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Monotherapy anticoagulation to expedite home treatment of patients diagnosed with venous thromboembolism in the emergency department: a pragmatic effectiveness trial

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Abstract

Background: The objective was to test if low-risk emergency department patients with VTE (including venous thrombosis and pulmonary embolism [PE]) can be safely and effectively treated at home with direct acting oral (monotherapy) anticoagulation in a large-scale, real-world pragmatic effectiveness trial.

Methods.—This was a single-arm trial, conducted from 2016–2019 in accordance with the Standards for Reporting Implementation Studies (StaRI) guideline in 33 EDs in the US. Participants had newly diagnosed VTE with low risk of death based upon either the modified Hestia criteria, or physician judgment plus the simplified PE severity index score of zero, together with non-high bleeding risk were eligible. Patients had to be discharged within 24 hours of triage and treated with either apixaban or rivaroxaban. Effectiveness was defined by the primary efficacy and safety outcomes, image-proven recurrent VTE and bleeding requiring hospitalization >24 hours, respectively, with an upper limit of the 95% confidence interval (CI) for the 30-day frequency of VTE recurrence below 2.0% for both outcomes.

Results: We enrolled 1421 patients with complete outcomes data, including 903 with venous thrombosis and 518 with PE. The recurrent VTE requiring hospitalization occurred in 14/1421 (1.0%, 95% CI 0.5–1.7%), and bleeding requiring hospitalization occurred in 12/1421 (0.8%, 0.4–1.5%). The rate of severe bleeding using ISTH criteria was 2/1421 (0.1%, 0–0.5%). No patient died, and serious adverse events occurred in 2.5% of venous thrombosis patients and 2.3% of PE patients. Medication non-adherence was reported by patients in 8.0% (6.6–9.5%), and was associated with a risk ratio of 6.0 (2.3 to 15.2) for VTE recurrence. Among all patients diagnosed with VTE in the ED during the period of study, 18% of venous thrombosis patients and 10% of PE patients were enrolled.

Conclusions: Monotherapy treatment of low risk patients with venous thrombosis or PE in the ED setting produced a low rate of bleeding and VTE recurrence but may be underused. Patients with venous thrombosis and PE should undergo risk-stratification prior to home treatment. Improved patient adherence may reduce rate of recurrent VTE.

Registration: ClinicalTrials.gov; NCT03404635

Keywords

anticoagulant drugs; hemorrhage; bleeding; emergency medicine; autonomy; anticoagulation; recurrent venous thromboembolism; implementation science; translational medical research; outcomes research

INTRODUCTION

Monotherapy anticoagulation using direct acting oral anticoagulants (DOACs) has gained attention as a method to facilitate home-based treatment of low-risk patients in the emergency department (ED) setting who are diagnosed with venous thromboembolism (VTE), including both venous thrombosis (which includes both deep vein thrombosis (DVT) and saphenous vein thrombosis) and pulmonary embolism (PE).[1] Early discharge of DVT is widely considered standard of care regardless of the anticoagulant regimen. Bolstered by data from seven randomized controlled trials, the home treatment of DVT for low-risk

patients has been suggested to be a best practice in clinical practice guidelines and published systematic reviews.[2–4] Despite these recommendations, literature reporting translation of these recommendations into practice have reported modest success for home treatment of DVT, even in the era of DOACs.[1, 5–7] The translation of home treatment of PE into practice has been slower. In the absence of an institutionally supported clinical pathway, and with limited evidence of efficacy and safety, many emergency clinicians remain wary of discharging patients with PE.[8] Only two randomized controlled trials have compared outcomes of treatment of PE at home versus in-hospital, and only one of these studies employed a DOAC as the anticoagulant.[9] Nonetheless, two clinical practice guidelines have endorsed outpatient treatment of low-risk patients with PE.[2, 10] Toward the goal of implementation, Vinson et al. randomized 21 sites in the Kaiser health system to either receive a targeted implementation strategy for outpatient treatment of PE (n=11 sites) or usual care (n=10), and found that implementation of the protocol resulted in 28% of eligible ED patients with PE being treated at home with the intervention, representing a 13% increase compared with hospitals using usual care.[11] That study used vitamin K antagonists (VKAs) as the primary modality of anticoagulation.

Thus in 2021, no multicenter data have been forwarded to evaluate the efficacy and safety of an outpatient treatment protocol that employs DOACs to treat both venous thrombosis and PE in the ED setting. This report presents the results of the implementation trial, Monotherapy Anticoagulation To expedite Home treatment of VTE (MATH VTE). The detailed rationale and methods of this trial have been previously published.[12] This pragmatic trial was designed with three underlying theoretical constructs: 1. The effectiveness of the protocol will be defined by its ability to prevent new or recurrent VTE whilst avoiding risk of bleeding in the short term after discharge; 2. Low-risk patients with VTE will benefit from home treatment;[8, 13] and 3. Patients with both venous thrombosis and PE should be risk-stratified identically, given that 1/3 of patients with DVT have undetected PE at the time of diagnosis, and proximal DVT can produce PE in any instant, and fewer than 50% of patients with DVT diagnosed in the ED are treated at home.[1, 5–7, 14, 15]

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request to the corresponding author.

Overview

This was a single-arm, multicenter study designed to be responsive to the data elements in the Standards in Reporting of Implementation (STARi) guidelines checklist (NCT03404635).[16, 17] We undertook a multifaceted approach to enhance behavior change, including education (didactic session and publications), advertisement (placards), electronic order sets, change in culture (multidisciplinary acceptance of sending DVT and PE home), system changes (prespecified clinical follow-up), and research procedures (IRB approval, protocolized data collection and archiving, 30 day follow-up).[16, 18] All sites obtained approval from local institutional review boards (IRB) prior to site initiation. We aimed to measure outcomes that include efficacy (VTE recurrence rate), safety (bleeding) with a

heterogenous group of providers with minimal training, with minimal exclusion criteria, and across a wide geography, the investigators view this as a real-world effectiveness trial.

Among all participating sites, only three (Indiana University School of Medicine, Intermountain Health and University of Colorado) had pre-existing protocols that guided the home treatment patients with DVT or PE on DOACs. Outcomes of patients treated with these protocols were previously published.[1, 19] For other sites, essentially no patients were treated with DOACs as outpatients.

