CHAPTER 4

Time course, predictors and prognostic implications of significant mitral regurgitation after ST-segment elevation myocardial infarction

Elena Abate*, Georgette E. Hoogslag*, Ibtihal Al Amri, Philippe Debonnaire, Ron Wolterbeek, Jeroen J. Bax, Victoria Delgado, Nina Ajmone Marsan
* Both authors contributed equally to this work

Submitted

ABSTRACT

Background: Ischemic mitral regurgitation (MR) is a known complication of ST-segment elevation myocardial infarction (STEMI). We evaluated changes in ischemic MR after STEMI, the incidence and predictors of significant (grade ≥2) MR at 12 months and the prognostic implications of significant MR at follow-up.

Methods: STEMI patients (n=1,599; 77% male; 60 ± 12 years) treated with primary percutaneous coronary intervention underwent echocardiography <48h of admission and at 12 months. MR was graded on a 3-point scale. Mortality data were collected during long-term follow-up.

Results: At baseline, significant MR was present in 103 (6%) patients. After 12 months, MR worsened ≥1 grade in 321 (20%) patients, remained stable in 963 (60%) and improved ≥1 grade in 315 (20%). Significant MR was present in 135 patients at 12 months (8%, p=0.01 vs. baseline). Age, left ventricular end-systolic volume (LVESV) and significant MR at baseline were independently associated with significant MR at follow-up, after correcting for other clinical and echocardiographic parameters. During follow-up (median 50 months), 121 (8%) patients died (48 [40%] of cardiovascular cause). Significant MR at follow-up was independently associated with all-cause (hazard ratio [HR] 1.65, 95% confidence interval [CI] 1.02–2.99) and cardiovascular mortality (HR 2.47, 95% CI 1.24–4.92).

Conclusions: The incidence of significant MR after STEMI increases over time. Age, baseline LVESV and baseline significant MR are independently associated with significant MR at follow-up. Significant MR at 12 months was associated with all-cause and cardiovascular mortality.

INTRODUCTION

In the acute phase of ST-segment elevation myocardial infarction (STEMI), ischemic mitral regurgitation (MR) may be observed in 8% to 64% of patients.[1-3] However, functional ischemic MR is a highly dynamic lesion that may improve after coronary revascularization or impair due to progressive adverse left ventricular (LV) remodelling and tethering of the mitral leaflets.[4-6] The prognostic implications associated with ischemic MR underscore the need of accurate identification and treatment of patients with STEMI that may develop MR after STEMI.[1,7] The time course of ischemic MR in the contemporary era of primary percutaneous coronary intervention (PCI) has not been explored. In addition, identification of baseline characteristics independently associated with the development of ischemic MR at follow-up is important. Therefore, the aim of the present evaluation was 3-fold: (1) to evaluate changes of MR grade during 12 months follow-up in a contemporary cohort of STEMI patients treated with primary PCI; (2) to assess the incidence and the early predictors of significant MR (moderate and severe) at 12 months follow-up; and (3) to determine the long-term prognostic implications of significant MR at 12 months follow-up.

METHODS

Study population and data collection

Patients admitted with STEMI at the Leiden University Medical Center were included in an ongoing registry (MISSION!).[8] According to the institutional MISSION! protocol, which is based upon the most recent American College of Cardiology/American Heart Association and European Society of Cardiology guidelines, all STEMI patients were treated with primary PCI.[8-10] Optimal medical therapy was initiated promptly during hospitalization and 2-dimensional echocardiography was performed within 48 hours of admission. All patients were followed at the outpatient clinic at 3, 6 and 12 months and echocardiography was repeated at each visit. Clinical and echocardiographic data were collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, The Netherlands) and in the echocardiography database, respectively, and all data were retrospectively analyzed. For this retrospective analysis of clinically acquired data, the Institutional Review Board waived the need of patient written informed consent.

In the present evaluation, consecutive STEMI patients treated with primary PCI, in whom echocardiography was available at baseline and at 12 months follow-up, were included. The infarct-related artery was identified by electrocardiographic criteria and confirmed by coronary angiography. Final Thrombolysis In Myocardial Infarction flow was assessed during PCI. The changes over time in MR grade were assessed from baseline to 12 months follow-up.

Echocardiography

Patients were examined at rest in the left lateral decubitus position using a commercially available ultrasound system (Vivid 7 and E9, General Electric-Vingmed, Horten, Norway). Data acquisition was performed with a 3.5-MHz transducer in the standard transthoracic echocardiographic views. Standard 2-dimensional, color, pulsed wave and continuous wave Doppler images were obtained and saved in cine-loop format. Data analysis was performed offline (EchoPAC 112.0.1; GE Medical Systems, Horten, Norway).

LV end-systolic volume (LVESV) and end-diastolic volumes were measured in the apical 4- and 2-chamber view and indexed to body surface area. Using the biplane Simpson's method, LV ejection fraction was subsequently calculated and expressed as a percentage.[11] Adverse LV remodelling was defined as an increase in LVESV ≥15% at 12 months follow-up.[12-15]

LV diastolic function was assessed by positioning the Doppler sample volume between the tips of the mitral leaflets and acquiring the pulsed wave Doppler spectral signal of the mitral valve inflow. Peak early (E) and late (A) diastolic velocities and E-wave deceleration time were assessed. E' was measured with tissue Doppler imaging at the septal side of the mitral annulus in the apical 4-chamber view and E/E' ratio was calculated.[16]

Severity of MR was evaluated using a multi-parametric integrative approach including qualitative and quantitative (vena contracta width in all patients and proximal isovelocity surrface area method when feasible) assessments as currently recommended.[7,17-19] Specifically, severity of MR was graded on a 3-point scale: mild=1, moderate=2 and severe=3. Significant MR was defined as a MR grade ≥2.[20]

Follow-up and endpoint definitions

After discharge, patients were followed according to the institutional MISSION! protocol.[8] By reviewing medical records, the occurrence of adverse events between baseline and follow-up echocardiogram were collected, including coronary revascularization and myocardial re-infarction. By retrieval of survival status through municipal civil registries in December 2012, data on the occurrence of death were collected. Cause of death was obtained from medical records, data from the municipal civil registries and patients' general practitioners. The primary endpoint was all-cause mortality. The secondary endpoint was cardiovascular mortality.

