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Cardiac Magnetic Resonance for Ventricular Arrhythmias: A Systematic Review and Meta-analysis

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Abstract

Background: Cardiac magnetic resonance (CMR) allows comprehensive myocardial tissue characterization, revealing areas of myocardial inflammation or fibrosis that may predispose to ventricular arrhythmias (VAs). With this study we aimed to estimate the prevalence of structural heart disease (SHD) and decipher the prognostic implications of CMR in selected patients presenting with significant VAs.
Methods: Electronic databases were searched for studies enrolling adult patients that underwent CMR for diagnostic or prognostic purposes in the setting of significant VAs. A random effects model meta-analysis of proportions was performed to estimate the prevalence of SHD. Hazard ratios (HRs) were pooled together in order to evaluate the prognostic value of CMR.
Results: The prevalence of SHD was reported in 18 studies. In all-comers with significant VAs, the pooled rate of SHD post-CMR evaluation was 39% (24% in the subgroup of premature ventricular contractions and/or non-sustained ventricular tachycardia vs. 63% in the subgroup of more complex VAs). A change in diagnosis after use of CMR ranged from 21% to 66% with a pooled average of 35% (29%-41%). A non-ischaemic cardiomyopathy was the most frequently identified SHD (56%), followed by ischaemic heart disease (21%) and hypertrophic cardiomyopathy (5%). After pooling together data from six studies, we found that the presence of late gadolinium enhancement was associated with increased risk of major adverse outcomes in patients with significant VAs (pooled HR: 1.79; 95% CI: 1.33-2.42).
Conclusion: CMR is a valuable tool in the diagnostic and prognostic evaluation of patients with VAs. CMR should be considered early after initial evaluation in the diagnostic algorithm for VAs of unclear etiology as this strategy may also define prognosis and improve risk stratification.

Keywords: cardiac magnetic resonance; ventricular arrhythmias; meta-analysis

What is already known on this topic

- The presence of SHD not only has important therapeutic implications, but also plays a central role in risk stratification of patients with significant VAs.
- CMR allows comprehensive myocardial tissue characterization, revealing areas of myocardial inflammation or fibrosis that may predispose to VAs.

What this study adds

- CMR represents an indispensable imaging tool in the armamentarium for the diagnosis and risk stratification of patients with significant VAs.
- Non-ischaemic causes of VAs are more frequently identified compared to ischaemic, when CMR is utilized.

How this study might affect research, practice or policy

- CMR may be considered early in the diagnostic evaluation of selected patients with VAs of unclear etiology, in order to aid decision making regarding the need for further investigations and define prognosis.

Abbreviations

ACM: Arrhythmogenic cardiomyopathy

CAD: Coronary artery disease

CMR: Cardiac magnetic resonance

HCM: Hypertrophic cardiomyopathy

IHD: Ischaemic heart disease

LGE: Late gadolinium enhancement

MACE: Major adverse cardiovascular events

NSVT: Non-sustained ventricular tachycardia

PVCs: Premature ventricular contractions

SCD: Sudden cardiac death

SHD: Structural heart disease

VA: Ventricular arrhythmia

VF: Ventricular fibrillation

Introduction

Ventricular arrhythmias (VAs) are a major cause of cardiovascular morbidity and mortality worldwide, accounting for the vast majority of sudden cardiac deaths (SCD)[1]. Although isolated premature ventricular contractions (PVCs) are commonly seen in individuals with structurally normal hearts, more complex forms of VAs (i.e. frequent/polymorphic PVCs, ventricular tachycardia – VT, ventricular fibrillation – VF) are usually a marker of underlying structural heart disease (SHD)[2]. The presence of SHD in patients with VAs not only has important therapeutic implications, but also plays a central role in risk stratification, representing a major determinant of unfavorable outcomes[3].

Echocardiography is the first-line imaging modality used to assess for SHD in patients with VAs[4]. However, normal or borderline/non-specific echocardiographic findings cannot exclude the possibility of underlying cardiomyopathy or an arrhythmogenic substrate[5]. On the other hand, cardiac magnetic resonance (CMR) bears the additional benefit of comprehensive myocardial tissue characterization, revealing areas of myocardial inflammation or fibrosis that may predispose to arrhythmias[6]. In fact, several studies have explored the diagnostic and prognostic value of CMR in selected patients with VAs, but their results have not yet been quantitatively synthesized in terms of a meta-analytic approach[7-11].

