Effect of a Rivaroxaban Patient Assistance Kit (R-PAK) for Patients Discharged With Rivaroxaban: A Randomized Controlled Trial

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Abstract

Background: The combination of poor health literacy and a complex dosing regimen/transition for rivaroxaban in venous thromboembolism (VTE) treatment may increase the likelihood of negative clinical outcomes secondary to nonadherence. **Objective:** The aim was to determine if a Rivaroxaban Patient Assistance Kit (R-PAK) given at hospital discharge increases proper dose transition and overall patient adherence. **Methods:** This prospective, randomized, controlled trial was conducted at an 859-bed academic medical center. Patients were randomized into 2 groups. In the treatment group, patients received the R-PAK with counseling at discharge, whereas patients in the control group received discharge counseling alone. In addition, patients were contacted after 21 days of therapy to assess dose transition, adherence, satisfaction, and safety. The primary outcome was percentage of patients who properly transitioned to rivaroxaban once daily on day 22. **Results:** Twenty-five patients were enrolled; 12 received an R-PAK, whereas 13 comprised the control group. No difference in the baseline assessment of health literacy status was noted ($P = 1.00$). Proper transition to daily administration on day 22 was no different between the groups ($P = .891$). Adherence was reported in 99.8% of R-PAK patients and 97.65% of control patients ($P = .074$). Side effects were rarely reported. **Conclusions:** The use of an R-PAK for the treatment of VTE was not associated with an improvement in transition to daily administration; however, both groups had high rates of overall adherence. Pharmacist counseling/education was provided in both groups and is an important component to include in any patient discharge, especially for medications with dose transitions.

Keywords

anticoagulant, discharge counseling, patient education, rivaroxaban, transitions of care

Background

Venous thromboembolism (VTE) is a disorder in which fibrin and red blood cells clot in the veins at sites of blood stasis and vascular damage, manifesting as a deep vein thrombosis (DVT) and/or a pulmonary embolism (PE).¹ Nearly 30% of patients who experience a VTE event will have another thrombotic event within 10 years, most commonly occurring within 2 years of the index event.²

Current VTE guidelines recommend treatment with non-vitamin K oral anticoagulants (NOACs) including dabigatran, rivaroxaban, apixaban, or edoxaban over the vitamin K antagonist (VKA) warfarin for most patients without cancer.³ Although all of the NOACs come with unique dosing strategies, rivaroxaban requires a transition of dose and frequency that may affect a patient's ability to use the medication appropriately.⁴ For VTE, rivaroxaban is dosed at 15 mg by mouth twice daily for 21 days, and then transitioned to 20 mg by mouth once daily.³ Patients require 3 or more months of

therapy, depending on patient-specific factors.⁴ Rivaroxaban has an onset of action of 1 to 2 hours and a predictable dose response eliminating the need for bridging with a parenteral agent and therapeutic drug monitoring required with VKA treatment. This favorable pharmacokinetic profile may decrease the overall cost of therapy and improve patient satisfaction.⁴ In addition, based on the Anti-clot Treatment Scale

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(ACTS), rivaroxaban has been associated with a lower medical burden, higher perceived benefits, and improved treatment satisfaction by patients when compared with treatment involving a combination of low molecular weight heparin (LMWH) and VKA.⁵⁻⁷

Although the short onset and offset of action is often considered one of the greatest benefits of rivaroxaban, it may also pose a risk. Patients must remain adherent to the intended dosing regimen to remain fully anticoagulated.⁴ With a half-life of 5 to 9 hours in healthy adults, one missed dose could result in loss of anticoagulation and subsequently increase the patient's risk for a thrombotic event.⁴ In addition, the combination of a short half-life and the change of medication dosage and frequency required on day 22 may increase the likelihood for patient error, especially in patients with limited health literacy. An error made during this critical transition phase may increase the risk of patients to experience a recurrent VTE or major bleed. Although the literature examining adherence to NOACs for treatment of VTE is lacking, it is hypothesized that factors related to NOAC nonadherence include increased number and severity of comorbid conditions, lack of access to resources, low degree of patient education, and negative patient perceptions of drug therapy.⁸ One recent cohort study found that, when compared with pooled data of patients prescribed dabigatran, rivaroxaban, and apixaban, initiation of warfarin was associated with a lower probability of adhering to anticoagulation in patients with atrial fibrillation ($P < .001$).⁹ Consistent monitoring and follow-up are vital to ensure continued compliance and beneficial clinical outcomes. With nearly 36% of adults in the United States proposed to have limited health literacy, improved patient education for this high-risk medication is critical to allow ample opportunity for beneficial clinical outcomes.¹⁰

