

Heart Failure and Death After Myocardial Infarction in the Community

The Emerging Role of Mitral Regurgitation

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Background—In case series, mitral regurgitation (MR) increased the risk of death after myocardial infarction (MI), yet the prevalence of MR, its incremental prognostic value over ejection fraction (EF), and its association with heart failure and death after MI in the community is not known.

Methods and Results—The prevalence of MR and its association with heart failure and death were examined among 1331 patients within a geographically defined MI incidence cohort between 1988 and 1998. Echocardiography was performed within 30 days after MI in 773 patients (58%), and MR was present in 50% of cases, mild in 38%, and moderate or severe in 12%. Among patients with MR, a murmur was inconsistently detected clinically. After 4.7 ± 3.3 years of follow-up, 109 episodes of heart failure and 335 deaths occurred. There was a graded positive association between the presence and severity of MR and heart failure or death. Moderate or severe MR was associated with a large increase in the risk of heart failure (relative risk 3.44, 95% CI 1.74 to 6.82, $P < 0.001$) and death (relative risk 1.55, 95% CI 1.08 to 2.22, $P = 0.019$) among 30-day survivors independent of age, gender, EF, and Killip class.

Conclusions—In the community, MR is frequent and often silent after MI. It carries information to predict heart failure or death among 30-day survivors independently of age, gender, EF, and Killip class. These findings, which are applicable to a large community-based MI cohort, suggest that the assessment of MR should be included in post-MI risk stratification. (*Circulation*. 2005;111:295-301.)

Key Words: mitral valve ■ regurgitation ■ myocardial infarction ■ prognosis ■ population

Mitral regurgitation (MR) can complicate myocardial infarction (MI),¹ is often unrecognized clinically, and has been reported to increase the risk of death after MI.²⁻⁴ These reports consist chiefly of case series or secondary analyses of clinical trials, which are subject to referral and selection biases and which compromise the generalizability of these findings by an unknown degree. Therefore, this matter should be studied in a different population with a more robust study design.

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Furthermore, despite the physiological link between MR and heart failure, previous studies that addressed the prognostic value of MR after MI seldom included heart failure as an outcome.³ This is important because of the increasing appreciation of the contribution of post-MI outcomes to the epidemic of heart failure.⁵ Moreover, characteristics associated with the presence of MR after MI remain to be fully delineated, because there is no agreement whether MR is

associated with the site and extent of MI. Finally, echocardiography is not universally used after MI.⁶ Thus, to enable clinicians to apply the findings derived from the analyses of clinically indicated tests to all patients with MI, a methodology suitable to draw inference to all patients should be used. Yet, to the best of our knowledge, this has not been the case in prior studies. Thus, the purpose of the present study was to address these gaps in knowledge by evaluating, in a geographically defined population and within a large MI incidence cohort, the prevalence of MR early after MI, the clinical characteristics associated with MR, and its association with subsequent heart failure and death.

Methods

Study Setting

This historical population-based cohort study was conducted in Olmsted County, Minnesota, where epidemiological studies are possible because the county is relatively isolated from other urban centers, and only a few providers (the Mayo Clinic, Olmsted Medical

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Center, and a handful of private practitioners) deliver nearly all health care to residents. Each provider uses a comprehensive medical record system. Under the auspices of the Rochester Epidemiology Project (AR-30582), all medical records of county residents are indexed, which enables the retrieval of records data for use in epidemiological studies and which ensures complete capture of all healthcare-related events occurring in the county for county residents. This centralized system encompasses the records of a population of 124 277 at the 2000 census, which represent an estimated 3 600 000 person-years of health care.

The MI Incidence Cohort

The cohort consisted of patients with incident MI; thus, all patients with prior MI were excluded from the study. This inception cohort was assembled by standardized surveillance methods described elsewhere.⁷ Briefly, the surveillance pertains to all patients discharged from Olmsted County hospitals with diagnoses compatible with an MI defined by the target codes from the 9th version of the International Classification of Diseases, specifically 410 (acute MI), 411 (other acute and subacute forms of ischemic heart disease), 412 (old MI), 413 (angina pectoris), and 414 (other forms of ischemic heart disease). Trained abstractors collected information on residency in Olmsted County, incident status, cardiac pain, and creatine phosphokinase (CK) values. Standardized criteria were applied to assign an MI diagnosis based on cardiac pain, enzyme values, and Minnesota coding of the ECG.⁸ The reliability of these criteria was published elsewhere.⁷ The study period was 1988 to 1998.

