Management of atrial fibrillation in rheumatic heart disease

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Rheumatic heart disease (RHD) is the underlying cause of a significant proportion of atrial fibrillation (AF) in the low- and middle-income countries, while nonvalvular AF is the most common cause of AF in high-income countries. RHD is also common among African Americans, migrants, and the indigenous population of high-income countries. The onset of AF in RHD patients is a clinical marker of worse outcomes and is associated with significant morbidity and mortality. Despite RHD being a major cause of morbidity and mortality in the young in many parts of the world, it is often neglected by policymakers, the media, and even the medical fraternity. Stroke risk assessment using various risk scores has not been systematically evaluated in rheumatic AF patients. Rate control may not be ideal for symptom control in rheumatic AF patients considering the young age and an active lifestyle. There is limited information regarding the nonpharmacological management of rheumatic AF. The current management guidelines based on nonvalvular AF do not apply to rheumatic AF patients who are often younger, are women, and have fewer comorbidities. This review critically looks at specific areas such as stroke prevention with reference to direct oral anticoagulants, cardioversion, rate and rhythm control strategies, and the role of nonpharmacological methods in rheumatic AF management. Future recommendations must be cognizant of local health care systems and resourcing considering the geographic distribution of the disease.

KEYWORDS Rheumatic heart disease; Atrial fibrillation; Rheumatic atrial fibrillation; Atrial fibrillation management; Valvular heart disease; Valvular heart disease management

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Introduction

Rheumatic heart disease (RHD) contributes to a significant proportion of AF in low- and middle-income countries (LMICs), while nonvalvular atrial fibrillation (AF) is the most common cause of AF in high-income countries (HICs). RHD is the delayed sequelae of acute rheumatic fever (ARF). While ARF afflicts children between 5 and 15 years of age, RHD is usually diagnosed between 20 and 50 years of age.[1] Whereas RHD and its antecedent ARF have diminished in HICs, it continues unabated in the LMICs and among vulnerable groups in the HICs.[2] RHD is a condition of global health importance and is estimated to affect over 33 million people, mostly in LMICs where the disease is endemic.[2] RHD poses a significant health burden among African Americans and immigrants from developing countries living in multiethnic urban America. In HICs, the condition is aggressive in immigrants and requires more interventions.[3] Existing international guidelines for the management of AF provide limited assistance in managing rheumatic AF.[4] Current guidelines based on nonvalvular AF have not been systematically studied and do not apply to rheumatic AF.

This review aims to look at the available literature on rheumatic AF and suggest possible management strategies based on the current evidence (Central Illustration).

Epidemiology

In 2015, there were an estimated 33.4 million cases of RHD, causing 319,400 deaths and 10.5 million disability-adjusted life years globally. The median age at death is 28 years, and case fatality at 24 months was highest in low-income countries (21%) and significantly lower in middle-income countries (12%–17%).[5] Oceania, South Asia, and central sub-Saharan Africa have the highest age-standardized mortality due to RHD.[3] A recent meta-analysis of 83 studies from 42 countries revealed the global prevalence of AF in RHD to be 32.8%, with substantial heterogeneity (4.3%–79.9%) based on the country's development level.[6] RHD remains a significant cause of AF in Africa, China, the Middle East, and India, where it is present in nearly one-third of patients with AF.[7] The prevalence of AF in RHD increases with age and varies from 7.6% in children and adolescents to 39.7% in adults.[6]

Patients with severe valvular disease have a higher prevalence of AF than those with mild/moderate disease. AF is more prevalent in mixed mitral valve (MMVD) disease,

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KEY FINDINGS

- Atrial fibrillation in rheumatic heart disease is under-recognized but is prevalent in many countries around the world.
- It causes significant morbidity and mortality, mainly in the young.
- There are no current guidelines for managing rheumatic atrial fibrillation.
- Randomized trials have excluded patients with rheumatic atrial fibrillation, especially mitral stenosis.

followed by isolated mitral stenosis (MS) and mitral regurgitation (MR).[6] Patients who have undergone surgical valve replacement have a higher prevalence of AF than patients who have undergone valvuloplasty.[8] In RHD patients with sinus rhythm, AF develops in about 20% over a median of 72 months, with an average annual event rate of 3.5% per year. However, patients with an enlarged left atrium (LA) (≥47 mm) have an average annual AF development rate of 6.0% per year.[9]

Differences between rheumatic vs nonrheumatic valvular AF

Valvular heart disease affects approximately 3% of the population in the United States and causes up to 30,000 deaths annually. RHD affects roughly 5% of the population worldwide and causes over 300,000 deaths annually.[10] There are several differences between rheumatic valvular disease (RVD) vs nonrheumatic valvular disease (NRVD) (Table 1). It is essential to understand the differences, as each group's risk stratification and treatment strategy are different. RVD can present as MMVD, MS, or MR. NRVD usually presents as MR due to mitral valve prolapse or, less commonly, as MS due to severe mitral annular calcification, and MMVD is uncommon. AF is more often seen in patients with RVD and less common in NRVD (52% vs 16%).[11] RVD is mainly seen in LMICs, whereas NRVD is more common in HICs.[11] RVD is seen in patients in their 20s and 30s with fewer comorbidities. NRVD patients present in their 60s and 70s and more often have hypertension, diabetes, chronic kidney disease, and coronary artery disease as comorbidities.[1,11,12] NRVD patients have more myocardial disease, causing a stiffer atrium and left ventricle, leading to diastolic dysfunction, compared with a more pliable atrium and ventricles in RHD patients.[11] The stroke risk for RVD patients with AF is far higher than for age-matched control subjects. AF patients with NRVD tend to be older, and rate control is preferred, which may not be the best option in younger rheumatic AF patients. The European Heart Rhythm Association has classified valvular heart disease. Type 1 refers to AF patients needing therapy with vitamin K antagonists (VKAs) (moderate-to-severe MS and mechanical prosthesis), and type 2 requires treatment with VKAs or direct oral anticoagulants (DOACs), taking into consideration the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, sex) score risk factor.[13]

