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Importance of Mitral Regurgitation in Patients Undergoing Percutaneous Coronary Intervention for Acute Myocardial Infarction

The Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Trial

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OBJECTIVES We sought to determine the prognostic importance of mitral regurgitation (MR) in patients undergoing percutaneous coronary intervention for acute myocardial infarction (AMI).

BACKGROUND Mitral regurgitation has been associated with a poor prognosis in patients treated with thrombolytic therapy for AMI. The prognostic significance of MR in patients undergoing mechanical reperfusion therapy for AMI is unknown.

METHODS Left ventriculography was performed during the index procedure in 1,976 (95%) of 2,082 non-shock patients enrolled in a prospective, multicenter, randomized trial of mechanical reperfusion strategies in AMI. The severity of operator-assessed MR was divided into four strata: none (n = 1,726), mild (n = 192), and moderate/severe (n = 58).

RESULTS Patients with progressively more severe MR were older ($p < 0.0001$), were more often women ($p < 0.0001$), and had higher Killip class ($p = 0.0007$). More severe grades of MR correlated with triple-vessel disease ($p < 0.0001$) and lower left ventricular ejection fraction (LVEF) as measured during the index procedure ($p = 0.0004$). Increasingly severe MR was strongly associated with a higher mortality at 30 days (1.4% vs. 3.7% vs. 8.6%, respectively; $p < 0.0001$) and at one year (2.9%, 8.5%, 20.8%, respectively; $p < 0.0001$). By multivariate analysis, the presence of even mild MR was an independent predictor of long-term mortality (mild MR, relative risk [RR] = 2.40, $p = 0.005$; moderate/severe MR, RR = 2.82, $p = 0.006$).

CONCLUSIONS Mitral regurgitation of any degree present on the baseline left ventriculogram during the index procedure is a powerful, independent predictor of mortality in patients undergoing mechanical reperfusion therapy for AMI. The presence of MR identifies high-risk patients in whom close out-patient follow-up is warranted, and who may benefit from aggressive adjunctive medical or surgical therapies. (J Am Coll Cardiol 2004;43:1368–74) © 2004 by the American College of Cardiology Foundation

Mitral regurgitation (MR) is a frequent complication of acute myocardial infarction (AMI) and has several etiologies (1). In the setting of AMI, mitral regurgitation is most commonly due to valvular dysfunction without structural disease (2–4), may result from altered ventricular geometry (5–7), incomplete mitral leaflet coaptation, papillary muscle dysfunction, and regional wall motion abnormalities (4,8). During AMI, mitral regurgitation carries an adverse prognosis (9–13), and it has been associated with high mortality in patients treated with fibrinolytic therapy (9,10). Emergent percutaneous coronary intervention (PCI) has been shown to improve the degree of MR at follow-up (14–17). However, the prognostic impact of MR in patients undergoing primary PCI for AMI is unknown. We therefore examined the relationship between baseline MR and clinical outcomes after primary PCI in a large prospective trial of patients with AMI without cardiogenic shock.

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METHODS

In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, 2,082 patients of any age with AMI within 12 h of

Abbreviations and Acronyms

AMI = acute myocardial infarction
CADILLAC = Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications
LV = left ventricle/ventricular
MR = mitral regurgitation
PCI = percutaneous coronary intervention
PVC = premature ventricular contraction
TIMI = Thrombolysis In Myocardial Infarction

onset were randomized to balloon angioplasty ± abciximab versus stenting ± abciximab. Both the design and the principal results of the CADILLAC trial have been reported previously (18). In brief, the main exclusion criteria were cardiogenic shock, bleeding diathesis, known serum creatinine >2.0 mg/dl, and baseline angiographic anatomy not eligible for stent implantation. Patients were pretreated with aspirin, a thienopyridine, heparin, and intravenous beta-blockade in the absence of contraindications. Contrast left ventriculography in the 30° right anterior oblique view was strongly recommended during the index procedure before coronary angiography to measure left ventricular (LV) systolic performance and end-diastolic pressure, assess valvular function, exclude mechanical complications of AMI, and to confirm infarct location. The protocol specified that at least two consecutive non-premature ventricular contraction (PVC) or post-PVC beats must be present; otherwise, the injection should be repeated. Angiography was then performed in multiple orthogonal views, followed by PCI if the anatomy was appropriate for stent implantation, as previously described (18).

