THE PRACTICAL MANAGEMENT OF EXTENSIVE DEEP VEIN THROMBOSIS

A SURVEY OF THROMBOSIS SPECIALISTS ON THE PRACTICAL MANAGEMENT OF EXTENSIVE DEEP VEIN THROMBOSIS AND A PROTOCOL FOR A RANDOMIZED TRIAL

By

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TITLE: A Survey of Thrombosis Specialists on the Practical Management of Extensive Deep Vein Thrombosis and a Protocol for a Randomized Trial

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ABSTRACT

BACKGROUND: Though direct oral anticoagulants (DOACs) have become a standard of care in the treatment of acute deep vein thrombosis (DVT), it is our observation that physicians tend to initiate heparin or low-molecular-weight heparin, hereafter called “heparin”, for the treatment of extensive DVT or phlegmasia cerulea dolens (PCD). This might be due to a perception that heparin might relieve DVT-related symptoms more quickly than DOACs. Whether these assumptions are true has not been evaluated.

METHODS: We conducted a survey of thrombosis specialists in North America to explore the practical management of anticoagulant therapy in patients with extensive DVT, and the underlying reasons for the selection of heparin over DOACs. A cross-sectional, web-based survey was distributed to thrombosis specialists who are members of four thrombosis societies.

RESULTS: Eighty-nine respondents provided consent. Most respondents selected DOACs over heparin in a case scenario representing mild DVT-related symptoms and limited thrombus involvement (81% vs. 19%). Most respondents selected heparin over DOACs in a case scenario representing early stage PCD (84% vs.16.3%) or a patient with high bodyweight (72% vs. 28%). In a case scenario representing extensive DVT, 57.4% of the respondents selected heparin, whereas, 42.6% selected DOACs. In the respondents who selected heparin over DOACs, the major reason was that heparin might relieve DVT-related symptoms more quickly because of its anti-inflammatory effects.

DISCUSSION: Severity of DVT-related symptoms, thrombus extent, and bodyweight play a role in the selection of anticoagulant therapy. Despite a lack of evidence to support the hypothesis with respect to which anticoagulant is superior, most thrombosis specialists selected heparin over DOACs in patients with severe DVT-related symptoms and extensive thrombus involvement. Observation of variations in the selection of anticoagulant therapy for the treatment of extensive DVT also indicates that clinical trials in this patient population are needed.

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Section I: Introduction

Primary thesis question

Can direct oral anticoagulants be effectively used as an initial anticoagulant therapy for the treatment of extensive deep vein thrombosis compared with the conventional anticoagulant treatment?

Overview of the thesis

The thesis comprises 4 parts including: introduction, a survey of thrombosis specialists on the practical management of extensive deep vein thrombosis, a protocol of a randomized trial investigating rivaroxaban vs. a short course of low-molecular-weight heparin in patients with extensive deep vein thrombosis, and a validation study for the deep vein thrombosis leg symptom index, a measurement tool that will be used in the randomized trial.

Background

Extensive deep vein thrombosis (DVT) predisposes its patient to severe symptoms. As a result of venous obstruction and inflammatory response, clinical signs and symptoms of extensive DVT include marked swelling, erythema, pain, and tenderness of the affected extremities. If left untreated, extensive venous thrombosis may lead to venous gangrene or "phlegmasia cerulea dolens" (PCD), a rare complication of DVT which is associated with high morbidity and mortality.[1] Extensive thrombus involvement also increases the risk of residual vein thrombosis (adjusted OR, 3.58; 95% CI, 2.19-5.86); residual vein thrombosis at 3 months increases the risk of post-thrombotic syndrome (PTS)[2], a chronic complication following DVT which occurs in 20-50% of patients.[3,4] Of those, severe PTS occurs in

up to 10%. Severe PTS has a negative impact on health-related quality of life and could result in long-term disability.[5]

The treatment of patients with extensive DVT or phlegmasia cerulea dolens (PCD) is of great clinical concern. The practical management of these patients is varied among physicians and there is no guideline recommendation for this specific population. Though randomized controlled trials have found no difference in the rates of recurrent venous thromboembolism (VTE) between direct oral anticoagulants (DOACs) and low-molecular-weight heparin (LMWH) transitioned to vitamin K antagonists (VKA) in unselected VTE patients[6], whether patients with extensive DVT who have severe DVT-related symptoms have been included in those trials have not been documented. It is our observation that physicians tend to initiate treatment with heparin or LMWH in these patients due to a perception that more severe symptoms require more intensive therapy, or heparin or LMWH have anti-inflammatory effects which could improve DVT-related symptoms more quickly. Whether DOACs can be effectively used in the acute treatment of extensive DVT, or early stage PCD, has not been studied.

Literature review

Definition and significance of extensive DVT

Though there is no standard definition of extensive DVT, it is acceptable to most physicians that venous thrombosis locates at the iliac or common femoral veins is considered "extensive". This is due to the fact that iliofemoral vein thrombosis is associated with the greatest risk for PTS morbidity and increases the risk of recurrent VTE.[4,7-9]

In most studies, extensive thrombus was defined objectively based on the location of thrombus involvement which was documented by compression ultrasound or venography. In case reports and modest size observational studies, "extensive thrombosis" was variably used to describe patients with varying degrees of DVT-related symptoms, but had a large thrombus burden, or a thrombus in the iliofemoral segment (table1).[10-19] In a prospective cohort study investigating the impact of residual vein thrombosis on recurrent VTE, and PTS development, extensive thrombosis was defined by thrombosis confined to the popliteal and common femoral veins.[2] In this study, 39% of 869 patients met the definition of extensive DVT. As for a randomized trial, in a pooled analysis of the EINSTEIN-DVT and EINSTEIN-PE studies in which 8,282 patients with acute VTE were randomized to receive either LMWH transitioned to vitamin K antagonists (VKA) or rivaroxaban, extensive clot burden was defined by thrombus involvement of the common femoral vein and/or the iliac veins. Of those, 32.5% of the patients met the objective definition of extensive clot burden (including both extensive DVT and extensive PE).[20] The Hokusai study in which patients with acute VTE were randomized to receive either LMWH transitioned to warfarin or LMWH/edoxaban, extensive DVT was defined by an event in which the most proximal site of thrombus was the common femoral or iliac veins. Of the 4,921 patients enrolled in the study, 25.3% met the definition of extensive DVT.[21] In the AMPLIFY study which enrolled 5,395 patients with acute VTE, though they did not specify the definition of extensive DVT, 43% of the patients had the most proximal location of DVT at the common femoral or iliac veins.[22]

Unlike extensive DVT that has objective definition, the diagnosis of PCD relies on clinical signs and symptoms suggestive of ischemia along with the

documentation of venous thrombosis. Four cardinal signs that are required for the diagnosis of PCD include edema, violaceous discoloration, pain, and severe flow obstruction.[23] The severity of PCD can be categorized into non-complicated PCD (grade I), impending venous gangrene (grade II), and venous gangrene (grade III). Non-complicated PCD is defined by the presence of cyanosis, preserving distal pulses of affected extremities without signs of neurologic impairments or venous gangrene. In this stage, the ischemic process can be reversed if anticoagulant treatment is given. Impending venous gangrene is defined by the presence of cyanosis, blistering skin, mild neurologic impairments, and diminishing of the distal pulses without signs of venous gangrene. In the last stage or venous gangrene, the ischemic process is irreversible and is associated with high mortality.[1]

Overall, extensive DVT is not uncommon and accounted for up to 40% of patients enrolled in the randomized trials.[20-22]Thrombus involvement at the iliofemoral segment was the most commonly used definition. Though extensive DVT usually associates with severe DVT-related symptoms, whether patients who had severe symptoms or who were suspicious of PCD have been included in the previous randomized trials compared DOACs with LMWH/warfarin has not been documented.

Current evidence of DOACs for the treatment of extensive DVT

To date, the evidence of DOACs' use in patients with extensive DVT was derived from randomized trials that compared DOACs with LMWH transitioned to warfarin in patients with acute VTE. In these trials, the results of a subgroup analysis on the location of thrombus or thrombus burden were reported. In the subgroup analysis of extensive clot burden from the pooled EINSTEIN DVT, PE studies,

recurrent VTE occurred in 35 of 1364 (2.6%) patients in the rivaroxaban group and occurred in 26 of 1327 (2%) in the LMWH/VKA group (hazard ratios, 1.29, 95% CI, 0.78-2.15). The interaction test between clot burden and the outcome revealed a non-significant result.[20] It was noted that the study had combined both extensive DVT and pulmonary embolism as the outcomes of interest. In the AMPLIFY study, the subgroup analysis based on the anatomical extent of DVT demonstrated that in patients with iliac or common femoral vein thrombosis, recurrent VTE occurred in 18 of 730 patients (2.5%) in the apixaban group, and in 26 of 725 patients (3.6%) in the LMWH/warfarin group.[22] In the RECOVER I, II, and the Hokusai studies, which investigated dabigatran and edoxaban, the results of the subgroup analysis according to the extent of thrombosis were not reported.[21,24,25]

In terms of bleeding outcomes, the subgroup analysis of extensive VTE from the pooled EINSTIEN DVT, PE studies demonstrated a comparable rate of major and clinically relevant non-major bleeding between the 2 groups (126 in 1359, 9.3% in the rivaroxaban vs. 134 in 1326, 10.1% in the LMWH/VKA groups, hazard ratio, 0.9, 95% CI 0.71-1.15). In the AMPLIFY study, the rate of major bleeding in the subgroup of patients with iliac or common femoral vein thrombosis was lower in the apixaban group compared with that in the LMWH/VKA group (2 in 746, 0.2% vs. 11 in 750, 1.46%, respectively). However, the interaction test between the extent of DVT and the bleeding outcome revealed a non-significant interaction.

Meta-analysis of the RCTs

To provide evidence regarding the efficacy and safety of DOACs compared with LMWH/VKA in the subgroup of patients with extensive DVT, a meta-analysis of

the 2 RCTs was conducted. The table summarizing the characteristics of the studies and risk of bias assessment using the Cochrane Collaboration's tool for assessing the risk of bias is presented (Table 2, Figure 1). The primary efficacy outcome was recurrent VTE and/or VTE-related death. The primary safety outcome was major bleeding. It is noted that the primary efficacy outcome of the pooled EINSTEIN DVT, PE studies was extensive clot burden including both DVT and PE, whereas the primary efficacy outcome in the AMPLIFY study was only DVT.

The data from the pooled EINSTEIN DVT, PE and AMPLIFY studies were meta-analyzed using the Mantel-Haenszel, random effects model. A random effects model was used based on the assumption that heterogeneity was expected as a result of variation in the type of DOAC, and the duration of treatment. The effect measures for each study were calculated and reported in relative risk and 95% confidence interval (CI). Heterogeneity was assessed using the Cochrane Q statistic and a p-value < 0.05 denoted significant heterogeneity. In addition, the I^2 statistic was calculated to provide a quantitative estimate of heterogeneity. However, due to unavailable data, subgroup analyses or an exploratory analyses for heterogeneity could not be performed. The meta-analyses were performed using Review Manager 5.3 software.

For the efficacy outcome, recurrent VTE occurred in 53 of 2,094 patients (2.53%) in the DOAC group, and in 52 of 2,052 patients (2.53%) in the LMWH/VKA group (Relative risk, 0.97, 95% CI, 0.52-1.82, $I^2 = 62\%$) (Figure 2).

For the safety outcome, major bleeding occurred in 13 of 2,105 (0.62%) in the DOAC group, and occurred in 39 of 2,076 patients (1.87%) in the LMWH/VKA group (Relative risk 0.34, 95% CI 0.18- 0.63, $p<0.001$, $I^2=0\%$) (Figure 3).

Despite moderate heterogeneity, the results of the pooled effect estimate from the two randomized trials demonstrated that the use of DOAC in extensive DVT was not associated with an increased risk of recurrent VTE. On the other hand, the use of DOAC was associated with a 66% relative reduction in risk of major bleeding.

Though data from only two phase III randomized trials were available, rivaroxaban and apixaban represent DOACs that can be initiated without a need for bridging heparin therapy. The population enrolled in the EINSTEIN and the AMPLIFY studies was homogeneous. The trials were well-designed and conducted. The outcomes were similarly defined and objectively measured. Thus, the results from this meta-analysis suggest a comparable efficacy of DOACs with LMWH/VKA in the prevention of recurrent VTE, and the DOAC use was associated with a lower risk of major bleeding in the subgroup of patients with extensive DVT.

Current evidence of DOACs in PCD

Based on anatomic and pathophysiologic knowledge, a thrombosis at the iliac or common femoral veins predisposes patients to severe DVT-related symptoms.[26] However, whether patients with iliofemoral vein thrombosis who were included in the randomized trials had severe DVT-related symptoms, or suspicion of PCD, was not documented. Thus, the evidence of DOAC use in patients with severe DVT-related symptoms or suspicion of PCD remains unknown.

Other treatment considerations in extensive DVT

Currently, there are several clinical trials investigating addition of catheter-direct thrombolysis (CDT) to standard anticoagulant therapy in patients with extensive

DVT. Rapid thrombolysis can restore valve function at sites of thrombosis and might prevent the development of PTS.[27] A randomized trial which enrolled 189 patients with the diagnosis of iliofemoral DVT found that the use of additional CDT to anticoagulant therapy was associated with a significant risk reduction of PTS development at 2 years, but also increased the risk of bleeding. In addition, quality of life at 2 and 5 years in the patients who received additional CDT was not significantly different when compared with those who received standard anticoagulant therapy.[28,29] In a larger randomized trial which enrolled patients with acute DVT involving the femoral, common femoral, and/or iliac vein, the preliminary results demonstrated that in patients who received an additional pharmacomechanical CDT to the standard anticoagulation, the rate of PTS at 2 years was not significantly different compared with that in patients who receive only standard anticoagulation. However, moderate to severe PTS occurred numerically less frequently in patients with iliofemoral DVT in the pharmacomechanical CDT group than those receiving standard anticoagulation; whether this was statistically significant was not presented.[30] Current guidelines do not generally recommend CDT for patients with DVT, but patients who are most likely to benefit from CDT are those who have iliofemoral vein thrombosis, symptoms for < 14 days, good functional status, life expectancy ≥ 1 years, and a low risk of bleeding.[31]

DVT-related symptoms and PTS as outcomes in a randomized trial

Though physicians usually determine response to anticoagulant therapy by clinical assessment, DVT-related symptom improvement has not been pre-specified as an outcome in most randomized studies. This might be due to the fact that the

improvement in DVT-related symptoms is a subjective measurement which is prone to observer error and reporting bias. In addition, the measurement of DVT-related symptoms might not be such an important outcome in general since anticoagulant therapy typically quickly relieves symptoms. However, in a subset of patients with extensive DVT, or suspected PCD who suffer from severe symptoms, the relief of symptoms is likely to be the first clinical indicator of the success of anticoagulant treatment and will guide physicians for further anticoagulant management.

To date, little evidence is available on the choice of anticoagulant therapy between either LMWH/warfarin or DOACs, and the development of PTS. A meta-analysis of two randomized trials found that long-term LMWH treatment lowers the risk of PTS development compared with LMWH transitioned to VKA.[32] A post-hoc analysis of 336 patients enrolled in the EINSTEIN-DVT study demonstrated that the cumulative PTS incidence at 60-months follow-up in the patients who received rivaroxaban was lower in number, but not statistically significant when compared with those given LMWH/VKA (29% vs. 40%, respectively).[33] In the previous randomized trials, PTS has not been pre-specified as an outcome.

Why the trial is needed?

Though rivaroxaban and apixaban can be initially administered without need for bridging therapy, and have a comparable efficacy in the prevention of recurrent VTE in the subset of patients with extensive DVT, it is our observation that physicians tend to give a short course of LMWHs instead of the DOACs as an initial anticoagulant therapy in patients with extensive DVT or those with severe DVT-related symptoms. This might be due to a perception that LMWHs are more effective,

or they have anti-inflammatory effects which could result in better outcomes in the acute phase of VTE treatment such as they might relieve the symptoms more quickly. In general, however, LMWHs are relatively costlier compared with the DOACs, and are inconvenient for patients or their caregivers because of the subcutaneous route of administration.

Therefore, in order to support our observations, we conducted a survey of thrombosis specialists to explore the practical management of anticoagulant therapy and their underlying reasons for the treatment of extensive DVT or early stage of PCD. The results of the survey illustrate gaps in knowledge and provide evidence supporting the need for the proposed randomized trial.