Therefore, herein, we performed a meta-analysis to estimate the prevalence of SHD in patients presenting with significant VAs. We also investigated the prognostic value of CMR in this patient population.

Methods

Eligibility criteria

Studies published in the English language reporting CMR data on diagnostic (SHD detection) or prognostic outcomes in the setting of significant VAs in adult patients were eligible for inclusion. The presence of SHD was defined as either diagnosis of SHD according to the investigators or structural abnormalities consistent with the presence of SHD (wall motion abnormalities, delayed gadolinium enhancement, intramyocardial fat signal). We defined significant VAs as any of the following: premature ventricular contractions (PVCs) that were considered by the study investigators to be of clinical importance based on their clinical presentation, complexity, or frequency; VT, either sustained or non-sustained (NSVT); VF; aborted SCD. Eligible studies

had to report the number of patients assigned to a new or alternative diagnosis following CMR, either directly or via proportion of the total number of patients.

For the prognostic meta-analysis, eligible studies had to report hazard ratio (HR) for the association of CMR with adverse outcomes.

Search strategy – Information sources

Electronic databases (Medline, Scopus, Cochrane Library) were searched for relevant studies, up to February, 2024. To this end, we used the following search algorithm: ("cardiac magnetic resonance" OR CMR) AND ("ventricular arrhythmias" OR sudden cardiac death OR ectopy OR "premature ventricular complexes"). The reference lists of the included studies and relevant reviews were also examined for further eligible studies.

Selection process – Data collection process

Two reviewers (CAP and MAB) independently screened retrieved studies at title and full-text level. Any discrepancies were resolved by consensus, with the involvement of a third reviewer (TK). A pre-specified form was used to extract epidemiological and clinical data of the included studies.

Outcomes of Interest

The primary outcome of interest was the rate of SHD post-CMR evaluation. In a secondary sub-analysis, we estimated the rate of change in diagnosis post-CMR as a secondary outcome, excluding studies that reported only data for structural abnormalities without assigning a final clinical diagnosis. We also determined the proportions of types of SHD post-CMR evaluation. Given the fact that some cardiomyopathies may have overlapping and indistinguishable features on CMR, we classified the most common SHDs into three main categories based on distinct anatomical and morphological characteristics: (i) ischaemic heart disease (IHD), (ii) non-ischaemic cardiomyopathy, including dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (ACM) and inflammatory cardiomyopathies (myocarditis and/or sarcoidosis) and (iii) hypertrophic cardiomyopathy (HCM).

For the prognostic meta-analysis, major adverse cardiovascular outcomes (MACE) that included death and/or arrhythmic endpoints were assessed.

Risk of bias of individual studies

The QUIPS tool was used for the quality assessment of the prognostic studies. Each study was assessed as being of low, moderate, or high risk of bias for any of the following domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis, and reporting.

Statistical analysis

Meta-analysis of proportions using the logit transformation method was performed in order to estimate the prevalence of SHD, to explore the impact of CMR on diagnostic reclassification and determine the distribution of the most common disease entities in patients with significant VAs[12]. A random effects model (Mantel-Haenszel method) was selected a priori given the heterogeneity in study design across the included studies. Between-study heterogeneity was assessed with the I^2 statistic. Values lower than 25% indicated low, while values greater than 70% indicated severe heterogeneity[13]. Funnel plot and Egger's test were used to assess the risk of publication bias. To evaluate the impact of each study on the overall effect size, one study removed sensitivity analysis was performed. Finally, potential sources of between-study heterogeneity were investigated via subgroup analysis based on the severity of presenting VAs (PVCs and/or NSVT vs. unstable VAs/aborted SCD).

HRs (unadjusted or adjusted) and corresponding 95% confidence intervals (CI) of individual studies were pooled together in order to evaluate the prognostic value of CMR. All analyses were performed using Revman version 5.3 (Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014) and Comprehensive Meta-analysis version 2 (Englewood, New Jersey).

Results

Electronic search yielded 3,189 studies. Following screening at titles and abstract level, 33 full-texts were assessed for eligibility. Finally, 21 unique studies (13 studies reporting data on the prevalence of SHDs, 3 studies reporting prognostic data and 5 studies reporting both diagnostic and prognostic data) met eligibility criteria and were included in this review[6-11, 14-21]. A detailed flow diagram is shown in **Figure 1**.

