Management of Acute Atrial Fibrillation

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PROVIDENCE
Ascension

Objectives: Pharmacists

- Explain the epidemiology, pathophysiology, and risks associated with atrial fibrillation (AF)
- Describe the management of acute AF
- Compare anticoagulation options for stroke prevention

Objectives: Pharmacy Technicians

- Describe the risks associated with AF
- Identify the therapy options for acute AF
- List anticoagulants used for stroke prevention

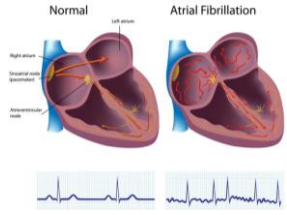
Epidemiology

- AF affects between 2.7 – 6.1 million American adults and is expected to continue to increase in prevalence
- Over 1/3 of patients with AF are ≥ 80 years of age
- Accounts for nearly 500,000 hospitalizations annually
- Estimated to contribute to > 99,000 deaths per year

Lip et al. *J Am Coll Cardiol*. 2015;66(21):2282-2284
January et al. *Circulation*. 2014; 130(23):2071-104

Pathophysiology

- Uncoordinated atrial activation and ineffective atrial contraction due to structural and/or electrophysiological abnormalities
  - **Structural** – HTN, CAD, valvular heart disease, cardiomyopathies, and HF
  - **Electrophysiological** – Ectopic focal triggers, autonomic stimulation



January et al. *Circulation*. 2014; 130(23):2071-104
Atrial fibrillation fact sheet. *CDC*. https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/images/afib_heart.jpg

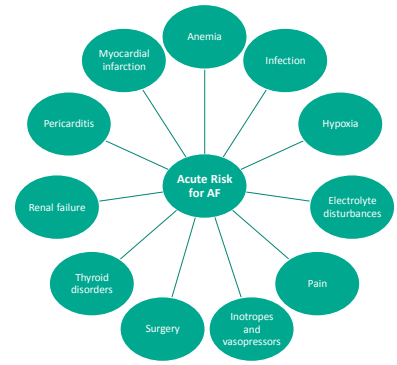
Pathophysiology (cont.)

- Cardiac output (CO) = Heart rate (HR) x **stroke volume (SV)**
- Reduced diastolic filling time and lack of atrioventricular synchrony leads to hemodynamic compromise
- **Complications**
  - Symptoms
    - Fatigue, dizziness/syncope, shortness of breath, palpitations
  - Tachycardia-induced cardiomyopathy
  - Stroke

Walkey et al. *CHEST*. 2015; 148(4):859-864
Marik et al. *J Intensive Care Med*. 2000; 15:181-190

Risk Factors

- Advanced age
- **Hypertension**
- **Diabetes mellitus**
- Myocardial infarction
- Heart failure
- Valvular heart disease
- **Obesity**
- **Obstructive sleep apnea**
- Surgery
- **Smoking**
- **Exercise**
- **Alcohol use**
- **Hyperthyroidism**
- Left atrial enlargement
- Male sex
- European ancestry
- Genetics
- COPD
- Chronic kidney disease



Atrial Fibrillation Definitions

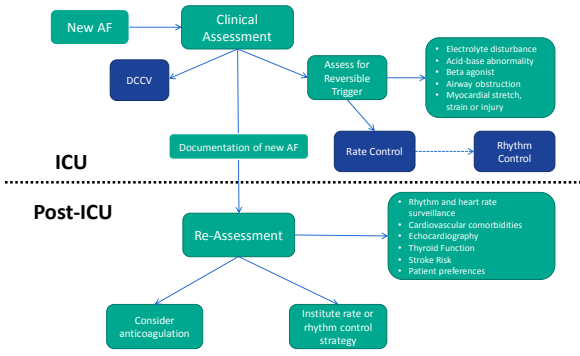
Paroxysmal
- AF terminates spontaneously or with intervention within 7 days

