ORIGINAL ARTICLE

Functional mitral regurgitation after a first non-ST segment elevation acute coronary syndrome: very-long-term follow-up, prognosis and contribution to left ventricular enlargement and atrial fibrillation development

Iván J Núñez-Gil, Irene Estrada, Leopoldo Pérez de Isla, Gisela Feltes, José Alberto De Agustín, David Vivas, Ana Viana-Tejedor, Javier Escaned, Fernando Alfonso, Pilar Jiménez-Quevedo, Miguel A García-Fernández, Carlos Macaya, Antonio Fernández-Ortiz

Cardiovascular Institute, Hospital Clínico San Carlos, Madrid, Spain

Correspondence to
Dr Iván J Núñez Gil, Cardiology Department, Hospital Clínico San Carlos, Plaza Cristo Rey, Madrid 28040, Spain; ibnsky@yahoo.es

Received 16 May 2013
Revised 11 July 2013
Accepted 16 July 2013
Published Online First 19 August 2013

ABSTRACT

Objective To assess the relationship between functional mitral regurgitation (MR) after a non-ST segment elevation acute coronary syndrome (NSTSEACS) and long-term prognosis, ventricular remodelling and further development of atrial fibrillation (AF), since functional MR is common after myocardial infarction.

Design and setting Prospective cohort study conducted in a tertiary referral centre.

Patients We prospectively studied 237 patients consecutively discharged in New York Heart Association class I–II (74% men; mean age 66.1 years) after a first NSTSEACS. All underwent an ECG the first week after admission and were echocardiographically and clinically followed-up (median 6.95 years).

Results MR was detected in 95 cases (40.1%) and became an independent risk factor for the development of heart failure (HF) and major adverse cardiovascular events (MACE) (per MR degree, HR_{HF} 1.71, 95% CI 1.138 to 2.588, p=0.01; HR_{MACE} 1.49, 95% CI 1.158 to 1.921, p=0.002). Left ventricular diastolic (grade I 12.7±40.7; grade II 26.8±12.4; grade III 46.3±50.9 mL, p=0.01) and systolic (grade I 10.4±37.3; grade II 10.12±12.7; grade III 36.8±46.0 mL, p=0.02) mean volumes were higher after follow-up in patients with MR, in proportion to the initial degree of MR. In the rhythm analysis (126 patients; previously excluding those with any history of AF) during follow-up, 11.4% of patients with degree I MR, 14.3% with degree II MR and 75% with degree III MR developed AF, while only 5.1% of those with degree 0 developed AF, p<0.001.

Conclusions MR is common after an NSTSEACS. The presence and greater degree of MR confers a worse long-term prognosis after a first NSTSEACS. This can in part be explained by increased negative ventricular remodelling and increased occurrence of AF.

INTRODUCTION

Ischaemic mitral regurgitation (MR) is common after a myocardial infarction. It has been deemed to be a predictor of long-term cardiac mortality and morbidity after either a Q-wave acute myocardial infarction (AMI) or a non-ST segment elevation acute coronary syndrome (NSTSEACS).[1–7] The mechanism linking MR and outcome is only partially understood.[7 8] Beeri *et al*[9] have described the role of moderate ischaemic MR in the development of left ventricle (LV) remodelling after a myocardial infarction. However, data on the influence of functional MR on LV dilation after an NSTSEACS are scarce.[8] LV enlargement related to the development of functional MR may be one of the main links between the two entities. In addition, atrial fibrillation (AF) seems to be the most common cardiac arrhythmia seen in clinical practice.[10] AF has also been reported as a common complication after an AMI with an incidence ranging between 5% and 23%.[11 12] Based on the latter, an association of AF with short- and long-term mortality among patients with ST segment elevation acute coronary syndrome (STSEACS) and NSTSEACS has been postulated.[13]

Our objective was to assess the contemporary long-term prognosis and the relationship between the presence and severity of functional MR after an NSTSEACS episode, and the development of LV enlargement and AF.

METHODS

Between November 2003 and September 2005, 311 consecutive patients were admitted for a first NSTSEACS episode. Patients with previous NSTSEACS, hypertrophic cardiomyopathy, mitral valve/subvalvular apparatus structural disease and acute mechanical post-infarction complications were not included. Twenty patients from the study group died during hospitalisation. The 237 remaining patients were discharged from hospital in New York Heart Association functional class I–II and constituted the study group. Thirty-three died during follow-up before the interim control echocardiogram. The diagnosis of NSTSEACS was based on the European Society of Cardiology criteria. All patients were prospectively selected and followed-up.

Before discharge, all patients underwent a complete transthoracic echocardiogram, in which mitral valve anatomy and function were specifically

To cite: Núñez-Gil IJ, Estrada I, Pérez de Isla L, *et al*. *Heart* 2013;**99**: 1502–1508.

studied during a median (IQR) of 2 (1–3) days after admission. It was performed using a Philips Sonos 5500 with 2.5–3.5 MHz probes. Patients with structural disease of the mitral valve and/or subvalvular apparatus were excluded from the cohort, in order to study only those with a clear functional cause of MR. The presence and degree of MR was evaluated using the proximal isovelocity surface area method and a validated nomogram for semiquantitative estimation.[14] Left atrial and ventricular diameters were measured in the parasternal view on M mode. The ejection fraction was calculated in two-dimensional mode, in the two- and four-chamber apical views, using the Simpson biplane method. Myocardial thickening was assessed by dividing the LV up as in the 16-segment model, following the recommendations of the American Society of Echocardiography.

