Safety and Efficacy of Anticoagulants

Written by Toni Rizzo

Apixaban is an oral factor Xa inhibitor with prompt onset and offset of anticoagulation, twice-a-day dosing, and no need for coagulation monitoring. Greg Flaker, MD, University of Missouri, Columbia, Missouri, USA, discussed the efficacy and safety of apixaban compared with warfarin in the Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation trial [ARISTOTLE; NCT00412984] and compared with aspirin in the Apixaban Versus Acetylsalicylic Acid to Prevent Strokes trial [AVERROES; NCT00496769].

In the ARISTOTLE trial [Granger CB et al. *N Engl J Med* 2011], 18,201 patients with atrial fibrillation (AF) and at least 1 additional risk factor for stroke were randomly assigned to treatment with apixaban 5 mg BID or warfarin (target INR 2-3). The primary outcome was stroke or systemic embolism (SE). The median duration of follow-up was 1.8 years.

The rate of stroke or SE was significantly lower with apixaban (1.27% per year) versus warfarin (1.60% per year), with a 21% relative risk reduction (RRR) in the apixaban group (HR, 0.79; 95% CI, 0.66 to 0.95; p=0.011). Event rates per year were significantly lower with apixaban versus warfarin for hemorrhagic stroke (0.24% vs 0.47%; p<0.001) and all-cause death (3.52% vs 3.94%; p=0.047) but not for ischemic (or uncertain) stroke, SE, or myocardial infarction (Table 1). Patients who were treated with apixaban had significantly lower rates of major bleeding (HR, 0.69; 95% CI, 0.60 to 0.80; p<0.001) and any bleeding (HR, 0.71; 95% CI, 0.68 to 0.75; p<0.001).

Table 1. Efficacy Outcomes.

Outcome	Apixaban (n=9120) Event Rate (% per Year)	Warfarin (n=9081) Event Rate (% per Year)	HR (95% CI)	p value
Stroke or SE*	1.27	1.60	0.79 (0.66-0.95)	0.011
Stroke	1.19	1.51	0.79 (0.65-0.95)	0.012
Ischemic or uncertain	0.97	1.05	0.92 (0.74-1.13)	0.42
Hemorrhagic	0.24	0.47	0.51 (0.35-0.75)	<0.001
SE	0.09	0.10	0.87 (0.44-1.75)	0.70
All-cause death*	3.52	3.94	0.89 (0.80-0.998)	0.047
Stroke, SE, or all-cause death	4.49	5.04	0.89 (0.81-0.98)	0.019
Myocardial infarction	0.53	0.61	0.88 (0.66-1.17)	0.37

SE=systemic embolism; *Part of sequential testing sequence preserving the overall type I error.

In the AVERROES trial, 5600 patients with AF were randomly assigned to apixaban 5 mg BID or aspirin 81 to 324 mg/day. The primary outcome was stroke or SE. Compared with aspirin, apixaban significantly reduced the risk of stroke or SE (RR, 0.46; 95% CI, 0.33 to 0.64; p<0.001). There was no significant difference in major bleeding risk with apixaban versus aspirin.

Dr. Flaker concluded that compared with warfarin, apixaban reduces stroke and SE, major bleeding, and mortality. Compared with aspirin, apixaban reduces stroke and SE and has comparable rates of major bleeding and tolerability.

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Anticoagulant Selection for Patients with AF

Peter R. Kowey, MD, Jefferson Medical College, Philadelphia, Pennsylvania, USA, discussed the challenge of choosing anticoagulation therapy for patients with AF. Warfarin is highly effective for this indication but has a narrow therapeutic target, frequent food and drug interactions, genetically determined metabolism, bridging issues, and a high rate of intracerebral and gastrointestinal bleeding and is difficult to reverse.

