**Introduction: Atrial Fibrillation**

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice. It is estimated that AF affects over 3 million adults in the United States, with prevalence increasing with age.1 Overall AF prevalence is around 1-2% in adults under 60 years old but rises to nearly 10% in those over 80 years. AF is characterized by rapid and disorganized electrical activation of the atria, leading to ineffective atrial contraction. This results in an irregularly irregular ventricular response as impulses conduct variably through the AV node. Hemodynamic consequences include loss of atrial kick, irregular ventricular filling, and potential for tachycardia-mediated cardiomyopathy. AF may be classified as first detected, paroxysmal, persistent, or permanent based on duration of arrhythmogenic episodes.

**Clinical Presentation**

The clinical manifestations of AF span a wide spectrum. Some patients are completely asymptomatic while others experience severe, debilitating symptoms related to rate, irregularity, and loss of atrial contraction:

* Palpitations
* Dyspnea
* Fatigue
* Dizziness
* Chest pain
* Polyuria
* Exercise intolerance

Symptoms like palpitations and dyspnea correlate with higher ventricular rates. Rapid, uncontrolled rates can precipitate myocardial ischemia, heart failure exacerbation, hypotension, and cardiomyopathy. Irregular R-R intervals also reduce cardiac output. Loss of atrial kick further compromises hemodynamics, especially in patients with diastolic dysfunction or conditions like mitral stenosis that rely heavily on atrial contraction.

* Risk factors: hypertension, obesity, smoking, cardiac disease, diabetes, chronic kidney disease, alcohol consumption, sleep apnea
* Signs: irregularly irregular pulse, rapid ventricular response

**Pathophysology**

Normal sinus rhythm depends on organized activation of the atria originating from the sinoatrial node and conduction to the ventricles through the AV node. This synchronized pattern is disrupted in AF. Rapid, disorganized electrical activity overwhelms the sinoatrial node and spreads continuously through the atrial myocardium in a chaotic manner. The irregular fibrillatory waves of AF prevent coordinated atrial contraction, reducing atrial emptying. Variable AV nodal conduction results in an irregular ventricular response, compromising cardiac output. Loss of atrial kick and irregular R-R intervals both contribute to hemodynamic impairment. Heart rate also becomes less responsive to autonomic modulation. Over time, persistent AF leads to electrical and structural remodeling of the atria, perpetuating the arrhythmia.

AF results from a complex interplay of triggers, substrate, and modulating factors. Ectopic foci near the pulmonary veins and superior vena cava provide triggers. Atrial stretch, fibrosis, conduction slowing, and tissue inflammation create an arrhythmogenic substrate. Autonomic tone, ischemia, valvular disease, endocrine factors, genetics, and lifestyle issues modulate AF risk.

### ****Diagnostic Approach****

The diagnosis of AF requires documentation of the arrhythmia on ECG, which will show the characteristics of an irregularly irregular rhythm with no discernible P waves.

Additional diagnostic evaluation aims to determine the onset, type, underlying causes, and hemodynamic impact of AF. Key components include:

* History and physical exam to elicit duration and nature of symptoms, precipitating factors, medical history, cardiovascular exam findings.
* 12-lead ECG to confirm diagnosis and evaluate ventricular rate, intervals, preexcitation.
* Assessment of vital signs including heart rate and blood pressure.
* Lab tests:
  + Complete blood count, electrolytes, renal function tests, thyroid function tests, cardiac enzymes and BNP to uncover contributing factors
  + Coagulation studies if anticoagulation is being considered
* Chest x-ray to evaluate heart size and pulmonary congestion
* Echocardiography to evaluate chamber sizes, left ventricular function, valvular disease.
* Additional cardiac imaging (eg, CT, MRI) may be warranted in certain cases to further evaluate anatomy and function.
* Ambulatory ECG monitoring to document pattern (paroxysmal, persistent) and burden of AF

The evaluation aims to determine the type of AF (first detected, paroxysmal, persistent, long-standing persistent), identify reversible precipitating causes, assess stroke and bleeding risks using CHA2DS2-VASc and HAS-BLED scores respectively, and evaluate the need for further monitoring.

Management Overview

### ****Management - Overview****

* The acute management priorities for AF are assessing hemodynamic stability, controlling ventricular rate, considering options for rhythm control when appropriate, and initiating anticoagulation based on stroke risk.

* Rate control involves use of AV nodal blocking agents to achieve a target heart rate of <110 bpm at rest for asymptomatic patients or <80 bpm for symptomatic patients.

* Rhythm control is achieved with electrical cardioversion or pharmacological cardioversion using antiarrhythmic medications. This is indicated for patients who remain symptomatic despite adequate rate control or in hemodynamically unstable patients.

* Anticoagulation with warfarin or direct oral anticoagulants reduces the risk of stroke and systemic embolism. The decision is based on stroke risk stratification using CHA2DS2-VASc score.