Cardiac catheterisation was performed according to the attending physician's preferences. The extent of coronary artery disease was characterised by the traditional diameter stenosis percentage and one-, two- or three-vessel disease classification.

After discharge, all patients were followed-up in the outpatient clinic or by telephone interview. A control echocardiogram was performed at least 1 year after the first NSTSEACS episode. Each event was recorded only once; for example, after a heart failure event, new episodes were not taken into account in the statistical analysis of major adverse cardiovascular events (MACE) (heart failure/angina-infarction/all-cause death). For all variables, the patient data were censored after the first event. Three sets of data are provided named the clinical, structural (remodelling) and rhythm arms. For the clinical arm, the full follow-up is considered. For the structural and rhythm arms, only the interim follow-up is considered (median follow-up 1126 days). Patients who were subsequently lost, died or had baseline AF were excluded from the rhythm analysis at the outset to avoid the loss of statistical power caused by the decrease in sample size secondary to lost or deceased patients years later.

Statistical analysis

The SPSS V.15 software package for Windows and Microsoft Office 2007 were used. The baseline characteristics of the patients are expressed as mean (SD), continuous variables as median (IQR), and categorical variables as an absolute figure (percentage). Between-group comparisons were performed using the Pearson χ^2 test for qualitative variables and the Student t test or Mann–Whitney U test for continuous variables,

Table 1 Baseline characteristics

Characteristic	Overall	No MR	MR	p Value
N	237	142 (59.9)	95 (40.1)	–
Age (years)*	66.1±12.9	63.8	69.8	0.007
Male	175 (73.8)	102 (71.8)	73 (69.4)	0.39
Hypertension	152 (64.1)	86 (60.5)	66 (69.4.2)	0.16
DM	70 (29.5)	34 (23.9)	36 (37.9)	0.02
Dyslipidaemia	86 (36.3)	53 (37.3)	33 (34.7)	0.68
Smoking	138 (58.2)	87 (61.2)	51 (53.7)	0.24
Atrial fibrillation	53 (22.4)	29 (20.4)	24 (25.3)	0.38
Renal insufficiency	24 (10.1)	10 (7.0)	14 (14.7)	0.054
COPD	19 (8)	12 (8.5)	7 (7.4)	0.76
Previous stroke	13 (5.5)	6 (4.2)	7 (7.4)	0.29
Previous diagnosis of CAD	49 (20.7)	25 (17.6)	24 (17.9)	0.154
Previous coronary revascularisation	37 (15.6)	16 (11.3)	21 (22.1)	0.024
ST segment depression during acute phase	124 (52.3)	66 (46.5)	58 (61.1)	0.028
Myocardial markers				
Peak CK†	400 (174.0–855.0)	399 (167.5–718.7)	404 (186.0–925.0)	0.40
Peak troponin I†	10 (2.6–23.0)	8.0 (2.4–22.0)	10.6 (3.1–23.5)	0.16
Onset ECG				
LVEF	55.69±15.0	59.59	51.03	<0.001
Wall (LV) motion segmental abnormalities	134 (56.5)	71 (50.0)	63 (66.3)	0.013
Cardiac catheterisation				
Coronary angiography during hospitalisation	212 (89.5)	130 (91.5)	82 (86.3)	0.19
Mean number of vessels	1.75±1.04	1.58±1.0	2.04±0.5	0.002
Location of significant coronary lesions				
LAD	132 (55.7)	72 (50.7)	60 (63.2)	0.059
Cx	107 (45.1)	66 (46.5)	41 (43.2)	0.61
RCA	29 (12.2)	19 (13.4)	10 (10.4)	0.51
LMA	16 (6.8)	8 (5.6)	8 (8.4)	0.40
Number of patients undergoing revascularisation procedures				
PCI	136 (57.4)	84 (59.2)	52 (54.7)	0.50
CABG	36 (15.2)	19 (13.4)	17 (17.9)	0.34

Overall (clinical arm) cohort.
Unless otherwise stated, values are number (%).
*Mean±SD.
†Median (IQR). Comparison test: Mann–Whitney U test.
CABG, coronary artery bypass graft; CAD, coronary artery disease; CK, creatine kinase; COPD, chronic obstructive pulmonary disease; Cx, circumflex coronary artery; DM, diabetes mellitus; LAD, left anterior descending coronary artery; LMA, left main coronary artery; LV, left ventricular; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PCI, percutaneous coronary intervention; RCA, right coronary artery.

as indicated by the dispersion of data. MR was classified as a dichotomous or categorical variable, depending on the analysis. To evaluate the reliability of the MR-grading method used in our laboratory and reported in this paper, intraobserver concordance (Iván J Núñez Gil) and between-observer concordance (Iván J Núñez Gil and Leopoldo Pérez de Isla) were calculated in 30 studies using the κ index. Thus, intraobserver (κ=0.91) and interobserver (κ=0.84) concordance were excellent. Long-term survival curves for the different groups were obtained using the Kaplan–Meier method, and comparisons were made using the log-rank test. The Cox proportional hazard regression model was used to analyse and select variables that were independently associated with the appearance of long-term events. An excessive number of variables in the multivariate analysis was avoided by reducing the number by using a prespecified model that included those known to be associated with prognosis and regarding the univariate findings. Thus, age (quantitative), diabetes mellitus and hypertension (present in discharge reports), kidney failure (creatinine clearance <60 mL/h according to the Cockroft–Gault formula), LV ejection fraction (LVEF), peak troponin level (quantitative), previous revascularisation, current multivessel disease (two or more vessels), AF, ventricular wall motion abnormalities (present) and MR (qualitative and quantitative) were included as covariates in the final models, and several clinical events were included as dependent variables. HR and 95% CI were calculated by backward stepwise regression analysis (Wald).

