

The current approach of atrial fibrillation management

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ABSTRACT

Atrial fibrillation (AF) is the most commonly encountered arrhythmia in clinical practice. Aging populations coupled with improved outcomes for many chronic medical conditions has led to increases in AF diagnoses. AF is also known to be associated with an increased risk of adverse events such as transient ischemic attack, ischemic stroke, systemic embolism, and death. This association is enhanced in select populations with preexisting comorbid conditions such as chronic heart failure. The aim of this review is to highlight the advances in the field of cardiology in the management of AF in both acute and long-term settings. We will also review the evolution of anticoagulation management over the past few years and landmark trials in the development of novel oral anticoagulants (NOACs), reversal agents for new NOACs, nonpharmacological options to anticoagulation therapy, and the role of implantable loop recorder in AF management.

Key words: Antiarrhythmic, anticoagulation, atrial fibrillation, drugs and ablation

INTRODUCTION

The prevalence of atrial fibrillation (AF) ranges from 0.5 to 1%. 70% of afflicted persons are between the ages 65 and 85 with a median age of diagnosis of 75 years.^[1-4] Discrepancies may be seen with gender, race, and the presence or absence of cardiovascular disease. There is an increased prevalence of AF in age-adjusted male population as compared to women. However, nearly 60% of AF patients over the age of 75 years are women. Caucasians have a higher prevalence of AF at 2.2 compared to 1.5% in African Americans over the age of 50 years.^[1] Lastly, patients with known clinical cardiovascular disease have been shown to have AF rates as high as 9.1% in both men and women compared to 4.6% in comparable groups with subclinical disease and 1.6% in patients without cardiovascular disease.^[2] Rates of hospitalizations have also increased 2–3 fold.^[5]

There is a well-established relationship between AF and chronic heart failure (CHF). A Framingham study showed AF accounts for 14% of deaths in the first few months of CHF diagnosis.^[6] In some CHF clinical trials, the prevalence of AF was 4% in functional class I patients, 10%–27% in those with functional class II–III, and 50% in those with functional class IV. This shows the strong correlation between worsening cardiac function, age, and AF.^[7] Net effects include an increase in cost to the health care system due to the annual cost of AF-related expenses, which are estimated to be nearly 16 billion dollars in the United States alone.^[8] We completed an extensive review of available evidence of the current American College of Cardiology (ACC), Heart Rhythm Society (HRS), and European Society of Cardiology (ESC) practice guidelines.

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PATHOPHYSIOLOGY

Mechanism of atrial fibrillation

AF requires a trigger to begin. The trigger is usually in the form of either automatic foci of tachycardia or multiple wavelets extending through the left atrium. The substrate used for maintenance of arrhythmia is commonly heterogeneous tissue.^[9] The prevailing hypothesis of enhanced focal automaticity in atrial tissue results in chaotic atrial activation. Enhanced focal automaticity occurs most commonly in the pulmonary veins (PVs), which generate microreentrant circuits that extend into adjacent left atrial tissue.^[9,10] Atrial stretch has been considered as a trigger of recurrent AF especially in patients with valvular heart diseases, CHF, and ischemic heart disease.^[11-14]

Systemic thromboembolism

The typical source of systemic thromboembolism in AF patients is the left atrial appendage (LAA). Duration of AF more than 48 h promote LAA stasis, endothelial dysfunction, and hypercoagulability. The risk of thromboembolism persists even after cardioversion secondary to a phenomenon known as atrial stunning. Atrial dysfunction is most pronounced immediately following restoration of sinus rhythm and abates typically within days but has been described as far out as 3–4 weeks.^[15]

INITIAL EVALUATION

Initial encounters with patients with AF should focus on the hemodynamic stability. Hemodynamic instability results from compromised ventricular diastolic filling and myocardial oxygen delivery, particularly in patients with AF with rapid ventricular response.^[16,17]

In the absence of hemodynamic compromise the management of AF is guided by symptomatology and its duration [Figure 1]. This specifically involves identifying exercise capacity and functional capacity, which is inferred from generalized complaints of fatigue and the absence or presence of syncope. Establishing the presence or absence of symptoms and their duration in AF patients is paramount in making decisions regarding long-term rate versus rhythm control strategy. Lastly, it is important to identify and effectively manage other risk factors such as obesity, thyroid disorder, and sleep apnea.

