Atrial Fibrillation, Diagnosis and Initial Treatment

Basic Information

Terminology

- Atrial fibrillation is a supraventricular tachyarrhythmia characterized by chaotic, disorganized electrical activation and inefficient atrial contraction

Epidemiology

- Atrial fibrillation is the most common sustained cardiac arrhythmia, with a worldwide prevalence of more than 37 million (0.5% of the global population)[1]
- Incidence and prevalence have risen steadily over the past 20 years, and they are projected to continue to rise[1]

Etiology and Risk factors

Etiology

- Atrial fibrillation episodes are initiated by premature atrial complexes
    - Typically originate in the pulmonary veins (called *pulmonary vein triggers*)
    - May also come from the other structures (called *non–pulmonary vein triggers*[2]), including:
        - Right atrium
        - Superior vena cava
        - Posterior wall of left atrium
        - Vein of Marshall
        - Left atrial appendage

Risk Factors

- Risk factors for atrial fibrillation
    - Cardiac factors
        - Hypertension
        - Coronary artery disease

- Heart failure
- Hypertrophic cardiomyopathy

- Extracardiac factors
  - Obesity
  - Metabolic syndrome
  - Sleep apnea
  - Diabetes mellitus
  - Excessive alcohol consumption
  - Hyperthyroidism

- Genetic factors
  - Sometimes familial
    - Patterns of autosomal dominant inheritance have been described in some families[3]
    - Numerous genetic mutations have been linked to atrial fibrillation, including:
      - Ion channel mutations (sodium and potassium channels)
      - Non–ion channel mutations (eg, lamin, connexin, ryanodine receptor, cardiac transcription factors)[3]
  - European ancestry is a risk factor[4]
- Advancing age

Diagnosis

Approach to Diagnosis

- Presence is suggested by findings on physical examination and confirmed by ECG

Staging or Classification

- Classified according to predominant duration of episodes
  - Paroxysmal (terminating spontaneously or by intervention in less than 7 days)
  - Persistent (more than 7 days, often requiring direct-current cardioversion)

- Long-standing persistent (continuous atrial fibrillation for 1 year or longer)
- Permanent (accepted as long-term by the patient and physician, with no plans to pursue rhythm control)

Workup

History

- Symptoms may include:
  - Palpitations
  - Dyspnea
  - Lightheadedness
  - Reduced exercise tolerance
  - Fatigue
  - Syncope
- Patients may be asymptomatic or have subtle symptoms during atrial fibrillation including decreased exercise tolerance and energy levels, which they recognize only in retrospect after restoration of sinus rhythm
- Atrial fibrillation increases risk of stroke, which is sometimes the initial presentation
  - Ischemic strokes related to atrial fibrillation have high morbidity and mortality[5]
- Atrial fibrillation may cause a tachycardia-mediated cardiomyopathy, in which case symptoms of left ventricular dysfunction may be present (eg, dyspnea, orthopnea, paroxysmal nocturnal dyspnea)
- Syncope due to atrial fibrillation with rapid ventricular rates is possible but not common
  - Atrial fibrillation commonly coexists with sinus node dysfunction and such patients may have syncope or near-syncope caused by sinus pauses upon termination of atrial fibrillation (“tachy-brady” syndrome[6])

Physical Examination

- Typical physical findings include:
  - Irregularly irregular pulse

- Apical-radial pulse deficit may occur in atrial fibrillation with rapid ventricular response
- Variable intensity of the first heart sound (S1)

- May have signs of congestive heart failure if associated with left ventricular systolic dysfunction (eg, peripheral edema, jugular venous distension, lung crackles)
- If the atrial fibrillation is related to valvular heart disease, systolic or diastolic murmurs may be audible
- If atrial fibrillation is secondary to hyperthyroidism, physical signs of hyperthyroidism may be present, including:
  - Tremor
  - Low BMI
  - Goiter
  - Thyroid eye disease

Diagnostic Procedures

- ECG confirms diagnosis: irregularly irregular intervals between QRS complexes and no organized p waves (only fibrillatory waves)

Laboratory Tests

- Routine laboratory tests should be performed, including:
  - CBC
  - Basic metabolic panel
  - Thyroid function tests

Imaging Studies

- Chest radiograph to assess for cardiomegaly, pulmonary congestion, and consolidation
- Transthoracic echocardiography to assess left ventricular size and function, assess left atrial size, and check for presence of valvular disease

Other Diagnostic Tools

- After initial diagnosis of atrial fibrillation, some form of continuous monitoring is usually established to distinguish whether pattern of atrial fibrillation is paroxysmal or persistent, which informs further management
  - If the patient is receiving in-patient hospital treatment, this may be performed with cardiac telemetry

- For patients undergoing outpatient evaluation, ambulatory monitoring is performed (such as Holter or other external loop recorder)
- Consider stress testing particularly if there is left ventricular systolic dysfunction or for screening for coronary artery disease if use of a class 1C antiarrhythmic drug is planned
- Perform invasive coronary angiography if stress testing or history prompts concern for myocardial ischemia

Differential Diagnosis

Table 1. Differential diagnosis.*

Condition	Description	Differentiated by
Premature atrial complexes	Premature or extra atrial beats originating outside sinus node will cause irregular pulse	ECG showing premature p waves of different morphology than sinus p waves
Premature ventricular complexes	Premature or extra beats originating in the right or left ventricles will cause irregular pulse	ECG showing premature beats that are not preceded by p waves and have different QRS morphology than conducted beats
Premature junctional complexes	Premature or extra beats originating from the region of the AV node/proximal His bundle will cause irregular pulse	ECG showing premature beats which have QRS morphology similar to conducted beats Usually not preceded by a p wave, but there may be a retrogradely conducted p wave

Atrial flutter or atrial tachycardia with variable AV conduction	Variability in the AV conduction of an atrial flutter or tachycardia will cause irregular pulse	ECG showing atrial flutter waves or abnormal p waves of atrial tachycardia, with variable conduction to the ventricle
Second-degree AV block	Intermittent nonconduction of sinus atrial beats to the ventricles will cause irregular pulse	ECG showing sinus p waves with intermittent AV block that may be preceded by PR prolongation (Mobitz type I, Wenckebach), or occur without PR prolongation (Mobitz type II)

AV, atrioventricular.

*Ectopy or second-degree atrioventricular block also cause pulse irregularities. Perform ECG to confirm atrial fibrillation (irregularly irregular QRS complexes with underlying fibrillatory waves and the absence of organized p waves).

Treatment

Approach to Treatment:

- Treatment of atrial fibrillation usually includes anticoagulation (depending on stroke risk), rate control, and/or rhythm control **(Figure 1)**
    - Anticoagulation
        - Strokes related to atrial fibrillation lead to greater mortality and disability than other forms of ischemic stroke[5]; therefore, assessment of stroke risk is a pillar of atrial fibrillation management
        - CHA_2DS_2-VASc is calculated by applying 1 or 2 points for several factors **(Table 2)**

Table 2. CHA_2DS_2-VASc score.

Component of CHA_2DS_2-VASc	Points assigned
Congestive heart failure (C)	1
Hypertension (H)	1
Age 75 or older (A_2)	2
Diabetes (D)	1
Stroke or transient ischemic attack (S)	2
Vascular disease	1
Age 65 to 74 (A)	1
Sex category, female (Sc)	1
Scoring	
- Score 0: do not anticoagulate - Score 1: consider anticoagulation - Score 2 or greater: anticoagulate	

- When assessing the risks and benefits of initiating oral anticoagulation, the HAS-BLED score can be applied to estimate the likelihood of major bleeding **(Table 3)**

Table 3. HAS-BLED score.

Component of HAS-BLED score	Points assigned

Uncontrolled hypertension (greater than 160 mm Hg systolic)	1
Renal disease (dialysis, transplant, or creatinine level greater than 2.26 mg/dL or 200 µmol/L)	1
Liver disease (cirrhosis or bilirubin greater than 2 times reference range with AST/ALT/AP greater than 3 times reference range)	1
Stroke history	1
Previous major bleeding or predisposition to bleeding	1
Labile INR (unstable/high INRs, time in therapeutic range less than 60%)	1
Age older than 65 years	1
Medication use that predisposes patient to bleeding (aspirin, clopidogrel, NSAIDs)	1
Alcohol use (8 or greater drinks/week)	1
Scoring	
- If score is less than 3, the bleeding risk is considered low or moderate	

- If score is 3 or greater, the bleeding risk is considered high and alternatives to anticoagulation should be considered[7]

- Agents for oral anticoagulation include:
  - Warfarin
  - Direct oral anticoagulants (ie, apixaban, rivaroxaban, dabigatran, and edoxaban)
    - At least noninferior to warfarin at reducing stroke and have lower rates of significant bleeding events, as demonstrated in 4 randomized controlled trials [8-11]
    - Considered preferable to warfarin except in patients with moderate or greater mitral stenosis or mechanical valve replacements in whom warfarin should be used[12]
- For patients with increased atrial fibrillation–related stroke risk who have significant contraindications to long-term oral anticoagulation, consider percutaneous or surgical occlusion of the left atrial appendage (the main source of atrial fibrillation–related cardioembolism)[12]

- Percutaneous left atrial appendage occlusion (with the Watchman device) has been compared with warfarin in patients with atrial fibrillation (in the absence of moderate or greater mitral stenosis or a mechanical heart valve) who are at increased risk of stroke in 2 randomized controlled trials[13,14]
  - A meta-analysis of data from these 2 trials has shown that patients receiving the Watchman device had significantly fewer hemorrhagic strokes than those receiving warfarin, but there was an increase in ischemic strokes in the device group
    - However, when periprocedural events were excluded, the difference in ischemic strokes was not significant[15]
  - Currently, complying with a period of periprocedural oral anticoagulation is mandated for patients undergoing percutaneous left atrial appendage occlusion, but randomized controlled trials are being performed using antiplatelet-only regimens[16]

