Cardiac magnetic resonance predictors of left ventricular remodelling following acute ST elevation myocardial infarction: The VavirimS study

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ABSTRACT

Background: Left ventricular (LV) remodelling (REM) ensuing after ST-elevation myocardial infarction (STEMI), has typically been studied by echocardiography, which has limitations, or cardiac magnetic resonance (CMR) in early phase that may overestimate infarct size (IS) due to tissue edema and stunning. This prospective, multi-center study investigated LV-REM performing CMR in the subacute phase, and 6 months after STEMI.

Methods and results: patients with first STEMI undergoing successful primary angioplasty were consecutively enrolled. CMR was done at 30-days and 6-months. Primary endpoint was prevalence at 6 months of LV-REM [$\geq$12% increase in LV end-diastolic volume index (LV-REM$_{EDV}$)]; LV-REM by end-systolic volume index increase $\geq$12% (LV-REM$_{ESV}$) was also calculated.

Of 325 patients enrolled, 193 with a full set of research-quality CMR images were analyzed. LV-REM$_{EDV}$ and LV-REM$_{ESV}$ were present in 36/193 (19%) and 34/193 (18%) patients, respectively. At follow up, LV ejection fraction (EF) improved in patients with or without LV-REM$_{EDV}$, whilst it decreased in those with LV-REM$_{ESV}$ ($p < 0.001$ for interaction). Considering predictors of LV-REM, IS in the highest tertile was clearly separated from the two lower tertiles. In LV-REM$_{EDV}$, the highest tertile was associated with significantly higher LV-EDV, LV-ESV, and lower EF.

Conclusions: In a contemporary cohort of STEMI patients studied by CMR, prevalence of LV-REM$_{EDV}$ was lower than previously reported. Importantly, our data indicate that LV-REM$_{EDV}$ might not be "adverse" per se, but

rather "compensatory", being associated with LV-EF improvement at follow-up. Conversely, LV-REM$_{ESV}$ might be an "adverse" phenomenon associated with decreased LV-EF, driven by IS.

1. Introduction

Adverse left ventricle remodelling (LV-REM) following STEMI has been defined as ≥20% increase in LV end-diastolic volume (LV-EDV) 6-months after the index event, measured using echocardiography, based on the upper limit of the 95% confidence interval of intra-observer variability for change (%Δ) in LV-EDV [1]. Although echocardiography remains an essential tool, Cardiovascular Magnetic Resonance (CMR) is considered the *gold-standard* imaging modality for quantitative and qualitative assessment of myocardial infarct size (IS), LV volumes and ejection fraction (LV-EF) [2,3], given its high reproducibility and lower operator dependence [4–6].

Studies of LV-REM using CMR have produced conflicting results [6] and this might be due to scans performed at different times after the index event or with different acquisition protocols.

Indeed, in the acute phase of STEMI, the extent of late gadolinium enhancement (LGE) is compounded by tissue oedema. The latter progressively vanishes in the subacute phase, leading to stable LGE distribution which identifies the permanent myocardial scar. Ibrahim et al. [7] reported that LGE% could decrease up to ~5% from day 1 to 7 after STEMI. Similar results have been reported by Dall'Armellina et al. [8] who showed that the mean volume of oedema was stable over the first week, with a reduction at 2 weeks and near resolution at 6-months. Furthermore, myocardial stunning in the peri-infarct areas contributes to alter function and geometry of the LV in the acute phase [9]. The combination of these factors may lead to a significant over-estimation of IS and LV-REM when baseline CMR is performed in the first week after STEMI. Finally, much information about LE-REM has been gathered years ago; aside from the limitations of echocardiographyic techniques used in earlier studies, the overall management of STEMI has markedly evolved since.

Based on this evidence, the prospective, multicenter VavirimS study (Valore predittivo della vitalità miocardica nell'identificazione del rimodellamento ventricolare sinistro 6 mesi dopo uno STEMI; NCT04699565) was carried-out to ascertain, in a contemporary series of STEMI patients, the prevalence of adverse LV-REM, defined as a percentage change in LV-EDV index (LV-EDVi) ≥12% [4] with a baseline CMR scan obtained at 30-days and follow-up scan at 6-months after index STEMI.

2. Methods

2.1. Study design and population

VavirimS is a prospective, multicenter study (including ten Institutions of the Italian Research Hospital [IRCCS] Cardiology Network) enrolling consecutive patients admitted for STEMI who had undergone primary PCI (pPCI). Inclusion criteria were: first STEMI, symptoms onset <12 h, successfully revascularization with p-PCI, and presence of regional LV systolic dysfunction in at least 2 adjacent segments in the territory of the culprit coronary artery, based on a baseline echocardiogram performed after p-PCI at the arrival of the patient in the coronary care unit. Exclusion criteria were: previous myocardial infarction, cardiomyopathies, valve disease, life-limiting non-cardiac diseases, CMR contra-indications and patients unable or unwilling to give informed consent.

Patients underwent coronary angiography and p-PCI according to institutional protocols, followed by guideline-directed medical therapy. All patients underwent CMR scan scheduled 30-days post-STEMI; further 10 day leeway were allowed to accommodate logistic needs; CMR scan was repeated after 6-month follow-up; blood tests included peak troponin (T or I), and NT-pro-BNP at discharge.

Study data were collected and managed using a web-based software platform (electronic Case Report Form-eCRF) based on REDCap (Research Electronic Data Capture) hosted at the IRCCS Cardiology Network [10,11].

The research protocol was approved by the Ethics Committees of participating centers and complied with the Declaration of Helsinki. Signed informed consent was obtained from all patients.

2.2. CMR acquisition protocol

CMR studies were carried out on different 1.5 T scanners: Aera (Siemens Healthcare, Erlangen, Germany); Discovery MR 450 (GE Healthcare, Milwaukee, WI); Philips Achieva DStream (Philips Healthcare, Best, The Netherlands), sharing the same acquisition protocol: 1- The scan acquired 30-days following STEMI included cine SSFP images for ventricular volumes, function and mass, short-tau inversion-recovery T2-weighted sequences (STIR) for myocardial oedema and Mag-IR (Magnitude only Inversion Recovery) T1-weighted sequences acquired 10 min after injection of ~0.15 mmol/kg of Gadobutrol for late gadolinium enhancement (LGE). 2- The scan acquired 6-months after index event consisted of cine SSFP images covering the entire left ventricle for the assessment of volume, function and mass.

2.3. Centralized analysis of DICOM images

After acquisition, DICOM images were transferred to the Core-Lab (Multimodality Cardiac Imaging at Policlinico San Donato, Milan) for centralized analysis by two expert cardiologists (S.P. and L.T., Level 3 EACVI accreditation) blinded to clinical information. Disagreements were solved by a third reader.

A dedicated workstation (Qmass, MR version 6.2.1, Medis Medical Imaging Systems, Leiden, Netherlands) was used for the analyses.

