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Myocardial Fibrosis Assessment by LGE Is a Powerful Predictor of Ventricular Tachyarrhythmias in Ischemic and Nonischemic LV Dysfunction

A Meta-Analysis

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ABSTRACT

OBJECTIVES The authors performed a meta-analysis to evaluate the predictive value of late gadolinium enhancement (LGE) cardiac magnetic resonance for ventricular tachyarrhythmia in ischemic cardiomyopathy (ICM) and nonischemic cardiomyopathy (NICM) patients with ventricular dysfunction.

BACKGROUND The use of LGE to detect myocardial fibrosis and its related arrhythmic substrate is well established. Several recent studies have described the predictive value of LGE for ventricular tachyarrhythmias; however, their validity is limited by small sample size and low number of events.

METHODS MEDLINE and the Cochrane Library electronic databases were systematically searched to identify studies that applied LGE in ICM and NICM patients with ventricular dysfunction and reported arrhythmic clinical outcomes (sudden death, aborted sudden death, ventricular tachycardia, ventricular fibrillation, and appropriate implantable cardioverter-defibrillator [ICD] therapy, including antitachycardia pacing). A meta-analysis was performed to determine pooled odds ratios (ORs) for these arrhythmic events.

RESULTS Nineteen studies that evaluated 2,850 patients with 423 arrhythmic events over a mean/median follow-up of 2.8 years were identified. The composite arrhythmic endpoint was reached in 23.9% of patients with a positive LGE test (annualized event rate of 8.6%) versus 4.9% of patients with a negative LGE test (annualized event rate of 1.7%; $p < 0.0001$). LGE correlated with arrhythmic events in the different patient groups. In the overall population, the pooled OR was 5.62 (95% confidence interval [CI]: 4.20 to 7.51), with no significant differences between ICM and NICM patients. In a subgroup of 11 studies (1,178 patients) with mean ejection fraction (EF) ≤30%, the pooled OR for the arrhythmic events increased to 9.56 (95% CI: 5.63 to 16.23), with a negative likelihood ratio of 0.13 (95% CI: 0.06 to 0.30).

CONCLUSIONS LGE is a powerful predictor of ventricular arrhythmic risk in patients with ventricular dysfunction, irrespective of ICM and NICM etiology. The prognostic power of LGE is particularly strong in patients with severely depressed EF, which suggests its potential to improve patient selection for ICD implantation. (J Am Coll Cardiol Img 2016;9:1046–55) © 2016 by the American College of Cardiology Foundation.

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The prognostic stratification of sudden death represents an open challenge for modern cardiology. Current guidelines for use of implantable cardioverter-defibrillators (ICDs) in primary prevention are mostly based on left ventricular ejection fraction (EF) values (1). Nonetheless, a severely depressed EF is a low-specificity marker in differentiating risk of sudden death from risk of death associated with comorbidities or the evolution of heart failure (2,3). Similarly, sudden death can occur in patients with normal or mildly depressed EF (4). Therefore, in recent years, efforts have been made to identify new markers to improve the prognostic stratification of sudden death.

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Ventricular fibrosis plays an important role in the genesis of ventricular arrhythmias in patients with ischemic cardiomyopathy (ICM) (5) and nonischemic cardiomyopathy (NICM) (6,7). Thus, the assessment of ventricular fibrosis by late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) has been recently suggested as a candidate marker for sudden death risk stratification (8–11). Although this topic has been investigated by several studies, their small sample size and low number of events limit their clinical significance. The aim of the present meta-analysis was to assess the role of LGE in risk stratification of ventricular tachyarrhythmic events in both ICM and NICM patients with ventricular dysfunction. Given the importance of EF values in ICD implantation (1), subgroup meta-analyses were performed in order to assess the performance of LGE in patients with different EF values.

METHODS

The systematic review and meta-analysis were conducted following the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement (12).

ELIGIBILITY CRITERIA. The search of published reports was performed to identify studies assessing the predictive value of LGE-CMR in the prognostic stratification of ventricular tachyarrhythmias in cardiomyopathy patients with ventricular dysfunction. Both ischemic and nonischemic etiologies were considered, while other cardiomyopathies were excluded. Studies presenting primary or secondary outcomes related to ventricular events, such as cardiac sudden death, aborted sudden death, sustained ventricular tachycardia (VT), ventricular fibrillation (VF), appropriate ICD therapy with the inclusion of antitachycardia pacing (ATP), were selected. Studies reporting a composite endpoint were included, provided that arrhythmic events could be analyzed separately. Many studies included a mixed population with both primary and secondary prevention of ventricular tachyarrhythmias. Because the focus of the study was the primary prevention population, studies including a fraction of secondary prevention patients ≥25% were not included. Additional inclusion criteria were a sample size greater than 50 and an average follow-up period longer than 6 months. The search was restricted to articles published in English in peer-reviewed journals. Abstracts and session presentations were excluded.

INFORMATION SOURCES, SEARCH STRATEGY, AND STUDY SELECTION. MEDLINE and the Cochrane Library electronic databases were systematically searched by 2 reviewers (M.D. and G.C.) to identify primary references up to April 2015. The database search was followed by a review of the citations from eligible studies. The following search terms were used: late gadolinium enhancement OR LGE OR delayed enhancement OR magnetic resonance AND sudden death OR ventricular tachyarrhythmias OR outcome AND cardiomyopathy OR coronary artery disease, in humans. The database search identified 1,547 relevant references, which were complemented by 14 references from the study citations (**Figure 1**). A total of 1,506 references were excluded after reading title and abstract, and 55 were retrieved for further evaluation. Thirty-six studies from the latter group were excluded because they did not fulfill all the inclusion criteria, leaving 19 studies for the subsequent qualitative and quantitative syntheses (8–11,13–27) (**Tables 1 and 2**).

