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ORIGINAL ARTICLE

Functional classification of left ventricular remodelling: prognostic relevance in myocardial infarction

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Abstract

Aims The current definition of post ST-segment elevation myocardial infarction (STEMI) left ventricular (LV) remodelling is purely structural (LV dilatation) and does not consider LV function (ejection fraction, EF), even though it is known to be a predictor of long-term post-STEMI outcome. This study aimed to reclassify LV remodelling after STEMI by integrating LV dilatation and function (LVEF) and to investigate the prognostic implications.

Methods and results Data from an ongoing registry of STEMI patients who were treated with primary percutaneous coronary intervention (PCI) were retrospectively evaluated. Four distinct remodelling subgroups were identified: (i) no LV dilatation, no LVEF impairment,(ii) no LV dilatation but LVEF impairment, (iii) LV dilatation but no LVEF impairment, and (iv) LV dilatation and LVEF impairment. The impact of functional LV remodelling on outcomes was analysed. A total of 2346 patients were studied (mean age 60 ± 11 years, 76% men). During a median follow-up of 76 (interquartile range 52 to 107) months, 282 (12%) died, while the composite of death and heart failure hospitalization occurred in 305 (13%) patients. Those with LV remodelling and LVEF impairment had a significantly lower survival rate ($P < 0.001$) and event-free survival rate ($P < 0.001$) compared with other functional LV remodelling groups.

Conclusions Employing a functional LV post-infarct remodelling classification has the potential to improve risk stratification beyond structural LV remodelling alone. Identification of patients with the worst prognosis by using a functional LV remodelling approach may allow institution of early preventative therapies.

Keywords STEMI; remodelling; mortality; HF hospitalization; prognosis

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Introduction

Left ventricular (LV) dilatation after myocardial infarction (MI) is defined as adverse LV remodelling.[1] Such LV remodelling after ST-segment elevation MI (STEMI) is characterized by a pathologic cascade comprising inflammation and fibrosis, cardiomyocyte loss leading to increased wall stress and subsequent LV dilatation.[2] Compared with the era before primary percutaneous coronary intervention (PCI) and the widespread use of angiotensin-converting enzyme inhibitors (ACEi)/angiotensin-receptor blocker (ARB),[3] the prevalence of LV remodelling after STEMI has markedly declined.[4,5] When LV remodelling does occur post-STEMI, it is still associated with worse long-term prognosis[4,5] although the impact is less than that described in earlier series.[6] Impairment of LV function after STEMI is less frequently observed in patients treated with primary PCI as compared with thrombolysis,[7,8] but likewise, retains a robust link to post-infarct outcomes including all-cause mortality and heart failure (HF) readmissions.[9] Both LV post-infarct remodelling and LV function impairment are therefore associated with adverse long-term outcomes (e.g. all-cause mortality and

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HF hospitalization[4,5,9,10]), but are usually considered in isolation.

Whether 'functional LV remodelling', that is, remodelling defined by integrating LV post-infarct remodelling and impairment in LV function on two-dimensional (2D) echocardiography, can provide superior prognostic information over LV structural remodelling alone, is unknown. In this study, we therefore investigated the association between functional LV remodelling and all-cause mortality and the composite endpoint of all-cause mortality and HF hospitalization by using data from a large, contemporary registry of STEMI patients who were treated with primary PCI and optimal medical therapy.

Methods

Study population and data collection

Patients with STEMI who were treated with primary PCI and optimal medical therapy at the Leiden University Medical Centre from September 2004 to December 2019, were included from an ongoing registry (MISSION!).[11] All patients were treated according to a standardized institutional protocol for management of patients with STEMI, which is based on contemporary European Society of Cardiology (ESC) guidelines.[12] Previous comorbidities including hypertension, hyperlipidaemia, family history of coronary artery disease (CAD), diabetes mellitus (DM), and previous MI were collected as last recorded in the MISSION! database before the index event in the current study. Clinical and echocardiographic data used in the current study were collected from the departmental information system (EPD-Vision, Leiden University Medical Centre, Leiden, The Netherlands) for routine clinical purposes and were retrospectively analysed.

The primary endpoint was all-cause mortality, while the composite secondary endpoint comprised all-cause mortality and HF hospitalization, analysed as the time to the first occurrence. Survival data were collected via municipal registries and telephonic follow-up, while data on HF hospitalization were acquired by review of medical records which were archived in the departmental information system (EPD-Vision, EPD-Vision, Leiden University Medical Centre, Leiden, The Netherlands). HF hospitalization was defined as admission for worsening HF which required intensification of intravenous diuretic or device therapy implantation specifically for HF. Haemodynamically stable patients who were admitted for elective CRT implantation were not included in the endpoint of 'worsening HF'. Follow-up time was calculated from the date of echocardiography at 6 months post-STEMI and patients who died before 6 months after STEMI, or who were lost to follow-up, were excluded because post-infarct LV remodelling could, by definition, not be diagnosed in them. All patients were followed up until occurrence of the endpoint, loss of follow-up or December 2019. All data used in the current study were collected for routine clinical purposes and handled anonymously. Written informed consent was waived by the Institutional Review Board on a patient level. The investigation conforms with the principles outlined in the *Declaration of Helsinki*.[13]

Echocardiographic data acquisition

According to the institutional protocol, all patients underwent transthoracic echocardiography within 48 h of admission, as well as at 3, 6, and 12 month follow-up visits. Patients were imaged in the left lateral decubitus position using a commercially available echocardiography system (Vivid 7, E9 and E95, GE Vingmed Ultrasound, Horten, Norway). M-mode and 2D images were obtained and saved in cine-loop format. Echocardiographic loops were digitally archived for off-line analysis (EchoPac 202 and 203, GE Vingmed Ultrasound, Horten, Norway).

