THROMBOPROPHYLAXIS IN PATIENTS WITH ACUTE SPINAL CORD INJURY

By

SIAVASH PIRAN, BSc (Hons), MSc, MD, FRCP(C)

Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the Requirements for the Degree Master of Science in Health Research Methodology McMaster University

TITLE: Thromboprophylaxis in patients with acute spinal cord injury

AUTHOR: Siavash Piran, BSc (University of Ottawa), MSc (University of Toronto), MD (University of Ottawa), FRCP(C) (Internal Medicine, University of Ottawa; Adult Hematology, McMaster University)

SUPERVISOR: Dr. Sam Schulman, MD PhD FRCP(C)

NUMBER OF PAGES: LXXVI, 76

Abstract

Patients with acute spinal cord injury (SCI) have a high risk of venous thromboembolism (VTE) despite receiving thromboprophylaxis. The current standard of care recommended by guidelines is to use low-molecular-weight heparin (LMWH) for thromboprophylaxis for 90 days. This entails once- or twice-daily subcutaneous injections of LMWH for this duration, which is inconvenient for the patients and only partially effective. There are uncertainties about risk factors and the true incidence of SCI-associated VTE, the optimal time to commence thromboprophylaxis, and the optimal duration of thromboprophylaxis. Furthermore, there are currently no studies on the use of direct oral anticoagulants (DOACs) for thromboprophylaxis in patients with SCI. The use of DOACs for prophylaxis in this group can eliminate the inconvenience associated with daily subcutaneous injections for 3 months.

To examine the incidence and risk factors of SCI-associated VTE, we performed a retrospective chart review of consecutive adult patients with acute SCI admitted to Hamilton General hospital from 2009 to 2015. The incidence of symptomatic VTE despite the use of thromboprophylaxis was 11% within 90 days of acute SCI; age and presence of other sites of injuries (such as lower limb fractures or pelvic fractures) along with SCI were independent risk factors for symptomatic VTE.

To determine the opinion of Canadian spine surgeons about the optimal timing of starting LMWH after acute SCI, a short 5-question electronic survey was sent to the Canadian Spine Society. Data from our survey showed that the understanding about thromboprophylaxis after acute SCI was variable and that most spine surgeons were comfortable with starting LMWH after consultation with the surgeon. Future studies should focus on educational strategies to improve the knowledge base in this area.

We will perform a pilot study at the Hamilton General Hospital comparing apixaban versus LMWH for thromboprophylaxis in patients with acute SCI. The use of apixaban for this indication can contribute to cost savings for the healthcare system and increased convenience for the patient. The protocol for the pilot study as well as steps towards a multi-center randomized controlled trial will be detailed in this thesis.

Acknowledgements

I would like to sincerely thank my thesis supervisor and mentor, Dr. Sam Schulman. I appreciate his guidance, patience, and support. I would like to also thank my thesis committee members, Drs. John Eikelboom and James Douketis for their insightful guidance. I am also grateful for the guidance and support of Dr. Clive Kearon, the Program Director of McMaster's Clinician Investigator Program.

List of Figures and Tables

List of Abbreviations

ACCP, American College of Chest Physicians

ASA, Aspirin

BMI, body mass index

CAD, coronary artery disease

CBC, complete blood count

CI, confidence interval

CKD, chronic kidney disease

CTPA, computed tomography pulmonary angiography

CVA, cerebrovascular accident

DASS, Duke Anticoagulation Satisfaction Scale

DOAC, direct oral anticoagulant

DVT, deep vein thrombosis

HR, hazard ratio

IPC, intermittent pneumatic compression

ISTH, International Society on Thrombosis and Haemostasis

IVC, inferior vena cava

Kg, kilogram

LDUH, low-dose unfractionated heparin

LMWH, low-molecular-weight heparin

LOS, length of hospital stay

ME, margin of error

NASS, North American Spine Society

N, number

NG, nasogastric

NSAIDs, non-steroid anti-inflammatory drugs

OR, odds ratio

PCC, prothrombin complex concentrate

PE, pulmonary embolism

QOL, quality of life

RCT, randomized controlled trial

RR, relative risk

SCI, spinal cord injury

SCITI, Spinal Cord Injury Thromboprophylaxis Investigators

VKAs, vitamin K antagonists

VTE, venous thromboembolism

V/Q, ventilation-perfusion

Declaration of Academic Achievement

The following is a declaration that the content of this document has been completed by Dr. Siavash Piran. The contributions of Drs. Sam Schulman, Drew Bednar, Brian Drew, James Douketis, and John Eikelboom in the preliminary work, research process and completion of the thesis are recognized and appreciated. The work takes the form of a sandwich thesis, consisting of two separate, but related published manuscripts (references 56 and 60) and a related pilot study protocol.

Chapter 1. Introduction

1.1 Incidence and Risk Factors for Venous Thromboembolism for Venous Thromboembolism in Patients with Acute Spinal Cord Injury

Patients with an acute spinal cord injury (SCI) have the highest incidence of venous thromboembolism (VTE) among hospitalized patients [1-2]. VTE is common within the first 3 months after SCI [3]. The overall incidence of symptomatic or asymptomatic deep vein thrombosis (DVT) in untreated SCI patients ranges from 50 to 100%, with the first two weeks following injury being the highest risk period [4-5]. Furthermore, pulmonary embolism (PE) is the third most common cause of mortality in patients with SCI, with an incidence of fatal PE estimated as high as 5% [6]. VTE after SCI is associated with significant morbidity and mortality [5] and it is, therefore, important for these high-risk patients to receive thromboprophylaxis.

There is very limited data on the risk factors associated with VTE in patients with an acute SCI. A few of the previously reported risk factors include the level of spinal injury, age, race, number of co-morbidities, and presence of paraplegia [7-11].

1.2 Mechanism Underlying the Increased Risk of VTE in Patients with Acute Spinal Cord Injury

The mechanism underlying the increased risk of VTE in the first 3 months after SCI is likely multifactorial and includes immobility and venous stasis after injury, endothelial vessel wall injury from surgeries, and other sites of injury which increase the risk of VTE such as lower limb and pelvic fractures [12]. Furthermore, the activation of the coagulation system after trauma might contribute to the increased risk of thrombosis and likely involves the release of tissue factor, diminished fibrinolysis, and depletion of endogenous anticoagulants such as antithrombin [13].

