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In nonvalvular atrial fibrillation, effects of rivaroxaban compared with warfarin did not differ by patient age

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Clinical impact ratings: ★★★★★★☆☆★★★★★★★☆☆★★★★★★☆☆

Question

In patients with nonvalvular atrial fibrillation (AF) and moderate-to-high risk for stroke, does the efficacy and safety of rivaroxaban compared with warfarin differ by patient age?

Methods

Design

Prespecified subgroup analyses of a 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]).

Allocation

{Concealed}^{*,†}

Blinding

Blinded[†] (patients, clinicians, and outcome assessors).

Follow-up period

Median 707 days.

Setting

{1178 centers in 45 countries}^{*}.

Patients

14 264 patients ({median age 73 y}^{*}, 44% ≥75 y, 60% men) who had nonvalvular AF and previous stroke, transient ischemic attack, or systemic embolism or ≥2 of heart failure or left ventricular systolic dysfunction, hypertension, age ≥75 years, and diabetes mellitus.

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

[†]See Glossary.

Exclusion criteria included mitral stenosis, prosthetic heart valves, AF due to reversible conditions, severe renal insufficiency, liver disease or increased serum liver enzyme levels, increased risk for bleeding, or concomitant treatment with other antithrombotic drugs (except aspirin) or thienopyridine.

Intervention

Rivaroxaban, 20 mg/d or 15 mg/d for patients with creatinine clearance 30 to 49 mL/min (0.50 to 0.82 mL/s) plus placebo warfarin (n = 7131), or warfarin adjusted to achieve a target international normalized ratio of 2.0 to 3.0 plus rivaroxaban placebo (n = 7133). Outcomes: Outcomes included a composite of ischemic or hemorrhagic stroke or systemic embolism, and major bleeding.

Patient follow-up

99% (intention-to-treat analysis).

Main results

Rates of stroke or systemic embolism and major bleeding were higher in the older age group. The main results are in the Table.

Rivaroxaban vs warfarin for nonvalvular atrial fibrillation [‡]				
Outcomes	Age group	Event rates		At a median 707 d RRR/RRI (95% CI) [§]
		Rivaroxaban	Warfarin	
Stroke or systemic embolism	75 y	4.0%	5.0%	RRR 20% (–2 to 36)
	< 75 y	3.6%	3.8%	RRR 5% (–19 to 24)
Major bleeding	75 y	7.2%	6.6%	RRI 11% (–8 to 32)
	< 75 y	4.3%	4.5%	RRR 4% (–18 to 22)
Hemorrhagic stroke	75 y	0.62%	0.88%	RRR 30% (–26 to 61)
	< 75 y	0.35%	0.75%	RRR 53% (12 to 75) ^{//}

[‡]Abbreviations defined in Glossary. RRR, RRI, and CI calculated from control event rates and hazard ratios in article.

[§]Treatment by age interaction: stroke or systemic embolism, $P = 0.31$; major bleeding, $P = 0.34$; hemorrhagic stroke, $P = 0.37$.

^{//}Number needed to treat 253 (CI 179 to 1118).

Conclusion

In patients with nonvalvular atrial fibrillation, the effects of rivaroxaban compared with warfarin did not differ by patient age.

Commentary

In this prespecified secondary analysis of the ROCKET AF trial, Halperin and colleagues report on the comparative efficacy and safety of rivaroxaban and warfarin in patients 75 years of age. Compared with patients < 75 years of age, those 75 years had increased risk for stroke or systemic embolism and major bleeding, regardless of treatment with warfarin

or rivaroxaban. Nevertheless, rivaroxaban was as effective and safe as adjusted-dose warfarin in elderly patients as in younger patients. Moreover, the net clinical benefit of rivaroxaban was greater in elderly than younger patients, due largely to prevention of ischemic stroke.

This analysis represents the largest study of older adults with nonvalvular AF receiving oral anticoagulants. These findings are consistent with the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, in which the benefits of apixaban were consistent across older and younger patients with nonvalvular AF (1). In contrast, in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, dabigatran, 150 mg twice daily, increased risk for major extracranial bleeding compared with warfarin in patients ≥ 75 years of age (2).

Older adults with nonvalvular AF have increased risk for stroke and major bleeding that must be carefully assessed when oral anticoagulants are being considered. Modifiable risk factors for bleeding, including uncontrolled hypertension, unnecessary aspirin or nonsteroidal antiinflammatory drug use, and excessive alcohol use, should be identified and eliminated. Finally, because elderly patients are a high-risk population, oral anticoagulants should be used carefully and with regular follow-up, regardless of the anticoagulant prescribed.

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