The LV end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were measured on the apical, two-chamber and four-chamber views using Simpson's biplane method and LVEF was derived.[14] LV mass was calculated with the linear method and indexed for body surface area.[14] Pulsed-wave Doppler of the mitral valve inflow was obtained by placing the Doppler sample volume between the tips of the mitral leaflets. Peak early (E) and late (A) diastolic velocities and deceleration time (DT) were recorded from the transmitral spectral trace. The e′ was measured on tissue Doppler traces from the basal septal and lateral segments and the E/e′ ratio was calculated. Mitral regurgitation was evaluated and graded according to current recommendations.[15,16]

Functional classification of left ventricular remodelling pattern

We developed a novel classification system for the interaction of LV post-infarct remodelling and LV systolic function, comprising changes in LVEDV and LVEF from baseline to 6 months post-STEMI. LV post-infarct remodelling was defined as LV dilatation (LVEDV increase of $\geq$20%),[4,5] while a significant change in LVEF was identified with a penalized spline curve analysis investigating the hazard ratio (HR) change for individual study endpoints across the range of absolute change in LVEF (*Figure 1*). An absolute reduction of 5% in LVEF at 6 months post-STEMI, derived from spline curve analysis, represents the value where the lower limit of the 95% confidence interval (CI) of the HR is greater than unity and was therefore considered as cut-off value to identify a significant LVEF reduction. Four distinct functional LV remodelling

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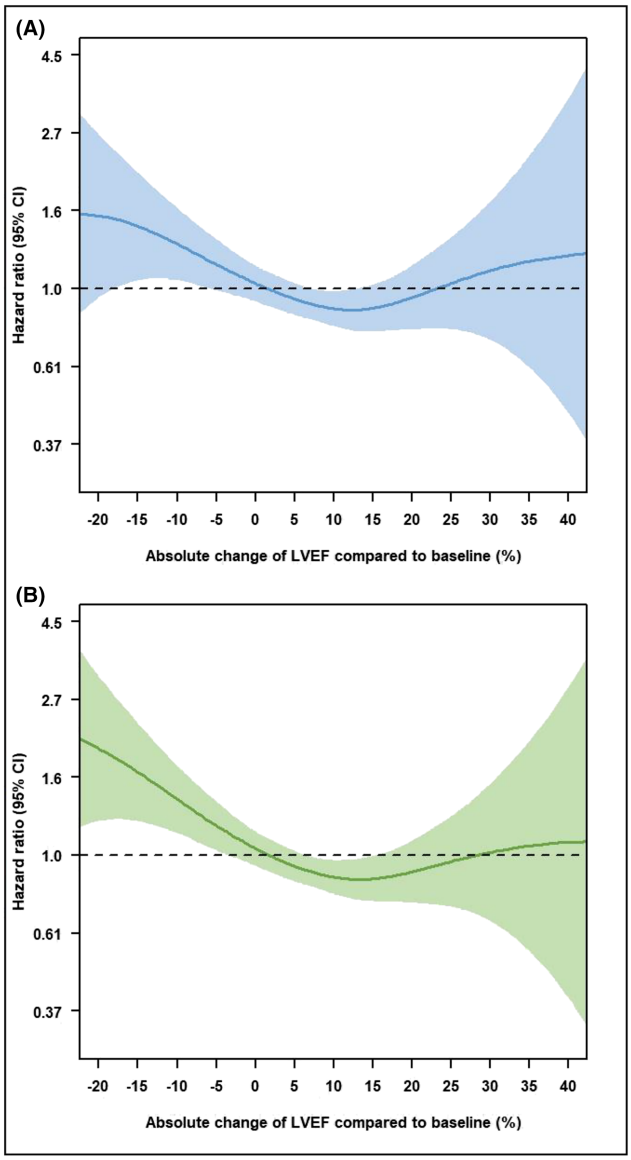
Figure 1 Spline curves for all-cause mortality (A) and the composite of all-cause mortality and HF hospitalization (B) across a range of absolute change in LVEF, plotted as a hazard ratio with overlaid 95% confidence intervals. CI, confidence interval; HF, heart failure; LVEF, left ventricular ejection fraction.



groups were defined as follows: (i) no LV dilatation, no LVEF impairment that included patients without LVEDV increase of ≥20% and no absolute reduction in LVEF of >5%; (ii) no LV dilatation but LVEF impairment that included patients without LVEDV increase of ≥20% but with absolute reduction in LVEF of >5%; (iii) LV dilatation but no LVEF impairment, comprising patients with LVEDV increase of ≥20% and no absolute reduction in LVEF of >5%; and (iv) LV dilatation and LVEF impairment that consisted of patients with LVEDV increase of ≥20% and absolute reduction in LVEF of >5%.

Statistical analysis

Continuous variables are presented as mean ± standard deviation when normally distributed (assessed by the Shapiro–Wilk test and distribution histograms) and as median [and interquartile range (IQR)] when not normally distributed. Categorical variables are presented as frequencies and percentages. Differences in continuous variables across the LV remodelling groups were evaluated using one-way ANOVA with Bonferroni correction (Jonckheere–Terpstra trend tests when indicated), while differences in categorical variables were compared by χ^2 tests (Fisher's exact test when indicated). Survival analysis, including estimation of mean survival time and event-free survival time, was performed with the Kaplan–Meier method and differences across the functional LV remodelling groups were compared with log-rank tests, including pairwise comparisons. Univariable and multivariable Cox proportional hazard regression analyses were used to determine the relationship between individual variables and the study endpoints. All continuous variables were assessed per one unit change in each variable. Multivariable analysis included variables, which showed significant association on univariable analysis. Because the definition of functional LV remodelling groups was predicated on LVEDV and LVEF, conventional echocardiographic parameters were excluded from multivariable analysis to avoid co-linearity. Incremental value of the functional classification of LV remodelling over the baseline clinical model (which comprised variables associated with primary and secondary endpoints in univariable Cox regression analysis) was investigated using the likelihood ratio test. Global χ^2 values were computed and compared. Additional receiver-operating characteristic curves and Harrell's concordance index analysis were conducted to assess the incremental model discriminative value.

