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# Incidence, etiology, and outcomes of pre- and post-operative atrial fibrillation in mitral valve procedures: a review

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## Abstract

Although pre-procedural and post-procedural atrial fibrillation occur commonly in mitral valve (MV) patients, the impact on patient outcomes and resource utilization has not been well documented. A comprehensive PubMed review was performed using a combination of MeSH terms related to atrial fibrillation, MV disease, MV and atrial fibrillation procedures, and medical management. Additional publications were selected from the reference lists of studies identified in the literature search. This review found that several studies conflict with the short-term outcomes associated with pre- and post-operative atrial fibrillation in MV patients. In general, both pre- and post-operative atrial fibrillation have clear negative long-term impacts on MV patients' mortality and risk of stroke, major bleeding and other thromboembolic events. Surgical ablation for pre-operative atrial fibrillation and transcatheter ablation for medically resistant post-operative atrial fibrillation appears to be safe and effective procedure; these percutaneous and surgical interventions have been documented to mitigate MV-related thromboembolic risk. For MV patients, evidence suggests that the first step should be to optimize the current medical therapy; for persistent symptoms not addressed medically, ablation procedures should be considered. To optimize MV patients' quality of care, however, additional research appears warranted to prevent long-term adverse outcomes.

**Keywords:** Atrial fibrillation, mitral valve repair, mitral valve replacement, mitral valve surgery, short-term outcomes, long-term outcomes

## INTRODUCTION

Mitral valve (MV) procedures are increasing in frequency. Pre- and post-operative atrial fibrillation are common in patients undergoing MV procedures, with approximately one-third of these patients meeting the criteria for pre-operative atrial fibrillation[1-4], and new-onset post-operative atrial fibrillation estimates range as high as 40%[5-8]. Mitral valve procedures have been associated with post-operative atrial fibrillation (OR = 1.91) and more frequently result in post-operative atrial fibrillation compared to other cardiac procedures[8,9]. In spite of their high rates of occurrence, significant challenges in patient management, and impact on morbidity and mortality of pre- and post-operative atrial fibrillation in patients with mitral valve disease are not well understood. There is a gap in the literature regarding the effects of AF on MV patients' outcomes and resource utilization. In this manuscript, the etiology, incidence, and outcomes of atrial fibrillation are summarized for MV patients with pre-operative and new-onset post-operative atrial fibrillation.

## PRE-OPERATIVE ATRIAL FIBRILLATION IN MITRAL VALVE DISEASE

### Etiology

Valvular heart disease has been associated with the development of atrial fibrillation[10]. Both mitral stenosis and mitral regurgitation can result in increased left atrial (LA) pressure and LA enlargement (LAE)[11-14]. Several studies report that age, LA diameter changes due to mitral regurgitation, severity of mitral stenosis, and reduced left ventricular function are associated with atrial fibrillation[15-21]. Vulnerability to atrial fibrillation at increased atrial pressure has been demonstrated in animal models[22] and in patients with mitral stenosis[23].

In addition to LA pressure, LAE has been associated with atrial fibrillation development[10,24-26]. Despite its enlargement, the LA undergoes loss of myocardium[27]. Loss and scarring of the atrial myocardium create conduction abnormalities and susceptibility to atrial fibrillation. This has been attributed to myocardial fibrosis, which prevents adequate transmission of electrical impulses[28]. Thus, interrupted electrical signals may instead follow reentry pathways. In mitral stenosis, the increased degree of fibrosis is associated with the increased incidence of atrial fibrillation[29]. Decreased LA strain and increased lateral wall electromechanical conduction time can predict the development of atrial fibrillation in mitral stenosis patients at 5-year follow-up[30]. These parameters can be monitored via speckle tracking echocardiography and may allow earlier detection of atrial fibrillation[31].

LA stretch is also thought to contribute to conduction anomalies arising from the pulmonary veins[31]. This location is commonly a point of origin of atrial fibrillation but has been poorly studied in atrial fibrillation induced by MV disease. An early report of a patient with mitral stenosis recorded atrial activation originating adjacent to and on the side of the left pulmonary veins, in addition to activation in the LA appendage[32]. Additional research on MV disease is needed to identify specific conduction abnormalities and their precise origins.

### Prevalence

MV operations are among the fastest growing cardiac procedures, with about a third of patients having pre-operative atrial fibrillation[33,34]. Noubiap *et al.*[1]' recent meta-analysis has shown atrial fibrillation to be prevalent in 33.9% of patients with rheumatic mitral stenosis and 21.6% of patients with rheumatic mitral

regurgitation globally. In patients with degenerative mitral regurgitation, between 32% to 45% present with atrial fibrillation[2-4]. Kim *et al.*[35]' recent study of ten-year trends in Korea further showed that 66.1% of patients with mitral stenosis had atrial fibrillation. Patients with atrial fibrillation and mitral disease were often older, presenting with more severe mitral disease and LA and left ventricular enlargement[2-4]. Thus, atrial fibrillation represents one of the most prevalent diseases occurring concomitant with MV repair and replacement procedures.

## Therapeutic interventions

Due to increased mortality risk from stroke, thromboembolic events and other adverse outcomes associated with pre-operative atrial fibrillation, treatment for patients with pre-operative atrial fibrillation and MV disease is focused primarily on preventing these complications through anticoagulation, medical rate and rhythm control, and ablation procedures when medical therapy is not sufficient[36-39].