DATA COLLECTION PROCESS. Two reviewers (M.D. and G.C.) independently extracted the demographic and clinical outcome data from the selected studies. When disagreement occurred, they reviewed the papers together to reach joint conclusions. The methodological quality of the studies was evaluated by applying the Newcastle-Ottawa Score (NOS) checklist for cohort studies (28).

STATISTICAL ANALYSIS. When available, patient characteristics were expressed as a percentage, mean ± SD, or median (interquartile range), as appropriate. In each study the outcomes of ventricular arrhythmic events were summarized by simple counts. Pooled odds ratio (OR) and 95% confidence interval (CI) were estimated by a random effects model based on the method used by DerSimonian and Laird (29). Data heterogeneity among studies was estimated

ABBREVIATIONS AND ACRONYMS

ATP = antitachycardia pacing

CMR = cardiac magnetic resonance

EF = ejection fraction

ICD = implantable cardioverter-defibrillator

ICM = ischemic cardiomyopathy

LGE = late gadolinium enhancement

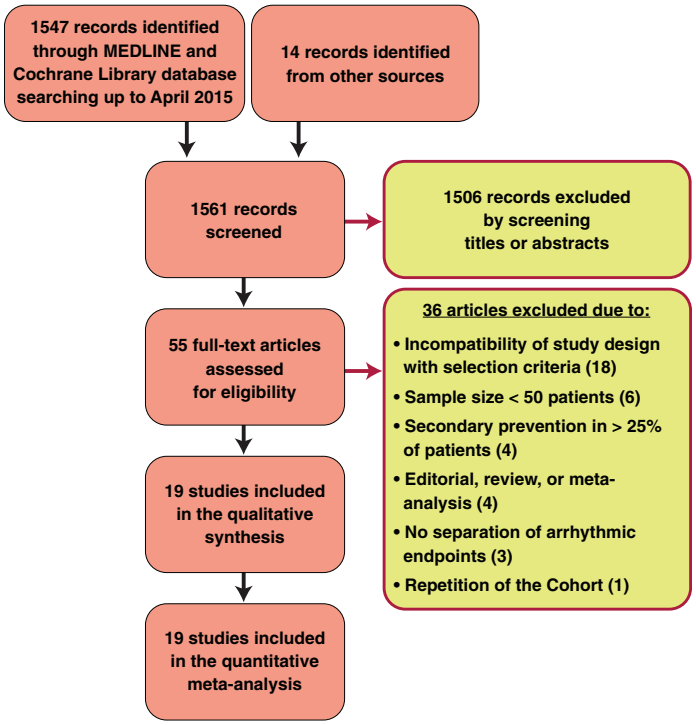
NICM = nonischemic cardiomyopathy

NLR = negative likelihood ratio

VF = ventricular fibrillation

VT = ventricular tachycardia

FIGURE 1 Selection Process for the Studies Included in the Systematic Review and Meta-Analysis



The PRISMA (Preferred Reporting Items for Systemic Reviews and Meta-Analyses) flow diagram depicts the number of records identified, included and excluded, and the reasons for exclusions, through the different phases of the systematic review and meta-analysis.

by chi-square test and I^2 and Tau^2 statistics, which were calculated by an inverse-variance fixed-effect model. Sensitivity analysis was performed to evaluate the influence of individual studies on the pooled ORs. Small study effects were assessed using the Harbord modified test (30). According to the etiology of the cardiomyopathy, subgroup meta-analyses were performed by pooling the studies into 3 subgroups: studies including ICM patients, those including NICM patients, or those with mixed ICM/NICM patients. Given the clinical importance of EF values, an additional subgroup evaluation was performed, separating studies with a mean EF ≤30% from those with a mean EF >30%. For each of the subgroups, the performance of a binary classification test based on LGE was calculated in terms of annualized event rate of positive and negative LGE (LGE+ and LGE−, respectively), sensitivity, specificity, positive likelihood ratios (PLR) and negative likelihood ratios (NLR). The annualized event rates were calculated by dividing the total number of events in the LGE+ and LGE− groups by the follow-up length. A 2-tailed p value <0.05 indicated statistical significance. Pooled sensitivity and specificity, PLR, and NLR were calculated using a bivariate model fitted by a generalized linear mixed model approach in order to consider potential correlation between sensitivity and specificity across the studies (31). All analyses were performed using the Cochrane Collaboration Software Review Manager (RevMan) [computer program] version 5.3. (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen, Denmark) and Stata Statistics/Data analysis version 13.1 (StataCorp, College Station, Texas).