- Rhythm control and rate control

- Management strategies include rhythm control (restore and maintain sinus rhythm) or rate control (accept atrial fibrillation and control the ventricular rate)
- Rhythm control may be achieved by the use of antiarrhythmic drugs, ablation, or a combination of both
    - For persistent atrial fibrillation:
        - Cardioversion is the first step to restore sinus rhythm
        - Rhythm control strategies are used to maintain sinus rhythm after cardioversion
- Rate control may be achieved by drug therapy to control the ventricular rate during atrial fibrillation
- If atrial fibrillation is symptomatic, rhythm control is preferred
- In atrial fibrillation of recent (less than 12 months) onset, rhythm control is associated with superior outcomes (regardless of symptom complex)[17]
- Atrial fibrillation and heart failure frequently coexist
    - If atrial fibrillation is associated with left ventricular systolic dysfunction, rhythm control is preferred
        - Restoration and maintenance of sinus rhythm may improve and even normalize left ventricular systolic function in patients with tachycardia-mediated cardiomyopathy, as well as improve quality of life[18,19]
        - Trials have demonstrated such improvements at left ventricular ejection fraction less than 45%,[19] but in clinical practice any degree of systolic dysfunction is considered significant and a rhythm control strategy should be considered

- If atrial fibrillation is longstanding, asymptomatic, and not associated with left ventricular systolic dysfunction, rate control is an acceptable alternative to rhythm control
- In patients where the duration of atrial fibrillation is unclear and the patient cannot identify any specific associated symptoms, a trial of cardioversion to restore sinus rhythm is helpful to ascertain whether sinus rhythm improves quality of life
    - If patient feels better in sinus rhythm, then continued rhythm control strategy to maintain sinus rhythm is indicated

Drug Therapy

- Rate control: β-blockers, calcium channel blockers, digoxin
- Rhythm control: class 1C agents (flecainide, propafenone), class III agents (sotalol, dofetilide, amiodarone, dronedarone)
    - Important considerations when selecting an antiarrhythmic drug include:
        - Presence of structural heart disease, which precludes use of class 1C agents
        - Presence of renal dysfunction, which requires careful monitoring and dose adjustment for sotalol and dofetilide
    - Preferably, long-term use of amiodarone is avoided in younger patients owing to potential for cumulative organ toxicity (particularly thyroid, liver, and lungs)

Table 4. Drug Therapy: Rate control in atrial fibrillation.*

Medication	Therapeutic use	Dosage†	Safety concerns	Notable adverse reactions	Special considerations
β-blockers					
Atenolol	First line agent in patients with concomitant hypertension or HFpEF[D1,D2] Oral medications may be administered in hemodynamically stable patients with rapid ventricular response[D1]	Usual dose: 25-100 mg PO once daily[D1,D2] Max dose, CrCl ≥ 35 mL/minute/1.73 m^2: 100-200 mg/day Max dose, CrCl = 15-35 mL/minute/1.73 m^2: 50 mg/day Max dose, CrCl < 15 mL/minute/1.73 m^2: 25 mg/day[D3]	Contraindicated in patients with significant bradycardia, second- or third-degree heart block, decompensated heart failure, or cardiogenic shock[D3] Abrupt discontinuation may result in severe exacerbations of angina, MI, and/or ventricular arrhythmia[D3] May acutely worsen heart failure[D3] β-blockers may mask signs and symptoms of hypoglycemia and	Bradycardia Dizziness Fatigue Hyperkalemia Hypotension[D3,D5]	Cardioselective[D2,D3]

			hyperthyroidism[D3] Use with caution in patients with renal impairment, bronchospastic disease, peripheral vascular disease, or pheochromocytoma[D3, D4]		
Bisoprolol	First line agent in patients with concomitant hypertension or heart failure (HFpEF or HFrEF)‡[D1,D2] Oral medications may be administered in hemodynamically stable patients with rapid ventricular response[D1]	Usual dose: 1.25-20 mg PO once daily[D1,D2] Adjust dose for CrCl ≤ 40 mL/minute or hepatic impairment[D4]	Contraindicated in patients with significant bradycardia, second- or third-degree heart block, decompensated heart failure, and cardiogenic shock[D4] Abrupt discontinuation may result in severe exacerbations of angina, MI, and/or ventricular arrhythmia[D4] May acutely worsen heart failure[D4] β-blockers may mask	Bradycardia Dizziness Fatigue Hyperkalemia Hypotension[D4,D5]	Cardioselective[D2,D4]

			signs and symptoms of hypoglycemia and hyperthyroidism[D3,D4] Use with caution in patients with renal impairment, hepatic impairment, bronchospastic disease, peripheral vascular disease, and pheochromocytoma[D3, D4]		
Carvedilol	First line agent in patients with concomitant hypertension or heart failure (HFpEF or HFrEF)‡[D1,D2] Oral medications may be administered in hemodynamically stable patients with rapid ventricular response[D1]	Usual dose: 3.125-50 mg PO twice daily[D1,D2]	Contraindicated in patients with asthma, significant bradycardia, second- or third-degree heart block, sick sinus syndrome, decompensated heart failure, cardiogenic shock, and severe hepatic impairment[D6] Abrupt discontinuation may result in severe exacerbations of angina, MI, and/or ventricular arrhythmia[D6]	Bradycardia Dizziness Fatigue Hyperkalemia Hypotension[D6,D5]	Nonselective β-blocker with α_1-blocking activity[D6] Dizziness and other adverse reactions may occur at a higher rate in patients who are poor metabolizers of CYP2D6 due to higher plasma drug concentrations[D6]

			May acutely worsen heart failure[D6] β-blockers may mask signs and symptoms of hypoglycemia and hyperthyroidism[D6] Use with caution in patients with bronchospastic disease, peripheral vascular disease, pheochromocytoma, and Prinzmetal variant angina[D6] Drug interactions: may need to avoid or adjust dosage of certain drugs[D6]		
Esmolol	First line agent for rapid control in patients without preexcitation and with concomitant hypertension or heart failure (HFpEF or HFrEF), in the acute setting[D1,D2]	500 mcg/kg IV bolus, then 50-300 mcg/kg/minute continuous IV infusion[D1,D2,D5]	Contraindicated in patients with significant bradycardia, second- or third-degree heart block, sick sinus syndrome, decompensated heart failure, cardiogenic shock, and pulmonary	Bradycardia Dizziness Fatigue Hyperkalemia Hypotension Infusion site reactions[D5]	Cardioselective[D2,D5]

	IV β-blockers are recommended to slow RVR in patients with ACS and no evidence of heart failure, hemodynamic instability, or bronchospasm[D1]		hypertension[D5] Abrupt discontinuation may result in severe exacerbations of angina, MI, and/or ventricular arrhythmia[D5] May acutely worsen heart failure[D5] β-blockers may mask signs and symptoms of hypoglycemia and hyperthyroidism[D5] Use with caution in patients with hypovolemia, bronchospastic disease, peripheral vascular disease, and pheochromocytoma[D5] Drug interactions: may need to avoid or adjust dosage of certain drugs[D5]		

Metoprolol tartrate, oral immediate-release	First line agent in patients with concomitant hypertension or HFpEF[D1,D2] Oral medications may be administered in hemodynamically stable patients with rapid ventricular response[D1]	Usual dose: 25-100 mg PO twice daily[D1,D2] Adjust dose for hepatic impairment[D7]	Contraindicated in patients with significant bradycardia, second- or third-degree heart block, sick sinus syndrome, decompensated heart failure, cardiogenic shock, and severe peripheral vascular disease[D7] Abrupt discontinuation may result in severe exacerbations of angina, MI, and/or ventricular arrhythmia[D7] May acutely worsen heart failure[D7] β-blockers may mask signs and symptoms of hypoglycemia and hyperthyroidism[D7] Use with caution in patients with hepatic impairment,	Bradycardia Dizziness Fatigue Hyperkalemia Hypotension[D5,D7]	Cardioselective[D2,D7] Cardioselectivity is decreased in poor metabolizers of CYP2D6 due to higher plasma drug concentrations[D7]

			bronchospastic disease, and pheochromocytoma[D7]		
Metoprolol tartrate, intravenous	First line agent for rapid control in patients without preexcitation and with concomitant hypertension or heart failure (HFpEF or HFrEF), in the acute setting[D1,D2] IV β-blockers are recommended to slow RVR in patients with ACS and no evidence of heart failure, hemodynamic instability, or bronchospasm[D1]	2.5-5 mg IV bolus; may repeat 3 times as needed[D1,D2] Adjust dose for hepatic impairment[D8]	Contraindicated in patients with significant bradycardia, second- or third-degree heart block, and decompensated heart failure[D8] Abrupt discontinuation may result in severe exacerbations of angina, MI, and/or ventricular arrhythmia[D8] May acutely worsen heart failure[D8] β-blockers may mask signs and symptoms of hypoglycemia and hyperthyroidism[D8] Use with caution in patients with hepatic impairment, bronchospastic	Bradycardia Dizziness Fatigue Hyperkalemia Hypotension[D5,D8]	Cardioselective[D2,D8] Cardioselectivity is decreased in poor metabolizers of CYP2D6 due to higher plasma drug concentrations[D8]

