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Long-Term Implications of Atrial Fibrillation in Patients With Degenerative Mitral Regurgitation

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ABSTRACT

BACKGROUND Scientific guidelines consider atrial fibrillation (AF) complicating degenerative mitral regurgitation (DMR) a debated indication for surgery.

OBJECTIVES This study analyzed the prognostic/therapeutic implications of AF at DMR diagnosis and long-term.

METHODS Patients were enrolled in the MIDA (Mitral Regurgitation International Database) registry, which reported the consecutive, multicenter, international experience with DMR due to flail leaflets echocardiographically diagnosed.

RESULTS Among 2,425 patients (age 67 ± 13 years; 71% male, 67% asymptomatic, ejection fraction 64 ± 10%), 1,646 presented at diagnosis with sinus rhythm (SR), 317 with paroxysmal AD, and 462 with persistent AF. Underlying clinical/instrumental characteristics progressively worsened from SR to paroxysmal to persistent AF. During follow-up, paroxysmal and persistent AF were associated with excess mortality (10-year survival in SR and in paroxysmal and persistent AF was 74 ± 1%, 59 ± 3%, and 46 ± 2%, respectively; $p < 0.0001$), that persisted 20 years post-diagnosis and independently of all baseline characteristics (p values <0.0001). Surgery (n = 1,889, repair 88%) was associated with better survival versus medical management, regardless of all baseline characteristics and rhythm (adjusted hazard ratio: 0.26; 95% confidence interval: 0.23 to 0.30; $p < 0.0001$) but post-surgical outcome remained affected by AF (10-year post-surgical survival in SR and in paroxysmal and persistent AF was 82 ± 1%, 70 ± 4%, and 57 ± 3%, respectively; $p < 0.0001$).

CONCLUSIONS AF is a frequent occurrence at DMR diagnosis. Although AF is associated with older age and more severe presentation of DMR, it is independently associated with excess mortality long-term after diagnosis. Surgery is followed by improved survival in each cardiac rhythm subset, but persistence of excess risk is observed for each type of AF. Our study indicates that detection of AF, even paroxysmal, should trigger prompt consideration for surgery.
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Degenerative mitral regurgitation (DMR) is the most prevalent moderate/severe valvular heart disease (1), which leads to frequent hospitalizations and cardiac surgery (2), but often remains untreated (3) despite specific criteria defined by clinical guidelines (4,5). In parallel to DMR, atrial fibrillation (AF) is also prevalent with aging, is associated with notable risks, and is a burden for health care systems worldwide (6–10). Although most cases of AF are nonvalvular, DMR can cause AF because DMR-induced volume overload leads to left atrial enlargement and, eventually, AF (11,12).

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These important epidemiological and pathophysiological data call for more effective strategies aimed at treating and possibly preventing the consequences of these 2 diseases (3). Nowadays, innovative technologies ranging from robotic surgery to percutaneous repair or replacement can provide previously unimagined treatment opportunities, but conversely render risk assessment in DMR even more crucial (13). Surprisingly, AF's prognostic impact in DMR remains widely debated as it is often found to be insignificant (14–17) or at other times important (11,18,19). These inconsistencies may be caused by small sample sizes (14,15,18,20), or single-center studies (11,14,15,18) of inconsistent regurgitation etiology (14,15,19), excluding medically treated patients (18,19,21). The unavoidable consequences of these gaps in knowledge are that American and European guidelines on valvular diseases consider AF a Class II (debated) indication for mitral surgery, with low levels of evidence, advocating for new and more powerful studies (4,5,22,23). Furthermore, AF guidelines highlight differences between paroxysmal and persistent AF (22,24), raising additional uncertainties on potential outcome or therapeutic implication differences in DMR.

To address these gaps in our knowledge, a large cohort gathered at multiple international centers is needed to limit potential selection biases characterizing individual single-center studies or national health care systems. Accordingly, we took advantage of the MIDA (Mitral Regurgitation International Database), the largest international registry of pure severe DMR patients consecutively diagnosed by echocardiography at the European and North American centers. We aimed to define the prevalence, clinical context, and prognostic implications of paroxysmal and persistent AF at diagnosis of DMR and during long-term follow-up.

METHODS

A fully detailed Methods section is available in the Online Appendix. A more concise version is reported in the following text.

STUDY DESIGN. The MIDA is an international registry based on routine clinical practice and assembled by merging a series of prospectively assembled electronic institutional databases (20,25–29). All centers participating in the registry are recruiting centers. Patients were screened for MIDA if they had flail mitral leaflet diagnosed by echocardiogram at 1 of the participating centers between 1980 and 2005 according to each center's database.

INCLUSION AND EXCLUSION CRITERIA. The MIDA inclusion/exclusion criteria are: 1) DMR diagnosis and flail leaflet at the index transthoracic echocardiography, which had to be performed at any of the participating centers; 2) comprehensive clinical/instrumental evaluation at index echocardiography; 3) exclusion of ischemic/functional regurgitation; and 4) absence of significant concomitant aortic disease, mitral stenosis, active endocarditis, congenital diseases, and previous valve surgery. For the specific purpose of the present study, cardiac rhythm had to be ascertained by an electrocardiogram, and patients showing pacemaker rhythm or rhythm other than sinus/AF were excluded. To obtain the most reproducible definition, AF was defined based on temporal patterns (24).

ECHOCARDIOGRAPHY. Because the MIDA Registry focuses on routine clinical practice, echocardiographic data were analyzed as collected at the time of echocardiography performed without subsequent modification or central review (see the Online Appendix).

BASELINE EVALUATION AND FOLLOW-UP. The patients' baseline clinical characteristics reported in the MIDA are those collected by personal physicians at the time of the echocardiogram, and were reported unaltered.

Subsequent patient management after the baseline echocardiogram (including if and when indicating surgery) was independently determined by personal physicians. Follow-up events recorded in the MIDA are those specifically linked to the natural history of DMR (4,5). Those events were ascertained by clinical note reviews and/or telephone calls with physicians, patients, and (if necessary) next of kin by investigators unaware of the subsequent analyses.