RESULTS

STUDY CHARACTERISTICS. Nineteen studies enrolling 2,850 patients with ICM and NICM were included in the meta-analysis (**Table 1**). In a study by Boyé et al. (13), the arrhythmic events could not be analyzed separately from cardiac death events, but the study was included in the analysis given the low percentage of cardiac death (13% [2 of 16 patients]). In the study by Muller et al. (21), arrhythmic events that were terminated by an appropriate ICD therapy (including ATP) were included in the analysis, while VTs with spontaneous resolution and low rate were excluded. In the studies by Wu et al. (25) and Mordi et al. (26), groups at low risk of arrhythmic events were defined according to LGE cutoffs and serum C-reactive protein and N-terminal pro-B-type natriuretic protein levels. The methodological quality of the studies in terms of NOS score is reported in **Table 1** (28). The score was generally good for the selection of patients (levels 3 to 4; maximal NOS score: 4) and for the outcome (levels 2 to 3; maximal NOS score: 3). All studies were observational, with 11 prospective studies (9-11,13,16-18,20,23,25,26). The patients had a mean age of 60.0 ± 15.3 years, and 77.7% were men (**Table 2**). The average follow-up period ranged from a minimum of 0.7 years to a maximum of 5.4 years.

The 19 selected studies were divided into 3 subgroups according to cardiomyopathy etiology. Five studies enrolled 358 patients with ICM, 8 studies enrolled 1,443 patients with NICM, and 6 studies enrolled 1,049 patients from a mixed ICM/NICM population (**Table 1**). When we subgrouped studies according to EF values, the mean EF was ≤30% in 11 studies (n = 1,178) and >30% in the remaining 8 studies (n = 1,672).

Late gadolinium enhancement was present in 25% to 71% of NICM patients and in almost all ICM patients. Thus, the presence of LGE (5 studies) or midwall LGE (3 studies) was the cutoff used for outcome assessment in studies that included only NICM patients. Conversely, outcome assessment was based

TABLE 1 Characteristics of the 19 Selected Studies, Subgrouped According to Cardiomyopathy Etiology

First Author (Ref. #)	Year	Patients (n)	Follow-Up (Months)	Arrhythmic Endpoint in the Meta-Analysis	% LGE-CMR Prevalence	LGE-CMR Cutoff in the Meta-Analysis	NOS
Studies including ischemic cardiomyopathy patients							
Roes et al. (8)	2009	91	9 (2–20)	ICD therapy†	100	Gray zone extent = 16.7 g	4,0,2
Boyé et al. (13)	2011	52	41 ± 11	ICD therapy†, CD	100	Relative infarct transmurality = 43%	3,0,3
De Hann et al. (14)	2011	55	24 (11–36)	ICD therapy, VT	100	Peri-infarct zone threshold, g	4,0,2
Alexandre et al. (15)	2013	66	42 (22–52)	ICD therapy†	100	2 segments with scar extent ≥50%	4,0,3
Demirel et al. (16)	2014	94	65 (54–79)	ICD therapy†, VT	100	Peri to core-infarct mass ratio = 0.6	4,0,3
Studies including nonischemic cardiomyopathy patients							
Assomull et al. (17)	2006	101	22 ± 12	Sudden death, VT‡	35	LGE presence in midwall	4,2,2
Iles et al. (18)	2011	61	19 (13–29)	ICD therapy†	51	LGE presence	4,2,2
Leyva et al. (19)	2012	97	35*	Sudden death ‡	26	LGE presence in midwall	4,2,3
Gulati et al. (11)	2013	472	64*	ICD therapy, sudden death, aSD‡	30	LGE presence in midwall	4,2,3
Neilan et al. (20)	2013	162	29 ± 18	ICD therapy†, sudden death‡	50	LGE presence	4,2,2
Muller et al. (21)	2013	185	21*	aSD, ICD therapy‡	51	LGE presence	4,2,3
Perazzolo-Marra et al. (22)	2014	137	36*	ICD therapy†, sudden death, VT/VF	56	LGE presence	4,0,3
Masci et al. (23)	2014	228	23 (13–37)	ICD therapy, aSD, sudden death‡	27	LGE presence	4,2,2
Studies including a mixed population of ischemic and nonischemic cardiomyopathy patients							
Fernandez-Armenta et al. (24)	2012	78 (41/37)	25 (15–34)	ICD therapy†	69	Border zone = 9.5 g	4,0,2
Gao et al. (9)	2012	124 (59/65)	21 ± 9	ICD therapy†, sudden death, aSD	100/71§	LGE extent = 38.7 g/20.8 g§	4,0,2
Klem et al. (10)	2012	137 (73/64)	24 (20–29)	ICD therapy, sudden death‡	96/58§	LGE = 5% LV mass	4,0,2
Wu et al. (25)	2012	235 (137/98)	43*	ICD therapy†	73	Gray zone extent = 8.7 g/0 g§	4,0,3
Mordi et al. (26)	2014	157 (61/96)	31*	ICD therapy†‡	100/25§	LGE percentage = 23%/0%§	4,0,2
Almehmadi et al. (27)	2014	318 (149/169)	16*	ICD therapy†, sudden death	78	LGE presence	4,0,2

Values are n, median (interquartile range), or mean ± SD. *Median; interquartile range not available. †Including antitachycardia pacing. ‡Secondary endpoint. §In ischemic/nonischemic cardiomyopathy patients.

aSD = aborted sudden death; CD = cardiac death; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; LGE-CMR = late gadolinium enhancement cardiac magnetic resonance; LV = left ventricle; NOS = Newcastle-Ottawa Scale for quality assessment of non-randomized studies.

upon either the scar extent (2 studies) or the peri-infarct zone/gray zone extent (3 studies) in the studies including ICM patients; the cutoffs used in each study are presented in Table 1. In the studies with mixed populations, the presence of LGE (1 study), the extent of the scar (3 studies), or the gray zone/border zone extent (2 studies) were alternatively adopted for outcome assessment; the cutoffs used in these studies are also presented in Table 1. Based on these criteria, the pooled prevalence of LGE positive test was 52.3% in the overall population and 58.4% in studies with a mean EF ≤30%.

