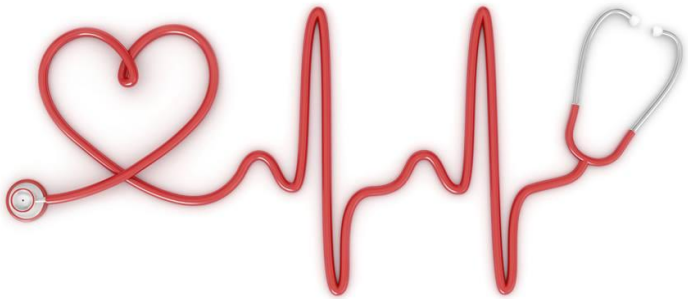
Atrial Fibrillation



LMPS Residents: Arjun Randhawa and Tessa Milic

Facilitator: Herb Wong

Learning Objectives

1. Describe the pathophysiology, clinical presentation and risk factors for atrial fibrillation (AF) and atrial flutter (AFL)
2. Describe the ECG features of AF/AFL and discuss diagnostic methods
3. Classify the different types of AF
4. Differentiate the treatment approaches for acute and chronic AF
5. Discuss antithrombotic therapy for AF

Background

- AF is the most common arrhythmia
  - Affects over 200 000 Canadians

- Nearly 25% of ischemic strokes in people over 40 are caused by AF

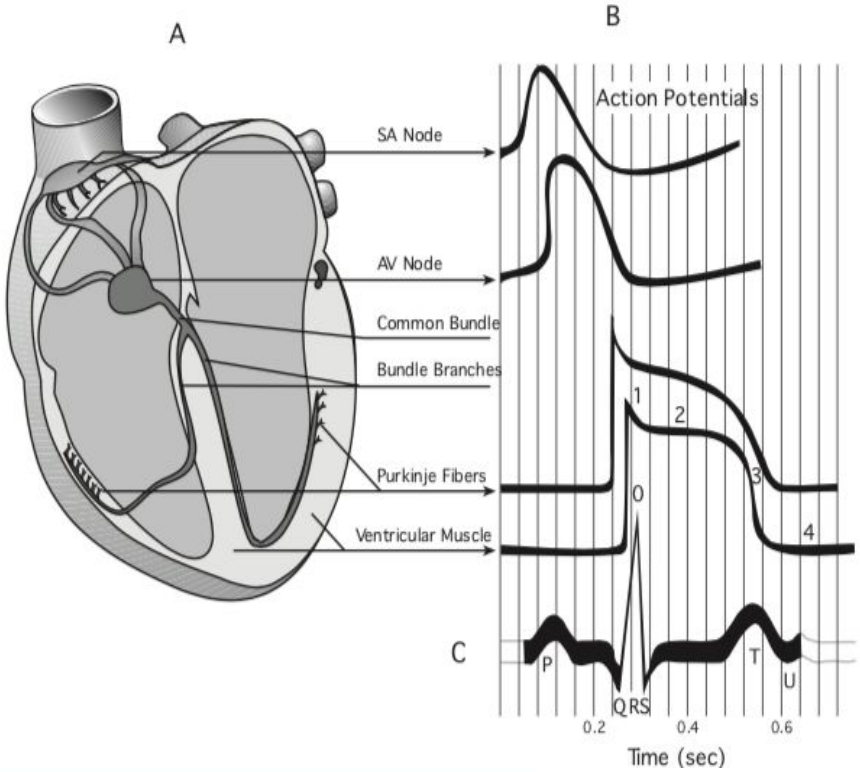
- Mean cost per AF hospital admission is $4735 (CAD)

1. https://www.heartandstroke.ca/heart/conditions/atrial-fibrillation
2. CJC. 2011 27; 401-403.

Pathophysiology

Cardiac Action Potential

- Phase 0: Na influx (depolarization)
- Phase 1: K efflux
- Phase 2: Ca influx, K efflux
- Phase 3: K efflux (repolarization)
- Phase 4: Limited K efflux (resting)



Applied Therapeutics. 2009; 19: 1-32.

Arrhythmia Pathophysiology

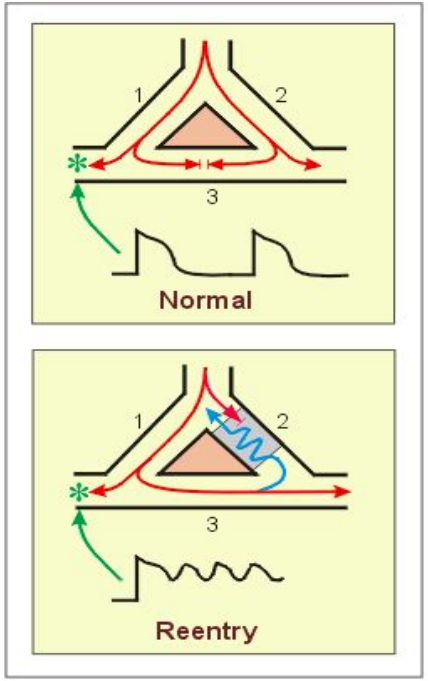
- Causes of arrhythmias:
  - **Abnormal impulse formation**
    - Abnormal automaticity
    - Triggered activity
  - **Abnormal impulse conduction**
    - Re-entry circuits
    - Block

Applied Therapeutics. 2009; 19: 1-32.

Re-entry Mechanism

- Caused by an excitatory wave traveling in a circular path → re-activation of site of origin

- Underlying cause of Atrial Flutter



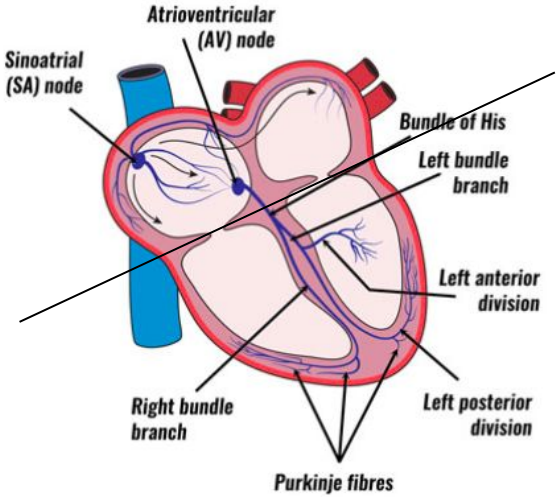
1. Applied Therapeutics. 2009; 19: 1-32.
2. https://www.cvphysiology.com/Arrhythmias/A008c

Classification of Arrhythmias

- Rate
  - Bradycardia
  - Tachycardia

- Origin
  - Supraventricular:
    - Sinus bradycardia/tachycardia, PSVT, **AFL**, **AF**, WPW
  - Ventricular:
    - PVCs, VT, VF

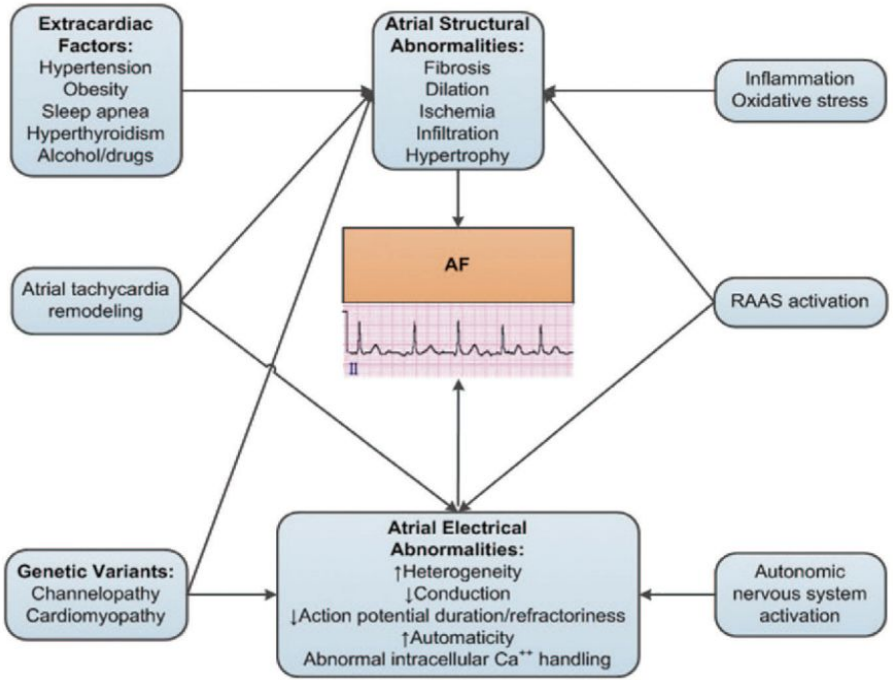
Supraventricular



Ventricular

1. JACC. 2014: 64 (No 21)
2. Applied Therapeutics. 2009; 19: 1-32.

AF Pathophysiology

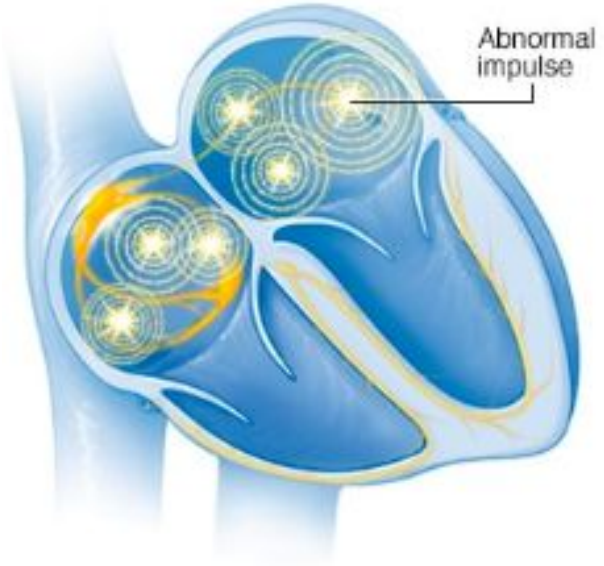


JACC. 2014: 64 (No 21)

AF Pathophysiology

- Multiple signals bombard the AV node → “irregularly irregular” rapid ventricular rate (**90-170 BPM**)

- Inefficient atrial contraction
  - ↑ risk of thromboembolic ischemic stroke



1. Applied Therapeutics. 2009; 19: 1-32.
2. https://www.mayoclinic.org/diseases-conditions/atrial-fibrillation/symptoms-causes/syc-20350624

AF Classification

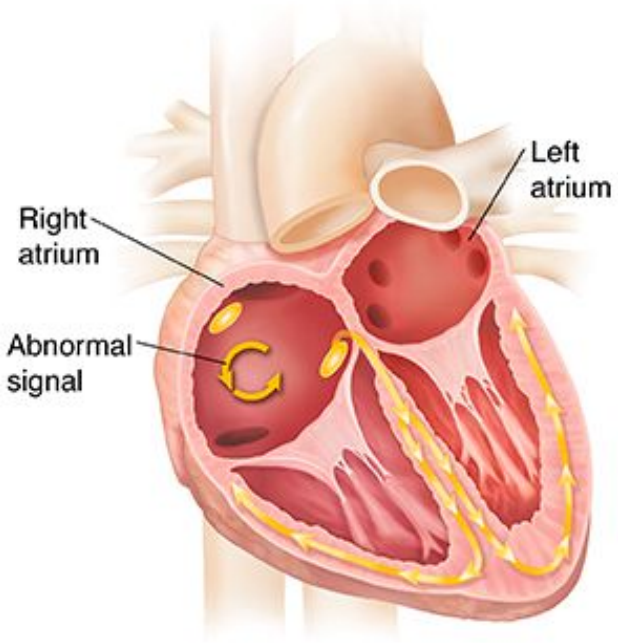
Paroxysmal	< 1 week and converts spontaneously to sinus rhythm
Persistent	> 1 week or requires an intervention to terminate
Long-standing persistent	> 1 year, but sinus rhythm could be restored
Permanent	Cannot be converted to sinus rhythm

JACC. 2014: 64 (No 21)

AFL Pathophysiology

- Secondary to a reentrant ectopic loop in the right atrium
  - Rapid atrial activity (**250-350 BPM**)
  - Loop typically can be ablated

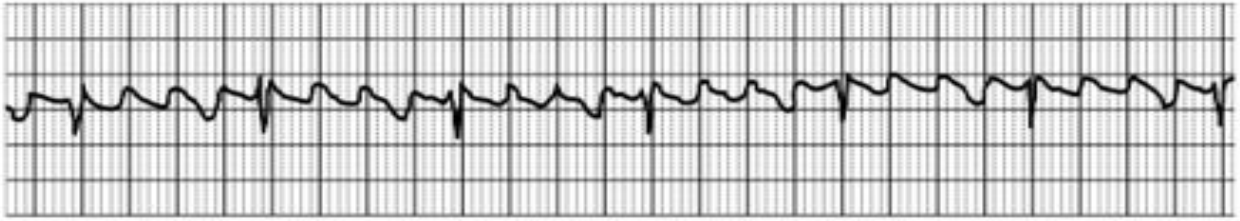
- AV node works as a “brake” to most circuit impulses
  - Ventricular rate **~150 BPM**



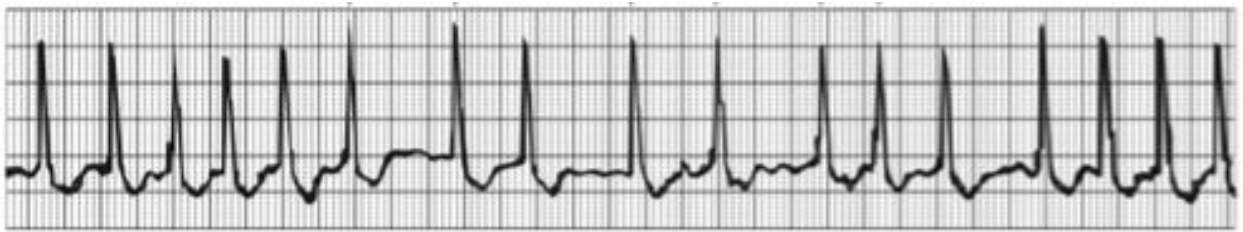
1. https://www.fairview.org/patient-education/90710
2. UptoDate, Phang et al, 2019.

