

**Diagnosis and prognosis in sudden cardiac arrest survivors without  
coronary artery disease:  
utility of a clinical approach using cardiac magnetic resonance imaging**

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## **ABSTRACT**

### **Background:**

Determining the etiology of sudden cardiac arrest or peri-arrest (sCA) without significant coronary artery disease (CAD) is crucial for management and prognosis. Cardiovascular magnetic resonance (CMR) can detect morphological, functional or tissue abnormalities, and we sought to evaluate the role of CMR in determining sCA etiology and prognosis in survivors.

### **Methods and Results:**

We retrospectively reviewed cardiac investigations and clinical outcomes in consecutive survivors of potentially fatal arrhythmias without CAD admitted to our institutions from 2008-2014. Following coronary angiography and echocardiography, all underwent CMR and, where indicated, electrophysiology studies. Major adverse cardiac events (MACE), comprising significant non-fatal ventricular arrhythmia or death, was the primary outcome.

Of 164 included subjects (65% male, mean age 48 (18-80) years), CMR contributed to the diagnosis in 80 (49%) and was decisive in 50 cases (30%). Dilated cardiomyopathy (n=27), myocarditis or sarcoidosis (n=22), occult myocardial infarction (n=13) and hypertrophic cardiomyopathy (n=9) were most frequent. Arrhythmic causes were found in 14%, while no cause was identified in 36%.

MACE occurred in 31% of subjects over a median follow-up of 32 months. MACE associated with presence of a CMR diagnosis, extent of late gadolinium enhancement (LGE), left and right ventricular ejection fraction (LVEF, RVEF). RVEF was an independent predictor of MACE.

**Conclusions:**

CMR identified a likely etiology for sCA in nearly half of survivors in whom CAD had been excluded. One in three subjects had MACE; risk doubled in those with a CMR diagnosis and some CMR parameters – LGE, LVEF and especially RVEF – associated with prognosis.

Word count: 250

**Key-words:** sudden cardiac arrest; cardiovascular magnetic resonance; late gadolinium enhancement; etiology; prognosis

## INTRODUCTION

Surviving sudden cardiac arrest or a peri-arrest event (sCA) is increasingly likely in societies investing in emergency response capabilities<sup>1</sup>. In the absence of coronary artery disease (CAD), determining the etiology of sCA is often challenging<sup>2-5</sup>.

Although most sCA survivors receive implantable cardiac defibrillators (ICDs), other aspects of their management and prognosis will depend on the underlying cause.

Additionally, although recurrent arrhythmia rates are high following the index sCA, some causes of sCA may be transient and only temporary secondary arrhythmia prevention may be needed – as indicated in the case of cardiac arrest immediately following an acute myocardial infarction<sup>6</sup>. Finally, inherited cardiac conditions are frequently identified as causes of sCA and an accurate diagnosis is essential for genetic testing and for family counselling and screening<sup>7,8</sup>.

Notably, most studies of sCA include patients both with and without coronary artery disease. In those excluding coronary disease, the majority are post-mortem studies in non-survivors<sup>2,9,10</sup> or focus only on the young and/or athletes. For example, diagnoses based on electrophysiology studies (EPS) and dynamic ECG changes can be missed<sup>11</sup>, as well as those sensitive to sampling errors<sup>12</sup>.

Cardiovascular magnetic resonance (CMR) can detect subtle structural, functional and tissue abnormalities of the cardiac muscle; in combination with other assessments, CMR can increase our ability to diagnose many of diseases affecting the heart muscle that are most commonly associated with sCA<sup>13,14</sup>. Alongside, late gadolinium enhancement (LGE) (both the presence and extent) has been found to be prognostic across a variety of cardiac diagnoses<sup>15-18</sup> and clinical settings, including cardiac arrest survivors<sup>13</sup>.

CMR is therefore likely to have an additional role in determining the substrate for the

ventricular arrhythmias in sCA survivors, and for identifying those patients at greatest risk of recurrent arrhythmias <sup>14,19,20</sup>.

Our aims were therefore to:

1. Provide a contemporary description of the non-coronary causes of sCA, their relative frequency in an adult population and estimate the frequency with which this carries implications for patient and family management.
2. Describe the diagnostic utility of a clinical strategy based on CMR for the evaluation of adult sCA survivors without coronary disease.
3. Assess the prognostic utility of CMR findings (LGE in particular) in this population of adult sCA survivors.

