Warfar–IN or Warfar-OUT? And Other Updates in the Management of Atrial Fibrillation

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Conflict of Interest

- I have no conflicts of interest to disclose

Objectives for Pharmacists

- Review general management principles in the treatment of atrial fibrillation
- Summarize updates in the 2014 AHA/ACC/HRS Atrial Fibrillation Guidelines
- Utilize risk stratification schemes to balance risks and benefits to antithrombotic therapy
- Discuss the role of various anticoagulants in stroke prevention management in patients with atrial fibrillation

Objectives for Technicians

- Identify novel oral anticoagulants (NOACs)
- Describe atrial fibrillation and discuss its complications
- Recognize the different doses for the NOACs available on the market

Atrial Fibrillation

- Definition
  - Supraventricular tachyarrhythmia characterized by uncoordinated atrial activity which results in impaired mechanical function
- Epidemiology
  - Affects between 2.3 and 6.1 million American adults
  - Expected to double over the next 25 years
  - Adds $26 billion in U.S. healthcare bill
- Prognosis
  - Mortality is double that of patients in normal sinus rhythm
  - Non-valvular AF: 5-fold increase risk of stroke
  - Mitral stenosis: 20-fold increase risk of stroke

Circulation 2014;129: 1-124

Pathophysiology

Normal Sinus Rhythm **Atrial Fibrillation**

rwjuh.edu

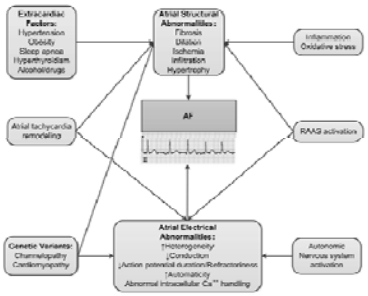
- Normal sinus rhythm
  - SA node→ AV node → ventricular response
- Atrial fibrillation
  - ≥ 1 rapidly firing foci, multiple reentrant wavelets, spiral or wave re-entrant circuits

Circulation 2014;129: 1-124
Image from rwjuh.edu

Pathophysiology

- Normal sinus rhythm
  - Every atrial impulse (SA node) generates a ventricular response
  - 1:1 conduction
  - Atrial and ventricular rate 60-100bpm
- Atrial Fibrillation
  - Multiple atrial stimuli blocked in a random fashion by the AV node
  - Variable conduction
  - Atrial rate ≥300bpm, ventricular rate variable

Pathophysiology



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Symptoms

- Non-existent→ severe
  - Fatigue, dizziness, palpitations, dyspnea, hypotension, syncope, heart failure
  - Decreased cardiac output
    - Suboptimal ventricular rate (too fast/slow)
    - Loss of coordinated atrial contraction
    - Beat to beat variability

Old Classification

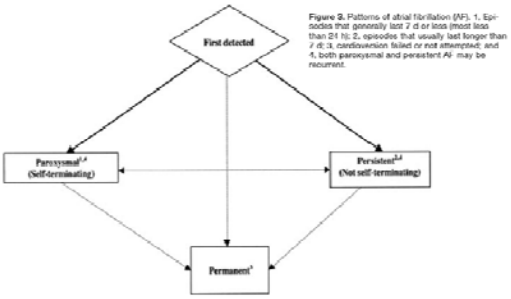

Figure 3. Patterns of atrial fibrillation (AF). 1, Episodes that generally last 7 d or less (most less than 24 h); 2, episodes that usually last longer than 7 d; 3, cardioversion failed or not attempted; and 4, both paroxysmal and persistent AF may be recurrent.

Circulation 2006;114:e257-354

Pharmacist: Question #1

- JC is a 47 year old male with atrial fibrillation interested in the NOACs. JC states that commercials on TV for the NOACs mention atrial fibrillation "not due to a heart valve problem." He turns to you for clarification. Which of the following conditions is considered a heart valve problem? (valvular AF)

A. Rheumatic mitral stenosis
B. Mechanical heart valve
C. Bioprosthetic heart valve
D. Mitral valve repair
E. All of the above

Classification Updated**

Type	Description
Paroxysmal	AF that terminates spontaneously or with intervention within 7 d of onset
Persistent	Continuous AF that is sustained > 7d
Longstanding persistent	Continuous AF of >12 mo duration
Permanent	When there is a joint decision by the patient and clinician to cease further attempts to restore sinus rhythm
Nonvalvular	AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral repair

Simplified scheme for AF classification, no more "lone" AF

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Technician: Question #2

- Which of the following is a devastating consequence of atrial fibrillation?

