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Effects of Atrial Fibrillation on Treatment of Mitral Regurgitation in the EVEREST II (Endovascular Valve Edge-to-Edge Repair Study) Randomized Trial

Howard C. Herrmann, MD,* Zachary M. Gertz, MD,* Frank E. Silvestry, MD,* Susan E. Wiegers, MD,* Y. Joseph Woo, MD,* James Hermiller, MD,† Douglas Segar, MD,† David Heimansohn, MD,† William Gray, MD,‡ Shunichi Homma, MD,‡ Michael Argenziano, MD,‡ Andrew Wang, MD,§ James Jollis, MD,§ Mark B. Lampert, MD,‖ John Alexander, MD,‖ Laura Mauri, MD,¶ Elyse Foster, MD,# Donald Glower, MD,§ Ted Feldman, MD‖

Philadelphia, Pennsylvania; Indianapolis, Indiana; New York, New York; Durham, North Carolina; Evanston, Illinois; Boston, Massachusetts; and San Francisco, California

Objectives The purpose of this study was to characterize patients with mitral regurgitation (MR) and atrial fibrillation (AF) treated percutaneously using the MitraClip device (Abbott Vascular, Abbott Park, Illinois) and compare the results with surgery in this population.

Background The EVEREST II (Endovascular Valve Edge-to-Edge Repair Study) randomized controlled trial compared a less invasive catheter-based treatment for MR with surgery, providing an opportunity to assess the impact of AF on the outcomes of both the MitraClip procedure and surgical repair.

Methods The study population included 264 patients with moderately severe or severe MR assessed by an independent echocardiographic core laboratory. Comparison of safety and effectiveness study endpoints at 30 days and 1 year were made using both intention-to-treat and per-protocol (cohort of patients with MR ≤2+ at discharge) analyses.

Results Pre-existing AF was present in 27% of patients. These patients were older, had more advanced disease, and were more likely to have a functional etiology. Similar reduction of MR to ≤2+ before discharge was achieved in patients with AF (83%) and in patients without AF (75%, p = 0.3). Freedom from death, mitral valve surgery for valve dysfunction, and MR >2+ was similar at 12 months for AF patients (64%) and for no-AF patients (61%, p = 0.3). At 12 months, MR reduction to <2+ was greater with surgery than with MitraClip, but there was no interaction between rhythm and MR reduction, and no difference in all-cause mortality between patients with and patients without AF.

Conclusions Atrial fibrillation is associated with more advanced valvular disease and noncardiac comorbidities. However, acute procedural success, safety, and 1-year efficacy with MitraClip therapy is similar for patients with AF and without AF. (J Am Coll Cardiol 2012;59:1312–9) © 2012 by the American College of Cardiology Foundation

From the *University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; †Care Group Heart Center, Indianapolis, Indiana; ‡Columbia University Medical Center, New York, New York; §Duke University Medical Center, Durham, North Carolina; ‖Northshore University Health System, Evanston, Illinois; ¶Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; and the #University of California San Francisco, San Francisco, California. Dr. Herrmann has received research funding from Abbott Vascular; and has equity in Micro Interventional Devices Inc. Dr. Hermiller is a consultant for Abbott Vascular. Dr. Gray has received research support and is a consultant for Abbott Vascular. Dr. Argenziano is a consultant receiving fees from Abbott Vascular. Dr. Wang has received research funding from Abbott Vascular and Gilead Sciences; and is on the clinical events committee for Edwards Lifesciences. Dr. Mauri has received grant support from Abbott Vascular, Boston Scientific, Cordis, Medtronic, Eli Lilly, Bristol-Myers Squibb, Sanofi-Aventis, and Daiichi Sankyo; is a consultant for Abbott Vascular, and Cordis; and is an expert witness for Cordis. Dr. Foster has received grant support from Abbott Vascular. Dr. Glower has received grant support from Abott Laboratories. Dr. Feldman is a consultant and receives research grants from Abbott, Boston Scientific, and Edwards. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Atrial fibrillation (AF) develops commonly in patients with mitral regurgitation (MR), with a reported rate as high as 5% per year (1). Patients with both AF and MR have increased rates of cardiac events (1,2). For this reason, the onset of AF is considered a class IIa indication for mitral valve surgery in patients with severe MR (3).

