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Late Gadolinium Enhancement and the Risk for Ventricular Arrhythmias or Sudden Death in Dilated Cardiomyopathy

Systematic Review and Meta-Analysis

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the association between late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging and ventricular arrhythmias or sudden cardiac death (SCD) in patients with dilated cardiomyopathy (DCM).

BACKGROUND Risk stratification for SCD in DCM needs to be improved.

METHODS A systematic review and meta-analysis were conducted. A systematic search of PubMed and Ovid was performed, and observational studies that analyzed the arrhythmic endpoint (sustained ventricular arrhythmia, appropriate implantable cardioverter-defibrillator [ICD] therapy, or SCD) in patients with DCM, stratified by the presence or absence of LGE, were included.

RESULTS Twenty-nine studies were included, accounting for 2,948 patients. The studies covered a wide spectrum of DCM, with a mean left ventricular ejection fraction between 20% and 43%. LGE was significantly associated with the arrhythmic endpoint both in the overall population (odds ratio: 4.3; $p < 0.001$) and when including only those studies that performed multivariate analysis (hazard ratio: 6.7; $p < 0.001$). The association between LGE and the arrhythmic endpoint remained significant among studies with mean left ventricular ejection fractions >35% (odds ratio: 5.2; $p < 0.001$) and was maximal in studies that included only patients with primary prevention ICDs (odds ratio: 7.8; $p = 0.008$).

CONCLUSIONS Across a wide spectrum of patients with DCM, LGE is strongly and independently associated with ventricular arrhythmia or SCD. LGE could be a powerful tool to improve risk stratification for SCD in patients with DCM. These results raise 2 major questions to be addressed in future studies: whether patients with LGE could benefit from primary prevention ICDs irrespective of their left ventricular ejection fractions, while patients without LGE might not need preventive ICDs despite having severe left ventricular dysfunction. (J Am Coll Cardiol HF 2017;5:28–38)

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Risk stratification for sudden cardiac death (SCD) among patients with dilated cardiomyopathy (DCM) remains inadequate, causing ongoing clinical challenges in the appropriate identification of candidates for primary prevention implantable cardioverter-defibrillators (ICDs).

Left ventricular ejection fraction (LVEF) continues to be used as the main criterion to select patients for primary prevention ICDs. However, LVEF has low sensitivity and low specificity for the prediction of SCD (1). Indeed, only about 20% of patients with DCM who have ICDs for primary prevention subsequently receive appropriate therapies from the devices during follow-up (2). Recently, the DANISH (Danish ICD Study in Patients With Dilated Cardiomyopathy) trial questioned the benefit of primary prevention ICDs in patients with nonischemic heart failure (3).

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Myocardial scar is the major substrate for ventricular arrhythmias (VAs) (4), but not all patients with DCM have identifiable scarring. Late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging can detect areas of localized myocardial fibrosis (5). Several studies have analyzed the association between LGE and outcomes, including VA or SCD, in patients with DCM. However, with regard to arrhythmic events, results have varied, and most analyses were from single-center studies including relatively small numbers of patients.

Therefore, we considered it appropriate to perform a meta-analysis that specifically addressed the association between LGE and SCD or VA in patients with DCM.

METHODS

The study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (6).

SEARCH STRATEGY. A systematic search was performed by 2 investigators in PubMed and Ovid using the following search string: "late gadolinium enhancement OR delayed gadolinium enhancement OR magnetic resonance AND cardiomyopathy OR arrhythmias OR ventricular tachycardia OR ventricular fibrillation OR sudden death OR sudden cardiac death." No language restrictions were applied. The search was finalized in August 2015. Abstracts from the 2015 Europace and Heart Rhythm Congresses were also screened for the same keywords, to avoid missing studies not yet published in journals. To ensure saturation, the reference lists of included reports and relevant reviews were also scanned.

ELIGIBILITY CRITERIA, OUTCOMES, SELECTION PROCESS, AND DATA COLLECTION PROCESS. Observational cohort studies, both prospective and retrospective, were included in the meta-analysis if they reported the rate of arrhythmic events in adult patients (>18 years of age) with DCM and provided information about the presence or absence of LGE. SCD, ventricular fibrillation, sustained ventricular tachycardia, and appropriate ICD therapies were considered arrhythmic events and represent the main outcome of this meta-analysis. Any pattern of nonischemic LGE was accounted for to define the presence or absence of LGE. Only studies that specified the exclusion of significant coronary artery disease in their DCM populations were included in this analysis.

Citations initially selected by systematic search were first retrieved as titles and abstracts and preliminarily screened. Potentially suitable citations were then retrieved as full-text reports and assessed for compliance with the inclusion criteria. The reasons for excluding studies were recorded. The search and screening were performed by 2 independent investigators.

When the population of a study also included patients with cardiomyopathies other than DCM, only those with DCM were considered for the present meta-analysis. For studies in which ICD therapies were the only arrhythmic endpoint analyzed and not all patients in the study had undergone ICD implantation, only patients with ICDs were included in the meta-analysis.