Statistical analysis

Continuous data are expressed as mean ± standard deviation or median with interquartile range, where appropriate. Categorical data are expressed as frequencies and percentages. Changes in MR grade from baseline to 12 months follow-up were assessed with the McNemar's test.

Patients were divided into 2 subgroups based on the presence or absence of significant MR at 12 months follow-up. Baseline clinical and echocardiographic data were compared between subgroups with the unpaired Student's *t*-test and χ^2 test.

In addition, univariate and multivariate binary logistic regression analyses were performed to identify potential baseline predictors of significant MR at 12 months follow-up. All variables with a p-value <0.10 in univariate analyses were entered in the multivariate model. To avoid multicollinearity between univariate parameters, LVESV was chosen among other variables (peak creatine phosphokinase level, peak cardiac troponin T level, LV end-diastolic volume, LV ejection fraction) as the parameter reflecting infarct size.

To assess the association between the presence of significant MR and adverse LV remodelling at 12 months follow-up, we evaluated the phi-coefficient value and odds ratio with associated 95% confidence interval.

Finally, survival analysis was performed with the date of the follow-up echocardiogram set as follow-up onset. Event rates of the primary and secondary endpoint were analyzed and displayed using Kaplan-Meier curves. The groups were compared using Cox regression modelling for all-cause and cardiovascular mortality. Relative risks, expressed as hazard ratios with associated 95% confidence intervals, were derived from Cox regression models. To evaluate the independent association between significant MR at 12 months follow-up and the primary and secondary endpoints, multivariate Cox proportional-hazards analyses were performed. Only clinical and 12-month echocardiographic parameters were considered as potential confounders. To avoid multicollinearity, adverse LV remodelling was chosen as the parameter reflecting infarct size. All variables with a p-value <0.10 in the univariate analyses were entered in the multivariate model. In order not to overfit the model, the number of variables included in the multivariate model was limited to the number of events. Survival analyses were also performed in the group of excluded patients evaluating the independent association between significant MR at baseline and the primary endpoint (Supplemental material). The date of the index infarction was set as follow-up onset. LV end-diastolic volume was chosen as parameter reflecting infarct size.

All statistical tests were 2-sided, a p-value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS software (IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.).

RESULTS

A total of 1,935 patients were included in the current evaluation. In 332 patients (17%), 12-month follow-up echocardiographic examination was not available (in 93 patients because of death before the 12-month visit) and in 4 (0.2%), MR quantification by echocardiography was not feasible. Comparison of baseline characteristics between patients with and without echocardiographic follow-up is included in the Supplemental material and revealed a higher cardiovascular risk profile, a larger myocardial infarction

and a suboptimal medical therapy in the patients without follow-up echocardiography, explained by the inclusion of patients who died within 12 month after STEMI. The final population consisted of 1,599 patients.

Baseline characteristics

Clinical and echocardiographic characteristics of the patient population are listed in Table 1. Multivessel disease (defined as the presence >1 vessel with luminal narrowing ≥50%) was present in 54% of patients. According to our institutional protocol,[8] all patients were optimally treated with antiplatelets, beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and statins. Regarding the baseline echocardiographic characteristics, LV systolic function was mildly reduced and LV volumes were within the normal range.

Table 1. *Baseline characteristics*

	Total patient population (n=1,599)	Significant MR at 12 months follow-up (n=135)	No significant MR at 12 months follow-up (n=1,464)	p*
Clinical characteristics				
Age (years)	60 ± 12	67 ± 12	60 ± 11	<0.001
Male gender	1,229 (77%)	92 (68%)	1,137 (78%)	0.01
Killip class ≥2	64 (4%)	9 (7%)	55 (4%)	0.10
Medical history				
Current smoking	765 (48%)	44 (33%)	721 (49%)	<0.001
Diabetes	170 (11%)	16 (12%)	154 (11%)	0.63
Family history of CAD	685 (43%)	46 (34%)	639 (44%)	0.03
Hypercholesterolemia	334 (21%)	28 (21%)	306 (21%)	0.95
Hypertension	563 (35%)	55 (41%)	508 (35%)	0.17
Previous MI	137 (9%)	15 (11%)	122 (8%)	0.27
Coronary angiography				
LAD as culprit vessel	690 (43%)	64 (47%)	626 (43%)	0.30
RCA as culprit vessel	627 (39%)	44 (33%)	583 (40%)	0.10
Multivessel disease	868 (54%)	83 (62%)	785 (54%)	0.08
TIMI 2–3 flow	1,575 (99%)	132 (98%)	1,443 (99%)	0.38