Persistent
- Sustained continuous AF for greater than 7 days

Long-standing Persistent
- Sustained continuous AF for greater than 12 months

Permanent
- Patient and clinician decide to stop further attempts to restore and/or maintain sinus rhythm

Treatment



Atrial Fibrillation in the ICU

- Encountered in 1 in 3 critically ill patients
- Frequently caused by a reversible underlying illness
- ~37% of critically ill patients with new-onset AF develop hemodynamic instability
  - 25% with HR greater than 150 bpm
- No guidelines for treatment of AF in critically ill patients

ICU Management

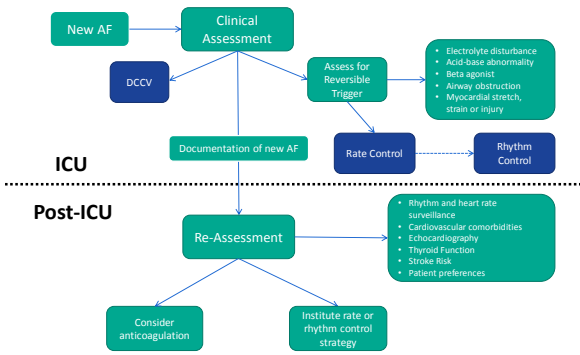
- **2014 AHA/ACC/HRS Atrial Fibrillation Guidelines**
  - Before initiating antiarrhythmic drug therapy, treatment of **precipitating** or **reversible** causes of AF is recommended (Class I; LOE C)

1. Removal of offending agents that increase risk of AF (e.g., beta-agonists)
2. Correction of reversible arrhythmogenic triggers (e.g., electrolyte imbalances, **fluid depletion**, airway obstruction, atrial stretch)

Rate Control	• Adverse effects of AF are due to elevated HR
Rhythm Control	• Adverse effects are due to a loss of atrial systole or where rate control is ineffective or intolerable
Cardioversion	• Hemodynamic instability

Hemodynamically Unstable

- **Direct current cardioversion**
  - Preferred in decompensated HF, ongoing myocardial ischemia, hypotension
- **Arrigo (2015)**
  - 71% have immediate conversion to sinus rhythm, 43% remain in sinus rhythm after one hour, 23% remain in sinus rhythm after 24 hours
- Consider concurrent rate or rhythm control
  - **Rate**
    - Beta-blockers, non-dihydropyridine calcium channel antagonists, digoxin
  - **Rhythm**
    - Amiodarone, magnesium
- **2014 AHA/ACC/HRS Atrial Fibrillation Guidelines**
  - Beta-blocker is preferred due to frequency of elevated catecholamines



Atrial Fibrillation Post-ICU

- AF spontaneously reverts to sinus rhythm within 24 hours in at least 50% of patients
- AF frequently reoccurs following resolution of critical illness
  - 55% of new-onset AF secondary to sepsis patients had AF occurrence within 5 years, compared to 16% of patients who did not have AF during sepsis hospitalization

Rate vs Rhythm

- **Rate control**
  - Attempts to reduce ventricular rate and prolong diastolic filling time
  - Mechanical or pharmacologic therapy
  - **Goal**
    - Minimize symptoms and prevent tachycardia-mediated cardiomyopathy
- **Rhythm control**
  - Attempts to restore atrial contribution to cardiac output
  - Mechanical or pharmacologic therapy
  - **Goal**
    - Clinically meaningful reduction in frequency, duration, and severity of episodes

Rate vs Rhythm (cont.)

- **AFFIRM (2002)**
  - Rate control (resting HR < 80 bpm) vs rhythm control
    - N = 4060
  - Patients ≥65 years with AF that was likely to be recurrent and with risk factors for stroke or death
  - **Primary outcome**
    - No difference in mortality (25.9% rhythm vs 26.7% rate; P = 0.08)
  - Increased hospitalization and side effects with rhythm control
  - **Limitations**
    - Only about 40% stayed in normal sinus rhythm by end of trial
    - Potential selection bias
    - Choice in rhythm control
    - Anticoagulation differences between groups

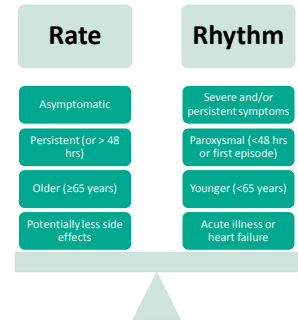
Reasonable to utilize either rate or rhythm control

Rate vs Rhythm (cont.)