Beyond the acute setting, the goals also include managing comorbidities, reducing AF burden, and preventing recurrences. Ablation procedures may be considered when antiarrhythmic medications fail to maintain sinus rhythm.

### ****Pharmacotherapy****

#### Rate Control

Beta-blockers

* Mechanism: Reduce conduction through the AV node by inhibiting beta-1 adrenergic receptors. Also provide cardioprotective benefits.
* Metoprolol:
  + Dose: 2.5-5 mg IV bolus over 2-5 minutes, repeat every 5 minutes for a total of 3 doses
  + Onset: 5-10 minutes, duration 6-8 hours
  + Adverse effects: Hypotension, bronchospasm, worsened heart failure
* Esmolol:
  + Dose: 500 mcg/kg IV bolus over 1 minute followed by 50-200 mcg/kg/min infusion
  + Onset: 2 minutes, duration 10-20 minutes
  + Adverse effects: Hypotension, bronchospasm

Calcium channel blockers

* Mechanism: Inhibit AV nodal conduction by blocking L-type calcium channels
* Diltiazem
  + Dose: 0.25 mg/kg IV bolus over 2 minutes, may repeat with 0.35 mg/kg after 15 minutes up to total dose of 1 mg/kg
  + Onset: 2-7 minutes, duration up to 4 hours
  + Adverse effects: Hypotension, worsened heart failure
* Verapamil
  + Dose: 2.5-5 mg IV over 2 minutes, may repeat with 5-10 mg after 15 minutes up to total dose of 20 mg
  + Onset: 3-5 minutes, duration 1-6 hours
  + Adverse effects: Hypotension, high-degree AV block

Digoxin

* Mechanism: Vagal mediated reduction in SA and AV nodal conduction
* Dose: 0.25 mg IV, may repeat 0.25 mg every 6 hours up to 1.5 mg daily
* Onset: 30-120 minutes, duration 6-8 hours
* Adverse effects: AV block, digoxin toxicity
* May be less effective in high adrenergic states
* Useful in heart failure patients

Amiodarone

* Mechanism: Potassium channel blockade prolongs repolarization. Also exerts beta blockade and mild calcium channel inhibition.
* Dose: 150 mg IV over 10 minutes, then 1 mg/min infusion for 6 hours
* Onset: 5-15 minutes when given IV
* Adverse effects: Hypotension, bradycardia, phlebitis with IV infusion

#### **Rhythm Control**

Electrical Cardioversion

* Delivers synchronized direct current shock using paddles or patches
* Recommended starting dose: 100 J biphasic
* Success rate around 90%
* Sedation recommended prior to procedure
* Resume anticoagulation immediately after procedure

Antiarrhythmic Medications

Flecainide

* Dose: Single oral dose 200-300 mg
* Mechanism: Sodium channel blockade slowing conduction velocity
* Efficacy around 60-80% in recent-onset AF
* Contraindicated in structural heart disease

Propafenone

* Dose: Single oral dose 450-600 mg
* Mechanism: Sodium channel blockade slowing conduction velocity
* Efficacy similar to flecainide
* Contraindicated in structural heart disease

Amiodarone

* Dose: 600 mg daily oral loading for 4 weeks, then 200 mg daily maintenance
* Mechanism: Multichannel (sodium, potassium, calcium channel) blocker
* Useful when structural heart disease present
* Slow onset limits utility for acute conversion

Ibutilide

* Dose: 1-2 mg IV over 10 minutes
* Mechanism: Potassium channel blockade prolonging repolarization
* Efficacy around 50% for acute conversion
* QT prolongation and torsades de pointes are primary risks
* Requires inpatient monitoring during administration

Procainamide: 15-18 mg/kg IV over 30-60 minutes

* Class Ia antiarrhythmic, sodium channel blocker
* Hypotension is primary adverse effect
* Avoid in structural heart disease

#### Anticoagulation

* Before cardioversion, patients with AF of 48 hours duration or longer should be anticoagulated for at least 3 weeks prior with warfarin (INR 2-3) or DOACs.
* After successful cardioversion back to normal sinus rhythm, anticoagulation should be continued for at least 4 more weeks regardless of stroke risk. This allows time for atrial mechanical function to recover.
* For patients undergoing cardioversion of AF less than 48 hours duration, anticoagulation is started as soon as possible but 3 weeks of pretreatment is not needed.
* If a thrombus is seen on transesophageal echocardiogram (TEE) prior to planned cardioversion, the procedure should be postponed and anticoagulation continued for several more weeks until resolution.

