

COMMENTARY

Studies in upper extremity deep vein thrombosis: Addressing the knowledge gaps

Alejandro Lazo-Langner MD MSc FRCPC^{1,2,3}  ¹Department of Medicine, Division of Hematology, Western University, London, ON, Canada²Department of Epidemiology and Biostatistics, Western University, London, ON, Canada³Department of Oncology, Western University, London, ON, CanadaThis is a commentary on *Woller et al* [2019]: <https://doi.org/10.1002/rth2.12208>**Correspondence**Alejandro Lazo-Langner, Hematology Division, London Health Sciences Centre, 800 Commissioners Rd E, Rm E6-216A, London, ON N6A 5W9, Canada.
Email: alejandro.lazolangner@lhsc.on.ca**Funding information**

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Upper extremity deep vein thrombosis (UEDVT) is a relatively uncommon form of venous thrombosis, accounting for 5% to 10% of all deep vein thromboses (DVTs), with an annual incidence of 0.5 to 1 case per 10 000 patient-years. This means that approximately 2500 to 5000 new cases will be diagnosed in Canada in a year.¹ As with other forms of thrombosis, the cornerstone of its treatment is the use of anticoagulant therapy to prevent recurrences and other complications including pulmonary embolism. However, given the relatively low frequency of this type of thrombosis, there is a paucity of high-quality data regarding many aspects of this condition, including diagnosis, prognosis, chronic complications, and, most importantly, treatment (Table 1).²

In this issue of *RPTH*, Woller and colleagues report the protocol for a large prospective management cohort (the ARM-DVT study) aiming to assess the use of apixaban at standard doses for 12 weeks in patients diagnosed with UEDVT involving any vein from the ulnar and radial to the internal jugular.³ The study outcomes will be assessed at 90 days and include a composite of clinically overt recurrent venous thromboembolism (VTE) and VTE-related death and a composite of major and clinically relevant nonmajor bleeding. Additionally, they also will assess a number of secondary outcomes, including postthrombotic syndrome and quality of life. The authors aim to enroll 357 patients and plan to match the apixaban population with a historic cohort treated with warfarin. If successful, this will be the largest study assessing apixaban in this setting and will add to the scant existing information about the use of oral direct factor Xa inhibitors, together with a recently published study⁴

and another study currently ongoing (ClinicalTrials.gov identifier: NCT03100071). Most importantly, the study proposed by Woller and colleagues highlights the many voids that exist regarding our knowledge about UEDVT.

The pathophysiology of UEDVT differs depending on the type of thrombosis. The primary form of UEDVT represents the venous subtype of the vascular thoracic outlet syndrome, also known as Paget-Schroetter syndrome, and is a rare condition accounting for <10% to 20% of all UEDVT events. The secondary forms of UEDVT are much more frequent, and most present in patients with cancer and are associated with central venous catheters or peripherally inserted central catheters.⁵ Additionally, some patients develop UEDVT secondary to external compression by tumors or to other nonmalignant conditions, such as the presence of pacemaker leads or recent surgical interventions. Given the different pathophysiology, it is not clear whether anticoagulation alone is effective in both forms. Two previous prospective studies evaluating the use of low-molecular-weight heparin (LMWH) followed by warfarin in patients with both forms of UEDVT found that anticoagulation alone seems to be equally effective in preventing thrombotic recurrences in either type.^{6,7} Therefore, for any study in this area it is important to evaluate thrombosis recurrence according to the subtype of UEDVT. Woller and colleagues plan to report outcomes separately for patients with cancer and for those with indwelling catheters. While this will certainly provide more information regarding the effectiveness and safety of apixaban in each type of UEDVT, it will also result in a reduction of the statistical power to detect clinically relevant event

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TABLE 1 Key research questions in studies evaluating upper extremity deep vein thrombosis

1. Is anticoagulant therapy alone equally effective in preventing thrombotic recurrences in patients with primary and secondary forms of UEDVT?
2. Are all classes of anticoagulants equally safe and effective in both primary and secondary forms of UEDVT and in particular in catheter-related UEDVT?
3. Is there any difference in the risk of postthrombotic syndrome in patients with primary UEDVT compared to patients with secondary forms?
4. Is there a role for adjuvant invasive interventions including thrombolysis, thrombectomy, and decompression surgery?
5. Is anticoagulation needed for patients with distal UEDVT?
6. What is the optimal duration of treatment in patients with primary UEDVT and in particular in patients with Paget-Schroetter syndrome?

UEDVT, upper extremity deep vein thrombosis.

rates in these subgroups. This will have to be considered when interpreting their final data.

