

## Management of atrial fibrillation-flutter: uptodate guideline paper on the current evidence

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### ABSTRACT

The term ‘flutter’ and ‘fibrillation’ were first coined to differentiate the differences between fast, regular contractions in Atrial Flutter (AFLUT) with irregular, vermiform contractions of Atrial Fibrillation (AFIB). Management of these two diseases has been a challenge for physicians. Rate control (along with rhythm control) is the first line of management for symptomatic AFIB/AFLUT with Rapid Ventricular Rate (RVR). In some situations, atrial rhythms may not be well controlled by these anti-arrhythmic drugs, making cardioversion to sinus rhythm necessary. Anti-coagulation therapy in both the disease population is essential. Catheter ablation is an effective treatment option in certain patients that have AFIB/AFLUT refractory to medical management. Newer techniques like left atrial appendage (LAA) has been developed and is a highly attractive concept for the future in the management of AFIB/AFLUT. Newer novel drugs targeting specific ion channels are approaching the stages of clinical investigation. However, while advances in technologies have helped elucidate many aspects of these diseases, many mysteries still remain. This literature review serves as one of the guideline papers for current up-to-date management on both AFIB and AFLUT.

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## 1. Introduction



Atrial Fibrillation (AFIB) and Atrial Flutter (AFLUT) are recognized as the most common cardiac arrhythmias in the world [1]. With the ever increasing population, the incidence rate of AFIB is thought to double by 2050 [2,3]. Some data suggests that the projected incidence may be as high as 8 million by 2050 [4]. Especially vulnerable is the geriatric population: known as the ‘disease of the old’, these 2 diseases have age as the major determinant in calculating prevalence. Consequently, these 2 diseases are rare in children and healthy young adults. Besides age, race and geographical location have a special preference for both AFIB and AFLUT. Studies have found white people over the age of 50 with higher prevalence when compared to black people [5]. In addition, North America had the greatest age-adjusted prevalence for both AFIB and AFLUT when compared with other continents [6]. Similar to the increasing prevalence of AFIB and AFLUT, the incidence of both these diseases is estimated to double with each passing decade of adult life [7].

The terms ‘flutter’ and ‘fibrillation’ were first coined in the early 20<sup>th</sup> century when Einthoven found out about atrial flutter. He compared the tactile rapid, regular atrial contractions (AFLUT) induced by faradic stimulation in animal hearts, in contrast with irregular, vermiform contractions (AFIB) [8–10]. Since then, the world of cardiovascular medicine has seen major

developments and changes in the management of these 2 interrelated atrial diseases. Due to the immense cardiovascular disease complications and economic burden of these two complicated pathologies, it is imperative to study on cost-effective means of treatment for these conditions. With the recent advances in technology, more and more evidence-based literature is available on newer and cost-effective methods of treating and managing these patients. This literature review serves as one of the key guiding stepping stones for current up-to-date management and treatment for both AFIB and AFLUT.

## 2. Etiology and types

Numerous risk factors have been indicated for both AFIB and AFLUT in multiple studies. There is a very strong genetic component playing a role in both abnormalities [11–13]. This was confirmed in the infamous Framingham Heart Study, done in 2004, which showed an increased genetic incidence in patients with AFIB [14]. Other modifiable risk factors include obesity, alcohol consumption, high caffeine intake and extreme endurance-bearing exercises [15–18]. These independent risk factors have a strong link to AFIB and AFLUT, however, the pathophysiology has not been fully elucidated.

