(PBL) Atrial Fibrillation: Outpatient Management of Non-Valvular A-Fib

Philip Dooley, MD, FAAFP

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- Some specific medications or dosage forms of individual beta-blockers, calcium channel blockers or other anti-arrhythmic medications recommended in evidence-based national guidelines may not be FDA approved for the treatment of non-valvular atrial fibrillation.

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Dr. Dooley joined the Via Christi Family Medicine Residency as core faculty in 2014 and was appointed Program Director in 2016. He now oversees the training for 54 residents, continues to precept in the two residency clinics, and rotates as an attending physician on the inpatient teams. He earned his medical degree from the University of Michigan Medical School in Ann Arbor, and completed his residency at the Headquarters Air Armament Center Family Medicine Residency at Eglin Air Force Base, Florida. He served as active-duty core residency faculty at Eglin for four years and Reserve Chief of Aerospace Medicine at McConnell Air Force Base in Wichita, Kansas, for three years. He has been recognized as Eglin's Residency Faculty of the Year (2014) and as Air Force Reserve Command Outstanding Field Grade Officer Assigned to a Reserve Medical Unit (2017). Dr. Dooley has special interests in cardiology and tropical medicine, and pursues his interest in the practical application of evidence-based medicine as the Co-Editor-in-Chief for the Family Physicians Inquiries Network's HelpDesk Answers.

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Learning Objectives

1. Practice applying new knowledge and skills gained from Atrial Fibrillation sessions, through collaborative learning with peers and expert faculty.

2. Identify strategies that foster optimal management of atrial fibrillation, within the context of professional practice.

3. Formulate an action plan to implement practice changes, aimed at improving patient care.

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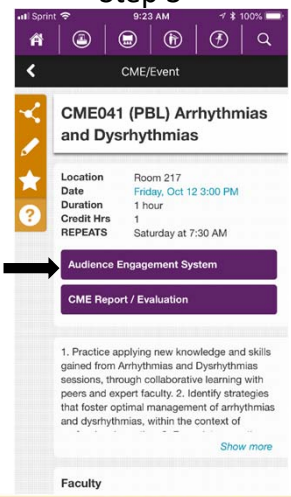
Audience Engagement System

Step 1

Step 2

Step 3



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Associated Session

- Atrial Fibrillation: Outpatient Management of Non-Valvular A-Fib

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Chronic Management of A-Fib

- Up to 4 cases today
- Not working on diagnosis, all cases are patients who have A-fib or A-flutter
- Two primary management goals
  - Stroke prevention (mortality/morbidity)
  - Alleviate symptoms (improve quality of life)

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Calculating Risks

- Risk of thromboembolism
  - $CHADS_2$ or CHA_2DS_2–VASc
- Risk factors for bleeding
  - HAS-BLED

www.sparctool.com

Risk Stratification "One Stop Shopping"

to facilitate **Shared Decision Making**

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Case #1

- 82 year old female
- Quit smoking 15 years ago after CABG
- Experienced a minor stroke 12 months ago while taking aspirin
- Switched to aspirin + dipyridamole

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Case #1 Continued

- Recently admitted for another stroke
- Paroxysmal A-fib detected on telemetry

- Declined the “rat poison” they wanted to start her on in the hospital because she wanted to talk about it with you…

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Case #1 – Meds / Vitals / Labs

- Aspirin / dipyridamole
- Lisinopril (for hypertension)
- Metoprolol (for rate-control)
- Atorvastatin
- Levothyroxine
- Omeprazole

- Normal echo
- BP: 135/80
- Pulse: 98 (regular)
- Labs: Normal

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Decision Point / AES Question #1-A

- What are the CHA_2DS_2–VASc and HAS-BLED scores for this patient?

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Case #1 - Key Facts

- 82 year old female
- Hypertension
- History of stroke
- Known coronary artery disease
- Taking aspirin
- Normal echo
- BP: 135/80
- Labs: Normal

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Calculated Scores

CHA_2DS_2–VASc = 7

- Hypertension
- Age (2 points)
- Stroke (2 points)
- Vascular disease
- Female

HAS-BLED = 3

- Stroke
- Elderly
- Drugs (aspirin)

SUPPLEMENTAL MATERIAL

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Decision Point / AES Question #1-B

- Do you want to change their medication regimen to reduce the risk of thomboembolism or bleeding?
- If yes, what would you recommend?
- If no, why would you keep them on their current regimen?

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Generally avoid dual anticoagulation…

- "The AAFP **strongly recommends against** dual treatment with anticoagulant and antiplatelet therapy in most patients who have atrial fibrillation (moderate-quality evidence)."

- European Guidelines following ACS and/or Stent
  - 1 to 6 months of triple therapy
  - 5 to 11 months of dual therapy

ANTICOAGULATION GUIDELINES

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Table Discussion Question #1

- What if the patient is concerned about the lack of a reversal agent for the direct oral anti-coagulants?

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Case #1 - Current Status

- Generally feeling well
- Only knows she's in A-fib if she checks her pulse and it is irregular, but denies SOB, DOE, fatigue, lightheadedness, dizziness, palpitations, orthopnea
- Resting HR usually 90s-100s

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Decision Point / AES Question #1-C

- What changes, if any, would you make to her treatment plan?

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Case #1 - Current Status (Take 2)

- Feels terrible when in A-fib with fatigue and palpitations, resting HR is 90s-100s
- Maxed out β-blocker, still symptomatic
- Switched to CCB (diltiazem or verapamil)
  - Titrated to maximum dose
  - Still remains symptomatic when in A-fib

STRICT/LENIENT TARGETS

SUPPLEMENTAL MATERIAL

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Decision Point / AES Question #1-D

- What changes, if any, would you make to her treatment plan?