### *Medical therapy*

According to the 2020 ACC/AHA guidelines, to prevent stroke and other thromboembolic events, non-vitamin K oral anticoagulants are recommended for patients with atrial fibrillation and nonrheumatic mitral stenosis or mitral disease (Class I, Level A). Patients with rheumatic mitral stenosis and atrial fibrillation should be given long-term vitamin K antagonist oral anticoagulants (Class I, Level C-EO)[36]. Recent studies have shown increased use of direct oral anticoagulants in patients with atrial fibrillation undergoing MV procedures[40,41]. Several meta-analyses demonstrate decreased risk of stroke and systemic embolism[42-44] and decreased risk of major bleeding with edoxaban[42], apixaban and dabigatran[43]. Furthermore, a recent randomized controlled trial in patients with atrial fibrillation and mitral or aortic valve disease showed a non-significant trend towards reduced stroke, systemic embolism, death, and major bleeding with apixaban compared to warfarin[45]. However, additional research appears warranted to conclusively determine the superiority of direct oral anticoagulants *vs.* vitamin K antagonists[43].

Additional 2020 ACC/AHA guidelines on valvular heart disease recommend that patients with rheumatic mitral stenosis and acute atrial fibrillation should be treated with negative dromotropic agents to slow ventricular contraction and decrease left atrial pressure (Class 2A, Level C-LD)[36]. Rate control therapy has been shown to have similar efficacy in conjunction with anticoagulation in controlling adverse outcomes compared to rhythm control therapy; it is recommended by the 2014 ACC/AHA/HRS guidelines on atrial fibrillation to address the symptoms of atrial fibrillation, improve the quality of life and reduce morbidity[37,46-52]. Rate control therapy can be used in patients with paroxysmal, persistent or permanent atrial fibrillation (Class I, Level B)[37,46]. Beta blockers are used most frequently, followed by nondihydropyridine calcium channel blockers, digoxin or amiodarone[37]. However, if atrial fibrillation persists with worsening symptoms despite rate control and anticoagulation therapy, antiarrhythmic drugs, such as amiodarone, may be recommended to alleviate the symptoms of atrial fibrillation (Class I, Level C)[37,46].

### *Ablation*

Ablation procedures can be performed through a surgical or transcatheter approach. Surgical ablations are often performed concomitantly with MV surgery to improve patient outcomes, restore sinus rhythm, and reduce the need for long-term use of anticoagulants and antiarrhythmic drugs[2,53-58]. According to the STS guidelines, concomitant surgical ablation is a Class I, Level A recommendation for patients undergoing MV surgery with pre-operative atrial fibrillation due to its effectiveness in restoring sinus rhythm without increased operative morbidity and mortality[53]. Surgical ablation involves creating lesions in the right and left atria, most commonly around the pulmonary veins, to disrupt the electrical conduction pathways of

atrial fibrillation and can be performed through a cut-and-sew-technique, radiofrequency ablation, or cryoablation[53,59,60]. The outcomes of concomitant surgical ablation for patients with pre-operative atrial fibrillation are detailed in Sections 1.4.2. and 1.4.6.

A subset of patients may have symptomatic pre-operative atrial fibrillation unresponsive to medical management with low severity of MV disease that does not warrant MV surgery. For these patients who are not candidates for MV surgery or who are at high risk for concomitant surgical ablation, transcatheter ablation, a more minimally invasive approach, is available[61]. According to the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation and 2014 AHA/ACC/HRS guidelines, transcatheter ablation is recommended for paroxysmal atrial fibrillation when Class I or Class III antiarrhythmic drugs are ineffective (Class I, Level A)[37,61]. Pulmonary vein isolation is considered to be the key element of transcatheter ablation; however, recent literature has demonstrated that it may not be enough, especially in cases of persistent AF. A recent meta-analysis has demonstrated that left atrial appendage ablation, in addition to pulmonary vein isolation, had decreased recurrence of AF when compared to patients who received pulmonary vein isolation ablation alone[62]. In a propensity score-matched study of persistent AF with a mean follow-up of 30.5 months, patients who received both left atrial appendage and pulmonary vein isolation (75.7%) had significantly greater freedom from atrial tachyarrhythmia with no difference in cerebrovascular events or all-cause mortality compared to patients who received only pulmonary vein isolation (61.6%). Furthermore, pulmonary vein isolation alone was a significant predictor of recurrent atrial tachyarrhythmia[63]. As such, transcatheter ablation now often involves a combination of pulmonary vein isolation and ablation of the left atrial appendage. The outcomes of left atrial appendage exclusion and transcatheter ablation for pre-operative atrial fibrillation are detailed in Sections 1.4.3 and 1.4.5-1.4.6, respectively.

When medical therapy is insufficient to address persistent or worsening symptoms of AF for MV patients, as a last option AV nodal ablation may be considered (Class IIa, Level B) by AHA/ACC/HRS guidelines[37,53,64]. Though successful in alleviating symptoms and improving quality of life, AV nodal ablation is often performed only when necessary, such as in patients for whom both medical therapy and catheter ablation are insufficient in addressing refractory, symptomatic and permanent AF and present with LVEF < 35% and NYHA functional class I or II, due to it requiring the patient to live with a permanent pacemaker and possible complications of sudden cardiac death and heart failure[65-71]. Permanent pacemakers may further worsen left ventricular function in patients with AF, increasing the likelihood of heart failure[68,71].

## Outcomes

*Mitral valve surgery*

Although studies differ on the impact of pre-operative atrial fibrillation on early mortality, studies with 5- to 10-year follow-up have shown pre-operative atrial fibrillation to be an independent predictor of increased long-term mortality and other long-term adverse outcomes[2,4,72]. Furthermore, a study including 382 patients found that survival at 15 years following surgery was significantly lower in those with atrial fibrillation (59.9%) compared to those without (86.5%). Patients with atrial fibrillation and/or pulmonary hypertension also had reduced freedom from major adverse cardiac and cerebrovascular events (52.7% *vs.* 74.5%) and a decreasing trend in freedom from recurrent mitral regurgitation (65.1% *vs.* 87.0%), suggesting decreased effectiveness of MV repair in that group[73]. These studies imply that atrial fibrillation, although often an independent variable for the outcome, may be a surrogate of worse myocardial conditions (e.g., heart failure).

