From The Medical Letter on Drugs and Therapeutics

Which Oral Anticoagulant for Atrial Fibrillation?

Direct-to-consumer advertisements continue to urge patients who take warfarin (Coumadin, and others) for atrial fibrillation to ask their doctors about the benefits of one or another of the newer oral anticoagulants.

Warfarin

In patients with nonvalvular atrial fibrillation, warfarin reduces the risk of thromboembolic stroke by about 60%.[1] If necessary, vitamin K, prothrombin complex concentrate, or fresh frozen plasma can reverse its anticoagulant effect.[2] Drawbacks of warfarin include unpredictability and variability in dosage requirements, dietary restrictions, interactions with many other drugs, and the need for close monitoring to keep the international normalized ratio (INR) in the therapeutic range (2-3).

Direct Oral Anticoagulants

The direct thrombin inhibitor dabigatran etexilate (Pradaxa) and the direct factor Xa inhibitors apixaban (Eliquis), edoxaban (Savaysa), and rivaroxaban (Xarelto) do not require routine monitoring of coagulation times and they have fewer drug interactions than warfarin (**Table 1**).

Drawbacks of the direct oral anticoagulants include absence of any method for monitoring the extent of their anticoagulant effect, short half-lives that increase the risk of thrombosis with missed doses, lack of data on their use in patients with end-stage renal disease, and higher drug costs.

Efficacy

In the pivotal clinical trials against warfarin that led to their approval by the FDA, all of the direct oral anticoagulants were at least noninferior to warfarin for prevention of stroke or systemic embolism in patients with atrial fibrillation. In patients taking warfarin, the INR was in the therapeutic range only 55-65% of the time.[3-6] Edoxaban was less effective than warfarin for prevention of stroke or systemic embolism in patients with a CrCl >95 mL/min; it was more effective in those with a CrCl between 50 and 80 mL/min.[7]

Bleeding

All of the direct oral anticoagulants had significantly lower rates of intracranial bleeding and hemorrhagic stroke than warfarin in the pivotal clinical trials (**Table 2**). Compared to warfarin, the rates

Table 1. Oral Anticoagulants for Atrial Fibrillation

Drug	Usual Dosage	Comments	Cost[a]
Direct Factor Xa Inhibitors			
Apixaban[b]—Eliquis (BMS)	5 mg bid[c]	Interacts with inhibitors and inducers of CYP3A4 and P-gp[d]	$333.60
Edoxaban[b]—Savaysa (Daiichi Sankyo)	60 mg once/d[e]	Should not be used in patients with a CrCl >95 mL/min; avoid use with the P-gp inducer rifampin	291.30
Rivaroxaban[b]—Xarelto (Janssen)	20 mg once/d[f]	Should be taken with the evening meal; interacts with inhibitors and inducers of CYP3A4 and P-gp[g]	333.30
Direct Thrombin Inhibitor			
Dabigatran etexilate[b]—Pradaxa (Boehringer Ingelheim)	150 mg bid[h]	Must be dispensed and stored in the original container (once the bottle is opened, use within 4 months); tablets should not be broken, crushed, or chewed; dyspepsia is common; interacts with inhibitors and inducers of P-gp[i]; reversal agent available; dialyzable	333.60
Vitamin K Antagonist			
Warfarin—generic	2-10 mg once/d[j]	Interacts with many other drugs; has dietary restrictions;	8.50
Coumadin (BMS)		INR monitoring required; reversal agents available	58.80

Abbreviations: INR, international normalized ratio; P-gp, P-glycoprotein.

[a] Approximate WAC for 30 days' treatment at the lowest usual dosage. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. March 5, 2016. Reprinted with permission by First Databank, Inc. All rights reserved. ©2016. www.fdbhealth.com/policies/drug-pricing-policy.

[b] FDA-approved for use in patients with nonvalvular atrial fibrillation.

[c] Dosage is 2.5 mg bid for patients with ≥2 of the following: age ≥80 years, weight ≤60 kg, serum creatinine ≥1.5 mg/dL.

[d] In patients taking strong inhibitors of both CYP3A4 and P-gp, reduce the dosage of apixaban by 50% to a minimum of 2.5 mg bid; avoid coadministration in patients already taking 2.5 mg bid. Avoid use with strong inducers of both CYP3A4 and P-glycoprotein.

[e] Dosage is 30 mg once/d for patients with a CrCl 15-50 mL/min. Not recommended for use in patients with a CrCl <15 mL/min.