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Furthermore, AFLUT can be divided into 3 different types depending on the specificity. The 3 most common AFIB types are paroxysmal AFIB, persistent AFIB and permanent AFIB. The first type is paroxysmal AFIB, which occurs spontaneously and generally resolves by itself or with treatment within 7 days [19]. It is characterized by episodes of irregular heart rhythm, which can occur with varying frequencies and periods of time before stopping. Persistent AFIB is sustained abnormal heart rhythm for more than 7 days even with treatment or direct current cardioversion [19]. Despite this, persistent AFIB may eventually cease via treatment or sometimes on its own [19]. Persistent AFIB is defined as Permanent AFIB when all means of treatment to restore normal heart rhythm have failed and the AFIB persists longer than 12 months [19]. The transition between Paroxysmal and Persistent AFIB may be regular, however, once diagnosed with Permanent AFIB, the disease stays there for the entire lifetime. Furthermore, distinguishing between Paroxysmal and Persistent AFIB is sometimes difficult as physicians often decide to terminate recent-onset AFIB via electrical or pharmacological means [19]. However, over time untreated Paroxysmal/Persistent AFIB may become worse and result in permanent AFIB [20].

### 3. Pathophysiology

Pathophysiology for both disease processes is different. However, both are inter-related diseases of the atrium.

#### 3.1. Atrial fibrillation

Many different mechanisms have been proposed regarding the pathophysiology of AFIB ranging from structural to electrical abnormalities which in turn leads to tissue remodeling [21]. When the atrial tissue contracts secondary to electrical or structural defects, there is uncoordinated blood flow to the ventricles causing an abnormal rhythm. Consequently, AFIB can cause large variations in blood pressure and cardiac output owing to irregular atrial contractions. AFIB is believed to be caused by certain triggers which could lead to rapid firing of the atria [21]. This can subsequently cause fibrillatory conduction through the heart [22]. Most common known place for these conduction is in the pulmonary veins [23]. In rare instances, there is myocardial tissue that can instigate repetitive firing causing episodic re-entrant activation of the veins [24].

Besides, the exact mechanism behind AFIB initiation have not been fully elucidated but it is believed that it involves enhanced automaticity or micro-entry [25]. Studies have further shown that the disease progression from Paroxysmal to

Persistent AFIB is due to structural and electrical changes within the atrium [26]. Fibrosis of the atria can lead to key structural changes in the atrium that may further worsen the AFIB [26]. Besides, fibroblasts act by electrically coupling to cardiac cells before proliferating. This promotes ectopic activity or re-entry within the atria [26]. These re-entrant circuits can further worsen the heart and enhance disease progression. Furthermore, electrophysiological changes can also occur very quickly after AFIB onset (sometimes within minutes), shortening the refractory period, and increasing the likelihood of Persistent AFIB [27].

#### 3.2. Atrial flutter

The pathophysiology for AFLUT is a little different as compared to AFIB. In majority of cases, however, flutter episodes alternate with fibrillation episodes. Various data suggests that low-voltage electrograms with slower conduction circuits within the right atrium results in myocardial remodeling [28–32]. This is thought to be the main pathology behind AFLUT rhythms. However, majority of the cases include structural and electrical abnormalities (similar to AFIB) as the main culprit behind the flutter waves [33–35]. One major difference in AFIB and AFLUT is that the thickness of the terminal crest of the atria and its capacity to block transverse conduction are increased in cases of AFLUT compared to AFIB [36,37]. Some literature also suggests left atrial dilatation as one of the strongest predictors of developing AFLUT in the recent future [38].

### 4. Clinical features

Two most common symptoms for both AFIB and AFLUT include palpitations and shortness of breath [39]. However, palpitations are more commonly seen in Paroxysmal AFIB as opposed to shortness of breath which is more common in Persistent/Permanent AFIB. Other common non-specific presentations include fatigue, lightheadness and lethargy [40]. However, not all the times atrial rhythm abnormalities are symptomatic: Paroxysmal AFIB patients more frequently present as asymptomatic [41]. Furthermore, due to the loss of effective atrial contraction in both AFIB/AFLUT, synchronized movements of ventricular contraction gets affected which in turn can lead to rapid ventricular rates which can result in angina, hypotension or syncope, making the patient seek medical help [42]. Occasionally, AFLUT can be asymptomatic for weeks or even months and the sustained tachycardia can lead to systolic ventricular dysfunction and heart failure symptoms (tachycardiomyopathy) [42].

