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Is Oral Rivaroxaban Safe and Effective in the Treatment of Patients With Symptomatic DVT?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not oral rivaroxaban is safe and effective in the treatment of patients with symptomatic DVT.

STUDY DESIGN: Review of three English language primary randomized controlled trial studies published from 2007-2011.

DATA SOURCES: Three randomized controlled trials studying the effectiveness and safety of rivaroxaban in the treatment of patients with symptomatic DVT in comparison to enoxaparin and placebo.

OUTCOMES MEASURED: Outcomes measured were episodes of recurrent DVT and bleeding. Patients were monitored for the proposed treatment period and seen at fixed intervals that were matching for the rivaroxaban and comparison groups. At this time a checklist was used to gather information on symptoms and signs of recurrent venous thromboembolism, bleeding, and adverse events.

RESULTS: The articles showed rivaroxaban is safe and effective in the treatment of patients with deep venous thrombosis. The primary efficacy outcome in all was episodes of recurrent DVT. The principle safety outcome in all studies was clinically relevant major and non-major bleeding.

CONCLUSIONS: This review supports the use of rivaroxaban in the treatment of patients with symptomatic deep venous thrombosis. More information is needed for the use of the drug in special populations such as cancer patients.

KEY WORDS: Rivaroxaban, Treatment, DVT

INTRODUCTION

Deep venous thrombosis (DVT) is a blood clot that most commonly forms in the deep veins of the arms or legs and may lead to emboli. A clot forms when something slows or causes an alteration in blood flow such as hospitalization. This paper evaluates three randomized, controlled trials (double blind, parallel group phase II, open label) in the safety and effectiveness of rivaroxaban in the treatment of patients with symptomatic DVT. The precise number of people affected by DVT is unknown, but estimates range from 300,000 to 600,000 (1 to 2 per 1,000, and in those over 80 years of age, 1 in 100) each year in the US.⁴ 33% of people with DVT will have a recurrence within 10 years.⁴ The total annual healthcare cost for a Venous Thromboembolism (VTE) ranged from \$7594 to \$16,644, depending on the type of event and whether it was a primary or secondary diagnosis.⁵ The recurrent DVT event was associated with 21% greater cost compared with the initial DVT event.⁵ DVT was diagnosed in an estimated annual average of 348,558 hospitalizations.⁶

Various factors can lead to DVT such as age, obesity, smoking, heart failure, oral contraception, venous stasis due to immobilization, cancer, stroke, pregnancy, polycythemia vera, factor deficiencies, etc. Among people who have had a DVT, 50% will have long-term symptoms such as swelling, pain, discoloration, and scaling in the affected limb.⁴ Numerous methods are used to treat the condition including unfractionated or low molecular weight heparin, vitamin K antagonists, selective factor Xa inhibitors, direct thrombin inhibitor, inferior vena cava filters, and fibrinolytic therapy. Current treatments of DVT have limitations due to the required laboratory monitoring for dose initiation and adjustment, narrow therapeutic window, and are subject to food and drug interactions.² Rivaroxaban is being proposed as an alternative in

treatment because it does not need laboratory monitoring, has a wide therapeutic window, is safe in long term use, and has oral route of administration.³

OBJECTIVE

The objective of this selective EBM review is to determine whether or not oral rivaroxaban is safe and effective in the treatment of patients with symptomatic DVT.

METHODS

Articles designated for this selective evidence based medicine (EBM) review have met precise requirements to explore the objective. The articles consisted of three randomized control trials. The articles were selected using the key words: rivaroxaban, treatment, and DVT. The author of this selective EBM review conducted the research in PubMed, Cochrane, and OVID. All articles were published in the English language in peer-reviewed journals. Articles were chosen if they targeted patients with DVT, included patient oriented outcomes, and population age greater than 18. Articles were excluded if they were systematic reviews, non- patient oriented outcomes, and population age less than 18. Statistics were reported using p-values, 95% confidence intervals (CI), relative risk reduction (RRR), absolute risk reduction (ARR), relative risk increase (RRI), absolute risk increase (ARI), number needed to treat (NNT), and number needed to harm (NNH).

