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ORIGINAL PAPER

# Redefining the risk of major arrhythmic events in non-ischaemic cardiomyopathy: insights from the DERIVATE-NICM study

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**Aims**

Selection of the patients for implantable cardioverter defibrillator primary prevention therapy in non-ischaemic cardiomyopathy (NICM) needs to be improved. To evaluate the additional prognostic value of a new cardiac magnetic resonance (CMR) score based on late gadolinium enhancement (LGE) pattern distribution (DERIVATE Risk Score 2.0) when compared with previously published DERIVATE Risk Score 1.0, which is based solely on quantitative parameters, in a cohort of NICM patients enrolled in the DERIVATE registry.

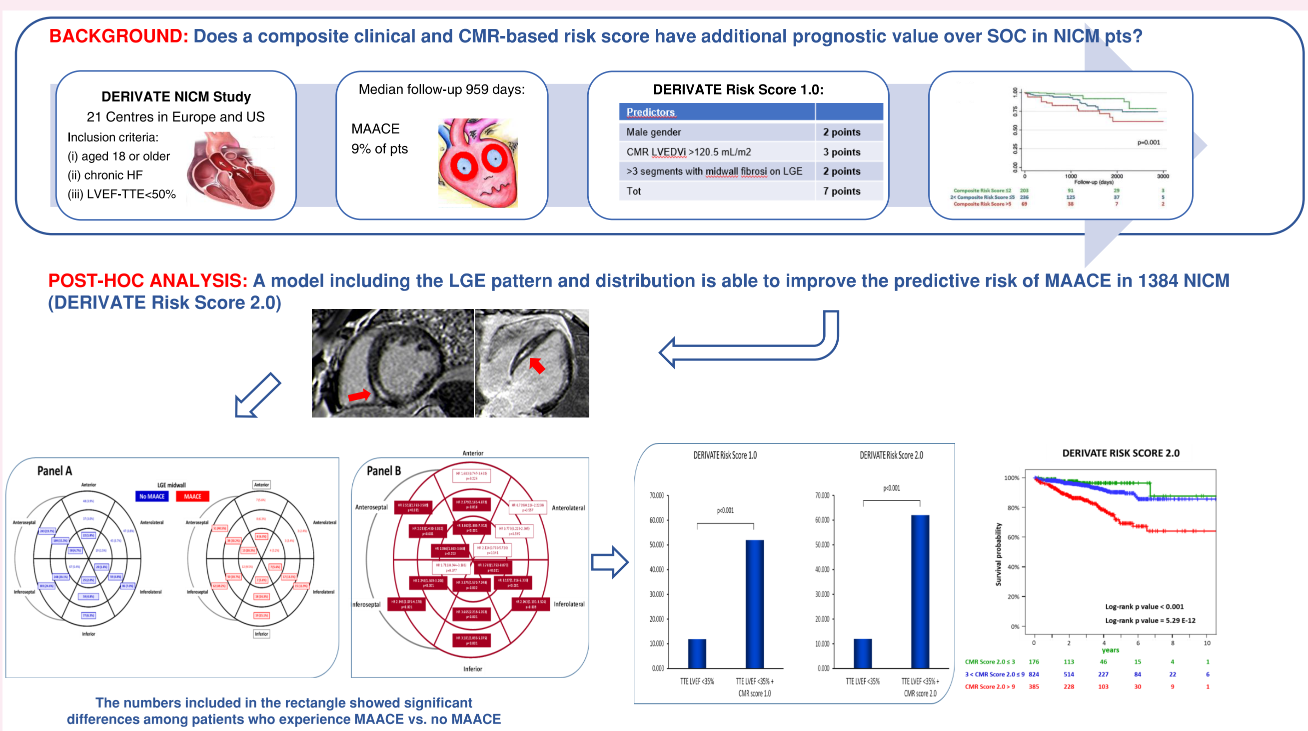
**Methods and results**

One thousand three hundred and eighty-four NICM patients with chronic heart failure and left ventricular ejection fraction (LVEF) $< 50\%$ were evaluated for primary sudden cardiac death prevention therapy. Major adverse arrhythmic cardiac events (MAACEs) were the primary endpoint. During a median follow-up of 959 days, MAACE occurred in 128 (9.2%) patients. In the multivariate analyses, male gender [hazard ratio (HR): 1.605 (95% confidence interval, CI: 1.051–2.451); $P = 0.028$], LVEF per point % [HR: 0.977 (95% CI: 0.961–0.993); $P = 0.005$] and presence and location of midwall LGE [weighted HR: 1.066 (95% CI: 1.045–1.086), $P < 0.001$] were independent predictors of MAACE. A multi-parametric CMR-weighted predictive-derived score (DERIVATE Risk Score 2.0) provided a higher additional prognostic value vs. transthoracic echocardiography–LVEF cut-off of 35% when compared with the previous published DERIVATE Risk Score 1.0 with a net reclassification improvement of 54.52% (95% CI: 36.52–72.52%; $P < 0.001$). These findings were confirmed in the validation cohort.

**Conclusion**

The presence of midwall LGE, but also the location of scar, confers an added and independent MAACE risk to a large NICM population influencing the choice of treatment.


**Graphical Abstract**




**Keywords** non-ischaemic dilated cardiomyopathy • heart failure • cardiac magnetic resonance • implantable cardioverter defibrillator therapy

# Introduction

Treatment with an implantable cardioverter defibrillator (ICD) has proven to be an effective prophylactic strategy for the prevention of sudden cardiac death (SCD) in patients with non-ischaemic dilated cardiomyopathy (NICM).[1] During the past two decades, an increasing number of studies have shown that the international guidelines recommending ICD implantation lead to limited clinical benefit.[2] Indeed, the left ventricle (LV) ejection fraction (EF) centred strategy excludes many patients who would need a ICD protection and, at the same

