


METHODOLOGICAL ARTICLE

Apixaban for Routine Management of Upper Extremity Deep Venous Thrombosis (ARM-DVT): Methods of a prospective single-arm management study

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Abstract

Background: Upper extremity deep vein thrombosis (UEDVT) constitutes approximately 10% of all deep vein thromboses (DVTs). The incidence of UEDVT is increasing in association with use of peripherally inserted central venous catheters. Treatment for UEDVT is derived largely from evidence for treatment of lower extremity DVT. Limited evidence exists for the use of a direct oral anticoagulant for the treatment of UEDVT.

Population: Sequential patients identified within the Intermountain Healthcare System and University of Utah Healthcare system with symptomatic UEDVT defined as the formation of thrombus within the internal jugular, subclavian, axillary, brachial, ulnar, or radial veins of the arm.

Intervention: Apixaban 10 mg PO twice daily for 7 days followed by apixaban 5 mg twice daily for 11 weeks.

Comparison: The historical literature review rate of venous thrombosis reported for recurrent clinically overt objective venous thromboembolism (VTE) and VTE-related death. If the confidence interval for the observed rate excludes the threshold event rate of 4%, we will conclude that treatment with apixaban is noninferior and therefore a clinically valid approach to treat UEDVT.

Sample Size: We elected a sample size of 375 patients so that an exact 95% confidence interval would exclude an event rate of VTE in the observation cohort of 4%.

Outcome: Ninety-day rate of new or recurrent objectively confirmed symptomatic venous thrombosis and VTE-related death. The primary safety outcome is the composite of major and clinically relevant nonmajor bleeding.

KEYWORDS

apixaban, cancer, central venous catheter, deep vein thrombosis, PICC line, treatment, upper extremity

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Essentials

- Limited evidence supports efficacy of direct oral anticoagulants for treating upper extremity deep vein thrombosis.
- We present the design of an open-label study of symptomatic upper extremity deep vein thrombosis.
- Recurrent thrombosis and bleeding will be reported among patients prescribed apixaban.

1 | BACKGROUND

Upper extremity deep vein thrombosis (UEDVT) refers to the formation of fibrin clots within the subclavian, axillary, and brachial veins of the arm.¹ UEDVT may be either primary (without apparent inciting factor) or secondary (often in conjunction with a central venous catheter [CVC]; malignancy, pregnancy, surgery, or trauma).² UEDVT constitutes approximately 10% of all deep vein thrombosis (DVT),³ with an increasing incidence largely secondary to the expanded use of peripherally inserted central venous catheters (PICCs) for both inpatient and outpatient care. Approximately 50% of all UEDVT is attributed to CVCs⁴⁻⁶ with a contemporary overall incidence of symptomatic UEDVT following CVC use approximating 2% to 6%.^{7,8}

No randomized controlled studies have evaluated anticoagulation for initial treatment of UEDVT; therefore, evidence for the treatment of acute UEDVT is extrapolated from recommendations for treatment of lower extremity deep vein thrombosis (LEDVT).¹ Prospective cohort studies have reported a clinically acceptable rate of recurrent thrombosis and hemorrhage when UEDVT is treated similarly to LEDVT.⁹⁻¹¹ Historically, the implementation of a parenteral anticoagulant (unfractionated heparin, low-molecular-weight heparin [LMWH], fondaparinux) in conjunction with warfarin has been the mainstay of treatment for acute venous thromboembolism (VTE). More recently, large prospective randomized clinical trials have demonstrated the efficacy and safety of the direct oral anticoagulants (DOACs) apixaban, dabigatran, edoxaban, and rivaroxaban for the acute treatment¹²⁻¹⁵ and secondary prevention^{12,16,17} of VTE. Pooled meta-analyses suggests DOACs compare favorably with LMWH/vitamin K antagonist (VKA) for outcomes of recurrent VTE, fatal pulmonary embolism (PE) overall mortality, and major bleeding.^{18,19}