## **METHODS**

*The data that support the findings of this study are available from the corresponding authors upon reasonable request.*

### Study population

We retrospectively studied consecutive patients admitted at the London Chest and University College London Hospitals NHS Trusts between 2008 and 2014 (now part of Barts Heart Centre, Barts Health NHS Trust), who survived a resuscitated cardiac arrest, or sustained ventricular tachycardia with hemodynamic instability requiring emergent cardioversion (a peri-arrest scenario), between 2008 and 2014. All subjects underwent coronary angiography and those without significant coronary artery disease (luminal obstruction < 30%) and that underwent CMR were included in this

study. If an underlying cause was not identified from the CMR or if the ECG raised concern regarding a primarily arrhythmic cause, electrophysiology (EP) assessment was made - including ECG analysis, sodium channel blockade, catecholamine infusion, treadmill test and/or EPS, where deemed clinically indicated.

The final clinical diagnosis for the etiology of the sCA was made during the index admission by the cardiology team managing the patient, using all available data (clinical, imaging and electrophysiological).

Consent and Ethical Approval: This study was conducted as audit (Clinical Management of the Inherited and Acquired Heart Muscle Diseases, Barts Health NHS Trust audit No. 5298). All clinical data were collected as part of standard care and all patient identifiable fields were removed prior to analysis.

#### CMR protocol

All CMR studies were undertaken during the index admission following cardiac arrest. Scanning was performed on Philips® and Siemens® 1,5 Tesla scanners. All protocols included cine imaging and late gadolinium enhancement imaging. T1-weighted imaging pre and post contrast and T2-weighted triple inversion recovery images (STIR) were acquired where deemed clinically indicated.

LV dimensions, mass and systolic function were assessed using steady-state free precession (SSFP) cine imaging. Late gadolinium enhancement images were acquired 10 minutes post injection of 0.1mmol/Kg gadoterate meglumine (Dotarem® Guerbet S.A. France) with an inversion-recovery segmented gradient echo (Turbo-Flash) sequence, with slice orientations corresponding to the cine images. In patients with limited breath holding ability or frequent ectopy, a single-shot SSFP-based

inversion recovery sequence was used.

A quantitative evaluation of edema was obtained from T2-weighted short-tau inversion-recovery (T2w) images, by measurement of myocardial signal intensity normalized to skeletal muscle in the same slice<sup>21</sup>.

Quantitative evaluation of the early gadolinium enhancement ratio (EGEr), a marker of hyperemia, analyzed from T1-weighted spin echo images, was obtained by measuring the signal intensity before and after contrast administration and normalized to the skeletal muscle<sup>21</sup>.

All studies were analyzed by two investigators blinded to the original CMR results, final clinical diagnosis and outcomes, in a central core laboratory using CVI42 ® software (Circle Cardiovascular Imaging, Calgary, AB, Canada). Standard volumetric analysis was performed (papillary muscles included as myocardium), and measurements indexed to body surface area. Late gadolinium enhancement was automatically quantified using a threshold of 5 standard deviations above the mean signal intensity of the remote myocardium<sup>22</sup>. The site of enhancement was classified as subendocardial/ transmural (ischemic), or as epicardial/ midwall/ patchy (non ischemic). Very small or poorly defined patches of LGE ( $\leq 1\%$  of total myocardium) were considered non specific.

Final CMR diagnosis was obtained by consensus between at least two investigators.

We followed the current criteria for defining ARVD<sup>23</sup>, DCM<sup>24</sup>, HCM<sup>25</sup> and myocarditis<sup>21</sup>, as published elsewhere.

### Final clinical diagnosis

We defined “final clinical diagnosis” as the cause of the sCA deemed responsible for the episode adjudicated by the medical team treating the patient, based on all clinical

information available (imaging, electrophysiological, biopsy, genetic). This did not need to coincide with the final CMR diagnosis.

### Outcome assessment

The primary endpoint was the occurrence of major adverse cardiac events (MACE), defined as a composite of significant non-fatal ventricular arrhythmia (appropriate anti-tachycardia pacing or ICD shock, sustained ventricular tachycardia [VT] or ventricular fibrillation [VF]) and death.

Clinical outcome information was obtained from electronic health records (EHR), with mortality data from linked national databases including NHS Spine. Follow-up arrhythmia data was obtained from implantable cardiac defibrillator (ICD) interrogation and from medical records.

### Statistical analyses

Continuous data are described as mean  $\pm$  standard deviation or median (25-75 interquartile range) for non-gaussian distributions. Shapiro-Wilk test was used to assess normality. Categorical data are presented as absolute frequencies (n) and percentages.

Baseline differences between patients with and without MACE were assessed, using univariable Cox regression analysis.

The hazard ratio for the prediction of the events was calculated for MACE using Cox regression models. Multivariable analysis was performed using Cox regression with a stepwise forward selection method. Parameters that were significantly associated with MACE in the univariable analysis ( $p < 0.1$ ) and without collinearity were

considered. Gender and age were also included because of their known clinical significance and impact on survival.