Test Your Knowledge

A

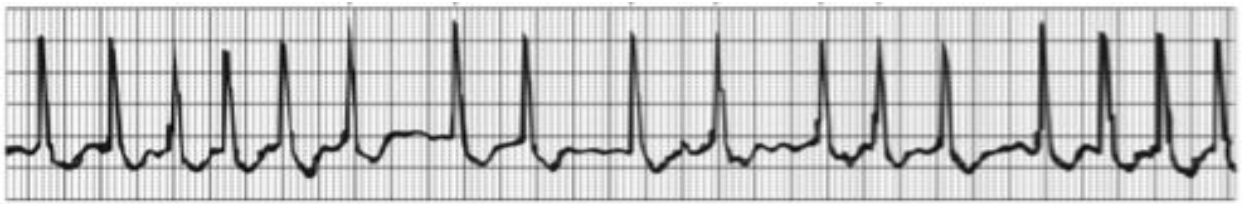


B



Applied Therapeutics. 2009; 19: 1-32.

ECG: Atrial Fibrillation

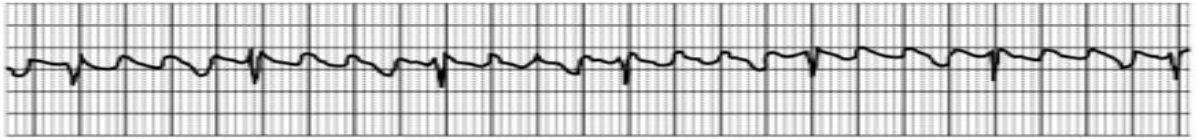


- Rapid ventricular rate (90 - 170 BPM)

- Abnormal ECG features:
  - P-wave absent (ectopic foci in right atrium)
  - R-R instability
  - Narrow QRS (exception: wide QRS with aberrant activation)

1. Applied Therapeutics. 2009; 19: 1-32.
2. UptoDate, Phang et al, 2019.

ECG: Atrial Flutter



- Sawtooth atrial waves (II, III, aVF)
- Variable ventricular rate dependant on AV block (~150 BPM)
  - AV block most commonly 2:1
- Regular R-R interval

1. Applied Therapeutics. 2009; 19: 1-32.
2. UptoDate, Kumar et al, 2019.

Risk Factors: AF

Modifiable	Non-modifiable
• Cardiac disease: hypertension, MI, VTE, CHF • Obesity • Obstructive sleep apnea • Heavy alcohol use • Hyperthyroidism • Electrolyte abnormalities • Infection • Diabetes mellitus	• Increasing age • Family history • European ancestry

JACC. 2014: 64 (No 21)

Clinical Presentation

Symptoms	Signs

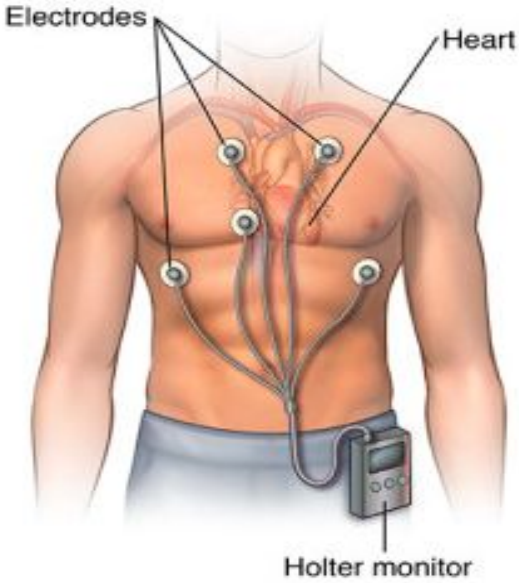
• **CNS:**
  ○ Fatigue, dizziness, presyncope/light-headedness
• **RESP:**
  ○ Dyspnea
• **CVS:**
  ○ Palpitations/"fluttering"
  ○ Chest pain
  ○ Hypotension
  ○ Heart failure
	• **Typically present:**
	  ○ Tachycardia
	  ○ Irregular pulse
	
	• **May be present:**
	  ○ Valvular heart disease or myocardial abnormalities

JACC. 2014: 64 (No 21)

Diagnosis

- Must be confirmed via ECG

- Various options to capture an ECG:
  - Holter monitor
  - Telemetry
  - Event recorders
  - Implantable loop recorder
  - Implantable devices: ICD, PPMs



JACC. 2014: 64 (No 21)

AF Evaluation

- Transthoracic echo (TTE): evaluate cardiac structure
- Blood tests: thyroid, renal, hepatic function

1. JACC. 2014: 64 (No 21)
2. https://myafibexperience.org/treatment/provider-s-office/diagnosis-of-afib/additional-testing/

Treatment Overview

1. Acute Management
2. Chronic Management
3. Non-Pharmacological Management
4. Stroke Prophylaxis
5. Other considerations

Goals of Treatment

- Prevent mortality
- Address any modifiable RF
- Alleviate symptoms/improve QOL:
  - Return to baseline ADL, improve exercise tolerance
- Prevent complications
  - Ischemic stroke is a major complication of AF that can lead to mortality, morbidity and healthcare costs
- Prevent ADRs from medications

JACC. 2014: 64 (No 21)

Acute Treatment

Overview

- Hemodynamically stable patients: acute rate control
  - **IV BB**: Metoprolol tartrate, Esmolol, Propranolol
  - **IV Non-DHP CCB**: Verapamil, Diltiazem

- Hemodynamically unstable and/or heavily symptomatic patients: electrical or pharmacological cardioversion

JACC. 2014: 64 (No 21)

Cardioversion

- Electrical/DCCV or pharmacological

- Two types of cardioversion:
  - **Elective:** part of a chronic management strategy for rhythm control
  - **Emergency:** acutely in circumstances of hemodynamic instability

- Chronic drug therapy required after to keep patient in sinus rhythm

JACC, 2019; 140: (No. 125-151)

Elective Cardioversion

- Electrical or pharmacological

- Two typical scenarios:
  - Planned in advance
  - Patients highly symptomatic but hemodynamically stable

JACC. 2014: 64 (No 21)

Emergency Cardioversion

- Typical method is electrical cardioversion
  - Faster onset and higher efficacy vs medications

- Indicated in hemodynamically unstable patients:
  - Decompensated CHF
  - Ongoing myocardial ischemia
  - Hypotension

JACC. 2014: 64 (No 21)

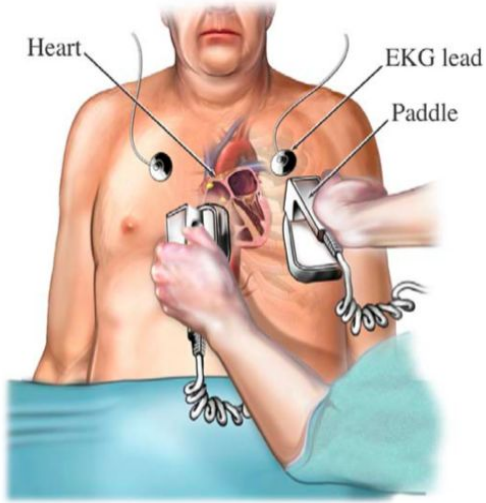
	Electrical Cardioversion	Pharmacological Cardioversion
Indications	Elective cardioversion for symptomatic control **Acute hemodynamic instability**	Elective cardioversion for symptomatic control **”Pill-in-the-pocket” strategy**
Efficacy	80-95%	25-95% (drug-dependent)
Safety	Uncomfortable; typically requires sedation	Many regimens potentially arrhythmogenic

JACC. 2014: 64 (No 21)

Electrical Cardioversion

- Direct shock synchronized with the QRS complex

- Multiple factors can increase chance of initial success:
  - Shock type (biphasic, higher energy)
  - Pre-treatment with PO Amiodarone



1. https://www.health.qld.gov.au/__data/assets/pdf_file/0022/145903/cardiac_10.pdf
2. Clin Exp Emerg Med. 2019; 6(1):64-69.

Amiodarone Before DCCV

Patients	N= 92, Persistent AF (>2 weeks duration), **first documented episode**
Interventions	Group A: Amiodarone PO Group B: Diltiazem PO + Glucose-Insulin-Potassium solution Group C: Diltiazem PO

Outcomes (Group A vs B/C)	• Rate of spontaneous conversion to SR:
	  ○ 25% vs 6%/3% (P < 0.005)
	• Success rate of DCCV:
	  ○ 88% vs 56%/65% (P<0.05)
	• AF recurrence:
	  ○ NSS at 24 hours, lower at 2 months (32% vs 56%/52%)

Conclusions: pre-treatment with Amiodarone increases success rate of DCCV and reduces AF recurrence.

EHJ. 2000; 21(1): 66-67

Electrical Cardioversion

Complications	● Thromboembolic ○ Up to 10 days post-procedure ● Sedative-related ● Arrhythmias: VT, VF, bradyarrhythmias ● Skin burn at site
Recurrence rate	Observational study: only 42% of patients in sinus rhythm at 1 year

1. Cochrane Database Syst. Rev. 2015; 3: No CD010824
2. JACC. 2014: 64 (No 21)

Pharmacological Cardioversion

Drug	Route	Onset	Efficacy	Regimen
Flecainide	PO	2-8 h	2-4 h: 57-68% 8 h: 75-91%	200 - 300 mg x 1 dose
Propafenone	PO	2-3 h	PO: 25% IV: 55 - 95%	450 - 650 mg x 1 dose

1. JACC. 2014: 64 (No 21)
2. Int J Cardiol. 203; 87(2-3): 121-128
3. J Am Coll Cariol. 2001;37(1):542-547

Pharmacological Cardioversion

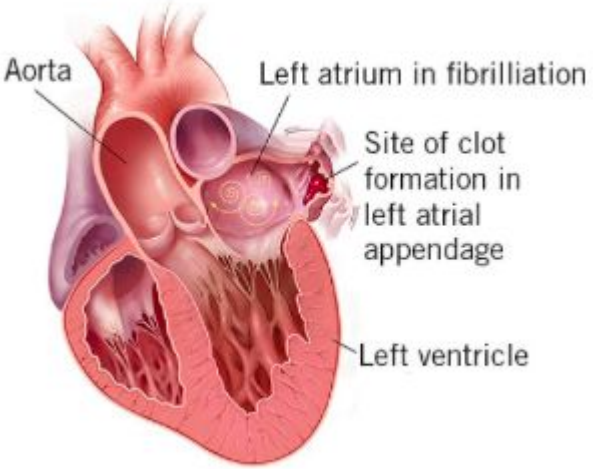
Drug	Route	Onset	Efficacy	Regimen	Other
Procainamide	IV	~1h	~ 50%	15-17 mg/kg over 30 minutes	Can cause QT prolongation and profound hypotension
Amiodarone	PO/IV	6-8 h	PO: 25% IV: 55 - 95%	PO: 600 - 800 mg daily in daily divided doses to a total load of up to 10 g, then 200 mg once daily as maintenance IV: 150 mg over 10 minutes, then 1 mg/min for 6 h, then 0.5 mg/min for 18 h or change to PO dosing	An option, but not typically used for acute cardioversion