Meta-analysis of SHD prevalence

Characteristics of included studies

18 studies enrolling 4,275 patients were included in the meta-analysis of SHD prevalence[6, 7, 9-11, 14-19, 22-28]. Two studies (Zorzi et al. 2021 and Zorzi et al. 2018) had overlapping populations but they reported data on different outcomes, and thus their results were used in different analyses[20, 28]. Specifically, the study of Zorzi et al. 2021[28], which was the larger one, was included in the main analysis of our study (for the prevalence of SHD)while the study of Zorzi et al. 2018[20] was included only in the sub-analysis for the diagnostic reclassification.

10 studies (including that of Zorzi et al. 2018) were prospective[6, 7, 10, 11, 20, 22-26], while the rest of the studies had a retrospective design[9, 14-19, 27, 28]. Six studies enrolled only patients with sustained VT/VF or aborted SCD[6, 15-17, 19, 20], seven studies included exclusively patients with PVCs and/or NSVT[11, 22-27] and the rest of the studies included patients from the entire spectrum of VAs[7, 9, 10, 14, 18]. Except for the study of William et al., where CMR was performed only in the subset of patients with no SHD based on the initial investigation, in all other eligible studies CMR was systematically performed in all participating patients. In all studies, the initial diagnostic work-up prior to CMR included clinical evaluation, electrocardiogram, and transthoracic echocardiography. In most studies, additional tests were performed (i.e. coronary anatomy assessment, electrophysiological study), when deemed appropriate by the treating physicians[6, 9-11, 14, 15, 17-20, 23, 25].

Baseline patient characteristics and CMR approach

Baseline characteristics of included studies are summarized in **Table 1**. The mean age of enrolled patients was 45±16 years. The mean left ventricular ejection fraction by CMR was 57%±9%. A multiparametric CMR approach, based on various parameters such as anatomical and functional indices, LGE, T1 and T2-weighted imaging, was adopted by all studies for SHD detection.

Visual inspection of the funnel plot and Egger's test (p=0.36) did not reveal any significant publication bias (**Supplementary Figure 1**).

Synthesis of individual results

In all-comers with significant VAs, the pooled prevalence of SHD post-CMR evaluation was 39% (29%-49%) (**Figure 2**). In the subgroup of patients with PVCs and/or NSVT (12 studies; 3,299 patients) the rate of SHD ranged from 11% to 40% with a pooled average of 24% (19%-30%) (**Supplementary Figure 2**). In the

subgroup of sustained VT and/or SCD (10 studies; 1,007 patients) the prevalence of SHD ranged from 25% to 83% with a pooled average of 63% (**Supplementary Figure 3**).

12 studies reported data on the ability of CMR to reclassify clinical diagnosis. In these studies, pre-CMR evaluation led to a diagnosis in 23% (14%-35%) of the patient population. A change in diagnosis after the use of CMR ranged from 21% to 66% with a pooled average of 35% (29%-41%) (**Figure 3**). The corresponding value was 29% for the subgroup of PVCs and/or NSV and 39% for the subgroup of sustained VT and/or SCD (**Supplementary Figure 4 and 5**, respectively). Types of SHD identified by CMR imaging are shown in **Table 2**. A non-ischaemic cardiomyopathy was the most frequently identified SHD (pooled proportion among CMR-detected heart diseases: 56%), followed by IHD (pooled proportion among CMR-detected heart disease: 21%), and HCM (pooled proportion among CMR-detected heart diseases: 5%) (**Figure 4**). Separate analyses for the specific diagnoses of non-ischaemic cardiomyopathy are shown in **Supplementary Figure 6**.

No significant change was detected in the rate of diagnosis change after performing one study removed sensitivity analysis (**Supplementary Figure 7**). After removing two studies[11, 17] that excluded patients with CAD from the analysis for IHD proportion, its pooled proportion was 24% (95% 0.16-0.34; I^2: 87%). Results remained unchanged in all sensitivity analyses (**Supplementary Figure 8**).

Meta-analysis of Prognostic Studies

Eight studies, comprising 2,889 patients in total, were included in the meta-analysis for the prognostic value of CMR[8, 9, 17, 21, 22, 24, 28, 29]. The median follow-up period ranged from 2.6 to 5.1 years among the included studies. Two studies included exclusively patients with sustained VT or aborted SCD[17, 28], four studies enrolled only patients with PVCs/NSVT[21, 22, 24, 29] and the rest of the studies included mixed patient populations[8, 9]. Six studies reported data on the prognostic value of late gadolinium enhancement (LGE)[8, 9, 17, 21, 28, 29]. Three studies evaluated the prognostic significance of myocardial abnormalities detected by CMR[9, 22, 24]. Details on baseline characteristics and quality assessment of prognostic studies are presented in **Table 3** and **Supplementary Table 1**, respectively.

