Formulary Flash

Volume 17, Issue 1 March 2017

A PUBLICATION OF THE PHARMACY AND THERAPEUTICS COMMITTEE (P&T) AND THE DEPARTMENT OF PHARMACY

Oral Anticoagulants: Considerations for Use of Warfarin, Apixaban and Rivaroxaban

Background

For decades, vitamin K antagonists (e.g. warfarin) were the only class of oral anticoagulants available to clinicians. In more recent years a new class of oral anticoagulants (OACs) commonly referred to as direct oral anticoagulants (DOACs) have gained FDA approval. Dabigatran (Pradaxa®) was approved in 2010, followed by rivaroxaban (Xarelto®), apixaban (Eliquis®), and edoxaban (Savaysa®). Of these, rivaroxaban and apixaban are currently on UHS formulary. Given the various differences among these agents vs warfarin, it is important to address a number of factors when deciding which OAC is best suited for a specific patient.

Warfarin treats and prevents clot formation by decreasing the hepatic synthesis of vitamin K dependent clotting factors II, VII, IX and X. The extended half-lives of clotting factors II and X result in a delayed full therapeutic effect of warfarin, necessitating initial concomitant therapy with a parenteral anticoagulant ("bridge") when immediate anticoagulation is indicated. Warfarin dose response varies depending on a multitude of environmental and genetic factors, therefore requiring routine therapeutic drug monitoring to promote efficacy and safety.[1]

Apixaban and rivaroxaban directly target and inhibit factor Xa and prothrombinase activity, thus inhibiting the conversion of prothrombin to thrombin. They exhibit predictable pharmacokinetics and therefore do not require routine therapeutic monitoring. Their faster onsets of action vs warfarin avoids the need for bridging with a parenteral anticoagulant, while their shorter half-lives require strict adherence to therapy. [2,3]

Clinical Trials

Randomized prospective clinical trials for venous thromboembolism (VTE) treatment and stroke prevention in non-valvular atrial fibrillation (NVAF) compared the DOACs to warfarin. **Table 1** summarizes efficacy and safety outcomes from the apixaban and rivaroxaban trials. Prospective trials comparing the DOACs to each other are lacking, therefore one must rely on indirect comparisons when choosing between one DOAC and another.[4,5]

OAC Selection

Differences in FDA approved indications and the risk/benefit ratio in subgroups where data is lacking must be recognized before initiating DOAC vs warfarin therapy. Renal and hepatic function, drug/diet interactions, compliance and access to medication must also be considered. **Table 2** highlights some of the key differences (*Continued on page 3)*

Table 1: Rivaroxaban and Apixaban vs Warfarin in VTE and NVAF Clinical Trials[6-10]

Outcome	Apixaban vs Warfarin	Rivaroxaban vs Warfarin
VTE Trials [6,7,8]		
Recurrent VTE	Non-inferior	Non-inferior
Major Bleeding	↓ with DOAC	↓ with DOAC
NVAF Trials[9,10]		
Stroke or systemic embolism	↓ with DOAC	No difference
- Hemorrhagic strokes	↓ with DOAC	No difference
- Ischemic strokes	No difference	No difference
Major Bleeding	↓ with DOAC	No difference
- ICH	↓ with DOAC	↓ with DOAC
- Major GI bleed	No difference	↑ with DOAC
Death from any cause	↓ with DOAC	No difference

VTE-Venous thromboembolism, DOAC- direct oral anticoagulant, NVAF-Non-valvular atrial fibrillation, ICH-intracranial hemorrhage, GI-gastrointestinal