All patients provided informed consent for anonymous publication of clinical data for scientific

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CVD = cardiovascular death

DMR = degenerative mitral regurgitation

SR = normal sinus rhythm

TABLE 1 Study Population

	Overall Patient Population (N = 2,425)	Sinus Rhythm (n = 1,646)	Paroxysmal Atrial Fibrillation (n = 317)	Persistent Atrial Fibrillation (n = 462)	p Value
Age, yrs	67 ± 13	65 ± 13	68 ± 13*	73 ± 11*	<0.0001
Male	1,732 (71)	1,200 (73)	223 (71)	309 (67)*	0.002
Body surface area, m^2	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.3	0.32
Asymptomatic	1,625 (67)	1,196 (73)	203 (64)*	226 (49)*	<0.001
Heart rate, beats/min	76 ± 16	75 ± 15	72 ± 14*	84 ± 20*	<0.001
History of coronary artery disease	256 (11)	175 (11)	26 (8)	55 (12)	0.16
Diabetes	176 (7)	103 (6)	28 (9)	45 (10)*	0.008
Hypertension	973 (40)	644 (39)	145 (46)	184 (40)	0.29
Chronic kidney disease	81 (4)	51 (3)	13 (4)	17 (4)	0.60
Left atrial diameter, mm	50 ± 9	48 ± 8	52 ± 9*	56 ± 10*	<0.001
Left ventricular end-diastolic diameter, mm	58 ± 7	58 ± 7	59 ± 7	59 ± 8*	0.029
Left ventricular end-systolic diameter, mm	36 ± 7	35 ± 6	37 ± 7*	38 ± 8*	<0.001
Left ventricular ejection fraction, %	64 ± 10	65 ± 9	63 ± 10*	61 ± 12*	<0.001
Severe mitral regurgitation	2,275 (94)	1,532 (94)	302 (96)	441 (96)	0.078
Right ventricular systolic pressure, mm Hg	44 ± 17	42 ± 16	45 ± 18*	48 ± 17*	<0.001
ACE inhibitors/angiotensin receptor blockers	1,018 (42)	640 (39)	140 (44)	238 (51)*	<0.001
Beta-blockers	438 (18)	275 (17)	79 (25)*	84 (18)	0.004
Diuretics	838 (35)	474 (29)	120 (38)*	244 (53)*	<0.001
Digoxin	571 (24)	237 (14)	97 (31)*	237 (51)*	<0.001

Values are mean ± SD or n (%). *p < 0.05 versus sinus rhythm.
ACE = angiotensin-converting enzyme.

research purposes; the study was approved by the locally appointed ethics committees.

STATISTICAL ANALYSIS AND QUALITY CONTROL OF THE DATA. Continuous variables are expressed as mean ± 1 SD, and/or as median (25th to 75th percentile). Categorical data are reported as numbers (percentages).

The primary endpoint was total mortality, while the secondary endpoint was death from cardiovascular causes (CVD). Endpoints were analyzed: 1) overall (i.e., considering the entire follow-up period from diagnosis and including the post-surgical phase if mitral operation was performed); 2) under medical (nonsurgical) follow-up (i.e., starting the observation at diagnosis and censoring the follow-up at the time of surgery if this was performed); and 3) during the post-operative follow-up (i.e., initiating the observation at the time of surgery and including the immediate post-surgical phase).

Rates of events were estimated by the Kaplan-Meier method. Landmark analysis was performed to take into account the impact of the length of time from diagnosis to surgery on outcome. Patients were grouped into those who had surgery before the landmark point (set at 3, 6, and 12 months from diagnosis), or medically managed up to the landmark point (followed by surgery whenever considered indicated). Patients deceased or censored prior to the landmark point were excluded (30).

The instantaneous rate of death across follow-up was quantified by hazard functions methodology (31).

Cox proportional hazards analysis was used to assess predictors of events; variables reaching $p < 0.10$ were entered in a multivariate model. To assess the influence of surgery and AF during follow-up on outcome, we performed time-dependent proportional hazards analysis.

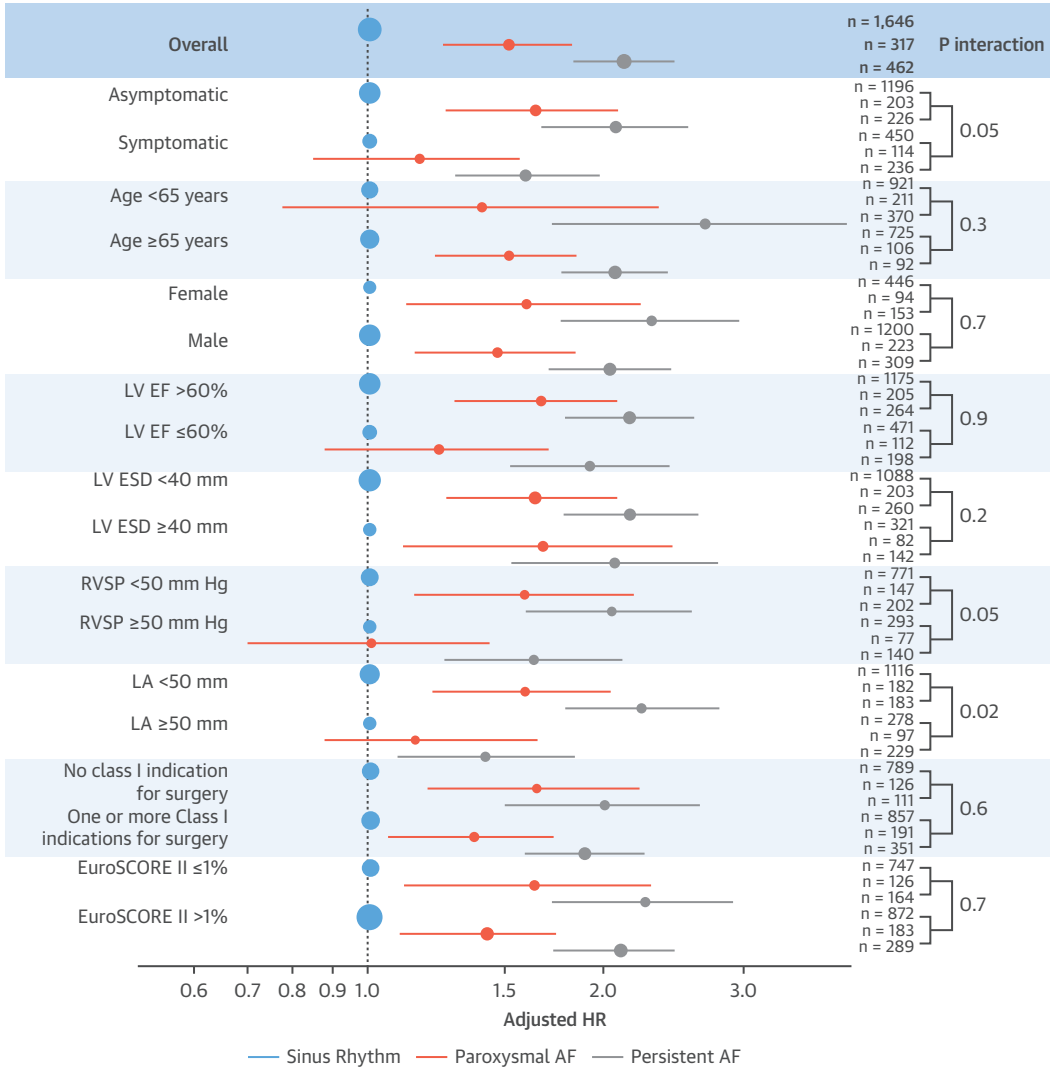
Because surgery is a competing risk event when analyzing survival under medical management (and so is non-CVD when analyzing CVD), we also performed competing risk analysis (32). A $p < 0.05$ was considered significant.

