

# Impact of ageing on presentation and outcome of mitral regurgitation due to flail leaflet: a multicentre international study

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Received 22 December 2012; revised 24 May 2013; accepted 10 June 2013; online publish-ahead-of-print 12 July 2013

## Aims

Define the impact of age at diagnosis on degenerative mitral regurgitation (MR) prognosis.

## Methods and results

The Mitral regurgitation International DAtabase (MIDA) is a multicentre registry of MR due to flail leaflets including 862 patients ( $65 \pm 12$  years) diagnosed by echocardiography. The 498 older patients ( $\geq 65$  years at diagnosis) were compared with the 364 younger ( $< 65$ ) with regard to presentation and the outcome was compared with that expected in the general population. Older vs. younger patients had MR of similar severity and ventricular overload but presented with more MR consequences and incurred higher mortality [risk ratio (rr) 95% confidence interval (95% CI) 4.7 (2.5–10.0),  $P < 0.001$ ] independently of co-morbidity. Compared with expected survival [relative risk (95% confidence interval)], excess mortality, non-significant in younger patients [1.1 (0.6–2.0),  $P = 0.65$ ], was prominent in older patients [1.4 (1.2–1.7),  $P < 0.001$ ]. Compared with expected, excess heart failure (HF) occurred in younger [9.3 (6.5–13.3),  $P < 0.0001$ ] and in older patients [6.7 (5.6–8.1),  $P < 0.0001$ ]. Excess atrial fibrillation (AF) was even higher in younger [6.9 (4.5–10.6),  $P < 0.0001$ ] than in older patients [3.5 (2.6–4.7),  $P < 0.0001$ ;  $P < 0.001$  for comparison between age groups]. Subsequent excess mortality [rr (95% CI)] was associated with occurrence of HF and/or AF in both age groups [13.5 (7.4–24.6),  $P < 0.001$ ]. Mitral surgery was associated with reduced long-term mortality in older patients and lower rate of HF in both the age groups (all  $P < 0.01$ ).

## Conclusions

Both older and younger patients incurred excess risk of complications. Older patients suffered excess mortality, AF, and HF, whereas younger incurred excess morbidity linked to subsequent long-term excess mortality. The excess risks of uncorrected degenerative MR should be considered in deliberating surgical management, which significantly reduced mortality in older patients and HF in younger patients.

## Keywords

Mitral regurgitation • Ageing • Congestive heart failure • Atrial fibrillation • Outcome • Mitral valve surgery

## Introduction

The prevalence of mitral regurgitation (MR) in the population is strongly linked to ageing<sup>1</sup> due to current predominance of degenerative causes of MR<sup>2</sup> but among patients presenting with degenerative MR the age distribution is wide.

Regarding clinical outcome, reports on the natural history of degenerative MR differ considerably. Observations of adverse prognosis, including excess mortality under medical management<sup>3,4</sup> even in asymptomatic patients,<sup>5,6</sup> are indeed contradicted by a report of benign outcome with low mortality.<sup>7</sup> Reported morbidity

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rates after diagnosis, specifically congestive heart failure (CHF) and atrial fibrillation (AF), are also notably discordant.<sup>3,7–9</sup>

Examining the baseline characteristics of various series, a critical difference relates to age at diagnosis, which is on average in the early-mid-50s in studies with a benign outcome<sup>7,10</sup> and in the mid-60s in studies with excess mortality.<sup>3–6</sup> It is well known that independently of any cardiac disease, age adversely affects the prevalence of symptoms, AF, left atrial (LA) size, and systolic pulmonary artery pressure (SPAP).<sup>11–13</sup> However, the influence of ageing *per se* on the tolerance of a specific disease such as organic MR is unknown and the critical issue of excess mortality and morbidity when compared with expected in the general population in each age group has not been reported in this setting.

The Mitral regurgitation International DAtabase (MIDA) offers the opportunity to provide large multicentre data, collected in Europe and USA, enrolling consecutive patients in routine practice with flail mitral.<sup>14,15</sup> The aims of the present study conducted in this large population of patients uniformly diagnosed with degenerative MR due to a flail leaflet were to investigate the association between age at diagnosis and subsequent mortality and morbidity and to analyse the rates of these complications in comparison with those expected in the general population in two age groups.

## Methods

### Study design

The design of the MIDA registry was previously reported.<sup>15</sup> Briefly, the registry includes consecutive patients prospectively entered in the electronic databases in four tertiary centres in Europe (University Hospitals in France—Amiens and Marseille, and Italy—Bologna and Modena) and one in the USA (Mayo Clinic, Rochester, MN, USA). The Mitral regurgitation International DAtabase centres and investigators are listed in the Appendix. Patients who denied authorization for anonymous publication of their clinical data for research purposes were excluded; the study was conducted in accordance with institutional guidelines, national legal requirements, and the revised Helsinki declaration.

Patients were eligible if they had degenerative MR with a flail leaflet diagnosed by two-dimensional echocardiography between 1980 and 2004 in the five participating centres. Specific eligibility criteria for entry in the MIDA registry were as follows: (i) transthoracic echocardiographical diagnosis of a flail mitral leaflet according to the validated criteria, i.e. failure of leaflet coaptation, with a rapid systolic movement of the involved leaflet tip in the left atrium,<sup>3,16</sup> (ii) comprehensive clinical/echocardiographical evaluation at diagnosis, (iii) exclusion of ischaemic MR [both organic due to papillary muscle rupture and secondary ischaemic MR due to left ventricular (LV) remodelling], and (iv) the absence of significant concomitant aortic valve disease, congenital diseases, mitral stenosis, and prior valve surgery. Concomitant coronary artery disease was not an exclusion criterion provided that MR was not the consequence of ischaemic LV dysfunction. A comorbidity index was calculated.<sup>17</sup> A total of 862 patients were enrolled in the MIDA registry. Previous reports on the MIDA population have respectively focused on the European population<sup>14</sup> and on the prognostic value of end-systolic LV diameter,<sup>15</sup> LA diameter,<sup>18</sup> and SPAP.<sup>19</sup> The current report is the first to report all patients enrolled in the MIDA registry.

