

STROKE PREVENTION IN ATRIAL FIBRILLATION: ROLE OF THE NEWER ORAL ANTICOAGULANTS

Until recently, warfarin was the only oral anticoagulant (OAC) available for prevention of stroke secondary to atrial fibrillation. Difficulties with achieving optimal anticoagulation with warfarin and the need for frequent blood work (INR) monitoring prompted the development of new oral anticoagulants that target different components of the coagulation cascade and do not require INR monitoring.¹ A review of these newer oral anticoagulant alternatives, which include apixaban (Eliquis®), dabigatran (Pradaxa®), and rivaroxaban (Xarelto®), is warranted.

THE NEWER ORAL ANTICOAGULANTS VS. WARFARIN

As a group, the newer OACs have been declared “as good as or better than warfarin in stroke prevention in patient populations included in the trials”.² The “Focused 2012 Update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines: Recommendations for Stroke Prevention and Rate/Rhythm Control” provides the following recommendations:³

- “We suggest, that when OAC therapy is indicated, most patients should receive dabigatran, rivaroxaban, or apixaban, in preference to warfarin.”
- “This recommendation places a relatively high value on comparisons with warfarin showing that dabigatran and apixaban have greater efficacy and rivaroxaban has similar efficacy for stroke prevention; dabigatran and rivaroxaban have no more major bleeding and apixaban has less; all 3 newer OACs have less intracranial haemorrhage and are much simpler to use. The recommendation places less value on the following features of warfarin: long experience with clinical use, availability of a specific antidote, and a simple and standardized test for intensity of anticoagulant effect.”

Following are some additional points to consider:

- Unlike warfarin, where vitamin K intake variation through food ingestion can affect the anticoagulant action of the drug, the newer anticoagulants are not associated with food interactions.
- The newer OACs have short half-lives; therefore, their anticoagulant effects diminish quickly after drug discontinuation. However, unlike warfarin, where vitamin K rapidly diminishes anticoagulant effect, no such antidote exists for the newer OACs.
- The newer OACs are contraindicated in patients with aortic or mitral mechanical heart valves.

Warfarin would be preferred over the newer OACs in patients in the following circumstances:²

- valvular heart disease
- at risk of dyspepsia or GI bleeding
- have been well controlled with warfarin
- no concerns regarding lab monitoring
- poor renal function
- concerns over medication cost
- have conditions that would have excluded them from newer OAC landmark trials

SWITCHING FROM WARFARIN TO A NEWER OAC

The therapeutic INR range for a patient taking warfarin is normally between 2.0 and 3.0. Because the peak effect of the newer OACs occurs one to three hours after dosing, if a switch from warfarin to a newer OAC is made, the INR of the patient should be 2.0 or lower before the newer OAC is started.⁴ **MPT**

References:

1. Gonsalves WI, Pruthi RK, Patnaik MM. *Mayo Clin Proc* 2013;88:495-511.
2. Kosar L, Jin M, Kamrul R, Schuster B. *Can Fam Physician* 2012;58:850-855.
3. Skanes AC, Healey JS, Cairns JA, et al. *Can J Cardiol* 2012;28:125-136.
4. Thrombosis Canada. Comparison of New Oral Anticoagulants and Frequently-Asked Questions from Patients and Physicians (2013). Available at http://thrombosiscanada.ca/guides/pdfs/NOACs_Comparison_and_FAQs.pdf.

Comparison of the Newer OACs

None of the studies conducted to date have compared the newer OACs “head to head.” All have been compared individually with warfarin for stroke prevention in atrial fibrillation or the treatment of venous thromboembolism (VTE). Because of the differences in trial designs, patient populations studied, and medication dose regimens used, it is difficult to directly compare the three newer OACs (dabigatran, rivaroxaban, apixaban) to each other.⁴ Therefore, when choosing a drug, the patient’s risk profile for stroke and for bleeding as well as the presence or absence of comorbid conditions (e.g., prior stroke, renal dysfunction) must be taken into consideration. **DN**

Table 1: Comparison of Newer Oral Anticoagulants⁴

| | Dabigatran | Rivaroxaban | Apixaban |
|-----------------------------------|--|---|---|
| Dose (Atrial Fibrillation) | 150 mg or 110 mg twice daily | 20 mg daily | 5 mg twice daily |
| Mechanism of Action | Direct factor IIa (thrombin) inhibitor | Direct factor Xa inhibitor | Direct factor Xa inhibitor |
| Renal Clearance | 80% | 33% (active drug) | 25% |
| Onset of Action | 1-3 hours | 1-3 hours | 1-3 hours |
| Half-life (normal renal function) | 11 hours | 9 hours | 9 hours |
| Drug Interactions | amiodarone, quinidine, azole antifungals (e.g., ketoconazole), rifampin, ritonavir | azole antifungals (e.g., ketoconazole), ritonavir, rifampin, clarithromycin, anticonvulsants (e.g., phenytoin, carbamazepine) | azole antifungals (e.g., ketoconazole), ritonavir, rifampin, clarithromycin, anticonvulsants (e.g., phenytoin, carbamazepine) |

Table 2: Dosing For Stroke Prevention in Atrial Fibrillation According to Renal Function⁴

| | CrCl mL/min | Dose | Comments |
|-------------|-----------------------------|-------------------|--|
| Dabigatran | Greater than 50 | 110 or 150 mg BID | Consider 110 mg BID in patients at increased risk for bleeding or in patients over 80 years. Measure CrCl every 12 months. |
| | 30-50 | 110 or 150 mg BID | Consider 110 mg BID in patients at increased risk for bleeding or in patients over 80 years. Measure CrCl every 6 months and with acute illness. |
| | Less than 30 | Avoid dabigatran | Consider warfarin as alternative anticoagulant. |
| Rivaroxaban | Greater than or equal to 50 | 20 mg daily | Measure CrCl every 12 months. |
| | 30-49 | 15 mg daily | Measure CrCl every 6 months and with acute illness. |
| | Less than 30 | Avoid rivaroxaban | Consider warfarin as alternative anticoagulant. |
| Apixaban | Greater than 50 | 5 mg BID | Measure CrCl every 12 months. |
| | 25-50 | 5 mg BID | 2.5 mg BID in patients with 2 of the following: <ul style="list-style-type: none"> • Cr greater than or equal to 133 µmol/L • Age over 80 • Body weight less than or equal to 60 kg Measure CrCl every 6 months and with acute illness. |
| | 15-24 | Limited data | Consider warfarin as alternative anticoagulant. |
| | Less than 15 | Avoid apixaban | Consider warfarin as alternative anticoagulant. |

This review is not comprehensive. Please refer to specific product monographs for more comprehensive information, including precautions, adverse reactions, and drug interactions.