PREDICTIVE POWER OF LATE GADOLINIUM ENHANCEMENT. Tachyarrhythmic event rates and ORs for the overall studies and subgroups of studies are reported in Table 3. In the overall meta-analysis, the 2,850 patients experienced 423 arrhythmic events, defined as a composite of sudden death, aborted sudden death, VT/VF, and appropriate ICD therapy, including ATP (prevalence: 14.8%; annualized event rate: 5.3%). The composite arrhythmic endpoint was reached in 23.9% of patients with a positive LGE test (annualized event rate of 8.6%) versus 4.9% of patients with a negative LGE test (annualized event rate of 1.7%; $p < 0.0001$). The pooled ORs for arrhythmic events were 5.62 (95% CI: 4.20 to 7.51) in the overall population, 5.05 (95% CI: 2.73 to 9.36) in the studies with ICM patients, 6.27 (95% CI: 4.15 to 9.47) in the studies with NICM patients, and 4.92 (95% CI: 2.70 to 8.98) in the studies with a mixed ICM/NICM population (Figure 2). Heterogeneity was low within each group, between groups, and in the overall population (chi-square = 14.55; $p = 0.69$; $I^2 = 0\%$; $Tau^2 = 0.00$). The sensitivity analysis showed that single-study exclusion did not affect the strength of the association between LGE and the arrhythmic endpoints. A trend toward small size effects was suggested by the Harbord test ($p = 0.085$).

When studies were grouped according to EF values, the meta-analysis showed that in the subgroup with mean EF ≤30%, the arrhythmic endpoint was reached in 25.8% of patients with positive LGE results (annualized event rate: 10.3%) versus 3.1% of patients with negative LGE results (annualized event rate 1.2%; $p < 0.0001$). The pooled ORs were 9.56 (95% CI: 5.63 to 16.23) in the subgroup of studies with EF ≤30% versus 4.48 (95% CI: 3.17 to 6.33) in the subgroup with EF >30% ($p = 0.02$) (Figure 3). Heterogeneity was low within each EF subgroup but

TABLE 2 Characteristics of the Patients in the 19 Selected Studies, Subgrouped According to Cardiomyopathy Etiology

First Author (Ref. #)	Age (yrs)	% of Males	EF (%)	Implanted ICD (%)	Sudden Death Secondary Prevention (%)
Studies including ischemic cardiomyopathy patients					
Roes et al. (8)	65 ± 11	81	28 ± 9	100	11
Boyé et al. (13)	70 ± 10	NR	29 ± 7	100	0
De Hann et al. (14)	65 ± 11	78	25 ± 7	100	0
Alexandre et al. (15)	63 ± 11	97	23 ± 8	100	23
Demirel et al. (16)	65 ± 11	86	32 ± 9	100	23
Studies including nonischemic cardiomyopathy patients					
Assomull et al. (17)	51 ± 13	69	36 ± 12	0	0
Iles et al. (18)	54 ± 13	77	25 ± 9	100	0
Leyva et al. (19)	66 ± 12	62	22 ± 10	3	3
Gulati et al. (11)	51 ± 15	69	37 ± 13	23	5
Neilan et al. (20)	55 ± 14	65	26 ± 8	100	0
Muller et al. (21)	51 ± 16	71	43 ± 16	31	0*
Perazzolo-Marra et al. (22)	49 ± 18	79	32 (28-40)	50	5
Masci et al. (23)	50 ± 15	79	43 ± 10	7	0
Studies including a mixed population of ischemic and nonischemic cardiomyopathy patients					
Fernandez-Armenta et al. (24)	64 ± 11	83	22 ± 7	100	0
Gao et al. (9)	61 ± 11	81	26 ± 7	64	8
Klem et al. (10)	59 ± 15	63	35 ± 18	75	9
Wu et al. (25)	57 ± 13	76	26 ± 9	100	0
Mordi et al. (26)	51 ± 14	78	28 ± 15	100	0
Almehmadi et al. (27)	62 ± 13	73	33 ± 12	NR	11

Values are mean ± SD, (%), or median (interquartile range). *8% hypertrophic cardiomyopathy or hypertensive heart disease, 2% storage disease.
NR = not reported; other abbreviations as in Table 1.

was present between the 2 subgroups (I^2 = 81.9%) (Figure 3).

Pooled sensitivity, specificity, PLR, and NLR of LGE for the prediction of arrhythmic events are reported in Table 4 for the overall population and for all subgroups of patients. In particular, in the subgroup of studies with a mean EF ≤30%, the pooled NLR was 0.13 (95% CI: 0.06 to 0.30).