Table 2: Considerations in Oral Anticoagulant Selection

	Warfarin (Coumadin®, Jantoven®)	Apixaban (Eliquis®)	Rivaroxaban (Xarelto®)
Indications for Use			
Non-valvular Afib	Yes	Yes	Yes
Valvular Afib	Yes	**No**	**No**
Heart Valve Replacements	Yes	**No**	**No**
DVT/PE Treatment and Secondary Prevention	Yes	Yes	Yes
DVT/PE Subgroups:[5] -Severe Renal failure -Extreme Weight (<40 kg or >150 kg)[11,12] -Thrombophilia[12] -Cancer Associated VTE[12] -Pregnancy/Breastfeeding &Pediatrics[12]	Yes Pregnancy- avoid during 1st trimester and close to delivery, consider LMWH instead Cancer Associated VTE- LMWH is first line, warfarin is 2nd line	**Limited data in these clinical subgroups** **> 18 yo- Weigh risk vs benefit** **< 18 yo- DO NOT use**	**Limited data in these clinical subgroups** **> 18 yo- Weigh risk vs benefit** **< 18 yo- DO NOT use**
DVT prophylaxis after hip/knee replacements	Yes (rare)	Yes	Yes
Time to Peak	**5-7 days**	3-4 hours	2-4 hours
Half-Life	Long and variable (20-60 hours)	12 hours	5-9 hours
Routine Therapeutic Monitoring	**Yes- INR**	Routine monitoring not recommended AntiXa level may be useful to assess adherence and bleeding potential-Send out lab	Routine monitoring not recommended AntiXa levels may be checked to assess adherence and bleeding potential-Send out lab
Food Interactions	**Yes (Vitamin K rich food)**	None	**Must be taken with food**
Drug Interactions	Substrate 2C9, 3A4, 2C19, 1A2 (May need to adjust dose per INR)	Substrate of 3A4 and P-gp (May need to adjust dose or avoid use)	Substrate of 3A4 and P-gp (May need to avoid use)
Renal Impairment	No dose change	**27% dependent on renal elimination**	**36% dependent on renal elimination**
Hepatic Impairment	Monitor INR closely	**Child-Pugh class C: Avoid use**	**Child-Pugh B or C: Avoid use**
Doses per day	Once daily	Twice daily	Once or twice daily per indication See Table 3
Cost	Generic Various retail pharmacy $5 programs	Brand Name Only Med and Co-pay Assistance Program Available	Brand Name Only Med and Co-pay Assistance Program Available
Hold before a procedure	5-6 days (consider bridging based on thrombotic risk)	24 hours- low risk of bleeding 48 hours- moderate/high risk of bleeding	At least 24 hours Consider 48 hours in elderly or if CrCl < 50mL/min
Reversal agents	Vitamin K, PCC, FFP	None currently available. Limited data for PCC	None currently available. Limited data for PCC

Afib- atrial fibrillation; DVT-deep vein thrombosis; FFP- fresh frozen plasma; PCC-prothrombin complex concentrate (Kcentra®); P-gp-P glycoprotein efflux pump; PE-pulmonary embolism;

(*Continued from page 1)*

between OACs currently on UHS formulary. Once an OAC is selected, special attention should be paid to ensure the correct dose is prescribed initially and throughout therapy. Starting doses, frequency, and dose adjustment criteria vary for apixaban and rivaroxaban based on the indication and often times require that the dose be changed during the course of therapy. Though routine therapeutic monitoring is not necessary with these agents, periodic follow up by a physician to review appropriateness of anticoagulation therapy is recommended. **Table 3** outlines dosing for the OACs currently on UHS formulary.

Table 3: Dosing based on Indication

	VTE Treatment and Secondary Prevention	DVT Prophylaxis	Non-Valvular Afib	Prosthetic Heart Valve or Afib with Valvular Disease
Apixaban (Eliquis®)	10mg twice daily x 7 days then 5mg twice daily for remainder treatment **Secondary Prevention:** (after at least 6 months initial therapy): 2.5mg twice daily *Scr >2.5 or CrCl < 25 mL/min were excluded from AMPLIFY trial[8]. Use with caution. Consider risk vs benefit.	2.5mg twice daily Hip x 35 days Knee x 12 days *Impaired renal function excluded from trials	5mg twice daily unless **2** of the following criteria are met, then adjust to 2.5mg twice daily: • **Scr > 1.5** • **≥ 80 years old** • **≤ 60 kg** *Scr >2.5 or CrCl < 25 mL/min were excluded from ARISTOTLE trial[10] Use with caution. Consider risk vs benefit.	Not approved
Rivaroxaban (Xarelto®)	15mg twice daily x 21 days w/ food, then 20mg once daily for remainder treatment **Secondary Prevention:** (after at least 6 months initial therapy): 20mg once daily CrCl < 30mL/min or on dialysis: Avoid use	10mg once daily Hip x 35 days Knee x 12 days CrCl < 30 mL/min or dialysis: Avoid use	CrCl > 50 mL/min: 20mg once daily w/ food CrCl 15–50 mL/min: 15mg once daily w/ food *CrCl < 30 mL/min was excluded from ROCKET trial.[9] Use with caution. Consider risk vs benefit. CrCl <15 mL/min or dialysis: Avoid use	Not approved
Warfarin (Coumadin®, Jantoven®)	Starting dose 2.5mg - 10mg once daily Adjust to target INR of 2.0-3.0			2.5mg - 10mg once daily adjust to target INR 2.0-3.0 - Afib, aortic mechanical valve (lifelong), bioprosthetic valves (3 months) 2.5-3.5 - mechanical valve plus 1 risk factor: Mitral position, low EF concomitant afib, caged ball valve, history of stroke/TIA

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