Using a database of more than 12000 patients with SCI, the risk of VTE in the first 3 months, 6 months, and one year after injury were 34%, 1.1%, and 0.4%, respectively [14]. The reduction in the risk of VTE over time might be due to the absence of the above risk factors except for immobility and the recovery of the muscle stretch reflexes and tone after the acute spinal shock period [15]. Given that the highest risk of

symptomatic VTE is the highest in the first 3 months and the reduced risk thereafter, eligible patients in our pilot study will receive thromboprophylaxis for 90 days or until fully mobilized whichever one comes first.

1.3 The Role of Screening Doppler Ultrasound

No randomized trials have assessed the benefit of routine screening of SCI patients for asymptomatic DVT. A systematic review examined the role of screening for asymptomatic DVT in patients with acute traumatic SCI who received pharmacologic thromboprophylaxis and concluded that there is insufficient evidence to support or refute this approach for patients with SCI [16]. The 2008 American College of Chest Physicians (ACCP) guidelines recommended screening for DVTs in patients who are at high risk of VTE (SCI, lower extremity or pelvic fracture, or major head injury) and who have suboptimal or no thromboprophylaxis (Grade 1C) [17]. The 2012 ACCP guidelines recommend against the routine screening for DVT in patients with major trauma (Grade 2C) [18]. Therefore, the VTE outcome examined in the retrospective chart review and the pilot study will be symptomatic and objectively verified events.

1.4 Low Molecular Weight Heparin as Standard Thromboprophylaxis

Low-molecular-weight heparins (LMWHs) have become the most utilized method of prophylaxis against VTE for patients with acute SCI [6, 19]. A randomized trial of 41 patients with SCI and complete paralysis compared tinzaparin, 3500 units daily, with low-dose unfractionated heparin (LDUH), 5000 units three times daily [20]. No patient in the tinzaparin group compared with 5 patients (23.8%) in the LDUH group had asymptomatic thrombotic events comprising 2 patients with a fatal PE and 3 with a DVT [20]. In addition, none of the patients who received tinzaparin had bleeding compared with 2 patients (9.5%) in the LDUH group who had severe bleeding requiring cessation of anticoagulation [20]. The authors concluded that LMWH is a safe and effective method for VTE prevention in patients with SCI and is superior to LDUH [20]. A randomized double-blind trial compared the efficacy and safety of LDUH, 5000 units twice daily, with LMWH, enoxaparin 30 mg twice daily, in 265 patients with major trauma, which included a subgroup of patients with SCI [21]. Thromboprophylaxis was started within 36 hours after injury and was continued for up to 14 days [21]. The primary outcome was DVT on or before day 14 after randomization. Bilateral leg venography was performed between day 10 and 14 or prior to discharge if that occurred earlier [21]. Sixty patients (44%) in the LDUH group compared with 40 patients (31%) in the enoxaparin group had a calf

DVT (P = 0.014) [21]. Proximal DVT occurred in 15% and 6%, respectively (p = 0.012). The relative risk reduction with enoxaparin was 30% (95% confidence interval [CI]; 4-50%) for calf DVT and 58% (95% CI; 12-87%) for proximal DVT [21]. There was no difference in the rate of major bleeding, as 6 patients (1.7%) had major bleeding with 1 in the LDUH group vs 5 in the enoxaparin group (P=0.12). The authors concluded that LMWH was more effective than LDUH in trauma patients and that despite the early start of thromboprophylaxis, the risk of major bleeding was low [21]. The event rates were not reported separately for the subgroup of patients with SCI.

The Spinal Cord Injury Thromboprophylaxis Investigators (SCITI) multicenter randomized trial compared the combination of LDUH, 5000 units every 8 hours, and intermittent pneumatic compression (LDUH-IPC) with enoxaparin, 30 mg twice daily, during the initial 2 weeks after acute SCI in 107 assessable patients (out of 476 patients initially randomized) [22]. Contrast venography and duplex ultrasound surveillance were performed 2 weeks after randomization. In addition, patients who developed clinical signs or symptoms of VTE underwent investigation. There was no difference in the rates of asymptomatic DVT amongst the enoxaparin (66%) and the LDUH-IPC (63%) groups (P = 0.81); however, the rate of PE was significantly lower in the enoxaparin group (5%) compared with the LDUH-IPC group (18%) (P = 0.03) [22]. There was no difference in rates of major bleeding. Therefore, in the acute treatment phase (the initial 2 week period), the safety and efficacy of LDUH-IPC and enoxaparin were similar [22].

These data suggest that LMWH appeared more effective in the prevention of VTE compared with LDUH. As a result, the ACCP guidelines recommend thromboprophylaxis using LMWH to be started once primary hemostasis is secured (Grade 1B) and recommend against LDUH alone (Grade 1A) [17]. Therefore, eligible patients in our pilot study patients will receive LMWH as the standard thromboprophylaxis control arm.

1.5 Intensity and Duration of Low-Molecular-Weight Heparin

Three observational studies have compared a standard low-dose LMWH (e.g. dalteparin 5000 units daily or enoxaparin 40 mg daily) to increased intensity LMWH (enoxaparin 30 mg twice daily) [23-25]. A retrospective study of 129 patients with SCI during rehabilitation compared the safety and effectiveness of enoxaparin 30 mg twice daily with enoxaparin 40 mg once daily [23]. There were no differences in the rates

of symptomatic VTE. The rates of symptomatic DVT and PE in the twice-daily compared with once-daily enoxaparin group were 2% vs 1.25%, and 2% vs none in the once-daily group, respectively [23]. The average length of time between SCI and initiation of thromboprophylaxis at admission to rehabilitation was similar (20.6 days for the twice-daily group and 23 .6 days for the once-daily group). In addition, there was no difference in the bleeding rates: 4.1% in the enoxaparin twice daily compared with 6.3% in the once daily enoxaparin group, although it was not specified how many of these events were major bleeding [23]. The authors concluded that enoxaparin once- or twice-daily has comparable efficacy in the prevention of VTE and both are associated with a low incidence of bleeding [23]. The rate of VTE in the acute phase (the first two weeks) after SCI was not evaluated in this study, which explains the low rate of VTE events observed.