Although studies [Hart RG et al. *Ann Intern Med* 2007] have demonstrated the efficacy of warfarin to prevent stroke in patients with AF, reducing stroke incidence by about 64%, many AF patients do not receive warfarin. A literature review [Bungard TJ et al. *Arch Intern Med* 2000] identified several barriers, including physicians' perceptions that 1) the risk of warfarin therapy is greater than the benefit; 2) patients are unreliable; and 3) maintaining therapeutic INR is difficult. Physicians also believe patients will refuse therapy, and they consider monitoring therapy inconvenient.

A number of therapies are under development (Table 2). The Randomized Evaluation of Long-Term Anticoagulant Therapy with Dabigatran Etexilate trial [RE-LY; Connolly SJ et al. *N Engl J Med* 2009] randomly assigned patients with AF and at least 1 additional risk factor to warfarin (INR, 2.0-3.0; n=6000), dabigatran etexilate (110 mg BID; n=6000), or dabigatran etexilate (150 mg BID; n=6000). Dabigatran 110 mg was noninferior to warfarin (p<0.001), and dabigatran 150 mg was superior to warfarin (p<0.001) for reduction of stroke and SE. Patients who were taking dabigatran 110 mg had significantly lower rates of major bleeding (p=0.003) and intracranial hemorrhage (p<0.001) versus patients who taking warfarin.

The Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation [ROCKET; Patel MR et al *N Engl J Med* 2011] demonstrated the noninferiority of rivaroxaban for reducing the rate of stroke and non-CNS embolism (HR, 0.79; 95% CI, 0.66 to 0.96; p<0.001). Apixaban was shown to significantly reduce cumulative risk of stroke or SE versus aspirin in the AVERROES trial (p<0.001). In the ARISTOTLE trial, apixaban was superior to warfarin for reducing the rate of stroke or SE (p=0.011). The factor Xa direct inhibitor edoxaban is currently undergoing investigation versus warfarin in the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation Thrombolysis in Myocardial Infarction trial [ENGAGE AF-TIMI 48; NCT00781391].

New anticoagulants present several clinical challenges. For example, therapeutic ranges have not been established, no validated tests exist to measure anticoagulation effect, and there are no antidotes for most agents. In addition, compliance assessment is more difficult with these agents than with vitamin K antagonists, and the potential exists for unknown long-term adverse events. Balancing cost against efficacy is another challenge, and there are no head-to-head studies that have compared new agents. In the absence of head-to-head trials, the choice of agent must be based on trial data and a patient's profile.

Table 2. Emerging Anticoagulants in AF.

Agent	Mechanism of Action	Dosing	Onset	Half Life	Reversibility	Clinical Development
Apixaban	Direct factor Xa inhibitor	Oral 2x daily	3 hr	12 hr	No	Phase 3; ARISTOTLE, AVERROES
Rivaroxaban	Direct factor Xa inhibitor	Oral 1-2x daily	3 hr	9 hr	No	Phase 3; ROCKET AF
DU 176b	Direct factor Xa inhibitor	Oral 1-2x daily	1-2 hr	9-11 hr	No	Phase 3; ENGAGE-AF
Betrixaban	Direct factor Xa inhibitor	Oral 2x daily	Not reported	19 hr	No	Phase 2; EXPLORE Xa
YM 150	Direct factor Xa inhibitor	Not reported	Not reported	Not reported	No	Phase 2
Idrabiotaparinux	Direct factor Xa inhibitor	Weekly SC Injection	1-2 hr	80-130 hr	Yes, IV avidin	Phase 3; BOREALIS-AF
Dabigatran etexilate	Direct thrombin inhibitor	Oral 1-2x daily	1-2 hr	12-17 hr	No	Phase 3; RE-LY
AZD 0837	Direct thrombin inhibitor	Oral 1-2x daily	1 hr	9 hr	No	Phase 2
ATI-5923 Tecarfarin	Vitamin K antagonist	Variable Oral 1x daily	Not reported	136 hr	Yes, vitamin K	Phase 2/3; EMBRACE AC

Sobieraj-Teague M et al. *Semin Thromb Hemost* 2009.