All statistical tests were two-sided, and a P value of <0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS for Windows version 25.0 (IBM Corporation, Armonk, New York, USA) and R version 4.0.0 (survival package v3.1-12, splines2 package v0.3.1, Greg package v1.3.4, R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline patient characteristics

A total of 2346 patients were included (mean age 60 ± 11 years, 76% men). Baseline characteristics of the overall population and functional LV remodelling pattern groups are summarized in *Table 1*. The baseline characteristics of patients who survived up to 6 months and beyond post-STEMI,

Table 1 Baseline patient characteristics

	Overall population (n = 2346)	Group I (n = 1485)	Group II (n = 173)	Group III (n = 594)	Group IV (n = 94)	P value
Age (years)	60 ± 11	60 ± 11	60 ± 11	61 ± 12	63 ± 11	0.129
Male, n (%)	1793 (76)	1127 (76)	134 (78)	462 (78)	70 (75)	0.768
BMI (kg/m^2)	26.6 ± 3.9	26.6 ± 4.0	26.3 ± 3.5	26.6 ± 3.9	26.9 ± 4.3	0.776
BSA (m^2)	1.99 ± 0.21	1.99 ± 0.21	2.00 ± 0.20	1.99 ± 0.21	2.00 ± 0.21	0.809
Current smoker, n (%)	1076 (46)	683 (46)	79 (46)	272 (46)	42 (46)	0.998
Ex-smoker, n (%)	291 (12)	190 (13)	18 (10)	71 (12)	12 (13)	0.807
Hypertension, n (%)	832 (35)	510 (34)[d]	72 (42)	202 (34)[d]	48 (51)[a,c]	0.003
Hyperlipidaemia, n (%)	479 (20)	302 (20)	30 (17)	125 (21)	22 (23)	0.676
Family history of CAD, n (%)	1009 (43)	648 (44)	75 (44)	256 (44)	30 (33)	0.223
DM, n (%)	218 (9)	137 (9)	10 (6)	58 (10)	13 (14)	0.173
Previous MI, n (%)	152 (6)	98 (7)	10 (6)	37 (6)	7 (7)	0.945
Admission heart rate (bpm)	74 ± 18	73 ± 18	72 ± 18	75 ± 19	77 ± 18	0.161
Admission SBP (mmHg)	135 ± 25	134 ± 24	137 ± 26	136 ± 25	135 ± 26	0.409
Admission DBP (mmHg)	81 ± 16	81 ± 15	82 ± 17	81 ± 16	81 ± 16	0.559
Killip class, n (%)						0.403
I	2241 (95)	1424 (96)	164 (95)	566 (95)	87 (93)	
II	64 (3)	40 (3)	6 (3)	13 (2)	5 (5)	
III	10 (1)	3 (<1)	1 (1)	5 (1)	1 (1)	
IV	31 (1)	18 (1)	2 (1)	10 (2)	1 (1)	
Peak TnI (ng/mL)	3.4 (1.3–7.1)	3.0 (1.2–6.1)	4.3 (1.4–7.3)	4.6 (1.7–9.0)	6.3 (3.2–13)	<0.001
eGFR (mL/min/1.73 m^2)	86.4 ± 17.6	86.8 ± 17.4	87.2 ± 16.7	85.4 ± 18.3	83.4 ± 18.0	0.125
LM/LAD culprit vessel, n (%)	1054 (45)	663 (45)[b]	61 (35)[a,c,d]	280 (47)	50 (53)	0.016
Multivessel disease, n (%)	1242 (53)	789 (53)	91 (53)	308 (52)	54 (57)	0.780
Discharge heart rate (bpm)	70 ± 12	69 ± 12[c]	69 ± 12	71 ± 12[a]	72 ± 12	0.005
Discharge SBP (mmHg)	115 ± 16	116 ± 16	116 ± 15	114 ± 17	113 ± 12	0.037
Discharge DBP (mmHg)	69 ± 11	70 ± 11	69 ± 11	69 ± 10	69 ± 10	0.475
DAPT, n (%)	2272 (97)	1446 (97)	168 (97)	569 (96)	89 (95)	0.144
ACEi/ARB, n (%)	2282 (97)	1445 (97)	168 (97)	579 (97)	90 (96)	0.787
Statin, n (%)	2331 (99)	1474 (99)	172 (99)	591 (99)	94 (100)	0.890
Beta-blocker, n (%)	2218 (94)	1409 (95)	163 (94)	557 (94)	89 (95)	0.720
LV mass (g)	202 ± 59	201 ± 60	208 ± 62	202 ± 57	213 ± 57	0.180
LVMI (g/m^2)	101 ± 27	101 ± 28	104 ± 26	102 ± 27	106 ± 27	0.166
LVEDV (mL)	102 ± 32	108 ± 33[c,d]	113 ± 34[c,d]	87 ± 25[a,b]	96 ± 33[a,b]	<0.001
LVESV (mL)	53 ± 23	56 ± 24[e]	50 ± 22[e]	48 ± 18[e]	48 ± 22[e]	<0.001
LVEF (%)	49 ± 10	48 ± 9[e]	57 ± 10[e]	46 ± 9[e]	51 ± 10[e]	<0.001
E/A	0.99 ± 0.39	0.99 ± 0.38	0.98 ± 0.29	0.96 ± 0.39	1.05 ± 0.58	0.096
DT time (ms)	209 ± 70	212 ± 70[d]	212 ± 80	204 ± 69	189 ± 67[a]	0.005
E/e′	11.9 ± 4.8	11.7 ± 4.7	12.1 ± 4.9	12.2 ± 4.7	12.9 ± 6.2	0.024
MR severity, n (%)						0.635
None	1373 (58)	851 (58)	110 (64)	357 (60)	55 (58)	
Mild	711 (30)	452 (31)	46 (27)	182 (31)	31 (33)	
Moderate to severe	237 (10)	160 (11)	17 (10)	52 (9)	8 (8)	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; DAPT, dual-antiplatelet therapy; DBP, diastolic blood pressure; DM, diabetes mellitus; DT, deceleration time; E/A, mitral valve early and late inflow velocity ratio; E/e′, mitral valve early inflow and annular early velocity ratio; eGFR, estimated glomerular filtration rate; LAD, left anterior descending coronary artery; LM, left mainstem; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index; MI, myocardial infarction; MR, mitral regurgitation; SBP, systolic blood pressure; TnI, troponin I.
Values are mean ± SD, n (%), or median (interquartile range).
[a] $P < 0.05$ vs. Group I,
[b] $P < 0.05$ vs. Group II,
[c] $P < 0.05$ vs. Group III,
[d] $P < 0.05$ vs. Group IV,
[e] $P < 0.05$ vs. other groups.

and those who did not are presented in Supporting information, *Table S1*.

At 6 months follow-up, 1485 (63%) patients demonstrated no LV remodelling and no impairment in LVEF (Group I), while 173 (7%) experienced no LV remodelling but impairment in LVEF (Group II). LV remodelling without impairment in LVEF was observed in 594 (25%) patients (Group III), whereas 94 (4%) patients showed LV remodelling and impairment in LVEF (Group IV).

Myocardial damage, as assessed by the troponin rise during the acute event, increased from Groups I to IV ($P < 0.001$). Patients in Groups I, III, and IV were more likely to have the left main coronary artery or left anterior descending coronary artery as the culprit vessel (45%, 47%, and 53%,

respectively), compared with Group II (35%, $P < 0.05$ vs. other groups).