Management of AF

The cornerstones for the management of AF in RHD involve 3 goals: (1) control symptoms and prevent or reverse tachycardiomyopathy by rate or rhythm control, (2) prevent stroke and peripheral embolism by therapeutic anticoagulation, and (3) improve survival by appropriate timing of valve interventions.

Stroke prevention in rheumatic AF

MS was estimated to be responsible for 25% of all deaths from a systemic embolism in the presurgical and preanticoagulant therapy era.[14] Nearly 80% of patients with MS and systemic embolism have AF on electrocardiography. One-third of embolic events occur within 1 month of the onset of AF, and two-thirds occur within 1 year.[15] In patients with RHD and prior embolism, the recurrence rate of 15 to

Table 1 Differences between rheumatic AF and nonrheumatic valvular atrial fibrillation

Parameter	Rheumatic AF	Nonrheumatic valvular AF
Presentation	Mitral stenosis, mitral regurgitation, mixed mitral valve disease	Mitral regurgitation, mitral stenosis
Age, y	20-50	>60
Geographic distribution	Low- and middle-income countries	High-income countries
Pathology	Fibrosis and commissural fusion	Myxomatous valve (mitral regurgitation) Calcification of annulus and leaflets (mitral stenosis)
Comorbidities	Lesser	Higher
Atrial fibrillation	Common (52%)	Less common (16%)
Left atrial volume	Larger	Moderate enlargement
CHA_2DS_2-VASc Score	Untested, not applied	Applicable

As presented in Pressman et al.[11]

AF = atrial fibrillation; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, sex category.

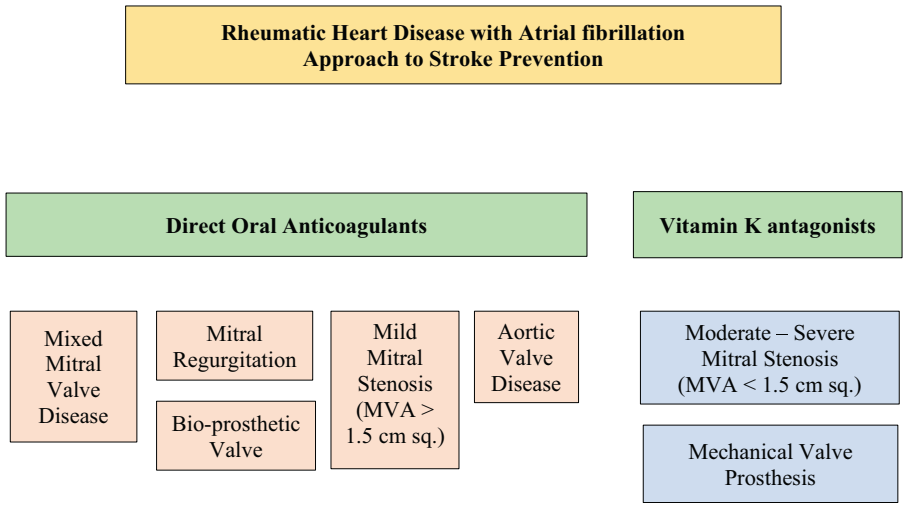

Figure 1 Stroke prevention in rheumatic atrial fibrillation. MVA = mitral valve area.

40 events per 100 patient-years is the highest reported in AF of any etiology.[14] There is no relation between the occurrence of embolism and mitral orifice dimensions, presence or absence of heart failure (HF), or patient symptoms. Embolism may be the first manifestation of MS, and it can occur even in patients with mild MS before symptom development.[14] In rheumatic mitral valve disease patients, thrombus can occur in areas outside the LA appendage (LAA)[16] and even in the right atrial appendage.[17]

Well-studied risk stratification scores in nonvalvular AF have not been validated for stroke risk assessment in rheumatic AF. A recent study of validation of CHA_2DS_2-VASc and HAS-BLED (hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol) scores in valvular AF patients showed that both scores were only modestly predictive of thromboembolism and bleeding events.[18] Less than 80% of eligible valvular AF patients are on oral anticoagulation, of whom <30% have a therapeutic international normalized ratio (INR).[19] While all patients with rheumatic MS with AF invariably require anticoagulation, the data are not very clear for other rheumatic valvular lesions. MS patients in sinus rhythm with dense left atrial spontaneous contrast have increased cardioembolic risk and may benefit from oral anticoagulation.[20]