Semi-automated contours were drawn on the short-axis cine images using the threshold segmentation option for the epicardial border and the automatic detection of endocardium. LV-EDV, LV-ESV, LV mass and LV-EF were quantified, with LV *trabecula* and papillary muscles included as part of the mass and indexed to body surface area. The basal cine slice was included if at least 50% of the ventricular circumference was surrounded by myocardium. %ΔLV-EDV, %ΔLV-ESV, and %ΔLV-EF were calculated as the difference between the measurements at 6-months and 30-days, expressed as percentage of the 30-day parameters.

Semi-quantitative assessment was used for regional wall motion abnormalities score (normal = 1, hypokinetic = 2, akinetic = 3, dyskinetic = 4, aneurismal = 5) at both 30-day and 6-month CMR, according to AHA 17-segments model; wall motion score index was also calculated.

Myocardial oedema was semi-quantitatively assessed considering signal hyperintensity +2-SD above normal myocardium according to AHA17-segments model. Myocardial haemorrhage was defined visually as a hypointense signal within the area of myocardial oedema.

2.3.1. Late gadolinium enhancement imaging analysis

IS was semi-automatically quantified using a signal intensity threshold of +5-SD above normal, remote myocardium on LGE short-axis images.

IS was expressed as grams (ISg) and percentage of the whole LV (IS %).

The difference of LV mass and LGE extent was measured to obtain the viable mass as a percentage of LV global mass.

MVO was defined as a hypointense signal within the infarct region, and was included in IS as part of infarcted myocardium.

Transmural extent of infarct was quantified for each segment as follows: no LGE, 1–25%, 26–50%, 51–75%, and 76–100%.

Furthermore, using a 17-segment model, the number of segments with >50% or >75% transmural hyper-enhancement was summed to calculate the segmental extent of transmural LGE.

2.4. Study outcomes

2.4.1. Primary endpoint

The primary endpoint was %ΔLV-EDV, defined by ≥12% increase in LV-EDV index at 6-months compared with the CMR evaluation at 30-days [4].

2.4.2. Secondary end-points

LV-REM was also assessed according the following definitions:

- ≥12% ΔLVESV increase at 6 months (LV-REM$_{ESV}$).
- LV-ESV (index) at 6 months >39 ml/m^2, + 2 SD above the normal reference range (LV-REM $_{6\text{-months}}$) [12].

Furthermore, the following clinical and CMR parameters at 30-days were evaluated as predictors of LV-REM according the above-mentioned definitions: age, gender, diabetes, symptoms-to-balloon time, ISg, number of segments with >50% LGE, MVO, haemorrhage.

2.5. Statistical analysis

Categorical variables are shown as count and percentage and compared with χ2 test; Continuous variables are expressed as mean ± SD and compared with *t*-test; non-normal variables are displayed as median and interquartile range and compared with Wilcoxon test.

We explored the longitudinal effect of LV-REM, time and the interaction LV-REM*time on LV-EDV (index), LV-ESV (index) and LV-EF, by fitting a mixed-effect model with a random-effect for subject-id and a fixed effect for LV-REM definition. Multiple post-hoc comparisons were adjusted with the Holm-Bonferroni method.

We further explored independent predictors of LV-REM$_{6\text{-months}}$ by fitting a logistic multivariable model. Age, gender, diabetes, symptoms-to-balloon time, ISg, number of segments with LGE >50%, MVO and haemorrhage were included as covariates.

Analyses were performed in R 4.1.2 version. A *p*-value <0.05 was considered significant.

3. Results

325 STEMI patients met the inclusion/exclusion criteria between November 2018 and September 2020. Due to the SARS-CoV-2 pandemic, STEMI hospitalizations in Italy significantly decreased during 2020 [13], and consequently enrolement was substantially affected; furthermore, because of logistic and social limitations during that period 92 patients could not undergo CMR examination at 30-days, and an additional 34 could not undergo CMR at 6-months. Six patients were excluded due to insufficient imaging quality, while 2 had a device implantation between scans, leaving 193 patients with paired CMR images for final analysis.

Table 1 shows baseline clinical, echocardiographic and angiographic characteristics of the study population.

Overall, in this cohort of patients with no prior history of myocardial infarction, the culprit vessel was the left anterior descending coronary artery in 55% of patients, left circumflex in 10%, and right coronary artery in 34%. The median symptoms-to-balloon time was 140 min. A TIMI-flow 3 after revascularization was achieved in 93% of patients.

Table 1

Clinical, echocardiographic and angiographic characteristics of the study population.

Clinical and echocardiographic variables	Patients (*n* = 193)
Age, mean (SD)	63(10)
Male gender n (%)	165(85)
Diabetes, n (%)	26(13)
Dyslipidemia, n (%)	60 (31)
Hypertension, n (%)	96 (50)
Smoking, n (%)	82 (43)
Heart rate, mean (SD)	75 (17)
Sinus rhythm, n (%)	187 (97)
Atrial fibrillation, n (%)	4 (2)
Left bundle branch block, n (%)	5 (3)
Systolic blood pressure, mean (SD)	133 (24)
Diastolic blood pressure, mean (SD)	81 (14)
Symptoms-to-balloon median [IQR])	140 [90, 240]
Diastolic function	
normal	59 (31)
altered relaxation	108 (56)
pseudonormal	12 (6)
restrictive	5 (3)
peak troponin T ng/ml, *n* = 90 (median [IQR])	3094 [1337, 7809]
peak troponin I ng/ml, *n* = 83 (median [IQR])	30,489 [200, 93,384]
NT-proBNP at discharge, median [IQR]	1114 [535, 2133]
Medical treatment at discharge	
Ace-Inhibitors, n (%)	152 (79)
Beta-blockers, n(%)	170 (88)
Calcium-Antagonist, n(%)	11 (6)
Statin, n(%)	187 (97)
Angiotensin receptor blockers, n (%)	14 (7)
Aspirin, n(%)	185 (96)
Clopidogrel, n(%)	19 (9)
Prasugrel, n(%)	48 (25)
Ticagrelor, n(%)	116 (60)
Diuretics, n(%)	53 (27)
Medical treatment at 6-months	
Ace-Inhibitors, n (%)	144 (75)
Beta-blockers, n(%)	152 (79)
Calcium-Antagonist, n(%)	14 (7)
Statin, n(%)	171 (89)
Angiotensin receptor blockers, n (%)	12 (6)
Aspirin, n(%)	165 (86)
Clopidogrel, n(%)	30 (16)
Prasugrel, n()	38 (20)
Ticagrelor, n(%)	96 (50)
Diuretics, n(%)	37 (19)
Angiographic variables	
Culprit artery, n (%)	
left anterior descending coronary artery	106 (55)
left circumflex	19 (10)
right coronary artery	65 (34)
Number of vessels, n (%)	
single vessel	79(45)
two vessel	62(35)
three vessel	34(20)
TIMI flow at presentation, n (%)	
0	121(72)
1	25(16)
2	7(4)
3	14(8)
TIMI flow post PCI, n (%)	
0	2(1)
1	1(1)
2	9(5)
3	158(93)

3.1. Patients with evidence of ≥ 12% increase of LV-EDV index at 6-months

Baseline CMR characteristics of the study population are shown in Table 2. Only 4% of patients had CMR evidence of a previous ischemic necrosis (<2% of LV mass) in territories other than the culprit artery territory.

