The Medical Letter®

on Drugs and Therapeutics

Volume 60 December 3, 2018

ISSUE No. 1561

IN THIS ISSUE

The Medical Letter®
on Drugs and Therapeutics

Volume 60 (Issue 1561) December 3, 2018

Take CME Exams

Rivaroxaban *(Xarelto)* plus Aspirin for Secondary Prevention of Cardiovascular Events

The FDA has approved a new 2.5-mg formulation of the direct factor Xa inhibitor rivaroxaban (*Xarelto* – Janssen) for use in combination with low-dose aspirin to reduce the risk of major cardiovascular events in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD). Rivaroxaban is the first direct oral anticoagulant to be approved for this indication. It was approved earlier for prevention and treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE) and for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.[1,2]

Pronunciation Key	
Rivaroxaban: riv" a rox' a ban	***Xarelto*:** zah rel' toe

SECONDARY PREVENTION — Most expert clinicians recommend aspirin 81-162 mg/day indefinitely for patients with atherosclerotic vascular disease (excluding those with aspirin hypersensitivity or a high risk of gastrointestinal bleeding).[3] In a meta-analysis of 16 secondary prevention trials, low-dose aspirin, compared to placebo, was found to reduce the annual incidence of serious vascular events (6.7% vs 8.2%), stroke (2.1% vs 2.5%), and coronary events (4.3% vs 5.3%); these differences were all statistically significant.[4]

CLINICAL STUDIES — In a double-blind trial (COMPASS), 27,395 patients with stable CAD and/or PAD were randomized to receive aspirin 100 mg once daily, rivaroxaban 5 mg twice daily, or dual therapy with rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily. Patients with a recent stroke or previous hemorrhagic or lacunar stroke, severe heart failure, or an estimated glomerular filtration rate (eGFR) <15 mL/min, and those at increased risk for bleeding (including those taking dual antiplatelet therapy, anticoagulants, or other antithrombotics) were excluded from the trial.[5]

A composite of cardiovascular death, stroke, or myocardial infarction, the primary endpoint, occurred in significantly fewer patients taking rivaroxaban plus aspirin than in those taking aspirin alone (4.1% vs 5.4%). The difference between those taking rivaroxaban alone and aspirin alone was not statistically significant (4.9% vs 5.4%). There were 313 deaths with rivaroxaban plus aspirin compared to 378 with aspirin alone (3.4% vs 4.1%), a statistically significant difference. The trial was stopped after a mean follow-up of 23 months when an interim analysis showed that dual therapy with rivaroxaban plus aspirin was superior to aspirin or rivaroxaban alone in reducing the rate of the primary endpoint. Trials that are stopped early for efficacy may overestimate the treatment effect.

Among the 7470 patients in the trial who had PAD, the incidence of major limb events, including major amputations, was reduced from 60 (2%) with aspirin alone to 32 (1%) with rivaroxaban plus aspirin.[6]

ADVERSE EVENTS — In the COMPASS trial, major bleeding (mostly gastrointestinal) occurred in significantly more patients taking dual therapy than in those taking aspirin alone (3.1% vs 1.9%). There was no significant increase in intracranial or fatal bleeding with dual therapy. Patients who took rivaroxaban

Table 1. Rivaroxaban Indications and Dosage

FDA-Approved Indications	Usual Adult Dosage
Reduction in risk of stroke and systemic embolism in nonvalvular atrial fibrillation	20 mg PO once/day CrCl ≤50 mL/min: 15 mg PO once/day
Treatment of DVT or PE	15 mg PO bid for 21 days, then 20 mg once/day CrCl <30 mL/min: avoid use
Reduction in risk of DVT or PE recurrence after ≥6 months of standard anticoagulant therapy	10 mg PO once/day CrCl <30 mL/min: avoid use
Prophylaxis of DVT after hip or knee replacement surgery	10 mg PO once/day for 35 days after hip or 12 days after knee replacement surgery CrCl <30 mL/min: avoid use
Reduction in risk of major cardiovascular events in chronic CAD or PAD	2.5 mg PO bid[1] No dosage adjustment required for renal impairment

CAD = coronary artery disease; CrCl = creatinine clearance; DVT = deep vein thrombosis; PAD = peripheral artery disease; PE = pulmonary embolism
1. Plus aspirin 75-100 mg PO once/day.

alone had significantly more hemorrhagic strokes than those who took aspirin alone (27 [0.3%] vs 10 [0.1%]).

DRUG INTERACTIONS — Rivaroxaban is a substrate of CYP3A4 and P-glycoprotein (P-gp). Concurrent use of drugs that are inhibitors of both P-gp and CYP3A4 could increase rivaroxaban serum concentrations and the risk of bleeding, and is contraindicated. Concomitant administration of drugs that are combined P-gp and strong CYP3A4 inducers could decrease rivaroxaban serum concentrations and its efficacy, and is also contraindicated.[7,8]

DOSAGE AND COST — The recommended dosage of rivaroxaban to reduce the risk of major cardiovascular events in patients with chronic CAD or PAD is 2.5 mg twice daily taken with aspirin (75-100 mg) once daily. The retail cost (without insurance) for 60 2.5-mg tablets of rivaroxaban is about $500. Over-the-counter aspirin 81 mg (30 tablets) costs about $2.50.

CONCLUSION — In one large randomized controlled trial, a low dose of the direct oral anticoagulant rivaroxaban *(Xarelto)* taken twice daily in addition to low-dose aspirin once daily was more effective than aspirin alone in preventing major cardiovascular events in patients with stable atherosclerotic vascular disease, but the combination caused significantly more major bleeding, mostly in the GI tract. Whether the benefits outweigh the drawbacks of taking two daily doses of an expensive second drug that is more likely to cause bleeding and to interact with other drugs is debatable. ■

1. Drugs for treatment and prevention of venous thromboembolism. Med Lett Drugs Ther 2018; 60:41.
2. Which oral anticoagulant for atrial fibrillation? Med Lett Drugs Ther 2016; 58:45.
3. R Jones et al. Clinician guide to the ABCs of primary and secondary prevention of atherosclerotic vascular disease. American College of Cardiology. April 2, 2018. Available at: www.acc.org/latest-in-cardiology/articles/2018/03/30/18/34/clinician-guide-to-the-abcs. Accessed November 20, 2018.
4. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009; 373:1849.
5. JW Eikelboom et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017; 377:1319.
6. SS Anand et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet 2018; 391:219.
7. Drug Interactions from The Medical Letter. Available at: https://secure.medicalletter.org/druginteractions.
8. Inhibitors and inducers of CYP enzymes and P-glycoprotein. Med Lett Drugs Ther 2017 September 18 (epub). Available at: medicalletter.org/downloads/CYP_PGP_Tables.pdf.