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Implementation and preliminary clinical outcomes of a pharmacist-managed venous thromboembolism clinic for patients treated with rivaroxaban post emergency department discharge

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Pharmacist-managed venous thromboembolism clinic for patients treated with rivaroxaban post emergency department discharge

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The authors [BMD, DMB, ZAW, KSD, CMD, ZAW, TAW] declare that they have no competing interests and have nothing to disclose with the exception of Jeffrey A. Kline. Dr. Kline serves as a consultant for Janssen Pharmaceuticals and Diagnostica Stago and has grants/research support from Mallinckrodt, NIH, and Roche Diagnostics.

**Abstract:**

**Objective.** To describe the implementation, work flow, and differences in outcomes

between a pharmacist-managed clinic for the outpatient treatment of venous

thromboembolism (VTE) using rivaroxaban versus care by a primary care provider.

**Interventions.** Patients in the studied health system that are diagnosed with low-risk VTE in the emergency department are often discharged without hospital admission. These patients are treated with rivaroxaban and follow up either in a pharmacist-managed VTE clinic or with their primary care provider. Pharmacists in the VTE clinic work independently under a collaborative practice agreement. An evaluation of thirty-four patients, seventeen in each treatment arm, was conducted to compare the differences in treatment-related outcomes of rivaroxaban when managed by a pharmacist versus a primary care provider.

**Results.** The primary endpoint was a six month composite of anticoagulation treatment-related complications that included a diagnosis of major bleeding, recurrent thromboembolism, or fatality due to either major bleeding or recurrent thromboembolism. Secondary endpoints included number of hospitalizations, adverse events, and medication

adherence. There was no difference in the primary endpoint between groups with one occurrence of the composite endpoint in each treatment arm ( $p=1.000$ ), both of which were recurrent thromboembolic events. Medication adherence assessment was formally performed in 8 patients in the pharmacist group versus 0 patients in the control group. No differences were seen amongst other secondary endpoints.

**Conclusions.** The pharmacist-managed clinic is a novel expansion of clinical pharmacy services that treats patients with low-risk VTEs with rivaroxaban in the outpatient setting. The evaluation of outcomes provides support that pharmacist-managed care utilizing standardized protocols under a collaborative practice agreement may be as safe as care by a primary care provider.

#### **Introduction:**

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), affects approximately 1 in 1000 people in the United States annually.<sup>1-2</sup>

Treatment consists of anticoagulation therapy, and evidence supports treating patients with low-risk VTEs as outpatients.<sup>3-5</sup> Novel oral anticoagulants such as rivaroxaban, an oral factor Xa inhibitor, are FDA approved for the treatment of VTE and serve as an alternative therapeutic option to a parenteral anticoagulant and warfarin, as it does not require bridging therapy. As demonstrated in the EINSTEIN clinical trial, benefits to using rivaroxaban for outpatient VTE therapy instead of warfarin include less frequent monitoring, less major bleeding, fewer drug interactions, and simpler dosing regimens.<sup>6</sup>

## Development of Outpatient Venous Thromboembolism Clinic

The outpatient VTE clinic, also known as the clot clinic, was originally developed by emergency department (ED) physicians in March of 2013 as an un-funded, ED fellowship research project. Protocols were established for the outpatient treatment of VTE that included initial clinic visits between two and five weeks to establish care and again three to six months after diagnosis to determine duration of therapy. In anticipation of the fellows' graduation, the physicians engaged the pharmacy department for assistance with transitioning the clinic's management to clinical pharmacists. During a six month overlap period, internal medicine and critical care-trained clinical pharmacists shadowed, trained, and created a hospital leadership approved collaborative practice agreement outlining specific protocols and medication management procedures. Upon completion of the fellowship, pharmacy assumed the responsibilities of the clot clinic as an opportunity to expand outpatient clinical pharmacy services. After clinic implementation, pharmacists performed a study evaluating the difference in outcomes between the outpatient treatment of VTE with rivaroxaban in the pharmacist-managed clinic versus management by a primary care provider (PCP).