After pooling together HRs of individual studies, we found that LGE was associated with increased risk of MACE in patients with significant VAs (pooled HR: 1.79; 95% CI: 1.33-2.42; I^2: 78%) (**Figure 5**). The

results remained significant even when we performed subgroup analysis based on VA type (pooled HR: 2.41; 95% CI: 1.8-3.22; I^2: 7% for sustained VT and/or SCD and pooled HR: 1.79; 95% CI: 1.25-2.56; I^2: 83% for PVCs and/or NSVT) (**Supplementary Figures 9 and 10,** respectively).

Discussion

This is a systematic review and meta-analysis on the diagnostic and prognostic role of CMR in patients presenting with new, significant VAs without a known underlying arrhythmogenic substrate. The main findings of our study can be summarized in the following key points: (i) CMR substantially improved the ability to detect SHD as the arrhythmogenic substrate compared to conventional investigations; (ii) CMR changed the initial diagnosis in one third of the patients; (iii) LGE was a powerful prognostic marker, conveying almost a two-fold higher risk of major adverse outcomes in patients with significant VAs.

Transthoracic echocardiography is the first-line imaging modality used for anatomic and functional assessment of the heart as well as SHD detection in patients with new VAs[4]. Apart from a detailed echocardiographic evaluation, contemporary guidelines recommend the exclusion of CAD either invasively or non-invasively based on the patient's pre-test probability as a first-step in the evaluation of patients presenting with significant VAs (i.e. NSVT, VT) or SCD[3, 4]. Nonetheless, a substantial proportion of these patients have non-specific or even normal echocardiographic findings and no or non-obstructive CAD. Thus, a structural abnormality may not be detected and patients receive an alternative diagnosis, such as right ventricular outflow tract or idiopathic VA, or no diagnosis at all. Our study aggregates the results of previous studies that investigated the role of CMR in this population and provides specific information regarding the true prevalence of SHD. As a result, the correct diagnosis is frequently achieved only post-CMR. In regards to the specific population of our study, most patients were relatively young with preserved or mildly reduced ejection fraction.

A non-ischaemic cardiomyopathy was more frequently detected than IHD in this population. In light of high morbidity and mortality rates associated with VAs, these findings have important clinical implications, since a rational diagnostic strategy would refine the treatment of patients with VAs[3].

CAD, in the form of scar from prior MI or acute coronary syndrome, is the leading cause of VT, and SCD. However, there are caveats in the presumed association of VAs with underlying CAD. Specifically, stable

obstructive CAD may just be a bystander in the setting of underlying non-ischaemic cardiomyopathies and in fact, a large proportion of patients with VAs are treated for coronary artery disease found in invasive angiograms without a CMR as part of their work-up. In other cases, myocardial fibrosis responsible for re-entrant VAs maybe due to myocardial infarction with non-obstructive coronary arteries (MINOCA) from plaque rupture and embolization or recanalization[30-32]. In both scenarios, CMR can be helpful in identifying the underlying substrate and reaching the correct diagnosis. In our study of young patients with new significant VAs and no known arrhythmogenic substrate upfront, our results suggest that non-ischaemic causes of VAs are more frequently identified compared to ischaemic, when CMR is utilized. These findings of our meta-analysis, together with the fact that CMR can accurately differentiate ischaemic from non-ischaemic cardiomyopathy based on the LGE distribution pattern[33], suggest that CMR may be considered early in the diagnostic evaluation of selected patients with VAs of unclear etiology, in order to aid decision making regarding the need for further investigations (e.g. coronary anatomy assessment) (**Figure 6**). Certainly, a one-size-fits-all diagnostic approach would be flawed by the fact that patients with VAs represent a heterogeneous population with diverse clinical characteristics. Therefore, the optimal diagnostic approach should be individualized based on patient's risk profile.