Table 1. *Baseline characteristics (continued)*

	Total patient population (n=1,599)	Significant MR at 12 months follow-up (n=135)	No significant MR at 12 months follow-up (n=1,464)	p*
Laboratory tests				
Peak CPK level (U/L)	2,136 ± 2,760	3,082 ± 2,576	2,049 ± 2,761	<0.001
Peak cTnT level (μg/L)	5.4 ± 5.4	8.1 ± 6.6	5.1 ± 5.3	<0.001
Medication at discharge				
ACE-inhibitors/ARBs	1,560 (98%)	129 (96%)	1,431 (98%)	0.18
Antiplatelets	1,594 (100%)	134 (100%)	1,460 (100%)	0.99
β-Blockers	1,514 (95%)	125 (93%)	1,389 (95%)	0.35
Statins	1,586 (100%)	132 (99%)	1,454 (100%)	0.09
Echocardiography				
LVESV (mL/m^2)	28.5 ± 10.9	32.9 ± 14.6	28.1 ± 10.4	<0.001
LVEDV (mL/m^2)	53.3 ± 15.5	57.1 ± 18.4	53.0 ± 15.2	0.003
LVEF (%)	47 ± 9	43 ± 10	47 ± 9	<0.001
MR grade				<0.001
MR grade 0	961 (60%)	39 (29%)	922 (63%)	
MR grade 1	535 (34%)	56 (42%)	479 (33%)	
MR grade 2	69 (4%)	26 (19%)	43 (3%)	
MR grade 3	34 (2%)	14 (10%)	20 (1%)	
E/A ratio	0.99 ± 0.39	1.12 ± 0.60	0.97 ± 0.36	0.009
DT (ms)	212 ± 74	211 ± 89	212 ± 73	0.84
E/E' ratio	12.8 ± 4.5	14.9 ± 5.6	12.6 ± 4.3	<0.001

ACE = angiotensin-converting enzyme; *ARB* = angiotensin receptor blocker; *CAD* = coronary artery disease; *CPK* = creatine phosphokinase; *cTnT* = cardiac troponin T; *DT* = deceleration time; *E/A* = mitral inflow peak early velocity (E)/mitral inflow peak late velocity (A); *E/E'* = mitral inflow peak early velocity (E)/mitral annular peak early velocity (E'); *MI* = myocardial infarction; *LAD* = left anterior descending coronary artery; *LVEDV* = left ventricular end-diastolic volume; *LVEF* = left ventricular ejection fraction; *LVESV* = left ventricular end-systolic volume; *MR* = mitral regurgitation; *RCA* = right coronary artery; *TIMI* = Thrombolysis In Myocardial Infarction.
Data are presented as mean ± standard deviation or as number (percentage).
* p-values are given for the comparisons of patients with and without significant mitral regurgitation (MR) at 12 months follow-up (defined as grade ≥2).

Time course of mitral regurgitation after acute myocardial infarction

At baseline, 961 (60%) patients showed no MR, 535 (34%) patients had MR grade 1, and significant MR (grade ≥2) was present in 103 (6%) patients. Figure 1 shows the evolution of MR grade from baseline to 12 months follow-up. At 12 months follow-up, MR improved ≥1 grade in 315 (20%) patients. On the other hand, MR grade remained stable over time in 963 (60%) patients. Moreover, MR worsened ≥1 grade in 321 (20%) patients; of note, 39 (4%) patients with no MR at baseline and 56 (10%) patients with MR grade 1 at baseline developed MR grade ≥2 at 12 months. Eventually, significant MR was present in 135 patients at 12 months follow-up (8%, p=0.01 compared to baseline).

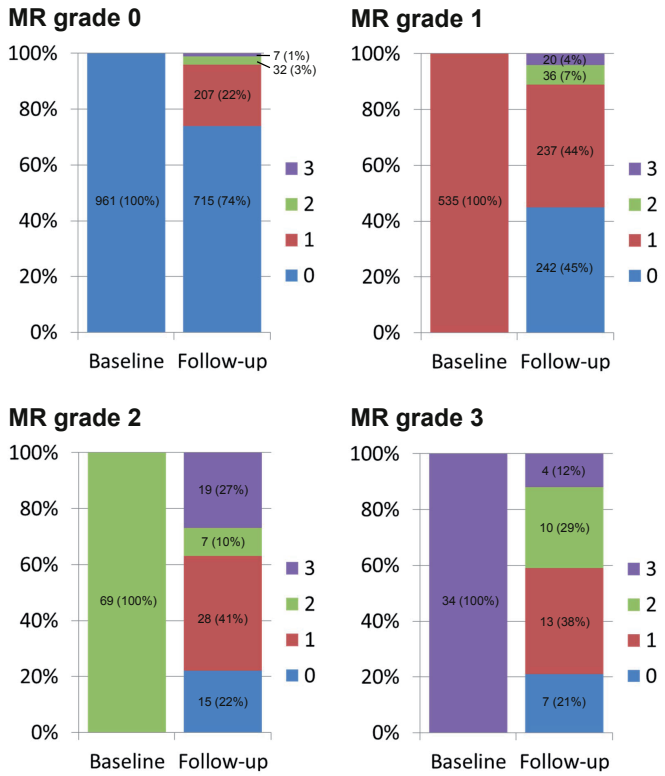

Figure 1. Time course of MR grade after STEMI from baseline to 12 months follow-up.
The patient population was divided according to MR grade at baseline (upper left panel, MR grade 0 n=961 [60% of the total population]; upper right panel, MR grade 1 n=535 [34%]; lower left panel, MR grade 2 n=69 [4%]; lower right panel, MR grade 3 n=34 [2%]).
MR = mitral regurgitation; *STEMI* = ST-segment elevation myocardial infarction.

Significant mitral regurgitation at follow-up

The clinical and echocardiographic characteristics of patients with and without significant MR at 12 months follow-up are presented in Table 1. Patients with MR grade ≥2 were older (p<0.001) and more likely to be women (p=0.01) compared to those with MR grade <2 at

12 months. This group of patients also included less current smokers (p<0.001) and a lower prevalence of family history for coronary artery disease (p=0.03). Furthermore, patients with MR grade ≥2 showed significantly higher peak cardiac enzymes (p<0.001 for both peak creatine phosphokinase and peak cardiac troponin T levels).