### **Methods:**

#### Study Setting

The clot clinic is located within an academic, safety-net, level 1 trauma center in a metropolitan city. The clinic takes place once monthly for four hours and provides services for up to twelve outpatients with low-risk VTE treated with rivaroxaban. The two clinical

pharmacists that manage the clot clinic and facilitate patient visits dedicate this time in addition to their normal, full-time jobs providing clinical pharmacy support to internal medicine and critical care teams. This equates to a combined total of 0.05 FTE monthly.

### Study Design

This prospective, observational cohort study evaluated the difference in outcomes between the outpatient treatment of VTE with rivaroxaban in a pharmacist-managed clinic versus management by a PCP. Outcomes were evaluated for patients seen between April 2015 and September 2015. The protocol was approved by the Indiana University Health Institutional Review Board prior to initiation of the study.

Patients in the pharmacist-managed group were diagnosed by a physician with a low-risk VTE based on the absence of any Hestia criteria in the ED.<sup>7</sup> For example, patients eligible for referral were required to have normal renal function (creatinine clearance > 30 ml/min), a systolic blood pressure above 100 mm Hg and a pulse oximetry reading above 94%, did not warrant admission for other medical or social conditions, and were not exhibiting coagulopathy based on international normalized ratio (INR) for the prothrombin time (PT) and had a normal platelet count. After diagnosis and ensuring eligibility criteria were met, patients were discharged from the ED with a prescription for rivaroxaban and a clot clinic appointment scheduled within one month from presentation. As a safety-net health-system, all referred patients are evaluated in clot clinic, regardless of payor source or insurance status.

Comparator group patients were selected using the hospital system's outpatient pharmacy dispense records. From the list of rivaroxaban prescriptions filled, patients were evaluated using the hospital's electronic medical record system and were included for potential matching if rivaroxaban was being used to treat a VTE. Once identified for potential matching, the control group patient was matched with a pharmacist-managed patient if they met all the following criteria: month and year of rivaroxaban initiation, age (same decade of life), and sex.

#### Study Protocol

The clot clinic pharmacist is able to order laboratory tests and manage medications in accordance with the collaborative practice agreement (CPA) between the clot clinic physicians and pharmacist. Laboratory tests including anti-Xa levels, basic metabolic panels, complete blood counts, D-dimers, and PT/INRs can be ordered based on the patient's history, presentation, or potential drug-drug interactions. Aspirin is considered an independent privilege, meaning it can be started, renewed, adjusted, or discontinued by the pharmacist. The pharmacist can renew, adjust, or discontinue rivaroxaban, warfarin, and enoxaparin prescriptions if originally prescribed by a physician. Any ED physician can write the original prescriptions for patients treated in the pharmacist-managed clinic. Prothrombin complex concentrate (PCC) and vitamin K can only be prescribed after provider consultation (but has not been used in any case).

Patient information collected at the pharmacist-managed clinic visit is summarized in Table

1. Prior to seeing the patient, the pharmacist reviews the patient's electronic medical record to analyze VTE diagnosis, laboratory data, and medication list. During each visit, the pharmacist identifies VTE symptoms, performs a focused physical exam (e.g. skin assessment, calf measurements, and pain evaluation), and evaluates for post-thrombotic syndrome (a syndrome resulting from thrombotic venous scarring and valve destruction leading to long term pain and changes in blood flow).<sup>8,9</sup> Assessment of adherence is performed using the 4-item Modified Morisky Adherence Scale, a validated questionnaire tool for measuring medication adherence.<sup>10</sup> Patients are counseled on laboratory results, medication use, adherence, side effects, drug interactions, lifestyle modifications, smoking cessation, and other issues as they arise. The pharmacist determines the duration of therapy, in alignment with the CHEST guidelines, primarily based on patient biological sex, location and nature of clot (i.e. DVT or PE, provoked or unprovoked) and if the patient has prior history of VTE. D-dimer concentrations can be used to help determine appropriate therapy duration in uncertain cases.<sup>11,12</sup> A unique contribution to clinic services provided by the pharmacists includes assistance with navigating insurance-related issues including prior authorizations, patient assistance programs, and other sources of sustainable funding to facilitate medication access and ensure completion of therapy.