Surgical series of mitral repair or replacement have demonstrated that patients with AF are older, have more comorbidities, and have more advanced disease (4–6). In some studies, the outcomes of surgery in patients with AF have been similar to those in patients without AF (4,7), whereas others have reported worse surgical outcomes (8,9). Persistent AF after surgery is associated with reduced medium- and long-term survival (4–6,8,10).

Recently, a less invasive catheter treatment for MR with the MitraClip device was compared with surgery in the EVEREST II (Endovascular Valve Edge-to-Edge Repair Study) randomized controlled trial (11,12). In the present analysis of the EVEREST II study, we sought to determine: 1) the effects of both surgery and MitraClip device (Abbott Vascular, Abbott Park, Illinois) therapy with core laboratory assessment of MR in AF patients who are older than those in most prior series; 2) whether a less invasive therapy than surgery would have a better outcome for AF patients than for those in previous surgical series; and 3) whether AF makes it more difficult to grasp leaflets with the MitraClip device.

Abbreviations and Acronyms

AF = atrial fibrillation
ITT = intention to treat
LA = left atrial
LV = left ventricular
MR = mitral regurgitation
NYHA = New York Heart Association
PP = per protocol

Methods

Study population. The study included 279 patients at 37 study centers in the United States and Canada who participated in the randomized EVEREST II study (11). A detailed description of the trial methodology, inclusion and exclusion criteria, and the results have been previously described (11,12). Briefly, all patients had moderately severe or severe mitral regurgitation (3+ or 4+) with a left ventricular (LV) ejection fraction >25%. Patients were symptomatic, or if asymptomatic, had a LV end-systolic diameter of 40 mm to 55 mm, new AF, or pulmonary hypertension. Patients were randomly allocated 2:1 to MitraClip repair or surgery and the primary composite endpoint for effectiveness was freedom from death, from surgery for mitral valve dysfunction, and from grade 3 or 4+ MR at 12 months. The primary safety endpoint was the rate of major adverse events at 30 days. All echocardiograms were assessed by an independent core laboratory, and quantitative and qualitative MR grading was performed according to the American Society of Echocardiography guidelines (11,12).

Flow chart of AF patients. For this post-hoc analysis of the EVEREST II randomized study, patients were classified on the basis of their baseline rhythm at the time of randomization. The rhythm data were missing in 15 patients, leaving a total of 264 subjects available for analysis. A flow chart detailing the patients available at various timepoints stratified by analysis group, rhythm, and treatment received is shown in Figure 1.

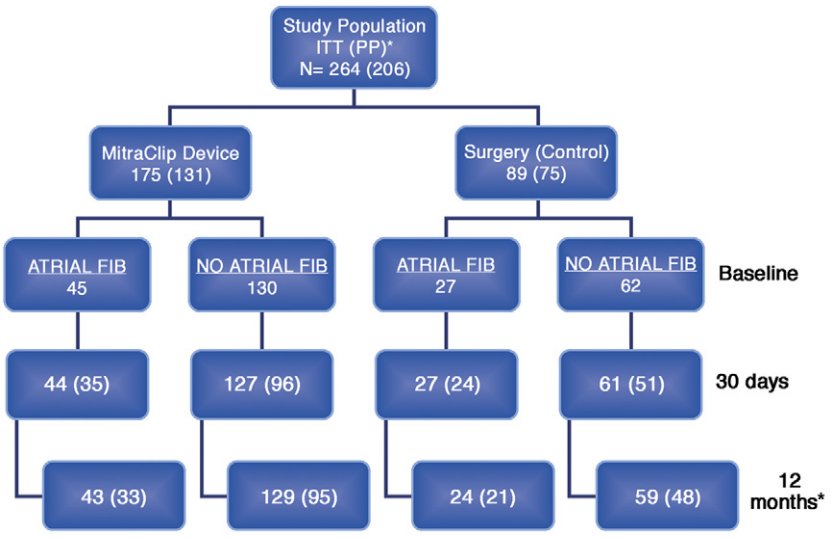

Figure 1 Flow Chart of Study Population

The number of patients available for analysis at each time point are shown for the intention-to-treat (ITT) population and also for the per-protocol cohort (PP [in parentheses]). *At 12 months, ITT patients who did not receive treatment (MitraClip device or mitral valve surgery) were assumed to have 3+ or 4+ MR and were included in the analysis. FIB = fibrillation.