Regarding baseline echocardiographic data, as compared to patients without significant MR, those with MR grade ≥2 had significantly larger LV volumes and lower LV ejection fraction (p<0.05 for all parameters). Furthermore, they demonstrated a higher grade of diastolic dysfunction measured by E/A ratio (p=0.009) and E/E' ratio (p<0.001).

At 12 months follow-up, in the group of patients that showed MR grade ≥2, 56 (42%) also demonstrated adverse LV remodelling. Conversely, among patients with MR grade <2 at 12 months, 343 (24%) showed adverse LV remodelling. The association between the presence of significant MR and adverse LV remodelling at follow-up was moderate but significant (odds ratio 2.37 [95% confidence interval 1.64–3.41]; phi-coefficient 0.12; p<0.001).

Associates of significant mitral regurgitation at follow-up

Significant baseline univariate associates of MR grade ≥2 at 12 months follow-up after STEMI were age, gender, multivessel disease, peak creatine phosphokinase level, peak cardiac troponin T level and baseline LVESV, LV end-diastolic volume, LV ejection fraction, significant MR, E/A ratio and E/E' ratio. Of note, between the baseline and follow-up echocardiogram, 180 (11%) patients were revascularized and 43 (3%) patients had a re-

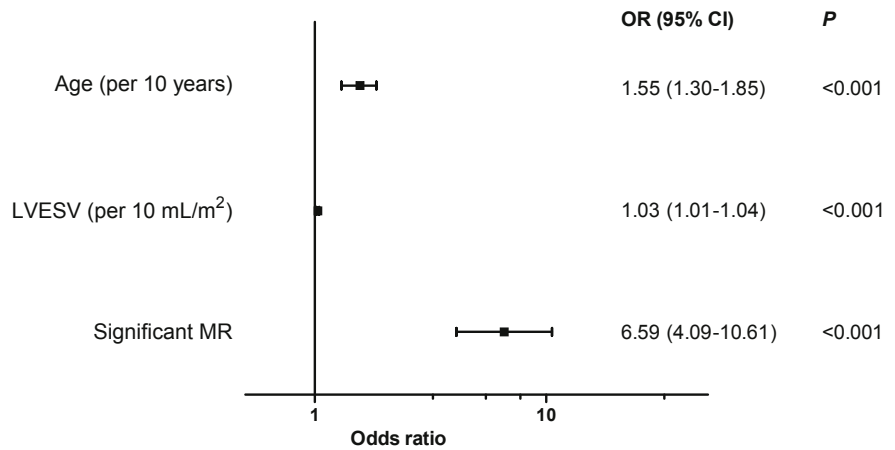

Figure 2. Prediction of significant MR.
Multivariate logistic regression analysis for the prediction of significant MR at 12 months follow-up following ST-segment elevation myocardial infarction. Significant MR was defined as grade ≥2.
CI = confidence interval; *LVESV* = left ventricular end-systolic volume; *MR* = mitral regurgitation; *OR* = odds ratio.

infarction. Both events were not significantly associated with MR grade ≥2 at follow-up (p=0.43 for revascularization and p=0.84 for re-infarction). At multivariate analysis, age, LVESV and MR grade ≥2 remained independent baseline predictors of MR grade ≥2 at 12 months while male gender and multivessel disease were not (Figure 2).

Significant mitral regurgitation and long-term outcome

During a median follow-up of 50 months, 121 (8%) patients died. The cause of death was cardiovascular in 48 (40%) patients. Non-cardiovascular deaths were mostly due to malignancy.

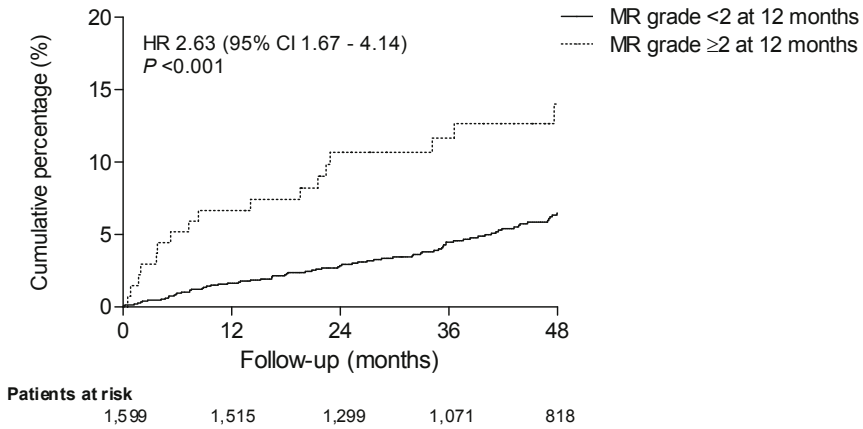

Figure 3. Kaplan-Meier curves for all-cause mortality.
Patients were divided according to the presence or absence of significant MR at 12 months follow-up (defined as grade ≥2) following ST-segment elevation myocardial infarction.
CI = confidence interval; *HR* = hazard ratio; *MR* = mitral regurgitation.