**Table 1 Baseline characteristics of NICM patients with and without MAACE**

| | All patients ($n = 1384$) | No MAACE ($n = 1256$) | MAACE ($n = 128$) | *P*-value |
|---|---|---|---|---|
| Demographic characteristics | | | | |
| Age, years | 56 ± 14 | 56 ± 14 | 58 ± 13 | 0.119 |
| Male | 948/1384 (68%) | 849/1256 (68%) | 99/128 (77%) | **0.023** |
| BSA, $m^2$ | 1.89 ± 0.25 | 1.89 ± 0.25 | 1.93 ± 0.22 | 0.327 |
| Cardiovascular risk factor | | | | |
| Family history | 421/1369 (31%) | 374/1243 (30%) | 47/126 (37%) | 0.095 |
| Smoking history | 465/1377 (34%) | 435/1249 (35%) | 30/128 (23%) | **0.009** |
| Hypertension | 558/1375 (41%) | 199/1247 (40%) | 59/128 (46%) | 0.182 |
| Hyperlipidaemia | 444/1377 (32%) | 403/1249 (32%) | 41/128 (32%) | 0.957 |
| Diabetes | 204/1380 (15%) | 183/1252 (15%) | 21/128 (16%) | 0.587 |
| NYHA class | | | | 0.538 |
| I and II | 1024/1303 (79%) | 930/1180 (79%) | 94/123 (76%) | |
| III and IV | 279/1303 (21%) | 250/1180 (21%) | 29/123 (24%) | |
| Medical therapy | | | | |
| Beta-blockers | 1145/1377 (83%) | 1024/1249 (82%) | 121/128 (95%) | **<0.001** |
| Ivabradine | 73/1233 (6%) | 67/1137 (6%) | 6/96 (6%) | 0.887 |
| ACE inhibitors/AT1 blockers | 1171/1377 (85%) | 1059/1249 (85%) | 112/128 (88%) | 0.413 |
| Diuretics | 967/1310 (66%) | 777/1191 (65%) | 90/119 (75%) | **0.022** |
| Calcium-blockers | 66/1309 (5%) | 54/1191 (5%) | 12/118 (10%) | **0.008** |
| Anti-thrombotic agents | 425/1309 (33%) | 390/1191 (33%) | 35/118 (30%) | 0.495 |
| Anti-coagulant therapy | 238/1309 (18%) | 209/1191 (18%) | 29/118 (25%) | 0.059 |
| Nitrates | 68/1308 (5%) | 61/1191 (5%) | 7/118 (6%) | 0.689 |
| Statins | 408/1309 (31%) | 362/1191 (30%) | 72/118 (39%) | 0.055 |
| Amiodarone/other anti-arrhythmics | 198/1309 (15%) | 168/1191 (14%) | 30/118 (25%) | **0.001** |

All continuous variables were expressed as mean ± SD or median and interquartile range. All discrete variables were expressed as an absolute number and percentage. All results shown in bold are considered statistically significant.
ACE, angiotensin converting enzyme; AT, angiotensin; BSA, body surface area; MAACE, major adverse arrhythmic cardiac events; NICM, non-ischaemic cardiomyopathy; NYHA, New York Heart Association.

time, overrates the anti-arrhythmic risk coverage among patients with severe LV systolic dysfunction.[1,3] Accordingly, an effort is being made to better identify patients at high arrhythmic risk worthy of prophylactic ICD implantation. As is well known, tissue characterization obtained by cardiac magnetic resonance (CMR) has emerged as a promising tool for this purpose.[4] In this regard, we designed an international registry collecting clinical and CMR-based data from a large cohort of NICM patients evaluated for SCD primary prevention and enrolled in several centres across Europe and the USA, where we developed a CMR-derived risk score model to predict major adverse arrhythmic cardiac events (MAACEs).[5,6] Current analysis has the scope to develop a new multi-parametric CMR score (the DERIVATE Risk Score 2.0) including late gadolinium enhancement (LGE) sequences and specifically considering its LV wall distribution and to compare it vs. the previously published DERIVATE Risk Score 1.0.[6]

# Methods

## Study design

DERIVATE (www.clinicaltrials.gov/registration: RCT#NCT03352648) is an international, multicentre, prospective, observational registry including consecutive patients from 21 sites across Europe and the US referred for heart failure (HF) work-up including transthoracic echocardiography (TTE) and CMR without a history of previous major ventricular arrhythmias in order to be evaluated for ICD primary prevention therapy. Study design and methods were already published.[5,6] Briefly, inclusion criteria were: (i) aged 18 or older, (ii) chronic HF according to the European Society of Cardiology Task force definition, and (iii) LVEF < 50% at initial TTE. All patients underwent TTE and CMR within 3 months. Patients with ischaemic cardiomyopathy, decompensated HF and acute myocarditis within 3 months of enrolment, severe valvular disease, primary and secondary cardiomyopathies, and congenital heart diseases were excluded. The following clinical information were collected: demographic characteristics, medical history, cardiovascular risk factors, and medical and device therapy. All data were recorded in a standardized case report form. The authors from each participating centre guarantee the integrity of data from their institution and had approval from a local ethics committee/internal review board.

## CMR protocols and analysis

CMR acquisition was performed according to current international recommendations.[7] After the acquisition of localizers, breath-hold cine steady-state free precession (SSFP) sequences were used for functional analysis with the following minimum requirements: in-plane spatial resolution of <2.0 mm × < 2.0 mm, slice thickness 8 mm, gap 0 mm, and temporal resolution 35–50 ms. Cine-SSFP were acquired in long-axis views, and a base-to-apex stack of short axis images was used to quantify LV volumes,

**Table 2 TTE and CMR characteristics of NICM patients with and without MAACE**

| | All patients ($n = 1384$) | No MAACE ($n = 1256$) | MAACE ($n = 128$) | P-value |
|---|---|---|---|---|
| TTE | | | | |
| LVEDVi, mL/m$^2$ | 101 ± 37 | 99 ± 37 | 121 ± 37 | **<0.001** |
| LVESVi, mL/m$^2$ | 68 ± 32 | 66 ± 31 | 86 ± 33 | **<0.001** |
| LVEF, % | 34 ± 11 | 34 ± 11 | 31 ± 10 | **0.001** |
| LVEF <35% | 815/1377 (59%) | 718/1251 (57%) | 97/126 (77%) | **<0.001** |
| CMR functional evaluation | | | | |
| LVEDVi, mL/m$^2$ | 131 ± 42 | 128 ± 40 | 154 ± 50 | **<0.001** |
| LVESVi, mL/m$^2$ | 89 ± 40 | 87 ± 39 | 111 ± 46 | **<0.001** |
| LV mass, g/m$^2$ | 82 ± 28 | 82 ± 28 | 85 ± 31 | 0.198 |
| LVSV, mL | 79 ± 27 | 78 ± 26 | 83 ± 29 | 0.056 |
| LVEF, % | 34 ± 11 | 34 ± 11 | 30 ± 10 | **<0.001** |
| LVEF <30% | 564/1384 (39.3%) | 486/1256 (39%) | 78/128 (61%) | **0.001** |
| RVEDVi, mL/m$^2$ | 79 ± 29 | 79 ± 29 | 80 ± 28 | 0.744 |
| RVESVi, mL/m$^2$ | 40 ± 25 | 40 ± 25 | 41 ± 24 | 0.722 |
| RVSV, mL | 73 ± 25 | 73 ± 25 | 75 ± 25 | 0.468 |
| RVEF, % | 51 ± 13 | 51 ± 13 | 51 ± 14 | 0.739 |
| CMR LGE evaluation | | | | |
| Prevalence of LGE-positive patients | 629/1358 (46%) | 543/1232 (44%) | 86/126 (68%) | **<0.001** |
| No. of segments with LGE | 0 (0–3) | 0 (0–3) | 2 (0–5) | **<0.001** |
| Presence of midwall LGE pattern | 544/1358 (40%) | 465/1232 (38%) | 79/126 (63%) | **<0.001** |
| Presence of epicardial LGE pattern | 171/1358 (13%) | 152/1232 (12%) | 19/126 (15%) | 0.377 |
| Prevalence of mixed LGE pattern | 86/1358 (6%) | 74/1232 (6%) | 12/126 (9%) | 0.126 |