Based on the pre-specified definition of LV-REM as at least 12% increase of LV-EDV index at 6-month follow-up CMR (LV-REM$_{EDV}$), 36/

Table 2

CMR characteristics of the study population, stratified according to LV-REM definition of LVEDV ≥12% increase from 30-days to 6-months CMR.

Variables	All patients (n = 193)	Patients without LV-REM (n = 157)	Patients with LV-REM (n = 36)	p
Bi-ventricular morpho-functional parameters at 30-days CMR				
LV EDV ml, mean (SD)	140 (38)	145 (37)	122 (36)	0.001
LV ESV ml, mean (SD)	65 (30)	67 (31)	56 (25)	0.052
LV EDV i ml/m2, mean (SD)	73 (18)	75 (18)	64 (18)	0.001
LV ESV i ml/m2, mean (SD)	34 (16)	35 (16)	29 (13)	0.061
LV EF %, mean (SD)	55 (12)	56 (12)	54 (13)	0.416
LV MASS g, mean (SD)	138 (31)	138 (32)	137 (28)	0.854
LV MASS i g/m2, mean (SD)	72 (14)	72 (14)	71 (14)	0.888
RV EDV ml, mean (SD)	117 (33)	120 (32)	101 (30)	0.001
RV ESV ml, mean (SD)	45 (17)	46 (17)	39 (16)	0.028
RV EDV i ml/m2, mean (SD)	61 (14)	62 (14)	52 (13)	<0.001
RV ESV i ml/m2, mean (SD)	23 (8)	24 (8)	20 (8)	0.018
RV EF %, mean (SD)	62.1 (7.9)	63 (7)	61 (9)	0.182
Bi-ventricular morpho-functional parameters at 6-months CMR				
LV EDV ml, mean (SD)	137 (38)	134 (36)	151 (45)	0.016
LV ESV ml, mean (SD)	58 (29)	56 (27)	67 (36)	0.046
LV EDV i ml/m2, mean (SD)	71 (19)	70 (17)	78 (23)	0.009
LV ESV i ml/m2, mean (SD)	30 (15)	29 (14)	35 (19)	0.2037
LV EF %, mean (SD)	59 (11)	59 (11)	58 (12)	0.362
LV MASS g, mean (SD)	135 (30)	134 (31)	139 (25)	0.368
LV MASS i g/m2, mean (SD)	70 (14)	69 (14)	72 (13)	0.288
RV EDV ml, mean (SD)	118 (33)	117 (33)	121 (37)	0.495
RV ESV ml, mean (SD)	43 (17)	43 (17)	44 (19)	0.825
RV EDV i ml/m2, mean (SD)	60 (14)	61 (14)	63 (17)	0.418
RV ESV i ml/m2, mean (SD)	23 (8)	22 (8)	23 (9)	0.77
RV EF %, mean (SD)	64 (7)	64 (7)	64 (7)	0.576
wall motion score index, mean (SD)	1.5 (0.4)	1.4 (0.3)	1.5 (0.4)	0.185
LA area cm2, mean (SD)	22 (5)	23 (5)	20 (5)	0.005
LA area i cm2/m2, mean (SD)	12 (3)	12 (2)	11 (3)	0.009
MR grading, n (%)				0.681
0	55(28)	43(27)	12(34)	
1	130(68)	111(70)	19(54)	
2	6(3)	2(1)	4(11)	
3	1(1)	1(1)	0	
AR grading, n (%)				0.568
0	136(71)	111(71)	26(71)	
1	50(26)	40(26)	10(29)	
2	5(3)	5(3)	0	
AS grading, n (%)				0.747
0	179(94)	147(94)	32(91)	
1	11(5)	8(5)	3(9)	
2	1(1)	1(1)	0	
Tissue characterization (30-days)				
Oedema presence, n (%)	168(89)	138 (90)	30 (84)	0.377
ISg, mean (SD)	22 (17)	22 (17)	20 (12)	0.478
IS%, mean (SD)	20 (10)	20 (10)	20 (10)	0.716
segments with LGE, n (%)	5.4 (2.6)	5.3 (2.6)	5.7 (2.8)	0.479
segments with LGE extent >50% of wall thickness, n(%)	3.2 (2.7)	3.3 (2.7)	2.9 (2.4)	0.451
	1.7 (2.2)	1.8 (2.2)	1.3 (2.0)	0.191

Table 2 (*continued*)

Variables	All patients (n = 193)	Patients without LV-REM (n = 157)	Patients with LV-REM (n = 36)	p
segments with LGE extent >75% of wall thickness, n(%)				
LGE of the LV apex>50%, n(%)	44 (23)	38 (25)	6 (17)	0.42
LGE of the RV, n(%)	5.0 (2.8)	12 (8)	2 (6)	0.937
prior myocardial ischemic necrosis g, mean (SD)	19 (10)	5.2 (3)	4.4 (0.8)	0.777
haemorrhage, n(%)	19 (10)	16 (10)	3 (8)	0.94
microvascular obstruction, n(%)	6 (3)	16 (10)	3 (9)	0.999
LV thrombus, n(%)	14 (7)	6 (4)	0	0.511
viable LV mass, g (mean (SD)	116 (28)	116 (28)	117 (29)	0.89
viable LV mass i, g/m2 (mean (SD)	60 (13)	60 (13)	61 (14)	0.819
viable LV mass, % (mean (SD)	80 (10)	80 (10)	80 (10)	0.716

p refers to LV-REM EDV vs no LV-REM EDV patients.

193 patients (19%) had evidence of LV-REM$_{EDV}$ (Table 2 **and** Fig. 1A and B**).**

Patients with LV-REM$_{EDV}$ did not differ for baseline clinical parameters, nor for symptoms-to-balloon time, TIMI flow after revascularization, or medical treatment, as compared to patients with no LV-REM$_{EDV}$. Peak troponin T and I were not statistically different in patients with evidence of LV-REM$_{EDV}$ compared to those with no LV-REM$_{EDV}$ ($p = 0.93$ and $p = 0.25$, respectively). Likewise, NT-proBNP values at discharge (median 1673 [497, 2249] vs 1101 [563, 2106] pg/ml, $p = 0.54$) were comparable in the two groups.

At baseline, patients with LV-REM$_{EDV}$ had smaller LV end diastolic volume index (LV-EDV$_i$), right ventricle end-diastolic (RV-EDV$_i$) and right ventricle end-systolic volume index (RV-ESV$_i$) compared to patients without LV-REM$_{EDV}$. By contrast, at 6-month CMR, patients with LV-REM$_{EDV}$ had larger LV-ESV$_i$ compared to those without LV-REM$_{EDV}$.