Baseline LVEDV was similar for patients in Groups I and II, but significantly larger in Groups III and IV ($P < 0.05$ vs. Groups III and IV). LVEF at baseline was significantly lower for patients in Groups I and III compared with patients in Groups II and IV ($P < 0.05$). There were no significant differences in discharge medication between functional LV remodelling groups.

Functional left ventricular remodelling pattern and all-cause mortality

During a median follow-up of 76 (IQR 52 to 107) months, 282 (12%) patients died (primary endpoint). Patients in Group IV (LV remodelling and impairment in LVEF) experienced a higher mortality (29%) compared with the other functional LV remodelling groups ($P < 0.05$ vs. other groups) (*Figure 2A*). Cumulative event rates for all-cause mortality at 120 months were 16%, 16%, 20%, and 32% for Groups I, II, III, and IV, respectively (*Figure 3A*). Patients in Group IV had a significantly lower survival rate compared to other functional LV remodelling groups (log-rank test with pairwise comparisons, $P < 0.001$ vs. Group I, $P = 0.003$ vs. Group II, $P < 0.001$ vs. Group III). Additional survival analysis with Kaplan–Meier curves for all-cause mortality and the composite of all-cause mortality and HF hospitalization, stratified according to functional LV remodelling group when using a threshold of 10% absolute change in LVEF was performed (*Figure S1*).

To investigate the association between the functional LV remodelling pattern and all-cause mortality, univariable and multivariable Cox proportional hazards models were

Figure 2 The occurrence of all-cause mortality (blue circles) (A), the composite of all-cause mortality and HF hospitalization (green circles) (B) and patients without events (grey circles) across the functional LV remodelling groups. Horizontal dashed line corresponds to the LVEF threshold used for the definition of remodelling groups, while the vertical dashed line corresponds to the LVEDV value used in the definition of remodelling groups. HF, heart failure; LV, left ventricular; LVEF, LV ejection fraction; LVEDV, LV end-diastolic volume.

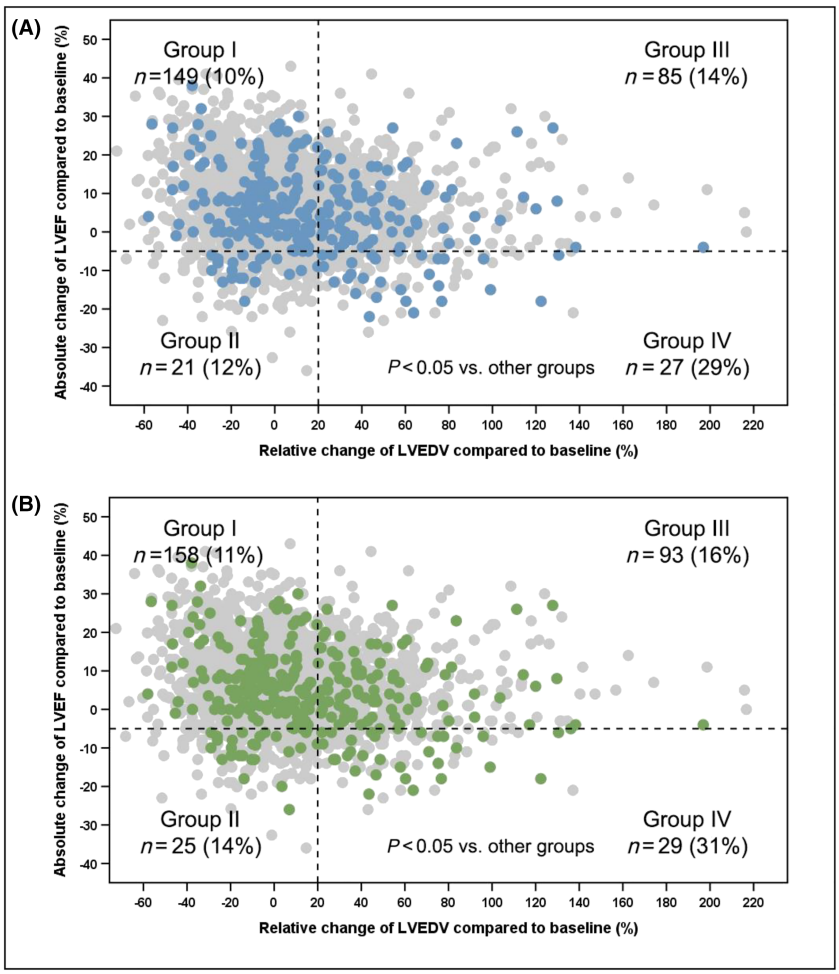
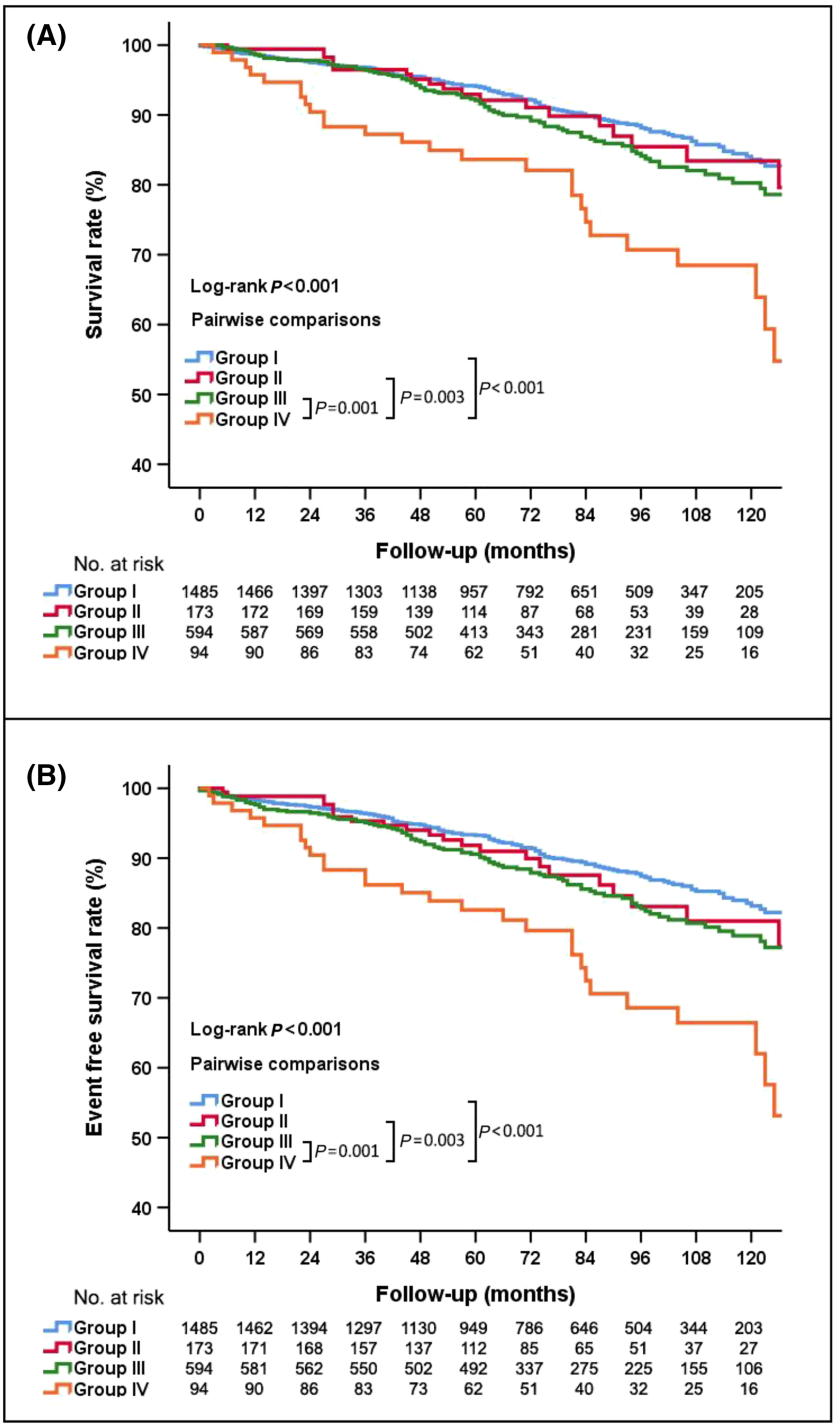