Raw data concerning the numbers of patients with and without arrhythmic events, stratified by the presence or absence of LGE, were extracted from original reports or obtained by contacting the corresponding investigator directly. Moreover, data on LVEF, percentages of patients undergoing ICD implantation, brain natriuretic peptide level, and New York Heart Association class were recorded if available.

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
DCM = dilated cardiomyopathy
ICD = implantable cardioverter-defibrillator
LGE = late gadolinium enhancement
LVEF = left ventricular ejection fraction
OR = odds ratio
SCD = sudden cardiac death
VA = ventricular arrhythmia

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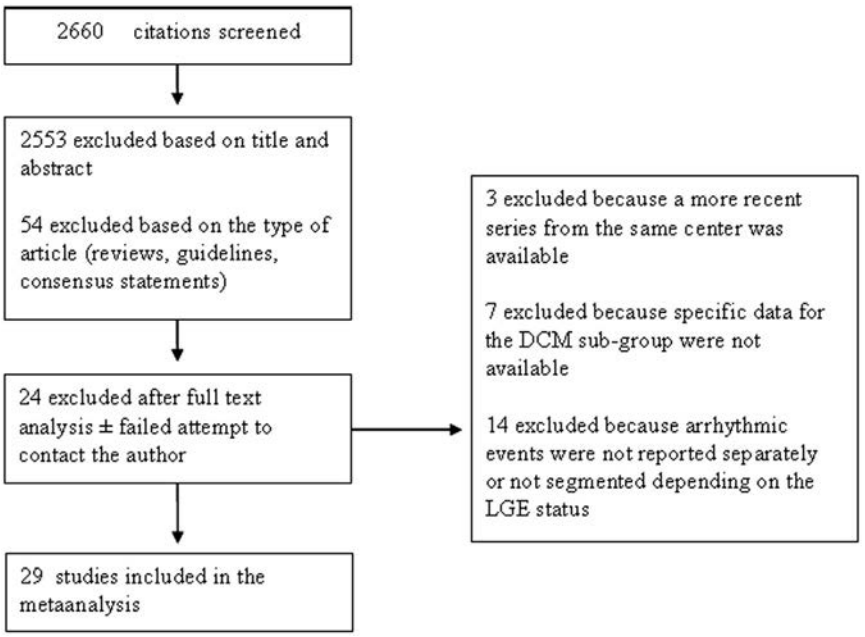
FIGURE 1 Selection Process of the Studies Included in the Meta-Analysis



DCM = dilated cardiomyopathy; LGE = late gadolinium enhancement.

QUALITY ASSESSMENT. The risk for bias within individual studies was evaluated according to the established methods of the Cochrane collaboration (7). Moreover, given the observational nature of the reports, further quality assessment was performed using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies (8).

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD or as median (interquartile range) and categorical variables as number (percentage).

Binary arrhythmic outcomes from individual studies were first combined in a fixed-effects model, leading to estimation of pooled odds ratio (OR), pooled hazard ratio, risk, or rate difference, all with 95% confidence intervals (CIs). Differences were considered statistically significant at a 2-sided p value <0.05. If significant heterogeneity was observed, a random-effects model was used. For a study with zero arrhythmic events in 1 of the 2 groups, an empirical continuity correction (9) was applied to calculate the OR.

Heterogeneity between studies was assessed using the chi-square homogeneity test. Heterogeneity was considered significant if the p value was <0.10. Inconsistency was calculated with the I^2 test, which describes the percentage of variability in effect estimates that is due to heterogeneity between studies. I^2 values of 25%, 50%, and 75% correspond to mild, moderate, and severe heterogeneity effects, respectively. The τ^2 parameter, which expresses interstudy variability, was also reported.

Publication bias was evaluated using the Egger test (10) and the Peters test (11) and was significant at $p < 0.10$. Because publication bias is influenced by sample size, we performed the evaluation of publication bias both in the entire group of studies and, selectively, only for those studies whose entire populations were taken into account in the meta-analysis.

All analysis were performed using Stata version 12 (StataCorp, College Station, Texas).

RESULTS

SEARCH RESULTS AND STUDY SELECTION. The search identified 2,660 citations. After the screening process, 53 full-text reports were carefully assessed. Of these, 21 were excluded because they did not meet the inclusion criteria. Three were excluded (12–14) because their data were included in more recent publications (15–17). In total, 29 studies were finally included in the meta-analysis (**Figure 1**) (15–43).

STUDY QUALITY AND RISK FOR BIAS WITHIN STUDIES. The assessment of study quality using the

Cochrane collaboration method showed that given the observational nature of all studies, the main bias that could not be ruled out was selection bias; attrition bias, related to loss of patients during follow-up, was present in just a few studies (**Table 1**).

The Newcastle-Ottawa scale revealed that in many cases, comparability of the study groups was not ensured on the basis of study design or analysis, because of the observational nature of all studies and the lack of multivariate analysis for the arrhythmic endpoint in many of them (Online Table 1); moreover, the majority of studies did not demonstrate that the outcome of interest was not already present at the beginning of the study (i.e., previous arrhythmic events were not listed as exclusion criteria). Apart from these limitations, most of the reports fulfilled all other criteria.