After PCI, medical therapy consisted of aspirin indefinitely, a thienopyridine for one month after stent implantation (optional in balloon angioplasty patients), and oral angiotensin-converting enzyme inhibitors and beta-blockers if not contraindicated. Clinical follow-up extended for 12 months. The primary end point was a composite of major adverse cardiovascular events, consisting of death, disabling stroke, reinfarction, or repeat revascularization of the target vessel due to ischemia, as previously defined (18).

Left ventriculographic analysis. All angiograms were analyzed at a central, independent core laboratory (the Cardiovascular Research Foundation, New York, New York). Left ventricular ejection fraction was calculated by the area–length method (19), and regional wall motion determined by the centerline chord method (20). Core laboratory quantitative assessment of MR was not contracted. Mitral regurgitation was assessed by the operator and divided into four strata: none = no systolic regurgitation of contrast into the left atrium; mild = partial opacification of the left atrium, which never equaled the extent of opacification of the LV; moderate = complete opacification of the left atrium equal to that of the LV but clearing more quickly; and severe = complete opacification of the left atrium greater than that of the LV in either systole or diastole. The severity of MR was graded only if at least two consecutive non-PVC or post-PVC beats were present.

Statistical analyses. Continuous variables are presented as medians and interquartile ranges, and these were compared using the Kruskal-Wallis nonparametric test. Categorical data are summarized as proportions and compared using the likelihood-ratio chi-square test. Survival was estimated using Kaplan-Meier methodology and compared using the log-rank test. Cox proportional hazards regression was used to determine the independent predictors of one-year mor-

Table 1. Baseline Clinical Characteristics Stratified by the Severity of Mitral Regurgitation

	Mitral Regurgitation			
	None (n = 1,726)	Mild (n = 192)	Moderate/Severe (n = 58)	p Value
Age (yrs)	58.5 (50, 67)	62.0 (52, 72)	70 (62, 77)	<0.0001
Male gender	74.7%	67.2%	46.6%*	<0.0001
Diabetes mellitus	16.3%	15.6%	20.7%	0.65
Systemic hypertension	48.1%	44.3%	60.3%	0.10
Hypercholesterolemia	38.7%	38.5%	29.3%	0.35
Current smoker	44.3%	37.0%	22.4%*	0.0009
Stable angina pectoris	17.6%	19.6%	10.5%	0.66
Prior myocardial infarction	14.2%	13.6%	12.1%	0.88
Prior percutaneous intervention	11.1%	13.0%	8.6%	0.59
Previous bypass surgery	2.0%	1.0%	5.2%	0.14
History of cerebrovascular disease	2.7%	4.7%	5.2%	0.19
Killip class ≥2	9.7%	12.1%	25.0%*	0.0007
Chest pain to balloon inflation (h)	3.97 (2.88, 6.18)	4.01 (2.90, 5.83)	3.83 (2.98, 7.13)	0.63
Medications prior to admission				
Aspirin	27.2%	29.2%	36.2%	0.28
Beta-blockers	14.5%	17.2%	31.0%*	0.002
ACE inhibitors or AR blockers	9.2%	10.9%	12.1%	0.58
Statins	11.7%	14.1%	13.8%	0.57

*$p < 0.01$ for moderate/severe mitral regurgitation vs. none/mild. Data are represented as median (25% and 75% interquartile ranges) or %.
ACE = angiotensin-converting enzyme; AR = angiotensin receptor.

Table 2. Baseline Angiographic Characteristics and Procedural Outcomes Stratified by the Severity of Mitral Regurgitation