Figure 3 Kaplan–Meier curves for all-cause mortality (A) and the composite of all-cause mortality and HF hospitalization (B), stratified according to functional LV remodelling group. HF, heart failure; LV, left ventricular.



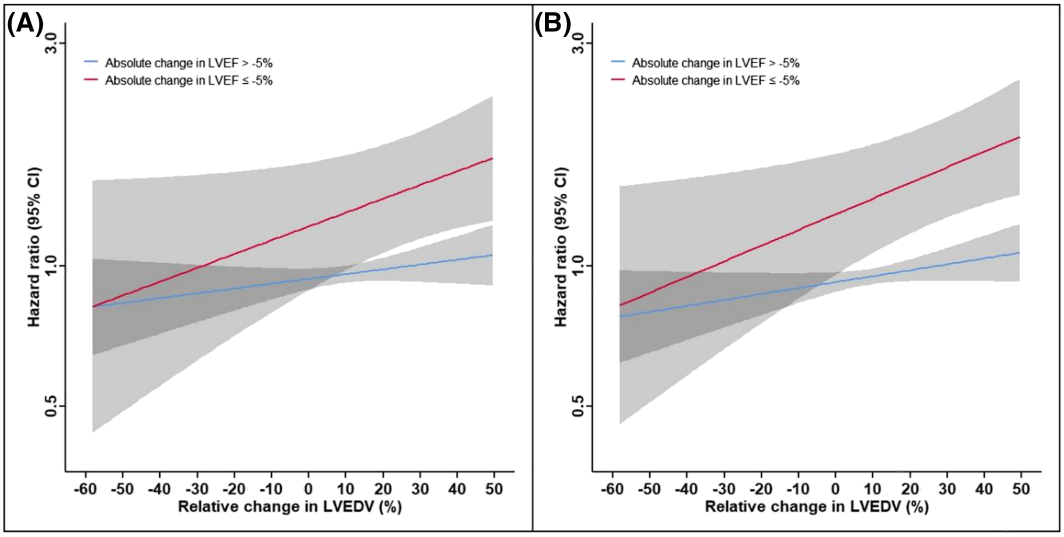
constructed (*Table 2*). All continuous variables (including the relative change in LVEDV and the absolute change in LVEF), which were used in the multivariable analysis, were formally tested for adherence to the assumption of linearity (*Table S2*). When testing this assumption with penalized spline estimation, all the continuous variables that were selected for multivariable analysis met the linearity assumption of Cox proportional hazard regression. The functional LV remodelling Group IV was significantly associated with higher risk of all-cause mortality compared with Group I (HR = 1.90, 95%

Table 2 Univariable and multivariable Cox regression analyses for all-cause mortality

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.09	1.07–1.10	<0.001	1.07	1.06–1.09	<0.001
Male	0.87	0.66–1.13	0.294	—	—	—
BMI (kg/m^2)	0.98	0.95–1.01	0.162	—	—	—
BSA (m^2)	0.30	0.17–0.52	<0.001	0.98	0.52–1.87	0.962
Current smoker	0.86	0.68–1.08	0.198	—	—	—
Ex-smoker	1.28	0.91–1.80	0.161	—	—	—
Hypertension	1.30	1.03–1.65	0.031	0.93	0.71–1.21	0.566
Hyperlipidaemia	0.99	0.74–1.32	0.917	—	—	—
Family history of CAD	0.61	0.47–0.78	<0.001	0.97	0.74–1.28	0.848
DM	2.25	1.66–3.06	<0.001	1.77	1.28–2.44	0.001
Previous MI	2.41	1.73–3.35	<0.001	1.75	1.22–2.50	0.002
Killip class ≥2	2.66	1.82–3.91	<0.001	1.27	0.83–1.93	0.266
Peak TnI (ng/mL)	1.04	1.02–1.06	<0.001	1.03	1.01–1.04	0.013
eGFR (mL/min/1.73 m^2)	0.97	0.97–0.98	<0.001	1.00	0.99–1.01	0.519
LM/LAD culprit vessel	0.95	0.75–1.20	0.667	—	—	—
Multivessel disease	1.70	1.34–2.17	<0.001	1.10	0.85–1.43	0.467
Discharge heart rate (bpm)	1.02	1.01–1.03	<0.001	1.01	1.00–1.02	0.007
Discharge SBP (mmHg)	1.00	0.99–1.01	0.596	—	—	—
Discharge DBP (mmHg)	0.98	0.97–0.99	0.003	0.99	0.98–1.00	0.042
DAPT	0.61	0.37–1.03	0.067	—	—	—
ACEi/ARB	0.39	0.23–0.65	<0.001	0.86	0.46–1.60	0.625
Statin	0.61	0.15–2.43	0.478	—	—	—
Beta-blocker	0.87	0.53–1.42	0.576	—	—	—
Functional LV remodelling Group I (reference)						
Group II	1.18	0.75–1.87	0.470	1.05	0.65–1.68	0.852
Group III	1.29	0.99–1.69	0.059	1.14	0.87–1.51	0.343
Group IV	2.71	1.79–4.09	<0.001	1.90	1.22–2.96	0.004

