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# Percutaneous Left Atrial Appendage Closure: Is there a Role in Valvular Atrial Fibrillation

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**Abstract**

Atrial fibrillation, a chronic and highly morbid cardiovascular condition which affects over 33 million people worldwide, can be broadly categorized as valvular vs non-valvular in etiology. However, definitions of valvular atrial fibrillation have varied widely in the literature, and there is no clear consensus definition to date. Historically, patients with atrial fibrillation in the setting of rheumatic mitral valve disease have constituted a particularly high risk group for cardioembolic stroke, and for this reason many contemporary trials of pharmaceutical and device therapies for atrial fibrillation have systematically excluded patients with valvular heart disease. Therefore, vitamin K antagonism remains the favored approach to mitigate stroke risk in valvular atrial fibrillation, and the optimal strategy to treat atrial fibrillation patients with valvular heart disease who cannot tolerate oral anticoagulation therapy is unknown. Recent trials have demonstrated an important role for percutaneous left atrial appendage occlusion devices in patients with non-valvular atrial fibrillation, but the role of these devices in patients with valvular atrial fibrillation is uncertain. Given the worldwide burden of valvular atrial fibrillation, future trials intended to clarify the role of percutaneous left atrial appendage closure devices in valvular atrial fibrillation should provide important insight for the care of millions of patients.

## Introduction

Atrial fibrillation (AF), which affects over 33 million people worldwide,[1] is a chronic illness predominantly impacting older adults and is associated with high rates of morbidity. AF is commonly associated with structural heart disease, and the term "valvular AF" has been used to describe a heterogenous group of patients with both AF and valvular heart disease. Among patients with AF, 30% have some form of valvular heart disease detectable by echocardiography.[2] Some prior studies have considered valvular AF to include only those patients with rheumatic mitral stenosis (MS) and mechanical heart valves while others have included patients with mitral bioprosthetic heart valves, mitral valve repair, and/or other moderate or severe valvular disease including aortic valve diseases.[3] In the developing world where rheumatic heart disease remains a highly morbid condition, most cases of AF are attributable to rheumatic heart disease and would be considered valvular AF.[4]

Stroke is a feared complication with an annual risk of about 5% in patients with AF who are not treated with anticoagulation,[5],[6] and the selection of rhythm vs rate control strategy does not mitigate the risk of stroke in the long-term.[7] With increasing comorbidities, the risk of stroke may also be substantially higher in a given patient.[8]

Therefore, oral anticoagulation (OAC) therapy to reduce the risk of left atrial (LA) thrombus and consequent stroke has been a cornerstone of AF therapy. However, many patients with AF are elderly with multiple bleeding risk factors, and long-term OAC poses a clinical dilemma. In practice, 2 out of 5 patients with AF do not receive OAC despite the risk of stroke, which reflects the complexity of prescribing OAC in older adults.[9] In fact, many of the risk factors that contribute to a high stroke risk as demonstrated by the CHA2DS2-VASc score also influence the bleeding rate with OAC as exhibited by the HAS-BLED score.[8],[10]

Recently, percutaneous left atrial appendage (LAA) closure has gained attention as a strategy non-inferior to OAC in reducing stroke risk of AF patients.[6],[11] However, due to a perceived higher risk of thromboembolic events in patients with valvular AF, most contemporary pharmaceutical and device trials for stroke reduction therapy in AF have excluded patients with valvular AF.[6],[11]-[14] Therefore, little is known about the optimal treatment of patients with valvular AF, and the role of LAA closure in patients with valvular AF is uncertain. OAC with vitamin K antagonism is the strategy recommended in the American and European AF guidelines to mitigate stroke risk in valvular AF,[2],[15] reflecting the lack of evidence for novel treatments in these patients.[16] In this review we discuss the role of the LAA in valvular AF related stroke and implications for percutaneous LAA closure in patients with valvular AF.

