



Rivaroxaban was not inferior to warfarin in the prevention of stroke or systemic embolism in patients with nonvalvular atrial fibrillation

Clinical Problem: A 75 year-old man with controlled hypertension and diabetes mellitus with known atrial fibrillation presents to your outpatient clinic for consideration of anti-coagulation for stroke prevention. The patient declines warfarin.

Clinical Question: Is Rivaroxaban oral anticoagulation treatment as safe and effective as dose-adjusted warfarin for the prevention of stroke in patients with nonvalvular atrial fibrillation at moderate-to-high risk for stroke?

Search Strategy: Medline search was performed using key words “Atrial Fibrillation” and “Anticoagulation” with limits “English, Human, Randomized Controlled Trial”. 150 articles were identified, only 1 randomized controlled trial comparing rivaroxaban to warfarin in patients with atrial fibrillation (ROCKET AF).

Clinical Bottom Lines:

1. Rivaroxaban at a dose of 20 mg daily was not inferior to warfarin for the prevention of stroke or systemic embolism.
2. There was a small, but statistically significant, decrease in the incidence of fatal bleeding (NNT=250, 95% CI 153-683) and intracranial hemorrhage (NNT=250, 95% CI 138-1366) with rivaroxaban as compared to warfarin.

The Evidence: A randomized, double-blind trial including 14,264 patients with nonvalvular atrial fibrillation and moderate-to-high risk of stroke.

Clinical Question: To determine whether rivaroxaban at a once-daily oral dose of 20 mg (or 15 mg in patients with CrCl 30-49 mL/min) was as safe and effective as dose-adjusted warfarin for the prevention of stroke or systemic embolism in patients with nonvalvular atrial fibrillation.

Inclusion criteria: 14,264 patients recruited from 1178 centres in 45 countries. Patients had documented nonvalvular atrial fibrillation and previous stroke, TIA or systemic embolus, or at least 2 of the following: 1) heart failure and/or LVEF ≤ 35%, 2) hypertension, 3) age ≥ 75, 4) diabetes mellitus.

Outcomes: The primary efficacy end point was a composite of stroke (ischemic or hemorrhagic) and systemic embolism. Primary safety end point was a composite of major and non-major clinically relevant bleeding. Secondary efficacy end points included composite of stroke, systemic embolism, or death from cardiovascular causes; a composite of stroke, systemic embolism, death from CV causes or MI; and individual components of the composite end points.

Data:

Primary end point for stroke or systemic embolism

	Rivaroxaban	Warfarin	Hazard Ratio (95% CI)	
Intention-to-treat (ITT) population	2.1%/year	2.4%/year	0.88 (0.75-1.03)	No significant difference

Secondary Outcomes and Adverse Events

	Rivaroxaban N=7111	Warfarin N=7125	Hazard Ratio (95% CI)	NNT (95% CI)
Ischemic Stroke	2.1%	2.3%	0.94 (0.75-1.17)	No significant difference
Hemorrhagic Stroke	0.41%	0.71%	0.59 (0.37-0.93)	333 (184-1821)
Non-CNS systemic embolism	0.07%	0.31%	0.23 (0.09-0.61)	417 (261-1030)
Myocardial Infarction	1.43%	1.78%	0.81 (0.63-1.06)	No significant difference
Major Bleeding	5.6%	5.4%	1.04 (0.90-1.20)	No significant difference
Intracranial Hemorrhage	0.8%	1.2%	0.67 (0.47-0.93)	250 (138-1366)
Fatal Bleeding	0.4%	0.8%	0.50 (0.31-0.79)	250 (153-683)
Deaths (ITT)	2.95%	3.53%	0.92 (0.82-1.03)	No significant difference

Rivaroxaban resulted in a small, but statistically significant increased risk of the following adverse events:

	Rivaroxaban N=7111	Warfarin N=7125	NNH (95% CI)
GI Bleeding	3.15%	2.16%	101 (66-216)
Epistaxis	10.14%	8.55%	63 (39-158)
Hematuria	4.16%	3.40%	132 (72-749)
Anemia (decrease in hemoglobin \geq 2 g/dl)	4.3%	3.6%	143 (75-1663)
Need for transfusion (\geq 2 units of whole blood or packed RBCs).	2.6%	2.1%	200 (100-42581)

Comments:

1. Overall, compelling study, as higher risk patients were included (mean and median CHADS₂ score of 3.5 and 3.0, respectively), as compared to studies of other oral anticoagulants versus warfarin in patients with atrial fibrillation (Connolly et al., 2009; Granger et al., 2011).
2. Proportion of time in therapeutic range with an INR 2-3 for warfarin (mean, 55%) was lower than in previous studies of other new anticoagulants in patients with atrial fibrillation. (Connolly et al., 2009; Granger et al., 2011).
3. The percentage of patients on antiplatelets was greater in the warfarin arm 36.2% versus the rivaroxaban arm 34.9%).
4. Cost is a factor as rivaroxaban is much more expensive, although warfarin requires frequent monitoring and dose-adjustment.

5. The study was funded by the manufacturer of the study drug. The Duke Clinical Research Institute performed the primary analyses independently.

References:

Patel, MR et al. (2011). Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 365:883-891. (ROCKET AF Trial)
Connolly et al. (2009). Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 361:1139-1151. (RE-LY Trial)
Granger et al. (2011). Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. [Epub ahead of print] (ARISTOTLE Trial)

Key Words: Rivaroxaban, Warfarin, Atrial Fibrillation, Stroke Prevention

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