The DETECT study compared the impact of switching from enoxaparin 30 mg twice-daily to dalteparin 5000 units once-daily for VTE prophylaxis in 135 critically-ill orthopedic trauma patients with pelvic or lower extremity fractures and/or acute SCI who had ICU admission (half of the patients) [24]. The design was a single center non-randomized, open-label, observational study with retrospective analysis. Phase 1 was from December 1, 2002, to November 30, 2003 (enoxaparin) and phase 2 was from January 1, 2004, to December 31, 2004 (dalteparin) [24]. Based on evidence supporting the use of dalteparin 5000 units daily in SCI patients [25], there was a switch from enoxaparin to dalteparin in phase 2. 63 received enoxaparin and 72 had dalteparin. The baseline characteristics in the two groups were similar [24]. The primary outcome was a composite of symptomatic proximal DVT and/or PE [24]. Symptomatic VTE occurred in 1.6% with enoxaparin and 9.7% with dalteparin (P = 0.103, absolute risk increase 8.1%; 95% CI, -0.6% to 15.6%). Given that the upper 95% CI for the difference in composite event rate exceeded the 5% threshold, the study failed to reject the null hypothesis that dalteparin is inferior to enoxaparin [24]. There was no difference in the rate of major bleeding: 4(6.4%) with enoxaparin versus 5 (6.9%) with dalteparin. The authors concluded that until an adequately powered non-inferiority trial is performed, enoxaparin 30 mg twice-daily should be the prophylactic regimen of choice [24]. However, this conclusion is limited by a low power of 64% and risk of bias from non-randomized treatment allocation, observational design, and changes in thromboprophylaxis over time. Nonetheless, an important finding from this study was that switching

from enoxaparin twice-daily to dalteparin once daily was associated with $12,485 CAD in LWMH acquisition cost savings [24].

A prospective, randomized, open-label study of 95 patients with acute SCI compared enoxaparin 30 mg twice daily with dalteparin 5000 units daily [25]. Thromboprophylaxis continued for 3 months for motor complete and 2 months for motor incomplete patients. DVT was detected on admission using ultrasound screening and during hospitalization, if DVT was clinically suspected [25]. There was no difference in DVT event rates: 6% developed a DVT while receiving enoxaparin versus 4% in those receiving dalteparin. There was also no difference in bleeding complications. After being discharged home, patients on enoxaparin twice daily reported significantly more inconvenience than those on dalteparin once daily [25]. In addition, the cost of enoxaparin was 1101 US dollars per month compared with 750 US dollars per month for dalteparin [25]. Taken together, low-dose LMWH (dalteparin 5000 units once-daily or enoxaparin 40 mg once-daily) seems to provide similar thromboprophylaxis compared to increased intensity LMWH (enoxaparin 30 mg twice-daily) and is the current standard for thromboprophylaxis in patients with acute SCI. Furthermore, once daily LMWH is less inconvenient for the patients and more cost-effective compared with twice daily LMWH.

An observational study examined the risk of VTE in 94 patients with acute SCI during the acute phase, during rehabilitation, and post-rehabilitation periods [3]. The cumulative incidence of VTE was 23% (22 of 94 patients) over a median period of 36 months after SCI [3]. Of the 22 VTE events, 21 were diagnosed during the acute and rehabilitation phases and only one in the post-rehabilitation period and 20 of 22 events (91%) occurred in the first 3 months after SCI [3]. A retrospective study evaluated the risk of VTE in 185 patients with SCI during the rehabilitation [26]. During a mean follow-up of 5 months, VTE occurred in 3 patients with a cumulative risk of 2% (95% CI 0 to 4%) [26]. There are no randomized trials that have compared various durations of thromboprophylaxis. The ACCP guidelines recommend that thromboprophylaxis should be continued for a minimum of 3 months or until completion of the inpatient phase of the rehabilitation (Grade 1A) [17-18]. This recommendation is based on the risk of symptomatic VTE being the highest 90 days after SCI. As a result, eligible patients in our pilot study will receive

thromboprophylaxis for 90 days or until fully mobilized whichever one comes first. However, the optimal duration of thromboprophylaxis has not yet been evaluated in an RCT.

1.6 Optimal Timing of Starting Low-molecular-weight Heparin

In addition to the ACCP guidelines, the North American Spine Society (NASS), the National Institute for Health and Clinical Excellence, and the AOSpine guidelines recommend that all SCI patients receive thromboprophylaxis [27-29]. However, the optimal timing of starting LMWH after acute SCI is unknown and is often challenging due to the balance against bleeding and the need for frequent surgical procedures in the first 2 weeks after injury. The AOSpine guidelines provide a weak recommendation to start thromboprophylaxis within the first 72 hours [29]. The latter recommendation from AOSpine is based on their systematic review of studies examining the efficacy, safety, and timing of thromboprophylaxis in the prevention of VTE in patients with acute SCI [30]. This systematic review found that combined mechanical and anticoagulant prophylaxis initiated within 72 hours of injury compared with starting >72 hours after injury resulted in a lower risk of DVT and the authors recommended that prophylaxis should be started within 72 hours of injury [30]. However, this finding and, thus, the recommendation is based on a single prospective study of 275 patients with SCI that examined early or late ($\leq$72 vs >72 hours after injury) initiation of prophylaxis using a combination of LMWH (nadroparin 0.4 mL once daily), graduated compression stockings, IPC, and early mobilization during the first 30 days after injury [31]. The rate of DVT was significantly lower in the early group (2 of 99; 2%) compared with the late group (46 of 176; 26%) with a relative risk (RR) of 12.9 (95% CI; 3.2 to 51.2; P <0.001) [31]. However, a limitation of this study is that bleeding complication rates were not reported [31].

A decision to commence thromboprophylaxis should be based on having a net clinical benefit of balancing the benefits (preventing symptomatic VTE and fatal PE) and the harms of therapy (major bleeding). Since fatal PE is the third most common cause of mortality in patients with acute SCI, the aim of thromboprophylaxis should be to reduce the rate of fatal PE. There is thus far a suggestion of LMWH being more effective in reducing the rate of fatal PE compared with LDUH [20, 22].