Survival analysis was completed with event curves, described according to the Kaplan-Meier method, and comparison of event rates was performed using the log-rank test.

We used SPSS® software (version 20) for statistical analyses, considering 2-sided tests with  $p < 0.05$  for statistical significance.

## **RESULTS**

We included 164 patients, 65% (107) were male, with a mean age at presentation of  $48 \pm 15$  years (range 18 – 80 years). Baseline characteristics are presented in Table 1; 9 patients had an arrest with a non-shockable rhythm (pulseless electric activity or asystole), 20 had sustained VT with hemodynamic instability (a peri-arrest scenario), and the remaining 135 had pulseless VT or VF.

An implantable cardiac defibrillator (ICD) was placed in 70% ( $n=114$ ). Follow-up data was available in all but one of the subjects.

### CMR findings and diagnoses

The main parameters analyzed in CMR imaging are described in Table 2.

Indexed cardiac volumes were normal in 71% of subjects and median LVEF was 59 (IQR 47-68), with 31.7% of the subjects presenting  $LVEF \leq 50\%$  (17.7% had LVEF 40-50%; 7.3% had LVEF 30-40% and 6.7% had  $LVEF \leq 30\%$ ).

*Tissue characterization with late gadolinium enhancement:*

Abnormal late gadolinium enhancement was detected in 61 (37%) of subjects – of these, it was predominantly subendocardial or transmural in 34% (n=21), midwall in 13% (n=8), subepicardial in 33% (n=20), in a diffuse discontinuous distribution in 11% (n=7) and 5 patients (8%) had more than one of these patterns. In almost all (n=54) of these subjects CMR provided a final diagnosis.

There was no late gadolinium enhancement in 81 patients (49%). In the remaining 22 patients (13%), subtle and/or non-specific LGE findings were present.

*Tissue characterization with T2-weighted imaging:*

T2-STIR imaging was available in 80 patients (49%). On visual assessment, there was evidence of myocardial edema (increased signal intensity in STIR images) in only 10 (6%) of the subjects – in 6 cases, this co-localized with LGE in a non-ischemic pattern, in 2 with myocardial infarct (MI) pattern and the remaining 2 had no LGE. In 13% (n=22) of subjects, the calculated ratio of STIR signal intensity normalized to skeletal muscle was  $\geq 2$ .

*Imaging-derived diagnosis:*

In 80 cases (49%), CMR findings contributed to determining the underlying etiology for the sCA (Table 3). The most frequent diagnoses made from CMR were dilated cardiomyopathy in 27 cases (17%), myocarditis or cardiac sarcoidosis in 22 (13%; 7 of those with possible sarcoidosis), occult myocardial infarction in 13 (8%) and hypertrophic cardiomyopathy in 9 (6%).

Minor and nonspecific changes not suggestive of a specific diagnosis were found in 30 CMR scans (18% of the total, 35% of those without a diagnosis) and 55 patients (34%) patients had a completely normal scan.

In order to assess the incremental diagnostic value of CMR, a cardiologist performed an adjudicated review of the clinical history and of the exams, blinded to CMR findings and final diagnosis by the medical team.

There were 50 patients in whom the final clinical diagnosis would not have been made without the additional morphological information and tissue characterization derived from the CMR scan. These included myocarditis (n=14), sarcoidosis (n=7), occult myocardial infarction (n=12), arrhythmogenic right ventricular dysplasia (n=3), non-ischemic dilated cardiomyopathy (n=11 cases where CMR was required to exclude alternative differential diagnoses) and 3 other cases where the final clinical diagnoses required exclusion of other CMR-detectable pathology.

It was also judged to be very relevant to support other diagnosis, for example hypertrophic cardiomyopathy (HCM).

#### Electrophysiology findings and diagnoses

An arrhythmic pathology was found in 26 cases and deemed to be the main cause for the sCA in 23 cases (14%): 13 patients had a channelopathy, 5 an accessory pathway and 5 an acquired arrhythmia with a reversible cause.

#### Final clinical diagnosis

After combining all clinical, imaging and EP findings, the most frequent final diagnoses made by the physicians were: dilated cardiomyopathy, myocarditis and prior myocardial infarction (Table 3). In 59 cases (36%), the clinicians felt that a specific diagnosis could not be determined; 41% of these were presumed to be idiopathic VT/VF according to the medical records. In 12 patients, more than one cause for the sCA was found, but one was felt to be predominant and was

considered the final diagnosis (Table 3).

### Follow-up - patient outcomes

Over a median follow-up of 32 months (interquartile range 17-52), MACE occurred in 51 patients (31%). In 47 patients (27%), a significant non-fatal ventricular arrhythmic event was recorded. A total of 9 patients (5.2%) died; 2 did not have an ICD – unfortunately we could not adjudicate the cause of death based on the available data. In 5 cases with ICD, a significant arrhythmic event had already been treated by the device before their death.