All continuous variables were expressed as mean ± SD or median and interquartile range. All discrete variables were expressed as an absolute number and percentage or as minimum and maximum value. All results shown in bold are considered statistically significant.

CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; LV, left ventricle; LVEDVi, left ventricle end-diastolic volume indexed; LVEF, left ventricle ejection fraction; LVESVi, left ventricle end-systolic volume indexed; MAACE, major adverse arrhythmic cardiac events; PAP, pulmonary artery pressure; RVEDVi, right ventricle end-diastolic volume indexed; RVEF, right ventricle ejection fraction; RVESVi, left ventricle end-systolic volume indexed; TTE, transthoracic echocardiography.

mass, and LVEF. Ten-to-fifteen minutes after an intravenous bolus of 0.1–0.2 mmol/kg gadolinium-based contrast agent according to the local acquisition protocol, LGE was acquired according to each centre's protocol, using segmented phase-sensitive gradient echo inversion-recovery sequences. LGE imaging was carried out in the same orientation as the cine-SSFP images, and the inversion time was adjusted on magnitude images to null normal myocardium. The CMR data set was transferred to the core laboratory and evaluated by certified expert readers with >5 years of experience. For LGE segmentation a second certified expert reader with >5 years of experience and in case of disagreement a third reader was involved to solve the conflict. Analysis of CMR was blinded to the patients' history, demographic data, echocardiographic data, and outcome. The following parameters were collected employing a segmentation process using CVI 4.2 software (Circle Software) by using automatic segmentation followed by manual correction: (i) standard LV and right ventricular (RV) volumetric parameters: LV end-diastolic volume indexed (LVEDVi), LV end-systolic volume indexed (LVESVi), LV stroke volume, LVEF, LV mass, RV end-diastolic volume indexed (RVEDVi), RV end-systolic volume (RVESVi), RV stroke volume, and RVEF; and (ii) for LGE, the analysis was performed defining hyperenhanced myocardium as any myocardial segment with a signal intensity increase >5 standard deviation (SD) above the mean signal intensity of remote myocardium for each patient, the number of myocardial segments involved by LGE was counted according to the American Heart Association myocardial segments classification.[8] The LGE was classified as midwall or subepicardial layers detectable in two perpendicular views, as previously described.[9,10] Patterns of non-ischaemic LGE consisted of midwall, epicardial, and mixed distribution.

## Follow-up

Patient follow-up was performed by each local institution by dedicated personnel. Event ascertainment was determined by (i) direct interviews during office visits or telephone contact with the patient or a close family member, (ii) contact of the patient's cardiologist or general physician in case of death, (iii) review of patient's medical records, (iv) device interrogation for patients who underwent device implantation, (v) 24 h ECG-Holter monitoring for those patients who did not receive device implantation. Study monitoring was performed in accordance with ICH E6GCP and applicable local regulations. A Clinical Monitoring Plan including project-specific operational guidelines was provided to define responsibilities of the Site Management/Monitoring Team, which ensured the quality and integrity of data collection.[11]

## Endpoint

The study endpoint of the current analysis was MAACE, defined as combination of SCD, aborted SCD (defined as appropriate ICD shock or anti-tachycardia pacing), and sustained ventricular tachycardia (ventricular tachycardia lasting >30 s and/or causing haemodynamic instability).

**Table 3 Univariable predictors of MAACE**

| | MAACE | |
|---|---|---|
| | HR (95% CI) | *P*-value |
| Demographic characteristics | | |
| Age, years (per 1 year) | 1.009 (0.996–1.022) | 0.166 |
| Male | 1.714 (1.133–2.594) | **0.011** |
| Cardiovascular risk factor | | |
| Family history | 1.305 (0.909–1.872) | 0.149 |
| Smoking history | 0.632 (0.420–0.952) | **0.028** |
| Hypertension | 1.306 (0.922–1.849) | 0.132 |
| Hyperlipidaemia | 0.960 (0.662–1.392) | 0.830 |
| Diabetes | 1.287 (0.806–2.056) | 0.290 |
| NYHA Classes III and IV | 1.228 (0.809–1.862) | 0.334 |
| Medical therapy | | |
| Beta-blockers | 3.161 (1.475–6.775) | **0.003** |
| Ivabradine | 1.178 (0.515–2.693) | 0.699 |
| ACE inhibitors/AT1 blockers | 0.981 (0.580–1.659) | 0.943 |
| Diuretics | 1.524 (1.003–2.316) | **0.049** |
| Calcium-blockers | 2.216 (1.218–4.033) | **0.009** |
| Anti-thrombotic agents | 0.818 (0.551–1.214) | 0.319 |
| Anti-coagulant therapy | 1.650 (1.085–2.510) | **0.019** |
| Nitrates | 0.961 (0.447–2.066) | 0.920 |
| Statins | 1.507 (1.041–2.182) | **0.030** |
| Amiodarone/other anti-arrhythmics | 1.980 (1.308–2.996) | **0.001** |
| TTE | | |
| LVEDVi (per 1 mL/m$^2$) | 1.012 (1.007–1.016) | **<0.001** |
| LVESVi (per 1 mL/m$^2$) | 1.014 (1.009–1.019) | **<0.001** |
| LVEF (per point %) | 0.975 (0.959–0.992) | **0.004** |
| LVEF <35% | 2.052 (1.354–3.110) | **0.001** |
| CMR functional evaluation | | |
| LVEDVi (per 1 mL/m$^2$) | 1.011 (1.008–1.014) | **<0.001** |
| LVEDVi >120.5 mL/m$^2$ | 3.238 (2.117–4.953) | **<0.001** |
| LVESVi (per 1 mL/m$^2$) | 1.011 (1.008–1.015) | **<0.001** |
| LV mass (per 1 g/m$^2$) | 1.003 (0.997–1.009) | 0.295 |
| LVSV (per 1 mL) | 1.007 (1.001–1.013) | **0.017** |
| LVEF (per point %) | 0.970 (0.954–0.985) | **<0.001** |
| LVEF <30% | 2.168 (1.520–3.093) | **<0.001** |
| RVEDVi, mL/m$^2$ | 1.003 (0.998–1.008) | 0.255 |
| RVESVi, mL/m$^2$ | 1.004 (0.998–1.010) | 0.178 |
| RVSV, mL | 1.003 (0.996–1.010) | 0.401 |
| RVEF, % | 0.996 (0.982–1.009) | 0.519 |
| CMR LGE evaluation | | |
| Prevalence of LGE-positive patients | 2.650 (1.821–3.857) | **<0.001** |
| No. of segments with LGE | 1.115 (1.073–1.159) | **<0.001** |
| Presence of midwall LGE pattern | 2.644 (1.843–3.794) | **<0.001** |
| Presence of epicardial LGE pattern | 1.319 (0.810–2.150) | 0.266 |
| Presence of mixed LGE pattern | 1.670 (0.921–3.027) | 0.091 |