A 2016 observational study investigated the relationship between the timing of thromboprophylaxis initiation and development of VTE in 1,425 neurosurgical trauma patients (877 with SCI and 548 with

traumatic brain injury) [32]. All patients had weekly screening duplex ultrasound of bilateral lower

extremities [32]. The authors reported that the patients who developed a VTE had a significantly longer time

to initiation of LMWH (6.7 ±4.9 d versus 4.7 ±4.9 d) [32]. Furthermore, patients with SCI received LMWH

significantly earlier (3.4 ±4.2 d vs 6.7 ±3.9 d) and had a significantly lower VTE rate compared with patients

who had a traumatic brain injury (4.4% vs 10.4%) [32]. Lastly, patients with the combination of subdural

and subarachnoid hemorrhage were started on LMWH significantly later than the overall traumatic brain

injury group (8.3 ± 6.1 d versus 6.7 ± 3.9 days) and had a trend towards a higher rate of VTE (14.4% vs

10.4%) [32]. The results of this study furthermore illustrate the importance of timing of starting LMWH

after trauma and the challenge of starting LMWH in patients with active bleeding. A 2018 retrospective

study examined the optimal timing of initiation of thromboprophylaxis in 3,554 patients with acute SCI in a

propensity-matched analysis [33]. There were 1,772 patients in the early (< 48 hours after operative

procedure) and late (≥ 48 hours after operative procedure) initiation of thromboprophylaxis [33]. The groups

were matched for demographics, admission vital signs, injury parameters, type of operative intervention,

hospital length of stay, and type of thromboprophylaxis (LMWH vs LDUH) [33]. The rate of DVT was

significantly lower in the early group compared with those in the late group (2.1% versus 10.8%,

respectively, $p < 0.01$), although the rate of PE was similar; there were also no differences in the rate of post-

prophylaxis red cell transfusions or overall mortality [33]. The authors concluded that early initiation of

thromboprophylaxis reduces the rate of DVT without increasing the risk of bleeding and mortality and that

thromboprophylaxis should be initiated within 48 hours of surgery. However, this conclusion has a

limitation in that a surrogate marker of bleeding (red cell transfusion requirements) instead of a validated

major bleeding definition was utilized and therefore the risk of major bleeding during this acute phase is

unknown.

1.7 Other Thromboprophylaxis Options

1.7.1 Inferior Vena Cava Filters

A retrospective study of 111 patients with SCI from a trauma registry evaluated whether routine

placement of prophylactic IVC filter is indicated in SCI patients [34]. IVC filters were placed for patients

with a PE despite anticoagulation or a contraindication to anticoagulation prophylaxis [34]. The incidence of

DVT and PE were 9%, and 1.8%, respectively [34]. The incidence of DVT in patients with a combination of SCI and long bone fractures was 37.5%, which was significantly higher than the total SCI group (p<0.02) [34]. The following patients received an IVC filter: 1) two patients for a contraindication to prophylaxis due to severe closed head injury and open pelvic fractures; 2) two patients with a PE; 3) three of 10 patients who developed DVT and had a contraindication to anticoagulation; and 4) one with a suspected PE who subsequently had negative pulmonary arteriography [34]. Based on a low incidence of PE in this study, the authors concluded that routine placement of prophylactic IVC filters is not recommended in patients with SCI [34]. In spite of this conclusion, they recommend that SCI patients at high risk of thrombosis with an occurrence of a DVT despite prophylactic anticoagulation, those with long bone fractures, or patients with a contraindication to anticoagulation could be considered for prophylactic IVC filter placement [34]. However, given the known complications (such as filter fracture, filter migration resulting in of nearby structures, IVC wall penetration, and IVC thrombosis) [35], and the high cost associated with IVC filter placement ($5000 US dollars per filter) [36], and the low incidence of PE, placement of IVC filter would be unnecessary.

Furthermore, a retrospective study of 112 patients acute SCI examined the role of prophylactic IVC filter placement [36]. There were 107 (95.5%) patients who received LMWH or LDUH for prophylaxis, of whom 54 (47%) had an IVC filter placement and 58 (53%) did not. In regards to baseline characteristics, the IVC filter group was younger, had more males, and a greater proportion of patients with tetraplegia compared with the group without an IVC filter. DVT occurred in 11 (20.4%) of those with an IVC filter compared with 3 (5.2%) in those without an IVC filter (P = 0.021) [36]. Only one patient in this study had a PE; this patient had an IVC filter placement. The authors concluded that placement of an IVC filter may increase the risk of DVT in patients with acute SCI [36].

The 2008 and 2012 ACCP guidelines recommend against the use of IVC filter as a thromboprophylaxis method in patients with spinal cord injury (Grade 1C) or major trauma (Grade 2C), respectively [17-18]. The 2008 ACCP recommendations are that an IVC filter is indicated for patients with a proximal DVT and either an absolute contraindication to full-dose anticoagulation or planned major surgery in the near future [17]. Moreover, they also recommend that in either case, even with an indwelling IVC

filter, therapeutic anticoagulation should be started as soon as contraindication resolves [17]. Given the undesirable complications listed above, the treating physician deciding whether to insert an IVC filter or not should weigh the benefit (prevention of PE) versus the risks (filter complications and cost), and consider patient's preference.

1.7.2 Mechanical Thromboprophylaxis

Two trials evaluated the role of the combination of anticoagulant prophylaxis and mechanical prophylaxis compared with mechanical prophylaxis alone [22, 37]. As described above, the SCITI trial found no differences in the rates of DVT but a significantly lower rate of PE in patients who received enoxaparin 30 mg twice-daily compared with those who received LDUH plus IPC during the first 2 weeks after injury [22]. A second trial compared the use of heparin 5,000 units every 8 hours versus LDUH 5,000 units every 8 hours and electric stimulation (bilateral tibialis anterior and gastrocnemius-soleus stimulation for 23 hours daily) in 48 patients with SCI less than 2 weeks after their injury [37]. Patients were randomized to LDUH, LDUH plus electric simulation, or saline placebo. The use of a combination of LDUH plus electric simulation significantly reduced the rate of DVT compared to the other two groups [37]. The 2012 ACCP guidelines recommend adding mechanical thromboprophylaxis to pharmacologic prophylaxis for patients at high risk of VTE including those with SCI, traumatic brain injury, or spinal surgery for trauma when there is no lower limb injury (Grade 2C) [18]. In addition, for trauma patients who cannot receive LMWH or LDUH, they suggest mechanical prophylaxis with IPC over no prophylaxis (Grade 2C) in the absence of a lower limb injury [18].