Although the MIDA Registry does not include a local audit, data collected at each institution undergo quality control before being merged into the database.

RESULTS

STUDY POPULATION. Of the 2,522 patients currently included in the general MIDA Registry, 2,425 satisfied the inclusion/exclusion criteria for the present analysis. The general baseline characteristics of the present study population are summarized in Table 1. The vast majority of patients presented with no symptoms and normal left ventricular function at the time of the index echocardiogram. The low prevalence of coronary artery disease is consistent with the nonischemic etiology of the regurgitation. Flail leaflet was idiopathic in 2,266 (93%) patients, and caused by

FIGURE 1 **Excess Risk of Mortality Linked to Atrial Fibrillation**

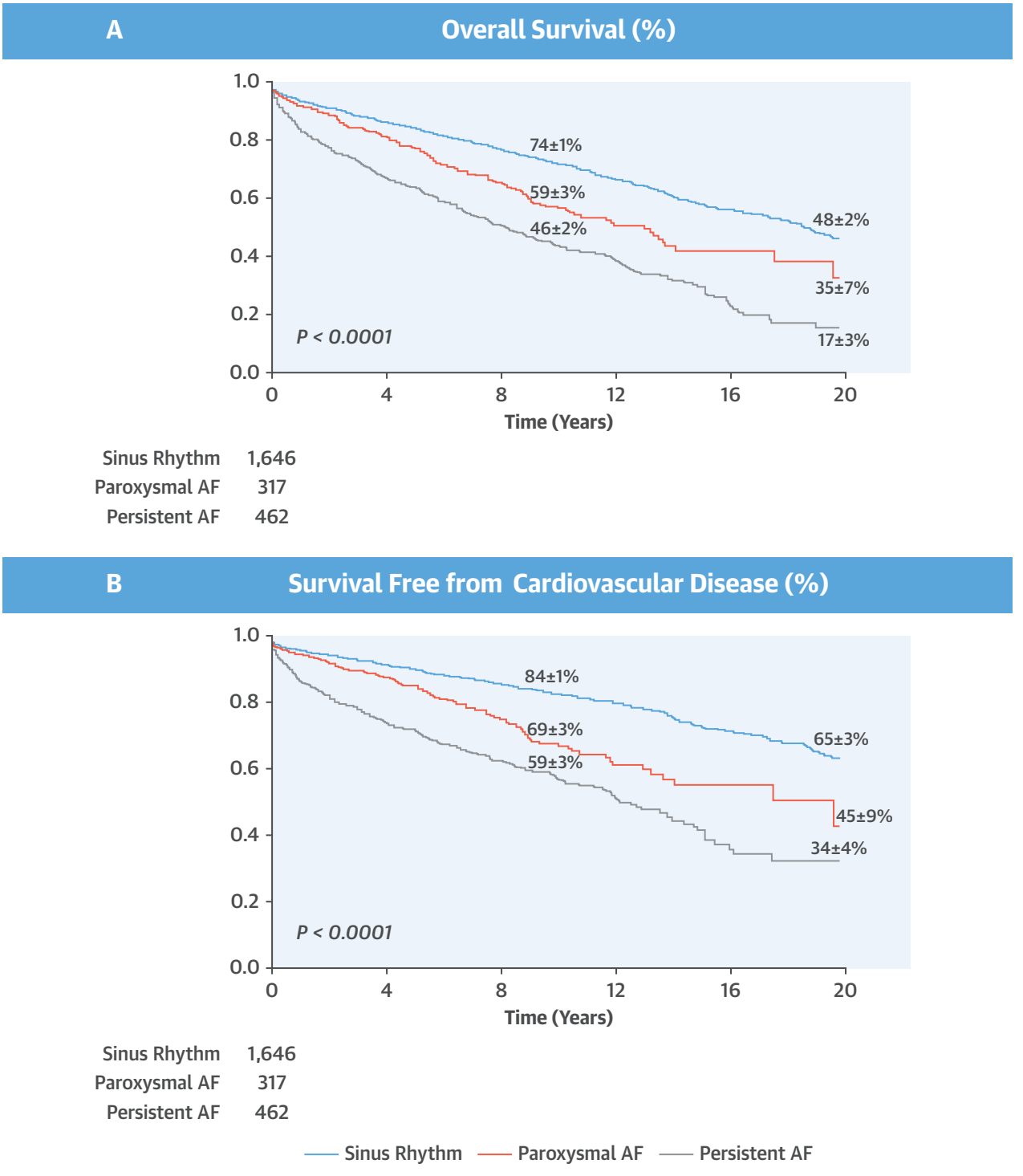


Forest plot illustrating the excess risk of overall mortality linked to paroxysmal and persistent atrial fibrillation (AF) in subgroups of patients pre-specified according to the presence/absence of guideline-endorsed predictors of outcome in degenerative mitral regurgitation. The hazard ratio (HR) is set at 1 for sinus rhythm and adjusted for age, sex, and the effects of surgery when performed. The p for interaction is reported on the **right**. The **size of the bullets** reflects the sample size of patients belonging to each specific subgroup, which is also reported as a number. The entire follow-up from diagnosis (including the post-surgical period in patients who underwent mitral operation) is considered in this specific analysis. See also the Methods section for more details. EF = ejection fraction; ESD = end-systolic diameter; LA = left atrium; LV = left ventricular; RVSP = right ventricular systolic pressure.