The last follow-up was conducted on 1 December 2012. The null hypothesis was rejected using a two-tailed p value <0.05 as cut-off.

RESULTS

Baseline characteristics

The mean age of the 237 patients studied was 66.1±12.9 years (29–91), and 175 (73.8%) were men. The incidence of MR was 40.1% (95 patients; 73 men). The distribution of the severity of MR, assessed on the first ECG, was: 71 patients degree I (30.0%), 15 degree II (6.3%), six degree III (2.5%) and three degree IV (1.26%). Epidemiological features and differences are depicted in table 1. On ECG, there were no differences in Q-wave development, the presence of a transient ST-segment elevation (<20 min), and the location of changes in repolarisation. However, a marked ST-segment depression was more common in the MR group. Medical therapies in patients with/without MR at the time of discharge showed no differences between the two groups (ACE inhibitors/angiotensin II receptor blocker (ARBs), β-blockers, calcium channel blockers, nitrates, diuretics, spironolactone; p>0.10). No patients in this study had the mitral valve repaired either because they had no indications for this procedure or because of the presence of contraindications or patient preference.

Coronary anatomy

A total of 212 patients (89.5%) underwent coronary angiography during the index hospitalisation. The results are displayed in table 1. The difference in the number of patients revascularised in each group did not reach significance.

Events and long-term follow-up

Patients were followed-up for a median of 2540 days (IQR 856–2843); there were no significant differences between groups (p=0.391). Admissions for unstable angina, heart failure or the combined event (MACE) were all more common in the MR group. Follow-up events are displayed in table 2 and figure 1.

Table 2 Incidence of long-term events

	No MR	MR	p Value
Clinical arm (overall)			
N (237)	142	95	–
Follow-up*	2567 (963–2894)	2010 (638–2894)	0.39
Death	30 (21.1)	23 (24.2)	0.57
Cardiovascular death	14 (9.9)	15 (15.8)	0.17
Sudden death	1 (0.7)	3 (3.2)	0.15
Acute myocardial (re) infarction	26 (18.3)	17 (17.9)	0.93
Unstable angina	27 (19.0)	28 (29.5)	0.062
CHF	16 (11.3)	17 (17.9)	0.14
MACE	54 (38.0)	56 (58.9)	0.002
Remodelling arm			
N (153)	94	59	–
Follow-up*	1107 (985–1244)	1109 (1002–1220)	0.80
Death	0	1 (1.6)	0.20
AMI	13 (13.5)	13 (22.0)	0.18
Unstable angina	16 (16.6)	21 (35.5)	0.009
CHF	8 (8.5)	12 (20.3)	0.035
Rhythm arm			
N (126)	79	47	–
Follow-up*	1106 (976–1242)	1144 (1047–1243)	0.31
AMI	10 (12.7)	11 (23.4)	0.11
Unstable angina	12 (15.2)	17 (36.2)	0.007
CHF	6 (7.6)	10 (21.3)	0.02

Unless otherwise indicated, values are number (%).
*Median (IQR) in days.
AMI, acute myocardial infarction; CHF, congestive heart failure; MACE, combined event—major adverse cardiovascular events (death or infarction or angina or heart failure); MR, mitral regurgitation.

Survival curves show that the development of MACE (figure 1A,B) and heart failure (figure 1C) depended on the presence or absence of MR and on its severity. Univariate analysis for MACE is provided in table 3. Cox regression multivariate analysis revealed age, diabetes mellitus, hypertension, previous revascularisation and the presence of functional MR to be relevant to the development of heart failure and MACE. However, only diabetes mellitus and MR were found to be independent predictors in the final multivariate analysis. The most relevant results in the multivariate analysis are shown in table 4.

Remodelling arm

A total of 153 patients were finally included in the structural analysis. Their epidemiological features were similar to those in the overall group. As shown in table 5, at baseline, LV end-systolic diameters were significantly greater, LV performance was diminished, the prevalence of LV wall motion abnormalities in the echocardiographic study was higher, and the left atrium diameter was larger in the patients with MR. No differences were found in volumes between groups at this stage.

After a similar follow-up (1108 days, IQR 995–1234), left atrial, LV end-diastolic and LV end-systolic diameters continued to be higher in the MR group compared with the group without MR. However, at that point, LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were higher in the MR group (table 5).

In addition, comparing the MR group evolution adjusted by degree of MR, we observed a significant proportional LV dilatation, with regard to mean LVEDV (figure 2A) and mean LVESV (figure 2B).