Few studies have examined the use of concomitant ablation for patients with pre-operative atrial fibrillation undergoing isolated MV surgery[17,74]. Further detailed in Section 1.4.2, concomitant ablation has been associated with reduced thromboembolic risk and atrial fibrillation recurrence[58,59]. In the few studies that have been reported on isolated MV surgery, pre-operative atrial fibrillation was associated with increased risk of stroke and bleeding complications. Bando *et al.*[17] conducted a multicenter retrospective study comparing outcomes in three groups of patients: patients in sinus rhythm who underwent isolated mitral valvuloplasty for mitral regurgitation, patients with pre-operative atrial fibrillation who underwent isolated mitral valvuloplasty, and patients with pre-operative atrial fibrillation who underwent concomitant ablation with mitral valvuloplasty. They observed that of the three groups, survival and eight-year freedom from stroke were worst for patients with pre-operative atrial fibrillation who underwent isolated mitral valvuloplasty[17]. A study by Ngaage *et al.*[74] comparing outcomes between patients with pre-operative atrial fibrillation and patients in sinus rhythm after isolated repair for MV regurgitation reported similar results with higher mortality and reduced freedom from cardiac death in patients with pre-operative atrial fibrillation compared to patients in sinus rhythm. Most importantly, pre-operative atrial fibrillation was reported to be an independent risk factor for adverse cardiac events and stroke[74].

To summarize, Tables 1 and 2 list several multivariate models predicting short- and long-term post-procedural morbidity and mortality where pre-operative atrial fibrillation was a model-eligible variable. Based on this evaluation of MV multivariable models', it is striking that pre-operative atrial fibrillation appears as an important risk factor predictive of adverse MV surgical outcomes; thus, additional research appears warranted to identify the atrial fibrillation-related management strategies to improve the future quality of MVR patient care.

*Mitral valve surgery with concomitant surgical ablation*

Concomitant surgical ablation therapy has been associated with decreased adverse outcomes in patients with pre-operative atrial fibrillation undergoing MV procedures. Due to increased long-term mortality risk with pre-operative atrial fibrillation, concomitant surgical ablation is recommended in patients undergoing MV procedures to restore sinus rhythm[2,54-58]. Although concomitant surgical ablation with MV surgery has been associated with increased risk for permanent pacemaker implantation compared to MV surgery alone[75], several studies have shown reduced incidence of late stroke[55], improved sinus rhythm[56,57], and lower risk of mortality in patients who underwent concomitant surgical ablation[58,76].

In a randomized multi-center clinical trial following patients with persistent or long-term persistent atrial fibrillation for 1 year, patients who underwent MV surgery and concomitant ablation via pulmonary-vein isolation or biatrial Maze procedure demonstrated greater freedom from atrial fibrillation at 6 months and 12 months than patients who only received medical therapy (63.2% *vs.* 29.4%). However, 1-year mortality and 1-year risk of MACCE were similar between both groups, with more frequent permanent pacemaker implantation in patients who received concomitant ablation (21.5% *vs.* 8.1%)[59]. A more recent study with longer follow-up demonstrated similar benefits in patients with pre-operative atrial fibrillation who underwent concomitant surgical ablation via Cox Maze III/IV using radiofrequency ablation, cryoablation, or both during only MV surgery. This sample of patients had freedom from atrial fibrillation without the need for antiarrhythmics at rates of 85%, 79% and 64% at 1, 5, and 7 years, respectively. Only 2% of patients experienced embolic stroke and 9% required pacemaker placement. Atrial fibrillation recurrence was associated with longer duration of pre-operative atrial fibrillation and the surgeon's experience with ablation[77]. Although pacemaker implantation is considered a negative outcome of ablation procedures, it may be associated with less morbidity than previously thought. A prospective study of pacemaker implantation following Cox Maze procedures for AF found that pacemakers are actually implanted at lower

**Table 1. Reported risk factors for short-term ( ≤ 1 year) mortality (M), complications (C), or mortality and/or complications (M/C) following mitral valve procedures in patients with pre-operative atrial fibrillation. Only multivariable models that considered number of risk factors per category are shown**

| | Pre-operative AF or early post-operative atrial tachyarrhythmias | Cardiovascular disease or devices | Other non-cardiovascular comorbidities | Procedural characteristics | Modifiable risk factors | Socioeconomic or demographic factors |
|---|---|---|---|---|---|---|
| Schueler *et al.*[140] 2016 | | | 1 M | | | |
| Labin *et al.*[57] 2017 | 2 C | | | 1 C | | |
| Saad *et al.*[89] 2020 | 1 C | 1 M<br>3 C | | | 1 M<br>1 C | 1 C |
| Mehaffey *et al.*[137] 2021 | | 3 M/C | 1 M/C | 1 M/C | | |

Cardiovascular disease or devices included heart failure, peripheral artery disease, dyslipidemia, hypertension, tricuspid regurgitation, and intra-aortic balloon pump. Other non-cardiovascular comorbidities included renal disease, diabetes, and chronic lung disease. Procedural characteristics included failure to use box-lesion to isolate posterior left atria and mitral valve repair (*vs.* replacement). Modifiable risk factors included smoking status. Socioeconomic/demographic factors included age.

rates than previously thought and are not associated with significant differences in survival or atrial arrhythmia compared to patients who did not require pacemaker implantation[78].