1. Int J Cariol. 2003;89(2-3):239-248
2. JACC. 2014: 64 (No 21)

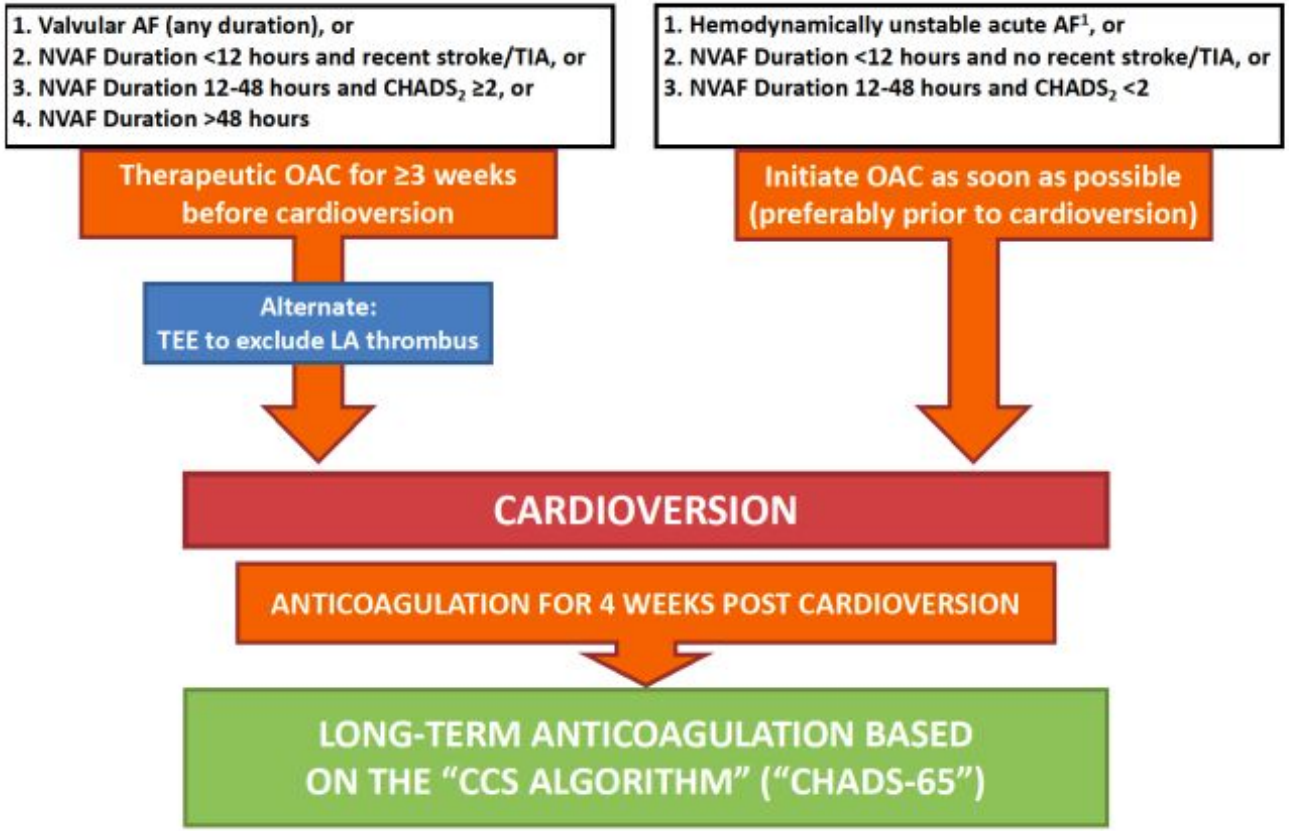
Anticoagulation

- Risk of thromboembolic complications highest in the 72 hours post-cardioversion

- Higher risk patients: female sex, CHF, diabetes mellitus



1. JACC. 2014: 64 (No 21)
2. https://www.dignityhealth.org/central-coast/locations/marianregional/services/cardiac-care/watchman-device-for-afib



CJC. 2018; 34 (No. 1375)

2-3-4 Rule

Patient presents with AF:		
For **GREATER** than	**2 days**	(or duration unknown)
We **ANTICOAGULATE** for:	**3 weeks**	Before cardioversion
AND **CONTINUE** for at least:	**4 weeks**	After cardioversion

UBC Medicine. Wong et al, 2018.

“Pill-in-the-Pocket” Strategy

- Drugs of choice: Flecainide, Propafenone
- Can be used in select patients with **paroxysmal AF**

1. N Eng J Med, 2004; 351: 2384-2389
2. https://www.livingwithatrialfibrillation.com.

“Pill-in-the-Pocket” Strategy

- Can cause bradycardia, atrial flutter and ventricular arrhythmias
  - Atrial flutter caused by 1:1 conduction
  - Monitor initial treatment in inpatient setting prior to endorsing outpatient use

- Administer a beta blocker or non-DHP CCB ≥ 30 minutes prior

1. N Eng J Med, 2004; 351: 2384-2389
2. JACC. 2014: 64 (No 21)

“Pill-in-the-Pocket” Strategy

- In appropriately selected patients, this strategy decreases hospitalization rate

- Limitations
  - Does not decrease number of episodes per month/symptomatic burden
  - Rate of thromboembolic complications not studied

NEJM, 2004; 351: 2384-2389

BREAK

Chronic Treatment

Rate vs Rhythm Control

Cochrane Review

- Included 3 RCTs (N=927) that compared **electrical cardioversion** (rhythm control) to rate control
  - RACE 2002, STAF 2003, HOT CAFE 2004

- Patient population: 18+ years, paroxysmal, chronic or persistent AF or AFL
  - Excluded patients with AF post-surgery

Cochrane SR. 2009; 1: 1-28.

Meta-Analysis Results

Mortality	NSS (OR 0.83, 95% CI 0.48-1.43, p=0.5)
Stroke Rate	NSS (OR 1.90, 95% CI 0.99-3.65, p=0.05)
Maintenance of SR	Rhythm > Rate (OR 0.09, 95% CI 0.03-0.34)
Quality of Life (RACE and STAF only)	Rhythm > Rate in: physical function, physical role function, vitality

Conclusions: a rhythm control strategy MAY increase stroke risk but is associated with improvements in several domains of QOL.

Cochrane SR. 2009; 1: 1-28.

Limitations

- Difficult to interpret the trend towards increased stroke risk with a rhythm control strategy
  - Use of OAC not consistently reported across the 3 studies
  - STAF stroke rate lower than expected

- Low success in achieving sinus rhythm in the rhythm control group

Cochrane SR. 2009; 1: 1-28.

AFFIRM

P	213 sites in US + Canada, N = 4030 ≥ 65 years of age with recurrent AF + additional risk factors for stroke
I	Rate control strategy + oral anticoagulation (Warfarin, INR 2-3)
C	Rhythm control strategy
O	**Rate vs Rhythm:** ● **Mortality:** 15% vs 17% (NSS) ● **Stroke/TIA:** 3.8% vs 3.9% (NSS) ● **MI:** 3.3% vs 3.6% (NSS) ● **Hospitalization:** 60.2 vs 67.6, NNT of 14

Conclusions: A rate control strategy was associated with a decreased risk of hospitalizations compared to a rhythm control strategy.

NEJM. 2002; 347: 1825-1833.

Limitations

- Patients with frequent or severe AF might have been considered unsuitable for rate-control and not enrolled
- Cannot conclude that anticoagulation can be discontinued if a patient is in SR
- Results not generalizable for younger patients or patients without risk factors for stroke

NEJM. 2002; 347: 1825-1833.

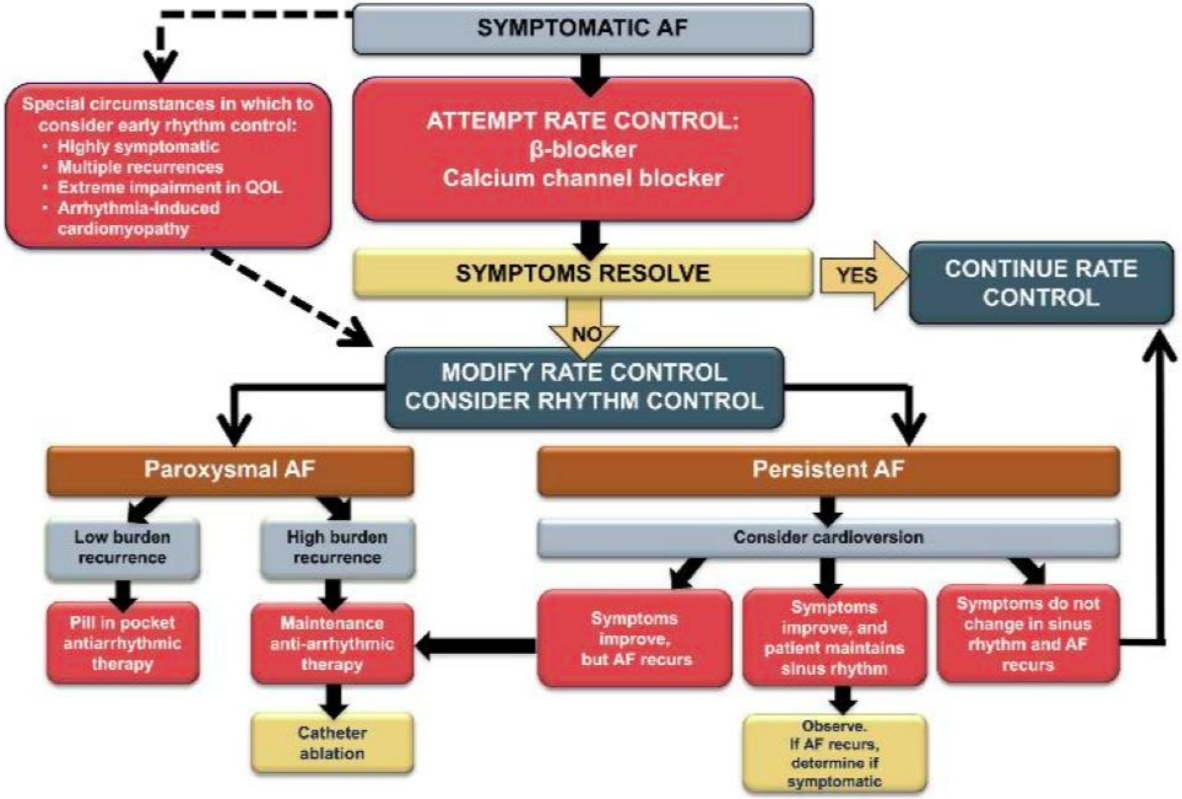
Rhythm Control Strategy

Rhythm Control Overview

- Aims to restore and maintain sinus rhythm through a combination of approaches
  - Restore:
    - Cardioversion (electrical or pharmacological)
  - Maintain:
    - Antiarrhythmic drug therapy
    - Catheter ablation

JACC. 2014: 64 (No 21)

Algorithm for Rate vs Rhythm Control for Patients With Symptomatic AF



CJC. 2018; 34 (No. 1375)

Antiarrhythmic Classes

Class	Mechanism	Drugs
I	Sodium channel blockade	1a: Quinidine, Procainamide 1b: Lidocaine, Phenytoin 1c: Flecainide, Propafenone
II	Beta-blockade	Eg. Metoprolol, Bisoprolol
III	Potassium channel blockade	Amiodarone Sotalol (also Class II) Dofetilide
IV	Calcium-channel blockade	Verapamil, Diltiazem

JACC. 2014: 64 (No 21)

Antiarrhythmic Drugs

- AHA guidelines recommend the following as options for a rhythm control strategy:
  - Ic: Flecainide, Propafenone
  - II/III: Sotalol, Dofetilide
  - III: Amiodarone, Dronedarone

- Selection based on patient-specific factors

JACC. 2014: 64 (No 21)

Antiarrhythmic Drugs: Efficacy

Patients	59 studies, Mean age: 65.5 years (46-72), 44% in permanent AF
Interventions	Classes: Ia, Ib, Ic, II, III (vs control or each other)
Outcomes	• **Mortality**: increased vs control for IA drugs (OR 2.39, 95% CI 1.03-5.59) and sotalol (OR 2.23, 95% CI 1.10-4.5) ○ NSS for other antiarrhythmic agents vs control • **AF recurrence**: Amiodarone reduced the recurrence of AF significantly more than combined class I drugs, dronedarone or sotalol.

Conclusion: Amiodarone is more effective at maintaining SR than other antiarrhythmic agents.