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Case #2

- 59 year old male with heart failure diagnosed 3 years ago, NYHA Class II
- Known paroxysmal and persistent A-fib for the last 5 months
- Currently treated with warfarin to reduce his risk of thromboembolism

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Case #2 – Past Medical History

- Heart failure with reduced ejection fraction of 32% (HFrEF), normal left heart cath, no valvular dz on echo, has AICD
- Hypertension
- Alcohol dependence (down to 2 beers/day)
- Knee osteoarthritis
- Bleeding gastric ulcer in 2014 and 2016
  - Stopped aspirin in 2014
  - Treated for H. pylori in 2016

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Case #2 – Meds / Vitals / Labs

- Warfarin
- Lisinopril
- Metoprolol succinate
- Furosemide
- Atorvastatin
- Naprosyn

- Afebrile
- BP: 165/95
- Pulse: 78 (irreg / irreg)
- Labs
  - INR 2.7, time in the therapeutic range ~55%
  - Otherwise normal

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Decision Point / AES Question #2-A

- What are the CHA_2DS_2–VASc and HAS-BLED scores for this patient?

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Case #2 - Key Facts

- 59 year old male
- Heart failure (EF 32%)
- History of upper GI bleed
- EtOH ~14 drinks/week
- NSAID for osteoarthritis
- No history of diabetes, stroke, MI, CAD or other vascular disease
- Afebrile
- BP: 165/95
- Pulse: 78 (irreg / irreg)
- Labs
  - INR 2.7, TTR ~55%
  - Otherwise normal

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Case #2 - Calculated Scores

CHA$_2$DS$_2$–VASc = 2

- HFrEF
- Hypertension

HAS-BLED = 5

- Uncontrolled HTN
- Bleeding
- Labile INR
- Drugs (NSAIDs)
- Drugs (EtOH >8/wk)

SUPPLEMENTAL MATERIAL

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Decision Point / AES Question #2-B

- Do you want to change their medication regimen to reduce the risk of thomboembolism?
- If yes, what would you recommend?
- If no, why would you keep them on their current regimen?

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Management of Bleeding Risk

- HAS–BLED score ≥3 warrants additional monitoring and efforts to reduce bleeding risk by addressing modifiable risk factors.
- Bleeding risk scores **should not be used to exclude patients** from anticoagulation therapy.
  - Highest bleeding risk associated with greatest benefit
  - Don't withhold VKA / DOAC only due to fall risk (2014 UK)

ANTICOAGULATION GUIDELINES

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HAS–BLED Modifiable Risks

SUPPLEMENTAL MATERIAL

Risk factors		Definitions	Points
H	Hypertension	Uncontrolled with systolic BP >160 mm Hg	1
A	Abnormal liver function	Cirrhosis, bilirubin >2x normal, or liver enzymes >3x normal	1
	Abnormal renal function	Dialysis, transplant, or serum creatinine >2.26 mg/dL	1
S	Stroke history	Including asymptomatic lacunar infarcts seen on imaging	1
B	Bleeding predisposition	History of major bleeding due to any cause	1
L	Labile INR	Time in therapeutic range <60%	1
E	Elderly	Age >65 years	1
D	Drug	Antiplatelet agents, including NSAIDs	1
	Alcohol use	>8 drinks per week	1

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Table Discussion Question #2

- How do you explain the risk / benefit balance of anticoagulation if they are concerned about experiencing another GI bleed?

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Case #2 – Current Status

- Feels okay when in sinus rhythm
- Symptoms are severe to disabling when in A-fib

SUPPLEMENTAL MATERIAL

FMX

Decision Point / AES Question #2-C

- What changes, if any, would you make to his treatment plan?

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Case #3

- 76 y/o female with longstanding persistent A-Fib
- Moderate rheumatic mitral stenosis
- Type 2 Diabetes, controlled with insulin
- Hypertension, well controlled
- End-state renal disease (CrCl 12 mL/min) with mature AV fistula
- Admitted to the hospital 9 mo ago due to HFpEF

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Case #3 - Calculated Scores

$\underline{CHA_2DS_2}$–VA$\underline{Sc}$ = 6

- HFpEF hospitalization
- Hypertension
- Age (2 points)
- Diabetes
- Female

H$\underline{A}$S-$\underline{B}$L$\underline{E}$D = 2

- Abnormal renal function
- Elderly

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Case #3 continued

- On warfarin and rate-controlled with a β-blocker
- 3 months ago she was a restrained passenger in MVA with airbag deployment, airlifted to Level 1 trauma center with subdural hematoma; INR 2.5; reversed
- 8 day admission followed by subacute rehab
- Has returned to living independently with complete hematoma resolution
- Her cardiologist and neurologist want her to restart warfarin, but she wants your opinion first…

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Case #3 - Calculated Scores

$\underline{CHA_2DS_2}–VA\underline{Sc}$ = 6

- HFpEF hospitalization
- Hypertension
- Age (2 points)
- Diabetes
- Female

H<u>A</u>S-<u>B</u>L<u>E</u>D = 3

- Abnormal renal function
- Bleeding
- Elderly

SUPPLEMENTAL MATERIAL

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Decision Point / AES Question #3

- How would you counsel this patient?

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Case #4

- 74 year old male with permanent A-fib
- A-fib diagnosed incidentally during preventive medicine visit
- On aspirin for primary prevention of CAD
- No significant PMH
- Rate controlled and asymptomatic on a CCB
- Normal echocardiogram
- BP: 127/65
- Pulse: 78 (irreg / irreg)
- Labs: Normal

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Case #4 - Calculated Scores

CHA_2DS_2–VASc = 1

- Age (1 point)

HAS-BLED = 2

- Age (1 point)
- Drugs (aspirin)

SUPPLEMENTAL MATERIAL

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Decision Point / AES Question #4

- Do you want to change their medication regimen to reduce the risk of thomboembolism or bleeding?
- If yes, what would you recommend?
- If no, why would you keep them on their current regimen?