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; CI, confidence interval; DAPT, dual-antiplatelet therapy; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LAD, left anterior descending coronary artery; LM, left mainstem; LV, left ventricular; MI, myocardial infarction; SBP, systolic blood pressure; TnI, troponin I.

Figure 4 Interaction between change in LVEDV and change in LVEF for all-cause mortality (A) and the composite of all-cause mortality and HF hospitalization (B). HF, heart failure; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction. The interaction between these two variables is confirmed by the non-parallel nature of the curves.



CI 1.22–2.96, *P* = 0.004). In contrast, the other functional LV remodelling groups were not significantly associated with higher risk of mortality as compared with Group I. Additional analyses were performed to investigate the interaction between a relative change in LVEDV and an absolute change in LVEF as a continuous variable (*Table 4* and *Figure 3*). In this

additional analysis, we identified a significant interaction between the change in LVEDV and the change in LVEF for all-cause mortality (HR = 0.97, 95% CI 0.94–0.99, P = 0.013) (*Table 4*). The risk of all-cause mortality was greater when LVEDV increase was accompanied by LVEF reduction of 5% or more (red line in *Figure 4A*).

Functional left ventricular remodelling pattern: implications for all-cause mortality and heart failure hospitalization

During a median follow-up of 75 (IQR 51 to 106) months, the composite of all-cause mortality and HF hospitalization (secondary endpoint) occurred in 305 (13%) patients, and was observed more frequently (31%) in the functional LV remodelling Group IV, compared with the other groups ($P < 0.05$ vs. other groups) (*Figure 2B*). The cumulative event rate for the composite of all-cause mortality and HF hospitalization at 120 months was 16%, 19%, 21%, and 34% for Groups I, II, III, and IV, respectively (*Figure 3B*). Patients in Group IV had a significantly lower event free survival rate compared with other remodelling groups during follow-up (log-rank test with pairwise comparisons, $P < 0.001$ vs. Group I, $P < 0.01$ vs. Group II, $P < 0.001$ vs. Group III).

Group IV was the only functional LV remodelling group, which was significantly associated with higher risk of experiencing the composite endpoint of all-cause mortality and HF hospitalization, compared with patients in Group I (HR = 1.80, 95% CI 1.17–2.78, P = 0.007) (*Table 3*). Analysis of interaction between the change in LVEDV and the change in LVEF showed a significant association with the composite of all-cause mortality and HF hospitalization (HR = 0.97, 95% CI 0.94–0.99, P = 0.007) (*Table 4*) and the risk was increased when LVEDV increase was accompanied with by a reduction in LVEF of 5% or more (red line in *Figure 4B*).

Incremental prognostic value of functional classification of left ventricular remodelling

In order to demonstrate the incremental value of the functional classification of LV remodelling, we tested the predictive value of this model using a likelihood ratio test. LVEDV, when added to a comprehensive baseline model (including age, body surface area, hypertension, family history of CAD, DM, previous MI, Killip Class ≥2, peak troponin I, estimated glomerular filtration rate, multivessel disease, discharge heart rate, discharge diastolic blood pressure, and use of an ACEi/ARB) did not add significant incremental value for either

Table 3 Univariable and multivariable Cox regression analyses for the composite of all-cause mortality and HF hospitalization

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.08	1.07–1.09	<0.001	1.07	1.06–1.09	<0.001
Male	0.87	0.68–1.13	0.303	—	—	—
BMI (kg/m^2)	0.99	0.96–1.02	0.381	—	—	—
BSA (m^2)	0.34	0.20–0.58	<0.001	1.06	0.58–1.96	0.843
Current smoker	0.83	0.66–1.05	0.116	—	—	—
Ex-smoker	1.27	0.92–1.77	0.152	—	—	—
Hypertension	1.25	0.99–1.57	0.059	—	—	—
Hyperlipidaemia	0.97	0.73–1.28	0.822	—	—	—
Family history of CAD	0.65	0.51–0.82	<0.001	1.02	0.79–1.32	0.890
DM	2.22	1.65–2.98	<0.001	1.71	1.25–2.33	0.001
Previous MI	2.49	1.81–3.42	<0.001	1.80	1.28–2.54	0.001
Killip class ≥ 2	2.55	1.74–3.72	<0.001	1.26	0.83–1.91	0.280
Peak TnI (ng/ml)	1.05	1.03–1.07	<0.001	1.04	1.02–1.05	<0.001
eGFR (mL/min/1.73 m^2)	0.98	0.97–0.98	<0.001	1.00	0.99–1.01	0.735
LM/LAD culprit vessel	0.99	0.79–1.24	0.935	—	—	—
Multivessel disease	1.70	1.34–2.14	<0.001	1.11	0.86–1.42	0.432
Discharge heart rate (bpm)	1.02	1.01–1.03	<0.001	1.02	1.01–1.03	0.002
Discharge SBP (mmHg)	1.00	0.99–1.00	0.441	—	—	—
Discharge DBP (mmHg)	0.98	0.97–0.99	0.004	0.99	0.98–1.00	0.035
DAPT	0.61	0.37–1.00	0.051	—	—	—
ACEi/ARB	0.40	0.24–0.66	<0.001	0.79	0.43–1.44	0.440
Statin	0.40	0.13–1.25	0.116	—	—	—
Beta-blocker	0.95	0.58–1.55	0.840	—	—	—
Functional LV remodelling Group I (reference)						
Group II	1.37	0.90–2.09	0.144	1.20	0.78–1.86	0.407
Group III	1.35	1.05–1.75	0.021	1.18	0.90–1.54	0.230
Group IV	2.72	1.82–4.06	<0.001	1.81	1.17–2.78	0.007

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; CI, confidence interval; DAPT, dual-antiplatelet therapy; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LAD, left anterior descending coronary artery; LM, left mainstem; LV, left ventricular; MI, myocardial infarction; SBP, systolic blood pressure; TnI, troponin I.