## 5. Management and treatment

Management of these two atrial diseases has been a challenge for physicians. Before both the diseases can be treated, it is important that the clinical significance of the arrhythmia is identified. This can be done through a detailed history and physical examination [43]. Along with that, basic labs and imaging studies including echocardiography and thyroid function tests should be done to evaluate cardiac and thyroid activity [43]. This process must be completed to ensure that the treatment plan for a specific patient does not have any potential side effects, which may be caused by other underlying heart conditions.

### 5.1. Rate control

Rate control is the first line of management for symptomatic AFIB/AFLUT with Rapid Ventricular Rate (RVR). For the majority of patients that are hemodynamically stable and do not require immediate cardioversion, anti-arrhythmic drug therapies can potentially be utilized. These include calcium-channel blockers and beta-blockers. Evidence suggests that initial administration of calcium-channel blockers, like diltiazem, and beta-blockers, like metoprolol, are the most effective drugs in rate-controlling atrial rhythm disturbance [43]. Initial administration of these drugs reduce mortality rates and are more effective than other drugs, including digoxin, as they elicit a quicker and faster response irrespective of the patient's sympathetic tone [43]. Furthermore, a study also showed some synergism between these drugs and digoxin [44]. Both the calcium-channel blockers and beta blockers have been highly effective in converting AFIB/AFLUT to normal sinus rhythm if promptly administered following onset of AFIB/AFLUT and at an adequately high dosage [44]. This should be followed by constant electrocardiographic monitoring of the patient for the first 48 to 72 hours to confirm the conversion following the initial anti-arrhythmic drug [43].

However, in some situations, AFLUT may not be well controlled by these anti-arrhythmic drugs (digoxin, beta-blockers and calcium channel blockers), making cardioversion to sinus rhythm necessary. Sometimes potassium-channel blockers, like dofetilide and Ibutilide, pure class III anti-arrhythmic drugs, are effective for interrupting AFLUT with a small risk of QT prolongation and subsequent *torsade de pointes* [43].

### 5.2. Rhythm control/cardioversion

Rhythm control could be achieved with medications or via synchronized cardioversion in both AFIB and AFLUT [45]. Synchronized current cardioversion

depolarizes the cardiomyocytes simultaneously in an attempt to restore normal sinus rhythm. During the early onset of AFIB, cardioversion is generally avoided unless the patient has other heart conditions like preexcitation [43]. More commonly, cardioversion is attempted if the AFIB is persistent (lasted longer than 7 days), as the probability of it spontaneously converting to normal sinus rhythm after then is very low. In many cases, electrical cardioversion is coupled with the administration of an anti-arrhythmic drug, usually a potassium-channel blocker like ibutilide. Studies suggest that the combination of electrical shock with an intravenous drug (like a potassium-channel blocker) increases the chances of restoring the normal sinus rhythm [43].

Often, the recurrence of AFIB rhythm occurs. If recurrence occurs within 3 months of the intervention, it may be necessary for a repeated current cardioversion in combination with another drug or an increased dosage of the drug used in the initial cardioversion procedure [43]. However, if the patient is asymptomatic, anti-arrhythmic drugs and long term anticoagulation can be used alternatively, and patient can be monitored overtime for any symptomatic events.

Rhythm control via cardioversion is more successful in AFLUT than AFIB: In 75% of cases, AFLUT rhythm interruption can be achieved by atrial pacing above the flutter rate or by programming fast atrial rates in patients with atrial or dual-chamber pacemakers [46]. AFLUT has a lower recurrence rate after the cardioversion as compared to AFIB, making a strategy of repeated cardioversions supported with anti-arrhythmic drugs and long term anti-coagulation therapy, a clinically applicable option [45]. Transthoracic direct-current cardioversion, under short-lasting sedation, is the quickest and most effective method to recover sinus rhythm in patients with AFLUT, with a lower energy delivery and higher success rate than in AFIB. Often, AFLUT cardioversion by pacing is painless and can be done without sedation or anesthesia [45].

