From the Midwestern Vascular Surgical Society

Safety and efficacy of rivaroxaban compared with warfarin in patients undergoing peripheral arterial procedures

Anjan Talukdar, MD,[a] S. Keisin Wang, MD,[a] Lauren Czosnowski, PharmD,[a,b] Nassim Mokraoui, MD,[a] Alok Gupta, MD,[a] Andres Fajardo, MD,[a] Michael Dalsing, MD,[a] *and* Raghu Motaganahalli, MD,[a]
Indianapolis, Ind

ABSTRACT

Objective: Rivaroxaban is a United States Food and Drug Administration-approved oral anticoagulant for venous thromboembolic disease; however, there is no information regarding the safety and its efficacy to support its use in patients after open or endovascular arterial interventions. We report the safety and efficacy of rivaroxaban vs warfarin in patients undergoing peripheral arterial interventions.

Methods: This single-institution retrospective study analyzed all sequential patients from December 2012 to August 2014 (21 months) who were prescribed rivaroxaban or warfarin after a peripheral arterial procedure. Our study population was then compared using American College of Chest Physicians guidelines with patients then stratified as low, medium, or high risk for bleeding complications. Statistical analyses were performed using the Student *t*-test and χ^2 test to compare demographics, readmissions because of bleeding, and the need for secondary interventions. Logistic regression models were used for analysis of variables associated with bleeding complications and secondary interventions. The Fisher exact test was used for power analysis.

Results: There were 44 patients in the rivaroxaban group and 50 patients in the warfarin group. Differences between demographics and risk factors for bleeding between groups or reintervention rate were not statistically significant ($P = .297$). However, subgroup evaluation of the safety profile suggests that patients who were aged ≤65 years and on warfarin had an overall higher incidence of major bleeding ($P = .020$). Patients who were aged >65 years, undergoing open operation, had a significant risk for reintervention ($P = .047$) when they received rivaroxaban.

Conclusions: Real-world experience using rivaroxaban and warfarin in patients after peripheral arterial procedures suggests a comparable safety and efficacy profile. Subgroup analysis of those requiring an open operation demonstrated a decreased bleeding risk when rivaroxaban was used (in those aged <65 years) but an increased risk for secondary interventions. Further studies with a larger cohort are required to validate our results. (J Vasc Surg 2017;■:1-6.)

Rivaroxaban, an oral direct anti-Xa agent, was approved by the United States Food and Drug Administration in 2011 for use in the United States. It is currently used for prevention of venous thromboembolism, deep venous thrombosis, stroke prevention in patients with nonvalvular atrial fibrillation, and secondary prevention of coronary events in patients with acute coronary syndrome.[1-9] There are no data available to support its use in patients with peripheral arterial occlusive disease after surgical or endovascular intervention. Warfarin, an oral vitamin K antagonist, has been in use in general since 1954 as well as in patients deemed high risk for failure after peripheral arterial intervention. This benefit is offset by food and drug interactions as well as a bleeding risk, which is best controlled with frequent coagulation monitoring and dose adjustments as needed.[8,10-13]

Efficacy and safety of these drugs are compared in the ROCKET AF trial[14] (The Rivaroxaban once daily oral Direct factor Xa inhibition compared with Vitamin K Antagonism for prevention of Stroke and Embolism Trial in Atrial Fibrillation) for recurrent stroke prevention in patients with nonvalvular atrial fibrillation. This randomized trial found that rivaroxaban was noninferior to warfarin in the primary analysis, which included patients in the per-protocol population, and also in the intention-to-treat analysis. The primary safety analysis found no significant difference between rivaroxaban and warfarin with respect to rates of major or no major clinically relevant bleeding.

The objective of our study was to compare the safety and efficacy of rivaroxaban vs warfarin in patients

From the Division of Vascular Surgery[a] and Department of Surgery,[b] Indiana University School of Medicine.

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Correspondence: Raghu Motaganahalli, MD, Division of Vascular Surgery, 1801 N Senate Blvd, MPC-2 #3500, Indianapolis, IN 46202 (e-mail: rmotagan@iupui.edu).