			disease, peripheral vascular disease, and pheochromocytoma[D5, D8]		
Metoprolol succinate, oral extended-release	First line agent in patients with concomitant hypertension or heart failure (HFpEF or HFrEF)‡[D1,D2] Oral medications may be administered in hemodynamically stable patients with rapid ventricular response[D1]	Usual dose: 50-400 mg PO once daily[D1,D2] Adjust dose for hepatic impairment[D9]	Contraindicated in patients with significant bradycardia, second- or third-degree heart block, sick sinus syndrome, decompensated heart failure, and cardiogenic shock[D9] Abrupt discontinuation may result in severe exacerbations of angina, MI, and/or ventricular arrhythmia[D9] May acutely worsen heart failure[D9] β-blockers may mask signs and symptoms of hypoglycemia and hyperthyroidism[D9] Use with caution in	Bradycardia Dizziness Fatigue Hyperkalemia Hypotension[D5,D9]	Cardioselective[D2,D9] Cardioselectivity is decreased in poor metabolizers of CYP2D6 due to higher plasma drug concentrations[D9]

			patients with hepatic impairment, bronchospastic disease, peripheral vascular disease, and pheochromocytoma[D9]		
Nadolol	First line agent in patients with concomitant hypertension or HFpEF[D1,D2] Oral medications may be administered in hemodynamically stable patients with rapid ventricular response[D1]	Usual dose: 10-240 mg PO once daily[D1] Adjust dose for CrCl ≤ 50 mL/minute[D10]	Contraindicated in patients with asthma, significant bradycardia, second- or third-degree heart block, decompensated heart failure, and cardiogenic shock[D10] Abrupt discontinuation may result in severe exacerbations of angina, MI, and/or ventricular arrhythmia[D10] May acutely worsen heart failure[D10] β-blockers may mask signs and symptoms of hypoglycemia and hyperthyroidism[D10]	Bradycardia Dizziness Fatigue Hyperkalemia Hypotension[D5,D10]	Nonselective β-blocker[D10]

			Use with caution in patients with renal impairment, bronchospastic disease, peripheral vascular disease, pheochromocytoma, and Prinzmetal variant angina[D6,D10]		
Nondihydropyridine calcium channel blockers					
Diltiazem, oral immediate-release	First line agent in patients with concomitant hypertension, HFpEF, or severe asthma/COPD[D1,D2] Do not use in patients with preexcitation[D1] Do not use in patients with LV systolic dysfunction and decompensated heart failure because of negative inotropic effects[D1]	Usual dose: 120-360 mg/day PO divided in 3-4 doses[D1,D2,D11]	Contraindicated in patients with second- or third-degree heart block, sick sinus syndrome, hypotension, or acute MI and pulmonary congestion[D11] May worsen heart failure[D11] Use with caution in patients with renal impairment and hepatic impairment[D2,D11] Drug interactions: may need to avoid or	AV block Bradycardia Constipation Hepatic enzymes increased Hypotension Rash[D11]	Reduces resting and exercise heart rates; can improve exercise tolerance[D1]

			adjust dosage of certain drugs[D11]		
Diltiazem, oral extended-release	First line agent in patients with concomitant hypertension, HFpEF, or severe asthma/COPD[D1,D2] Do not use in patients with preexcitation[D1] Do not use in patients with LV systolic dysfunction and decompensated heart failure because of negative inotropic effects[D1]	Usual dose: 120-360 mg PO once daily[D1,D2]	Contraindicated in patients with second- or third-degree heart block, sick sinus syndrome, hypotension, or acute MI and pulmonary congestion[D12] May worsen heart failure[D12] Use with caution in patients with renal impairment and hepatic impairment[D2,D13] Drug interactions: may need to avoid or adjust dosage of certain drugs[D12]	AV block Bradycardia Constipation Hepatic enzymes increased Hypotension Rash[D12]	Reduces resting and exercise heart rates; can improve exercise tolerance[D1]
Diltiazem, intravenous	First line agent for rapid control in patients with concomitant hypertension, HFpEF, or severe asthma/COPD, in	0.25 mg/kg IV bolus, then 5-15 mg/hour continuous IV infusion[D1,D2]	Contraindicated in patients with second- or third-degree heart block, sick sinus syndrome, hypotension, cardiogenic shock,	AV block Bradycardia Constipation Hepatic enzymes increased Hypotension Rash[D13]	

	the acute setting[D1,D2] Do not use in patients with preexcitation[D1] Do not use in patients with LV systolic dysfunction and decompensated heart failure because of negative inotropic effects[D1]		WPW, or Lown-Ganong-Levine syndrome[D13] May worsen heart failure[D13] Use with caution in patients with renal impairment and hepatic impairment[D13] Drug interactions: may need to avoid or adjust dosage of certain drugs[D13]		
Verapamil, oral immediate-release	First line agent in patients with concomitant hypertension, HFpEF, or severe asthma/COPD[D1,D2] Do not use in patients with preexcitation[D1] Do not use in patients with LV systolic dysfunction and decompensated	Usual dose: 240-480 mg/day PO divided in 3-4 doses[D14]	Contraindicated in patients with severe left ventricular dysfunction, second- or third-degree heart block, sick sinus syndrome, hypotension, cardiogenic shock, WPW, or Lown-Ganong-Levine syndrome[D14] Use with caution in patients with renal impairment, hepatic	AV block Bradycardia Constipation Hepatic enzymes increased Hypotension[D14]	Reduces resting and exercise heart rates; can improve exercise tolerance[D1]

	heart failure because of negative inotropic effects[D1]		impairment, myasthenia gravis, or Duchenne muscular dystrophy[D14] May worsen heart failure[D14] Drug interactions: may need to avoid or adjust dosage of certain drugs[D14]		
Verapamil, oral extended-release	First line agent in patients with concomitant hypertension, HFpEF, or severe asthma/COPD[D1,D2] Do not use in patients with preexcitation[D1] Do not use in patients with LV systolic dysfunction and decompensated heart failure because of	Usual dose: 180-480 mg PO once daily[D1,D2]	Contraindicated in patients with severe left ventricular dysfunction, second- or third-degree heart block, sick sinus syndrome, hypotension, cardiogenic shock, WPW, or Lown-Ganong-Levine syndrome[D15] May worsen heart failure[D15] Use with caution in patients with renal impairment, hepatic impairment,	AV block Bradycardia Constipation Hepatic enzymes increased Hypotension[D15]	Reduces resting and exercise heart rates; can improve exercise tolerance[D1]

	negative inotropic effects[D1]		myasthenia gravis, or Duchenne muscular dystrophy[D15] Drug interactions: may need to avoid or adjust dosage of certain drugs[D15]		
Verapamil, intravenous	First line agent for rapid control in patients with concomitant hypertension, HFpEF, or severe asthma/COPD, in the acute setting[D1,D2,D16] Do not use in patients with preexcitation[D1] Do not use in patients with LV systolic dysfunction and decompensated heart failure because of negative inotropic effects[D1]	0.075-0.15 mg/kg IV bolus; if no response after 30 minutes, may give an additional 10 mg IV bolus, then 0.005 mg/kg/minute continuous IV infusion[D1,D16]	Contraindicated in patients with severe congestive heart failure, second- or third-degree heart block, sick sinus syndrome, hypotension, cardiogenic shock, WPW, Lown-Ganong-Levine syndrome, or wide-complex ventricular tachycardia[D16] May worsen heart failure[D16] Use with caution in patients with renal impairment, hepatic impairment, myasthenia gravis, or Duchenne muscular	AV block Bradycardia Constipation Hepatic enzymes increased Hypotension[D15,D16]	

			dystrophy[D14,D16] Drug interactions: may need to avoid or adjust dosage of certain drugs[D16]		
Digitalis glycosides					
Digoxin, oral	Add-on to β-blocker and/or nondihydropyridine calcium channel blocker when rate control is insufficient[D1,D2] Not an optimal agent when rapid rate control desired[D1] May be useful in patients with HFrEF[D1,D2] Do not use as sole therapy in patients with preexcitation[D1]	Usual dose: 0.0625-0.25 mg PO once daily[D1,D2] Adjust dose in patients with renal impairment[D17]	Avoid in patients with myocarditis or acute MI[D17] Use with caution in patients with WPW, sinus node disease, AV block, or hypothyroidism[D17] Risk of ventricular arrhythmia during electrical cardioversion[D17] Advanced age, low body weight, renal impairment, and electrolyte abnormalities increase the risk of toxicity[D17] Drug interactions:	Anorexia AV block Bradycardia Nausea Ventricular arrhythmia Vision changes Vomiting[D1,D17]	Correct hypocalcemia before initiation[D17] Does not possess negative inotropic effects[D1] Not effective in patients with high sympathetic tone[D2] Longer onset of action compared to β-blockers and nondihydropyridine calcium channel blockers[D1,D2] High plasma concentrations are associated with increased

			may need to avoid or adjust dosage of certain drugs[D17]		mortality[D2] Serum digoxin concentrations < 0.5 ng/mL have been associated with diminished efficacy while toxicity is associated with concentrations > 2 ng/mL, although symptoms may occur at lower concentrations[D17,D18]
Digoxin, intravenous	Add-on to β-blocker and/or nondihydropyridine calcium channel blocker when rate control is insufficient[D1,D2] Not an optimal agent when rapid rate control desired[D1] May be useful in patients with HFrEF[D1,D2]	Loading dose: 0.25-0.5 mg IV once with repeat dosing every 6-8 hours to a maximum of 1.5 mg/24 hours[D1,D2,D19] Transition to oral digoxin[D1,D2] Adjust dose in patients with	Avoid in patients with myocarditis or acute MI[D19] Use with caution in patients with WPW, sinus node disease, AV block, or hypothyroidism[D19] Risk of ventricular arrhythmia during electrical cardioversion[D19]	Anorexia AV block Bradycardia Nausea Ventricular arrhythmias Vision changes Vomiting[D1,D19]	Correct hypocalcemia before initiation[D19] Does not have negative inotropic effects[D1] Not effective in patients with high sympathetic tone[D2] Longer onset of action compared to β-blockers and