The upfront use of CMR can have significant prognostic impact in these patients. CMR with LGE, as shown in our study, can help identify patients at higher risk for future adverse events. Similar results have been also reported for other tissue characterization CMR techniques. Zorzi et al. showed that the presence of myocardial edema, as detected on T2-weighted imaging, was independently associated with a lower risk of ICD discharge for arrhythmic events during follow-up in SCD survivors (HR: 0.22; 95% CI: 0.05-0.94)[28]. Moreover, based on the results of our subgroup analysis, CMR can effectively risk-stratify patients with PVCs/NSVT. Therefore, a close follow-up would be beneficial in patients with NSVT and LGE on CMR imaging, even in the absence of a specific diagnosis. Taken together, CMR represents an indispensable imaging tool in the armamentarium for the diagnosis and risk stratification of patients with VAs.

Study Limitations and Strengths

Our study has several limitations that should be acknowledged. First, some of the cardiac conditions studied in our meta-analysis (i.e. ACM, DCM, myocarditis) may have overlapping and indistinguishable features on CMR. This limitation makes the accurate differentiation of these conditions based only on CMR somewhat problematic, introducing a kind of misclassification bias in the existing literature. Second, a high degree of heterogeneity was observed in most analyses, likely due to differences in study design (patient selection, type of VAs studied, CMR techniques used to diagnose SHD, pre-CMR work-up used to assign an initial diagnosis) among the included studies. Patients with VAs represent a heterogeneous population and thus the reported between-study heterogeneity was anticipated and is inevitable. However, in an attempt to homogenize the existing data, we performed a subgroup analysis based on VAs severity (PVCs/NSVT vs. VT/SCD). Finally, some of the included studies were at high risk of bias, mainly due to patient selection.

Conclusion

CMR is a valuable tool in the diagnostic and prognostic evaluation of patients with VAs, by revealing an underlying SHD in a significant proportion of the patient population. Moreover, CMR reclassified the initial diagnosis based on conventional assessment in one third of the patients. CMR should be considered early after initial evaluation in the diagnostic algorithm for VAs of unclear etiology as this strategy may improve risk stratification of these patients and alter prognosis.

Contributorship statement

Conception: CAP, TDK

Design: CAP, PNK, MAB, TDK

Electronic search: CAP, MAB

Data extraction: DGK, IT

Statistical analysis: CAP, DGK, TZ

Risk of bias: CAP, DP

Writing: CAP, PNK, MAB TDK

Editing/final review: All authors

Guarantor is TDK

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Table 1: Baseline Characteristics of Included Studies