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Table 1 Baseline Characteristics of the Study Population

Characteristics	Pre-Existing AF	No AF	p Value
n	72 (27%)	192 (73%)	
Male, female	67%, 33%	63%, 37%	0.67
Age, yrs	72 ± 11	65 ± 13	<0.0001
Age >75 yrs	44%	23%	0.0013
Congestive heart failure	93% (67/72)	84% (162/192)	0.0690
Coronary artery disease	59% (42/71)	40% (76/192)	0.0053
History/myocardial infarction	33% (24/72)	16% (30/191)	0.0032
Peripheral vascular disease	13% (9/72)	7% (13/192)	0.14
Hypertension	82% (59/72)	71% (136/192)	0.0834
Diabetes mellitus	13% (9/72)	7% (14/192)	0.22
Chronic kidney disease	6% (4/72)	2% (3/192)	0.0906
COPD	21% (15/71)	12% (23/192)	0.0752
History of CABG	22% (16/72)	17% (33/192)	0.38
History of PCI	26% (19/72)	18% (35/191)	0.17
History of PPM	13% (9/70)	3% (5/192)	0.0027
History of ICD	14% (10/70)	3% (6/192)	0.0021
NYHA III and IV	56 (40/72)	47% (90/192)	0.22
LVEF, %	58 ± 10 (n = 72)	62 ± 9 (n = 130)	0.0010
Afterload-reducing drugs	93% (42/45)	80% (104/130)	0.0386

Values are n (%), %, mean ± SD, or % (n/N).

AF = atrial fibrillation; CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PPM = prior pacemaker.

Statistical analysis. We performed all analyses according to the intention-to-treat (ITT) principle. Where more appropriate to compare actual treatments received, a per-protocol (PP) analysis comparing only patients who had successful percutaneous or surgical therapy (grade ≤2+ MR at the time of hospital discharge) was utilized and specified in the text. The PP analysis included 206 patients with known rhythm. Binary variables were compared with Fisher's exact test, and continuous variables were compared with Student's *t* test. A modified ridit analysis was used to compare clinical success rates (freedom from death, mitral valve surgery, and MR >2+) between device and control groups at 12 months (13). Changes in MR grade and New York Heart Association (NYHA) functional class from baseline to 12 months are compared using Bowker's test (14). All statistical analyses were performed with the use of SAS for Windows software, version 9.1 or higher (SAS Institute, Cary, North Carolina).

Results

Baseline characteristics. The study population included 72 (27%) patients with AF and 192 (73%) patients without pre-existing AF. Comparison of these patients is shown in Table 1. Patients with AF were significantly older (72 ± 11 years vs. 64 ± 13 years, p < 0.0001) with a larger percentage >75 years of age (44% vs. 23%, p =

Table 2 Baseline Echocardiographic Parameters, Intention-to-Treat Cohort

	All Patients		Device Patients		Control Patients	
Parameters	With AF (n = 72)	No AF (n = 192)	With AF (n = 45)	No AF (n = 130)	With AF (n = 27)	No AF (n = 62)
MR etiology functional	40% (29/72)	19%* (36/192)	33% (15/45)	21% (27/130)	52% (14/27)	15%* (9/62)
MR grade 3	74% (53/72)	68% (131/192)	78% (35/45)	67% (87/130)	67% (18/27)	71% (44/62)
MR grade 4	18% (13/72)	28% (54/192)	18% (8/45)	29% (38/130)	19% (5/27)	26% (16/62)
LV EDV, ml	150 ± 43 (n = 72)	160 ± 40 (n = 190)	150 ± 43 (n = 45)	158 ± 38 (n = 128)	151 ± 44 (n = 27)	163 ± 46 (n = 62)
LV ESV, ml	64 ± 27 (n = 72)	62 ± 25 (n = 190)	64 ± 27 (n = 45)	62 ± 24 (n = 128)	65 ± 28 (n = 27)	62 ± 27 (n = 62)
LV EF, %	58 ± 10 (n = 72)	62 ± 9* (n = 190)	58 ± 10 (n = 45)	62 ± 9* (n = 128)	58 ± 10 (n = 27)	63 ± 10* (n = 62)
LA volume, ml	94 ± 34 (n = 70)	81 ± 26* (n = 184)	95 ± 33 (n = 44)	82 ± 25* (n = 123)	91 ± 37 (n = 26)	80 ± 27* (n = 61)
Septolateral annulus EDD, cm	3.9 ± 0.4 (n = 69)	3.9 ± 0.5 (n = 190)	3.9 ± 0.4 (n = 43)	3.9 ± 0.5 (n = 128)	3.9 ± 0.5 (n = 69)	3.9 ± 0.5 (n = 190)
Septolateral annulus ESD, cm	3.4 ± 0.4 (n = 69)	3.4 ± 0.5 (n = 190)	3.4 ± 0.4 (n = 43)	3.4 ± 0.5 (n = 128)	3.4 ± 0.5 (n = 69)	3.4 ± 0.5 (n = 190)