ACUTE MANAGEMENT OF ATRIAL FIBRILLATION

Patients presenting with evidence of hemodynamic or myocardial compromise should receive immediate interventions to restore sinus rhythm or rapidly reduce

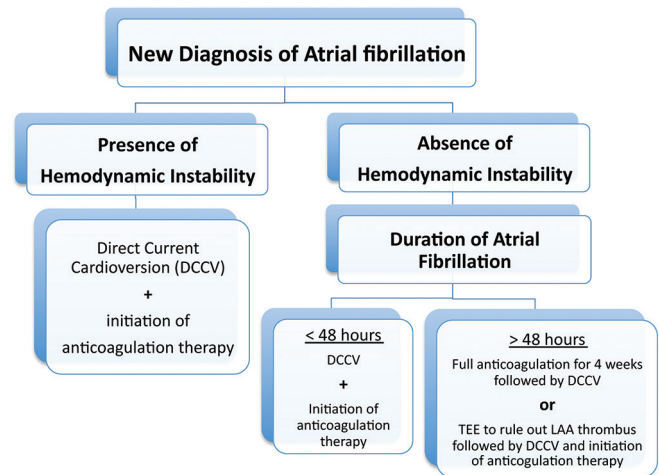


Figure 1: Acute Management of new onset atrial fibrillation (LAA: Left atrial appendage; Full anticoagulation: either with 4 consecutive weeks of warfarin therapy with weekly therapeutic INR (2-3) or four weeks of the novel oral anticoagulants (NOACs) without any interruption even for one dose)

ventricular rates. In the absence of hemodynamic instability, synchronized direct-current cardioversion (DCCV) should be an elective procedure. Particular attention should be given to the ability of patients to tolerate anticoagulation for at least 4 weeks post DCCV.

For acute rate control, beta blockade (BB), calcium channel blockade (CCB), digoxin, or amiodarone may be considered. Selection of one agent over another is guided primarily by comorbid conditions including the presence or absence of CHF and the potential for an existing accessory pathway of atrioventricular (AV) conduction (preexcitation). Beta-adrenergic antagonists are most effective in states of high catecholamine release, including the perioperative period and critical illness. Intravenous esmolol (BB) and diltiazem (CCB) have similar heart rates achieved at 2 and 12 h, respectively.^[18] CCB and BB should be judiciously examined in patients with CHF or preexcitation. Both portend a negative inotropic effect in concert with preferential AV node slowing which may accelerate ventricular activation in patients with accessory pathways leading to ventricular rate acceleration and ventricular fibrillation.

In the setting of a patient with CHF, consideration may be given to digoxin though a vagotonic mechanism of action digoxin may transiently slow AV conduction.^[19] Coupled with significant drug-drug interactions, the use of digoxin in the acute setting has largely fallen out of favor, which shows that effects are reduced in high catecholamine states.

In the setting of advanced CHF or preexcitation amiodarone may be considered.^[20] In the United States, amiodarone for

rate control is considered off-label and must be weighed carefully against the potential for acute pulmonary and hepatic injury as well as hemodynamic consequences including hypotension and bradycardia in high doses^[20] [Figure 2].

LONG-TERM MANAGEMENT OF ATRIAL FIBRILLATION

Long-term management of AF involves effectively managing symptoms with either rate or rhythm control strategies in addition to prevention of thromboembolism. These goals are not mutually exclusive.^[21] The long-term management of AF focuses on:

Quality of life

Quality of life (QOL) evaluations have demonstrated no significant difference between patients ascribed to rate control strategies versus those placed on rhythm control strategies, with the exception of one study; which was a status postsurgical Maze procedures.^[22] Symptomatic improvement with improved exercise capacity has been reported in rhythm control patients versus rate control patients.^[23,24] This has led to controversy regarding the evaluation of QOL in AF patients. Similarly, concurrent anticoagulant therapy appears to negatively affect perceived QOL. However, novel anticoagulants are significantly reducing the burden associated with routine anticoagulation monitoring.^[25]