- No formal recommendations from guidelines

Factors	
	Nature, frequency, and severity/urgency of symptoms
	Length of continuous AF in patients with persistent AF
	Left atrial size
	Potential precipitants of AF
	Comorbidities (e.g., heart failure)
	Response to previous medications and/or cardioversions
	Age
	Side effects
	Patient preference

Rate vs Rhythm (cont.)



Audience Question

- Which of the following is not a factor favoring rhythm control?

a) Young patient

b) Persistent symptoms

c) Asymptomatic

d) Paroxysmal AF

Rate Control Agents

Beta-blockers	Non-dihydropyridine calcium channel blockers
Digoxin	Amiodarone

Rate Control Target

- **RACE II (2010)**
  - **Lenient** (resting HR < 110 bpm) vs **strict** (resting HR < 80 bpm)
  - N = 614
  - Mean age 68 years, permanent AF, mean follow-up of 2.3 years
  - Primary outcome (non-inferiority):
    - Composite of CV mortality, CHF, stroke, VTE, major bleeding, and arrhythmic events
    - 12.9% lenient vs 14.9% strict control ($p < 0.001$)
  - Target HR achieved in 97.7% lenient vs 75.2% strict
    - Mean HR 93 bpm in lenient and 76 bpm in strict

- Reasonable to target a resting HR < 110
  - Stricter HR control warranted if symptoms are worse with higher HR

Rate Control

- **Beta-blockers (BB)**
  - Negative chronotropic, dromotropic, and bathmotropic effects
    - Slows HR, delays conduction at AV node, and reduces myocardial excitability
    - Also may have vasodilatory and negative inotropic effects
  - Most commonly used drug class for rate control
- **Options**
  - **IV**: Metoprolol, esmolol, propranolol
  - **PO**: Metoprolol, atenolol, nadolol, propranolol, carvedilol
- **Pearls**
  - BB associated with lower risk of in-hospital mortality and need for second agents compared to other rate control options
  - Ideal in hyperadrenergic state or increased sympathetic tone (e.g., thyrotoxicosis, post-operative, pulmonary embolism, etc.)
  - Oral administration can be considered in hemodynamically stable patients
  - Risk for bronchospasm

Rate Control (cont.)

- **Non-dihydropyridine calcium channel blockers**
  - Direct AV nodal effects through blocking of L-type calcium channels
    - Also have vasodilatory and negative inotropic effects
- **Diltiazem**
  - **IV**: 0.25 mg/kg IV bolus over 2 min, then 5-15 mg/h
  - **PO**: 120-360 mg/day
- **Verapamil**
  - **IV**: 0.075-0.15 mg/kg IV bolus over 2 min, then 0.005 mg/kg/min
  - **PO**: 180-480 mg/day
- **Pearls**
  - Diltiazem may have fastest reduction in ventricular rate but experience higher rates of hypotension
  - Verapamil more negatively inotropic than diltiazem
  - Contraindicated in LV dysfunction (negative inotropic effects)
  - May be favored for COPD and asthma patients
  - Oral administration is appropriate unless immediate rate control is required or enteral route is not available

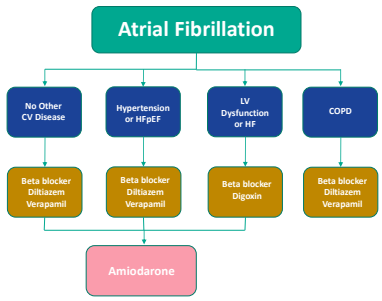
Bosch et al. *CHEST*. 2018; 3692(18)30545-2
Sibley et al. *Can Respir J*. 2015; 22(3):179-182
January et al. *Circulation*. 2014; 130(23):2071-104

Rate Control (cont.)