### Echocardiography

Baseline transthoracic echocardiograms were performed within routine clinical practice, using standard methods<sup>20</sup> and prospective

measurements of LV diameters and ejection fraction (EF), LA diameter, and SPAP whenever possible were entered in each of the original institutional databases. Severity of MR was assessed semi-quantitatively on a scale from 1 to 4+ by Doppler echocardiography.<sup>14</sup> Diagnosis of a flail mitral leaflet was based on the failure of leaflet coaptation, with a rapid systolic movement of the involved leaflet tip in the LA.<sup>14</sup>

### Follow-up

Follow-up extended from the baseline evaluation until the closure of the study or death, so that 99% of patients provided follow-up information until death, mitral surgery, study closure, or at least 5 years post-diagnosis. During the follow-up, patients were monitored by their personal physicians and information was harvested on a 2-year schedule basis. Baseline clinical variables were obtained by review of medical records. Events were ascertained by clinical interviews, detailed questionnaires completed by review of clinical documents of outside institutions, or by telephone calls to physicians and patients. Autopsy records and death certificates were consulted for attribution of causes of death.

### Statistical analysis

Variables are expressed as mean  $\pm$  SD or percentages. Two age groups were separated based on the mean age at diagnosis, 65 years, which is a common landmark used in previous studies<sup>8</sup> and also administratively to mark older age. In addition, analysis of relative risk (RR) of mortality and morbidity expressed as a spline function of age as a continuous variable suggested that this age cut-off was an acceptable threshold of increased risk of adverse events.

Comparison between age groups used  $\chi^2$  or *t*-test. Endpoints were mortality, CHF, and new AF in patients in sinus rhythm at diagnosis, under medical management, censoring patients at death or mitral surgery. Survival curves were obtained by Kaplan–Meier method. To assess the impact of age *per se* on outcome, comparison of observed-to-expected event rates were stratified by age groups, using specific US and European life tables for mortality, CHF,<sup>21,22</sup> and AF.<sup>23</sup> Briefly, these reported incidence rates were used to estimate each individual's expected events over their respective follow-up time. These expected events were then used as offset terms within a Poisson regression model to estimate RR of events within the cohort with that expected in the population and allowed the estimation of the excess risk between age groups by adjusting for their expected event rates. The independent impact of older age was confirmed by Cox proportional hazards multivariable models used to calculate adjusted risk ratios (rr) and 95% confidence intervals (95% CI) for the following covariates defined *a priori*, i.e. sex, co-morbidity, symptoms, AF, LV end-systolic diameter, and EF. Co-morbidity used the validated Charlson comorbidity index that takes into account the number and severity of associated comorbid conditions, providing a single variable which was used in Cox proportional hazards analyses.<sup>18</sup> In addition to fitting age as a continuous variable, age was also fit using cubic splines in the Cox models. This allows for a robust fit of age and allows assessing the functional relationship of hazard with respect to age. All analyses were repeated after stratification by medical centre in order to have a natural adjustment of a possible centre effect. For the analysis concerning the effect of CHF or new AF on subsequent mortality, these events were considered as time-dependent covariates. Although not the focus of the present study which primarily aimed to report the natural history of flail leaflets according to age, the impact of mitral surgery on mortality, CHF, and AF was analysed using mitral surgery as a time-dependent variable within the entire follow-up, medical and post-surgical in multivariable models using same covariates, i.e. sex, co-morbidity, symptoms, AF, LV end-systolic diameter, and EF. All statistical tests were two-sided and *P* values <0.05 were considered

statistically significant. Analyses were performed using R free (version 2.8.1), SAS, and JMP software.

## Results

### Baseline characteristics

The baseline characteristics of all 862 patients with a flail mitral leaflet from the five participating centres are presented in *Table 1*. The age at diagnosis was  $65 \pm 12$  years, the majority of patients were males and the average co-morbidity index was low. The majority of patients

(789 patients, 92%) had  $MR \geq$  grade III, attesting the almost uniform severity of the regurgitation in agreement with current guidelines mentioning the flail leaflets as a specific marker of severe MR. The remaining patients had Grade II MR.

Most patients presented with no or minimal symptoms in the sinus rhythm. Comparison between younger ( $<65$ ) and older ( $\geq 65$ ) patients revealed important differences (*Table 1*). Older patients included more women and therefore their LV dimensions were smaller. However, once normalized for the body surface area, there was no difference between age groups in LV enlargement in agreement with similar percentage of patients with Grade 3 or 4

**Table 1** Baseline clinical and echocardiographical characteristics of 862 patients with flail leaflet and comparison between the two age groups