## Outcomes

The primary outcome was the composite occurrence of anticoagulation treatment-related complications defined as an episode of major bleeding, recurrent thromboembolic event, or fatal event due to either bleeding or thromboembolism within six months of the original VTE

diagnosis. The study defined major bleeding using the International Society for Thrombosis and Hemostasis definition of greater than or equal to a 2 g/dL reduction in hemoglobin or greater than or equal to 2 units of blood transfusion, bleeding in a critical area, or bleeding contributing to death.<sup>13</sup> Secondary endpoints included individual components of the primary outcome, number of hospitalizations after VTE diagnosis, adverse events, and Morisky medication adherence score.

#### Data Analysis

Statistical tests were performed using Minitab® 16 statistical software (Minitab Inc., State College, PA). Normally distributed data were reported with mean (standard deviation), whereas non-normally distributed data were reported with median (interquartile range). Normality was tested using the Anderson-Darling Normality Test. The student's t-test was used to detect differences between normally distributed continuous data. For continuous data that was not normally distributed, a Mann-Whitney U test was used to examine potential differences. The Fisher's exact or Chi-square tests were used to detect differences in nominal data. The significance level (alpha) was pre-determined to be less than 0.05. A sample size calculation was not conducted as this was a convenience sample limited to the number of patients seen and treated in the described clinic with a corresponding number of control patients.

## Results:

Seventeen patients were seen in the pharmacist-managed clinic during the six-month study period. The mean patient age was 50 ( $\pm 12$ ) years, and six patients were male (35%).

Seventeen patients served as matching cohorts in the control group with a mean patient age of 54 ( $\pm 12$ ) years, six of whom were male (35%). Patients were well-matched in terms of age, gender, weight, smoking status, and occurrence of either DVT and/or PE. Complete demographic information is summarized in Table 2.

### *Primary Outcome*

There was one occurrence (6%) of the composite primary endpoint in each study arm, each of which were due to recurrent thromboembolic events ( $p=1.000$ ). These events were within the first six months of original VTE diagnosis and both were recurrent DVTs.

### *Secondary Outcomes*

All secondary outcomes are summarized in Table 3. There was one instance (6%) of VTE-related hospitalization in each study arm ( $p=1.000$ ). All other hospitalizations were not related to the patients' VTE diagnosis or treatment. Adverse events described by patients included pain, headache, and minor bleeding including menorrhagia. Overall, there were seven (41%) reported adverse events in the pharmacist care group and four (24%) in the control group ( $p=0.465$ ).

Pharmacists began using the Modified Morisky Adherence Scale to formally evaluate medication adherence three months after starting in the clot clinic since it had not been studied in this patient population to our knowledge. While this could influence the secondary endpoint of medication adherence, it was determined to be a necessary part of our study protocol because a lack of adherence could negatively affect patient care, directly impacting the primary outcome. All patients assessed (n=8) had a score of 0 or 1, signifying high adherence. Although a few PCP notes commented on a patient's medication adherence informally, no patients in the control group had a documented assessment of medication adherence using a formal tool. The lack of formal assessment in the control group could represent a confounder to the results.

#### **Discussion:**

Pharmacists have demonstrated the importance of their role in the outpatient health care setting based on studies showing improved patient outcomes, medication adherence, and compliance to evidence-based guidelines. Examples include increased percentage of patients on optimally dosed heart failure medications, increased medication adherence leading to decreased heart failure-related ED visits, increased percentage of patients with hypertension achieving goal blood pressures, and decreases in hemoglobin A1c in patients with diabetes.<sup>14-17</sup> Previously published studies on pharmacist-managed warfarin clinics describe the pharmacist's ability to achieve goal INRs more frequently than PCPs, improve patient satisfaction scores, and decrease costs by optimizing the number of INRs checked.<sup>18-</sup>

<sup>20</sup> The pharmacist-managed clot clinic is a unique expansion of outpatient clinical pharmacy services. In the clot clinic, not only are pharmacists managing and monitoring

anticoagulants, they are also independently managing VTE treatment duration, assessing adherence, and ensuring sustainability of drug therapy.

