Atrial Fibrillation and Anticoagulation: Risk and Benefit

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To lower health-care costs, many physicians are teaming up with airport security.

$CHA2DS_2$-VASc score

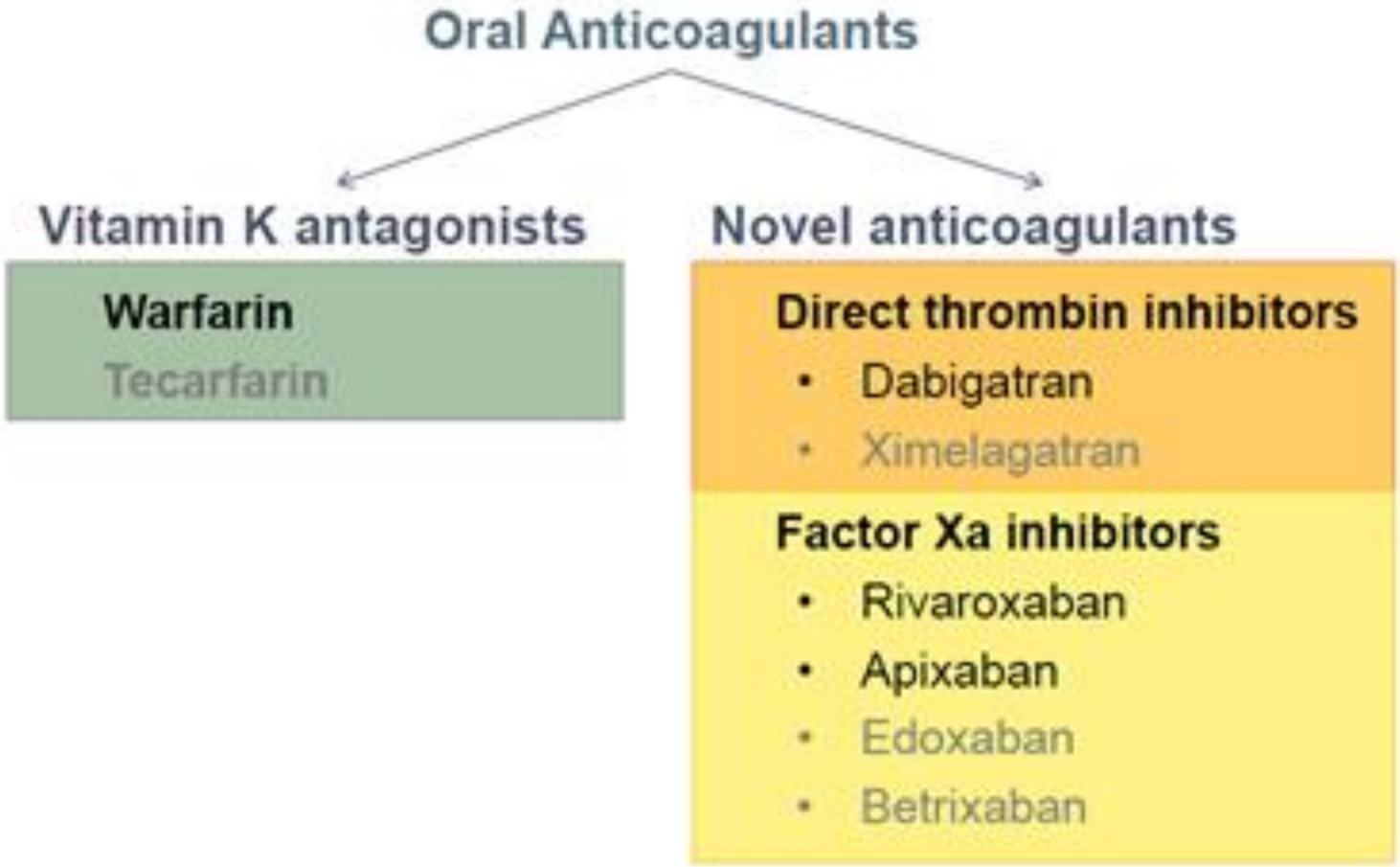
- Estimates stroke risk in patients with A. fib
- Acronym:
  - C = HF or LV dysfunction
  - H = HTN
  - A = Age (≥ 75 = 2 points)
  - D = DM
  - S = Stroke/TIA/emboli history = 2 points
  - S = gender
  - VASc = prior MI, PAD, aortic plaque