## Epidemiology and classification

AF is one of the most common chronic cardiovascular conditions affecting nearly 1 in 10 United States medicare beneficiaries > 65 years old and accounting for nearly 500,000 hospital admissions and 100,000 deaths in the United States annually.15 The incidence of AF doubles with each advancing decade of life, and the number of patients affected with AF is estimated to reach nearly 16 million

**Key Words**

Atrial fibrillation,Valvular heart disease,Left atrial appendage closure,Watchman

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cases in the United States by 2020 as the population ages.[6],[17] Over half of all patients with AF suffer from concomitant heart failure, ischemic heart disease, and/or hypertension.[15] However, in the developing world rheumatic heart disease is by far the most common cause of AF, far outpacing coronary artery disease, hypertension, or other cardiomyopathies.[4]

Even in the developed world, AF is commonly associated with valvular heart disease and can be broadly categorized as valvular vs non-valvular AF. The term valvular AF is not well defined, and various definitions have been employed both in major society guidelines and prior clinical trials ([Table 1]).[3],[5] For example, the most recent American AF guidelines include prior mitral valve repair in the group of patients with valvular AF while the most recent European AF guidelines do not consider prior mitral valve repair as a criteria for valvular AF.[2],[15] Such discrepancies have resulted in considerable confusion among practicing clinicians. In a survey of internists and cardiologists, 1 in 3 considered isolated aortic valve disease to constitute valvular AF,[18] whereas neither the American nor European guidelines would consider such patients as having valvular AF. It is widely accepted that patients with rheumatic MS and prior mechanical heart valves should be included amongst those with valvular AF, and many authors also include those with mitral bioprosthetic valves and mitral valve repair (although the risk of stroke varies considerably between these groups).[3],[5]

**Table 1: Definitions of valvular atrial fibrillation in clinical trials and practice guidelines**

| Author | Year | Study Design | Valvular AF Definition |
|---|---|---|---|
| Holmes et al.[6] | 2009 | PROTECT AF trial: RCT of percutaneous LAA closure vs warfarin to prevent stroke in nonvalvular AF | Not defined |
| Connolly et al.[12] | 2009 | RE-LY trial: RCT of dabigatran vs warfarin to prevent stroke in nonvalvular AF | Severe heart valve disorder |
| Patel et al.[14] | 2011 | ROCKET AF trial: RCT of rivaroxaban vs warfarin to prevent stroke in nonvalvular AF | Hemodynamically significant MS or prosthetic heart valve |
| Granger et al.[13] | 2011 | ARISTOTLE trial: RCT of apixaban vs warfarin to prevent stroke in nonvalvular AF | Moderate or severe MS or prosthetic heart valve |
| Connolly et al.[57] | 2011 | AVERROES trial: RCT of apixaban vs aspirin to prevent stroke in nonvalvular AF | Valvular disease requiring surgery |
| Giugliano et al.[58] | 2013 | ENGAGE AF-TIMI 48 trial: RCT of edoxaban vs warfari prevent stroke in nonvalvular AF | Moderate or severe MS or mechanical heart valve |
| January et al.[15] | 2014 | AHA/ACC/HRS guidelines for the treatment of AF | Rheumatic MS, mechanical or bioprosthetic heart valve, MVR |
| Holmes et al.[11] | 2014 | PREVAIL trial: RCT of percutaneous LAA closure vs warfarin to prevent stroke in nonvalvular AF | Significant MS or mechanical heart valve |
| Kirchhof et al.[2] | 2016 | ESC/EACTS guidelines for the management of AF | Rheumatic valvular disease or mechanical heart valve |

ACC = American College of Cardiology. AF = atrial fibrillation. AHA = American Heart Association. EACTS = European Association for Cardiothoracic Surgery. ESC = European Society of Cardiology. HRS = Heart Rhythm Society. LAA = left atrial appendage. MS = mitral stenosis. MVr = mitral valve repair. RCT = randomized controlled trial.

## Risk of stroke and role of the left atrial appendage in valvular atrial fibrillation

Historical data from the Framingham heart study illustrated that AF is associated with a 5-fold increased risk of stroke. Among octogenarians in that study, AF was the only independent cardiovascular risk factor for stroke with the risk of stroke attributable to AF equaling 23.5% in that age group.[19] It has long been understood that most strokes related to AF result from cardioembolism due to LA thrombus.[20] The primary importance of differentiating valvular vs non-valvular etiology of AF pertains to prognostication about the risk of future stroke. The Framingham heart study data demonstrated a 17-fold increased risk of stroke in patients with AF and rheumatic heart disease compared to a 5-fold increased risk of stroke in patients with AF without rheumatic heart disease in reference to patients without AF.[21] In patients with rheumatic MS, low cardiac output with reduced transmitral flow has been implicated as a potential mechanism for increased rate of thrombus formation.[5],[22] In a study of 1544 patients with severe MS by Mahmood and colleagues, LA thrombus was identified by transesophageal echocardiogram (TEE) in 55.7% (161/289) of patients with AF and 10.2% (128/1255) of patients without AF.[23] The finding that 1 in 10 patients in the non-AF group had LA thrombus further supports the concept that rheumatic mitral valve disease may contribute to LA thrombus formation regardless of the underlying cardiac rhythm. Moreover, multiple studies have suggested that increasing severity of mitral regurgitation in the setting of both rheumatic and non-rheumatic mitral valve disease may be a protective factor for stroke, which also supports the concept that reduced transmitral flow may be related to thrombus formation. [24]-[26]