	Mitral Regurgitation			
	None (n = 1,726)	Mild (n = 192)	Moderate/Severe (n = 58)	p Value
One-vessel disease	52.8%	42.7%	37.9%*	0.003
Two-vessel disease	32.7%	38.5%	27.6%	0.18
Three-vessel disease	14.4%	18.8%	34.5%†	<0.0001
Ejection fraction (%)	58 (49, 65)	53 (39, 59)	51 (45, 68)	0.0004
Infarct zone regional wall motion (SD/chord)	− 1.30 (−1.65, −0.84)	−1.44 (−1.70, −1.08)	−1.38 (−1.76, −1.09)	0.02
Infarct vessel				
Left anterior descending	35.8%	40.6%	27.6%	0.17
Left circumflex	17.7%	18.8%	22.4%	0.63
Right coronary	46.5%	40.1%	50.0%	0.20
Left main (protected)	0%	0.5%	0%	0.96
Baseline				
TIMI flow grade 3	23.1%	19.7%	12.1%	0.09
Diameter stenosis (%)	100 (75, 100)	100 (75, 100)	100 (73, 100)	0.54
Stent(s) implanted	55.8%	63.5%	58.6%	0.12
Abciximab administered	52.3%	54.2%	63.8%	0.21
Final				
TIMI flow grade 3	95.8%	96.3%	93.1%	0.57
Diameter stenosis (%)	23 (17, 31)	22 (15, 30)	22 (17, 31)	0.35

*p = 0.04 for moderate/severe mitral regurgitation vs. none/mild. †p < 0.001 for moderate/severe mitral regurgitation vs. none/mild. Data are represented as median (25% and 75% interquartile ranges) or %.
SD = standard deviation; TIMI = Thrombolysis In Myocardial Infaraction.

tality. Clinical (Table 1), angiographic (Table 2), and treatment assignment variables were selected using stepwise selection, entering those with a significant or borderline univariate association with mortality ($p \leq 0.10$). Candidate predictors of one-year mortality were: none versus mild versus moderate/severe MR, use of stent, use of abciximab, age, gender, Killip class (1 or >1), previous myocardial infarction, diabetes mellitus, hypertension, hypercholesterolemia, baseline Thrombolysis In Myocardial Infarction (TIMI) flow grade 3, left anterior descending infarct artery, three-vessel disease, time from symptom onset to balloon angioplasty, creatinine clearance < 60 cc/min, and ejection fraction. A p value of <0.05 was defined as significant.

RESULTS

Baseline clinical characteristics. Left ventriculography was performed during the index procedure in 1,976 (95%) of the 2,082 randomized patients. Mitral regurgitation was absent in 1,726 patients (87.4%), mild in 192 patients (9.7%), moderate in 45 patients (2.2%), and severe in 13 patients (0.7%). For subsequent analyses, the moderate and severe groups were combined into one strata. As seen in Table 1, patients with progressively more severe MR were older, were more often women, were less frequently current smokers, and had higher Killip class on admission. Medication use before admission was similar in the three groups, except that patients with progressively more severe MR were more likely to be taking beta blockers (Table 1).

Angiographic features and procedural outcomes. The severity of MR strongly correlated with triple-vessel disease and LV dysfunction, as measured by both global ejection fraction and infarct zone regional wall motion (Table 2). Of note, AMI location was not associated with the severity of MR. There was a trend toward lower rates of baseline TIMI flow grade 3 in the infarct vessel in patients with a higher severity of MR. Stent and abciximab use were equally distributed among the three groups. Procedural success, as assessed by final epicardial TIMI flow and lesion diameter stenosis, was independent of the severity of MR.

Clinical outcomes. Corrective mitral valve surgery was performed in only one patient before discharge (a mitral valve repair during bypass surgery in a patient with initially mild MR). The duration of the hospitalization correlated with the severity of MR (3.5 vs. 3.9 vs. 4.1 days with no, mild, and moderate/severe MR, respectively, p = 0.006). Medications at the time of discharge were similar in the three groups except for greater use of angiotensin converting enzyme inhibitors and receptor blockers in patients with more severe grades of MR (33.5%, 40.9%, and 50.0% in patients with no, mild, and moderate/severe MR, respectively, p = 0.008).

As seen in Table 3 and Figure 1, survival was markedly reduced in patients with MR at both 30 days and one-year, with mortality progressively increasing with increasing MR severity. Disabling stroke was significantly more common in patients with moderate/severe MR at 30 days, but not at one year. By multivariate analysis, mild and moderate/severe MR during the index procedure were the two strongest independent predictors of one-year mortality (Fig. 2). Survival in patients with MR was unaffected by randomization to stenting versus balloon angioplasty, or abciximab versus no abciximab (Fig. 3).