Rate control strategy

Pharmacologic intervention

Oral BB has been shown to be the best single agent for rate control. It has achieved specified heart rate points

of between 60 and 80 beats/min at rest and a maximum heart rate of 110 beats/min with exercise in 70% of the AFFIRM study patients.^[26] CCB is preferentially used for patients with coexistent pulmonary diseases. Digoxin is used in patients with CHF.^[27] Newer evaluations of rate control compared lenient rate control (resting heart rates as high as 110 beats/min) to strict rate control similar to the AFFIRM study and showed a 2% absolute reduction in the death from cardiovascular cause, hospitalization for CHF, life-threatening arrhythmogenic events, stroke or systemic embolism, and bleeding in the lenient rate control arm compared to the strict rate control arm.^[28] The AFFIRM study described an overall increase in mortality in the rhythm control arm especially in patients with CHF, coronary artery disease, and the elderly as demonstrated by subset hazard ratio.^[25,29]

Nonpharmacologic intervention

AV node and permanent pacemaker are a well-established rate control strategy in medically refractory AF. Significant improvement in QOL, left ventricular ejection fraction (LVEF) as well as exercise endurance improves in patients who underwent AV node ablation and pacing as a rate control strategy.^[30] Chronic right ventricular pacing post AV ablation could compromise the cardiac performance and possibly induce CHF. There was no significant change in the NYHA class, and LV ends diastolic diameter in patients with normal LV function in the clinical study. Hospitalization for CHF occurs in patients with low LVEF and CHF at the time of AV node ablation and pacemaker implantation.^[31] Therefore, biventricular pacemaker implantation post AV node ablation is recommended in patients with medically refractory AF, symptomatic CHF, and low LVEF. This was concluded from the PAVE study, which showed a significant improvement in 6 min walk distance and LVEF.^[32]

Rhythm control strategy

Antiarrhythmic therapy

Antiarrhythmic therapy is tailored upon structural cardiac features and guided by evidence-based both on the type of AF and side effect profile of the antiarrhythmic drugs (AAD) considered. Classification of the AAD is based on the mechanism of action. Class I AAD blocks sodium channels with different potency, IC being the most potent. Class II AAD blocks beta-receptors. Class III AAD blocks potassium channels, and class IV AAD blocks calcium channels.

- Class IC AADs: Flecainide and propafenone have superior rhythm control at 6–12 months compared to the placebo.^[33] Class IC AADs should be utilized in

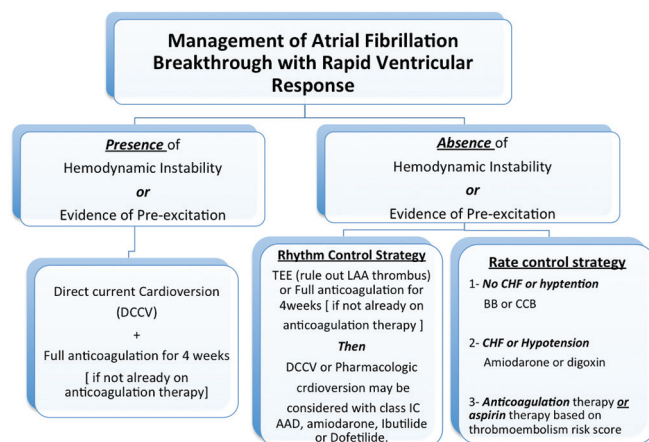


Figure 2: Management of atrial fibrillation breakthrough with rapid ventricular response (AAD: antiarrhythmic drug; BB: beta blocker; CCB: calcium channel blocker; CHF: chronic heart failure; DCCV: Direct current cardioversion; TEE: Transesophageal echocardiogram and LAA: Left atrial appendage. Full anticoagulation: either with 4 consecutive weeks of warfarin therapy with weekly therapeutic INR (2-3) or four weeks of the novel oral anticoagulants (NOACs) without any interruption even for one dose. Ibutilide is an intravenous AAD, which is usually used for pharmacologic cardioversion in normal heart structure and normal QT interval

patients with structurally normal hearts, especially in patients with coronary artery disease and significant LV hypertrophy. Flecainide increases in mortality in patients with coronary artery disease.^[34]