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Wrap Up

- Use CHA_2DS_2–VASc to assess thromboembolism risk (SOR C)
- Assess bleeding risk & address modifiable risk factors (SOR C)
- Consider DOACs over warfarin for **non-valvular** AF (SOR B)
  (prevent more strokes and lower all-cause mortality)
- Warfarin is only option for valvular AF or severe CKD (SOR A)
- Rate-control strategy for most patients (SOR B)
  - Rhythm-control if symptoms are refractory
  - Rhythm-control if < 65 yo with symptoms
  - Invasive management if symptoms persist

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Questions

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Contact Information

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Case #1 – Supplemental Material

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CHA_2DS_2–VASc (0-9 scale)

Return to case 1 2

Risk factor	Points
Congestive heart failure (current HFrEF or hospitalization due to HFpEF)	1
Hypertension (history of, regardless of control)	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke/TIA/Thromboembolism (to include PE)	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65-74 years	1
Sex **c**ategory (ie, female sex)	1

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Annual rate of hospital admission or death due to thromboembolism

CHA_2DS_2–VASc score	Annual Risk (%) †	95% CI
0	0.7	0.6-0.8
1	1.5	1.3-1.6
2	2.9	2.8-3.1
3	4.3	4.1-4.5
4	6.5	6.2-6.7
5	10.0	9.5-10.4
6	12.5	11.8-13.3
7	14.0	12.6-15.5
8	14.1	10.9-18.2
9	15.9	8.0-31.8

†10-year follow-up data for a Danish cohort of 73,538 patients with AF who did not receive anticoagulation.

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"CHADS-VASc better identifies truly low risk individuals who are unlikely to benefit from oral anticoagulation."

CHA_2DS_2–VASc score	Annual Risk (%) †	95% CI
0	0.7	0.6-0.8
1	1.5	1.3-1.6
2	2.9	2.8-3.1
3	4.3	4.1-4.5
4	6.5	6.2-6.7
5	10.0	9.5-10.4
6	12.5	11.8-13.3
7	14.0	12.6-15.5
8	14.1	10.9-18.2
9	15.9	8.0-31.8

$CHADS_2$ of 0-1

Female patient ≥75 years with vascular disease would have a CHADS2 of 1 but a CHADS-VASc of 4

Olesen JB, Torp-Pedersen C, Hansen ML, et al. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study. *Thromb Haemost.* 2012;107:1172-1179.

†10-year follow-up data for a Danish cohort of 73,538 patients with AF who did not receive anticoagulation.

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HAS–BLED (0-9 scale)

Return to case 1 2

Risk factors		Definitions	Points
H	Hypertension	Uncontrolled with systolic BP >160 mm Hg	1
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	Abnormal renal function	Dialysis, transplant, or serum creatinine >2.26 mg/dL	1
S	Stroke history	Including asymptomatic lacunar infarcts seen on imaging	1
B	Bleeding predisposition	History of major bleeding due to any cause	1
L	Labile INR	Time in therapeutic range <60%	1
E	Elderly	Age >65 years	1
D	Drug	Antiplatelet agents, including NSAIDs	1
	Alcohol use	>8 drinks per week	1

Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093-1100.

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Return to case
1 2

A-fib & A-flutter Anticoagulation Guidelines

CHA_2DS_2-VASc	Men	Women
0	No anticoagulation	N/A
1	Discuss the risks and benefits of anticoagulation*	No anticoagulation
≥2	Oral anticoagulation strongly recommended (DOAC preferred**)	

*Aspirin and/or clopidogrel only if there is an indication other than stroke prevention (e.g. post-MI, recent stent)

**This point is only included in Canadian and European guidelines.

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Generally avoid dual anticoagulation…

- "The AAFP **strongly recommends against** dual treatment with anticoagulant and antiplatelet therapy in most patients who have atrial fibrillation (moderate-quality evidence)."

- European Guidelines following ACS and/or Stent
  - 1 to 6 months of triple therapy
  - 5 to 11 months of dual therapy

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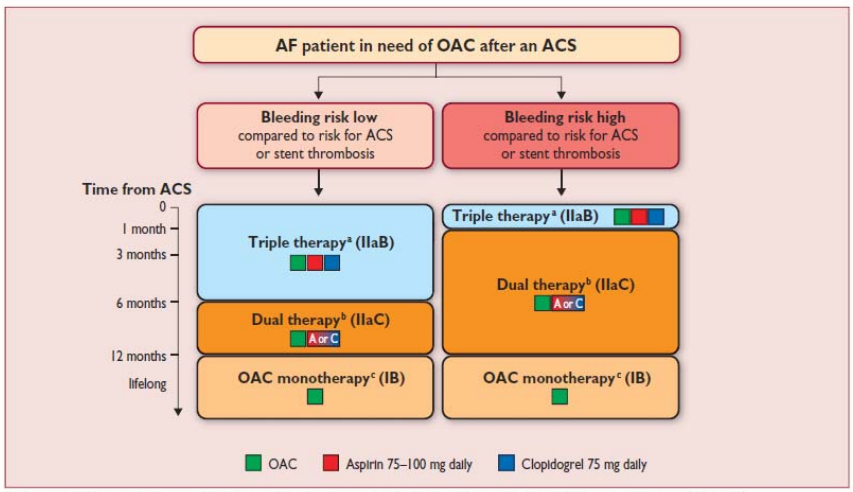

ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.
[a]Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients, especially those not receiving a stent or patients at a longer time from the index event.
[b]OAC plus single antiplatelet.
[c]Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events.