According to recent guidelines, VKAs are the only treatment with established safety in AF patients with rheumatic mitral valve disease (Figure 1).[4] Disadvantages of VKAs are, a narrow therapeutic window requiring frequent INR monitoring and dose adjustments, need for adequate time in therapeutic range, teratogenicity, and food and drug interactions.[21] Time in therapeutic range (TTR) of >70% (based on the Rosendaal method or the percentage of therapeutic INRs) is necessary for effective stroke prevention. A low TTR is associated with higher stroke risk, and a very high TTR is associated with increased bleeding risk.[4] In the Randomized Evaluation of Long-Term Anti- coagulation Therapy in AF registry, the proportion of INR values between 2.0 and 3.0 was highest in Western Europe, at 67%, and lowest in India, at 35%. The TTR was between 51% and 62% in Western countries compared with 32% to 40% in India, China, and Southeast Asia.[7] It is also of concern that Asians have higher rates of intracranial hemorrhage with VKAs than Caucasians.[22] In a large longitudinal study of Korean patients by Kim and colleagues[23] that included 27,824 MS and AF patients, though there was an increase in the use of VKAs over time, the thromboembolic stroke rate plateaued out. The increased intracranial hemorrhage rates in Asian patients indicate the necessity of an alternative anticoagulant strategy.[23]

All randomized trials of DOACs have excluded patients with moderate-to-severe MS and mechanical heart valves.[21] In a retrospective observational Korean study of 2230 MS with AF patients comparing DOACs with VKAs, showed that patients on DOACs had significantly lower thromboembolic rates than VKAs. The all-cause mortality was significantly lower in the DOAC group, with no significant difference in the incidence of intracranial hemorrhage between the 2 groups.[24] The limitations of this study are its retrospective nature, and inability to ascertain the severity of MS, which may have biased the result. The European Society of Cardiology guidelines recommend against the use of DOACs in patients with AF and moderate-to-severe MS (mitral valve area <1.5 cm^2) (Class 3, Level of Evidence C).[4] The American College of Cardiology/American Heart Association guidelines recommend only VKAs in the previous subset.[25]

The INVICTUS (INVestIgation of rheumatiC AF Treatment Using VKAs, rivaroxaban, or aspirin Studies) registry is an observational registry of 17,000 patients from 23 countries with rheumatic MS and AF and a randomized noninferiority trial of rivaroxaban vs VKAs. The final analysis had 4531 patients with mean age of 50.5 years, 72.3% women, and a mean duration of follow-up of 3.1 ± 1.2 years. Patients with a CHA_2DS_2-VASc score of at least 2 with a mitral valve

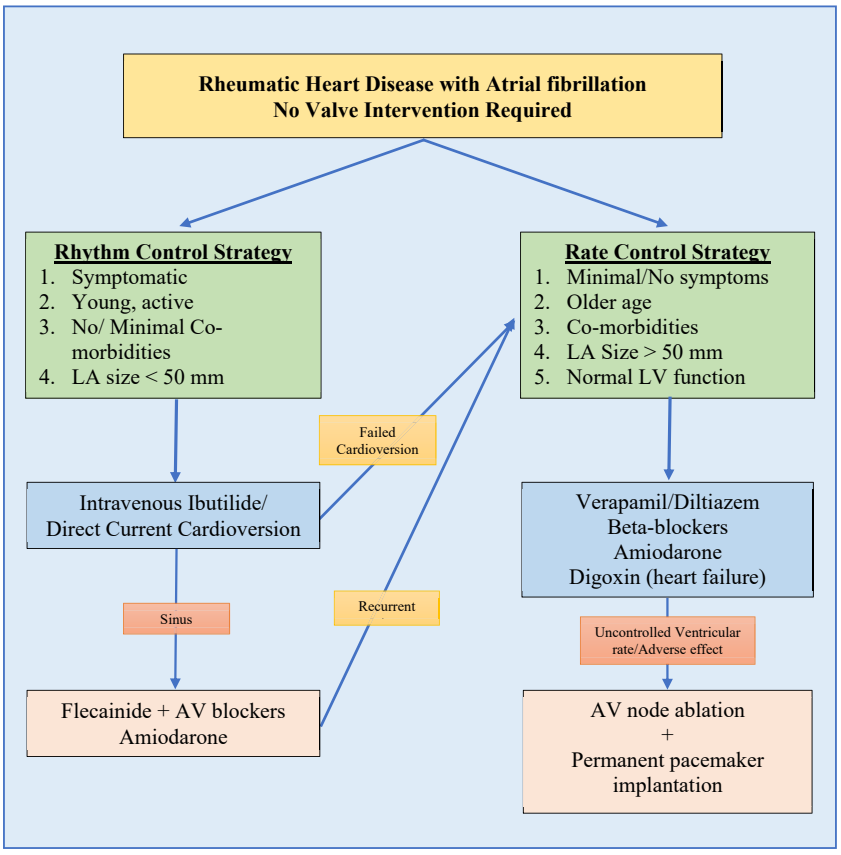

Figure 2 Suggested management strategy of rheumatic atrial fibrillation not requiring valve intervention. AF = atrial fibrillation; AV = atrioventricular; LA = left atrial; LV = left ventricular.

area of <2 cm^2, LA spontaneous echo contrast, or LA thrombus were randomized to standard doses of rivaroxaban or dose-adjusted VKAs. There was a significantly higher incidence of death in the rivaroxaban arm than in the VKA arm, with no significant group difference in the rate of major bleeding.[26] The results of the INVICTUS registry support current guidelines, which recommend VKAs for the prevention of stroke in patients with RHD with AF.