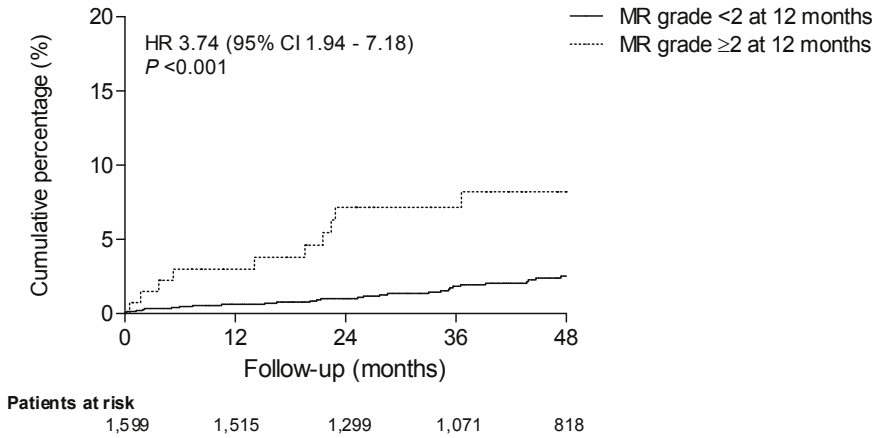

Figure 4. Kaplan-Meier curves for cardiovascular mortality.
Patients were divided according to the presence or absence of significant MR at 12 months follow-up (defined as grade ≥2) following ST-segment elevation myocardial infarction.
CI = confidence interval; *HR* = hazard ratio; *MR* = mitral regurgitation.

Kaplan-Meier curves for all-cause and cardiovascular mortality with patients divided according to the presence or absence of significant MR at 12 months follow-up are shown in Figure 3 and 4, respectively. Event rates of all-cause mortality at 12, 24, 36 and 48 months were 6.7%, 10.7%, 11.7% and 14.0%, respectively, for patients with significant MR and 1.6%, 2.9%, 4.5% and 6.5%, respectively, for patients without significant MR (p<0.001). Event rates of cardiovascular mortality at 12, 24, 36 and 48 months were 3.0%, 7.2%, 7.2% and 8.2%, respectively, for patients with significant MR and 0.6%, 1.0%, 1.8% and 2.5%, respectively, for patients without significant MR (p<0.001). Univariate analysis showed that significant MR at 12 months follow-up was associated with a significant increased risk of all-cause mortality (hazard ratio 2.63, 95% confidence interval 1.67–4.14, p<0.001; Figure 3) and cardiovascular mortality (hazard ratio 3.74, 95% confidence interval 1.94–7.18, p<0.001; Figure 4).

At multivariate level, significant MR at 12 months was independently associated with all-cause mortality (hazard ratio 1.65, 95% confidence interval 1.02–2.66) together with age, multivessel disease and diabetes (Table 2). Finally, significant MR at 12 months was also independently associated with cardiovascular mortality together with age, multivessel disease, diabetes, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers treatment and adverse LV remodelling (Table 2). Revascularization and re-infarction between the baseline and follow-up echocardiogram were not significantly associated with the primary or secondary endpoint (p=0.16 and p=0.20 for revascularization and p=0.27 and p=0.05 for re-infarction, respectively).

DISCUSSION

The main findings of the current evaluation can be summarized as follows. First, the incidence of significant MR after STEMI increases over time and significant MR was observed in 8% of STEMI patients at 12 months follow-up. Secondly, age, baseline systolic LV volume and significant MR were independent correlates of significant MR at follow-up. Lastly, significant MR at 12 months was associated with all-cause and cardiovascular mortality.

Time course of mitral regurgitation after acute myocardial infarction

The reported incidence of significant MR after STEMI is variable depending on the methodology of MR assessment (angiography versus qualitative/quantitative echocardiographic measurements) and the timing of MR evaluation (acutely before hospital discharge or during follow-up).[21] Furthermore, data on the course of ischemic MR over time after acute myocardial infarction treated with PCI are scant.[22,23] It is well known that the degree of ischemic MR can change over time, either improving due to successful revascularization (in the acute phase) or worsening due to adverse LV remodelling (in the chronic phase).[5-7,24] Neskovic et al reported a 38% incidence of MR at 1 year after acute

Table 2. *Determinants of all-cause and cardiovascular mortality following STEMI*

	Univariate		Multivariate	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
All-cause mortality				
Age (years)	1.08 (1.06–1.10)	<0.001	1.06 (1.04–1.08)	<0.001
Diabetes	2.07 (1.31–3.26)	0.002	1.88 (1.18–2.99)	0.008
Family history of CAD	0.58 (0.39–0.86)	0.006	0.85 (0.56–1.28)	0.43
Multivessel disease	2.23 (1.51–3.28)	<0.001	1.73 (1.16–2.58)	0.007
ACE-inhibitors/ARBs	0.34 (0.16–0.72)	0.005	0.57 (0.25–1.29)	0.18
β-Blockers	0.45 (0.25–0.80)	0.007	0.72 (0.37–1.37)	0.32
MR grade ≥2	2.63 (1.67–4.14)	<0.001	1.65 (1.02–2.66)	0.04
Adverse LV remodelling*	1.59 (1.09–2.33)	0.02	1.47 (0.99–2.17)	0.06
Cardiovascular mortality				
Age (years)	1.08 (1.05–1.11)	<0.001	1.06 (1.03–1.09)	<0.001
Diabetes	2.61 (1.33–5.11)	0.005	2.31 (1.17–4.57)	0.02
Multivessel disease	2.61 (1.38–4.94)	0.003	2.00 (1.04–3.85)	0.04
ACE-inhibitors/ARBs	0.23 (0.08–0.63)	0.004	0.30 (0.11–0.86)	0.03
MR grade ≥2	3.74 (1.94–7.18)	<0.001	2.47 (1.24–4.92)	0.01
Adverse LV remodelling*	2.34 (1.31–4.18)	0.004	2.12 (1.17–3.84)	0.01

