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ORIGINAL ARTICLE

Implications of Atrial Fibrillation on the Mechanisms of Mitral Regurgitation and Response to MitraClip in the COAPT Trial

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BACKGROUND: Atrial fibrillation (AF), mitral regurgitation (MR), and left ventricular (LV) ejection fraction have a complex interplay. We evaluated the role of AF in patients with heart failure and moderate-to-severe or severe secondary MR enrolled in the randomized COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) and its impact on mechanisms and outcomes with the MitraClip.

METHODS: Patients in the COAPT trial were stratified by the presence (n=327) or absence (n=287) of a history of AF and by assignment to treatment group. Clinical, echocardiographic, and outcome measures were assessed. The primary outcome was the composite rate of death or heart failure hospitalization at 24 months.

RESULTS: Patients with history of AF were older and more often male. They had a higher LV ejection fraction, larger left atrial volumes and mitral valve orifice areas, smaller LV volumes, and similar MR severity. Patients with AF compared with those without a history of AF had a higher unadjusted (hazard ratio [HR], 1.32 [95% CI, 1.06–1.64], P=0.01) and adjusted (HR, 1.30 [1.03–1.64], P=0.03) 2-year rate of the primary outcome. Treatment with the MitraClip compared with guideline-directed medical therapy alone reduced death or heart failure hospitalization in both those with (HR, 0.61 [0.46–0.82]) and without (HR, 0.46 [0.33–0.66]) a history of AF (P_{int}=0.18). Treatment with the MitraClip was associated with a lower risk of stroke in patients with a history of AF (HR, 0.18 [0.04–0.86]) but not in those without a history of AF (HR, 1.64 [0.58–4.62]; P_{int}=0.02).

CONCLUSIONS: In the COAPT trial, patients with a history of AF had larger left atrial and mitral valve orifice areas with higher LV ejection fraction and smaller LV volumes, suggesting an atrial mechanism contribution to functional MR. Despite the worse prognosis of heart failure patients with a history of AF, MR reduction with the MitraClip still afforded substantial clinical benefits. Treatment with MitraClip was associated with a lower risk of stroke in patients with a history of AF.

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Key Words: atrial fibrillation ■ heart failure ■ hospitalization ■ mitral valve ■ stroke

Atrial fibrillation (AF), mitral regurgitation (MR), and reduced left ventricular (LV) ejection fraction (EF) have a complex interplay. MR may lead to LV enlargement and reduced left ventricular ejection fraction (LVEF), while LV dilatation with resultant displacement of the papillary muscles, tethering of the mitral

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WHAT IS KNOWN

- Atrial fibrillation, reduced left ventricular ejection fraction, and mitral regurgitation have a complex interplay, each with the potential to cause and be exacerbated by the other.
- In the COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation), patients with reduced left ventricular ejection fraction and secondary mitral regurgitation had reduced mortality and hospitalizations when treated with the MitraClip.

WHAT THE STUDY ADDS

- Patients with a history of atrial fibrillation in the COAPT trial likely had a mixed cause of mitral regurgitation, with components of an atrial and ventricular mechanism of functional mitral regurgitation.
- Patients with a history of atrial fibrillation in the COAPT trial had worse outcomes than those without but still benefited from treatment with the MitraClip.
- Patients with a history of atrial fibrillation in the COAPT trial treated with the MitraClip also had fewer strokes compared with those patients randomized to guideline-directed medical therapy.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
COAPT	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation
EF	ejection fraction
GDMT	guideline-directed medical therapy
HF	heart failure
LA	left atrial
LV	left ventricle
LVEF	left ventricular ejection fraction
MR	mitral regurgitation
TMVr	transcatheter mitral valve repair

leaflets, and reduced closing forces may lead to MR.[1,2] Both MR and reduced LVEF may lead to AF via left atrial (LA) dilatation, while AF may lead to reduced LVEF due to dysrhythmia.[3,4] AF may also cause functional MR by dilatation of the mitral annulus in the absence of LV dilation, so-called atrial functional MR.[5]

Patients with reduced LVEF who develop MR are usually assumed to have functional MR secondary to LV dysfunction, and studies of atrial functional MR have excluded patients with reduced LVEF.[5,6] It is likely that atrial and ventricular functional MR pathologies can coexist, although patients with this combination have not been well studied.

AF is frequently associated with worse outcomes in patients with MR, whether it occurs after surgery[7] or in the setting of low LVEF.[8] The COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) showed that transcatheter mitral valve repair (TMVr) with the MitraClip reduces mortality and hospitalization in patients with reduced LVEF and secondary MR.[9] Whether patients with a history of AF derive similar benefit with TMVr compared with those with sinus rhythm has not been well studied.