- Dofetilide is a class III AAD and has been established as an appropriate antiarrhythmic option in patients with structurally normal hearts as well as those with CHF or prior myocardial infarction.^[35-37] Dofetilide demonstrated superiority to the placebo in pharmacologic cardioversion in the first month as well as one-year maintenance of sinus rhythm.^[36]
- Amiodarone is a multichannel AAD. Sotalol is class III AADs. Amiodarone has been shown to be superior to sotalol and propafenone in maintaining sinus rhythm in paroxysmal and persistent AF. A comparative study showed 69% of patients on amiodarone maintain sinus rhythm compared to 39% of patients on propafenone or sotalol therapy [Figure 3].^[38] Similarly in the AFFIRM study, 60% of patients on amiodarone maintained sinus rhythm compared to 38% of patients on sotalol at one year [Figure 3].^[25]
- Dronedarone is a class III AAD. It is related to amiodarone but lacks the iodine moieties with the expectation of reducing toxic effects on the thyroid, lungs, and liver.^[39] Dronedarone is effective in maintaining sinus rhythm in patients with paroxysmal and persistent AF and atrial flutter (AFL) and normal LVEF.^[40] However, dronedarone increases mortality in patients with AF and AFL and symptomatic NYHA III and IV CHF and LVEF <35%.^[41] Another study showed significant reduction of hospitalization or death in patients with AF and AFL and LVEF <40% without any decompensated CHF for at least 4 weeks.^[42]

Therefore, dronedarone is contraindicated in patients with NYHA IV or NYHA II-III heart failure with a recent

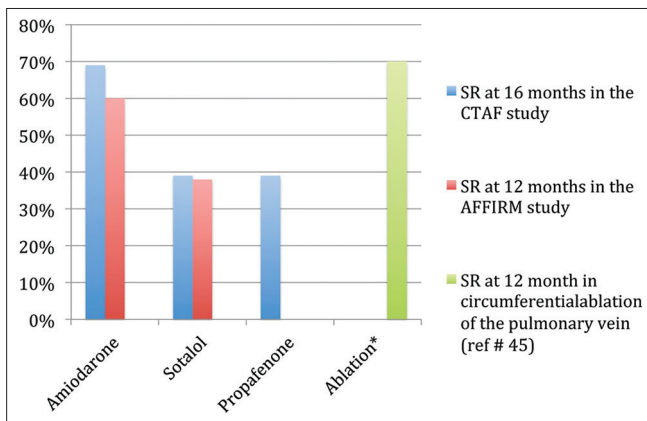


Figure 3: Efficacy of anti-arrhythmic drugs on maintaining sinus rhythm (SR: Sinus rhythm; Ablation*: maintained sinus rhythm after one ablation in patients with either paroxysmal and persistent atrial fibrillation)

decompensation and in patients with permanent AF.^[41-43] Postmarketing, dronedarone was also associated with a rare case of severe liver damage. Therefore, we recommend checking liver function test frequently in the first few weeks.

Ablation therapy of atrial fibrillation

The relatively low rates of success for AADs coupled with the specific long-term potential side effects have resulted in ablative therapy as an alternative second-line therapy for the maintenance of sinus rhythm. Current protocols seek to isolate the PVs via radiofrequency ablation or balloon cryoablation.

Efficacy of the ablative therapy

Catheter radiofrequency ablation or balloon cryoablation is superior over AADs in patients with paroxysmal or persistent AF. It results in nearly 70% of patients maintaining sinus rhythm over a 12-month period [Figure 3].^[10,44,45] Therefore, referrals for ablation therapy should be considered for individuals seeking to maintain sinus rhythm and who have an AF breakthrough while on AAD.^[21]

Outcome of atrial fibrillation ablation in patients with chronic heart failure

Successful catheter ablation and restoration of sinus rhythm improve LV function, exercise endurance, and QOL in patients with AF and CHF.^[46] The outcome of catheter ablation of AF in patients with CHF is significantly better compared to AV node ablation with biventricular pacing.^[47] Successful ablation of persistent AF in patients with symptomatic CHF and LVEF ≤ 35% is superior in improving exercise capacity, symptoms, QOL, as well as B-type natriuretic peptide compared to optimal rate control strategy.^[48]

Complications of atrial fibrillation ablation

Complications of AF ablation therapy have been reported in 4.5%. Death accounts for 0.15% of total complications. Atrio-esophageal (AE) fistula is the deadly complication and accounted for 0.04%. Other complications include cardiac tamponade (1.31%) as well as PV stenosis requiring surgical dilation (0.3%). Minor complications include femoral pseudoaneurysm and arteriovenous fistula.^[49]

Contraindications of ablation therapy

Absolute contraindications to ablation include intolerance to anticoagulation. This is since anticoagulation therapy is required postablation. The presence of LAA thrombus is also an indication as well as severe mitral valve disease or mechanical mitral valve prosthesis and severe pulmonary hypertension.