[f] Dosage is 15 mg once/d for patients with a CrCl 15-50 mL/min. Not recommended for use in patients with a CrCl <15 mL/min.

[g] Avoid use with combined P-gp and strong CYP3A4 inhibitors or inducers.

[h] The American College of Chest Physicians and Health Canada do not recommend use for atrial fibrillation in patients with a CrCl <30 mL/min. The US labeling recommends a dosage of 75 mg twice daily in patients with a CrCl 15-30 mL/min; this dose is based on pharmacokinetic modeling and has not been studied in clinical trials.

[i] Avoid use with P-gp inducers. The dose should be reduced to 75 mg bid during coadministration with dronedarone or systemic ketoconazole in patients with a CrCl 30-50 mL/min. Avoid use with P-gp inhibitors in patients with a CrCl 15-30 mL/min.

[j] Should be coadministered with a parenteral anticoagulant for ≥5 days and until the INR is in the therapeutic range (2-3) for ≥24 h.

Table 2. Direct Oral Anticoagulants vs Warfarin

	Stroke or Systemic Embolism[a]	Hemorrhagic Stroke	Ischemic Stroke (or unspecified)	Intracranial Bleeding	Major Bleeding	INR in Therapeutic Range[b]
Dabigatran[c,d]	RR 0.66[e]	RR 0.26[e]	RR 0.76[e]	RR 0.40[e]	RR 0.93	64%
Rivaroxaban[f]	HR 0.88[g]	HR 0.59[e]	HR 0.94	HR 0.67[e]	HR 1.04	55%[h]
Apixaban[i]	HR 0.79[e]	HR 0.51[e]	HR 0.92	HR 0.42[e]	HR 0.69[e]	62%
Edoxaban[j,k]	HR 0.79[e,l]	HR 0.54[e]	HR 1.00[m]	HR 0.47[e]	HR 0.80[e]	65%

Abbreviations: HR, hazard ratio; INR, international normalized ratio; RR, relative risk.

[a] The primary endpoint in all four trials.

[b] Mean percentage of time in the therapeutic range (2-3).

[c] SJ Connolly et al. *N Engl J Med*. 2009;361:1139.

[d] Results for the 150-mg dose. A 110-mg dose was also studied, but was not approved by the FDA for treatment of atrial fibrillation.

[e] Statistically significant.

[f] MR Patel et al. *N Engl J Med*. 2011;365:883.

[g] Statistically significant for noninferiority, but not superiority.

[h] The device used to measure the INR was later found to be inaccurate in patients with certain conditions, such as acute and chronic inflammatory conditions and low hematocrit. A post-hoc analysis of the results in these patients and those without the implicated conditions determined that the malfunction of the device did not have a significant effect on the results (MR Patel and AS Helkamp. *N Engl J Med*. 2016;374:785).

[i] CB Granger et al. *N Engl J Med*. 2011;365:981.

[j] RP Giugliano et al. *N Engl J Med*. 2013;369:2093.

[k] Results for the 60-mg dose. A 30-mg dose was also studied, but is not the usual recommended dose for treatment of atrial fibrillation.

[l] About 50% of the edoxaban dose is renally eliminated. The HR was 1.87 in patients with a CrCl >95 mL/min and 0.53 in those with a CrCl >50 and ≤80 mL/min.

[m] The HR in patients with CrCl >95 mL/min was 2.16.

of major bleeding with dabigatran and rivaroxaban were similar and the rates with apixaban and edoxaban were significantly lower.

Reversibility

In 2015, the FDA approved idarucizumab (Praxbind) for urgent reversal of the anticoagulant effect of dabigatran.[8] No specific antidote is available in the US for the three direct factor Xa inhibitors, but in one study in healthy volunteers, an investigational synthetic product (andexanet alfa) reversed the anticoagulant effects of apixaban and rivaroxaban within minutes.[9] The results of some studies suggest that the anticoagulant effects of all of the direct oral anticoagulants may be reversed by prothrombin complex concentrate.[10]

Conclusion

The direct oral anticoagulants dabigatran (Pradaxa), apixaban (Eliquis), edoxaban (Savaysa), and rivaroxaban (Xarelto) have been at least as effective as warfarin (Coumadin, and others) in preventing stroke or systemic embolism in patients with nonvalvular atrial fibrillation, and they appear to be safer. Patients well controlled on warfarin (INR stable in the therapeutic range) could stay on it. For all others, one of the direct oral anticoagulants might be a better choice. Head-to-head comparisons of the new drugs are lacking.

ARTICLE INFORMATION

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