- **Digoxin**
  - Suppresses AV nodal conduction and enhances vagal tone
    - Also inhibits the sodium-potassium pump to increase contractility
- **Dosing**
  - **IV**: 0.25 mg with repeat dosing to a maximum of 1.5 mg over 24 hours
  - **PO**: 0.125 – 0.25 mg daily
- **Pearls**
  - Not recommended for monotherapy (except decompensated HF)
  - Slow onset of action and does not peak until ~6 hours
  - Loses effectiveness during high sympathetic tone
  - May help reduce hospitalizations in HF
  - Monitor renal function
  - Typically target serum digoxin levels of 0.5-0.9 ng/mL

Arrigo et al. *Crit Care Res Pract*. 2014; 2014:840615
January et al. *Circulation*. 2014; 130(23):2071-104
Ziff et al. *BMJ*. 2015; 351:h4451

Rate Control (cont.)



January et al. *Circulation*. 2014; 130(23):2071-104

Audience Question

- Which of the following are first-line agents for rate control?

a) Beta-blockers

b) Digoxin

c) Non-dihydropyridine calcium channel blockers

d) Amiodarone

e) A and C

Rhythm Control

- **2014 AHA/ACC/HRS Atrial Fibrillation Guidelines**
  - The following antiarrhythmic drugs are recommended to maintain sinus rhythm, depending on underlying heart disease and comorbidities (Class I; LOE A):

Amiodarone	Dofetilide	Dronedarone
Flecainide	Propafenone	Sotalol

January et al. *Circulation*. 2014; 130(23):2071-104

Rhythm Control (cont.)

2014 AHA/ACC/HRS Atrial Fibrillation Guidelines

- Difficulty in achieving adequate rate control
- Persistent AF symptoms
- Young patient age
- Tachycardia-mediated cardiomyopathy
- First episode of AF
- AF precipitated by an acute illness
- Patient preference

Mechanisms

- Antiarrhythmic medications (scheduled and pill-in-the-pocket)
- Catheter ablation
- Cardioversion (electrical and pharmacological)
- Surgical

January et al. *Circulation*. 2014; 130(23):2071-104

Rhythm Control (cont.)

- Most drugs offer 50-60% reduction in odds of recurrent AF during 1 year of treatment
  - Amiodarone has 60-70% efficacy but not first-line due to toxicities
- **Goal**
  - Transition from frequent to infrequent, well-tolerated recurrences
- Pill-in-the-pocket approach reasonable for patients with infrequent symptomatic episodes of paroxysmal AF
  - Establish safety of cardioversion in hospital setting initially
  - Propafenone and dofetilide

January et al. *Circulation*. 2014; 130(23):2071-104
Morady et al. *Braunwald's Heart Disease*. 798-820

Rhythm Control (cont.)

- **Amiodarone**
  - Multichannel blocker which inhibits adrenergic receptors, and affects sodium, potassium, and calcium channels
    - Prolongs cardiac repolarization, refractory period, and conduction rate
- **Dosing** (rhythm control)
  - **IV**: 150 mg IV over 10 minutes, then 1 mg/min for 6 hours, then 0.5 mg/min for 18 hours or change to oral dosing
  - **PO**: 600-800 mg orally daily in divided doses to a total load of up to 10g, then 200 mg daily as maintenance
- **Dosing** (rate control)
  - **IV**: 300 mg over 1 hour, then 10-50 mg/h for 24 hours
  - **PO**: 100-200 mg daily after loading dose

January et al. *Circulation*. 2014; 130(23):2071-104
Khan et al. *Int J Cardiol*. 2003; 89(2-3):239-48

Rhythm Control (cont.)

