Te Awakairangi Health NETWORK

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Rivaroxaban – oral anticoagulant

Rivaroxaban is a direct oral anticoagulant (DOAC).[1,2] Its mode of action is to inhibit activated factor Xa which prevents the conversion of prothrombin to thrombin (and consequently the conversion of fibrinogen to fibrin) – refer Fig 1.

Rivaroxaban is now fully subsidised without restriction for all licensed indications, including prevention of stroke and systemic embolism in non-valvular atrial fibrillation (AF), treatment of DVT/PE and prevention of recurrent DVT/PE.

NOTE: this bulletin provides an overview of rivaroxaban prescribing information – please refer to the NZ Formulary, Xarelto® datasheet and recent bpac article[2] (main source of information used for TeAHN bulletin) for detailed advice.

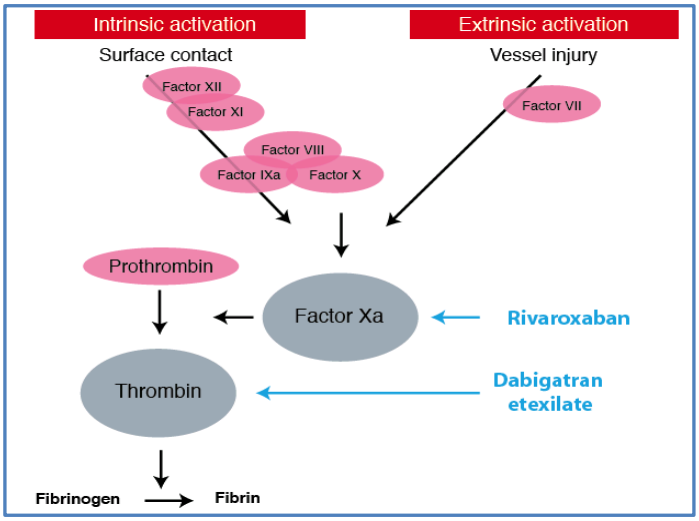

Fig 1: Site of action in coagulation cascade (rivaroxaban & dabigatran)[3]

Comparison to other anticoagulants[2]

- similar levels of protection against stroke are expected from warfarin, dabigatran and rivaroxaban
- versus **warfarin**: rivaroxaban has similar rates of *major* bleeding (except for higher association for gastrointestinal) but less intracranial bleeding
- versus **dabigatran**: rivaroxaban may be associated with higher risk of both major and intracranial bleeding
- rivaroxaban has not been associated with an elevated risk of myocardial infection

Contraindications

These include: ● active or high risk of major bleed ● prosthetic heart valve ● CrCl <30 mL/min ● moderate to severe hepatic dysfunction ● age < 18 yrs (no data) ● pregnancy ● breastfeeding

Key Messages

- Available in 10mg*, 15mg and 20mg tablets
- Once daily dosing
- Does not require initial enoxaparin when treating DVT/PE
- Dose adjustments needed in renal dysfunction
- Do not use if CrCl < 30 mL/min
- Test patient's renal function before starting and at least annually
- Also metabolised by the liver
- Do not use in patients with prosthetic heart valves
- Associated with more major bleeding than dabigatran
- No reversal agent available in NZ
- Easier to blister pack than dabigatran
- May be better tolerated in dyspepsia

*subsidy for 10mg strength limited to one tablet per day

Points to consider when deciding between dabigatran and rivaroxaban:

The decision to use a DOAC remains largely unchanged. When you have decided a DOAC is preferred over warfarin then the following should be considered:

Dabigatran may be preferred to rivaroxaban when:	Rivaroxaban may be preferred to dabigatran when:
Multiple risk factors for bleeding are present, e.g. • Age over 65 years • Elevated blood pressure • Previous stroke • Hepatic dysfunction • High alcohol intake	• Once daily dosing is preferred • Moderate renal dysfunction is present (dose adjustments still needed if CrCl <50 mL/min) • Treating DVT/PE* (no enoxaparin required) • Patient has a history of dyspepsia • Blister packing is required**

* 3DHB Health Pathways recommends rivaroxaban as first line for management of DVT/PE

**Dabigatran is more difficult to blister pack as the foil around each capsule must remain intact

Rivaroxaban dosing [1,2,6]

Creatinine Clearance (mL/min) Use Cockcroft & Gault equation	Indications		
	Prevention of stroke and systemic embolism in non-valvular AF (plus at least one risk factor for stroke*)	Treatment of DVT/PE and prevention of recurrent DVT/PE	Prevention of VTE following joint replacement surgery
>49	20mg, once daily with food	15mg twice daily with food for 21 days, then 20mg once daily with food	10mg once daily, starting six to ten hours post-surgery, for 2 weeks following a knee replacement or 5 weeks following a hip replacement.
30-49	15mg, once daily with food	As above, however consider a maintenance dose of 15mg once daily, if risk of bleeding outweighs risk of recurrent DVT or PE	No change required
15-29	Contraindicated	Contraindicated	Use with caution
<15			Contraindicated

*congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or TIA

Quick reference guide for switching between anticoagulants [1,2, 7]

***Note**: there is unlikely to be any clinical benefit in switching patients from warfarin if they spend ≥70% of the time within the therapeutic range (TTR).[2]*

		Switching to:		
		Warfarin	**Rivaroxaban**	**Dabigatran**
Switching from:	**Warfarin**	–	Stop warfarin, measure INR daily, start rivaroxaban **when INR is ≤ 3.0*** if taking for stroke/systemic embolism prevention, or **when INR ≤ 2.5*** if taking for treatment/prevention of recurrent DVT/PE	Stop warfarin, measure INR daily, start dabigatran **when INR is < 2.0***
	Rivaroxaban	Initiate warfarin while still taking rivaroxaban, withdraw rivaroxaban when INR is ≥ 2.0. Initiation of warfarin: start at a standard dose and adjust dose based on INR after two days.**	–	Take first dose of dabigatran 24 hours after last dose of rivaroxaban.
	Dabigatran	If CrCl ≥ 50ml/min, start warfarin three days before stopping dabigatran. If CrCl 30 – 49 ml/min, start warfarin two days before stopping dabigatran.	Take first dose of rivaroxaban 12 hours after last dose of dabigatran.	–

*Once patient has started taking rivaroxaban or dabigatran, the INR is not a reliable measure of the anticoagulant effect

** Rivaroxaban can contribute to an elevated INR, so INR measurements made during co-administration with warfarin may not be useful for determining the appropriate dose of warfarin. For the first two days of the conversion period, standard initial dosing of warfarin should be used and, after the first two days, warfarin dosing should be guided by INR testing. While patients are on both rivaroxaban and warfarin, INR should be tested just prior to the next dose of rivaroxaban (not earlier than 24 hours after the previous dose). Once rivaroxaban is discontinued INR testing may be done reliably at least 24 hours after the last dose.

Monitoring[2]

- Routine testing of anticoagulant effect not required[2,5]
- Testing may be required in certain clinical situations e.g. prior to surgery, in event of bleeding (refer www.bpac.org.nz/bleeding-guidelines.aspx and 3D HealthPathways)
- Annual testing of renal function recommended (more frequently in some patients e g. in progressive kidney disease, dehydration, hypovolaemia or if nephrotoxic medicines started)

Missed doses

- If taking **once**-daily rivaroxaban → can take missed dose **later that same day**. Continue normal dosing on the next day (do not take 2 doses at once).[1]

- If taking **twice**-daily rivaroxaban (i.e. for DVT/PE treatment or prevention of recurrent DVT/PE) → the missed dose should be **taken as soon as possible**; two doses may be taken at once. Normal dosing should resume the next day.[1]

Drug Interactions[1,2]

Rivaroxaban is mainly cleared via cytochrome P450-mediated (CYP 3A4, CYP 2J2) hepatic metabolism and renal excretion of the unchanged drug, involving the P-glycoprotein (P-gp) / breast cancer resistance protein (Bcrp) transporter systems. It does not however induce or inhibit CYP3A4 itself.[1]

It is *contraindicated* in patients receiving concomitant systemic treatment with *azole-antifungals* (e.g. ketoconazole) or *HIV protease inhibitors* (e.g. ritonavir) as these substances are strong inhibitors of both CYP 3A4 and P-gp and increase rivaroxaban levels.[1] However, fluconazole, a less potent CYP3A4 and P-gp inhibitor has less effect on rivaroxaban and may be co-administered.[1] Some anticonvulsants can reduce the activity of rivaroxaban[6].

Use with caution in patients with moderate renal impairment (CrCL 30 - 49 mL/min) who are also prescribed medications that increase rivaroxaban levels (including moderate inhibitors of CYP3A4 or P-gp).

Similar to other anticoagulants the risk of bleeding is increased in combination with NSAIDs, platelet aggregation inhibitors, other antithrombotics, or selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs).

Not all drug interactions are listed here - check for interactions before prescribing rivaroxaban using the NZF Interaction checker: **https://nzf.org.nz**

Other

- 15mg and 20mg tablets should be taken with food to aid absorption.[1]
- 10mg tablet can be taken with or without food[1]

References:

1. Bayer New Zealand Ltd. Xarelto data sheet 2017. Available from Medsafe: http://www.medsafe.govt.nz/profs/datasheet/x/Xareltotab.pdf (Accessed Aug 2018)
2. Rivaroxaban: a fully-subsidised oral anticoagulant. Bpac 2018. Available on-line at: www.bpac.org.nz/2018/rivaroxaban.aspx (Accessed Aug 2018)
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4. 3D Health Pathways. Available via https://3d.healthpathways.org.nz/index.htm (accessed Aug 2018).
5. Tran H, Joseph J, Young L et al. New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management. Internal Medicine 2014; 44: 525-536
6. New Zealand Formulary (NZF). NZF v73. Available from: www.nzf.org.nz (accessed Aug 2018)
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