The DAVID-MS (DAbigatran for Stroke PreVention In Atrial Fibrillation in MoDerate or Severe Mitral Stenosis) trial is another ongoing noninferiority trial comparing dabigatran vs VKAs in the prevention of stroke or systemic embolism.[27]

The optimal anticoagulation strategy for patients with bioprosthetic valves and AF is uncertain. A recent meta-analysis included 4 randomized controlled trials and 6 observational studies of 6405 patients with bioprosthetic valves and AF. It showed that DOACs were equivalent to VKAs in preventing stroke and all-cause mortality, resulting in lesser major bleeding than VKAs.[28] However, even though the recent European Society of Cardiology guidelines suggest that DOACs may be used in patients with bioprosthetic valves, it does not make a firm recommendation.

Along with stroke prevention, the management of rheumatic AF depends on the need for valve intervention. If valve intervention is unnecessary, then a decision to follow a rate or rhythm control strategy is considered (Figure 2). If valve intervention is necessary, the decision on rate or rhythm control strategy is decided at the time of valvular intervention (Figure 3).

Rate control in rheumatic AF

Acute rate control is necessary for symptomatic hemodynamically stable patients for symptom alleviation. AF in MS or MMVD patients results in an increased gradient across the mitral valve. The preferred strategy is to reduce the resting ventricular rate to <80 beats/min using intravenous atrioventricular (AV)-blocking drugs.[29] AV-blocking drugs such as beta-blockers, calcium-channel blockers (diltiazem, verapamil), digoxin, or amiodarone may be used for rate control. The short-acting intravenous beta-blocker esmolol is the initial treatment of choice in the acute setting in patients with stable hemodynamics. Nondihydropyridine calcium-channel blockers (diltiazem, verapamil) are an alternative for patients with contraindications to beta-blockers. Intravenous amiodarone is preferred in the intensive care unit for rate control because of the lesser negative inotropic effect and safety in patients with structural heart disease or HF.[30] However, amiodarone should be used with caution, as it

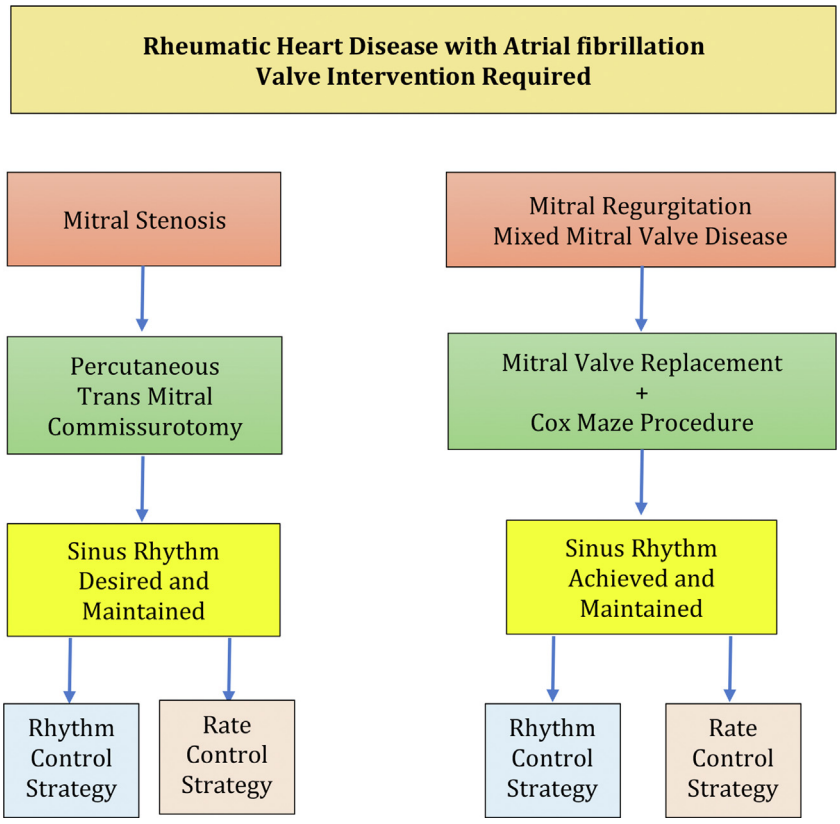

Figure 3 Suggested management strategy for rheumatic atrial fibrillation requiring valve intervention.

may convert AF to sinus rhythm, and in patients with LA thrombus, it can potentially result in a stroke.

AV-blocking drugs such as nondihydropyridine calcium-channel blockers, beta-blockers, or digoxin are used for chronic rate control. In a study of digoxin, verapamil, or metoprolol for rate control in improving symptoms and exercise capacity, digoxin produced the least and verapamil the maximum symptomatic improvement.[31] RHD patients with AF and HF may potentially derive some benefit from digoxin use.[32] Digoxin controls the resting heart rate due to increased vagal tone. Upright exercise decreases vagal tone and enhances AV conduction due to increased sympathetic tone, resulting in fast ventricular rates.[33] Hence, digoxin is ineffective in ventricular rate control after exercise and in young patients with a high sympathetic tone. With the limited data available, verapamil can be the drug of choice in patients with AF with no left ventricular dysfunction or HF. Beta-blockers approved for HF should be preferred in patients with rheumatic AF with left ventricular dysfunction or HF. Digoxin should be avoided in patients with rheumatic AF not in HF. The aim of rate control should be to achieve a resting heart rate of 60 to 80 beats/min and an exercise rate of 110 beats/min. A tight heart rate control will reduce the gradient across the mitral valve and reduce symptoms. Control of ventricular rate in MS patients with AF has shown a reduction in coagulation system activation and may decrease the risk of thrombosis.[34,35]