- **Amiodarone Pearls**
  - Extensive adverse effects and drug interactions
  - Large volume of distribution and relatively slow onset
    - Time to conversion is ~6-8 hours after initiation
  - Potential for worsening hemodynamics
  - May precipitate cardioversion and increase risk for embolization
  - Recommended as last resort option for rate control
    - Slows HR by ~10-12 bpm after 8-12h when given IV
  - **Monitoring**
    - **Baseline**: Liver function tests, chest X-ray, thyroid function tests, pulmonary function tests, electrocardiogram
    - **6 months**: Liver function tests, thyroid function tests
    - **Annual**: Chest X-ray

January et al. *Circulation*. 2014; 130(23):2071-104
Khan et al. *Int J Cardiol*. 2003; 89(2-3):239-48
Cherian et al. *Am J Pharm Benefits*. 2017; 9(4):108-115

Rhythm Control – Catheter Ablation

- **2014 AHA/ACC/HRS Atrial Fibrillation Guidelines**
  - Useful for symptomatic **paroxysmal** or **persistent** AF refractory or intolerant to at least 1 antiarrhythmic medication
  - Reasonable **initial** strategy for **recurrent symptomatic paroxysmal** AF before trials of antiarrhythmic drug therapy
- Strongest evidence for paroxysmal AF in younger patients with little to no structural heart disease
  - Triggers of paroxysmal AF arise from the pulmonary veins in ~90%
- Ablation has higher efficacy than antiarrhythmics in most populations but has major complications in up to 5-6% of patients
  - Antiarrhythmic drug therapy commonly given for 8-12 weeks after ablation

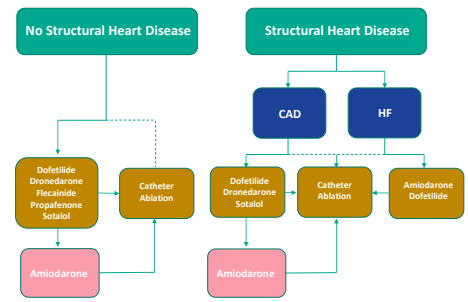
January et al. *Circulation*. 2014; 130(23):2071-104
Morady et al. *Braunwald's Heart Disease*. 798-820
Kirchhof et al. *Eur Heart J*. 2016; 37(38):2893-2962
Bunch et al. *J Thorac Dis*. 2015;7(2):132-141

Rhythm Control – Catheter Ablation

- **CASTLE-AF (2018)**
  - Multicenter, open-label, randomized controlled trial
  - N = 363
  - Catheter ablation vs medical therapy (rate or rhythm control) in medically managed heart failure patients
  - **Primary outcome**: Composite of all-cause mortality or hospitalization for HF
    - Catheter ablation favored [28.5% vs 44.6%; HR, 0.62 (0.43-0.87); **p = 0.007**]
- **CABANA (2018)**
  - Open-label, randomized controlled trial to be published in 2018
  - N = 2204
  - Patients with new-onset or untreated AF
  - **Primary outcome**: Composite of death, disabling stroke, serious bleeding, or cardiac arrest at 5 years
    - Ablation is not superior to drug therapy (8% vs 9.2%; p=0.3)
  - Catheter ablation significantly reduced:
    - Composite death or CV hospitalization (51.7% vs 58.1%; **p = 0.002**)
    - Time to first AF recurrence [HR 0.53 (0.46-0.61); **p < 0.0001**]

Marrouche et al. *N Engl J Med*. 2018;378(5):417-427
Packer et al. *Heart Rhythm Society Scientific Session*. Presentation.

Rhythm Control (cont.)



January et al. *Circulation*. 2014; 130(23):2071-104

Audience Question

- Amiodarone is a first-line option for rhythm control
  a) True
  b) False

Anticoagulation

Anticoagulation

- Atrial fibrillation associated with a 5-fold increased risk of stroke
  - Risk is the same between paroxysmal, persistent, and permanent AF
- Can experience cardioembolic stroke with as little as 6 minutes to 5.5 hours of AF duration
- **2014 AHA/ACC/HRS Atrial Fibrillation Guidelines**
  - Antithrombotic therapy should be **individualized** based on shared decision making after discussion of **risks and risk reductions** of stroke and bleeding and the **patients values and preferences** (Class I; LOE C)

January et al. *Circulation*. 2014; 130(23):2071-104
Passman et al. *Stroke*. 2016; 47:570-576

Anticoagulation (cont.)