	Do not use as sole therapy in patients with preexcitation[D1]	renal impairment[D19]	Advanced age, low body weight, renal impairment, and electrolyte abnormalities increase the risk of toxicity[D19] Drug interactions: may need to avoid or adjust dosage of certain drugs[D19]		nondihydropyridine calcium channel blockers[D1,D2] High plasma concentrations are associated with increased mortality[D2] Serum digoxin concentrations < 0.5 ng/mL have been associated with diminished efficacy while toxicity is associated with concentrations > 2 ng/mL, although symptoms may occur at lower concentrations[D18, D19]
Antiarrhythmics					
Amiodarone, oral	Reserve for chronic rate control in patients who do not respond to or are intolerant to	Usual dose: 400-600 mg/day PO in divided doses for 2-4 weeks, then 100-200 mg PO once daily§¶[D1,D2]	**BOXED WARNING:** risk for pulmonary toxicity, hepatotoxicity, and/or arrhythmia exacerbation[D20]	Arrhythmias Bradycardia Corneal microdeposits Hepatotoxicity Hyperthyroidism	Correct hypokalemia, hypomagnesemia, and hypocalcemia before initiation[D20]

	other therapy[D1,D2] Consider as an add-on second-or third-line agent in patients with HFrEF and suboptimal rate control[D2] Do not use in patients with preexcitation[D1]		Contraindicated in patients with significant bradycardia, second- or third-degree heart block, sick sinus syndrome, and cardiogenic shock[D20] Use with caution in patients with pulmonary disease[D1] Drug interactions: may need to avoid or adjust dosage of certain drugs[D20]	Hypothyroidism Nausea Optic neuropathy/neuritis Peripheral neuropathy Photosensitivity Pulmonary toxicity QT prolongation Skin discoloration (blue-gray) Torsade de pointes Vomiting[D1,D2,D20]	Monitor chest x-ray, PFTs, thyroid function tests, LFTs, and ophthalmic examination[D20] Food significantly increases the rate and extent of absorption and may minimize GI symptoms[D1,D20] Many potential toxicities limit long-term use[D1] Limited data for chronic oral therapy; efficacy may be similar to digoxin[D1] Longer time to effect compared to β-blockers and nondihydropyridine calcium channel blockers[D1] Long half-life; toxicity and

					potential drug interactions can persist for several weeks after drug discontinuation[D20]
Amiodarone, intravenous	Useful in critically ill patients with severe LV systolic dysfunction or hemodynamic instability[D1,D2] Consider as an add-on second-or third-line agent in patients with HFrEF and suboptimal rate control[D2] Do not use in patients with preexcitation[D1]	300 mg IV over 1 hour then 10-50 mg/hour continuous IV infusion for 24 hours§[D1,D2] Transition to oral amiodarone[D21]	Contraindicated in patients with significant bradycardia, second- or third-degree heart block, and cardiogenic shock[D21] Use with caution in patients with pulmonary disease[D1] Drug interactions: may need to avoid or adjust dosage of certain drugs[D21]	Arrhythmias Bradycardia Hepatoxicity Hyperthyroidism Hypotension Hypothyroidism Optic neuropathy/neuritis Phlebitis Pulmonary toxicity QT prolongation Torsade de pointes[D1,D21]	Correct hypokalemia, hypomagnesemia, and hypocalcemia before initiation[D21] Use a large peripheral vein and avoid administration > 24 hours to avoid phlebitis[D2] Longer time to effect compared to β-blockers and nondihydropyridine calcium channel blockers[D1] Long half-life; toxicity and potential drug interactions can persist after drug discontinuation[D21]

ACS = acute coronary syndrome, AV = atrioventricular, COPD = chronic obstructive pulmonary disease, CrCl = creatinine clearance, GI = gastrointestinal, HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, LFT = liver function tests, LV = left ventricular, MI = myocardial infarction, PFT = pulmonary function tests, RVR = rapid ventricular response, WPW = Wolff-Parkinson-White syndrome.

*When selecting therapy, consider the patient's degree of symptoms, hemodynamic status, comorbidities, potential precipitants of atrial fibrillation, and potential adverse effects of treatment. In general, β-blockers are the most common pharmacologic agents used, followed by nondihydropyridine calcium channel blockers, digoxin, and amiodarone.[D1,D2]

†Titrate dose to heart rate < 110 bpm (lenient control) or if symptoms persist, < 80 bpm (strict control) at rest.[D1,D2]

‡Bisoprolol, carvedilol, and metoprolol succinate have been shown to reduce mortality in HFrEF and should be used preferentially over other β-blockers.[D22]

§Multiple dosing regimens used.[D1,D2]

¶Onset of action is accelerated by a high-dose amiodarone loading regimen.[D1]

Table 5. Drug Therapy: Rhythm control in atrial fibrillation.*†

Medication	Therapeutic use	Dosage	Safety concerns	Notable adverse reactions¶	Special considerations
Class IC antiarrhythmics					
Flecainide	Pharmacologic cardioversion‡ in patients without ischemic or structural heart disease[D1,D2] "Pill-in-the-pocket" to terminate paroxysmal AF out of hospital§[D1,D2]	200-300 mg PO once#[D1,D2]	**BOXED WARNING**: increased mortality in patients with prior MI and asymptomatic non-life-threatening ventricular arrhythmias; risk for ventricular arrhythmias in patients with AF or atrial flutter[D23] Contraindicated in patients with second- or third-degree heart block, right bundle	Atrial flutter with 1:1 conduction AV block Bradycardia Dizziness Hypotension QT prolongation	Correct hypokalemia or hyperkalemia before initiation[D23] Obtain ECG at baseline and after 1-2 weeks[D2]

			branch block associated with a bifascicular block, or cardiogenic shock[D23] May worsen heart failure[D23] Use with caution in patients with renal or hepatic impairment, sick sinus syndrome, permanent pacemakers, temporary pacing electrodes, sinus or AV node dysfunction, atrial flutter, or Brugada syndrome[D1,D23] Drug interactions: may need to avoid or adjust dosage of certain drugs[D23]	Torsade de pointes Ventricular arrhythmia Visual disturbance[D1,D23]	Possesses negative inotropic effects[D1,D23] Use with a β-blocker or nondihydropyridine calcium channel blocker to reduce the risk of rapid ventricular response; class IC agents can cause slowing of the atrial rate in atrial flutter, promoting 1:1 AV conduction and an increased ventricular rate[D1,D2] Associated with a low proarrhythmic risk in properly screened patients[D2]
	Maintenance of sinus rhythm in patients with normal LV function and no structural heart disease, including significant LVH and myocardial ischemia[D1,D2]	Usual dose: 50-200 mg PO every 12 hours[D1,D2] Adjust dose for CrCl ≤ 35 mL/minute/1.73m^2[D23]			
Propafenone, oral immediate-release	Pharmacologic cardioversion‡ in patients without ischemic heart disease or structural heart disease [D1,D2] "Pill-in-the-pocket" to terminate paroxysmal AF out of hospital§[D1,D2]	450-600 mg once#[D1,D2]	**BOXED WARNING**: increased mortality in patients with prior MI and asymptomatic non-life-threatening ventricular arrhythmias[D24] Contraindicated in patients with heart failure, cardiogenic shock, AV block, sick sinus syndrome, Brugada syndrome, bradycardia, significant hypotension,	Agranulocytosis Atrial flutter with 1:1 conduction AV block Dizziness Hypotension Metallic taste	Obtain ECG at baseline and after 1-2 weeks[D2] Structurally similar to β-blockers with negative inotropic effects[D1,D24]

	Maintenance of sinus rhythm in patients with normal LV function and no structural heart disease including significant LVH and myocardial ischemia[D1,D2]	Usual dose: 150-300 mg PO every 8 hours[D1,D2] Adjust dose for hepatic impairment, significant QRS widening, or second- or third-degree AV block[D24]	bronchospastic disease, or significant electrolyte imbalance[D24] May affect artificial pacemaker function[D24] May worsen heart failure[D24] Use with caution in patients with renal or hepatic impairment, myasthenia gravis, or atrial flutter[D1,D24] Drug interactions: may need to avoid or adjust dosage of certain drugs[D24]	Nausea Positive ANA titers QT prolongation Torsade de pointes Ventricular arrhythmia Vomiting[D1,D24]	Metabolism influenced by genetic variations in CYP2D6[D1,D24] Use with a β-blocker or nondihydropyridine calcium channel blocker to reduce the risk of rapid ventricular response; class IC agents can cause slowing of the atrial rate in atrial flutter, promoting 1:1 AV conduction and an increased ventricular rate[D1,D2] Associated with a low proarrhythmic risk in properly screened patients[D2]
Propafenone, oral extended-release	Maintenance of sinus rhythm in patients with normal LV function and no structural heart disease including significant LVH and myocardial ischemia[D1,D2]	Usual dose: 225-425 mg PO every 12 hours [D1,D2] Adjust dose for hepatic impairment, significant QRS widening, or second- or third-degree AV block[D25]	**BOXED WARNING**: increased mortality in patients with prior MI and asymptomatic non-life-threatening ventricular arrhythmias[D25] Contraindicated in patients with heart failure, cardiogenic shock, AV block, sick sinus syndrome, Brugada syndrome, bradycardia, significant hypotension, bronchospastic disease, or significant electrolyte imbalance[D25]	Agranulocytosis Atrial flutter with 1:1 conduction AV block Dizziness Hypotension Metallic taste Nausea Positive ANA titers QT prolongation Torsade de pointes Ventricular	Obtain ECG at baseline and after 1-2 weeks[D2] Structurally similar to β-blockers with negative inotropic effects[D1,D25] Metabolism influenced by genetic variations in CYP2D6[D1,D25] Use with a β-blocker or