Figure 12 Antithrombotic therapy after an acute coronary syndrome in atrial fibrillation patients requiring anticoagulation.

European guidelines regarding simultaneous anticoagulation & antiplatelets **After ACS**

Kirchhof P, et al. 2016 ESC Guidelines. *Europace*. 2016;18(11):1609-1678. [1]

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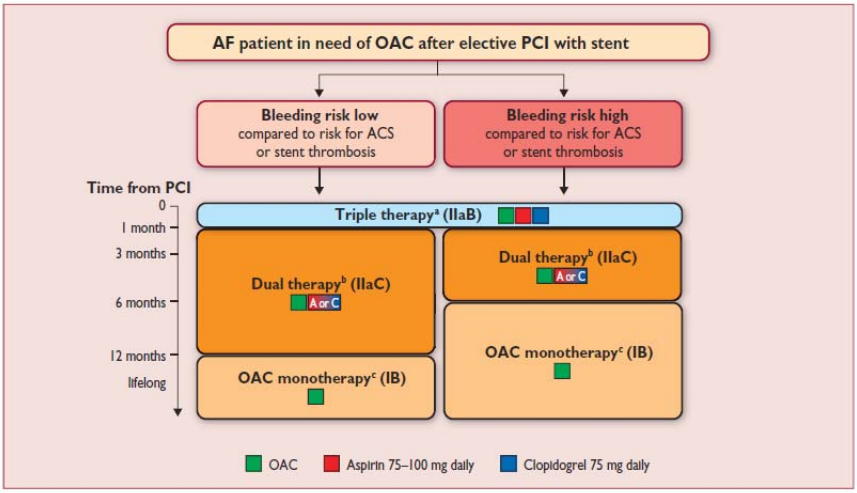

ACS = acute coronary syndrome; AF = atrial fibrillation; OAC = oral anticoagulation (using vitamin K antagonists or non-vitamin K antagonist oral anticoagulants); PCI = percutaneous coronary intervention.
[a]Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients.
[b]OAC plus single antiplatelet.
[c]Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events.

Figure 13 Antithrombotic therapy after elective percutaneous intervention in atrial fibrillation patients requiring anticoagulation.

European guidelines regarding simultaneous anticoagulation & antiplatelets **After PCI with stent**

Kirchhof P, et al. 2016 ESC Guidelines. *Europace*. 2016;18(11):1609-1678. [1]

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Rate-control Strategy Targets

- Strict
  - Resting HR target <80
  - Used in the AFFIRM trial, equivalent to or better than rhythm control in elderly patients
- Lenient
  - Resting HR target <110
  - Equivalent to strict target, with fewer side effects if patients' symptoms were controlled

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Rate Control Medications

Drug	Loading dose	Maintenance dose	Specific indications	Cautions or adverse effects
Beta-blockers				
Atenolol	N/A	25-100 mg/d	None	Blunts response to exercise Contraindicated in the presence of bradycardia, pre-excitation, decompensated HF
Bisoprolol	N/A	2.5-10 mg/d	HFrEF	
Carvedilol	N/A	3.125-25 mg BID	HFrEF	
Esmolol	500 mcg/kg bolus IV over 1 min, then 50-300 mcg/kg/min IV	N/A	Short duration, use if uncertain that beta-blocker will be tolerated	
Metoprolol succinate (XL)	N/A	50-400 mg/d	Used in high adrenergic tone (ie, post-operative AF) Following acute MI HFrEF (only XL)	
Metoprolol tartrate	2.5-5.0 mg IV bolus over 2 min (Max: 3 doses)	25-100 mg BID		
Nadolol	N/A	10-240 mg/d	None	
Propranolol	1 mg IV over 1 min, up to 3 doses at 2-min intervals	10-40 mg TID or QID	None	

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From Dooley, Doolittle, Knauss and Crowl, *J Fam Pract*, Vol 66, No 1. Jan 2017.

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Rate Control Medications

	Loading dose	Maintenance dose	Specific indications	Cautions or adverse effects
Non-dihydropyridine CCBs				
Diltiazem	0.25 mg/kg IV bolus over 2 min, then 5-15 mg/hr	120-360 mg/d (ER)	Chronic obstructive pulmonary disease Asthma	Contraindicated in the presence of HFrEF or pre-excitation
Verapamil	0.075-0.15 mg/kg IV bolus over 2 min; may give additional 10 mg after 30 min if no response, then 0.005 mg/kg/min infusion	180-480 mg/d (ER)		
Other				
Amiodarone	300 mg IV over 1 hr, then 10-50 mg/hr over 24 hr	100-200 mg/d	HFrEF	Pre-excitation
Digoxin[†]	0.25 mg IV with repeat dosing (Max: 1.5 mg in 24 hr)	0.125-0.25 mg/d	HFrEF Additive when combined with beta-blocker or CCB	Not optimal for rapid control Pre-excitation

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From Dooley, Doolittle, Knauss and Crowl, *J Fam Pract*, Vol 66, No 1. Jan 2017.