For abbreviations, see *Table 2*.

## Statistical method

Statistical analysis was performed using SPSS 25 (SPSS Inc.), R version 3.3, and Stata version 14 (StataCorp LLC). Continuous variables were expressed as mean ± SD or median (25th–75th percentile) as appropriate and discrete variables as absolute numbers and percentages. Student's *t*-test or Mann–Whitney *U* test was used as appropriate to compare continuous variables between patients with and without MAACE while $\chi^2$ test or Fisher's exact test was used to study differences regarding categorical data.

The overall analytic goal was to test whether a new DERIVATE Risk Score 2.0 including LGE location provides a higher additional prognostic value vs. current guidelines based on TTE–LVEF in order to predict MAACE when compared with the CMR-derived risk score model previously published and now referred to as DERIVATE Risk Score 1.0.[6] Briefly, the DERIVATE Risk Score 1.0 comprised 7 points with 2 points assigned to male gender, 3 points to CMR LVEDVi > 120.5 mL/m$^2$, and 2 points to the presence of >3 segments with midwall fibrosis on LGE regardless the location of the scar.

In order to develop the DERIVATE Risk Score 2.0, we did the following steps, as previously described.[12] First, we evaluated the univariate Cox proportional hazard ratio (HR) of MAACE prediction of all baseline characteristics, including the presence of LGE for each myocardial segment. Second, we estimated the regression coefficients of the multiple logistic regression of variables significant at univariate Cox analysis after excluding collinear predictors. Third, we selected a referent risk factor profile by choosing a base category for each risk factor (the base category was the category assigned 0 points in the scoring system). Four, we computed how far each category of each risk factor is from the base category in terms of regression units. Five, we defined the number of regression units that will correspond to 1 point. Finally, we determined the risks that are associated with each point total.

The incremental value of CMR-DERIVATE Risk Score 1.0 and CMR-DERIVATE Risk Score 2.0 in addition to TTE–LVEF clinical data was assessed and compared by the $\chi^2$ using Omnibus test of model coefficients.

Reclassification of patients of the new score was determined using net reclassification improvement (NRI) analysis for MAACE.

Finally, event-free survival related to the study endpoints was estimated using the Kaplan–Meier method, and survival curves were compared by means of the log-rank test among low, intermediate, and high-risk populations for MAACE according to the first, second/third, and fourth quartiles of CMR-DERIVATE Risk Score 2.0.

An independent validation cohort of patients who met the inclusion criteria of the study was subsequently identified to test the ability of the DERIVATE Risk Score 2.0 to adequately predict events in a different study population.

All results were considered significant with values of $P < 0.05$.

# Results

According to the specified inclusion and exclusion criteria, the entire cohort consisted of 1384 subjects [mean age: 56 ± 14 years, male: 948 (68.4%)]. Patient baseline characteristics are listed in *Table 1*. TTE and CMR tests were performed successfully in all patients with a median interval of 3 days (25th–75th percentile: 2–5 days) between TTE and CMR.[6] The median follow-up time was 959 days (25th–75th percentile: 559.5–1590). MAACE occurred in 128 (9.2%).

## Characteristics of the population according to the events

Patients who experienced MAACE were predominantly male, with no history of smoking and with more frequent use of beta-blockers, diuretics,

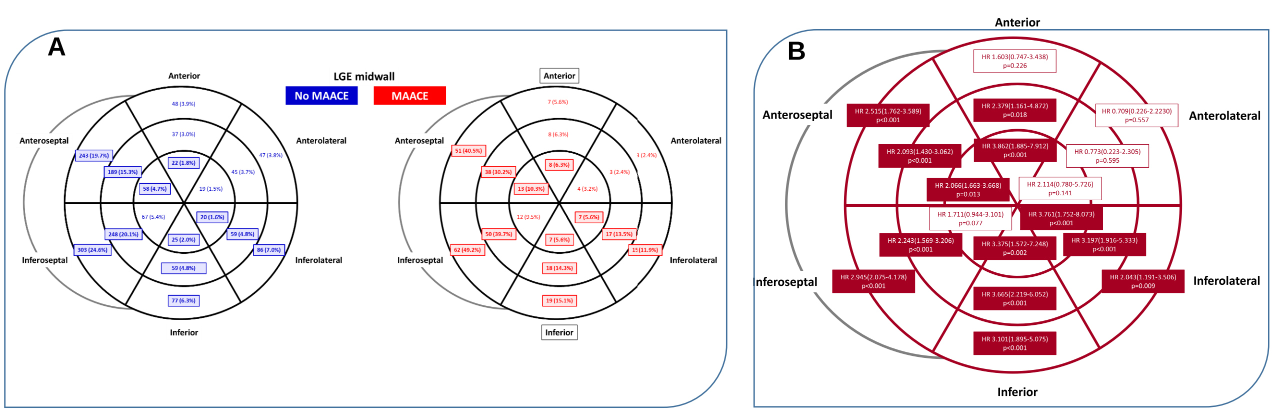



**Figure 1** (*A*) Prevalence of midwall LGE in the LV myocardial segments between patient without MAACE (left) vs. patient who experienced MAACE (right). (*B*) HR to predict MAACE according to the LGE distribution. LGE, late gadolinium enhancement; MAACE, major arrhythmic adverse cardiac events. The numbers included in the rectangle showed significant differences among patients who experience MAACE vs. no MAACE.

