Degenerative mitral regurgitation (MR) due to leaflet prolapse is the most frequent mitral valve disease referred to surgery in Western populations and is often complicated by left ventricular (LV) dysfunction, which may cause poor outcome even after surgery.\(^1\) Both European and US guidelines\(^2\),\(^3\) define LV dysfunction as starting with ejection fraction (EF) ≤60%, with mild/moderate LV dysfunction between 30% and 60% and severe LV dysfunction <30%. However, this apparent agreement is based on thin evidence (level C) and leaves many questions unanswered. Indeed, the 60% cutoff applied to patients medically managed is supported by analysis of limited patient numbers and is based almost exclusively on postoperative outcomes\(^4\) that were collected in older series with few patients.

**Background**—Ejection fraction (EF) as a marker of left ventricular (LV) dysfunction and the appropriate thresholds for diagnosing severe or mild/moderate LV dysfunction in mitral regurgitation are doubted and poorly followed in clinical practice. We aimed at assessing the role of EF in a large registry of organic mitral regurgitation to objectively establish thresholds for various degrees of LV dysfunction and to analyze whether mitral surgery remains beneficial in those subsets of patients.

**Methods and Results**—We investigated the relation between EF and mortality in 1875 patients with mitral regurgitation due to flail leaflets in sinus rhythm (65±13 years; median EF, 66% [60%–71%]) enrolled in the Mitral Regurgitation International Database (MIDA) registry. With EF <60%, mortality after diagnosis increased precipitously under medical management (adjusted hazard ratio [HR], 1.59 [1.19–2.12]) and during the entire follow-up (adjusted HR, 1.51 [1.22–1.87]). Severe LV dysfunction, if defined by EF <30%, would affect a minuscule number of patients (0.3%). Conversely, EF <45% was more frequent (2.9%) and was associated with considerable mortality under medical management (adjusted HR, 2.43 [1.50–3.95]) and during the entire follow-up (adjusted HR, 2.46 [1.67–3.61]). The group with EF of 45 to 60% represented a large proportion of patients (23%), exhibited rarely overt symptoms, and had higher mortality compared with EF >60%. Above 60%, no EF threshold further determined survival. The benefit of surgery remained considerable in the groups with EF <45% (adjusted HR, 0.28 [0.17–0.56]) and with EF of 45 to 60% (adjusted HR, 0.34 [0.21–0.64]).

**Conclusions**—EF is valuable in defining presence and severity of LV dysfunction in organic mitral regurgitation. Patients with EF <45% have severe LV dysfunction, catastrophic outcome under medical management, and should not be denied surgery. Although there is no survival gain with EF ranges >60%, with EF dropping <60%, mortality increases precipitously and prompt surgical referral is critical to outcome. (Circ Cardiovasc Imaging. 2014;7:363-370.)

**Key Words:** mitral valve ■ mitral valve insufficiency ■ mortality ■ surgery ■ systole

---

**Editorial on p 220**

**Clinical Perspective on p 370**

---

Received August 22, 2013; accepted December 19, 2013.

From the Department of Cardiology, Université de Amiens, Amiens, France (C.T., D.R., C.S., F.L.); INSERM U-1088, Jules Verne University of Picardie, Amiens, France (C.T.); Cardiovascular Department, University of Bologna, Bologna, Italy (F.G., A.R.); Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic College of Medicine, Rochester, MN (H.I.M., S.V.P., M.E.-S.); Department of Cardiology, Catholic University of Louvain, Brussels, Belgium (J.-L.V., A.P.); Department of Cardiology, Aix-Marseille University, Marseille, France (J.-F.A., A.T.); and Department of Cardiology, University of Modena, Modena, Italy (A.B.).

*A list of all MIDA investigators is given in the Appendix in the Data Supplement.


Correspondence to Christophe Tribouilloy, MD, PhD, INSERM U-1088, Amiens, France and University Hospital Amiens, France, Department of Cardiology, Avenue Rene Laennec, 80054 Amiens Cedex 1, France. E-mail tribouilloy.christophe@chu-amiens.fr

© 2013 American Heart Association, Inc.

Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org

DOI: 10.1161/CIRCIMAGING.113.001251

---

Valvular Heart Disease

Long-Term Mortality Associated With Left Ventricular Dysfunction in Mitral Regurgitation Due to Flail Leaflets