Values are % (n/N) or mean ± SD. *p < 0.05 atrial fibrillation (AF) versus no AF.

EDD = end-diastolic dimension; EDV = end-diastolic volume; EF = ejection fraction; ESD = end-systolic dimension; ESV = end-systolic volume; LA = left atrial; LV = left ventricular; MR = mitral regurgitation.

Table 3 Procedural Results, Treatment Received, Per-Protocol Cohort

	Device Patients		Control Patients	
	With AF (n = 35)	No AF (n = 96)	With AF (n = 24)	No AF (n = 51)
Post-procedure ICU/CCU time, h	34 ± 21 (n = 35)	24 ± 17‡ (n = 94)	150 ± 116 (n = 22)	55 ± 48‡ (n = 50)
Post-procedure hospital stay, days	2.4 ± 1.5 (n = 35)	1.6 ± 1.0‡ (n = 96)	9.6 ± 5.3 (n = 24)	6.6 ± 3.0‡ ((n = 51)
Discharged home	97% (34/35)	98% (94/96)	58% (14/24)	77% (39/51)
MitraClip procedure time,* min	177 ± 78 (n = 34)	183 ± 72 (n = 95)	NA	NA
MitraClip device time,† min	130 ± 61 (n = 33)	141 ± 69 (n = 93)	NA	NA
1 MitraClip implanted	54% (19/35)	62% (59/96)	NA	NA
2 MitraClips implanted	46% (16/35)	39% (37/96)	NA	NA

Values are mean ± SD or % (n/N). *MitraClip procedure time is measured from the time the transseptal procedure starts until the time the steerable guide catheter (SGC) is removed. †MitraClip device time is measured from the time the SGC is placed in the intra-atrial septum until the time the MitraClip Delivery System is retracted into the SGC. ‡$p < 0.05$ atrial fibrillation (AF) versus no AF.
CCU = cardiac care unit; ICU = intensive care unit; NA = not applicable.

0.0013). In addition, AF patients had more comorbidities, including a history of congestive heart failure, coronary artery disease, previous myocardial infarction, chronic kidney disease, chronic obstructive lung disease, prior pacemaker, and lower LV ejection fraction. More patients with AF were in NYHA functional class III or IV and had a greater need for afterload-reducing medications (Table 1).

Echocardiographic parameters at baseline as assessed by the echocardiographic core laboratory are compared by treatment and rhythm in Table 2. The etiology of MR was more likely to be functional in AF patients (40%) as compared with patients without AF (19%), although the majority of patients in all groups had degenerative valve disease. The volume of the left atrium (LA) was larger in AF patients (94 ± 34 ml vs. 81 ± 26 ml, $p < 0.05$). The grade of MR and LV volumes were similar in patients with and patients without AF, and there were no differences between the device group and control group (Table 2).

Acute procedural results. In MitraClip patients, acute procedural success rates, procedural time, device time, and number of clips implanted were similar in patients with AF and patients without AF (Table 3). Procedural reduction of MR to ≤2+ occurred at similar rates in MitraClip patients with AF (83%, 35 of 42) compared with MitraClip patients without AF (75%, 96 of 128; $p = 0.30$). When comparing all patients with AF or without AF, patients with AF required longer post-procedure stays both in the intensive care unit/cardiac care unit and in the hospital (Table 3). The difference was more marked in the control (surgical) patients. The presence of AF added 0.8 days to the length of stay for MitraClip patients, and 3.0 days for surgical patients. Only 67% of surgical patients with AF could be discharged to home as compared with >90% in the other groups.