STUDY CHARACTERISTICS. A total of 2,948 patients from 29 studies were included in the meta-analysis. DCM was usually defined as a reduction in LVEF in the absence of significant coronary artery disease, significant valve disease, hypertensive heart disease, infiltrative heart diseases, and hypertrophic cardiomyopathy (Online Table 2), in line with the suggestions of the position statement of the European Society of Cardiology (44).

The characteristics of the studies are detailed in **Table 2**. The studies covered a wide spectrum of patients with DCM, with mean LVEFs ranging from 20% to 43%. The majority of studies evaluated the presence or absence of LGE by visual analysis (15,17,18,21,24–31,33,35–41,43). Duration of follow-up ranged from 1 to 5.3 years; mean follow-up duration was 3 years. The majority of studies considered composite arrhythmic endpoints formed by SCD and/or aborted cardiac arrest, sustained VAs, and/or appropriate ICD therapies (15,16,18,19,21,24,25,27–29,31,33,36,39–42).

In 2 studies, history of arrhythmic events was the endpoint analyzed (20,43). These data were not used to calculate annual event rates but were included in the evaluation of pooled ORs. However, pooled ORs were also calculated without the inclusion of these 2 studies.

Additional data about arrhythmic events and/or LGE status were obtained for several studies by contacting the investigators (16,17,21,24–35,37–40).

DATA SYNTHESIS: LGE AND VAs. LGE was present in a variable proportion of patients with DCM (21% to 70%), and overall, 1,305 patients (44%) had LGE. The clinical characteristics of patients with and without LGE, when available, are presented (Online Table 3).

The arrhythmic endpoint occurred in 350 patients (12%), 272 of them with LGE (21% of LGE-positive patients) and 78 without LGE (4.7% of LGE-negative patients), with a weighted risk difference between LGE-positive and LGE-negative patients of 14.4% (95% CI: 9.6% to 19.2%; $p < 0.001$). The annual event rates were 6.9% and 1.6%, respectively, in patients with and without LGE (weighted rate difference 4%; 95% CI: 2.6% to 5.5%; $p < 0.001$). The presence of LGE was associated with significantly higher occurrence of the arrhythmic endpoint (pooled OR: 4.3; $p < 0.001$) (**Table 3**, **Figure 2**).

Heterogeneity was not significant ($p = 0.18$), and inconsistency was low (19%); in consequence, the fixed-effects model yielded very similar results to the random-effects model (Online Table 4). The Egger and Peters tests suggested the absence of publication bias, both including all studies and taking into account only those studies whose entire populations were used for the meta-analysis (**Table 4**). After the exclusion of the 2 studies that analyzed history of arrhythmic events, the pooled OR remained 4.3.

TABLE 1 Quality Assessment Using Cochrane Method

First Author (Ref. #)	Selection Bias	Performance Bias	Attrition Bias	Detection Bias	Reporting Bias
Wu (18)	Yes	No	No	No	No
Yokokawa (20)	Yes	No	NA	No	No
Kono (19)	Yes	No	Yes	No	No
Looi (21)	Yes	No	No	No	No
Iles (22)	Yes	No	No	No	No
Fernández-Armenta (23)	Yes	No	No	No	No
Klem (24)	Yes	No	No	No	No
Leyva (25)	Yes	No	No	No	No
Masci (26)	Yes	No	No	No	No
Gulati (15)	Yes	No	No	No	No
Müller (27)	Yes	No	No	No	No
Neilan (28)	Yes	No	No	No	No
Šramko (29)	Yes	No	No	No	No
Yoshida (30)	Yes	No	Yes	No	No
Almehmadi (16)	Yes	No	No	No	No
Hasselberg (31)	Yes	No	Yes	No	No
Machii (32)	Yes	No	Yes	No	No
Masci (33)	Yes	No	No	No	No
Mordi (34)	Yes	No	No	No	No
Nabeta (35)	Yes	No	Yes	No	No
Perazzolo Marra (36)	Yes	No	No	No	No
Rodríguez-Capitán (37)	Yes	No	No	No	No
Yamada (38)	Yes	No	No	No	No
Amzulescu (39)	Yes	No	No	No	No
Barison (40)	Yes	No	No	No	No
Chimura (41)	Yes	No	No	No	No
Buss (17)	Yes	No	No	No	No
Piers (42)	Yes	No	No	No	No
Tachi (43)	Yes	No	NA	No	No

NA = not applicable.

