Canterbury District Health Board
Te Poari Hauora o Waitaha

Clinical Pharmacology Bulletin

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Rivaroxaban – a new oral anticoagulant

Rivaroxaban (Factor Xa inhibitor) and dabigatran etexilate (a direct thrombin inhibitor) are alternatives to warfarin for oral anticoagulation, and to low-molecular weight heparins (LMWH) post-orthopaedic surgery. This bulletin discusses the use of rivaroxaban - important characteristics and potential issues - with a particular focus on treatment of atrial fibrillation (AF). A previous bulletin (005/12) has discussed the use of dabigatran etexilate.

Indications: Rivaroxaban is *licensed* for:

- treatment of deep vein thrombosis (DVT)
- prevention of recurrent venous thromboembolism (VTE)
- thromboprophylaxis after total knee/hip replacement
- thromboprophylaxis in non-valvular AF patients at moderate to high risk (e.g. congestive heart failure, hypertension, age ≥ 75 years, diabetes, prior stroke/transient ischaemic attack)

However, it is currently only *funded* via Special Authority for post- knee or hip surgery, for a course of up to 2 or 5 weeks, respectively.

Mechanism of action: Rivaroxaban is a direct Factor Xa inhibitor. Factor Xa is a key enzyme in the coagulation cascade that directly converts prothrombin to thrombin, leading to fibrin clot formation and platelet activation.

Pharmacokinetics: Rivaroxaban is well absorbed orally (66 - 100%; increased with food). It has a terminal half-life of 5 - 13 hours, and is highly protein bound. Rivaroxaban is partially renally cleared (~30%) via active secretion, with ~50% of a dose hepatically cleared (~30% involving CYP enzymes, in particular CYP 3A4/5/7). Rivaroxaban is also a substrate of the efflux transporter protein, P-glycoprotein (P-gp).

Interactions: Rivaroxaban serum concentrations may be altered by drugs that inhibit/induce liver enzymes or P-gp, particularly if both are potently inhibited or induced (e.g. with ketoconazole or rifampicin), and the patient has renal impairment. Drugs that potently inhibit/induce both CYP 3A4/5/7 and P-gp should ideally be avoided (see the 'Pink Book').

Monitoring: Routine monitoring for rivaroxaban is not currently recommended. However, prothrombin time (PT) may be of use to determine patient adherence; or prior to a procedure, to ensure normal coagulation for surgery.

Dosing:

- Treatment of DVT/recurrent VTE: Week 1-3: 15mg Q12H**,** then 20 mg Q24H if prophylaxis required
- Non-valvular AF: 20mg Q24H
- Post-hip/knee-surgery:10mg Q24H started 6-10 hrs post-op for 5 weeks (hip) or 2 weeks (knee)

Evidence for use in AF: This is mostly based on a double-blind, randomised, non-inferiority trial (Rocket AF Study; n=14,264) comparing rivaroxaban 15 or 20mg Q24H versus warfarin in patients with moderate-major risk of thrombosis, without valve abnormalities. Rivaroxaban was found to be non-inferior to warfarin in reducing stroke and systemic embolism in non-valvular AF patients. There appears to be no clear advantage over warfarin in adverse effects.

The incidences of overall mortality, systemic embolism or stroke, major bleeding and overall bleeding were not significantly different between the two arms. Rivaroxaban was associated with fewer intracranial bleeds, but more gastrointestinal bleeding, epistaxis and haematuria. (Note that a therapeutic INR was achieved in only 55% of the time in the warfarin arm).

Rivaroxaban has not been trialled head-to-head with dabigatran or other new anticoagulants.

Additional adverse effects: The most common non-bleeding adverse effects were peripheral oedema and dizziness. Others include gastrointestinal disorders (e.g. nausea, vomiting, diarrhoea, dyspepsia and abdominal pain), raised transaminases, syncope, anaphylaxis and kidney failure.

Management of bleeding: There is no specific antidote for rivaroxaban. Usual treatment measures should be instituted (e.g. compression, surgery, fluid replacement, blood products (e.g. packed red cells, fresh frozen plasma or platelets)). If the patient is still bleeding, procoagulants, such as activated prothrombin complex concentrate, prothrombin complex concentrate or factor VIIa can be considered, although data on use are limited. Discuss with Haematology. Neither protamine sulphate, vitamin K nor dialysis are expected to be beneficial. There are no data on administration of tranexamic acid.

Place in therapy: Rivaroxaban is an alternative to LMWHs for thromboprophylaxis after total knee or hip replacements. Rivaroxaban is expensive and not funded for AF. Therefore, use in this patient group is limited. It is reserved for patients unable to have warfarin e.g. adverse effects, and difficulty monitoring or achieving a therapeutic INR.

Table: Comparison of currently available oral anticoagulants in NZ

Anticoagulant	Indications	Advantages	Disadvantages / Cautions	Daily Cost
Rivaroxaban (direct Factor Xa inhibitor)	DVT/recurrent VTE Non-valvular AF Prophylaxis post-hip/knee-surgery	No routine monitoring in most Rapid onset	No antidote. Expensive. Drug interactions. Rapid offset. Anticoagulant effect not easily measured. Caution in renal/hepatic impairment (contraindicated if GFR<15mL/min)	$10 - 20
Warfarin (vitamin K antagonist)	Treatment and prevention of most thromboembolic conditions, including valvular AF and MI:	Antidote available Inexpensive Anticoagulation effect easily measured Vast experience	Regular monitoring and dose changes. Drug interactions. Food interactions. Warfarin resistance. Slow onset. Caution in hepatic impairment	< 20 cents
Dabigatran etexilate (direct thrombin inhibitor)	Non-valvular AF Prophylaxis post-hip/knee surgery	No routine monitoring in most Quick onset	No antidote. Expensive. Drug interactions. Rapid offset. Anticoagulant effect not easily measured. Dose reduce in renal impairment (contraindicated if GFR<30mL/min)	$5