Permanent or persistent AF developed more often after surgery (31%) than after MitraClip repair (16%). Among patients undergoing surgery, a maze procedure was performed in 11% of patients (37% of those with pre-operative AF). An LA appendage ligation procedure was done in 22%

Table 4 Safety to 30 Days, Intention-to-Treat Population

	Device Patients Patients With Event		Control Patients Patients With Event	
	With AF (n = 45)	No AF (n = 130)	With AF (n = 27)	No AF (n = 62)
Death	2.2% (1/45)	0.8% (1/130)	3.7% (1/27)	1.6% (1/62)
Myocardial infarction	0% (0/45)	0% (0/130)	0% (0/27)	0% (0/62)
Reoperation for failed MV surgery	0% (0/45)	0% (0/130)	3.7% (1/27)	0% (0/62)
Nonelective CV surgery for AE	6.7% (3/45)	0.8% (1/130)	7.4% (2/27)	3.2% (2/62)
Renal failure	2.2% (1/45)	0% (0/130)	0% (0/27)	0% (0/62)
Stroke	2.2% (1/45)	0.8% (1/130)	3.7% (1/27)	1.6% (1/62)
Deep wound infection	0% (0/45)	0% (0/130)	0% (0/27)	0% (0/62)
Septicemia	0% (0/45)	0% (0/130)	0% (0/27)	0% (0/62)
Ventilation >48 h	0% (0/45)	0% (0/130)	14.8% (4/27)	0% (0/62)
GI complication requiring surgery	2.2% (1/45)	0.8% (1/130)	0% (0/27)	0% (0/62)
Transfusion ≥2 units of blood	18% (8/45)	12% (15/130)	63% (17/27)	37% (23/62)
Total number patients with MAE*	22% (10/45)	12% (16/130)	67% (18/27)	40% (25/62)

Values are % (n/N). *Total number of patients with major adverse events (MAE) may not equal sum of patients in each row because individual patients may experience >1 MAE.
AE = adverse event; AF = atrial fibrillation; CV = cardiovascular; GI = gastrointestinal; MV = mitral valve.

Table 5 Efficacy at 12 Months, Intention-to-Treat Population

	All Patients With AF (n = 57)	All Patients With No AF (n = 157)	p Value
Change baseline to 12 months			
LV EDV, ml	−21 ± 26 (n = 50)	−34 ± 33 (n = 147)	0.0032
LV ESV, ml	0.3 ± 13.3 (n = 50)	−7.8 ± 16.8 (n = 147)	0.0023
LA volume, ml	−8 ± 22 (n = 43)	−16 ± 27 (n = 130)	0.08
NYHA functional class I/II at 12 months	89% (47/53)	97% (148/152)	0.020
MR grade (≤2+) at 12 months	96% (50/52)	85% (130/153)	0.046
SF-36 QOL change at 12 months			
Mental component summary	6.6 ± 10.8 (n = 45)	4.8 ± 10.0 (n = 137)	0.30
Physical component summary	3.2 ± 10.1 (n = 45)	5.3 ± 9.8 (n = 136)	0.20

Values are mean ± SD or % (n/N).
QOL = quality of life; SF-36 = Short Form 36-Item Questionnaire; other abbreviations as in Tables 1 and 2.

of control (surgery) patients, half of whom had pre-operative AF.

Device attachment to a single leaflet occurred more often in patients with AF (13%) compared with patients not having AF (3%, p = 0.0194). Other protocol-defined major adverse events to 30 days in device patients and control patients stratified by rhythm are shown in Table 4. The need for blood transfusion was higher for surgical patients and trended higher for AF patients. There was 1 death and 1 stroke in each of the 4 study groups (device and surgery with or without AF). The stroke in the device patient with AF occurred after randomization but 1 month before MitraClip treatment. In the device patient without AF, a stroke occurred after mitral valve surgery after MitraClip treatment and resulted in death. The 2 strokes in the control (surgery) patients occurred immediately post-operatively, and 1 resulted in death. There were no other differences in major adverse events between patients with AF or without AF.