TABLE 2 Description of the Studies Included in the Meta-Analysis

First Author, Year (Ref. #)	Type of Study	n	Population Considered for Meta-Analysis	Mean Age (yrs)	Mean LVEF (%)	LGE-Positive	Method for Evaluation of LGE	Median Follow-Up Duration	Arrhythmic Endpoints Evaluated
Wu, 2008 (18)	Prospective cohort, consecutive pts	65	DCM Primary prevention ICD	55	24	24 (42%)	Visual analysis	17 months	SCD, ICD therapies
Yokokawa, 2009 (20)	Cohort of consecutive pts	29*	DCM Admitted for HF, CRT, or VT	65	24	18 (62%)	Intensity >6 SDs of normal myocardium	–	VT
Kono, 2010 (19)	Observational cohort study	32	DCM LVEF<40%	61	28	18 (56%)	Intensity >2 SDs of normal myocardium	31 months (mean)	SCD, VT, VF
Looi, 2010 (21)	Prospective cohort	103	DCM	58	32	31 (30%)	Visual analysis	660 days (mean)	SCD, VA
Iles, 2011 (22)	Prospective cohort	61*	DCM Primary prevention ICD	54	25	31 (52%)	Intensity >2 SDs of normal myocardium	573 days†	ICD therapies
Fernández-Armenta, 2012 (23)	Prospective cohort, consecutive pts	37*	DCM, primary prevention CRT-D	64	22	15 (41%)	Intensity >2 SDs of normal myocardium	25 months†	ICD therapies
Klem, 2012 (24)	Prospective study	64*	DCM	52	41	37 (58%)	Visual analysis	24 months†	SCD, ICD therapies
Leyva, 2012 (25)	Observational cohort	97*	DCM with CRT	66	22	20 (21%)	Visual analysis	1,038 days†	SCD, secondary prevention CRT-D
Masci, 2012 (26)	Prospective cohort	125	DCM, LVEF<50%, NYHA class I–II	58	34	50 (40%)	Visual analysis	14 months	SCD
Gulati, 2013 (15)	Prospective cohort, consecutive pts	472	DCM Absence of subendocardial LGE	51	37	142 (30%)	Visual analysis	5.3 yrs	SCD, ICD therapies, VF or VT
Müller, 2013 (27)	Observational cohort	167*	Recent onset HF, DCM including myocarditis	51	43	85 (51%)	Visual analysis	21 months†	rCA, VT, ICD therapies
Neilan, 2013 (28)	Prospective cohort, consecutive pts	162	DCM Primary prevention ICD	55	26	81 (50%)	Visual analysis	26 months	SCD, ICD therapies
Šramko, 2013 (29)	Cohort of consecutive pts	42	DCM, LVEF <45%, HF symptoms <6 mo	44	22	28 (67%)	Visual analysis	25 months	SCD, VT, ICD therapies
Yoshida, 2013 (30)	Retrospective cohort of consecutive pts	50	DCM, LVEF <45%	57	25	21 (42%)	Visual analysis	33 months	VT, ICD therapies
Almehmadi, 2014 (16)	Cohort of consecutive pts	169*	DCM, LVEF ≤55%	62	33	107 (63%)	Intensity >5 SDs of normal myocardium	467 days†	SCA, ICD therapies
Hasselberg, 2014 (31)	Cohort of consecutive pts	13*	DCM, mutations in lamin A/C	52	32	4 (31%)	Visual analysis	29 months†	SCD, VT, ICD therapies
Machii, 2014 (32)	Retrospective cohort, multicenter	72*	DCM, LVEF<45%	64	25	48 (67%)	Intensity >3 SDs of normal myocardium	36 months (mean)†	SCD, VT
Masci, 2014 (33)	Prospective cohort, consecutive pts	228	DCM, no history of HF	50	43	61 (28%)	Visual analysis	23 months	SCD, VT, VF, ICD therapies
Mordi, 2014 (34)	Prospective cohort, consecutive pts	96*	DCM, primary prevention ICD	46	27	24 (25%)	Intensity >5 SDs of normal myocardium	915 days	ICD therapies
Nabeta, 2014 (35)	Observational cohort	75	DCM, LVEF <45%	56	30	36 (48%)	Visual analysis	326 days	Sustained ventricular arrhythmias
Perazzolo Marra, 2014 (36)	Cohort of consecutive pts	137	DCM, LVEF <50%	49	36	76 (55%)	Visual analysis	3 yrs	SCD, VT, VF, ICD therapies
Rodríguez-Capitán, 2014 (37)	Retrospective cohort of consecutive pts	18*	DCM	56	29	23 (36%)	Visual analysis	32 months†	ICD therapies
Yamada, 2014 (38)	Cohort of consecutive pts	57	DCM, LVEF <50%	55	33	25 (44%)	Visual analysis	71 months	VT, VF
Amzulescu, 2015 (39)	Prospective cohort, consecutive pts	162	DCM, LVEF <40%	55	25	63 (39%)	Visual analysis	3.4 yrs	SCD, VT, VF, ICD therapies

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Meta-regression analysis showed that neither the quality of the reports (adjusted $R^2 = -0.03$, $p = 0.26$) nor the mean LVEF of each study (adjusted $R^2 = -0.04$, $p = 0.52$) had any significant impact over interstudy variability.

SUBGROUP ANALYSIS. The significant association between LGE and VA or SCD was maintained in both prospective and retrospective studies, in studies that performed visual analysis of LGE, and in studies that used threshold-based methods to detect it (Table 5).