ANTICOAGULATION THERAPY

Regardless of the strategy of symptom control, every patient needs to be evaluated for thromboembolic risk. An appropriate strategy must also be identified at the time of diagnosis and re-evaluated with each clinical encounter. Maintenance of anticoagulation in the immediate setting is critical to prevent systemic thromboembolism including stroke following pharmacologic or electrical cardioversion, which occurs within the first 3 days of restoration of sinus rhythm.^[50]

Epidemiologic studies showed the lowest incidence of thromboembolism at 1.3% over 3 decades in patients with lone AF.^[51] Whereas, patient with hypertension and/or cardiomegaly developed a stroke with an incidence of 28.2% during 11 years follow-up.^[52] This difference is best reconciled by the understanding that several independent risk factors for thromboembolism in AF exist. A history of ischemic stroke or TIA is the largest single risk factor for recurrent stroke with a relative risk of 2.5 in patients with nonvalvular AF.^[21] Advancing age remains a predictor of stroke risk with a relative risk of 1.4.^[53] Hypertension and diabetes are independent predictors of stroke with a relative risk of 1.6 and 1.7, respectively. Echocardiographic evidence of CHF is an independent risk factor for stroke.^[54]

Risk factors of systemic thromboembolism

The rationale for anticoagulant or antiplatelet therapy should be guided by the interaction of these known risk factors. The most common risk stratification algorithm is currently utilized is either the CHADS₂ or CHA₂DS₂-VASC risk classification scheme [Table 1].^[21] The rates of stroke on aspirin therapy alone linearly correlated with a CHADS₂ score with individuals having a CHADS₂ score of 0 maintaining an annual stroke risk of 1.9% in comparison to patients with a score of 5 or 6 having a stroke rate of 12.5–18.2%, respectively.^[54,55]

The CHA₂DS₂-VASC score has been used in the 2012 ESC guidelines and the 2014 ACC/AHA Task Force. It

CHADS ₂ risk factors (0-9)		CHA ₂ DS ₂ -VASC risk factors (0-9)	
Risk factors	Points	Additional risk	Extra points
History of stroke/TIA	2	Age >65 years	1
Age >75 years	1	Age >75 years	2
Hypertension	1	vascular disease	1
Diabetes mellitus	1	Female gender	1
Heart failure	1		

This score was created based on the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014^[21,55,58]

is recommended that patients with a CHA₂DS₂-VASC score of 2 and above should be on oral anticoagulation therapy (OAC).^[18] Antiplatelet agents are often considered for stroke prophylaxis in individuals at presumed low risk for stroke and those with a high-risk feature for bleeding. Aspirin has been evaluated independently in 6 trials. A meta-analysis of this demonstrates only marginal protection against stroke with a stroke rate of 1.5%–2.2% in patients treated with aspirin for a CHADS₂ score of 1.^[56,57] There is a 33% reduction in stroke risk during oral anticoagulation compared to aspirin therapy for a CHADS₂ score >1. Similarly, high-risk populations benefit most from oral anticoagulation compared to aspirin therapy.

Vitamin K antagonist therapy in atrial fibrillation

Warfarin is a Vitamin K antagonist, and it functions by inhibiting clotting factor production (factor II, VII, IX, X Protein C, and S). It has a slow onset that often requires bridging with intravenous heparin or subcutaneous low molecular heparin. Warfarin therapy demonstrated a 62% risk reduction of stroke.^[58] Current recommendations utilize an INR guided warfarin dosing with a target INR between 2.0 and 3.0.^[21] In the last half decade, with the emergence of novel oral anticoagulant (NOAC) medications, more patients prefer NOACs due to lower incidence of drug interactions, dietary restriction, and routine monitoring in an outpatient setting compared to warfarin therapy.^[59,60]

Novel oral anticoagulants therapy in atrial fibrillation

NOACs are used in patients with nonvalvular AF for the prevention of embolic stroke. NOACs include either direct thrombin inhibitor (Dabigatran [Pradaxa]) or Factor Xa inhibitors (Rivaroxaban [Xarelto], Apixaban [Eliquis], and Edoxaban [Savaysa]).^[61,62] NOACs usually have a rapid onset and more predictable dosing compared to warfarin.