Patient selection

Inclusion criteria required patients to be over the age of 18 years with image-proven venous thrombosis or PE in the ED setting. The diagnosis of PE or venous thrombosis required a positive interpretation of either a pulmonary vascular imaging method or venous ultrasound by a board-certified radiologist. Patients could have a filling defect interpreted as acute PE in any pulmonary vessel, and thrombosis in any vein in an extremity or a jugular vein, with any degree of chronicity (i.e., acute or chronic clot), as long as in the opinion of the clinician, the patient required systemic anticoagulation. We allowed isolated saphenous vein thrombosis as an inclusion, as prior clinical practice guidelines and expert recommendations published shortly before the trial began recommended anticoagulation under certain circumstances.[20, 21] Exclusions included current use of full-dose anticoagulation, known pregnancy, any contraindication listed on the label for either apixaban or rivaroxaban (active bleeding or known hypersensitivity to the drug) or high bleeding risk. Patients referred from an outside facility with imaging performed elsewhere were eligible. To assess bleeding risk as non-high, clinicians could use their own unstructured estimate of a non-high probability of bleeding in 30 days, or define low risk using the method of Ruiz-Gimenez, which the protocol suggested as an alternative.[22] Eligibility required that the patient be deemed low risk of adverse outcomes by either the modified Hestia criteria as previously defined or clinical judgment plus all items negative on the simplified Pulmonary Embolism Severity Index (sPESI).[12] For patients with active cancer (defined as “currently under the care of an oncologist”), the protocol suggested that patients be excluded if they had a probability of death >5%, as estimated by the prediction of mortality from pulmonary embolism in cancer (POMPE-C) tool.[12, 23] All patients had to be discharged from either the ED, or an ED managed observation unit <24 hours from the time of registration at ED triage.

Primary outcomes

Clinical effectiveness was defined as the composite of a treatment efficacy outcome and a safety outcome as previously defined in detail.[12] The primary treatment efficacy outcome was a point estimate of the 30 day frequency of recurrent or new VTE requiring hospitalization >24 hours, with an associated upper limit 95% confidence interval, calculated from exact binomial formula, below 2.0%.[19, 24, 25] The primary outcome for safety was the point estimate of the 30-day frequency of bleeding requiring hospitalization >24 hours, with an associated upper limit 95% confidence interval below 2.0%.[19, 24, 25] The data collection form (available from corresponding author on request) was designed to measure the 30-day frequency of six other secondary outcomes: 1. The rate of International Society for Thrombosis and Haemostasis (ISTH)-defined major hemorrhage[26]; 2.

Discontinuation of the prescribed DOAC as indicated by the patient or electronic medical record; 3. Patient-reported unscheduled emergency department (ED) or clinic visit; 4. Hospitalization > 24 hours for any reason; 5. Patient reported bleeding requiring any unscheduled medical care (meeting a criterion necessary for the ISTH definition of clinically relevant non-major hemorrhage)[27]; 6. Any event satisfying the Good Clinical Practice/ International Committee on Harmonization definition of a serious adverse event.[28]

Source of funding

This work was funded by two separate investigator-initiated studies (IIS) awards from pharmaceutical companies, first from Pfizer-BMS, and later from Janssen Scientific Affairs, LLC. All funding went to Indiana University School of Medicine. None of the investigators received money for the work, and none of the investigators are paid consultants or serve on speaker's bureaus for the companies. Both IIS applications were written and submitted by an author (JAK) in 2015. The funding sources otherwise had no role in study design, inclusion criteria, outcomes, project management, the choice of sites, protocol execution or data collection. Each contract specified that the sponsor of record was Indiana University. Sites were paid by Indiana University on a capitated basis based upon patient enrollment milestones.

Plan for protocol implementation

In April 2016 the first of 33 sites were onboarded, with the last initiated in March 2019. To facilitate a multifaceted approach, study site investigators, research staff, staff physicians and residents were provided the protocol, guidance document and other educational materials in advance of site qualification. The research team ensured that both apixaban and rivaroxaban were included as preferred drugs by state Medicaid agencies. Site investigators engaged ED stakeholders (pharmacists, social workers and case managers) in advance to streamline help with qualification from either the Johnson and Johnson Patient Assistance Foundation or the Bristol Meyers Squibb Patient Assistance Foundation to provide free drug to patients without insurance. Site investigators were encouraged to contact representatives of other specialties (e.g., hematology, pulmonology and family medicine) to gather their input and plan for patient clinical follow-up. The study principal investigator traveled to all participating institutions to qualify the sites; deliver a Powerpoint® lecture to introduce the protocol (attendees were at least the research team, and often included residents and staff physicians in a "grand rounds" format); and meet and train site principal investigators, emergency physicians and research personnel on the implementation of the protocol. All sites posted placards in the ED and/or physician offices, and made announcements at faculty and resident meeting to introduce protocol. To facilitate adoption post-initiation, research team members sent emails to physicians of patients who were discovered to be eligible, but who were admitted to remind them of the protocol's existence. Each site developed a specific order set for their electronic medical record (EMR) for the MATH-VTE study, with examples provided in the protocol publication.[12] The initial duration of anticoagulation the ED prescription was suggested to be a minimum of three months for all thromboses.[2] Patients were instructed to follow-up with either their primary care provider or specific thrombosis clinics within 30 days.

Methods of assessing outcomes

The primary efficacy and safety outcomes are assessed from three sources: 1. From patient follow-up at dedicated clinic visit results (which require a qualified health care provider to specifically complete a data form to assess for the primary outcomes), 2. Medical record review and 3. Telephone call at or after 30 days. These sources were used to determine any unscheduled visit to an emergency department or other healthcare provider, re-hospitalizations, with directed questioning about VTE diagnoses, or bleeding events. Details of procedures for follow-up, including the script for the phone call, handling disconnected numbers, and non-answers were addressed in a detailed guidance document which was previously published.[12]

The definitions of new or recurrent VTE were based upon chart review to confirm suspected recurrent PE or DVT, and the requirement of explicit radiographic or ultrasonic evidence of PE/DVT.[12] The definition of re-hospitalization for bleeding required chart review demonstrating explicit written decision-making by the admitting emergency physician that a patient was admitted (requiring >24 hour stay) for medical or procedural care to manage objective or suspected bleeding. To assess secondary objectives, study associates use a combination of patient report and medical record documentation, for example, to determine if patients discontinued rivaroxaban or apixaban and why. To better understand reasons for non-adherence at 30 days, patients who indicated they either never filled or discontinued the initial DOAC prescription were asked to explain why, and their answer was recorded verbatim in the electronic data collection form (REDCap®) and this text was later categorized into discrete explanatory themes.[12]

To assess the frequency with which the protocol was used among patients with VTE, we used administrative data (e.g., international classification of disease codes) to determine the total number of patients diagnosed with PE and DVT in the EDs during the period of enrollment, and use these data as the denominator.