Cochrane SR. 2015; 3: 1-190

Antiarrhythmic Drugs: Safety

Drug	Dose	ADRs: Cardiac	ADRs: Non-cardiac	Cautions
Propafenone (IC)	IR: 150-300 mg po every 8h ER: 225-425 mg po every 12h	↑ PR and QRS intervals 1:1 conduction and ↑ ventricular rate (AFL)	Dizziness Visual disturbances Metallic taste (Propafenone)	CAD HF/LVH AFL Interactions (CYP2D6)
Flecainide (IC)	50-200 mg po every 12h			
Sotalol (III/III)	40-160 mg po every 12h	↑ QT ↓ HR	Headache N/V Blurred vision	↑ QT HFrEF (EF < 40) CKD (Cl CrCl < 40 mL/min)

1. JACC. 2014: 64 (No 21)
2. Lexicomp Online. Clinical Drug Information Inc, 2013.

Antiarrhythmic Drugs: Safety

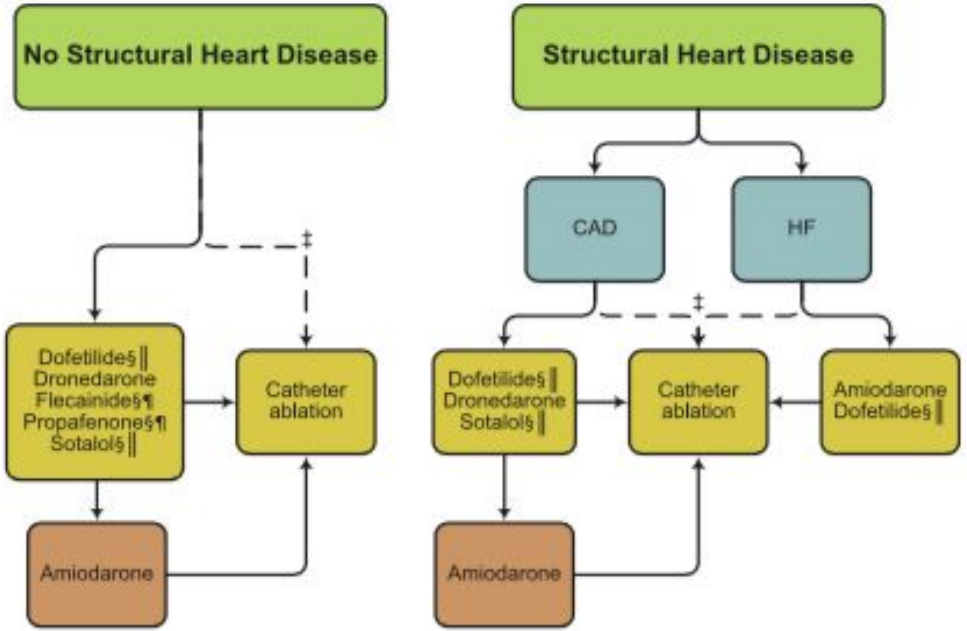
Drug	Dose	ADRs: Cardiac	ADRs: Non-cardiac	Cautions
Dronedarone (III)	400 mg po every 12h	↓ HR ↑ QT	Hepatotoxicity	NYHA class III/IV Permanent AF
Amiodarone (III)	100 - 200 mg po once daily		See next slide	Sinus/AV node dysfunction ↑QT at baseline Pre-excitation

1. JACC. 2014: 64 (No 21)
2. Lexicomp Online. Clinical Drug Information Inc, 2013.

Amiodarone

CNS	Abnormal gait, fatigue, dizziness, HA
HEENT	Blurred vision, corneal deposits
CVS	Hypotension (IV > PO), bradycardia, phlebitis (IV), QTc prolongation, TdP (rare)
RESP	Pulmonary fibrosis, pneumonitis, ARDS
GI/Liver	N/V, hepatotoxicity
ENDO	Hyper/hypothyroidism
DERM	Photosensitivity/blue man's
CI	Sick sinus syndrome, 2nd or 3rd degree AV block, cardiogenic shock
Monitoring	HR, ECG, LFTs, TSH/fT4, ophthalmologic exam, CXR, drug interactions (Digoxin, Warfarin, Flecainide)

Antiarrhythmic Drug Selection



JACC. 2014: 64 (No 21)

Catheter Ablation

- Mostly studied in younger patients with symptomatic **paroxysmal** AF refractory to ≥ 1 antiarrhythmic medications or in HF
  - AHA recommends:
    - Potential first-line option in patients with paroxysmal AF or HF
    - Second-line option in patients with persistent AF refractory to antiarrhythmic therapy

JACC. 2014: 64 (No 21)

Rate Control Strategy

Target Heart Rate

- Controversial area with limited evidence.
- AHA recommends a resting HR of < 80 BPM in most patients and < 110 BPM in select patients.
- Recommendations on targets for exercise are based on consensus

JACC. 2014: 64 (No 21)

Target Heart Rate: RACE-II

P	N= 614, permanent AF, **preserved LV systolic function**
I	"Lenient" rate-control (resting HR < 110 bpm)
C	"Strict" rate-control (resting HR < 80 bpm)

O	• Primary composite endpoint at 3 years:
	  ○ CV death, hospitalization for HF, stroke, embolism, bleeding, or life-threatening arrhythmic events
	  ■ 12.9% "lenient" vs 14.9% "strict" (NSS)

Conclusion: in a patient population with preserved LV function, it may be reasonable to have a more lenient HR target (≤ 110 BPM).

Card Electrophysiol Rev. 2003;7(2):118-21

Rate Control Overview

Pharmacological	**First line:** Beta-blocker, non-DHP CCB (Diltiazem, Verapamil)
	Other options: Digoxin, Amiodarone
Non-pharmacological	AV nodal ablation

JACC. 2014: 64 (No 21)

Rate Control Drugs

Class	Mechanism	Dosing Regimen
Beta Blocker	• Blockade of beta-adrenergic receptors • Slow AV conduction	• See later slides
Non-DHP CCB	• Blockade of L-type calcium channels → prolonged refractory period of AV node + slower conduction	• See later slides
Digoxin	• Blockade of Na/K pump • Direct suppression of AV node conduction	• PO: 0.125-0.25 mg daily • IV: 0.25-0.5 mg over several minutes; repeat 0.25 mg doses q6h to a max of 1.5 mg over 24 hours
Amiodarone	• Potassium channel antagonism	• See rhythm control slides

Beta Blockers

Drug	Dose	Selectivity
Atenolol	50-100 mg po daily	Beta 1
Bisoprolol	2.5-10 mg po daily	Beta 1
Metoprolol	25-200 mg po daily	Beta 1
Carvedilol	3.125-25 mg po bid	Mixed alpha and Beta
Nadolol	20-160 mg po bid	Non-selective
Propranolol	80-200 mg po tid	Non-selective

Beta Blockers

CNS	Fatigue, headache, insomnia, dizziness
CVS	Hypotension, bradycardia, orthostasis,
RESP	Dyspnea, exercise intolerance
GI	Nausea, vomiting
ENDO	Mask hypoglycemia, impair insulin sensitivity => hyperglycemia
Monitor	HR, BP, ECG, BG (in diabetics), renal function
Caution	Sudden discontinuation, CHF, diabetes, lung disease
Contraindications	Bradycardia or hypotension, 2° or 3° AV block, peripheral arterial circulatory disorder, SSS or SA block

Non-DHP CCB

Drug	PO	IV
Verapamil	120-240 mg daily Available in IR (tid-qid) or SR (daily or bid)	5-10 mg IV bolus; give 2nd bolus of 10 mg if no response in 15-30 min
Diltiazem	120-480 mg daily Available in IR (tid-qid) or SR (daily or bid)	0.25 mg/kg IV; give 2nd bolus of 0.35 mg /kg if no response in 30 mins

Non-DHP CCB

CVS	Bradycardia, hypotension
GI	Constipation
MSK	Peripheral edema
Monitor	HR, BP ECG
Caution	Heart failure
Contraindications	Bradycardia or hypotension, SSS, 2° or 3° AV block, Post-MI with EF<40%

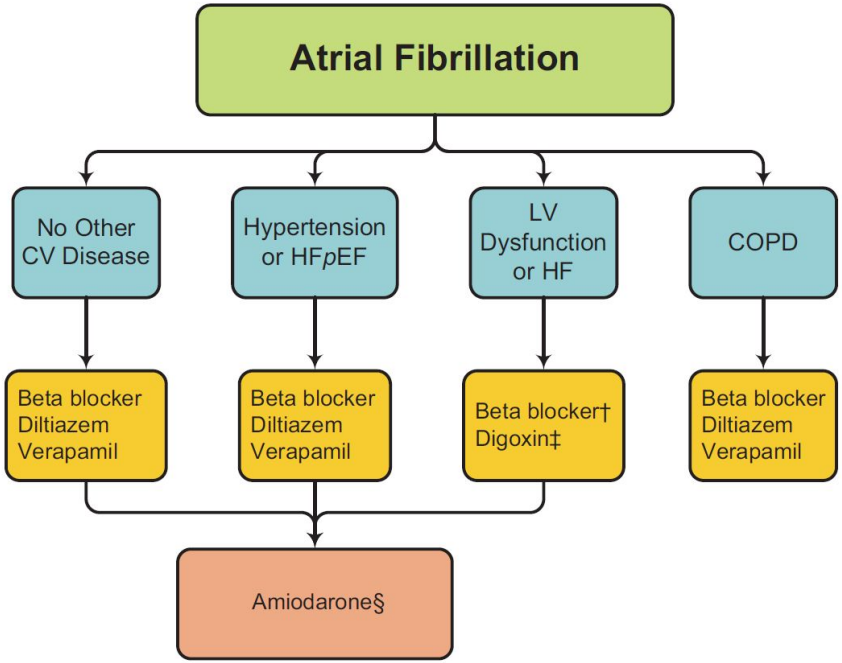
Digoxin

CNS	Dizziness, headache, confusion, delirium, hallucinations (visual disturbances)
CVS	Atrial tachycardia, heart block, VT or VF
RESP	Laryngeal edema
GI	Nausea, vomiting, diarrhea
Caution	Renal dysfunction, elderly
Contraindications	Hypersensitivity, VF

When to monitor level:

1. Not achieving HR control
2. Patient presents with symptoms of toxicity (N/V, visual halos)
3. Poor renal function (requires dose-adjustment in CKD)

Rate Control Drug Selection



AV Nodal Ablation

- AHA recommends only if:
  - Not a candidate for rhythm control
  - Unable to achieve rate control on medical therapy

- Requires pacemaker implantation

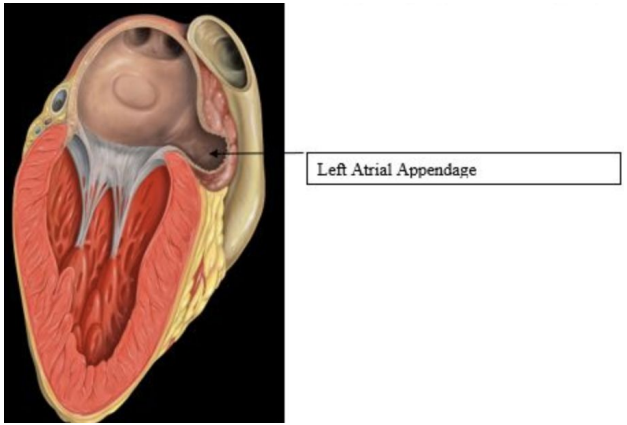
- Drugs for rate control no longer required BUT anticoagulation still required

JACC. 2014: 64 (No 21)

Chronic Treatment: Antithrombotic Therapy

Stroke Pathophysiology

- Thrombus or Embolus
- Atrial Fibrillation:
  - Embolic
- 3-5 fold increased risk of ischemic stroke in AF



BMJ 1999

Navigating Risk Assessment Tools

CHADS2 & CHADS2-VASc

Table 1	
CHADS2 Risk Factors	Score
Congestive heart failure	1
Hypertension (BP > 140/90 mm Hg or treated HTN)	1
Age ≥75 years	1
Diabetes mellitus	1
Stroke/TIA (prior)	2
Maximum Score	6

Table 2	
CHA2DS2-VASc Risk Factors	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease	1
Age 65–74 years	1
Sex category (i.e., female sex)	1
Maximum Score	9