AV node ablation with permanent pacemaker implantation is an effective treatment strategy in AF patients resistant to other treatment modalities. The ablate-and-pace approach offers much better ventricular rate control and regularization of the R-R intervals. AV nodal ablation in patients with uncontrolled AF improves the quality of life and exercise tolerance and decreases HF episodes and hospital admissions.[36]

Guidelines recommend AV node ablation for rate control in (1) patients with inadequate rate control with pharmacological agents, (2) patients with intolerable side effects to drugs, or (3) patients in whom catheter ablation (CA) or surgical ablation of AF is not indicated, has failed, or is rejected.[4] Though there are no ablate-and-pace trials in patients with rheumatic AF, it can be considered in a select subset of patients with uncontrolled ventricular rates or adverse drug effects.

Rate control is the preferred option in older patients, those with minimal symptoms, those with extremely large LA (>5.5 cm), and those who fail the rhythm control strategy.

Rhythm control in rheumatic AF

Acute rhythm control

The primary indication for rhythm control is to reduce AF-related symptoms, improve quality of life, and improve left ventricular function in tachycardiomyopathy patients.[4] To evaluate the response, an attempt to restore sinus rhythm is a logical first step. Restoration of sinus rhythm in rheumatic

AF patients has several benefits, including increased cardiac output, better exercise capacity, reduced heart rate at rest and exercise, and alleviation of symptoms.[37,38] Restoration of sinus rhythm also increases LAA velocities, resulting in reverse remodeling of the LA.[34]

In a study of intravenous loading of amiodarone post–balloon valvotomy, amiodarone did not cardiovert any patient to sinus rhythm at 12 hours.[39] In another study of oral amiodarone loading for 1 to 6 weeks after balloon valvotomy, 26% to 40% of rheumatic AF patients converted to sinus rhythm.[38,40] Amiodarone's class III activity is a delayed effect observed days to weeks following drug loading; hence, acute intravenous loading is ineffective in sinus rhythm restoration.[41]

In a pilot study of 50 rheumatic AF patients, a single oral dose of 4 mg/kg of flecanide effectively cardioverted 4% to sinus rhythm, and 72% achieved sinus rhythm with direct current cardioversion (DCCV).[42] In a study of 165 patients with rheumatic AF, ibutilide successfully restored sinus rhythm in 77%, with a mean conversion time of 7.9 ± 4.1 minutes. Torsades de pointes requiring defibrillation developed in 1.8% of patients at a mean interval of 55 ± 37 minutes, and there were no deaths.[43] Use of 4 gm. of intravenous magnesium and esmolol along with ibutilide enhances cardioversion than ibutilide alone in patients with nonvalvular AF with a reduced incidence of QTc prolongation and diminished risk of ventricular tachycardia.[44]

DCCV is effective and safe in restoring sinus rhythm in most rheumatic AF patients, especially after valvular interventions such as balloon valvotomy.[42] To improve cardioversion success and prevent relapses, DCCV should be done after at least 1 month of oral amiodarone loading.[45]

Cardioversion should preferably be done after antiarrhythmic drug loading to prevent recurrences. Ibutilide should be considered the first choice for pharmacological cardioversion of rheumatic AF. DCCV should be considered if pharmacological cardioversion fails.

Pharmacological maintenance of sinus rhythm

Most studies of rheumatic AF of rhythm control strategy have with amiodarone. In the Control of Rate versus Rhythm in rheumatic Atrial Fibrillation Trial study of 144 rheumatic AF patients, Vora and colleagues[37] performed DCCV after oral amiodarone loading. At 1-year follow-up, 70% maintained sinus rhythm on amiodarone 200 mg maintenance dose. The patients in the study were young (38.6 ± 10.3 years), with an LA size of <50 mm, and 72% had undergone valvular interventions.[37] In a randomized study of 183 patients who had undergone successful balloon valvuloplasty, 96% maintained sinus rhythm at 1 year on low-dose amiodarone (mean of 130 mg/d).[38] In a small randomized study to evaluate the efficacy of early DCCV along with intravenous loading dose followed by low-dose short duration (100 mg/d during 6 weeks) amiodarone after balloon valvotomy, 87% remained in sinus rhythm at a short follow-up period of 6 to 9 months.[46] In a recent randomized placebo-controlled trial of amiodarone, 77.5% in the amiodarone group and 34.1% in the placebo group remained in sinus rhythm at 3 months of follow-up. At 12 months, 55% in the amiodarone group and 17.1% in the placebo group maintained sinus rhythm.[39]

In a pilot study of 50 patients, oral flecainide successfully maintained sinus rhythm in 60% of patients at 1-year follow-up.[42] Further larger randomized studies of flecanide are necessary to confirm its efficacy. Rheumatic AF patients tend to be young, with fewer comorbidities, have a normal left ventricular function, and need long-term antiarrhythmic therapy to maintain sinus rhythm. Flecanide, along with an AV-blocking drug, is the first option. Those with AF recurrence on flecainide can be considered for treatment with amiodarone, preferably in a low dose. Most small studies have shown that maintenance of sinus rhythm was superior to rate control on exercise capacity, quality of life, morbidity, and mortality.[37–39] There are no large randomized rate vs rhythm control studies in rheumatic AF patients.