Statistical Analysis Methods

The primary analysis consisted of the point-estimate of the treatment efficacy outcome (either new or recurrent VTE) and treatment safety outcome (bleeding requiring hospitalization) at 30 days with 95% confidence intervals (CIs), calculated from the exact binomial formula. The definition of study success requires both the efficacy and safety outcomes have upper limits of the 95% CI below 2.0%, calculated from the exact binomial method. Other secondary outcomes were similarly analyzed. Confidence intervals were calculated using StatsDirect v 3.2.8 (Cheshire, England). Graphs plotting the frequency of veins (for DVT diagnoses) and pulmonary arteries affected (for PE diagnoses) were produced with GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA.

A minimum sample size of 1300 patients was estimated by iterative analysis using the method of Arkin et al to produce upper limit 95% CI below 2.0% using assumptions of the point estimate proportions of the efficacy and safety outcomes ranging from best case (0.1%) to worst case (1.5%).[29] Thus, with 1300 subjects, trial success required that within

30 days, fewer than 17 patients could be hospitalized with new or recurrent VTE, and fewer than 17 patients could be hospitalized with bleeding.

RESULTS

Overview of enrollment

The implementation was initiated in April 2016, starting in Indianapolis. All 33 sites were enrolling as of March 2019. The sample size of 1300 was reached in January 2020, but sites were allowed to enroll until March 2020 as data verification and cleaning proceeded. This resulted in 1434 patients enrolled. Thirteen participants voluntarily withdrew prior to the 30-day endpoint, leaving 1421 patients available for analysis for the primary efficacy and safety outcomes (Figure 1). Apixaban was prescribed as the initial anticoagulant in 1027 participants (73%) and rivaroxaban in 394 participants (27%). Physicians used the modified Hestia criteria as the method of risk stratification in 753 (53%) patients and clinical judgment plus sPESI in the remainder. At the time of enrollment, PE without DVT was diagnosed in 480 (34%) participants, and PE with DVT was diagnosed in 38 (2.7%) participants. Hereafter, these 518 (36%) patients are referred to as having PE. Venous thrombosis without PE was diagnosed 903 (64%) patients. In all but one participant who had a high probability ventilation-perfusion scintillation lung scan, the diagnosis of PE was made on computed tomographic pulmonary angiography. To determine the percentage of patients diagnosed with VTE during the study period who were treated with the pathway, we considered patients with PE and DVT as PE patients. With this assumption, 10% of all patients diagnosed with PE (range 0–24%) and 18% of all patients diagnosed with venous thrombosis (range 5–50%) in the 33 EDs during the periods of enrollment at each hospital were enrolled.

Anatomic locations of clots

Figure 2 shows the anatomical distribution of pulmonary artery filling defects as read by a board-certified radiologist. Regarding the range of PE size from low to high, 41 patients (8%) had isolated subsegmental PE, and 27 (5%) had bilateral main pulmonary artery PE, 207 had at least one lobar artery affected, and 243 had at least one segmental filling defect. The diagnosis of venous thrombosis was made in all cases with compression ultrasound and Figure 3 shows the distribution of veins affected, and the impression of whether the clot was chronic or acute. Regarding range of venous thrombosis size from low to high, only the saphenous vein was affected in 55 (6% of all venous thrombosis participants) and only one or more calf veins were affected 164 (18% of all venous thrombosis participants), whereas 168 (19%) had abnormal compressibility in the iliofemoral venous system.

Clinical features of patients

Table 1 shows the clinical features of the 1421 participants, including demographic information and potential factors that increase VTE risk, stratified by PE versus DVT diagnosis. Biomarkers are absent from Table 1 because of large numbers of missing data. For example, troponin was measured in only 327 patients. Table 1 suggests that the difference in proportions of higher risk features were small (i.e., <5% difference) between PE and venous thrombosis patients with the exception of prior VTE, which was present in

63% of PE participants, compared with 21% of venous thrombosis patients. Although at site training, we recommended against enrolling patients taking CYP 3A4 inhibitors, eleven patients who were being treated for human immunodeficiency virus infection were enrolled, and 10 were prescribed apixaban and one was prescribed rivaroxaban.

Outcomes

Table 2 presents the primary efficacy data, and shows that 14 participants had new venous thrombosis or PE within 30 days that required hospitalization, producing an upper limit 95% CI of 1.7% thus meeting the prespecified requirement for efficacy. The DOAC prescribed to these 14 participants with treatment failures was apixaban in 9 cases and rivaroxaban in five cases. An additional 3 participants had imaging done during an ED visit within 30 days that showed evidence of new venous thrombosis (n=1) or PE (n=2, subsegmental in both cases), but no change was made to therapy and the patient was not admitted. If those three were included as treatment failures, the top limit of the 95% CI would still be below 2.0% (17/1421 = 1.2%, 95% CI 0.7–1.9%). However, if PE were considered alone, the top limit 95% CI extended to 2.8%.

Table 3 presents the primary safety data and shows that 12 participants had bleeding that led to hospitalization, producing an upper limit 95% CI of 1.5%, thus meeting the prespecified requirement for safety. The DOAC prescribed to these 12 patients with bleeding was apixaban in 8 cases and rivaroxaban in 4 cases. Table 3 also presents the frequency of the prespecified secondary outcome, ISTH-defined severe bleeding. Only two patients met the ISTH criteria for severe bleeding; both were severe because of blood transfusions, one in a patient with lower gastrointestinal bleeding and another with menorrhagia.

Table 4 presents the 30-day frequency of five other preplanned secondary adverse outcomes. These data show much higher rates of undesirable outcomes, including an 8.0% rate of failure to take the anticoagulant as prescribed, a 22.6% rate (n=321 patients) of unscheduled medical care (for any reason), with about half (10.5%) of those visits related to bleeding and about one-quarter (5.6%) leading to hospitalization >24 hours, and one in ten (2.3%) qualifying as a serious adverse event. For the 321 patients with a return visit for unscheduled care, their first day of return occurred a median of 8 days after diagnosis (1^{st}-3^{rd} quartiles 3–16.5 days) and 51% of these occurred after 7 days. Physicians ordered a diagnostic test for possible recurrent DVT in 71 visits (only 40 had an venous ultrasound ordered), and a test for possible recurrent PE in 35 visits (33 had a CTPA done). The most frequent chief complaint or reason for visit was body pain other than chest pain (33%), chest pain (15%), possible infection (15%), bleeding (10.5%), dyspnea (5%) and fall or trauma (5%) with the other 17% for multiple other reasons. No patient died within 30 days, although one patient suffered cardiac arrest at day 26 and survived until day 31.