UEDVT often occurs in the setting of a concomitant CVC and cancer. Limited evidence exists to inform the uncertainty regarding the influence of CVCs and anticoagulation therapy. Published evidence suggests that outcomes of bleeding and thrombosis may differ among patients with foreign body devices that receive a DOAC vs. warfarin.²⁰ This concern is theoretical and attributed to differences in the mechanism of action of warfarin and the DOACs. DOACs including apixaban selectively inhibit free and clot-bound activated factor X alone.²¹ Warfarin inhibits the activation of both tissue factor-induced coagulation (upon inhibiting factor VII synthesis) and contact pathway-induced coagulation (upon inhibiting the synthesis of factor IX), as well as inhibiting the synthesis of factor X and thrombin in the common pathway.²²

Recent Level 1 evidence suggests that the DOAC edoxaban is safe and effective for the treatment of cancer-associated thrombosis

(CAT).²³ Prospective randomized clinical trials assessing the safety and effectiveness of apixaban and rivaroxaban among patients with CAT are ongoing,²⁴⁻²⁶ and preliminary results suggest that the effectiveness of DOACs among patients with CAT may be a class effect.^{27,28} Prospective management study reported outcomes with apixaban among patients with UEDVT and CAT would meaningfully inform clinical decision making and contribute to the limited evidence that exists for the use of DOACs among patients with UEDVT and cancer.²⁹

To date, the use of a DOAC for the treatment of UEDVT has been limited to a small study among patients with central venous catheters.²⁹ Recurrent VTE among patients receiving a DOAC for the acute treatment of thrombosis is low (on-treatment rate of recurrent VTE, 2%; 95% confidence interval [CI], 1.6%-2.4%), and the rate compares favorably with the on-treatment rate of recurrent VTE reported recently among patients with acute VTE treated with heparin/VKA (2.2%; 95% CI, 1.8%-3%).¹⁸ Apixaban has been compared with warfarin for the treatment of mostly unprovoked acute PE and DVT of the lower extremities. In a randomized double-blind study apixaban compared favorably with usual care for the outcome of recurrent venous thrombosis and VTE-related death (2.3% vs. 2.7%) with a favorable comparative rate of major bleeding (0.6% vs. 1.8%).¹³ Guidelines presently recommend therapeutic anticoagulation for a minimum duration of 3 months among patients with UEDVT¹ and possibly longer should the thrombosis occur in the setting of a CVC that must remain in place.³⁰⁻³³

Evidence of efficacy for the treatment of UEDVT with an oral anticoagulant that requires no monitoring and delivers reliable therapeutic anticoagulation would be of great interest and would be applicable to large number of patients. In clinical use, apixaban has been observed to have a favorable therapeutic and safety profile.^{34,35}

2 | STUDY AIMS AND OUTCOMES

We hypothesize that apixaban for 12 weeks (10 mg BID for 7 days followed by apixaban 5 mg BID for 11 weeks) will be noninferior to the rate of recurrent VTE and VTE-related death as reported in the literature among patients treated with LMWH/VKA should the event rate we observe exclude 4%. The primary efficacy outcome will be the 90-day rate of clinically overt recurrent symptomatic VTE and VTE-related death. The primary safety outcome will be the combined 90-day rate of major bleeding and clinically relevant nonmajor bleeding as formerly defined.^{13,36} All outcomes occurring during the 90 days following signed informed consent will contribute to the

TABLE 1 ARM-DVT inclusion and exclusion criteria

Inclusion
Age ≥ 18 y
Have received no more than 6 doses of any therapeutic anticoagulant, or intravenous therapeutic heparin for longer than 72 h
Women of childbearing potential (WOCBP) must have a negative pregnancy test, agree to contraception associated with the time of therapy, and not be breastfeeding
Males who are sexually active with WOCBP must use contraception
Exclusion
An indication for anticoagulation for which no FDA approval of apixaban exists (eg, prosthetic heart valves)
Life expectancy of less than 6 mo
Unable to engage in reliable follow-up as per protocol
Participating in a clinical trial or has participated in a clinical trial within the last 30 d
Receiving concomitant dual antiplatelet therapy
Requires aspirin dose of >165 mg daily
A hemoglobin level of <8 mg/ dL
A platelet count of $<50\,000$ per cubic mm
A calculated creatinine clearance of <25 mL/ min calculated by Cockcroft-Gault equation
Alanine aminotransferase or aspartate aminotransferase level >2 times the upper limit of the normal range
A total bilirubin >1.5 times the upper limit of the normal range
Intend pregnancy or breastfeeding within the next year
Known allergy to apixaban, rivaroxaban, or edoxaban
Active pathological bleeding
Any condition that at the discretion of the investigator is thought to prohibit active participation and follow-up in the trial (eg, active substance dependency disallowing reliable follow-up)
UEDVT that occurs while therapeutic anticoagulation is being taken by the patient ("event on therapy")
Concomitant VTE diagnosed elsewhere except for DVT with the most proximal aspect isolated to the distal lower extremity circulation (eg DVT of the lower extremity or PE)