For this reason, we conducted a subanalysis from the COAPT trial, comparing baseline characteristics and outcomes of those patients with and without a history of AF. The purposes of our study were 3-fold: (1) to evaluate the role of AF in the mechanism of MR in patients with reduced LVEF (via atrial functional MR); (2) to determine the impact of history of AF on patient outcomes; and (3) to compare the benefit of TMVr in patients with and without a history of AF.

METHODS

Study Population

The data, analytic methods, and study materials are proprietary to the sponsor and at this time are not available to nonstudy participants. Details of the study protocol and design were previously published.[9] The COAPT trial was approved by the institutional review board at each site, and written informed consent was obtained from all patients. Briefly, COAPT was a multicenter, randomized, open-label clinical trial of TMVr with the MitraClip (Abbott Vascular, Santa Clara, CA) plus guideline-directed medical therapy (GDMT) compared with GDMT alone in patients with heart failure (HF) and moderate-to-severe (3+) or severe (4+) functional MR as confirmed at an independent echocardiographic core laboratory before enrollment. Inclusion criteria included LVEF 20% to 50% and LV end-systolic dimension ≤70 mm. Exclusion criteria included a primary (degenerative) cause of MR, severe pulmonary hypertension, severe tricuspid regurgitation requiring surgery or intervention, and moderate or severe right ventricular dysfunction, among others. Heart teams at the participating centers identified patients for whom surgery was not the standard of care and with mitral valve anatomy suitable for TMVr. Patients who remained symptomatic despite maximally tolerated GDMT were randomized in 1:1 ratio to either TMVr in addition to GDMT or GDMT alone. Follow-up in COAPT will be performed through 5 years, but at the present time is complete through 24 months in all patients. Transthoracic echocardiograms were performed at baseline and at 1, 6, 12, 18, and 24 months after randomization. Echocardiographic findings were assessed by an independent echocardiographic core laboratory as previously described.[10] Follow-up 12-lead electrocardiograms were not obtained, but heart rhythms were assessed at the time of each echocardiogram.

End Points

For the present retrospective post hoc analysis, patients were stratified by the presence or absence of a history of AF as assessed in all patients before randomization. The principal end point of interest for the present study was the time to the first occurrence of all-cause mortality or HF hospitalization within 2 years. Additional analyses were performed to assess the rates of stroke and transient ischemic attack. Adverse events in COAPT were adjudicated by an independent clinical events committee.

Statistical Plan

Continuous data are expressed as mean ±SD and were compared with *t* tests. Categorical variables are summarized as percentages and were compared using the χ^2 test. Time-to-event variables are summarized as Kaplan-Meier event rates and were compared by the log-rank test. Hazard ratios and 95% CI were determined using Cox proportional hazards regression. Multivariable analyses were performed with adjustment for the reported clinical variables. A 2-sided *P* value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Clinical and Echocardiographic Characteristics

All 614 randomized patients from the COAPT trial were included in the present analysis, of whom 327 (53.3%) had a history of AF. Patient characteristics are shown in Table 1. Patients with a history of AF were older, more often male and more frequently had hypertension. Echocardiographic characteristics are shown in Table 2. Patients with a history of AF had smaller LV dimensions and larger LA volumes as well as larger mitral annular size compared with those without a history of AF. The degree of MR was similar between groups. Baseline clinical and echocardiographic characteristics in the randomized subgroups according to AF history were generally well matched (Tables I through IV in the Data Supplement).

Table 1. Baseline Clinical Characteristics Stratified by History of Atrial Fibrillation

	History of atrial fibrillation		
	Yes (n=327)	No (n=287)	*P* value
Age, y	74.7±9.4	69.4±12.3	<0.0001
Male sex	72.2% (236)	54.7% (157)	<0.0001
Body mass index, kg/m^2	27.2±5.6	26.9±6.2	0.53
Diabetes	35.8% (117)	39.0% (112)	0.41
Hypertension	83.5% (273)	77.0% (221)	0.04
Prior stroke	11.3% (37)	12.2% (35)	0.74
Prior myocardial infarction	49.2% (161)	54.0% (155)	0.24
Kidney disease (creatinine clearance ≤60 mL/min)	76.3% (244)	70.1% (197)	0.09
New York Heart Association class III or IV	60.6% (198)	61.2% (175)	0.87

Values are mean±SD or % (n).