Development of LV-REM$_{EDV}$ was not associated with a greater mean ISg in LV-REM$_{EDV}$ vs no LV-REM$_{EDV}$ ($20 \pm 10\%$ in both groups, $p = 0.72$), nor with a higher number of segments with LGE $> 50\%$ or $> 75\%$ (3 ± 2 segments in LV-REM$_{EDV}$ vs 3 ± 3 segments in no LV-REM$_{EDV}$, $p = 0.45$ and 1 ± 2 vs 2 ± 2 segments, respectively, $p = 0.19$). Similarly, no differences were observed when considering viable LV mass ($80 \pm 10\%$ in both groups, $p = 0.72$). Myocardial haemorrhage and MVO were equally prevalent in the two groups, 3 (8%) vs 16 (10%), and 3 (9%) vs 16 (10%) respectively, $p > 0.9$ (Table 2**).**

3.2. Patients with evidence of ≥ 12% increase of LV-ESV index at 6 months

When a 12% change in LV-ESV index was considered, 34/193 patients (18%) had evidence of LV-REM$_{ESV}$, of whom only 17 met the criteria also for LV-REM$_{EDV}$ (Table 3).

LV-REM$_{ESV}$ patients did not differ for baseline clinical parameters, nor for symptoms-to-balloon time, TIMI flow after revascularization, or medical treatment, compared to patients with no LV-REM$_{ESV}$.

Peak troponin T and I were not statistically different in patients with evidence of LV-REM$_{ESV}$ compared to those with no LV-REM$_{ESV}$ ($p = 0.21$ and $p = 0.25$, respectively).

Likewise, NT-proBNP values at discharge (median 842 [510, 2285] vs 1213 [570, 2093] pg/ml, $p = 0.57$) were comparable in the two groups.

At baseline, patients with LV-REM$_{ESV}$ had smaller LV-EDV$_i$, LV-ESV$_i$, RV-EDV$_i$, RV-ESV$_i$ and higher LV and RV-EF compared to patients
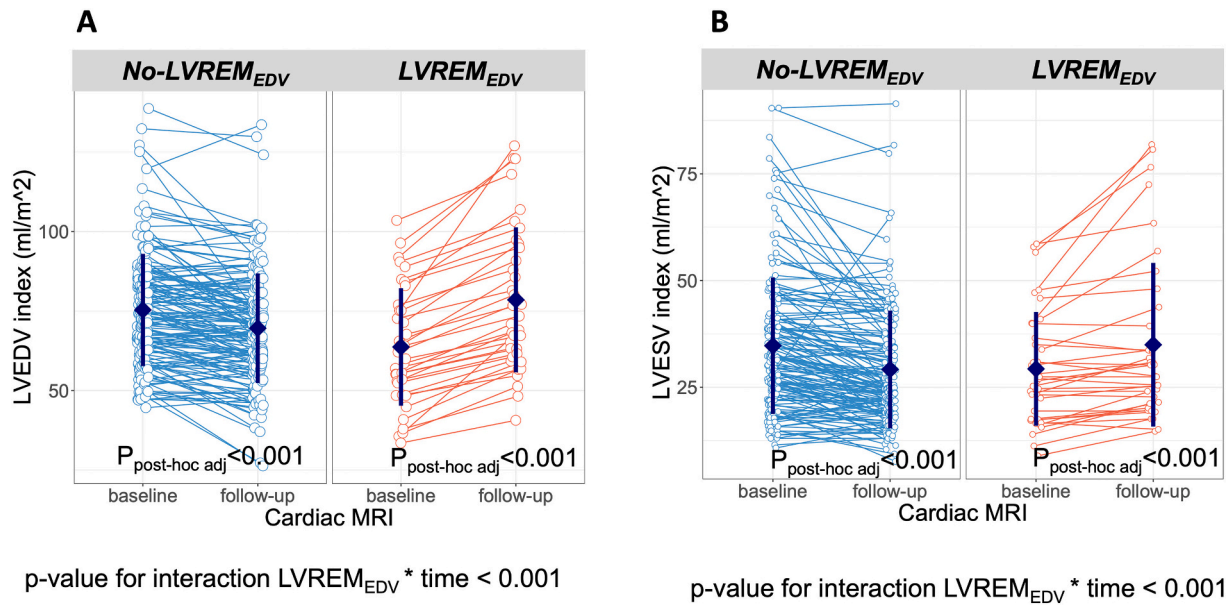
Fig. 1. A and B: Individual patient change in left ventricular end-diastolic volume index (Panel 1A) and left ventricular end-systolic volume index (Panel 1B), assessed by CMR, 30-days and 6-months after the index event, stratified by an increase of LV end-diastolic volume (%ΔLV-EDV) of at least 12%. Dark blue bars show mean +/− standard deviation for the parameter. Overall statistics was obtained by fitting a mixed model for repeated measures. Subject id was included as random effect, while remodelling (LV-REM$_{EDV}$), time and the interaction term between LV-REM$_{EDV}$ * time were included as fixed effects. Multiple post-hoc comparisons were adjusted with the Holm-Bonferroni method. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

without LV-REM$_{ESV}$, whilst all these parameters were comparable in the two groups at 6-month CMR.

3.3. Changes in LV ejection fraction at follow-up based on remodelling definition

At follow-up, patients with LV-REM$_{EDV}$ and patients with no LV-REM$_{EDV}$ both improved LV-EF. By contrast, when LV-REM$_{ESV}$ was considered, patients with LV-REM$_{ESV}$ at follow-up showed a reduction in LV-EF, whilst patients with no LV-REM$_{ESV}$ showed improvement in LV-EF, this trend being significantly different between the two groups (i.e. LV-REM$_{EDV}$ vs LV-REM$_{ESV}$ $p < 0.001$ for interaction (Fig. 2 **and B**).

3.4. CMR predictors of LV remodelling

Fig. 3A, B and C show tertiles of distribution of IS% across LV-EDV, LV-ESV and LV-EF at 30-day CMR and at 6-month follow-up, according to development of LV-REM$_{EDV}$ or not.

IS showed a clear separation of the highest tertile from the two lower tertiles. This pattern was evident at 30-days CMR and was maintained at 6-months. In patients with evidence of LV-REM$_{EDV}$, the highest tertile (i.e. greatest LGE extent) was associated to significantly higher LV-EDV, LV-ESV and lower EF compared to the two lower tertiles. Patients in the highest tertile of IS% also increased volumes and function between the two scans, and the increase was more evident than for the lower tertiles. By contrast, patients with no evidence of LV-REM$_{EDV}$, had significant decreases in LV-EDV and LV-ESV, and increased EF at 6-month follow-up (Fig. 3A, B, C).

3.5. Evidence of LV remodelling based on the cut-off of LV-ESV$_i$ > 39 ml/m^2 at 6-month CMR and Multivariable analysis

When defining LV-REM$_{6-months}$ by the absolute value of LV-ESV$_i$, i.e. 2-SD above the upper normal value, 40 patients (21%) met this criterion.