This study compares patient outcomes in the pharmacist-managed clinic versus those managed by a PCP. Because the pharmacist-managed clinic is the only formalized outpatient service treating patients with low-risk VTE, there were challenges in selecting a control group. A few control group patients were hospitalized as a result of their original VTE diagnosis, potentially selecting for a higher-risk control group. It was not possible to retrospectively evaluate the severity of VTE using the Hestia criteria in the control group due to documentation limitations in the electronic medical record. Restrictive, pre-determined inclusion criteria were used for control group patients to ensure they were matched as closely as possible with intervention group patients. The goal of a matched control group was to minimize confounders allowing for a more accurate comparison of pharmacist-managed versus PCP-managed care.

Although a power calculation was not performed due to the convenience sample of our study, the primary outcome indicated pharmacist-managed care was potentially as safe as care by a PCP and helped justify long-term pharmacist management in the clinic. The similar secondary outcome results further support the safety of a pharmacist-managed clinic. A post-hoc power calculation demonstrated that in order to achieve 80% power to detect at least a 10% difference in the primary outcome between study groups, 153 patients would

need to be enrolled in each arm of the study. Based on current enrollment rates, this would take at least 6 years with our single center.

There were a higher number of documented adverse events noted in the pharmacist-managed group, which could be due to recall bias. However, given the small number of events overall, this may have been due to differences in the questions asked to the patient and documentation practices. By using a standardized question list and note template, pharmacists ensured they would not omit asking about or reporting adverse events.

Menorrhagia was the most common adverse event reported by female patients in the clot clinic. To address this concern, the pharmacist-managed protocol specifies holding no more than one dose of rivaroxaban if the patient has heavy uterine bleeding (i.e. menstrual bleeding considered heavy by the patient and lasting five or more days, or two consecutive days requiring ten or more pads).

There are several strengths and limitations of our study. Strengths include the unique expansion of clinical pharmacy services in a safety-net healthcare system, use of a matched control group, prospective data collection related to VTE outcomes, and the use of a verified tool to evaluate medication adherence in the intervention group. An additional strength evident in the study due to clinical pharmacist involvement includes detailed medication profile reviews which encompass formal drug-drug interaction screening, side effect evaluation, and renal dose adjustments. Pharmacists also spend a significant portion of each clinic appointment counseling and educating patients on medication use, disease state,

lifestyle modifications, and smoking cessation if applicable. Limitations include slow patient recruitment at the start of the study, limited ability to determine the true rate of adverse events due to variation in documentation practices, and the use of only one anticoagulant in the clinic. All of these may have contributed to our small sample size and the inability to achieve power, as highlighted above. The retrospective nature of the data collection in the control group has the potential to bias results due to potential lack of documentation by the PCP. While most of these limitations are unavoidable, clinic volumes have since increased and pharmacists have added apixaban to their CPA to broaden the list of anticoagulants that can be prescribed. The small size of the convenience sample included in our study made statistical analysis demonstrating significance difficult which could have resulted in a type II error. Also, while we attempted to control for confounders by matching patients to historical controls, using a propensity score may allow for a more rigorous comparison in a future study utilizing a larger sample size. However, our results should be seen as hypothesis-generating, warranting further studies with larger patient populations or across multiple sites.

#### *Financial Justification of Services*

Outpatient treatment of VTE using rivaroxaban can result in significant cost savings. In a previously published evaluation of low-risk VTE outpatient treatment costs for 97 patients within the same study institution, the median cost for the first six months of care for patients treated with enoxaparin and warfarin was \$9,016 [interquartile range (IQR) = \$3,535 to \$10,622] versus \$5,932 (IQR = \$4,745 to \$8,594) with rivaroxaban (n=45). This six-month median difference per patient of \$3,084 approximates \$515 of cost savings per

month of VTE treatment using rivaroxaban instead of enoxaparin and warfarin.<sup>21</sup> We hypothesize that the cost savings associated with outpatient treatment of VTE using rivaroxaban, as compared to warfarin, is due to the decreased need for laboratory monitoring and subsequent provider visits.

During the first 10 months of pharmacist-management in clinic, 27 unique outpatients were treated though not all were included in the data analysis due to not being six months from diagnosis. Amongst these patients, there were 182 treatment months which yields an estimated \$93,730 of cost savings for VTE treatment using rivaroxaban instead of enoxaparin and warfarin (based on the cost savings described above).<sup>21</sup> It is important to note that this cost savings originates from the ED physician's decision to treat the patient with a low-risk VTE as an outpatient. With this decision, cost savings allowed for resources to be allocated toward the expansion of clinical pharmacy services, into the clot clinic. Additional savings could be realized when comparing the salaries and benefits required for clinical pharmacist hours versus primary care provider hours spent in clinic. As the time spent per patient visit was not documented in either group, and due to the retrospective nature of this study, this was not included in the estimate above.