Although not specific to rivaroxaban and not statistically significant, a study by Shore and colleagues showed that pharmacist-led adverse event and adherence monitoring was associated with improved dabigatran adherence (RR, 1.25; 95% confidence interval [CI], 1.11-1.41, $p > 0.05$).¹¹ Collaboration with physicians to tailor monitoring to manage nonadherent patients was associated with higher adherence rates (RR 1.31; 95% CI, 1.16-1.47, $p > 0.05$). This finding suggests that multidisciplinary clinics with close monitoring and patient specific follow-up can improve medication adherence regardless of patient factors that may be nonmodifiable.¹¹

The Rivaroxaban Patient Assistance Kit (R-PAK) trial was designed to measure the ability of a novel discharge strategy to enhance the dose transition period and improve medication adherence, patient safety and satisfaction.

Methods

Study Design and Oversight

This is a prospective, randomized, single-center, active-treatment trial conducted at an 859-bed, comprehensive,

not-for-profit, community-teaching hospital in patients with confirmed symptomatic DVT and/or PE who were prescribed rivaroxaban. After obtaining informed consent, patients who met inclusion/exclusion criteria were assigned to either the standard rivaroxaban group with no discharge kit or to the rivaroxaban discharge kit (R-PAK) group. On the day of discharge, all patients received standardized verbal education by a pharmacist on rivaroxaban including indication, dosing regimen, administration, common adverse effects, and required monitoring. Patients were also given a written educational handout titled "A Patient's Guide to Rivaroxaban." Patients assigned to the R-PAK group were additionally given a rivaroxaban discharge kit, which consisted of a pillbox to organize medication doses based on the date of drug initiation and hospital discharge as well as a dose transition card.

Assignments were randomly allocated in blocks of 10 and investigators were blinded to the treatment group until the patient was enrolled. The study was supported by an internal institutional research fund. The investigators coordinated the trial and performed all statistics independently from the sponsors.

The investigators had final responsibility for the study design, clinical protocol, study oversight, and data verification and analyses. The protocol was reviewed and approved by all affiliated institutional review boards. Written informed consent was obtained from all patients. The data were collected and securely maintained by the investigators. The investigators wrote the manuscript and vouch for the accuracy and completeness of the reported data and analyses and the fidelity of the study to the protocol.

Recruitment

Using the electronic medical record and reporting system, a daily report was generated to identify patients diagnosed with a current VTE and prescribed rivaroxaban twice daily. An investigator confirmed all inclusion criteria were met and screened for exclusion criteria.

Study Subjects

Patients 18 years of age at the time of diagnosis, with one or more newly diagnosed acute VTE(s) treated with rivaroxaban were included in this study. Patients who met criteria and consented to participation for study entry were screened for health literacy using a single item-screening tool (Figure 1). Patients were screened for drug interactions and needed to consent to an outpatient follow-up phone call. Patients being discharged to long-term care facilities or skilled nursing facilities or on rivaroxaban prior to admission were excluded.

Intervention

Patients were randomized to receive verbal education by a pharmacist plus the R-PAK or to a control group to receive

Single Item Screening Tool

How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor or pharmacy?

(1) Never (2) Rarely (3) Sometimes (4) Often (5) Always

Figure 1. Single item-screening tool.

education by a pharmacist alone. The R-PAK included a reminder card stating the dates of dose transition and a customizable pillbox. Patients who received the R-PAK were taught how to properly fill and utilize the pillbox. All patients were educated on the indication, dosing regimen, adverse effects, and monitoring required for rivaroxaban as previously described. Additional details on the R-PAK and information provided to each patient has been previously published.¹²

