Maine Medical Center
MaineHealth

Clinical Guideline for Anticoagulation in Atrial Fibrillation

The approval of three novel oral anticoagulants for the prevention of ischemic stroke due to atrial fibrillation presents a clinical dilemma for prescribers. These clinical guidelines are intended to provide evidence-based recommendations regarding which oral anticoagulant should be used in certain clinical scenarios. These guidelines include the direct thrombin inhibitor, dabigatran (Pradaxa®); the direct factor Xa inhibitors, rivaroxaban (Xarelto®) and Apixaban (Eliquis®); and the vitamin-K antagonist, warfarin (Coumadin®).

Risk Assessment

Stroke Risk = CHA_2DS_2-VASc[1]

	Risk Factor	Score
C	Heart failure (LVEF ≤40%)	1
H	Hypertension	1
A_2	Age ≥75	2
D	Diabetes	1
S_2	Previous stroke, TIA, or TE	2
V	Vascular disease (CAD, PAD, Aortic plaque)	1
A	Age 65-75	1
Sc	Sex = female	1
	Total	/9

Total Score	Annual Risk (%/year)
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

Bleeding Risk = HAS-BLED[2,3]

	Risk Factor	Score
H	Uncontrolled Hypertentions	1
A	Abnormal renal* or liver function† (1 each)	2
S	Previous stroke	1
B	Bleeding history or predisposition (anemia)	1
L	Labile INRs	1
E	Elderly: Age >65	1
D	Drugs (antiplatelets or NSAIDs) or alcohol use	1
	Total	/9

*Abnormal renal function: HD, transplant, or SCr >2.3 mg/dL
†Abnormal liver function: chronic hepatic disease or bilirubin >2x ULN with AST, ALT, AlkPhos >3x ULN

Total Score	Annual Risk[3] (%/year)
0	0.9
1	3.4
2	4.1
3	5.8
4	8.9
5	9.1
≥6	N/a

Therapy Recommendations

For patients new to anticoagulation therapy for AF, please reference www.afib.ca for a useful clinical tool weighing risk assessment (stroke risk vs. bleeding risk) as well as other patient characteristics and guiding you to therapy recommendations. Also see below for specific clinical scenarios that favor one agent over another. Consultation with MMC's anticoagulation pharmacy specialist is also available (pager: 741-7933).

MMC Specific Exclusion Criteria

- Dabigatran:
  - CL_{Cr} (per Cockcroft-Gault) <30 mL/min
  - Weight <50 kg
  - Age >75 years *plus* CL_{Cr} 30-50 mL/min
  - Age >75 years *plus* weight <60 kg
- Rivaroxaban: CL_{Cr} (per CG) <30 mL/min
- Apixaban: CL_{Cr} (per CG) <30 mL/min OR SCr >2.5 mg/dL

Clinical Pearls

	Dabigatran	Rivaroxaban	Apixaban	Warfarin
Drug class	Direct Thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Vitamin-K antagonist
Dosing	150 mg BID	20 mg daily (CL_{Cr} >50) 15 mg daily (CL_{Cr} 30-50)	5 mg BID 2.5 mg BID (≥2: age ≥80, SCr ≥1.5, wt <60 kg)	Patient specific, target INR 2-3
Protein Binding (%)	35	>90	87	99
Bioavailability (%)	6	80	50	100
Tmax (hr)	1-3	2-4	1-3	5-7 days
Half-life (hr)	12-17	5-9	8-15	20-60
Elimination	80% Renal	36% Renal	25% Renal	Liver
Dialyzable	Yes	Unlikely	Unlikely	No
CYP interactions	No	3A4, 2J2	3A4	2C9, 3A4
p-glycoprotein interactions	Yes	Yes	Yes	No
Food alterations	Less dyspepsia w/ food	Take with food	None	Vitamin K

Clinical Scenarios

The following list includes several common scenarios where selecting alternative agents may be warranted. This list is not inclusive of all possible scenarios. Consultation with MMC's anticoagulation pharmacy specialist is also available (pager: 741-7933).