previous endocarditis in the remaining 159 (7%). Isolated involvement of the posterior leaflet was diagnosed in 1,921 patients (79%) and of the anterior leaflet in 345 (14%), while both leaflets were involved in 159 patients (7%).

Patients' baseline characteristics according to the type of rhythm are also listed in Table 1. Although the vast majority of patients (68%) (n = 1,646) presented in normal sinus rhythm (SR) at the time of echocardiographic diagnosis of DMR, AF (either persistent or paroxysmal) was present in 779 patients (32%). Median duration of persistent AF recorded at index evaluation was 47 months (interquartile range: 7 to 74 months). As expected, a progressive impairment in baseline clinical instrumental parameters was recorded when comparing patients in SR to those presenting with paroxysmal and eventually persistent AF (Table 1).

CENTRAL ILLUSTRATION **Long-Term Prognostic Implications of Atrial Fibrillation Complicating Degenerative Mitral Regurgitation**



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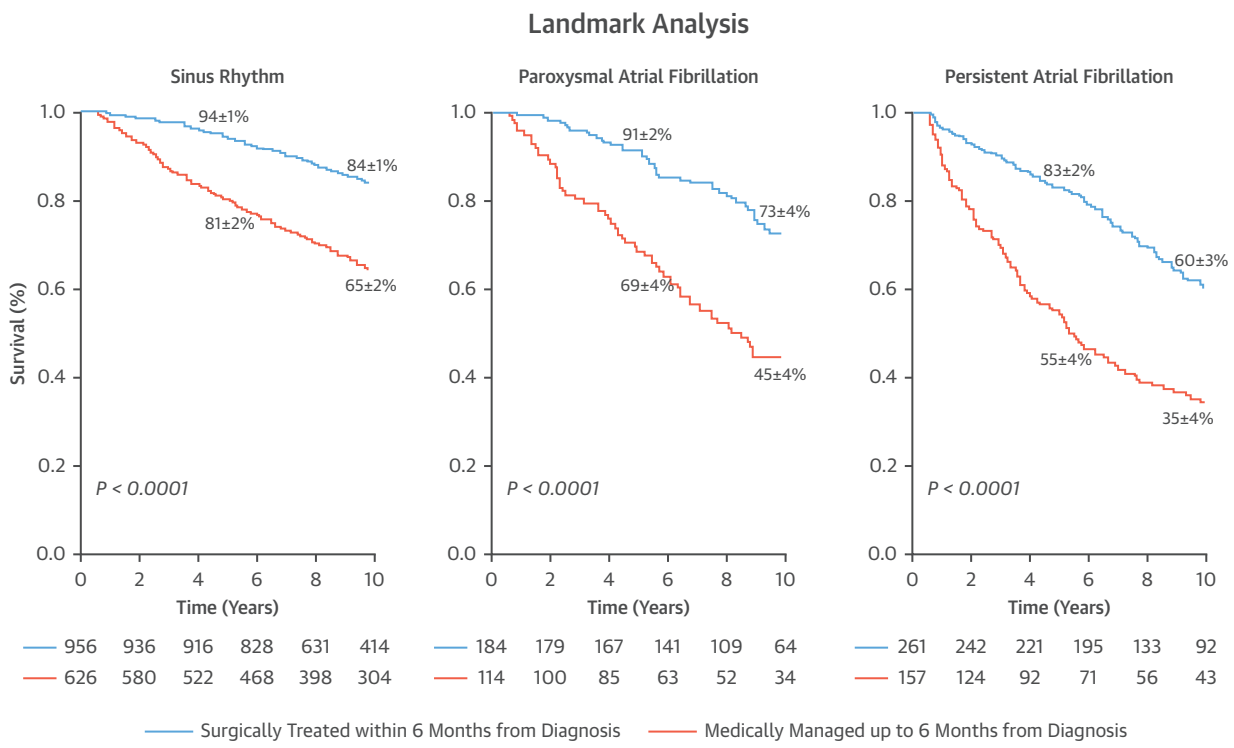
Long-term estimated overall survival **(A)** and survival free from cardiovascular (CV) disease **(B)** according to cardiac rhythm at degenerative mitral regurgitation diagnosis. The entire follow-up from diagnosis is considered in this specific Kaplan-Meier analysis (including the post-surgical period in patients who underwent mitral operation). AF = atrial fibrillation.

