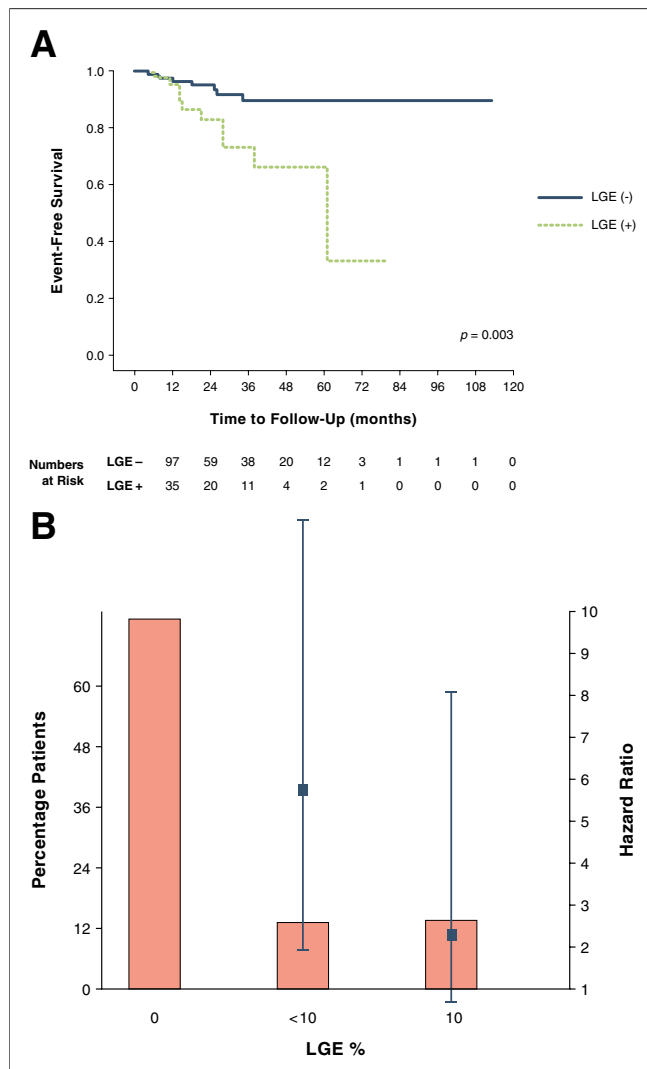


Figure 3. NSVT Group: Survival Analysis by LGE and Proportional Hazards Relative to Extent of Fibrosis

(A) Kaplan-Meier estimated freedom from reaching the combined endpoint in the 169 patients with nonsustained ventricular tachycardia (NSVT) according to presence or absence of fibrosis. (B) NSVT group: proportional hazards relative to extent of fibrosis. Hazard ratios for reaching the composite endpoint for the 169 NSVT patients grouped into 3 categories: no fibrosis, <10% fibrosis, or $\geq 10\%$ fibrosis. Abbreviations as in Figure 1.

only significant predictor of events, warrants further exploration. Although current guidelines for AICD implantation as secondary prevention list those with sustained VT and structural heart disease as a Class I, Level of Evidence: B indication, it is conceivable that in vivo detection of fibrosis may be able to identify those patients with structural heart disease who could derive particular benefit from AICD prescription. Our findings are in agreement with the findings of Iles et al. (24), who showed a significant difference between groups of patients

with structural heart disease who had fibrosis versus those without fibrosis with respect to recurrence of ventricular arrhythmia episodes.

Of the randomized controlled studies that compared AICD implantation with antiarrhythmic medication for secondary prevention, only AVID demonstrated a statistically significant survival benefit. This implies that better discrimination of those patients who will use an AICD is desirable. If confirmed by other studies, our findings have the potential to refine the criteria for secondary prevention, as already challenged by post hoc analyses of landmark studies that identified that patients at lower risk may not benefit from AICD implantation (7). Risk stratification inclusive of LV fibrosis may contribute as a robust biomarker for arrhythmia recurrence in these patients.

Implications for primary prevention. The primary prevention of ventricular arrhythmias remains a subject of intense debate. The group we studied has an element of self-selection, as they already presented with an NSVT episode rather than being arrhythmia naive (the same applied to randomized controlled studies of primary prevention, for example, in those with nonischemic cardiomyopathy enrolled in the DEFINITE [Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation] trial [33]). Although a depressed EF ($\leq 35\%$) is the mainstay for favoring AICD therapy in the current guidelines, almost irrespective of etiology, our results were unable to confirm this because we had very few patients in the NSVT subgroup with severely impaired EF ($\leq 35\%$): 12 of 169. This is, of course, expected, as in accordance with current guidelines, those with poor EF would have been prescribed an AICD by their attending cardiologist, and further investigation before device placement would often be deemed unnecessary. For the remaining majority of patients presenting with NSVT, our results showed that the presence of fibrosis was the only predictor of the combined outcome. This result is interesting because it opens new avenues of consideration for primary prevention in groups that are not included by guidelines and are treated by individual consideration in current medical practice.