Indications for anticoagulation

- **Valvular AF**
  - Mitral stenosis, mitral valve repair, mechanical or bioprosthetic heart valve
- **Hypertrophic cardiomyopathy**
- **Nonvalvular AF with risk factors for stroke**
  - CHA_2DS_2-VASc

January et al. *Circulation*. 2014; 130(23):2071-104
Kirchhof et al. *Eur Heart J*. 2016; 37(38):2893-2962

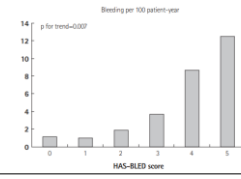
Stroke Risk Estimation

Risk Assessment	Score	Total Patient Score	Adjusted Annual Stroke Rate
$CHADS_2$		0	1.9%
• Heart failure	1	1	2.8%
• Hypertension	1	2	4.0%
• Age ≥ 75	1	3	5.9%
• Diabetes	1	4	8.5%
• Stroke, TIA, thromboembolism	2	5	12.5%
		6	18.2%
CHA_2DS_2-VASc		0	0%
• Congestive heart failure	1	1	1.3%
• Hypertension	1	2	2.2%
• Age ≥ 75	2	3	3.2%
• Diabetes	1	4	4.0%
• Stroke, TIA, thromboembolism	2	5	6.7%
• Vascular disease	1	6	9.8%
• 65-74 years	1	7	9.6%
• Sex category (female)	1	8	6.7%
		9	15.2%

January et al. *Circulation*. 2014; 130:e199-e267
Kirchhof et al. *Eur Heart J*. 2016; 37:2893-2962

Bleed Risk Estimation

Risk Factor Assessment	Score	Total Patient Score	Bleeds/100 patient-years of warfarin
HAS-BLED		0	1.13
• Hypertension	1	1	1.02
• Abnormal renal or liver function (1 point each)	1 or 2	2	1.88
• Stroke	1	3	3.74
• Bleeding	1	4	8.70
• Labile INRs	1	5	12.5
• Elderly (>65 years)	1	6	0
• Drugs or alcohol (1 point each)	1 or2	Any score	1.56



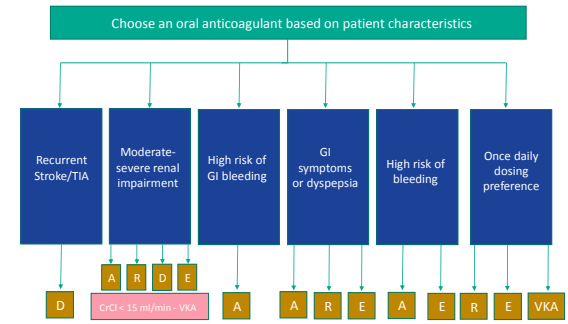
January et al. *Circulation*. 2014;130:e199-e267
Senoo et al. *Korean Circ J*. 2014;44(5):281-290

Oral Anticoagulant Comparison

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Factors II, VII, IX, X, Protein C & S	Thrombin (Factor II)	Factor Xa	Factor Xa	Factor Xa
Dosing (adjustment)	qDay	150 mg BID (75 mg BID)	20 mg qDay (15 mg QD)	5 mg BID (2.5 mg BID)	60 mg qDay (30 mg QD)
Monitoring	INR	None	None	None	None
Peak level (hrs)	4	2-3	3	3-4	1-2
Half-life (hrs)	40	12-17	5-13	10-14	10-14
Renal clearance	< 1%	80%	36%	25%	50%