A. Deep venous thrombosis (DVT)
B. Stroke and systemic embolism
C. High blood pressure
D. Coronary artery disease

Pathophysiology

- Embolism formation
  - Loss of organized atrial contraction causes decreased blood velocity and stasis in the left atrium and left atrial appendage

Management

- Rate control
- Rhythm control
- Anticoagulation

Rate Control

- Improves quality of life, decreases potential for tachycardia induced cardiomyopathy, reduces mortality
- Patients remain in atrial fibrillation
  - Little to no effect on *atrial* rate or rhythm*
  - Decreases conduction through the AV node
  - Slower ventricular rate (heart rate)

*depending on cause

The NEW ENGLAND JOURNAL of MEDICINE

Lenient versus Strict Rate Control in Patients with Atrial Fibrillation

- RACE-II Trial
- Prevention of: Composite of death from CV causes, hospitalization for HF, stroke, systemic embolism, bleeding, life threatening arrhythmias
- <110bpm vs. <80bpm
- Lenient heart rate control is non-inferior to strict heart rate control
  - 12.9% vs 14.9% HR 0.84 (0.58-1.21)

N Eng J Med 2010;362:1363-73

ORIGINAL ARTICLE

Dronedarone in High-Risk Permanent Atrial Fibrillation

- PALLAS Trial
- Dronedarone increased risk of heart failure, stroke and death from CV causes in patients with permanent AF

Table 2. Study Outcomes.*

Outcome	Dronedarone		Placebo		Hazard Ratio (95% CI)†	P Value
	No. of Events	Rate/100 Patient-Yr	No. of Events	Rate/100 Patient-Yr		
First coprimary outcome	43	8.2	19	3.6	2.29 (1.34–3.94)	0.002
Second coprimary outcome	127	25.3	67	12.9	1.95 (1.45–2.62)	<0.001
Death						
From any cause	25	4.7	13	2.4	1.94 (0.99–1.79)	0.049
From cardiovascular causes	21	4.0	10	1.9	2.11 (1.00–4.49)	0.046

N Eng J Med 2011;365:2268-76

2014 Rate Control Update**

- Less than 80 bpm resting (Class IIa)
- Less than 110 bpm (Class IIb)
- Rate controlling agents
  - Beta blockers (Class I)
  - Non-dihydropyridine CCBs (Class I)
  - Digoxin
  - Amiodarone (Class IIb)
  - Dronedarone NOT recommended for rate control in permanent AF (Class III)

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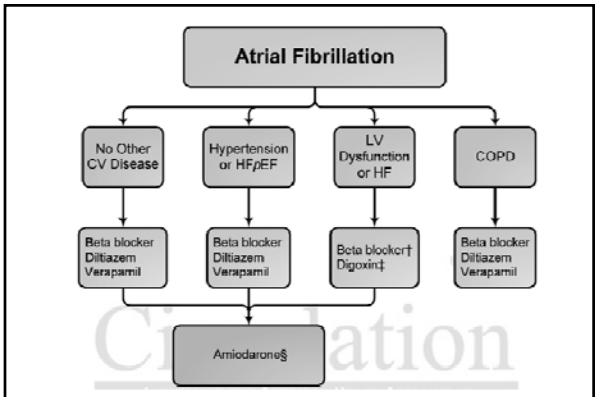
Pharmacist: Question 3

- According to the 2014 Guidelines, which of the following is an appropriate management strategy for a patient in atrial fibrillation?