There has been concern over the efficacy of ablation in patients with giant left atria, which is a rare sequela of MV disease that may pose a greater risk of surgical ablation failure due to a larger area requiring ablation and a more intensive cut-and-sew Maze procedure[79,80]. A recent propensity-matched analysis evaluating patients with giant left atria reported ablation-induced restoration of sinus rhythm with and without the use of antiarrhythmic drugs and a success rate comparable to that of patients without giant left atria[80].

Surgical ablation appears to be a safe procedure for patients with pre-operative atrial fibrillation undergoing MV surgery. The long-term outcomes following MV surgery in patients with pre-operative atrial fibrillation are generally poor compared to non-atrial fibrillation patients, but concomitant surgical ablative therapy provides a viable and effective treatment option to mitigate adverse sequelae and restore sinus rhythm in this high-risk population. Further research appears warranted, as the degree to which sinus rhythm may facilitate long-term recovery of damaged myocardium and to what degree damaged myocardium may be restored.

*Mitral valve surgery with concomitant left atrial appendage exclusion*

Another consideration to address atrial fibrillation is performing concomitant left atrial appendage (LAA) exclusion at the time of MV intervention. One study reported decreased risk of ischemic stroke in pre-operative atrial fibrillation patients who underwent concomitant MV replacement and LAA obliteration as

**Table 2. Reported risk factors for long-term (≥ 1 year) mortality (M), complications (C), or mortality and/or complications (M/C) following mitral valve procedures in patients with pre-operative atrial fibrillation. Only multivariable models that considered number of risk factors per category are shown**

| | Pre-operative AF | Cardiovascular disease or devices | Other non-cardiovascular comorbidities | Procedural characteristics | Socioeconomic or demographic factors |
|---|---|---|---|---|---|
| Chua *et al.*[141] 1994 | | 1 M | | 1 M | 1 M |
| Leon *et al.*[142] 1999 | | 4 M/C | | | 1 M/C |
| Tribouilloy *et al.*[143] 1999 | | 1 M | | | |
| Jessurun *et al.*[144] 2000 | | 1 C | | 1 C | 2 C |
| Lim *et al.*[145] 2001 | | 1 M | | | |
| Bando *et al.*[55] 2002 | | | | 1 C | |
| Bando *et al.*[146] 2003 | 1 C | 1 M | | 1 C | 1 M |
| Bando *et al.*[17] 2005 | 1 M<br>1 C | 1 M | | 1 C | 1 M<br>1 C |
| Eguchi *et al.*[3] 2005 | 1 M<br>1 C | 2 C | | | 1 M |
| Itoh *et al.*[147] 2006 | 1 C | 1 C | | | |
| Alexiou *et al.*[4] 2007 | 1 M | 1 M | | | |
| Ngaage *et al.*[74] 2007 | 1 C | 2 M<br>1 C | | | |
| Funatsu *et al.*[148] 2009 | 1 C | 1 C | | | |
| Fujita *et al.*[149] 2010 | | 1 C | | | |
| Weerasooriya *et al.*[97] 2011 | | 2 C | | | |
| Wang *et al.*[72] 2012 | 1 M<br>1 C | 2 M<br>1 C | 1 C | 1 C | 1 M |
| Saint *et al.*[150] 2013 | | 2 M | 2 M | | 1 M |
| Yoo *et al.*[151] 2013 | 1 C | | | | 1 C |
| Tomai *et al.*[152] 2014 | 1 M/C | 2 M/C | | | 2 M/C |
| Nickenig *et al.*[153] 2014 | | 2 M/C | | 1 M/C | |
| Coutinho *et al.*[73] 2015 | 1 M | | 2 M | | 1 M |
| Capodanno *et al.*[154] 2015 | | 2 M | | 1 M | |
| Giannini *et al.*[155] 2016 | | 1 M | 1 M | | |
| Puls *et al.*[156] 2016 | | 5 M | 2 M | 1 M | |
| Labin *et al.*[57] 2017 | 1 C | | | 1 C | |
| Jabs *et al.*[157] 2017 | 1 M | | | | |
| Sorajja *et al.*[158] 2017 | | 3 M | 2 M | | 1 M |

| | | | | | |
|---|---|---|---|---|---|
| | | 3 M/C | 2 M/C | | 1 M/C |
| Ad *et al.*[77] 2018 | 1 C | | | 2 C | |
| Keßler *et al.*[91] 2018 | 1 M | | | | |
| Spieker *et al.*[159] 2018 | 1 M | 3 M | | | |
| Kim *et al.*[160] 2018 | | 2 M/C | | | |
| Kitamura *et al.*[161] 2019 | | 2 M | | | 1 M |
| Ailawadi *et al.*[162]2019 | | 1 M | | 4 M | 1 M |
| Grigioni *et al.*[2] 2019 | 1 M | 2 M | | 1 M | 1 M |
| Wu *et al.*[96] 2020 | 1 C | 1 C | 1 C | | |

Cardiovascular disease or devices included left ventricular ejection fraction, post-operative mitral regurgitation, echocardiographic score, post-operative mitral valve area, post-operative mean pulmonary artery pressure, New York Heart Association functional class, right ventricular pressure, left atrial dimension, left ventricular fractional shortening, cardiomegaly, heart failure, left ventricular diastolic diameter, valvular heart disease, cardiomyopathy, cardiovascular disease, myocardial infarction, European System for Cardiac Operation Risk Evaluation, mitral regurgitation etiology, right ventricular systolic dysfunction, peripheral artery disease, tricuspid regurgitation, mitral regurgitation, N-terminal pro b-type natriuretic peptide, tricuspid annular plane systolic excursion, stroke, mitral valve pressure gradient, previous coronary artery bypass graft, and previous aortic valve intervention. Other non-cardiovascular comorbidities included chronic obstructive pulmonary disease, lung disease, renal failure, renal dysfunction, dialysis, serum creatinine, anemia, and diabetes. Procedural characteristics included the need for coronary artery bypass graft at the time of surgery, tricuspid valve repair, omission of the Cox maze procedure, failure to use box lesion, procedural success or failure, surgeon experience, cryothermal energy source, heart failure hospitalization, transfusion of blood, length of hospital stay, and type of surgery performed. Socioeconomic/demographic factors included age and gender.