DVT, deep vein thrombosis; FDA, Food and Drug Administration; PE, pulmonary embolism; UEDVT, upper extremity deep vein thrombosis; VTE, venous thromboembolism.

respective efficacy or safety outcome. For the composite outcome of major bleeding and clinically relevant nonmajor bleeding, assuming a rate reported in the literature of 9.7%, should we observe that the upper bound of the 95% CI for event rate excludes 13%, we will consider apixaban as noninferior to warfarin. Additional outcomes will include all-cause mortality, VTE-related mortality, vein-specific quality-of-life assessment as measured by a standardized questionnaire,³⁷ anticoagulant use quality-of-life assessment as measured by a standardized questionnaire,³⁸ and postthrombotic syndrome measured using a standardized technique.³⁹ We will report how the event rate we observe compares to a historical control of case-matched patients for the primary efficacy outcome recurrent

symptomatic VTE and VTE-related death. The Apixaban for Routine Management of Upper Extremity Deep Venous Thrombosis (ARM-DVT) clinical trial is funded through an investigator-initiated grant provided by the Bristol-Myers Squibb Pfizer Pharmaceutical Alliance (CV185-512) and by a grant from the Intermountain Research and Medical Foundation (Project 790) and is registered at ClinicalTrials.gov Identifier: NCT02945280.

3 | STUDY DESIGN

3.1 | Overview

ARM-DVT is a prospective, open-label, single-arm management study recruiting consecutive adults (age ≥ 18 years) who provide signed informed consent with a qualifying UEDVT. The complete protocol may be found in Appendix S1, and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist is found in Appendix S2.

3.2 | Diagnosis

Patients eligible for enrollment will include those for whom acute UEDVT is identified upon compression ultrasound performed using the classic method⁴⁰ to assess venous compressibility, except in veins inaccessible to compression (eg, the subclavian vein), in which case lumen echogenicity and Doppler flow characteristics will be used. Examination will consist of comprehensive venous compression, color flow imaging of the upper extremity including the proximal upper extremity deep veins (internal jugular vein, subclavian vein, axillary vein, brachial vein), distal upper extremity deep veins (radial vein, ulnar vein), and upper extremity superficial veins (basilic, cephalic) at 2-cm intervals in the transverse plane. Ultrasound results will be categorized as (1) normal (no DVT) if all imaged venous segments are fully compressible or if there is absence of intraluminal echogenic material and normal flow in veins inaccessible to compression; (2) inadequate for interpretation; or (3) abnormal, defined as a noncompressible segment being present in the internal jugular vein, subclavian vein, axillary vein, brachial vein, ulnar vein, or radial vein, or echogenic material with evidence of compromised flow in segments inaccessible to compression. Patients with clinically overt DVT involving the internal jugular, subclavian, axillary, brachial, ulnar, and radial veins for which anticoagulation is indicated at the discretion of the treating physician are eligible. Should DVT be identified on computed tomography in the qualifying deep venous distribution and anticoagulation is indicated at the discretion of the treating physician, the patient will be considered eligible for enrollment.

3.3 | Patient demographics and recruitment

Potentially eligible patients (eligibility criteria in Table 1) will be identified through the peripheral vascular labs and clinical service lines at the Intermountain Medical Center and University of Utah Hospital.

Screening logs will be kept, and reasons for exclusion will be reported. The Intermountain Medical Center is the flagship 502-bed tertiary care academic hospital of Intermountain Healthcare located in Murray, Utah. The University of Utah Hospital is the 527-bed flagship hospital of University of Utah Health and is a tertiary care center located in Salt Lake City, Utah. At Intermountain Medical Center a computer algorithm that uses natural language processing to identify radiology reports demonstrative of acute venous thrombosis has been developed⁴¹ and iteratively refined.⁴² This program then emails an alert to the research coordinator in real time. A Spanish language short form will be used to facilitate enrollment of native Spanish-speaking patients. Patients with concomitant venous thrombosis of another anatomic location or PE are ineligible. While initially patients with cancer were considered ineligible, with the advent of Level 1 evidence supportive for use of the DOACs in treatment among patients with CAT, the ARM-DVT protocol was modified to permit enrollment of patients with active cancer.²³ We estimate that we will be able to enroll approximately 12 patients monthly.