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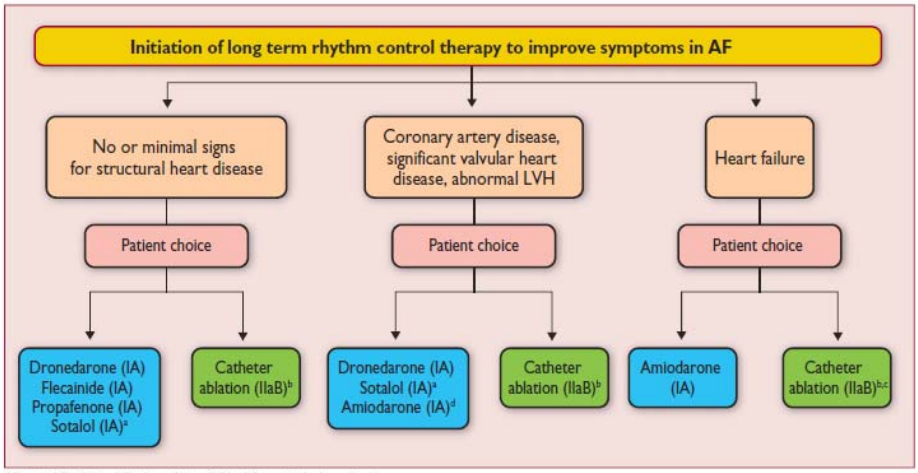

AF = atrial fibrillation; HF = heart failure; LVH = left ventricular hypertrophy;
[a]Sotalol requires careful evaluation of proarrhythmic risk.
[b]Catheter ablation should isolate pulmonary veins and can be performed using radiofrequency or cryoballoon catheters.
[c]Catheter ablation as a first-line therapy is usually reserved for heart failure patients with tachycardiomyopathy.
[d]Amiodarone is a second-choice therapy in many patients because of its extracardiac side-effects.

Figure 17 Initiation of long-term rhythm control therapy in symptomatic patients with atrial fibrillation.

European guidelines regarding initial rhythm control options

Start Case 2

1

Kirchhof P, et al. 2016 ESC Guidelines. *Europace*. 2016;18(11):1609-1678.

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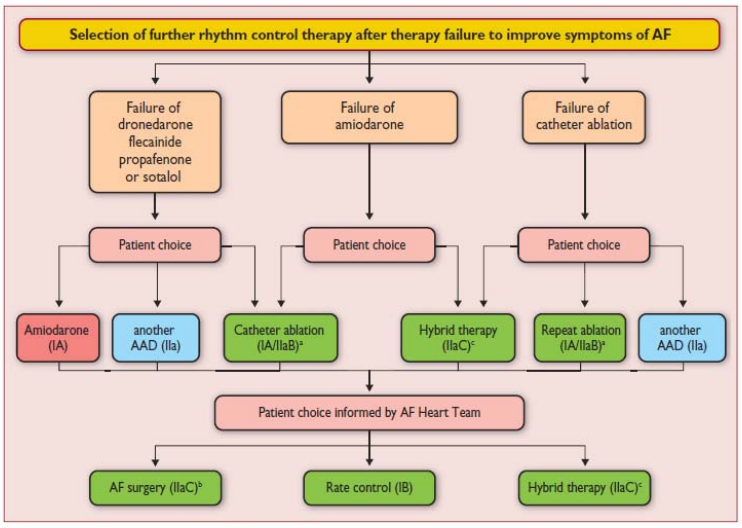

AAD = antiarrhythmic drug; AF = atrial fibrillation; PVI = pulmonary vein isolation.
[a]catheter ablation should target PVI. IA for paroxysmal AF, IIaB for persistent and long-standing persistent AF.
[b]AF surgery may be PVI (e.g. in paroxysmal AF) or maze surgery (e.g. in therapy-refractory or persistent and long-standing persistent AF).
[c]Hybrid therapy involves combination of antiarrhythmic drugs, catheter ablation, and/or AF surgery.

Figure 20 Choice of rhythm control therapy following treatment failure.

European guidelines regarding rhythm control after failure of first line options

Start Case 2 1

Kirchhof P, et al. 2016 ESC Guidelines. *Europace*. 2016;18(11):1609-1678.

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Rhythm Control Medications

RHYTHM CONTROL

Drug	Cardioversion dose	Maintenance of sinus rhythm dose	Specific indications	Cautions or adverse effects
Class IC – For cardioversion, give beta-blocker or CCB ≥30 min prior to a IC agent‡				
Flecainide	Oral: 200-300 mg x 1‡	50-200 mg q12 hr	AF without structural heart disease Pill-in-the-pocket‡	Sinus or AV node dysfunction Heart failure CAD Atrial flutter Brugada syndrome Renal or liver disease
Propafenone	Oral: 450-600 mg x 1‡	IR: 150-300 mg q8 hr ER: 225-425 mg q12 hr	AF without structural heart disease Pill-in-the-pocket‡	Sinus or AV node dysfunction Heart failure CAD Atrial flutter Brugada syndrome Liver disease Asthma

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Start Case 2

1

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Rhythm Control Medications

RHYTHM CONTROL

Drug	Cardioversion dose	Maintenance of sinus rhythm dose	Specific indications	Cautions or adverse effects
Class III				
Amiodarone	Oral: 600-800 mg/d divided doses, max total load of 10 g IV: 150 mg over 10 min, then 1 mg/min for 6 hr, then 0.5 mg/hr for 18 hr	Oral: 400-600 mg/d for 2-4 wks, then 100-200 mg/d IV: 150 mg over 10 min, then 1 mg/min for 6 hr, then 0.5 mg/hr for 18 hr	LV hypertrophy HF CAD Previous MI	Phlebitis (with IV route) Hypotension Bradycardia QT prolongation Torsades de pointes GI upset Constipation Increased INR
Dofetilide	Oral: 125 to 500 mcg q12 hr based on renal function	125-500 mcg q12 hr. Must monitor QTc interval and dose accordingly	None	Prolonged QT interval Renal disease Hypokalemia Hypomagnesemia Diuretic therapy
Sotalol	N/A	40-160 mg q12 hr	None	Prolonged QT interval Renal disease Hypokalemia Hypomagnesemia Diuretic therapy Sinus or AV nodal dysfunction HF Asthma

From Dooley, Doolittle, Knauss and Crowl, *J Fam Pract*, Vol 66, No 1. Jan 2017.