Dabigatran is direct thrombin inhibitor

The recommended dose is 150 mg twice daily for patient's creatinine clearance (CrCl) >30 mL/min and 110 mg (75 mg is only approved the USA) twice daily for patients with CrCl 15–30 mL/min [Figure 4a]. In patients with a CrCl <30 mL/min, that effect dabigatran can last >4 days. Hemodialysis can rapidly reduce the dabigatran blood concentration and anticoagulant effect for few hours.^[63,64] In perioperative management, it is recommended to hold dabigatran for 1–2 days if CrCl ≥50 mL/min, 3–5 days if the CrCl <50 mL/min for patients who may require major surgery.

Dabigatran is noninferior to warfarin in preventing systemic thromboembolism. Dabigatran has significantly lower

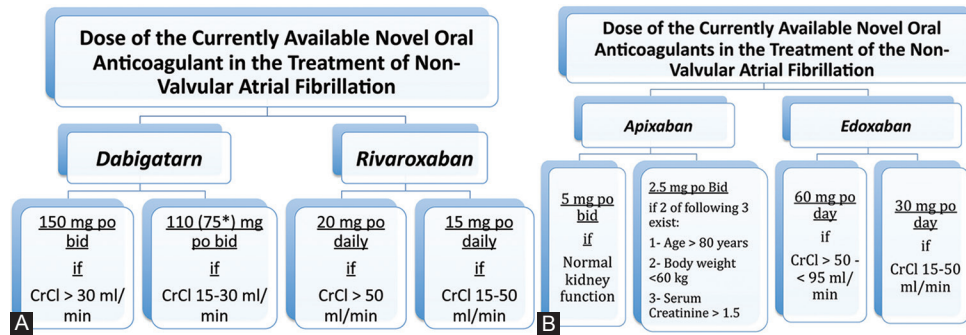


Figure 4: (A,B) Dose adjustment of the novel oral anticoagulants (NOACs) (*Approved dose in the USA) (mg: milligram; po: Oral, Bid: twice daily; CrCL: creatinine clearance; kg: Kilogram; min: minute)

incidence of hemorrhagic stroke, but a higher incidence of gastrointestinal bleeding compared to warfarin therapy.^[63]

Rivaroxaban is factor Xa inhibitor

The recommended dose is 20 mg daily for patients with CrCl >50 mL/min and 15 mg daily for patients with CrCl between 15 and 50 mL/min [Figure 4a].^[60] For perioperative management, it is recommended to hold for ≥24 h prior to surgery or consider longer times for elderly patients or high bleeding risk procedures. Rivaroxaban is noninferior to warfarin in patients with nonvalvular AF and a history of stroke or a CHADS₂ score of 2.^[65] However, significantly higher incidence of stroke or systemic embolism was observed when transitioning to warfarin therapy from rivaroxaban.^[65,66] Therefore, rivaroxaban should be continued with warfarin until a therapeutic INR is achieved.^[67] No significant difference between rivaroxaban and warfarin in regards to major or nonmajor bleeding.

Apixaban is factor Xa inhibitor

The recommended dose is 5 mg twice daily for patients with nonvalvular AF and preserved renal function. Apixaban 2.5 mg twice daily for patients with nonvalvular AF and two of the following characteristics [Figure 4b]:

- Age >80 years
- Body weight <60 kg
- Serum creatinine >1.5 mg/dl.