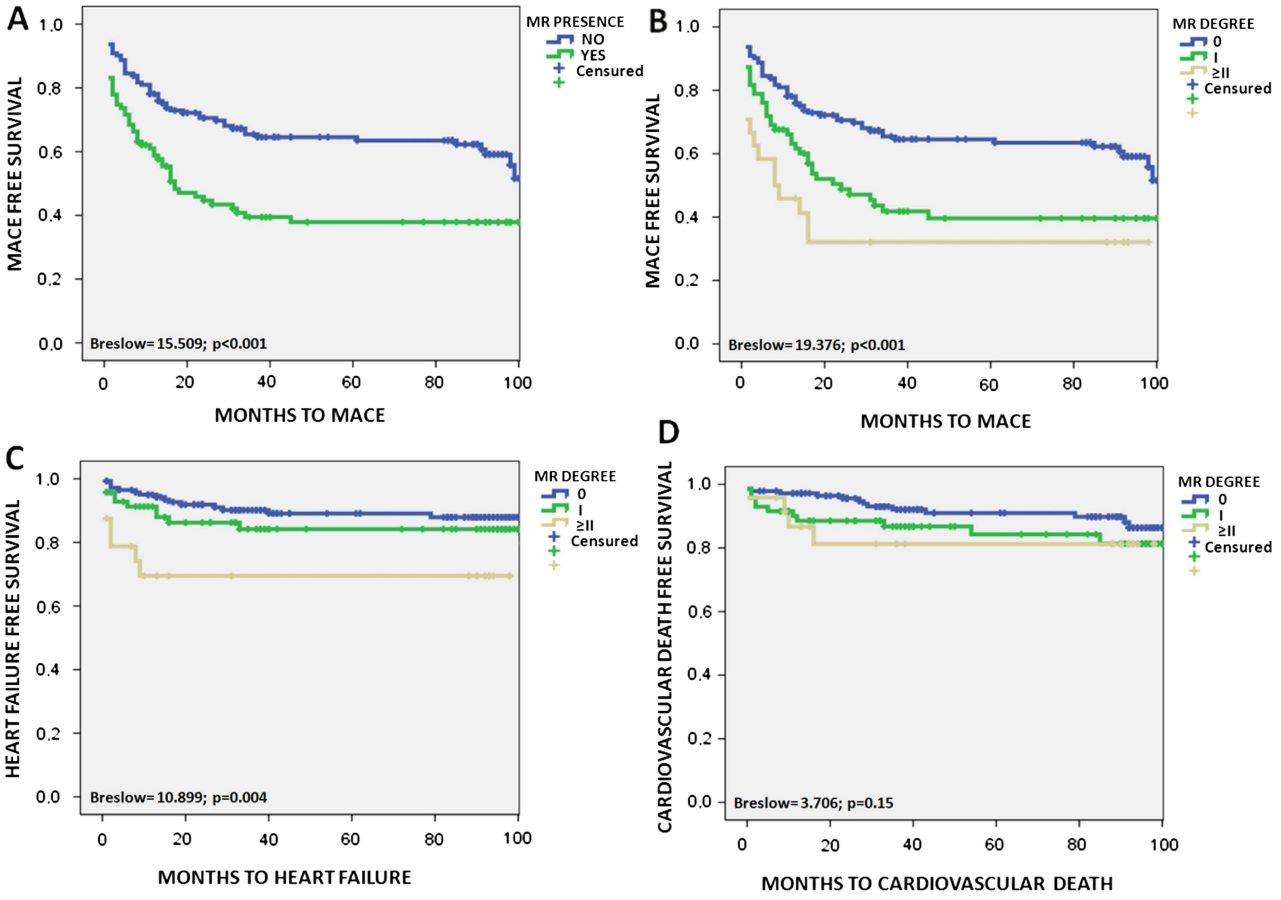

Figure 1 Clinical arm: Kaplan–Meier graphs, with Breslow analysis. (A) Long-term follow-up to hospital re-admission due to major adverse cardiovascular events (MACE) depending on the presence or absence of mitral regurgitation (MR). (B) Long-term follow-up to hospital re-admission due to MACE depending on the severity of MR. (C) Long-term follow-up to hospital re-admission due to congestive heart failure depending on the severity of the MR. (D) Long-term follow-up to cardiovascular death depending on the severity of the MR. Access the article online to view this figure in colour.

Rhythm arm

The number of patients included in this study group was 126. Baseline characteristics and discharge drugs were also similar to the overall cohort. The difference in the number of patients revascularised in each group did not reach significance. Patients were followed-up for rhythm for a median of 1126 days. During this follow-up period, no patients died (previously excluded). Admissions for AMI, unstable angina and heart failure were all more common in the MR group (table 2).

Baseline LV end-systolic and diastolic diameters were significantly greater (p=0.005, p=0.001, respectively), LV performance was diminished (LVEF 59.3±16.8% vs 51.5±15.0%, p=0.012), the prevalence of LV wall motion abnormalities in the echocardiographic study was higher (41.8% vs 61.7%, p=0.03), and the left atrial diameter was slightly larger (37.9 ±5.4 vs 42.0±8.0 mm) in the group of patients with MR.

AF was significantly more common in the MR group (19.2% vs 3.8%, p=0.009; figure 3A). In addition, comparing the MR group evolution adjusted by MR degree, we observed a statistically significant proportional AF development. Interestingly, AF appeared in 5.1% of patients with MR degree 0, 11.4% with MR degree 1, 14.3% with MR degree 2, and 75% with MR degree 3 (p<0.001) (figure 3B).

DISCUSSION

To our knowledge, this study is the first to assess the very-long-term prognostic implications of the development of MR after a first NSTSEACS. In addition, it is the first study to specifically address the relationship between MR and long-term structural and rhythm outcomes, establishing interesting relationships.

Ischaemic or functional MR occurs with a structurally preserved mitral valve as a result of an altered force balance on the leaflets. Causal mechanisms comprise annulus dilatation, ischaemia or a scar at the level of the papillary muscles, papillary muscle rupture, and most commonly, a change in the ventricular geometry causing tethering of the mitral leaflets. In addition, systolic dysfunction has been considered to be another factor that contributes to MR caused by restricted movement of the leaflets.[1 4–7 14–23] However, all the circumstances surrounding the development of ischaemic MR are still not well clarified.