LV-REM$_{6-months}$ patients did not differ for baseline clinical parameters, nor for symptoms-to-balloon time, culprit artery, number of involved vessels, TIMI flow after revascularization, or medical treatment, compared to patients with no LV-REM$_{6-months}$. Peak troponin-T was above the median in 78% of patients with LV-REM$_{6-months}$, compared to 44% of those with no LV-REM$_{ESV}$ (p 0.002). Peak troponin-I was above the median in 60% of patients with evidence of LV-REM$_{6-months}$, compared to 47% in those with no LV-REM$_{6-months}$ ($p = 0.44$). NT-pro-BNP values at discharge (median 2080 (812–3954) vs 959 (481–1898), pg/ml, $p = 0.003$) were significantly higher in patients with LV-REM$_{6-months}$ (Table 4).

LV-REM$_{6-months}$ patients showed significantly higher LV-EDVi (94 ± 18 ml/m^2 vs 68 ± 14 ml/m2), LV-ESVi (54 ± 15 ml/m2 vs 28 ± 11 ml/m^2) and lower EF (42 ± 8% vs 59 ± 10%) at 30-days examination as compared to no LV-REM$_{6-months}$ (all $p < 0.001$); this trend persisted at 6-month CMR.

Presence of LV-REM$_{6-months}$ was associated with a greater mean LGE extent (IS% 38% vs 19%, p < 0.001), with a higher segmental extension of transmural LGE (6 vs 2 segments with >50% LGE, p < 0.001, and 4 vs 1 segments with LGE >75% of transmurality, respectively, p < 0.001). LV-REM$_{6-months}$ patients also had 70% of viable LV mass vs 90% in those with no LV-REM$_{6-months}$, p < 0.001.

Myocardial haemorrhage and MVO had similar prevalence in LV-REM$_{6-months}$ patients (5% vs 14% and 5% vs 14% respectively, $p > 0.7$) (Table 4).

By multivariable analysis, LGE extent in grams (ISg) was an independent predictor of the study endpoint LV-REM$_{6-months}$ [OR = 1.05 (1.01–1.10), $p = 0.019$]. Another independent predictor of the study endpoint was the segmental extent of transmural LGE [OR = 1.43 (1.09–1.87), p = 0.01]. Conversely, age, male gender, diabetes, symptoms-to-balloon >120′, haemorrhage and MVO were not independently associated with the outcome measure ($p > 0.07$) (Fig. 4).

3.6. Intra and inter-observer reproducibility

Intra-class correlation coefficient (ICC) for LGE extent (IS%) assessment was ICC = 0.98 (0.96–0.99) for intra-observer and ICC 0.96 (0.85–0.99) for inter-observer reproducibility analysis.

Table 3

CMR characteristics of the study population stratified according to LV-REM definition of LVESV ≥12% increase from 30-days to 6-months CMR.

Variables	Patients without REM (n = 159)	Patients with REM (n = 34)	p
Bi-ventricular morpho-functional parameters at 30-days CMR			
LV EDV ml, mean (SD)	145 (37)	121 (33)	0.001
LV ESV ml, mean (SD)	69 (30)	45 (25)	<0.001
LV EDV i ml/m2, mean (SD)	75 (18)	64 (16)	0.001
LV ESV i ml/m2, mean (SD)	36 (15)	24 (13)	<0.001
LV EF %, mean (SD)	54 (11.0)	63 (13)	<0.001
LV MASS g, mean (SD)	142 (32)	122 (21)	0.001
LV MASS i g/m2, mean (SD)	74 (15)	64 (8)	0.001
RV EDV ml, mean (SD)	119 (33)	105 (25)	0.019
RV ESV ml, mean (SD)	46 (18)	36 (9)	0.003
RV EDV i ml/m2, mean (SD)	62 (15)	55 (10)	0.02
RV ESV i ml/m2, mean (SD)	24 (9)	19 (4)	0.003
RV EF %, mean (SD)	62 (8)	65 (6)	0.037
Bi-ventricular morpho-functional parameters at 6 months CMR			
LV EDV ml, mean (SD)	136 (37)	140 (45)	0.607
LV ESV ml, mean (SD)	57 (26)	62 (40)	0.336
LV EDV i ml/m2, mean (SD)	71 (18)	74 (22)	0.361
LV ESV i ml/m2, mean (SD)	30 (14)	33 (20)	0.282
LV EF %, mean (SD)	59 (10)	60 (13)	0.634
LV MASS g, mean (SD)	137 (31)	125 (23)	0.031
LV MASS i g/m2, mean (SD)	71 (15)	66 (9)	0.057
RV EDV ml, mean (SD)	118 (34)	116 (31)	0.791
RV ESV ml, mean (SD)	43 (17)	42 (18)	0.823
RV EDV i ml/m2, mean (SD)	61 (15)	61 (13)	0.905
RV ESV i ml/m2, mean (SD)	24 (9)	19 (4)	0.003
RV EF %, mean (SD)	64 (7)	64 (8)	0.888
wall motion score index, mean (SD)	1.5 (0.4)	1.3 (0.4)	0.017
LA area cm2, mean (SD)	23 (5)	20 (4)	0.002
MR grading, n (%)			0.797
0	43(27)	12(35)	
1	110(70)	20(59)	
2	4(2)	2(6)	
3	1(1)	0	
AR grading, n (%)			0.202
0	111(71)	25(74)	
1	41(26)	9(26)	
2	5(3)	0	
AS grading, n (%)			0.707
0	148(94)	32(91)	
1	8(5)	3(9)	
2	1(1)	0	
Tissue characterization (30-days)			
Oedema presence, n(%)	143(92)	25(76)	0.019
IS g, mean (SD)	23.4 (17.2)	15.6 (11.3)	0.014
IS %, mean (SD)	20 (10)	10 (10)	0.102
segments with LGE, n(%)	5.6 (2.6)	4.4 (2.6)	0.018
segments with LGE extent >50% of wall thickness, n (%)	3.4 (2.7)	2.3 (2.3)	0.041
segments with LGE extent >75% of wall thickness, n (%)	1.8 (2.3)	1.2 (1.7)	0.153
LGE of the LV apex >50%, n(%)	37 (24)	7 (21)	0.949
LGE of the RV, n(%)	14 (9)	0	0.152
prior myocardial ischemic necrosis g, mean (SD)	5 (3)	4 (11)	0.777
haemorrhage, n(%)	17 (11)	2 (6)	0.602
microvascular obstruction, n (%)	16 (10)	3 (9)	0.999
LV thrombus, n(%)	6 (4)	0	0.544
viable LV mass, g (mean (SD)	118 (29)	107 (22)	0.044
viable LV mass, % (mean (SD)	80 (10)	90 (10)	0.100
viable LV mass i, g/m2 (mean (SD)	61 (13)	56 (9)	0.038

4. Discussion

The main findings of the present study, conducted in a contemporary cohort of first STEMI patients including more than half anterior STEMI

successfully reperfused with p-PCI, using a *gold-standard* approach with serial CMR scans to capture subtle changes in LV anatomy, function and tissue characterization, were: a) six months after the index event, significant LV volume changes were observed in one-fifth of patients, a figure lower than previously reported; b) the impact on LV-EF was found to be different depending of the definition of LV-REM used: LV-EDVi increase was paralleled by improvement in LV-EF, and therefore may not be necessarily "adverse", but rather "compensatory", whereas an increase in LV-ESV$_i$ unfavourably affected LV-EF and therefore should be considered as "adverse" phenomenon; c) IS and segmental extension of transmural LGE showed an independent impact on LV-REM adverse (systolic) remodelling.

