Management of Bleeding

Apixaban, Rivaroxaban, Edoxaban or Dabigatran		Warfarin		
Minor Bleed	Hold anticoagulant. Provide supportive measures	**No Significant Bleed**	INR 4.5 - 9	Omit 1 – 2 doses. Reduce dose by 10 – 20%
			INR > 9	Hold warfarin. Give vitamin K, 5 – 10mg PO. Monitor daily INR then reduce dose once in therapeutic INR
Life-threatening Bleed	Discontinue anticoagulant Supportive measures Overdose: Charcoal by mouth if ingested within 2 – 6 hrs Dialysis: Not expected to have any effect on apixaban/rivaroxaban **Apixaban, Rivaroxaban, Edoxaban**: Kcentra® 50 units/kg **Dabigatran**: Praxbind® 5 g intravenously once	**Severe Bleed**	Hold warfarin Give vitamin K, 10mg slow IV plus fresh frozen plasma or Kcentra® 25 – 50 units/kg Repeat vitamin K every 12 hrs as needed	
		Life-threatening Bleed	Hold warfarin Give Kcentra® 25 – 50 units/kg plus vitamin K, 10mg slow IV Repeat vitamin K as needed	

Kinetics

Medication	Apixaban	Rivaroxaban	Warfarin
Onset of action	3 – 4 hrs	2 – 4 hrs	24 – 72 hrs, up to 2 wks to reach steady state
Half-life	12 hrs	5 – 9 hrs, 11 – 13 hrs in elderly	20 – 60 hrs
Bioavailability	50%	10mg: 80 – 100% 20mg: 66% without food, 100% with food	100%
Protein binding	~87%	92 – 95%	99%
Metabolism	Primarily CYP3A4P-glycoprotein substrate Minor: CYP1A2, 2C8, 2C9, 2C19	Primarily CYP3A4 and P-glycoprotein substrate Minor: CYP2J2	Primarily CYP2C9 (metabolizes more active S enantiomer) Minor: CYP2C8, 2C19, 1A2, and 3A4

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Approved by: Anticoagulation Safety Committee: 2/2018
Pharmacy and Therapeutics Committee: 3/2018

University Health System

Oral Anticoagulation Pocket Card

Drug	Indication	Dose	Renal Impairment	Hepatic Impairment
Apixaban (Not approved for use in patients < 18 years old)	Nonvalvular atrial fibrillation	5mg by mouth twice daily	2.5mg by mouth twice daily if patient has at least **2** of the following: SCr ≥ 1.5mg/dL, Age ≥ 80 years, weight ≤ 60 kg	Caution Child-Pugh class C: **Do not use**
	DVT and/or PE	10mg by mouth twice daily for 7 days, then 5mg by mouth twice daily	No adjustment necessary however Patients with SCr > 2.5 mg/dL or CrCl < 25 ml/min were excluded from the AMPLIFY clinical trials	
	DVT/PE Secondary prevention after >/= 6 months initial therapy	2.5mg by mouth twice daily		
	VTE Prophylaxis following hip or knee replacement surgery	2.5mg by mouth twice daily for 35 days (hip replacement) or 12 days (knee replacement)	No adjustment necessary Patients with impaired renal function were excluded from the ADVANCE trials	
Rivaroxaban (Not approved for use in patients < 18 years old)	Nonvalvular atrial fibrillation	20mg by mouth once daily with food	CrCl 15 – 50 mL/min: 15mg by mouth once daily with food CrCl < 30 mL/min: excluded from ROCKET trial CrCl < 15 mL/min: **Do not use**	Child-Pugh class B or C: **Do not use** Any hepatic disease associated with coagulopathy: **Do not use**
	DVT and/or PE	15mg by mouth twice daily with food for 21 days, then 20mg by mouth once daily	CrCl < 30 mL/min: **Do not use**	
	DVT/PE Secondary prevention after >/= 6 months initial therapy	10mg by mouth once daily		
	VTE Prophylaxis following hip or knee replacement surgery, or in acutely ill medical patients	10mg by mouth once daily for 35 days (hip replacement) or 12 days (knee replacement), or up to 39 days total (medical illness)	CrCl 30 – 50 mL/min: Use with caution CrCl < 30 mL/min: **Do not use**	
	Reduction of risk of major cardiovascular events in CAD/PAD	2.5mg by mouth twice daily plus aspirin 81mg once daily	CrCl < 15 mL/min or on dialysis: Excluded from COMPASS trial	
Warfarin	See warfarin dosing nomograms (pages 2 and 3)		No renal adjustment necessary	

