Title

ACP Journal Club. Review: new oral anticoagulants reduced stroke and systemic embolism compared with warfarin in AF.

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Apixaban reduced stroke and systemic embolism compared with warfarin in atrial fibrillation

Granger CB, Alexander JH, McMurray JJ, et al. ***Apixaban versus warfarin in patients with atrial fibrillation.*** *N Engl J Med. 2011;365:981-92.*

Clinical impact ratings: GM ★★★★★★☆ C ★★★★★★★ H ★★★★★★★ N ★★★★★★★

Question

In patients with atrial fibrillation (AF), how does apixaban compare with warfarin for prevention of stroke or systemic embolism?

Methods

Design: Randomized controlled trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation [ARISTOTLE] study). ClinicalTrials.gov NCT00412984.

Allocation: {Concealed}*.†

Blinding: Blinded (patients, clinicians, outcome assessors, and {data collectors and analysts}*).†

Follow-up period: Median 1.8 years.

Setting: 1034 centers in 39 countries.

Patients: 18 201 patients (median age 70 y, 65% men, mean $CHADS_2$ score 2.1) with AF or atrial flutter at enrollment or ≥ 2 episodes of AF or atrial flutter ≥ 2 weeks apart in the 12 months before enrollment, and ≥ 1 of age ≥ 75 years; previous stroke, transient ischemic attack, or systemic embolism; systolic heart failure within 3 months or left ventricular ejection fraction ≤ 40%; diabetes mellitus; and hypertension requiring pharmacologic treatment. Exclusion criteria included AF due to a reversible cause, moderate or severe mitral stenosis, need for anticoagulation other than for AF, stroke within 7 days, need for aspirin at a dose > 165 mg/d or for both aspirin and clopidogrel, and severe renal insufficiency.

Intervention: Apixaban, 5 mg twice daily, plus warfarin placebo (n = 9120), or warfarin, adjusted to achieve a target international normalized ratio (INR) of 2.0 to 3.0, plus apixaban placebo (n = 9081). Apixaban patients received 2.5 mg twice daily if they had ≥ 2 of age ≥ 80 years, body weight ≤ 60 kg, and serum creatinine level ≥ 133 μmol/L (1.5 mg/dL).

Outcomes: Primary efficacy outcome was a composite of stroke or systemic embolism. Primary safety outcome was major bleeding. Secondary outcomes included all-cause mortality and a composite of major bleeding and clinically relevant nonmajor bleeding.

Patient follow-up: 97.9% for vital status (intention-to-treat analysis).

Apixaban vs warfarin in atrial fibrillation‡

Outcomes	Event rate (%/y)		RRR (95% CI)	NNT (CI)
	Apixaban	Warfarin		
Stroke§ or systemic embolism‖	1.3	1.6	21% (5 to 34)	166 (102 to 695)
All-cause mortality	3.5	3.9	11% (0.2 to 20)¶	128 (70 to 7051)
Major bleeding	2.1	3.1	31% (20 to 40)¶	65 (50 to 101)
Major or clinically relevant nonmajor bleeding	4.1	6.0	32% (25 to 39)¶	34 (28 to 43)

‡Abbreviations defined in Glossary. RRR, NNT, and CI calculated from hazard ratios and control event proportions in article.

§Focal neurologic deficit, from a nontraumatic cause, lasting ≥ 24 h.

‖Stroke (RRR 21%, CI 5 to 35), systemic embolism (RRR 13%, CI −75 to 56).

¶Information provided by author.

Main results

The main results are in the Table.

Conclusion

In patients with atrial fibrillation, apixaban reduced stroke and systemic embolism compared with warfarin.

**Information provided by author.*

†See Glossary.

Sources of funding: Bristol-Myers Squibb and Pfizer.

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Commentary

Although warfarin prevents stroke in patients with nonvalvular AF, interactions with food and drugs and genetics necessitate frequent monitoring and dose adjustments, making it difficult for many patients to use warfarin effectively and safely. Hence, alternative oral anticoagulants that are equally efficacious and safe, but more easily administered, have long been sought by clinicians and patients.

The first of such anticoagulants to be tested was a direct thrombin inhibitor; the Randomized Evaluation of Long-Term Anticoagulation Therapy trial (RE-LY) showed that dabigatran reduced the risk for stroke or systemic embolism by 34%, without increasing bleeding, compared with warfarin (1).

The results of 2 trials assessing factor Xa inhibitors are reported here. The ARISTOTLE trial, which included patients at high risk for stroke (mean $CHADS_2$ score 2.1), showed that, at 2 years of follow-up, apixaban reduced stroke or systemic embolism (mostly due to a decrease in hemorrhagic stroke), all-cause mortality, and major bleeding, compared with warfarin. The risk for gastrointestinal bleeding, a source of major bleeding in the elderly, was numerically lower in patients treated with apixaban. Interestingly, patients with moderate-to-severe renal impairment were most likely to benefit from the lower risk for bleeding with apixaban.

The ROCKET AF assessed the effect of rivaroxaban in an older population (mean age 73 y vs 70 y) with more comorbid conditions and higher risk for stroke (mean $CHADS_2$ score 3.5 vs 2.1) than ARISTOTLE. Compared with warfarin, rivaroxaban reduced stroke and systemic embolism but without a reduction in major bleeding, although it did decrease intracranial hemorrhage and fatal bleeding.