Follow-up

Using a standardized questionnaire, patients were contacted via telephone after at least 22 days of therapy to assess the date of transition based on the date of initiation while hospitalized, medication adherence including missed doses and doses taken more than 12 hours from appropriate timing, treatment satisfaction (via ACTS), understanding of dosing regimen, and side effects. The ACTS is a validated tool used to assess patient benefit and burden associated with anticoagulation therapy; the burden portion of the scale ranges from 12 to 60, with higher scores indicating more treatment hindrance and the benefit portion ranges from 3 to 15, with higher scores indicating more treatment satisfaction.⁶ Each patient's pharmacy was also contacted to obtain a refill history for both strengths of rivaroxaban. Patients were considered lost to follow-up if they were unable to be contacted by phone after 5 attempts or if greater than 30 days of therapy had been completed prior to patient contact.

Outcome Assessment

The primary outcome of this trial was the percentage of patients who properly transitioned to rivaroxaban 20 mg once daily on day 22. Predefined secondary outcomes included total adherence, percentage of patients with greater than 90% adherence, percentage of patients who stopped rivaroxaban for any reason, patient understanding of correct dose and timing of medication, and overall satisfaction. Safety outcomes assessed self-reported side effects including minor bleeds, events that required contacting physician or visiting an emergency department, recurrent VTE, and death.

Statistical Analysis

Statistics were run utilizing the per-protocol principal. An alpha level of 0.05 was set a priori. The primary outcome

was analyzed using the Fisher exact test to assess the difference between the percentage of patients who properly transitioned to rivaroxaban 20 mg once daily on day 22 within the treatment and control group. A clinically significant difference was considered greater than or equal to 5% difference between groups. The Fisher exact test was used for nominal data, whereas the Mann-Whitney *U* and Student *t* tests were used for ordinal and continuous data, respectively.

Results

From October 2014 through April 2016, a total of 29 patients underwent randomization (Figure 2). Baseline characteristics, including data on indication and treatment with rivaroxaban, for the patients in this trial are shown in Table 1. There were no baseline statistical differences noted between treatment groups ($P > .05$). Eight (32%) patients enrolled had an indication of PE with DVT whereas 13 (52%) patients had a single diagnosis of PE alone; no difference was found between treatment groups. In addition, 13 (52%) of the thromboses were thought to be unprovoked in nature. Patients who were assigned the R-PAK received a median of 4 doses while hospitalized, whereas patients in the control group received 2 doses ($P = .47$). Twenty-five patients were contacted for follow-up; 3 patients were lost to follow-up and 1 patient declined consent for follow-up after enrollment. One patient in the R-PAK group, who verified full medication adherence to study investigators, discontinued therapy prematurely due to recurrent VTE.

Treatment

The primary outcome of proper transition on day 22 was observed in 67% of R-PAK patients and 69% of control patients ($P = .89$; Table 2). When assessed for understanding of dose and interval, 100% of patients in both arms were able to verbalize comprehension of the intended dosing regimen for rivaroxaban. Adherence to the dosing regimen was found in 99.8% of R-PAK and 97.65% of control patients ($P = .07$). Minor bleeding, defined as epistaxis or ecchymosis without a known cause, was reported in 1 R-PAK patient and 4 control patients ($P = .16$). No patients involved with the trial reported bleeding requiring medical attention or death. No difference was found between patients when reporting benefit or burden of therapy via ACTS ($P = .054$ and $P = .68$, respectively).

Discussion

To the investigators' knowledge, this is the first prospective study evaluating the implementation of a discharge kit to help facilitate the appropriate transition of rivaroxaban in the treatment of VTE. Although most patients were diagnosed with a PE, PE severity index (PESI) scores indicated low mortality risk among patients in both groups, correlating with the observation of a low number of in-hospital doses administered to

Figure 2. Patient enrollment.

Note. VTE = venous thromboembolism.

patients in each group, prior to being discharged. This study found that there was no difference in dose transition at day 22 to once daily therapy between treatment and control groups. However, there was a nonsignificant improvement in adherence, in favor of the R-PAK patients.