Another important step is to anti-coagulate the patient before, during and after cardioversion [47]. This reduces the chances of stroke via dislodged emboli into systemic circulation. Patients with AFIB/AFLUT of longer duration should be anticoagulated for atleast 4 weeks before cardioversion is attempted. Also left atrial thrombi should be ruled out by transoesophageal echocardiography (TEE) before any cardioversion is planned, to lower the risk of dislodging an emboli. Following cardioversion, anticoagulation should be maintained for a minimum of 3 weeks in patients with low embolic risk patients [47]. If high embolic risk is present, anticoagulation should be continued indefinitely, unless prolonged follow-up monitoring demonstrates an absence of recurrence [47].

### 5.3. Anti-coagulation therapy

Anti-coagulation therapy is essential in both these diseases since these patients are more susceptible to forming blood clots in the atria which can be dislodged into the systemic circulation causing a stroke. The choice of anticoagulant medication is very important and should take into account the potential drug interactions, patient's comorbidities and the patient's ability to strictly adhere to the medication schedule. Furthermore, if the onset of AFIB/AFLUT cannot be accurately determined, patients undergoing cardioversion should receive anti-coagulation before, during and after the procedure. A strict compliance to the schedule is essential as a missed dose can significantly increase the risk of a thrombotic event.

The type of medication recommended is dependent upon the patient's risk of stroke determined by the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, which is a clinical predictor estimating the risk of stroke in these patients. For patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 or greater, it is recommended that they use warfarin or factor Xa inhibitors such as rivaroxaban or apixaban [19]. If the CHA<sub>2</sub>DS<sub>2</sub>-VASc score is 1, anti-coagulant therapy may not be necessary but the physician, using his clinical judgement, may still consider using an aspirin [19]. A patient with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 requires no necessary anticoagulation therapy [19]. For patients requiring a treatment that involves interruption of anticoagulation, low molecular weight heparin or heparin in unfractionated form can be used. Studies have also demonstrated similar efficacy profiles for rivaroxaban and warfarin [48]. Ultimately, assessing the risk of stroke is essential for determining the treatment that will be most effective in improving outcomes, hospitalization stays and quality of life of patients with AFIB and AFLUT.

### 5.4. Catheter ablation

Catheter ablation for the treatment of AFIB/AFLUT is increasingly being used as an alternative to medical management, or when medical management has been ineffective or not tolerated [43]. Patients who have AFIB/AFLUT refractory to medical management and those with systolic heart failure are the ones most beneficial from catheter ablation [43,45]. Studies have also shown that catheter ablation improves quality of life in these patients [45]. Hence, some clinicians use it as the treatment of choice. During the procedure, energy is delivered to the myocardium to destroy areas of the heart resulting in electrically isolate small areas of tissue where abnormal electrical signals originate [43]. Again, as with cardioversion,

patients undergoing catheter ablation procedure should be anticoagulated and the anti-coagulation should be continued for at least 8 weeks after the procedure [45]. Following the procedure a permanent pacemaker must be implanted to maintain the heart rate [43].

While ablation does not eliminate the AFIB/AFLUT per se, it can limit the ventricular rate by eliminating triggers and altering electrophysiological connections in the heart in a similar fashion to rate control anti-arrhythmic drugs [49]. Multiple studies and trials have demonstrated superior results for restoration of normal sinus rhythm with catheter ablation compared with antiarrhythmic drug therapy alone [50]. Several studies have also shown that the success rate is much higher when catheter ablation is used in combination with antiarrhythmic drug therapy, as compared to using antiarrhythmic drug therapy alone [50]. Furthermore, the recurrence rate with catheter ablation was far lower as compared to antiarrhythmic drug therapy alone [51,52]. Overall, radiofrequency catheter ablation is a treatment method that has been shown to enhance the patient's quality of life and also improves ventricle function in a large portion of patients [53,54]. Therefore, this in the long-term is very effective in the management of AFIB/AFLUT.