Characteristic	All patients (n = 862)	Age < 65 (n = 364)	Age $\geq$ 65 (n = 498)	P-value
Age (years)	$65 \pm 12$	$54 \pm 9$	$74 \pm 6$	<0.001
Male sex %	70	80	62	<0.001
History				
Coronary artery disease %	9	5	11	0.002
Infective endocarditis %	11	13	9	0.03
Hypertension %	34	28	38	0.004
ID diabetes mellitus %	1	0.80	1.60	0.3
Dyslipidaemia %	31	32	31	0.7
Comorbidities				
Renal disease %	6	2	8	<0.001
Cerebrovascular disease %	3	2	4	0.3
Pulmonary disease %	9	6	12	0.004
History of neoplasia %	10	6	13	<0.001
Charlson comorbidity index	$1.07 \pm 1.22$	$0.78 \pm 1.07$	$1.29 \pm 1.28$	<0.001
Symptoms %				
None or minimal	70	79	63	<0.001
Class NYHA III	21	15	26	
Class NYHA IV	9	6	11	
Atrial fibrillation %	20	11	28	<0.001
Echocardiographical data				
Flail location %				
Posterior leaflet	83	83	83	0.7
Anterior leaflet	6	5	6	
Both leaflets	11	12	10	
LV diastolic diameter (mm)	$59 \pm 8$	$61 \pm 8$	$58 \pm 7$	<0.001
LV diastolic diameter/BSA ( $\text{mm}/\text{m}^2$ )	$33 \pm 5$	$33 \pm 5$	$33 \pm 5$	0.2
LV systolic diameter (mm)	$36 \pm 7$	$37 \pm 7$	$35 \pm 7$	0.002
LV systolic diameter/BSA ( $\text{mm}/\text{m}^2$ )	$20 \pm 4$	$19 \pm 4$	$20 \pm 4$	0.2
Ejection fraction %	$65 \pm 10$	$66 \pm 9$	$64 \pm 10$	0.08
Ejection fraction $\geq$ 60%	80	81	79	0.4
LA diameter (mm)	$50 \pm 9$	$49 \pm 9$	$50 \pm 9$	0.13
LA diameter/BSA ( $\text{mm}/\text{m}^2$ )	$28 \pm 6$	$27 \pm 5$	$29 \pm 6$	<0.001
SPAP (mmHg)	$44 \pm 15$	$40 \pm 14$	$46 \pm 16$	<0.001

Values are expressed as mean  $\pm$  SD or percentages.

BSA, body surface area (all measurement indicated/BSA are those normalized for BSA and are expressed in  $\text{mm}/\text{m}^2$ ); ID, insulin-dependent; LA, left atrium; LV, left ventricle; NYHA, New York Heart Association; SPAP, systolic pulmonary artery pressure.

MR (91 vs. 92% in younger vs. older patients,  $P = 0.62$ ). Compared with younger, severe symptoms and AF were more frequent in older patients, indexed LA diameter was larger, and SAP higher. Older patients presented more frequently with past history of cardiovascular (CV) disease, risk factors, and co-morbid conditions.

## Mortality under medical management

During 1941 person-year of follow-up under medical management (mean:  $6.0 \pm 3.7$ ; median: 6.3 years), 113 patients died, 83 from CV cause. At 5 and 10 years after the diagnosis, the survival rates were  $75 \pm 3\%$  and  $54 \pm 4\%$ , respectively, which reflected the overall excess mortality vs. expected in the general population of same age and sex [RR (95% CI) vs. expected 1.4 (1.1–1.6),  $P < 0.001$ ]. As expected, most deaths occurred in the older age group and the 10-year survival was  $89 \pm 3\%$  in the younger group vs.  $34 \pm 6\%$  in the older group ( $P < 0.0001$ ). Higher mortality in the older group was only partially explained by co-morbidity and risk factors. Indeed in Cox proportional hazards analysis, the risk ratios associated with age  $\geq 65$  were 6.4 (3.7–12.3),  $P < 0.0001$  univariably and 4.7 (2.5–10.0),  $P < 0.001$  in multivariable modelling. The 10-year CV mortality was of  $7 \pm 3\%$  in patients  $< 65$  compared with  $56 \pm 7\%$  in patients  $\geq 65$  ( $P < 0.0001$ ), a difference confirmed in multivariable analysis [rr (95% CI): 5.5 (2.5–14.8),  $P < 0.0001$ ].

Comparison of observed mortality of our MR cohort with that expected for age and sex showed in older patients a 40% excess mortality [rr (95% CI): 1.4 (1.2–1.7),  $P < 0.001$ ], whereas the difference was not significant in patients  $< 65$  [RR (95% CI): 1.1 (0.65–2.0),  $P = 0.65$ , Figure 1B and A, respectively]. When the risk of death was analysed as a function of age as a continuous variable in a spline function format (Figure 2A), the mortality risk increased regularly with age at diagnosis and crossed the average (RR = 1 on the y-axis) in the 55–65 years range. The risk of excess mortality between the MR cohort and the general population, according to age as a continuous variable is presented in Figure 2B. The curve was flatter than that

regarding mortality according to age within the cohort, and showed in younger patients a 95% range covering the RR = 1 line denoting the absence of significant excess mortality. Subsequently, the curve crossed the line of RR = 1 denoting excess mortality and trending upward indicating an excess risk not abating with more ageing.

## Morbidity under medical management

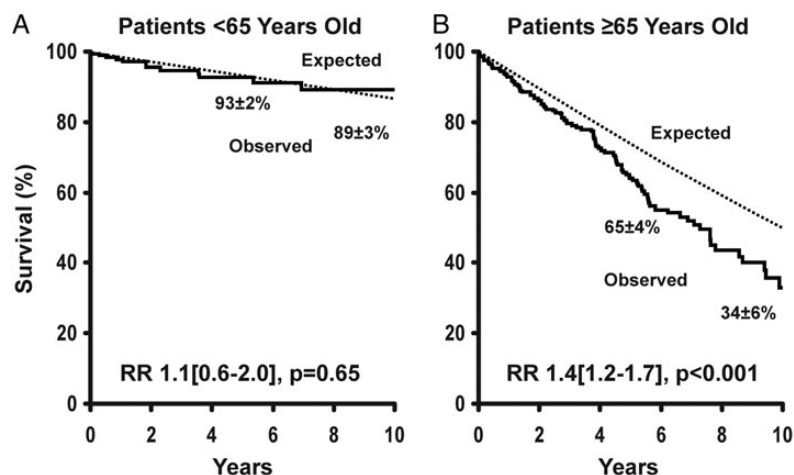
### Influence of age on rates of congestive heart failure and atrial fibrillation

Under medical management, 145 patients experienced CHF ( $56 \pm 4\%$  at 10 years).