Patient Outcomes

Overall, patients with a history of AF were more likely than patients without a history of AF to experience the primary composite outcome of death or hospitalization for HF (61.3% versus 49.8%, hazard ratio [HR], 1.32 [95% CI, 1.06–1.64], *P*=0.01; Figure 1). By multivariable analysis, history of AF was a significant independent predictor of the primary outcome (HR, 1.35 [95% CI, 1.07–1.70], *P*=0.01; Figure I in the Data Supplement). Evaluating the components of the primary end point separately, patients with a history of AF were more likely to die (40.2% versus 30.1%, *P*=0.02) or be hospitalized for HF (50.9% versus 39.6%, *P*=0.02) during 2 years of follow-up.

Stratifying by history of AF and treatment group, patients with AF derived similar relative benefits from TMVr as did those without a history of AF for reduction of death or HF hospitalization (Figure 2 and Table 3). Within the group of patients with a history of AF, those treated with TMVr were less likely to experience the primary end point compared with those in the control group (52.1% versus 71.6%, *P*=0.0007). Evaluating the components of the primary end point separately, patients with a history of AF treated with TMVr were also less likely to die (32.9% versus 48.6%, *P*=0.02) or be hospitalized for HF (42.9% versus 59.6%, *P*=0.02) than patients in the control group during 2 years of follow-up.

All evaluated outcomes, stratified by history of AF and treatment group, are shown in Table 3. In addition to reductions in death and hospitalization, patients with a history AF randomized to TMVr had fewer strokes compared with those randomized to GDMT alone (Figure 3). In contrast, among patients without a history of AF, there were no differences in stroke rates between those randomized to device or control ($P_{interaction}$=0.02).

We performed several analyses to better understand the nature of the lower incidence of stroke among patients with a history of AF randomized to TMVr compared with GDMT alone. Both groups had similar $CHADS_2$ scores (Table I in the Data Supplement). Numerically more patients were treated with anticoagulation at baseline in the device group, although that difference was not statistically significant. Use of anticoagulation at 30 days tended to be more common in the device arm (77.2% versus 67.5%, *P*=0.055). LA and LV chamber dimensions at baseline as well as the severity of MR were similar in the randomized groups with a history of AF (Table 2). The site-reported baseline heart rhythm was AF in similar proportions of both groups (46.8% versus 40.3%, respectively, *P*=0.25), as was the percentage with history of paroxysmal versus persistent/permanent AF (38.1% versus 42.8%, *P*=0.39). At follow-up

Table 2. Baseline Echocardiographic Characteristics Stratified by History of Atrial Fibrillation

	History of atrial fibrillation		
	Yes (n=327)	No (n=287)	*P* value
Left ventricular ejection fraction, %	32.1±9.7	30.4±8.8	0.03
Left ventricular end-systolic volume index, mL/m^2	67.8±29.3	74.7±28.6	0.005
Left ventricular end-diastolic volume index, mL/m^2	97.4±34.1	105.8±34.1	0.003
Left atrial volume index, mL/m^2	52.3±24.6	44.0±17.0	<0.0001
Mitral valve orifice area, cm^2	5.3±1.3	5.0±1.1	0.0002
Mitral annular diameter, cm	3.34±0.40	3.18±0.36	<0.0001
Effective regurgitant orifice area, cm^2	0.41±0.16	0.40±0.14	0.45
Regurgitant volume, mL/beat	27.6±17.6	25.9±14.6	0.39
Stroke volume index, mL/m^2	26.5±8.3	27.2±9.0	0.39
Tricuspid regurgitation ≥2+	17.4% (56/322)	15.2% (42/277)	0.46
Right ventricular ejection fraction, %	31.6±9.5	32.5±8.5	0.34
Right ventricular systolic pressure, mm Hg	44.0±12.8	44.5±14.7	0.69

Values are mean±SD or % (n).

echocardiographic rhythm assessments, the proportion of patients in AF increased from baseline in the device group but remained stable in the control group such that more patients in the device group were in AF at 30 days (57.8% versus 40.2%, *P*=0.004) and at 1 year (52.5% versus 35.4%, *P*=0.02). There were no significant differences in terms of reverse remodeling of the LA or LV based on treatment group, and both groups had similar, nonsignificant changes in chamber dimensions throughout follow-up (Tables V and VI in the Data Supplement).

DISCUSSION

We performed a subanalysis of the COAPT trial to evaluate the role of a history of AF in patients with reduced LVEF and secondary MR. Our study has 4 main findings: (1) Despite the fact that all enrolled patients had LV dysfunction and presumed ventricular functional MR, there was evidence of a component of atrial functional MR in those with a history of AF, based on echocardiographic differences in chamber sizes and annular dimensions; (2) patients with a history of AF were at higher risk of adverse outcomes, even after adjustment for other clinical variables; (3) patients with a history of AF derived similar benefit compared with those without a history of AF for reduction of death and HF hospitalization after TMVr with the MitraClip; and (4) patients with a history of AF had a lower risk of stroke after treatment with the MitraClip.