In this study, larger LV systolic size, together with lower LVEF and segmental wall motion abnormalities, were more common in patients with functional MR. This suggests an effect of extensive coronary artery disease on the degree of cardiomyopathy in our patients and it is probably the factor most closely related to the development of functional MR.

Of note, although the development of ischaemic MR was associated with a worse long-term outcome, it did not show a clear worse in-hospital outcome in our series (excluding previously unstable patients or mechanical complications). This finding is logical, since progressive LV remodelling takes time to develop and the in-hospital stay is quite short.

As the protocol was not designed to evaluate this point, an alternative analysis was performed on patients with LVEF ≥ or

Table 3 Univariate analysis for MACE (combined event—major adverse cardiovascular events: death or infarction or angina or heart failure)

	No MACE	MACE	p Value*	OR	95% CI
Men	70.9%	77.3%	0.26	1.39	0.77 to 2.51
Hypertension	63.8%	64.5%	0.90	1.03	0.60 to 1.76
Diabetes mellitus	16.5%	44.5%	<0.001	4.05	2.22 to 7.39
Smoking habit	60.6%	55.5%	0.42	0.80	0.48 to 1.35
Dyslipidaemia	34.6%	38.2%	0.57	1.16	0.68 to 1.98
Renal failure	4.7%	16.4%	0.003	3.94	1.50 to 10.33
Previous coronary artery disease	12.6%	30.0%	<0.001	2.97	1.53 to 5.77
Previous revascularisation	7.1%	25.5%	<0.001	4.47	2.00 to 9.98
Cardiac catheterisation	85.0%	94.5%	0.018	3.04	1.17 to 7.93
Left main disease	3.1%	10.9%	0.018	3.76	1.17 to 12.03
LAD disease	45.7%	67.3%	0.001	2.44	1.44 to 4.15
Circumflex disease	37.8%	53.6%	0.015	1.90	1.13 to 3.19
Right coronary disease	11.8%	12.7%	0.83	1.08	0.50 to 2.37
Onset revascularisation	28.7%	28.7%	0.19	1.40	0.83 to 2.36
PCI	48.0%	47.3%	0.90	0.97	0.58 to 1.61
CABG	10.2%	20.9%	0.02	2.31	1.11 to 4.83
Onset rhythm (sinus vs atrial fibrillation)	81.9%	72.7%	0.09	0.59	0.31 to 1.09
LV segmental abnormalities	52.8%	60.9%	0.20	1.39	0.83 to 2.34
Mitral regurgitation (present)	30.7%	50.9%	<0.001	2.34	1.37 to 3.97
	No MACE		MACE		p Value†
Age (years)	63.9±13.8		68.7±11.31		0.005
Troponin I (ng/dL)	17.7±20.08		17.6±22.75		0.99
LVEF (%)	59.07±12.04		52.06±17.6		0.001
Follow-up (days)	2053.7±1032.8		1700.5±1146.0		0.013

All previous medical treatment showed no significant differences.
*χ^2 test.
†Student t test.
CABG, coronary artery bypass grafting; LAD, left anterior descendent coronary artery; LV, left ventricular; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

<45%. The results for those with LVEF ≥45% were similar to those in patients with preserved systolic function (per MR degree, HR_{MACE} 1.5, 95% CI 1.096 to 2.095, p=0.012), but with a lack of statistical significance in the cohort with depressed LVEF. These findings should be considered with caution because of the small numbers enrolled in each group.

Table 4 Multivariate (Cox-Wald) predictors of development of congestive heart failure or MACE*

	HR	95% CI	p Value
MACE			
Age (per year)	1.018	0.998 to 1.038	0.071
Diabetes mellitus	2.497	1.537 to 4.057	<0.001
Previous revascularisation	1.621	0.968 to 2.715	0.066
MR (per degree)	1.491	1.158 to 1.921	0.002
Heart failure			
Diabetes mellitus	5.347	2.374 to 12.044	<0.001
Hypertension	2.939	1.009 to 8.554	0.048
Atrial fibrillation	2.528	0.991 to 6.450	0.052
MR (per degree)	1.716	1.138 to 2.588	0.010

Long-term follow-up (median=6.95 years). See text for more details.
*Clinical arm. Variables included in the model: age (quantitative), diabetes mellitus and hypertension (present in discharge reports), kidney failure (creatinine clearance <60 mL/h according to the Cockroft–Gault formula), LVEF, peak troponin level (quantitative), previous revascularisation, current multivessel disease (two or more vessels), atrial fibrillation (or history of), ventricular wall motion abnormalities (present), and MR (qualitative and quantitative) were included as covariates.
LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; MR, mitral regurgitation.

Table 5 Echocardiographic variables (remodelling arm)