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undergoing peripheral arterial procedures who are deemed of sufficiently high risk of failure to warrant anticoagulation.

METHODS

The study was approved by the Indiana University Institutional Review Board as an exempt study, and hence, no patient consent was obtained. This single-center retrospective study included all sequential patients from December 2012 to August 2014 who were prescribed rivaroxaban after an open or endovascular intervention for lower extremity arterial occlusive disease or acute embolic occlusion. Comparisons were made with matched sequential patients who were prescribed warfarin during the same time for similar indications. Patients were identified from a database with Pharmacy, which kept a log of patients who were prescribed rivaroxaban or warfarin.

Patients were prescribed warfarin or rivaroxaban according to physician preference, potential undesirable drug interactions, history of difficulty maintaining a therapeutic anticoagulation profile with warfarin, concern for hypercoagulable state, use of a nonautogenous conduit with poor runoff, and presence of a proximal embolic source. Patient demographics (Table I), readmission with cause, and need for secondary interventions were identified from inpatient record reviews.

The American College of Chest Physicians (ACCP) guidelines were used to stratify patients into low, medium, or high risk for bleeding complications.[15] The patient demographics that were recorded included age, any previous bleeding episodes, history of cancer, either primary or metastatic disease, including hematologic, history of chronic renal insufficiency or chronic liver disease, thrombocytopenia (<150,000/mm^3), previous stroke, diabetes, anemia (<13.4 g/dL in men and <12 g/dL in women), use of antiplatelet (aspirin or clopidgrel), poor anticoagulant control, failure to thrive, recent surgery, frequent falls, and alcohol abuse. Low-risk patients had no risk factors, medium-risk patients had one risk factor, and high-risk patients had two or more risk factors.

Major bleeding complications were defined as any bleeding requiring hospitalization or transfusion. Secondary interventions were defined as any intervention performed after the index operation to maintain graft/stent patency. Interventions included open, endovascular, or hybrid procedures. Patients receiving rivaroxaban or warfarin were compared by age (≤65 or >65 years), risk of bleeding, and type of primary and secondary interventions. Patients who required reintervention were managed case-by-case. Decision for an urgent intervention was dictated by an imminent threat to an extremity rather than the use of an anticoagulant. For patients requiring emergency intervention, we used either or a combination of reversal agents (vitamin K, fresh frozen plasma for warfarin) and blood transfusions. Agents to reverse effects of rivaroxaban were not available commercially during the time of our data collection.

Statistical analyses were performed with IBM SPSS 23 software (IBM Corp, Armonk, NY) using the Student *t*-test and χ^2 test to compare demographics, readmissions due to bleeding, and need for secondary interventions. Logistic regression models were used to evaluate variables associated with major bleeding complications and secondary interventions. A *P* value of <.05 was defined as statistically significant. A post hoc power

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective case control study
- **Take Home Message:** In 94 patients undergoing peripheral arterial procedures rivaroxaban was equally safe and effective compared with warfarin but carried less risk of bleeding complications.
- **Recommendation:** The data suggest that in patients who require anticoagulation after lower extremity open or endovascular revascularization, rivaroxaban is preferred over warfarin.

Table I. Patient demographics and risk for bleeding

Variable[a]	Rivaroxaban (n = 44)	Warfarin (n = 44)	*P* value
Age, years	60.5 ± 15	63.8 ± 14	.278
Gender			.833
Male	27	32	
Female	17	18	
Race			.541
Caucasian	41	44	
African American	3	5	
Other	0	1	
Risk category			.297
Low	0	0	
Medium	6	3	
High	38	47	
Risk factors, No.	2.4 ± 0.8	2.7 ± 0.9	.199
Intervention type			.312
Endovascular	7	11	
Open	36	35	
Hybrid	1	4	
Antiplatelet use	31	45	.016
Diabetes mellitus	14	14	.686
Anemia	32	33	.481
Stroke	3	2	.544
Cancer	4	1	.126
Thrombocytopenia	5	4	.58

[a]Continuous data are shown as the mean ± standard deviation and categoric data as number of patients.