Because of the change over time in normal values, peak CK ratio was defined as the ratio of the maximum CK value to the upper limit of normal. ST-segment elevation was defined with the Minnesota code. Time to presentation was defined as the interval (in hours) from the self-reported onset of acute symptoms (which defined the inception date) to the first recorded ECG. Killip class was assessed within 24 hours of admission to the hospital. Comorbidity was measured by the Charlson index.⁹ Clinical diagnoses as documented in the record were used to ascertain cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, and family history of coronary disease); former and current smoking were combined in the analysis.

Echocardiographic Evaluation

All patients who received an echocardiogram within 30 days of the MI were identified, and the results of all echocardiograms were reviewed by the principal investigator (FB) without knowledge of patients' outcomes and histories. After exclusion of patients with papillary muscle rupture, the severity of MR was evaluated semi-quantitatively from the area of the regurgitant jet by color Doppler.¹⁰ MR was classified as absent or trivial, mild, and moderate or severe, a classification that is associated with outcomes in nonischemic mitral valve disease.¹⁰ Ejection fraction (EF) was calculated by the biplane Simpson method or with left ventricular systolic and diastolic diameters by the Quinones method¹¹ or visually estimated, a method comparable to other assessments of left ventricular EF.¹² Left ventricular wall-motion score index was calculated according to a 16-segment model.¹³ Diastolic function was evaluated by the deceleration time of the early mitral inflow. Ventricular size was analyzed as a categorical variable: normal or borderline enlarged versus enlarged.

Follow-Up

Follow-up was provided by passive surveillance through the community (inpatient and outpatient) medical records, a process quite complete because >90% of the population receives care at Mayo Clinic or Olmsted Medical Center, and residents are seen on average every 3 years at Mayo Clinic.¹⁴ Both inpatient and outpatient records were reviewed to ascertain heart failure during the entire follow-up period, which was validated with the Framingham criteria.¹⁵ All heart failure events were identified, including outpatient cases. Only incident episodes of heart failure after the index MI were considered

in the analysis of the association between MR and heart failure after MI.

The ascertainment of death incorporates death certificates filed in Olmsted County, autopsy reports, obituary notices, and electronic files of death certificates obtained from the State of Minnesota Department of Vital and Health Statistics. Death after 30 days was a prespecified cutoff driven by the recognition that left ventricular remodeling is a heterogeneous process^{16,17} and that MR is an important component of its later stage.^{3,4,18}

Statistical Analyses

The data are presented as frequency or mean \pm SD. Characteristics were compared across groups with χ^2 tests for categorical variables and ANOVA for continuous variables. For highly skewed variables, presented as median and first and third quartiles, the Kruskal-Wallis nonparametric test of rank scores was used. Logistic regression analysis was used to identify the baseline variables independently associated with MR. Survival and event-free survival of patients with and without MR were determined by the Kaplan-Meier method and compared by the log-rank test. Patients were censored at the time of last follow-up. Cox proportional hazards models were constructed to evaluate the risk of death or heart failure according to the presence and degree of MR. Results were summarized as relative risk (RR) and 95% CI. Variables included in the proportional hazards models were chosen from those known to be of clinical interest in post-MI risk stratification, with the goal of keeping the models as parsimonious as possible.

Because most of the analyses were conducted with the subset of patients who underwent echocardiography, the results were generalized to the entire cohort by estimating the probability of moderate or severe MR for each person with a multivariable logistic regression model, constructed from the persons subjected to an echocardiogram. The predictor variables were selected by the backward-elimination selection method with consideration of age, gender, body mass index, linear and quadratic terms of year of MI, hypertension, tobacco use, hyperlipidemia, history of familial or personal coronary disease, Charlson comorbidity index, CK ratio, and Killip class. The variables included in the final model were age, gender, linear and quadratic terms of year of MI, history of familial or personal coronary disease, and Killip class. The c-statistic of the model was 0.77, which indicates satisfactory discrimination. The cutoff to estimate moderate or severe MR from the estimated probabilities was determined from the receiver operating characteristic curve. The model and the cutoff were then used to estimate moderate or severe MR in the entire MI cohort, and the Cox proportional hazards models that evaluated the risk of death or heart failure were repeated with no or mild MR as the referent.