TABLE 3 Tachyarrhythmic Event Rate and Odds Ratio in the Different Subgroups of Studies

				LGE-CMR			
	Studies	Patients	% AER	% of LGE+ AER*	% LGE− AER*	OR (95% CI)	p Value
Total	19	2,850	5.3	8.6	1.7	5.62 (4.20-7.51)	<0.00001
ICM	5	358	8.9	13.2	3.3	5.05 (2.73-9.36)	<0.00001
NICM	8	1,443	3.7	7.6	1.3	6.27 (4.15-9.47)	<0.00001
Mixed population	6	1,049	6.8	8.8	1.8	4.92 (2.70-8.98)	<0.00001
Mean EF ≤30%	11	1,178	6.6	10.3	1.2	9.56 (5.63-16.23)	<0.00001
Mean EF >30%	8	1,672	4.6	7.4	2.0	4.48 (3.17-6.33)	<0.00001

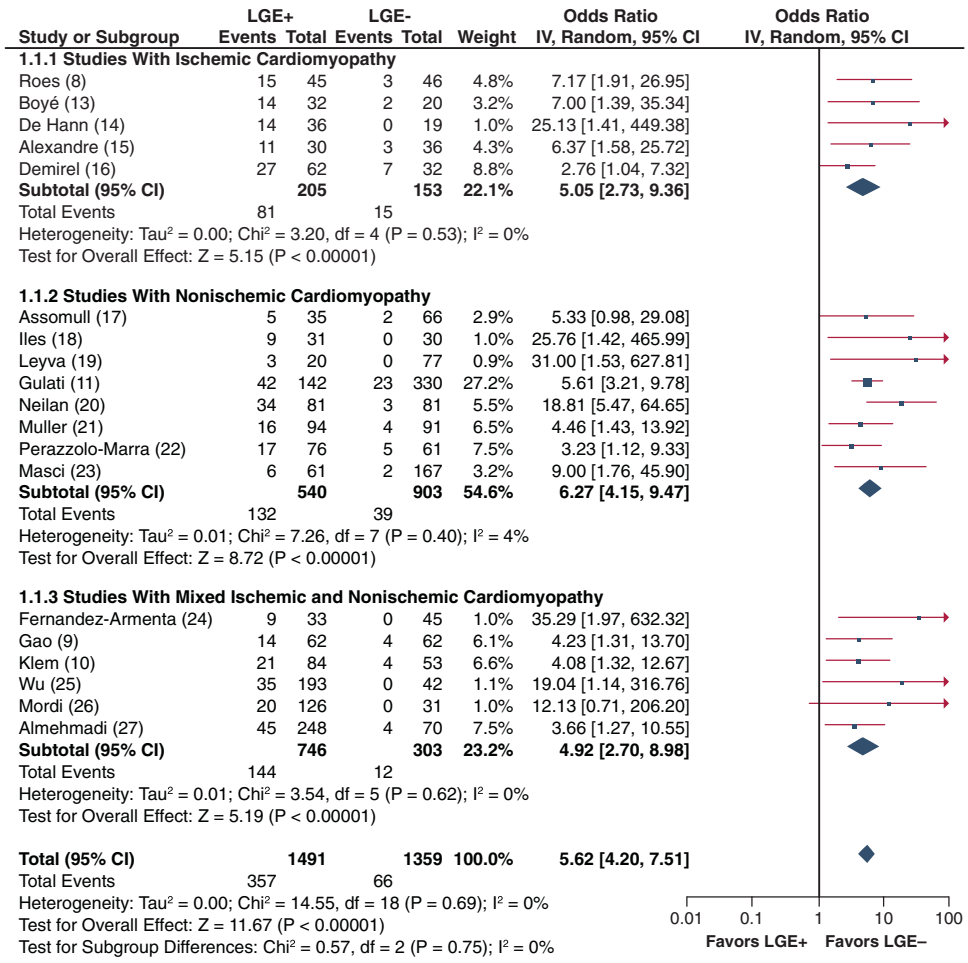
Values are n or %. *LGE+/− test results based on the criteria reported in Table 1.
AER = annualized event rate; ICM = ischemic cardiomyopathy; NICM = nonischemic cardiomyopathy; OR = odds ratio; other abbreviations as in Table 1.

EXTENT OF LATE GADOLINIUM ENHANCEMENT AND ARRHYTHMIC RISK. In addition to the LGE patterns adopted for the dichotomous categorization of patients (LGE+ and LGE−) in the meta-analysis reported earlier (Table 1), some of the studies evaluated the existence of a dose-response effect between the degree of ventricular fibrosis and the arrhythmic endpoint by Cox or logistic regression analysis (Table 5). The fibrotic burden was quantified by 2 main descriptors: the total extent of the scar (in mass or percentage) and the extent of the zone of fibrosis heterogeneity (defined as gray zone or border zone or peri-infarct zone). Fourteen of the selected studies quantified the relationship between the total extent of LGE and the arrhythmic endpoints (Table 5). Despite differences in regression strategy and covariates, 10 studies (n = 1,760) (9-11,15,17,20,23-26) reported a statistically significant ($p < 0.05$) increase of the arrhythmic risk at the increase of total LGE extension. The effect was observed in both ICM and NICM patients. In the largest published study, including 472 NICM patients with median follow-up of 5.3 years, both the presence and the extent of fibrosis were independent predictors of the arrhythmic risk, with adjusted hazard ratios of 4.61 (95% CI: 2.75 to 7.74; $p < 0.001$) and 1.10 (95% CI: 1.05 to 1.16 at 1% LGE increase; $p < 0.001$), respectively (11). The relationship between the extension of the heterogeneous zone and the arrhythmic endpoint was quantitatively assessed in 5 studies and was shown to be statistically significant in 4 studies (n = 498) (8,16,24,25). When either the total scar or the gray zone was considered as a potential descriptor of the fibrosis extent, a statistically significant relationship with the arrhythmic endpoint was observed in 12 of 14 studies (8-11,15-17,20,23-26).