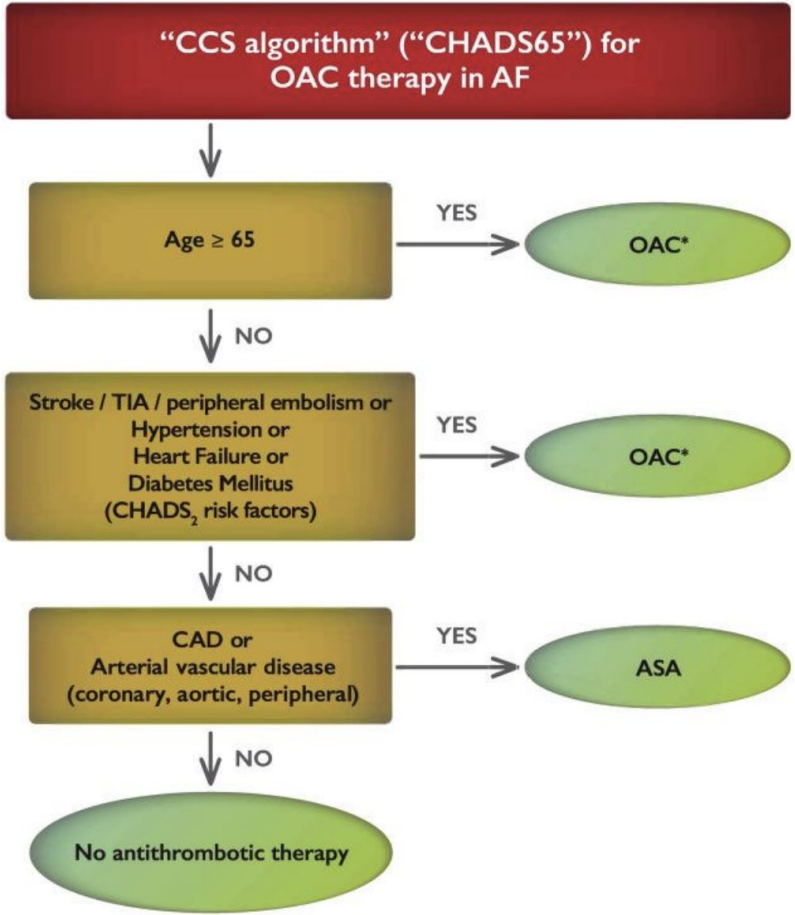
Stroke risk stratification with the $CHADS_2$ and CHA_2DS_2-VASc scores	
$CHADS_2$ acronym	**Unadjusted ischemic stroke rate (% per year)***
0	0.6%
1	3.0%
2	4.2%
3	7.1%
4	11.1%
5	12.5%
6	13.0%
CHA_2DS_2-VASc acronym	**Unadjusted ischemic stroke rate (% per year)***
0	0.2%
1	0.6%
2	2.2%
3	3.2%
4	4.8%
5	7.2%
6	9.7%
7	11.2%
8	10.8%
9	12.2%

Table 2. Event rates (95% CI) and hazard ratios for hospital admission and death due to thromboembolism according to components of CHA2DS2-VASc score at 5-years follow-up

Risk Factor	Annual Risk (95% CI)	Hazard Ratio (95% CI)	*P*
CHA_2DS_2-VASc = 0	0.69 (0.59-0.81)	1.0	
CHA_2DS_2-VASc = 1			
- **Heart failure**	2.35 (1.30-4.24)	3.39 (1.84-6.26)	< 0.0001
- **Diabetes mellitus**	2.28 (1.42-3.66)	3.31 (2.00-5.46)	< 0.0001
- **Hypertension**	1.60 (1.26-2.01)	2.32 (1.75-3.07)	< 0.0001
- **Age 65-74**	2.13 (1.85-2.46)	3.07 (2.48-3.80)	< 0.0001
- **Vascular disease**	1.40 (0.91-2.15)	2.04 (1.29-3.22)	0.002
- **Female sex**	0.86 (0.70-1.06)	1.25 (0.96-1.63)	0.10

CHADS2 Vs CHA2DS2-VASc

- CHA2DS2 -VASc includes arterial vascular disease and emphasizes the importance of age greater than 74 years, and female sex as risk factors to the CHADS2 score
- CHA2DS2 -VASc readily identifies those patients truly at low risk compared to CHADS2
- CHA2DS2 -VASc places more emphasis on high risk patients
- American and European Guidelines prefer CHA2DS2-VASc


"CCS algorithm" ("CHADS65") for OAC therapy in AF
Age ≥ 65
YES
OAC*
NO
Stroke / TIA / peripheral embolism or Hypertension or Heart Failure or Diabetes Mellitus (CHADS2 risk factors)
YES
OAC*
NO
CAD or Arterial vascular disease (coronary, aortic, peripheral)
YES
ASA
NO
No antithrombotic therapy

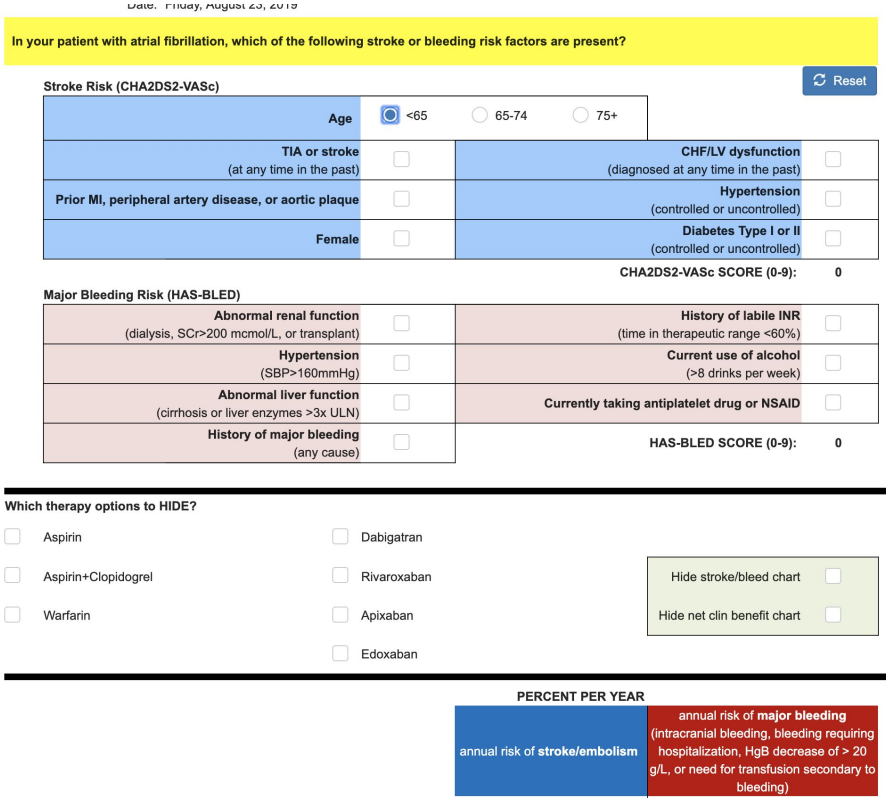
CCS,2014

HASBLED

HAS-BLED score for bleeding risk on oral anticoagulation in atrial fibrillation

Letter	Clinical Characteristic	Score (if present)
H	Hypertension (systolic ≥ 160 mmHg) – on treatment	1
A	Abnormal renal function (Dialysis, transplant, Cr > 2.6 mg/dL or > 200 µmol/L)	1
A	Abnormal liver function (Cirrhosis or bilirubin >2xNormal or AST/ALT/AP >3xNormal)	1
S	Stroke in past	1
B	Prior major bleeding or predisposition to bleeding	1
L	Labile INRs (Unstable/high INRs, time in therapeutic range <60%)	1
E	Elderly – age ≥ 65 years	1
D	Drugs: Medication usage predisposing to bleeding (antiplatelet agents, NSAIDs)	1
D	Drugs: Concomitant alcohol intake (≥8 drinks/week)	1
	Total HAS-BLED Score	Maximum score = 9

SPARCtool



Date: Friday, August 23, 2019

In your patient with atrial fibrillation, which of the following stroke or bleeding risk factors are present?

Reset

Stroke Risk (CHA2DS2-VASc)

Age	◉ <65	○ 65-74	○ 75+		
TIA or stroke (at any time in the past)	☐		**CHF/LV dysfunction** (diagnosed at any time in the past)	☐	
Prior MI, peripheral artery disease, or aortic plaque	☐		**Hypertension** (controlled or uncontrolled)	☐	
Female	☐		**Diabetes Type I or II** (controlled or uncontrolled)	☐	
			CHA2DS2-VASc SCORE (0-9):		**0**

Major Bleeding Risk (HAS-BLED)

Abnormal renal function (dialysis, SCr>200 mcmol/L, or transplant)	☐		**History of labile INR** (time in therapeutic range <60%)	☐	
Hypertension (SBP>160mmHg)	☐		**Current use of alcohol** (>8 drinks per week)	☐	
Abnormal liver function (cirrhosis or liver enzymes >3x ULN)	☐		**Currently taking antiplatelet drug or NSAID**	☐	
History of major bleeding (any cause)	☐		**HAS-BLED SCORE (0-9):**		**0**

Which therapy options to HIDE?

☐ Aspirin	☐ Dabigatran	
☐ Aspirin+Clopidogrel	☐ Rivaroxaban	☐ Hide stroke/bleed chart
☐ Warfarin	☐ Apixaban	☐ Hide net clin benefit chart
	☐ Edoxaban	

PERCENT PER YEAR

annual risk of **stroke/embolism**	annual risk of **major bleeding** (intracranial bleeding, bleeding requiring hospitalization, HgB decrease of > 20 g/L, or need for transfusion secondary to bleeding)

http://sparctool.com/

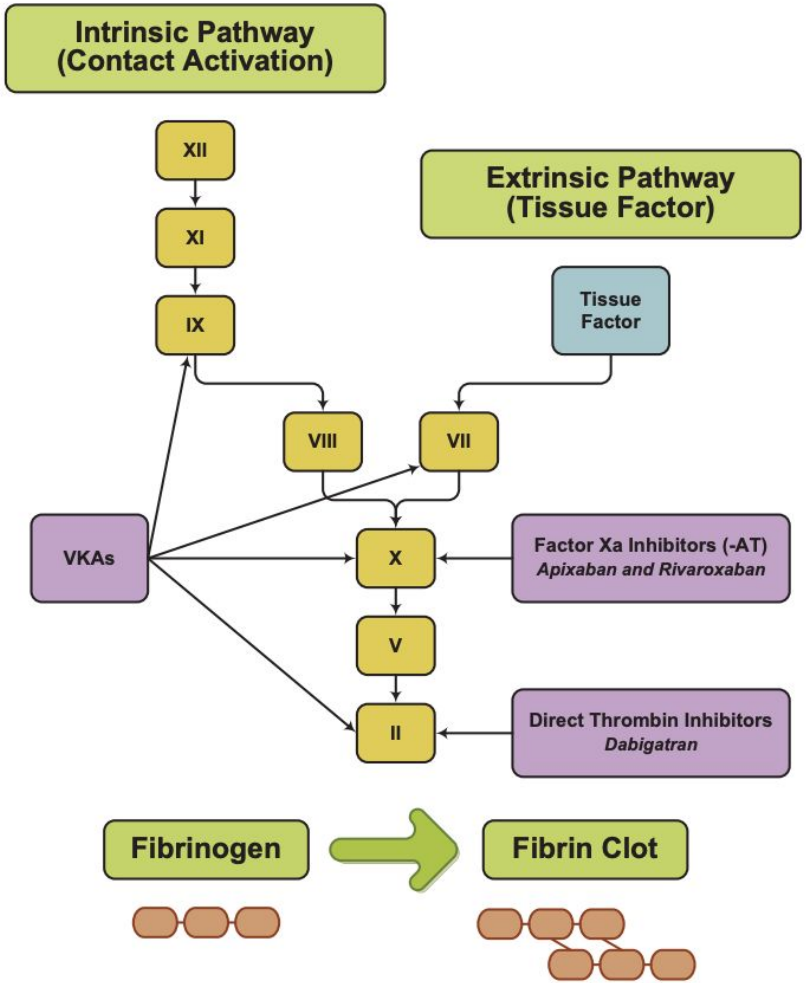
Shared Decision Making

- Efficacy
- Safety
- Cost
- Benefits vs Risks

Stroke Prophylaxis

Goals of Therapy

- Prevent mortality
- Prevent thromboembolic complications
- Prevent ADRs
  - Major Bleeds



JACC. 2014: 64 (No 21)

Therapeutic Options

- **Anticoagulants**
  - Warfarin
  - DOACs: Apixaban, Rivaroxaban, Dabigatran, Edoxaban

- **Antiplatelets**
  - ASA

- **Other**
  - Watchman device

Anticoagulants: Warfarin

	Mechanism	ADRs	Special Indications	Dosing	Contraindications
Warfarin	Vitamin K antagonist	Bleeding, and skin necrosis	Mechanical valve	INR 2-3, 2.5-3.5 (with mechanical valve)	Active bleed, pregnancy (1st trimester), and previous warfarin skin necrosis

Antithrombotic: ASA

	Mechanism	Landmark Trials	ADRs	Dosing	Contraindications
Acetylsalicylic Acid	COX-1 and COX-2 inhibitor	ACTIVE W and ACTIVE A	Bleeds, tinnitus, rash	75-100 mg po daily	Active bleed, hypersensitivity to NSAIDs

ACTIVE W

P	N= 6,706, Follow up: 1.3 years Baseline: age: 70 y/o, 67% male, $CHADS_2$: 2, 69% permanent AF Inclusion: AF, 1 RF on $CHADS_2$ Exclusion: Mitral stenosis, 6 month history of PUD, Prior ICH
I	Aspirin 75-100mg daily + Clopidogrel 75mg daily
C	Warfarin (INR: 2-3)