compared to LAA preservation[81]. A retrospective study compared pre-operative atrial fibrillation patients undergoing MV surgery with or without LAA exclusion and/or ablation[82]. Among patients who did not receive ablation, preservation of the LAA was associated with higher risks of thromboembolism and death. There was no significant impact of LAA exclusion versus preservation in patients who received concomitant ablation[82]. Similarly, one study of pre-operative atrial fibrillation patients undergoing MV surgery with concomitant radiofrequency ablation did not find a significant impact of LAA exclusion on 2-year freedom from atrial fibrillation[83]. In contrast, another study found LAA occlusion was only associated with decreased rate of cerebrovascular events following MV surgery in pre-operative atrial fibrillation patients when concomitant surgical ablation was performed[84].

The impact of LAA obliteration during MV procedures to address atrial fibrillation is not clear. Additionally, surgical ablation may modulate the effect of LAA obliteration. Randomized control trials are needed to evaluate the effectiveness of LAA exclusion with or without ablation in reducing risk of thromboembolism for pre-operative atrial fibrillation patients.

*Transcatheter mitral valve repair*

Similar to its impact on MV surgery, pre-operative atrial fibrillation has also been associated with adverse long-term outcomes in patients undergoing transcatheter MV repair via MitraClip but with conflicting results on short-term outcomes such as in-hospital mortality, in-hospital complications and resource utilization[85-90]. One study reported greater in-hospital ischemic stroke, in-hospital hemorrhagic stroke, length of hospitalization, and increased 30-

day mortality in patients with pre-operative atrial fibrillation undergoing repair with MitraClip compared to those without pre-operative atrial fibrillation. However, both groups had a similar rate of stroke at 30-day[89]. Although studies conflict on short-term outcomes, many report pre-operative atrial fibrillation as an independent predictor of 1-year mortality[86,87] and 3-year mortality with increased MACCE[91]. A multicenter study with 5-year follow-up also showed an association between atrial fibrillation and reduced long-term survival in patients with MitraClip repair but showed no difference in stroke incidence[92]. Most recently, randomized clinical data from the COAPT trial for Heart Failure Patients with Functional Mitral Regurgitation trial has shown that history of atrial fibrillation is associated with increased mortality or hospitalization for heart failure within two years of follow-up compared to patients without a history of atrial fibrillation. Despite these adverse outcomes, patients with a history of atrial fibrillation still experienced many benefits, such as reduced rates of mortality and heart failure hospitalization after MitraClip compared to patients without this intervention[93].

Although the association between atrial fibrillation and increased risk of stroke is well-known[94], recent meta-analyses of transcatheter MV repair without ablation procedures have reported no significant difference in risk of stroke between patients with and without atrial fibrillation. Instead, these studies have shown increased risk of bleeding in patients with atrial fibrillation, which they suggest may be due to the administration of oral anticoagulant therapy after MV procedures to prevent stroke[88,90].

While the impact of pre-operative atrial fibrillation on short-term outcomes of MitraClip intervention is controversial, it has a clear negative influence on long-term outcomes. Nevertheless, transcatheter interventions are generally considered last resort options - normally reserved for patients at prohibitive surgical risk. The pre-operative atrial fibrillation patient population tends to be older and have more comorbidities[87]. Thus, these patients may more frequently be poor surgical candidates, necessitating transcatheter interventions instead. Additional research to mitigate the poor outcomes of transcatheter MV repair in patients with pre-operative atrial fibrillation is warranted.

*Transcatheter ablation*

In a recent 3-dimensional echocardiographic study, patients with persistent atrial fibrillation and less than severe mitral regurgitation were provided radiofrequency catheter ablation and not only maintained sinus rhythm after 6 months, but also had MV apparatus remodeling with significantly decreased left atrial volume, decreased mitral annular diameter, and improved annular contraction[95]. A more recent retrospective cohort study with a longer mean follow-up time of 20.7 months for patients with paroxysmal or persistent atrial fibrillation and functional mitral regurgitation showed similar results with decreased left atrial size in patients who maintained sinus rhythm, but required multiple ablation procedures[96]. This finding was in agreement with previously published studies with 5- and 10-year follow-up that reported success in maintenance of sinus rhythm or decreased rates of permanent atrial fibrillation development with repeated transcatheter ablation[97,98].

*Comparison of outcomes between mitral valve surgery with concomitant ablation and transcatheter ablation*

Both transcatheter and surgical ablation are recommended for the treatment of atrial fibrillation, but few studies exist comparing the efficacy of transcatheter ablation to mitral valve surgery with concomitant surgical ablation. Studies on transcatheter ablation have shown that at 12 months, 24%-39% of patients with MV disease maintained sinus rhythm after a single procedure and 32%-52% after multiple procedures[96,99]. Studies on concomitant surgical ablation have shown higher rates of success with 63%-90% of patients maintaining sinus rhythm at 12 months[59,77,100,101]. Similar results were seen in studies directly comparing concomitant surgical ablation with MV surgery to transcatheter ablation in patients with MV disease. In a