A Multicenter Analysis

Christophe Tribouilloy, MD, PhD; Dan Rusinaru, MD, PhD; Francesco Grigioni, MD, PhD; Hector I. Michelaena, MD; Jean-Louis Vanoverschelde, MD, PhD; Jean-François Avierinos, MD; Andrea Barbieri, MD; Sorin V. Pislaru, MD; Antonio Russo, MD; Agnès Pasquet, MD, PhD; Alexis Théron, MD; Catherine Szymanski, MD, PhD; Franck Lévy, MD; Maurice Enriquez-Sarano, MD; on behalf of the Mitral Regurgitation International Database (MIDA) Investigators*
reparations performed. On the contrary, the 30% EF threshold is purely based on expert opinions without any supportive data, so that the effectiveness of this threshold as marker and sensitive detector of severe LV dysfunction is untested. Furthermore, the interpretation of LV systolic function based on EF has always been contested in MR because LV dysfunction may be concealed behind a normal EF attributable to the ejection in a low impedance atrial chamber. These doubts are supported by the fact that EF often decreases markedly after mitral valve surgery in contrast to frequent increase after aortic valve surgery.\(^1\) 4\(^}\(6\)\(^\)\(^7\) Other reasons to doubt these thresholds in the current era are the facts that mitral valve repair tends to result in improved postoperative LV function, that there is increased use of valve repair (despite center to center variation), and that in this context, late improvement in LV function postrepair has been recently reported.\(^5\) These combined sources of uncertainty have left doubts on whether EF is at all an appropriate current marker of LV dysfunction and outcome, whether EF <30% is the appropriate level for severe LV dysfunction, and whether EF ≤60% should continue to be used as a marker of mild/moderate LV dysfunction. These uncertainties translate into clinical inconsistencies demonstrated by US and European registries, showing poor adherence to guidelines, specifically demonstrating that patients with severe organic MR are currently often treated medically despite the presence of EF ≤60%.\(^8\)\(^\)\(^9\) Indeed, cardiologists sometimes remain passive in patients with severe MR and EF ≤60% as long as those present with no/minimal symptoms and wait for severe symptoms or further decrease in EF to decide referral for surgery.\(^10\) Thus, it is essential to improve credibility and consistent application of guidelines to reassert the link between EF and outcome under medical management and under medical/surgical management and to define appropriate thresholds for detecting overt LV dysfunction mild/moderate and severe. In those redefined subsets, it is also essential to analyze whether mitral surgery remains beneficial or should be contraindicated.

The Mitral Regurgitation International Database (MIDA)\(^1\)\(^1\)\(^2\) is a multicenter international registry of the medical and surgical outcome of MR in routine practice which includes patients with echocardiographically diagnosed flail mitral valve. In the current analysis, we aimed to reassert the link between EF and outcome irrespective of clinical management and to define specific thresholds of EF based on their sensitivity and association to clinical outcome.

### Methods

**Study Design**

The MIDA registry was assembled by merging the consecutive experience with MR due to flail leaflets of 6 tertiary centers: 2 in France (University Hospitals of Amiens and Marseille), 2 in Italy (University Hospitals of Bologna and Modena), 1 in Belgium (Brussels), and 1 in the United States (Mayo Clinic, Rochester, MN). The process of forming each center data set involved retrospective identification of consecutive patients diagnosed with MR due to flail leaflets by transthoracic echocardiography and has been previously described.\(^1\)\(^1\)\(^2\) Echocardiographic variables were obtained by download of standardized measurements, prospectively entered in the databases. We obtained institutional review board authorizations before conducting the study. The study was conducted in accordance with institutional policies, national legal requirements, and the revised Declaration of Helsinki.

Patients were enrolled in the study if they had degenerative MR with flail leaflet diagnosed by 2-dimensional (2D) echocardiography. Specific eligibility criteria\(^1\)\(^1\)\(^2\) were as follows: (1) presence of echocardiographically diagnosed flail leaflet; (2) availability of a comprehensive clinical/instrumental evaluation at the time of baseline echocardiography; (3) exclusion of ischemic MR attributable to previous or ongoing myocardial infarction; and (4) absence of significant concomitant aortic valve disease, congenital diseases, mitral stenosis, and prior valve surgery. Patients were excluded if they denied authorization for research participation. A comorbidity index summing the patient’s individual comorbidities was calculated.\(^1\)\(^3\) For the present analysis, we considered only MIDA registry patients in sinus rhythm at diagnosis in whom a measurement of EF at diagnosis was available (n=1875).

**Echocardiography**

Transthoracic echocardiograms were performed within routine clinical practice using standard methods. LV dimensions were assessed from parasternal long-axis views by 2D-guided M-mode echocardiography using the leading edge methodology at end diastole and end systole. EF was estimated by the Simpson biplane method or visually. Severity of MR was assessed semiquantitatively on a scale from 1 to 4 by Doppler echocardiography. Diagnosis of flail leaflet was based on the failure of leaflet coaptation, with rapid systolic movement of the involved leaflet tip in the left atrium.\(^1\)\(^1\)\(^2\) Echocardiograms were used as collected at the time of the index echocardiography, without subsequent modification.

**Follow-Up**

Patients were followed by their personal physicians within each participating center or outside. Information on follow-up events was obtained by direct patient interview and clinical examination or by repeated follow-up letters and questionnaires. Documentation of testing and surgical reports were reviewed and validated by the investigators. Follow-up was 98% complete. The main end point was overall survival after diagnosis starting at baseline echocardiographic evaluation and was analyzed under medical management and under medical and surgical management. Survival analysis under medical management reached up to last follow-up under medical management (censored at surgery). Survival under medical and surgical management encompassed medical and surgical management. Other end points were postoperative survival in patients who underwent surgery and cardiac mortality (after adjudication of noncardiac mortality by review of clinical records, autopsy records, and death certificates).