A. Dronedarone for rate control
B. Resting heart rate target of < 110
C. Diltiazem for rate control in a patient with an EF <40%
D. None of the above are appropriate



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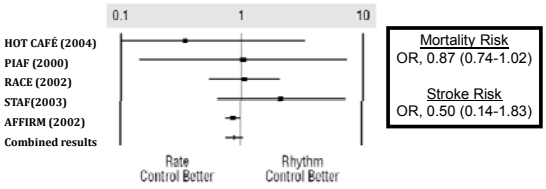
Rate vs. Rhythm Control

- Meta-analysis: rate vs rhythm control



- No mortality difference
- Similar stroke risk, fewer adverse drug effects, hospitalizations

Arch Intern Med 2005;165:258-262

Rhythm Control

- Restoration and maintenance of sinus rhythm
  - Cardioversion
    - Electrical (Class I)
    - Chemical (Class I)
  - Catheter ablation***
- Pharmacologic agents to *maintain* sinus rhythm
  - Increase refractory period
  - Decrease automaticity

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Drugs Recommended for Cardioversion

Drug	Route of Administration	Dosage	
Amiodarone	Oral	600–800 mg daily in divided doses to a total load of up to 10 g, then 200 mg QD as maintenance	
	IV	150 mg over 10 min, then 1 mg/min for 6 h, then 0.5 mg/min for 18 h or change to oral dosing	
Dofetilide	Oral	CrCl (mL/min)	Dose (mcg BID)
		>60	500
		40–60	250
		20–40	125
		<20	Not recommended
Flecainide	Oral	200–300 mg x 1*	
Ibutilide	IV	1 mg over 10 min; may repeat 1 mg once if necessary (weight <60 kg use 0.01 mg/kg)	
Propafenone	Oral	450–600 mg x 1*	

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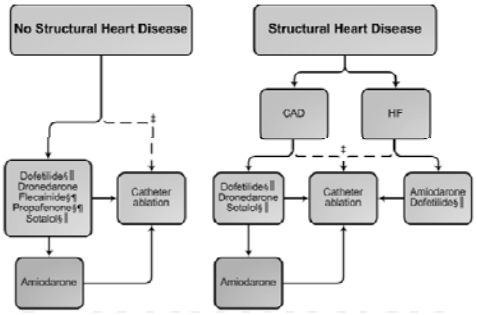
Maintenance of Sinus Rhythm



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Rate vs. Rhythm Control

- Tolerability of rhythm
  - Palpitations
  - Shortness of breath
  - Inability to adequately control rate
- Ability to maintain sinus rhythm
  - Reversibility of precipitants
    - Surgery
    - Alcohol intake
  - Structural changes
  - Number of occurrences

Stroke and Systemic Embolism Prevention

Individualized based on absolute and relative risk of stroke and bleeding and patient values and preferences

(Class I)

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Technician: Question #4

Which of the following agents is not yet approved by the FDA but has a new drug application submitted for stroke prevention in atrial fibrillation?

A. Edoxaban
B. Dabigatran
C. Vorapaxar
D. Apixaban
E. Rivaroxaban

Risk Stratification Updated**

- CHA_2DS_2-VASc scoring
- Irrespective of paroxysmal, persistent or permanent AF
- Limitation with $CHADS_2$
  - Lowest risk patients are not identified with $CHADS_2$ score of 1

CHA_2DS_2-VASc	%/yr
0	0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

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CHA_2DS_2-VASc (Class I)

Risk Factor	Score
C (Heart failure)	1
H (HTN)	1
Age (≥ 75 y)	1
D (diabetes)	1
S (stroke or TIA)	2
Total Score	6

Risk Factor	Score
C (Heart failure)	1
H (HTN)	1
A (age ≥ 75 y)	2
D (diabetes)	1
S (stroke or TIA)	2
V (Vascular Dz)	1
Age (64 to 75 y)	1
Sc (Female)	1
Total Score	9

- Non-valvular AF only
- Age is only counted once

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Pharmacist: Question #5

RF is a 67 year old female with hypertension and type II diabetes. She has newly diagnosed atrial fibrillation and her primary care physician asks you to help estimate her annual risk of stroke.

What is her CHA_2DS_2-VASc score?

A. 1
B. 2
C. 3
D. 4
E. 5

Recommendations Updated**

Old Recommendations	
No risk factors ($CHADS_2$=0)	aspirin 81 to 325mg
1 moderate risk factor ($CHADS_2$=1)	aspirin 81 to 325mg or warfarin
1 high risk* or 2 moderate risk factors	Warfarin

2014 Recommendations (CHA_2DS_2-VASc)§	
0	Reasonable to omit therapy (Class IIa)**
1	No anticoagulation, oral anticoagulation or aspirin (Class IIb)**
≥2	Oral anticoagulation w/ dabigatran, apixaban, or rivaroxaban (Class I)**