Analyses were performed with SAS, version 8.0 (SAS Institute Inc). The Mayo Foundation Institutional Review Board approved this study.

Results

Characteristics of Patients With MR After MI

During the period 1988 to 1998, 1331 county residents were hospitalized for an incident MI; 773 (58%) of them underwent an echocardiogram within 30 days after the index MI. Sixteen patients were excluded from the analysis because their echocardiographic data were not retrievable. The mean time between the index MI and the echocardiogram was 3.0 ± 4.5 days. MR was present in 386 subjects (50%); among these, MR was mild in 297 (38%) and moderate or severe in 89 (12%).

The clinical characteristics indicate that patients with any degree of MR were older, had greater comorbidity, and were more likely to be women and nonsmokers ($P < 0.001$). They were more likely to present in higher Killip class, and a murmur was inconsistently present, because more than half of

TABLE 1. Characteristics of 773 Patients Who Underwent Echocardiography Within 30 Days After MI by Degree of MR

	No MR (n=387)	Mild MR (n=297)	Moderate/Severe MR (n=89)	P for Trend
Demographics				
Age, y, mean±SD	66±14	72±13	77±10	<0.001
Male gender, n (%)	226 (58)	147 (49)	24 (27)	<0.001
Charlson index, n (%)				<0.001
0	180 (47)	91 (31)	18 (20)	
1–2	144 (37)	117 (39)	38 (43)	
3+	63 (16)	89 (30)	33 (37)	
Cardiovascular risk factors				
Hypertension, n (%)	216 (56)	184 (62)	64 (72)	0.004
Diabetes, n (%)	69 (18)	82 (28)	24 (27)	0.005
Current/former smoker, n (%)	272 (71)	168 (57)	38 (43)	<0.001
Hyperlipidemia, n (%)	140 (36)	125 (42)	29 (33)	0.800
Family history of CAD, n (%)	72 (20)	58 (20)	17 (20)	0.830
BMI, kg/m ² , mean±SD	27±6	27±5	27±5	0.950
Clinical presentation, n (%)				
Murmur	121 (32)	135 (46)	61 (69)	<0.001
Killip class				<0.001
I	267 (70)	177 (60)	33 (37)	
II	23 (6)	16 (5)	3 (3)	
III	69 (18)	89 (30)	44 (49)	
IV	21 (6)	13 (4)	9 (10)	
CK ratio				0.951
Tertile 1	126 (34)	88 (32)	30 (32)	
Tertile 2	109 (30)	83 (30)	28 (32)	
Tertile 3	116 (32)	94 (34)	26 (30)	
Non-ST elevation	216 (56)	183 (63)	55 (63)	0.117
Q-wave MI	181 (52)	149 (58)	37 (44)	0.980
Anterior MI	142 (40)	109 (40)	30 (34)	0.490

CAD indicates coronary artery disease; BMI, body mass index.

the patients with mild MR and one third of the patients with moderate or severe MR did not have any murmur detected on cardiac auscultation (Table 1). No association was found between the presence of MR and location of MI, CK ratio, or presence of Q waves on the ECG. There was a graded positive association between the presence of MR and the presence of hypertension and diabetes. The echocardiographic characteristics of the patients indicate that those with MR had a lower EF, larger left ventricular volumes, greater

wall-motion score index, and higher right ventricular systolic pressures than patients without MR (*P* for trend <0.001; Table 2).

Survival Analysis

After 4.7±3.3 years, 109 episodes of heart failure and 335 deaths occurred. At 5 years, survival free of heart failure was 74% (95% CI 67% to 82%) for persons with mild MR and 35% (95% CI 17% to 72%) for persons with moderate or

TABLE 2. Echocardiographic Findings in 773 Patients Who Underwent Echocardiography Within 30 Days After MI

	No MR (n=387)	Mild MR (n=297)	Moderate/Severe MR (n=89)	P for Trend
LVEF, %, mean±SD	49±13	45±14	40±15	<0.001
LV enlargement, n (%)	87 (28)	118 (46)	49 (60)	<0.001
WMSI, median (Q1–Q3)	1.4 (1.1–1.7)	1.5 (1.2–1.9)	1.6 (1.3–2.1)	<0.001
RV systolic pressure, mm Hg	38±9	45±11	49±10	<0.001
Deceleration time, ms, mean±SD	209±48	210±57	178±63	<0.001

LVEF indicates left ventricular EF; WMSI, left ventricular wall-motion score index; and RV, right ventricular.