In the Einstein's study which was an open label, randomized, event driven, non-inferiority study patients were assigned to receive oral rivaroxaban 15mg twice daily for the first three weeks, followed by 20mg once daily for the anticipated 3, 6, or 12 months of treatment.¹ In Agnelli's group phase II trial study the oral rivaroxaban group received doubled blinded doses of 10, 20, or 30mg twice daily or 40mg once daily, with food for 12 weeks.² In both studies patients

in the standard anticoagulant group received subcutaneous enoxaparin 1mg/kg twice daily followed by vitamin K antagonist such as warfarin. In Roumaldi's double blind, placebo controlled superiority study, patients were assigned to receive rivaroxaban 20mg or placebo for 6-12 months.³ Outcomes measured include incidence of recurrent DVT and bleeding. The demographics of the studies included are demonstrated in Table 1.

OUTCOMES MEASURED

The primary efficacy outcomes of the studies was the incidence of symptomatic recurrent VTE, defined as a composite of DVT and pulmonary embolism.³ The safety outcome measured in all the studies is bleeding. Bleeding was considered major if it was fatal, affected a critical organ, led to treatment cessation, or transfusion of two or more units of packed red blood cells or whole blood.² Patients were monitored for the proposed treatment period and seen at fixed intervals that were matching for the rivaroxaban and comparison groups. At this time a checklist was used to gather information on symptoms and signs of recurrent venous thromboembolism, bleeding, and adverse events.

RESULTS

Three randomized control trials evaluated in this review include a parallel group phase II trial, an open label event driven, noninferiority study and a double blind, event driven superiority study. Two of the studies compared rivaroxaban to enoxaparin plus vitamin K antagonist while one compared rivaroxaban to placebo. Patients included in the studies were all of legal age for consent and had symptomatic DVT. The primary efficacy outcome in all studies was episodes of recurrent DVT. The principle safety outcome in all studies was clinically relevant major and non-major bleeding. The principle safety outcome was measured via events such as treatment

Table 1: Demographics and Characteristics of included studies

Study	Type	# pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Einstein ¹ , 2010	RCT Open label, randomized, even driven, noninferiority study	3449	18 years or older	-legal age of consent -confirmed DVT -no symptoms of PE	-Pts with heparin, VKA treatment for >48 hrs, treatment with thromboectomy, vena cava filter, or fibrinolytic agent, liver disease, active bleeding, BP>180/110, pregnancy, CrCl<30ml/min, bacterial endocarditis, life expectancy<3mos	66	-regimen of 15 mg bid or 20mg QD PO rivaroxaban -1.0 mg/kg of body weight bid subQ enoxaparin + VKA
Agnelli ² , 2007	RCT parallel-group phase II trial	636	18 years or older	-age 18+ -no symptoms of PE -not received VKA -no more than 36 hrs of treatment with LMWH	-cerebral ischemia, intracerebral bleeding or GI bleeding within past 6 months, surgery within past 4 weeks, active PUD, known bleeding disorder, prolonged INR, platelet count <100X10 ⁹ /L, body wt <45kg, uncontrolled HTN, heart failure, CrCl<30ml/min, pregnancy	32	-rivaroxaban 10, 20, or 30 mg BID or 40mg once daily -enoxaparin 1 mg/kg BID followed by vitamin K antagonist
Romualdi ³ 2011	RCT double blind, placebo controlled superiority study	1197	Mean age 58 years	-Patients with confirmed DVT	-indication for VKA, renal insufficiency, liver disease, bacterial endocarditis, active bleeding or high risk of bleeding, uncontrolled HTN, pregnancy	N/A	-rivaroxaban 20mg once daily

cessation and blood transfusions. The primary efficacy outcome was measured via checklist used to identify signs and symptoms of recurrent DVT.

This review also looked at safety outcomes measured by percentage of treatment emergent adverse events. The percentages reported were used to calculate Relative Risk Increase (RRI) and Absolute Risk Increase (ARI). The ARI value is used to calculate the Numbers Needed to Harm (NNH). The NNH tells the clinician how many patients can be treated with the experimental treatment over the control treatment before one patient will be harmed.