randomized controlled trial of patients with long-lasting persistent atrial fibrillation and rheumatic heart disease, Liu *et al.*[102] observed that 82% of patients who underwent concomitant surgical ablation with MV surgery maintained sinus rhythm at 12 months compared to 55% of patients who underwent a single procedure of radiofrequency catheter ablation after MV surgery ($P < 0.001$). More recently, Chen *et al.*[103] conducted a retrospective observational study on patients with nonparoxysmal atrial fibrillation and moderate mitral regurgitation and observed that significantly more patients who underwent concomitant surgical ablation with MV surgery maintained sinus rhythm at 12 months (69.6%) compared to patients who underwent a single procedure of radiofrequency catheter ablation (38.8%). At 24 months, concomitant surgical ablation with MV surgery remained superior with 64.2% of patients maintaining sinus rhythm compared to 38.3% of patients maintaining sinus rhythm after multiple procedures of radiofrequency catheter ablations. Patients with radiofrequency catheter ablation were also more likely to have recurrent atrial tachyarrhythmia[103]. However, complications were also present in concomitant surgical ablation patients with a few developing pneumonia and requiring permanent pacemaker implantations, similar to reports in other studies[75,103]. Considering the risk of permanent pacemaker implantation following concomitant surgical ablation and the possible need for multiple procedures of transcatheter ablation, concomitant surgical ablation with MV surgery at present appears to offer better long-term outcomes than transcatheter ablation for patients with MV disease and pre-operative atrial fibrillation.

## POST-OPERATIVE ATRIAL FIBRILLATION IN MITRAL VALVE SURGERY

### Etiology

New-onset post-operative atrial fibrillation (POAF) is a condition that is neither well understood nor defined, particularly in patients undergoing MV procedures. POAF is frequently grouped with perioperative atrial fibrillation due to unclear consensus on the timing of POAF[104-107]. Mitral stenosis and LAE are identified risk factors for the development of atrial fibrillation after cardiac surgery[108]. POAF following MV replacement occurs more often in rheumatic than non-rheumatic mitral stenosis[109]. Age and concomitant aortic or tricuspid valve surgery have been identified as important risk factors associated with POAF following MV surgery[5].

LA size prior to MV surgery for mitral regurgitation has been associated with risk of early POAF[7,110], while LA diameter and pressure half time are risk factors for late POAF, occurring after hospital discharge[111]. LA volume index after MV surgery also independently predicts the development of POAF[112]. In a cohort of patients with rheumatic MV disease undergoing MV replacement, transmitral A waves as measured on echocardiogram were predictive of POAF occurring or lasting 1 year after surgery[113].

Electrocardiogram findings may yield insights into the etiology of this condition as well. Mitral regurgitation patients undergoing percutaneous MV repair via MitraClip had several changes in electrocardiogram findings after surgery, including decreased P wave duration, P wave amplitude, and PR interval, which suggest alterations in atrial conduction patterns[114]. Similarly, in percutaneous MV commissurotomy for rheumatic mitral stenosis, atrial effective refractory periods (AERP) increased and AERP dispersion decreased after resolution of atrial stretch[115]. These changes in conduction may be of significance in delaying or preventing the development of atrial fibrillation.

Genetic factors may be involved in the development of POAF, as demonstrated by RNA sequencing of tissue samples from the LA collected just prior to MV surgery[116]. Expression of genes involved in potassium current-modulated resting membrane potential, metabolism of cyclic GMP, and wingless integrated (Wnt) signaling varied between patients with and without POAF. Alterations in resting membrane potential due to changes in potassium currents provide a feasible explanation for arrhythmogenesis. Cyclic GMP is involved

in the nitric oxide signaling pathway, which has influences on myocardial ion currents, such as the potassium current. Wnt signaling may promote cardiac fibrosis, which can also contribute to arrhythmias[116].

Although POAF may be common, it may be a transient condition[117]. The transient nature of POAF suggests surgical techniques or approaches may be related to the development of this potentially temporary post-procedural complication. For example, POAF occurs at similar frequencies following transcatheter MV (MitraClip) procedures[118], as it does following transcatheter ablation for AF itself[119], POAF may be related to fluid shifts, oxidative stress, inflammation, catecholamine release, and altered sympathetic and parasympathetic activity during cardiac surgery[120,121]. Additionally, direct injury to the atria either from manipulation or incision during surgery may disrupt electrical conduction[120]. This may contribute to refractoriness and the formation of reentry wavelets. However, minimizing cardiac manipulation using an off-pump technique did not lead to a POAF post-CABG decrease[103].

POAF is a complex and multifactorial condition. Development of POAF likely depends on both pre-operative patient-specific factors, such as LA size and genetic alterations, and factors related to surgery. Understanding the etiology and predictors of POAF development is essential for risk stratification and treatment decisions in patients undergoing MV repair or replacement. While some risk factors predisposing to new-onset POAF have been identified for specific cardiac surgery populations, there is a paucity of data regarding the longer-term impact on MV patients. Future research will be necessary to evaluate the role of these patient risk characteristics *vs.* the role of surgery-specific factors, such as surgical "low touch" (i.e., reduced manipulation) techniques. Furthermore, to date very little is known about pharmacologic prophylaxis in this patient population.

### Incidence

New-onset POAF is especially common after MV procedures compared to other cardiac procedures[8,9]. New-onset POAF has been seen in 24% of patients after surgery for mitral regurgitation[7] and in 39% of patients after surgery for mitral stenosis[8]. Overall, the incidence of new-onset POAF in patients undergoing MV procedures is between 14%-42%[5,6], with approximately 23% of patients developing new-onset POAF after MV replacement and 15% after MV repair[5], In patients with transcatheter MV repair using MitraClip, the incidence of new-onset POAF was very rare with one study reporting 1.5%[122].