Start Case 2

1

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Start Case 2

"Pill-in-the-Pocket"

- For patients with infrequent AF episodes
- Reduces burden of daily medicine administration and risks from side effects
- Efficacy and safety should first be proven in a monitored setting
  - Flecainide or propafenone are preferred agents
  - Diltiazem or beta-blocker 30 minutes prior to Class IC antiarrhythmic if not using chronic AV nodal blocker*

*A-fib can convert to A-flutter (or can be A-flutter) and the slowed rate may lead to 1:1 conduction (which usually does not happen with A-flutter at a rate of 300)

2014 AHA/ACC/HRS Guideline

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Case #2 – Supplemental Material

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Management of Bleeding Risk

- HAS–BLED score ≥3 warrants additional monitoring and efforts to reduce bleeding risk by addressing modifiable risk factors.
- Bleeding risk scores **should not be used to exclude patients** from anticoagulation therapy.
  - Highest bleeding risk associated with greatest benefit
  - Don't withhold VKA / DOAC only due to fall risk (2014 UK)

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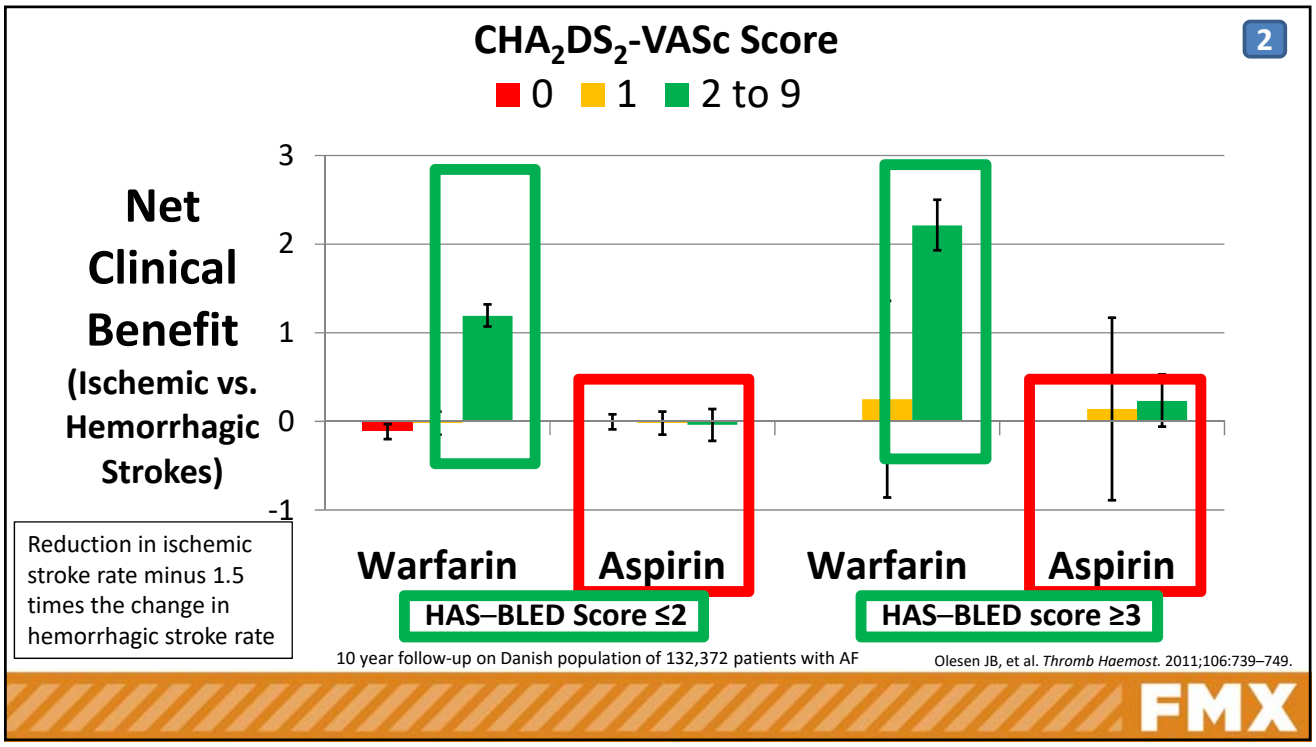

Rate vs. Rhythm Control

- Rate-control is generally first line AAFP
  - No mortality difference & ↓ hospitalizations vs. rhythm-control
  - Younger patients (<65 yo) not included in most trials
- Target resting heart rate less than 110 bpm AAFP
  - Less than 80 if symptomatic at higher rates
- Persistent symptoms is the #1 indication for strategy change
- Digoxin associated with ↑ all-cause mortality (even in HFrEF)

2014 AHA/ACC/HRS Guideline & 2017 AAFP Guideline

FMX

Rate-control is generally first line

The Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825-1833.

Target resting heart rate <110 bpm if asymptomatic

Lenient HR target outcomes are similar to strict HR targets in patients with AF

Van Gelder IC, Groenveld HF, Crijns HJGM, et al. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med*. 2010;362:1363-1373.

Digoxin is associated with increased all-cause mortality regardless of heart failure status

Wang ZQ, Zhang R, Chen MT, et al. Digoxin is associated with increased all-cause mortality in patients with atrial fibrillation regardless of concomitant heart failure: a meta-analysis. *J Cardiovasc Pharmacol*. 2015;66:270-275.

Digoxin all-cause mortality (HR=1.4, 95% CI 1.2-1.6, P=.0001)

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Multiple national guidelines

First Line Rhythm Control?