**Conclusions:**

The pharmacist-managed VTE clinic using non-warfarin oral anticoagulants is a unique expansion of pharmacy services not yet described in the literature. Pharmacists are now independently managing all clot clinic patient care activities under a CPA, and have

expanded responsibilities to include apixaban. Pharmacists contribute distinct insight to clot clinic patient care by performing detailed reviews of medication lists, screening for drug interactions, counseling on adherence and disease state education, and ensuring sustainable access to their medication for the complete duration of therapy. Future directions include evaluating outcomes with a larger sample size, matching patients to controls using a propensity score, and conducting a survey to assess patient and provider satisfaction with the pharmacist-managed clot clinic. This study supports the expansion of pharmacy services in the clot clinic to promote safety, efficacy, and cost savings.

**Tables:**

Table 1. Patient Information Collected and Documented During Clinic Visits

- Name
- Age
- Gender
- Serum creatinine/creatinine clearance
- Diagnosis (deep vein thrombosis/pulmonary embolism) and date of diagnosis
- Provoked or unprovoked VTE
- Previous doppler date and findings
- D-dimer trends
- Pertinent past medical history
- Family or personal history of clots

- Smoking status
- Patient's primary care provider
- Current symptoms: pain, shortness of breath, chest pain, coughing, weight changes, bleeding symptoms
- Leg exam: level of swelling, calf measurements, ulceration presence, pigmentation changes
- Medication information: concomitant anticoagulants, rivaroxaban start date, last rivaroxaban fill date, frequency in which patient takes rivaroxaban, current dosing, missed doses, pharmacy used, insurance coverage, assessment of medication adherence
- Duration of rivaroxaban therapy

Table 2. Demographic Information

Demographic Information (N=34)	Pharmacist-managed Care Group (n=17)	Primary Care Provider Group (n=17)	<i>P Value</i>
Age (years), mean (SD)	50 (12)	54(12)	0.333
Male, n (%)	6 (35%)	6 (35%)	1.000
Weight (kg), median (IQR)	104 (90-121)	83 (68-112)	0.098
CrCl (mL/min), median (IQR) <sup>a</sup>	120 (120-120)	83 (68-112)	0.014
CrCl (mL/min), median (IQR) <sup>b</sup>	81 (73-99)	69 (65-90)	0.215

<b>Smoker, n (%)</b>	5 (29%)	2 (12%)	0.215
<b>DVT occurrence, n (%)</b>	14 (82%)	15 (88%)	0.398
<b>PE occurrence, n (%)</b>	4 (24%)	5 (29%)	1.000
<b>Both DVT and PE occurrence, n (%)</b>	1 (6%)	3 (18%)	0.601

<sup>a</sup> Calculated using actual body weight per prescribing information recommendations

<sup>b</sup> Calculated using ideal body weight per Cockcroft-Gault creatinine clearance equation

Table 3. Secondary Outcomes Results

<b>Secondary Endpoints (N=34)</b>	<b>Pharmacist Care (n=17)</b>	<b>Primary Care Provider Group (n=17)</b>	<b>P-Value</b>
<b>Number of hospitalizations, n</b>	5	3	0.688
<b>VTE-related, n</b>	1	1	1.000
<b>Thromboembolic event, n (%)</b>	1 (6%)	1 (6%)	1.000
<b>Fatality due to thromboembolism or bleeding, n (%)</b>	0 (0%)	0 (0%)	1.000
<b>Major bleeding, n (%)</b>	0 (0%)	0 (0%)	1.000
<b>Adverse events, n (%)</b>	7 (41%)	4 (24%)	0.465

<b>Formal medication adherence evaluation performed, n (%)</b>	8 (47%)	0 (0%)	0.003
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<sup>a</sup> Morisky Adherence Questionnaire score ranges from 0-8. A score of 0 indicates high adherence. A score of 1-2 indicates medium adherence. A score of >2 indicates low adherence.<sup>10</sup>

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