Laboratory Monitoring	Apixaban	Rivaroxaban	Warfarin
	Baseline and periodic SCr, LFTs, & CBC. Routine coagulation monitoring is not recommended. INR and aPTT will be prolonged, but should not be used to assess effectiveness		Assess INR for efficacy and safety See nomograms on pages 2 and 3

New Start Warfarin Dosing Nomograms

5mg Warfarin [A]		
Day	INR	Warfarin Dose (mg)
1		5 mg
2		5 mg
3	< 1.5	10 mg
	1.5 – 1.9	5 mg
	2.0 – 3.0	2.5 mg
	> 3.0	0
4	< 1.5	10 mg
	1.5 – 1.9	7.5 mg
	2.0 – 3.0	5 mg
	> 3.0	0
5	< 2.0	10 mg
	2.0 – 3.0	5 mg
	> 3.0	0
6[B]	< 1.5	12.5 mg
	1.5 – 1.9	10 mg
	2.0 – 3.0	7.5 mg
	> 3.0	0

2.5mg Warfarin [A]		
Day	INR	Warfarin Dose (mg)
1		2.5 mg
2	< 1.5	5 mg
	1.5 – 1.9	2.5 mg
	2.0 – 2.5	1 – 2.5 mg
	> 2.5	0
3	< 1.5	5 – 7.5 mg
	1.5 – 1.9	2.5 – 5 mg
	2.0 – 3.0	0 – 2.5 mg
	> 3.0	0
4	< 1.5	10 mg
	1.5 – 1.9	5 – 7.5 mg
	2.0 – 3.0	0 – 5 mg
	> 3.0	0
5	< 1.5	10 mg
	1.5 – 1.9	7.5 – 10 mg
	2.0 – 3.0	0 – 5 mg
	> 3.0	0
6[B]	< 1.5	7.5 – 12.5 mg
	1.5 – 1.9	5 – 10mg
	2.0 – 3.0	0 – 7.5 mg
	> 3.0	0

[A] Consider 2.5mg start if elderly, malnourished, liver disease, high bleeding risk, CHF exacerbation, or interacting drugs

[B] For dose adjustments beyond day 6, see the "Maintenance Dose Warfarin Nomogram" on page 3

Consult to Anticoagulation Clinic for INR Monitoring

EMR entry titled "Anticoag Clinic Consult"

Clinic Phone Number 210-358-6518

Drug and Food Interactions

Apixaban	**Strong inhibitors of both CYP3A4 and P-gp** Ketoconazole, itraconazole, ritonavir, or clarithromycin: **Reduce dose** from 5 mg twice daily to 2.5 mg twice daily **Avoid** if patient is already taking 2.5 mg twice daily or if patient has 2 of the following: SCr ≥ 1.5mg/dL, Age ≥ 80 years, weight ≤ 60 kg **Strong inducers of both CYP3A4 and P-gp** Rifampin, carbamazepine, phenytoin, St. John's Wort, phenobarbital, and primidone: **Avoid use**
Rivaroxaban	**Strong inhibitors or inducers of both CYP3A4 and P-gp** Inhibitors: **Avoid** if on ketoconazole, itraconazole, indinavir-ritonavir, lopinavir-ritonavir, ritonavir, or conivaptan Inducers: **Avoid** if on carbamazepine, phenytoin, or rifampin