**Table 4 Multivariate predictors of MAACE to build DERIVATE Risk Score 2.0**

| | HR (95% CI) | *P*-value | Categories | Points |
|---|---|---|---|---|
| Male | 1.605 (1.051–2.451) | 0.028 | Female | 0 |
| | | | Male | 4 |
| LVEF (per point %) | 0.977 (0.961–0.993) | 0.005 | <24.9% | 6 |
| | | | 25.0–34.9% | 4 |
| | | | 35.0–44.9% | 2 |
| | | | >45.0% | 0 |
| LGE location—HR segment sum (per point) | 1.066 (1.045–1.086) | <0.001 | 0 | 0 |
| | | | >1 and ≤5 | 1 |
| | | | >5 and ≤10 | 3 |
| | | | >10 | 8 |

For abbreviations, see *Table 2*.

calcium-blockers, and anti-arrhythmics drugs when compared with the patients without MAACE (*Table 1*). Regarding imaging variable LVEDi, LVESi were higher and LVEF lower in MAACE group for both TTE and CMR when compared with patients without MAACE (*Table 2*). Moreover, the presence, the extent of LGE, and the midwall LGE pattern significantly differed among MAACE vs. non-MAACE (*Table 2*).

## Predictors of MAACE

Regarding the imaging variables at univariate analysis (*Table 3*) LVEDi, LVESi and LVEF for both TTE and CMR were predictive of MAACE. Regarding the tissue characteristics, the presence, the extent of LGE, and the midwall LGE pattern also were predictive of MAACE. Regarding the role of midwall LGE distribution, *Figure 1* shows the prevalence of LGE in each myocardial segment between patients who experienced MAACE vs. patients who had no events during the follow-up and the HR at univariate analyses for MAACE according to the LGE distribution.

According to the univariate analysis and after excluding collinear predictors, we built a new DERIVATE Risk Score 2.0 measuring the regression coefficients of the multiple logistic regression of variables significant at univariate Cox analysis, and we assigned a scoring for each variable (*Table 4*). Based on these results, the study population was divided into 4 quartiles by considering low (176 subjects), intermediate (824 subjects), and high-risk patients (385 subjects) who fell into the first (Q1), second to third (Q2 and Q3), and fourth quartiles (Q4), respectively (*Figure 2*). All results shown in bold are considered statistically significant.

The omnibus test of model coefficients showed a higher additional prognostic value vs. TTE–LVEF cut-off of 35% when compared with the previously published DERIVATE Risk Score 1.0 with an NRI of 54.52% [95% confidence interval (CI): 36.52–72.52%; $P < 0.001$] (*Figure 3*).

Additionally, as shown in *Figure 4*, 85 patients out of 1031 with less than three segments with middle-wall LGE who experienced MAACE, 35 and 58% had high and intermediate risk, respectively, based on the DERIVATE Risk Score 2.0. Conversely, among the 41 patients out of 201 with more than three segments with midwall LGE who experienced MAACE, the DERIVATE Risk Score 2.0 upgraded all patients classified as intermediate risk according to the DERIVATE Risk Score 1.0 to high risk.

The validation cohort consisted of 244 patients with baseline characteristics listed in Supplementary data online, *Table S1*. MAACE occurred in 19 (8%) cases. As for the derivation cohort, the DERIVATE Risk Score 2.0 provided an NRI for MAACE of 38.1% (95% CI: 20.82–55.37%; $P < 0.001$) when compared with TTE–LVEF with Kaplan–Meier showing again significantly different event-free rates ($P < 0.001$; Supplementary data online, *Figure S1*).

*Figure 5* shows two case examples and the main findings of the study are synthetized in the *Graphical Abstract*.

# Discussion

The present sub-analysis of the entire DERIVATE-NICM cohort population demonstrates that: (i) the prevalence of LGE in the anteroseptal, inferoseptal, inferior, and inferolateral wall is higher in patients who experienced MAACE, while no differences there were in terms of LGE presence in the anterior and anterolateral wall among patients with MAACE vs. patients without MAACE; (ii) a new multi-parametric score (DERIVATE-NICM Risk Score 2.0) weighted on multivariate analysis and including gender, LVEF, and LGE location provides incremental