Tables and figures

Table 1 Extensive DVT definition in case reports and observational studies

Author, year of publication	Type of study (n)	Clinical presentation	Definition of extensive DVT
Bendrups, 1988[10]	Case report	PCD	Iliofemoral DVT
Frazee, 2006[34]	Case report	Leg pain and swelling	Common femoral vein thrombosis
Max Senna Mano, 2006[14]	Case report	Bilateral leg pain and edema	Extending from both popliteal veins up to the thoracic segment of the inferior vena cava, close to the entrance to the right atrium
Ioannidou-Papagiannak, 2009[11]	Case report	Upper limb edema	Left brachiocephalic, subclavian and internal jugular veins, extensive thrombosis of the right femoral and popliteal veins
La Spada, 2010[13]	Case report	Acute bilateral swelling of the legs and elevated pain.	Complete acute DVT extending from the popliteal veins to the suprarenal vena cava and with thrombosis of the right renal vein
Telich-Tarriba, 2012[18]	Case report	Swelling and pitting edema over the affected lower extremity, PCD	Extensive echolucent density that was not compressible through the deep venous system extending from the tibial veins upward, with a total occlusion of the outflow from the extremity

Wormald, 2012[19]	Case report	Markedly swollen and comparatively cooler with impalpable left popliteal	Complete occlusion extending from the left posterior tibial vein to the common iliac vein
Sagar, 1970[17]	Observational (84)	Not reported	Femoral vein thrombi
Mumme, 2002[15]	Observational (53)	Occlusive DVT, PCD	DVT, three segments, four segments
Kölbel, 2007[12]	Observational (37)	Limb swelling, severe limb pain	Iliocaval segment
O'Connell, 2009[16]	Observational (667)	Not reported	Proximal iliofemoral or extensive femoral DVT

PCD = phlegmasia cerulea dolens, DVT = deep vein thrombosis

Table 2 Characteristic of included studies

Study	Indication	Type and dose	Comparator	Primary efficacy outcome	Primary safety outcome
Pooled EINSTEIN DVT-PE	Acute VTE	Rivaroxaban 15 mg bid x3 weeks, then 20 mg OD	Enoxaparin/ VKA	Recurrent symptomatic VTE	Major bleeding
AMPLIFY	Acute VTE	Apixaban 10 mg bid x7 days, then 5 mg bid	Enoxaparin /warfarin	Recurrent symptomatic VTE or VTE-related death	Major bleeding

VTE= venous thromboembolism, VKA= vitamin K antagonist, bid= twice a day, OD= once a day

Figure 1 Risk of bias assessment

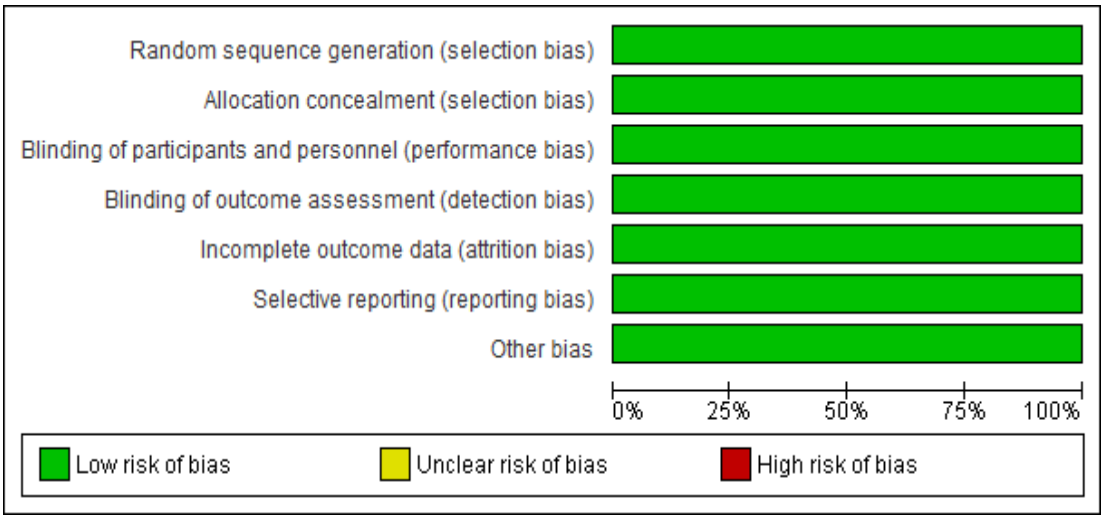


Figure 2 Primary efficacy outcome

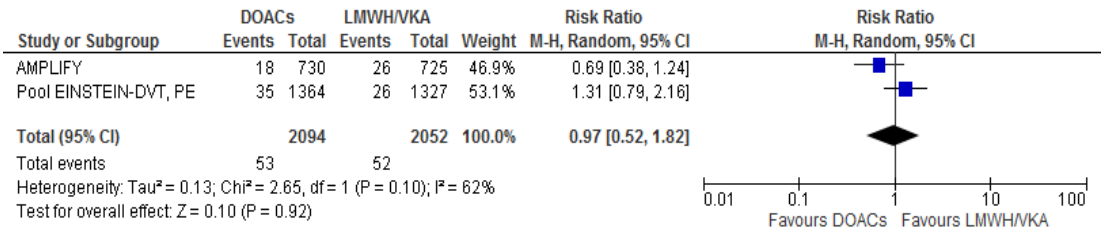
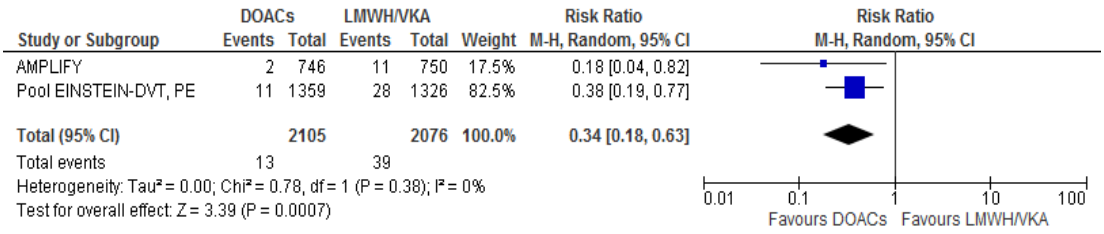


Figure 3 Primary safety outcome



References

1. Chinsakchai K, Ten Duis K, Moll FL, de Borst GJ. Trends in management of phlegmasia cerulea dolens. *Vasc Endovascular Surg*. 2011;45(1):5-14.

2. Prandoni P, Lensing AW, Prins MH, et al. The impact of residual thrombosis on the long-term outcome of patients with deep venous thrombosis treated with conventional anticoagulation. *Semin Thromb Hemost*. 2015;41(2):133-140.

3. Prandoni P, Lensing AW, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med*. 1996;125(1):1-7.

4. Kahn SR, Shrier I, Julian JA, et al. Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med*. 2008;149(10):698-707.

5. Kahn SR, Hirsch A, Shrier I. Effect of postthrombotic syndrome on health-related quality of life after deep venous thrombosis. *Arch Intern Med*. 2002;162(10):1144-1148.

6. van Es N, Coppens M, Schulman S, Middeldorp S, Buller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood*. 2014;124(12):1968-1975.

7. Delis KT, Bountouroglou D, Mansfield AO. Venous claudication in iliofemoral thrombosis: long-term effects on venous hemodynamics, clinical status, and quality of life. *Ann Surg*. 2004;239(1):118-126.

8. Tick LW, Kramer MH, Rosendaal FR, Faber WR, Doggen CJ. Risk factors for post-thrombotic syndrome in patients with a first deep venous thrombosis. *J Thromb Haemost*. 2008;6(12):2075-2081.

9. Douketis JD, Crowther MA, Foster GA, Ginsberg JS. Does the location of thrombosis determine the risk of disease recurrence in patients with proximal deep vein thrombosis? *Am J Med*. 2001;110(7):515-519.

10. Bendrups A, van der Weyden MB, Doyle T, Downey WF, Cummings M, Whitworth JA. A 61-year-old man with extensive thrombosis. *Aust N Z J Med*. 1988;18(4):639-644.

11. Ioannidou-Papagiannaki E, Diamantidis MD, Livanis I, et al. Fatal chylous ascites, pericarditis and extensive venous thrombosis, due to an aggressive T cell non-Hodgkin lymphoma. *Ann Hematol*. 2009;88(4):371-373.

12. Kolbel T, Lindh M, Holst J, et al. Extensive acute deep vein thrombosis of the iliocaval segment: midterm results of thrombolysis and stent placement. *J Vasc Interv Radiol*. 2007;18(2):243-250.

13. La Spada M, Stilo F, Carella G, et al. Thrombectomy and surgical reconstruction for extensive iliocaval thrombosis in a patient with agenesis of the retrohepatic vena cava and atresia of the left renal vein. *Ann Vasc Surg*. 2011;25(6):839 e831-834.

14. Mano MS, Guimaraes JL, Sutmoller SF, Reiriz AB, Sutmoller CS, Di Leo A. Extensive deep vein thrombosis as a complication of testicular cancer treated with the BEP protocol (bleomycin, etoposide and cisplatin): case report. *Sao Paulo Med J*. 2006;124(6):343-345.

15. Mumme A, Heinen W, Geier B, Maatz W, Barbera L, Walterbusch G. Regional hyperthermic fibrinolytic perfusion after unsuccessful venous thrombectomy of extensive deep venous thrombosis. *J Vasc Surg*. 2002;36(6):1219-1224.

16. O'Connell JB, Chandra A, Russell MM, et al. Thrombolysis for acute lower extremity deep venous thrombosis in a tertiary care setting. *Ann Vasc Surg*. 2010;24(4):511-517.

17. Sagar S, Nairn D, Stamatakis JD, et al. Efficacy of low-dose heparin in prevention of extensive deep-vein thrombosis in patients undergoing total-hip replacement. *Lancet*. 1976;1(7970):1151-1154.

18. Telich-Tarriba JE, Anaya-Ayala JE, Davies MG, El-Sayed HF. Percutaneous mechanical thrombectomy for extensive acute lower-extremity deep venous thrombosis in a patient after double-lung transplantation. *Ann Vasc Surg*. 2012;26(4):573 e571-574.

19. Wormald JR, Lane TR, Herbert PE, Ellis M, Burfitt NJ, Franklin IJ. Total preservation of patency and valve function after percutaneous pharmacomechanical thrombolysis using the Trellis(R)-8 system for an acute, extensive deep venous thrombosis. *Ann R Coll Surg Engl*. 2012;94(2):e103-105.

20. Prins MH, Lensing AW, Bauersachs R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J*. 2013;11(1):21.

21. Hokusai VTEI, Buller HR, Decousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369(15):1406-1415.

22. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808.

23. Mumoli N, Invernizzi C, Luschi R, Carmignani G, Camaiti A, Cei M. Phlegmasia cerulea dolens. *Circulation*. 2012;125(8):1056-1057.

24. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014;129(7):764-772.

25. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361(24):2342-2352.

26. Jaff MR, McMurtry MS, Archer SL, et al. Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension. *A Scientific Statement From the American Heart Association*. 2011;123(16):1788-1830.

27. Nyamekye I, Merker L. Management of proximal deep vein thrombosis. *Phlebology*. 2012;27 Suppl 2:61-72.

28. Enden T, Haig Y, Klow NE, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet*. 2012;379(9810):31-38.

29. Haig Y, Enden T, Grøtta O, et al. Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial. *The Lancet Haematology*. 2016;3(2):e64-e71.

30. Lou N. Catheter-Based Tx Disappoints for Deep Vein Thrombosis Thrombolytic tx didn't cut post-thrombotic syndrome in trial. March 7, 2017. Retrieved from https://www.medpagetoday.com/meetingcoverage/sir/63676.

31. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for vte disease: Chest guideline and expert panel report. *Chest*. 2016;149(2):315-352.

32. Hull RD, Liang J, Townshend G. Long-term low-molecular-weight heparin and the post-thrombotic syndrome: a systematic review. *Am J Med*. 2011;124(8):756-765.

33. Cheung YW, Middeldorp S, Prins MH, et al. Post-thrombotic syndrome in patients treated with rivaroxaban or enoxaparin/vitamin K antagonists for acute deep-vein thrombosis. A post-hoc analysis. *Thromb Haemost*. 2016;116(4):733-738.

34. Frazee BW, Price DD. Images in emergency medicine. Extensive deep venous thrombosis with dilated collaterals and confirmatory emergency department ultrasound. *Ann Emerg Med*. 2006;47(3):292, 308.

Section II: Practical management of extensive deep vein thrombosis: a survey of thrombosis specialists in North America

Introduction

As discussed in the introduction section, physicians might tend to initiate heparin or low-molecular-weight heparin (hereafter referred to as "heparin" for simplicity) for the treatment of extensive deep vein thrombosis (DVT) due to a perception that heparin is more effective, or can relieve DVT-related symptoms more quickly, than direct oral anticoagulants (DOACs). Whether this assumption is true has not been evaluated.

Research questions

1. Among thrombosis specialists, what are the anticoagulant treatments of choice and the underlying reasons for selecting heparin instead of DOACs in patients with extensive DVT?
2. What are the opinions of thrombosis specialists on the effect of heparin on the duration of DVT-related symptoms and the development of post-thrombotic syndrome compared with DOACs?

Overview of the survey

This cross-sectional web-based survey comprised 4 case-based scenarios representing DVT patients with varying degrees of DVT-related symptoms and thrombus extent. The target population of the survey was thrombosis specialists in North America. The main objective of this survey was to provide evidence to support the development of a randomized trial. Observation of variations in practical anticoagulant management among thrombosis specialists would suggest a gap in knowledge in this specific population; understanding the reasons for the selection of

heparin over DOACs would help us understanding practical management considerations in patients with this condition. In addition, the survey aimed to provide evidence supporting a rationale for using DVT-related symptoms and the development of post-thrombotic syndrome (PTS) as outcomes.

Specific aims

1. To demonstrate variations in anticoagulant selection among thrombosis specialists in patients with extensive DVT.
2. To describe the underlying reasons for the selection of anticoagulant therapy in patients with extensive DVT.
3. To demonstrate the opinions among thrombosis specialists on how heparin or DOACs effects on the duration of DVT-related symptoms and the development of PTS in patients with extensive DVT.
4. To explore the practical duration of initial heparin therapy in patients with extensive DVT.

Hypotheses

1. Most thrombosis specialists would select DOACs in patients with mild DVT-related symptoms and limited thrombus extent, whereas they would select heparin in patients with plegmasia cerulea dolens (PCD). In patients with extensive DVT, variations in the selection of anticoagulant therapy would be substantial.
2. Thrombosis specialists would select heparin in preference to DOACs in patients with extensive DVT or PCD due to a perception that heparin is more

effective than DOACs, or that heparin might relieve DVT-related symptoms more quickly because of its anti-inflammatory effects.

3. The degree of uncertainty around if, and how, heparin or DOACs effects the duration of DVT-related symptoms and the development of PTS in patients with extensive DVT, would be considerable.

Methods

Target population

The target population was thrombosis specialists in North America. However, thrombosis specialists in other countries could participate if they were on the email lists of the participating organizations. The sampling frame for the target population was the members of thrombosis societies including Thrombosis Canada, Canadian Venous Thromboembolism Clinical Trials and Outcomes Research (CANVector) network, the Anticoagulant Forum and the International Society on Thrombosis and Hemostasis (ISTH). The sampling technique used was simple random sampling of all members of the stated thrombosis societies. Within those societies participation was limited to those with a contact email address and access to the web-based survey.

Survey development

As the survey aimed to explore practical anticoagulant management, a case-based scenario question was the most reasonable approach. Each case scenario was formulated to evaluate different degrees of clinical severity of DVT and thrombus extent. The concept was derived from the hypotheses that the majority of thrombosis specialists tend to select heparin instead of DOACs in patients with the most severe-

DVT related symptoms, and they tend to select DOACs in patients with more mild DVT-related symptoms.

The definition of extensive DVT in this survey was aligned with the definition of extensive DVT in randomized trials, however, some modifications were made. Extensive DVT was defined as the extension of thrombus from at least the common femoral vein to the popliteal vein, unlike the definition in the randomized trials which used the most proximal location at the common femoral vein. Extensive thrombus involvement usually associates with severe DVT-related symptom and those symptoms can be varied from markedly swollen with or without signs of local inflammation (extensive DVT), purplish discoloration suggestive of relative venous ischemia (uncomplicated PCD), to the worst-case scenario, venous gangrene. Since impending venous gangrene and venous gangrene are life-threatening conditions in which interventional or surgical management is urgently needed, these case scenarios were not included in the survey.

Each case scenario was developed using a prototypical clinical situation within which uncertainty might be observed in day-to-day clinical practice. Four clinical scenarios with varying in a degree of DVT-related symptoms and thrombus involvement were developed. The first case scenario aimed to represent a patient with mild DVT-related symptoms (mildly swollen leg [2-centimeter difference between the diameter of the affected and unaffected legs], without signs of inflammation) and with limited thrombus involvement. This case scenario represented the most common clinical situation encountering in clinical practice. The second case scenario aimed to represent a patient with extensive DVT (marked swollen leg [5-centimeter difference

between the diameters of the affected vs. unaffected legs], with signs of local inflammation) and extensive thrombus involvement. This case scenario represented the population of interest in which substantial variations in the selection of anticoagulant therapy was expected. The third case scenario aimed to represent a patient with uncomplicated PCD (marked swollen leg [7.5-centimeter difference between the diameters of the affected vs. unaffected legs], with signs of local inflammation and relative ischemia) with extensive thrombus involvement (similar thrombus extent as in the second case). After these three case scenarios were developed, another case scenario with a special condition was added. This condition represented a patient with extremely high bodyweight. Because of they are used at a fixed dose, concerns have arisen about the use of DOACs in those with extreme bodyweight. These concerns might contribute to the decision of selecting heparin rather than DOACs. The clinical scenario was similar to the case with extensive DVT (marked swollen leg [5-centimeter difference between the diameters of the affected vs. unaffected legs], with local signs of inflammation] and extensive thrombus involvement), except for a high bodyweight.

In each scenario question, sub-questions were developed based on the objectives to explore the underlying reasons for selecting heparin as well as the practical duration of initial heparin treatment. Only participants who selected heparin as their initial anticoagulant treatment were asked the sub-questions. In the participants who selected heparin because it might improve DVT-related symptoms more quickly, further underlying reasons such as the anti-inflammatory effects of heparin were explored. For all participants, opinions on how they think heparin would

affect the duration of DVT-related symptoms and the development of PTS, compared with DOACs, were sought.

The response categories and formats were developed based on the type of questions and anticipated responses. The choices of anticoagulant treatment given in each case scenario question were in accordance with the approved anticoagulants for the indication of acute VTE treatment in Canada. Unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) were combined in one response category. The combination was based on the hypothesis that the heparins, regardless of type, have similar anti-inflammatory effects which might influence the participant's selection of anticoagulant treatment. The response formats given in the survey were nominal, or binary. An intermediate response ("I do not know") was included in questions where uncertain responses were anticipated. An open response ("others") was included in the questions in which unanticipated responses were expected. The open responses also helped to identify new themes.

After the case scenarios and the response formats were formed, the questions were transformed into a web-based survey according to the principles described by Dillman[1], when they were applicable. As a respondent-friendly questionnaire is one of the elements that increases response rate[1,2], the questions were intended to be short and concise but to provide sufficient clinical information. The survey was created using the Real Time Electronic Digitally Controlled Analyzer Processor (REDCap) application. REDCap is a mature and secure web application for building and managing online surveys and databases; the implementation in this case is housed at St Joseph's Healthcare, Hamilton.