Warfarin

Increase potency or bleed risk		Decrease potency
Acetaminophen	NSAIDs	Azathioprine
Alcohol	Omeprazole	Barbiturates
Amiodarone	Phenytoin	Carbamazepine
Amoxicillin	Propafeone	Cholestyramine
Anabolic steroids	Quinidine	Cyclosporine
Antiplatelet agents	Salicylates	Dicloxacillin/nafcillin
Cephalosporins	SSRIs	Griseofulvin
Cimetadine	Tamoxifen	Rifampin
Fluoroquinolones	Thyroxine	Sucralfate
Disulfiram	Tramadol	Trazodone
Doxycycline	Trimethoprim-sulfamethoxazole	**Foods**
Tetracycline	**Herbal products**	Enteral feeds with high vitamin K amounts
Erythromycin	Danshen	Green leafy vegetables
Fluconazole/itraconazole	Devil's claw	Broccoli, Avocados
Influenza vaccine	Dong quai	Mayonnaise, Liver
Isoniazid	Garlic	Green tea
Lovastatin	Ginkgo	**Herbal products**
Metronidazole	Papain	Coenzyme Q10
Miconazole	Vitamin E	Ginseng
		St. John's Wort

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University Health System

Oral Anticoagulation Pocket Card

Warfarin Maintenance Dose Nomogram

Based on Total Weekly Dose

INR target 2.0 – 3.0			INR target 2.5 – 3.5		
INR	**Adjustment**	**Next INR**	**INR**	**Adjustment**	**Next INR**
< 1.5	Increase dose 10 – 20%, consider extra dose	14 days	< 1.5	Increase dose 10 – 20%, consider extra dose	14 days
1.5 – 1.9	Increase dose 5 – 10%[A]	7 – 14 days	1.5 – 2.4	Increase dose 5 – 10%[B]	7 – 14 days
2.0 – 3.0	No change	Number of consecutive in-range INR x 1 wk (max 4 weeks)[C]	2.5 – 3.5	No change	Number of consecutive in-range INR x 1 wk (max 4 weeks)[C]
3.1 – 3.9	Decrease dose 5 – 10%[A]	7 – 14 days	3.6 – 4.5	Decrease dose 5 – 10%[B]	7 – 14 days
4.0 – 4.9	Hold 0 – 1 days Decrease dose 10%	4 – 8 days	4.5 – 6.0	Hold 0 – 1 days Decrease dose 10%	4 – 8 days
> 5.0	See "Management of Bleeding" table on page 4		> 6.0	See "Management of Bleeding" table on page 4	

[A]: If INR is 1.7 – 1.9 or 3.1 – 3.3 consider no change with repeat INR in 7 – 14 days

[B]: If INR is 2.3 – 2.4 or 3.6 – 3.7, consider no change with repeat INR in 7 – 14 days

[C]: For example, if a patient has had 4 consecutive in-range INR values, recheck in 4 weeks

Warfarin Target INR and Treatment Duration

Indication		Therapy Duration	Target INR
DVT or PE	First episode, provoked	3 months	2.0 – 3.0
	First episode, unprovoked	At least 3 months but extended therapy is preferred if no contraindications and low-moderate bleeding risk	
	First episode, patient with cancer	Therapeutic LMWH for 6 months then warfarin or continue LMWH. Treat until cancer is resolved.	
	Recurrent DVT	Indefinitely	
Atrial Fibrillation	Atrial fibrillation	Indefinitely	
	Anticoagulation after cardioversion	At least 4 weeks after cardioversion. Refer to CHA2DS2-VASc for subsequent treatment	
Valvular Heart Disease	Bioprosthetic valve: Aortic – ASA or warfarin	3 months	
	Bioprosthetic valve: Mitral – Warfarin		
	Mechanical valve	Indefinitely	
	Mechanical valve plus one of the following risk factors: Mitral valve position, low EF (<50%), caged ball valve, history of TIA/stroke, atrial fibrillation	Indefinitely	2.5 – 3.5