A rhythm control strategy should be considered in young, symptomatic patients leading an active lifestyle with mild-moderate mitral valve disease or early after valvular interventions. The patients should preferably have a LA diameter <5.0 cm and little or no comorbidities.

Catheter ablation

There is minimal data on CA of rheumatic AF. Most of the studies of CA of rheumatic AF are small, with limited follow-up data. In an early study of 13 patients, induced atrial arrhythmia was successfully terminated by radiofrequency CA near the coronary sinus ostium by Nair and colleagues.[47] A careful look at the cycle length and the activation sequence suggest that the arrhythmias were organized atrial flutter rather than AF.[47] A study of 20 rheumatic AF patients compared simultaneous balloon valvotomy and pulmonary vein isolation or DCCV, followed by antiarrhythmic therapy. At 4 years of follow-up, 80% of CA group patients were in sinus rhythm compared with 10% who were only on antiarrhythmic medication.[48] In a recent retrospective study comparing CA in rheumatic AF vs nonvalvular AF, the long-term (23–140 months) outcomes of CA for rheumatic AF were modest. Compared with nonvalvular AF, the results were worse in rheumatic AF patients (32% vs 56%).[49] CA of LA and right atrial reentrant arrhythmias is feasible in patients with RHD with a high acute success rate. However, there is a significant incidence of arrhythmia recurrence and late AF development.[50]

The limited data in RHD patients shows that CA of atrial arrhythmias, including AF, is associated with modest acute success and a high recurrence rate. Hence, CA cannot be considered a primary therapeutic option.

Surgery

James Cox introduced the Cox maze III, the cut-and-sew approach using multiple incisions in the left and the right atria to eliminate circulating wavelets of AF while allowing the sinus impulse to reach the AV node.[51] A recent meta-analysis of 4 randomized controlled trials and 4 observational studies involving 1931 patients evaluated the safety and efficacy of concomitant surgical AF ablation during rheumatic mitral

valve surgery. Concomitant SA during rheumatic MV surgery does not increase perioperative adverse events more effective in sinus rhythm restoration than MV surgery alone at discharge and 1- and 3-year follow-up.[52] Surgical AF ablation has a class IIa recommendation in patients with valvular heart disease undergoing surgery in the recent AF guidelines.[4]

LAA closure

In a retrospective study of 860 patients, LAA exclusion during mitral valve replacement was safe and effective in preventing postoperative ischemic stroke in rheumatic AF.[53] In another observational study of 136 patients of LAA exclusion during mitral valve surgery, there was a significant incidence of thromboembolic events in patients not prescribed warfarin therapy at hospital discharge.[54]

Percutaneous LAA closure, an established treatment in nonvalvular AF, is limited to case reports and has not been tested systematically in rheumatic AF.[55] Considering the frequent presence of thrombus outside appendage in RHD patients, LAA closure alone may not be beneficial in patients with rheumatic mitral valve disease, and all patients need to be on oral anticoagulants.

Public health statement

RHD is a cause of significant morbidity and mortality in young and middle-aged individuals. Contrary to the assumption that ARF and RHD are on the decline, the Global Burden of Disease Study indicates that there has been hardly any decline in the last 25 years. It is especially true in LMICs, migrants, and indigenous populations in HICs. Though the prevention, control, and eradication of RHD is an essential public health issue, it has not attracted the attention of policymakers. Barriers to controlling and eliminating RHD are neglect of ARF and RHD in national health policies, inadequate budget allocation, lack of data, poor access to primary health care, and an insufficient number of trained health care staff.

The strategies for prevention, control, and elimination of RHD consist of primordial, primary, and secondary prevention. Primordial prevention aims to avoid episodes of streptococcal pharyngitis by tackling overcrowding and poverty and improving living and housing standards. Primary prevention of ARF involves early recognition and effective treatment of streptococcal pharyngitis with penicillin. Health care professionals and the public need to be educated about prompt and complete antibiotic treatment of streptococcal pharyngitis. Secondary prevention involves the monthly administration of injections of benzathine benzylpenicillin to patients with a previous history of ARF and RHD. Ensuring a consistent supply of quality-assured antibiotics is essential for the success of primary and secondary prevention. In established RHD, education of the professionals and the patient regarding regular follow-up for secondary prophylaxis and proper timing of surgery is necessary. Early diagnosis of AF is essential to initiate an appropriate rate or rhythm control strategy and anticoagulation for stroke prevention to prevent clinical deterioration. Planning, development, and implementation of a feasible program for the prevention and control of RHD should be an integral component of the national health system.

Conclusion

RHD is still prevalent in many parts of the world. It affects mainly the young and underprivileged causing significant morbidity and mortality. Even though rheumatic AF is common in many countries, all major guidelines have neglected this disease entirely. There are no guideline recommendations for managing rheumatic AF. There are no large randomized trials of rheumatic AF, and all major trials have excluded patients with RHD. There is an urgent need for large randomized trials of patients with rheumatic AF. It is time for the various guideline writing committees to give recommendations for managing rheumatic AF.