TABLE 2 Continued

First Author, Year (Ref. #)	Type of Study	n	Population Considered for Meta-Analysis	Mean Age (yrs)	Mean LVEF (%)	LGE-Positive	Method for Evaluation of LGE	Median Follow-Up Duration	Arrhythmic Endpoints Evaluated
Barison, 2015 (40)	Prospective cohort	89	DCM	59	41	39 (44%)	Visual analysis	24 months	SCD, sustained VA
Buss, 2015 (41)	Prospective cohort, consecutive pts	23*	DCM, LVEF ≤50%, NYHA class ≤III, ICD implanted	52	36	12 (52%)	Visual analysis	5.3 yrs†	ICD therapies
Chimura, 2015 (17)	Retrospective study	175	DCM, LVEF <35%, NYHA class II–III	60	29	122 (70%)	Visual analysis	5.1 yrs (mean)	SCD, VT, VF, ICD therapies
Piers, 2015 (42)	Cohort of consecutive pts	87	DCM Primary or secondary prevention ICD	56	29	55 (63%)	≥35% of maximal myocardial signal intensity	45 months	ICD therapies, aborted SCD
Tachi, 2015 (43)	Cohort of consecutive pts	41	DCM	60	20	21 (51%)	Visual analysis	–	VT

*The population considered for this meta-analysis is a part of the total population of the original study. †Data derived from the entire population of the original study.

CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy defibrillator; DCM = dilated cardiomyopathy; HF = heart failure; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; pt = patient; rCA = resuscitated cardiac arrest; SCD = sudden cardiac death; VA = ventricular arrhythmias; VF = ventricular fibrillation; VT = ventricular tachycardia.

Among studies that reported mean LVEFs >35%, the arrhythmic endpoint occurred in 23.9% of patients with LGE and 5.6% of patients without LGE, and the annual event rates were 7.3% and 1.6%, respectively ($p < 0.001$ for weighted risk and rate difference) (Figure 3). In studies with mean LVEFs <35%, the arrhythmic endpoint occurred in 19.6% and 4.1% of patients, and the annual event rates were 6.7% and 1.6%, respectively, in patients with and those without LGE ($p < 0.001$ for weighted risk and rate difference). A significant association between LGE and VA or SCD was observed both when the mean LVEF was <35% (OR: 4.2; 95%: CI 2.4 to 7.2) and when it was >35% (OR: 5.2; 95% CI: 3.4 to 7.9) (Table 5).

Considering studies that included only patients with primary prevention ICDs, LGE was present in 42% of patients, the mean follow-up duration was 2 years, the overall incidence of the arrhythmic event was 17.1%, and the overall annual event rate was 8.4%. The incidence of the arrhythmic endpoint was 34% versus 4.5% ($p = 0.004$), and the annual rate was 17.2% versus 2.1% ($p = 0.007$), respectively, in patients with and those without LGE. In this group of patients, LGE had the highest OR for the arrhythmic endpoint (OR: 7.8; 95% CI: 1.7 to 35.8; $p = 0.008$).

ANALYSIS ADJUSTING FOR CONFOUNDING COVARIATES. Potential confounding covariates for the association between LGE and the arrhythmic endpoint were analyzed in 4 studies with a large population ($n = 946$) (15,28,36,41). The pooled adjusted hazard ratio (hazard ratio: 6.7; 95% CI: 3.6 to 12.5) indicates that LGE is an independent predictor of the arrhythmic endpoint (Online Table 5).

To further assess the potential role of LVEF as a confounding covariate, we estimated pooled ORs in both studies in which LVEF did and did not significantly differ between patients with and those without LGE. The significant association between LGE and VA or SCD was maintained in both groups of studies (Table 5).

LVEF IN RELATION TO LGE AND TO THE ARRHYTHMIC ENDPOINT. No significant correlation was identified between the proportion of patients with LGE and the mean LVEF in each study ($r = -0.23$; 95% CI: −0.55 to +0.15; $p = 0.22$).

Mean LVEF did not correlate with the overall proportion of arrhythmic events ($r = 0.02$, $p = 0.90$) or the overall annual event rate from each study ($r = 0.07$, $p = 0.70$).

When studies with mean LVEFs >35% or <35% were considered separately, there was no significant difference between them in terms of overall percentage of arrhythmic events (12.2% vs 11.7%, $p = 0.70$) or annual event rate (3.5% vs 4.2%, $p = 0.10$)

DISCUSSION

This meta-analysis, based on 2,948 patients enrolled in 29 studies, represents the first systematic review to specifically evaluate the association between LGE and VAs or sudden death among patients with DCM. The results clearly show that LGE is a robust predictor of VA or SCD across a wide spectrum of patients with DCM.