- Consider early rhythm control in some
  - AF has a reversible cause
  - HF primarily caused by AF (ablation for LVEF ≤ 35%)
  - Newly detected AF
  - Atrial flutter suitable for ablation
  - More suitable based on clinical judgment (i.e. younger patients)
- If symptoms remain, change your strategy

Start Case 3

2

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CASTLE-AF (Feb 2018)

Start Case 3

- 397 patients with HFrEF (of 3,013 assessed for eligibility)
- Candidate for rhythm control (failed or refused meds)
- Implanted defibrillator was required
- Ablation (intervention) vs. Meds (control) for rhythm-control
  - ↓ AF burden, ↑ LVEF, ↑ 6-minute walk distance
  - All-cause mortality (13 vs 25%; *P*=.01; number needed to treat [NNT]=9)
  - Cardiovascular hospitalizations (36 vs 48%; *P*=.04; NNT=8)
  - Worse outcomes in patients with LVEF <25%
- Supported by industry (device manufacturer)
- "At five years 63% of patients in the ablation group were in sinus rhythm, as compared with 22% of those in the medical-therapy group (P<0.001). It is notable that ablation did not completely eliminate atrial fibrillation in all patients but rather decreased the time in atrial fibrillation to roughly 25%, whereas the time in atrial fibrillation among patients who received medical therapy was 60%."

EAST trial investigating rhythm control including early use of catheter ablation within the first year after the onset of A-fib

FMX

Surgical Options

- Thromboembolism prophylaxis
  - Percutaneous left atrial appendage (LAA) occlusion
  - Surgical excision of the LAA*
- Rhythm Control
  - Catheter directed ablation (Radiofrequency or Cryoballoon)
    - All guidelines require periprocedural anticoagulation
    - 2017 guidelines update now recommends continued long-term anticoagulation in most patients after ablation
  - Atrial maze procedure*
- Rate Control
  - AV nodal ablation with ventricular pacemaker

*If undergoing cardiac surgery for another reason (ex: CABG)

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1. None of the surgical options are great for refractory cases and are still undergoing long term follow-up studies or technique refinement
2. Should have failed at least one antiarrhythmic medication before trying catheter ablation (except for things like WPW)
3. Recurrence of AF after ablation is 3-7 times more likely to be asymptomatic and can recur late
4. Stroke rates post CA are low, but studies suffer from inadequate follow-up for high stroke risk patients
5. 90% of patients in both arms of CASTLE-AF were anticoagulated at final follow-up.

- CABANA Trial comparing ablation, rate-control and rhythm control
  - Prelim results: http://www.acc.org/latest-in-cardiology/clinical-trials/2018/05/10/15/57/cabana
  - More to be released at ESC meeting in late August (FMX slides due in July)

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Case #3 – Supplemental Material

FMX

Chai-Adisaksopha C, et al. *Thromb Haemost*. 2015;114:819–825

After major GI bleeding?

- Restart warfarin after a single GI bleed

Outcome	Hazard Ratio	95% CI
Mortality	**0.76**	**0.66–0.88**
Thromboembolism	**0.68**	**0.52–0.88**
Recurrent GI bleed	1.2	0.97 to 1.5

Meta-analysis of observational / cohort studies

Start Case 4 3

- Restarting DOACs has not been systematically studied
  - Consider a DOAC with a lower risk of GI bleeding
  - Dabigatran 110 mg BID, Apixaban 5 mg BID or Edoxaban 30 mg/d

FMX

Nielsen PB, Larsen TB, Skjøth F, Lip GY. *JAMA Intern Med*. 2017;177(4):563-570.

After intracranial hemorrhage?

- Restart warfarin after a single ICH (single retrospective cohort)

Outcome	Type of ICH	Adjusted Hazard Ratio	95% CI
Mortality	**Hemorrhagic Stroke**	**0.51**	**0.37–0.71**
	Traumatic	**0.35**	**0.23–0.52**
Ischemic stroke or Systemic embolism	Hemorrhagic Stroke	0.49	0.24–1.02
	Traumatic	0.40	0.15–1.11
Recurrent ICH	Hemorrhagic Stroke	1.31	0.68–2.50
	Traumatic	**0.45**	**0.26–0.76**

- Restarting DOACs has not been studied
  - Consider a DOAC with a lower risk of ICH
  - Dabigatran 110 mg BID or Edoxaban 30 mg/d

Start Case 4 3

FMX

Nielsen PB, Larsen TB, Skjøth F, Lip GY. *JAMA Intern Med*. 2017;177(4):563-570.

1. Nationwide Danish retrospective cohort (1998-2016) identified 2,415 patients with ICH (1,325 hemorrhagic / 1090 traumatic) Approx 2/3 did not resume warfarin while ~1/3 resumed warfarin.
2. Adjusted for Age, CHADS-VASc and HAS-BLED, sex, previous TE, vascular disease, HTN, DM, ASA, beta-blocker, NSAID, statin, hospital LOS after index event (**but not quality of warfarin treatment, no INR information or size of ICH**)
3. Mean CHADS-VASc = 3.7-4.1; Mean HAS-BLED = 3.6 Start Case 4
4. 96 ischemic strokes, 139 recurrent ICH, 514 deaths (25.4%!)-34.9% (discontinued warfarin) vs. 15.5% (resumed warfarin) 3

- APACHE-AF (phase II trial of apixaban after ICH is in progress)

European Society of Cardiology Guidelines recommend Dabigatran 150 mg after an ischemic stroke in patients on Rivaroxaban or Apixaban

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Case #4 – Supplemental Material

FMX

Adapted and modified from Verdecchia, Angeli, Bartolini et al. *Expert Opin Drug Saf*, 2014

Relative Efficacy (from a network meta-analysis)

Stroke or Embolism	SUCRA
Dabigatran 150 mg	98
Apixaban 5 mg	75
Edoxaban 60 mg	55
Rivaroxaban 20 mg	54
Dabigatran 110 mg	46
Warfarin	**21**
Edoxaban 30 mg	1