1.7.3 Vitamin K Antagonists

Other thromboprophylaxis options include vitamin K antagonists (VKAs) such as warfarin administered to attain an international normalized ratio (INR) range of 2.0 to 3.0. A 2009 systematic review that examined different thromboprophylaxis options in patients with acute SCI found only 4 non-randomized studies that compared VKA and non-VKA strategies (untreated control or received LMWH) [38]. Meta-analyses of these four studies showed a lower rate of PE in the VKA group but no difference in the rates of DVT or bleeding compared with the non-VKA group [38]. The authors did not find any head-to-head randomized controlled trials (RCTs) that compared oral anticoagulants with heparin-based anticoagulants

[38]. Furthermore, the use of VKA has some limitations including a delayed onset, interactions with dietary vitamin K and numerous drugs, a need for frequent INR monitoring which is inconvenient, and the prolonged effect. The latter issue is problematic in this patient population who may require frequent interruption of anticoagulation for procedures.

1.7.4 Direct Oral Anticoagulants

There have been no studies comparing the current standard LMWH with a direct oral anticoagulant (DOAC) for thromboprophylaxis in patients with acute SCI. A single center non-randomized study of rivaroxaban in 84 patients with pelvic trauma examined its safety and efficacy (47 also had injuries to the lower limbs) [39]. Patients with SCI, severe neurological injuries, hepatosplenic injuries, or hemodynamic instability were excluded [39]. Rivaroxaban 10 mg daily was initiated within 24 hours of injury or upon hemodynamic stability, withheld on the day of surgery and re-started 12 hours postoperatively or upon hemodynamic stability and continued for 30 days [39]. Patients were screened for DVT using a duplex ultrasound on the day of admission, within 48 hours after surgery, and 30 days after surgery [39]. Furthermore, patients had a ventilation-perfusion scan if there were signs or symptoms suggestive of a PE. One patient had a fatal PE, 2 had a proximal DVT, and 12 had an asymptomatic below knee DVT [39]. There were no complications such as excessive bruising, bleeding, or prolonged wound oozing associated with rivaroxaban [39]. Patients receiving prophylaxis within 24 hours after fracture had a lower rate of DVT (6 of 64; 9.4%) than those receiving delayed prophylaxis (8 of 20; 45%) (P=0.02) [39].

Three studies have compared rivaroxaban 10 mg once daily with enoxaparin 40 mg once daily for thromboprophylaxis in patients undergoing total hip and knee replacements [40- 42]. The RECORD 1 and 2 trials compared rivaroxaban 10 mg once daily (given for total of 35 days for both trials) with enoxaparin 40 mg once daily (given for 35 days in RECORD1 and 12 ±2 days in RECORD 2) in patients undergoing total hip replacement and showed that rivaroxaban was superior to enoxaparin for the reduction of VTE and there were no differences in major bleeding events [40-41]. Similarly, the RECORD 3 trial compared rivaroxaban 10 mg once daily with enoxaparin 40 mg once daily in patients undergoing total knee replacement and reported that rivaroxaban was superior to enoxaparin in the reduction of VTE [42]. Both anticoagulants were given for a total of 12 ±2 days.

It is interesting to note that rivaroxaban demonstrated in major orthopedic surgery superiority to LMWH, not only with respect to any VTE (relative risk [RR] 0.42, 95% CI, 0.20–0.84) but also for symptomatic VTE (RR 0.49, 95% CI, 0.34–0.72) and for major VTE (RR 0.42, 95% CI, 0.20–0.84) [43]. However, two meta-analyses comparing all DOACs with enoxaparin for thromboprophylaxis in patients who underwent a major orthopedic surgery reported that the risk of bleeding was the highest with rivaroxaban and lowest with apixaban [44 - 45]. In both meta-analyses, compared with enoxaparin, dabigatran was the least effective of all DOACs for VTE prevention [44 - 45]. Furthermore, dabigatran should not be crushed as this may result in increased drug absorption and, thereby, increase the risk of bleeding [46 - 47]. Therefore, dabigatran cannot be administered via a nasogastric (NG) tube and cannot be used in patients with acute SCI as some of these patients are initially intubated in the intensive care unit. Given the described limitations of rivaroxaban and dabigatran, apixaban is an ideal DOAC of choice as it has the lowest risk of major bleeding among all DOACs and can be administered via an NG tube [48].

Apixaban is an oral direct factor Xa inhibitor that is absorbed rapidly, with a peak plasma levels 3 to 4 hours post intake, oral bioavailability more than 50% and has a terminal half-life of 10 to 14 hours [49]. Apixaban is only 25% renally cleared [50]. Apixaban has shown to have similar efficacy compared with VKA for treatment of acute VTE and for extended VTE prophylaxis in the AMPLIFY [50] and AMPLIFY-EXT trials [51]. In patients with atrial fibrillation, apixaban significantly reduced the risk of stroke without increasing the risk of major bleeding when compared to aspirin in the AVERROES trial [52].

Two studies have compared apixaban 2.5 mg twice daily with enoxaparin 40 mg once daily for thromboprophylaxis in patients undergoing total hip and knee replacements [53 - 54]. ADVANCE-2 trial compared apixaban 2.5 mg twice daily with enoxaparin 40 mg once daily in patients undergoing knee replacement [53]. Both anticoagulants were given for a total of 10-14 days. Apixaban 2.5 mg twice daily was superior to enoxaparin 40 mg once daily for prevention of VTE with no increased risk of major bleeding [5]. ADVANCE-3 trial compared apixaban 2.5 mg twice daily with enoxaparin 40 mg once daily in patients undergoing hip replacement [54]. Both anticoagulants were given for a total of 35 days [54]. Apixaban had lower rates of VTE compared to enoxaparin without increasing bleeding [54].