DISCUSSION

Although several studies have investigated the effect of LGE in risk stratification of ventricular tachyarrhythmic events in ICM and NICM patients with ventricular dysfunction, these studies have been limited by their small sample size and low number of events. This meta-analysis is the first to include such a large number of studies (19 studies; n = 2,850), which allowed us to demonstrate that LGE is a powerful predictor of ventricular tachyarrhythmic events in patients with ventricular dysfunction of ischemic and nonischemic etiology. In particular, by performing subgroup meta-analyses, we assessed the performance of LGE in different studies, including moderately versus severely depressed EF patients. The pooled ORs showed no differences in LGE

FIGURE 2 **Individual and Pooled ORs for LGE Cardiac Magnetic Resonance in Different Cardiomyopathy Etiologies**



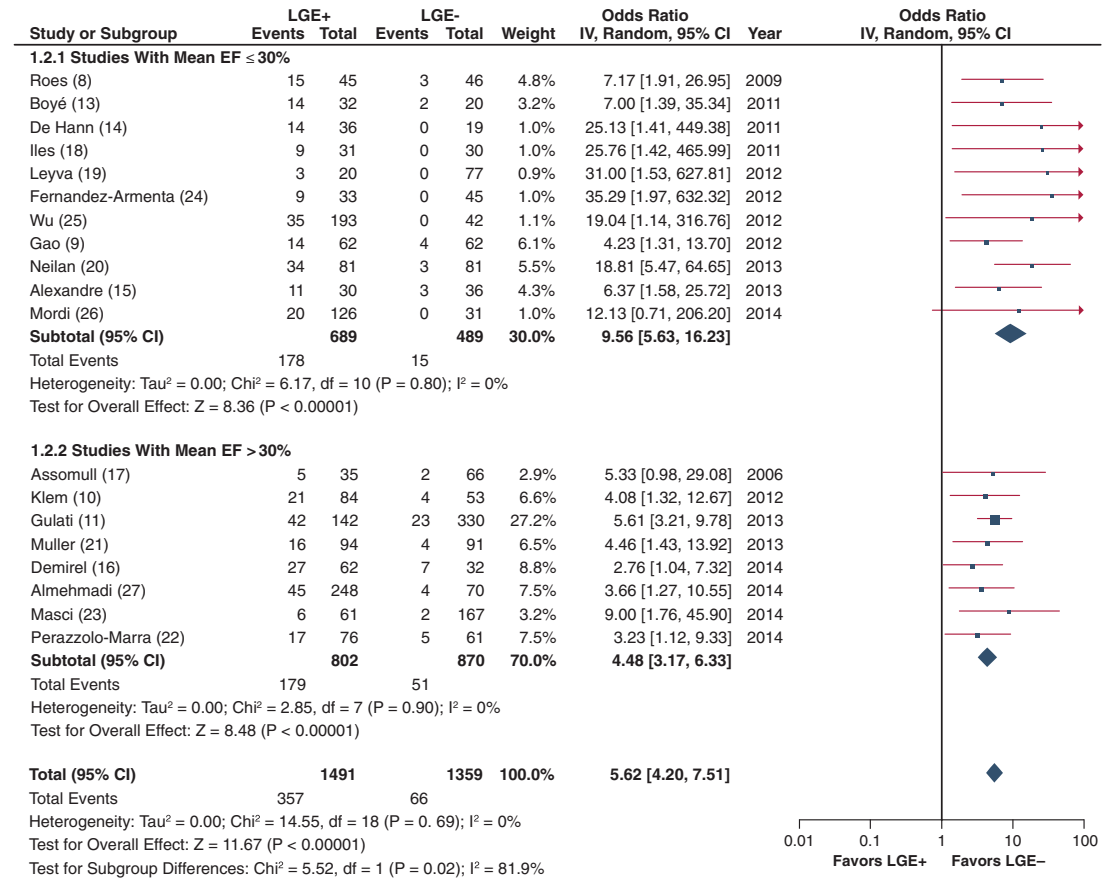
Forest plot compares the composite arrhythmic endpoint in patients with positive (LGE+) and negative test (LGE−) in the ischemic cardiomyopathy **(top)**, nonischemic cardiomyopathy **(center)**, and mixed ischemic/nonischemic cardiomyopathy **(bottom)** populations. LGE = late gadolinium enhancement; ORs = pooled odds ratios.

prognostic power between ICM and NICM patients (Figure 2), while the OR was almost double in the studies with a mean EF ≤30% versus a mean EF >30%. This highlights the fact that the prognostic power of LGE for ventricular arrhythmias is particularly strong in patients with severely depressed EF (Figure 3).

LATE GADOLINIUM ENHANCEMENT AND ARRHYTHMIC SUBSTRATE. In both ischemic and nonischemic cardiomyopathy the remodeling process is characterized by changes in the extracellular matrix, including the formation of fibrosis (32). The ability of LGE-CMR to detect myocardial fibrosis is supported by mounting evidence, which has been recently complemented by histological correlations (11,33). The fibrotic tissue may constitute a substrate for ventricular arrhythmias (5-7), where slow and heterogeneous conduction associated with fibrosis may favor the instauration of re-entrant circuits, increasing the vulnerability to VT/VF (6,34). In particular, the gray zone (or peri-infarct zone or border zone) is a heterogeneous medium, where areas with different levels of fibrosis coexist, resulting in both viable and nonviable myocardium (34). Conduction channels in the gray zone detected by 3-dimensional LGE-CMR corresponded to those identified by endocardial voltage mapping (35), which supports their role in arrhythmia maintenance.