**Statistical Analysis**

Continuous variables were expressed as mean values±1 SD, and categorical variables were summarized as frequency percentages. EF was analyzed as categorical variable, and because EF <30% affected a minuscule number of patients (n=5; 0.3%), we used clinically meaningful cutoff values (<45%, 45%–60%, and >60%). The relationship between continuous baseline variables and EF categories was explored using 1-way ANOVA or the Kruskal–Wallis test, as appropriate. Pearson \(\chi^2\) statistic or Fisher exact test was used to examine the association between EF categories and baseline categorical variables. The significance between the highest EF group (EF >60%) and the others was examined if there was a significant difference across categories. \(P\) values were not adjusted for multiple comparisons and therefore are provided only for descriptive purposes.

For the analysis of outcome under conservative treatment, data were censored at the time of cardiac surgery, if performed. The entire follow-up was used to analyze outcome under conservative and surgical treatment. The effect of surgery on outcome was analyzed as a time-dependent covariate using the entire follow-up. Event rates±1 SE were estimated according to the Kaplan–Meier method and were compared with 2-sided log-rank tests. Univariate and multivariable analyses of time to events were performed using Cox proportional hazards models. For multivariable analyses of time to events, we used predefined Cox proportional hazards multivariable
models that included covariates considered of potential prognostic impact (sex, comorbidity index [includes age], symptoms at baseline, and presence of coronary artery disease). The proportional hazards assumption was confirmed using statistics and graphs based on the Schoenfeld residuals. For continuous variables, the assumption of linearity was assessed by plotting residuals against independent variables. We used penalized smoothing splines (P-splines) to illustrate the association of EF as a continuous variable and the risk of overall mortality under medical management. Cardiac death was analyzed by censoring those with noncardiac deaths in Cox proportional hazards multivariable models at last follow-up. A significance level of 0.05 was assumed for all statistical tests. All P values were results of 2-tailed tests. Data were analyzed with SPSS 13.0 (SPSS Inc., Chicago, IL) and S-Plus 8.0 (Insightful Inc., Seattle, WA).

### Results

#### Baseline Characteristics

The baseline characteristics of the 1875 patients are presented in Table 1. Mean age was 65±13 years, and male sex was predominant (72% of patients). About 25% of patients (n=460)

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients (n=1875)</th>
<th>&lt;45% (n=53)</th>
<th>45%–60% (n=438)</th>
<th>&gt;60% (n=1384)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65.0±13.4</td>
<td>71.0±11.3*</td>
<td>66.5±13.3†</td>
<td>64.3±13.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>72.2% (1354)</td>
<td>71.7% (38)</td>
<td>76.0% (333)</td>
<td>71.0% (983)</td>
<td>0.12</td>
</tr>
<tr>
<td>Overt symptoms</td>
<td>24.5% (460)</td>
<td>67.9% (36)*</td>
<td>29.2% (128)†</td>
<td>21.4% (296)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New York Heart Association class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>45.4% (851)</td>
<td>13.2% (7)*</td>
<td>46.8% (205)*</td>
<td>46.2% (639)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>II</td>
<td>30.1% (564)</td>
<td>18.9% (10)</td>
<td>24.0% (105)</td>
<td>32.4% (449)</td>
<td>0.02</td>
</tr>
<tr>
<td>III</td>
<td>19.0% (357)</td>
<td>56.6% (30)</td>
<td>23.5% (103)</td>
<td>16.2% (224)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>5.5% (103)</td>
<td>11.3% (6)</td>
<td>5.7% (25)</td>
<td>5.2% (72)</td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>9.8% (183)</td>
<td>39.6% (21)*</td>
<td>15.5% (68)*</td>
<td>6.8% (94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37.6% (705)</td>
<td>56.6% (30)†</td>
<td>38.1% (167)</td>
<td>36.7% (508)</td>
<td>0.013</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6.0% (113)</td>
<td>15.1% (8)†</td>
<td>7.5% (33)</td>
<td>5.2% (72)</td>
<td>0.02</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>34.3% (644)</td>
<td>35.8% (19)</td>
<td>32.4% (142)</td>
<td>34.9% (483)</td>
<td>0.62</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>5.7% (106)</td>
<td>17.0% (9)†</td>
<td>6.4% (28)</td>
<td>5.0% (69)</td>
<td>0.001</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>10.6% (198)</td>
<td>18.9% (10)</td>
<td>11.4% (50)</td>
<td>10.0% (138)</td>
<td>0.09</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>4.0% (75)</td>
<td>5.7% (3)</td>
<td>5.9% (26)†</td>
<td>3.3% (46)</td>
<td>0.04</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>7.9% (149)</td>
<td>5.7% (3)</td>
<td>8.4% (37)</td>
<td>7.9% (109)</td>
<td>0.76</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>4.6% (86)</td>
<td>17.0% (9)†</td>
<td>6.4% (28)†</td>
<td>3.5% (49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>1.0±1.3</td>
<td>2.2±1.9*</td>
<td>1.2±1.5†</td>
<td>0.9±1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Echocardiographic data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic size, mm</td>
<td>58.5±7.2</td>
<td>62.4±7.1*</td>
<td>59.1±7.9†</td>
<td>58.2±6.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-systolic size, mm‡</td>
<td>35.2±6.5</td>
<td>49.7±7.1*</td>
<td>39.6±6.6*</td>
<td>33.7±5.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>65.5±8.9</td>
<td>36.1±6.5*</td>
<td>56.7±4.1†</td>
<td>69.5±5.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left atrium size, mm</td>
<td>48.6±8.0</td>
<td>51.1±7.9</td>
<td>48.9±9.2</td>
<td>48.4±7.6</td>
<td>0.08</td>
</tr>
<tr>
<td>Systolic pulmonary artery pressure, mmHg§</td>
<td>43.0±16.0</td>
<td>51.8±19.5†</td>
<td>44.5±15.9†</td>
<td>42.3±16.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Flail posterior leaflet</td>
<td>85.5% (1604)</td>
<td>67.9% (36)*</td>
<td>82.4% (361)†</td>
<td>87.2% (1207)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>40.2% (754)</td>
<td>60.4% (32)†</td>
<td>38.4% (168)</td>
<td>40.0% (554)</td>
<td>0.008</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>17.9% (335)</td>
<td>24.5% (13)</td>
<td>20.8% (91)</td>
<td>16.7% (231)</td>
<td>0.07</td>
</tr>
<tr>
<td>Diuretics</td>
<td>31.0% (581)</td>
<td>67.9% (36)†</td>
<td>32.4% (142)</td>
<td>29.1% (403)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nitrates</td>
<td>10.2% (192)</td>
<td>22.6% (12)†</td>
<td>10.5% (46)</td>
<td>9.7% (134)</td>
<td>0.009</td>
</tr>
<tr>
<td>Warfarin</td>
<td>14.1% (265)</td>
<td>15.1% (8)</td>
<td>19.4% (85)†</td>
<td>12.4% (172)</td>
<td>0.001</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>27.9% (524)</td>
<td>28.3% (15)</td>
<td>30.0% (132)</td>
<td>27.2% (377)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