Table 3. Clinical Outcomes Stratified by the Severity of Mitral Regurgitation

	Mitral Regurgitation			
	None (n = 1,726)	Mild (n = 192)	Moderate/Severe (n = 58)	p Value
30-day events				
Death	1.4%	3.7%	8.6%*	<0.0001
Reinfarction	0.9%	0.5%	1.9%	0.67
Target-vessel revascularization	3.6%	2.7%	5.4%	0.64
Percutaneous intervention	2.5%	1.6%	1.9%	0.68
Bypass graft surgery	1.1%	1.1%	3.6%	0.22
Mitral valve repair/replacement	0%	0.5%	0%	0.99
Disabling stroke	0.1%	0.5%	1.8%†	0.002
Composite adverse events	5.2%	6.3%	15.5%*	0.004
Subacute thrombosis	1.0%	0.5%	1.9%	0.69
Moderate or severe bleeding	3.1%	2.7%	10.6%‡	0.007
1-year events				
Death	2.9%	8.5%	20.8%*	<0.0001
Reinfarction	2.6%	0.5%	1.8%	0.23
Target-vessel revascularization	13.6%	10.1%	19.2%	0.22
Percutaneous intervention	10.5%	8.4%	13.8%	0.55
Bypass graft surgery	3.4%	2.2%	5.6%	0.44
Mitral valve repair/replacement	0%	0.5%	1.8%	0.92
Disabling stroke	0.5%	1.1%	1.8%	0.24
Composite adverse events	16.8%	18.0%	34.5%*	0.001

*$p < 0.001$ for moderate/severe mitral regurgitation vs. none/mild. †$p < 0.01$ for moderate/severe mitral regurgitation vs. none/mild. ‡$p = 0.002$ for moderate/severe mitral regurgitation vs. none/mild.

DISCUSSION

The principal findings of this analysis are: 1) in an AMI population undergoing primary PCI (with the important caveat that patients with cardiogenic shock were not enrolled), MR at the time of the baseline procedure is evident in 12.6% of patients; 2) the presence of MR is associated with advanced age, female gender, reduced LV function, and triple-vessel coronary artery disease, but not a specific infarct artery of electrocardiographic AMI location; and 3) even the presence of mild MR at baseline is a powerful independent predictor of reduced survival after primary PCI.

Frequently, MR is present in the early phases of AMI, though its incidence is dependent upon the detection technique. Mitral regurgitation, within several days to one week after AMI, has been reported to be present in 9% to 55% of patients by auscultation (11,21,22), and in 20% to 56% of patients by echocardiography (11,23,24). More recently, two angiographic studies have detected MR in 13% and 17.9% of patients within 7 h of admission for AMI (9,10), and in 19.4% of patients at a mean of four days (12). The 12.6% incidence of MR present on the index angiogram during the early hours of evolving AMI in the present study is consistent with these findings. The incidence would have been higher had patients not been excluded for cardiogenic shock (25,26).

Compared to those without MR, patients with MR in the CADILLAC trial were older and more often female, similar to previous reports (9,10,12). In addition, MR was strongly associated with global and regional LV dysfunc-

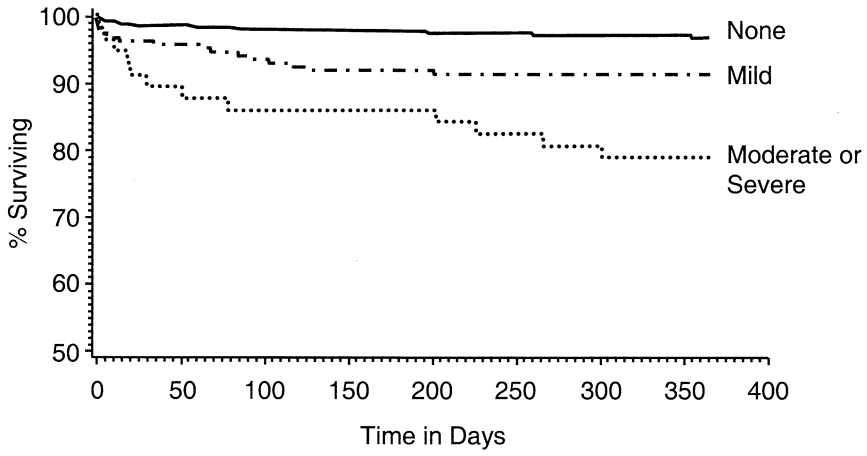

Figure 1. One-year survival stratified by the severity of baseline mitral regurgitation.