Efficacy. The effects of therapy at baseline and 12 months are shown for AF versus no AF in the entire (ITT) population in Table 5, and stratified by treatment received (PP population) in Figures 2, 3, and 4. Overall clinical success in the ITT population, defined as freedom from death, mitral valve surgery for valve dysfunction, and MR >2+, was similar for AF patients (64%, 43 of 67) and no-AF patients (61%, 114 of 188; p = 0.33). The percent of patients on afterload-reducing medication at 12 months was lower in the no-AF group (65%) compared with the AF group (72%), although the difference was not statistically significant (p = 0.31). A reduction in LV and LA volumes was observed in both AF and no-AF patients, but was significantly greater in patients without AF. A reduction in MR grade (to ≤2+) occurred more often in AF patients

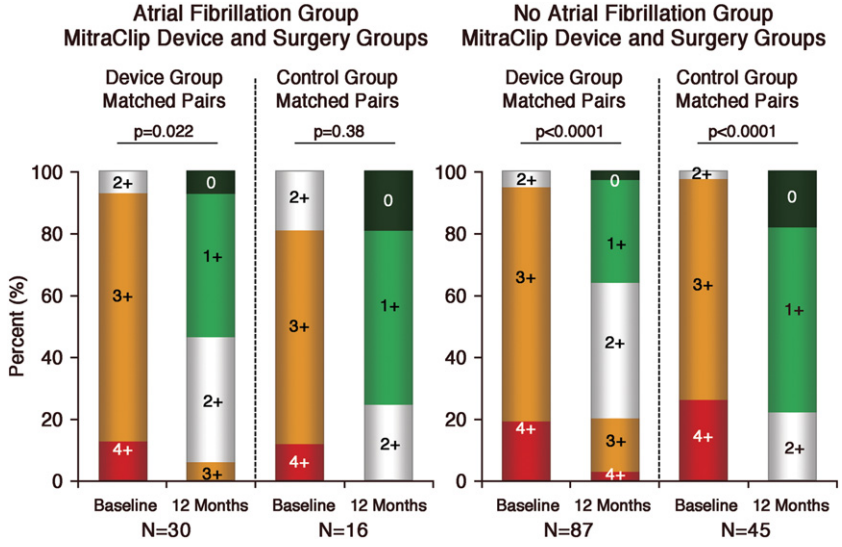

Figure 2 MR Grade at Baseline and at 12 Months

The change in mitral regurgitation (MR) grade (0 to 4+) by rhythm (with or no atrial fibrillation) is shown at baseline and at 12 months in the per-protocol cohort. Comparisons are between matched pairs of patients with percentages in each labeled grade.