However, there are some complications during the catheter ablation procedure which needs to be addressed as well. Recent data suggests a high rate of post-procedural complications in patients undergoing catheter ablation [52]. These included a high incidence of life-threatening cardiac tamponade [52]. Furthermore, sometimes during the procedure, identification of the exact location of abnormal firing can be difficult for the cardiologist, hence, greater expertise is needed [55]. Also, there are some scattered reported cases of myocardial infarction caused by damage to the right coronary artery, in patients with pre-existing coronary atherosclerotic lesions [56].

### 5.5. Percutaneous left atrial appendage (LAA) closure

In many patients anticoagulation is contra-indicated due to high bleeding risk, life-threatening bleeds of unknown cause while on anticoagulation, or due to high risk of falls, especially in elderly population [57,58]. Furthermore, International Normalized Ratio (INR) control of patients is generally poor, possibly due to no-compliance or lifestyle variations. An alternative approach to prevention of cardiac embolism in patients with AFIB/AFLUT is therefore desirable. One that can be used in all patients and

does not require anticoagulation other than low-dose aspirin.

It is on this basis that the left atrial appendage (LAA) has been developed and is a highly attractive concept for the future in the novel management of AFIB/AFLUT [59,60]. LAA occlusion in these typical patients helps prevent the vast majority of intracardiac thrombus formation especially for those patients who are unable to take any form of oral anticoagulant therapy. The patients, however, must be made aware that exclusion of the LAA, similar to when using warfarin, does not absolutely exclude risk of future strokes [59]. Currently many randomized clinical trials are underway assessing the efficacy and safety profile of these devices. If approved, however, this procedure could potentially become a first-line consideration in patients with AFIB/AFLUT facing a lifetime of anticoagulation.

## 6. Conclusion

Management of these two atrial diseases has been a challenge for physicians. For years, the first line treatment for AFIB/AFLUT has been rate control (along with rhythm control). However, with the advent of technology and many new drugs/devices under clinical investigation, this might change in the future. However, while advances in technologies have helped elucidate many aspects of these diseases, many mysteries still remain. With continued research, we can expect more cost-effective and patient-friendly drug therapies to be developed in the near future.

## 7. Future prospects

In the past few decades, research into the management of AFIB/AFLUT has increased tremendously. With it, our understanding of the relevant pathophysiology and treatment options has improved as well. Newer novel drugs targeting specific ion channels are approaching the stages of clinical investigation. Similarly, newer techniques like LAA has been developed and is a highly attractive concept for the future in the management of AFIB/AFLUT. There are also new and exciting areas such as gene therapy and microRNAs and their function on tissue remodeling and structural changes in the pathology behind the atrial rhythm disturbances. With our ageing population and ever increasing prevalence of AFIB/AFLUT, optimized treatment plans for individuals are essential. Better therapeutic strategies for AFIB/AFLUT should be focused on disease-specific targets that aim to control pathophysiologic remodeling. The hope in the end will be a cure or a prevention strategy

that will prevent triggers, substrate, or both from occurring.

Future in the management of AFIB/AFLUT looks bright. Currently various randomized controlled trials are underway regarding many new drugs aiming at different pathophysiology regarding AFIB/AFLUT. Besides, the ORBIT AF II (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II) and GUIDE-IT (GUIDing Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure) trials are under various phases of completion. The goal of these prospective trials is to identify treatment patterns in patients with AFIB/AFLUT and will attempt to define current treatment patterns and their relationship with outcomes, including stroke, all-cause mortality, and quality-of-life. Regardless, with the advent of technology, we can always expect a decrease in the mortality rates from these diseases. With continued research, we can expect more cost-effective and patient-friendly drug therapies and ablation techniques to be developed in the near future. It is anticipated that the results of these trials will soon be implemented in international guidelines.

## Disclosure statement

No potential conflict of interest was reported by the author.

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- Note: (\*=of importance, \*\*= of considerable importance)  
These are important articles with previous current evidence on AFIB/AFLUT management
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