A pooled analysis of the ADVANCE-2 and ADVANCE-3 trials reported that apixaban was superior to enoxaparin in major orthopedic surgery with respect to major VTE, which occurred in 23 of 3394 (0.7%) apixaban patients and in 51 of 3394 (1.5%) enoxaparin patients (risk difference, -0.8% 95% CI -1.2 to -0.3; p = 0.001 for superiority) [55]. This was achieved without increased risk of major bleeding. There is thus a potential to reduce the high risk of symptomatic VTE in patients with SCI by using apixaban instead of LMWH.

1.8 Conclusions

There is a lack of high-quality data in thromboprophylaxis in patients with SCI. In addition, there are many unanswered questions in this area, which include the safety and efficacy of a DOAC compared with LMWH, the optimal timing of starting thromboprophylaxis and duration of thromboprophylaxis after injury, and the optimal strength of LMWH (once daily versus twice daily). We will aim to answer the first question in a feasibility pilot study. If the primary feasibility outcome is met we will then proceed with a multicenter RCT to examine the safety and efficacy of LMWH against a DOAC.

Chapter 2. Incidence and Risk Factor of Venous Thromboembolism in Patients with Acute Spinal Cord Injury: A Retrospective Study

2.1 Aims

As mentioned in Chapter 1 (section 1.1), given the limited available data, our aims were to 1) evaluate the incidence and risk factors of symptomatic VTE in patients with acute SCI who received LMWH, and 2) investigate the appropriate intensity and duration of VTE prophylaxis in patients with acute SCI [56].

2.2 Methods

Inclusion and exclusion criteria

A retrospective chart review of consecutive adult patients with acute SCI from 2009 to 2015 was conducted at the Hamilton Health Sciences-General Hospital. Patients were included if they met the following criteria: 1) acute traumatic or non-traumatic SCI; and 2) presenting within 1 week of injury. We excluded patients who were already on therapeutic oral anticoagulation, those who had a short hospital admission (≤7 days), and patients who had an early transfer to a different hospital location (≤30 days from the initial admission) without a possibility to follow up [56]. Patients who had a short hospital admission were excluded as they had a mild degree of SCI and were mobilizing well when discharged home.

The study was approved by the Hamilton Integrated Research Ethics Board without the need for informed consent.

Baseline characteristics

Demographic and clinical characteristics were collected, including factors previously suggested as being predictive of acute SCI-associated VTE: age, gender, body weight, year of injury, presence of spinal fracture, degree of neurological impairment, level of injury, presence of other sites of injury, length of hospital stay (LOS), and co-morbidities including hypertension, diabetes mellitus, coronary artery disease (CAD), cerebrovascular accident (CVA), chronic kidney disease, respiratory diseases, and cancer. Body weight was available for 107 patients and missing for the remaining 44 patients.

Presence of diabetes mellitus was defined as documented prior history thereof or use of anti-hyperglycemic agents. LOS referred to the total duration of days the patient was a hospital inpatient during

the acute admission at Hamilton General Spinal Cord Service and, whenever applicable, the inpatient rehabilitation admission.

Thromboprophylaxis

We also examined the intensity and duration of thromboprophylaxis. Low-dose LMWH included the use of enoxaparin 40 mg daily, dalteparin 5000 units daily, fondaparinux 2.5 mg daily, or heparin 5000 units twice daily. Increased intensity LMWH was defined as enoxaparin 30 mg twice daily. Low-dose LMWH was sequentially combined with warfarin (INR range of 2 to 3) in 5 patients.

Primary and secondary outcomes

The primary outcome was the incidence of symptomatic, objectively verified DVT via venous Doppler ultrasound and/or PE diagnosed using computerized tomography pulmonary angiogram (CTPA) within 90 days. Secondary outcomes were major bleeding, all-cause mortality, and fatal PE. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis (ISTH) recommendations [57]. Fatal PE was defined as objectively verified PE on CTPA or diagnosed on autopsy [56].

Statistical analyses

The association between different baseline characteristic variables and the presence of VTE was investigated with univariable analyses using the Fisher's exact test. These variables included gender, age (≤51 years vs >51 years), body weight (<100 kg vs ≥100 kg), year of injury (2009 to 2011 vs 2012 to 2015), presence of leg paresis vs no neurological impairment, SCI with versus without injury, SCI with additional sites of injury versus spinal only, level of injury (cervical vs others), short versus long duration of hospital stay (≤79 days vs >79 days), and low-dose LMWH versus increased intensity LMWH. The effect sizes are reported as ORs with 95% CIs. Other levels of injury include thoracic, lumbar, and ≥2 levels.

Step-wise Cox modeling with forward selection analyses was also performed to identify independent risk factors for VTE. The effect sizes are reported as hazard ratio (HR) with 95% CI. These analyses were performed using the SAS, version 9.3. For all analyses, the values of $P < 0.05$ were considered as indicative of statistical significance.

2.3 Results

A total of 151 consecutive patients with acute SCI met our inclusion criteria. Sixty patients were excluded: 34 patients had short hospital admissions (≤7 days), 17 were transferred to a different hospital location (median time of 11 days, range 5 to 29 days), 3 had another reason for admission, and 6 patients were already on therapeutic anticoagulation. The baseline characteristics of the patients are summarized in **Table 1**. Patients were followed for a median of 90 days (range, 1 to 90) and the median length of hospital stay was 79 days (range, 1 to 90).

One hundred and eleven patients (73.5%) had paraplegia or tetraplegia, 10 patients (6.6%) had no neurological impairment, and the degree of impairment was unspecified in 30 patients (19.9%). A total of 112 patients (74.2%) had a traumatic SCI with a fracture, 34 (22.5%) had a traumatic SCI without a fracture, and 5 (3.3%) had a non-traumatic SCI. Ninety-four patients (62.2%) had SCI alone versus 57 (37.8%) who had additional sites of injury. The majority of patients (52.3%, 79 of 151) had cervical SCI followed by thoracic (21.9%), ≥2 levels (15.9%), and lumbar SCI (9.9%).