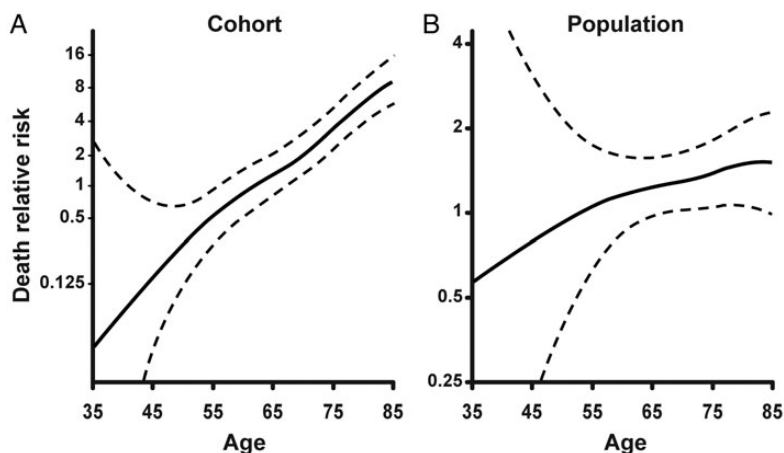
Five- and 10-year rates of CHF after diagnosis were  $19 \pm 4$  and  $28 \pm 5\%$  in patients  $< 65$  and were  $42 \pm 4$  and  $76 \pm 6\%$  in patients  $\geq 65$  ( $P < 0.0001$ , Figure 3). In multivariate analysis, age  $\geq 65$  years remained predictive of higher rates of CHF [rr (95% CI): 2.7 (1.7–4.3,  $P < 0.001$ ].

Analysis of the within-cohort risk of CHF according to age as a continuous variable (Figure 4A) showed a progressive increase of CHF risk with age with the excess risk above the average of the cohort (RR > 1) around the age of 65. However, due to increase of expected rates of CHF with age in the general population, RR compared with the general population were 9.3 (6.5–13.3),  $P < 0.0001$  for patients  $< 65$  (Figure 3A) and 6.7 (5.6–8.1),  $P < 0.0001$  for patients  $\geq 65$  (Figure 3B). This difference in RR between age groups did not reach statistical significance ( $P = 0.11$ ). The curve of variation of excess CHF with age in the MR cohort compared with the general population (Figure 4B) was relatively flat with a trend for declining RR after age 75. Therefore, for the endpoint of CHF under medical management, the younger subset of the MR cohort ( $< 65$ ) incurred at least the same excess risk than the older subset ( $\geq 65$ ).

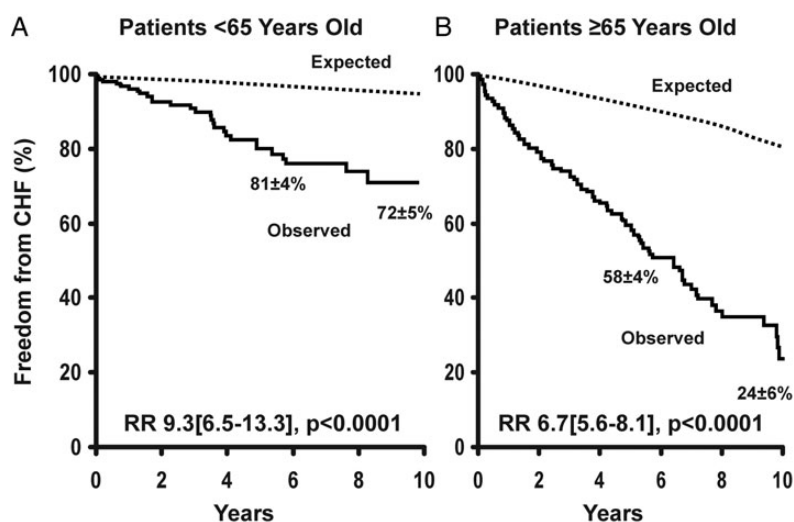
Among patients in the sinus rhythm at diagnosis ( $n = 686$ ), 227 had at least one episode of new AF during follow-up ( $44 \pm 5\%$  at 10 years). Five- and 10-year rates of AF after diagnosis were  $14 \pm 3$



**Figure 1** Survival under medical management after the diagnosis of MR due to flail leaflets. Observed survival (solid line) is compared with the expected survival in the general population (dotted line) in patients  $< 65$  years old (left panel) and  $\geq 65$  years old at diagnosis (B). The relative risk, 95% confidence interval and  $P$ -value apply to the comparison with the expected survival.



**Figure 2** Mortality relative risk expressed as a spline function of age as a continuous variable. (A) Displays the relative risk of mortality within the cohort and (B) the mortality risk relative to the general population. The mean risk is shown as a solid line and the dashed lines mark the 95% confidence interval.



**Figure 3** Freedom from congestive heart failure under medical management after the diagnosis of MR due to flail leaflets. Observed freedom from congestive heart failure (solid line) is compared with the expected rate in the general population (dotted line) in patients <65 years old (A) and ≥65 years old at diagnosis (B). The relative risk, 95% confidence interval and *P*-values apply to the comparison with expected rates.