Adherence rates observed in our trial were found to be higher than those found in other trials assessing NOAC adherence.¹¹ Although average adherence rates among the NOACs have been shown to be greater than 80%, with rivaroxaban showing the greatest patient adherence, the adherence rates for this study were greater than 95%.⁸ One reason for the higher adherence rate found within our study could be due to the increased accountability and motivation the patients had knowing that pharmacists were going to follow up with them after 3 weeks of treatment. The high rate of adherence among our patients is supported by the low incidence of safety related outcomes that were reported by patients at follow-up. Possible reasons for the higher rate of adherence could be the high rate of health literacy seen in the sample population studied, with the majority of patients saying they rarely or never required help to read instructions, pamphlets, or other written materials from their doctor or pharmacy. Another hypothesis would be that focused education on the new medication about the indication and dosing by a pharmacist helped both groups. This explanation could further support the observation that 100% of patients understood the intended dosing regimen of rivaroxaban for treatment of their acute VTE.

When this project was initiated, Mercy Hospital St. Louis, a community-teaching hospital, had established protocols for

pharmacist-led discharge medication education on high-risk medications including dofetilide, enoxaparin and warfarin. With this project, we were able to expand pharmacist involvement in the discharge process to include individualized medication education for rivaroxaban. The investigators found that when asked, a majority of patients stated that they had received little to no education about rivaroxaban by their health care providers before pharmacist intervention, which often times occurred on the day of anticipated discharge.

Some aspects related to study methodology and potential limitations of the study require discussion. First, the lack of adequate sample size likely contributes to our inability to detect a difference in the primary and secondary outcomes. On analysis, a reverse power was calculated to be 3.6% and the study did not meet power to appropriately detect a difference between groups. Particular outcomes at high risk of type 2 error include total adherence, self-reported side effects, minor bleeding, and ACTS benefit score. Enrollment was limited by a large percentage of potential patients discharged to long-term care or skilled nursing facilities, a majority of VTE patients being treated with LMWH bridging to warfarin, and time constrictions.

This project may be hard to implement without pharmacists with time dedicated to enrolling and seeing patients. The time requirement to review patient charts for inclusion, set up the individualized R-PAK, and to educate the patients was substantial. However, in hospitals with pharmacists dedicated to discharge counseling and/or transitions of care, the ability to initiate and maintain these efforts may be more feasible.

Table 1. Baseline Characteristics.

	R-PAK n = 12	Control n = 13	P value
Age, mean, y	54	61	.20
Weight, mean, kg	111.3	96.9	.18
Male (%)	5 (42)	8 (62)	.32
Caucasian (%)	10 (83)	12 (92)	.49
No. of PTA medications, mean	5.3	5.6	.84
Health literacy score			1.00
At risk (%)	0 (0)	0 (0)	
Not at risk (%)	12 (100)	13 (100)	
Insurance (%)			.14
Uninsured	1 (8)	1 (8)	
Government	2 (17)	7 (54)	
Private	9 (75)	5 (38)	
History of VTE (%)	2 (17)	9 (69)	.41
History of cancer (%)	3 (25)	3 (23)	.91
History of heart failure (%)	0 (0)	1 (8)	.33
History of lung disease (%)	1 (8)	1 (8)	.49
Thrombophilia (%)	1 (8)	1 (8)	.95
Indication (%)			.29
PE only	4 (33)	9 (69)	
Distal DVT only	2 (17)	1 (8)	
Proximal DVT only	1 (8)	0 (0)	
PE + DVT	5 (42)	3 (23)	
PESI score, median	71	82	.69
Primary etiology (%)			.72
Unprovoked	5 (42)	8 (62)	
Recent surgery	4 (33)	4 (31)	
Immobilization	2 (17)	1 (8)	
Estrogen therapy	1 (8)	0 (0)	
Cancer	0 (0)	1 (8)	
Other	2 (17)	2 (15)	
Hgb, mean, g/dL	13	12.3	.53
Hct, mean (%)	36.3	35.9	.95
Platelets, mean, $\times 10^9/L$	237.9	285.8	.25
SCr, mean, mg/dL	0.87	0.93	.31

Note. R-PAK = Rivaroxaban Patient Assistance Kit; PTA = prior to admission; VTE = venous thromboembolism; PE = pulmonary embolism; DVT = deep vein thromboembolism; PESI = PE severity index; Hgb = hemoglobin; Hct = hematocrit; SCr = serum creatinine.