Study limitations. Inevitably, there will be some referral bias dependent on referring physician practice. It is conceivable that those at greatest risk were not referred because an AICD was considered mandatory on the basis of current guidelines. Also, risk in this work is determined on the basis of a fixed rather than a progressive review based on stratified assess-

Table 3. Unadjusted and Adjusted HR for the Cox Proportional Models

	Univariate Cox (Unadjusted) HR	CI	p Value	Chi-Square	Multivariate Cox (Adjusted) HR	CI	p Value	Chi-Square
All patients								
LVEF ≤35%	2.49	1.17-5.30	0.018	6.0	1.44*	0.66-3.17	0.36	10.7
LVEF <55%	2.34	1.36-4.03	0.002	10.0	1.38†	0.74-2.53	0.31	10.3
Presence of LGE	3.51	2.01-6.13	<0.001	22.2	3.26*	1.83-5.82	<0.001	
LGE 0%	1.00		Overall <0.001	23.5				
LGE 0.1% to 9.9%	3.53	1.87-6.67	<0.001					
LGE ≥10%	3.74	1.91-7.34	<0.001					
LGE per 5% extra fibrosis	1.12	1.03-1.22	0.01	0.95				
VT								
LVEF ≤35%	4.10	1.78-9.46	0.001	12.8	2.54*	1.05-6.18	0.038	19.1
LVEF <55%	1.86	0.95-3.64	0.069	3.4	1.21†	0.59-2.49	0.61	12.0
Presence of LGE	3.23	1.60-6.49	0.001	12.1	2.95*	1.39-6.25	0.001	
LGE 0%	1.00		Overall 0.002	13.9				
LGE 0.1% to 9.9%	2.88	1.21-6.87	0.017					
LGE ≥10%	3.79	1.75-8.20	0.001					
LGE per 5% extra fibrosis	1.13	1.02-1.25	0.025	5.3				
NSVT								
LVEF ≤35%	0.67	0.09-5.05	0.70	0.15	0.35*	0.05-2.70	0.31	10.7
LVEF <55%	3.34	1.31-8.53	0.012	7.2	1.83†	0.57-5.85	0.31	10.3
Presence of LGE	3.73	1.47-9.50	0.006	8.8	4.27*	1.66-10.99	0.003	
LGE 0%	1.00		Overall 0.005	12.9				
LGE 0.1% to 9.9%	5.89	2.00-17.33	0.001					
LGE ≥10%	2.44	0.74-8.12	0.15					
LGE per 5% extra fibrosis	1.09	0.92-1.29	0.34	0.95				

*HR, 95% CI, and p value when LVEF ≤35 is fitted in a model with presence of fibrosis. †HR, 95% CI, and p value for LVEF <55% when fitted in a model with presence of fibrosis. CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

ment. Our quantitative analysis of fibrosis assumed calibration of signal intensity to a remote area of myocardium considered normal—in practice it is also conceivable that in disease states, diffuse fibrosis may be present in the remote myocardium, and if so, this would slightly alter the amount of calculated replacement fibrosis by this technique.

CONCLUSIONS

In this study, we evaluated the prognostic significance of LV fibrosis in patients presenting with a ventricular arrhythmia. Patients with detectable myocardial fibrosis had a significantly higher risk of reaching the combined outcome of cardiac

death, cardiac arrest, new episode of sustained VT or VF, and appropriate AICD discharge. The presence of fibrosis was the most significant independent predictor in multivariate analyses and may have merit as an important biomarker for further risk stratification. These findings have the potential to bring significant refinement in prescribing AICD therapy for both primary and secondary prevention.

Reprint requests and correspondence: Dr. Dana K. Dawson, Cardiovascular Medicine Research Unit, School of Medicine and Dentistry, University of Aberdeen, Aberdeen, AB25 2ZD, United Kingdom. *E-mail:* dana.dawson@abdn.ac.uk

REFERENCES

- Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices). *J Am Coll Cardiol* 2008;51:e1-62.
- Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated