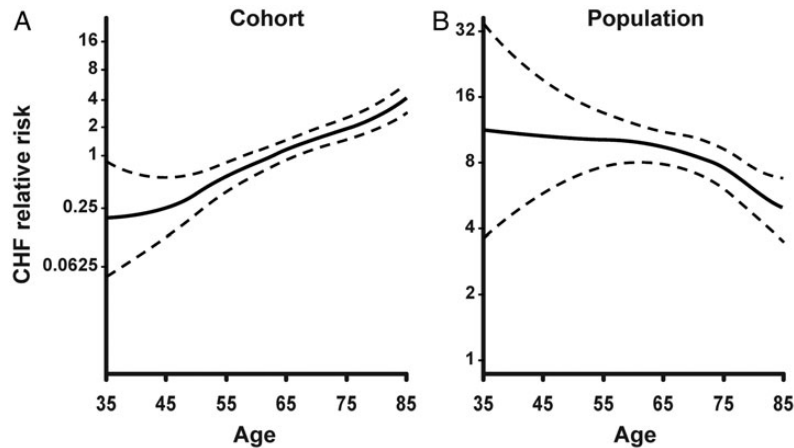
and  $26 \pm 5\%$  in patients <65 and were  $26 \pm 4$  and  $65 \pm 9\%$  in patients  $\geq 65$  ( $P < 0.0001$ , Figure 5). In multivariate analysis, the age  $\geq 65$  predicted a new episode of AF in patients in the sinus rhythm at diagnosis [rr (95% CI): 2.1 (1.3–3.7),  $P < 0.001$ ]. The within-cohort AF risk according to age as a continuous variable plotted in Figure 6A showed a progressive increase of absolute AF risk with age with the excess risk above the average cohort risk (RR > 1) around the age of 65. However, due to increase in the expected AF rate with age in the general population, the excess risk of new AF in patients <65 [rr (95% CI): 6.9 (4.5–10.6),  $P < 0.0001$ , Figure 5A] was higher ( $P < 0.001$ ) than the excess risk noted in patients  $\geq 65$

[rr (95% CI): 3.5 (2.6–4.7),  $P < 0.0001$ , Figure 5B]. The curve of variation of excess AF risk in the MR cohort compared with the general population plotted in Figure 6B, tended to show declining RR with age throughout the age span. Therefore, for the endpoint of new AF, the younger subset of the MR cohort (<65) incurred a higher excess risk than the older subset ( $\geq 65$ ).

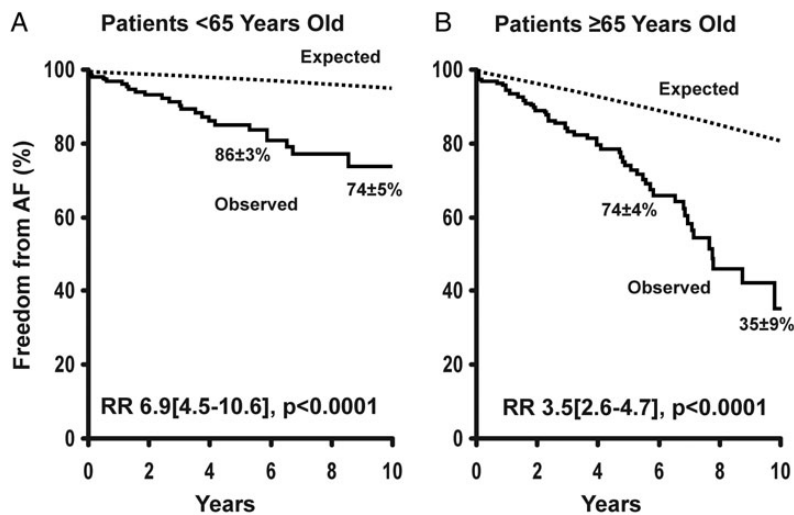
### Survival implications

Among 371 patients who developed either CHF or new AF after diagnosis, 63 died subsequently under medical management. In multivariable models, the occurrence of either CHF or new AF during





**Figure 4** Congestive heart failure relative risk expressed as a spline function of age as a continuous variable. (A) Displays the congestive heart failure risk within the cohort, while (B) the congestive heart failure risk relative to the general population. The mean risk is shown as a solid line and the dashed lines mark the 95% confidence interval.



**Figure 5** Freedom from new atrial fibrillation under medical management after the diagnosis of MR due to flail leaflets in sinus rhythm. Observed freedom from atrial fibrillation (solid line) is compared with the expected rate in the general population (dotted line) in patients <65 years old (A) and ≥65 years old at diagnosis (B). The relative risk, 95% confidence interval and *P*-values apply to the comparison with expected rates.

follow-up, tested as a time-dependent variable, was a strong independent risk factor of subsequent mortality under medical management [rr (95% CI): 13.5 (7.4–24.6),  $P < 0.001$ ] and remained so in both age groups (both  $P < 0.01$ ).

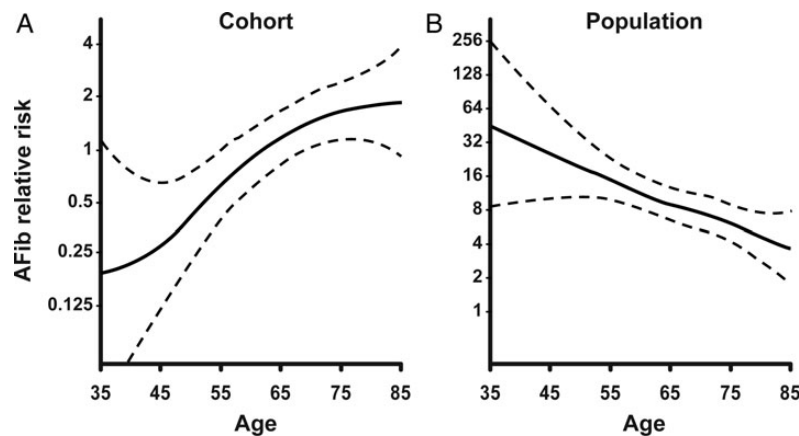
### Surgical management

During follow-up, 615 patients underwent mitral surgery (491 repair, 80%), 291 in patients <65 and 324 in patients ≥65. The mean time to surgery was 2.2 years ± 3.1 and the median time 0.6 years.