HAS-BLED Score

	Clinical Characteristic	Score
H	Hypertension	1
A	Abnormal renal or liver function (1 each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly age	1
D	Drugs or alcohol (1 each)	1 or 2
	Maximum Score	9

Hypertension: SBP > 160 mmHg; Abnormal renal function: Chronic dialysis, renal transplant, serum creatinine ≥ 200μmol/L; Abnormal liver function: Chronic hepatitis, bilirubin > 2x upper limit of normal (ULN) in association with AST/ALT/ALP > 3 x ULN; Bleeding: Previous history, predisposition; Labile INRs: unstable/high INRs, in therapeutic range < 60%; Age > 65 years; Drugs/alcohol: Concomitant use of antiplatelet agents, non-steroidal anti-inflammatory drugs, etc.

Options for Anticoagulation



Pharmacology

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism	Reduced synthesis of Factors II, VII, IX,X	Direct competitive reversible inhibition of thrombin	Direct competitive reversible inhibition of Factor Xa	Direct competitive reversible inhibition of Factor Xa	Direct competitive reversible inhibition of Factor Xa
Dosing	QD	BID	QD	BID	QD
Time to peak AC	3-5 days	1-2 hr	2.5-4 hr	3 hr	1-2 hr
Half life	40 hr	14-17 hr	11-13 hr	8-15 hr	9-12 hr
Antidote	Vitamin K	None (60% dialyzabe, ?PCC, ?rFVIIa)	None (PCC, ?rFVIIa)	None (?PCC, ?rFVIIa)	None (?PCC, ?rFVIIa)
Renal excretion	0%	~80%	35%	25%	60%
Drug interaction potential	Multiple, especially CYP2C9	P-glycoprotein inhibitor (possible PPI)	CYP3A4 substrate and P-glycoprotein inhibitor	CYP3A4 substrate and P-glycoprotein inhibitor	CYP3A4 substrate and P-glycoprotein inhibitor
Monitoring	PT/INR	None	None	None	None

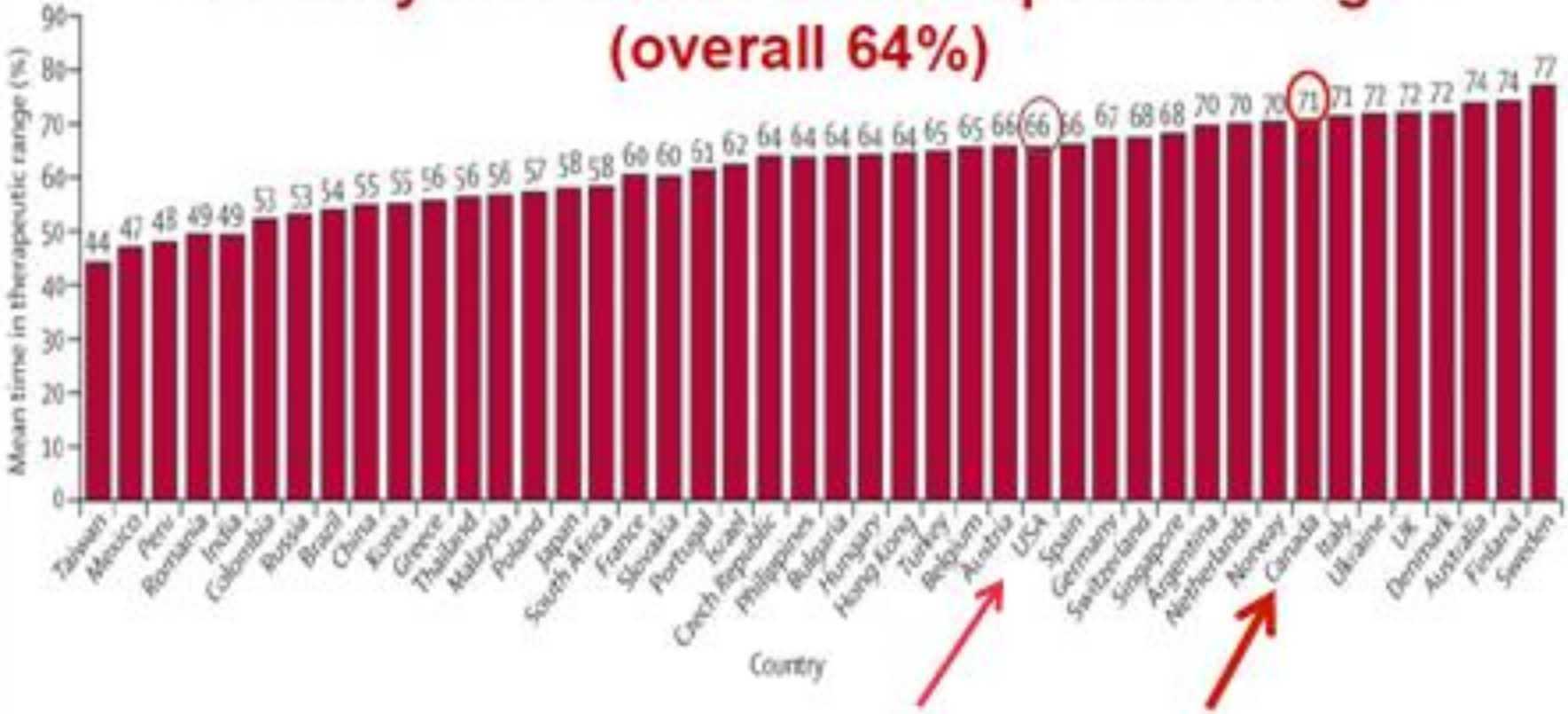
*Inhibitors of P-glycoprotein transporter include amiodarone and verapamil