4 | SAMPLE SIZE, POWER CALCULATION, STATISTICAL ANALYSIS, AND DATA INTEGRITY

A literature review was performed to ascertain an event rate that would allow for sample size estimate. We estimate a 90-day rate of recurrent VTE and VTE-related death of 1.5%, based on recurrent VTE from prior observational studies (Table 2). A sample size of 357 patients who meet eligibility criteria was chosen so that an exact 95% CI would exclude an event rate of 4% for 90-day recurrent symptomatic venous thrombosis and venous thromboembolism-related death with 80% power. Primary analyses will be conducted based on intention to treat. Excluding an event rate of 4%, especially taking into account the presence of patients with CAT would suggest a standard by which this diagnostic strategy would be clinically acceptable. Anticipating a 5% rate of withdrawal, a total of 375 patients are to be enrolled. For the primary efficacy analysis a 2-sided CI for the composite event rate of objectively confirmed VTE and VTE-related death will be calculated for the observation cohort by exact methods. If the CI for the event excludes the event rate of 4%, we will conclude that treatment with apixaban is noninferior to the reference value in the literature. A per-protocol analysis among all patients who complete treatment will be performed as a sensitivity analysis. All events, regardless of whether they occur as on- or off-treatment events, will be assessed in a blinded fashion. Additionally, we will report the number of events that occurred on and off treatment and conduct sensitivity analyses including only on-treatment events (including all events up to 3 days following cessation of therapy). Thrombosis and bleeding rates among patients in 2 subgroups—those with cancer and those who have a PICC/CVC—will also be reported separately. For the composite safety outcome of major bleeding and clinically relevant nonmajor bleeding assuming a rate reported in the literature of 9.7%, should we observe the

upper bound of the 95% CI for event rate excludes 13%, we will consider apixaban as noninferior to warfarin. The value was derived from the observed rate of major bleeding and clinically relevant non-major bleeding observed among patients randomized to warfarin in the Apixaban for the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis as First-Line Therapy (AMPLIFY) study. At Intermountain Medical Center, we have reported an annual rate of UEDVT ranging from 1.9% to 3%.^{43,44} A Safety Monitoring Committee (SMC) that is empowered to provide recommendations to the Institutional Review Board regarding the continuation status of ARM-DVT was empaneled. The SMC meets annually (or at a greater frequency at the members' discretion) to review outcome events. Auditing of ARM-DVT occurs at the discretion of the Intermountain Healthcare Office of Research.

All individual patient personal health information will be stored in a secure, password-protected, deidentified database that resides behind the Intermountain Healthcare firewall. Upon study completion, the results of ARM-DVT will be submitted for publication to a peer-reviewed journal.

As a secondary analysis, we will compare the individual event rates of clinically important outcomes (recurrent VTE, VTE-related death, and major and clinically relevant nonmajor bleeding) to a historical control of case-matched patients treated with warfarin. We will reserve matching only for risk factors whose confounding effects need to be controlled for but that are not of scientific interest as independent risk factors in the study.

We anticipate exact matching enrolled patients to those from the historical control group on the following important variables whose confounding effects need to be controlled for: age, sex, cancer, presence of a PICC/CVC, and presentation service line (emergency department, inpatient, and outpatient). We will consider k:1 exact matching (where k represents the ratio of controls to 1 case) and determine k based on the matched sample size and covariate balance. We will assess covariate balance by comparing the standardized difference in means for each covariate before and after matching. Should exact matching yield a small or poorly balanced sample, we will instead use a nearest neighbor approach with k:1 greedy or optimal caliper matching without replacement, where the distance metric used, k, and the matching algorithm are chosen by which combination yields the most balanced matched sample. Once the matched sample has been finalized, the relationship between the outcomes and apixaban treatment, controlled for cancer-associated thrombosis, will be analyzed using generalized estimating equations, which accounts for the paired nature of the data introduced by matching. We will use McNemar's test to assess unadjusted outcomes between the groups.