The first page of the survey was an electronic informed consent which provided a brief introduction, objectives, instruction to complete the survey, and contact information of the researchers. The survey consisted of 2 parts and a total of 29 questions. The first part of the survey was intended to collect background information and experience in the field of thrombosis. The second part of the survey comprised 4 case-based scenario questions. Each scenario question contained 5 sub-questions. The case scenarios were logically ordered from the mildest to the most severe clinical symptoms. Thus, the first case scenario was a patient with mild DVT-related symptoms. The second case scenario was a patient with extensive DVT. The third case was an extreme bodyweight patient with extensive DVT. Finally, the fourth case scenario was a patient with uncomplicated PCD. Each question was created in a similar format and each page contained only 1 question. The logic function was used for the participants who selected heparin. The REDCap application provided a specific link to the survey. A "return function" was available for the participants who discontinued the survey- a specific code was provided so that the participants could resume the survey at their convenience.

Properties of the survey

Reliability

To evaluate the reliability of the survey, test-retest reliability was performed. Test-retest reliability assesses whether the same question posed to the same individual yielded consistent results at a different time. The survey link was sent via email to a group of 3 thrombosis specialists at the St. Joseph's hospital. After the survey was

completed by the thrombosis specialists, it was then repeated by the same individuals within 1-2 weeks. An unweighted Kappa was calculated for agreement. The mean duration of the time between the tests was 1.5 weeks. The unweight Kappa statistic was 0.68. The Kappa statistics were 0.65, 0.44, 0.62 and 0.74 for the 1st, 2nd, 3rd and 4th case scenarios, respectively. A Kappa value of more than 0.6 indicates adequate agreement. [3]

Validity

The survey was validated by content validation. As the survey aimed to explore the practical management of the thrombosis specialists on a specific patient population, clinical expertise is required. Hence, content validation by experts in the field is the most appropriate. Validation by construct or concurrent validity was not plausible because there is no preexisting standardized survey on this specific issue. Face validity was not appropriate since the interpretation of each case scenario requires clinical skills and expertise. The survey was sent to a group of thrombosis specialists who validated whether the survey contents met the objectives and whether each case scenario well represented the intended patient population.

Pilot testing

After content validation, the survey was sent to a group of thrombosis specialists for pilot testing. Pilot testing was performed to test the logic function of the survey, to evaluate flow and the dynamics of the survey, and to identify unusual, redundant, or poorly worded question-stem and response categories. The survey was then revised until the specialists were satisfied with the format of the questions, the response categories, the logic function, and the flow of the survey. Estimated time to

complete the survey was 5-7 minutes. Pilot testing of the survey on different internet browsers and different electronic devices was performed to ensure accuracy and consistency of the survey formats through all platforms.

Survey administration and data collection

Methods to increase the response rate to mail surveys were used.[1,2] Multiple contacts, and offering a financial incentive were the 2 elements that could be applied for this survey. Three reminders were planned at 1, 3, and 7 weeks for non-respondents. In addition, a prize was offered to a random participant who had completed the survey and who provided their email address.

Four thrombosis organizations were contacted and asked if they could distribute the survey to their members. The overview and objectives of the project and the invitation letter, including the survey link, were sent to each organization. Thrombosis Canada and the CANVector network agreed to send the survey link to their members' contact email address. The Anticoagulation Forum and the ISTH agreed to publicize the survey link on their monthly newsletters. Reminders were not able to be sent, as planned, because of the mechanism of dissemination of the survey link – further because of the mechanism of dissemination and because of the likelihood of overlapping membership between organizations, we were unable to obtain the total number of individuals who could have completed the survey. This limitation then prevented us from calculating a response rate.

All records were stored online within REDCap. All data were anonymized and accessed online through a secure password by authorized researchers. After the 2

month study period, all data were exported using available export tools provided by the REDCap application.

Ethical consideration

The ethical considerations of this research were privacy breach and the identification of the respondents. To protect the identity of the respondents, the survey was anonymized. It did not contain any questions that could identify the participants. Participants who elected to participate in the draw were required to enter their email address. All data were kept confidential, securely stored online within the REDCap application where they can only be accessed only by an authorized researcher. After the survey was completed, data were exported to an encrypted file in a secured password-protected computer that can be accessed by an authorized researcher. In addition, participation was voluntary. The research protocol was reviewed and approved by the Hamilton Integrated Research Ethics Board.

Sample size estimation

Since the survey was an exploratory analysis, we selected a target sample size of convenience. In addition, information on the number of thrombosis specialists in North America was not available. However, if the number of thrombosis specialists was 200, 132 respondents would be required to achieve a margin of error of 5% and confidence interval of 95% (Table1).

Statistical analysis

Descriptive statistics were used. Percentages of response categories in the case scenarios and sub-questions were calculated and reported. In each scenario question,

the responses were categorized into 2 groups, either "heparin group" (including UFH/LMWH to start) or "DOAC group" (including UFH/LMWH transitioned to dabigatran, rivaroxaban, and apixaban – the survey was designed prior to approval of edoxaban). Simple proportion comparisons were performed for each case scenario question. A p-value <0.05 was considered statistically significant. The unanticipated reasons for the selection of anticoagulant therapy were analyzed and reported. All statistical analyses were performed using SPSS version 22.

Results

Between February and April 2017, a total of 91 participants responded to the survey. Eighty-nine respondents signed the electronic informed consents. Of the 86 respondents who provided their responses, 30 respondents (34.5%) were aged between 35-44 years old, 27 respondents (31%) were aged between 45-54 years old, and 18 respondents (21%) were aged between 55-64 years old (Figure 1). For their area of specialization, respondents could select more than 1 choice. Of the 82 respondents who provided their responses, 61 respondents (74.4%) specialized in thrombosis. Nineteen respondents (23.2%) specialized in internal medicine and a similar proportion of the respondents specialized in benign hematology. Thirteen (15.9%), 3 (3.7%) and 12 respondents (14.6%) specialized in hematology/oncology, family medicine, and others, respectively (Figure 2). Of the 82 respondents who provided their responses, 49 respondents (60.5%) worked in Canada. Eighteen (21%), and 15 respondents (18.5%) worked in the United States, and other countries, respectively (Figure 3).

In term of experience in the field of thrombosis, of the 80 respondents who gave their responses, 46 respondents (57.5%) saw more than 10 patients with new or prevalent VTE in a month. Twenty-two (27.5%), and 12 respondents (15%) saw 4-10 cases, and less than 3 cases in a month, respectively (Figure 4). Of the 77 respondents who gave their responses, 44 respondents (57.1%) have practiced in the field of thrombosis for more than 10 years. Twenty (27%) and 13 respondents (16.9%) have practiced in the field of thrombosis for 5-10 years, and less than 5 years, respectively (Figure 5).

First case scenario (mild DVT-related symptoms with limited thrombus involvement)

Of all 89 respondents, 74 respondents (83.1%) gave their responses. Forty-five respondents (60.8%) selected rivaroxaban as their anticoagulant of choice followed by apixaban in 14 respondents (19%). One respondent (1.4%) selected heparin transitioned to dabigatran. Five respondents (12.2%) selected heparin to start, with close follow-up to determine long-term anticoagulant choice, and 9 respondents (6.8%) selected heparin transitioned to warfarin (Figure 6, 7).

When the choice of anticoagulant was categorized as "heparin" or "DOAC" groups, 60 of 74 responses (81%) were in the DOAC group, whereas, 14 of 74 responses (19%) were in the heparin group (Figure 8, 9). A simple proportion comparison demonstrated a significant difference between the 2 groups ($p<0.001$). In this case scenario, the proportion of the respondents who selected DOACs for their initial anticoagulant therapy was significantly higher than those who selected heparin.

Among 14 respondents who selected heparin for their initial anticoagulant treatment, 4 respondents (29%) gave heparin for 4-6 days and a similar proportion of

the respondents gave heparin for 1-2 weeks before the next clinical assessment or before transitioning to warfarin. Three respondents (21.4%) started heparin and warfarin concurrently. Two respondents (14.3%) gave heparin for 2-3 days, and one respondent (7.1%) gave heparin for 3-4 weeks (Figure 10).

For the sub-question exploring the reasons why the respondents selected heparin instead of DOACs, the respondents could select more than 1 reason. Nine respondents (64.3%) thought that heparin might relieve DVT-related symptoms more quickly than DOACs, 2 respondents (14.3%) thought that heparin might lower the risk of recurrent VTE, and 2 respondents (14.3%) thought that the patient might have underlying cancer. Other reasons were given by 4 respondents (28.5%) (Figure 11). The alternative reasons included: the ability to measure anti-factor Xa level with LMWH, limited experience use of DOACs in large thrombus burden, rapid onset of action and low bleeding profile of LMWH, and coverage issues with DOACs.

For the sub-question exploring the reasons why the respondents thought that heparin might improve DVT-related symptoms more quickly than DOACs, the respondents were able to select more than 1 reason. Of the 9 respondents, 8 respondents (88.8%) thought that heparin might relieve DVT-related symptoms more quickly because heparin had an anti-inflammatory effect and 3 respondents (33.3%) thought that heparin might improve DVT-related symptoms more quickly because of its weight-adjusted dose. One respondent gave an alternative reason that UFH might have more predictable bioavailability given that it was parenteral (Figure 12).

For the question asking the opinion on how the anticoagulant therapy could affect the development of PTS, of the 71 respondents, 35 respondents (49%) were

uncertain whether heparin influenced the development of PTS compared with alternative anticoagulants. Seven respondents (10%) thought that heparin influenced the development of PTS, whereas, 29 respondents (41%) did not think that heparin had such effect (Figure 13, 14).

For the question asking the opinion on the expected duration of relevant DVT-related symptoms, 70 respondents gave their responses. Thirty-one respondents (44%) thought that heparin relieved DVT-related symptoms similarly with DOACs, whereas, 18 respondents (26%) thought that heparin relieved DVT-related symptoms more quickly than DOACs. Twenty-one respondents (30%) were uncertain whether the duration of relevant DVT-related symptoms would be different (Figure 15, 16).

Though most respondents selected heparin because of a perception that it might relieve DVT-related symptoms more quickly, internal inconsistency was observed. Among 9 respondents who selected heparin because it might relieve DVT-related symptoms more quickly, 7 respondents (77.8%) thought that heparin relieved DVT-related symptoms more quickly than DOACs which indicates a consistent idea. However, inconsistent responses were observed in 2 respondents who either thought that heparin relieved DVT related symptoms similarly with DOACs or were uncertain whether the duration of the symptoms would be different.

Second case scenario (Extensive DVT)

Of all 89 respondents, 68 respondents (76.4%) gave their responses. Nineteen respondents (28%) selected rivaroxaban and 10 respondents (15%) selected apixaban as their anticoagulant of choice. Thirty-three respondents (48.5%) selected heparin, with close follow-up to determine long-term anticoagulant choice, and 4 respondents

(6%) selected heparin transitioned to warfarin. Two respondents indicated that they would give LMWH for a week and then transitioned to DOAC (Figure 6, 7).

When categorized, the responses of anticoagulant choice as heparin or DOAC, 39 of 68 responses (57.4%) were in the heparin group, whereas, 29 of 68 responses (42.6%) were in the DOAC group (Figure 8, 9). A simple proportion comparison found no significant difference between the 2 groups (p=0.225).

Among 41 respondents who selected heparin for their initial anticoagulant treatment, 16 respondents (39%) gave heparin for 1-2 weeks, 10 respondents (24%) gave heparin for 4-6 days, 9 respondents (22%) gave heparin for 2-3 days, and 3 respondents (7%) gave heparin for 3-4 weeks before the next clinical assessment or before transitioning to warfarin. Two respondents (5%) started heparin and warfarin concurrently. One respondent gave alternative option indicating that he would continue LMWH for 4-6 days and then switch to rivaroxaban (Figure 10).

For the sub-question exploring why respondents selected heparin instead of DOACs, the respondents were able to select more than 1 reason. Of the 37 respondents who gave their reasons, 26 respondents (70%) thought that heparin might improve DVT-related symptoms more quickly. Three respondents (8%) thought that heparin might lower the risk of recurrent VTE, and 7 respondents (19%) thought that the patient might have underlying cancer (Figure 11). Ten respondents (27%) gave alternative reasons. Some respondents indicated that they gave heparin because catheter-directed thrombolysis (CDT) might be needed. For instance, the respondents explained that "I would consider transfer for thrombolytic therapy if symptoms worsened in first 24 hours.", or "If symptoms do not improve, I would consider

transferring the patient to another center for thrombolysis." Some respondents commented on the preferable pharmacologic or pharmacokinetic properties of LMWH over DOACs. For instance, the respondents mentioned that "Might provide more effective acute anticoagulation.", "…worsening of the venous obstructive symptoms - if present these might result in the intensification of LMWH e.g. BD instead of OD dosing or might lead to referral for CDT", "Possible reduced likelihood of PTS". Other reasons were related to the ability to measure anti-factor Xa level with LMWH to ensure adequate anticoagulation or coverage issues of DOACs. Few respondents noted that they selected heparin because the patient was very symptomatic, or iliofemoral vein thrombosis was suspected.

For the sub-question exploring the reasons why the respondents thought that heparin might improve DVT-related symptoms more quickly than DOACs, the respondents were able to select more than 1 reason. Of the 26 respondents, 22 respondents (85%) thought that heparin might improve DVT-related symptoms more quickly because it had an anti-inflammatory effect, 6 respondents (23%) thought that heparin might improve DVT-related symptoms more quickly because of its weight-adjusted dose, and 3 respondents gave alternative reasons (Figure 12). The other reasons were related to the preferable pharmacologic and pharmacokinetic properties of heparin such as "UFH has a better pharmacokinetics as it is a parenteral drug", "Perhaps more intense anticoagulant effect", and "Rapid thrombin inhibition results in more lysable clot".

For the question asking the opinion on how the anticoagulant therapy could affect the development of PTS, of the 68 respondents, 37 respondents (54%) were

uncertain whether heparin had an effect on the development of PTS compared with other alternative anticoagulants. Eight respondents (12%) thought that heparin influenced the development of PTS, whereas, 23 respondents (34%) did not think that heparin had such effect (Figure 13, 14).

For the question asking the opinion on the expected duration of relevant DVT-related symptoms, 67 respondents gave a response. Twenty-seven respondents (40%) thought that heparin relieved DVT-related symptoms similarly with DOACs, whereas, 17 respondents (25%) thought that heparin relieved DVT-related symptoms more quickly than DOACs. Twenty-three respondents (34%) were uncertain whether the duration of DVT-related symptoms between the 2 treatments would be different (Figure 15, 16).

Of the 26 respondents who selected heparin over DOACs because of a perception that it might relieve DVT-related symptoms more quickly, 25 respondents gave their opinions on the expected duration of DVT-related symptoms. Consistent responses were observed in 14 respondents (56%) who thought that heparin relieved DVT-related symptoms more quickly than DOACs. Inconsistent responses were observed in 1 respondent who thought that heparin relieved DVT related symptoms similarly with DOACs, and in 10 respondents who were uncertain whether the duration of the symptoms would be different.

<u>Third case-scenario (Extensive DVT with high bodyweight)</u>

Of all 89 respondents, 61 respondents (68.5%) gave their responses. Twenty-five respondents (41%) selected heparin to start, with close follow-up to determine long-term anticoagulant choice followed by 19 respondents (31%) who selected

heparin transitioned to warfarin. Ten (16%), and 6 (10%) respondents selected rivaroxaban, and apixaban, respectively. One respondent (2%) selected heparin transitioned to dabigatran as their anticoagulant of choice (Figure 6, 7).

When categorized the responses of anticoagulant choice into heparin or DOAC groups, 44 of 61 responses (72%) were in the heparin group, whereas, 17 of 61 responses (28%) were in the DOAC group (Figure 8, 9). A simple proportion comparison found a significant difference between the 2 groups ($p< 0.001$). In this case scenario, the proportion of the respondents who selected heparin for their initial anticoagulant therapy was significantly higher than the proportion of the respondents who selected DOACs.

Among 43 respondents who selected heparin for their initial anticoagulant treatment, 14 respondents (33%) gave heparin for 1-2 weeks, 10 respondents (23%) gave heparin for 4-6 days, 7 respondents (16%) gave heparin for 2-3 days and 1 respondent (2.3%) gave heparin for 3-4 weeks before the next clinical assessment or before transitioning to warfarin. Ten respondents (23.3%) started heparin and warfarin concurrently. One respondent indicated that he would give LMWH for 4-6 days and then switch to DOAC (Figure 10).

For the sub-question exploring the reasons why the respondents selected heparin over DOACs, the respondents could select more than 1 reason. Nineteen respondents (43%) thought that heparin might improve DVT-related symptom more quickly than DOACs, 3 respondents (7%) thought that heparin might lower the risk of recurrent VTE, and 2 respondents (4.5%) thought that the patient might have underlying cancer. Alternative reasons were given by 27 respondents (61%) (Figure

11). The major reason (89% of the reasons given) was that the patient had extremely high bodyweight, for instance, the respondents explained "Current recommendation of the ISTH SSC 2016 is a suggestion not to use DOAC in patients with a body weight >120kg", "Less data on the efficacy of DOACs with high BMI the use of DOACs in extremely high bodyweight", "Obese patients not included in trials with DOAC", "Weight too high for initial treatment with DOAC". Other alternative reasons were the ability to measure anti-Factor Xa level with LMWH such as "Ability to measure an anti-Xa level to make sure dosing of anticoagulant is adequate…", and the need for clinical assessment for thrombolytic therapy such as "I might transfer for thrombolytic therapy if no clinical improvement in first 24 hours.", " ..If the patient remains very symptomatic, I can consider transferring him to another center for thrombolysis."

For the sub-question exploring the reasons why the respondents thought that heparin might improve DVT-related symptoms more quickly than DOACs, the respondents were able to select more than 1 reason. Of the 19 respondents, 14 respondents (74%) thought that heparin might improve DVT-related symptoms more quickly because heparin had an anti-inflammatory effect, 8 respondents (42%) thought that heparin might improve DVT-related symptoms more quickly because of its weight-adjusted dose and 2 respondents gave alternative reasons (Figure 12). The alternative reason was related to the preferable pharmacologic or pharmacokinetic properties of LMWH. For instance, the respondents explained "Perhaps more intense anticoagulant effect as in cancer patients.", and "related to the tensile strength of the clot."