Because the treatment of isolated saphenous vein thrombosis may be considered controversial, we performed a sensitivity analysis removing them from the primary analysis. These 55 patients accounted for zero cases of recurrent VTE and one case of bleeding requiring hospitalization within 30 days and no serious adverse events. Thus, for the primary outcome of recurrent VTE, removal of isolated saphenous thrombosis (n=55) led to a recurrence of 14/1355 (1.0%, 0.5–1.7%) and a bleeding rate of 11/1355 (0.5%, 0.2–1.1%).

Of relevance to the primary efficacy aim, six patients who had new VTE within 30 days had discontinued or not filled their prescribed anticoagulant, producing a risk ratio [incidence of new VTE in non-adherent/incidence of new VTE in adherent=(6/113)/(8/1308)=8.7, 95% CI 3.0 to 22.4.

Protocol adherence

The protocol and data collection form were designed to determine reasons for non-adherence. This required that data be obtained from both telephone contact and a structured review of the EMR to extract explicit reasons, captured in short text descriptions, which the authors grouped into five specific categories. These are listed by frequency in Table 5 and stratified by initially prescribed anticoagulant. Areas of potential modification include financial limitations, and patient choices, which included a high rate of concern instilled by television ads regarding class action lawsuits over anticoagulants.

DISCUSSION

This work presents the results from the first large multicenter real-world effectiveness trial designed to facilitate home treatment using monotherapy anticoagulation with DOACs using a bundled approach for both patients with DVT and PE, stratified as low risk using validated criteria for PE. Using this approach, we found similar differences in outcome between patients with DVT and PE. These similar outcomes address a gap in current literature regarding the rates of treatment failure and significant hemorrhage for the outpatient treatment of venous thrombosis and PE with DOACs. A major finding is that outpatient treatment of patients with PE is equally safe as is the outpatient treatment of patients with DVT. Overall, with venous thrombosis and PE combined, we found the 30-day rate of VTE recurrence was 1.0%, with an upper limit of the 95% of 1.7%, below the prespecified threshold of 2.0%, suggesting an acceptable “treatment failure” rate. In a sensitivity analysis, removal of patients with isolated saphenous vein thromboses did not significantly affect these findings. In terms of safety, the rates of significant hemorrhage were considerably lower with only 12/1421 (0.8%, 95% CI 0.4 to 1.5%) participants experiencing bleeding associated with a hospital admission, and only 2/1421 (0.1%, 95% CI 0–0.5%) experience severe bleeding, in both cases requiring two units of packed red blood cell transfusion. No patient died. No patient had hemorrhage requiring emergent reversal of coagulopathy, or catheter or surgical treatment to control hemorrhage.

However, the secondary outcomes provide some concerning findings. Chief among these concerns was the 8.0% rate of non-adherence at 30 days, where non-adherence was defined as either never filling the prescription, or completely stopping the medication without consulting a physician. Non-adherence was associated with increased risk of VTE recurrence (risk ratio 6.0, 95% CI 2.3 to 15.2). Assuming that financial barriers and patient personal decisions could be addressed, 30% of the stated reasons for non-adherence could be addressed at the time of discharge from the ED. Thus, taken together, these data indicate overall safety and efficacy, and identify opportunities to improve transition of care from the ED to the home setting, including ensuring financial access to drugs and taking steps to ensure that patients immediately fill their prescriptions.

Our finding that only 18% of patients with DVT and 10% of ED patients with PE were treated in the MATH VTE protocol are consistent with previous real-world data showing that a low percentage of US ED patients diagnosed with DVT or PE are treated at home.[5–7] The fraction of patients treated with our protocol was disappointing for both DVT and PE, despite a funded and multifaceted approach to disseminate the protocol and encourage adoption. We did not include methodology to assess patients who were eligible but not enrolled in this study, but we speculate that the low rate of enrollment was largely secondary to comorbidities and adverse social determinates of health that led clinicians to believe the patients would be better served in hospital. The MERCURY trial offered ED patients deemed low risk by a modified version of Hestia to be randomized to home treatment with rivaroxaban. Out of 1894 patients with PE who were screened and only 114 (6%) were enrolled, with the most common reason for exclusion being either social or medical reasons to admit to the hospital.[30]

In terms of advancement across the spectrum of knowledge translation, this work provides the first prospective multicenter evidence to support the transition from “T2 to T3” (from clinical trials into practice), with evidence specific to monotherapy anticoagulation in the outpatient treatment of patients with VTE. In a 2017 review of current and ongoing trials for DOACs, Schulman et al., posited that “Valuable information on persistence, adherence, satisfaction, quality of life, outcomes in specific subsets, long-term outcomes, treatment patterns, and health resource utilization” can only be measured with an open-label design.[31] As reviewed by Schulman et al, the results of many large registries reporting outcomes of patients treated with DOACs for VTE have been recently published, or are ongoing.[31] Many of these large registries use administrative codes to define outcomes, which clearly have limitations compared with prospective study that includes explicit EMR review supplemented by direct patient contact.[32, 33] To our knowledge, no prior outpatient treatment study has risk-stratified both DVT and PE with the same procedure and prospectively followed them for adverse outcomes.