### Prophylaxis

Prophylactic management of new-onset POAF for patients undergoing MV surgery is primarily through medical therapy as recommended by the 2014 AHA/ACC/HRS guidelines on the management of atrial fibrillation (Class IIa, Level A; Class IIb, Level B). Under these guidelines, amiodarone (Class IIa, Level A) may be recommended prior to surgery or sotalol (Class IIb, Level B) post-surgery when patients are at high risk of POAF[37]. A recent randomized control trial using one prophylactic dose of intravenous amiodarone and magnesium sulfate showed significant differences in post-cardiopulmonary bypass arrhythmia incidence in patients undergoing surgical MV replacement. This study population included patients with and without pre-operative atrial fibrillation. At discharge, 30% of patients treated with amiodarone and magnesium sulfate had atrial fibrillation, compared to 73.3% of patients who did not receive this intervention[123]. This finding was in agreement with a previous study of the same framework but using only a single dose of amiodarone prior to valve replacement[124].

As POAF may be in part due to post-surgical inflammation, anti-inflammatory therapies have been suggested as prophylaxis following cardiac surgery. Several meta-analyses found that prophylactic treatment with colchicine or dexamethasone decreased POAF after cardiac surgery[125,126]. However, evidence from

randomized control trials for the use of these anti-inflammatory treatments following MV surgery specifically is lacking.

Currently, studies on prophylactic surgical or transcatheter ablation in MV surgery are few to none due to the uncertainty in benefits and risks of ablation in patients who present with sinus rhythm and the frequently transient nature of POAF[127,128]. Prophylactic surgical ablation has been reported for "high risk" (e.g., rheumatic heart disease patients undergoing MV repair) procedures[129]. As these high-risk patient populations are rarely found within the United States; however, this prophylactic approach to prevent atrial fibrillation is not commonplace. A recent study with a mean follow-up of 23 months has shown prophylactic maze surgical ablation to be effective in patients with congenital heart disease, resulting in reduced burden or freedom from arrhythmias without early or late mortality but not without recurrence[129]. Further research on how to optimize the prevention of new-onset POAF in high-risk patients undergoing specific surgery procedures (i.e., MV-related) is warranted. As of now, for patients with POAF that persists after either MV surgery or concomitant surgical ablation, transcatheter ablation is an option, and its outcomes are detailed in Section 2.4.2[130,131].

## Outcomes

*Surgical and transcatheter mitral valve procedures*

There is not a clear consensus on the impact of POAF on short- and long-term outcomes following MV procedures. One study with 361 MV surgery patients and median follow-up of 3.1 years demonstrated that POAF was an independent predictor of all-cause late mortality, defined as death beyond 30 days, but was not associated with increased early mortality. This group experienced significantly more in-hospital cerebrovascular events, which may have contributed to increased late mortality in these patients[6]. Another study by Doshi *et al.*[132] with 2580 transcatheter MV repair patients showed no significant differences in adjusted MACCE rates and in-hospital mortality for patients with and without POAF. However, patients with POAF had longer median lengths of stay and higher associated resource utilization costs, which they state may have been due to atrial fibrillation, older age and increased comorbidities in patients with POAF[132]. Other studies have shown similar non-significant differences in mortality between patients with and without POAF after MV surgery, but show an increasing trend toward mortality or stroke and increased risk of recurrent myocardial infarction[5,7,111]. Table 3 lists several multivariate models for long-term morbidity and mortality in which POAF was model-eligible. Although more studies are needed on short-term outcomes, POAF generally appears to have a harmful impact on long-term MV outcomes.

Additionally, the burden of pre-operative atrial fibrillation may be important as a predictor of short- and long-term outcomes in MV repair procedures. Persistent atrial fibrillation has been associated with higher mortality and hospitalization due to heart failure at 30 days compared to paroxysmal atrial fibrillation, but showed similar 1-year outcomes[87]. In a cohort study with a mean follow-up of 9 years, the risk of mortality was greatest in patients with persistent atrial fibrillation compared to that of patients with paroxysmal atrial fibrillation and least in patients with sinus rhythm, regardless of age, sex and comorbidities[2]. However, a more recent study of the Nationwide Readmission Database compared paroxysmal atrial fibrillation to non-paroxysmal atrial fibrillation and did not show any significant difference in death, stroke or 30-day readmission after transcatheter MV repair[54].

*Transcatheter ablation*

Although the optimal timing of transcatheter ablation after MV surgeries or surgical ablation is not yet clear, transcatheter ablation generally appears to be safe and effective after both procedures. Performed a median of 224 days [73.0; 424.8] after the original procedure, transcatheter ablation in patients with atrial

**Table 3. Reported risk factors for long-term (≥ 1 year) mortality (M), complications (C), or mortality and/or complications (M/C) following mitral valve procedures in patients with post-operative atrial fibrillation. Only multivariable models that considered number of risk factors per category are shown**

| | Post-operative AF | Cardiovascular disease or devices | Other non-cardiovascular comorbidities | Procedural characteristics | Socioeconomic or demographic factors |
|---|---|---|---|---|---|
| Kernis *et al.*[7] 2004 | 1 C | | | | |
| De Santo *et al.*[163] 2005 | 1 M<br>1 C | | | 2 C | |
| Bramer *et al.*[6] 2011 | 1 M | 4 M | 2 M | | 2 M |

Cardiovascular disease or devices included pre-operative cerebrovascular accident, left ventricular ejection fraction, intra-aortic balloon pump, and perioperative myocardial infarction. Other non-cardiovascular comorbidities included pre-operative hemoglobin and diabetes. Procedural characteristics included type of prosthesis and prosthetic model. Socioeconomic/demographic factors included age and gender.

fibrillation who previously underwent transcatheter MV repair using MitraClip showed similar arrythmia-free survival (64.8% *vs.* 68.3%) compared to patients without prior repair, with only a few patients requiring antiarrhythmic drugs and no minor or major complications after 1-year follow-up[133]. In another 1-year follow-up study, radiofrequency catheter ablation was shown to be safe and effective without increased risk of complications or difficulties with catheter entrapment in patients with prior MV replacement. As of the patient's last follow-up, approximately 83% maintained sinus rhythm and 69% no longer required antiarrhythmic drugs. However, compared to those without prior MV replacement, patients with prior MV replacement experienced more repeat ablations (1.5 per person)[134]. Transcatheter ablation has also been effective in patients with recurrent atrial fibrillation after concomitant surgical ablation with MV replacement. In a small study of 10 patients with rheumatic valve disease and long-persistent atrial fibrillation despite undergoing concomitant surgical ablation, all patients underwent catheter ablation 1-3 years after surgery with 100% of patients successfully in sinus rhythm at 12 months[131].