ACE = angiotensin-converting enzyme; *ARB* = angiotensin receptor blocker; *CAD* = coronary artery disease; *CI* = confidence interval; *HR* = hazard ratio; *LV* = left ventricular; *MR* = mitral regurgitation; *STEMI* = ST-segment elevation myocardial infarction.
* Adverse left ventricular remodelling was defined as an increase in left ventricular end-systolic volume ≥15% at 12 months follow-up.

myocardial infarction, with 40% of patients having moderate MR and 6% severe MR.[22] However, the population was mostly treated with thrombolysis. Another study by Meris et al evaluated the degree of MR until 20 months after myocardial infarction in 610 high-risk patients with LV dysfunction, heart failure or both.[23] At 20 months follow-up, 150 (44%) patients had no detectable MR, 139 (41%) patients had mild MR and 52 (15%) patients had moderate to severe MR.[23] In the present study, although 60% of patients had no MR at baseline and MR grade remained stable in the vast majority of patients, there was also a large group of patients (20%) in whom MR worsened ≥1 grade and 4% of patients progressed from no MR to significant MR at 12 months; consequently, we noted an increase in the incidence of significant MR over time (8%, p=0.01 compared to baseline). Therefore, the present study supports the need for further surveillance of MR after STEMI since the prognostic consequences of significant MR at follow-up are not benign.

Associates of significant mitral regurgitation at follow-up

It is known that ischemic MR can be considered as a ventricular, rather than valvular, disorder.[21] In fact, local and global adverse LV remodelling are key determinants of ischemic MR progression, leading to mitral annular dilatation and papillary muscle displacement with malcoaptation of the mitral valve leaflets. In addition, the reduced LV contractility that can result after a myocardial infarction, further impairs the mitral valve closing forces and increases the grade of MR.[21] Supported by these pathophysiological mechanisms, we found significant association between the presence of significant MR and adverse LV remodelling. Furthermore, in the present study, baseline LVESV (a marker for infarct size) was a significant correlate of MR grade ≥2 at follow-up; this finding emphasizes that the LV enlargement already present in the acute phase after a myocardial infarction has a negative influence on MR progression. Moreover, the current study underscored the importance of baseline MR as correlate of MR progression: presence of MR immediately after infarction not only has per se an important prognostic value, as previously demonstrated,[1,7] but also contributes to volume overload and further LV enlargement over time, which further impairs mitral leaflet coaptation, increasing the grade of MR during follow-up.[23] Data from the Valsartan in Acute Myocardial Infarction Echo substudy showed that baseline tenting area (as a measure of leaflet tethering) and worsening by ≥1 grade in MR at 1-month follow-up were independently associated with MR progression ($p=0.018$ and $p<0.001$, respectively).[23]

Significant mitral regurgitation and outcome

Ischemic MR has shown to be an independent predictor of mortality and cardiovascular morbidity.[1,25] In the Survival And Ventricular Enlargement (SAVE) study, even mild MR predicted cardiovascular mortality during 3.5 years follow-up.[25] In another study including 711 patients with acute coronary syndrome undergoing PCI, only 58% of patients with moderate to severe MR were alive at 5 years in contrast to 97% of those without MR.[26]

However, the majority of existing data on ischemic MR and outcome did not include STEMI patients treated with primary PCI.[25,26] More recent data on STEMI patients19 confirmed the negative prognostic role of moderate to severe MR assessed in the early postinfarction period. Furthermore, Uddin et al[7] demonstrated that MR detected within 72 hours after PCI for STEMI stratified mortality risk, although it was not an independent predictor of mortality when accounting for age.

Importantly, in the previous reports MR was assessed only in the acute phase.[7,19] Therefore, the prognostic role of significant MR detected at follow-up was not well elucidated. One of the few studies evaluating the relationship between MR at follow-up and prognosis involved 496 high-risk myocardial infarction patients, including 66% with Q-wave myocardial infarction, 39% treated with thrombolytic therapy and 19% treated with primary PCI.[24] Progression of MR from baseline to 1 month was associated with a significantly increased risk of death or heart failure hospitalization; furthermore, progression of MR over 20 months follow-up was related to increased likelihood of hospitalizations

for heart failure.[24] The current study provides new data in the setting of contemporary STEMI patients treated with primary PCI, confirming that significant MR at 12 months is independently associated with all-cause mortality and cardiovascular mortality. It might therefore represent a further therapeutical target including heart failure medications, device implantation and surgical treatment.

Study limitations

The present study was retrospective and included patients from a single center. Therefore, the results of the present evaluation should be confirmed by prospective studies. Furthermore, the present study was limited by survivor bias, since patients who died before the 12 months echocardiographic assessment were excluded. Similarly, absence of echocardiographic follow-up in excluded surviving patients may also introduce a bias. However, analysis in the excluded patients is provided in the Supplemental material. Finally, patients with clearly organic MR due to flail or Barlow disease were excluded. However, there may be cases with mild forms of organic MR that cannot be differentiated from ischemic MR from transthoracic echocardiography.

CONCLUSIONS

Ischemic MR is a frequent complication after STEMI and has a dynamic nature. Age, baseline systolic LV volume and baseline significant MR are independent correlates of significant MR at 12 months follow-up. Finally, significant MR at 12 months is independently associated with all-cause and cardiovascular mortality.