When compared with directly relevant precedent literature, our results generally indicate a favorable overall rate of adverse outcomes for outpatient treatment of low-risk VTE patients with a DOAC. First, the 1.0% rate of VTE recurrence at 30 days compares favorably to pooled data from 31 randomized treatment trials of VTE, which found a 1.5% (95% CI 1.25–1.80%) rate of new or recurrent VTE in the first month after the index VTE.[34] Regarding hemorrhage, our 0.8% 30-day rate of hospitalization associated with hemorrhage was comparable to the 30-day hemorrhage rates data from EINSTEIN DVT and PE studies and the AMPLIFY study. In pooled data from EINSTEIN DVT and PE, the rate of ISTH major hemorrhage in rivaroxaban-treated patients at 30 days was 10/3191 or 0.3%, and the 30-day rate of clinically relevant non-major bleeding was 3.7%.[24] For all patients treated with apixaban in the AMPLIFY trial, the 30 day rate of severe bleeding was approximately 0.2% and the rate of clinically relevant non-major bleeding was 3.8%.[35, 36] In comparison to data obtained from a more real-world setting, our findings are similar to the 14% rate of any bleeding that DeCamillo et al found in retrospective chart review of VTE patients treated with either apixaban or rivaroxaban from two institutions.[37] In a retrospective study of 671 VTE patients treated apixaban for usual care, with 74% treated as outpatients, and outcomes assessed at 3 months, Hendriks et al found a 0.3% (95% CI 0.08 to 1.1%) rate of VTE

recurrence, but considerable higher 1.8% (95% CI 0.9 to 2.9%) rate of ISTH defined major bleeding.[38] Using outcomes from linkage of multiple administrative databases, Weycker et al found a 7.0% rate of clinically relevant non-major bleeding for 17,878 VTE patients treated with apixaban and without hospitalization.[39] It should be noted that variations exist in defining clinically relevant non-major bleeding, even if standardized criteria are used.[27] In the present work, in Table 4, question 3, it is likely that many of the 10.5% who had unscheduled care stated as "because of" bleeding also had other reasons that they sought unscheduled care, but we did not measure these possible confounders. The 10.5% number may overestimate the frequency with which overt bleeding compelled the participants to seek medical care—it is possible that the patients conflated the memory of any bleeding with their reason for an ED visit. Of relevance to this point, although these patients were chosen to be low risk, they had a high rate of all-cause return ED visits in the first month. The 30-day rate of return to an ED or clinic for any reason was 22.6% (20.3–25.0%), which was considerably higher than to the 16.6% (16.6–16.6%) 30 day return rate observed in a much larger sample of discharged ED patients in the HealthCare Cost Utilization Project.[40] The reasons and chief complaints associated for return visits were heterogenous and more about symptom management than for bleeding or suspected recurrence of VTE inasmuch as fewer than 1/3 led to a diagnostic test for DVT or PE. Regarding the 8.0% rate of absolute non-adherence at 30 days, this frequency is in relative agreement with analyses from linked administrative databases (Optum Clinical and Research databases) which found approximately 14% of 151 patients diagnosed with VTE, who were treated initially with a DOAC, but not admitted to the hospital did not fill a prescription within 30 days.[41] Had we used a wider definition of non-adherence, the frequency may have increased. Using the 4-item Morisky scale, Castellucci et al found a 42% rate of non-adherence among 99 patients taking rivaroxaban, assessed after a mean treatment duration of 24 months.[42]

The data in Table 1 provide the inference that emergency physicians in the US employ similar risk tolerance for treating patients with DVT and PE as an outpatient. The unexpected component of the inference arises from the generally accepted belief that outpatient treatment of patients with DVT is considered a best practice, whereas the outpatient treatment of PE is more controversial. However, the data in Table 1 show that with the exception of "prior VTE", clinicians chose home treatment of relatively similar proportions of DVT and PE patients with higher risk conditions. Then, when the cumulative rates and severity of adverse outcomes are compared between DVT and PE patients (in Tables 2–4), it is apparent that the overall proportion of patients who had adverse outcomes was not substantially different. For example, the overall rate of Good Clinical Practice-defined serious adverse events was 2.3% for PE patients versus 2.5% for DVT patients. These data suggest overall equipoise in risk associated with home treatment of patients with PE and DVT, and that scrutiny of risk should be focused equally on the two conditions.

Methodological limitations inherent to an implementation study were that this was an open-label, single arm study, without a VKA control group, a hospitalized treatment group, or any randomization to use apixaban or rivaroxaban. The 95% confidence interval for VTE recurrence in PE patients exceeded 2.0%, which may limit adoption. The problems associated with affordability of the DOACS revealed an area for improvement in this implementation trial, inasmuch as all patients should have been informed of the 30-day free

cards, which were available for both apixaban and rivaroxaban during the conduct of the study. We did not measure patient reported quality of life. Lastly, as a real-world implementations study, we did not use a core radiology laboratory, nor did we use centralized, blinded adjudication of outcomes. The method of follow-up varied both between sites and by patient at each site, allowing for either a dedicated thrombosis treatment unit, or use of primary care. The method of assessing participant non-adherence by directly asking the patient could lead to error as differences could exist in the skill of the research personnel asking questions and patients may be hesitant to discuss non-compliance, or alternatively, they could possibly overstate reasons such as financial limitations. This heterogeneity could reduce reproducibility.

Methods to increase the relatively low rate of enrollment warrants discussion. On one hand, the 10% frequency of outpatient management of PE is higher than the 4.1% outpatient treatment rate that was recently found among 61,070 of patients with new PE were discharged from the emergency department.[43] However, the 10% rate of discharge for PE and 18% rate of discharge of DVT patients collectively, appear to show low adoption rate of the protocol. Up to one-half of all patients with PE diagnosed in the emergency department are low risk by sPESI, and another DOAC-based management protocol led to outpatient treatment of over 50% of DVT patients.[6, 44] In the view of the present findings and prior literature, the authors suggest that the first step to enhance adoption would be a mandatory quiz to ensure that every physician was aware and knowledgeable of the protocol components (e.g. how to access the order set, drug prescribing information, discharge instructions and follow-up options). In the ED setting, it is feasible to propose that a clinical decision support tool could calculate the PESI score from the electronic medical record and remind physicians of eligibility. Second, physicians should be monitored and provided feedback when they admit, rather than discharge, a potentially eligible patient.[18] Lastly, compliance might increase if clinician behavior is tied to financial incentives.