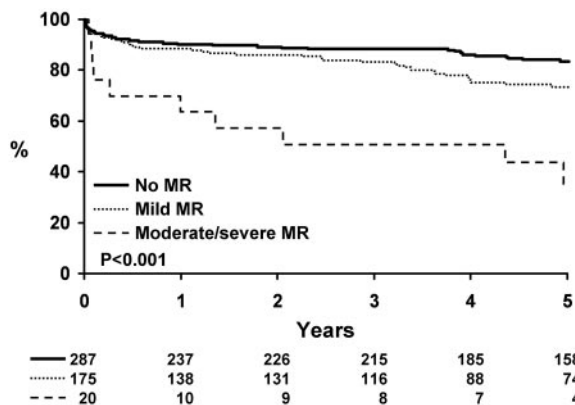


Figure 1. Survival free of heart failure according to degree of MR in 773 patients who underwent echocardiography within 30 days after MI (solid line indicates no MR, dotted line mild MR, and dashed line moderate or severe MR). Number of patients at risk of heart failure in each MR group appears below figure at yearly intervals.

severe MR versus 84% (95% CI 79% to 89%) for patients without MR ($P<0.001$; Figure 1). With proportional hazards regression modeling, there was a strong, graded, positive association between MR and heart failure, and MR was associated with a >3-fold excess risk of heart failure, independently of age, gender, EF, and Killip class (Table 3).

A similar relationship was observed between MR and death (Figure 2). At 5 years, the overall survival was 62% (95% CI 57% to 68%) for persons with mild MR and 40% (95% CI 31% to 52%) for persons with moderate or severe MR versus 72% (95% CI 68% to 77%) among patients without MR ($P<0.001$). After adjustment for age, gender, and EF, the presence of moderate or severe MR was associated with a 45% increase in the risk of death (RR 1.45, 95% CI 1.05 to 1.99, $P=0.023$). Further adjustment for Killip class

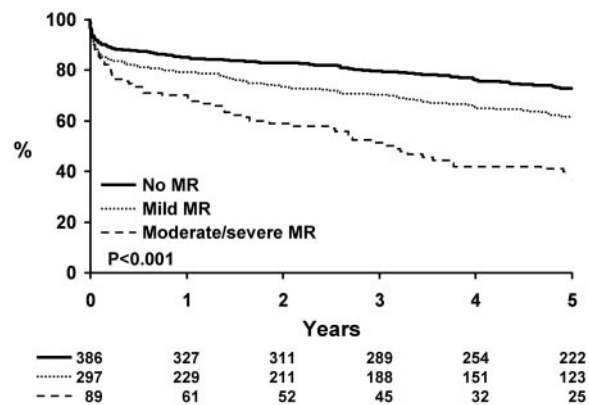


Figure 2. Overall survival according to degree of MR in 773 patients who underwent echocardiography within 30 days after MI (solid line indicates no MR, dotted line mild MR, and dashed line moderate or severe MR). Number of patients at risk of death in each MR group appears below figure at yearly intervals.

attenuated the association between MR and death only if early deaths were included; by contrast, when we focused on 30-day survivors, moderate or severe MR increased the risk of death by 55% independently of Killip class. For all end points, adjustment for hypertension, diabetes, non-ST-elevation MI, and comorbidity did not attenuate these associations.

Some patients did not undergo an echocardiogram within 30 days after MI, which reflects the practice in the community; these patients were younger, more likely to be men, and more likely to have non-ST-elevation MIs. Echocardiograms were also less likely to be performed in the absence of a murmur on auscultation and in the setting of lower Killip class and smaller MI size as measured by CK and Q waves ($P<0.05$ for all comparisons). We examined the applicability

TABLE 3. MR, Heart Failure, and Death After MI in 773 Patients Who Underwent Echocardiography Within 30 Days After MI