Einstein's 2010 study consisted of 3449 patients in whom 1731 were given rivaroxaban while 1718 were given enoxaparin plus vitamin K antagonist. Patients were assigned to receive oral rivaroxaban 15mg twice daily for the first three weeks, followed by 20mg once daily for the anticipated 3, 6, or 12 months of treatment.¹ Patients who received standard therapy received subcutaneous enoxaparin 1.0 mg/kg, and either warfarin or acenocoumarol. Patients were followed for the treatment duration and seen at fixed intervals that were identical for experimental and comparison groups, at which time a checklist was used to elicit information on symptoms and signs of recurrent VTE, bleeding, and adverse events.¹ Adverse events leading to discontinuation of study drug occurred in 4.9% of patients receiving rivaroxaban and 4.7% of patients in the control group. Recurrent DVT occurred in 14 patients of the rivaroxaban group compared to 28 patients receiving enoxaparin plus vitamin K antagonist. The primary efficacy outcome occurred in 2.1% of patients in the rivaroxaban group and in 3% of patients in the standard therapy group causing a hazard ratio of .68 and 95% CI of .44-1.04. The principal safety outcome occurred in 139 patients in the rivaroxaban group and 138 patients receiving standard therapy. The hazard ratio was .97 and 95% CI was .76 to 1.22. 196 patients in the rovaroxaban discontinued treatment due to adverse events, consent withdrawn or lost to follow up. The NNH

value was 0 indicating no difference in major bleeding rates between the experimental and control groups. The NNT value was -111 indicating for every 111th person treated with rivaroxaban, DVT occurred in one less person. These results are summarized in tables 2 and 3.

Table 2: Adverse Event Data for Rivaroxaban

HARM	CER (enoxaparin/VKA)	EER (rivaroxaban)	RRI	ARI	NNH	CI	P-value
Einstein, 2010	.081	.081		0	0	.76-1.22	.77

Table 3: Efficacy of Rivaroxaban in the Prevention of DVT

Prevention	CER (enoxaparin/VKA)	EER (rivaroxaban)	RRR	ARR	NNT	CI	P-value
Einstein, 2010	.03	.021	-.30	-.009	-111	.44- 1.04	<.001

In Roumaldi's 2011 study, 1197 patients were enrolled in the study. 34.1% completed the DVT study, 19.1% completed the PE study and 47.5% came from routine care.³ The average age of patients was 58 years. The primary efficacy outcome occurred in 8 out of 602 patients in the rivaroxaban group and 42 out of 594 patients in the placebo group for a hazard ratio of .18, 95% CI of .09-.39 and P-value <.001.³ Major bleeding occurred in 4 patients receiving rivaroxaban with no episodes in patients receiving placebo. The net clinical benefit defined as the composite of primary efficacy outcome and major bleeding, occurred in 12 patients receiving rivaroxaban and in 42 patients receiving placebo, for a hazard ratio of .28 and 95% confidence interval of .15-.53. 76 patients in the rivaroxaban group discontinued treatment due to adverse events, withdrawn consent or lost to follow up. Non-major bleeding which consisted of mucosal bleeding was increased from 1.2% in placebo group to 5.4% in those treated with rivaroxaban. However patients continued treatment and overall benefits outweighed risks. The NNH value

was 143, which means for every 143 patients one more patient would have an episode of major bleeding with rivaroxaban than with control after a period of time of 6 months. The NNT value was -17 meaning for every 17th patient treated with rivaroxaban DVT occurred in one less person with a 95% CI of .09-.39 and p-value<.001. These values are summarized in tables 4 and 5.

Table 4: Adverse Event Data for Rivaroxaban

HARM	CER (placebo)	EER (rivaroxaban)	RRI	ARI	NNH	CI	P-value
Roumaldi, 2011	0	.007		.007	143		.11

Table 5: Efficacy of Rivaroxaban in the Prevention of DV T

Prevention	CER (placebo)	EER (rivaroxaban)	RRR	ARR	NNT	Ci	P-value
Roumaldi, 2011	.071	.013	-.82	-.058	-17	.09-.39	<.001

In Agnelli's 2007 study 636 patients were enrolled in the study. 613 patients were randomized while 23 could not be randomized due to violation of protocol. An additional 9 patients did not receive treatment due to protocol violation or withdrawn consent leaving 602 patients who received study drug. Patients in the rivaroxaban were split up to receive either 10, 20, 30 milligrams twice daily or 40 milligrams once daily of rivaroxaban compared with enoxaparin 1 mg/kg twice daily followed by vitamin K antagonist. Patients received treatment for 12 weeks. The primary safety endpoint was major bleeding. Bleeding was considered major if it was fatal, affected a critical organ, led to treatment cessation, or transfusion of two or more units of blood.² Major bleeding was observed in 1.7%, 1.7%, 3.3%, and 1.7% of patients receiving rivaroxaban 10, 20, 30, milligrams twice daily or 40 milligrams once daily

respectively.² No episodes of major bleeding occurred in the enoxaparin group. A total of 18 patients discontinued treatment due to protocol violation or lack of compliance. Table 6 summarizes incidence of major and non-major bleeding. The NNH value was 59 meaning for every 59 patients one more patient would have an episode of major bleeding with rivaroxaban than with control for a period of time of 12 weeks and a p-value of .39. These results are summarized in table 7.