LV indicates left ventricular.

*P<0.001 individual category vs >60%.
†P<0.05 individual category vs >60%.
‡Missing in 296 patients.
§Missing in 695 patients.
had symptoms of heart failure (class III and IV) at the time of the echocardiography.

Overall, EF at diagnosis was 65.5±8.9% (median, 66%; interquartile range, 60%–71%). EF was ≤60% in 491 patients (26%) and >60% in the remaining 1384 patients (74%). Only 5 patients (0.3%) had EF <30%, so that this threshold cannot be a clinically meaningful definition of severe LV dysfunction and new thresholds need to be defined. We therefore separated 438 patients with EF of 45% to 60% from 53 patients with EF <45%. Compared with patients with EF >60%, patients with EF between 45% and 60% were slightly older, and although they had more frequent symptoms at diagnosis, most had no or minimal symptoms (Table 1). The subgroup with EF of 45% to 60% also had significantly greater LV dilatation, more frequent coronary artery disease, and overall slightly higher comorbidity index (Table 1). The subgroup with EF <45% was older (71±11 versus 64±13 years; \( P < 0.001 \)), had higher comorbidity index (2.2±1.9 versus 0.9±1.2; \( P < 0.001 \)), and had greater frequency of coronary artery disease (39% versus 7%; \( P < 0.001 \)). Patients with EF <45% had more frequently overt symptoms (68% versus 23%; \( P < 0.001 \)) than patients with EF ≥45%, but almost a third remained with no or minimal symptoms. EF <45% was also associated with greater LV diameters and more frequent prescription of angiotensin-converting enzyme inhibitors, diuretics, and nitrates (Table 1).

In 432 patients (23%), management was solely medical, whereas 1443 patients (77%) were initially managed medically and then underwent surgery. Mean duration of follow-up with medical and surgical treatment was 9.3±5.5 years.

### Outcome in Conservatively Managed Patients

Overall, the Kaplan–Meier estimate of 8-year all-cause mortality was 40±2%, and estimated mortality according to EF categories (<45%, 45%–60%, and >60%) is displayed in Figure 1. The best outcome was observed in patients with EF >60% (Figure 1). Patients with EF between 60% and 75% and patients with EF >75% had practically identical estimated 8-year all-cause mortality (35±3% versus 33±4%; \( P = 0.87 \)).