For the question asking the opinion on how the anticoagulant therapy could affect the development of PTS, of the 60 respondents, 35 (58%) were uncertain whether heparin influenced the development of PTS compared with other alternative anticoagulants. Seven respondents (12%) thought that heparin influenced the development of PTS, whereas, 18 respondents (30%) did not think that heparin had such an effect (Figure 13, 14).

For the question asking the opinion on the expected duration of relevant DVT-related symptoms, 59 respondents gave their responses. Twenty-three (39%) respondents thought that heparin relieved DVT-related symptoms similarly with DOACs, whereas, 16 respondents (27%) thought that heparin relieved DVT-related symptoms more quickly than the DOACs. Twenty respondents (34%) were uncertain whether the duration of DVT-related symptoms between the 2 treatments would be different (Figure 15, 16).

Of the 19 respondents who selected heparin instead of DOACs because it might relieve DVT-related symptoms more quickly, 18 respondents gave their opinions on the expected duration of DVT-related symptoms. Consistent responses were observed in 11 respondents (61%) who thought that heparin relieved DVT-related symptoms more quickly than DOACs. Inconsistent responses were observed in 1 respondent who thought that heparin relieved DVT related symptoms similarly with DOACs, and in 6 respondents who were uncertain whether the duration of the symptoms would be different.

Fourth case-scenario (uncomplicated PCD)

Of all 89 respondents, 59 respondents (66.3%) gave their responses. Thirty-six respondents (61%) selected heparin to start, with close follow-up to determine long-term anticoagulant choice. Four respondents (7%) selected heparin for an extended period without a plan for transition to another anticoagulant. Four (7%), and 3 (5%) respondents selected rivaroxaban, and apixaban, respectively. One respondent (2%) selected heparin transitioned to dabigatran. Ten respondents (17%) gave alternative anticoagulant options (Figure 6, 7). The majority of the alternative options were to give UFH or LMWH prior to a referral for consideration of catheter-directed thrombolysis. The respondents explained their opinions, for instance, "Urgent referral to CDT site. Give a single dose of LMWH while waiting for referral", "LMWH, and consider CDT as adjunctive therapy", "Would start UFH and urgently refer for consideration for catheter-directed thrombolysis…", "LMWH in bid doses with admission to hospital and plan to try to transfer to a hospital with catheter-directed thrombolysis; if the transfer is not possible, continue bid LMWH until significant symptomatic improvement than transitioned to DOAC or warfarin according to patient preference."

When categorized by anticoagulant choice into heparin or DOAC groups, 41 of 49 responses (83.6%) were in the heparin group, whereas, 8 of 49 responses (16.3%) were in the DOAC group (Figure 8, 9). A simple proportion comparison found a significant difference between the 2 groups (p=0.001). In this case scenario, the proportion of the respondents who selected heparin for their initial anticoagulant therapy was significantly higher than that who selected DOACs.

Among 37 respondents who selected heparin for their initial anticoagulant treatment, 17 respondents (46%) gave heparin for 1-2 weeks, 11 respondents (30%) gave heparin for 2-3 days, 6 respondents (16%) gave heparin for 4-6 days, and 2 respondents (5%) gave heparin for 3-4 weeks before the next clinical assessment or before transitioning to warfarin (Figure 10). One respondent gave an alternative option that the patient should be assessed at least twice a day and considered for thrombolysis.

For the sub-question exploring the reasons why the respondents selected heparin instead of DOACs, the respondents were able to select more than 1 reason. Twenty-two respondents (54%) thought that heparin might improve DVT-related symptoms more quickly. Five respondents (12%) thought that heparin might lower the risk of recurrent VTE, and 8 respondents (19.5%) thought that the patient might have underlying cancer. Fifteen respondents (37%) gave alternative reasons (Figure 11). The major reason was due to a possible referral for thrombolytic therapy, and limited experience with the use of DOAC in PCD. For instance, some respondents explained "If the leg symptoms worsen, the patient might need aggressive intervention and I want him on an anticoagulant with which interventional radiology is familiar", "Limited evidence of the use of DOACs in such extreme cases of DVT", "Phlegmasia cerulea dolens. The patient should be transferred to another institution for intervention procedure." Some respondents mentioned the preferable pharmacologic or pharmacokinetic properties of heparin such as "LMWH might inhibit thrombosis faster than DOAC", "Treatment may need to be interrupted for thrombectomy if/when he can get to a treatment center that has this available". Other reasons were related to

the ability to measure anti-Factor Xa level to ensure adequate anticoagulation and coverage issues of DOACs.

For the sub-question exploring the reasons why the respondents thought that heparin might improve DVT-related symptoms more quickly than DOACs, the respondents were able to select more than 1 reason. Of the 22 respondents, 19 respondents (86%) thought that heparin might improve DVT-related symptoms more quickly because heparin had an anti-inflammatory effect. Three respondents (14%) thought that heparin might improve DVT-related symptoms more quickly because of its weight-adjusted dose, and 3 respondents gave alternative reasons (Figure 12). The other reasons were "rapid thrombus inhibition with heparin", "little experience of DOACs in phlegmasia cerulea dolens", and "for an unknown reason."

For the question asking the opinion on how the anticoagulant therapy could affect the development of PTS, of the 58 respondents, 33 respondents (64%) were uncertain whether heparin had an effect on the development of PTS compared with other alternative anticoagulants. Seven respondents (12%) thought that heparin influenced the development of PTS, whereas, 18 respondents (31%) did not think that heparin had such effect (Figure 14, 15).

For the question asking the opinion on the expected duration of relevant DVT-related symptoms, 58 respondents gave their responses. Twenty-two respondents (38%) thought that heparin relieved DVT-related symptoms similarly with DOACs, whereas, 15 respondents (26%) thought that heparin relieved DVT-related symptoms more quickly than DOACs. One respondent (1.7%) thought that heparin relieved DVT-related symptoms less quickly than DOACs. Twenty respondents (34.5%) were

uncertain whether the duration of DVT-related symptoms between the 2 treatment groups would be different (Figure 16, 17).

Among 22 respondents who selected the heparin because it might relieve DVT-related symptoms more quickly, consistent responses were observed in 11 respondents (50%) who thought that heparin relieved DVT-related symptoms more quickly than DOACs. Inconsistent responses were observed in 2 respondents who thought that heparin relieved DVT related symptoms similarly with DOACs, and in 9 respondents who were uncertain whether the duration of the symptoms would be different.

Sensitivity analysis

To explore the impact of payment and coverage issues of DOACs, the data were analyzed only in respondents who worked in North America. The comparison of the proportions between the heparin and DOACs groups provided similar results to those in all respondents.

Discussion

Through case-based scenarios with varying degrees of DVT-related symptoms and thrombus burden, most of the respondents selected DOACs as their initial anticoagulant therapy in the case with mild DVT-related symptoms and limited thrombus involvement. Most of the respondents selected heparin as their initial anticoagulant therapy in the case with the most severe DVT-related symptoms or uncomplicated of PCD and extensive thrombus involvement. Despite similar extent of thrombus involvement, the proportion of the respondents who selected heparin was not significantly higher than that of who selected DOACs in the case with less severe in clinical symptoms. These findings support the assumption that physicians use heparin in patients with severe DVT-related symptoms, or in other words, the clinical severity of DVT, as well as the extent of thrombus, play a major role in the selection of anticoagulant therapy, either heparin or DOACs. The findings also demonstrated variations in the anticoagulant choice for the treatment of extensive DVT despite little or no evidence to support the hypothesis with respect to which anticoagulant is "better". In extreme bodyweight with extensive DVT, most respondents opted for heparin. This finding indicates that extreme body weight has an impact on the selection of anticoagulant therapy even though no bodyweight limitations were present in the randomized trials of DOACs.[4-7]

The duration of initial heparin treatment varied between respondents. However, in all scenarios, most respondents who selected heparin as their initial therapy would assess clinical response at 1-2 weeks before consider switching to an oral anticoagulant, either warfarin or DOAC. The proportion of the respondents who

selected 1-2 week duration was highest in the case with uncomplicated PCD, followed by that in the case with extensive DVT. These findings might reflect the fact that physicians tend to give a short course of LMWH in patients with severe clinical symptoms or with extensive thrombus involvement. The findings also suggest that DVT-related symptom improvement are important in the clinical assessment of such patients.

The major underlying reason for the selection of heparin over DOACs was that heparin might relieve DVT-related symptoms more quickly. In the case with extensive DVT, up to 70% of the respondents selected this reason, while only 8% of the respondents thought that heparin might lower risk of recurrent VTE. These findings also support the hypothesis that DVT-related symptom improvement is a crucial concern for physicians in the initial treatment of extensive DVT. However, the uncertainty in such perception was substantial. The observation of inconsistent responses suggests that more evidence is needed to guide clinical reasoning in this area.

Among the respondents who thought that heparin might improve DVT-related symptoms more quickly, the major underlying reason was that heparin contained anti-inflammatory effects. As local inflammatory responses caused by venous thrombosis partly contribute to the clinical signs and symptoms of DVT, the anti-inflammatory effects of heparin might attenuate the local inflammatory responses. Therefore, heparin might relieve DVT-related symptoms more rapidly compared with other anticoagulants. The anti-inflammatory effects of heparin have been established and can occur by multiple mechanisms.[8] Heparin inhibits neutrophil recruitment and

impairs its function, and thus consequently attenuates inflammatory process. Heparin prevents inflammatory mediator expression by interacting with vascular endothelium. Anticoagulant properties of heparin also prevent further thrombus formation and may reduce the inflammatory responses. Like UFH, multiple studies showed that LMWHs can reduce inflammatory cytokines and inflammation.[9,10] One study found that LMWH can reduce the inflammatory responses to a similar degree of those with UFH.[11]

Though most thrombosis specialists believed that heparin might relieve DVT-related symptoms more quickly than DOACs because of its anti-inflammatory effects, whether the anti-inflammatory effects of heparin would actually relieve clinical symptoms more rapidly than DOACs in acute VTE setting has not been studied. Several randomized trials investigated the anti-inflammatory effects of heparin in other clinical settings such as chronic obstructive pulmonary disease, asthma, or acute coronary syndrome. The effect of the anti-inflammatory properties of heparin on inflammatory markers, and on clinical outcomes was inconsistent.[12] As for DOACs, a randomized trial investigating the anti-inflammatory effects of rivaroxaban, and dabigatran, is ongoing.[13] To date, whether DOACs are able to provide similar anti-inflammatory effects as heparin remains unknown.

Alternative reasons why the respondents selected heparin were given. Many respondents preferred LMWHs due to their pharmacokinetic properties over DOACs as these advantages could result in more effective acute anticoagulation. For DOACs, only rivaroxaban and apixaban can be initially administered without the need for "bridging therapy". As UFH is less effective than LMWH in the acute treatment of

VTE [14], it is usually reserved for patients who need intensive anticoagulation monitoring or those with a high risk of bleeding. Further discussion will focus on the pharmacokinetic properties of LMWHs and the DOACs as the initial anticoagulant therapy for acute VTE.

In term of the mechanisms of action, LMWHs are indirect anticoagulants which exert their anticoagulant effects by binding to antithrombin through a specific pentasaccharide sequence. LMWHs have greater inhibition activity against factor Xa than thrombin with a ratio ranging from in 2:1 to 4:1 depending on the type of LMWHs.[15] Unlike LMWHs, rivaroxaban and apixaban directly exert their anticoagulant effects by specifically inhibiting factor Xa activity. The bioavailability of LMWHs given subcutaneously is 90-100%. For rivaroxaban, the bioavailability given their oral route of administration is dose-dependent. The bioavailability of the 10 mg of rivaroxaban is up to 80% but is decreased to as low as 66% with the 15 or 20 mg of rivaroxaban. However, the bioavailability of the high-dose rivaroxaban can be increased to more than 80% if it is taken with foods.[16] The bioavailability of apixaban is 50% and is not affected by food intake.[17] In term of time to peak effect of the anticoagulant activity, the peak effect can be reached within 3-4 hours following LMWH injection, 2-4 hours following rivaroxaban, and 1-3 hours following apixaban intake. The half-life of LMWHs is approximately 4-6 hours depending on the type and frequency of injection. The half-life of rivaroxaban is 5-9 hours, whereas the half-life of apixaban is 9-14 hours. Monitoring of anti-factor Xa activity is generally not recommended for LMWHs and the DOACs because of their predictable anticoagulant response. Although testing for levels of both Xa inhibitor, and LMWH, can be

performed it is rarely indicated given the predictable pharmacokinetic profiles of these drugs.

As previously discussed, the pharmacodynamic advantages of LMWHs over the DOACs are that LMWHs have broader anticoagulant effects as they inhibit both factor Xa and thrombin while the DOACs only inhibit factor Xa. LMWHs also have a higher bioavailability compared with the DOACs. In addition, LMWHs probably have an anti-inflammatory effect, whereas it is unknown if DOACs have this effect. However, their pharmacokinetic properties are similar in term of rapid achievement of the peak anticoagulant effect, predictable anticoagulant activity without the need for dose adjustment, and short half-life. It might be true that LMWHs might provide a superior acute anticoagulation effect, but whether these pharmacokinetic advantages impact physician- and patient-important outcomes in acute extensive DVT treatment remains unknown.

Another reason given by the respondents who selected heparin over DOACs was that patients with extensive DVT or uncomplicated PCD might need a frequent clinical assessment and patients might be considered for CDT. However, in patients who can be managed as outpatients, the use of either LMWHs or DOACs should not affect the frequency of clinical assessment, or preclude a consideration for CDT. DOACs are substantially less costly than LMWHs. Their oral route of administration is more convenient to patients and might improve compliance to the treatment. Furthermore, recent evidence suggesting CDT to be ineffective [18-20] in many patients with proximal DVT may reduce the use of this technique and thus reduce the use of this as a reason to select a treatment course with LMWH over DOAC.

In term of PTS, only 9-12% of the respondents thought that heparin influenced the development of PTS, whereas 20-40% of the respondents did not think that heparin influenced the development of PTS. More than 50% of the respondents were uncertain whether heparin influenced the development of PTS. These findings suggest that clinical trials investigating the development of PTS as an outcome in patients with extensive DVT, who do not require CDT, are needed.

The findings of the survey support a rationale for a randomized trial by demonstrating variations in anticoagulant selection between DOACs and heparin among thrombosis specialists. This could be stated as "clinical equipoise" in which there are controversy and uncertainty among thrombosis specialists regarding the preferred treatment of extensive DVT. The results of the survey also inform the intervention arms of the proposed randomized trial. Rivaroxaban, the most common DOAC selected by the thrombosis specialists will be an intervention treatment. In addition, since there is no standard treatment for extensive DVT, a 1-2 week course of LMWH, which representing the most common practical anticoagulant management of extensive DVT and early stage PCD among the thrombosis specialists, will be a control treatment of the proposed randomized trial.

The survey has several strengths. This is the first survey that demonstrated the practical anticoagulant management and the underlying reasons for the anticoagulant selection among thrombosis specialists for the treatment of extensive DVT. In addition, the survey had an adequate reliability and had been content validated by thrombosis experts. Furthermore, the respondents well represented the target population.

The survey has limitations worth discussing. The response rate of the survey cannot be determined due to unavailability of the number of thrombosis specialists in North America, the possible overlapping of members in thrombosis societies, and the differences in the methods of survey dissemination. When the response rate is low or cannot be measured, it cannot be assumed that nonresponse bias is not significant. However, the response rate of a survey is not as important as response representativeness.[21] In this survey, the majority of the respondents were specialized in thrombosis, and more than half of them have extensive experience in the field of thrombosis. Hence, the respondents well represented the target population. Although some respondents were not specialized in the field of thrombosis, the survey was distributed to the members of thrombosis societies which ensured that those respondents were interested, or have practiced in the field of thrombosis.

Moderate proportions of incomplete response were observed. Of all respondents who signed the informed consent, 34% of the respondents did not complete the entire survey. The proportion completed was highest in the first scenario question (83.1%), and lowest in the last scenario question (66.3%). These observations might reflect the unattractiveness of the survey questions or its format. However, because declining rates of response through the case scenarios was expected, the number of case-scenario questions was limited to 4, and the questions were ordered from the most common to the rarest case. The clinical scenario of greatest interest was ordered second and had a completion rate of 76%.

Another issue was that one might argue that a low number of respondents could result in a low power to detect the difference between the 2 treatment groups as

shown in the second case scenario. However, this survey was an exploratory analysis. In addition, the results of the survey were aligned with the pre-specified hypotheses.

Conclusion

In summary, the survey demonstrated variations in the anticoagulant therapy selection in patients with extensive DVT among thrombosis specialists. Most thrombosis specialists selected heparin instead of DOACs as their initial anticoagulant therapy in patients with severe DVT-related symptoms and in a patient with high bodyweight. The major underlying reason for selecting heparin instead of DOACs in such patients was that heparin might relieve DVT-related symptoms more quickly because of its anti-inflammatory effect. Improvement of DVT-related symptoms at 1-2 weeks is a crucial assessment for response to the anticoagulant therapy. Uncertainty around the effect of heparin or DOACs on the duration of DVT-related symptoms and PTS development was considerable.

Overall, the objectives of the survey were met. Variations in the anticoagulant selection and practical management, the importance of clinical assessment, and a certain degree of uncertainty on the effect of heparin on the duration of DVT-related symptoms and in the development of PTS were demonstrated. The findings support a randomized trial by demonstrating clinical equipoise in which whether DOAC or heparin is the preferred treatment for extensive DVT among thrombosis specialists. The findings also inform the interventions for the proposed randomized trial and support the use of DVT-related symptoms and PTS as outcomes for such a study.