Occurrence of LV remodelling has long been recognized as a frequent negative sequela of STEMI. This notion derives from earlier studies, which investigated and defined post-infarction changes in LV geometry and function by echocardiography [1]. However, it has now become evident that CMR affords a more accurate and less operator-dependent assessment of LV dimension and function compared to echocardiography [4,5]. Furthermore, in the two decades that have passed since the initial description of post-infarction remodelling, medical and interventional management of STEMI patients has substantially evolved. Thus, there is a need to assess this phenomenon in a contemporary population, by means of accurate methodology.

According to our pre-specified criteria, 36/193 patients (19%) had evidence of LV-REM$_{EDV}$. Patients with evidence of LV-REM$_{EDV}$ did not differ for baseline parameters, nor for symptoms-to-balloon time, TIMI flow after revascularization, or medical treatment, nor for LGE extent, compared to patients with no LV-REM$_{EDV}$.

Bolognese et al. reported a higher (30%) incidence of LV-REM$_{EDV}$ using the definition of LV-EDV increase of at least 20% by echocardiography at 6-month follow-up. Several reasons may explain the lower incidence of LV-REM$_{EDV}$ in our study: Bolognese et al. performed baseline echocardiograms earlier (i.e. within 24 h), therefore likely overestimating LV-REM by including myocardial stunning [9]. Furthermore, Bolognese et al. included 13% of patients with prior myocardial infarction. Finally, over the past two decade, STEMI management has markedly evolved: stream-lined paths to early reperfusion, use of latest generation drug-eluting stents, more powerful anti-platelet drugs, and more complete revascularization before discharge [14], all have likely contributed to reduce the impact of STEMI on global LV function, and remodelling.

Comparing our result with the CMR study of Bulluck et al. [4], we also found that LV-REM$_{EDV}$ may be not necessarily "adverse", but rather "compensatory", i.e. linked to increased LV-EF at 6-month-follow-up. This may be explained through the Frank-Starling mechanism leading to increased myocardial fiber stretch, so that LV-EF and cardiac output may remain relatively preserved. The ultimate impact of these two LV-REM conditions on long-term prognosis remains to be investigated.

When remodelling was assessed based on % changes in LV end-systolic volume, 34/193 patients (18%) had evidence of LV-REM$_{ESV}$. Although the percentage of patients with LV-REM$_{ESV}$ is very similar to that of patients with LV-REM$_{EDV}$, these two groups include two different populations. Notably, patients with evidence of LV-REM$_{ESV}$, but not those with LV-REM$_{EDV}$, showed a significant reduction of LV-EF at 6-months (Fig. 2**A and B**) and therefore LV-REM$_{ESV}$ should be considered the "adverse" component of LV-REM.

Similar to patients with LV-REM$_{EDV}$, those with LV-REM$_{ESV}$ did not differ for baseline or angiographic parameters, as compared to patients with no LV-REM$_{ESV}$.

When considering the tertiles of distribution of potential predictors of LV-REM across LV-EDV$_i$, LV-ESV$_i$ and EF at 30-days CMR and at 6-month follow-up, IS showed a clear separation of the highest tertile from the two lower tertiles. In patients with evidence of LV-REM$_{EDV}$, the highest tertile was associated with significantly higher LV-EDV$_i$, LV-ESV$_i$ and lower EF compared to the two lower tertiles. Patients in the highest tertile of IS also increased volumes and function between the two scans
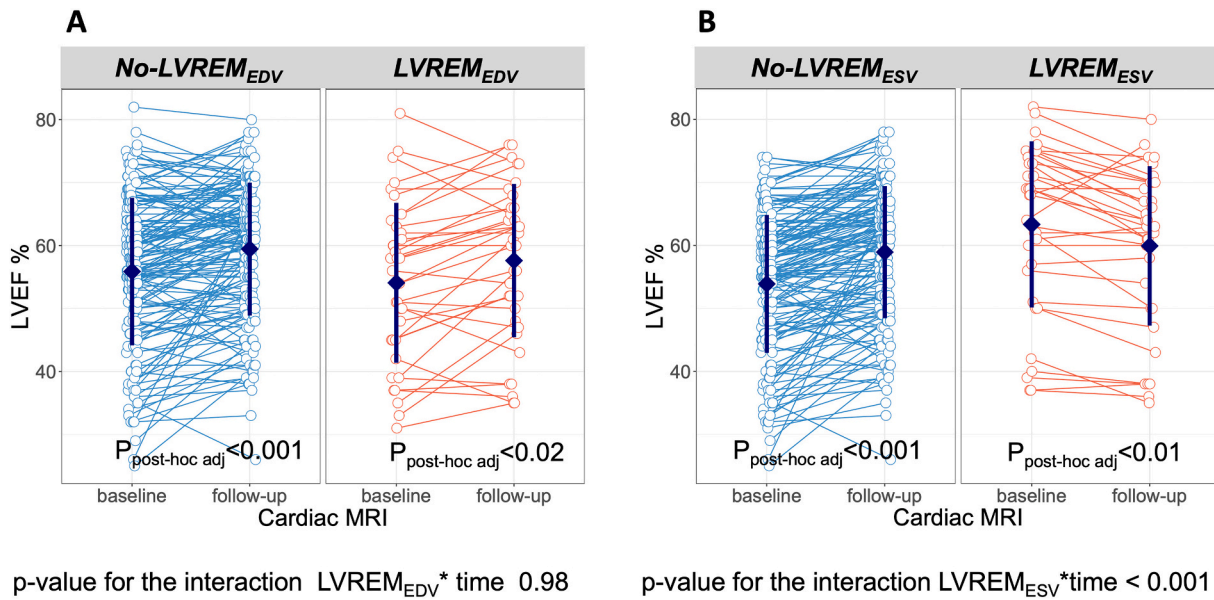
Fig. 2. A and B: Individual patient change in left ventricular ejection fraction (LV-EF) stratified by an increase of LV end-diastolic volume (%ΔLV-EDV) of at least 12% (Panel A) or by an increase of LV systolic volume (%ΔLV-ESV) of at least 12%. Dark blue bars show mean $+/-$ standard deviation for the parameter. Statistics as in Fig. 1.