Atrial functional MR, classified as Carpentier Type I, arises secondary to mitral annular dilatation (typically due to long-standing AF) and a failure of compensatory mitral leaflet enlargement leading to lack of leaflet coaptation.[5,6] It was first studied in patients with preserved LVEF, allowing differentiation of the atrial mechanism from the more common pathophysiology of functional MR—that is lack of leaflet coaptation due to leaflet tethering from

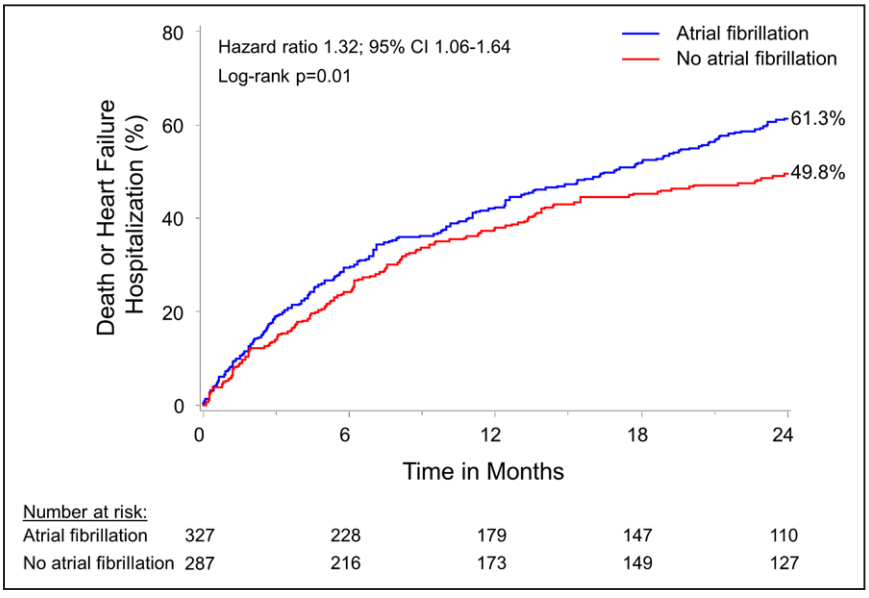

Figure 1. Kaplan-Meier curves for the primary composite outcome of all-cause death or hospitalization for heart failure stratified by history of atrial fibrillation.

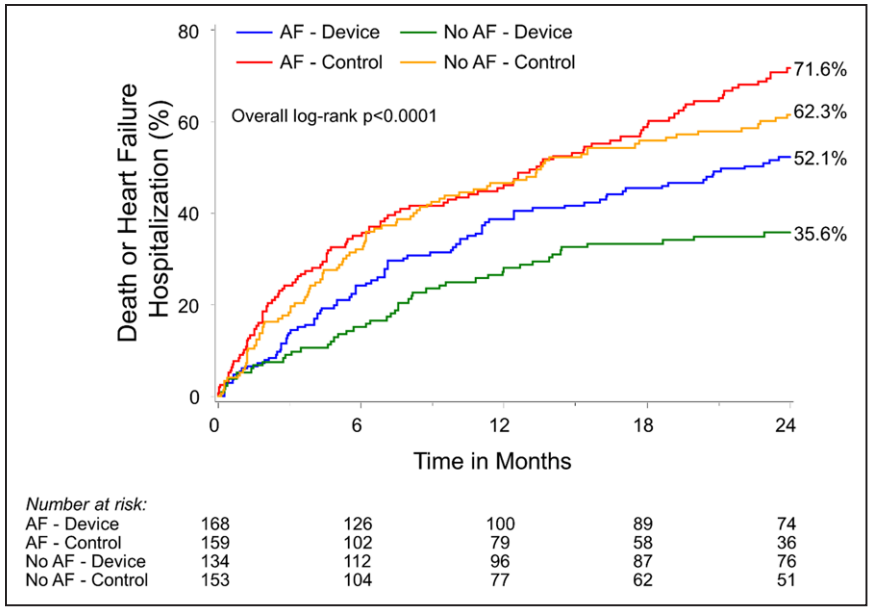

Figure 2. Kaplan-Meier curves for the primary outcome stratified by history of atrial fibrillation (AF) and treatment group.