	No MR (Reference)	Mild MR	Moderate or Severe MR
Heart failure			
Number of events	51	47	11
Unadjusted RR	1.00	1.78 (1.20–2.65)	5.30 (2.75–10.2)
RR* (95% CI)	1.00	1.32 (0.87–1.99)	3.07 (1.57–6.00)
RR† (95% CI)	1.00	1.35 (0.89–2.05)	3.44 (1.74–6.82)
Death at all times			
Number of events	146	127	62
Unadjusted RR	1.00	1.40 (1.10–1.77)	2.69 (1.99–3.63)
RR* (95% CI)	1.00	1.04 (0.81–1.33)	1.45 (1.05–1.99)
RR† (95% CI)	1.00	1.00 (0.78–1.28)	1.27 (0.92–1.75)
Death among 30-day survivors			
Number of events	115	90	50
Unadjusted RR	1.00	1.33 (1.01–1.75)	3.11 (2.23–4.35)
RR* (95% CI)	1.00	1.03 (0.78–1.37)	1.74 (1.22–2.49)
RR† (95% CI)	1.00	1.01 (0.76–1.34)	1.55 (1.08–2.22)

RRs are presented with no MR as the referent; other variables in the models include *age, male gender, and EF; †age, male gender, EF, and Killip class.

of our results to the entire MI cohort using the estimated probability of MR among patients without echocardiograms. Moderate or severe MR was present in 18% of all patients with MI and was associated with increased risk of heart failure (unadjusted RR 3.43, 95% CI 2.58 to 4.57, $P < 0.001$) and death (unadjusted RR 3.62, 95% CI 3.03 to 4.33, $P < 0.001$). These results were qualitatively comparable to those obtained with the complete case analysis, which attests to their robustness and suggests that they may be applicable to all patients with MI, irrespective of echocardiographic referral practices.

Discussion

The data from this large community-based cohort of persons experiencing their first MI indicate that MR is frequent and cannot be reliably identified from auscultation or MI characteristics. There was a strong, positive, graded association between MR and heart failure or death beyond 30 days that was independent of age, gender, EF, and Killip class, which indicates that MR brings incremental value to recognized clinical characteristics in predicting 2 major outcomes after MI. This association did not differ according to the location of the MI and remained robust when assessed within the entire cohort, which underscores its relevance to all patients with MI irrespective of practice patterns. To the best of our knowledge, the present study is the largest to examine the prevalence of MR after MI and is the only one to address its role in subsequent heart failure and death in a geographically defined incidence cohort.

Frequency and Characteristics of MR After MI

Previous studies reported a prevalence of MR after MI ranging from $< 20\%$ in angiographic studies^{2,3,19} to 40% in echocardiographic series.^{1,20} These large discrepancies reflect the selection biases inherent to most of these studies, which involved either patients selected in clinical trials (thus subject to the “healthy participant effect”²¹) or convenience samples of patients referred to the catheterization laboratory or admitted to the coronary care unit. These patients do not reflect all subjects with MI in the community,²² which leaves uncertainties with regard to the broad applicability of these findings. After MI, MR is frequent and often silent, and this clinical observation in a large community-based cohort extends previous reports^{1-3,23} that indicated that in ischemic MR, the intensity of the murmur does not reflect the degree of regurgitation. Indeed, severe MR may even be silent, because reduced ventricular function minimizes the atrioventricular gradient, regurgitant flow, and subsequent murmur. In the existing literature, the association between the location of MI and the presence of MR remains questionable. Although often reported as a complication of inferior MI,²⁴ MR is also described as chiefly associated with anterior MI,² whereas other studies reported no association^{1,20} with MI location. Because previous reports are affected by the aforementioned selection biases and did not consistently exclude prior MI in their analyses, it is challenging to reconcile these contradictory findings. The present study provides incremental knowledge in this regard by indicating that after a first MI, the presence of MR is not associated with the location of MI, the

presence of Q waves on the ECG, or CK levels. Investigation of the mechanism of MR is not within the scope of the present study; however, these data are consistent with emerging concepts on the pathophysiology of ischemic MR, which may be more related to local and global ventricular remodeling than to papillary muscle dysfunction.^{24,25} Ventricular remodeling results in valvular tenting,²⁶ loss of annular contraction, and ventricular deformation, all elements that converge to generate and increase the presence and severity of MR.^{27,28}

Implications of MR Among Patients With MI

Patients with MR had worse outcomes, which exhibited a graded “dose-response” relationship with the severity of MR, a pattern that supports causality.²⁹ Heart failure is recognized as an emerging epidemic to which MI survivors contribute,⁵ yet little is known about the determinants of post-MI heart failure, and there is even less information about the role of MR in heart failure after MI.³ The present results bring important new knowledge to the field by indicating that MR plays a central role in the development of post-MI heart failure independently of age, gender, EF, and Killip class.