5 | OUTCOMES ASSESSMENT AND FOLLOW-UP

All patients enrolled will be scheduled for a 90-day follow-up visit, and every attempt will be made to see the patient in person. Pill counts

TABLE 2 Extant literature for treatment of UEDVT¹

Author year	Study type	Enrolled	Intervention	Outcomes	Follow-up	Results
Savage 1999 ¹⁰	Prospective cohort, 2 center	46 outpatients with UEDVT (16 CVC)	Dalteparin 200 IU/kg daily for 5-7 d and VKA with target INR 2.0-3.0 Duration of VKA not provided	Symptomatic recurrence/extension of DVT, PE, MB, death	3 mo	Recurrence/extension DVT: 1/46 (2%) PE: 0/46 MB: 1/46 (2%) (on VKA) Death: 7/46 (15%) (none from PE or bleeding)
Karabay 2004 ¹¹	Prospective cohort, single center	36 inpatients with UEDVT (includes 13 with CVC)	Nadroparin s.c. BID, 86 anti-Xa IU/kg for 7 d then VKA (started on d 3; target INR 2-2.5) for mean of 4.7 mo	Symptom relief Lysis of thrombus on ultrasound Recurrent DVT PE Death	12 mo	Significant symptom relief, day 7: 32/36 (89%) Lysis, day 10: ≥35%: 16/36 (45%), <35%: 17/36 (47%) None: 3/36 (8%) Recurrent DVT: 0/36 PE: 0/36 Death: 9/36 (25%) (none due to PE or bleeding)
Prandoni 2004 ⁹	Prospective cohort, number of centers not stated	53 patients with first UEDVT (included 6 with CVC)	Therapeutic-dose heparin (81% received UFH, 19% received LMWH) then VKA (median, 3 mo)	Recurrent VTE Death	Median 48 mo	Results not presented by initial Rx with UFH vs. LMWH Recurrent VTE: 3/53 (5.7%) (2 arm, 1 leg) Cumulative incidence 1, 2, and 5 y: 2.0%, 4.2%, 7.7% Death: 11/53 (20.8%) (due to cancer, PE, congestive heart failure [numbers not provided])
Kovacs 2007 ⁴⁵	Prospective cohort, multicenter	74 cancer patients with UEDVT (all had CVC)	Dalteparin 200 IU/kg daily for 5-7 d and VKA to achieve target INR of 2.0-3.0	Recurrent VTE, PE, MB, death, CVC failure 2/2 DVT or inability to infuse	3 mo	Recurrent VTE: 0/74 PE: 0/74 MB: 3/74 (4%) Death: 7/74 (6 cancer, 1 MB) Catheter failure due to DVT or inability to infuse: 0/74
Baumann-Kreuziger 2015 ⁴⁶	Subset of prospective international registry of consecutive patients with objectively confirmed VTE	558 (all had CVC and thrombosis and 45 had concomitant PE at time of CVC-related DVT)	LMWH 67%, VKA 27%	VTE recurrence MB	Median 106 d	Recurrent VTE: 7/100 pt-years MB: 8.9/100 pt-years Fatal PE: 1.85/100 pt-years Fatal bleeding: 2.32/100 pt-years
Delluc 2014 ⁴⁷	Retrospective cohort study	89 consecutive cancer outpatients with UEDVT (all CVC related)	1 mo of full therapeutic weight-adjusted dose of LMWH followed by an intermediate dose	VTE recurrence MB	Mean 124 d	Recurrent VTE: 0/89 MB: 2/89

(Continues)

TABLE 2 (Continued)

Author year	Study type	Enrolled	Intervention	Outcomes	Follow-up	Results
Laube 2017 ⁴⁸	Retrospective cohort	83 cancer patients (53 completed 90-d) with CVC and UEDVT	Rivaroxaban (Dosing not reported)	Line function, line removal, bleeding, death, other VTE	90 d	Preserved line function: 50/53 MB: 2/53 CRNMB: 1/53 Death: 6/53 New VTE: 3/53
Davies 2018 ²⁹	Prospective cohort, multicenter	70 consecutive cancer patients with UEDVT (all CVC related)	Rivaroxaban 15 mg BID for 21 d then 20 mg daily for 9 wk	Line function, recurrent VTE, bleeding	12 wk	Preserved line function: 100% Recurrent VTE: 1.43% (1/70) Bleeding: 12.9%

Table 2 is constructed in part from AT9 Table S46.