			May affect artificial pacemaker function[D25] May worsen heart failure[D25] Use with caution in patients with renal or hepatic impairment, myasthenia gravis, or atrial flutter[D1,D24] Drug interactions: may need to avoid or adjust dosage of certain drugs[D25]	arrhythmia Vomiting[D1,D24]	nondihydropyridine calcium channel blocker to reduce the risk of rapid ventricular response; class IC agents can cause slowing of the atrial rate in atrial flutter, promoting 1:1 AV conduction and an increased ventricular rate[D1,D2] Associated with a low proarrhythmic risk in properly screened patients[D2]
Class III antiarrhythmics					
Amiodarone, oral	Pharmacologic cardioversion‡ in patients with heart failure or structural heart disease[D1,D2]	600-800 mg/day PO in divided doses to a total load of up to 10 g, then 200 mg PO once daily**[D1]	**BOXED WARNING**: risk for pulmonary toxicity, hepatotoxicity, and/or arrhythmia exacerbation[D20] Contraindicated in patients with significant bradycardia, second- or third-degree heart block, sick sinus syndrome, and cardiogenic shock[D20] Use with caution in patients with pulmonary disease[D1] Drug interactions: may need to avoid or adjust dosage of certain drugs[D20]	Arrhythmias Bradycardia Corneal microdeposits Hepatotoxicity Hyperthyroidism Hypothyroidism Nausea Optic neuropathy/neuritis Peripheral neuropathy	Correct hypokalemia, hypomagnesemia, and hypocalcemia before initiation[D20] Monitor chest x-ray, PFTs, thyroid function tests, LFTs, and ophthalmic examination[D20] Obtain ECG at baseline and after 4 weeks[D2]
	Maintenance of sinus rhythm in all AF patients, including those with heart failure (HFrEF or HFpEF), ischemic heart disease and/or prior MI, or LV hypertrophy; however, not considered first line due to potential extracardiac toxicities[D1,D2]	Usual dose: 400-600 mg/day in divided doses for 2-4 weeks, then 100-200 mg PO once daily**[D1,D2]			

	May be useful to prevent recurrent AF in patients with hypertrophic cardiomyopathy, in combination with a β-blocker or nondihydropyridine calcium channel blocker[D1]			Photosensitivity Pulmonary toxicity QT prolongation Skin discoloration (blue-gray) Torsade de pointes Vomiting[D1,D2,D20]	Food significantly increases the rate and extent of absorption and may minimize GI symptoms[D1,D20] Most effective antiarrhythmic agent for maintenance of sinus rhythm in patients with paroxysmal or persistent AF (more effective than dronedarone, sotalol, or propafenone)[D1,D2] Many potential toxicities limit long-term use[D1] Use for rhythm control has the added benefit of effective rate control and may eliminate the need for other rate control agents[D1] Long half-life; toxicity and potential drug interactions can persist for several weeks after drug discontinuation[D20]
	Pharmacologic cardioversion‡ in	150 mg IV over 10 minutes, then 1	Contraindicated in patients with significant bradycardia, second- or third-	Arrhythmias	Correct hypokalemia, hypomagnesemia, and

Amiodarone, intravenous	patients with heart failure or structural heart disease[D1,D2] Facilitation of electrical cardioversion[D2]	mg/minute continuous IV infusion for 6 hours, then 0.5 mg/minute for 18 hours or transition to oral dosing**[D1]	degree heart block, and cardiogenic shock[D21] Use with caution in patients with pulmonary disease[D1] Drug interactions: may need to avoid or adjust dosage of certain drugs[D21]	Bradycardia Hepatoxicity Hyperthyroidism Hypotension Hypothyroidism Optic neuropathy/neuritis Phlebitis Pulmonary toxicity QT prolongation Torsade de pointes[D1,D21]	hypocalcemia before initiation[D21] Obtain ECG at baseline and after 4 weeks[D2] Use a large peripheral vein and avoid administration > 24 hours to avoid phlebitis[D2] Long half-life; toxicity and potential drug interactions can persist after drug discontinuation[D21]
	Maintenance of sinus rhythm in all AF patients, including those with heart failure (HFrEF or HFpEF), ischemic heart disease and/or prior MI, or LV hypertrophy; however, not considered first line due to potential extracardiac toxicities[D1,D2]	Usual dose: 150 mg IV over 10 minutes, then 1 mg/minute continuous IV infusion for 6 hours, then 0.5 mg/minute for 18 hours or transition to PO dosing; after 24 hours, consider decreasing dose to 0.25 mg/minute**[D1]			
Dofetilide	Pharmacologic cardioversion‡[D1]	500 mcg PO every 12 hours[D1] Adjust dose for CrCl ≤ 60 mL/minute[D1,D26]	**BOXED WARNING:** initiation or reinitiation requires at least 3 days in a care setting capable of continuous ECG monitoring and presence of personnel trained in the treatment of ventricular arrhythmias[D26] Contraindicated in patients with long QT syndrome, baseline QT interval > 440 msec (500 msec in patients with ventricular conduction abnormalities), or severe renal impairment (CrCl < 20 mL/minute)[D26]	Chest pain Dizziness Headache QT prolongation Torsade de pointes Ventricular arrhythmia[D1,D26]	Correct hypokalemia before initiation[D26]
	Maintenance of sinus rhythm in patients at low risk for torsade de pointes induced by QT prolongation[D1] Preferred in patients with ischemic heart	Usual dose: 125-500 mcg PO every 12 hours[D1] Adjust dose for CrCl ≤ 60 mL/minute[D26] Further adjust based on			

	disease or heart failure[D1] May be considered for rhythm control in patients with hypertrophic cardiomyopathy[D1]	degree of QT prolongation[D25]	Use with caution in patients with hepatic impairment or electrolyte imbalance[D26] Drug interactions: may need to avoid or adjust dosage of certain drugs[D26]		
Dronedarone	Maintenance of sinus rhythm in patients with normal or mildly impaired but stable LV function or HFpEF, ischemic heart disease, or valvular heart disease[D1,D2] May be considered for rhythm control in patients with hypertrophic cardiomyopathy[D1]	Usual dose: 400 mg PO every 12 hours[D1,D2]	**BOXED WARNING**: increased risk of death, stroke, and heart failure in patients with decompensated heart failure or permanent AF[D27] Contraindicated in patients with permanent AF, recently decompensated heart failure requiring hospitalization or NYHA Class IV heart failure, second- or third-degree heart block, bradycardia, hepatic or pulmonary toxicity related to previous amiodarone use, severe hepatic impairment, or QTc Bazett ≥500 msec[D27] May worsen heart failure[D27] Use with caution in patients with electrolyte imbalance[D27] Drug interactions: may need to avoid or adjust dosage of certain drugs[D27]	Asthenia Bradycardia Diarrhea Hepatotoxicity Hypokalemia Hypomagnesemia Nephrotoxicity Pulmonary toxicity QT prolongation Serum creatinine elevation†† Torsade de pointes[D1,D27]	Correct hypokalemia before initiation[D27] Obtain ECG at baseline and after 4 weeks[D2] Decreased efficacy compared to amiodarone, but improved adverse reaction profile[D1,D2] Associated with increased mortality in patients with recent decompensated or permanent heart failure[D1,D2]
Ibutilide	Pharmacologic cardioversion‡[D1,D2]	Weight ≥ 60kg: 1 mg IV over 10 minutes	**BOXED WARNING:** requires a care setting capable of continuous ECG monitoring and presence of personnel trained in the	Hypotension QT prolongation Torsade de pointes	Correct hypokalemia and hypomagnesemia before initiation[D28]

	Recommended to restore sinus rhythm or slow ventricular rate in patents with preexcited AF and RVR who are not hemodynamically compromised[D1]	Weight < 60 kg: 0.01 mg/kg IV over 10 minutes May repeat once 10-20 minutes after initial dose if needed[D1,D2,D28]	treatment of ventricular arrhythmias; ensure appropriate patient selection in that expected benefits outweigh risks[D28] Avoid in patients with QT prolongation, severe LVH, marked hypokalemia, or EF < 30%[D1,D2] Drug interactions: may need to avoid or adjust dosage of certain drugs[D28]	Ventricular arrhythmia[D1,D28]	Monitor ECG for ≥ 4 hours after infusion or until QTc has returned to baseline[D1,D28] Pretreatment with ibutilide improves the efficacy of transthoracic electrical cardioversion[D1] Some experts administer magnesium sulfate prior to ibutilide to lower the risk of ventricular arrhythmias[D1]
Sotalol	Maintenance of sinus rhythm in patients without structural heart disease; consider in patients with ischemic heart disease if close monitoring is provided[D1,D2] May be considered for rhythm control in patients with hypertrophic cardiomyopathy[D1] Prophylactic use may be considered for patients	Usual dose: 40-160 mg PO every 12 hours[D1,D2] Adjust dose for CrCl ≤ 40-60 mL/minute[D29,D30]	**BOXED WARNING:** initiation or reinitiation requires a care setting capable of continuous ECG monitoring and presence of personnel trained in the treatment of ventricular arrhythmias[D29,D30] Contraindicated in patients with CrCl < 40 mL/minute, bradycardia, second- or third-degree heart block, sick sinus syndrome, long QT syndrome, baseline QT interval > 450 msec, cardiogenic shock, uncontrolled heart failure, serum potassium < 4 mEq/L, or bronchospastic disease[D29,D30] Do not use in patients with HFrEF or significant LVH[D2] Use with caution in patients with recent	AV block Bradycardia Dizziness Fatigue Hyperkalemia Hypotension QT prolongation Torsade de pointes[D1,D5,D29,D30]	Correct hypokalemia and hypomagnesemia before initiation[D29] Obtain ECG at baseline, after 1 day, and after 1-2 weeks[D2] Class III antiarrhythmic effects only if dosing > 160 mg/day[D2]

	with AF risk after cardiac surgery[D1]		MI or electrolyte imbalance[D29] Abrupt discontinuation may result in severe exacerbations of angina, MI, and/or ventricular arrhythmia[D29,D30] May worsen heart failure[D29,D30] β-blockers may mask signs and symptoms of hypoglycemia and hyperthyroidism[D29,D30] Drug interactions: may need to avoid or adjust dosage of certain drugs[D29,D30]		

AF = atrial fibrillation, ANA = antinuclear antibodies, AV = atrioventricular, CrCl = creatinine clearance, ECG = electrocardiogram, EF = ejection fraction, GI = gastrointestinal, HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, LFT = liver function test, LV = left ventricular, LVH = left ventricular hypertrophy, MI = myocardial infarction, PFT = pulmonary function test, RVR = rapid ventricular response.