When patients who initially refused surgery ( $n = 60$ ) or were considered to have notable co-morbidity ( $n = 50$ ) were excluded, 5 years after diagnosis 75 ± 2% (<65) vs. 70 ± 2% (≥65)

underwent mitral surgery ( $P = 0.02$ ). In the multivariable analysis of time to surgical correction of MR, among the patients considered operable, the age ≥65 was independently associated with a lower rate of surgery [rr (95% CI) 0.72 (0.60–0.87),  $P < 0.001$ ].

Used as a time-dependent variable in the entire follow-up including medical and post-surgical, mitral surgery was associated with improved survival [adjusted rr (95% CI) 0.54 (0.40–0.72),  $P < 0.0001$  and with decreased CHF incidence [adjusted rr (95% CI) 0.44 (0.33–0.58),  $P < 0.0001$ ]. Survival benefit was mostly driven by repair [adjusted rr (95% CI) 0.48 (0.33–0.69),  $P < 0.0001$ ] with much less effect of replacement, although still significant [adjusted rr (95% CI): 0.60 (0.38–0.96),  $P = 0.03$ ].



**Figure 6** New atrial fibrillation relative risk expressed as a spline function of age as a continuous variable. (A) Displays the atrial fibrillation risk within the cohort, while the (B) atrial fibrillation risk relative to the general population. The mean risk is shown as a solid line and the dashed lines mark the 95% confidence interval.

Beneficial impact on CHF incidence was highly significant for repair [adjusted rr (95% CI) 0.39 (0.27–0.57),  $P < 0.0001$ ] but was also observed after replacement [adjusted rr (95% CI): 0.48 (0.28–0.83),  $P = 0.009$ ].

The survival improvement was considerable in patients  $\geq 65$  [adjusted rr (95% CI) 0.51 (0.37–0.71),  $P < 0.0001$ ]. In patients  $< 65$  who did not experience excess mortality under medical treatment, survival improvement was logically not significant [0.92 (0.44–1.93),  $P = 0.82$ ]. Conversely, the CHF preventive effect of mitral surgery was similar in patients  $\geq 65$  [adjusted rr (95% CI) 0.43 (0.31–0.61),  $P < 0.0001$ ] and in patients  $< 65$  [adjusted rr (95% CI) 0.48 (0.28–0.82),  $P = 0.008$ ], consistent with excess CHF rates observed in both age groups. Mitral surgery was not associated with new AF reduction [adjusted rr (95%CI) 0.94 (0.70–1.28),  $P = 0.71$ ].

## Discussion

The present study conducted to our knowledge in the largest population of patients with degenerative MR reported so far, provides new information on the influence of ageing on presentation and outcome of patients with MR due to flail leaflets. Compared with younger patients, older patients had MR of comparable severity and similar LV consequences but presented with more clinical manifestations. In addition, older patients despite normal EF in the vast majority of them incurred marked excess mortality, while in younger excess mortality was not significant. Morbid consequences of MR displayed more complex patterns. Absolute rates of CHF and of new AF were higher in older than in younger patients. However, compared with the expected rates, similar high excess risk of CHF was observed in younger and older patients, whereas the excess risk of new AF was higher in younger patients. Lastly, surgical correction of MR was associated with a reduced risk of CHF both in younger and older patients, and markedly improved survival in older patients.

## Contrasting presentation of mitral regurgitation in older and younger patients

In the current study, the flail leaflet was associated with similar MR severity in younger and older patients and similar LV volume overload, once the differences in the body size due to the higher prevalence of women among the older patients was accounted for, suggesting a similar duration of the leak in both age groups. The reason of the predominant representation of women in older patients, already reported<sup>24</sup> has not been elucidated. Noteworthy, differences were observed at diagnosis between younger and older patients. A higher pulmonary pressure, more frequent symptoms, larger LA, and more frequent AF were noted in older patients. These patterns suggest more MR consequences in older patients despite comparable MR degree. Impaired myocardial intrinsic pathological properties and cardiomyocyte apoptosis of the senescent heart<sup>25,26</sup> could explain a reduced LV adaptation to the volume overload in older patients.

## Clinical outcome of mitral regurgitation due to flail leaflets in younger and older patients

The optimal timing of surgical correction of organic MR continues to cause a flourishing debate focused around the natural history of the disease under medical management.<sup>27,28</sup> This contentious issue stems from differences in observed mortality between studies reporting mediocre outcome under medical management<sup>3,5,6,8</sup> and other showing no excess mortality under medical treatment.<sup>7</sup> One explanation relates to intensity of 'watchful waiting' as a potential source of favorable prognosis.<sup>7</sup> However, a recent study demonstrated that even with a tight follow-up, patients with organic MR incurred excess mortality under close medical management.<sup>6</sup> Other hypotheses did not pan out, whether examining geographical origin (European vs. American) as a source of outcome differences, with studies showing similar outcomes in Europe<sup>6,14</sup> and the USA<sup>3,5,8</sup> or whether examining potential referral bias.<sup>4</sup> However, the age at

diagnosis of MR remains an important unexplored issue. Indeed, series with high mortality<sup>3,5,6,14,15</sup> and those with lower mortality<sup>7,10</sup> displayed ~10–15 years difference in age at diagnosis. It is a truism that older age is linked with higher complication rates both in various valve diseases<sup>8,14,29–31</sup> and in the general population irrespective of underlying cardiac diseases.<sup>22,23,32,33</sup> In analysing the impact of ageing on MR mortality and morbidity, it was thus essential to account for naturally increasing co-morbidity and rates of events in an ageing subset. Accounting for co-morbidity differences between younger and older patients, we observed that the age at diagnosis strongly affected outcome. Moreover, the risk attached to ageing was not due to increasing severity of MR, as both MR grading and LV overload were comparable in the older and younger groups.