## Future treatment considerations

It is well known that atrial fibrillation is not an isolated event and is a life-altering disease with a considerable increased risk of stroke and long-term mortality that requires life-long anticoagulation and rate and rhythm control drug therapy[135,136]. However, there has been little progress in developing the optimal treatment for patients with POAF after cardiac surgery. POAF in the field of MV disease has great potential to dramatically reduce the incidence of POAF, reduce mortality, and improve the quality of life for patients undergoing MV procedures due to the high incidence of POAF in these patients and opportunities for concomitant prophylactic ablative therapy. As of now, few studies exist to determine if prophylactic ablation in addition to MV surgery, is safe without increasing the risk of developing POAF and effective in reducing the incidence of POAF for patients who present with sinus rhythm but may be at risk for POAF[127,128]. The delayed progress in prophylactic ablation may be in part due to the hesitancy in pursuing concomitant surgical ablation in patients with atrial fibrillation undergoing MV surgery. Mehaffey *et al.*[137] recently reported decreasing use of concomitant surgical ablation from 2011 to 2018 despite the increasing incidence of pre-operative atrial fibrillation and positive outcomes associated with ablation. With no difference in STS morbidity or mortality and pacemaker implantation over 30 days, patients who underwent concomitant surgical ablations had fewer incidences of atrial fibrillation at hospital discharge and lower healthcare costs. Surgeon mitral surgery volume was a significant predictor of concomitant surgical ablation use, with higher volume

surgeons more likely to perform the procedure[137]. The risk and benefit of concomitant surgical ablation are patient and surgeon dependent and more time is needed to evaluate the long-term outcomes of concomitant surgical ablation before it can be expanded for prophylactic use in patients who are in sinus rhythm but at risk for POAF. However, prophylactic ablation is promising, especially due to the high likelihood of developing POAF after MV surgery and may likely become standard therapy for these patients. For prophylactic ablation to be considered, it will be critical to identify risk factors in patients that predict specifically persistent POAF and compare its efficacy to prophylactic medical therapy in combination and alone[127,128]. Other important prophylactic therapy to consider are routine concomitant LAA closure for all patients undergoing MV surgery and transcatheter ablation prior to MV surgery for patients with pre-operative atrial fibrillation as a less invasive alternative procedure to concomitant surgical ablation.

Thrombi from atrial fibrillation are most commonly found in the LAA, and its surgical closure may reduce the risk of stroke and the need for life-long anticoagulation. Ando *et al.*[138] conducted a meta-analysis evaluating the impact of LAA closure in patients undergoing cardiac surgery and observed lower 30-day or in-hospital mortality and incidence of cerebrovascular accidents in patients who underwent LAA closure, especially in patients with pre-operative atrial fibrillation. A weaker association was seen in patients without pre-operative atrial fibrillation undergoing valve surgery[138]. Due to the high risk of POAF and associated increased risk of stroke in patients undergoing MV surgery, prophylactic LAA for all patients undergoing MV surgery may be a promising beneficial therapy.

Transcatheter ablation may also serve as a less invasive and intensive alternative procedure to concomitant surgical ablation in patients with pre-operative atrial fibrillation undergoing MV surgery. Concomitant surgical ablation lengthens the MV surgery, may require longer bypass time and is associated with permanent pacemaker implantation[75]. Previous studies with transcatheter ablation have shown successful long-term cardioversion albeit requiring repeat ablations[96-98]. Due to its shorter procedural time and less invasive nature, transcatheter ablation may serve as a safer prophylactic ablative therapy and in combination with catheter ablation of the cavotricuspid isthmus has been shown in a meta-analysis to reduce the incidence of atrial fibrillation in patients with atrial flutter[139].

## CONCLUSION

Both pre- and post-operative atrial fibrillation are common in the MV disease population, yet the reasons behind the development, optimal treatment, and longer-term impact of these arrhythmic conditions are not yet completely understood. Pre-operative atrial fibrillation is likely attributable to left atrial enlargement associated with MV stenosis and regurgitation. If it is by itself a significant risk factor or if it is a surrogate for impaired myocardium is yet to be determined. Regardless, the management of these high-risk patients warrants careful consideration. Therapeutic strategies to address pre-operative atrial fibrillation include medical management and ablation. The etiology of POAF is most likely multifactorial and has been linked to other pre-operative risks, intra-operative processes of care, as well as surgeon-based experience. Although there is no consensus regarding the impact of POAF on long-term outcomes, POAF appears to negatively impact mortality, and thus with more studies would warrant prophylactic therapy through left atrial appendage closure, transcatheter ablation, or concomitant surgical ablation.

## DECLARATIONS

### Authors' contributions

Substantive intellectual contribution, conception, and design: Dokko J, Novotny S, Santore LA, Shroyer ALW, Bilfinger T

Writing the initial abstract/manuscript: Dokko J, Novotny S, Santore LA
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