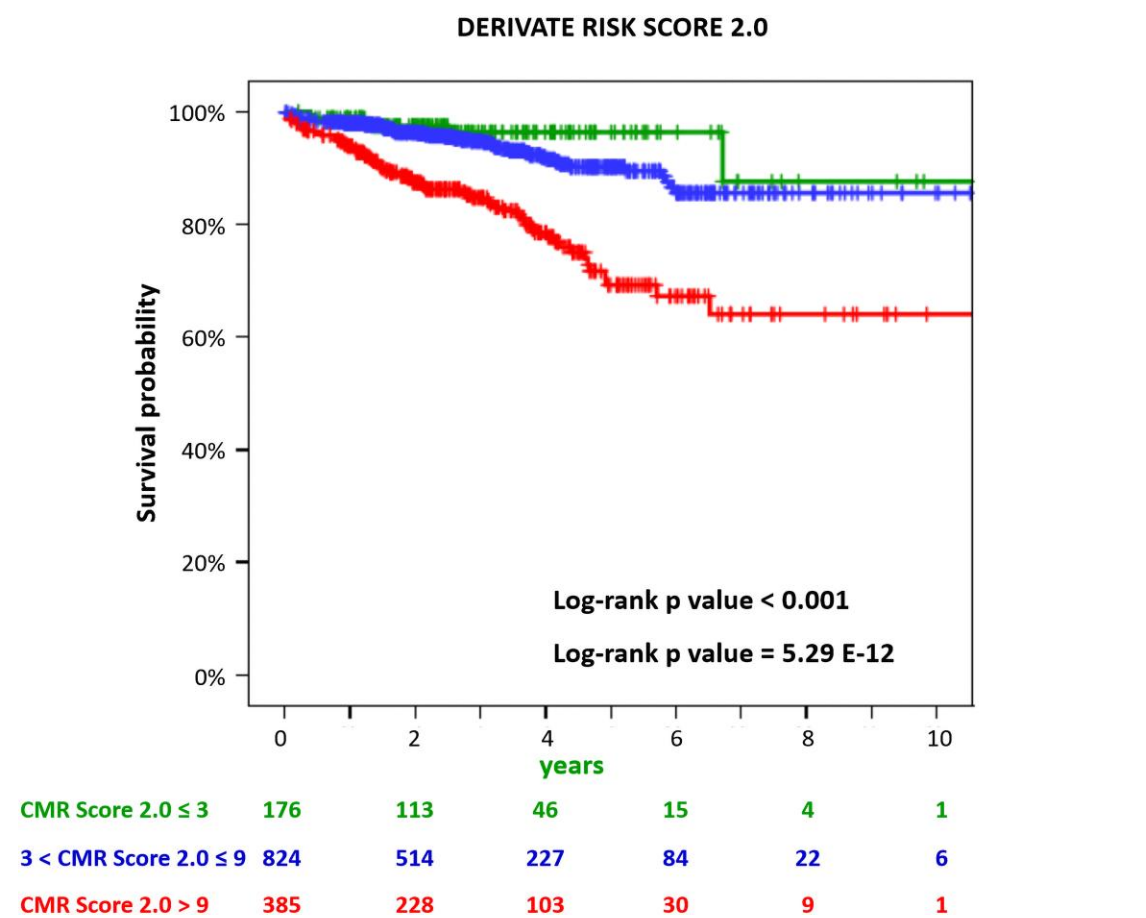



**Figure 2** Kaplan–Meier curves according to the DERIVATE Risk Score 2.0 derived from multivariate analysis in the derivation cohort.

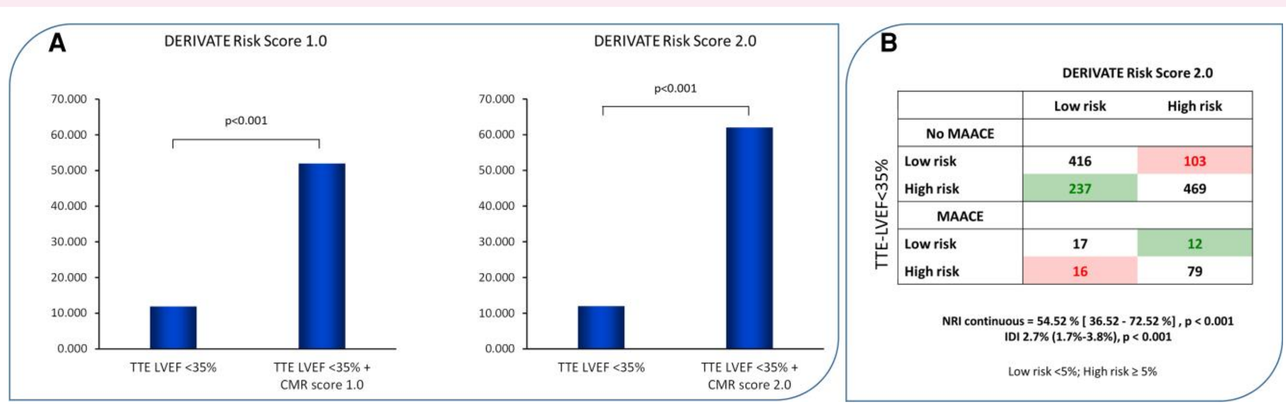



**Figure 3** Incremental prognostic value of DERIVATE Risk Score 1.0 and 2.0 vs. TTE–LVEF < 35% (*A*) with a table of reclassification (*B*). CMR, cardiac magnetic resonance; IDI, integrated discrimination improvement; LVEF, left ventricle ejection fraction; NRI, net reclassification improvement; TTE, transthoracic echocardiography.

prognostic value when compared with the previously published CMR-derived risk score (DERIVATE-NICM Risk Score 1.0); (iii) accordingly with the survival analysis, the patients who belong to the highest quartile of DERIVATE-NICM Risk Score 2.0 had the worst outcome with an NRI of 54% when compared with a model based on TTE–LVEF.

Based on the last European guidelines,[13] LGE-derived information should be considered for assessing aetiology and the risk of MAACE