REFERENCES

1. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 2001;103:1759–64.
2. Van Dantzig JM, Delemarre BJ, Koster RW, Bot H, Visser CA. Pathogenesis of mitral regurgitation in acute myocardial infarction: importance of changes in left ventricular shape and regional function. Am Heart J 1996;131:865–71.
3. Yiu SF, Enriquez-Sarano M, Tribouilloy C, Seward JB, Tajik AJ. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: a quantitative clinical study. Circulation 2000;102:1400–6.
4. Chua S, Hung J, Chung SY, Lin YC, Fu M, Wu CJ et al. Primary percutaneous coronary intervention lowers the incidence of ischemic mitral regurgitation in patients with acute ST-elevated myocardial infarction. Circ J 2010;74:2386–92.
5. Soleimani M, Khazalpour M, Cheng G, Zhang Z, Acevedo-Bolton G, Saloner DA et al. Moderate mitral regurgitation accelerates left ventricular remodeling after posterolateral myocardial infarction. Ann Thorac Surg 2011;92:1614–20.
6. Agricola E, D'Amato R, Stella S, Oppizzi M, Slavich M, Ancona MB et al. Effects of mild ischemic mitral regurgitation on ventricular remodeling and its contribution to congestive heart failure. J Am Soc Echocardiogr 2011;24:1376–82.
7. Uddin AM, Henry TD, Hodges JS, Haq Z, Pedersen WR, Harris KM. The prognostic role of mitral regurgitation after primary percutaneous coronary intervention for acute ST-elevation myocardial infarction. Catheter Cardiovasc Interv 2012;80:779–86.
8. Liem SS, van der Hoeven BL, Oemrawsingh PV, Bax JJ, van der Bom JG, Bosch J et al. MISSION!: optimization of acute and chronic care for patients with acute myocardial infarction. Am Heart J 2007;153:14 e1–11.
9. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;61:e78–140.
10. 1Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012;33:2569–2619.
11. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.
12. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987;76:44–51.
13. Himelman RB, Cassidy MM, Landzberg JS, Schiller NB. Reproducibility of quantitative two-dimensional echocardiography. Am Heart J 1988;115:425-31.
14. Hung CL, Verma A, Uno H, Shin SH, Bourgoun M, Hassanein AH et al. Longitudinal and circumferential strain rate, left ventricular remodeling, and prognosis after myocardial infarction. J Am Coll Cardiol 2010;56:1812–22.
15. Nucifora G, Marsan NA, Bertini M, Delgado V, Siebelink HM, van Werkhoven JM et al. Reduced left ventricular torsion early after myocardial infarction is related to left ventricular remodeling. Circ Cardiovasc Imaging 2010;3:433–42.
16. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. Eur J Echocardiogr 2009;10:165–93.
17. Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). Eur J Echocardiogr 2010;11:307–32.
18. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.
19. López-Pérez M, Estévez-Loureiro R, López-Sainz A, Couto-Mallón D, Soler-Martin MR, Bouzas-Mosquera A et al. Long-term prognostic value of mitral regurgitation in patients with ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention. Am J Cardiol 2014;113:907–12.
20. Mollema SA, Liem SS, Suffoletto MS, Bleeker GB, van der Hoeven BL, van de Veire NR et al. Left ventricular dyssynchrony acutely after myocardial infarction predicts left ventricular remodeling. J Am Coll Cardiol

2007;50:1532-40.
21. Bursi F, Enriquez-Sarano M, Jacobsen SJ, Roger VL. Mitral regurgitation after myocardial infarction: a review. Am J Med 2006;119:103–12.
22. Neskovic AN, Marinkovic J, Bojic M, Popovic AD. Early predictors of mitral regurgitation after acute myocardial infarction. Am J Cardiol 1999;84:329–32.
23. Meris A, Amigoni M, Verma A, Thune JJ, Kober L, Velazquez E et al. Mechanisms and predictors of mitral regurgitation after high-risk myocardial infarction. J Am Soc Echocardiogr 2012;25:535–42.
24. Amigoni M, Meris A, Thune JJ, Mangalat D, Skali H, Bourgoun M et al. Mitral regurgitation in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both: prognostic significance and relation to ventricular size and function. Eur Heart J 2007;28:326–33.
25. Lamas GA, Mitchell GF, Flaker GC, Smith SC, Jr., Gersh BJ, Basta L et al. Clinical significance of mitral regurgitation after acute myocardial infarction. Survival and ventricular enlargement investigators. Circulation 1997;96:827–33.
26. Pastorius CA, Henry TD, Harris KM. Long-term outcomes of patients with mitral regurgitation undergoing percutaneous coronary intervention. Am J Cardiol 2007;100:1218–23.

SUPPLEMENTAL MATERIAL

Differences in baseline characteristics between patients who completed echocardiographic follow-up (n=1,599) and patients who did not (n=332) are outlined in the Supplementary Table 1.

Supplementary Table 1. *Baseline characteristics of patients with and without echocardiographic follow-up*

	Echocardiographic follow-up		p*
	Yes (n=1,599)	No (n=332)	
Clinical characteristics			
Age (years)	60 ± 12	66 ± 13	<0.001
Male gender	1,229 (77%)	235 (71%)	0.02
Killip class ≥2	64 (4%)	41 (12%)	<0.001
Medical history			
Current smoking	765 (48%)	134 (42%)	0.04
Diabetes	170 (11%)	54 (16%)	0.003
Family history of CAD	685 (43%)	116 (37%)	0.03
Hypercholesterolemia	334 (21%)	65 (20%)	0.73
Hypertension	563 (35%)	140 (43%)	0.01
Previous MI	137 (9%)	35 (11%)	0.24
Coronary angiography			
LAD as culprit vessel	690 (43%)	148 (45%)	0.52
RCA as culprit vessel	627 (39%)	118 (36%)	0.27
Multivessel disease	868 (54%)	202 (61%)	0.03
TIMI 2–3 flow	1,575 (99%)	314 (95%)	<0.001
Laboratory tests			
Peak CPK level (U/L)	2,136 ± 2,760	2,368 ± 2,378	0.16
Peak cTnT level (μg/L)	5.4 ± 5.4	8.4 ± 18.9	0.004
Medication at discharge			
ACE-inhibitors/ARBs	1,560 (98%)	269 (95%)	0.002
Antiplatelets	1,594 (100%)	282 (100%)	0.99
β-Blockers	1,514 (95%)	254 (89%)	<0.001
Statins	1,586 (100%)	274 (96%)	<0.001