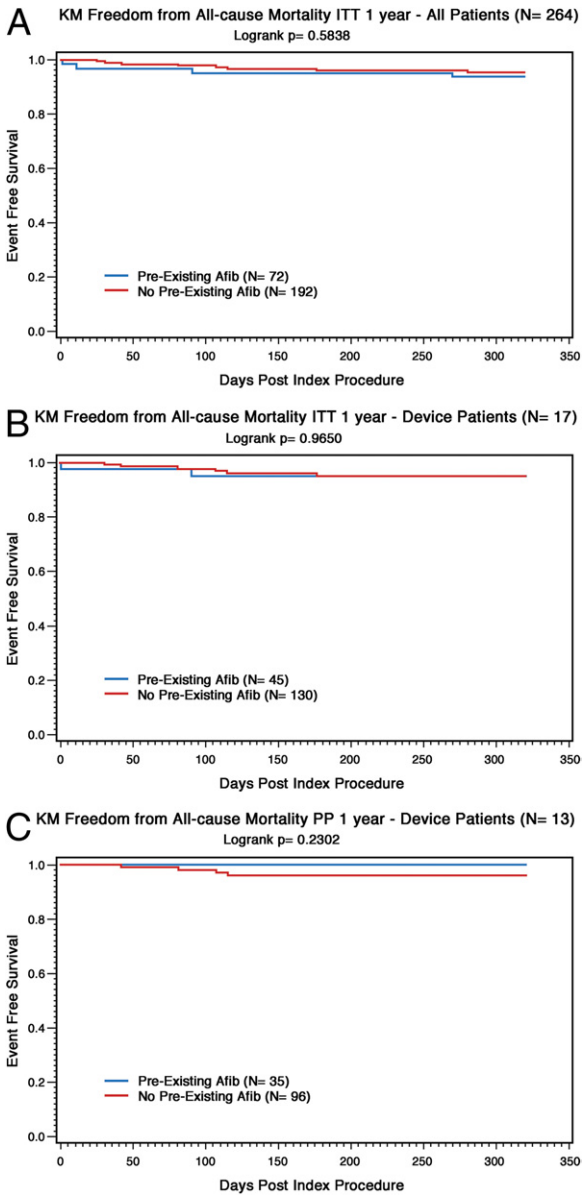

Figure 3 **Freedom From All-Cause Mortality**

Kaplan-Meier (KM) curves are shown for freedom from all-cause mortality during 1 year for patients with pre-existing atrial fibrillation (Afib) **(blue lines)** or no pre-existing atrial fibrillation **(red lines)**. Groups shown are **(A)** all patients (intention-to-treat [ITT] cohort); **(B)** patients receiving the MitraClip device (ITT cohort); and **(C)** patients receiving the MitraClip device (per-protocol [PP] cohort.

(97%) as compared with no-AF patients (85%), with similar improvement in NYHA class and Short Form-36 Health Survey quality of life score (Table 5, Figs. 2 and 3).

The effects of therapy received (PP population) on MR reduction is shown in Figure 2. Consistent with the overall study, MR reduction was greater with surgery as compared with MitraClip. However, there was no significant interaction between rhythm and MR reduction to ≤2+ at 12 months for the entire study population, device, or control groups (p = 0.99). The freedom from all-cause mortality at 1 year did not differ between AF and no-AF patients (Fig. 3A), nor for MitraClip patients examined both by ITT (Fig. 3B) or by therapy received (Fig. 3C). Similarly, the freedom from mitral valve surgery did not differ by rhythm in the same 3 analyses (Fig. 4).