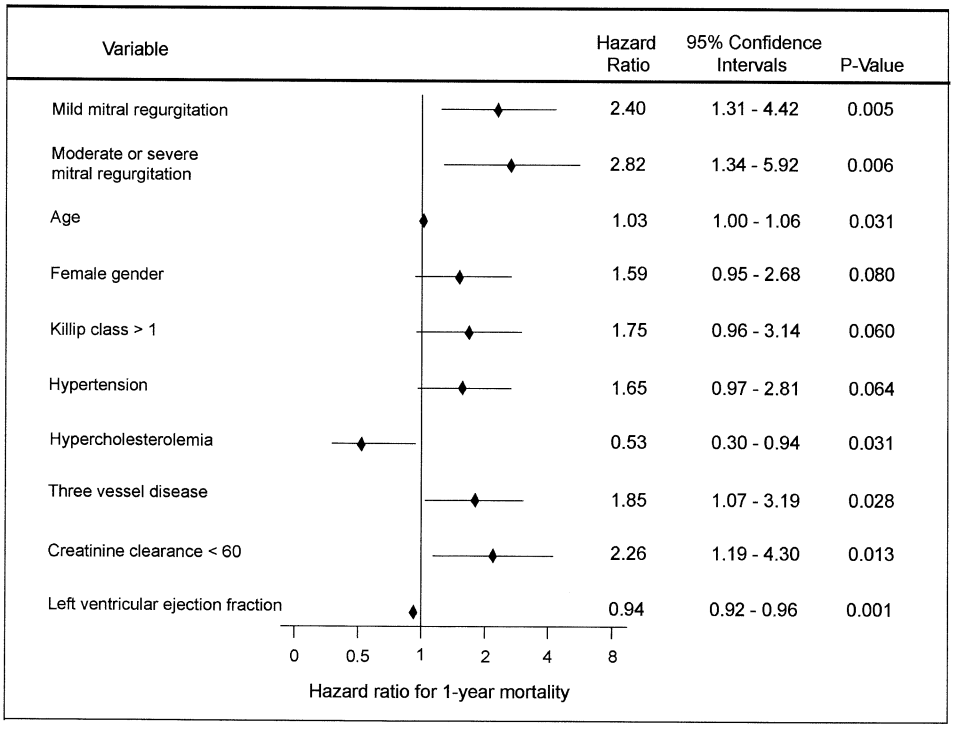

Figure 2. Multivariate predictors of one-year mortality.

tion, as well as with signs of clinical congestive heart failure on admission, also consistent with earlier observations in fibrinolytic studies (9,10,12). The extent of coronary artery disease also correlated with the frequency and severity of MR, consistent with some (8,10,12), but not all (9) prior reports. Of note, no relationship was present in the current study between the specific infarct vessel and MR, whereas other investigators have reported the presence and severity of MR to be related to either inferior/posterior (3,10,12) or anterior (9) AMI location. These conflicting data likely indicate that in different patient populations the predominant mechanism of MR may involve either more or less ischemic papillary muscle dysfunction (3,8) versus valvular dysfunction from LV dilation and/or dysynchronous myocardial contraction (5,6,12). Numerous experimental studies have emphasized the importance of the geometry of the LV for normal mitral leaflet coaptation (5–7).

The most important finding of this study is that the presence of MR of any degree on the baseline left ventriculogram during the immediate intervention was a powerful, independent predictor of mortality after primary PCI for AMI. After multivariate adjustment for differences in baseline characteristics between patients with and without MR, even mild MR was as strong or stronger a predictor of