O

Outcomes	ASA + Clopidogrel (%/year)	Warfarin	RR & P Value
Composite (Stroke, non-CNS systemic embolism, MI, Vascular Death)	5.6	3.90	1.44 (1.18-1.76), p=0.0003
Stroke	2.39	1.40	1.72 (1.24-2.37), p=0.0001
Non-CNS embolism	0.43	0.10	4.66 (1.58-13.8), p=0.0001
Composite (Major hemorrhage, death)	8.32	6.45	1.31 (1.12-1.54), p=0.0008
Major Hemorrhage	2.42	2.21	1.10 (0.83-1.45), p=0.53

Limitations: Open label, many patients on warfarin prior to trial entry (selection bias)
Bottom line: Warfarin is superior to DAPT

ACTIVE A

P	N= 7,554, Follow up: 3.6 years Baseline: age: 71 y/o, 58% male, $CHADS_2$: 2, 64% permanent AF Inclusion: AF at enrollment or ≥ 2 episodes in last 6 months , 1 RF on $CHADS_2$ Exclusion: Mitral stenosis, 6 month history of PUD, Prior ICH, History of alcohol abuse			
I	Aspirin 75-100mg daily + Clopidogrel 75mg daily			
C	Aspirin 75-100mg daily + placebo			
O	Outcomes	ASA + Clopidogrel (%/year)	ASA + Placebo	RR & P Value
	Composite (Stroke, non-CNS systemic embolism, MI, Vascular Death)	6.8	7.6	0.89 (0.81-0.98), p=0.01
	Stroke	2.4	3.3	0.72 (0.63-0.83), p<0.0001
	MI	0.7	0.9	0.78 (0.59-1.03), p=0.08
	Major Hemorrhage	2.0	1.3	1.57 (1.29-1.92), p<0.001

Limitations: Warfarin deemed inappropriate for many pts but not clear as to why

Bottom line: DAPT reduces the risk for major vascular events, but increases bleed risk

Anticoagulants: Dabigatran

	Mechanism	Landmark Trial	ADRs	Dosing	Contraindications
Dabigatran	Direct Thrombin inhibitor	RE-LY	Bleeds, dyspepsia	150 mg po BID 110 mg BID if ≥ 80 y/o or ≥ 75 y/o with at least one other bleed risk factor including CrCl 30-50 ml/min	Active bleed, CrCl < 30 ml/min

P	N= 18,113, Follow up: 2 years Baseline: 71 y/o, 36% female, 32% persistent AF, 35% CHADS2 of 2, 40% ASA Inclusion: Age ≥75 years or 65-74 years with T2DM, HTN, or CAD, ECG confirmed AF Exclusion: history of heart valve disorder (prosthetic valve or hemodynamically relevant valve disease)					
I	Dabigatran 150 mg po BID or 110 mg po BID					
C	Warfarin INR of 2.0-3.0					
O	Outcomes	Dabigatran 110 mg bid (%/year)	Warfarin	RR & P Value	Dabigatran 150 mg bid (%/year)	RR & P Value
	Stroke or systemic embolism	1.53	1.69	0.91 (0.74-1.11) <0.0001	1.11	0.66 (0.53-0.82) <0.0001
	Stroke	1.44	1.57	0.92 (0.74-1.13) <0.0001	1.01	0.64 (0.51-0.81) <0.0001
	Major Bleed	2.71	3.36	0.8 (0.69-0.93) 0.003	3.11	0.93 (0.81-1.07) 0.31

Limitations: TTR: ~64%, ASA use in 40% of patients

Bottom line: Dabigatran reduces stroke without increasing the risk for major bleed when compared to warfarin

Anticoagulants: Rivaroxaban

	Mechanism	Landmark Trial	ADRs	Dosing	Contraindications
Rivaroxaban	Direct factor Xa inhibitor	ROCKET-AF	Bleeds	20 mg po cc 15 mg po cc (CrCl 30-49 ml/min)	Active bleed, hepatic disease, CrCl < 30 ml/min

P	N= 14,262, Follow up: 2 years Baseline: 73 y/o, 39% female, 81% persistent AF, 42% CHADS2 of 3, 90% HTN, 38% on ASA Inclusion: ≥ 18 y/o, nonvalvular AF, CHADS2 ≥ 2 Exclusion: significant mitral valve stenosis, and prosthetic heart valve			
I	Rivaroxaban 20 mg po daily, or 15 mg po daily in those with CrCl 30-40 ml/min			
C	Warfarin 2 mg adjusted to attain an INR of 2.0-3.0			
O	Outcomes	Rivaroxaban (%/year)	Warfarin	RR & P Value
	Stroke or systemic embolism	2.1	2.4	0.88 (0.75-1.03) P < 0.0001
	Major Bleed	3.6	3.4	1.04 (0.90-1.20) P = 0.58
	Nonmajor clinically relevant bleed	11.8	11.4	1.04 (0.96-1.13) P= 0.35

Limitations: TTR: ~55%, ASA use in 38% of patients

Bottom line: Rivaroxaban is noninferior to warfarin in preventing stroke and systemic thromboembolism, and possess similar bleed risks

Anticoagulants: Apixaban

	Mechanism	Landmark Trial	ADRs	Dosing	Contraindications
Apixaban	Factor Xa inhibitor	ARISTOTLE	Bleeds, menorrhagia	5 mg po bid 2.5 mg po bid (age ≥ 80, ≤ 60 Kg, SCr ≥ 133 µmol/L)	Active bleed, CrCl < 15 ml/min

P	N=18,201, Follow up: 1.8 years Baseline: 70 y/o, 35% female, 24% North American, 84% persistent AF, 35% CHADS score of 2, 87% HTN requiring treatment, 31% on ASA Inclusion: AF on ECG 2 weeks apart in prior year + ≥ 1 CHADS2 Exclusion: moderate or severe mitral stenosis, prosthetic heart valve
I	Apixaban 5mg po BID or Apixaban 2.5mg po BID (2.5 mg po bid (age ≥ 80, ≤ 60 Kg, SCr ≥ 133 µmol/L)
C	Warfarin 2 mg adjusted to attain an INR of 2.0-3.0

O

Outcomes	Apixaban (%/year)	Warfarin	RR & P Value
Stroke or systemic embolism	1.27	1.60	0.79 (0.66-0.95) P=0.01
Stroke	1.19	1.51	0.79 (0.65-0.95) P=0.01
Major Bleed	2.13	3.09	0.69 (0.60-0.80) P<0.0001

Limitations: TTR: ~66%, ASA use in 31% of patients,

Bottom line: Apixaban is superior at reducing vascular events, and is associated with a lower bleed risk compared to warfarin

Anticoagulants: Edoxaban

	Mechanism	Landmark Trial	ADRs	Dosing	Contraindications
Edoxaban	Factor Xa inhibitor	ENGAGE-TIMI 48	Bleeds	60 mg daily 30 mg daily in patients with CrCl 30-50 ml/min, ≤ 60 kg	Active bleed, CrCl > 95 ml/min or <30 ml/min

P	N= 21,105, Follow up: 2.8 years Baseline: 72 y/o, 37% female, 22% North American, 77% CHADS2 ≤ 3, 30% on ASA Inclusion: Patients >21 years with documented AF within 12 months prior to randomization, Score of >2 on $CHADS_2$ Exclusion: moderate-to-severe mitral stenosis
I	Edoxaban 60 mg po daily or 30 mg po daily (patients with CrCl 30-50 ml/min, ≤ 60 kg, or the concomitant use of verapamil or quinidine (potent P-glycoprotein inhibitors))
C	Warfarin 2 mg adjusted to attain an INR of 2.0-3.0

O

Outcomes	Edoxaban 60 mg (%/year)	Warfarin	HR P value	Edoxaban 30 mg (%/year)	HR P value
Stroke or systemic embolism	1.18	1.50	0.79 (0.63-0.99) <0.001	1.61	1.07 (0.87-1.31) 0.005
Stroke	1.49	1.69	0.88 (0.75-1.03) 0.11	1.91	1.13 (0.97-1.31) 0.12
Major Bleed	2.75	3.43	0.80 (0.71-0.91) <0.001	1.61	0.47 (0.41-0.55) <0.001

Limitations: Study did not show reduction in ischemic stoke for CrCl >95ml/min TTR: ~68%, ASA use in 30% of patients

Bottom line: Edoxaban is noninferior to warfarin with regards to Vascular events and is associated with a lower bleed risk

DOAC vs Warfarin Summary

	Dabigatran 110 mg bid 150 mg bid	**Rivaroxaban** 20 mg daily	**Edoxaban** 60 mg daily	**Apixaban** 5 mg bid
Landmark Trial	RE-LY	ROCKET-AF***	ENGAGE AF-TIMI 48	ARISTOTLE
Stroke or SE*	✗ ↓	✗	↓	↓
All cause death	✗	✗	✗	↓
GI Bleed	✗ ↑	↑	↑	✗
Major Bleed	↓ ✗	✗	↓	↓
Intracranial Bleed	↓	↓	↓	↓
INR TTR**	64%	55%	68%	66%

* Systemic Embolism (SE)
**Time in Therapeutic Range (INR 2-3)
***Statistical significance achieved in per-protocol analysis

✗ Non-significant difference ↓ Significant reduction ↑ Significant increase

DOAC Dosing

CrCl	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
CrCl >50 mL/min	Dose adjusted for INR 2.0-3.0	150 mg bid*	20 mg daily	5 mg bid	60 mg daily∞
CrCl 30-49 mL/min	Dose adjusted for INR 2.0-3.0	Consider 110 mg bid in preference to 150 bid	15 mg daily	5 mg bid (Consider 2.5 mg bid)†	30 mg daily
CrCl 15-29 mL/min	No RCT Data **	No RCT Data¶	No RCT Data	Very limited RCT Data§	No RCT Data¶
CrCl < 15 mL/min (or on dialysis)	No RCT Data‡	No RCT Data¶	No RCT Data¶	No RCT Data¶	No RCT Data¶

bid, twice daily; INR, international normalized ratio; RCT, randomized clinical trial.

* Consider Dabigatran 110 mg po bid if age >75 years
† Consider Apixaban 2.5 mg po bid if 2 of the 3 following criteria are present: 1) age >80 years, 2) body weight <60 kg, or 3) serum creatinine >133 μmol/L
∞ Consider Edoxaban 30mg daily if weight ≤60 kg or concomitant potent P-Gp inhibitor therapy
** Dose adjusted warfarin has been used, but data regarding safety and efficacy is conflicting
‡ Dose adjusted warfarin has been used, but data regarding safety and efficacy is conflicting and may lean towards causing harm.
§ The ARISTOTLE trial did include patients with a CrCl as low as 25 mL/min, but this was a very small number of patients (1.5% of patients in the trial).
¶ No published randomised studies support a dose for this level of renal function; product monographs suggest the drug is contraindicated for this level of renal function.

DOAC Drug Interactions

DRUG INTERACTIONS THAT MAY AFFECT DOAC DRUG LEVELS			
Potential ↑ in Apixaban	**Potential ↓ in Apixaban**	**Potential ↑ in Dabigatran**	**Potential ↓ in Dabigatran**
*Diltiazem** *Ketoconazole, itraconazole, voriconazole, posaconazole = azole-antimycotics‡* *Naproxen** *Ritonavir (all HIV protease inhibitors)‡* *Strong inhibitors of both P-glycoprotein and CYP 3A4‡*	*Carbamazepine¥* *Phenobarbital¥* *Phenytoin¥* *Rifampin¥* *St. John's Wort¥* *Strong inducers of both P-glycoprotein and CYP-3A4¥*	*Amiodarone** *Clarithromycin** *Cyclosporine** *Dronedarone¥* *Itraconazole** *Ketoconazole‡* *Nelfinavir** *Posaconazole** *Quinidine*§* *Ritonavir** *Saquinavir** *Tacrolimus** *Tipranavir¥* *Ticagrelor¥* *Verapamil*§* *Strong P-glycoprotein inhibitors‡*	*Antacids§* *Atorvastatin*** *Carbamazepine¥* *Proton Pump Inhibitors** *Rifampin¥* *St. John's Wort¥* *Tenofovir¥* *Strong P-glycoprotein inducers‡* *Phenytoin¥*
Potential ↑ in Edoxaban	**Potential ↓ in Edoxaban**	**Potential ↑ in Rivaroxaban**	**Potential ↓ in Rivaroxaban**
*Amiodarone** *Cyclosporine£* *Digoxin** *Dronedarone£* *Erythromycin£* *Ketoconazole£* *Quinidine£* *Verapamil** *Protease Inhibitors¥*	*Atorvastatin** *Carbamazepine¥* *Esomeprazole** *Phenobarbital¥* *Phenytoin¥* *Rifampicin¥*	*Clarithromycin** *Erythromycin** *Fluconazole** *Ketoconazole‡* *Itraconazole‡* *Posaconazole‡* *Ritonavir‡* *Strong inhibitors of both P-glycoprotein and CYP 3A4‡*	*Carbamazepine¥* *Phenobarbital¥* *Phenytoin¥* *Rifampin¥* *St. John's Wort¥* *Strong inducers of both P-glycoprotein and CYP 3A4¥*

Note that drug interaction data with the DOACs is limited and this table reflects currently available data. Consider Pharmacist consult as needed. Dabigatran etexilate and edoxaban are substrates for the P-glycoprotein transporter (P-gp) and as such any strong inhibitors or inducers should be avoided. Rivaroxaban and apixaban are eliminated by both P-gp and cytochrome P-450 3A4 (CYP-450 3A4). As such the concomitant use of strong inhibitors and inducers of both P-gp and 3A4 should be avoided.