CRNMB, clinically relevant nonmajor bleeding; CVC, central venous catheter; DVT, deep vein thrombosis; INR, international normalized ratio; LMWH, low-molecular-weight heparin; MB, major bleeding; PE, pulmonary embolism; UEDVT, upper extremity deep vein thrombosis; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

will be performed at the 90-day follow-up encounter. A standardized questionnaire assessing for primary and secondary outcomes will be administered at the 90-day follow-up visit. If the patient is unable to follow up in person, a telephone call or electronic (email) questionnaire will be substituted and considered adequate 90 day follow-up upon completion. Any therapy beyond the 90-day study period will be administered per clinical routine. Study involvement will be considered complete 90 days after the date of signed informed consent.

The primary efficacy and primary safety outcome ascertainment among patients prospectively enrolled will be assessed by three independent adjudicators. Each adjudicator will have established expertise in vascular medicine and will be named to adjudicate all suspected events of DVT or PE and all diagnostic tests for these occurring during the follow-up period. The adjudicators will be blinded to the adherence of the patient with recommended study dosing. The kappa statistic of interobserver agreement will be reported as similarly performed by others,⁴⁹ and discussion leading to consensus will resolve disputes. All deaths will be adjudicated as to whether attributable to venous thrombosis, bleeding, or another cause by the same group of adjudicators. To limit interobserver variability, patient information will be redacted and entered in specific data fields on a form generated for this purpose for events identified both in the study and historical control cohorts.

Suspected recurrent or progressive DVT will be defined as thrombosis objectively confirmed by a Doppler ultrasound performed using the classic method⁴⁰ as described above or upon venography as per clinical care and routine that is present in an anatomic distribution in the deep venous circulation not formerly seen. Evaluation of suspected PE will occur at the discretion of the clinician caring for the patient and defined in a standard fashion upon objective assessment using computed tomography pulmonary arteriography (contrast material outlining an intraluminal defect or a vessel occluded by low attenuation material read by a board-certified radiologist), ventilation-perfusion (V/Q) scan (interpreted as positive in the setting of a high-probability V/Q lung scan in a patient with no prior PE, and high or intermediate pretest probability for PE by a clinical assessment, or a positive venous ultrasound in a patient with no

prior LEDVT in a patient with a nondiagnostic V/Q scan and high or intermediate clinical probability by a pretest probability score as described by others.^{50,51} Likewise, criteria exist for the diagnosis of PE using pulmonary angiography or magnetic resonance imaging as others have previously described in the unlikely event that this should occur.^{50,52} An elevated D-dimer test alone will not be sufficient for a diagnosis of VTE. PE identified incidentally upon imaging indicated for another indication will be adjudicated as described above.

6 | MINIMIZATION OF BIAS

To minimize selection bias, consecutive patients that meet eligibility will be approached for consent, and all eligible consenting subjects enrolled without exception. Risk for biased assessment of clinical outcomes will be mitigated by evaluating suspected VTE and bleeding in a standard manner. Strict diagnostic criteria and subsequent interpretation by an independent adjudication panel will guard against differential interpretation of these tests. A kappa statistic for interobserver agreement will be reported. For the secondary analysis comparing outcomes to a historical control, all consecutive qualified patients identified with UEDVT prior to the advent of Food and Drug Administration approval of DOACs (January 1, 2011) are considered eligible to avoid ascertainment bias in the historical control group. Outcomes of 90-day new or recurrent VTE, major bleeding, and clinically relevant nonmajor bleeding will be verified and recorded. To limit attrition bias, patients will be registered in a central study cohort that will allow for 90-day follow-up. Initial patient informed consent will allow family members and referring physicians to be contacted if there is difficulty contacting patient.