Patients with valvular AF have been long considered a particularly high-risk subset for stroke due to higher likelihood of LA thrombus[27] in the setting of low transmitral flow, mechanical heart valves, and the risk of LA thrombus that occurs in the atrium itself. In the aforementioned study by Mahmood et al., among 1544 patients with severe MS, LA thrombus was identified in 14.5% of patients regardless of the underlying cardiac rhythm, and 10.3% of patients with an LA thrombus also had LA cavity thrombus outside of the LAA.[23] In a systematic review by Blackshear and colleagues, only 57.0% of patients with rheumatic AF and documented LA thrombus had LA thrombus located in the LAA compared with 90.5% of patients with nonrheumatic AF who had their LA thrombus isolated to the LAA.[28] These data highlight the potentially different mechanisms of LA thrombus formation in patients with valvular and non-valvular AF and the increased risk for LA cavity thrombus in valvular AF ([Table 2]).

## Surgical left atrial appendage closure in valvular atrial fibrillation

Over the past 2 decades closure of the LAA has gained considerable attention as a strategy to mitigate the risk of AF-related stroke based on data supporting the LAA as the primary source of thrombus in AF-related stroke.[29]-[32] Surgical LAA closure can be accomplished by a variety of techniques, but the technical success of surgical LAA closure is highly variable, ranging from 17-93%.[1],[33] In a meta-analysis of surgical LAA closure, the operation was associated with a 54% reduction in the odds of 30-day stroke, [34] supporting the notion that LAA closure in patients with valvular AF may warrant further study. Very few studies have evaluated the

benefit of surgical LAA closure solely in patients with underlying valvular heart disease, and the results have been mixed ([Table 3]). A large multicenter randomized controlled trial of surgical LAA closure is currently underway to better elucidate this issue.[35] Currently, both the American and European AF guidelines give a class IIb recommendation to consider LAA closure in patients with AF undergoing cardiac surgery, and there is no specific distinction between valvular and non-valvular operations.[2],[15]

**Table 2: Location of LA thrombus in patients with valvular heart disease with or without AF**

| Author | Year | Study Population | Study Design | Prevalence of LA thrombus | Location of LA thrombus |
|---|---|---|---|---|---|
| Aschenberg et al.[59] | 1986 | 21 patients with mitral stenosis. AF present in 85.7% (n=18). | Single center series | 28.6% (n=6) | 100% (n=6) isolated to LAA |
| Hwang et al.[60] | 1993 | 147 patients with rheumatic MS. | Single center series | 20.4% (n=30)<br>93% of (n=28) with LA thrombus had chronic AF | 36.7% (n=11) isolated to LAC, 46.7% (n=14) isolated to LAA, 16.7% (n=5) in both LAC and LAA |
| Blackshear et al.[28] | 1996 | 3504 patients with rheumatic AF and 1,288 patients with nonrheumatic AF. | Systematic review of 23 studies | Rheumatic AF: 12.7% (n=446)<br>Nonrheumatic AF: 17.2% (n=222) | Rheumatic AF: 57.0% (n=254) involving LAA<br>Nonrheumatic AF: 90.5% (n=201) involving LAA |
| Kaymaz et al.[61] | 2001 | 474 patients with rheumatic mitral valve disease. AF present in 56.3% (n=267). | Single center series | 22.1% (n=105) | 14.3% (n=15) isolated to LAC, 61.0% (n=64) isolated to LAA, 24.8% (n=26) in both LAC and LAA |
| Sriman-narayana et al.[27] | 2003 | 490 patients with rheumatic MS and AF | Single center series | 33.2% (n=163) | 46.0% (n=75) involving LAC, 54.0% (n=88) isolated to LAA |
| Parashar et al.[62] | 2016 | 1330 patients with AF and isolated moderate or severe AS. | Single center series | 3.6% (n=48) | 100% (n=48) isolated to LAA |

AF = atrial fibrillation. AS = aortic stenosis. LA = left atrium. LAC = left atrial cavity. LAA = left atrial appendage. MS = mitral stenosis.