papillary muscle dislocation in patients with LV dilatation due to ischemic or nonischemic cardiomyopathy. While the COAPT trial required that all patients have reduced LVEF, those with compared with those without a history of AF had a different echocardiographic phenotype, with larger LA volumes, smaller LV volumes, and larger mitral annular orifice areas, that is, likely including a contribution of an atrial mechanism to the MR (Figure 4). Patients in COAPT with and without a history of AF had similar mitral effective regurgitant orifice areas despite smaller LV dimensions, denoting relatively more severe MR (ie, a higher percentage of patients with disproportionate MR).[11] These data support the hypothesis that atrial functional MR, via mitral annular dilatation, contributed to the mechanism of the MR in the AF cohort. The CASTLE-AF trial (Catheter Ablation Versus Standard Conventional Therapy in Patients With Left Ventricular Dysfunction and Atrial Fibrillation)[4] showed that AF ablation could improve LVEF and outcomes in patients with AF and reduced LVEF but did not evaluate the importance of baseline MR or the impact of ablation on MR at follow-up. Further studies, examining the role of AF ablation, either before or after treatment with MitraClip, may be warranted.

Patients with a history of AF in our analysis had a worse prognosis than patients without AF. This remained true after controlling for the higher-risk characteristics of this population, such as older age and male sex. This finding is in line with other studies that have shown that AF portends a worse prognosis in patients with HF and reduced LVEF.[8] Patients with degenerative MR and AF

Table 3. Outcomes Based on History of Atrial Fibrillation and Treatment Group

	History of atrial fibrillation			No history of atrial fibrillation			
	MitraClip+GDMT (n=168)	GDMT alone (n=159)	HR (95% CI)	MitraClip+GDMT (n=134)	GDMT alone (n=153)	HR (95% CI)	*P* interaction
Death or hospitalization for heart failure	52.1% (86)	71.6% (108)	0.61 (0.46–0.82)	35.6% (47)	62.3% (93)	0.46 (0.33–0.66)	0.18
Death							
All-cause	32.9% (54)	48.6% (71)	0.65 (0.46–0.93)	22.3% (29)	37.2% (54)	0.55 (0.35–0.87)	0.54
Cardiovascular	28.0% (44)	41.4% (57)	0.66 (0.44–0.98)	16.1% (20)	31.6% (45)	0.46 (0.27–0.77)	0.25
Hospitalization							
All-cause	73.4% (120)	87.4% (130)	0.71 (0.56–0.92)	62.5% (80)	73.7% (106)	0.77 (0.58–1.04)	0.69
Cardiovascular	56.2% (88)	70.8% (101)	0.68 (0.51–0.91)	42.7% (53)	62.9% (89)	0.58 (0.41–0.81)	0.43
Heart failure related	42.9% (65)	59.6% (84)	0.60 (0.44–0.84)	24.7% (30)	52.8% (74)	0.37 (0.24–0.57)	0.07
Neurological events*	2.1% (3)	10.9% (12)	0.21 (0.06–0.74)	8.2% (10)	5.3% (7)	1.58 (0.60–4.16)	0.02
Stroke	1.4% (2)	8.4% (9)	0.18 (0.04–0.86)	7.5% (9)	4.7% (6)	1.64 (0.58–4.62)	0.02
TIA	0.7% (1)	2.6% (3)	0.29 (0.03–2.82)	1.7% (2)	0.7% (1)	2.20 (0.20–24.29)	0.24

Values are % (n). Event rates are Kaplan-Meier estimated percentages (number of events). GDMT indicates guideline-directed medical therapy; HR, hazard ratio; and TIA, transient ischemic attack.

*Stroke or TIA.