In perioperative management, apixaban should be held for ≥48 h for elective surgery or procedures with moderate to high bleeding risk, or ≥24 h for elective surgery or procedures with low bleeding risk. Apixaban is not only more effective than warfarin at preventing stroke, but also safer in terms of bleeding risk and risk of death.^[68] Apixaban has significantly lower rate of stroke or systemic embolism compared with the aspirin without an increase in rates of major bleeding.^[69]

Edoxaban is a factor Xa inhibitor

The recommended dose is 60 mg daily for CrCl >50 and <95 mL/min and 30 mg daily for CrCl between 15 and 50 mL/min

[Figure 4b].^[70] In perioperative management, edoxaban should be held for ≥48 h for elective surgery or procedures with moderately high bleeding risk or ≥24 h for elective surgery or procedures with low bleeding risk.^[62] Edoxaban is noninferior to warfarin with respect to the prevention of stroke or systemic embolism in patients with nonvalvular AF. Edoxaban is associated with significantly lower rates of bleeding and death from cardiovascular causes compared to warfarin.^[70]

Reversal agents of the novel oral anticoagulants

Andexanet alfa is an antidote for patients anticoagulated with apixaban and rivaroxaban. Whereas, Idarucizumab is an antidote for patients anticoagulated with dabigatran. Both agents should be utilized if patients develop major bleeding or need an emergent surgery.^[71-73]

Risk stratification for bleeding

Anticoagulant therapy carries the potential of bleeding complications; HAS-BLED score calculates the major bleeding risk utilizing clinical history in patients with AF.^[74,75] The score accounts for hypertension, abnormal liver or renal function, stroke, bleeding tendency, or diathesis, Labile INR, age >65 years, and aspirin/nonsteroidal anti-inflammatory drugs or alcohol use. Higher scores confer increased bleeding risk in a nonlinear fashion with a score of zero suggesting a bleeding rate of 0.9% per year compared to a score of 5 which predicts 9.1% annual major bleeding rate. Scores more than 5 were too rare to predict outcomes. Routine use of the (HAS-BLED and CHADS₂) scoring system should be utilized to guide the initiation of anticoagulation therapy.

Left atrial appendage closure devices

These devices are intended to prevent thromboembolism in patients with AF, who are intolerant to OAC. These devices primarily occlude the LAA with the intent to reduce the incidence of thrombus formation and thereby obviate the need for anticoagulation. Current closure devices include the WATCHMAN, the Amplatzer cardiac plug, and the LARIAT (snare device) system.^[76-78]

Summary

Due to the high prevalence of AF, almost every cardiologist and internist have a decent sized patient population with a diagnosis of AF. The initial encounter could occur during an acute and unstable hemodynamic presentation that requires an immediate DCCV then initiation of anticoagulation if not contraindicated. Systematic and detailed evaluation of the patient with stable AF should be implemented including assessment of the risk of thromboembolism, presence of CHF, tachycardia-induced cardiomyopathy, presence of preexcitation, and other comorbidities that will influence the management of AF such as sleep apnea, thyroid disorder, pulmonary disease, obesity, and diabetes mellitus.

The long-term management depends on the symptoms and the duration of AF. Less than 48 h AF could be cardioverted safely back to sinus rhythm followed with the initiation of anticoagulation therapy. Any AF of more than 48 h needs either initiation of full anticoagulation for 4 weeks followed by DCCV/pharmacologic cardioversion or initiation of full anticoagulation, then implementation transesophageal echo-guided DCCV or pharmacologic cardioversion. Drug therapy that is used for rate control strategy is guided by patient symptoms such as palpitations, decreased functional capacity, and exercise intolerance as well as tolerance to the medications. Pacemaker and AV node ablation are an alternative to rate control therapy if the patient is intolerant to the drug therapy.

AAD in rhythm control strategy is guided by the cardiac function as well as the pharmacokinetic, drug-drug interaction, and metabolism of AAD.

Ablation therapy is an alternative option for the AAD in rhythm control therapy. 2014, the HRS guidelines of evaluation and management of AF recommend ablative therapy for symptomatic AF refractory or intolerant to at least one AAD and for symptomatic AF prior to initiation of AAD therapy with an AAD.^[16] Pros and cons of anticoagulation therapy concerning Warfarin and NOACs need to be discussed with the patient in details, including the cost of the INR monitoring, dietary interaction, drug interaction, as well as the NOACs. LAA closure is also an alternative option for thromboembolic prevention therapy in patients who are intolerant to Warfarin or NOACs.

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Conflicts of interest

There are no conflicts of interest.

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