Both patients with LV-REM$_{EDV}$ and no LV-REM$_{EDV}$ improved LV-EF at follow-up. On the contrary, patients with LV-REM$_{ESV}$ as compared with no LV-REM$_{ESV}$ showed a reduction in LV-EF at follow-up. Change in LV-EF was significantly different between the two LV-REM criteria (LV-REM$_{EDV}$ vs. LV-REM$_{ESV}$), p for interaction <0.001. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

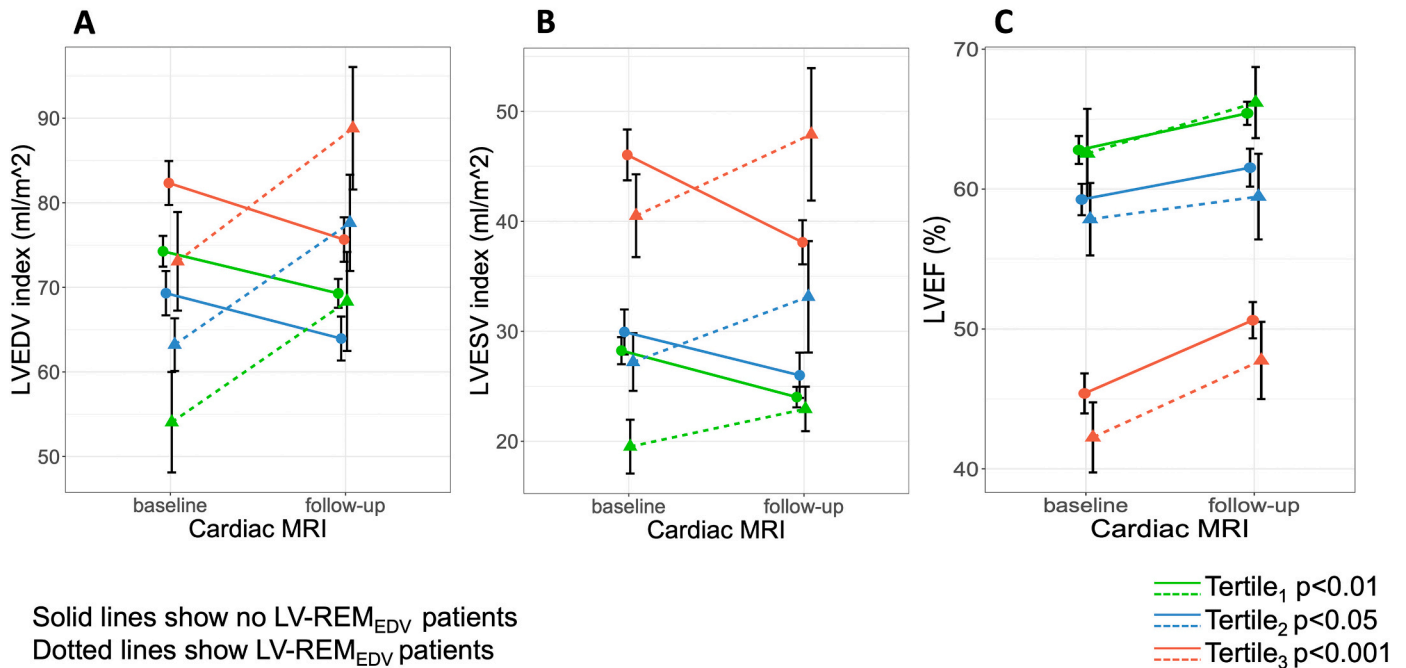## Tertiles of late gadolinium enhancement as percentage of left ventricular mass

Fig. 3. A, B, C Tertiles of late gadolinium enhancement as percentage of left ventricular mass: change in CMR parameters: left ventricular end-diastolic volume index (panel A), left ventricular end-systolic volume index (panel B) and left ventricular ejection fraction (Panel C), stratified by percentage of late gadolinium enhancement (LGE) - left ventricular mass-ratio. Solid lines show change in parameters for patients without adverse remodelling criteria (LV-REM$_{EDV}$), dotted lines for patients with LV-REM$_{EDV}$. Statistics as in Fig. 1. In the highest tertile of infarct size %, compared with the two lower tertiles, there is evidence of higher LV-EDV index, LV-ESV index and lower LV-EF.

and the increase was more evident than for the lower tertiles. Similar patterns were observed for MVO and haemorrhage (**Supplementary Fig. 1 and 2**).

The definitions of adverse LV-REM used in the present work derives from a CMR study of Bulluck et al., who observed similar accuracy of both % changes of EDV$_i$ and ESV$_i$ to discriminate patients with LV-REM,

Table 4

Clinical and CMR characteristics of the study population stratified according to LV-REM definition of LVESV index >39 ml/m2 at 6-months CMR.

Variables	Patients without REM (n = 153)	Patients with REM (n = 40)	p
Symptoms-to-balloon median [IQR]	140 [90, 207]	150 [90, 247]	0.918
peak troponin T ng/ml, n = 90 (median [IQR])	2832 [1302, 5241]	9943 [4337, 15,114]	0.007
peak troponin I ng/ml, n = 83 (median [IQR])	26,900 [193, 67,474]	90,939 [11,547, 150,986]	0.034
NT-proBNP at discharge, median [IQR]	959.2 [481.0, 1898.5]	2080.0 [812.5, 3954.8]	0.003
Culprit artery, n (%)			0.384
descending coronary artery	81(54)	25(64)	
left circumflex	14(9)	5(1)	
right coronary artery	56 (36.6)	9 (22.5)	
Number of vessels, n (%)			0.785
single vessel disease	71(47)	17(43)	
two vessel disease	52(34)	16(40)	
three vessel disease	29(19)	7(17)	
TIMI flow after primary PCI, n (%)			0.517
0	106(70)	31(82)	
1	24(16)	3(8)	
2	6(4)	1(2)	
3	16(10)	3(8)	
Bi-ventricular morpho-functional parameters at 30-days CMR			
LV EDV i ml/m2, mean (SD)	68 (14)	94 (18)	<0.001
LV ESV i ml/m2, mean (SD)	28 (11)	54 (15)	<0.001
LV EF %, mean (SD)	59 (10)	42 (8)	<0.001
LV MASS i g/m2, mean (SD)	70 (13)	78 (18)	0.002
RV EDV i ml/m2, mean (SD)	60 (14)	62 (15)	0.463
RV ESV i ml/m2, mean (SD)	22 (8)	25 (10)	0.071
RV EF %, mean (SD)	63 (7)	60 (9)	0.05
Bi-ventricular morpho-functional parameters at 6-months CMR			
LV EDV i ml/m2, mean (SD)	65 (13)	88 (20)	<0.001
LV ESV i ml/m2, mean (SD)	23 (6)	49 (15)	<0.001
LV EF %, mean (SD)	64 (7)	46 (7)	<0.001
LV MASS i g/m2, mean (SD)	67 (12)	77 (16)	<0.001
RV EDV i ml/m2, mean (SD)	61 (15)	61 (15)	0.864
RV ESV i ml/m2, mean (SD)	22 (7)	24 (10)	0.075
RV EF %, mean (SD)	65 (6)	62 (8)	0.055
wall motion score index, mean (SD)	1.4 (0.3)	1.9 (0.3)	<0.001
Tissue characterization (30-days)			
IS%, mean (SD)	18.7 (13)	37.7 (18)	<0.001
segments with LGE, n(%)	4.8 (2.4)	7.7 (2.2)	<0.001
segments with LGE extent >50% of wall thickness, n (%)	2.5 (2.3)	5.7 (2.5)	<0.001
segments with LGE extent >75% of wall thickness, n (%)	1.2 (1.8)	3.6 (2.5)	<0.001
LGE of the LV apex >50%, n (%)	23 (15)	21 (54)	<0.001
viable LV mass, % (mean SD)	90 (10)	70 (10)	<0.001
haemorrhage, n(%)	14(9)	5(13)	0.729
microvascular obstruction, n (%)	14(9)	5(12)	0.797
Oedema presence, n(%)	123(91)	45(83)	0.20
LV thrombus, n(%)	1 (0.7)	5 (12)	0.001
prior myocardial ischemic necrosis g, mean (SD)	2 (1.1)	2 (1.3)	0.327