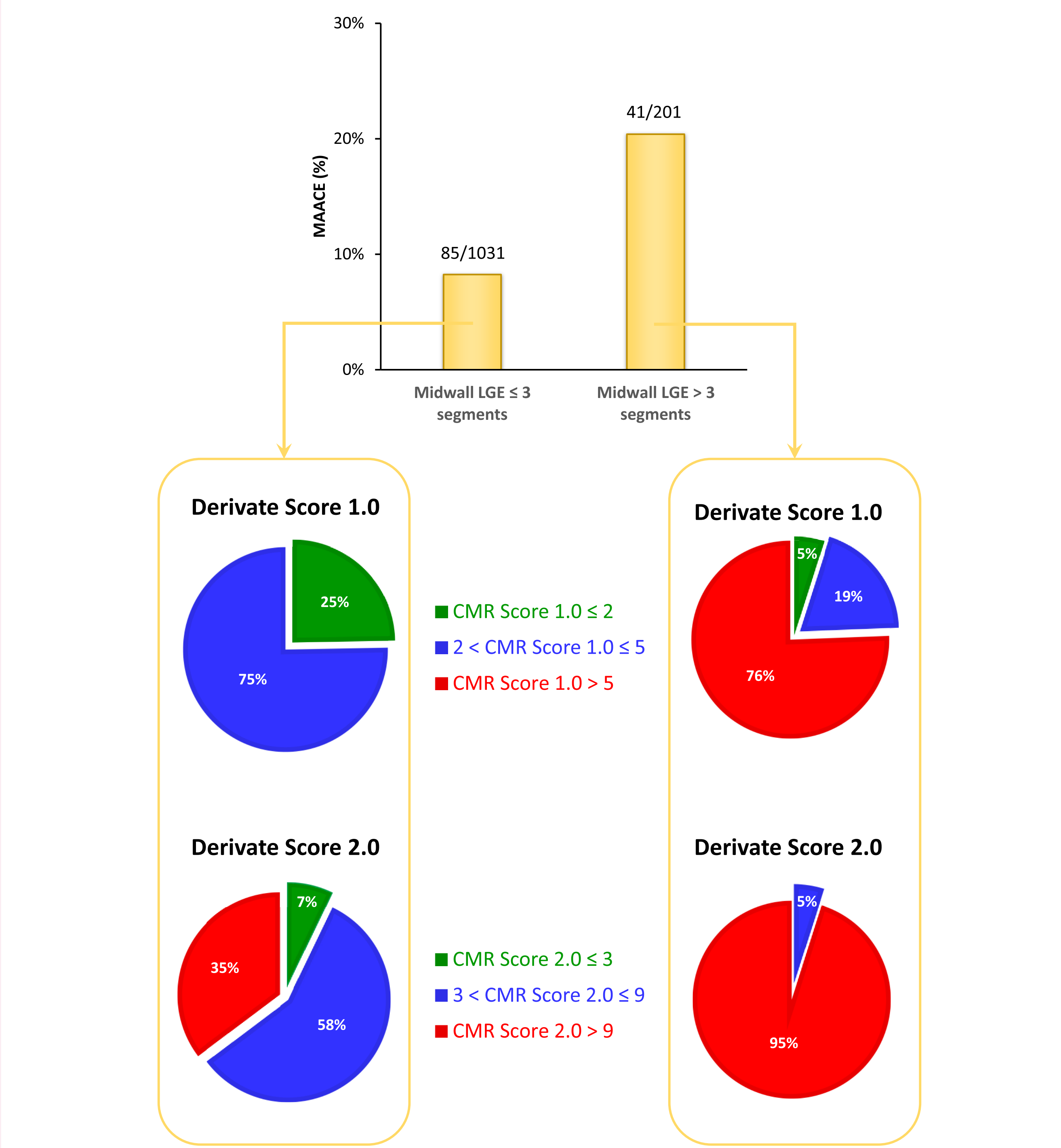



**Figure 4** Reclassification rate of DERIVATE Risk Score 2.0 vs. DERIVATE Risk Score 1.0. CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement.

occurrence in dilated cardiomyopathy. Accordingly, ICD implantation should be considered not only in dilated cardiomyopathy patients but also in hypokinetic non-dilated cardiomyopathy patients with an LVEF <50% and ≥2 risk factors, where such risk factors include LGE on CMR and unexplained syncope. An emerging body of evidence supports contrast-enhanced CMR imaging as a useful technique for prediction of SCD and other outcomes in patients with NICM.[9,14] Pathophysiologic observations indicate that myocardial scar promotes ventricular arrhythmia via heterogeneous conduction and electric re-entry in patients with NICM. Notably, across a wide spectrum of LVEF in patients with NICM, LGE was strongly and independently associated with ventricular arrhythmia.[15]

Thus, the current approach of ICD implantation based on echo LVEF measurement alone, i.e. <35%, for NICM patients appears no longer

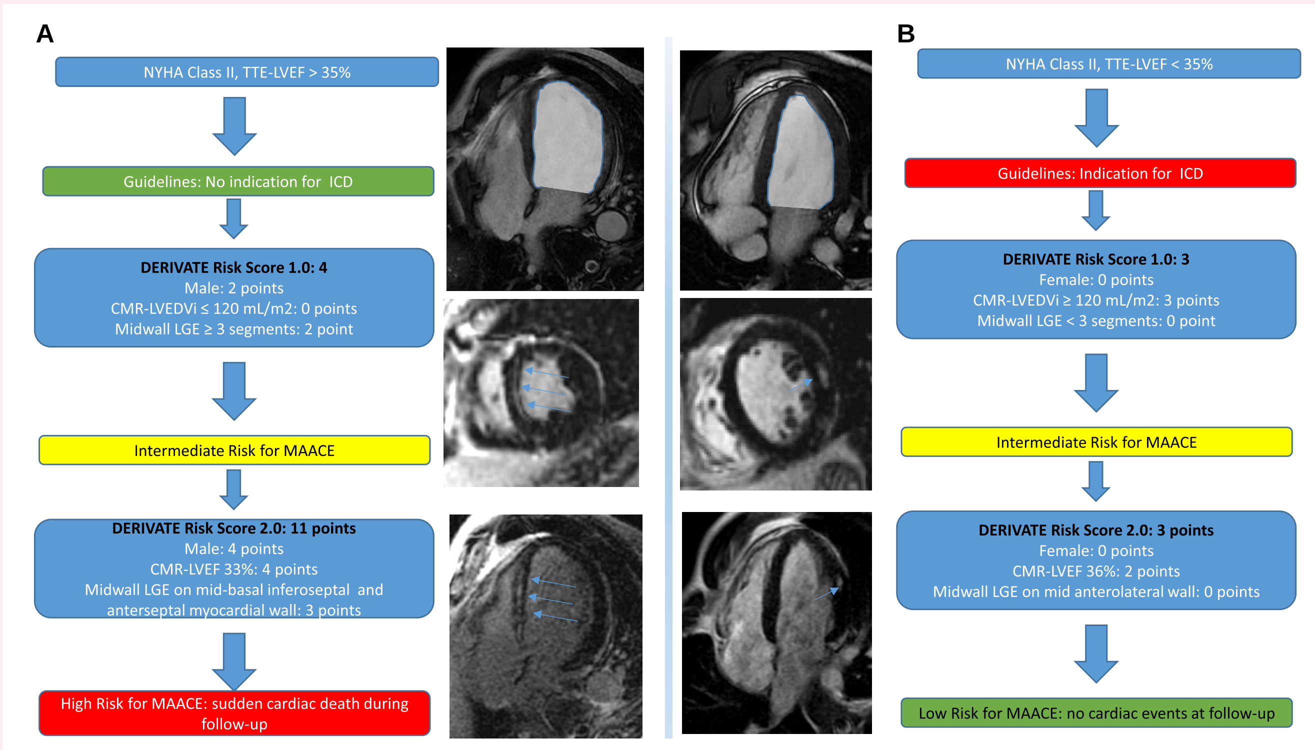



**Figure 5** Patient A: Patient with TTE–LVEF > 35% (i.e. not fulfilling current guidelines criteria for ICD implantation) showing a DERIVATE Risk Score 1.0 and 2.0 of 4 points (intermediate risk for MAACE) and 11 points (high risk for MAACE), respectively. The 3 points related to the midwall LGE are attributed to the category '>5 & ≤10' (*Table 4*) which identifies the sum of the HRs of the corresponding segments (middle inferoseptal 2.2 + basal inferoseptal 2.9 + middle anteroseptal 2.1 + basal anteroseptal 2.5 = 9.7, *Figure 1*B). The patient experienced SCD during the follow-up. Patient B: Patient with TTE–LVEF < 35% (i.e. fulfilling current guidelines criteria for ICD implantation) showing a DERIVATE Risk Score 1.0 and 2.0 of 3 points (intermediate risk for MAACE) and 2 points (low risk for MAACE), respectively. No events occurred during the follow-up. CMR, cardiac magnetic resonance; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricle ejection fraction; MAACE, major arrhythmic adverse cardiac events; TTE, transthoracic echocardiography.