## Percutaneous catheter based devices for left atrial appendage closure

The WaveCrest LAA occluder device is a nitinol frame with PTFE covering which is also available in Europe and has a very high rate of successful deployment >95%, but also has not been evaluated in patients with valvular AF.[1] In contradistinction to the Amplatzer and WaveCrest devices, which are deployed endocardially, the Lariat device is a combined endocardial and epicardial device that consists of a percutaneously delivered suture to ligate the LAA. Widespread adoption of the Lariat has been limited by concerns about technical challenges and procedural safety with complete LAA closure achieved in only 86% and major bleeding in 9% in 1 series.[41] The Lariat device has not been tested in patients with valvular AF, and robust clinical trial data for the device is lacking.

The Watchman LAA occlusion device, which gained approval from the United States Food and Drug Administration (FDA) in 2015, is the favored percutaneous device for percutaneous LAA closure in the United States.[42]-[50] The device is a nitinol occlusion cage with PTFE covering that is delivered endocardially to the LAA via transseptal approach through a 14-french delivery sheath. In the PROTECT AF trial, 707 patients with non-valvular AF were randomized 2:1 to the Watchman device or OAC with dose-adjusted warfarin therapy and studied in regards to the primary composite endpoint of stroke, cardiovascular death, or systemic embolism.6 The device was successfully implanted in 88% of cases, and the primary endpoint occurred in 3.0 per 100 patient years in the Watchman group and 4.9 per 100 patient years in the warfarin group (relative risk 0.62, 95% confidence interval 0.35 – 1.25). Based on these results the Watchman was considered to be non-inferior to OAC with warfarin, and by 5-years Watchman placement proved superior to OAC for the primary efficacy endpoint (relative risk 0.61, 95% CI 0.38 – 0.97).[51] The rate of the primary safety endpoint (composite of major bleeding, pericardial effusion, device embolization) was initially higher in the Watchman group (7.4 per 100 patient years vs 4.4 per 100 patient years, relative risk 1.69, 95% confidence interval 1.10 – 3.19). However, by 5-year follow-up the difference was no longer significant (relative risk 1.21, 95% CI 0.78 – 1.94), mainly due to a significantly higher rate of hemorrhagic stroke in the warfarin group (3.3 vs 0.4%, p = 0.005).

**Table 3: Studies of surgical left atrial appendage closure in valvular heart disease**

| Author | Year | Study Design | Population | Proportion with AF | Findings |
|---|---|---|---|---|---|
| Lee et al.[63] | 2014 | Propensity matched observational series | 238 patients (119 with and 119 without LAA resection) undergoing mitral valve surgery and maze. | 100% (n=238) | No difference in stroke-free survival at mean follow-up of 3.1 +/- 2.8 years. |
| Nagpal et al.[64] | 2009 | RCT | 43 patients (22 with and 21 without LAA resection) undergoing mitral valve surgery. | 18.6% (n=8) | No difference in rate of post-operative cerebrovascular events. |
| Garcia-Fernandez et al.[55] | 2003 | Single center series | 205 patients (58 with and 157 without LAA ligation) undergoing mitral valve replacement. | Not specified | Absence of LAA ligation was independently associated with subsequent embolic events (OR 6.7, 95% CI 1.5 – 31.0, P=0.02) |
| Zapolanski et al.[65] | 2013 | Single center series | 1777 patients (808 with and 969 without LAA ligation) undergoing bypass and/or valvular surgery. Valvular surgery performed in 50.8% (n=903). | 14.9% (n=262) | No difference in rates of stroke or TIA. |

AF = atrial fibrillation. LAA = left atrial appendage. RCT = randomized controlled trial. TIA = transient ischemic attack.