although an imperfect link between IS and LV remodelling was observed (4). Westman and colleagues, using a definition of LV-REM of >10 mL/m2 increase of LV-EDV$_i$ by CMR at 4-months, also reported results consistent with our observations: patients with small IS (~15% of cases) could still show progressive LV-REM, while up to 60% of patients with larger IS did not develop LV-REM [15].

We also explored the definition of LV-REM based on the absolute value of LV-ESV$_i$ measured at 6-month-CMR of >39 ml/m^2 according to the cut-off value of 2 SD above the normal reference range of the general

population (LV-REM$_{6-months}$) [12]. Based on this definition, 40/193 patients (21%) had evidence of LV-REM (Table 4).

LV-REM$_{6-months}$ patients did not differ for baseline or angiographic parameters, as compared to patients with no LV-REM$_{6-months}$. However, LV-REM$_{6-months}$ patients showed higher enzymatic release during the index event and higher NT-proBNP levels at discharge. Most importantly, IS at 30-days and number of segments with transmurality of LGE > 50% were the most significant independent predictors of LV-REM$_{6-months}$, while myocardial haemorrhage and MVO had similar prevalence in LV-REM$_{6-months}$ patients.

Incidence of heart failure remains high in STEMI population, prompting a precise evaluation and early prediction of LV remodelling to improve patients' management.

IS and segmental extent of transmural LGE, should be considered "hard endpoints" in STEMI clinical trials as linked to adverse remodelling and clinical outcome; in this respect, our analysis supports the use of LGE characterization by CMR as gold-standard for its assessment.

In the present study, we purposely avoided to perform baseline CMR scans during the acute phase of STEMI. Although it is possible that we might have missed initial signs of remodelling that may have occurred early on, we felt it would be more accurate to avoid the confounding effects of multiple factors that characterize the acute phase of STEMI, and/or which may vary in the immediate post-discharge phase, including structural and functional changes extending beyond infarction area (e.g., myocardial edema, stunning, tethering), hemodynamic alterations (instability, transient use of drugs), staged revascularization of non-culprit vessel. Togther, these factors might tend to influence the correct estimation of degree and distribution of LV contractile dysfunction and geometry.

4.1. Limitations

SARS-CoV-2 pandemic impacted severely on enrolment, and on the availability of CMR slots for this study, therefore loss of patients at follow-up is mainly justified by a time-bias rather than a selection bias. Also, we cannot comment on possible further changes in LV dimensions and geometry after a longer follow-up, or on the prognostic impact of our findings.

In the present work we did not explore changes in the extracellular matrix of the remote (salvaged) myocardium in patients with STEMI and its association with adverse LV remodelling, using mapping technique and extracellular volume quantification.

Adverse LV remodelling is undoubtedly complex and likely involves multiple mechanisms: excessive inflammatory response is, in addition to IS, a possible contributor [16]. Whether these tissue changes could independently predict those at risk of adverse events remains to be tested in future. Finally, we did not use the most recent techniques to quantify myocardial viability in patients with acute infarction by means of manganese-enhanced-CMR, a measure of intracellular calcium handling, which permits to differentiate scarred from stunned myocardium [9]; however, the choice of not performing baseline CMR in the acute phase should have allowed sufficient time for stunning to resolve.

5. Conclusions

The prevalence of LV-REM$_{EDV}$ observed in the present study, as assessed by CMR in a contemporary population, is lower than that reported using echocardiography in earlier studies (19 vs 30%). Our findings suggest that LV-REM$_{EDV}$ is not necessarily "adverse", but rather "compensatory" and linked to increased LV-EF at follow-up.

Conversely, LV-REM$_{ESV}$ should be considered "adverse" and associated to reduced LV-EF at 6-month follow-up. IS and LGE transmural extent, assessed by CMR, are the most important drivers of adverse LV-REM. Further studies are necessary to ascertain the impact of all these definitions of LV-REM on long-term follow-up in contemporary STEMI patients.

Multivariable-adjusted predictors of Left Ventricular Adverse Remodeling
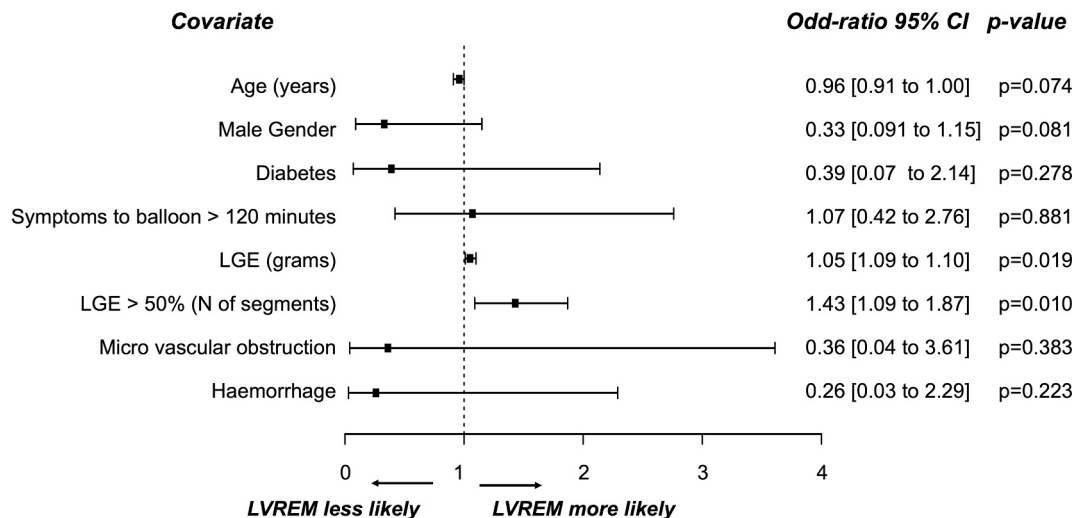

Fig. 4. Multivariable-adjusted predictors of LVREM.
LV-REM was defined as 2 standard deviations above normal values of ESV index at 6-months follow-up.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.11.006.

Authors statement

All authors takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

Declaration of Competing Interest

None.

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