Monitoring

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
PT/INR	Prolongs, high sensitivity	Prolongs, low sensitivity	Prolongs, poor sensitivity at low concentrations	Prolongs, unknown variability	Prolongs, variable sensitivity
aPTT	Prolongs, low sensitivity	Prolongs, curvilinear relationship, variable sensitivity	Prolongs, variable and generally low sensitivity	Prolongs, unknown variability	Prolongs, variable sensitivity

INR Control and Dabigatran in RE-LY

Country Mean Time in Therapeutic Range (overall 64%)



Wallentin – Lancet 2010;376:975

Warfarin vs Dabigatran & TTR

Event	Warfarin (n=6,022)	Warfarin Q4 TTR <53%	Warfarin Q1-2 TTR >67%	Dabig 110 mg (n=6,015)	Dabig 150 mg (n=6,076)
Stroke + SE	1.7%/yr	2.2%/yr	1.3%/yr	1.5%/yr	1.1%/yr
Major bleed	3.4%/yr	4.6%/yr	2.7%/yr	2.7%/yr	3.1%/yr
Composite	7.6%/yr	11.9%/yr	5.3%/yr	7.1%/yr	6.9%/yr

Patients on warfarin with TTR >67% did at least as well as those on dabigatran

Considerations

Warfarin	New Anticoagulant	No Anticoagulant
• Excellent INRs while on warfarin • Need for dual antiplatelet therapy • Other indications for warfarin (e.g. prosthetic valves) • Least expensive	• Labile INRs on warfarin • Refusal to take warfarin • Averse to monitoring • Inconsistent diet • High risk for stroke • Low risk for GI bleed	• Intractable problems with bleeding • Prior hemorrhagic intracerebral event

Caveats

Warfarin	New Anticoagulant	No Anticoagulant
• Need to control INRs • Need stable diet • Screen for multiple potential for drug interactions (i.e. in polypharmacy)	• Avoid if patient has high risk for bleed, especially GI bleed • If existing or impending renal dysfunction, avoid dabigatran and caution in rivaroxaban • Screen for a few key drug interactions • Prohibitive cost	• Consider aspirin • ?LAA occlusion

One Approach

1. Does the patient need oral anticoagulation? (CHADSvasc)
2. What is the patient's bleed risk? (HAS-BLED)
3. Is there a compelling indication for a newer anticoagulant?
   - Patient refuses warfarin
   - Patient has unstable INRs on warfarin 
4. Are there contraindications to newer agents?
   - Severe renal and/or liver disease, valve disease
5. If choosing warfarin, optimize time in therapeutic range
   - Centers can have TTRs ranging from 40% to 70%
6. If choosing newer agent, carefully consider dosing issues
   - Avoid high dose dabigatran in patients >75 to 80 yrs
   - Screen for risk of GI bleed (ulcer, NSAIDs, etc.)

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Thank You!