With EF <45%, 8-year estimated mortality was extremely high (89±7%; Figure 1). The group of patients with EF of 45% to 60% had intermediate estimated 8-year mortality (49±5%), lower compared with EF <45% but higher compared with EF >60% (\( P = 0.006 \) for EF between 45% and 60% versus >60%). The risk of death associated with EF ≤60% was almost 2-fold greater compared with EF >60% (hazard ratio [HR], 1.89 [1.43–2.50]). After adjustment for sex and comorbidity index (includes age), EF ≤60% was independently associated with all-cause mortality (adjusted HR, 1.70 [1.28–2.25]). Further adjustment for symptoms and coronary artery disease did not influence this independent relationship (adjusted HR, 1.59 [1.19–2.12]). To estimate the character of the relationship between EF and the risk of all-cause mortality, we used spline functions for EF (Figure 2). On multivariable analysis, there was no increase in mortality risk with decreasing EF when it remained >60% (adjusted HR, 0.98 [0.92–1.06] per 1% EF decrement; \( P = 0.56 \)). With EF ≤60%, there was important increase in mortality risk with decreasing EF (adjusted HR, 1.12 [1.02–1.20] per 1% EF decrement; \( P = 0.005 \)). Compared with patients with EF >60%, patients with EF <45% had >4-fold increase in the risk of all-cause death under medical management (Table 2). This strong association remained valid after adjustment for sex, comorbidity index, symptoms, and coronary artery disease (adjusted HR, 2.43 [1.50–3.95]; Table 2). The group with EF of 45% to 60% exhibited moderate increase in all-cause mortality on univariate analysis (adjusted HR, 1.42 [1.04–1.95]; Table 2). However, this was lower than the risk observed in patients with EF <45% (\( P = 0.002 \) for EF between 45% and 60% versus EF <45%). Further adjustment for the leaflet involved did not influence the results (adjusted HR, 1.42 [1.05–1.96]; \( P = 0.029 \) for EF 45%–60% versus EF >60% and adjusted HR, 2.41 [1.48–3.92]; \( P < 0.001 \) for EF <45% versus EF >60%).

Compared with EF >60%, cardiac mortality under conservative management was considerable for patients with EF <45% (adjusted HR, 3.21 [1.93–5.34]; \( P < 0.001 \)), but did not reach statistical significance with EF of 45% to 60% (adjusted HR, 1.14 [0.78–1.68]; \( P = 0.49 \)). The excess risk of cardiac mortality according to ejection fraction (EF) in patients with organic mitral regurgitation under conservative management.

![Figure 1. All-cause mortality according to ejection fraction (EF) in patients with organic mitral regurgitation under conservative management.](image1)

![Figure 2. Association between ejection fraction and the risk of all-cause death under conservative management. Hazard ratio (solid line) and 95% confidence intervals were estimated in a Cox multivariable model with ejection fraction represented as a spline function and adjusted for sex, comorbidity index, symptoms, and coronary artery disease.](image2)
Table 2. Relative Risk of All-Cause Mortality Associated With EF Levels

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted for comorbidity index and sex</th>
<th>Adjusted for comorbidity index, sex, symptoms, and CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medical Management</td>
<td>Medical and Surgical Management*</td>
<td>Postoperative Outcome</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>EF &gt;60%</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>EF 45%–60%</td>
<td>1.54 (1.13–2.10)</td>
<td>0.006</td>
<td>1.50 (1.19–1.87)</td>
</tr>
<tr>
<td>EF &lt;45%</td>
<td>4.76 (3.02–7.48)</td>
<td>&lt;0.001</td>
<td>3.92 (2.70–5.71)</td>
</tr>
<tr>
<td>EF &gt;60%</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>EF 45%–60%</td>
<td>1.41 (1.03–1.92)</td>
<td>0.032</td>
<td>1.40 (1.12–1.76)</td>
</tr>
<tr>
<td>EF &lt;45%</td>
<td>3.75 (2.37–5.92)</td>
<td>&lt;0.001</td>
<td>3.16 (2.17–4.60)</td>
</tr>
</tbody>
</table>

Charlson comorbidity index includes age. CAD indicates coronary artery disease; CI, confidence interval; EF, ejection fraction; and HR, hazard ratio.

*Analysis of outcome with medical and surgical management also includes surgery as time-dependent covariate.

death associated with EF <45% was of comparable magnitude in younger (<65 years) and in older (≥65 years) patients (P for interaction=0.12).

Outcome With Medical and Surgical Treatment

Mitral valve surgery was performed in 1443 patients (77%), and in 85% of cases, the surgical procedure was valve repair. As expected, compared with surgical patients, those in whom management was solely medical were older, had milder symptoms, and had less severe markers of volume overload by echocardiography (all P<0.01).

Operative mortality was 1.7% with EF ≤60% and 1.1% with EF >60% (P=0.30). The lowest long-term mortality was observed with EF >60% (at 8 years, the Kaplan–Meier estimate of mortality was 20±2% versus 32±2% with EF ≤60%; P=0.001), but was not different whether EF was 60% to 75% or >75% (20±4% versus 19±5%; P=0.95). In comparison, estimated mortality was higher with EF of 45% to 60% (28±2%; P<0.001) and dramatically higher with EF <45%, (62±7%; P<0.001).