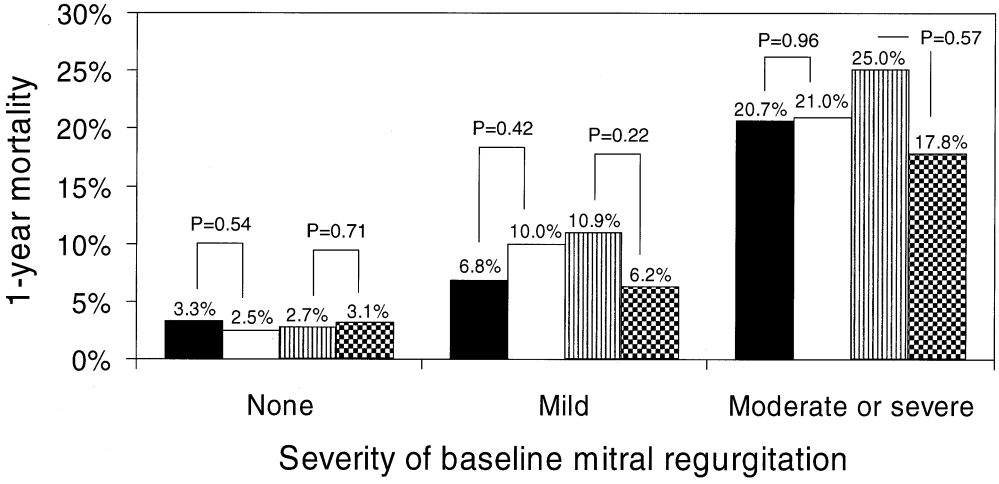

Figure 3. Impact of randomization to stenting versus balloon angioplasty (pooled regardless of abciximab administration), and to abciximab versus no abciximab (pooled regardless of stent use) on one-year mortality as a function of the severity of baseline mitral regurgitation. **Solid bars** = percutaneous transluminal coronary angioplasty; **open bars** = stent; **striped bars** = no abciximab; **checkered bars** = abciximab.

mortality than advanced age, renal insufficiency, and triple-vessel disease, independent from the degree of LV dysfunction. More severe MR was directly and independently associated with an even higher risk of mortality than mild MR. These findings confirm and extend the results of earlier investigations demonstrating incremental mortality with increasingly severe grades of MR in patients with AMI treated predominantly with thrombolytic therapy (9,10,12). Of note, procedural success rates were similar in patients with and without MR. Moreover, neither stent implantation nor abciximab administration improved the poor prognosis of patients with MR. Thus, the existence and severity of ischemic MR remains an important determinate of decreased survival even after successful primary PCI in AMI using contemporary reperfusion strategies.

The mechanisms by which MR may increase mortality after primary PCI for AMI cannot be answered by this study. Altered filling pressures and volume overload with resultant LV remodeling have both been directly related to late mortality after AMI (27–29). Associated regional infarct zone akinesis can serve as a nidus for LV mural thrombus with subsequent stroke (30,31). Moreover, MR resulting from papillary muscle rupture, although uncommon, usually results in cardiogenic shock and subsequent high mortality whether managed medically or with valve surgery (32). However, mitral valve repair and/or replacement was rarely performed in the non-shock patients randomized in the CADILLAC trial, reflecting a low rate of structural valvular damage in this series.

Study limitations. This study is a post hoc analysis of prospectively collected data. These findings thus identify associations but do not confirm causality. However, they are consistent with previous reports and confirm the importance of MR in the setting of AMI (independent of ejection fraction), even after successful primary PCI. In addition, the underlying cause of MR was not determined in this study, and whether or not its existence pre-dated the AMI is unknown. The angiographic grading of MR is a semi-quantitative measurement and may be at variance with measured regurgitant volume index, particularly in patients with enlarged LVs in whom the degree of MR may be underestimated (33). Finally, MR was operator-assessed in the present study, and thus interpretation bias cannot be excluded. Moreover, whether the extent of MR as evaluated by core laboratory analysis would have been more or less prognostically predictive is unknown. However, the fact that operator-assessed MR provided such powerful prognostic information in this study suggests that awareness of this condition may offer immediate "on-line" prognostic utility.

Clinical implications. Currently, the management of ischemic MR is not well defined. Previous longitudinal studies have suggested that the severity of MR may improve after successful reperfusion with fibrinolytic therapy (34,35) and primary PCI (14–17). Oral vasodilator therapy has been shown to reduce MR and LV end-systolic and end-diastolic volumes, and it may improve clinical outcomes (28,29). Lacking randomized studies, mitral valve surgery for functional MR, even when severe, cannot be routinely recommended unless refractory heart failure or cardiogenic shock develops (1,36–38). At a minimum, however, the presence of MR identifies patients at high risk, in whom close outpatient follow-up is warranted, and who may benefit from aggressive adjunctive medical therapy.

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