§ Non-valvular AF only

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HAS-BLED Score

- New scoring system to assess bleeding risk
- Not studied in combination with CHA_2DS_2-VASc
- No guideline recommendation on use

Risk Factor	Score
H (SBP >160)	1
A (renal/hepatic)	1 each
S (stroke)	1
B (bleeding)	1
L (labile INR)	1
E (elderly >65)	1
D (drugs/alcohol)	1 each
Total	9

*Abnormal renal function: chronic HD, renal transplant, 2.26mg/dL, Abnormal liver function: cirrhosis, bilirubin 2-3x ULN with AST/ALT/Alk Phos 3xULN, Labile INR: <60% TTR, Drugs: excess alcohol use, antiplatelets

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Helpful Hint

- ApiXaban
- RivaroXaban
- EdoXaban

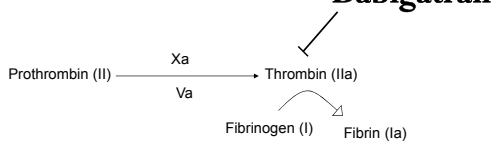
} Anti-Xa Inhibitors

- Dabigatran

} Direct Thrombin Inhibitor

Dabigatran

- Oral direct thrombin inhibitor
- FDA approved October 19, 2010



RE-LY Trial

- Prevention of stroke or systemic embolism
  - Warfarin INR 2-3 (TTR 63%)
  - Dabigatran 150mg PO BID or 110mg PO BID
  - Mean $CHADS_2$ = 2.1

	Dabigatran 150mg	Warfarin	P-value
Stroke or systemic embolism	1.11%	1.69%	<0.001 (non-inferiority)
Bleeding Total	3.11%	3.36%	0.052

- Dabigatran150mg BID is superior to warfarin in stroke and SE prevention
- Similar bleeding risk

N Eng J Med 2009;361:1139-51

ORIGINAL ARTICLE

Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

- Dabigatran should NOT be used in patients with AF and mechanical heart valves (Class III recommendation)
  - RE-ALIGN trial
  - Within 7 days (population A), 3 months out (population B)
  - Dabigatran 150, 220, or 300mg BID based on CrCl
    - Adjusted to serum level of 50ng/mL
- Stopped early do to a high incidence of thromboembolic and bleeding complications

N Eng J Med 2013;369:1206-18

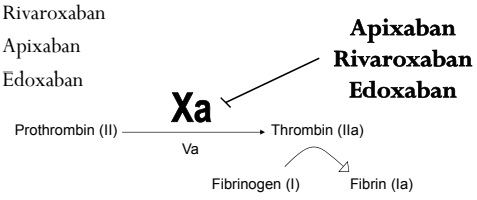
Technician: Question # 6

- Which of the following doses of Dabigatran is FDA approved?

A. 220mg
B. 150mg
C. 110mg
D. 300mg

Oral Anti-Xa Inhibitors

- Direct, competitive anti-Xa inhibitors
  - Does not require AT like fondaparinux
- Rivaroxaban
- Apixaban
- Edoxaban



Rivaroxaban

ROCKET-AF

- Prevention of stroke and systemic embolism
  - Warfarin INR target 2.5 (TTR 57.8%)
  - Rivaroxaban 20mg daily, (15mg CrCl: 30-49)
- High Risk Patients
  - Mean $CHADS_2$ = 3.4

	Rivaroxaban (n=7081)	Warfarin (n=7090)	p-value
Stroke or systemic embolism	1.71%	2.6%	<0.001
Major bleeding	3.6%	3.4%	0.58

- Rivaroxaban is ***non-inferior*** to warfarin
- Similar bleeding risk

N Engl J Med 2011;365:883-891

Apixaban

ARISTOTLE

- Prevention of stroke or systemic embolism
  - Warfarin targeted INR 2.5 (TTR 62.2%)
  - Apixaban 5mg BID*
  - Mean $CHADS_2$=2.1

	Apixaban (n=9120)	warfarin (n=9081)	p-value
Stroke or systemic embolism	1.27%	1.6%	0.01
Major bleeding	2.13%	3.09%	<0.01

- Apixaban is superior to warfarin
- Less bleeding than warfarin

*2.5mg BID >2 of ≥80yo, ≤60kg, 1.5mg/dL

N Engl J Med 2011:365:981-92

AVERROES

- Prevention of stroke and systemic embolism prevention in pts unsuitable for VKA
  - Aspirin 81-324mg daily OR Apixaban 5mg BID
  - Mean $CHADS_2$=2