FIGURE 2 **Long-Term Survival in Degenerative Mitral Regurgitation Using Landmark Analysis**



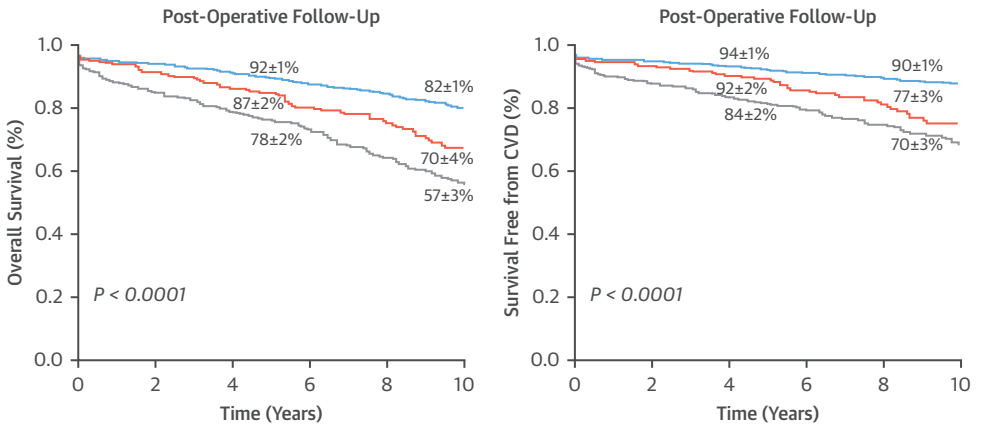
Patients were grouped into those who had surgery before the landmark point (i.e., within 6 months from diagnosis), or medically managed up to the landmark point with surgery performed later on during follow-up when considered indicated. Patients deceased or censored prior to 6 months were excluded. See also the Methods section.

LONG-TERM PROGNOSTIC IMPLICATIONS OF AF. During a mean overall follow-up of 9.1 ± 5.4 years (median 9 years; 25th to 75th percentile 6 to 12 years), 933 deaths occurred, of which 598 (64%) were cardiovascular. Surgery was eventually performed in 1,889 patients (78%) (in 1,463 patients within 6 months of diagnosis). Estimated overall survival at 5, 10, 15, and 20 years was 80 ± 1%, 67 ± 1%, 53 ± 1%, and 41 ± 2%, respectively. The overall incidence of new AF during follow-up in SR and paroxysmal AF (n = 458) was, respectively, 24 ± 1% and 36 ± 3% at 10 years ($p < 0.001$).

At Cox proportional hazard analysis, paroxysmal (adjusted hazard ratio [HR]: 1.51; 95% confidence interval [CI]: 1.24 to 1.82) and persistent AF at diagnosis (adjusted HR: 2.12; 95% CI: 1.82 to 2.46) were independent of age, sex, and whether surgery was performed or not associated with an increased risk of death (p values <0.0001). When all Class I indicators for surgery indicated by ACC/AHA guidelines (i.e., symptoms, LVEF ≤60%, left ventricular end-systolic diameter ≥40 mm) were additionally factored into the multivariable model reported in the previous text, the negative prognostic implications on mortality were retained both for paroxysmal (adjusted HR: 1.46; 95% CI: 1.20 to 1.76) and persistent (adjusted HR: 1.94; 95% CI: 1.66 to 2.24) AF ($p \leq 0.001$). When further adjusted for associated comorbidities, paroxysmal and persistent AF at diagnosis retained their prognostic significance independently of peripheral vascular disease ($p < 0.0001$), chronic kidney disease ($p < 0.0001$), diabetes ($p < 0.0001$), lung disease ($p < 0.0001$), and/or cancer ($p < 0.0001$). Surgery as a time-dependent variable was associated with better survival regardless of all baseline characteristics and rhythm (adjusted HR for surgery performed: 0.26; 95% CI: 0.23 to 0.30; $p < 0.0001$). The absence of significant interaction between surgery performed and AF (or between the time of surgery and AF) ($p \geq 0.36$) confirmed the beneficial effects of surgery, particularly when performed early in all subsets of rhythm (Online Tables 1 and 2, Online Figure 1).

Figure 1 shows the Forest plot in selected subgroups of patients pre-specified according to the presence/absence of outcome predictors endorsed by current scientific guidelines. The prognostic value of

FIGURE 3 Long-Term Survival in Degenerative Mitral Regurgitation After Surgery



Sinus Rhythm	1,257	1,187	1,142	1,012	775	511	1,257	1,187	1,142	1,012	775	511
Paroxysmal AF	238	216	198	170	128	78	238	216	198	170	128	78
Persistent AF	394	337	303	268	187	136	394	337	303	268	187	136

Long-term survival **(left)** and survival free from cardiovascular disease (CVD) **(right)** after surgery (Kaplan-Meier analysis). In these analyses, the observation started at the time of mitral valve operation. See also the statistical analysis section for a more detailed explanation.
AF = atrial fibrillation.

AF was particularly evident in patients without Class I indications for surgery, when additional indicators of outcome helping decision-making are currently most needed. The **Central Illustration** depicts estimated 20-year overall survival (panel A) and survival free from CVD (panel B) according to the type of rhythm at diagnosis. The landmark analysis (**Figure 2**) confirms the negative prognostic implications of AF regardless of whether patients within the first 6 months from diagnosis underwent surgery or medical management followed by surgery whenever considered indicated (surgery was eventually performed in 1,827 patients [80%]). Notably, in all rhythm subsets, patients operated within 6 months from diagnosis showed a better survival compared with those initially assigned to medical management (**Figure 2**). Those results were confirmed setting the landmark point at 3 or 12 months ($p \leq 0.001$).

Cox proportional hazard analysis showed that paroxysmal (adjusted HR: 1.78; 95% CI: 1.41 to 2.25) and persistent AF (HR: 2.55; 95% CI: 2.12 to 3.06) at diagnosis were independent of age, sex, and the effects of surgery, associated with an increased risk of CVD ($p < 0.0001$). Analogously, the transition from SR to AF during follow-up was independent from age, symptoms, sex, ejection fraction, baseline rhythm, and surgery performed associated with an increased risk of death (adjusted HR for AF occurrence: 1.24; 95% CI: 1.05 to 1.46; $p = 0.010$).

When CVD and non-CVD were considered in a competitive risk analysis, the independent negative prognostic implications of AF at diagnosis were retained ($p \leq 0.001$) (Online Tables 3 to 5). The same applied considering death and surgery as competing endpoints (Online Table 6).