*Identify and correct precipitating or reversible factors of AF prior to initiation of antiarrhythmic drug therapy. Drug selection is guided by safety rather than drug efficacy. The aim of drug therapy is to reduce AF-related symptoms; efficacy is modest. If one agent fails, another agent may be tried. Do not continue antiarrhythmic drug therapy for rhythm control when AF becomes permanent.[D1,D2]

†Carefully individualize the decision about whether to initiate antiarrhythmic drugs in an inpatient or outpatient setting; practice parameters vary widely both in terms of patient selection and length of hospitalization. Data supporting outpatient initiation is best established for amiodarone and dronedarone.[D1] Do not initiate dofetilide on an outpatient basis.[D26]

¶In general, antiarrhythmic agents have the potential to precipitate or worsen bradycardia due to sinus node dysfunction or abnormal AV conduction. Patients with significant bradyarrhythmias may require a pacemaker.[D1]

‡Pharmacologic cardioversion is indicated in hemodynamically stable patients and is most effective in within 7 days of episode onset.[D1,D2]

§A self-administered oral dose of flecainide or propafenone is slightly less effective than in-hospital pharmacologic cardioversion but may be preferred (permitting an earlier conversion) as along as drug safety and efficacy have been previously established in a monitored setting.[D1,D2] After self-administration, avoid exercise until cessation of AF and at least 2 drug half-lives have passed.[D2]

#Administer a β-blocker or nondihydropyridine calcium channel blocker ≥ 30 minutes before cardioversion with flecainide or propafenone to reduce the risk of a rapid ventricular response.[D1]

**Multiple dosing regimens used.[D2]

††Modest increase in serum creatinine is common after initiation and is a result of inhibition of creatinine's tubular secretion vs. a decline in renal function.[D2,D27]

Table 6. Drug Therapy: Anticoagulant therapy in atrial fibrillation.

Medication	Therapeutic use	Dosage	Safety concerns	Notable adverse reactions
Non-vitamin K oral anticoagulants (NOAC)*				
Direct thrombin inhibitors				
Dabigatran	Preferred over warfarin[D1,D2,D31] May be preferred in Asian patients†[D31] 150 mg dose may be preferred in patients at high stroke risk or recurrent stroke[D31,D32] 110 mg dose (where available) may be preferred in patients with high bleed risk	Usual dose: 150 mg PO twice daily[D33,D34] Low dose: 110 mg PO twice daily[D34] Adjust dose for patients with CrCl 15-30 mL/minute[D33]	**BOXED WARNING:** risk for thrombotic events with premature discontinuation and spinal or epidural hematoma[D33] Contraindicated in patients with mechanical prosthetic heart valve[D33] Not recommended for use in patients with severe mitral stenosis, triple-positive APS, or CrCl < 15 mL/minute[D1,D2,D31,D33,D35]	Major bleeding‡: 150 mg vs. warfarin: no difference[D34] 110 mg vs. warfarin: lower[D34]

	(HAS-BLED ≥3) or high GI bleed risk[D31]		Drug interactions: may need to avoid or adjust dosage of certain drugs[D33] Routine therapeutic drug monitoring not necessary[D2,D31] Reversal strategy: idarucizumab, PCC or aPCC, or hemodialysis[D2,D31,D36-D38]	
Factor Xa inhibitors				
Apixaban	Preferred over warfarin[D1,D2,D31] May be preferred in patients with high bleed risk (HAS-BLED ≥3), high GI bleed risk, ESRD, or Asian patients†[D2]	5 mg PO twice daily[D39,D40] Adjust dose if 2 of the following: age ≥ 80 years, body weight ≤ 60 kg, or SCr ≥ 1.5 mg/dL[D39]	**BOXED WARNING:** risk for thrombotic events with premature discontinuation and spinal or epidural hematoma[D39] Not recommended for use in patients with prosthetic mechanical heart valve, severe mitral stenosis, triple-positive APS, or Child-Pugh Class C hepatic impairment[D1,D2,D31,D35,D39,] Drug interactions: may need to avoid or adjust dosage of certain drugs[D39]	Major bleeding‡ vs. warfarin: lower[D40]

			Routine therapeutic drug monitoring not necessary[D2,D31] Reversal strategy: andexanet alfa, aPCC or PCC[D2,D31,D36-D38,D41]	
Edoxaban	Preferred over warfarin[D1,D2,D31] May be preferred in patients with high bleed risk (HAS-BLED ≥3), Asian patients†, and those who want a reduced pill burden[D31,D32] 60 mg dose may be preferred in patients with high stroke risk[D31]	Usual dose: 60 mg PO once daily[D42] Low dose: 30 mg PO once daily[D43] Adjust dose in patients with CrCl 15-50 mL/minute[D42]	**BOXED WARNING:** risk for thrombotic events with premature discontinuation and spinal or epidural hematoma; reduced efficacy in patients with CrCl > 95 mL/minute[D42] Not recommended for use in patients with prosthetic mechanical heart valve, severe mitral stenosis, triple-positive APS, CrCl > 95 mL/minute or < 15 mL/minute, or Child-Pugh Class B or C hepatic impairment[D1,D2,D31, D35,D42] Drug interactions: may need to avoid or adjust dosage of certain drugs[D42] Routine therapeutic drug monitoring not necessary[D2,D31]	Major bleeding‡ 30 or 60 mg vs. warfarin: lower[D43]

			Reversal strategy: andexanet alfa, aPCC or PCC[D2,D31,D36-D38]	
Rivaroxaban	Preferred over warfarin[D1,D2,D31] May be preferred in patients with ESRD or those who want a lower pill burden[D31]	20 mg PO once daily with food Adjust dose in patients with CrCl < 50 mL/minute[D44]	**BOXED WARNING:** risk for thrombotic events with premature discontinuation and spinal or epidural hematoma[D44] Not recommended for use in patients with prosthetic mechanical heart valve, severe mitral stenosis, triple-positive APS, or Child-Pugh Class B or C hepatic impairment[D1,D2,D31, D35,D44] Drug interactions: may need to avoid or adjust dosage of certain drugs[D44] Routine therapeutic drug monitoring not necessary[D2,D31]	Major bleeding§ vs. warfarin: no difference[D45]

			Reversal strategy: andexanet alfa, aPCC or PCC[D2,D17,D31, D36-D38,D41]	
Vitamin K antagonists (VKA)				
Warfarin	Preferred in patients with ESRD, mechanical heart valve, or moderate/severe mitral stenosis[D1,D2,D31,D46,D47] To aid in determining if a patient will do well on warfarin therapy, a score of 0-2 on the SAMe-TT_2R_2 is recommended; for score > 2, NOAC preferred or more frequent INR monitoring necessary¶[D2,D31]	Initial dose: 2.5-10 mg PO once daily#[D48]	**BOXED WARNING:** bleeding risk[D48] Monitor INR at least weekly until stable, then monthly; adjust dose to INR 2-3[D1,D2,D31] Genetic polymorphisms, changes in diet and concomitant drugs affect therapeutic efficacy and safety[D48] Reversal strategy: vitamin K, PCC, FFP[D2,D31,D36-D38]	Bleeding Skin necrosis Systemic atheroemboli[D48]

aPCC = activated prothrombin complex concentrates, APS = antiphospholipid syndrome, CrCl = creatinine clearance, ESRD = end-stage renal disease, FFP = fresh frozen plasma, GI = gastrointestinal, INR = international normalized ratio, NOAC = novel oral anticoagulant, PCC = activated prothrombin complex concentrates, SCr = serum creatinine.