With regard to mortality after diagnosis, younger patients enjoyed RR of death compared with the general population barely above 1.0, not reaching statistical significance and demonstrating a possible excess mortality in young patients would require series of considerable size. Conversely, older patients incurred a marked excess mortality which demonstrates the multiplier effect of ageing on the vital risk imparted by MR under medical management. This observation allows better understanding of previous natural history studies and reports of favourable outcome in young subsets<sup>7,10</sup> become easily explainable in the context of low mortality of such patients.

Analyses of morbid events compared with their age-specific expected rates provided additional information on the complex interactions between age and MR outcome. Rates of CHF increased with older age at diagnosis, but younger as well as older patients incurred excess CHF risk compared with the general population. Thus, the volume overload due to MR, although appearing well tolerated, multiplies the risk of subsequent CHF even in the younger population despite their most adaptable myocardium. While AF was of a higher absolute frequency in older patients as previously reported with MR<sup>8</sup> the excess risk of new AF was almost 7 times higher than expected in young patients and declined in the older group to 3.5 times that expected. This contrasting excess risk is in part due to AF rarity in the younger general population compared with the older general population.<sup>23</sup> Importantly, these morbid events were associated with similar subsequent mortality, irrespective of age, emphasizing the importance of preventing such events in both age groups.

## Clinical implications

The present data emphasize the shifting and contrasting risks imparted by organic MR of similar degree according to age. Older patients with MR due to a flail leaflet have the negative perspective of increasing excess mortality under medical management in contrast to decreasing surgical indications even accounting for baseline co-morbid conditions and patients' personal choices. However, recent series reported declining operative mortality in older patients, increasing valve reparability irrespective of age<sup>34</sup> and similar long-term post-operative relative survival in younger and older patients.<sup>34</sup> These observations are congruent with ours showing a marked improvement in survival afforded by mitral surgery in older patients and should be discussed with these patients in planning follow-up and surgical decision.

Younger patients have an apparent more favourable outcome without an abrupt perspective of excess mortality with medical management. However, these patients incur high RR of morbidity compared with their peers of same age. The occurrence of CHF or new AF is frequent and not inconsequential, carrying an excess risk of long-term mortality under medical management,<sup>10</sup> which may persist after surgical correction.<sup>29</sup> In young patients, survival improvement by mitral surgery was not significant, maybe due in part to lack of statistical power in this subset but also to lack of excess mortality under medical treatment in this group consistent with lack of mortality reduction by surgery. Conversely, CHF incidence, which was excessive in young as in older patients, was reduced by surgery in both subsets. These points are crucial to share with younger patients afflicted by organic MR due to flail leaflets in order to go beyond the apparent benign nature of the MR in this subset.

## Study limitations

We have assembled the largest series of patients with organic MR diagnosed with a uniform mechanism (flail leaflet). This diagnosis ensures that >90% of patients have severe MR but quantitative ascertainment of MR severity was not required and may have revealed a wider distribution of severity. The present study was not a longitudinal follow-up study of individuals from youth to death or surgery and impact of ageing was inferred from outcome differences in the two groups of patients distinct by age at diagnosis. Precise timing of occurrence of severe MR was not known and longer evolution of MR in the oldest age group when compared with the youngest rather than decreased tolerance of the leak by older age cannot be excluded. However, patients were included after first echocardiographical diagnosis of the flail leaflet in both age groups and comparison of indexed left ventricular diameters—similar in both age groups—does not favour this hypothesis. The low mortality of young patients was observed in the context of mitral surgery available and often performed early in the course of the disease. Whether such a benign survival would be observed under true 'natural history' conditions is not possible to address. Comparison of observed vs. expected morbidity rates was performed for the first time in MR, using the only available data to date.<sup>21–23</sup> A potential change in heart failure incidence would affect our analysis but fortunately more recent published data show that overall incidence rates of heart failure in the population have not changed over time so that the impact on our RR analysis is probably limited.<sup>35</sup> In this recent paper however, age-specific heart failure rates were not reported and more detailed heart failure incidence data are needed.

Regarding surgical management, the impact of surgery was inferred from time-dependent analysis, which accounted for potential confounders by adjusting for clinically significant covariates. It was not the result of a randomized study neither of propensity matching between patients with and those without surgery. Such propensity score analysis on outcome benefit of early surgery vs. medical treatment would require larger populations in both groups and will be the specific focus of future studies. Importantly, the main hypothesis examined in the present study did not relate to the impact of surgery on prognosis but was to analyse the natural history of severe degenerative MR due to the flail leaflet according to age at diagnosis in order to understand previous discordant reports.



## Conclusions

The present large and multicentre study shed a new light on the contrasting vital and morbid complications of MR due to the flail leaflet at different life stages. The absolute rates of mortality and morbidity are higher in older patients but the excess risk of these complications compared with that observed in the age-peer general population is more complex. Indeed, excess mortality under medical management is prominent in older patients. Conversely, excess morbidity, CHF, and new AF is observed in young as in older patients. Thus, the long-term excess risks of adverse events of uncorrected degenerative MR do not spare any age group and should be considered in deliberating surgical management.