All Strokes	SUCRA
Dabigatran 150 mg	97
Apixaban 5 mg	73
Rivaroxaban 20 mg	64
Edoxaban 60 mg	52
Dabigatran 110 mg	41
Warfarin	**21**
Edoxaban 30 mg	2

Ischemic Stroke	SUCRA
Dabigatran 150 mg	94
Apixaban 5 mg	68
Rivaroxaban 20 mg	66
Warfarin	**48**
Edoxaban 60 mg	47
Dabigatran 110 mg	26
Edoxaban 30 mg	1

All-cause Mortality	SUCRA
Edoxaban 30 mg	77
Dabigatran 150 mg	65
Apixaban 5 mg	61
Edoxaban 60 mg	49
Dabigatran 110 mg	49
Rivaroxaban 20 mg	44
Warfarin	**5**

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Adapted and modified from Verdecchia, Angeli, Bartolini et al. *Expert Opin Drug Saf*, 2014

Relative Safety (from a network meta-analysis)

Major Bleeding	SUCRA
Edoxaban 30 mg	100
Apixaban 5 mg	80
Edoxaban 60 mg	61
Dabigatran 110 mg	58
Dabigatran 150 mg	28
Warfarin	**14**
Rivaroxaban 20 mg	9

Intracranial Bleeding	SUCRA
Dabigatran 110 mg	89
Edoxaban 30 mg	87
Dabigatran 150 mg	56
Apixaban 5 mg	55
Edoxaban 60 mg	45
Rivaroxaban 20 mg	19
Warfarin	**0.1**

GI Bleeding	SUCRA
Edoxaban 30 mg	99
Apixaban 5 mg	79
Warfarin	**65**
Dabigatran 110 mg	53
Edoxaban 60 mg	35
Dabigatran 150 mg	15
Rivaroxaban 20 mg	5

Myocardial Infarction	SUCRA
Rivaroxaban 20 mg	90
Apixaban 5 mg	78
Edoxaban 60 mg	69
Warfarin	**57**
Edoxaban 30 mg	24
Dabigatran 150 mg	18
Dabigatran 110 mg	15

FMX

Stroke or Embolism	SUCRA
Dabigatran 150 mg	98
Apixaban 5 mg	75
Edoxaban 60 mg	55

All Strokes	SUCRA
Dabigatran 150 mg	97
Apixaban 5 mg	73
Rivaroxaban 20 mg	64

Ischemic Strokes	SUCRA
Dabigatran 150 mg	94
Apixaban 5 mg	68
Rivaroxaban 20 mg	66

All-cause Mortality	SUCRA
Edoxaban 30 mg	77
Dabigatran 150 mg	65
Apixaban 5 mg	61

Major Bleeding	SUCRA
Edoxaban 30 mg	100
Apixaban 5 mg	80
Edoxaban 60 mg	61
Dabigatran 110 mg	58

Intracranial Bleeding	SUCRA
Dabigatran 110 mg	89
Edoxaban 30 mg	87
Dabigatran 150 mg	56
Apixaban 5 mg	55

GI Bleeding	SUCRA
Edoxaban 30 mg	99
Apixaban 5 mg	79
Warfarin	65
Dabigatran 110 mg	53

Myocardial Infarction	SUCRA
Rivaroxaban 20 mg	90
Apixaban 5 mg	78
Edoxaban 60 mg	69
Warfarin	57

OVERALL BALANCE?

Wrap-Up

FMX

Stroke or Embolism	SUCRA
Dabigatran 150 mg	98
Apixaban 5 mg	75
Edoxaban 60 mg	55

All Strokes	SUCRA
Dabigatran 150 mg	97
Apixaban 5 mg	73
Rivaroxaban 20 mg	64

Ischemic Strokes	SUCRA
Dabigatran 150 mg	94
Apixaban 5 mg	68
Rivaroxaban 20 mg	66

All-cause Mortality	SUCRA
Edoxaban 30 mg	77
Dabigatran 150 mg	65
Apixaban 5 mg	61

Major Bleeding	SUCRA
Edoxaban 30 mg	100
Apixaban 5 mg	80
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Edoxaban 30 mg	87
Dabigatran 150 mg	56
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Apixaban 5 mg	79
Warfarin	65
Dabigatran 110 mg	53

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Rivaroxaban 20 mg	90
Apixaban 5 mg	78
Edoxaban 60 mg	69
Warfarin	57

MAXIMIZE EFFICACY?

Adapted and modified from Verdecchia, Angeli, Bartolini et al. *Expert Opin Drug Saf*, 2014

Wrap-Up

FMX

Stroke or Embolism	SUCRA
Dabigatran 150 mg	98
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All Strokes	SUCRA
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Edoxaban 30 mg	87
Dabigatran 150 mg	56
Apixaban 5 mg	55

GI Bleeding	SUCRA
Edoxaban 30 mg	99
Apixaban 5 mg	79
Warfarin	65
Dabigatran 110 mg	53

Myocardial Infarction	SUCRA
Rivaroxaban 20 mg	90
Apixaban 5 mg	78
Edoxaban 60 mg	69
Warfarin	57

MINIMIZE SIDE EFFECTS?

Adapted and modified from Verdecchia, Angeli, Bartolini et al. *Expert Opin Drug Saf*, 2014

Wrap-Up

FMX

- Verdecchia, Angeli, Bartolini et al. *Expert Opin Drug Saf*, 2014

1. Bayesian network meta-analysis may give some hints but is not conclusive (compare with a frequentist approach which just says they're all the same "non-inferior")
2. "SUCRA is a numerical summary that would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst."
3. DOACs are generally safer, especially for intracranial bleeding, despite the lack of a reversal agent

Wrap-Up

FMX