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References

1. Marijon E, Mirabel M, Celermajer DS, Jouven X. Rheumatic heart disease. Lancet 2012;379:953–964.
2. Watkins DA, Johnson CO, Colquhoun SM, et al. Global, regional, and national burden of rheumatic heart disease, 1990–2015. N Engl J Med 2017;377:713–722.
3. Doukky R, Abusin SA, Bayissa YA, Kelly RF, Ansari AH. Rheumatic heart disease in modern urban America: a cohort study of immigrant and indigenous patients in Chicago. Int J Cardiol 2014;175:178–180.
4. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2021; 42:373–498.
5. Watkins DA, Beaton AZ, Carapetis JR, et al. Rheumatic heart disease worldwide: JACC Scientific Expert Panel. J Am Coll Cardiol 2018;72:1397–1416.
6. Noubiap JJ, Nyaga UF, Ndoadoumgue AL, Nkeck JR, Ngouo A, Bigna JJ. Meta-analysis of the incidence, prevalence, and correlates of atrial fibrillation in rheumatic heart disease. Glob Heart 2020;15:38.
7. Oldgren J, Healey JS, Ezekowitz M, et al. Variations in cause and management of atrial fibrillation in a prospective registry of 15 400 emergency department patients in 46 countries: The RE-LY atrial fibrillation registry. Circulation 2014; 129:1568–1576.
8. Diker E, Aydogdu S, Ozdemir M, et al. Prevalence and predictors of atrial fibrillation in rheumatic valvular heart disease. Am J Cardiol 1996;77:96–98.
9. Kim H-J, Cho G-Y, Kim Y-J, et al. Development of atrial fibrillation in patients with rheumatic mitral valve disease in sinus rhythm. Int J Cardiovasc Imaging 2015;31:735–742.
10. Ryu R, Tran R. DOACs in Mechanical and bioprosthetic heart valves: a narrative review of emerging data and future directions. Clin Appl Thromb 2022; 28:107602962211035.
11. Pressman GS, Ranjan R, Park DH, Shim CY, Hong G-R. Degenerative mitral stenosis versus rheumatic mitral stenosis. Am J Cardiol 2020;125:1536–1542.
12. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on valvular heart disease. Eur Heart J 2003;24:1231–1243.
13. Lip GYH, Collet JP, De Caterina R, et al. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). Europace 2017;19:1757–1758.
14. De Caterina R, Camm AJ. Non-vitamin K antagonist oral anticoagulants in atrial fibrillation accompanying mitral stenosis: the concept for a trial. Europace 2016; 18:6–11.