An ICD complication was registered in 15 patients during follow-up (infection in 1, extrusion in 2, inappropriate shocks in 4 and lead displacement in 7 patients; 1 patient had infection, extrusion and inappropriate shocks). Notably, the 50 patients without an ICD had fewer registered major adverse cardiac events (MACE) - 8% vs 41%,  $p=0.008$  (Cox regression). Most cases who did not get an ICD were driven by a conclusion that the underlying cause had resolved or could be managed with appropriate medication, or due to patient refusal or loss of follow-up. The final diagnosis and extension of LGE were not significantly different, but LVEF was higher (58% vs 56%,  $p= 0.041$ ) and the presence of LGE was less common (24% vs 44%;  $p=0.022$ ) in patients without an ICD. As far as we could determine, none of the patients included was totally dependent or in a vegetative state at the time of discharge. However, a standardized evaluation of their neurologic status was not available.

### Clinical outcomes

There was no statistically significant relationship between MACE and baseline demographic characteristics, conventional cardiovascular risk factors or clinical features of the SCA peri-arrest (Table 1).

MACE were seen in 41% of the 80 patients with a CMR diagnosis, in 13% of the 23 with a predominant EP diagnosis and in 25% of the 59 with “idiopathic” sCA.

There was a non-significant trend towards lower MACE in the group with “idiopathic” sCA compared with those with a final etiologic diagnosis (24% versus 34%;  $p=0.338$ ).

Having a CMR-defined diagnosis was significantly associated with more MACE (41% vs 21%;  $p=0.022$ ) and a shorter event-free survival – Figure 1. Considering the most common diagnoses, MACE occurred in 41% of patients with dilated cardiomyopathy and in 43% of those with myocarditis/sarcoidosis (50% of patients with myocarditis and 29% of those with sarcoidosis), 50% of those with missed MI and 38% with HCM (Table 2). In the 24 patients with an arrhythmic etiology there was significantly lower MACE when compared to all other patients (13% vs 34%;  $p=0.034$ ).

We did not find a statistically significant association between individual diagnoses and prognosis.

In the cohort as a whole, several CMR parameters were associated with MACE in the univariable analysis (Table 2). These included the presence and extent of LGE (Figure 2), LV and RV ejection fraction (Supplementary Figures 1 and 2), left and right atrial area and ventricular volumes.

The pattern of LGE (ischemic versus non ischemic) was not significantly related to the occurrence of MACE.

Two methods of multivariable analysis for predicting MACE were considered. Covariates included LVEF, RVEF and LGE, all significantly associated with MACE in

the univariable analysis. Ventricular volumes were not included in the model (to avoid collinearity, since EF was included and derives from end-diastolic and end-systolic left ventricular volumes). A significant interaction between LVEF and RVEF in predicting MACE was excluded. We also included age and gender in the model (Methods section). We tested two models, using LGE as either a binary (clearly present or absent) or a continuous variable (% of myocardial mass).

RVEF was independently associated with MACE in both models (Supplementary Tables 1 and 2).

MACE rates were similar in patients with subtle/non-specific changes and those with a totally normal scan (respectively 20% and 22%). This lack of association between outcome and non-specific CMR changes remained when cases diagnosed with a primary arrhythmic cause were excluded (21% versus 25%;  $p=0.769$ ) and when studying only cases without a final diagnosis.

## **DISCUSSION**

To date, this is the largest published cohort of cardiac arrest survivors in whom coronary disease had been excluded as the cause by coronary angiogram. By incorporating CMR into the diagnostic algorithm for investigation of sCA, the etiology was determined in nearly two thirds of patients, with the most common causes in this cohort being non-ischemic dilated cardiomyopathy, myocarditis and missed myocardial infarction. The prognosis following sCA however remains poor, with MACE in almost one in three within a median follow-up of less than 3 years, despite defibrillator implantation in 70%. Those with a CMR-defined diagnosis had especially high MACE rates, with the presence of LGE and particularly RVEF as independent

predictors of future events.

Worldwide, coronary artery disease is the leading cause for sCA<sup>26</sup>, hence coronary angiography is frequently recommended, particularly if an acute coronary syndrome is suspected<sup>27,28</sup>. CMR is not specifically recommended in recent cardiac arrest guidelines, although the indication for a thorough investigation to find an etiology was reinforced<sup>27,28</sup>.