In conclusion, the MATH-VTE implementation trial demonstrated adequate efficacy and safety of monotherapy oral anticoagulation to treat DVT and PE patients in the emergency care setting who are deemed low risk by either the modified Hestia criteria or sPESI, plus clinical judgment. These data help support the contention that outpatient treatment of low-risk patients with DVT and PE with a DOAC should be considered a reasonable and prudent standard of care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Participating institutions in MATH-VTE: Indianapolis area hospitals: IU Health Methodist Hospital, IU Health West Hospital, Sidney and Lois Eskenazi Hospital. Dallas area hospitals: Baylor University Medical Center, Baylor-Garland, Baylor-Grapevine, Baylor-Irving, Baylor – Waxahachie, University of Texas Southwestern, Dallas, TX. Intermountain Healthcare, Salt Lake City, UT: Intermountain Medical Center, Riverton Hospital, Alta View Hospital, LDS Hospital, McKay Dee Hospital, Utah Valley Hospital, American Fork Hospital. Carillion Clinic, Roanoke, VA; Carolinas Medical Center, Charlotte, NC; George Washington University, Washington DC; John Peter Smith Hospital, Fort Worth, TX; Maine Medical Center, Portland, ME; Medical University of South Carolina, Charleston, SC; Northwell Health, Long Island, NY; Northwestern Memorial Hospital, Chicago, IL; Spirit of

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Abbreviations

DOAC	direct acting oral anticoagulant
DVT	deep vein thrombosis
ED	emergency department
ISTH	International Society for Thrombosis and Haemostasis
IRB	Institutional Review Board
MATH VTE	Monotherapy Anticoagulation To expedite Home treatment of VTE
PE	pulmonary embolism
POMPE-C	prediction of mortality from pulmonary embolism in cancer
StaRI	Standards for Reporting Implementation Studies
sPESI	simplified Pulmonary Embolism Severity Index
VKA	vitamin K antagonist
VTE	venous thromboembolism

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What is known:

- Outpatient treatment of venous thromboembolism (VTE) from the emergency department (ED) may be effective but a large-scale implementation trial is lacking.

What this study adds:

- In 1421 patients with VTE stratified as low risk and treated with monotherapy oral anticoagulation, the overall 30-day VTE recurrence and bleeding rates requiring hospitalization were both below 2%, suggesting overall safety and efficacy.