Tables and figures

Table 1. Sample size estimation

Sample size of the survey if the total number of thrombosis specialists were assumed

Total = 100	Confidence interval	
Margin of error	95%	90%
5%	80	74
10%	50	41

Total = 200	Confidence interval	
Margin of error	95%	90%
5%	132	115
10%	66	51

Total = 500	Confidence interval	
Margin of error	95%	90%
5%	218	176
10%	81	60

Figure 1. Age

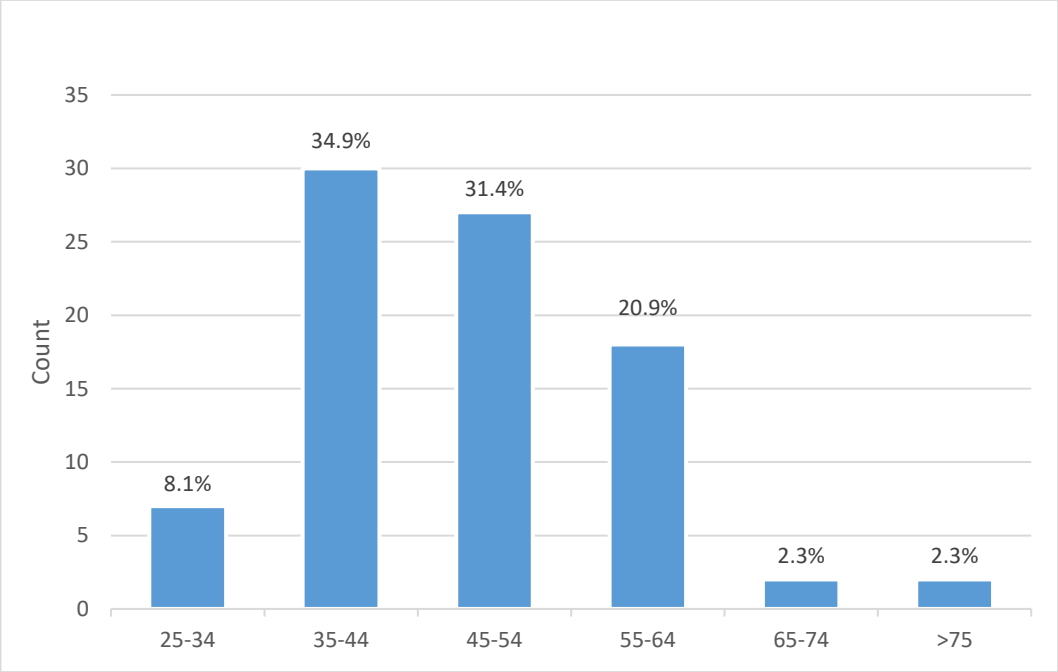


Figure 2. Area of specialization

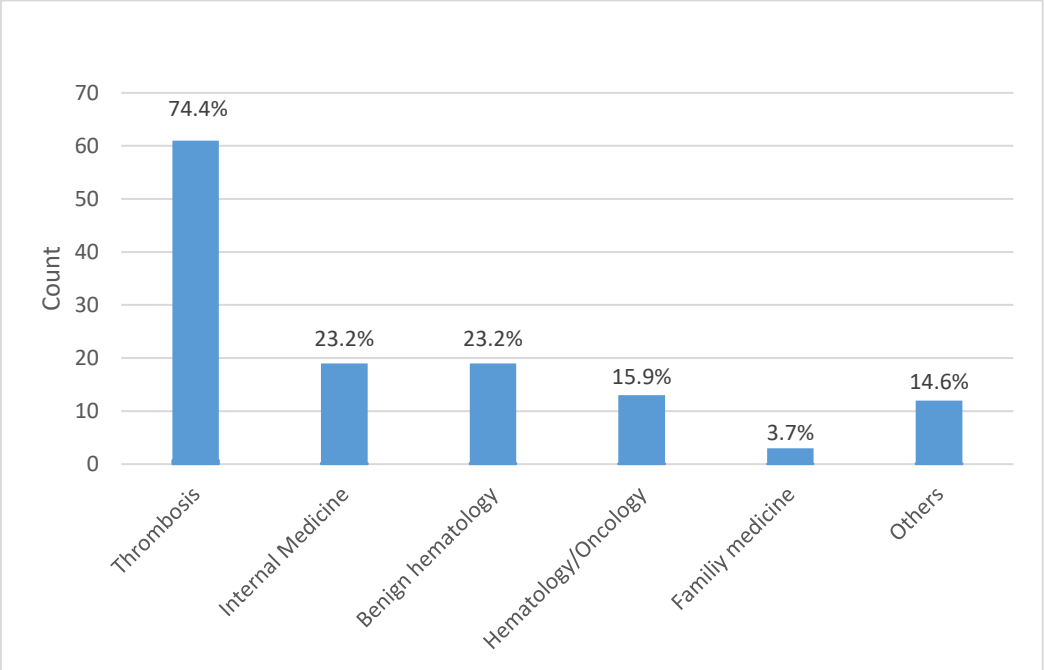


Figure 3. Workplace

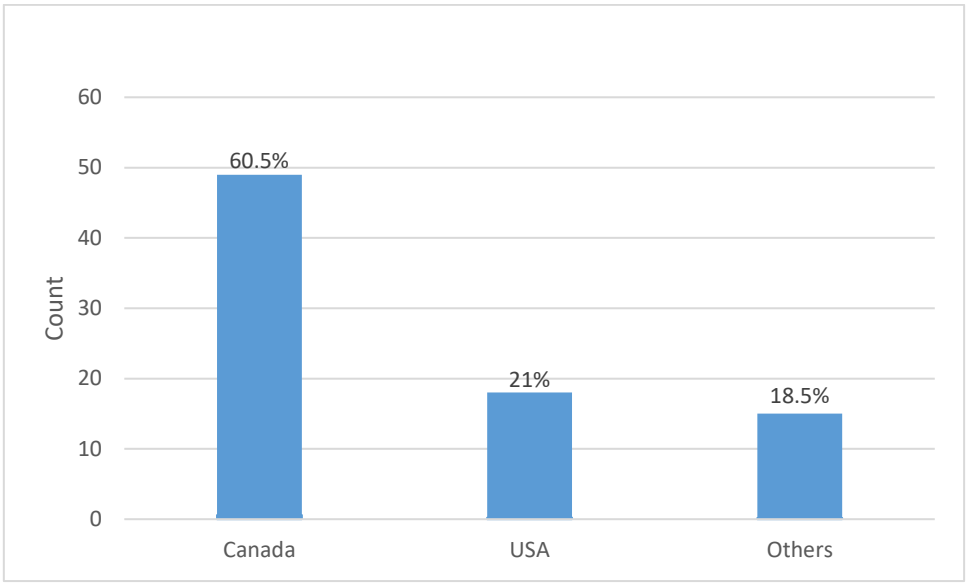


Figure 4. Number of new or prevalence of VTE seen per month

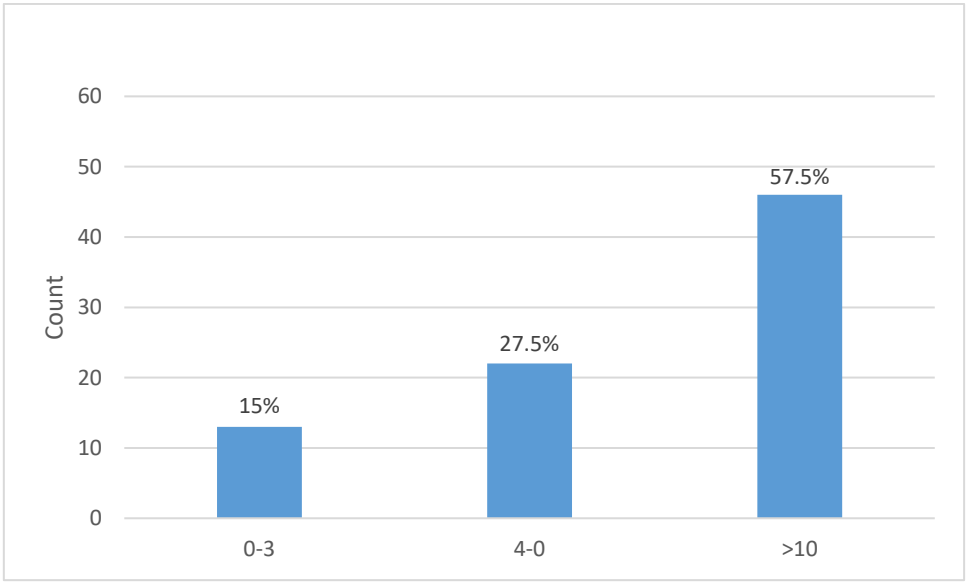


Figure 5. Experience in the field of thrombosis

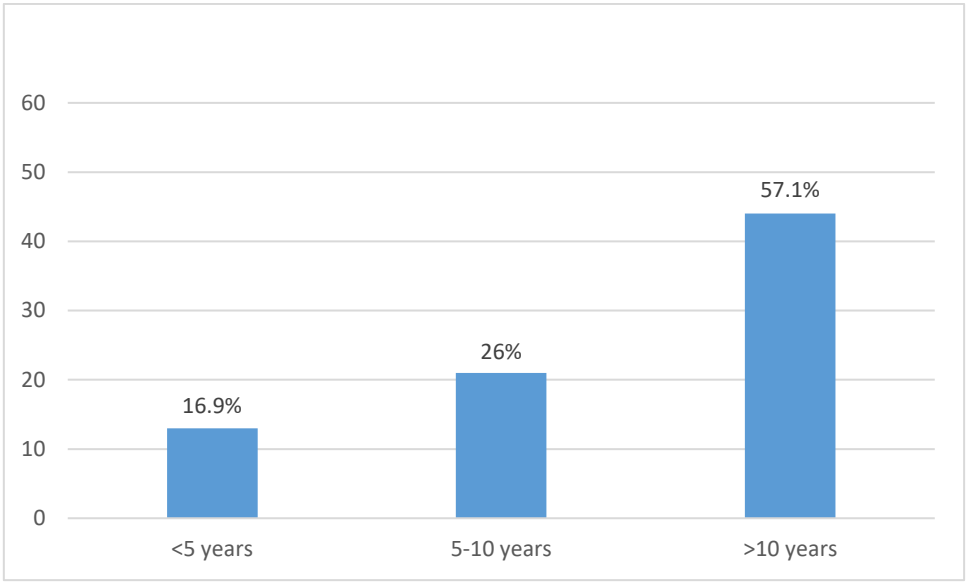


Figure 6. Choices of anticoagulant therapy, categorized by responses (in percentage)

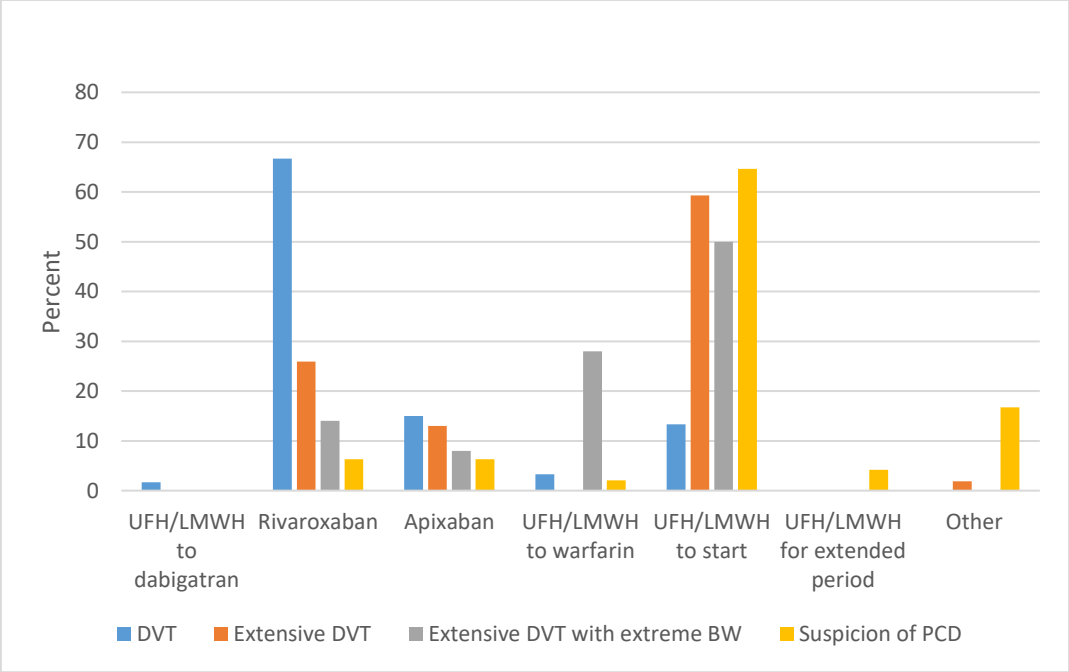


Figure 7. Choices of anticoagulant therapy, categorized by case scenario (in percentage)

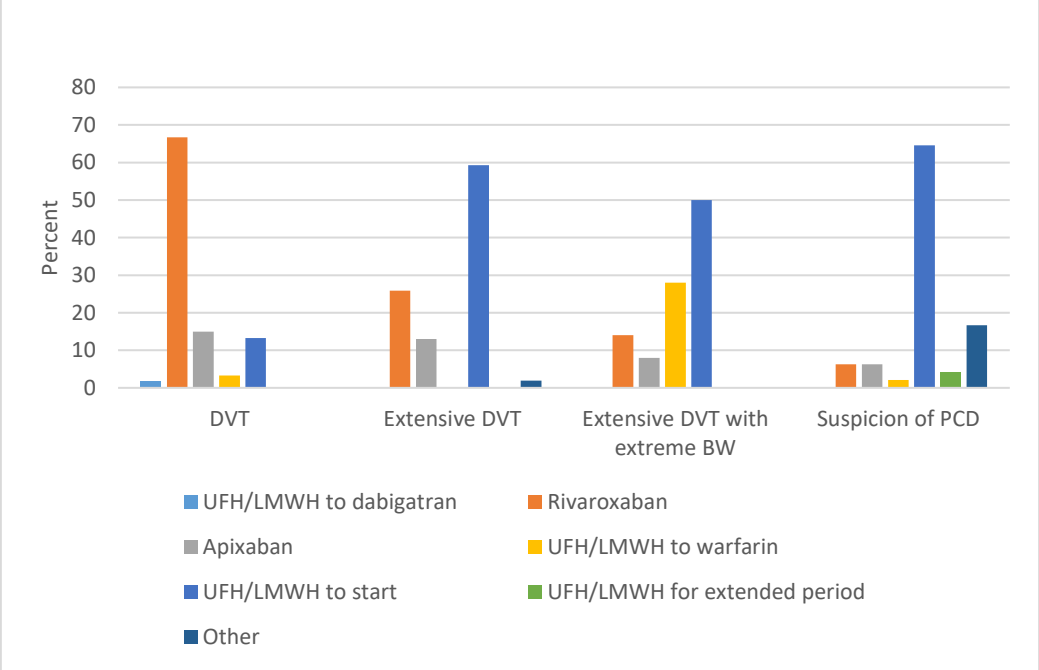


Figure 8. Choices of anticoagulant treatment categorized into the heparin or DOAC groups, by type of anticoagulant

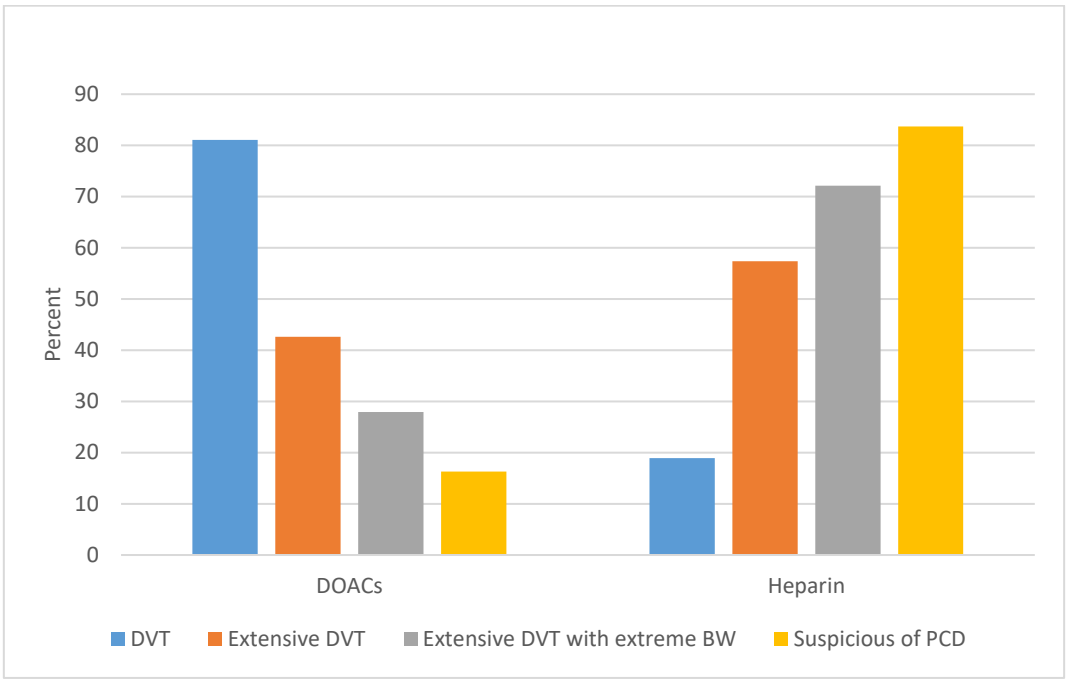


Figure 9. Choices of anticoagulant treatment categorized into the heparin or DOAC groups, by case scenario