The study investigators also received a grant to help provide funds to obtain adequate supplies required for the implementation of this project. Without necessary funds and supplies, it may be hard to implement this project into other community and teaching hospitals. However, the benefit of compliance to the recommended treatment regimen likely outweighs the cost of the supplies required for the implementation of this project.

Another limitation was that patient recall was heavily relied on when performing the follow-up phone call, after at least 22 total days of therapy. This type of investigation could lead to both recall and/or reporting biases. Although the investigators attempted to reach every individual the day

Table 2. Results.

	R-PAK n = 12	Control n = 13	P value
Primary outcome			
Proper transition at day 22 (%)	8 (67)	9 (69)	.89
Secondary Outcome			
Understanding of dose/interval (%)	12 (100)	13 (100)	1.00
Total adherence, %	99.8	97.65	.07
$\geq 90\%$ adherence (%)	12 (100)	12 (92)	.33
Contacted by nurse prior to follow-up (%)	1 (8)	0 (0)	.29
Self-reported side effects (%)	0 (0)	3 (23)	.08
Self-reported VTE (%)	1 (8)	0 (0)	.29
Minor bleed (%)	1 (8)	4 (30)	.16
Bleed requiring medical attention (%)	0 (0)	0 (0)	1.00
VTE recurrence (%)	1 (8)	0 (0)	.29
Reported death (%)	0 (0)	0 (0)	1.00
Early discontinuation (%)	1 (8)	0 (0)	.29
ACTS benefit score, median	10	12	.05
ACTS burden score, median	15	15	.68
In-hospital doses, median	4	2	.47
Cost of hospitalization, mean (2016 dollars)	27,257.99	33,838.48	.48

Note. R-PAK = Rivaroxaban Patient Assistance Kit; VTE = venous thromboembolism; ACTS = Anti-clot Treatment Scale.

after transition, most patients could not be contacted on day 22 of therapy. The majority of patients were contacted within the 30-day time frame. However, the accuracy of data is more likely to be lost, the farther out the day of contact is from the day of transition.

A confounding factor presented in the Fall of 2015 when the investigators realized that many patients were being sent home with the Xarelto StarterPack™, produced by the manufacturer. The StarterPack™ contains 42 doses of 15 mg tablets, totaling 21 days of twice daily therapy, and 9 doses of 20 mg to help ease the transition between different dosage strengths and frequencies. Unlike the StarterPack™, the R-PAK can be customized for each specific patient by factoring in doses taken while hospitalized to individualize each patient's outpatient treatment regimen at discharge. A total of 6 patients, 2 patients in the R-PAK group and 4 patients in the control group, were prescribed the Xarelto StarterPack™ while 19 patients were sent home with 2 prescriptions (1 for 15 mg twice daily and 1 for 20 mg once daily) on hospital discharge. The education in this study was not appropriately tailored to the patients receiving the StarterPack™, as patients received an average of 4 days of therapy while hospitalized. As such, patients were not thoroughly educated to omit tablets contained within the StarterPack™ based on doses administered in the hospital, but all patients received education on

how many additional days of twice daily therapy they required on discharge. If it is known that the patient will be prescribed the StarterPack™, additional education as to how many tablets to omit should be provided. As this was felt to be no fault of the patient, patients were stated to be adherent if they followed the instructions of the StarterPack™, even if they took more than the recommended 21 days of twice daily dosing; however, the transition date (primary outcome) would not be deemed appropriate. There was no difference in patient compliance to the recommended dosing regimen between these 2 subsets of patients ($P = .94$). Thus, the StarterPack™ seemed to have little effect on overall patient adherence.

In addition, the study population included young and generally healthy adult patients with high health literacy. Although baseline characteristics were similar between groups, it is possible the benefits of the R-PAK would be better seen in patients with a higher risk of nonadherence or patients with lower baseline health literacy.

Conclusion

These results suggest that the further implementation of pharmacists into patient discharge may prove advantageous to provide continuity of care and improve patient satisfaction. The investigators believe the outcomes found in this trial may provide additional evidence that pharmacists can be relied on to educate patients effectively to ensure adequate understanding of medications before patient discharge. Pharmacist counseling/education is an important component to include in any patient discharge, especially for new medications and those that require high compliance or dose transitions.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Stacy serves as a consultant and speaker for Janssen Pharmaceuticals.

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