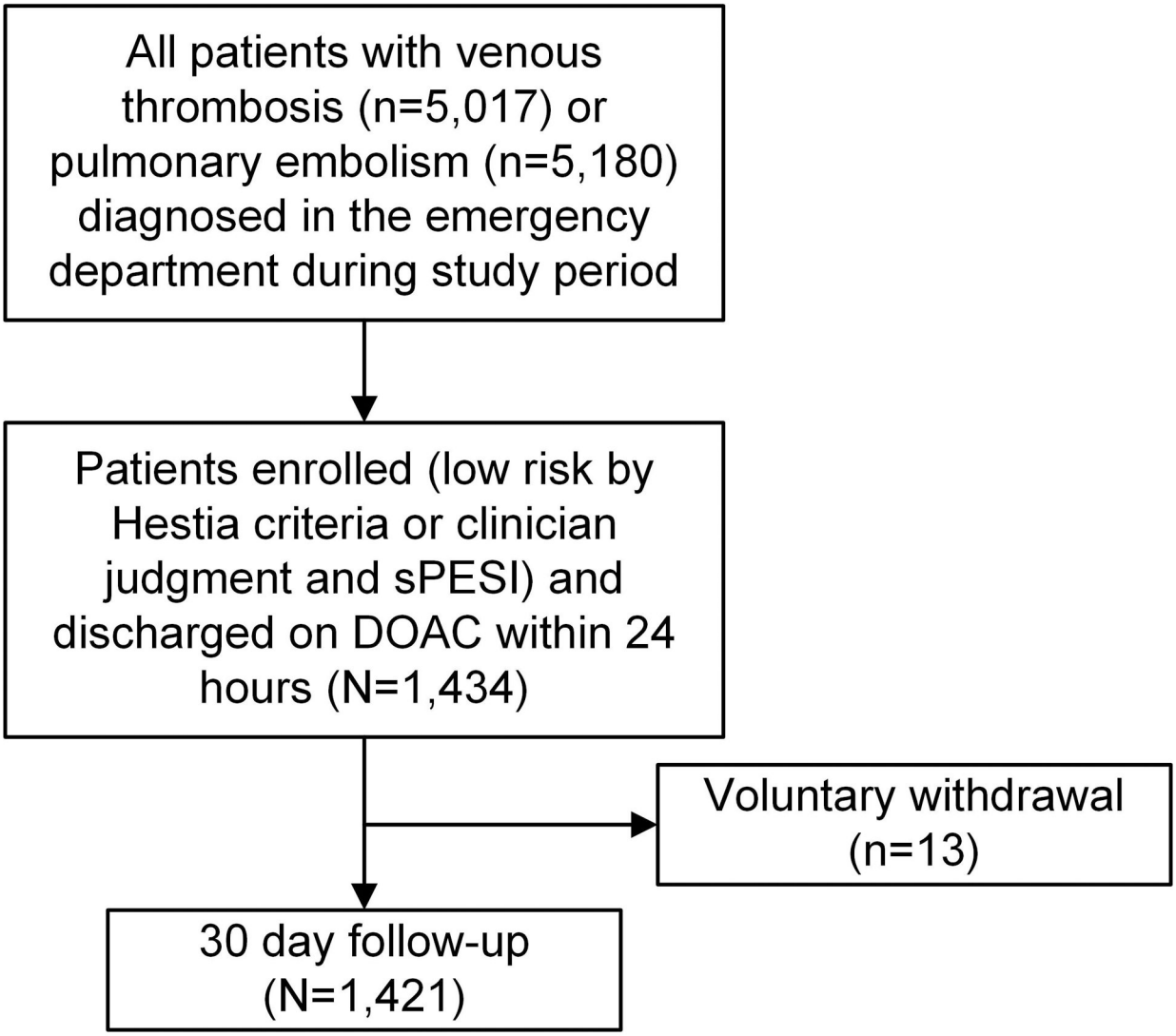

Figure 1.
Flow diagram of patients

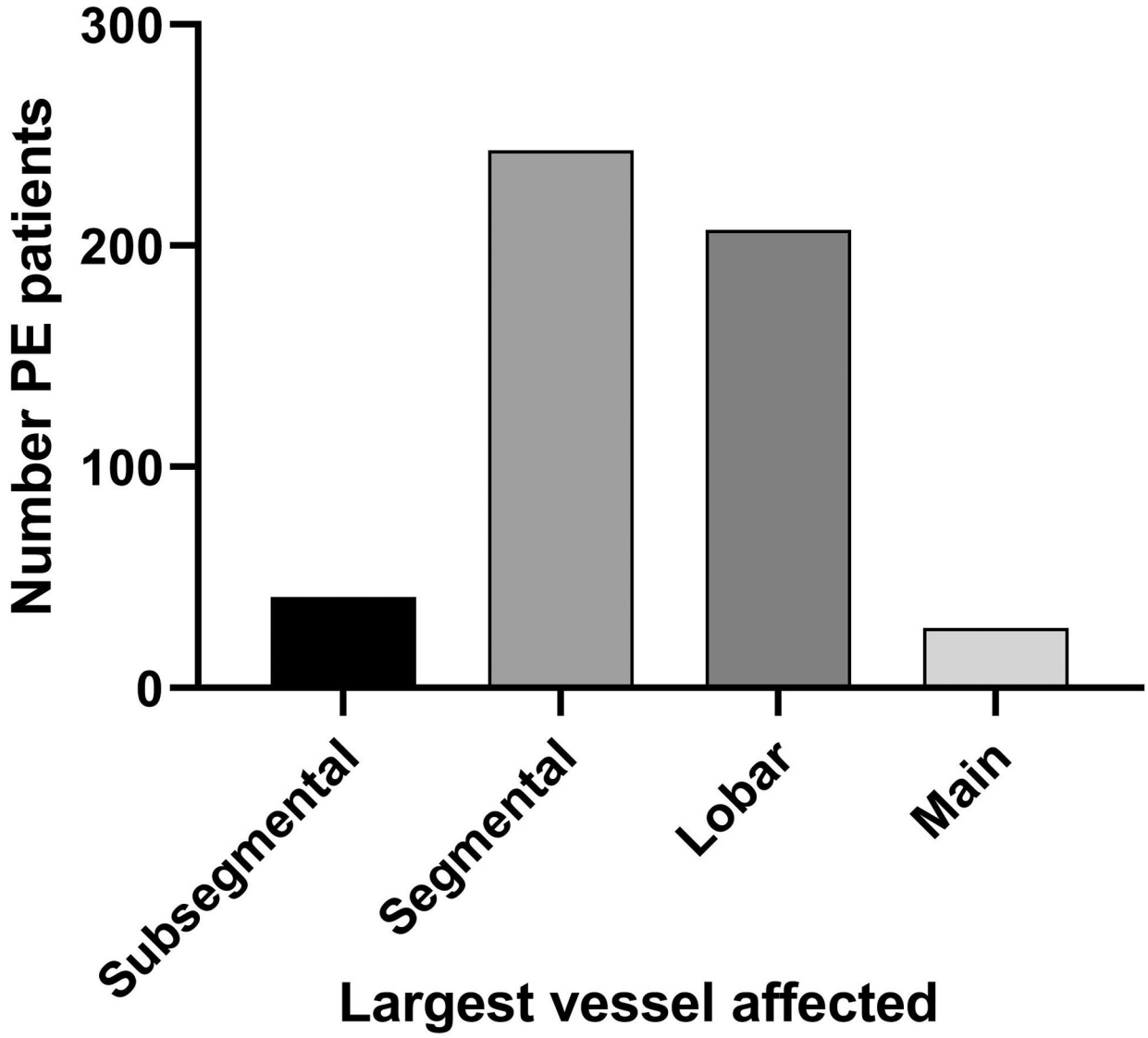

Figure 2.
Anatomic location of largest pulmonary arterial filling defects among 518 patients with pulmonary embolism (PE) treated at home.

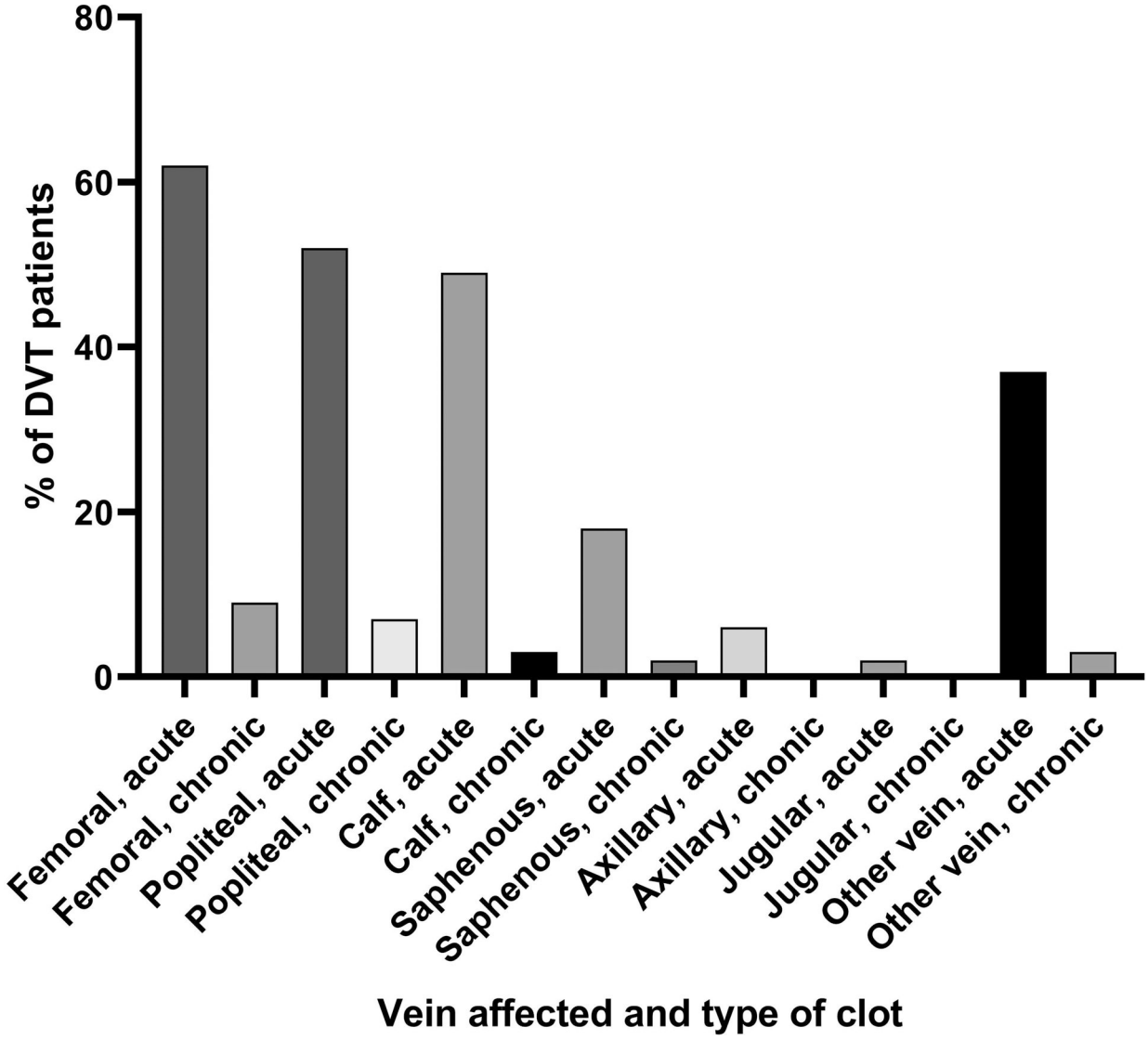

Figure 3.