- from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). *Circulation* 2000;102:748-54.
3. Connolly SJ, Gent M, Roberts RS, et al. Canadian Implantable Defibrillator Study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000;101:1297-302.
 4. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med* 1997;337:1576-83.
 5. Moss AJ, Greenberg H, Case RB, et al. Long-term clinical course of patients after termination of ventricular tachyarrhythmia by an implanted defibrillator. *Circulation* 2004;110:3760-5.
 6. Domanski MJ, Sakseena S, Epstein AE, et al. Relative effectiveness of the implantable cardioverter-defibrillator and antiarrhythmic drugs in patients with varying degrees of left ventricular dysfunction who have survived malignant ventricular arrhythmias. *J Am Coll Cardiol* 1999;34:1090-5.
 7. Hallstrom AP, McAnulty JH, Wilkoff BL, et al. Patients at lower risk of arrhythmia recurrence: a subgroup in whom implantable defibrillators may not offer benefit. *J Am Coll Cardiol* 2001;37:1093-9.
 8. Soejima K, Stevenson WG, Sapp JL, Selwyn AP, Couper G, Epstein LM. Endocardial and epicardial radiofrequency ablation of ventricular tachycardia associated with dilated cardiomyopathy: the importance of low-voltage scars. *J Am Coll Cardiol* 2004;43:1834-42.
 9. Bello D, Fieno DS, Kim RJ, et al. Infarct morphology identifies patients with substrate for sustained ventricular tachycardia. *J Am Coll Cardiol* 2005;45:1104-8.
 10. Kim RJ, Fieno DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation* 1999;100:1992-2002.
 11. Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 2000;343:1445-53.
 12. Kwong RY, Chan AK, Brown KA, et al. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. *Circulation* 2006;113:2733-43.
 13. Yokota H, Heidary S, Katikireddy CK, et al. Quantitative characterization of myocardial infarction by cardiovascular magnetic resonance predicts future cardiovascular events in patients with ischemic cardiomyopathy. *J Cardiovasc Magn Reson* 2008;10:17.
 14. Cheong BYC, Muthupillai R, Wilson JM, et al. Prognostic significance of delayed-enhancement magnetic resonance imaging. *Circulation* 2009;120:2069-76.
 15. Assomull RG, Prasad SK, Lyne J, et al. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. *J Am Coll Cardiol* 2006;48:1977-85.
 16. Kwong RY, Sattar H, Wu H, et al. Incidence and prognostic implication of unrecognized myocardial scar characterized by cardiac magnetic resonance in diabetic patients without clinical evidence of myocardial infarction. *Circulation* 2008;118:1011-20.
 17. Leonardi S, Raineri C, De Ferrari GM, et al. Usefulness of cardiac magnetic resonance in assessing the risk of ventricular arrhythmias and sudden death in patients with hypertrophic cardiomyopathy. *Eur Heart J* 2009;30:2003-10.
 18. Rubinshtein R, Glockner JF, Ommen SR, et al. Characteristics and clinical significance of late gadolinium enhancement by contrast-enhanced magnetic resonance imaging in patients with hypertrophic cardiomyopathy. *Circ Heart Fail* 2010;3:51-8.
 19. Adabag AS, Maron BJ, Appelbaum E, et al. Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. *J Am Coll Cardiol* 2008;51:1369-74.
 20. O'Hanlon R, Grasso A, Roughton M, et al. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2010;56:867-74.
 21. Wu KC, Weiss RG, Thieman DR, et al. Late gadolinium enhancement by cardiovascular magnetic resonance heralds an adverse prognosis in nonischemic cardiomyopathy. *J Am Coll Cardiol* 2008;51:2414-21.
 22. Roes SD, Borleffs CJW, van der Geest RJ, et al. Infarct tissue heterogeneity assessed with contrast-enhanced MRI predicts spontaneous ventricular arrhythmia in patients with ischemic cardiomyopathy and implantable cardioverter-defibrillator. *Circ Cardiovasc Imaging* 2009;2:183-90.
 23. Heidary S, Patel H, Chung J, et al. Quantitative tissue characterization of infarct core and border zone in patients with ischemic cardiomyopathy by magnetic resonance is associated with future cardiovascular events. *J Am Coll Cardiol* 2010;55:2762-8.
 24. Iles L, Pfluger H, Lefkowitz L, et al. Myocardial fibrosis predicts appropriate device therapy in patients with implantable cardioverter-defibrillators for primary prevention of sudden cardiac death. *J Am Coll Cardiol* 2011;57:821-8.
 25. Nazarian S, Bluemke DA, Lardo AC, et al. Magnetic resonance assessment of the substrate for inducible ventricular tachycardia in nonischemic cardiomyopathy. *Circulation* 2005;112:2821-5.
 26. Bogun FM, Desjardins B, Good E, et al. Delayed-enhanced magnetic resonance imaging in nonischemic cardiomyopathy: utility for identifying the ventricular arrhythmia substrate. *J Am Coll Cardiol* 2009;53:1138-45.
 27. 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;8:417-26.
 28. Wood MA, Stambler BS, Damiano RJ, Greenway P, Ellenbogen KA, for the Guardian ATP 4210 Multicenter Investigators Group. Lessons learned from data logging in a multicenter clinical trial using a late-generation implantable cardioverter-defibrillator. *J Am Coll Cardiol* 1994;24:1692-9.
 29. Mahesh K, Parmar B, Machin D. Cox's proportional hazards model. In: Machin D, Cheung YB, Parmar M, editors. *Survival Analysis: A Practical Approach*. Chichester, United Kingdom: Wiley, 1995:138-40.
 30. Pencina MJ, D'Agostino RB Sr., D'Agostino RB Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;27:157-72.
 31. Ashikaga H, Sasano T, Dong J, et al. Magnetic resonance-based anatomical analysis of scar-related ventricular tachycardia. *Circ Res* 2007;101:939-47.
 32. Kwon DH, Smedira NG, Rodriguez ER, et al. Cardiac magnetic resonance detection of myocardial scarring in hypertrophic cardiomyopathy: correlation with histopathology and prevalence of ventricular tachycardia. *J Am Coll Cardiol* 2009;54:242-9.
 33. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004;350:2151-8.

Key Words: cardiac magnetic resonance ■ fibrosis ■ late gadolinium enhancement ■ nonsustained ventricular tachycardia ■ ventricular tachycardia.