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Table 4 Interaction between change in LVEDV and change in LVEF for all-cause mortality and the composite of all-cause mortality and HF hospitalization

	HR	95% CI	*P* value
All-cause mortality			
Relative change in LVEDV (10-unit change)	1.05	1.02–1.08	0.004
Absolute change in LVEF (10-unit change)	0.97	0.86–1.10	0.598
Interaction between relative change in LVEDV and absolute change in LVEF	0.97	0.94–0.99	0.013
The composite of all-cause mortality and HF hospitalization			
Relative change in LVEDV (10-unit change)	1.05	1.02–1.09	0.001
Absolute change in LVEF (10-unit change)	0.93	0.82–1.04	0.203
Interaction between relative change in LVEDV and absolute change in LVEF	0.97	0.94–0.99	0.007

CI, confidence interval; HR, hazard ratio; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction.

the primary endpoint (χ^2 difference = 3.2, P = 0.083) (*Figure* 5) or the secondary endpoint (χ^2 difference = 3.2, P = 0.083) (*Figure* 4,5) (Model 2). In contrast, adding the functional classification of LV remodelling to the baseline model (Model 3) demonstrated clear incremental benefit in risk-stratifying post-infarct patients for mortality (χ^2 difference = 5.5, P = 0.031) (*Figure* 4,5) and all-cause mortality and HF hospitalization (χ^2 difference = 6.1, P = 0.024) (*Figure* 4,5). Model discriminative values were also compared by receiver-operating characteristic curve analysis (*Figure S2*) and Harrell's concordance index of model discriminative value (*Table S3*). Receiver-operating characteristic analysis does not take into account follow-up time when calculating the sensitivity and specificity and is therefore less suitable for analysis of time-to-event data. Harrell's concordance index is a good descriptor of predictive discrimination for a single model but not generally suited to the comparison of separate models. Therefore, those analyses were not a first choice to compare model discriminative values in the present study.

Discussion

The main findings from the current study of STEMI patients who were treated with primary PCI and optimal medical therapy, are as follows: (i) 6 months post-infarct, patients who experienced both LV remodelling and LV function impairment, comprised only a relatively small percentage (4%) of the overall population; and (ii) LV dilatation accompanied by LV dysfunction is associated with the worst prognosis.

Definition and outcome implications of LV post-infarct remodelling

A 20% increase in the LVEDV (compared to baseline) is a commonly-used definition of post-infarct adverse LV remodelling,[4] and has been validated in various studies by demonstrating an association with outcomes.[5,17] The use of primary PCI and the widespread use of ACEi/ARB in STEMI management have led to a substantial decline in the incidence of LV remodelling, and more recent series demonstrate LV remodelling rates of 30–40%.[5] In some studies, an even lower incidence (<30%) of post-STEMI LV remodelling was documented when primary PCI was used as a revascularization strategy.[18,19]

Despite the declining incidence of post-STEMI LV remodelling with the use of primary PCI and guideline-directed medical therapy, the occurrence of LV remodelling is still associated with worse clinical outcomes. Bolognese *et al*. demonstrated the association of LV post-STEMI remodelling with cardiac death, nonfatal acute MI and HF hospitalization.[4] Van der Bijl *et al*. also linked LV remodelling at 6 months post-infarct to higher rates of HF hospitalization during long-term follow-up.[5]

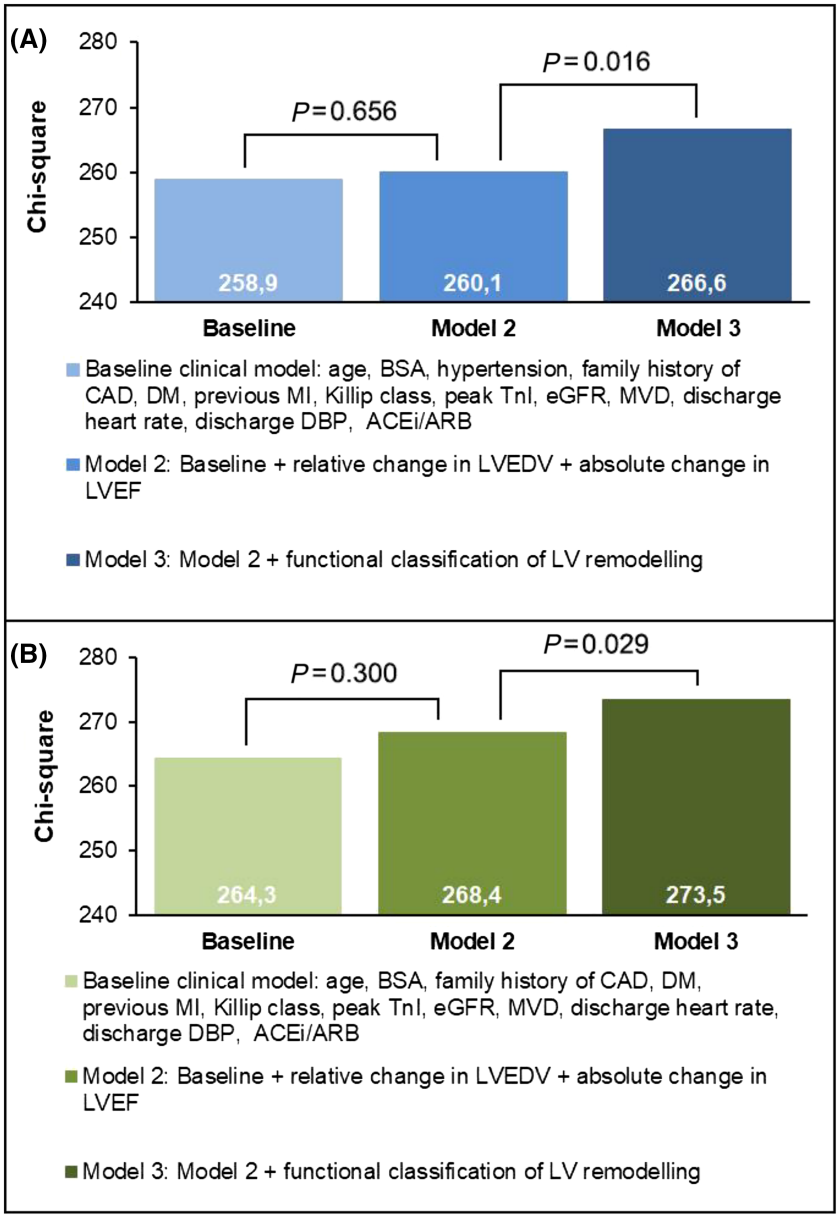
The current definition of post-STEMI LV remodelling is purely structural and does not take LV function into account, even though it is known to be a potent predictor of long-term post-STEMI outcome.[9]