Table 6: Incidence of Adverse Events

	Rivaroxaban				Enoxaparin/VKA N=126
	10mg bid (n=119)	20mg BID (n=117)	30mg BID (n=121)	40mg QD (n=121)	
Any bleeding	6 (5%)	11 (9.4%)	13 (10.7%)	14 (11.6%)	8 (6.3%)
Major bleeding	2 (1.7%)	2 (1.7%)	4 (3.3%)	2 (1.7%)	0
Bleeding leading to transfusion	2 (1.7%)	0	2 (1.7%)	1 (.8%)	0
Bleeding warranting treatment cessation	1 (.8%)	2 (1.7%)	3 (2.5%)	1 (.8%)	0
Minor bleeding	4 (3.4%)	9 (7.7%)	11 (9.1%)	12 (9.9%)	8 (6.3%)
95% CI	.2-5.9	.2-.6	.9-8.3	.2-5.8	.0-2.9

Table 7: Adverse Event Data for Rivaroxaban

HARM	CER (enoxaparin/VKA)	EER (rivaroxaban)	RRI	ARI	NNH	CI	P-value
Agnelli, 2007	0	.017		.017	59	varied	.39

DISCUSSION

Rivaroxaban, a factor Xa inhibitor provides an advantage over other therapies due to its oral route of administration, single drug approach, and does not require laboratory monitoring.

This provides advantages for physicians and patients, along with improving compliances. Rivaroxaban is also a cost effective drug.

One of the most common uses of rivaroxaban includes DVT prophylaxis for patients receiving hip or knee replacement surgery. Other indications of its use include pulmonary embolism prophylaxis, atrial fibrillation and non-valvular cerebrovascular accident. Contraindications to using rivaroxaban consist of active bleeding and hypersensitivity reaction to the drug. There is insufficient evidence in relation to its use in pregnancy and is a category C drug. The black box warning states that stopping rivaroxaban increases a patient's risk of thrombotic events such as stroke. Patients receiving neuraxial anesthesia or undergoing spinal puncture and are using rivaroxaban can get epidural or spinal hematomas, which may result in long term or everlasting paralysis. Aspirin, non-steroidal anti-inflammatory drugs, heparin, and warfarin are amongst drugs that can cause increased risk of bleeding if taken with rivaroxaban.

The use of newer drugs may change the way anticoagulation clinics currently work. For example the measurement of alternative blood tests such as D-dimer, ultrasound testing and immediate availability in case of signs and symptoms or recurrence, bleeding, or other clinical problems can be important.³

One limitation of Agnelli's study is that study populations were younger, and few had active cancer, which may have reduced the likelihood of thrombus extension or bleeding events.² The Einstein study had an open design which allowed potential for a diagnostic suspicion bias.¹

CONCLUSION

Rivaroxaban provides a solo drug approach to the short term and continued treatment of venous thrombosis that may expand the benefits of anticoagulation. The studies presented in this

review support the safety and efficacy of using rivaroxaban in the treatment of DVT. The large p-values for adverse events mean the prevention of bleeding may have occurred by chance or coincidence. Rivaroxaban provides alternative treatment to other regimens such as enoxaparin plus vitamin K antagonist. One of the major advantages of using rivaroxaban is that it does not require laboratory monitoring and has decreased food and drug interactions. Another advantage includes the drug's oral route of administration.

Future studies should focus on finding the most effective and safe dosages for the use of rivaroxaban. Dosages can be individualized to patients and also depend on other co-morbidities present. Another area of interest is to assess the safety of rivaroxaban in distinct populations including elderly, obese patients, patients with liver or renal impairment, and patients with cancer. These are amongst some of the populations that were poorly represented in these studies. Although DVT is less common in adolescents; the treatment of DVT with rivaroxaban in adolescents with DVT should also be incorporated in future studies.

In conclusion, the factor Xa inhibitor rivaroxaban proves to be a safe and effective single drug approach in the treatment of patients with symptomatic deep vein thrombosis.

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