Variable	No MR	MR	p Value
Baseline			
LVEDD	46.0±6.8	50.7±7.7	0.01
LVESD	29.8±8.2	34.8±8.6	0.03
LVEF (%)	59.3±17.0	51.1±14.7	0.05
WMA	41 (43.6)	37 (62.7)	0.02
LAD (mm)	36.1±9.6	41.7±9.6	0.03
E wave peak-velocity*	64 (49.7–75.5)	74.0 (60.7–87.5)	0.03
A wave peak-velocity*	75.0 (59.0–87.0)	79.0 (57.7–98.2)	0.45
PASP (mm Hg)	38.1±17.9	36.5±17.1	0.83
LVEDV*	73.5 (54.0–90.7)	77.0 (58.0–104.5)	0.33
LVESV*	31.0 (21.2–44.0)	37.0 (21.5–51.0)	0.25
After follow-up			
LVEDD	46.7±7.8	49.4±8.8	0.05
LVESD	30.2±7.1	33.5±9.8	0.02
LVEF (%)	59.4±11.4	53.7±15.5	0.01
WMA	27 (29.0)	26 (44.1)	0.05
LAD (mm)	40.0±6.7	45.0±9.7	0.03
E wave peak velocity*	68.5 (57.5–80.7)	78 (58.5–94.0)	0.03
A wave peak velocity*	75.0 (64.5–89.0)	81.5 (66.7–109.0)	0.05
PASP (mm Hg)	27.3±6.7	32.7±12.0	0.001
LVEDV*	70.0 (56.2–99.0)	87 (66.2–125.2)	0.001
LVESV*	26.5 (20.0–34.8)	35 (23.0–68.75)	0.001

Values are number (%), mean±SD or as indicated.
*Median (IQR). Comparison test: Mann–Whitney U test.
LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; WMA, wall motion abnormalities.

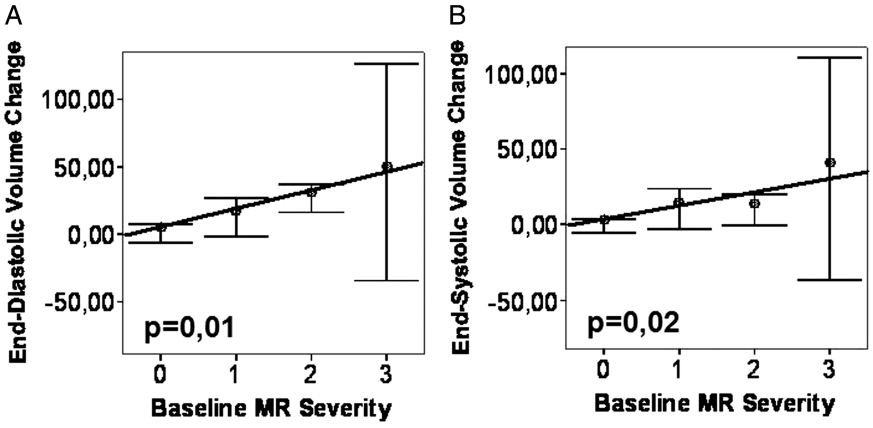

Figure 2 Remodelling arm. (A) Mean left ventricular (LV) end-diastolic volume change (mL), depending on the severity of mitral regurgitation (MR), after follow-up. (B) Mean LV end-systolic volume change (mL), depending on the severity of MR, after follow-up.

Remodelling arm

Beeri *et al*[9] described the role of moderate ischaemic MR in the development of LV enlargement in a sheep controlled model, which created a standardised moderate MR-like regurgitant flow and a provoked anteroapical infarction, which by itself does not cause MR. Moderate MR was shown to worsen post-AMI remodelling, with reduced contractility, independently of the accompanying infarction.

Furthermore, our results in humans also show that a greater severity of functional MR is associated with greater remodelling after long-term follow-up. Our patients with MR developed more complications than patients without MR, in spite of previous selection to exclude patients who died before the control ECG, as previously published elsewhere.[5 7 8 16] Therefore, identification of factors related to a bad prognosis in patients in an adequate functional class at the time of hospital discharge after the acute coronary syndrome is very important in order to optimise their therapeutic management.[24] De Bonis *et al*[25] found that, in patients with an effective repair of the functional MR, a better clinical outcome is associated with reverse LV remodelling compared with patients with persistence, or progression, of the remodelling process.

MR, caused by alterations in LV architecture and function after infarction, can itself initiate the remodelling process. It alters the load on the LV. It increases diastolic wall stress, which can induce eccentric LV hypertrophy and subsequent dilatation and failure.[8] Therefore, MR may represent both a cause and a result of LV remodelling. The contribution of MR to LV remodelling was previously assessed by a study using a posterolateral infarction sheep model in which either MR was treated using an undersized prosthetic annuloplasty ring or the myocardium was restrained with a mesh. The MR group showed greater remodelling, and the authors concluded that MR is not a cause of post-infarction remodelling.[26] These results were later questioned because of the theoretically proper deleterious effects of undersized rings.[8] This LV remodelling, which seems to be related to the degree of MR, may partly explain the worse prognosis for the MR group compared with the cohort without MR, as even low degrees of MR can result in LV enlargement and promote the development of heart failure and arrhythmias.