The median duration of thromboprophylaxis was 65 days (interquartile range, 18 to 90) (**Table 2**). The majority of patients (59.6%) received low-dose LMWH either alone (85 of 151, 56.3%) or sequentially with warfarin (5 of 151, 3.6%) with INR range of 2 to 3 compared to 48 patients (31.8%) who received increased intensity LMWH (enoxaparin 30 mg twice daily), either alone (9 of 151, 6%) or sequentially with low-dose LMWH (39 of 151, 25.8%). Thirteen patients (8.6%) had no thromboprophylaxis. Of the 151 patients included, 29 (19.2%) were taking aspirin during the follow-up period.

Of the 151 patients enrolled, 17 patients (11%, 95% CI: 7 to 17%) had symptomatic VTE (9 PE, 6 lower extremity DVT, 1 upper extremity DVT, 1 with both a DVT and PE and nobody with fatal PE). The survival without a VTE is shown in **Figure 1**. There was no statistical difference in the rate of VTE between low-dose LMWH and increased intensity LMWH (13.3% versus 8.3%, respectively; OR 0.59, 95% CI, 0.13-2.1, p = 0.58).

The incidence and time to major bleeding or death are shown in **Table 3**. The cause of death in these patients included: 7 neurogenic shock (33.3%), 5 respiratory failure (23.8%), 3 sepsis (14.3%), 3 multi-factorial (14.3%), 2 unspecified (9.5%), and 1 hemorrhagic shock (4.8%).

Of the 13 patients who did not receive thromboprophylaxis, 6 patients (46.1%) died early and 7 (53.9%) had mild or no lower extremity neurological impairment. The cause of death in these patients included: 4 neurogenic shock, 1 respiratory failure, and 1 hemorrhagic shock. Of the 13 patients, 1 patient (7.7%) had bilateral DVTs.

In the univariable analyses, male sex (OR 14.95; 95% CI, 1.05 to 49.1, p = 0.003) and having additional sites of injuries along with SCI (OR 2.6; 95% CI. 0.8 to 8.7, p = 0.049) were significantly associated with the risk of VTE (**Table 4**). The majority of the patients (75%, 43 of 57) with additional sites of injuries were males.

In stepwise Cox modeling, independent contributors to risk for VTE were other sites of injuries, age, and the presence of leg paresis, whereas hypertension appeared to reduce the risk (**Table 5**). The gender variable could not be included due to zero events for females. Similarly, co-morbidity variables including diabetes mellitus, CAD, CVA, cancer, CKD, and respiratory diseases could not be evaluated due to zero events in one of the subsets. There was no association between the following variables and risk of VTE: the presence of a spinal fracture, level of injury, and use of aspirin.

2.4 Discussion

In our study, we found an incidence of 11% of symptomatic VTE within 90 days of acute SCI. Age and presence of other sites of injuries along with SCI were independent risk factors for symptomatic VTE. In our subgroup analysis, we found that there was no difference in the rate of VTE between those who received low-dose LMWH compared to the increased intensity LMWH group suggesting that the latter might not provide the additional thromboprophylactic effect.

We found that male gender was associated with an increased risk of VTE in our univariable analysis. The gender variable could not be included in our stepwise Cox model due to zero events for females. This association has also been reported in three other studies [8, 11, 58]; however, the mechanism for this it is not well understood. In contrast, Furlan et al examined the effects of gender on neurological and clinical outcomes in patients with acute cervical SCI and reported a trend towards an increased rate of DVT in women [59]. This finding was limited by a very small sample size of 55 patients and was confined to the cervical spine only, which has been reported to have the lowest risk of VTE among spinal cord levels [9].

We found that males were more likely to have other sites of injuries in addition to SCI, which might explain the association. However, the younger age of males would, in fact, reduce this risk as we also found that VTE risk increases with age. The presence of other sites of injuries might outplay the effect of age as a risk factor for VTE as also reflected by the hazard ratios.

In our step-wise Cox model, we found a statistically significant association between the presence of additional sites of injuries and an increased risk of VTE. This finding is in keeping with the results of a prospective study that examined the rate of VTE in patients with major trauma and reported that 56% of patients with a lower limb or pelvic injury and 40% of patient who had face, chest, or abdominal injury had a DVT [12]. In addition, the increased rate of VTE in patients with multiple trauma might be explained by the challenge in the management of thromboprophylaxis due to the balance against bleeding and the delay in starting thromboprophylaxis. In our study, thromboprophylaxis was started at a median of 3 days (range, the day of admission to 8 days) in 14 patients with VTE events and 3 patients were not on thromboprophylaxis prior to being diagnosed with a VTE.

Older age was also an independent risk factor for VTE. This finding is consistent with the previously reported literature [3, 7, 10]. It is interesting to note that males were younger than females in our study (median age 48 versus 57), suggesting that age did not contribute to the increased VTE risk seen in males.

The presence of leg paresis/para- or tetraplegia increased the risk of VTE in our analysis, but this was not statistically significant. Two previous retrospective chart review studies reported an association between leg paresis and an increased risk of VTE [2, 7]. Worley et al found that paraplegia compared with tetraplegia was the sole independent VTE risk factor in their study [2]. Green et al reported that flaccid paralysis compared with spastic paralysis was an independent VTE risk factor [7]. The presence of hypertension appeared to reduce the risk of VTE in our model, which we are unable to explain.

In our subgroup analysis, we found that there was no difference in the rate of VTE between those who received low-dose LMWH compared to those who received increased intensity LMWH. Six patients had a major bleeding episode in our study, 5 received low-dose LMWH during the follow-up period compared to one patient who received a sequential combination of low-dose LMWH and increased intensity LMWH. As described in chapter 1, section 1.5, low-dose LMWH (dalteparin 5000 units once daily or

enoxaparin 40 mg once daily) seems to provide similar thromboprophylaxis compared to increased intensity LMWH (enoxaparin 30 mg twice daily) and is less inconvenient for the patients and more cost-effective compared with twice daily LMWH [23-25].

2.5 Conclusions

Symptomatic SCI-associated VTE is a frequent complication in patients with acute SCI. Age and presence of other sites of injuries along with SCI were independent risk factors for VTE. The current standard of care thromboprophylaxis method entails once- or twice-daily subcutaneous injections of LMWH for 90 days, which is inconvenient for the patients, costly, and only partially effective. Therefore, future randomized trials assessing the role of direct oral anticoagulants versus LMWH among these higher risk patients are needed.