*NOACs include dabigatran, apixaban, edoxaban, and rivaroxaban.[D1,D2,D31]

†Incidence of intracranial hemorrhage (ICH) was significantly lower compared to warfarin in clinical trials; Asian patients with atrial fibrillation are at higher risk for ICH vs. White patients.[D31]

‡Major bleeding is defined as reduction in the hemoglobin level of at least 2 g/dL, transfusion of at least 2 units of blood, symptomatic bleeding in a critical area or organ, or fatal bleeding.[D34,D40,D43]

§Major bleeding is defined as decrease in hemoglobin > 2 g/dL, requiring transfusion, critical or fatal bleeding.[D45]

¶The SAMeTT$_2$R$_2$ score predicts success on warfarin therapy.[D2,D31]

#Initial dose is very individualized and based on expected maintenance dose; consideration and testing of genotypes may help determining initial dosing.[D48]

Nondrug and Supportive Care

- Risk factor modification
  - Treat obesity, hypertension, and obstructive sleep apnea
    - For patients with obesity, weight loss is associated with regression of atrial fibrillation substrate and improved arrhythmia-free survival after treatment[20]
  - Optimize glycemic control
  - Limit any identifiable triggers, including excessive caffeine and alcohol intake, dehydration, and sleep deprivation

Treatment Procedures

- Cardioversion:
  - Electrical cardioversion
    - Initially performed to restore sinus rhythm in persistent atrial fibrillation
    - Direct-current energy of 150 to 360 J is delivered from an external defibrillator, synchronized with the QRS complex, via chest pads that are usually placed in an antero-posterior configuration
      - Performed using conscious sedation
    - Acute success rate of direct-current cardioversion at restoring sinus rhythm is greater than 90%
      - Rate is lower in the presence of longstanding persistent atrial fibrillation, high BMI, and atrial dilatation[21]
    - If cardioversion fails to restore any sinus beats, attempts to improve efficacy can be made, including:
      - Repositioning the pads
      - Applying pressure on the anterior pad
      - Increasing the energy delivered
      - Pretreatment with ibutilide [22]
  - Chemical cardioversion
    - Cardioversion with antiarrhythmic drugs may be successful if atrial fibrillation is within 7 days onset[21]; drugs include:

        - Ibutilide
        - Vernakalant (not available in the United States)
        - Flecainide
        - Procainamide
        - Amiodarone
    - High-dose oral flecainide (200-300 mg) or propafenone (450-600 mg) has been used as a "pill-in-the-pocket" approach to achieve chemical cardioversion in patients presenting within an average of 30 minutes of atrial fibrillation onset
    - Overall rate of conversion with this approach is greater than 85%, but it must be restricted to patients without structural heart disease and a β-blocker must always be coadministered[23]
        - First time using "pill-in-the-pocket" class 1C anti-arrhythmic drugs should be in a monitored setting
    - Acute success rate of direct-current cardioversion is higher than chemical cardioversion[24]
    - Direct-current cardioversion is performed if there is hemodynamic instability related to atrial fibrillation with rapid ventricular response
- Therapeutic anticoagulation for at least 3 weeks (or from the onset of the atrial fibrillation episode) is required before cardioversion of atrial fibrillation to reduce risk of thromboembolic stroke
    - If patient has not been anticoagulated, perform transesophageal echocardiography to assess for left atrial appendage thrombus before performing cardioversion
    - Anticoagulation is continued for at least 1 month following cardioversion or indefinitely depending on the CHA_2DS_2-VASc score
- Atrial fibrillation ablation:
    - Atrial fibrillation ablation may be considered as a first line treatment for patients with paroxysmal and persistent atrial fibrillation, particularly those patients who prefer not to take antiarrhythmic drugs or have adverse effects with or contraindications to antiarrhythmic drugs[25]
    - Electrical isolation of the pulmonary veins (pulmonary vein isolation) is the cornerstone of the procedure with the goal of

preventing pulmonary veins triggers from reaching the left atrium and initiating atrial fibrillation

- Percutaneous, endocardial ablation (via femoral venous sheaths and access to the left atrium by 1-2 transseptal punctures) is performed with cryoablation or radiofrequency, laser, or pulsed electric field ablation **(Figure 2)**
- Catheter ablation is more effective than antiarrhythmic drugs at maintaining sinus rhythm[26-28]
- Success rate of atrial fibrillation ablation is generally 80% for paroxysmal atrial fibrillation and about 70% for persistent atrial fibrillation[29]

Admission Criteria

- In patients with atrial fibrillation, admission for inpatient investigation and treatment is required if patients have any of the following:
  - Rapid ventricular rates
  - Symptoms or signs suggestive of congestive heart failure
  - Chest pain concerning for acute coronary syndrome
  - Syncope

- Any acute focal neurological deficits concerning for transient ischemic attack or stroke

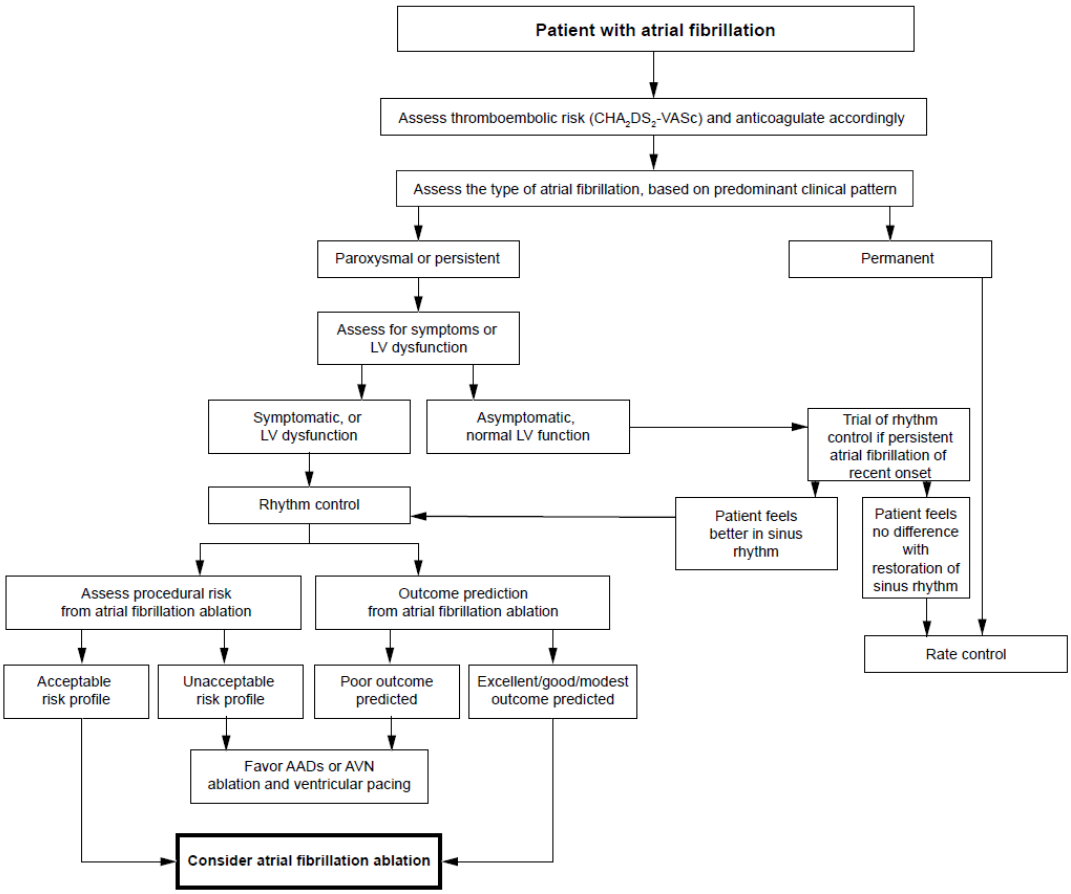

Figure 1. Factors to consider in choosing an atrial fibrillation management strategy.

AF, atrial fibrillation; LV, left ventricular; AAD, antiarrhythmic drugs; AVN, atrioventricular node.

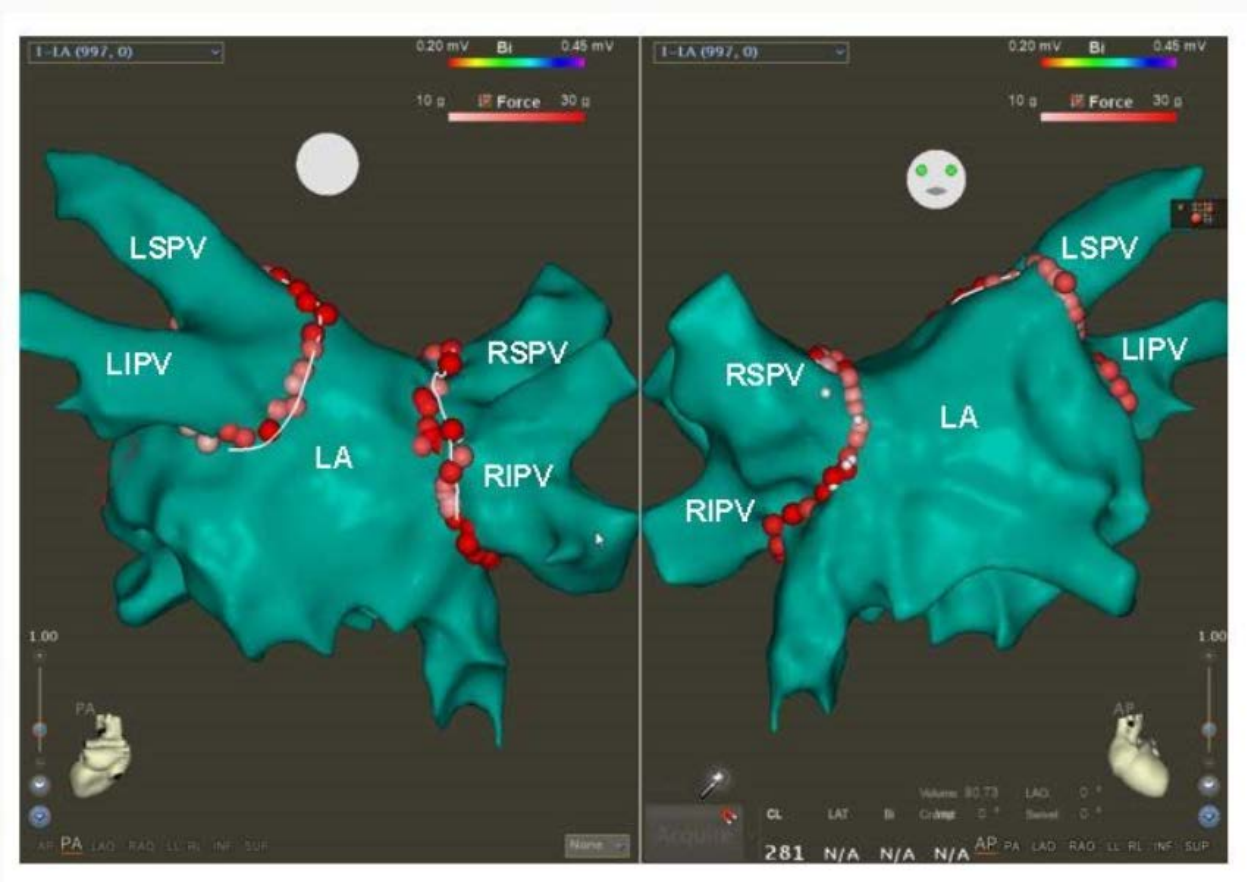

Figure 2. Left atrial map showing radiofrequency ablation lesions (red tags) encircling the pulmonary vein antra.