PRIOR STUDIES. Two meta-analyses evaluated the prognostic value of LGE in patients with DCM (45,46). However, in these two analyses, arrhythmic events were a secondary endpoint and therefore were not the main focus of the analyses. Significant associations with LGE were found, but this result was based on fewer studies compared with the present meta-analysis (7 and 12 studies, respectively). Moreover,

TABLE 3 Results of Data Synthesis

First Author (Ref. #)	LGE-Positive		LGE-Negative		Weight (%)	OR (95% CI)
	Events	No Events	Events	No Events		
Wu (18)	4	23	3	35	3.3	2 (0.4–9.9)
Yokokawa (20)	12 (12.88)	6 (6.88)	0 (0.12)	11 (11.12)	0.3	169.8 (0.6–50,900)
Kono (19)	4	14	2	12	2.4	1.7 (0.3–11.1)
Looi (21)	6	25	1	71	1.8	17 (2–148.6)
Iles (22)	9 (9.82)	22 (22.82)	0 (0.18)	30 (30.18)	0.4	71.6 (0.7–7,701.2)
Fernández-Armenta (23)	7 (7.75)	8 (8.75)	0 (0.25)	22 (22.25)	0.5	78.4 (1.4–4,499.2)
Klem (24)	9	28	2	25	3.1	4 (0.8–20.4)
Leyva (25)	3 (3.53)	17 (17.53)	0 (0.47)	77 (77.47)	0.9	33.3 (1.5–733.6)
Masci (26)	0 (0.74)	50 (50.74)	1 (1.26)	74 (74.26)	1.0	0.9 (0.1–15.6)
Gulati (15)	42	100	23	307	26.7	5.6 (3.2–9.8)
Müller (27)	18	67	6	76	8.6	3.4 (1.3–9.1)
Neilan (28)	38	43	3	78	5.4	23 (6.7–78.8)
Šramko (29)	3 (3.90)	25 (25.90)	0 (0.10)	14 (14.10)	0.2	20.7 (0.04–10,000)
Yoshida (30)	1 (1.76)	20 (20.76)	0 (0.24)	29 (29.24)	0.4	10.3 (0.1–761.7)
Almehmadi (16)	16	91	6	56	8.3	1.6 (0.6–4.4)
Hasselberg (31)	2 (2.66)	2 (2.66)	0 (0.34)	9 (9.34)	0.6	27.5 (0.6–1,255.2)
Machii (32)	2 (2.90)	46 (46.90)	0 (0.10)	24 (24.10)	0.2	14.5 (0.03–7,470.7)
Masci (33)	6	55	2	165	3.1	9 (1.8–45.9)
Mordi (34)	3	21	5	67	3.6	1.9 (0.4–8.7)
Nabeta (35)	2 (2.80)	34 (34.80)	0 (0.20)	39 (39.20)	0.4	15.9 (0.2–1,539.6)
Perazzolo Marra (36)	17	59	5	56	7.3	3.2 (1.1–9.3)
Rodríguez-Capitán (37)	0	8	2	8	1.1	0.3 (0.02–5.1)
Yamada (38)	1 (1.77)	24 (24.77)	0 (0.23)	32 (32.23)	0.4	10.2 (0.1–833.3)
Amzulescu (39)	6	57	6	93	5.9	1.6 (0.5–5.3)
Barison (40)	5	34	2	48	2.9	3.5 (0.6–19.3)
Buss (41)	9	3	3	8	2.4	8 (1.2–51.5)
Chimura (17)	18 (18.91)	104 (104.91)	0 (0.09)	53 (53.09)	0.2	105.8 (0.2–73,500)
Piers (42)	23	32	5	27	6.9	3.9 (1.3–11.6)
Tachi (43)	6	15	1	19	1.7	7.6 (0.8–70.2)
Total	272	1,033	78	1,565	100.0	4.3 (3.3–5.8)

For studies with zeroes, the empirical correction for zeroes was applied, and the corrected raw data are presented in parentheses. Weighted overall OR was calculated using the fixed-effects model.

CI = confidence interval; LGE = late gadolinium enhancement; OR = odds ratio.

detailed subgroup analysis or confounders-adjusted analysis was not performed with regard to the arrhythmic endpoint. Finally, some differences in study inclusion are present (Online Table 6).

Given the wealth of studies published in the past 2 years and the absence of a meta-analysis that specifically focused on the arrhythmic endpoint in DCM, we considered that the present work was appropriate and necessary.

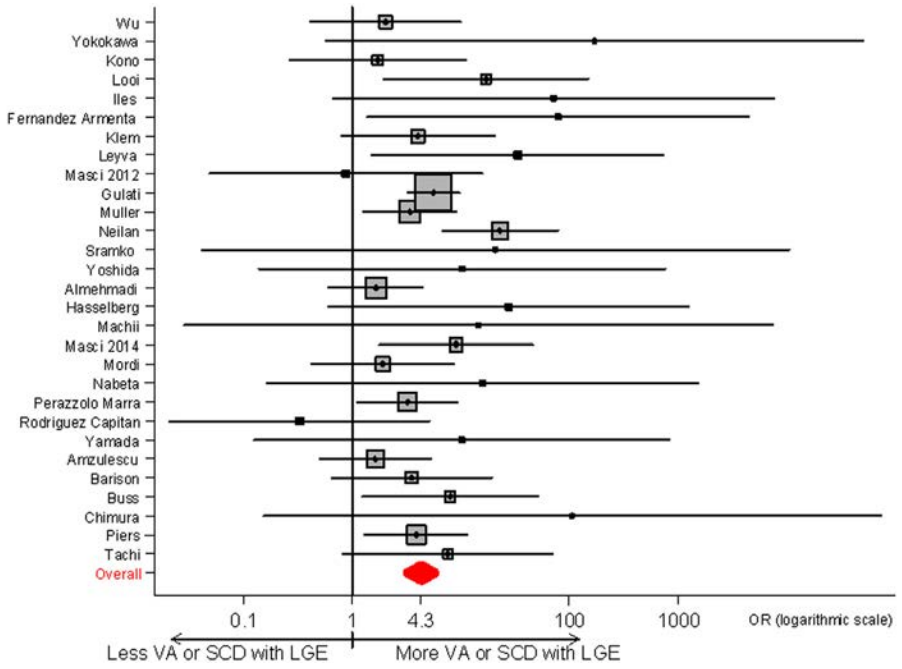
The present report significantly strengthens and clarifies the evidence available to date about the association between LGE and VA or SCD in patients with DCM. Thanks also to the collaboration of many investigators of the primary studies, it was possible to include a great number of reports and, from each study, to analyze only the population that precisely fitted the inclusion criteria of the meta-analysis. The specific focus on the arrhythmic outcome and the relevant number of studies included allowed a thorough subgroup analysis that contributed greatly to the relevance of this work.

