Clinical Pharmacology & Toxicology Pearl of the Week

~Pros and cons of direct oral anticoagulants (DOACs), warfarin & LMWH~

Anticoagulation is commonly initiated in the Emergency Department for patients with newly diagnosed venous thromboembolism (VTE) or atrial fibrillation (Afib). Options for outpatient management of VTE and stroke prevention in Afib include DOACs, warfarin, or low molecular weight heparin (LMWH). Despite the increasing popularity of DOACs, there is still a role for warfarin and low molecular weight heparin in certain cases. An understanding of pros and cons of these agents is helpful in selecting the most suitable therapy.

Comparison among different DOACs				
Drug	**Apixaban**	**Rivaroxaban**	**Edoxaban**	**Dabigatran**
Mechanism of action	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Direct Thrombin (FII) inhibitor
Pro	Lower risk of bleeding, more effective in preventing short-term VTE recurrence compared to rivaroxaban. Lower risk of bleeding compared to dabigatran & rivaroxaban.	Once daily dosing (but comes at a cost, see below).	Some evidence suggesting non-inferiority to LMWH in VTE management in patients with non-gastrointestinal malignancy.	Has a reversal agent, Praxbind (Idarucizumab)
Con	Twice daily dosing. Reversal agent not yet available, but is on the horizon (Andexanet Alpha).	Observational data also shows increased risk of bleeding & recurrent thrombotic risk compared to apixaban*. *This is due to the pharmacokinetics of rivaroxaban: in order to be a once-daily drug, a higher dose is administered, causing a high peak, followed by low trough serum concentrations, leading to periods of both supra- & sub-therapeutic anticoagulation in a 24 hour period.	For acute VTE, Requires bridging with parenteral anticoagulant (e.g. LMWH) for at least 5 days during the acute initiation phase.	Observational data shows increased risk of bleeding compared to apixaban. Increased risk of gastrointestinal bleeding compared to apixaban, rivaroxaban For acute VTE, Requires bridging with parenteral anticoagulant (e.g. LMWH) for at least 5 days during the acute initiation phase. Twice daily dosing.

Comparison of DOACs vs. warfarin vs. LMWH			
	DOACs	**Warfarin**	**LMWH**
Pro	Convenience (no need for INR check). May be better for patient with poor venous access, frequent travel, remote locations. Superior reduction in all-cause stroke and systemic embolism, lower risk of major bleeding, clinically relevant minor bleeding and hemorrhagic stroke compared to warfarin.	Anticoagulation is maintained for a couple of days if missing dose (better prevention of VTE/stroke in patients with poor compliance) Can be used in mechanical heart valves, valvular Afib. Very cheap Reversable with FFP/Octaplex/Vit K.	Can be used in pregnancy/breastfeeding, mechanical heart valves, valvular Afib. Preferred agent for anticoagulation for VTE in patients with malignancy. Can be used as bridging therapy during perioperative period or initiation of warfarin or edoxaban. Reversable with protamine.
Con	Requires patient to be very diligent in taking medications and not miss any dose as there is no protection against VTE/stroke if missed a dose. Safety is not established (not recommended) in pregnancy/breastfeeding, mechanical heart valves, valvular Afib. Requires stable hepatic and renal function (Creatinine clearance > 30ml/min) due to risk of accumulation. More costly than warfarin but less costly than LMWH. No readily available reversal agents (except idarucizumab for dabigatran). Drug-drug interactions (without ability to monitor the effect like warfarin)	Requires therapeutic drug monitoring with regular INR checks. - Now there are portable point of care INR monitoring devices available for patients to purchase for self testing (e.g. Coaguchek XS™). - There are also mobile labs in Calgary for patients who have mobility issues to have INR lab drawn at home. Not safe for pregnancy. Generally safe for breastfeeding. Multiple drug-drug interactions but able to monitor the effect using INR	Requires regular subcutaneous injection Very costly ~1% risk of heparin induced thrombocytopenia +/- thrombosis (HITT) Requires stable renal function Creatinine clearance > 20ml/min) if used for longer periods of time (more than a week or so) due to risk of accumulation Therapeutic drug monitoring can be done using Anti-Xa level but is more costly and time consuming.

References →

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The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-call physician is listed in ROCA. Click HERE for clinical issues the CP service can assist with.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.