**Long Term Anticoagulation**  
Decisions about long-term anticoagulation after cardioversion are based on the patient's stroke risk (CHA2DS2-VASc score), not on whether they are in sinus rhythm. Anticoagulation is recommended for most patients with atrial fibrillation to reduce the risk of ischemic stroke and other thromboembolic events. The decision to initiate anticoagulation is based on the patient's stroke risk, which can be assessed using the CHA2DS2-VASc score. Patients with a score ≥2 in males or ≥3 in females should receive oral anticoagulation.

The benefits of anticoagulation typically outweigh the increased bleeding risk. However, the bleeding risk should also be evaluated using the HAS-BLED score. While a high HAS-BLED score identifies patients at elevated bleeding risk, it should not be used alone to exclude patients from anticoagulation. Additional risk factors like frequent falls, comorbidities, and patient preferences should be considered.

**CHA2DS2VASc**

|  |  |
| --- | --- |
| Risk Factor | Points |
| Congestive heart failure | 1 |
| Hypertension | 1 |
| Age ≥75 | 2 |
| Diabetes mellitus | 1 |
| Prior stroke or TIA | 2 |
| Age 65-74 | 1 |
| Vascular disease\* | 1 |
| Sex category (female) | 1 |

\*Prior MI, PAD, or aortic plaque

Recommend anticoagulation if score ≥2 for males, ≥3 for females

**HAS-BLED Risk Score**

|  |  |
| --- | --- |
| Risk Factor | Points |
| Hypertension | 1 |
| Abnormal renal/liver function | 1 each |
| Stroke | 2 |
| Bleeding | 1 |
| Labile INRs | 2 |
| Elderly (Age >65 yea old) | 1 |
| Drugs (antiplatelets/NSAID) /alcohol (> 8 drinks) | 1 each |
|  |  |

**Score ≥3 indicates high risk for bleeding with anticoagulation**

**Specific Oral Anticoagulant Agents**

Warfarin

* Target INR 2-3
* Dose adjusted based on INR monitoring to maintain therapeutic range
* Lower INR target of 2-2.5 appropriate for low thromboembolic risk settings like post-cardioversion or post-ablation
* TTR should be >70% for optimal efficacy and safety
* PK
  + Half life: 40 hr
  + CYP2C9 primary, (CYP3A4, 1A2, 2C19 minor pathways)
  + Elimination: Renal, primarily as metabolites
* Initiate along with overlapping parenteral anticoagulant (heparin) in high thromboembolic risk patients
* Food and drug interactions require close monitoring
* Regular INR testing needed (weekly after initiation, every 4-6 weeks once stable)
* Reversal agents available (vitamin K, 4-factor PCC)

Apixaban

* Direct factor Xa inhibitor
* Dose: 5 mg PO BID
* PK
  + Half life: 12 hr
  + Renal (27% unchanged drug)
  + Metabolized, primarily by CYP3A4
  + P-gp substrate
* Dose reduction to 2.5 mg PO BID if ≥2 of: age ≥80, weight ≤60 kg, Cr ≥1.5 mg/dL
* No dose adjustment if Cr ≥15 mL/min
* Lower drug interaction potential than other DOACs
* Lower  bleeding risk compared to warfarin

Rivaroxaban

* Direct factor Xa inhibitor
* Dose: 20 mg PO daily with evening meal
* Reduce dose to 15 mg PO daily if CrCl 15-50 mL/min
* Avoid if CrCl <15 mL/min
* PK
  + Half life: 5-9 hr, 11-13 hr in elderly
  + Elimination: Renal (36% unchanged drug)
  + Metabolized, primarily by CYP3A4 and CYP2J2
  + P-gp substrate
* Lower major bleeding risk compared to warfarin
* Higher drug interaction potential than other DOACs
* Once daily dosing may improve compliance over warfarin

Dabigatran

* Direct thrombin inhibitor
* Dose: 150 mg PO BID
* Reduce dose to 75 mg PO BID if CrCl 15-30 mL/min
* Avoid if CrCl <15 mL/min
* PK
  + Half life:12-17 hr, up to 27 hr in renal failure
  + Over 80% cleared by the kidney
  + P-gp substrate
* Adverse effect: Dyspepsia
* Reversal agent available (idarucizumab)
* Capsules should not be crushed or chewed
* Higher GI bleeding risk compared to warfarin
* Lower drug interaction potential than warfarin or rivaroxaban

Edoxaban

* Direct factor Xa inhibitor
* Dose: 60 mg PO daily
* Reduce dose to 30 mg PO daily if: CrCl 15-50 mL/min, weight <60 kg, or using P-gp inhibitors
* Avoid if CrCl >95 mL/min or <15 mL/min
* PK
  + Half life: 10-14 hr
  + 50% cleared by the kidney
  + Undergoes minimal CYP metabolism
* Once daily dosing may improve compliance
* Lower GI bleeding risk than other DOACs
* Minimal drug interactions

### ****Tips for Board Exam Questions:****

* Stroke Risk Scores - Know that a CHA2DS2-VASc score of ≥2 for men or ≥3 for women indicates the need for anticoagulation.