The studies analyzed in the present meta-analysis adopted different LGE parameters and detection cutoffs for the arrhythmic risk stratification of

FIGURE 3 Individual and Pooled ORs for LGE Cardiac Magnetic Resonance in Patients With Different EF Values



Forest plot compares the composite arrhythmic endpoint in patients with positive (LGE+) and negative (LGE−) test and mean EF ≤30% **(top)** and >30% **(bottom)**. EF = ejection fraction; other abbreviations as in Figure 2.

patients. In NICM patients, the presence and absence of fibrosis or midwall fibrosis were most widely used as indicators to differentiate patients at high versus low risk of arrhythmic events. In ICM patients, LGE-CMR was used not only to detect the presence of a scar (present in almost all patients) but also to measure its extent. In addition to the binary categorization of myocardium into normal versus scarred myocardium, some of the studies evaluated scar tissue heterogeneity, characterizing the scar as core or gray-zone areas. In the majority of studies analyzing total LGE or gray-zone extent, a statistically significant dose-response effect with arrhythmic risk was shown. The larger and more heterogeneous the scar was, the higher the probability of ventricular arrhythmias during the follow-up (Table 5). Interestingly, total LGE or gray-zone extents were predictors of arrhythmic risk not only in ICM patients but also in NICM patients. The additive value of a scar characterization by LGE was suggested by numerous studies that showed the gray-zone extent to be consistent with the total scar extent in the prediction of arrhythmic endpoints (24,25), or even to outperform

TABLE 4 Performance of the LGE-CMR Test in Predicting the Composite Arrhythmic Endpoint in the Different Subgroups of Studies*

Subgroups	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)
Total	85.5% (78.7-90.5)	53.2% (44.6-61.7)	1.83 (1.57-2.13)	0.27 (0.19-0.38)
ICM	84.3% (75.5-90.4)	52.5% (44.9-59.9)	1.77 (1.48-2.13)	0.30 (0.18-0.49)
NICM	79.7% (68.1-87.9)	66.0% (57.7-73.4)	2.35 (1.88-2.93)	0.31 (0.19-0.49)
Mixed population	92.4% (79.0-97.5)	36.7% (24.2-51.3)	1.46 (1.20-1.77)	0.21 (0.08-0.54)
Mean EF ≤30%	92.9% (83.1-97.2)	52.9% (41.2-64.3)	1.97 (1.58-2.45)	0.13 (0.06-0.30)
Mean EF >30%	78.3% (69.1-85.4)	54.4% (41.6-66.6)	1.72 (1.38-2.13)	0.40 (0.30-0.52)

*Parameters were estimated by a bivariate generalized linear mixed model.

CI = confidence interval; EF = ejection fraction; ICM = ischemic cardiomyopathy; NICM = nonischemic cardiomyopathy; NLR = negative likelihood ratio; PLR = positive likelihood ratio.

TABLE 5 Association Between the Risk of Ventricular Arrhythmias and the Extent of the Total/Heterogeneous Scar, Assessed by LGE-CMR

First Author (Ref. #)	Scar Patterns From LGE-CMR Image Analysis	HR (95% CI)	p Value
Studies including ischemic cardiomyopathy patients			
Roes et al. (8)	Total scar mass (g), HR per 10 g increase	1.15 (0.99–1.33)*	0.06
	Gray zone mass (g), HR per 10 g increase	1.49 (1.01–2.20)†	0.04
Alexandre et al. (15)	Total scar mass (g)	3.15 (1.35–7.33)†	<0.001
Demirel et al. (16)	Total scar mass (g)	1.01 (0.99–1.03)*	0.18
	Peri to core-infarct mass ratio	2.01 (1.17–3.44)†	0.01
Studies including nonischemic cardiomyopathy patients			
Assomull et al. (17)	Total scar extent (% of LV mass)	1.12 (1.03–1.24)†‡	0.02
Gulati et al. (11)	Total scar extent (% of LV mass), HR per 1% increase	1.10 (1.05–1.16)†	<0.001
Neilan et al. (20)	Total scar extent (% of LV mass), HR per 1% increase	1.17 (1.12–1.22)†	<0.0001
Perazzolo Marra et al. (22)	Total scar extent (% of LV mass)	1.04 (0.98–1.09)*	0.18
Masci et al. (23)	Total scar extent (number of segments)	1.24 (1.11–1.38) †§	<0.001
Studies including a mixed population of ischemic and nonischemic cardiomyopathy patients			
Fernandez-Armenta et al. (24)	Total scar extent (% of LV volume), HR per 1% increase	1.10 (1.06–1.15)†	<0.01
	Border zone mass (g), HR per 1 g increase	1.06 (1.04–1.09)†	< 0.01
Gao et al. (9)	Total scar mass (g), HR per 10 g increase	1.38 (1.18–1.62)†	<0.001
	Gray-zone mass (g), HR per 10 g increase‖	1.47 (0.96–2.26)*	0.074
Klem et al. (10)	Total scar extent (% of LV mass)	1.04 (1.00–1.07)*	0.03
Wu et al. (25)	Total scar mass (g, tertiles), HR 3RD tertile versus reference	3.40 (1.60–7.00)*§	0.001
	Gray-zone mass (g, tertiles), HR 3RD tertile versus reference	4.60 (1.40–15.4)†§	0.01
Mordi et al. (26)	Total scar extent (% of LV mass), HR per 1% increase	1.04 (1.01–1.07)†	0.004
Almehmadi et al. (27)	Total scar extent (% of LV mass), HR per 1% increase	1.00 (0.90–1.00)†	0.22