Study	Study design	Cohort Size	Inclusion criteria/type of VA studied	Diagnostic work-up prior to CMR	CMR parameters assessed	Age, years (mean)	Male, %	LVEF by CMR, % (mean)	No. of patients with SHDs, (%)	Definition of SHD
Studies including patients from the entire spectrum of VAs										
Andreini et al., 2020	Prospective	946	1)VEBs>1000/24h; NSVT; sustained VT/ Aborted SCD 2) absence of any pathological findings at TTE	Clinical evaluation; ECG; TTE	Anatomical and functional parameters; LGE; T2-weighted imaging	41±16	64	58±8	241 (25)	Definite clinical diagnosis (e.g. IHD, myocarditis, ACM) based on established criteria
Weisser et al., 2014	Retrospective	76	VEBs (Lown≥2); VT; VF	Clinical evaluation; ECG; TTE; EPS	Anatomical and functional parameters; LGE; T2-weighted imaging	45±17	51	NR	20 (26)	Definite clinical diagnosis (e.g. IHD, myocarditis, ACM) based on established criteria
Cabanelas et al., 2013	Retrospective	113	Complex VEB; NSVT; VT/VF of unclear etiology based on initial evaluation	Clinical evaluation; ECG; TTE; stress testing	Anatomical and functional parameters; LGE; T1-weighted imaging	42±16	58	NR	48 (42)	Definite clinical diagnosis (e.g. IHD, myocarditis, ACM) based on established criteria
Ge et al., 2023	Retrospective	642	1) NSVT; VT/Aborted SCD 2) without ACS	Clinical evaluation; laboratory investigations; ECG; TTE; EPS; stress testing; C/A or CCTA	Anatomical and functional parameters; LGE	54±15	60	57±10	333 (52)	Definite clinical diagnosis (e.g. IHD, myocarditis, ACM) based on established criteria
Henning et al., 2018	Prospective	157	1) NSVT; VT, VF/Aborted SCD 2) without ACS<3 months	Clinical evaluation; laboratory investigations; ECG, TTE; signal average ECG; C/A or CCTA	Anatomical and functional parameters; LGE	54±17	75	55±14	105 (67)	Definite clinical diagnosis (e.g. IHD, myocarditis, ACM) based on established criteria
Studies including exclusively patients with sustained VT/VF and/or SCD										
Marçal et al., 2023	Retrospective	64	Unstable VAs (VT, VF)/ Aborted SCD	Clinical evaluation; laboratory investigations; ECG; TTE	Anatomical and functional parameters; LGE; T2-weighted imaging	55±15	72	44±14	53 (83)	Definite clinical diagnosis (e.g. IHD, myocarditis, ACM). The criteria for each diagnosis were not specified.
White et al.,2012	Prospective	82	1) Sustained VT/Aborted SCD 2) without ACS≤30 days	Clinical evaluation; ECG; TTE; C/A	Anatomical and functional parameters; LGE; T1 and T2-weighted imaging	52±15	67	51±19	61 (74)	Definite clinical diagnosis (e.g. IHD, myocarditis, ACM) based on established criteria
Rodrigues et al., 2017	Retrospective	164	1) Sustained VT/Aborted SCD 2) without CAD (defined as luminal obstruction<30%)	Clinical evaluation; ECG; TTE; C/A; EPS	Anatomical and functional parameters; LGE; T1 and T2-weighted imaging	48±15	65	58±16	80 (49)	Definite clinical diagnosis (e.g. IHD, myocarditis, ACM) based on established criteria
Zorzi et al., 2021*	Retrospective	101	Aborted SCD	Clinical evaluation; ECG; TTE; C/A	Anatomical and functional parameters; LGE; T2-weighted imaging	46±21	71	NR	72 (71)	Definite clinical diagnosis (e.g. IHD, myocarditis, ACM) based on established criteria
Zorzi et al., 2018*	Prospective	44	Aborted SCD	Clinical evaluation; ECG; TTE; C/A	Anatomical and functional parameters; LGE; T2-weighted imaging	NR	84	NR	37 (84)	Definite clinical diagnosis (e.g. IHD, myocarditis, ACM). The criteria for each diagnosis were not specified.
William et al., 2023	Retrospective	32	Unstable VAs; sustained VT of unclear etiology based on initial evaluation	Clinical evaluation; ECG; TTE; CA or CCTA	NA	NR	NR	NR	8 (25)	Definite clinical diagnosis (e.g. IHD, myocarditis, ACM). The criteria for each diagnosis were not specified
Gil et al., 2023	Retrospective	35	Aborted SCD of unclear etiology based on initial evaluation	Clinical evaluation; ECG; TTE; C/A or CCTA	Anatomical and functional parameters; LGE; T1 and T2-mapping	47±14	57	49±13	26 (74)	Definite clinical diagnosis (e.g. IHD, myocarditis, ACM) based on established criteria
Studies including exclusively patients with PVCs and/or NSVT										
Nikolaidou et al., 2021	Prospective	72	1) PVCs (≥500/24 h) or NSVT 2) absence of any pathological findings at TTE 3) No CAD	Clinical evaluation; ECG; TTE; anatomical or functional assessment of coronary anatomy	Anatomical and functional parameters; LGE; T2-weighted imaging; FT-CMR	46±16	47	60±6	24 (33)	Definite clinical diagnosis (e.g. IHD, myocarditis, ACM) based on established criteria or PVC-induced cardiomyopathy
Scorza et al.,2022	Prospective	51	1) PVCs>10,000/24h 2) Normal findings at TTE and exercise test	Clinical evaluation; ECG; TTE; Exercise testing	Anatomical and functional parameters; LGE; T2-weighted imaging	59±21	55	55±4	10 (20)	Abnormal LV or RV volume, abnormal wall thickness, regional dyskinesia, myocardial edema, fibrosis and EF lower than 55%.
Crescenzi et al., 2021	Prospective	251	1) Athletes with >100 PVCs/24 h or ≥1 repetitive VA (couplets, triplets, or NSVT)/24h 2) Negative FH, ECG, TTE	Clinical evaluation; ECG; TTE; Exercise testing; CCTA or imaging stress testing	Anatomical and functional parameters; LGE; T1 and T2-weighted imaging	27±16	74	63±7	28 (11)	Presence of LGE, fatty infiltration and/or edema
Hosseini et al., 2022	Prospective	255	1) PVCs≥5%/24h 2) Negative initial diagnostic work-up	Clinical evaluation; ECG; TTE	Anatomical and functional parameters; LGE	55±16	47	53±9	35 (14)	Presence of LGE and/or regional WMAs
Yokokawa et., 2017	Retrospective	321	Patients with frequent PVCs referred for ablation	NR	Anatomical and functional parameters; LGE	52±15	49	51±12	64 (20)	Definite clinical diagnosis (e.g. IHD, myocarditis, ACM). The criteria for each diagnosis were not specified
Aquaro et al., 2010	Prospective	396	1) PVCs>1,000/24h 2) Negative initial diagnostic work-up	Clinical evaluation; ECG; TTE; exercise testing	Anatomical and functional parameters; FSE	34±17	68	60±8	124 (31)	RV WMAs, RV dilation and/or dysfunction and/or fatty infiltration based on established criteria
Muser et al., 2020*	Prospective	518	1) PVCs>1,000/24h 2) Negative routine diagnostic work-up	Clinical evaluation; ECG; TTE; Exercise testing or CCTA or imaging stress testing or C/A	Anatomical and functional parameters; LGE	44±15	57	63±7	85 (16)	WMAs, fatty infiltration and/or presence of LGE