Previous studies investigating causes of sCA (without systematic use of CMR) have mainly focused on manifestations of coronary artery disease<sup>29</sup>. Dilated cardiomyopathy has been the second most frequent cause of sCA observed in adults<sup>4</sup>. The few studies that extensively explore the non-ischemic causes of sCA are mainly in children or young athletes, with hypertrophic cardiomyopathy/ left ventricular hypertrophy usually the most common etiology, while myocarditis and congenital coronary abnormalities are more common than in older cohorts<sup>10,30</sup>. In those studies, most of them post mortem, between 5 to 18% of the cases had no identifiable etiology<sup>2,10,30-32</sup>, reaching around a third of the patients in studies with survivors<sup>13,14</sup>. This often leaves patients, their families and clinicians with significant uncertainty regarding clinical management. A diagnostic approach with routine use of CMR and upstream angiography appears to be a successful method for determining the etiology, with CMR alone providing a cause in nearly half of patients. The relatively unique ability of CMR to perform tissue characterization allows detection of myocardial edema and focal scar, enabling identification of many conditions that are difficult to diagnose using other modalities. Our results show that CMR, being able to give information about RVEF and LGE, offers additional prognostic value compared to echocardiographic findings.

CMR was crucial for the main final clinical diagnosis in 50 cases (30%), while it gave

an important contribution to all the other cases where it was diagnostic. Cases of myocardial inflammation and specially 'occult' MI would not have been detected without CMR's tissue characterization. CMR was also pivotal in the diagnosis of ARVD. In fact, CMR can help confirm a diagnosis, suggest a hitherto unexpected diagnosis and contribute to eliminate differential diagnoses.

These data also highlight the wide range of potential causative underlying diseases in sudden cardiac arrest or peri-arrest cases, and illustrate the importance of identifying a diagnosis to facilitate treatment, prognosis and family screening. Despite all subjects having undergone coronary angiography and echocardiography, the frequency of occult infarcts was high; CMR provides a sensitive method for detection and enables administration of appropriate secondary preventative therapies. A recent study of 137 cardiac arrest survivors<sup>13</sup> without a clear diagnosis before performing CMR reported a higher prevalence of myocardial infarction (58% of patients), possibly related to the application of different angiographic criteria for inclusion (we excluded coronary disease with any stenosis >30%).

From our data, over one in four subjects were diagnosed with a potential inherited condition and one in five had an acquired cause, thereby facilitating targeted family screening and genetic testing. This not only helps to diagnose subclinical conditions in family members, but also to alleviate concern in family members of those with non-inherited conditions.

Patients with an identified etiology for their sCA had a worse prognosis than those labelled as 'idiopathic VF', with higher event rates in those with structural or functional cardiac abnormalities identified by CMR. Similar to studies of specific cardiomyopathies, the presence of LGE, lower LVEF and RVEF were associated with shorter event-free survival. LGE extent was not prognostic in this cohort, although

this may be because of study power or the method for scar quantification used<sup>22,33,34</sup>.

However, over a third of the cohort received no etiological cardiac diagnosis, and these patients remain a difficult group to manage clinically, particularly given the high MACE rates of one in four. In other studies with sCA survivors the percentages of cases without a final determined etiology are identical to ours<sup>13,14</sup>. Therefore, given the high recurrence of events and lack of ability to identify truly low-risk patients, ICD implantation must always be considered in these patients.

Our data also demonstrate that cardiac arrest and resuscitation do not necessarily produce detectable changes by CMR. This means that if changes are seen in a CMR scan in this context, we cannot assume that they are solely due to consequences of the arrest *per se*. However, subtle non-specific CMR abnormalities did not influence prognosis.

#### *Limitations and strengths*

This is a retrospective study that used a relatively standardized approach to survivors of cardiac arrests and CMR exams were blindly reviewed by at least two observers.

Given the design of the study, we can only derive association between the CMR findings and sCA; causality can only be hypothesized.

Non-survivors were not included and diseases with a more malignant course may therefore be under-represented. Patients with a presumed coronary etiology for their arrests were excluded and this may have included patients with dual pathology or bystander coronary disease. Patients who could not undergo CMR because of hemodynamic instability, functional deficits that precluded breath-holding, severe renal failure, claustrophobia or magnetic devices were also excluded.

Validation of CMR tissue characterization is currently incomplete. Notably, endomyocardial biopsy was not performed as a component of this clinical pathway and might have added valuable additional information.

The cohort size prevents more detailed study of etiologic subgroups and we must be cautious in interpreting the prognostic value of individual CMR parameters (including EF and LGE) without first considering them within a diagnostic framework.

Finally, we analyzed all-cause mortality rather than cardiovascular death, since the exact cause of death could not be determined in most cases.