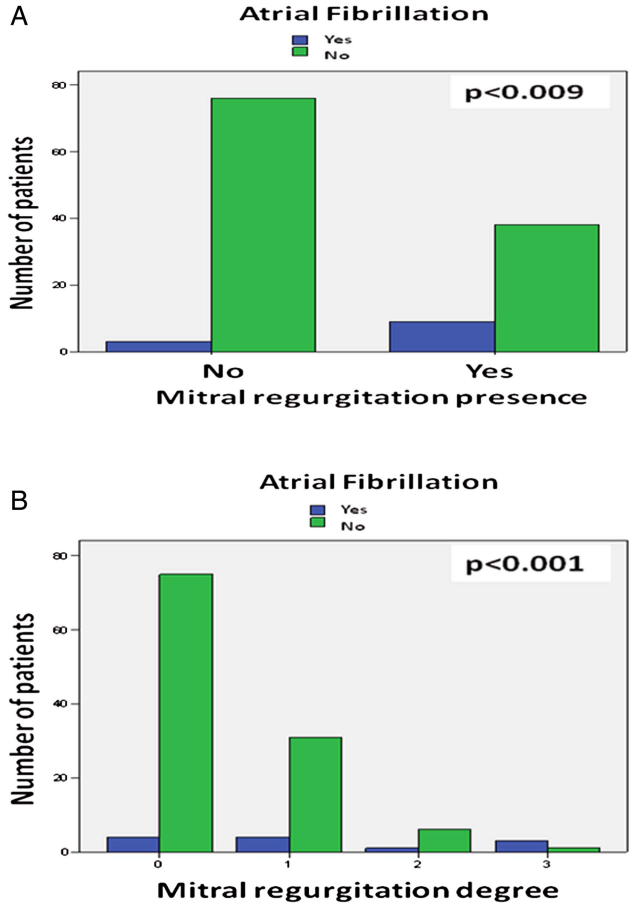

Figure 3 Rhythm arm. Bar graphs depicting the relationship between onset mitral regurgitation (MR) presence (A) or MR degree (B) with incident atrial fibrillation rhythm after the follow-up. Access the article online to view this figure in colour.

Rhythm arm

AF is a common arrhythmia[10] which has often been linked to increased left atrium diameters predicting risk of cardiovascular events.[27] Furthermore, AF is a common finding in both STSEACS and NSTSEACS.[12 13 28] A large meta-analysis by Lopes *et al*,[13] including more than 100 000 patients in 10 large clinical trials, reported that AF is independently associated with worse outcomes across the spectrum of acute coronary syndrome (both STSEACS and NSTSEACS), and is a predictor of increased short- and long-term mortality. Unfortunately, the presence of MR was not assessed by the latter study. In fact, clinical factors related to ischaemic cardiomyopathy and MR,[5 7] such as age, heart failure and infarction, were correctly reported to be predictors of non-valvular AF a long time ago by the SPAF investigators.[29] Their data also showed that an enlarged left atrium was associated with recurrent intermittent AF, and an enlarged left ventricle predicted conversion to constant AF. Thus, clinical and echocardiographic variables predicted AF in patients with non-valvular AF.[27 29]

The results of the present work agree with their data. We observed larger cavities in the MR cohort, lower LVEF, more adverse outcomes and a higher percentage of patients with AF with regard to the initial degree of MR. MR, caused by alterations in LV architecture and function after infarction, can itself stimulate AF. Thus, MR may represent the missing link between these two approaches, explaining in part the adverse outcomes related to MR degree in NSTSEACS. Again, MR may represent both a cause and a result of AF.

Clinical implications

In brief, as previously discussed, we feel that the presence of MR, even in mild degrees, must be carefully considered as a marker of a risk of a bad prognosis, from the standpoint of both heart failure and AF development. Since, in isolation, the haemodynamic relevance of minor degrees of MR is probably trivial, one should pay attention to the cardiomyopathy itself. Thus, we consider that any degree of MR warrants careful monitoring, with strict compliance with the treatments recommended by the guidelines for secondary prevention.

Limitations

We cannot be sure that, in the patients included in our study, any degree of MR was present before the index event, since we cannot distinguish between pre-existing MR and new-onset MR. Pre-AMI MR is a well-described prognostic factor.[4] In previous studies analysing prognosis after a Q-wave myocardial infarction, the presence of pre-AMI MR was not analysed either. However, we feel that this limitation is only minor if we consider previously published papers. With regard to the high prevalence of MR, many factors are probably involved in its development, but it would be difficult to reach any definitive conclusion about what they are because it would be necessary to have a group of patients with Q-wave AMI for comparison to obtain any concrete conclusions.

Not all patients in our series underwent a cardiac catheterisation procedure, but it is of note that this study is not an intervention study. Thus, the management of our patients was the standard in our hospital at that time and depended on the attending physician. So, we think our results come close to real life clinical practice.

Conclusions

MR is common after an NSTSEACS. The presence and degree of MR confers a worse long-term prognosis on patients after a first NSTSEACS. This can in part be explained by increased negative remodelling and increased occurrence of AF. Thus, the degree of MR should be carefully appraised in all patients after an NSTSEACS.

Contributors All the authors contributed significantly to this work, and all meet the full criteria and requirements for authorship. IJN-G, IE and LPdI were responsible for conception and design of the study. The remaining authors contributed to inclusion of patients, analysis and interpretation of data, and revising the manuscript. All approved the manuscript submitted.

Competing interests None.

Patient consent Obtained.