LGE AND VAs: A STRONG, CONSISTENT, AND INDEPENDENT ASSOCIATION. LGE was present in a considerable proportion of patients with DCM (44%), and it had a strong and significant association with the arrhythmic endpoint. This association was consistently observed across studies that included patients at different stages of their cardiomyopathy and was independent of potential confounders in subgroup analysis.

LGE could therefore add strong prognostic information across the entire spectrum of patients with DCM.

The differences in mean LVEF reported by each study did not influence the association between LGE and the arrhythmic endpoint. Mean LVEF did not

FIGURE 2 Forest Plot of Odds Ratios



LGE = late gadolinium enhancement; OR = odds ratio; SCD = sudden cardiac death; VA = ventricular arrhythmias.

correlate with the proportion of patients with LGE from each study and did not correlate at all with the overall proportion of arrhythmic events in each study. These data confirm that LVEF is not the optimal predictor of arrhythmic events in DCM and suggest that the prognostic value of LGE is superior and independent from LVEF.

POTENTIAL CLINICAL IMPLICATIONS. The present observations may have important clinical implications and may help address 2 major unresolved issues.

Most sudden deaths occur in patients without severely impaired LVEF (47), who are usually not protected by ICDs, because they fall outside current indications for a primary prevention device.

The association between LGE and the arrhythmic endpoint was present in studies with mean LVEFs <35% but was even stronger when the mean LVEF was >35%. Moreover, patients with LGE had a similar proportion of the arrhythmic endpoint in studies with mean LVEFs <35% and >35%. One may speculate if primary prevention ICDs might be beneficial in patients with LGE, independent of LVEF.

However, it must be underscored that none of the studies included in this meta-analysis focused solely on patients with mild or moderate systolic impairment, excluding patients with severely reduced LVEFs; therefore, specific analysis just of patients with LVEFs >35% was not possible. This is a key aspect that should be addressed in future studies.

The second important clinical issue is the low rate of appropriate ICD therapies among patients with DCM who receive primary prevention ICDs (2) and the absence of survival benefit from primary prevention ICD in a contemporary cohort of patients with nonischemic cardiomyopathy, as outlined by the recently published DANISH trial (3). This trial found that patients with nonischemic cardiomyopathy implanted with primary prevention ICDs have a low arrhythmic risk; an improved risk stratification for sudden death is therefore urgently needed, to select only those patients who could benefit most from ICDs.

TABLE 4 Analysis of Publication Bias

	All Studies (p Value)	Studies Whose Entire Populations Were Included in the Meta-Analysis (p Value)
Egger's method	0.13	0.49
Peters' method	0.43	0.56

TABLE 5 Subgroup Analysis

Type of Study or Population	OR (95% CI)	p Value	Number of Patients	Number of Studies
Prospective studies	4.2 (2.5–7.1)	<0.001	1,970	14
Retrospective or not specified	4.1 (2.4–7.1)	<0.001	978	15
Visual analysis of LGE	4.9 (3.3–7.3)	<0.001	2,383	21
Threshold-based LGE detection	3.4 (1.6–7.7)	0.002	591	8
Mean LVEF <35%	4.2 (2.4–7.2)	<0.001	1,892	22
Mean LVEF >35%	5.2 (3.4–7.9)	<0.001	1,056	7
ICD primary prevention	7.8 (1.7–35.8)	0.008	421	5
LVEF not different between LGE-positive and LGE-negative patients	6 (3.3–10.9)	<0.001	1,156	12
LVEF significantly different between LGE-positive and LGE-negative patients	5 (3.1–7.9)	<0.001	861	4

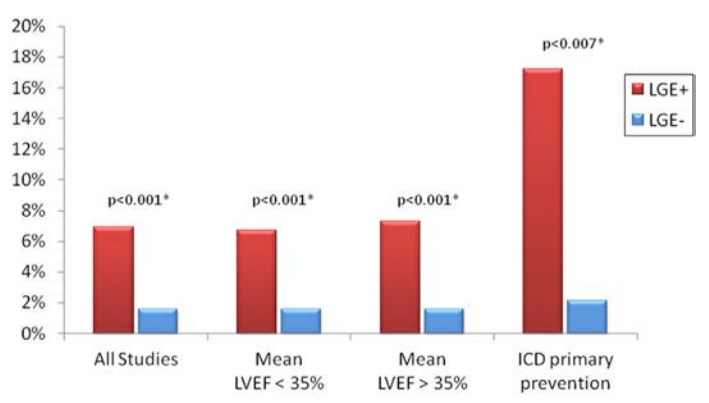
Abbreviations as in Tables 2 and 3.