PROGNOSTIC IMPLICATIONS OF AF AT THE TIME OF MITRAL SURGERY AND DURING LONG-TERM POST-SURGICAL OUTCOME. A perioperative death (defined as death within 30 days of the operation) occurred in 39 of 1,189 patients who underwent surgery (2.06%). Patients in SR at the time of surgery had an operative mortality of 1.67% (n = 21 of 1,257). The operative mortality for paroxysmal AF was 2.10% (n = 5 of 238) and 3.30% for persistent AF (n = 13 of 394) ($p = 0.16$). Mitral repair was accomplished in 1,664 patients (88%). In 1 patient operated outside of the MIDA centers, the surgical report could not be retrieved, and consequently, the type of procedure (repair vs. replacement) could not be ascertained. The rate of repair was 90% in patients in SR (n = 1,130 of 1,257), 90% in those with paroxysmal AF (n = 213 of 238), and 82% in patients with persistent AF (n = 321 of 394) ($p < 0.001$). An associated Maze procedure was performed in 62 patients (41 patients with persistent AF).

In patients in SR without any Class I indication for surgery (e.g., symptoms, and/or left ventricular ejection fraction ≤60%, and/or end-systolic

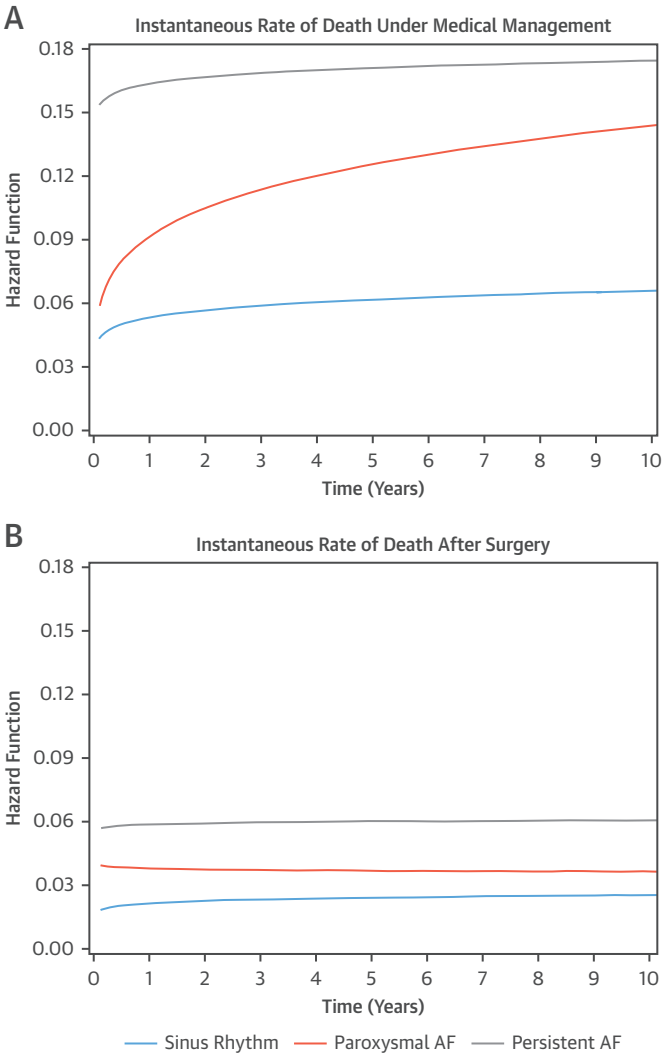
diameter ≥40 mm), operative mortality was 0.69% overall (4 of 580), and 2.67% in those either with a history of AF and/or any Class I indication for surgery (35 of 1,309) ($p = 0.002$).

During a post-surgical follow-up of 9.1 ± 4.8 years (median 9 years [interquartile range: 6 to 12 years]), 534 deaths occurred (including the perioperative deaths), of which 341 were CVDs (64%). The 10-year post-surgical incidence of AF was 23 ± 1% in those operated in SR and 36 ± 3% in those operated with paroxysmal AF ($p < 0.001$).

Confining the analysis to the post-operative phase, paroxysmal (adjusted HR: 1.58; 95% CI: 1.21 to 2.04; $p = 0.001$) and persistent AF (adjusted HR: 2.06; 95% CI: 1.70 to 2.50; $p < 0.0001$) were associated with a higher risk of mortality regardless of age, sex, EuroSCORE II, the type of surgery (repair/replacement), and the association of a Maze procedure with the mitral operation.

The results were further confirmed by selecting post-surgical CVD as the endpoint of the previously mentioned model (adjusted HR for paroxysmal AF: 1.92; 95% CI: 1.38 to 2.62; $p < 0.001$; adjusted HR for persistent AF: 2.34; 95% CI: 1.83 to 2.98; $p < 0.001$). Overall survival and survival free from CVD after surgery according to rhythm at the time of the operation are depicted in **Figure 3**. The instantaneous rate of death across time after surgery and under medical management is depicted in **Figure 4**.

FIGURE 4 Hazard Functions



Hazard functions depicting the instantaneous rate of death across follow-up in patients treated medically **(A)** and after surgery **(B)**. AF = atrial fibrillation.

DISCUSSION

The present study used the MIDA, the largest multicenter international registry enrolling consecutive patients with pure, isolated, severe DMR diagnosed by echocardiography. We found that AF, either paroxysmal or persistent, is common at DMR diagnosis and is not an isolated phenomenon. It is associated with older age and more severe clinical and echocardiographic presentation of DMR. Despite these collinearities, the unequaled sample size of our cohort demonstrates that the magnitude of the mortality risk progressively increases from sinus to paroxysmal to persistent AF independently of all underlying patient characteristics. Although the mortality risk is reduced by surgery in all subsets of patients (vs. the risk under medical management), we also found that paroxysmal and persistent AF are linked to excess post-surgical mortality that persists long-term throughout the follow-up. Although current guidelines mainly focus on paroxysmal AF, the findings of the present study suggest that prompt surgery should be considered in patients with DMR and AF of any type.

In routine clinical practice, DMR and AF are often diagnosed separately, but as the present study shows, the 2 pathological disorders are interlinked in many cases (11). In addition, due to the aging and increase in the general population, the prevalence, complications, and direct costs of both conditions are expected to increase significantly in the near future (1).