7 | DISCUSSION

While UEDVT is less common than thrombosis of the lower extremities, UEDVT accounts for approximately 50% of hospital-acquired

VTE.^{53,54} Because of the limited evidence that is available to inform the treatment of UEDVT a prospective management study reporting rates of patient important outcomes can inform clinical care. Greater physician familiarity with the DOACs has led to their broad use among patients with VTE, including adoption among subgroups of patients with unusual site thrombosis such as UEDVT. We perceive the routine use of DOACs among patients with UEDVT as a potential challenge associated with ARM-DVT enrollment. Identification of patients within 72 hours of initiating anticoagulation represents a challenge among those discharged from the emergency department (ED). Also, patients who have presented to the ED and have been discharged may be less likely to wish to return to participate in a clinical study. Likewise, given the increasing familiarity of ED physicians with the DOACs and emerging evidence for the use of DOACs among patients with malignancy, we acknowledge that physicians will be increasingly adopting use of the DOACs routinely, which could diminish enrollment in our study. For these reasons, our ED physician co-investigators have routinely interfaced with their ED physician colleagues to remind them of the study, and we have placed fliers in the ED physician work stations and engage our peripheral vascular laboratory technicians to aid in patient identification. We have continued to highlight the value of prospective evidence regarding the use of DOACs in this patient population during routine ED physician meetings in the hopes of mitigating this challenge.

It is estimated that 30% to 40% of all UEDVT occurs in the setting of cancer. The odds for thrombosis of the upper extremity among cancer patients when compared with patients without cancer has been estimated to be as high as 18% (95% CI, 9.4%-35%).^{53,55} Understanding the safety and efficacy of apixaban among patients with cancer-associated UEDVT (CAUEDVT) is an unmet need. Because of this and with the advent of evidence supportive of the use of DOACs among patients with CAT, we elected to modify our protocol to permit the enrollment of patients with cancer. Our experience among patients with CAUEDVT in conjunction with that from clinical trials enrolling exclusively patients with CAUEDVT²⁹ will provide valuable information regarding the use of apixaban among these patients. Patients with CAUEDVT were not eligible in our initial study design, and therefore our power calculation was not informed by taking into consideration the risk for recurrent thrombosis among this group. The inclusion of these patients introduces a limitation, given that they may be at an increased risk for recurrent thrombosis as compared with patients who experience UEDVT without cancer. The decision to include these patients may adversely affect our ability to refute the null hypothesis that apixaban is noninferior to our historical control. To mitigate this limitation, we will report outcome rates separately among patients with CAUEDVT and perform sensitivity analyses with and without patients with cancer.

Most patients with CAUEDVT experience thrombosis in the setting of a triad of Virchow's risk factors (stasis, endothelial injury, and hypercoagulability). Catheter presence promotes endothelial interruption and irritation, facilitating thrombin generation and fibrin

sheath development over the catheter itself (which may begin as soon as 1 hour after insertion).⁵⁶ PICCs in particular have been described as being associated with an increased risk for thrombosis when compared with other CVCs,^{57,58} and lumen diameter in conjunction with duration present appear to be additional risks.^{43,59,60} Anticoagulant thromboprophylaxis in randomized controlled trials among high-risk patients with CVCs has not demonstrated efficacy,^{7,61,62} and guidelines presently recommend against thromboprophylaxis among patients with CVCs.^{31,33,63} For these reasons, assuring that safe and effective therapy exists when UEDVT is present continues to be of paramount importance.

We anticipate that the prospective administration of apixaban for clinically symptomatic UEDVT will be associated with a rate of recurrent VTE that is acceptable when compared with the historical controls reported in the literature, and a favorable safety profile analogous to that seen in former studies of apixaban.

8 | CONCLUSION

ARM-DVT will represent the largest prospective clinical study assessing anticoagulant therapy for the treatment of UEDVT. Subgroup analyses, including those among patients with UEDVT and cancer, will be hypothesis generating and contributory to ongoing and possible future studies treating patients with cancer and UEDVT using apixaban. If this study achieves outcomes as defined, in the absence of a randomized clinical trial, these results may inform standard therapy for the treatment of UEDVT.

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AUTHOR CONTRIBUTIONS

SCW, SMS, RSE, and EW designed the research; SCW, SMS, SAJ, JL, BA, JB, and EW are performing the research; SCW, SMS, and EW undertook the statistical analysis planning; SCW, SMS, and SAJ are responsible for clinical aspects; and SCW, SMS, SAJ, JB, BG, RSE, and EW wrote the paper. All authors contributed to and approved the final version of the paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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