*Univariate analysis. †Multivariate analysis. ‡Odds ratio from binary logistic regression. §Composited endpoint with cardiac death. ‖Limited to ischemic cardiomyopathy patients. HR = hazard ratio; other abbreviations as in Table 1.

it in ICM patients (8,16). Further studies with larger populations are necessary to assess the actual performance of the gray-zone in risk stratification. Moreover, LGE quantification and, in particular, gray-zone detection protocols need to be optimized and standardized for clinical implementation, because they involve complex and operator-dependent procedures (36).

LATE GADOLINIUM ENHANCEMENT IN PATIENTS WITH SEVERELY DEPRESSED EJECTION FRACTION. Due to its limited sensitivity and specificity (2–4), EF is considered an unsatisfactory risk marker for sudden death. Nonetheless, given the multifactorial origin of sudden death, it is unlikely that another single marker would achieve better predictive accuracy. In order to overcome this limitation, combined markers integrating EF evaluation with tests able to investigate different arrhythmic mechanisms (3,37) should be used. The present work showed that the prognostic value of LGE for ventricular arrhythmias was improved in the studies with a mean EF ≤30% in comparison to those with a mean EF >30%, as confirmed by an increase of ORs from 4.48 (95% CI: 3.17 to 6.33) to 9.56 (95% CI: 5.63 to 16.23). Accordingly, in the EF ≤30% group, the pooled NLR of LGE was low (Table 4), and the annualized arrhythmic event rate was slightly above 1% for LGE-negative patients (Table 3). This suggests that patients with severely depressed EF but a negative LGE test result have relatively lower-risk of arrhythmic events. However, it is noteworthy that in 9 of 11 studies with mean EF ≤30%, all patients underwent ICD implantation and that the arrhythmic endpoint was defined as appropriate ICD therapy. This aspect may have partially affected the evaluation of clinical outcomes, because appropriate ICD therapy represents a surrogate endpoint. Appropriate ICD therapy may indeed overestimate sudden death and the beneficial effects of ICD by a factor of 2 (38), with more evident effects in the case of ATP.

Current ICD implantation guidelines for primary prevention of sudden death are based on EF values and suggest appropriate ICD implantation for ICM and NICM patients with EF ≤35% (1). Nonetheless, as confirmed by our results, patients with severely depressed EF constitute a heterogeneous group that includes patients at lower risk of sudden death who may not benefit from ICD implantation and may instead suffer from collateral effects (39). According to our data, the combination of the LGE test and EF evaluation may aid in the identification of lower risk patients, thus improving the appropriateness of ICD implantation.

STUDY LIMITATIONS. Arrhythmic endpoints differ from each other, and some, such as appropriate ICD therapy, overestimate sudden death risk. LGE-CMR techniques and diagnostic cutoffs are not uniform, and the assessment of fibrosis extent and heterogeneity by LGE, is still a complex and operator-dependent procedure (36). The majority of the studies analyzed in the present meta-analysis were performed in single, tertiary cardiologic centers. Finally, it was not possible to completely separate the results in ICM and NICM patients, because of a subgroup of 6 studies with a mixed ICM/NICM population.

CONCLUSIONS

This meta-analysis showed that the assessment of ventricular fibrosis by LGE-CMR is a powerful predictor of ventricular tachyarrhythmic events in both ICM and NICM patients. The prognostic power of LGE is particularly strong in patients with severely depressed EF. LGE testing may thus improve the appropriateness of ICD implantation in patients with severely depressed EF by identifying a lower-risk group unlikely to benefit from ICD. However, to be put into practice, LGE-CMR protocols need to be standardized with respect to execution modalities and the setting of diagnostic thresholds.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The prognostic stratification of sudden death represents an open challenge for modern cardiology. The assessment of ventricular fibrosis by LGE-CMR has been recently suggested as a candidate marker for sudden death risk stratification. Ventricular fibrosis could be the substrate of ventricular tachyarrhythmias in patients with ventricular dysfunction. This meta-analysis shows that LGE is a powerful predictor of ventricular tachyarrhythmic events in patients with ventricular dysfunction, irrespective of ischemic and nonischemic etiology. Moreover, the prognostic power of LGE for ventricular arrhythmias is particularly strong in patients with EF ≤30%.

TRANSLATIONAL OUTLOOK: Currently, the guidelines for ICD therapy in primary prevention of sudden death are based on EF values and suggest appropriate ICD implantation in patients with EF ≤35%. However, EF is considered an unsatisfactory risk marker for sudden death, because of its limited sensitivity and specificity. The combination of the LGE test and EF evaluation could aid in improving the appropriateness of ICD therapy. In patients with severely depressed EF a negative LGE test could identify patients at relatively low risk of arrhythmic events, who may have limited benefit from ICD therapy. Nevertheless, LGE-CMR protocols must be standardized.

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