Frequency and anatomic location of non-compressible veins among 903 patients diagnosed with DVT. Because many patients had more than one clot location, the total number of sites exceeds 903.

Table 1.

Patient features

	PE	% of PE	Venous thrombosis*	% of Venous thrombosis	Total	% of total
N	518		903		1421	
Female gender	254	49%	436	48%	690	49%
White Race	324	63%	609	67%	933	66%
Black Race	166	32%	246	27%	412	29%
Other Race	28	5%	28	3%	56	4%
Latino ethnicity	24	5%	45	5%	69	5%
Age > 80 years	24	5%	36	4%	60	4%
Systolic blood pressure <100 mm Hg)	10	2%	6	1%	16	1%
Pulse oximetry reading <95%	53	10%	62	7%	115	8%
Heart rate > 100 beats/min	95	18%	147	16%	242	17%
Body mass (Kg) >120 kg	56	11%	118	13%	174	12%
Hemoglobin <10 g/dL	29	6%	45	5%	74	5%
Serum creatinine >1.3 mg/dL	43	8%	89	10%	132	9%
Charlson Comorbidity Index >2	47	9%	92	10%	139	10%
HIV treatment	2	0%	7	1%	9	1%
Prior VTE	326	63%	190	21%	516	36%
Cancer, active	16	3%	38	4%	54	4%
Cancer, remission	24	5%	45	5%	69	5%
Heart failure	19	4%	25	3%	44	3%
Chronic lung disease	40	8%	62	7%	102	7%
Diabetes	63	12%	129	14%	192	14%
Surgery within 4 weeks	41	8%	87	10%	128	9%
Hospitalization within 3 weeks	46	9%	63	7%	109	8%
Limb immobility	12	2%	35	4%	47	3%
Generalized immobility	9	2%	17	2%	26	2%
Active smoker	129	25%	222	25%	351	25%

*Includes 55 cases of saphenous vein thrombosis

Table 2.

Primary efficacy outcomes*

VTE diagnosis at enrollment	New PE	New venous thrombosis	New venous thrombosis and PE	Total	Frequency	95% CI
Any VTE	7	4	3	14	14/1421 = 1.0%	0.5 to 1.7%
PE	4	1	2	7	7/518 = 1.4%	0.5 to 2.8%
Venous thrombosis	3	3	1	7	7/903 = 0.8%	0.3 to 1.6%

Abbreviations: VTE venous thromboembolism, PE pulmonary embolism, , CI confidence interval.

*Defined as image-proven new or extended thrombosis requiring hospital admission. An additional 3 patients had new VTE but were not admitted: 2 patients with initial DVT had new PE diagnosed and 1 patient with initial PE had new DVT diagnosed

Table 3.

Primary safety outcomes

VTE diagnosis at enrollment	Bleeding requiring hospitalization*	Frequency	95% CI	ISTH severe bleed	Frequency	95% CI
Any VTE	12	12/1421 = 0.8%	0.4 to 1.5%	2	2/1421 = 0.1%	0–0.5%
PE	4	4/518 =0.8%	0.2 to 1.9%	1	1/518 =0.2%	0–1.0%
Venous thrombosis	8	8/903 = 0.9%	0.3 to 1.7%	1	1/903 = 0.1%	0–0.6%

Abbreviations: VTE venous thromboembolism, PE pulmonary embolism, CI confidence interval, ISTH-International Society for Thrombosis and Haemostasis;

*Causes of bleeding: Lower gastrointestinal (5), Hematemesis (4), hematuria (1), menorrhagia (1), epistaxis (1)

Table 4.

Other adverse outcomes within 30 days

Adverse outcome stratified by VTE diagnosis at enrollment	Frequency	95% CI
1. Discontinued anticoagulant (patient or EMR reported) *		
PE	40/518 = 7.8%	5.5 to 10.3%
Venous thrombosis	73/903 = 8.1%	6.4 to 10.1%
Any VTE	113/1421 = 8.0%	6.6 to 9.5%
2. Patient reported unscheduled ED or clinic visit†		
PE	120/427 = 28.1%	24.0 to 32.5%
Venous thrombosis	167/842 = 20.0%	17.2 to 22.7%
Any VTE	287/1269 = 22.6%	20.3 to 25.0%
3. Patient reported bleeding requiring any unscheduled medical care†		
PE	52/425 = 12.2%	9.3 to 15.7%
Venous thrombosis	79/829 = 9.5%	7.6 to 11.7%
Any VTE	131/1254 = 10.5%	8.8 to 12.3%
4. Hospitalized > 24 hours		
PE	32/518 = 6.1%	4.2 to 8.6%
Venous thrombosis	47/903 = 5.2%	3.9 to 6.9%
Any VTE	79/1421 = 5.6%	4.4 to 6.9%
5. Any serious adverse event		
PE	12/518 = 2.3%	1.3 to 4.0%
Venous thrombosis	23/903 = 2.5%	1.6 to 3.8%
Any VTE	35/1421 = 2.5%	1.7 to 3.4%

Abbreviations: VTE venous thromboembolism, PE pulmonary embolism

* Failure to fill the prescription or completely stopping the medication without physician advice. Excludes patients with recurrent VTE who had medication changes. †Missing data result from lack of direct contact, uncertainty of answer, or refusal to answer

Table 5.

Patient or charted reasons for non-adherence

Reason	Apixaban	% of 1006	Rivaroxaban	% of 415
Financial or prior authorization difficulties	15	1.5%	5	1.2%
Perceived side effect other than bleeding	13	1.3%	3	0.7%
Bleeding as perceived by patient	11	1.1%	3	0.7%
Prescription not filled/patient choice	7	0.7%	4	1.0%
Worsened clot symptoms without new diagnosis	2	0.2%	1	0.2%
Other or unknown	35	3.5%	14	3.4%
Total	83	8.3%	30	7.2%