In this meta-analysis, LGE had the strongest association with the arrhythmic outcome (OR: 7.8) among studies that included only patients with primary prevention ICDs. Patients with LGE had a relatively high annual event rate (17.2%), while patients without LGE, who represented 58% of the population included in primary prevention ICD studies, had a considerably lower event rate (2.1% per year). Therefore, incorporating LGE status into the selection criteria for primary prevention ICD might allow treating a subgroup of patients at higher arrhythmic risk (LGE positive), while sparing patients without LGE the risk of complications from a device that is unlikely to improve their prognosis.

Further large registries would be useful to confirm the present data, and randomized trials would be necessary to evaluate the impact of preventive ICD on mortality in patients with DCM without LGE.

In addition, recent evidence suggests that the absence of LGE is a predictor of left ventricular remodeling after cardiac resynchronization therapy (48). Given the baseline low arrhythmic event rate in patients without LGE, and the lower rate of arrhythmic events observed in responders to cardiac resynchronization therapy (49), a sensible approach to patients without LGE and no histories of VAs who need cardiac resynchronization therapy devices could be to implant them with pacemakers, not defibrillators; such a strategy should be evaluated in future studies.

FIGURE 3 Annual Rate of the Arrhythmic Endpoint According to Late Gadolinium Enhancement Status



*p values for weighted rate difference. ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction.

POSSIBLE SUBSTRATES FOR VAs IN THE PRESENCE OR ABSENCE OF LGE. The association between LGE and VAs can be explained by the key role of myocardial scar as the main substrate for re-entrant VAs in patients with structural heart disease (3).

However, a small proportion of patients without LGE still experienced the arrhythmic endpoint. Diffuse fibrosis is commonly found in patients with DCM, and it can be quantified by T1 mapping. Such abnormality can alter the electric properties of the myocardium, and it might be especially important as a substrate for ventricular fibrillation; as such, it could complement the information provided by LGE, which in 1 study was found to have stronger association with ventricular tachycardia than ventricular fibrillation (42). Further studies using T1 mapping and extracellular volume fraction should address this issue. Indeed, T1 mapping and extracellular volume fraction have been associated with worse outcomes in patients with DCM (40,50).

STUDY LIMITATIONS. The main limitation of the present meta-analysis is the inclusion of observational studies, which all share an intrinsic risk for selection bias and can detect associations but not causality. However, it must be underscored that no randomized trials are available on this theme.

Precise data about ICD programming were not provided in the majority of the reports, and ICD settings significantly influence the rate of appropriate therapies (51).

Most of the studies used visual analysis to detect the presence or absence of LGE, while a minority used threshold-based methods. It is important to stress that regardless of this disparity, no significant heterogeneity was observed across studies. Moreover, when analyzed separately, both studies that used visual analysis and those that used threshold-based methods found a significant association between LGE and VA or SCD.

Patients with DCM may have different patterns and variable extension of LGE, and these factors might influence arrhythmic risk. However, very few studies evaluated the association between LGE pattern (36,41) or extension (15,20,28,36,42) and arrhythmic events specifically in patients with DCM. The limited data available and the differences in methods used not only to measure but also to report the quantification of LGE make these factors less suitable to be the target of a meta-analysis at present.

The main result is a pooled unadjusted OR. However, pooled data from studies that performed multivariate analysis confirmed that LGE is an independent predictor of VA.

CONCLUSIONS

Across a wide spectrum of patients with DCM, the presence of LGE is associated with an important and significant increase in the occurrence of VAs or sudden death. The association between LGE and the arrhythmic outcome was independent of other covariates, including LVEF. LGE could therefore be a powerful tool to improve risk stratification in patients with DCM.

The present findings raise 2 major issues that should be addressed in further studies: whether patients with LGE could benefit from primary prevention ICDs irrespective of LVEF and whether patients without LGE might not need preventive ICDs despite having severe left ventricular dysfunction.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The presence of LGE on cardiac magnetic resonance imaging is associated with a significant and relevant increase in the risk for VAs or SCD in patients with DCM.

TRANSLATIONAL OUTLOOK 1: Further studies, especially randomized controlled trials, should evaluate whether patients with DCM and LGE could benefit from a primary prevention ICD regardless of LVEF.

TRANSLATIONAL OUTLOOK 2: Further studies, especially randomized controlled trials, should assess if patients with DCM and severe left ventricular dysfunction but without LGE actually derive a survival benefit from primary prevention ICDs.

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KEY WORDS cardiac magnetic resonance, dilated cardiomyopathy, late gadolinium enhancement, sudden death, ventricular arrhythmias

APPENDIX For supplemental tables, please see the online version of this article.