* Studies with overlapping population. Data from these studies were used only in different analyses

ACM: Arrhythmogenic cardiomyopathy; C/A: Coronary angiography; CCTA: Coronary computed tomography angiography; ECG: Electrocardiogram; EF: Ejection fraction; EPS: Electrophysiological study; FH: Family history; FSE: Fast spin echo images; FT: feature-tracking; IHD: Ischaemic heart disease; LGE: Late gadolinium enhancement; NR: Not reported; NSVT: Non-sustained ventricular tachycardia; PVC: Premature ventricular contractions; SCD: Sudden cardiac death; TTE: Transthoracic echocardiography; VEBs: Ventricular ectopic beats; VF: Ventricular fibrillation

Table 2: Distribution of Structural Heart Diseases and Diagnosis Reclassification based on CMR, as reported by Individual Studies

Study	**No. of patients with non-CMR based diagnosis, n (%)**	**Change in diagnosis, n (%)**	**IHD, n (%)**	**Non-ischemic cardiomyopathy (ACM, DCM, inflammatory cardiomyopathies), n (%)**	**HCM, n (%)**
Andreini et al., 2020	0 (0)	241 (26)	22 (9)	185 (77)	13 (5)
Marçal et al., 2023	38 (59)	15 (23)	11 (21)	9 (17)	2 (4)
White et al.,2012	42 (51)	41 (50)	29 (48)	23 (38)	1 (2)
Rodrigues et al., 2017	53 (32)	50 (31)	13 (16)	27 (34)	9 (11)
Henning et al., 2018	73 (46)	48 (31)	46 (44)	52 (65)	3 (3)
Ge et al., 2023	167 (26)	214 (33)	106 (32)	149 (45)	17 (5)
Zorzi et al., 2021	32/44 (73)*	11/44 (25)*	21 (29)	24 (33)	3 (4)
Cabanelas et al., 2013	0 (0)	48 (43)	7 (15)	40 (83)	1 (2)
William et al., 2023	8 (21)	8 (25)	1 (13)	6 (75)	0 (0)
Gil et al., 2023	3 (9)	23 (66)	6 (23)	15 (58)	4 (15)
Nikolaidou et al., 2021	0 (0)	39 (54)	1 (3)	23 (59)	0 (0)
Weisser et al., 2014	4 (5)	16 (21)	2 (10)	17 (85)	1 (5)

* Results from Zorzi et al. 2018. Data on diagnostic reclassification were presented only in the study of Zorzi et al. 2018.

ACM: Arrhythmogenic cardiomyopathy; CMR: Cardiovascular magnetic resonance; HCM: Hypertrophic cardiomyopathy; IHD: Ischemic heart disease; DCM: Dilated cardiomyopathy