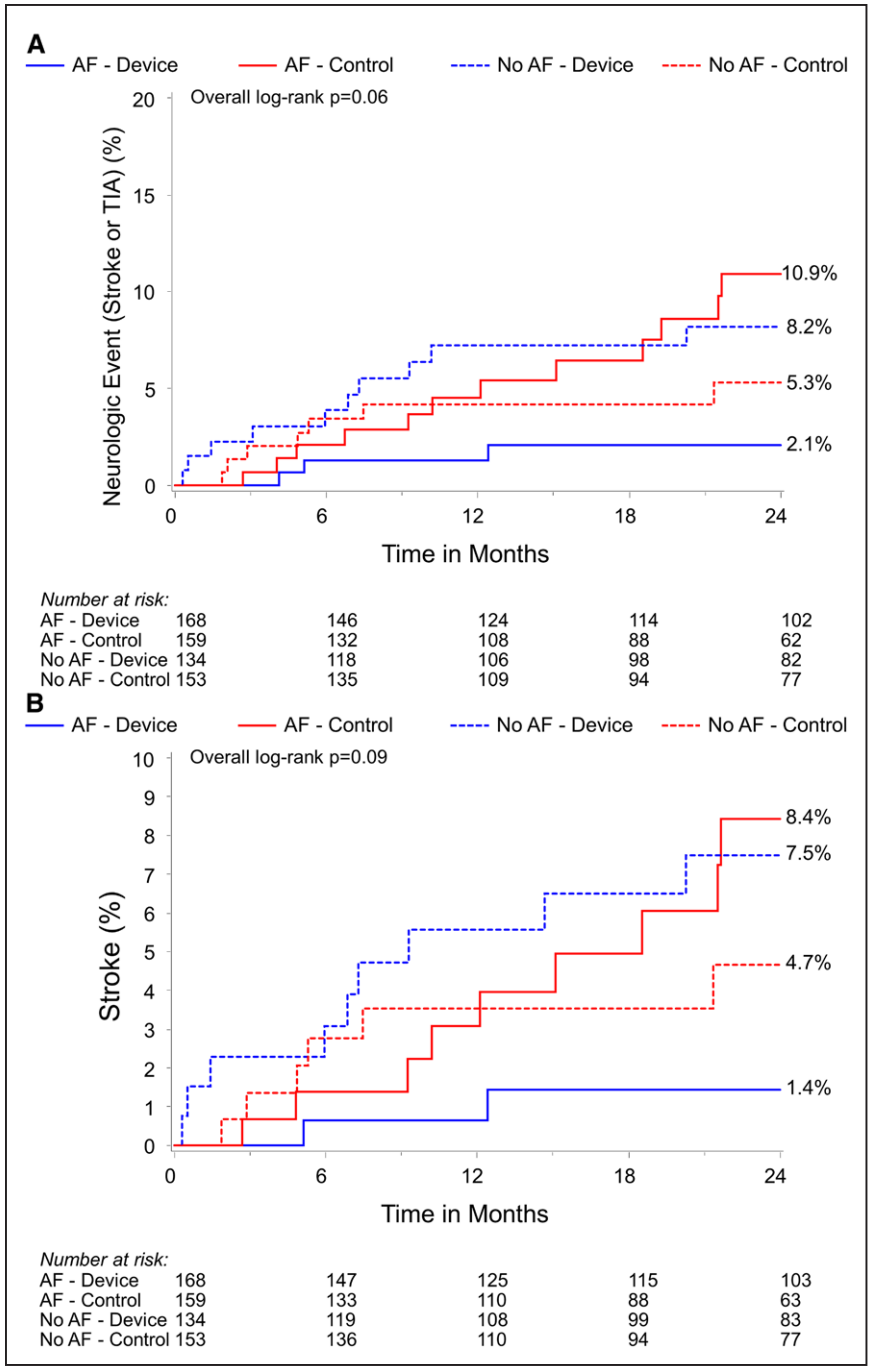

Figure 3. Kaplan-Meier curves for stroke or neurological events.
A, Neurological events (stroke or transient ischemic attack [TIA]) and (**B**) stroke in all patients stratified by history of atrial fibrillation and treatment group. Comparing just those with history of atrial fibrillation, there was a significant reduction in neurological events (P=0.008) and strokes (P=0.02) among patients treated with MitraClip.

also have been reported to have worse outcomes than those without AF,[7] although not all studies have agreed.[12] It is notable that the AF cohort in our study had higher rates of death or hospitalization for HF despite smaller LV volumes, a common marker of poorer outcomes in other settings,[13] perhaps reflecting the greater percentage of disproportionate MR. Despite the worse outcomes associated with AF, consistent relative reductions in death and HF hospitalization were realized after TMVr in patients with and without a history of AF. Similarly, surgical repair provides benefits in higher-risk patients with degenerative MR and AF.[7]

A lower risk of stroke during the 2-year follow-up period was observed among patients with a history of AF treated with the MitraClip compared with GDMT alone. Such a difference was not observed in patients without a history of AF. We examined several possible explanations for this finding, including differences in medical therapy, LA dimensions, and heart rhythm. There were numerically more patients treated with anticoagulation during follow-up in the device group, possibly due to the paradoxically increased rates of AF observed in the MitraClip group during follow-up. Although these differences in anticoagulation use did not reach statistical significance, it is

