Rivaroxaban in Patients with Atrial Fibrillation and a Bioprosthetic Mitral Valve

Background: There are few clinical trials that determine the safety and efficacy of using an oral direct factor Xa inhibitor in patients with atrial fibrillation and bioprosthetic valves. Warfarin requires careful monitoring of INR and lifestyle choices due to interactions with food and other medications. A DOAC would ease the burden of monitoring, while being anticoagulated to decrease the risk of a thromboembolism. There is always concern with bleeding risks when place on an anticoagulant of any kind. In the recent ROCKET AF trial, rivaroxaban was shown to be noninferior to warfarin in the prevention of stroke in nonvalvular atrial fibrillation. This trial expands upon the previous trials by examining patients with atrial fibrillation and a bioprosthetic mitral valve.

What They Did: A multicenter, randomized, noninferiority, open-label design trial that had blinded adjustment of outcomes that compared rivaroxaban to warfarin for anticoagulation for thromboembolism prophylaxis in patients that have atrial fibrillation and a bioprosthetic valve. The patient was to receive Rivaroxaban 20 mg daily for CrCl greater than 49 mL/min or Rivaroxaban 15 mg daily for CrCl of 30-49 mL/min vs warfarin dose adjusted to a target INR of 2.0-3.0. The noninferiority margin is 8 days. Intention-to-treat, as-treated, and per-protocol analysis were used.

Inclusion Criteria:

- Men and Women over the age of 18 at the time of inclusion
- Patients with paroxysmal, permanent, or persistent atrial fibrillation or flutter and a biological prosthetic mitral valve
- Planned or existing use of oral anticoagulants for prophylaxis of thromboembolism
- Consent of the patient obtained

Exclusion Criteria:

- Active endocarditis
- Uncontrolled hypertension: SBP > 180 mmHg and/or DBP > 100 mmHg
- Active internal bleeding
- History of, or a condition associated with increased risk of bleeding
- History of a severe stroke within the last 3 months or an acute thrombosis in last 14 day
- ASA > 100 mg or double antiplatelet, oral or IV, within 5 days before randomization
- Long-term treatment with a NSAID
- Treatment with a P450 3A4 inhibitor or inducer 4 days before randomization
- Anemia
- Pregnancy or breastfeeding
- CrCl < 30 mL /min
- Liver Disease

Outcomes

Primary Outcomes:

- Composite of death, major cardiovascular events, or major bleeding at 12 months.
    - Major cardiovascular events include stroke, transient ischemic attack, systemic embolism, myocardial infarction or hospitalization for heart failure

Secondary Outcomes:

- Composite of death from cardiovascular causes or thromboembolic events

Safety

- Bleeding events

Results

- 1005 patients randomized: 500 received rivaroxaban and 505 received warfarin
- Reported for primary outcome as restricted mean survival time (RMST)
    - RMST is the mean free time from an outcome event up to a prespecified time point
    - A negative value indicates an increased risk from rivaroxaban treatment

Primary Outcomes:

- Intention to treat analysis: The mean time an event occurred was 347.5 days in the rivaroxaban group and 340.1 days in the warfarin group
    - RMST difference 7.4 days; 95% CI, -1.4 to 16.3, P<0.001 for noninferiority
- As-treated analysis: The mean time an event occurred in 350.1 days in the rivaroxaban group and 339.6 days in the warfarin group
    - RMST difference 10.5 days; 95% CI, 1.9 to 19.1, P<0.001 for noninferiority
- Per-protocol analysis: The mean time an event occurred in 356.7 days in the rivaroxaban group and 347.1 days in the warfarin group
    - RMST difference 9.6 days; 95% CI, 2.2 to 16.9, P<0.001 for noninferiority

Secondary Outcomes:

- Death from cardiovascular causes of thromboembolic events
    - 17 patients in the rivaroxaban group vs 26 in the warfarin group
        - HR 0.65; 95% CI, 0.35 to 1.20
- Incidence of total stroke was 0.6% in the rivaroxaban group vs 2.4% in the warfarin group
    - HR 0.25; 95% CI, 0.07 to 0.88
- Valve thrombosis occurred in 5 patients in the rivaroxaban group vs 3 in the warfarin group
    - HR 1.67; 95% CI, 0.40 to 7.01

Safety

- At 12 months, bleeding occurred in 5 patients in the rivaroxaban group vs 3 in the warfarin group
    - HR 0.54; 95% CI, 0.21 to 1.35

Strengths

- Large multicenter trial with blinding of randomization
- Well balanced baseline characteristics between the two treatment groups
- Used intention-to-treat analysis, per-protocol analysis, and as-treated analysis
- Meaningful primary outcomes (death)
- Blinded adjudication of outcomes
- Stroke and bleeding risks asses using CHA_2DS_2 VASc Scale
    - Commonly used and easy to understand to assess risk

Limitations

- Only included bioprosthetic valves and not an artificial valve made from an alloy or plastic
- Included patients with mitral valve replacement only
- INR was therapeutic 65% of the time for patients on warfarin
- Open label could lead to bias
- Study was conducted in Brazil
- The as-treated and per-protocol groups rely on patient adherence to drug therapy
- Received grant support and consulting fees from many large pharmaceutical companies such as Bayer, Bristol Myers Squibb, Pfizer, and Medtronic

Study Author Conclusion

"In patients with atrial fibrillation and a bioprosthetic mitral valve, rivaroxaban was noninferior to warfarin with respect to the mean time until occurrence of major clinical events."

Discussion: Rivaroxaban demonstrates noninferiority to warfarin in time to composite of death, major cardiovascular events, or major bleeding in all three treatment groups (as-treated, per-protocol, and intention-to-treat). Hospitalizations for congestive Heart Failure (CHF) were included in the composite. The rate for hospitalization for CHF was similar in both treatment groups. No single major cardiovascular event such as a stroke, TIA, valve thrombosis, or hospitalization for CHF seemed to power the difference between the two treatments. The number of patients followed over a 12-month time frame experienced a low incidence of events, thus requiring the use of composite endpoints. In all three analysis models, the time to a cardiovascular event was longer. In looking at the life of an individual by years, seven days may not make that much of an impact on quality of life. The adverse effect of bleeding was lower in the rivaroxaban group by 6 people. Other adverse events of intracranial bleeding, fatal bleeding, and clinical nonmajor bleeding were similar between both groups. This study is limited in showing only noninferiority in patients with atrial fibrillation and mitral bioprosthetic valves.

Clinical Take Home Point: The results of this trial show rivaroxaban to be noninferior to warfarin in death from a composite of cardiovascular events and major bleeding over relatively short period of 12 months. The study shows that rivaroxaban is not worse than warfarin in causing death or bleeding, but the study cannot state that rivaroxaban is a better choice than warfarin in patients with bioprosthetic valves. This is a new treatment so caution should be taken when placing a patient on this treatment. The trial followed the patient for 12 months and the impact on the rest of the patient's life is not known at this time. The choice to place a patient with a bioprosthetic valve on rivaroxaban instead of warfarin

should be made on an individual based process and not be common practice until further studies are completed to show safety and efficacy.

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Peer Reviewer: Cody Null, PharmD, BCCCP, BCPS

Reference: Guimaraes H.P., Lopes R.D., de Barros e Silva P.G.M., et al. “Rivaroxaban in Patients with Atrial Fibrillation and a Bioprosthetic Mitral Valve”. The New England Journal of Medicine. 2020. 383:2117-2126.