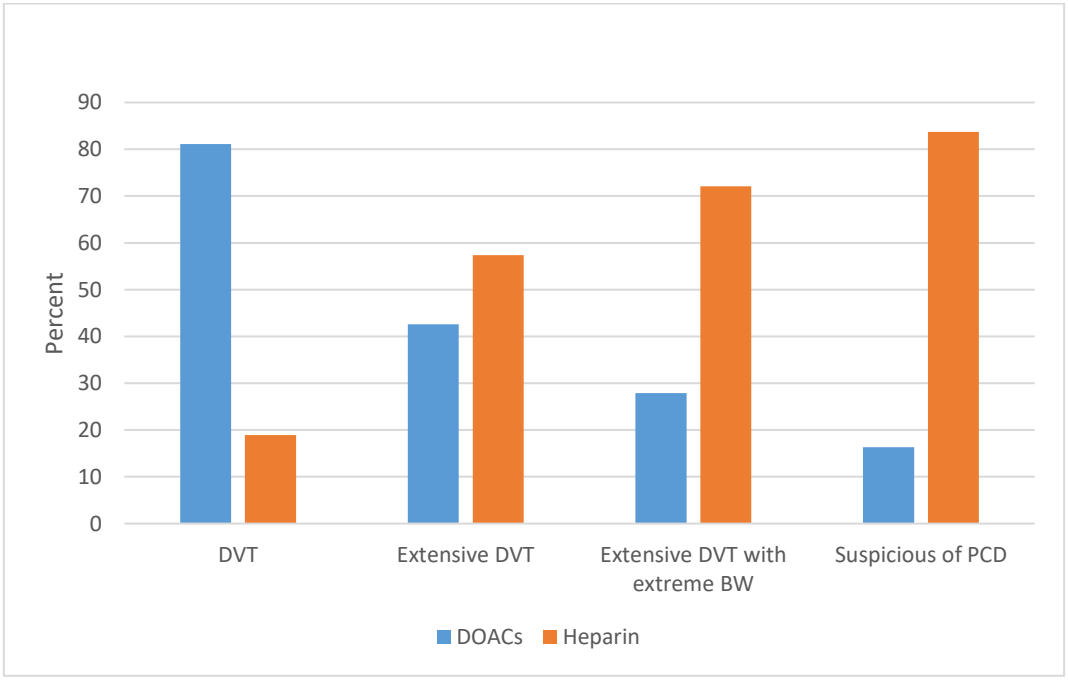


Figure 10. Duration of anticoagulant before next clinical assessment or transitioning to warfarin

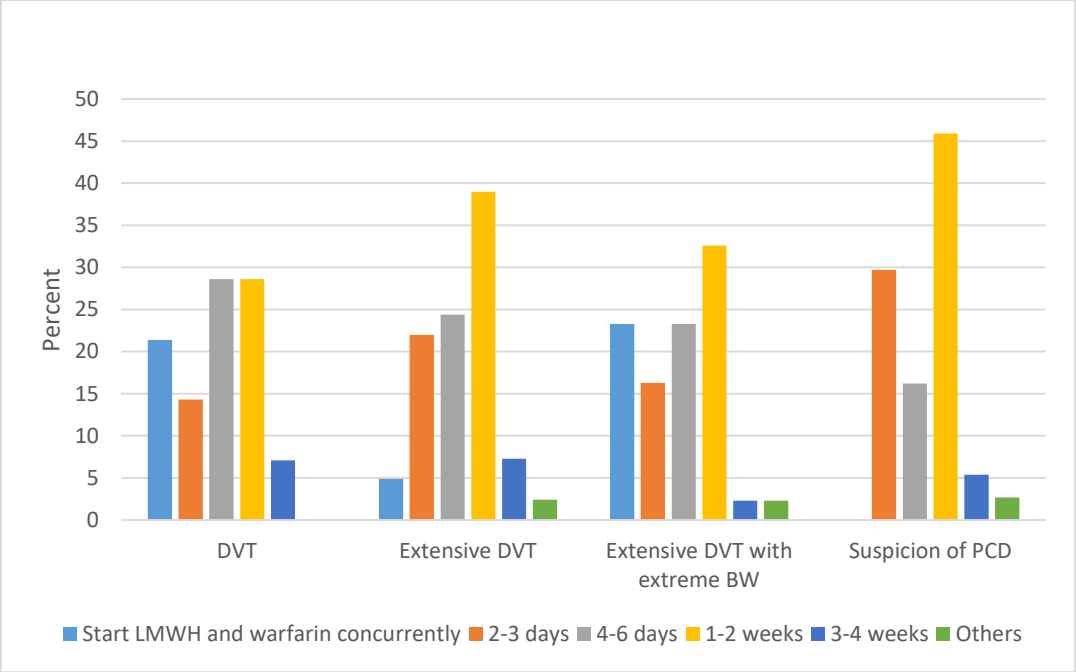


Figure 11. Reasons why selected heparin instead of DOACs, categorized by case scenario (in percentage)

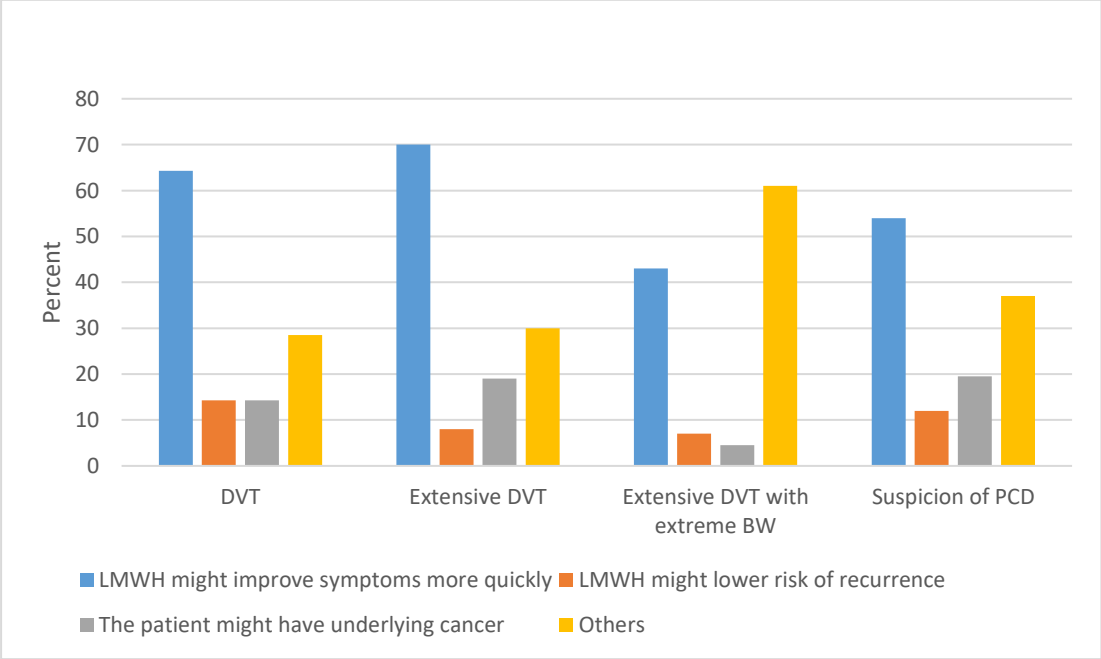


Figure 12. Reasons why participants thought that heparin might relieve symptoms more quickly than DOACs, categorized by case scenario (in percentage)

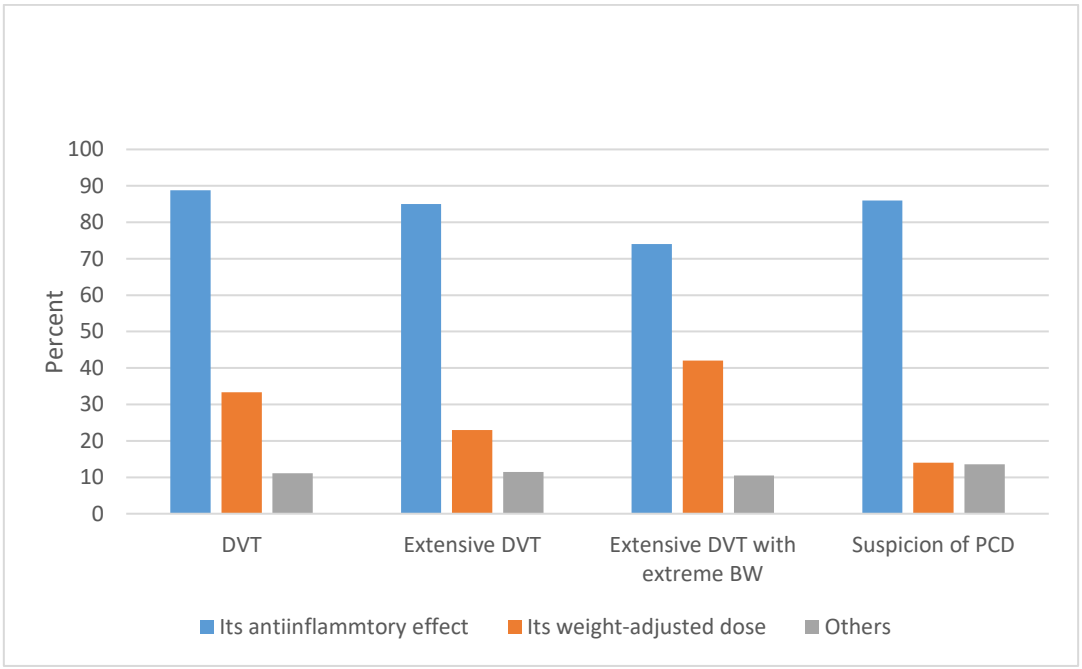


Figure 13. Opinions on the effect of heparin on the development of PTS, categorized by responses

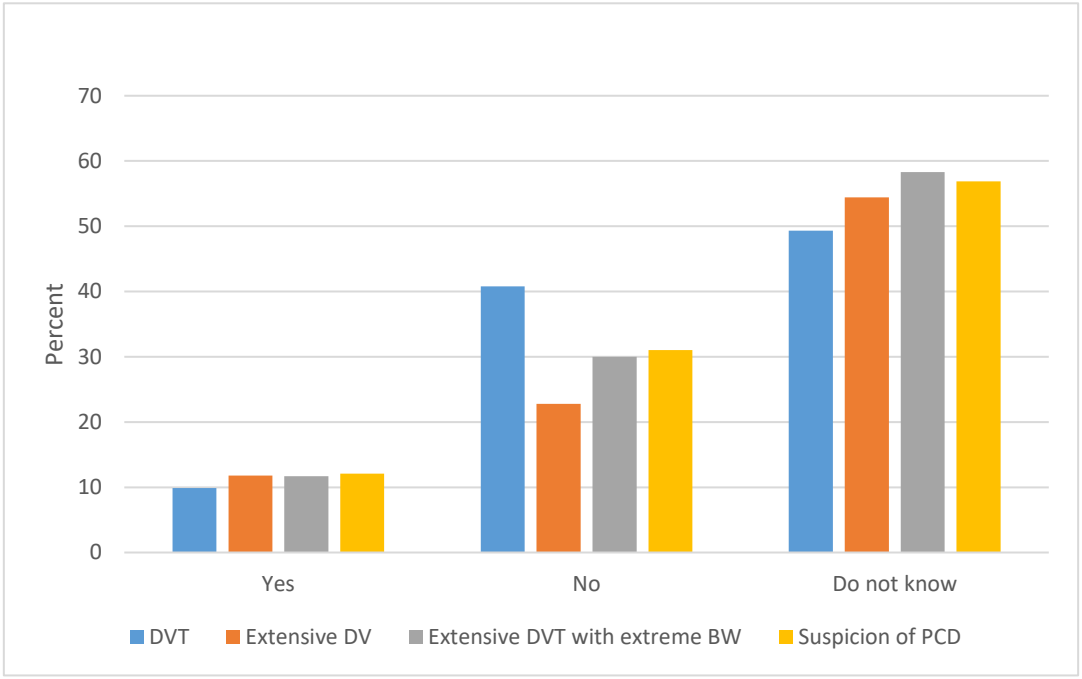


Figure 14. Opinions on the effect of heparin on the development of PTS, categorized by case scenario

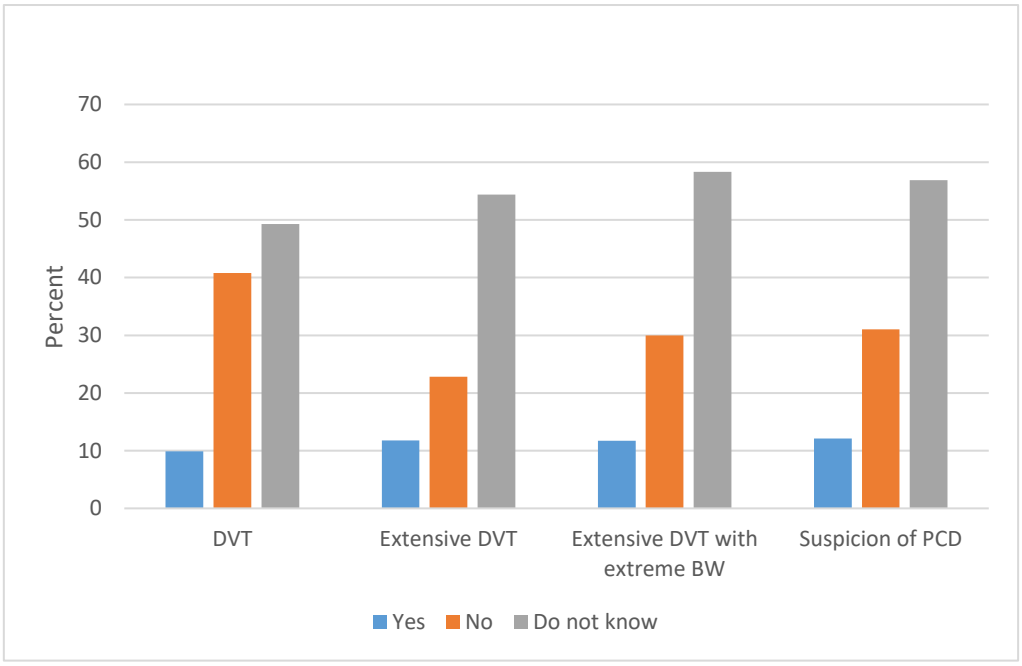


Figure 15. Opinions on the expect duration of relevant DVT-related symptoms, categorized by responses

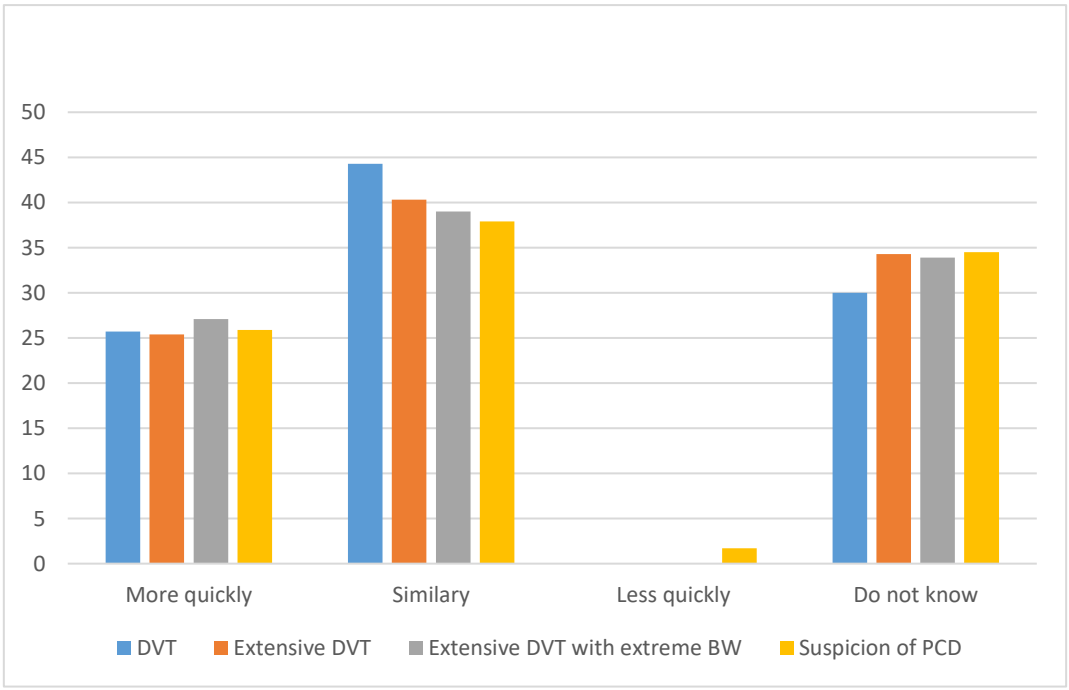
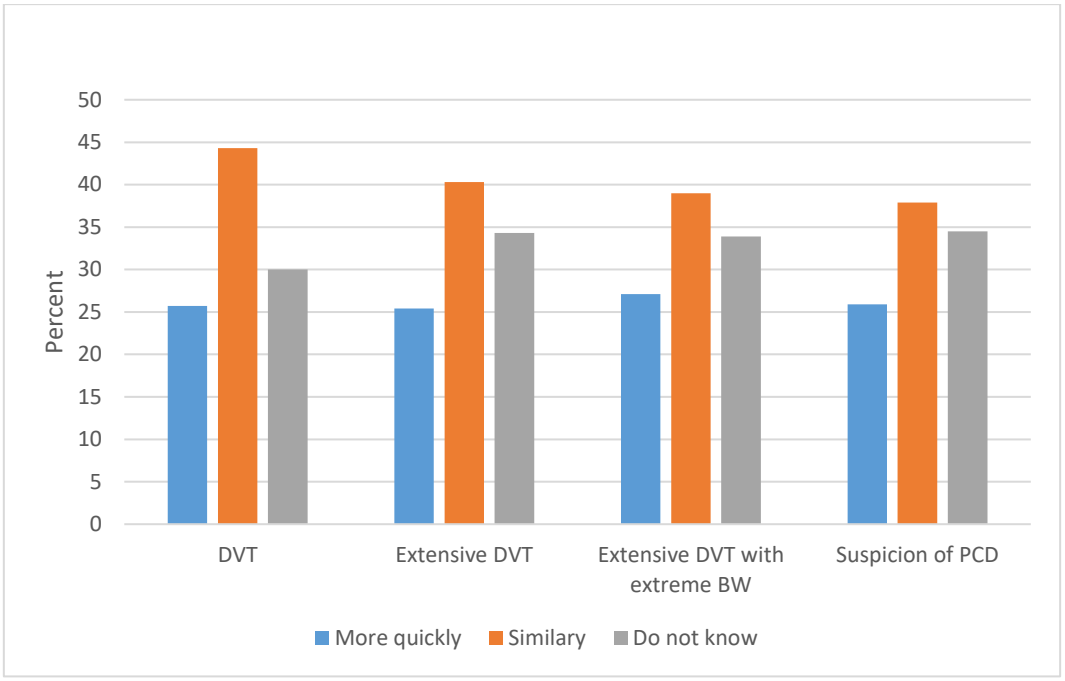


Figure 16. Opinions on the expect duration of relevant DVT-related symptoms with heparin compared with DOACs, categorized by case scenario



References

1. Dillman DA. Mail and Internet Surveys. Hoboken, UNITED STATES: Wiley; 2006.

2. Edwards PJ, Roberts I, Clarke MJ, et al. Methods to increase response to postal and electronic questionnaires. *Cochrane Database Syst Rev*. 2009(3):Mr000008.