LA, left atrium; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein.

Special Considerations

Athletes

- Atrial fibrillation is not uncommon in athletes in whom it is associated with high vagal tone
- Rhythm control is generally preferred
- Adverse effects of antiarrhythmic drugs and rate control agents may be more troublesome in athletes owing to lower resting heart rates in sinus rhythm
- Ablation has high success rates

Older Adults

- Often less symptomatic with atrial fibrillation than younger people
- More prone to adverse effects of medications including antiarrhythmic drugs and rate control agents and have slightly higher risk of complications during ablation
- Atrioventricular nodal ablation and permanent pacing may be a good option for older adults who have symptomatic atrial fibrillation with rates that are difficult to control and failure of rhythm control attempts

Hypertrophic cardiomyopathy

- Atrial fibrillation is common in patients with hypertrophic cardiomyopathy
    - Patients with hypertrophic cardiomyopathy tend to be highly symptomatic in atrial fibrillation; therefore, rhythm control strategy is generally preferable
- Anticoagulation is recommended in patients with atrial fibrillation and hypertrophic cardiomyopathy regardless of their CHA_2DS_2-VASc score because they have significant thromboembolic risk

Wolff-Parkinson-White Syndrome

- In patients with an accessory pathway that is capable of rapid antegrade conduction (about 25% of Wolff-Parkinson-White patients),[30] preexcited atrial fibrillation can conduct to the ventricles at very fast rates, which can cause syncope and degeneration to ventricular fibrillation
- Use of drugs that preferentially delay atrioventricular nodal conduction can promote rapid conduction down an accessory pathway
- For stable patients presenting in preexcited atrial fibrillation, ibutilide or procainamide are the preferred agents
- Avoid amiodarone, adenosine, digoxin, verapamil, and diltiazem
- Unstable patients should undergo direct-current cardioversion and be referred for catheter ablation of the accessory pathway

Follow-up

Monitoring

- Monitoring of rate and rhythm
  - Patients should be encouraged to report any symptoms concerning for atrial fibrillation recurrence
  - Methods of monitoring include ECGs, Holter monitors, and other longer-duration monitors
  - Portable single-lead ECG recordings using smartphone applications and other wearable devices (eg, watches[27]) increasingly allow reliable atrial fibrillation detection
  - Insertable cardiac monitors offer continuous, longer-term monitoring to detect recurrent atrial fibrillation (up to 4 years); clinical scenarios in which this technique might apply include:
    - Patients with tachycardia-mediated cardiomyopathy whose tachyarrhythmia is asymptomatic and may go undetected, exacerbating the cardiomyopathy
    - Patients who are being managed without anticoagulation (eg, whose CHA_2DS_2-VASc score does not mandate it) in order to detect recurrent atrial fibrillation
    - Long-term monitoring is also a useful research tool
- Therapeutic drug monitoring **(Tables 5 and 6)**
  - Follow-up ECGs are recommended after institution of certain antiarrhythmic drugs:
    - Flecainide and propafenone: at 1 to 2 weeks[31]
    - Dronedarone: at 4 weeks [31]
    - Sotalol: at 1 day and 1 to 2 weeks[31]
    - Ibutalide: continuous ECG monitoring for 4 hours or longer after infusion (until QTc returns to baseline)[32, 33]
    - Amiodarone: at 4 weeks[31]

- Additional routine follow-up for patients on amiodarone includes periodic monitoring for toxicity and other adverse effects, using[34]:
    - Chest radiograph
    - Pulmonary function studies
    - Thyroid and liver function studies
    - Ophthalmology examination

- Anticoagulation
    - Direct oral anticoagulants do not require therapeutic drug monitoring[31,35]
    - Monitor INR of patients on warfarin weekly or more until stable at a level of 2 to 3, and then monthly[31, 32, 35]

Complications

- Heart failure
    - Atrial fibrillation can lead to or exacerbate both heart failure with reduced ejection fraction (ie, tachycardia-mediated ventricular systolic dysfunction) and heart failure with preserved ejection fraction
        - Restoration and maintenance of sinus rhythm may improve and even normalize left ventricular systolic function in patients with tachycardia-mediated cardiomyopathy, as well as improve quality of life[18,19]

- Embolic stroke
    - 5-fold increased risk of stroke with nonvalvular atrial fibrillation[36,37]
    - 20-fold increased risk of stroke with atrial fibrillation associated with mitral stenosis[37]
    - Stroke associated with atrial fibrillation is associated with greater disability and higher mortality than stroke not associated with atrial fibrillation, and recurrence is more likely[5]

  - Anticoagulation (if patient is eligible using CHA_2DS_2-VASc score) and control of other stroke risk factors (eg, hypertension, dyslipidemia) can greatly reduce stroke risk[32]

- Peripheral thromboembolism (rare)

Prognosis

- Atrial fibrillation tends to progress from paroxysmal to persistent over time and may eventually become irreversible
- Outcomes for specific therapies tend to be better for paroxysmal atrial fibrillation than for persistent atrial fibrillation[32]
- Atrial fibrillation is associated with cognitive impairment and 2-fold increased mortality risk. The extent to which these outcomes can be mitigated by restoring sinus rhythm is uncertain[38,39]

Referral

- For patients with a new diagnosis of atrial fibrillation, referral to a cardiologist is recommended
- Consider further referral to a cardiac electrophysiologist for those who require a rhythm control strategy and those with ventricular rates that are difficult to control
- For patients with strong contraindications to oral anticoagulation and high atrial fibrillation–related stroke risks, consider referral to a cardiac electrophysiologist or interventional cardiologist with experience in percutaneous left atrial appendage closure

Screening and Prevention

Screening

- Screening for asymptomatic atrial fibrillation may be opportunistic or systematic and can be performed using several methods with varying sensitivity:
  - Manual pulse palpation
  - 12-lead ECG
  - Holter or longer-term wearable monitors
  - Insertable cardiac monitors

- Smartphones and watches
- Increased availability and popularity of wearable technologies will increase atrial fibrillation screening
- Population-based screening for atrial fibrillation[40]
  - Potential benefit of picking up unrecognized atrial fibrillation in patients who would benefit from anticoagulation to prevent stroke, as well as an opportunity to intervene with rate or rhythm control at an earlier stage
  - Potential downsides include:
    - Risk of false-positive results
    - Increased cost of confirmatory testing
    - Increased patient anxiety
    - Potential higher bleeding complications from increased use of anticoagulation
  - Because of absence of certainty regarding the risk/harm balance of population based screening for atrial fibrillation, differing guideline suggestions exist
    - Generally, current consensus statements recommend targeting screening only in higher risk groups (eg, those older than 65 years)

Prevention

- Atrial fibrillation can happen in healthy and young individuals and may not always be preventable
- When it is associated with obesity, hypertension, diabetes, coronary artery disease, and obstructive sleep apnea, optimal management of these risk factors may reduce the risk of development of atrial fibrillation

Summary

Key Points

- Atrial fibrillation is a supraventricular tachyarrhythmia characterized by chaotic, disorganized electrical activation and inefficient atrial contraction; it is the most common sustained cardiac arrhythmia

- It may be asymptomatic, produce only mild symptoms, or may result in more severe presentations including heart failure secondary to tachycardia-mediated cardiomyopathy
- Diagnosis is made by ECG followed by monitoring to determine whether arrhythmia is persistent or paroxysmal
- Workup includes evaluation of basic metabolic function, assessment of potential triggers (eg, thyroid function), chest radiograph, and echocardiography
- Differential diagnosis includes other arrhythmias that result in irregular and/or rapid rhythms (eg, premature atrial, ventricular, or junctional complexes); atrial flutter or atrial tachycardia with variable atrioventricular conduction; and second-degree atrioventricular block
    - Distinguished by characteristic ECG findings
- Pillars of managing atrial fibrillation include anticoagulation to reduce embolic stroke risk and either rate control or rhythm control
- Rate control is achieved through medication; rhythm control may be achieved by chemical or electrical cardioversion followed by medication or ablation
- Restoration of sinus rhythm improves quality of life, may reduce associated heart failure, and potentially has other benefits including reducing stroke and cardiovascular mortality[41]
- Without intervention, atrial fibrillation tends to progress from paroxysmal to persistent over time and may eventually become permanent
- Data and recommendations about screening are mixed; preventive measures apply to risk factors that can be altered or controlled (eg, obesity, hyperthyroidism)

Alarm Signs and Symptoms

- Alarms signs/symptoms in a patient with atrial fibrillation that should prompt urgent referral to hospital for evaluation include:
    - Sudden focal neurologic deficit
    - Decompensated heart failure symptoms
    - Chest pain/angina symptoms
    - Syncope or near-syncopal episodes

- Significant bleeding in patients on oral anticoagulation for atrial fibrillation
- Head trauma in patients on oral anticoagulation for atrial fibrillation
- Sudden headache in patients on oral anticoagulation for atrial fibrillation

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Figure Legends

Figure 1. Factors to consider in choosing an atrial fibrillation management strategy.

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Figure 2. Left atrial map showing radiofrequency ablation lesions (red tags) encircling the pulmonary vein antra.

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