About one-third of the MIDA registry patients with severe DMR in this study had a medical history remarkable for AF (**Table 1**). AF is the most common sustained cardiac arrhythmia, occurring in 1% to 2% of the general population (33,34), and DMR is another

public health problem whose burden is expected to increase in line with an aging population (1). Somewhat surprisingly, the exact prevalence of AF complicating isolated pure severe DMR is still debated, ranging in previous studies from 20% to 55% (11,15,18–21,35). This is the first study providing data on the prevalence of AF at the time of DMR diagnosis derived from a large sample size collected consecutively and internationally (and, consequently, at lower risk of referral bias). By highlighting the magnitude of the epidemiological link between these 2 costly and lethal conditions (assessed by adopting the most recent diagnostic criteria) (22,24), our findings call for prompt preventive and therapeutic strategies aimed at properly managing this already enormous but still growing number of patients (3).

Our study provides multiple and convergent results indicating that AF is associated with a higher risk of death. Since we recorded a more significant impairment of associated clinical/instrumental parameters in patients with AF (**Table 1**), whether AF may merely represent an indicator of a more severe underlying cardiac disease or conversely, once established, it independently contributes to disease progression remains unclear. These uncertainties apply more in general to AF from any etiology, including nonvalvular AF (36), and cannot be definitively answered without a prospective randomized study. Nevertheless, our results provide major evidence for the management of DMR until prospective studies are—hopefully—performed. Indeed, for the first time, we showed that AF maintained an independent association with a higher mortality in almost all subgroups of patients pre-defined according to the presence/absence of all risk factors currently endorsed by scientific guidelines (4,5), either taken alone or in combination (**Figure 1**). In this respect, the greater prognostic value of AF in patients without concomitant Class I indications for surgery is of particular value, because these are the patients for whom further data on decision-making are most needed. At the same time, the smaller magnitude of the prognostic impact of AF in patients already showing the severe consequences of volume overload (symptomatic patients who have already developed ventricular dysfunction complicated by pulmonary hypertension) should be considered expected, because these patients are already at the highest risk and their management is already established. Finally, the independent association between AF and CVD presents additional arguments toward considering even paroxysmal AF a marker of an impelling unfavorable adaptation to the volume overload.

Concerning the surgical phase, we found a significantly lower rate of mitral repair performed in patients with AF compared to the repair rate obtained in patients in SR (although the overall rate of repair in the whole series was satisfactory, being almost 90%). The lower rate of mitral repair in patients with AF has been previously reported (14) and could be attributed to the questionable perception of a diminished beneficial effect of repair over replacement in this group of patients (37,38). We also found a trend toward higher operative mortality in patients operated in AF, and this finding may provide additional arguments in favor of bringing forward the surgical correction to an earlier stage. Previous studies found a similar trend toward higher mortality for mitral repair when performed in patients with AF (15,18).

Although mitral surgery was beneficial independently of patient characteristics (Online Figure 1), AF was nevertheless linked to an unfavorable long-term post-surgical outcome (**Figures 3 and 4**), which was also confirmed at multivariate analysis ($p < 0.001$) and which increased moving from SR to paroxysmal to persistent AF. Current guidelines consider AF a Class II indication for surgery in DMR, reflecting current uncertainties on this topic and advocating "additional studies with focused objectives" (5,22). Taken together, the results of the present study make a notable contribution in this direction.

STUDY LIMITATIONS AND STRENGTHS. We found a high prevalence of systemic hypertension in our study population. The epidemiological association between hypertension and DMR has been described, and raises the hypothesis that long-term exposure to higher blood pressure could lead to structural changes in the mitral valve (39). Future studies are needed to establish whether lowering blood pressure might reduce the risk of DMR.

Current ablation techniques are reported to be safe (40), but the small number of procedures performed in the present series precluded a specifically dedicated analysis. The notable 10-year post-surgical incidence of AF we found is in keeping with the advice that ablation techniques should be more liberally applied at the time of open atrial procedures (40).

Because this is not a randomized trial, we should be prudent in concluding that operating on patients in SR (who displayed the lowest operative mortality, the highest rate of repair, and the most favorable long-term post-surgical outcome) may provide incremental beneficial effects compared with waiting for the occurrence of AF. Nevertheless, data obtained

from registries provide important outcome information, which is vital while awaiting appropriate clinical trials. The firm observation that any type of AF independently increases the risk of mortality should raise the concern that once it arises, AF increases the risk of mortality, which can only partially be reversed by surgery.

The risk of residual confounding cannot be definitively ruled out in any observational study, and the decision to recommend surgery could be linked to a subset of patients who are at lower risk (41). Nevertheless, surgery showed a remarkably strong independent association with total and CVD. The HR did not show significant variation, although it was tested in multiple models including up to 233 events per variable and adjusted for all Class I triggers for surgery (Online Tables 1 to 5). Despite a comparable ($p = 0.50$) EuroSCORE II (which includes a very comprehensive and established set of cardiovascular and noncardiovascular prognostic factors), an earlier surgical treatment was independently associated with a better outcome (Online Figure 1).

CONCLUSIONS

AF is a frequent complication of DMR due to flail leaflets, present in about 30% of consecutive patients diagnosed by transthoracic echocardiography. Although paroxysmal and persistent AF are associated with older age and worse clinical and echocardiographic presentation, their progressively negative prognostic implications are confirmed by multivariable analysis and in subgroup analyses. Thus, once established, AF may either contribute to DMR disease progression or unfavorably influence prognosis on its own, or both. Furthermore, as rhythm disturbances progress from SR to paroxysmal and to persistent AF, the superimposed excess risk of total and cardiovascular mortality is only mitigated (but not corrected) by mitral surgery, with lower rates of repair and worse long-term post-surgical outcomes.

Taken together, our findings indicate that the detection of even paroxysmal AF should trigger prompt consideration for surgery to minimize risks under medical management and prevent suboptimal operative results with a reduced long-term post-operative outcome.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: The development of AF in a patient with DMR identifies a subgroup at high risk of adverse outcomes that can be improved with valve repair surgery.

TRANSLATIONAL OUTLOOK: More research is needed to understand the factors associated with onset of AF in patients with DMR and determine whether intervention to prevent AF or correct MR improves long-term clinical outcomes.

REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005–11.

2. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003;24:1231–43.

3. Mirabel M, Iung B, Baron G, et al. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? Eur Heart J 2007;28:1358–65.

4. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57–185.

5. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739–91.

6. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation 2004;110:1042–6.

7. Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med 1995;98:476–84.

8. Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. Stroke 1997;28:316–21.

9. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med 2002;113:359–64.

10. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. Circulation 2003;107:2920–5.

11. Grigioni F, Avierinos JF, Ling LH, et al. Atrial fibrillation complicating the course of degenerative mitral regurgitation: determinants and long-term outcome. J Am Coll Cardiol 2002;40:84–92.

12. Grigioni F, Branzi A. Management of asymptomatic mitral regurgitation. Heart 2011;96:1938–45.

13. Suri RM, Taggarse A, Burkhart HM, et al. Robotic mitral valve repair for simple and complex degenerative disease: midterm clinical and echocardiographic quality outcomes. Circulation 2015;132:1961–8.

14. Jessurun ER, van Hemel NM, Kelder JC, et al. Mitral valve surgery and atrial fibrillation: is atrial fibrillation surgery also needed? Eur J Cardiothorac Surg 2000;17:530–7.

15. Chua YL, Schaff HV, Orszulak TA, Morris JJ. Outcome of mitral valve repair in patients with preoperative atrial fibrillation. Should the Maze

procedure be combined with mitral valvuloplasty? J Thorac Cardiovasc Surg 1994;107:408–15.

16. Obadia JF, el Farra M, Bastien OH, Lievre M, Martelloni Y, Chassignolle JF. Outcome of atrial fibrillation after mitral valve repair. J Thorac Cardiovasc Surg 1997;114:179–85.

17. Lim E, Barlow CW, Hosseinpour AR, et al. Influence of atrial fibrillation on outcome following mitral valve repair. Circulation 2001;104:I59–63.

18. Szymanski C, Magne J, Fournier A, Rusinaru D, Touati G, Tribouilloy C. Usefulness of preoperative atrial fibrillation to predict outcome and left ventricular dysfunction after valve repair for mitral valve prolapse. Am J Cardiol 2015;115:1448–53.

19. Bando K, Kasegawa H, Okada Y, et al. Impact of preoperative and postoperative atrial fibrillation on outcome after mitral valvuloplasty for nonischemic mitral regurgitation. J Thorac Cardiovasc Surg 2005;129:1032–40.

20. Grigioni F, Tribouilloy C, Avierinos JF, et al. Outcomes in mitral regurgitation due to flail leaflets a multicenter European study. J Am Coll Cardiol Img 2008;1:133–41.

21. Eguchi K, Ohtaki E, Matsumura T, et al. Preoperative atrial fibrillation as the key determinant of outcome of mitral valve repair for degenerative mitral regurgitation. Eur Heart J 2005;26:1866–72.

22. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014;64:e1–76.

23. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace 2010;12:1360–420.

24. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016;18:1609–78.

25. Tribouilloy C, Grigioni F, Avierinos JF, et al. Survival implication of left ventricular end-systolic diameter in mitral regurgitation due to flail leaflets a long-term follow-up multicenter study. J Am Coll Cardiol 2009;54:1961–8.

26. Rusinaru D, Tribouilloy C, Grigioni F, et al. Left atrial size is a potent predictor of mortality in mitral regurgitation due to flail leaflets: results from a large international multicenter study. Circ Cardiovasc Imaging 2011;4:473–81.

27. Avierinos JF, Tribouilloy C, Grigioni F, et al. Impact of ageing on presentation and outcome of mitral regurgitation due to flail leaflet: a multicentre international study. Eur Heart J 2013;34:2600–9.

28. Tribouilloy C, Rusinaru D, Grigioni F, et al. Long-term mortality associated with left ventricular dysfunction in mitral regurgitation due to flail leaflets: a multicenter analysis. Circ Cardiovasc Imaging 2013;7:363–70.

29. Suri RM, Vanoverschelde JL, Grigioni F, et al. Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets. JAMA 2013;310:609–16.

30. Dafni U. Landmark analysis at the 25-year landmark point. Circ Cardiovasc Qual 2011;4:363–71.

31. Blackstone EH. Outcome analysis using hazard function methodology. Ann Thorac Surg 1996;61:S2–7.

32. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.

33. Fitzmaurice DA, Hobbs FD, Jowett S, et al. Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial. BMJ 2007;335:383.

34. Hobbs FD, Fitzmaurice DA, Mant J, et al. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. Health Technol Assess 2005;9. iii–iv, ix–x, 1–74.

35. Varghese R, Itagaki S, Anyanwu AC, Milla F, Adams DH. Predicting early left ventricular dysfunction after mitral valve reconstruction: the effect of atrial fibrillation and pulmonary hypertension. J Thorac Cardiovasc Surg 2014;148:422–7.

36. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825–33.

37. Enriquez-Sarano M, Schaff HV, Orszulak TA, Tajik AJ, Bailey KR, Frye RL. Valve repair improves the outcome of surgery for mitral regurgitation. A multivariate analysis. Circulation 1995;91:1022–8.

38. Lazam S, Vanoverschelde JL, Tribouilloy C, et al. Twenty-year outcome after mitral repair versus replacement for severe degenerative mitral regurgitation. analysis of a large, prospective, multicenter international registry. Circulation 2017;135:410–22.

39. Rahimi K, Mohseni H, Otto CM, et al. Elevated blood pressure and risk of mitral regurgitation: a longitudinal cohort study of 5.5 million United Kingdom adults. PLoS Med 2017;14:e1002404.

40. Badhwar V, Rankin JS, Damiano RJ Jr., et al. The Society of Thoracic Surgeons 2017 clinical practice guidelines for the surgical treatment of atrial fibrillation. Ann Thorac Surg 2017;103:329–41.

41. Kahlert J, Gribsholt SB, Gammelager H, Dekkers OM, Luta G. Control of confounding in the analysis phase - an overview for clinicians. Clin Epidemiol 2017;9:195–204.

KEY WORDS atrial fibrillation, mitral regurgitation, mitral repair, percutaneous treatment, prognosis, surgery

APPENDIX For a complete list of the MIDA investigators, an expanded Methods section, and supplemental tables and a figure, please see the online version of this paper.