EF ≤60% was independently predictive of all-cause mortality during the entire follow-up (adjusted HR, 1.51 [1.22–1.87]). Patients with EF <45% had >3-fold increase in the risk of all-cause death compared with patients with EF >60% (Table 2). After adjustment for covariates, the risk of death was still almost 2 times greater for EF <45% compared with EF >60% (adjusted HR, 2.46 [1.67–3.61]; Table 2). The group with EF of 45% to 60% had moderate increase in mortality on univariable (Table 2) and multivariable analysis (adjusted HR, 1.37 [1.09–1.72]; Table 2) compared with EF >60%. This risk was lower compared with that observed with EF <45% (P=0.02). Results were unaffected after further adjustment for the leaflet involved (adjusted HR, 1.21 [1.04–1.40]; P=0.011 for EF 45%–60% versus EF >60% and adjusted HR, 1.69 [1.24–2.26]; P=0.001 for EF <45% versus EF >60%).

During the entire follow-up, both mild/moderate (EF 45%–60%) and severe (EF <45%) LV dysfunction were associated with increased risk of cardiac death (adjusted HR, 1.40 [1.10–1.78]; P=0.006 for EF 45%–60% versus EF >60% and adjusted HR, 2.58 [1.74–3.83]; P<0.001 for EF <45% versus EF >60%). There was no interaction (P for interaction=0.29) between the risk of cardiac death associated with EF <45% and age groups (<65 and ≥65 years).

One hundred ninety-four deaths were recorded in operated patients during postoperative follow-up (6.6±2.2 years). EF <60% remained independently predictive of death (adjusted HR, 1.39 [1.03–1.88]) during postoperative follow-up. Compared with EF >60%, the subgroup with EF <45% remained at high risk of death (Table 2) after surgery, whereas this risk was lower but still significant for the subgroup with EF of 45% to 60% (Table 2). Excess risk of cardiac death associated with mild/moderate and severe LV dysfunction was also observed during postoperative follow-up (adjusted HR, 1.74 [1.28–2.37]; P<0.001 for EF 45%–60% versus EF >60% and adjusted HR, 2.33 [1.21–4.50]; P=0.011 for EF <45% versus EF >60%). Postoperative survival was overall better with valve repair compared with valve replacement (8-year survival: 89±1% versus 73±4%; P<0.001). However, postoperative survival was significantly different between EF categories both in those who underwent valve repair and those with valve replacement (both P<0.01).

Using surgery as a time-dependent variable, the overall benefit of surgery was considerable (adjusted HR, 0.51 [0.43–0.65]). There was no interaction between EF at diagnosis and the magnitude of survival benefit after surgery using this time-dependent analysis (P for interaction=0.67). Thus, a considerable benefit of surgery was observed in all strata of EF (Figure 3) but was, in absolute terms, impressive in patients with EF <45% despite their excess postoperative mortality. Specific analysis of the EF <45% strata showed no
interaction with the magnitude of survival benefit after surgery ($P$ for interaction=0.78). Finally, there was no interaction between EF and valve repair on overall survival ($P=0.73$) so that repair does not negate the excess mortality associated with decreased EF.

**Discussion**

The present study based on a large international registry of degenerative MR demonstrates that grading LV dysfunction requires MR-specific thresholds. First, EF, despite the criticisms related to the loading conditions, is a major independent determinant of long-term outcome under medical or surgical management. Second, defining severe LV dysfunction by EF <30% is clinically ineffective because this level affects a minuscule percentage of patients. Conversely, EF <45% is more frequent and is associated with considerable mortality under medical management. Thus, EF <45% truly defines severe LV dysfunction in these patients with degenerative MR. The spline analysis shows that EF dropping <60% is a turning point of mortality and the group with EF of 45% to 60% represents a large proportion of patients (23%) and is not clinically distinguishable, as few of these patients present with overt symptoms of heart failure. This range of EF is associated with a more moderate increase in mortality and can be considered as mild/moderate LV dysfunction. With EF >60%, outcome is not affected by further EF stratification, so that this measure remains insensitive to incipient LV dysfunction in the normal EF range. In this EF range, mitral surgery is associated with lower long-term mortality. The risk of cardiac death follows the same pattern; it is considerable in the setting of EF <45%, more moderate with EF of 45% to 60%, and it persists after mitral surgery. Importantly, in the subgroups in which EF identifies overt LV dysfunction, the benefit of surgery remains considerable in both groups with EF <45% and with EF of 45% to 60%. Hence, the diagnosis of severe or mild/moderate LV dysfunction based on EF is not a rationale to deny surgical treatment of the MR but conversely an incentive to indicate a rescue surgical treatment promptly.