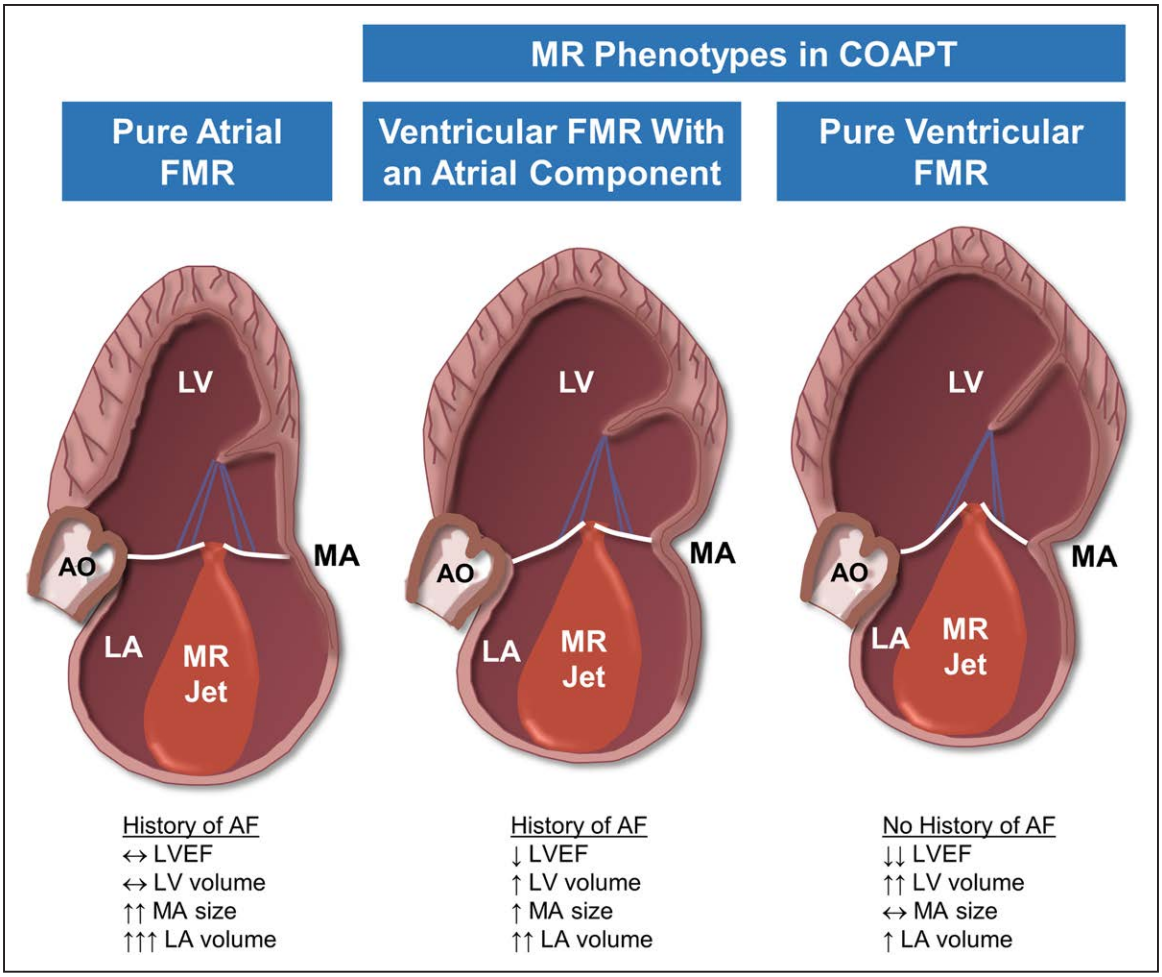

Figure 4. Representative examples of pure atrial functional mitral regurgitation (FMR), pure left ventricular FMR, and mixed (atrial and ventricular) FMR.

FMR usually develops due to left ventricular dysfunction with papillary muscle dislocation resulting in mitral leaflet tethering (**right**). In a minority of patients FMR may develop from primary mitral annular enlargement typically due to long-standing atrial fibrillation (AF; **left**). Per the COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) enrollment criteria, all patients had left ventricular dysfunction; however, those with a history of AF had higher left ventricular ejection fractions (LVEF), larger left atrial (LA) volumes and mitral annular (MA) orifice areas, and smaller LV volumes (**middle**) than those without a history of AF (**right**), suggesting an atrial component to their cause of FMR. The severity of FMR as quantified by the effective regurgitant orifice area was similar in both of the COAPT phenotypes.

possible that better medical therapy for stroke prevention may have contributed to the lower incidence of stroke with TMVr. LA dimension is closely linked with stroke risk.[14] While the EVEREST II trial (Endovascular Valve Edge-to-Edge Repair Study) did show a modest reduction in LA volume from baseline to 1 year after MitraClip treatment of patients with predominantly degenerative MR (albeit less so in patients with AF),[12] a significant decrease in LA volume was not observed in the functional MR patients in COAPT, either in those with or without a history of AF. We cannot exclude an improvement in LA function in patients treated with MitraClip, despite the unchanged LA volume. LA function has been linked to stroke risk, independent of LA dimension and AF burden,[15] but that question will require further study. Finally, the burden of AF has also been linked to stroke risk[16]; however, the available echocardiographic data from the present study demonstrates that there may actually have been an increase in AF after TMVr (despite the sustained reduction in MR with the MitraClip), perhaps due to the disruption of the interatrial septum. Given the lack of an obvious pathophysiologic explanation for the lower occurrence of stroke in the treatment group and the small number of total events, our findings require validation in future studies.