Age, Weight, and Renal Function

Severe renal impairment (CL_{Cr} <30 mL/min)

- Warfarin is preferred agent

Age ≥80

- Weight <60 kg OR CL_{Cr} >30 mL/min: Apixaban 2.5mg BID or Warfarin

- CL_{Cr} <30 mL/min: Warfarin

Age <80

	Weight	<60 kg	60-100* kg
CL_{Cr}	>50 mL/min	Apixaban 5 mg BID or Warfarin	Apixaban 5mg BID Rivaroxaban 20mg daily Dabigatran 150mg BID Warfarin
	30-50 mL/min	Apixaban 2.5 mg BID or Warfarin	Apixaban 5mg BID Rivaroxaban 15mg daily Dabigatran 150mg BID Warfarin
	<30 mL/min	Warfarin	

*Clinical trials of NOACs did not include large numbers of patients with body weight >100kg, thus their efficacy in AF patients is not well understood; Pharmacokinetic studies demonstrated no definitive alterations in drug concentrations of dabigatran, rivaroxaban, and apixaban in patients up to 110kg, 140kg, and 120kg, respectively.

Patients with mechanical heart valves

- Warfarin only
- Oral Xa inhibitors (rivaroxaban, apixaban) have not been studied for this indication; Dabigatran has showed an increased risk of both thromboembolic and bleeding complications in this patient population

Patient requiring dual antiplatelet therapy (DAPT) – recent cardiac stent, TAVR, off-pump CABG

- Very little data involving novel agents and DAPT, thus warfarin is the preferred agent
- If $CHADS_2$ score is 0 or CHA_2DS_2-VASc score <2, could consider aspirin + clopidogrel as alternative to anticoagulation in patients with a recent coronary stent (within 1 month for bare-metal stent, within 1 year for drug-eluting stent)

Patient requiring aspirin therapy

- Aspirin doses should be minimized to 81 mg daily during concomitant anticoagulant therapy
- If doses >81 mg daily are indicated, warfarin is preferred agent

Moderate to severe liver disease (Child Pugh B or C)

- Warfarin is preferred agent

Potential for non-adherence with medication dosing

- Warfarin is preferred agent due to ability to monitor INR
- Rivaroxaban is preferred novel agent given once-daily dosing in AF

Financial issues (insurance coverage, copay, etc.)

- Warfarin is preferred agent
- Financial assistance programs are available through the manufacturers of all novel oral agents.

Recent TIA/Stroke

- Patients with recent stroke were excluded from clinical trials of novel agents (w/in 14 days for dabigatran or rivaroxaban; w/in 7 days for apixaban)

Known drug-interactions with p-glycoprotein inhibitors/inducers or strong 3A4 inhibitors/inducers

- Warfarin is preferred agent due to ability to monitor INR

	Inhibitor	**Inducer**
p-glycoprotein (All three NOACs)	Amiodarone Dronedarone Macrolide antibiotics Azole antifungals Verapamil Protease Inhibitors	Rifampin Phenytoin Carbemazepime St. John's wort
CYP 3A4 (Rivaroxaban, Apixaban)	Amiodarone Dronedarone Macrolide antibiotics Azole antifungals Verapamil Diltiazem	Rifampin Phenytoin Carbemazepime St. John's wort

Perioprocedural management

Novel Agents[4-7]	**ClCr (ml/min)**	**Half-life, hr (range)**	**Bleeding Risk**	
			Low	High
Preprocedure				
Dabigatran	>80 51-79 30-50 <30	13 (11-22) 15 (12-34) 18 (13-23) 27 (22-35)	1-1.5 days 1-2 days ≥2 days 2-4 days	2-3 days 2-3 days 4 days >5 days
Rivaroxaban	>30	9	2 days	3 days
Apixaban	>50 30-50	9 17-18	2 days 3 days	3 days 4 days
Postprocedure				
Dabigatran	---	---	1-4 hours (at ½ dose) Or 6-12 hours	2-3 days
Rivaroxaban	---	---	24 hours	2-3 days
Apixaban	---	---	24 hours	2-3 days

References

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7. Connolly G, Spyropoulos AC. Practical issues, limitations, and periprocedural management of the NOAC's. *J Thromb Thrombolysis* 2013;36:212-222.