With regard to death, previous reports pertained to selected patients, such as subjects with reduced EF in the Survival and Ventricular Enlargement (SAVE) trial³ or patients after percutaneous coronary interventions.³⁰ Among 2 echocardiographic case series, 1 series²⁰ was restricted to patients admitted to a coronary care unit, whereas a case-control study from our group⁴ evaluated patients with chronic MR after Q-wave MI in the referral practice. Thus, all studies were affected by selection and survivor biases, and the reported association between MR and death after MI should be considered as hypothesis generating. The present study extends these findings by indicating that MR is associated with a large excess risk of death after MI, independently of age, gender, and EF. With regard to Killip class, the results should be interpreted cautiously because of the link between MR and Killip class, an indicator intended to predict^{31,32} deaths in the early post-MI phase. The present study underscores the role of MR in the prediction of death beyond 30 days, independently of age, gender, EF, and Killip class.

These findings are consistent with the heterogeneous process of left ventricular remodeling^{16,17,28} and underscore the dynamic nature of post-MI risk stratification. Because MR often lacks the typical auscultatory presentation and is not related to MI severity, its detection cannot rely on clinical assessment, thereby requiring imaging studies, most often echocardiography. Its detection would imply more systematic echocardiographic evaluation after MI than in current practice, where the use of echocardiography remains incomplete.⁶ Importantly, this approach would not lead to additional testing above current recommendations for left ventricular function assessment after MI³³ and could help delineate a novel therapeutic target for patients with MI.²⁷

Limitations and Strengths

Potential limitations should be kept in mind in the interpretation of these data. The evaluation of MR was semiquantitative; however, this is unlikely to affect the results, because in ischemic MR, the regurgitant jet is usually central and

correlates well with the regurgitant volume.¹⁰ Furthermore, we observed a graded, positive association between the severity of MR measured semiquantitatively and outcomes, commonly interpreted as indicating causality.²⁹ EF was evaluated by combining quantitative measurements with visual estimation, which reflects standard clinical practice with methods shown to have a similar accuracy. Because the method used to assess EF is not related to the presence of MR, the associations between MR and outcome are not confounded by the method of EF assessment.

Our echocardiographic findings were observed after MI and do not exclude that some MR was present beforehand in some patients, a limitation shared by all studies on this topic.^{1–4,19,20} However, the frequency of MR observed herein largely exceeded that reported in the general population,^{34,35} such that it can be attributed chiefly to the MI. The 30-day cutoff for the analysis of all-cause death was arbitrary, like all cut points. This was selected to address the dynamic nature of post-MI outcomes; within this framework, the alternative of selecting in-hospital versus postdischarge outcomes appeared less satisfactory given the gradual reduction in hospital stay.

The strengths of the present study include a rigorously ascertained, population-based MI incidence cohort. Thus, the results presented herein are less subject to confounding by changing case mix due to varying definitions or referral bias. Because they apply to all incident cases within a community, they are not confounded by incidence-prevalence bias²⁹ or by prior MI, which in turn can affect both the presence and extent of MR and its prognostic implications owing to unknown duration of left ventricular remodeling.^{1,3} These crucial methodological elements lead to compelling internal validity. Because echocardiography is not always performed after MI, it is important to examine the validity of the results of echocardiograms for all patients with MI so that clinicians can apply these results, yet this is seldom done. The present study addresses this gap in knowledge by suggesting that the present results are applicable to all patients with MI in the community. Finally, results of the present study provide insight into a mechanism of heart failure, a major source of post-MI morbidity, while including all episodes of post-MI heart failure, including outpatient cases.

Conclusions

MR is frequent and often silent among patients with MI. It is strongly associated with heart failure and death among 30-day MI survivors independently of age, gender, EF, and Killip class, which indicates that MR adds prognostic information incremental to known clinical indicators for post-MI risk stratification. These findings, which are applicable to a large community-based MI cohort, suggest that the assessment of MR should be included in post-MI risk stratification.

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