Left ventricular function: incidence and prognostic impact post-STEMI

Due to its importance as a prognostic marker, echocardiographic measurement of LVEF is recommended in all STEMI patients.[12] In earlier studies from the era before thrombolysis or primary PCI, an LVEF <40% was recorded in one third of STEMI patients[20] and represented a major determinant of mortality.[20,21] Because the use of primary PCI has become widespread over the past two decades, the incidence of post-STEMI LV functional impairment has decreased dramatically. In a previous analysis of the MISSION! cohort from 2004 to 2013, the prevalence of LV functional impairment (LVEF <40%) during the index admission was only 13%, when receiving guideline-based therapy.[7] Investigators of the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial infarction (HORIZONS-AMI) Trial reported an even lower incidence of LVEF <40% in STEMI patients treated with primary PCI (<10%).[22]

It is therefore clear that LV function has a significant impact on outcome post-STEMI, and because the primary objective of

Figure 5 Likelihood ratio test for the incremental value of functional classification of LV remodelling for all-cause mortality (A) and the composite of all-cause mortality and HF hospitalization (B). BSA, body surface area; CAD, coronary artery disease; DM, diabetes mellitus; EDV, end-diastolic volume; ESV, end-systolic volume; MI, myocardial infarction; TnI, troponin I; MVD, multivessel disease; DBP, diastolic blood pressure; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LV, left ventricular.



identifying post-STEMI LV remodelling is prognostication, the integration of LV function with post-STEMI LV remodelling is logical.

Functional left ventricular remodelling post-STEMI

Rodriguez-Palomares *et al.*[23] explored post-STEMI LV remodelling and function with cardiac magnetic resonance (CMR) in 374 STEMI patients. CMR imaging was performed after 1 week, as well as 6 months post-infarct. Optimal thresholds of LVEDV increase and LVEF decrease for predicting outcome were identified by HR curves, and the primary endpoint, which was a composite of cardiovascular death, HF hospitalization, and ventricular arrhythmias, occurred most frequently in the patients with an increase in LVEDV >15% and a decrease in LVEF >3%. In summary, the investigators demonstrated that by integrating CMR-derived LVEDV and LVEF, post-STEMI patients could be risk stratified more pre-

cisely than with an LVEDV-based approach alone.[23] In a large population of post-STEMI patients, where LVEDV and LVEF were measured with 2D echocardiography, we similarly found a functional LV remodelling approach superior to a structural definition alone when performing outcome analysis.

A corollary of our data is that not all LV dilatation (classic LV post-STEMI remodelling) is associated with poor prognosis, but only that accompanied by LV functional impairment.

Left ventricular functional post-infarct remodelling: clinical implications

The application of LV functional remodelling to post-infarct patients may allow more accurate risk stratification of patients with STEMI. We are entering the era of precision medicine, which will require a greater amount of granular data in order to accurately phenotype an individual patient.[24] Because LV remodelling with impairment in LVEF at 6 months post-STEMI is associated with poor long-term outcome despite primary PCI and the use of guideline-directed medical therapy, considering additional/alternative therapeutic options, for example, angiotensin receptor-neprilysin inhibitors[25] or oral soluble guanylate cyclase stimulators[26] might be reasonable for this group of patients. Such strategies however will require prospective evaluation.

Study limitations

The current study data originate from a single centre and were retrospectively analysed. The data do however represent real world data from a large, ongoing STEMI registry. Clinical events were not adjudicated by a central committee, and echocardiographic data were not analysed by a core laboratory. Different PCI techniques could not be accounted for in our analysis, and we were unable to integrate information on change in medication during follow-up. Mortality data were only available for all-cause mortality and not for cardiac mortality. Also, HF hospitalization data were only available for patients who were readmitted to the LUMC with decompensated HF. If a patient was admitted to a secondary hospital, this event would not have been captured by the LUMC database. If a patient died or was lost to follow-up within 6 months post-infarct, LV remodelling could not be diagnosed in such an individual. The relation between adverse LV remodelling and long-term outcomes could therefore not be investigated for such patients.

Conclusions

A functional LV post-infarct remodelling classification, representing changes in LVEDV and LVEF at 6 months post-infarct, has the potential to improve risk stratification beyond a purely structural definition of LV remodelling. In addition, LV dilatation accompanied by LV dysfunction is associated with the worst prognosis. Identification of patients after STEMI with the worst prognosis (i.e. increased LVEDV and impaired LV function at 6 months post-STEMI) may allow preventative therapies to be directed at this group.

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Conflict of interest

The Department of Cardiology, Heart Lung Centre, Leiden University Medical Centre has received research grants from Abbott Vascular, Bayer, Biotronik, Bioventrix, Boston Scientific, Edwards Lifesciences, GE Healthcare, Ionis and Medtronic. Victoria Delgado received speaker fees from Abbott Vascular, Edwards Lifesciences, GE Healthcare, Medtronic, MSD, and Novartis. Nina Ajmone Marsan received speaker fees from Abbott Vascular and GE Healthcare. Jeroen J. Bax received speaker fees from Abbott Vascular.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of patients included and excluded from the present study.
Table S2. Linearity assumption of continuous predictors used in the multivariable analysis for all-cause mortality and the composite of all-cause mortality and heart failure (HF) hospitalization.
Table S3. Harrell's concordance index of model discriminative value.

Figure S1. Kaplan-Meier curves for all-cause mortality (A) and the composite of all-cause mortality and HF hospitalization (B), stratified according to functional LV remodelling group, when using a threshold of 10% absolute change in LVEF. EF, ejection fraction; HF, heart failure; LV, left ventricular.

Figure S2. Discriminative value of predictive models for all-cause mortality (A) and the composite of all-cause mortality and HF hospitalization (B). HF, heart failure; LV, left ventricular; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction.

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