EF is a classical index of LV systolic function, but in MR it has been decried because LV dysfunction may be concealed behind a normal EF because of profoundly modified loading conditions. Over time, patients with severe chronic MR develop an irreversible impairment in LV systolic function and exhibit progressive decline in EF. Previous single-center studies in organic MR have suggested in limited patient samples that reduced EF at diagnosis is associated with greater mortality under medical management. Most available evidence regards the association of decreased preoperative EF with increased postoperative occurrence of LV dysfunction, heart failure, and death. Accordingly, despite physiological reluctance to use EF in the context of MR, it has been clinically recognized as providing value in clinical decision making and reduced (≤60%) EF is currently a class I indication for considering mitral surgery. In contrast to apparently coherent guidelines, recent registry data show that too often patients with severe MR and overt LV dysfunction based on low EF are still not referred to surgery and are exposed to unacceptably high risk of death with medical management. In a survey conducted among adult cardiologists in Canada, Tolendano et al. report that when considering surgery in patients with significant organic MR and New York Heart Association class II symptoms, 21% of respondents would refer when EF decreases to 40% to 49%. For asymptomatic patients, >30% of respondents would wait for EF to fall <50% to consider surgery. US data show that almost approximately half the patients with severe organic MR are not referred for surgery despite clear surgical indications, particularly low EF. This low rate of surgical referral is not rationalized as related to greater operative risk but to unconvincing guidelines recommendations. In the EuroHeart Survey on valvular heart disease, almost 50% of patients with severe symptomatic MR were not referred for surgery because of high comorbidity, old age, or reduced EF. Interestingly, EF between 30% and 60% instead of being considered an indication for surgery was associated with a frequent decision not to operate, independently of all other characteristics. These behavioral divergences are probably explained by uncertainties or insufficient evidence regarding the link between EF and excess risk of long-term mortality, the EF thresholds in organic MR, and the benefit of an eventual rescue surgery.

---

**Figure 3.** Outcome in ejection fraction (EF) subsets of patients with organic mitral regurgitation compared between surgical and medical management. Curves are adjusted for sex, comorbidity index, symptoms, and coronary artery disease, and surgery is treated as a time-dependent variable. A, Normal left ventricular (LV) function. B, Mild/moderate LV dysfunction. C, Severe LV dysfunction. HR indicates hazard ratio.
Our large registry demonstrates that undoubtedly EF at diagnosis is a valuable marker of LV dysfunction and that decreased EF is associated with poor outcome in patients with severe organic MR under conservative management. In terms of thresholds, our study provides new evidence that should allow more data-driven and convincing guidelines. We confirm that the threshold of EF of 60% is a turning point in terms of risk. However, other thresholds mentioned in clinical guidelines as a result of expert opinions do not fit with our results. The threshold of EF <30% in defining severe LV dysfunction by similarity to cardiomyopathies is not relevant because the overloaded LV of organic MR rarely reaches such a level. Including EF of 30% to 45% among the mild/moderate LV dysfunction underestimates the bleak outlook of these patients, and it seems more relevant to define severe LV dysfunction as EF <45%, not only in term of number of patients but also because when EF falls <45%, outcome under medical management is extremely poor. In the light of these findings, we think that EF <45% must be considered a threshold of severe LV dysfunction in severe organic MR, whereas EF values between 45% and 60% should represent mild-to-moderate LV dysfunction. In term of surgical management for these different categories, our data suggest that operative mortality is low in all EF strata and that the fear of operative risk should not be part of undue surgical delay. The survival benefit of patients with severe MR and EF <45% who undergo surgery is similar to that with EF ≥45%. Therefore, these patients with EF <45% should not be denied rescue surgery if comorbidity burden is not excessive particularly if mitral valve repair is feasible. Despite the large size of the MIDA registry, few patients with severely depressed EF (<30%) and organic MR are ever diagnosed and guidelines based on our data or even on clinical experience are impossible to draw, particularly regarding the ethically charged subject of not offering surgical treatment. For such patients who are symptomatic, current guidelines recommend surgery if mitral valve repair is feasible. It is our practice with organic MR and reduced EF to also ascertain the severity of the MR quantitatively to indicate mitral surgery.

On the contrary, previous studies have demonstrated that the long-term postoperative survival of patients with EF >60% rejoins the survival of the general population even after taking into account operative mortality. Cardiologists should be aware of the excellent postoperative outcome of these patients and consider referring patients for surgery before EF falls <60%, a class II recommendation of clinical guidelines, which avoids the excess risk associated with preoperative LV dysfunction. Indeed, our results show that surgery for EF ≤60% is followed by excess risk of death and that the best outcome is achieved when surgery is considered when EF is >60%.

Limitations
A limitation of the present study was that whereas echocardiographic data were prospectively collected, clinical and nonechocardiographic data were obtained by review of medical records. However, clinical ambiguities are not relevant to the present analysis based on the objective report of EF and its implication in regard to all-cause mortality. Quantitative assessment of MR severity (proximal isovelocity surface area method or width of the vena contracta) was not required for enrollment in the MIDA registry, and semiquantitative classification of MR severity was performed. The MIDA database used flail leaflet as a surrogate for severe MR. Although prominent flail usually is associated with severe MR, not all flail leaflets are associated with severe MR but most patients in the present study were felt to have severe MR (92%) at the time of echocardiography interpretation. Thus, we think that these findings can be extrapolated to most patients with degenerative MR and more generally to chronic severe organic MR.