## Funding

The present study was supported by a grant from the University of Bologna donated by the Foundation 'Luisa Fanti Melloni' for the purpose of furthering cardiovascular research. The study was also funded by the Mayo Foundation.

**Conflict of interest:** Dr Enriquez Sarano received grant from Abott vascular. Dr Avierinos received honorarium from Edwards.

## Appendix

### List of the MIDA investigators

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University of Modena, Italy: Andrea Barbieri, Francesca Bursi, T. Grimaldi, A. Nuzzo, and M. G. Modena.

Mayo Clinic, Rochester MN, USA: Maurice Enriquez-Sarano, Hector I Michelena, R Suri, and Douglas W Mahoney.

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## CARDIOVASCULAR FLASHLIGHT

doi:10.1093/eurheartj/eh254

Online publish-ahead-of-print 4 July 2013

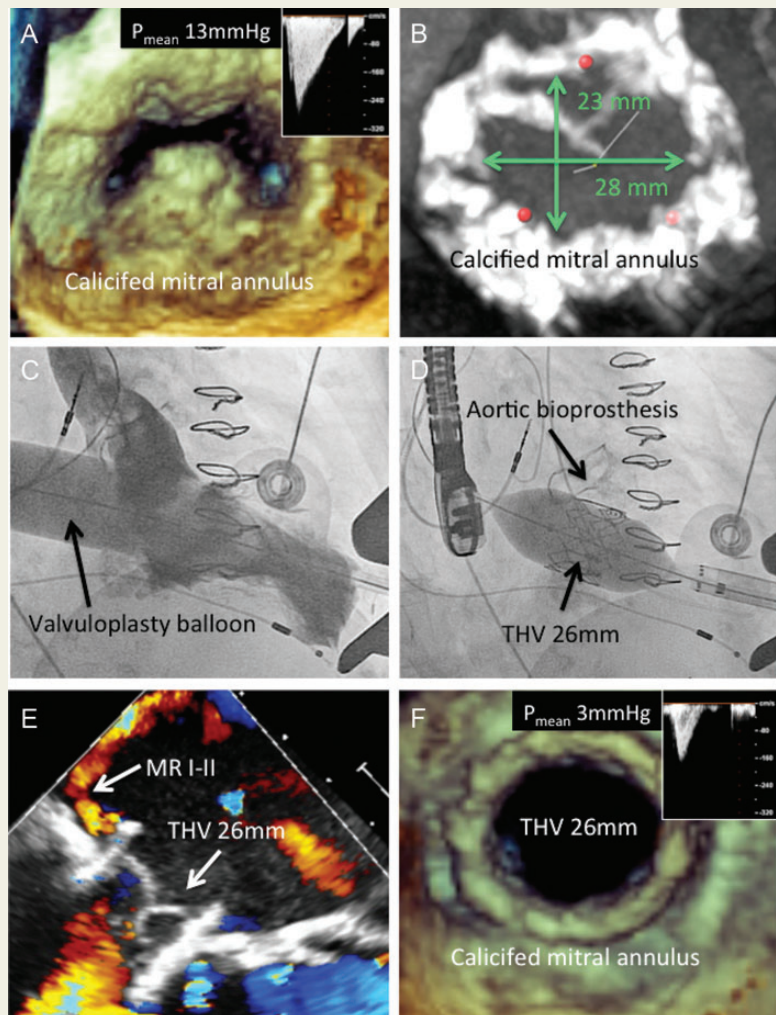
# Transcatheter mitral valve replacement using a balloon-expandable prosthesis in a patient with calcified native mitral valve stenosis

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A 75-year-old female presented with progressive dyspnoea NYHA functional class IV. Echocardiography revealed moderate regurgitation and severe stenosis ( $P_{\text{mean}}$  13 mmHg) of degenerated mitral valve (MV) with severe mitral annular calcification (MAC) (Panel A). Multislice computed tomography (MSCT) showed a ring-like pattern of the MAC with involvement of both MV leaflets (Panel B, MSCT of the MV annulus: inner diameter 28 × 23 mm, perimeter 82 mm). Owing to severe co-morbidities (STS score 13.8%) and a history of surgical aortic valve replacement in 2008, the Heart Team decided to perform transcatheter MV replacement (TMVR) via transapical access with implantation of a balloon-expandable Edwards-SAPIEN XT prosthesis (Edwards Lifesciences, Irvine, USA). For proper MV annular sizing, we used a 24-mm balloon valvuloplasty catheter (Osypka AG, Rheinfeld-Herten, Germany) for preparatory balloon mitral valvuloplasty with simultaneous left ventriculography (Panel C). Since no contrast regurgitation into the left atrium was obvious, we selected a 26-mm transcatheter heart valve (THV), which was implanted under transoesophageal echocardiographic (TEE) and fluoroscopic guidance (Panel D). Three dimensional-TEE and fluoroscopy confirmed proper TAVR valve positioning with only mild paravalvular MV regurgitation after valve expansion and acute reduction of the transvalvular mean pressure gradient to 3 mmHg (Panel E, two dimensional-TEE with MV regurgitation grade I–II; Panel F, 3D-TEE en-face-view of the acute procedural result with Doppler trace of the MV). After the procedure, the patient improved with a decrease in functional NYHA class to grade II. This case demonstrates that MV disease with calcified MV annulus may be treated by TMVR in selected high-risk patients.



After the procedure, the patient improved with a decrease in functional NYHA class to grade II. This case demonstrates that MV disease with calcified MV annulus may be treated by TMVR in selected high-risk patients.