Table 3: Baseline Characteristics and Results of Prognostic Studies

Study	Cohort size	Patient population	Study design	Follow-up, years (median)	Male, %	Age, years (mean ± SD)	LVEF, % (mean ± SD)	CMR findings assessed for prognosis	Study Outcomes	Results, HR (95% CI)
Ge et al., 2023	642	NSVT; sustained VT/aborted SCD	Retrospective	4.4	60	54±15	57±10	LGE; abnormal CMR findings (LVEF <50%, presence of any wall WMA in the LV or RV, presence of LGE, and abnormal LV wall thickness meeting criteria for HCM)	Composite of death, recurrent VT/VF requiring therapy, and HF hospitalization	HR: 3.18 (1.8-5.5) for NSVT, HR: 2.69 (1.8-4) for sustained VT/SCD
Zorzi et al., 2021	101	Aborted SCD	Retrospective	3.9	71	46±21	NR	LGE; ME	Appropriate ICD intervention	HR: 1.46 (0-6-3.54); HR: 0.22 (0.05-0.94)
Rodrigues et., 2017	164	Sustained VT/Aborted SCD	Retrospective	2.7	65	48±15	58±16	LGE	Composite of significant nonfatal VAs (appropriate antitachycardia pacing or ICD shock, sustained VT or VF) and death	HR: 1.9 (1.1-3.4)
Dawson et al., 2013	373	NSVT/sustained VT	Prospective	2.6	64	51±15	60±13	LGE	Composite of cardiac death/arrest, new episode of sustained VT, or appropriate ICD discharge	HR: 3.3 (1.8-5.8)
Muser et al., 2021	686	PVCs/NSVT	Retrospective	5.1	59	NR	NR	LGE	Composite of all-cause death, resuscitated cardiac arrest and appropriate ICD therapy	HR: 1.27 (1.21-1.33)
Aquaro et al., 2010	396	PVCs>1000/24h of LBBB morphology	Prospective	3.4*	68	60±8	34±17	RV abnormalities (WMA, dilation and/or dysfunction, signal alteration)	Composite of cardiac death, resuscitated cardiac arrest, and appropriate ICD shock.	HR: 32 (4.2-244.8)
Ghannam et al., 2019	272	Patients with frequent PVCs referred for ablation	Retrospective	4*	49	52±15	52±12	LGE	Long-term VT	HR: 1.4 (1.1-1.7)
Hosseini et al., 2022	255	PVCs>5%/24h	Prospective	3	47	55±16	53±9	Myocardial abnormalities (presence of LGE and/or regional WMAs)	Composite of mortality, VF, sustained VT, or reduction in LVEF≥10%.	HR: 4.35 (1.34-14.15)

* mean value

CI: Confidence interval; CMR: Cardiac magnetic resonance; HR: Hazard ratio; ICD: Implantable cardioverter defibrillator; LGE: Late gadolinium enhancement; LVEF: Left ventricular ejection fraction; ME: Myocardial edema; NSVT: Non sustained ventricular tachycardia; PVCs: Premature ventricular complexes; SCD: Sudden cardiac death; VT: Ventricular tachycardia; VF: Ventricular fibrillation; WMA: Wall motion abnormality

Figure Legends

Figure 1: **PRISMA flow chart**. The selection process is reported according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

Figure 2: Meta-analysis results. Forest plot demonstrating rates of structural heart disease post-CMR. CI: Confidence interval; CMR: Cardiac magnetic resonance; SHD: Structural heart disease

Figure 3: Meta-analysis results. Forest plot demonstrating rates of change in diagnosis post-CMR. CI: Confidence interval; CMR: Cardiac magnetic resonance; SHD: Structural heart disease

Figure 4: Meta-analysis results. Forest plots demonstrating pooled proportions of (A) Non ischaemic cardiomyopathy (Inflammatory cardiomyopathy, ACM, DCM); (B) Ischemic heart disease; (C) Hypertrophic cardiomyopathy, post-CMR evaluation. ACM: Arrhythmogenic cardiomyopathy; CI: Confidence interval; CMR: Cardiac magnetic resonance; DCM: Dilated cardiomyopathy; HCM: Hypertrophic cardiomyopathy; SHD: Structural heart disease

Figure 5: Meta-analysis results. Forest plot demonstrating pooled hazard ratios for major adverse cardiovascular outcomes. CI: Confidence interval

Figure 6: Summary of the meta-analysis main findings and their clinical implications. CMR: Cardiac magnetic resonance; HCM: Hypertrophic cardiomyopathy; IHD: Ischemic cardiomyopathy; LGE: Late gadolinium enhancement; MACE: Major adverse cardiovascular outcomes; NSVT: Non-sustained ventricular tachycardia; PVCs: Premature ventricular contractions; SHD: Structural Heart Disease; SCD: Sudden cardiac death; SVT: Sustained ventricular tachycardia; VAs: Ventricular arrhythmias