3. McHugh ML. Interrater reliability: the kappa statistic. *Biochemia Medica*. 2012;22(3):276-282.

4. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808.

5. Investigators E, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499-2510.

6. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361(24):2342-2352.

7. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014;129(7):764-772.

8. Poterucha TJ, Libby P, Goldhaber SZ. More than an anticoagulant: Do heparins have direct anti-inflammatory effects? *Thromb Haemost*. 2017;117(3):437-444.

9. Downing LJ, Strieter RM, Kadell AM, Wilke CA, Greenfield LJ, Wakefield TW. Low-dose low-molecular-weight heparin is anti-inflammatory during venous thrombosis. *J Vasc Surg*. 1998;28(5):848-854.

10. Poyrazoglu OK, Dogukan A, Yalniz M, Seckin D, Gunal AL. Acute effect of standard heparin versus low molecular weight heparin on oxidative stress and inflammation in hemodialysis patients. *Ren Fail*. 2006;28(8):723-727.

11. Hochart H, Jenkins PV, Smith OP, White B. Low-molecular weight and unfractionated heparins induce a downregulation of inflammation: decreased levels of proinflammatory cytokines and nuclear factor-kappaB in LPS-stimulated human monocytes. *Br J Haematol*. 2006;133(1):62-67.

12. Mousavi S, Moradi M, Khorshidahmad T, Motamedi M. Anti-Inflammatory Effects of Heparin and Its Derivatives: A Systematic Review. *Adv Pharmacol Sci*. 2015;2015:507151.

13. Yokohama City University Medical C, Yokohama City U. Anti-inflammatory Effects of Rivaroxaban Versus Dabigatran; 2015.

14. Robertson L, Jones LE. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for the initial treatment of venous thromboembolism. *Cochrane Database Syst Rev*. 2017;2:CD001100.

15. Weitz JI. Low-molecular-weight heparins. *N Engl J Med*. 1997;337(10):688-698.

16. Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. *Clin Pharmacokinet*. 2014;53(1):1-16.

17. Raghavan N, Frost CE, Yu Z, et al. Apixaban metabolism and pharmacokinetics after oral administration to humans. *Drug Metab Dispos*. 2009;37(1):74-81.

18. Enden T, Haig Y, Klow NE, et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep

vein thrombosis (the CaVenT study): a randomised controlled trial. *Lancet*. 2012;379(9810):31-38.

19. Haig Y, Enden T, Grøtta O, et al. Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial. *The Lancet Haematology*. 2016;3(2):e64-e71.

20. Lou N. Catheter-Based Tx Disappoints for Deep Vein Thrombosis Thrombolytic tx didn't cut post-thrombotic syndrome in trial. March 7, 2017.Retrieved from https://www.medpagetoday.com/meetingcoverage/sir/63676.

21. Cook C, Heath F, Thompson RL. A Meta-Analysis of Response Rates in Web- or Internet-Based Surveys. *Educational and Psychological Measurement*. 2000;60(6):821-836.

Section III: Rivaroxaban vs. low-molecular-weight heparin for the treatment of extensive deep vein thrombosis: a protocol of a non-inferiority randomized trial

Background and rationale

The treatment of extensive deep vein thrombosis (DVT) or phlegmasia cerulea dolens (PCD) is of great concern for both physicians and patients. In our survey of thrombosis specialists, variations in the practical management and anticoagulant selection in patients with extensive DVT were demonstrated. In addition, most thrombosis specialists tended to initiate a short course of low-molecular-weight-heparin (LMWH) in patients with severe DVT-related symptoms or early stage PCD due to a perception that LMWH might improve symptoms more quickly because of its anti-inflammatory effects, or LMWH might be more effective for acute anticoagulation. This is despite the fact that direct oral anticoagulants (DOACs) have a comparable efficacy in the prevention of recurrent VTE.[1,2] The survey also demonstrated substantial uncertainty regarding the effect of heparin compared with DOACs on DVT-related symptoms and the development of post-thrombotic syndrome (PTS). To date, no consensus or recommended guideline is available specifically in this patient population.

Rivaroxaban, one of direct oral anticoagulants (DOACs), is in widespread use and has become a standard of care in the treatment of acute venous thromboembolism (VTE). Our survey found that rivaroxaban was the most commonly selected DOACs among thrombosis specialists. This finding is aligned with trends in DOAC use in Canada.[3] Unlike LMWH, rivaroxaban is administered orally which potentially reduces the burden related to LMWH injection on patients and their caregivers. Also, the cost of rivaroxaban is less than that of LMWH.

Therefore, in order to provide evidence supporting the use of rivaroxaban for the treatment of patients with extensive DVT and early PCD, this randomized study is proposed to demonstrate non-inferiority of rivaroxaban to a short course of LMWH in term of improvement in DVT-related symptoms and the incidence of post-thrombotic syndrome (PTS).

Research question

In adult patients newly diagnosed with extensive DVT or early stage PCD is rivaroxaban non-inferior to a 10-day course of LMWH followed by rivaroxaban in term of DVT-related symptom improvement at 10 days, and PTS development at 6 months?

Primary objective

To determine if rivaroxaban is non-inferior to a 10-day course of LMWH followed by rivaroxaban for the treatment of extensive DVT or early stage PCD on DVT-related symptom improvement at 10 days, and PTS development at 6 months.

Secondary objectives

1. To determine the proportion of patients who need therapy changed at 10 days because of failure to relieve symptoms between the rivaroxaban and LMWH groups.
2. To determine the incidence of PTS at 6 months between the rivaroxaban and LMWH groups.
3. To determine the frequency of symptomatic recurrent VTE at 6 months in the rivaroxaban and LMWH groups.

Primary research hypothesis

Rivaroxaban is non-inferior to a 10-day course of LMWH followed by rivaroxaban for the treatment of extensive DVT or early stage PCD in term of DVT-related symptom improvement and the development of PTS.

Secondary research hypotheses

1. The proportion of patients who need therapy changed at 10 days because of failure to relieve symptoms between the rivaroxaban and LMWH group is similar.
2. The incidence of PTS at 6 months in the rivaroxaban group is similar with that in the LMWH group.
3. The frequency of recurrent VTE at 6 months in the rivaroxaban group is similar to that in the LMWH group.

Methods

Study design

This will be a 1:1 active controlled, parallel-group, double-blind, double-dummy randomized study.

Study setting

Patients who visit thrombosis or hematology outpatient clinics at the St. Joseph's Hospital, Hamilton General Hospital, Juravinski Hospital, McMaster University Medical Centre, and Ramathibodi Hospital, Thailand will be screened and assessed for eligibility criteria. Eligible patients will be asked to participate in the

study by physicians or research nurses. Expected recruitment duration of the study is 2 years. For all patients, the study treatment duration will be at least 6 months.

Study population

Eligibility criteria

1. Adults at least 18 years old, newly diagnosed with symptomatic extensive DVT with or without pulmonary embolism (PE). Patients must meet the requirements of extensive DVT including:
    - Severe DVT-related symptoms including pain and swelling of the entire affected leg *or* non-complicated PCD not felt to mandate thrombolytic therapy or surgical intervention, and
    - Patients can be managed as outpatient, and
    - Complete thrombosis of the proximal deep veins at least from the iliofemoral or common femoral veins and extends to the popliteal vein or the trifurcation, demonstrated by imaging with:
        - compression ultrasound (CUS) or
        - CT or MR venography

    Non-complicated PCD is defined by the presence of cyanosis, preserving distal pulses of affected extremities without signs of neurologic impairments or venous gangrene.

2. Patients are able to give written informed consent

Exclusion criteria

1. DVT or PE treatment with more than two doses of once-daily LMWH, or three doses of twice-daily dosing DOACs, or UFH infusion > 24 hours.
2. Patients with unstable hemodynamics.
3. Patients with active cancer.
4. Patients with known antiphospholipid antibody syndrome.
5. Patients with a mechanical heart valve.
6. Patients with body weight more than 120 kg.
7. Patients with active bleeding or high risk for bleeding contraindicating to anticoagulation.
8. Patients with a creatinine clearance calculated by Cockcroft-Gault of less than 30 ml/min.
9. Patients with severe hepatic impairment.
10. Patients with platelet count <100,000/mm^3, or hemoglobin <9 g/dL.
11. Allergic to LMWH or rivaroxaban.
12. Previously documented a history of heparin-induced thrombocytopenia.
13. Pregnancy or suspected pregnancy or unable or unwilling to use an acceptable method of birth control.

Randomization

Patients who provide consent will be enrolled in the study. Participants will be randomly assigned to receive either LMWH or rivaroxaban. Random allocation will be achieved through central randomization by a random number table, varying in block sizes, generated using a computer-based statistical program by an independent

statistician. Participants will be stratified based on clinical center. The randomization list will be encrypted in a secured computer with password protection and can be accessed by authorized study staff at a study coordinating center. Practically, investigators will call the study coordinating center. After confirming the eligibility, research coordinators at the study coordinating center will contact pharmacists at the enrolling clinical centers and inform them of the treatment allocation. Pharmacists will dispense the study drugs to participants according to the assigned treatments. Physicians, research personnel, and participants will be concealed and blinded to the treatment allocation. Pharmacists of the enrolling clinical centers will be aware of the treatment allocation.

Intervention

The study intervention comprises 2 phases including an initial phase and a short-term treatment phase (Figure 1). The initial phase will be double-blind, and double-dummy in which physicians, research personnel, and participants will be blinded to study drug. The LMWH group will receive dalteparin 200 IU/kg subcutaneously for 10 days and matching placebo tablets for rivaroxaban. The rivaroxaban group will receive rivaroxaban 15 mg orally twice a day for 10 days and matching placebo syringes for dalteparin. In the short-term treatment phase, both groups will receive rivaroxaban 15 mg orally twice a day for 11 days to complete a 3-week period and then will be switched to rivaroxaban 20 mg orally once daily. This phase will be an open-label. The study drugs will be administered within 24 hours after randomization. All patients will continue anticoagulant therapy for a minimum of six months.

At the 10-day follow-up visit, a decision should patients be switched to the short-term treatment phase will be made by their primary physicians. If primary physicians feel that participants should not be switched to the short-term treatment phase regardless of reasons, and not felt to mandate thrombolytic therapy or other interventional or surgical management, the intensification phase will be employed. The study drugs will be adjusted according to the pre-specified protocol to maintain blinding of the study treatment. The LMWH group will receive a 25% increase in the doses of LMWH subcutaneously once a day. The rivaroxaban group will receive dalteparin 200 IU/kg subcutaneously once a day instead of rivaroxaban. Participants in both groups will continue to receive matching placebo tablets/syringes. Participants will be followed and will be switched to either 15 mg of rivaroxaban orally twice daily to complete a 3 week period, or 20 mg of oral rivaroxaban once daily according to the primary physician's judgment. In this phase, physicians, research personnel, and participants will continue to be blinded to the study drug until participants have switched to rivaroxaban.

Baseline visit

Demographic data and baseline characteristics of participants will be collected. Blood work for a complete blood count, serum creatinine, and liver function test will be performed. DVT-related symptoms will be assessed using the DVT-Leg Symptom Index (DVT-LSI) by research assistants. Research personnel will teach participants how to inject dalteparin/placebo and advise participants to take rivaroxaban/placebo with food to increase drug absorption. Participants will be allowed to take pain control

medications except for non-steroidal anti-inflammatory drugs/aspirin as it may increase the risk of bleeding.

Follow-up visit

An in-person follow-up visit will be scheduled at 10 days, and 1, 3, and 6 months after randomization. At the 10-day follow-up visit, DVT-related symptoms will be assessed using the DVT-LSI. If primary physicians feel that participants need to be followed before 10 days, they can arrange in-person follow-up visits based on their clinical judgment. During each follow-up visit, compliance will be evaluated by pill and syringe count. Participants will be instructed to report to the study center if they experience symptoms suggestive of recurrent VTE or bleeding or other complications they attribute to their participation in the study

Outcomes and measurements

The primary outcome will be an improvement in DVT-related symptoms at 10 days. A change in the DVT-LSI score at the baseline and at the 10-day visit will be used to define either clinical improvement or no clinical improvement. DVT-related symptom improvement will be defined by a decrease in the DVT-LSI score of more than a certain cutoff which will be determined in the validation study. A decrease in the score less than a certain cutoff or an increase in the score will indicate no clinical improvement.

Secondary outcomes

1. The frequency of therapy changed because of failure to relieve DVT-related symptoms at 10 days.

2. The incidence of PTS at 6 months.
3. The frequency of symptomatic recurrent VTE at 6 months.

Outcome measurements

As previously mentioned, the DVT-LSI will be utilized for an outcome measurement tool. The improvement in DVT-related symptoms will be assessed by a change in the DVT-LSI score at the baseline visit and at the 10-day follow-up visit. The DVT-LSI is a 7-item patient self-reported questionnaire assessing the severity of a patients' DVT-related symptoms. The scale queries patients on the following symptoms: leg pain, swelling, leg-related sleep problems, skin discoloration, cosmetic appearance, activity limitation, and emotional distress.

The DVT-LSI was originally developed in patients with chronic venous insufficiency in order to assess clinical symptom improvement after wearing compression stocking at 1 and 16 months.[4] The mean values of symptom severity scores reported by the patients at 1 months were significantly decreased for all categories compared with the initial scores. The tool was subsequently validated in patients with acute DVT in another study. In this study, the DVT-LSI score was calculated by a total score divided by the number of main categories. Patients who admitted with acute DVT were assessed for the DVT-LSI scores in the affected and unaffected legs at 3-7 days, 30-40 days and 12 months following hospital discharge. The study demonstrated adequate reliability and validity of the score in distinguishing the affected and unaffected legs at 3-7 days and 30-40 days.[5]

For this randomized study, the DVT-LSI adapted from the previous validation study will be employed. Participants will be instructed to rate the score on a 5-point

adjectival scale (0=no problem at all, 1= minimal problem, 2= somewhat a problem, 3= major problem, 4= very much problem). A total score will be calculated by a combination of scores from all categories. Due to a lack of data on minimally clinically important differences of the DVT-LSI score, a validation study will be incorporated in this randomized trial. The objective of the validation study is to determine a minimally clinically important difference of the DVT-LSI score which will be used as a cutoff to determine symptom improvement. Details of the validation study will be discussed separately.

For the secondary outcomes, participants who require a therapy change because of failure to relieve DVT-related symptoms will be assessed at 10 days. The decision to switch therapy will be made by primary physicians mainly involve in the care of participants. Changes of therapy include one of the followings: a need for additional interventional or surgical therapy, switching to unfractionated heparin or other anticoagulant therapy, and switching to the intensification phase of the study. The duration of the intensification phase and reasons for changes of therapy will be recorded.

The incidence of PTS will be assessed at 6 months by using the Villalta scale[6] The Villalta scale is a standard tool for the diagnosis of PTS. It incorporates five patient-rated venous symptoms and clinician-related venous signs. The score will be assessed by research assistants who have experience using the scale.

The frequency of symptomatic recurrent VTE at 6 months will be reported. Symptomatic recurrent VTE including DVT and/or PE is defined by symptomatic patients with a new or progression of pre-existing thrombus objectively confirmed by

Doppler ultrasound of the legs, or computerized tomography pulmonary angiography (CTPA) or chest computerized tomography scan or high probability of ventilation-perfusion scan.

Major and clinically relevant non-major bleeding defined according to ISTH criteria[7] occur during the study period will be reported.

Minimizing bias

Because the primary outcome is a patient-reported outcome, physicians, study personnel, participants, and outcome assessors will be blinded to the assigned treatment. This will minimize outcome reporting bias and ascertainment bias. Secondary outcomes will be adjudicated by a committee who will be blinded to the treatment allocation. Pharmacists who are aware of the treatment allocation will not be part of any outcome assessments or statistical analyses.

Statistical analysis

Descriptive statistics will be summarized for baseline characteristics. Statistical analyses for the primary and secondary outcomes will be based on intention-to-treat population. The primary outcome will be reported in percentage. For the primary outcome analysis, the difference in risk and its 95% confidence interval will be calculated.

To demonstrate non-inferiority for the primary outcome, it is necessary to demonstrate that the proportion of the primary outcome in the rivaroxaban group, is not unacceptably lower in that in the LMWH group, as measured by the absolute risk difference of 0.1 ($p_l - p_r$), where p_l and p_r represent the proportions of patients with

DVT-related symptom improvement in the LMWH and rivaroxaban groups, respectively. Non-inferiority will be concluded if the following condition is satisfied;

The upper bound of 95% confidence interval for the risk difference ($p_l - p_r$) is less than 0.1. This corresponds to a test of the hypothesis H_0: $p_l - p_r \geq 0.1$ against H_a: $p_l - p_r < 0.1$, performed at the one-sided alpha at 0.025 level.

The non-inferiority margin is derived from literature review and clinical acceptance of thrombosis experts. The risk difference of 10% will be used based on the value that will preserve at least 50% of the treatment effect and is clinically acceptable by the experts (appendix).

Secondary outcomes will be reported in percentages and compared using a Fisher exact or a Chi-square test as appropriate. A p-value of <0.05 will indicate a statistical significance. No subgroup analysis and interim analysis will be performed.