## **CONCLUSIONS**

By incorporating CMR in clinical pathway for investigation of sudden cardiac arrest in the absence of CAD, a cause can be identified in nearly two thirds of patients. Many of the most frequent etiologies identified using CMR (idiopathic dilated cardiomyopathy, myocarditis and occult myocardial infarction) have important implications with regard to specific clinical management, family screening and prognosis. Although the risk of recurrent ventricular arrhythmias and death is high across this patient population, patients diagnosed with a structural or functional cardiac abnormality by CMR had a two-fold increased risk. LGE and biventricular systolic function were associated with prognosis, with RVEF being an independent predictor. We therefore advocate consideration of CMR for investigation and prognostication of all patients without culprit coronary disease post sCA.

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## FIGURE LEGENDS

**Figure 1** - Kaplan-Meier curves displaying the event-free survival according to the findings in CMR: patients with a CMR-defined diagnosis had a worse prognosis than those with a normal scan or one with minor nonspecific changes ( $p=0.018$  in the Log-rank test; HR=2, CI 95%= 1.1-3.5).

**Figure 2** - Kaplan-Meier curves of the MACE-free survival according to the presence of LGE (late gadolinium enhancement), which showed a significant relationship (Log-rank test  $p=0.014$ ; HR=1.9, CI 95%= 1.1-3.4 in Cox regression).

**TABLES:**

**Table 1 - Patients' characteristics according to the occurrence of MACE during follow-up.**

<b>Patients' characteristics</b>	<b>Total cohort (n=164)</b>	<b>No MACE (n=113)</b>	<b>MACE (n=51)</b>	<b>p</b>
Age (median (IQR); years)	48 (23)	47 (23)	52 (23)	0.100
Gender (% male)	65.2	61.9	72.5	0.265
Hypertension (n; %)	24 (15%)	13 (12%)	11 (22%)	0.100
Diabetes mellitus (n; %)	5 (3%)	1 (0.9%)	4 (8%)	0.082
Smoking history (n; %)	12 (7%)	10 (9%)	2 (4%)	0.595
Dyslipidemia (n; %)	5 (3%)	3 (3%)	2 (4%)	0.157
Obesity* (n; %)	3 (2%)	1 (0.9%)	2 (4%)	0.106
Excessive alcohol intake (n; %)	9 (5%)	6 (5%)	3 (6%)	0.256
Illicit drug use (n; %)	5 (3%)	5 (4%)	0	0.681
Chemotherapy (n; %)	3 (2%)	3 (3%)	0	0.698
Family history of SCD or IHD (n; %)	6 (4%)	5 (4%)	1 (2%)	0.727
Autoimmune disease (n; %)	4 (2%)	4 (4%)	0	0.650
OOHCA (n; %)	122 (74%)	86 (76%)	36 (71%)	0.226
Time to return to spontaneous circulation (median (IQR); minutes)	15 (10)	15 (10)	15 (24)	0.227
Shockable rhythm identified by first responder (n; %)	155 (94%)	105 (93%)	50 (98%)	0.241

Length of hospital admission (median (IQR); days)	10 (10)	10 (12)	10 (5)	0.370
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Abbreviations: MACE – major adverse cardiac events (a composite of significant non-fatal arrhythmia and death); SCD – sudden cardiac death; IHD – ischemic heart disease; OOHCA – out of hospital cardiac arrest; VT – ventricular tachycardia. IQR – interquartile range (quartile 75 - quartile 25). SD – standard deviation.

\*Defined as a body mass index above 30 Kg/m<sup>2</sup>.