Supplementary Table 1. *Baseline characteristics of patients with and without echocardiographic follow-up (continued)*

	Echocardiographic follow-up		p*
	Yes	No	
	(n=1,599)	(n=332)	
Echocardiography			
LVESV (mL/m^2)	28.5 ± 10.9	29.2 ± 11.0	0.35
LVEDV (mL/m^2)	53.3 ± 15.5	53.1 ± 15.6	0.84
LVEF (%)	47 ± 9	45 ± 10	0.003
MR grade			<0.001
MR grade 0	961 (60%)	177 (55%)	
MR grade 1	535 (34%)	109 (34%)	
MR grade 2	69 (4%)	32 (10%)	
MR grade 3	34 (2%)	3 (1%)	
Significant MR (grade ≥2)	103 (6%)	35 (11%)	0.005
E/A ratio	0.99 ± 0.39	1.07 ± 0.59	0.02
DT (ms)	212 ± 74	200 ± 79	0.01
E/E' ratio	12.8 ± 4.5	15.3 ± 9.2	<0.001

ACE = angiotensin-converting enzyme; *ARB* = angiotensin receptor blocker; *CAD* = coronary artery disease; *CPK* = creatine phosphokinase; *cTnT* = cardiac troponin T; *DT* = deceleration time; *E/A* = mitral inflow peak early velocity (E)/mitral inflow peak late velocity (A); *E/E'* = mitral inflow peak early velocity (E)/mitral annular peak early velocity (E'); *MI* = myocardial infarction; *LAD* = left anterior descending coronary artery; *LVEDV* = left ventricular end-diastolic volume; *LVEF* = left ventricular ejection fraction; *LVESV* = left ventricular end-systolic volume; *MR* = mitral regurgitation; *RCA* = right coronary artery; *TIMI* = Thrombolysis In Myocardial Infarction.
Data are presented as mean ± standard deviation or as number (percentage).
* p-values are given for the comparisons of patients with echocardiographic follow-up in whom MR quantification by echocardiography was feasible and patients without echocardiographic follow-up.

In the 332 excluded patients, we performed survival analyses with all-cause mortality as endpoint and date of index infarction as follow-up onset and analyzed the impact of baseline MR on survival. At baseline 177 (55%) patients showed no MR, 109 (34%) patients had MR grade 1 and 35 (11%) patients had MR grade ≥2. In 11 patients, MR quantification was not feasible at baseline. During a median follow-up of 62 months (interquartile range 51–81 months), 135 (41%) patients died. Event rates at 12, 24, 36, 48 and 60 months were 55.8%, 58.7%, 58.7%, 61.7% and 61.7%, respectively, for patients with significant MR and 23.4%, 26.4%, 28.6%, 30.1% and 34.2%, respectively, for patients without significant MR (log-rank p<0.001). Univariate Cox regression analysis showed that significant MR at baseline was associated with a significant increased risk of all-cause mortality (hazard ratio 2.35, 95% confidence interval 1.46–3.78, p<0.001). At multivariate level, significant MR

at baseline was independently associated with all-cause mortality (hazard ratio 2.78, 95% confidence interval 1.39–5.54, p=0.004) together with age, diabetes and baseline LV end-diastolic volume (Supplementary Table 2).

Supplementary Table 2. *Determinants of all-cause mortality following STEMI in the 332 excluded patients*

	Univariate		Multivariate	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
All-cause mortality				
Age (years)	1.06 (1.04–1.07)	<0.001	1.03 (1.01–1.06)	0.01
Killip class ≥2	4.14 (2.74–6.26)	<0.001	1.55 (0.59–4.03)	0.37
Diabetes	2.75 (1.90–3.98)	<0.001	2.72 (1.54–4.79)	0.001
Family history of CAD	0.40 (0.26–0.61)	<0.001	0.84 (0.46–1.53)	0.56
Previous MI	1.62 (1.01–2.61)	0.05	1.43 (0.63–3.28)	0.40
Multivessel disease	1.81 (1.25–2.62)	0.002	1.23 (0.72–2.12)	0.45
TIMI 2–3 flow	0.18 (0.10–0.32)	<0.001	0.30 (0.07–1.30)	0.11
ACE-inhibitors/ARBs	0.36 (0.19–0.69)	0.002	0.97 (0.38–2.51)	0.95
β-Blockers	0.27 (0.17–0.44)	<0.001	0.50 (0.24–1.03)	0.06
Statins	0.38 (0.17–0.88)	0.02	0.75 (0.23–2.44)	0.63
MR grade ≥2	2.35 (1.46–3.78)	<0.001	2.78 (1.39–5.54)	0.004
LVEDV (mL/m^2)	0.98 (0.96–0.99)	0.001	0.98 (0.96–1.00)	0.04
E/E' ratio	1.05 (1.03–1.06)	<0.001	1.00 (0.98–1.03)	0.80

ACE = angiotensin-converting enzyme; *ARB* = angiotensin receptor blocker; *CAD* = coronary artery disease; *CI* = confidence interval; *E/E'* = mitral inflow peak early velocity (E)/mitral annular peak early velocity (E'); *HR* = hazard ratio; *LVEDV* = left ventricular end-diastolic volume; *MI* = myocardial infarction; *MR* = mitral regurgitation; *STEMI* = ST-segment elevation myocardial infarction; *TIMI* = Thrombolysis In Myocardial Infarction.