In light of the unfavorable safety signal initially detected in the PROTECT AF trial, the PREVAIL study was designed to further clarify these concerns. Importantly, 39% of implants were performed by new operators. Overall, 407 patients were randomized 2:1 to the Watchman device or warfarin therapy and studied in regards to

the primary composite endpoint of stroke, systemic embolism, and cardiovascular or unexplained death.[11] At 18 months, the rate of the primary endpoint was similar between the Watchman and warfarin groups (0.064 vs 0.063, relative risk 1.07, 95% confidence interval 0.57 – 1.89) but did not achieve the prespecified cutoff for non-inferiority. However, for the secondary composite endpoint (stroke or systemic embolism >7 days after randomization), the Watchman device did meet the prespecified criteria for non-inferiority compared to warfarin. Moreover, the rate of 7-day procedural complications was 4.5% in the PREVAIL study compared to 8.7% in the PROTECT AF study. A subsequent meta-analysis of 2406 patients including both trials and their respective registries demonstrated that use of the Watchman was associated with significantly fewer hemorrhagic strokes, cardiovascular or unexplained deaths, and non-procedural bleeding episodes compared to warfarin. [46] However, the Watchman group did have a significantly higher risk of ischemic stroke (1.6% vs 0.9%, hazard ratio 1.95, P=0.05) at mean follow-up of 2.7 years. Taken together, these data have supported a role for the Watchman in patients with nonvalvular AF in whom long-term OAC is not suitable.

### A role for percutaneous left atrial appendage closure in valvular atrial fibrillation?

Valvular AF patients were systematically excluded from both the PROTECT AF and PREVAIL trials, and so the role of the Watchman device in these patients is unknown. The use of the Watchman in patients with valvular AF is limited to case reports, [52-54] and to our knowledge no large registry or clinical trial to date has evaluated the use of the Watchman or any other LAA closure device in valvular AF. As aforementioned, patients with rheumatic AF are more likely to have LA thrombus outside of the LAA alone compared to patients with nonvalvular AF. For this reason, LAA closure with the Watchman (or other percutaneous device) may seem to offer inadequate stroke risk reduction in patients with valvular AF. However, the aforementioned study by Garcia-Fernandez et al., demonstrated that lack of LAA ligation was an independent risk factor for future embolic events among patients with predominantly valvular AF treated with cardiac surgery, [55] and contemporary American and European AF guidelines support the use of surgical LAA closure at the time of cardiac surgery in all patients with AF regardless of the presence or absence of underlying valvular heart disease. [2,15] Moreover, a post hoc analysis of the PROTECT AF trial and continued access registry demonstrated that the net clinical benefit of the Watchman device was greatest in patients with the highest risk for thromboembolic stroke as assessed by the CHADS2 score. [56] Given that patients with valvular AF represent a group at particularly high risk for thromboembolic stroke, these data support the need for future research into the role of LAA closure in valvular AF patients. Importantly, the role of LAA closure in patients with valvular AF who cannot tolerate OAC remains unknown and ripe for investigation given the worldwide burden of rheumatic heart disease. Additionally, much of the literature on LAA closure devices has focused on LAA closure in place of long-term OAC. However, there may be a complimentary role of LAA closure in addition to long-term OAC to reduce residual stroke risk in patients with AF and high risk of stroke. OAC does not completely eliminate the risk of stroke, and in patients with valvular AF and high risk of stroke it may be reasonable to test a strategy of combined LAA closure and OAC to improve outcomes.

## Conclusions and future directions

AF is a common and highly morbid condition that impacts older adults worldwide. Stroke is a devastating complication of AF, and strategies to reduce the risk of AF related stroke include OAC or LAA closure. Patients with valvular AF, which is a heterogenous group without unified definition, have been largely excluded from major pharmaceutical and device trials in this field. Therefore, the optimal strategy to mitigate stroke risk in patients with valvular AF is unknown. OAC with vitamin K antagonism is the favored strategy for stroke risk reduction in patients with valvular AF, despite recent evidence that novel OAC medicines may be superior to warfarin for stroke risk reduction in nonvalvular AF and recent device trials demonstrating a role for LAA closure in patients who cannot take long-term OAC. There is clinical equipoise about the role of percutaneous LAA closure in patients with valvular AF. LAA closure, either as monotherapy in those who cannot tolerate long-term OAC or as combination therapy in those who can tolerate long-term OAC but have high risk for stroke, may improve outcomes in valvular AF. Future studies are needed to address these potential applications. Given the worldwide burden of rheumatic heart disease and valvular AF, clarity on the role of novel percutaneous LAA closure devices in valvular AF should provide important insight for the care of millions of patients.

## Conflict Of Interests

None.

## Disclosures

None.

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