**Table 2 – CMR findings in the total sample and divided according to the occurrence of MACE during follow-up.**

<b>CMR parameter</b>	<b>Total cohort (n=164)</b>	<b>No MACE (n=113)</b>	<b>MACE (n=51)</b>	<b>p</b>
LVEDV, indexed to BSA (mL/m <sup>2</sup> )	83 (31)	80 (28)	91 (45)	<b>0.021</b>
LVESV, indexed to BSA (mL/m <sup>2</sup> )	33 (30)	30 (26)	42 (38)	<b>0.002</b>
LV mass, indexed to BSA (g/m <sup>2</sup> )	70 (22)	69 (22)	75 (30)	0.276
LVEF (%)	59 (21)	62 (19)	53 (23)	<b>0.001</b>
LV RWMA (% of patients)	28	20	46	<b>0.003</b>
Cardiac output (L/min)	5.9 (1.8)	6.0 (1.8)	5.6(1.9)	0.237
Stroke volume, BSA-indexed (mL/m <sup>2</sup> )	46 (15)	48 (14)	44 (17)	0.115
RVEDV, indexed to BSA (mL/m <sup>2</sup> )	81 (25)	77 (27)	83 (21)	<b>0.029</b>
RVESV, indexed to BSA (mL/m <sup>2</sup> )	34 (18)	31 (16)	41 (17)	<b>0.001</b>
RVEF (%)	57 (10)	59 (11)	54 (12)	<b>&lt;0.001</b>
RV RWMA (% of patients)	6	4	11	0.735
TAPSE (mm)	20 (8)	22 (7)	18 (7)	<b>0.070</b>
Left atrial area (cm <sup>2</sup> )	21 (7)	21 (7)	24 (8)	<b>0.002</b>
Right atrial area (cm <sup>2</sup> )	20 (8)	20 (7)	23 (9)	<b>&lt;0.001</b>
Pericardial abnormalities (%of patients)	2	2	2	0.778
Mean EGEr in T1 *	1.0(0.01)	1.0 (0.01)	1.0 (0.3)	0.364
T2 STIR (mean ratio) †	2.0 (0.6)	2.0 (0.4)	2.3 (1.1)	0.128
STIR visually abnormal (% of patients)‡	6	6	6	0.907
LGE present (% of patients)	37	30	51	<b>0.020</b>
LGE distribution (% of patients)				<b>0.064</b>
-No LGE	49	55	38	
-Subendocardial or transmural LGE	13	12	14	
-Epicardial, midwall or patchy LGE	24	18	38	
-Minor nonspecific LGE§	13	15	10	

LGE quantification as % of LV mass	0.001 (4)	0.001 (3)	3.0 (11)	<b>0.022</b>
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Results are presented as median (interquartile range) or as a percentage.

Abbreviations: CMR – cardiovascular magnetic resonance; MACE – major adverse cardiac events (potentially fatal arrhythmia or death); BSA – body surface area; LVEDV – left ventricular end diastolic volume; LVESV - left ventricular end systolic volume; LV mass – left ventricular mass; LV – left ventricle; LVEF – left ventricular ejection fraction (measured on short axis stack pictures; using the biplane method, on 4-chamber and 2-chamber views); RWMA – regional wall motion abnormalities; MAPSE - mitral annular plane systolic excursion; RVEDV – right ventricular end diastolic volume; RVESV - right ventricular end systolic volume; RVEF – right ventricular ejection fraction; RV – right ventricle; TAPSE – tricuspid annular plane systolic excursion; LGE – late gadolinium enhancement.

\* Early gadolinium enhancement ratio (EGEr) - normalized to the skeletal muscle.

† T2-weighted STIR (short tau inversion recovery) ratio of signal intensity normalized to skeletal muscle.

‡ Increased signal intensity in STIR images clearly seen visually.

§ Very small or poorly defined patches of LGE ( $\leq 1\%$  of total myocardium).

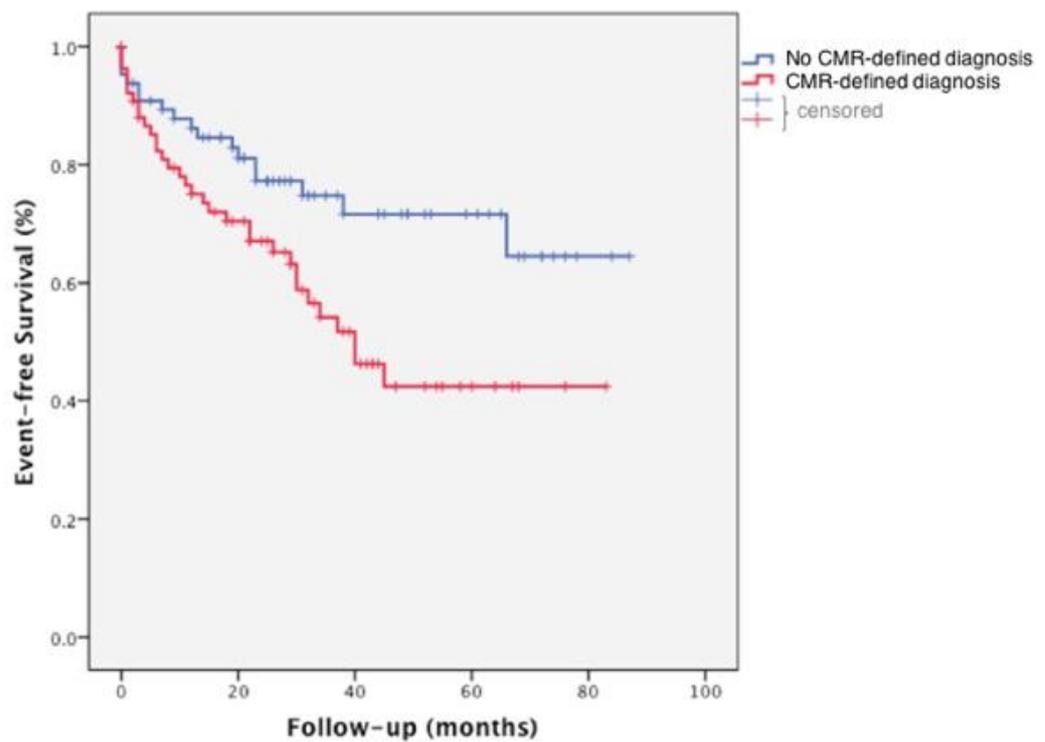
**Table 3 – Predominant diagnosis identified by CMR and final clinical diagnosis as per the medical team, considering all clinical investigation and features.**