All 3 new anticoagulants reduced risk for stroke (mostly hemorrhagic, by preservation of tissue factor VIIa complexes in the brain [2]) and systemic embolism as well as serious bleeding compared with warfarin; apixaban also reduced rates of major and gastrointestinal bleeding.

(continued on page 3)

Rivaroxaban reduced stroke and systemic embolism compared with warfarin in nonvalvular AF

Patel MR, Mahaffey KW, Garg J, et al. ***Rivaroxaban versus warfarin in nonvalvular atrial fibrillation.*** *N Engl J Med. 2011;365:883-91.*

Clinical impact ratings: C ★★★★★★★ H ★★★★★★★ N ★★★★★★☆

Question

In patients with nonvalvular atrial fibrillation (AF) at moderate-to-high risk for stroke, how does rivaroxaban compare with warfarin for prevention of stroke or systemic embolism?

Methods

Design: Randomized controlled trial (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation [ROCKET AF]). ClinicalTrials.gov NCT00403767.

Allocation: Concealed.*

Blinding: Blinded (patients, clinicians, and outcome assessors).*

Follow-up period: Median 590 days.

Setting: 1178 centers in 45 countries.

Patients: 14 264 adults ≥ 18 years of age (median age 73 y, 60% men, mean $CHADS_2$ score 3.5) who had electrocardiography-documented nonvalvular AF and a history of stroke; transient ischemic attack; systemic embolism; or ≥ 2 of heart failure or left ventricular ejection fraction ≤ 35%, hypertension, age ≥ 75 years, and diabetes mellitus. Exclusion criteria included AF due to a reversible cause, hemodynamically significant mitral valve stenosis, need for anticoagulation other than for AF, stroke within 14 days, and treatment with aspirin > 100 mg/d.

Intervention: Rivaroxaban, 20 mg/d or 15 mg/d in patients with creatinine clearance of 30 to 49 mL/min, plus warfarin placebo (n = 7131), or warfarin, adjusted to achieve a target international normalized ratio (INR) of 2.0 to 3.0, plus rivaroxaban placebo (n = 7133).

Outcomes: Primary efficacy outcome was a composite of stroke or systemic embolism. Primary safety outcome was a composite of major or nonmajor clinically relevant bleeding. Secondary efficacy endpoints included a composite of stroke, systemic embolism, cardiovascular death, or myocardial infarction; and individual components of the composite outcomes.

Patient follow-up: 97.8%.

Rivaroxaban vs warfarin in nonvalvular atrial fibrillation†

Outcomes	Number of events/100 patient-y		At a median 590 d	
	Rivaroxaban	Warfarin	RRR (95% CI)	NNT (CI)
Stroke or systemic embolism‡	1.7	2.2	21% (5 to 35)	141 (85 to 593)
Stroke, systemic embolism, CV death, or MI‡	3.9	4.6	15% (4 to 25)	94 (54 to 354)
			RRI (CI)	NNH (CI)
Major or nonmajor clinically relevant bleeding	14.9	14.5	2.7% (–4 to 10)	Not significant

†CV = cardiovascular; MI = myocardial infarction; other abbreviations defined in Glossary. RRR, RRI, NNT, NNH, and CI calculated from hazard ratios and control event proportions in article.

‡Stroke (RRR 15%, CI –3 to 30), systemic embolism (RRR 77%, CI 39 to 91), CV death (RRR 11%, CI –10 to 27), MI (RRR 19%, CI –6 to 37).

Main results

The main results are in the Table.

Conclusion

In patients with nonvalvular atrial fibrillation, rivaroxaban reduced stroke and systemic embolism compared with warfarin.

**See Glossary.*

Sources of funding: Johnson & Johnson Pharmaceutical Research and Development and Bayer HealthCare.

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Commentary *(continued from page 2)*

In addition, apixaban reduced mortality compared with warfarin, a trend that was observed with dabigatran (1) and rivaroxaban.

Despite their similarities, there are important differences among the trials of these anticoagulants. Whereas patients and clinicians were not blinded to treatment in the RE-LY trial (1), the ROCKET AF and ARISTOTLE trials were double-blind. Dabigatran and apixaban were given twice daily, wheras rivaroxaban was given only once daily. Patients in the ROCKET AF were older and had more comorbid conditions and higher risk for stroke than those in the RE-LY and ARISTOTLE trials. Finally, the average amount of time in which the INR was in the therapeutic range (assessing the quality of warfarin dosing) was 64% in the RE-LY trial (1) and 62% in the ARISTOTLE trial but only 55% in the ROCKET AF.

Although direct thrombin and factor Xa inhibitors overcome the need for routine blood monitoring and are more effective and safer than warfarin, switching to a newer agent may not be necessary for individual patients in whom INR has been well-controlled with warfarin for years. As well, agents to reverse the effect of the newer anticoagulants are still under development and not routinely available (3). Finally, future data on cost-effectiveness will further influence clinical decision-making. Thus, although newer anticoagulants are attractive alternatives, warfarin may continue to be used worldwide in many patients with AF.

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References

1. **Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators.** Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139-51.
2. **del Zoppo GJ, Eliasziw M.** New options in anticoagulation for atrial fibrillation. N Engl J Med. 2011;365:952-3.
3. **Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al.** Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation. 2011;124:1573-9.