**no empiric dosage adjustment required, however use with caution, § recommend to give 2 hours after dabigatran, ‡ contraindicated, ¥ caution advised if co-administering, should be avoided, £ reduce dose of edoxoban to 30mg daily, **no dose adjustment is required*

Valvular AF: Anticoagulation

- Valvular AF is AF in the setting of moderate to severe valvular stenosis OR a mechanical heart valve

- Less studied population
  - Trials frequently exclude valvular AF patients
  - Valvular AF (mechanical valves) is considered an automatic indication for long-term anticoagulation with Warfarin

DOACs and Valvular AF

Landmark Trials	Exclusion
RE-LY	History of heart valve disorder (prosthetic valve or hemodynamically relevant valve disease)
ROCKET-AF	Significant mitral valve stenosis, and prosthetic heart valve
ARISTOTLE	Moderate or severe mitral stenosis, prosthetic heart valve
ENGAGE-TIMI 48	Moderate-to-severe mitral stenosis

RE-ALIGN

Patients	N=252, aortic and/or mitral valve replacement
Interventions	Dabigatran group: Dabigatran was adjusted to goal trough ≥50 ng/mL, starting doses at 150 mg PO BID if CrCl <70 mL/min, 200mg PO BID if 70-109 mL/min, 300mg PO BID for CrCl ≥110 mL/min.
Comparator	Warfarin targeting an INR of 2.5-3.5
Outcomes	**Primary:** Trough **Secondary:** Stroke, systemic embolism, transient ischemic attack, valve thrombosis, bleeding, venous thromboembolism, myocardial infarction, and death

Conclusions: Dabigatran in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin

N Engl J Med 2013; 369:1206-1214

Expert Opinion on Anticoagulation

NOAC use is contraindicated	NOAC use is reasonable
Mechanical heart valves • In any position (100% agreement)	Bioprosthetic heart valve • aortic position (82% agreement) • mitral position (73% agreement)
Rheumatic mitral stenosis • mild (47% agreement) • moderate-severe (88% agreement) • post commissurotomy (42% agreement)	Mitral annuloplasty • with or without prosthetic ring (88% agreement)
	Non-Rheumatic mitral stenosis • mild (97% agreement)
	Mitral regurgitation • mild (97% agreement) • moderate-severe (>90% agreement)
	Tricuspid regurgitation • Any severity (98% agreement)
Non-rheumatic mitral stenosis • moderate or severe (69% agreement)	Aortic Stenosis or Regurgitation • Mild (98% agreement) • Moderate-Severe (80% agreement)

NOAC, novel non-vitamin K antagonist

Mechanical Valve Location	INR Target and Range	Recommendation for ASA (81 mg daily)‡
Aortic	2.5 (range 2.0-3.0)†	Yes
Mitral	3.0 (range 2.5-3.5)	Yes
Combined aortic and mitral	3.0 (range 2.5-3.5)	Yes
Pulmonic	2.5 (range 2.0-3.0)	No
Tricuspid	3.0 (range 2.5-3.5)	No
Combined pulmonic and tricuspid	3.0 (range 2.5-3.5)	No

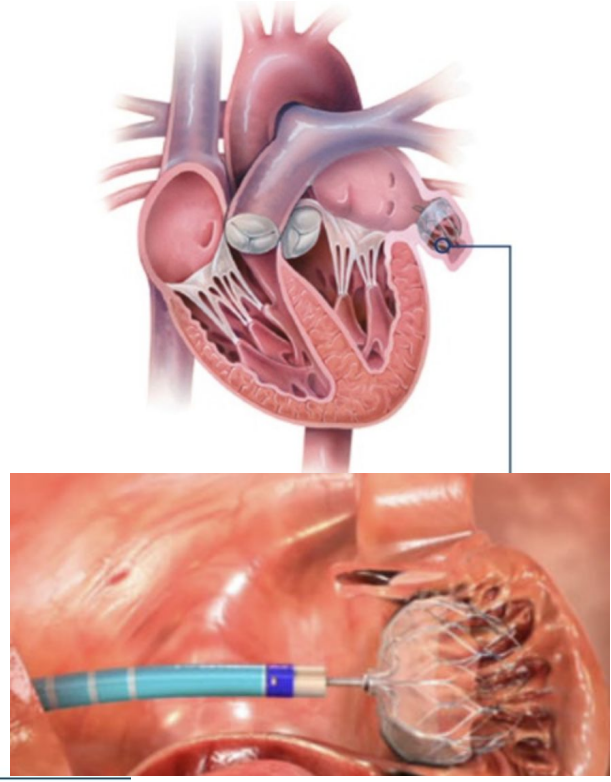
Thrombosis Canada, 2019

Bottom Line

1. Valvular AF pts are high risk for ischemic stroke
2. Warfarin is the drug of choice for valvular AF
3. Depending on bleed risk ASA should be added

WATCHMAN Device

- Percutaneous occlusion of the left atrial appendage (LAA)
- PROTECT-AF & PREVAIL: WATCHMAN inferior to warfarin for ischemic stroke prevention
- **Guidelines recommend WATCHMAN for those patients who have contraindications for oral anticoagulation**



Post-ACS Complicated by AF

- AF complicates 10-21% of ACS cases
- Both ACS and AF require anticoagulation strategies
- 2 general approaches to managing comorbid AF and ACS if both conditions require anticoagulation:
  - Dual pathway: OAC + P2Y12 inhibitor (typically clopidogrel)
  - Triple therapy (TT): OAC + DAPT

Dual Pathway vs TT

Trial	Interventions	Bleeding Rate
PIONEER AF-PCI	**Dual:** P2Y12 inhibitor + Rivaroxaban **TT:** DAPT + Rivaroxaban OR Warfarin	↓ in Rivaroxaban groups
RE-DUAL PCI	**Dual:** Dabigatran + Clopidogrel OR Ticagrelor **TT:** Warfarin + ASA + Clopidogrel OR Ticagrelor	↓ in dual vs TT
WOEST	**Dual:** Warfarin + Clopidogrel **TT:** Warfarin + DAPT	↓ in dual vs TT

1. NEJM. 2016; 375:2423-2434
2. Lancet. 2013; 381(9872): 1107-1115
3. NEJM. 2017; 377:1513-1524

AUGUSTUS

Patients	CHADS-VASc score 3.9, HAS-BLED 2.9, Recent ACS or PCI
Interventions	P2Y12 Inhibitor (x 6 months) and: ● Randomization 1: Apixaban vs Warfarin ● Randomization 2: Aspirin vs Placebo
Outcomes	**Primary: Bleeding** ● Apixaban vs Warfarin: 10.5% vs 14.7%; HR 0.69 (95% CI 0.58-0.81) ● Aspirin vs Placebo: 16.1% vs 9.0%; HR 1.89 (95% CI 1.59-2.24) **Secondary:** ● Apixaban vs Warfarin: ↓ mortality or hospitalization, ↓ hospitalization, ↓ stroke ● Aspirin vs placebo: NSS on all secondary outcomes

Conclusions: Dual therapy with Apixaban and Clopidogrel decreases bleed risk and improves multiple cardiac outcomes.

NEJM. 2019; 380:1509-1524

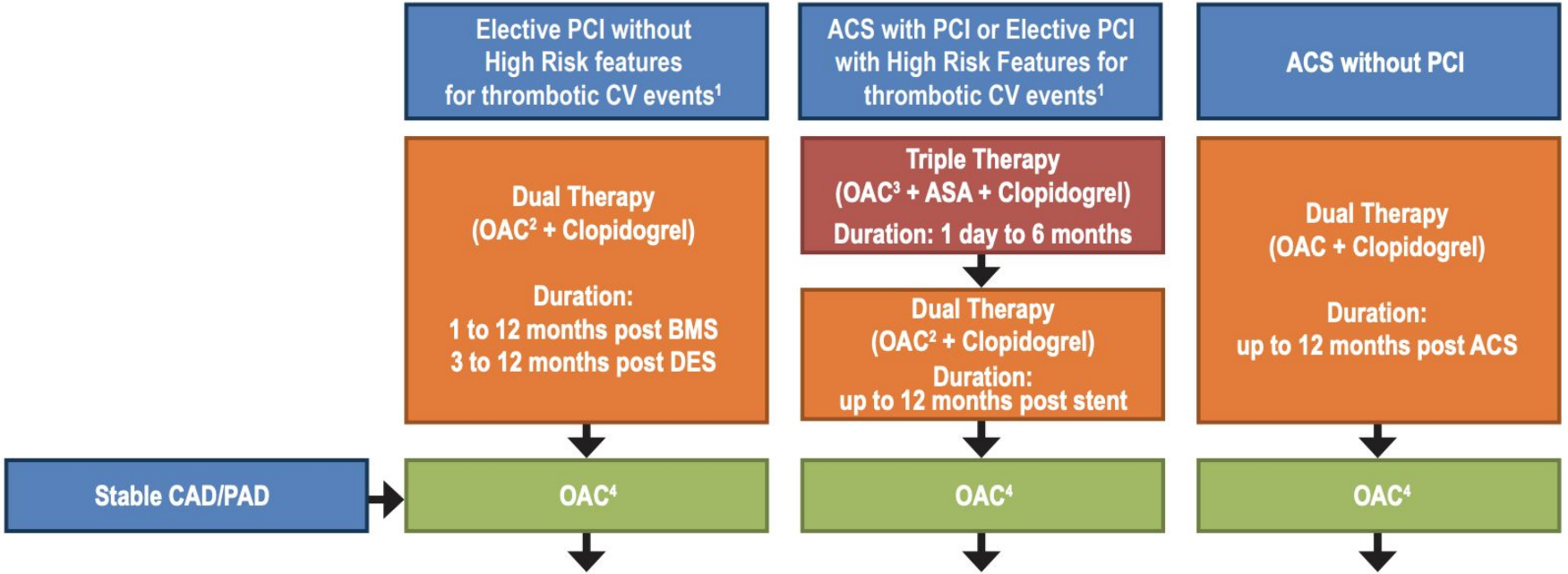
Duration of TT: ISAR-TRIPLE

Patients	Patients with an indication or OAC and drug-eluting stent implantation (82.7% with AF), CHADS2-Vasc Score ≥ 2
Interventions	Warfarin + ASA + Clopidogrel (x 6 weeks OR 6 months)
Outcomes	**Primary:** Composite (Death, MI, stent thrombosis, stroke, major bleeding): NSS **Secondary:** NSS: cardiac death, major bleeding, death ↓ Any BARC bleeding: 20.5% vs 27.9% (HR 0.68, 95% CI 0.47-0.98)

Conclusion: in patients receiving a drug-eluting stent and TT, step-down to double therapy can be considered at 6 weeks.