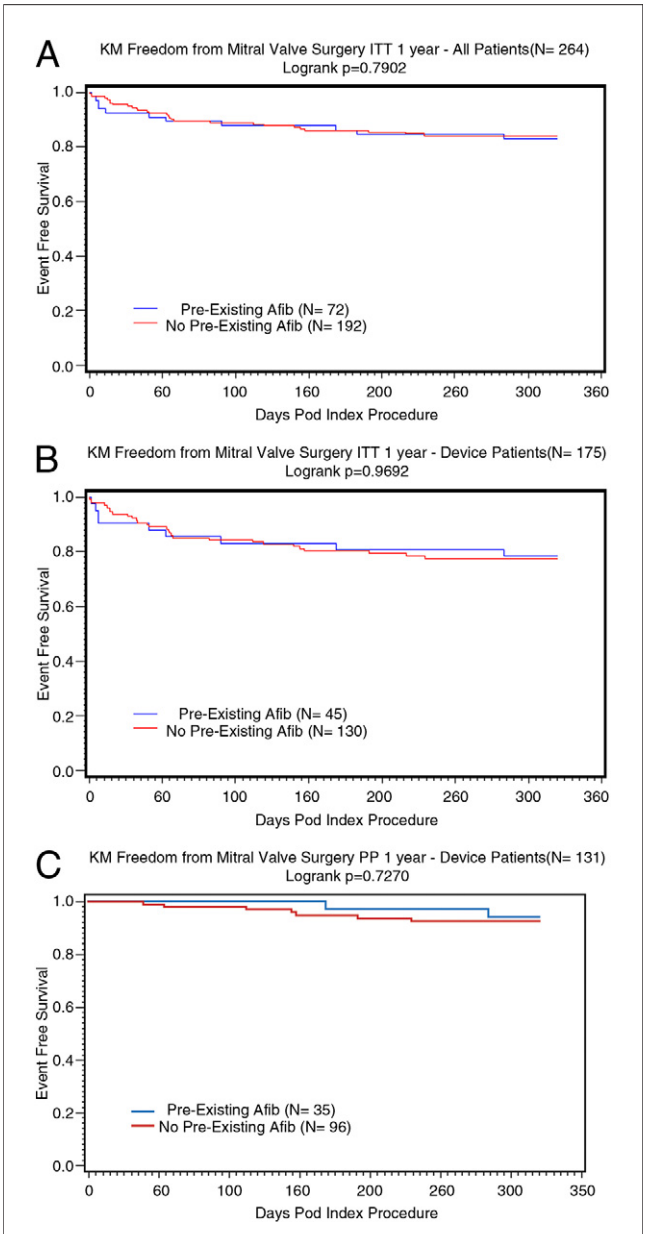

Figure 4 **Freedom From Mitral Valve Surgery**

Kaplan-Meier (KM) curves are shown for freedom from mitral valve surgery during 1 year for patients with pre-existing atrial fibrillation (Afib) **(blue lines)** or no pre-existing atrial fibrillation **(red lines)**. Groups shown are **(A)** all patients (intention-to-treat [ITT] cohort); **(B)** patients receiving the MitraClip device (ITT cohort); and **(C)** patients receiving the MitraClip device (per-protocol [PP] cohort.

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Discussion

Atrial fibrillation is common in patients with mitral regurgitation referred for therapy, occurring at baseline in 27% of the EVEREST II study population. Similar to prior surgical series, patients with MR and AF are older and have more advanced valvular disease and noncardiac comorbidities. Our patients with moderately severe or severe MR as assessed by echocardiographic analysis in a core laboratory were older than in most prior surgical series. In addition, the patients with AF were on average 7 years older than patients without AF, had more comorbidities, and required more medications. Although the grade of MR and left ventricular dimensions were similar between patients with AF and without AF, those with AF had larger left atria and were more likely to have a functional etiology of MR.

Despite the greater severity of MR and other illnesses in patients with MR and AF, it appeared that the acute procedural success of MitraClip therapy was similar for patients with AF and without AF. Unlike some prior surgical studies (8,9), surgery was not associated with worse early outcome for AF patients in this study. However, hospital length of stay was prolonged in AF patients more after surgery (3 days) than after MitraClip repair (0.8 days). This difference may be due, in part, to other baseline differences between patients with AF and without AF.

One might surmise that it would be more difficult to grasp the mitral leaflets in patients with an irregularly irregular rhythm; however, the MitraClip procedure and device time were similar in patients with AF and without AF. Device attachment to a single leaflet occurred in 10 patients, and significantly more frequently in AF patients (13% vs. 3%). That may reflect greater difficulty in assessing leaflet insertion echocardiographically during AF and suggests the need for an even more careful assessment of leaflet insertion in AF patients before clip release. It is tempting to speculate as to whether conversion to sinus rhythm before the procedure would reduce this risk.

There was little difference in effectiveness as assessed by the primary study endpoint (freedom from death, mitral valve surgery for valve dysfunction, or MR $>2+$) or by MR reduction between AF patients and no-AF patients. In fact, a reduction of MR to grade $\leq 2+$ occurred more often in patients with AF (96%) than in patients without AF (85%) (Table 5). At 1-year follow-up, there was no effect of rhythm on all-cause mortality or the need for mitral valve surgery.

The reduction in LA and LV volumes post-repair was smaller in the patients with AF (Table 5). This finding may reflect the larger initial chamber volumes in these patients, as well as the potential for less LA and LV remodeling or more persistent annular dilation after MR repair in AF patients. It also raises the potential need for additional rhythm strategies (pulmonary vein isolation and/or surgical maze procedure) as an adjunctive therapeutic strategy.

Study limitations. This study is limited by its observational design and by the small number of patients with AF. This analysis was not pre-specified, and the data collected on rhythm at various time points are limited. We cannot, therefore, differentiate between paroxysmal and persistent or permanent AF, nor do we have data on the duration of AF before enrollment. Finally, we do not have data on the conversion rates to sinus rhythm during follow-up.

Conclusions

Patients with MR and AF are sicker than patients who do not have AF, but can undergo MitraClip repair with overall procedural success, safety, and short-term efficacy similar to that for patients without AF. The development of AF is an indication for repair of MR. If a patient is suitable for MitraClip repair, this therapy should be considered independent of the presenting rhythm.

Reprint requests and correspondence: Dr. Howard C. Herrmann, Director, Interventional Cardiology and Cardiac Catheterization Labs, Hospital of the University of Pennsylvania, 3400 Spruce Street, 9 Gates West, Philadelphia, Pennsylvania 19104-4283. E-mail: howard.herrmann@uphs.upenn.edu.

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