appropriate, as suggested by the DANISH trial.[1] Notably, therapeutic interventions with guideline-directed medical and device therapies can result in reverse remodelling with improvements in LVEF for patients with NICM.[16,17] Recently, the DELIVER trial demonstrated the beneficial effect of sodium-glucose transport protein 2 inhibitors (SGLT2i) for the prevention of mortality and hospitalization in a wide spectrum of HF patient including those with mildly reduced and preserved EF, challenging the approach of guideline direct optimal medical therapy based only on reduced EF.[18] During SGLT2i treatment, reverse LV remodelling may occur by reducing the LV mass in HF patients with reduced EF representing one potential positive mechanism of these drugs.[19] Thus, during such treatment, EF may change over time. Therefore, the detection of focal scar burden by CMR for arrhythmic risk stratification may be more reliable than EF, which may change over time. Ultimately this also means that the selection criterion for ICD implantation of LVEF ≤35% may not be stable over time, implying that LVEF may lack specificity and sensitivity for identifying patients with NICM at risk for SCD.

The previously published DERIVATE-NICM Risk Score 1.0 from DERIVATE trial suggested that based on the selected pattern of LGE (more than three myocardial segments with midwall LGE patterns) the ICD implantation may be beneficial in HF patients throughout a broad range of LVEF especially if they are male with LV dilatation.[6] However, a more phenotypical approach, considering the location, in addition to the extension, of myocardial fibrosis on CMR, may help clinicians to better manage NICM patients.

Previous studies have already tested the impact of LGE location on outcome. In this perspective, in agreement with our study, Halliday *et al.*[20] showed that patients with LGE in the septum had adjusted HRs for the primary endpoint of 1.96 ($P < 0.001$) compared with those without LGE. Moreover, in our registry, we also found the inferior wall and inferior-lateral wall as predictors of MAACE. This evidence was consistent with the data published by Tat *et al.*[21] that showed in patients with NICM, anterior, inferior, and apical segment midwall LGE were independent predictors of the primary endpoint.

The underlying mechanism for how LGE location correlates to worse outcomes is not yet understood, and it is beyond the scope of this study. However, some hypotheses could be proposed. First, the association between regional sympathetic innervation related to fibrosis and inducibility of ventricular arrhythmias during electrophysiologic study with relevant differences between septum and inferior and inferior-lateral wall[22] related to the different architecture of fibrosis. In a patient with anteroseptal involvement, diffuse fibrosis with islands of viable myocardium can be observed in histologic staining. Along the fibrosis, an abundant number of neuronal fibres, mainly sympathetic, can still be distinguished. As a consequence, a pathologic relative 'hyper-innervation', which has been also associated with an increased risk of arrhythmias, could explain the increased risk for MAACE.[23] On the contrary, in inferior and inferior-lateral segments where the scar is more confluent and dense and associated with sympathetic denervation,[22] a potential mechanism responsible for MAACE could be the one observed in the context of mitral valve prolapse.[24] Indeed, the continuous stretching in this region could be the trigger for susceptible tissue when LGE is present.

Finally, the contribution of LGE located in the anterior and anterolateral walls to MAACE is not significant. This could reflect a different aetiology of the condition, as anterior and anterolateral LGE might conceal cases of patients with undiagnosed myocarditis, which, as is known, has a better prognosis compared with true NICM.

## Limitations

Firstly, the results of our registry are possibly affected by referring biases. However, the sites included in the registry represent referral centres, where the CMR is part of the usual care. Secondly, in this registry, a relatively low MAACE rate was observed, likely due to the inclusion of patients without a history of ventricular arrhythmias, and the exclusion of patients with hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy, which was done by intention to investigate the prognostic yield of CMR in a lower risk population.

Furthermore, in the current analysis, we intended to ensure a pure population of NICM patients without the contribution of ischaemic aetiology. According to the original study design, the ischaemic aetiology of LV dysfunction was defined as, among others, 'evidence of ischaemic scar at LGE–CMR explaining the degree of LV systolic dysfunction'. By applying a more restrictive interpretation of that criterion, we excluded all patients showing a concomitant non-ischaemic and ischaemic LGE pattern. This choice allowed us to obtain more refined prognostic results at the expense of a smaller population than in the previously published analysis.

Thirdly, our registry did not include NICM patients on treatment with SGLT2i, which may potentially improve the clinical outcome of these patients, nor did it include patients with sacubitril/valsartan treatment, which potentially may reduce the risks of ventricular arrhythmia compared with angiotensin converting enzyme inhibitors/angiotensin receptor blockers therapy in HF patients.[25] However, during the enrolment period of our registry, the two drug concepts had not yet reached full acceptance in the cardiology community worldwide. Moreover, we did not include biomarkers of HF, such as brain natriuretic peptide, or biomarkers of myocardial fibrosis, such as serum ST2, nor did we use novel CMR techniques such as quantitative T1 mapping (due to the limited availability of T1 mapping in several study centres). In addition, an arrhythmic composite risk model, which also includes genetics, will likely be able to improve the predictive performance of our model for MAACE. Thus, caution is needed in extending the results of our registry to NICM patients with different genotypes.

Fourthly, our registry does not include genetic tests. There is a growing body of evidence in the literature that genetic mutations correlate with LGE amount and distribution.[26] The majority of data showed that genes can be classified into three categories according to the predominant LGE pattern distribution as subepicardial/ring-like (DMD, DSP, and FLNC), unspecific (TTN, BAG3, LMNA, and MYBPC3), and absent/rare (TNNT2, RBM20, and MYH7) with a complementary role in terms of prognostic stratification.[27] However, whether tissue characterization and genetic tests are faces of the same coin is still under investigation, and moreover, these tests are not still widespread in clinical practice.

Finally, even larger studies are warranted to minimize the underpowering issue related to the uneven prevalence of scarring in the different ventricular sectors. Notwithstanding these limitations, the results of our registry add important new information on how to best use LGE–CMR in risk stratification of NICM patients.

# Conclusion

The incremental value of the DERIVATE Risk Score 2.0 is mainly related to the integration of LGE pattern and location in a model including gender and continuous value of LVEF that is a unique prerogative of CMR (*Graphical Abstract*). Further randomized trials to test a CMR-guided strategy for ICD implantation vs. standard of care are now needed.

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# Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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## Data availability

The original data generated during the study are available at the following link upon request: https://zenodo.org/records/14590431.

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