J Am Coll Cardio. 2015;16:1619-1629

AF Patients with Coronary or Peripheral Arterial Disease and an Indication for OAC (Age ≥ 65 or $CHADS_2$ ≥ 1)



CCS,2018

Postoperative AF: Background

- Atrial tachyarrhythmias most common postoperative complication of cardiac surgery requiring intervention

- Peak incidence of POAF occurs between postoperative days 2 and 4

CJC. 2011; 27(1): 91-97

POAF: Risk Factors

Patient-Related	Procedure-Related

• **Older age**
• Prior AF episodes
• Male gender
• History of hypertension
• Requirement for intraoperative balloon pump
• Withdrawal of beta-blocker therapy
	• Procedure type: isolated CABG, valve repair/replacement
	• Number of bypass grafts
	• Longer duration of:
	  ○ Surgery
	  ○ Aortic cross-clamp

CJC. 2011; 27(1): 91-97

POAF: Prophylaxis

- Mainstay of therapy is beta-blockers
  - Must be started **preoperatively** to have a benefit
  - ↓ POAF (29.6% vs 40.1% OR 0.63)

- Other options:
  - Amiodarone
  - Sotalol
  - IV Magnesium
  - Biatrial pacing
  - Combination therapy

CJC. 2011; 27(1): 91-97

POAF: Treatment

- Most patients will no longer have POAF 6-12 weeks after cardiac surgery
  - Reassess therapy at 6 weeks

- CCS recommends 2 components of therapy:
  - Rate or rhythm control
  - Anticoagulation (if POAF persists for > 72 hours)

CJC. 2011; 27(1): 91-97

CASE 1

Meet Our Patient: SC

ID: 40-year-old female, wt = 60 kg, ht = 165 cm

CC: Presenting to ED with chest tightness radiating to her neck and jaw

HPI:

- SC is finally wrapping up the year as a pharmacy residency coordinator and has been under a lot of stress recently
- Chest tightness and intermittent SOB started 5 days ago after a preceptor left unexpectedly, and she had to scramble to find a new rotation for one of her residents

PMHx

- Hypertension
- Dyslipidemia
- Type 2 diabetes mellitus
- Paroxysmal atrial fibrillation (diagnosed in 2018)
- Asthma since childhood
- Migraine headaches

Meet Our Patient: SC

Social Hx:

- Non-smoker, drinks socially once a week

Allergies: NKDA

Medications:

- Edoxaban 60 mg po daily
- Bisoprolol 5 mg po daily
- Rosuvastatin 5 mg po daily
- Ramipril 5 mg po daily
- Metformin 500 mg po BID
- Fluticasone 250 mcg 1 puff BID
- Salbutamol 100 mcg/inhalation 1-2 puffs q4h PRN
- Ibuprofen 200 mg po q6h PRN

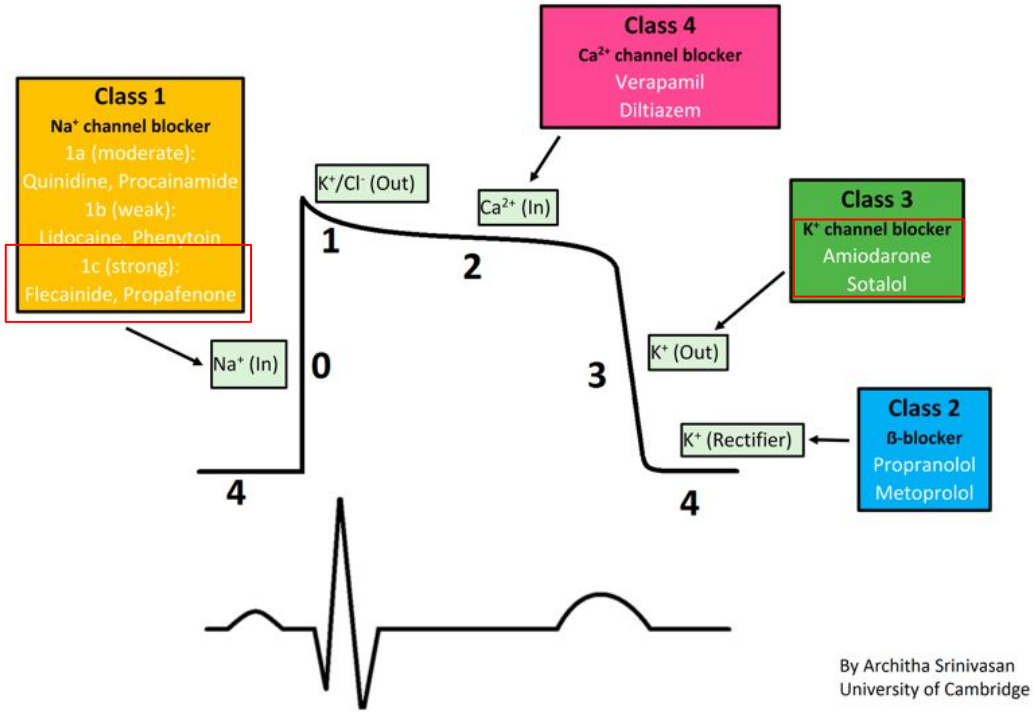
ROS:

- Vitals: T = 36.7, BP = 140/90, HR = 90, RR = 20, O2 Sat 98% RA
- Weight = 60 kg (same as baseline)
- CNS: A+O x3, dizzy, denies any cognition changes
- RESP: clear bilaterally
- CVS: Normal S1, S2; any ongoing chest discomfort/tightness?
- GI: abdomen soft and nontender
- DERM: unremarkable
- HEME: Hgb = 130 g/L
- Labs:
  - High sensitivity troponin: 480 ng/L initially, then 7030 ng/L
  - SCr= 60, eGFR > 120 mL/min

Jeopardy

Supplementary

Drugs Affecting the Cardiac Action Potential



By Architha Srinivasan
University of Cambridge

Anticoagulation Timing

	FinCV
P	N= 3123, Age = 62.2 years, 36.6% female, CHA2DS2-VAsc: 2, AF < 48 h
I	Prophylactic anticoagulation
C	No prophylactic anticoagulation
O	Stroke or systemic embolism (SSE) overall (prophylaxis vs none) 0.1% vs 0.7%, 82% RRR, p = 0.001 **BUT subgroup analysis showed NSS in SSE rate in patients with a CHA2DS2-VASc score of 0 or 1**

Conclusion: in patients with nonvalvular AF and symptoms for < 48 hours with a CHA2DS2-VASc score of < 2, it may be acceptable to not anticoagulate prior to cardioversion.

RACE 2002

P	N = 522, 68 years, 60% male, documented recurrence of AF/AFL after cardioversion
I	Rate control (target HR < 100 BPM)
C	Rhythm control
O	**Rate vs rhythm:** ● **Primary (composite):** 44/256 vs 60/266 ● **Secondary:** ○ Mortality: 18/256 vs 18/266 ○ Stroke: 13/256 vs 19/266 ○ SR at 2-year follow up: 10% vs 39% ○ Major ADRs: 2/256 vs 12/266

Conclusions: in patients with AF, rate control is non-inferior to rhythm control and associated with less ADRs.

STAF 2003

P	N= 200, patients at “moderate to high risk” for AF recurrence
I	Rate control (medications or AV node ablation +/- pacemaker implantation)
C	Rhythm control (dependent on LV function)
O	**Rate vs Rhythm:** ● **Primary outcome (composite):** 10/100 vs 9/100 (NSS) ● **Secondary outcomes:** ○ Mortality: 8/100 vs 4/100 (NSS) ○ Stroke/TIA: 1% vs 3% (NSS) ○ SR at 1-year follow up: 11/100 vs 26/100 ($p < 0.001$) ○ **Hospitalization for CV causes: 26/100 vs 54/100 ($p < 0.001$)**

Conclusions: a rhythm control strategy was associated with increased rate of hospitalization compared to a rate control strategy.

HOT CAFE 2004

P	N = 205, AF duration 7 days to < 2 years
I	Rate control (target HR < 70-90 BPM)
C	Rhythm control
O	**Rate vs rhythm:** ● **Primary (composite):** 44/256 vs 60/266 ● **Secondary:** ○ Mortality: 1/100 vs 3/104 ○ Stroke: 0/100 vs 3/104 (NSS) ○ SR at 2-year follow up: 0% vs 63% ○ Hospitalizations: 12% vs 74% (p < 0.001)

Conclusions: a rhythm control strategy was associated with an increased rate of hospitalizations compared to a rate control strategy.

Dual Pathway vs TT

Trial	Patients	Interventions	Bleeding
PIONEER AF-PCI	NVAF undergoing PCI for ACS (51%) or stable CAD	**Dual:** P2Y12 inhibitor (x 12 months) + Rivaroxaban 15 mg/day **TT:** DAPT (1, 6 or 12 mo) + Rivaroxaban 2.5 mg BID OR Warfarin (INR 2-3)	↓ Rivaroxaban groups (Dual: 16.8%, TT: 18.0%) vs Warfarin-based TT (26.7%)
RE-DUAL PCI	NVAF (CHADS2-VAsc 3.8) undergoing PCI	**Dual:** Dabigatran (110 or 150 mg) + P2Y12 inhibitor (x 12 months) **TT:** Warfarin + ASA (x 1-3 mo) + P2Y12 inhibitor (x 12 months)	↓ in dual vs TT (11.5% ARR with D110, 5.5% ARR with D150)
WOEST	Indication for OAC and undergoing PCI	**Dual:** Warfarin + Clopidogrel **TT:** Warfarin + DAPT	↓ in dual vs TT (19.4% vs 44.4%, HR 0.36; 95% CI 0.26-0.50)

AUGUSTUS

Patients	CHADS-VASc score 3.9, HAS-BLED 2.9, Recent ACS or PCI
Intervention	P2Y12 inhibitor→ Randomization 1: Apixaban (N=2306) vs warfarin (N=2308)--> Randomization 2: Aspirin (N=2307) vs placebo (N=2307)
Outcomes	**Primary: ISTH major or clinically relevant non-major bleeding** Apixaban vs Warfarin: 241 (10.5%) vs 332 (14.7%); HR 0.69 (95% CI 0.58-0.81) Aspirin vs Placebo: 367 (16.1%) vs 204 (9.0%); HR 1.89 (95% CI 1.59-2.24) **Secondary:** Apixaban vs Warfarin: ↓ death or hospitalization (23.5% vs 27.4%, HR 0.83, 95% CI 0.74-0.93), ↓ hospitalization (22.5% vs 26.3%, HR 0.93, 95% CI 0.74-0.93), ↓ stroke (0.6% vs 1.1%, HR 0.50, 95% CI 0.26-0.97)

Conclusions: in patients with concurrent AF and ACS, the combination of Apixaban and Clopidogrel is associated with a decreased rate of bleeding, and may have an impact on mortality and hospitalization.

Valvular AF: Anticoagulation

Study	Patients	Interventions	Outcomes
Cannegieter et al. (1995)	All patients with mechanical heart valves (AVR or MVR) primarily single-valve replacement	Warfarin at varying INRs	Optimal INR between 2.5 and 3.9.
AREVA (1996)	Single-valve replacement, mechanical heart valve	Warfarin to a target INR of 3.0-4.5 OR 2.0 to 3.0	↓ in risk of any bleeding with INR 2-3 (p=0.011) and no significant difference in thromboembolic events
GELIA (2005)	AVR (N= 2024), MVR (N=553), combined (N=158)	Warfarin at target INR 3.0-4.5 OR 2.5-4.0 OR 2.0-3.5	No significant difference in thromboembolic rates or bleeding between the 3 targets

POAF: Prophylaxis

Therapy	Evidence	Recommendation
Beta blocker	BLOS study (Metoprolol vs placebo): ↓ POAF (29.6% vs 40.1% OR 0.63) ONLY if BB initiated pre-op.	Strong evidence to continue a BB if started pre-op. Standard doses of BBs: ≥ 2 days pre-op, day of surgery, ≥ 6 days post-op.
Amiodarone	Meta-analysis (19 RCTs vs placebo): ↓ POAF (OR 0.60, 95% CI 0.43-0.59)	Consider in patients with CI to BB therapy. Weight-based dosing (10 mg/kg/d div BID): ≥ 6 days pre-op, day of surgery, ≥ 6 days post-op).

POAF: Prophylaxis

Therapy	Evidence	Recommendation
Sotalol	**Meta-analysis (Sotalol vs placebo or BBs):** ↓ POAF vs placebo (OR 0.34, 95% CI 0.26-0.45) and vs standard BB (OR 0.42, 95% CI 0.26-0.65) ADRs: 7.2% (Sotalol) vs 4.8% (BB), p=0.25 (NSS)	Can be used as prophylaxis for patients at high risk of POAF. May have ↑ efficacy but ↑ ADRs vs BB.
IV Magnesium	**Meta-analysis (vs placebo):** ↓ POAF (26.7% vs 20%, OR 0.66, CI 0.51-0.87)	Can use as POAF prophylaxis if patients have CI to BB and amiodarone therapy (other option: biatrial pacing)

POAF: Prophylaxis

Therapy	Evidence	Recommendation
Biatrial pacing	**Meta-analysis (14 RCTs):**↓ POAF vs placebo (17.7% vs 35.3%, p<0.01) **AFIST-II:** Amiodarone prevented POAF better than biatrial pacing (RR 0.50, 95% CI 0.30-0.82, P < 0.05)	Can use as POAF prophylaxis if patients have CI to BB and amiodarone therapy (other option: IV magnesium)
Combination Therapy	**2 RCTs:** **Forlani et al:** Placebo (38%) vs Sotalol (11.8%) vs IV Mag (14.8%) vs Sotalol + IV Mag (1.9%) **AFIST-II:** Prophylactic pacing vs amiodarone vs both vs neither (NSS)	Consider combination therapy in high risk patients for POAF of ≥ 2 of: beta-blocker, amiodarone, IV magnesium or biatrial pacing