Sample size calculation

The sample size is estimated based on a pre-specified non-inferiority margin. Assuming that 72% of participants in the LMWH group and 62% of participants in the rivaroxaban group have symptom improvement at 10 days, and a non-inferiority margin of 10% for the risk difference, the study requires 87 enrolled participants per group to have 80% power to show the non-inferiority of rivaroxaban, at a one-sided alpha level of 0.025 (table1).

Trial management

Informed consent

Physicians or research assistants who are knowledgeable about the study will obtain informed consents. In obtaining consent, all potential participants will have the goals of the study, the course of the study, and the interventions explained and will have an opportunity to ask any questions they wish. The information regarding efficacy and safety of both rivaroxaban and LMWH will be provided. Patients will be reassured that a refusal to participate in the study will not effect on clinical management.

Ethical considerations

The study will be conducted in accordance with the Declaration of Helsinki. All patients will be explained regarding potential risks for both interventions. Confidentiality and anonymity will be secured by using numbers or alphabetically order codes for each participant. All study drugs and placebo will be provided by the study. The study protocol will be submitted for approval from Hamilton Health Science research ethics board.

Research team

The research team will comprise principal investigator, co-investigators, research coordinators, research assistants, pharmacists, and statisticians. The study will be coordinated through an academic research unit based at McMaster University in Hamilton.

Data management plan

All data collection and entry will be recorded using electronic case record forms (CRFs). The patient-reported outcomes (DVT-LSI score) will be recorded using paper record forms and will be transcribed into electronic CRFs by research personnel on a day-to-day basis. Study data will be managed using the Real Time Electronic Digitally Controlled Analyzer Processor (REDCap) application. The REDcap is a secure, web-based application designed to support data capture for research studies. Research personnel who are responsible for data collection will have an access password for the REDCap application.

Trial documentation

All protocol amendments with justification will be recorded. Standard operating procedures will be provided to all study sites. Standard operating procedures will conform to the expectations of GCP – we anticipate using those available through the N2Canada website (http://n2canada.ca/)

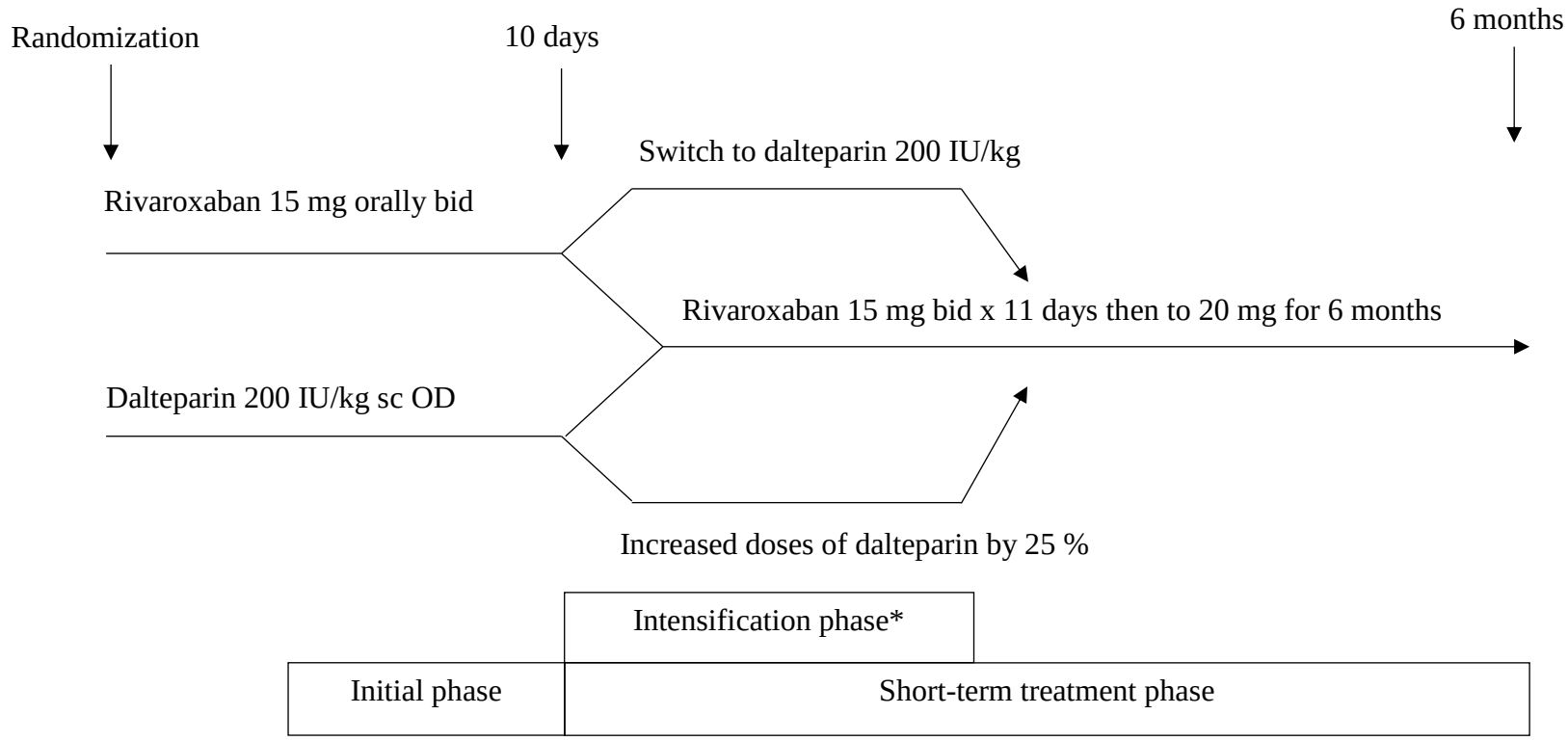
Tables and figures

Table 1. Sample size estimation

Assuming the proportion of improvement in symptoms in control group to be 0.72 and the proportion of improvement in symptoms in the intervention group to be 0.62 with absolute risk difference of 10%, the study requires 87 enrolled participants per group to have 80% power to show the non-inferiority of rivaroxaban, at a one-sided alpha level of 0.025. We selected a sample size of 174 patients due to feasibility issue as we expected to recruit at least 8 patients/months in a 2-year period.

Alpha	Power	
	80%	90%
1-sided 2.5%	174	232

Figure 1 Schematic of the randomized trial



*The intensification phase will only be used if required

Appendix

Determination of Non-inferiority margin

A non-inferiority margin was determined based on both statistical reasoning and clinical judgment. The statistical margin was derived from literature review. Clinical acceptance of the margin was reviewed and agreed upon by thrombosis experts. The process for determining the margin is outlined below.

Literature review

In order to demonstrate the efficacy of LMWH over placebo, randomized studies which compared the use of LMWH with placebo in acute VTE setting were searched for. However, such a study does not exist. The only available study compared the efficacy of heparin and placebo was published in 1960 and does not reflect current practice.[8] This study found an unacceptably high mortality rate in patients with acute PE who received no anticoagulant treatment.[8] Though randomized studies that compare LMWH with placebo in patients with acute VTE setting are not available, randomized studies compared LMWH with "less effective therapy", such as heparin or currently known to be inadequate anticoagulant treatment, are available. Moreover, because symptom improvement at 10 days has not been specified as an outcome in previous randomized trials, randomized trials that measure thrombus reduction at 7-14 days as one of their outcomes were selected for calculating the non-inferiority margin. This is based on a biological reason that thrombus reduction should relate to the improvement in DVT-related symptoms. Through the literature search, ten studies met the criteria and were included in the analysis (Table 2).

Table 2. LMWH vs. "less effective therapy" for clot reduction at 1-2 weeks in acute DVT: randomized controlled trials

Study, year of publication	Intervention	Long term AC	Control	Outcome	Number of patients with thrombus reduction (%)	
					LMWH	UFH
Faivre, 1988[9]	CY222 (LMWH) 10 days	-	UFH sc	Change in thrombus size (Marder's score) baseline vs. last day of treatment	11/30 (36.7)	10/29 (34.5)
Ninet, 1991[10]	Fraxiparine for 10 days.	-	UFH iv	Change in thrombus size (Marder's score) Repeated venography on day 0 and day 10	24/78 (30.8)	30/75 (40)
Lopaciuk, 1992[11]	Fraxiparine fixed dose for 10 days.	VKA on day 7	UFH sc	Change in thrombus size (Arnesen score) at 10 days	45/68 (66.2)	32/66 (48.5)
Prandoni, 1992[12]	Fragmin 7 days	VKA on day 7	UFH iv	Change in extent of thrombosis by venogram between d 0-10	50/83 (60.2)	36/85 (42.3)
Thery, 1992[13]	Fraxiparine for 14 days	-	UFH iv	Bilateral venography including ascending contrast venography was performed at day 0 and 8	29/31 (93.5)	21/21 (100)

Simonneau, 1993[14]	Enoxaparin 10 days	VKA on day10	UFH iv	Extension in size of thrombus at 10 days	35/60 (58.3)	18/57 (31.6)
Luomanmaki, 1996[15]	Dalteparin 5-10 days	VKA during initial heparin treatment	UFH iv	Change in thrombus size (Marder's score) after termination of heparin (day 6-10)	47/92 (51.1)	61/98 (62.2)
Kirchmaier, 1998[16]	Certoparin at least 14 days	VKA started on day 12-14	UFH iv	Change in thrombus size at day 12-16	55/128 (43)	42/131(32.1)
Harenberg, 2000a[17]	Certoparin 7 to 15 days.	-	UFH iv	Change in thrombus size (Marder's score), second venography between day 7 and15	60/198 (30)	48/192 (25)
Kakkar, 2003[18]	Bemiparin 12 weeks	VKA started on day 3	UFH iv	Change in thrombus size (Marder's score) between baseline and day 14 by venography	76/105 (72.4)	51/98 (52)

AC= anticoagulant, sc = subcutaneous, iv = intravenous infusion, VKA = vitamin K antagonist, UFH= unfractionated heparin

As shown in table 2, the proportion of thrombus reduction with LMWH ranges from 30.8- 72.4%% (10^{th} to 90^{th} percentile). The proportion of thrombus reduction with less effective therapy ranges from 31-62.2% (10^{th} to 90^{th} percentile).

To estimate an effect size for absolute risk difference in conservative manner, the difference between the maximum proportion in the less effective therapy group and the minimum proportion in the LMWH group of thrombus reduction was used. Therefore, assuming the percent of thrombus reduction in the less effective therapy group to be 62.2% and the percent of thrombus reduction in the LMWH group to be 30.8%, the non-inferiority margin preserving 50% of the treatment effect, based on absolute difference, is 15%.

Since extensive DVT can be life-threatening, most experts thought that an absolute risk difference of 15% was too large and proposed a risk difference of 10% would be clinically meaningful and acceptable. Thus, a risk difference of 10 % which corresponds to a non-inferiority margin preserving 68% of the treatment effect, will be used.

References

1. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799-808.

2. Prins MH, Lensing AW, Bauersachs R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J*. 2013;11(1):21.

3. Weitz JI, Semchuk W, Turpie AGG, et al. Trends in Prescribing Oral Anticoagulants in Canada, 2008–2014. *Clinical Therapeutics*;37(11):2506-2514.e2504.

4. Motykie GD, Caprini JA, Arcelus JI, Reyna JJ, Overom E, Mokhtee D. Evaluation of therapeutic compression stockings in the treatment of chronic venous insufficiency. *Dermatol Surg*. 1999;25(2):116-120.

5. Hudgens SA, Cella D, Caprini CA, Caprini JA. Deep vein thrombosis: validation of a patient-reported leg symptom index. *Health Qual Life Outcomes*. 2003;1:76.

6. Villalta S, Bagatella P, Piccioli A, Lensing A, Prins M, Prandoni P. Assessment of validity and reproducibility of a clinical scale for the post-thrombotic syndrome. *Haemostasis*. 1994;24(Suppl 1):158a.

7. Schulman S, Kearon C, the SOCOAOTS, Standardization Committee Of The International Society On T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *Journal of Thrombosis and Haemostasis*. 2005;3(4):692-694.

8. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. *Lancet*. 1960;1(7138):1309-1312.

9. Faivre R, Neuhart Y, Kieffer Y, et al. [A new treatment of deep venous thrombosis: low molecular weight heparin fractions. Randomized study]. *Presse Med*. 1988;17(5):197-200.

10. Ninet J BP, Prandoni P, Ruol A, Vigo M, Barret A. A randomized trial of subcutaneous low molecular weight heparin (CY216) compared with intravenous unfractionated heparin in the treatment of deep vein thrombosis. *Thrombosis and Haemostasis*. 1991;65(3):251-256.

11. Lopaciuk S, Meissner AJ, Filipecki S, et al. Subcutaneous low molecular weight heparin versus subcutaneous unfractionated heparin in the treatment of deep vein thrombosis: a Polish multicenter trial. *Thromb Haemost*. 1992;68(1):14-18.

12. Prandoni P, Lensing AW, Buller HR, et al. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. *Lancet*. 1992;339(8791):441-445.

13. Thery C, Simonneau G, Meyer G, et al. Randomized trial of subcutaneous low-molecular-weight heparin CY 216 (Fraxiparine) compared with intravenous unfractionated heparin in the curative treatment of submassive pulmonary embolism. A dose-ranging study. *Circulation*. 1992;85(4):1380-1389.

14. Simonneau G, Charbonnier B, Decousus H, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. *Arch Intern Med*. 1993;153(13):1541-1546.

15. Luomanmaki K, Grankvist S, Hallert C, et al. A multicentre comparison of once-daily subcutaneous dalteparin (low molecular weight heparin) and continuous

intravenous heparin in the treatment of deep vein thrombosis. *J Intern Med*. 1996;240(2):85-92.

16. Kirchmaier CM, Wolf H, Schafer H, Ehlers B, Breddin HK. Efficacy of a low molecular weight heparin administered intravenously or subcutaneously in comparison with intravenous unfractionated heparin in the treatment of deep venous thrombosis. Certoparin-Study Group. *Int Angiol*. 1998;17(3):135-145.

17. Harenberg J, Schmidt JA, Koppenhagen K, Tolle A, Huisman MV, Buller HR. Fixed-dose, body weight-independent subcutaneous LMW heparin versus adjusted dose unfractionated intravenous heparin in the initial treatment of proximal venous thrombosis. EASTERN Investigators. *Thromb Haemost*. 2000;83(5):652-656.

18. Kakkar VV, Gebska M, Kadziola Z, Saba N, Carrasco P. Low-molecular-weight heparin in the acute and long-term treatment of deep vein thrombosis. *Thromb Haemost*. 2003;89(4):674-680.

Section IV: Validation study of the Deep Vein Thrombosis- Leg Symptom Score

Objectives

1. To determine a cutoff for a change in the Deep Vein Thrombosis- Leg Symptom (DVT-LSI) score that will indicate a minimally clinically important difference.
2. To validate a change in the DVT-LSI in the assessment of DVT-related symptom improvement.

Method

Study design

The validation study will be incorporated in the first part of the randomized trial. A first 50 consecutive patients who are enrolled in the randomized trials will be included.

Index test

As discussed in the previous section, the DVT-LSI comprises 7 categories of DVT-related symptoms: leg pain, swelling, leg-related sleep problems, skin discoloration, cosmetic appearance, activity limitation, and emotional distress.[1,2] The response consists of 5-point adjectival scale: 0=no problem at all, 1= minimal problem, 2= somewhat a problem, 3= major problem, 4= very much a problem. The maximum score is thus 28. All participants will be assessed for the DVT-LSI score before the initiation of anticoagulant therapy at the baseline visit and at the 10-day in-person follow-up visit. Research assistants who are blinded to the treatment allocation will query participants and record the results using a standardized form. A difference

between the score at baseline and at 10-day assessment will be calculated and recorded.

Reference standard

Doppler ultrasound will be a reference standard. Doppler ultrasound of the affected extremities will be performed at baseline visit and at the 10-day follow-up visit by independent technicians. All participants will be verified with the reference standard. The outcome will be adjudicated by a panel of radiologists who are blinded to patient's clinical symptoms and treatment allocation. Thrombus burden at the 10-day follow-up visit will be compared with that at the baseline visit. The outcome will be categorized into 2 groups: thrombus reduction or no thrombus reduction (stable or progressive thrombus burden). Thrombus reduction will be defined by a reduction in thrombus burden of more than 4 mm compared to that in the baseline visit. Stable thrombus burden will be defined by a reduction in thrombus burden of less than 4 mm or an extension of thrombus of 0 to 4 mm compared to that in the baseline visit. Progressive thrombus burden will be defined by an extension of thrombus of more than 4 mm compared with that in the baseline visit.

Statistical analysis

Discrimination power will be evaluated by Receiver Operating Characteristic analysis. [3] The area under the curve of > 0.7 will indicate an acceptable discriminability.[4] The cutoff of a change in the DVT-LSI score will be determined by selecting the change in the score that maximizes sensitivity and specificity on the receiver operator curve. In order to select the optimal cutoff, the Youden index will be calculated and the cutoff that maximizes the index will be selected. [5] The selected

score will be used as a cutoff in the proposed randomized trial and will represent a minimally clinically important difference of the DVT-LSI. Sensitivity and specificity with 95% confidence intervals of the selected cutoff will be calculated and reported. In order to demonstrate the validity of the index test, the sensitivity, as well as the specificity of the index test, are expected to be more than 70%.

References

1. Hudgens SA, Cella D, Caprini CA, Caprini JA. Deep vein thrombosis: validation of a patient-reported leg symptom index. *Health Qual Life Outcomes*. 2003;1:76.

2. Motykie GD, Caprini JA, Arcelus JI, Reyna JJ, Overom E, Mokhtee D. Evaluation of therapeutic compression stockings in the treatment of chronic venous insufficiency. *Dermatol Surg*. 1999;25(2):116-120.

3. Hajian-Tilaki K. Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation. *Caspian J Intern Med*. 2013;4(2):627-635.

4. Hosmer DWJ, Lemeshow S. Applied Logistic Regression. 2004.

5. Youden WJ. Index for rating diagnostic tests. *Cancer*. 1950;3(1):32-35.