DOAC Clinical Trials

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Trial	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE-AF
$CHADS_2$ (mean)	2.1	3.5	2.1	2.8
Stroke (risk vs warfarin)	↓	↔	↓	↔
Major bleed (risk vs warfarin)	↔	↔	↓	↓
ICH bleed (risk vs warfarin)	↓	↓	↓	↓
GI bleed (risk vs warfarin)	↑	↑	↔	↑



D = dabigatran; A = apixaban; R = rivaroxaban; E = edoxaban; VKA = warfarin

Lip et al. *J Am Coll Cardiol*. 2015;66(21):2282-2284

Peri-cardioversion Anticoagulation

- Cardioversion promotes formation and migration of thrombi
  - Electrical cardioversion may cause atrial stunning

Pre-cardioversion

- Provide anticoagulation for at least 3 weeks prior to cardioversion or perform transesophageal echocardiography (TEE)
- If duration of AF < 48 hours or hemodynamically unstable then can provide cardioversion immediately

Post-cardioversion

- Provide anticoagulation for ≥ 4 weeks for most patients
- If duration of AF < 48 hours and low thromboembolic risk can withhold anticoagulation (Class IIb; LOE C)
- Long-term anticoagulation should be based on thromboembolic risk

January et al. *Circulation*. 2014;130(23):2071-104
Kirchhof et al. *Eur Heart J*. 2016;37(38):2893-2962

Peri-cardioversion - DOAC

- **2014 AHA/ACC/HRS Atrial Fibrillation Guidelines**
  - Anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for ≥ 3 weeks before and 4 weeks after cardioversion (Class IIa; LOE C)
- **Advantages**
  - Fast onset of action and shorter duration until cardioversion than warfarin
  - No monitoring required
  - Fewer drug-drug interactions
- **Limitations**
  - Data primarily from post-hoc analyses of AF trials and retrospective studies
- DOACs perform comparably to optimally managed warfarin
  - Lack of data with renal dysfunction

January et al. *Circulation*. 2014;130(23):2071-104
Gibson et al. *Ann Pharmacother*. 2018;52(3):277-284

Peri-ablation Anticoagulation

2014 AHA/ACC/HRS Atrial Fibrillation Guidelines

- Anticoagulation is indicated to prevent thromboembolism around the time of catheter ablation **regardless of baseline thromboembolic risk**
- Provide intraprocedural heparin followed by oral anticoagulation for **≥ 2 months** post-procedure
- Anticoagulation beyond 2 months should be **based on patient's thromboembolic risk**

ICU Stroke Risk

- New-onset AF during sepsis associated with 3x risk of stroke than septic patients without new-onset AF
- Increased risk in critically ill patients due to ongoing inflammation and pro-coagulatory state
- **Walkey (2016)**
  - Retrospective cohort of septic AF patients receiving anticoagulation
  - ~1/3 of patients received anticoagulation
  - No difference in stroke events with anticoagulation [1.3% vs 1.4%; RR 0.94 (0.77-1.15)]
  - Increased bleeding [8.6% vs 7.2%; **RR 1.21** (1.1-1.32)]

Walkey et al. *CHEST*. 2015; 148(4):859-864
Arrigo et al. *Crit Care Res Pract*. 2014; 2014:840615
Walkey et al. *JAMA Cardiol*. 2016; 1(6): 682-690

Post-Presentation Questions

Question 1

- Which of this following is a risk factor for atrial fibrillation?
  - a) Advanced age
  - b) Female sex
  - c) Asian descent
  - d) None of the above

Question 2

- Atrial fibrillation that continues for 2 weeks prior to resolution is defined as which of the following?
  - a) Paroxysmal
  - b) Persistent
  - c) Long-standing persistent
  - d) Permanent

Question 3

- Which of the following would not be considered for rate control?
  - a) Beta-blockers
  - b) Non-dihydropyridine calcium channel antagonists
  - c) Dofetilide
  - d) Digoxin

Question 4

- An advantage of using apixaban for stroke prevention is the ability to perform therapeutic drug monitoring
  - a) True
  - b) False