Whether all thromboses of the deep veins in the upper extremity should be anticoagulated is not clear. It has been our institutional practice to anticoagulate only those patients with thromboses involving the axillary or more proximal veins, and in fact such is the most recent recommendation of the American College of Chest Physicians.⁸ In those patients with thromboses affecting the brachial or more distal veins, we use nonsteroidal anti-inflammatory drugs and perform sequential ultrasounds to rule out proximal extension. To date, no study has compared anticoagulation versus active surveillance in either UEDVT or DVT of the lower extremity, but a recent randomized trial in patients with isolated DVT of the calf comparing nadroparin with placebo found that anticoagulation did not reduce the risk of proximal extension and increased the risk of bleeding.⁹ In the study proposed by Woller and colleagues, the authors will include patients with both distal and proximal thromboses. It is not clear if they plan to analyze separately the outcomes according to the anatomic location of the thrombosis. The ARM-DVT study would be a unique opportunity to answer this pending question.

Another important area that is not well studied in UEDVT is chronic complications, and in particular the development of postthrombotic syndrome (PTS). The best way to evaluate the presence of PTS is through the use of the Villalta scale modified for the upper extremity, which has been validated for this purpose.¹⁰ A careful evaluation of this outcome is particularly important, especially because previous studies have shown that the presence of PTS is associated with higher disability scores.¹¹ Our recent systematic review found that the overall risk of PTS in UEDVT is around 19% and maybe lower in patients with catheter-related UEDVT, although this may be confounded by the presence of a competing risk of death in cancer patients.¹ Although there is no information about PTS in patients treated with direct oral anticoagulants, it has been shown that in patients treated with LMWH followed by warfarin, the occurrence

of PTS is similar in patients with primary or secondary UEDVT.⁶ However, indirect evidence suggests that in patients treated with anticoagulants alone, the occurrence of PTS is higher compared to patients treated with surgery and/or thrombolysis,¹ although the lack of direct comparisons prevent drawing any definitive conclusions. On the other hand, in patients with DVT of the lower extremities, the use of thrombolysis is associated with higher bleeding risk but no reduction in PTS,^{12,13} and thus the current guidelines suggest reserving thrombolysis only for cases with impending risk to the affected limb for both lower and upper extremity DVT.⁸ Nonetheless, given the difference in the pathophysiology of UEDVT, and specifically in patients with Paget-Schroetter syndrome, the jury is still out.

Regarding the safety of anticoagulation in patients with UEDVT, our recent meta-analysis reported an overall occurrence of major bleeding events of 5%, although the data were limited by the use of different clinical definitions of bleeding, and all but 1 study used warfarin.¹ To date, only 1 prospective study evaluating the use of rivaroxaban has been published in patients with UEDVT associated with catheters.⁴ This study reported 13% of bleeding events (8% major), most of them during the first 30 days, as well as 1 fatal pulmonary embolism while on treatment. To the best of my knowledge, no other prospective studies using direct oral anticoagulants have been published. Furthermore, recent studies of oral direct factor Xa inhibitors in cancer patients have suggested a higher risk for bleeding in this population, especially in patients with gastrointestinal tumors.^{14,15} Given that a large proportion of patients with UEDVT have cancer, the use of these agents in this population should be carefully pondered, and safety monitoring should be required in any study conducted in this area.

Finally, the optimal duration of anticoagulant treatment in this population is not well established. Whereas in catheter-related UEDVT, a minimum of 3 months of treatment is recommended, or for as long as the catheter is in place, in patients with primary UEDVT and proven Paget-Schroetter syndrome this is not clear. Our group conducted a previous prospective study using standardized regimens for patients with UEDVT: For catheter-related UEDVT, patients received LMWH for at least 5 days, followed by warfarin for a minimum of 3 months or for as long as the line was in place, whereas for those with events that were not related to catheters, all patients received 6 months of anticoagulation. This study found similar rates of VTE recurrence and PTS in both groups of patients at 2 years of follow-up.^{6,11} However, a limitation of the study is that patients were not systematically assessed for the presence of thoracic outlet syndrome.

In summary, our knowledge about UEDVT is currently limited by the lack of systematic high-quality data, standardized outcome definitions, and inadequate analysis of the different UEDVT subtypes. In addition to the urgent need for a consensus in this area, future studies should consider these limitations at the design stage.

RELATIONSHIP DISCLOSURE

The author reports nothing to disclose.

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ORCID

Alejandro Lazo-Langner  <https://orcid.org/0000-0001-6869-8431>

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