15. Olesen KH. The natural history of 271 patients with mitral stenosis under medical treatment. Heart 1962;24:349–357.
16. Mahla H, Harlalka KK, Bhairappa S, Manjunath CN. Spectrum of left atrial thrombus in rheumatic heart disease. Case Rep 2014;2014:bcr2014204370.
17. Rohila AK, Kumar S, Khichar S, Meena DS, Pandit SK. Right atrial thrombus in a patient of rheumatic heart disease with severe mitral regurgitation: a rare association. Cardiovasc Hematol Disord Drug Targets 2021;21:202–205.
18. Lip GYH, Jensen M, Melgaard L, Skjøth F, Nielsen PB, Larsen TB. Stroke and bleeding risk scores in patients with atrial fibrillation and valvular heart disease: evaluating 'valvular heart disease' in a nationwide cohort study. Europace 2019; 21:33–40.
19. da Silva RMFL. Anticoagulation in atrial fibrillation associated with mitral stenosis. Cardiovasc Hematol Agents Med Chem 2022;20:172–174.
20. Gupta A, Bhatia R, Sharma G, Prasad K, Singh MB, Vibha D. Predictors of ischemic stroke in rheumatic heart disease. J Stroke Cerebrovasc Dis 2015; 24:2810–2815.
21. Fanaroff AC, Vora AN, Lopes RD. Non-vitamin K antagonist oral anticoagulants in patients with valvular heart disease. Eur Hear J Suppl 2022;24:A19–A31.
22. Shen AY-J, Yao JF, Brar SS, Jorgensen MB, Chen W. Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. J Am Coll Cardiol 2007;50:309–315.
23. Kim JY, Kim S-H, Myong JP, et al. Ten-year trends in the incidence, treatment and outcomes of patients with mitral stenosis in Korea. Heart 2020;106:746–750.
24. Kim JY, Kim SH, Myong JP, et al. Outcomes of direct oral anticoagulants in patients with mitral stenosis. J Am Coll Cardiol 2019;73:1123–1131.
25. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation 2019; 140:e125–e151.
26. Connolly SJ, Karthikeyan G, Ntsekhe M, et al. Rivaroxaban in rheumatic heart disease–associated atrial fibrillation. N Engl J Med 2022;387:978–988.
27. Zhou M, Chan EW, Hai JJ, et al. Protocol, rationale and design of DAbigatran for Stroke PreVention In Atrial Fibrillation in MoDerate or Severe Mitral Stenosis (DAVID-MS): a randomised, open-label study. BMJ Open 2020;10:e038194.
28. Yokoyama Y, Briasoulis A, Ueyama H, et al. Direct oral anticoagulants versus vitamin K antagonists in patients with atrial fibrillation and bioprosthetic valves: a meta-analysis. J Thorac Cardiovasc Surg 2021 Jul 29 [E-pub ahead of print].
29. Hill JA, Panza JA, Michler RE, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2016;358:1511–1520.
30. Arrigo M, Bettex D, Rudiger A. Management of atrial fibrillation in critically ill patients. Crit Care Res Pract 2014;2014:840615.
31. Ahuja RC, Sinha N, Saran RK, Jain AK, Hasan M. Digoxin or verapamil or metoprolol for heart rate control in patients with mitral stenosis — a randomised cross-over study. Int J Cardiol 1989;25:325–331.
32. Karthikeyan G, Devasenapathy N, Zühlke L, et al. Digoxin and clinical outcomes in the Global Rheumatic Heart Disease Registry. Heart 2019;105:363–369.
33. Beasley R, Smith DA, McHaffie DJ. Exercise heart rates at different serum digoxin concentrations in patients with atrial fibrillation. Br Med J (Clin Res Ed) 1985;290:9.
34. Atak R, Turhan H, Senen K, et al. Relationship between control of ventricular rate in atrial fibrillation and systemic coagulation activation in patients with mitral stenosis. J Heart Valve Dis 2004;13:159–164.
35. Yusuf J, Goyal M, Mukhopadhyay S, et al. Effect of heart rate control on coagulation status in patients of rheumatic mitral stenosis with atrial fibrillation–A pilot study. Indian Heart J 2015;67:S40–S45.
36. Vlachos K, Letsas KP, Korantzopoulos P, Liu T, Efremidis M, Sideris A. A review on atrioventricular junction ablation and pacing for heart rate control of atrial fibrillation. J Geriatr Cardiol 2015;12:547–554.
37. Vora A, Karnad D, Goyal V, et al. Control of rate versus rhythm in rheumatic atrial fibrillation: a randomized study. Indian Heart J 2004;56:110–116.
38. Hu CL. Comparison of rate control and rhythm control in patients with atrial fibrillation after percutaneous mitral balloon valvotomy: a randomised controlled study. Heart 2006;92:1096–1101.
39. Vilvanathan VK, Srinivas Prabhavathi Bhat BC, Nanjappa MC, et al. A randomized placebo-controlled trial with amiodarone for persistent atrial fibrillation in rheumatic mitral stenosis after successful balloon mitral valvuloplasty. Indian Heart J 2016;68:671–677.
40. Kapoor A, Kumar S, Singh RK, Pandey CM, Sinha N. Management of persistent atrial fibrillation following balloon mitral valvotomy: safety and efficacy of low-dose Amiodarone. J Heart Valve Dis 2002;11:802–809.
41. Chow MSS, Monsanto HA, Plante M. Intravenous amiodarone: pharmacology, pharmacokinetics, and clinical use. Ann Pharmacother 1996;30:637–643.
42. Ghosh A, Kapoor A, Khanna R, et al. A pilot study on the acute conversion and maintenance of sinus rhythm in rheumatic atrial fibrillation using oral Flecainide. Indian Heart J 2020;72:383–388.
43. Shenthar J, Banavalikar B, Valappil SP, et al. Safety and efficacy of ibutilide for acute pharmacological cardioversion of rheumatic atrial fibrillation. Cardiology 2021;146:624–632.
44. Fragakis N, Bikias A, Delithanasis I, et al. Acute beta-adrenoceptor blockade improves efficacy of ibutilide in conversion of atrial fibrillation with a rapid ventricular rate. Europace 2008;11:70–74.
45. Iung B, Leenhardt A, Extramiana F. Management of atrial fibrillation in patients with rheumatic mitral stenosis. Heart 2018;104:1062–1068.
46. Sharma G, Anantha Krishnan R, Bohra V, et al. Evaluation of early direct current cardioversion for maintenance of sinus rhythm in rheumatic atrial fibrillation following successful balloon mitral valvotomy. Indian Heart J 2016;68:486–492.
47. Nair M, Shah P, Batra R, et al. Chronic atrial fibrillation in patients with rheumatic heart disease. Circulation 2001;104:802–809.
48. Machino T, Tada H, Sekiguchi Y, et al. Hybrid therapy of radiofrequency catheter ablation and percutaneous transvenous mitral commissurotomy in patients with atrial fibrillation and mitral stenosis. J Cardiovasc Electrophysiol 2010; 21:284–289.
49. Chen J, Wang H, Zhao L. Long-term outcomes of radiofrequency catheter ablation for atrial fibrillation in rheumatic heart disease patients with mild mitral stenosis. J Interv Card Electrophysiol 2019;56:313–319.
50. Chen H, Yang B, Ju W, et al. Substrate characteristics and ablation outcome of left atrial tachycardia in rheumatic mitral valve disease. Pacing Clin Electrophysiol 2017;40:924–931.
51. Cox JL, Schuessler RB, Boineau JP. The development of the maze procedure for the treatment of atrial fibrillation. Semin Thorac Cardiovasc Surg 2000;12:2–14.
52. Ma J, Wei P, Yan Q, et al. Safety and efficacy of concomitant ablation for atrial fibrillation in rheumatic mitral valve surgery: a meta-analysis. J Card Surg 2022; 37:361–373.
53. Jiang S, Zhang H, Wei S, et al. Left atrial appendage exclusion is effective in reducing postoperative stroke after mitral valve replacement. J Card Surg 2020; 35:3395–3402.
54. Almahameed ST, Khan M, Zuzek RW, et al. Left atrial appendage exclusion and the risk of thromboembolic events following mitral valve surgery. J Cardiovasc Electrophysiol 2007;18:364–366.
55. Murdoch D, McAulay L, Walters DL. Combined percutaneous balloon mitral valvuloplasty and left atrial appendage occlusion device implantation for rheumatic mitral stenosis and atrial fibrillation. Cardiovasc Revasc Med 2014;15:428–431.