Limitations

Several limitations to our study must be noted. Our results cannot be generalized to patients who do not meet the inclusion and exclusion criteria of the COAPT trial including those patients with primary MR and AF. Likewise, patients with pure atrial functional MR and AF without LV dysfunction were excluded from the trial; whether the MitraClip is beneficial in such patients is

unknown. The benefits observed with MR reduction in the present study apply to treatment with the MitraClip only; whether devices other than the MitraClip that reduce MR by different mechanisms (eg, direct or indirect annuloplasty, or transcatheter mitral valve replacement) may be more or less safe and effective is uncertain and such effects may depend on whether the etiology of MR is predominantly atrial or ventricular in origin. We relied on site-reported history of AF. Patients who were in sinus rhythm during screening and did not report a history of AF may still have had a history of AF, clinical or subclinical, that was not captured. Still, this would only have been expected bias our findings to the null and does not explain the subsequent lower incidence of stroke after TMVr. Finally, given the lack of detailed follow-up data on rhythm, we were unable to assess the impact of TMVr on AF burden, nor could we evaluate the incidence of new AF during follow-up.

Conclusions

The present substudy from the COAPT trial demonstrates evidence of an atrial mechanism contributing to the cause of functional MR in the cohort of patients with a history of AF. Overall outcomes in such patients were worse than in those without a history of AF, although patients with and without a history of AF derived a consistent relative reduction in death and hospitalization for HF after treatment with TMVr compared with GDMT alone. Patients with a history of AF treated with TMVr also had a lower incidence of stroke during 2-year follow-up, a finding that merits further study.

ARTICLE INFORMATION

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Disclosures

Dr Herrmann reports institutional research funding from Abbott Vascular, Ancora, Boston Scientific, Edwards Lifesciences, Medtronic; consultant fees from Abbott Vascular, Edwards Lifesciences, Medtronic; equity in Microinterventional Devices. Dr Lim reports research grant support from Abbott, Edwards, Medtronic, Gore; consulting fees from Abbott, Edwards, Keystone Heart, Pipeline, Siemens, Valgen, Venus; advisory board position with Ancora, Venus; equity in 510Kardiac, Venus. Dr Kar reports consulting fees/advisory board position with Boston Scientific; consulting fees/stock equity from Valcare; consulting fees from W.L. Gore and Medtronic. Dr Kapadia reports stock options in Navigate Cardiac Structures, Inc. Dr Puri reports stock options in Centerline Biomedical. Dr Gersh reports consulting fees from Boston Scientific, Medtronic, and Edwards. Drs Weissman and Asch report institutional contracts with Abbott, Neovasc, Ancora, Mitralign, Medtronic, Boston Scientific, Edwards Lifesciences, Biotronik, and Livanova. Dr Grayburn reports consulting fees from Abbott Vascular, Edwards Lifesciences, W.L. Gore, Medtronic, 4C Medical; grant support from Abbott Vascular, Boston Scientific, Cardiovalve, Edwards Lifesciences, W.L. Gore, Medtronic, and Neochord. Dr Abraham reports research grant support from Abbott Vascular; consulting income from Abbott Vascular. Dr Lindenfeld reports research grant support from AstraZeneca; consulting income from Abbott Vascular, AstraZeneca, CVRx, Edwards Lifesciences, Impulse Dynamics, Boehringer Ingelheim, VoluMetrix, and V-Wave. Dr Stone reports speaker or other honoraria from Cook, Terumo, Qool Therapeutics and Orchestra Biomed; Consultant to Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, Matrizyme, Cardiomech; Equity/options from Ancora, Qool Therapeutics, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, MedFocus family of funds, Valfix. Dr Mack reports served as coprimary investigator for the PARTNER trial (Placement of Aortic Transcatheter Valves) for Edwards Lifesciences and COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) for Abbott; served as study chair for the APOLLO trial for Medtronic. The other authors report no conflicts.

Supplemental Materials

Tables I–VI
Figure I

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