In the present study, patients were followed by their individual physicians. This is a potential source of variability and inconsistency in medical care but conversely has the advantage to make our results relevant to standard clinical practice in diverse practice settings. We acknowledge that among included cases, there were some patients who presented with characteristics now known as class I surgical indications by guidelines. Surgery was delayed because physicians judged that these patients were well initially with medical management. We did not perform any multiple comparison correction, therefore some results significant at the 5% level, but not the 1% level, might be false positives. Finally, the MIDA registry did not require collection of serial EF measurements. Therefore, our analysis cannot link baseline EF and follow-up EF with medical or surgical treatment.

Clinical Implication
This analysis of a large international registry of organic MR in routine clinical practice shows that in the setting of severe MR, EF is a valuable parameter in defining the severity of LV dysfunction and in predicting survival after diagnosis. EF <30% is exceptional and therefore is not a useful threshold for clinical management. EF <45% defines severe LV dysfunction with catastrophic mortality under medical management. However, surgery is still beneficial in these patients who should not be denied the correction of the valvular defect. Furthermore, in patients with severe organic MR and EF dropping <60%, the risk of mortality increases precipitously and these patients should be promptly operated.

This new evidence emphasizes the importance of educating physicians on data-driven thresholds of LV dysfunction with organic MR because delayed surgery might lead to irreversible myocardial damage, exposing the patient to unacceptably high risk of adverse events.

Sources of Funding
This study was supported by a grant from the University of Bologna, Italy, donated by the Foundation Luisa Fanti Melloni and contributions from the Banca del Monte Foundation, Italy.

Disclosures
Dr Grigioni has received payment for lectures from Edwards Lifesciences. Dr Enriquez-Sarano serves as board member for Valtech and received grant funding from Abbott Vascular. The other authors have no conflicts to report.

References
Ejection fraction (EF) as marker of left ventricular (LV) dysfunction and the thresholds for severe or mild/moderate LV dysfunction in mitral regurgitation are debated and, in general, not diligently followed in clinical practice. We assessed the prognostic role of EF in 1875 patients with mitral regurgitation due to flail leaflets in sinus rhythm enrolled in the Mitral Regurgitation International Database (MIDA) registry. The main finding of our analysis is that grading LV dysfunction in mitral regurgitation requires specific thresholds. First, EF is a major independent determinant of long-term outcome under medical or surgical management. Second, defining severe LV dysfunction by EF <30% is clinically inadequate because this level affects few patients. Conversely, EF <45% is more frequent, is associated with considerable long-term mortality, and likely reflects severe LV dysfunction. EF dropping <60% is an important threshold for mortality. The group with EF between 45% and 60%, which represents a large proportion of patients (23%), is associated with a more moderate increase in mortality and can be considered as mild/moderate LV dysfunction. With EF >60%, outcome is not affected by further EF stratification, so that this measure remains insensitive to incipient LV dysfunction in the normal EF range. In this EF range, mitral surgery is associated with lower long-term mortality. Importantly, in the subgroups in which EF identifies overt LV dysfunction (EF <45% and EF 45%–60%), the benefit of surgery remains considerable.
Long-Term Mortality Associated With Left Ventricular Dysfunction in Mitral Regurgitation Due to Flail Leaflets: A Multicenter Analysis
Christophe Tribouilloy, Dan Rusinaru, Francesco Grigioni, Hector I. Michelena, Jean-Louis Vanoverschelde, Jean-François Avierinos, Andrea Barbieri, Sorin V. Pislaru, Antonio Russo, Agnès Pasquet, Alexis Théron, Catherine Szymanski, Franck Lévy and Maurice Enriquez-Sarano
on behalf of the Mitral Regurgitation International Database (MIDA) Investigators*

Circ Cardiovasc Imaging. 2014;7:363-370; originally published online December 20, 2013; doi: 10.1161/CIRCIMAGING.113.001251
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/7/2/363

Data Supplement (unedited) at:
http://circimaging.ahajournals.org/content/suppl/2013/12/20/CIRCIMAGING.113.001251.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org//subscriptions/
APPENDIX

MIDA investigators

Bruxelles, Belgium
Jean-Louis Vanoverschelde, Agnes Pasquet, Christophe de Meester, Patrick Montand, Fabien Chenot, Bernhard Vancrayenest, and Gebrine El-Khoury

Bologna, Italy
Francesco Grigioni, Antonio Russo, Elena Barbaresi, Giuseppe Marinelli, Marinella Ferlito, Elena Biagini, Claudio Rapezzi, and Angelo Branzi.

Modena, Italy
Andrea Barbieri, Roberta Lugli, Francesca Mantovani, Chiara Manicardi, Francesca Bursi, and Maria Garzia Modena

Amiens, France
Christophe Tribouilloy, Dan Rusinaru, Catherine Szymanski, Gilles Touati, Thierry Caus, Jean Paul Remadi, Franck Lévy, and Faouzi Trojette

Marseille, France
Jean-Francois Avierinos, Alexis Théron, and Gilbert Habib

Mayo Clinic, Rochester, MN, US
Maurice Enriquez-Sarano, Rakesh M. Suri, Hector I. Michelena, Hartzell V. Schaff, Marianne Huebner, and Douglas Mahoney