<b>DIAGNOSIS</b>	<b>Diagnosis by CMR n (%)</b>	<b>Main final clinical diagnosis n (%)</b>	<b>MACE (within main clinical diagnosis)</b>
Unknown cause	84 (51%)	59 (36%)	14 (24%)
DCM (“idiopathic”)	27 (17%)	22 (13%)	9 (41%)
Myocarditis	22 (13%)	14 (9%)	7 (50%)
Cardiac sarcoidosis		7 (4%)	2 (29%)
IHD	13 (8%)	12 (7%)	6 (50%)
Long QT syndrome		11 (7%)	1 (9%)
HCM	9 (6%)	8 (5%)	3 (38%)
Arrhythmia due to drugs or ionic disturbance		5 (3%)	0
Accessory pathway with fast conduction		5 (3%)	0
DCM due to cardiotoxic substance		4 (2%)	2 (50%)
Severe valvular disease	4 (2%)	4 (2%)	1 (25%)
ARVD	3 (2%)	3 (2%)	2 (67%)
Probable coronary vasospasm		3 (2%)	1 (33%)
Undetermined cardiomyopathy/ other cardiac disease	1 (1%)	3 (2%)	1 (33%)
Brugada syndrome		2 (1%)	2 (100%)
Takotsubo cardiomyopathy	1 (1%)	1 (1%)	0
Non-cardiac cause		1 (1%)	0

Note: In 12 patients, there were multiple diagnoses made, however all patients were given one final clinical diagnosis thought to be the main cause of the arrhythmic event.

**FIGURES:**

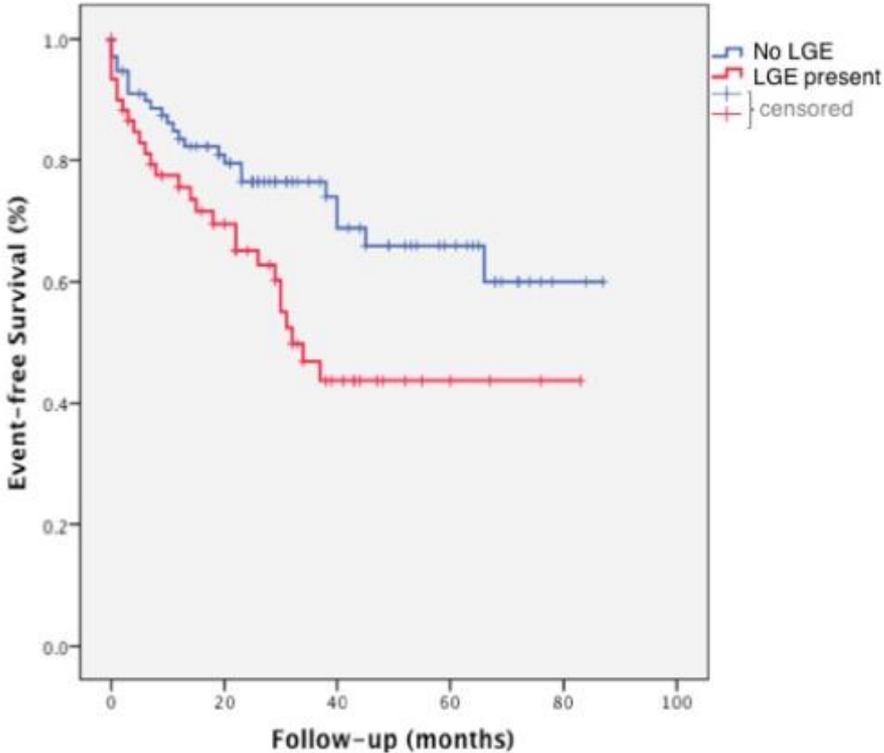
**Figure 1**



**Number at risk**

No CMR-defined diagnosis	84	46	22	12	2	0
CMR-defined diagnosis	80	43	18	5	1	0

Figure 2



Number at risk		0	20	40	60	80	100
No LGE	102	56	28	14	2	0	0
LGE present	62	32	11	2	1	0	0