	Apixaban (n=2808)	ASA (n=2791)	P-value
Stroke or systemic embolism	1.6%	3.7%	<0.001
Major Bleeding	1.4%	1.2%	0.57

- Trial terminated early due to clear benefit of apixaban
- Apixaban appears to be superior to ASA
- Similar bleeding risk

N Eng J Med 2011:364:806-17

ENGAGE AF-TIMI 48

- Prevention of stroke or systemic embolism
  - Edoxaban 60mg (30mg*) OR warfarin
  - Mean $CHADS_2$=2.8

	High Dose Edoxaban	Low Dose Edoxaban	Warfarin
Stroke or systemic embolism	1.18 % (p<0.001)	1.61 % (p=0.005)	1.5 %
Major Bleeding	2.75 % (<0.001)	1.61 % (<0.001)	3.43%

- Both doses are non-inferior to warfarin
- Both doses had lower rates of bleeding

* CrCl 30-50mL/min, < 60kg, DDI

N Engl J Med 2013:369:2093-2104

Pharmacist: Question #7

- RF is our 67 year old female with hypertension and type II diabetes. Her PCP asks for your recommendation on which anticoagulant therapy to select for stroke prevention. What do you recommend?
  - Home meds: atorvastatin, lisinopril, metformin, metoprolol
  - Crcl: 60mL/min, weight: 85 kg

A. Apixaban 5mg BID
B. Rivaroxaban 20mg daily
C. Warfarin titrated to an INR of 2-3
D. Dabigatran 150mg BID

Chronic Kidney Disease

	Dose	Renal Dose	Studied dose
Dabigatran	150mg BID	Crcl 15-30: 75mg BID CrCl <15: avoid use	RELY: 150mg BID PK data: 75mg
Rivaroxaban	20mg daily	Crcl: 15-50: 15mg daily Crcl < 15: avoid use	ROCKET-AF Crcl 30-50:15mg
Apixaban	5mg BID	2.5mg BID if ≥ 2 of Scr ≥1.5mg/dL, age ≥80, wt ≤60 kg	AVERROES/ARISTOLTE Excluded Scr >2.5mg/dL, Crcl <25

- For patients with non-valvular AF with a CHA_2DS_2-VASc of ≥ 2 and who have ESRD or are on HD, it is reasonable to prescribe warfarin (Class IIa)

End Stage Renal Disease

- FDA approval: Dose for ESRD patients maintained on hemodialysis (HD)
  - 5 mg orally twice daily
  - 2.5mg BID with ≥80 years or body weight ≤60 kg
- Pharmacokinetic study in 16 patients
  - 8 normal renal function, 8 ESRD
- 1 dose of apixaban

Wang X, Song Y, Tirucheraiet G, et al. Poster 2012 American College of Clinical Pharmacology Annual Meeting

Special Circumstances Updated**

- Valvular AF
  - Mitral stenosis: warfarin
  - Mechanical valves: warfarin based on type and location of valve
- Post coronary revascularization w/ CHA_2DS_2-VASc ≥ 2
  - Reasonable to use clopidogrel with anticoagulant without ASA
- Cardioversion
  - Stable patients with ≥ 48 hrs in AF or Aflutter
    - Anticoagulation 3 wks before/4 wks after regardless of CHA_2DS_2-VASc
      - Warfarin (Class I)
      - NOACs (Class IIa)

Circulation 2014;129: 1-124

Conclusions

- Updates
  - Acceptance of lenient heart rate control
  - Recommendation against of dronedarone for rate control in permanent AF
  - Use of the CHA_2DS_2-VASc instead of $CHADS_2$
  - Reasonable to omit therapy for CHA_2DS_2-VASc of 0
  - De-emphasis on the use of aspirin for stroke prevention
  - Recommendation for the use of NOACs
  - Recommendation against dabigatran for mechanical heart valves
  - Recommendations in special circumstances
  - ***Catheter ablation in patients with symptomatic, paroxysmal AF who have not responded to or tolerated antiarrhythmic medications (Class I) or in selected patients with symptomatic, paroxysmal AF *prior* to a trial of medical therapy

Circulation 2014;129: 1-124

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