* Anticoagulation - For most patients, choose a DOAC (apixaban, rivaroxaban, edoxaban, dabigatran) over warfarin for stroke prevention based on trials like ARISTOTLE and ENGAGE-AF.

* Rate vs. Rhythm Control - Remember that rate control has equal mortality to rhythm control in AF from the AFFIRM trial. Choose rate control.
* Rate Control Drugs - For rate control, pick beta-blockers or non-DHP CCBs as first-line agents over digoxin or amiodarone.

* Cardioversion - If a patient undergoes cardioversion, oral anticoagulation is needed for at least 3 weeks before and 4 weeks after the procedure.

### ****Key Guidelines and Evidence****

* American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) Guidelines for the Management of Patients with Atrial Fibrillation:
  + Rate Control - In hemodynamically stable patients without an accessory pathway, an intravenous (IV) beta-blocker (e.g. metoprolol) or non-dihydropyridine calcium channel blocker (e.g. diltiazem) is recommended for acute rate control.
  + Rhythm Control - For pharmacologic cardioversion of acute AF, a class Ic antiarrhythmic like propafenone or flecainide is recommended, or dofetilide/ibutilide in patients without structural heart disease. Amiodarone can also be considered.
  + Anticoagulation - Anticoagulation with heparin or low molecular weight heparin is recommended as soon as possible for AF greater than 48 hours or of unknown duration before cardioversion.
  + Cardioversion - If rapid pharmacologic cardioversion is unsuccessful or not feasible, electrical cardioversion should be performed. This also allows cardioversion without prolonged anticoagulation.
  + Maintenance of Sinus Rhythm - After successful cardioversion, an oral antiarrhythmic like amiodarone, dofetilide, dronedarone, flecainide, propafenone, or sotalol can be considered for maintaining sinus rhythm depending on the presence of structural heart disease.

* Key Studies
  + RE-LY
    - In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.
  + ROCKET AF
    - In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.
  + Hasbrouck M, Nguyen TT. Acute management of atrial fibrillation in congestive heart failure with reduced ejection fraction in the emergency department. Am J Emerg Med. 2022 Apr 6;58:39-42.
    - In HFrEF patients with AF, there was no difference in total adverse events in patients treated with IV diltiazem compared to metoprolol. However, the diltiazem group had a higher incidence of worsening CHF symptoms defined as increased oxygen requirement within four hours or initiation of inotropic support within 48 h.

### ****Clinical Scenarios****

* Scenario 1:
  + A 65-year-old male presents to the emergency department with palpitations and lightheadedness. His ECG shows irregularly irregular rhythm with absence of P waves. He has a history of hypertension and well-controlled diabetes. After initial stabilization, what is the most appropriate pharmacotherapy for this patient's atrial fibrillation?

* Answer and Explanation
  + The most appropriate pharmacotherapy for a patient with atrial fibrillation (AF) depends on several factors, including the patient's underlying medical conditions and the presence of symptoms. In this scenario, the patient is experiencing palpitations and lightheadedness, indicating that his AF may be causing hemodynamic instability. Therefore, the primary goal of treatment is to control the patient's heart rate and prevent further complications.

* The recommended first-line pharmacotherapy for controlling heart rate in AF is a beta-blocker, such as metoprolol or esmolol. Beta-blockers slow down the heart rate by blocking the effects of adrenaline on the heart. They are also effective in reducing symptoms and improving exercise tolerance in patients with AF.

* If the patient's heart rate is not adequately controlled with a beta-blocker, other options include calcium channel blockers, such as diltiazem or verapamil, or digoxin. These drugs also slow down the heart rate but work through different mechanisms.
* It is important to note that in certain cases, such as when the patient has underlying heart disease, more aggressive rhythm control strategies may be necessary, such as cardioversion or antiarrhythmic drugs. However, in this scenario, the primary goal is to control the patient's heart rate and stabilize his symptoms.
* In summary, the most appropriate pharmacotherapy for this patient's AF is a beta-blocker, such as metoprolol or esmolol, to control his heart rate and improve his symptoms.

### ****Summary:****

* Atrial Fibrillation is prevalent and clinically significant conditions in cardiology. Clinical pharmacists play a critical role in the management of these arrhythmias, ensuring optimal treatment outcomes for patients. Understanding the clinical presentation, pathophysiology, diagnostic approach, pharmacotherapy, and key guidelines is essential for providing comprehensive care.
* Atrial Fibrillation can present with a range of symptoms, including palpitations, irregular heart rate, shortness of breath, and syncope. Several risk factors, such as advanced age, hypertension, and structural heart disease, contribute to their development. Key guidelines, such as ACC/AHA/HRS and ESC guidelines, provide evidence-based recommendations for the management of atrial fibrillation.

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