Ethics approval Hospital Clinico San Carlos.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Grigioni F, Enriquez-Sarano M, Zehr KJ, *et al*. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. *Circulation* 2001;103:1759–64.
2 Lamas GA, Mitchell GF, Flaker GC, *et al*. Clinical significance of mitral regurgitation after acute myocardial infarction. Survival and Ventricular Enlargement Investigators. *Circulation* 1997;96:827–33.
3 Perez de Isla L, Zamorano J, Martinez Quesada M, *et al*. Prognostic significance of ischemic mitral regurgitation after non-Q-wave acute myocardial infarction. *J Heart Valve Dis* 2005;14:742–8.
4 Zamorano J, de Isla LP, Oliveros L, *et al*. Prognostic influence of mitral regurgitation prior to a first myocardial infarction. *Eur Heart J* 2005;26:343–9; discussion 19–21.
5 Perez de Isla L, Zamorano J, Quezada M, *et al*. Prognostic significance of functional mitral regurgitation after a first non-ST-segment elevation acute coronary syndrome. *Eur Heart J* 2006;27:2655–60.
6 Grigioni F, Detaint D, Avierinos JF, *et al*. Contribution of ischemic mitral regurgitation to congestive heart failure after myocardial infarction. *J Am Coll Cardiol* 2005;45:260–7.
7 Perez de Isla L, Zamorano J, Quezada M, *et al*. Functional mitral regurgitation after a first non-ST-segment elevation acute coronary syndrome: contribution to congestive heart failure. *Eur Heart J* 2007;28:2866–72.
8 Bursi F, Enriquez-Sarano M, Jacobsen SJ, *et al*. Mitral regurgitation after myocardial infarction: a review. *Am J Med* 2006;119:103–12.
9 Beeri R, Yosefy C, Guerrero JL, *et al*. Mitral regurgitation augments post-myocardial infarction remodeling failure of hypertrophic compensation. *J Am Coll Cardiol* 2008;51:476–86.
10 Ryder K, Benjamin E. Epidemiology and significance of atrial fibrillation. *Am J Cardiol* 1999;84:131R–8R.
11 Pedersen O, Baggar H, Kober L, *et al*. The occurrence and prognostic significance of atrial fibrillation/-flutter following acute myocardial infarction. *Eur Heart J* 1999;20:748–54.
12 Pizzetti F, Turazza F, Franzosi M, *et al*. Incidence and prognostic significance of atrial fibrillation in acute myocardial infarction: the GISSI-3 data. *Heart* 2001;86:527–32.
13 Lopes R, Pieper K, Horton J, *et al*. Short- and long-term outcomes following atrial fibrillation in patients with acute coronary syndromes with or without ST-segment elevation. *Heart* 2008;94:867–73.
14 Moya J, Catalan M, Garcia-Lledo A, *et al*. A semiquantitative method based on proximal convergence zone to estimate the severity of the mitral regurgitation: design and clinical application. *Eur J Echocardiogr* 2001;2:163–9.
15 Feinberg MS, Schwammenthal E, Shlizerman L, *et al*. Prognostic significance of mild mitral regurgitation by color Doppler echocardiography in acute myocardial infarction. *Am J Cardiol* 2000;86:903–7.
16 Nunez Gil IJ, Perez de Isla L, Garcia-Rubira JC, *et al*. Ischemic mitral regurgitation and non-ST-segment elevation acute myocardial infarction: long-term prognosis. *Rev Esp Cardiol* 2009;62:1267–75.
17 Bertrand M, Simoons M, Fox K, *et al*. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. The Task Force on the Management of Acute Coronary Syndromes of the European Society of Cardiology. *Eur Heart J* 2002;23:1809–40.
18 Enriquez-Sarano M, Miller FJ, Hayes S, *et al*. Effective mitral regurgitant orifice area: clinical use and pitfalls of the proximal isovelocitysurface area method. *J Am Coll Cardiol* 1995;25:703–9.
19 Gorman J, Gorman R, Plappert T, *et al*. Infarct size and location determine development of mitral regurgitation in the sheep model. *J Thorac Cardiovasc Surg* 1998;115:615–22.
20 Tibayan F, Rodríguez F, Zasio M, *et al*. Geometric distortions of the mitral valvular-ventricular complex in chronic ischemic mitral regurgitation. *Circulation* 2003;108:II-116–II-21.
21 Lancellotti P, Gerard PL, Pierard LA. Long-term outcome of patients with heart failure and dynamic functional mitral regurgitation. *Eur Heart J* 2005;26:1528–32.
22 Lancellotti P, Moonen M, Zacharakis D, *et al*. Ischemic mitral regurgitation. *Arch Mal Coeur Vaiss* 2007;100:1056–62.
23 Campwala SZ, Bansal RC, Wang N, *et al*. Mitral regurgitation progression following isolated coronary artery bypass surgery: frequency, risk factors, and potential prevention strategies. *Eur J Cardiothorac Surg* 2006;29:348–53.
24 The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992:685–91.
25 De Bonis M, Lapenna E, Verzini A, *et al*. Recurrence of mitral regurgitation parallels the absence of left ventricular reverse remodeling after mitral repair in advanced dilated cardiomyopathy. *Ann Thorac Surg* 2008;85:932–9.
26 He S, Fontaine A, Schwammenthal E, *et al*. Integrated mechanism for functional mitral regurgitation: leaflet restriction versus coapting force: in vitro studies. *Circulation* 1997;96:1826–34.
27 Olshansky B, Heller E, Mitchell L, *et al*. Are transthoracic echocardiographic parameters associated with atrial fibrillation recurrence or stroke? Results from the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study. *J Am Coll Cardiol* 2005;45:2026–33.
28 Goldberg R, Seeley D, Becker R, *et al*. Impact of atrial fibrillation on the in-hospital and long-term survival of patients with acute myocardial infarction: a community-wide perspective. *Am Heart J* 1990;119:996–1001.
29 Flaker G, Fletcher K, Rothbart R, *et al*. Clinical and echocardiographic features of intermittent atrial fibrillation that predict recurrent atrial fibrillation. Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. *Am J Cardiol* 1995;76:355–8.

Heart

Functional mitral regurgitation after a first non-ST segment elevation acute coronary syndrome: very-long-term follow-up, prognosis and contribution to left ventricular enlargement and atrial fibrillation development

Iván J Núñez-Gil, Irene Estrada, Leopoldo Pérez de Isla, et al.

Heart 2013 99: 1502-1508 originally published online August 19, 2013
doi: 10.1136/heartjnl-2013-304298