Chapter 3. Optimal Timing of Starting Thromboprophylaxis for Patients with Acute Spinal Cord Injury: A Survey of Canadian Spine Surgeons

3.1 Aims

We aimed to determine the opinion of Canadian spine surgeons about the optimal timing of starting LMWH and to assess their knowledge about the ACCP recommended thromboprophylaxis method and duration [60].

3.2 Methods

An electronic questionnaire with 5 questions (see **Appendix 1**) was sent via email to 144 spine surgeons from the Canadian Spine Society in July 2017. A reminder was sent two weeks later and no incentives were used. In an attempt to further increase the response rate and the potential number of participants, the survey was sent to the NASS and the international AOSpine Foundation, however, these societies did not support dissemination of a third-party survey [60]. The questions examined their understanding of the recommended prophylaxis type and duration by the ACCP guidelines and the optimal timing of commencing LMWH after acute SCI. Questionnaires were completed anonymously and no identifying data were collected outside of the participant's occupation and the number of years in practice. Participation in this survey was completely voluntary. Descriptive statistics were used to describe the proportion of surgeons with an understanding of appropriate thromboprophylaxis method and duration [60].

3.3 Results

A total of 32 responses were received: 31 from spine surgeons and 1 from a neurosurgeon. The completion rate was 88% and the response rate was 22% [60]. The median duration of years in practice was 10.5 years (range 2 to 40 years). Most of the respondents (26 of 32; 81%) correctly identified that the currently recommended prophylaxis by ACCP is LMWH. One (3%) chose unfractionated heparin, and 5 (16%) did not know the ACCP recommended thromboprophylaxis method. Only 10 respondents (31%) correctly identified that the recommended duration of prophylaxis is 90 days. The other responses were: 120 days (1 of 32; 3%), 60 days (5 of 32; 16%), 30 days (4 of 32, 12.5%), and the rest (12 of 32; 37.5%) did not know the duration of thromboprophylaxis [60].

Majority of the spine surgeons (20 of 32; 62.5%) recommended a consultation with the surgeon prior to starting LMWH. Four (12.5%) recommended starting LMWH if there is no para-spinal hematoma on the computerized tomography scan; 3 (9.4%) recommended waiting for a week after acute SCI; the rest (15.6%) indicated that they do not know the optimal timing of starting LMWH after acute SCI. None of the respondents selected the option of waiting for 2 weeks after acute SCI before starting LMWH [60].

3.4 Conclusions

Data from our survey suggest that the understanding after acute SCI was variable and that most spine surgeons recommended starting LMWH after consultation with the surgeon. In addition to calling for larger studies examining the understanding of all physicians involved in treating patients with SCI around thromboprophylaxis, future studies should focus on educational strategies (for example about guideline recommendations) to improve the knowledge base in this area [60]. Our results may also be explained by the uncertainty about the most effective method and duration of thromboprophylaxis due to a lack of high-quality evidence.

Chapter 4. Apixaban Compared with Low-Molecular Weight-Heparin For Thromboprophylaxis In Patients With Acute Spinal Cord Injury: A Pilot Study Protocol

4.1 Rationale

The current standard of care thromboprophylaxis method, LMWH, is inconvenient, costly, and only partially effective. There is no study on the use of a DOAC in this patient population and no RCT examining the safety and efficacy of LMWH against a DOAC after spinal surgery. The use of an oral anticoagulant such as apixaban can eliminate the inconvenience associated with daily subcutaneous injections with LMWH and eliminate the need for regular laboratory monitoring of VKA. The cost of apixaban 2.5 mg twice daily compared to low-dose LMWH (for example enoxaparin 40 mg daily) is crucial to consider. Apixaban 2.5 mg twice daily costs $ 3.50 compared to $9.35 for enoxaparin 40 mg once daily, and $11.77 for dalteparin 5000 units daily at Hamilton Health Sciences outpatient pharmacy. This would translate to approximate savings of $526.50 and $744.30 if apixaban were to be given for 90 days instead of enoxaparin or dalteparin, respectively. However, this cost difference does not include the healthcare expenses such as outpatient nursing care for injection of enoxaparin if thromboprophylaxis were to be continued as an outpatient. Therefore, the use of apixaban can contribute to cost savings for the healthcare system and increased convenience for the patient. A trial demonstrating the safety and efficacy of apixaban compared to the current standard thromboprophylaxis with LMWH will have a strong impact on the evidence-based guidelines. We will first assess the feasibility of performing a trial by conducting a pilot study comparing apixaban with LWMH in the prevention of VTE. The study is a randomized, open-label feasibility study with blinded endpoint adjudication.

4.2 Objectives

1) To determine the likely recruitment rate of eligible patients into an RCT in which patients with acute SCI will be randomized to a prophylactic dose of LMWH or apixaban for prevention of VTE

2) To assess for protocol violations pertaining to eligibility criteria and randomization procedures, the retention rate for primary end-point assessment at 3 months, and the estimates of endpoint rates in the RCT population

4.3 Patient Selection

4.3.1 Inclusion Criteria

1) Adult patients (≥18 years old) with acute SCI presenting to the hospital within 1 week of SCI and at least 36 h after the injury

2) Traumatic SCI

3) SCI with or without other injuries

4.3.2 Exclusion Criteria

1) Already on therapeutic oral anticoagulation prior to enrolment

2) Active bleeding, intracranial or peri-spinal hematoma, or acquired or congenital bleeding disorder

3) Pregnancy or breastfeeding

4) Severe renal failure (creatinine clearance ≤30 ml/min)

5) Severe liver cirrhosis Child-Pugh class C

6) Severe thrombocytopenia (platelets <50)

7) Attending physician believes that the patient is not suitable for the study (for example, psychiatric disorder; history of non-compliance)

8) Geographic inaccessibility: planned transfer to another site where follow-up not possible

9) Failure to obtain written consent

10) Previous hypersensitivity reaction to study drugs

11) Patients with expected short hospital admission (≤7 days) due to a minor injury.

The selected electronic data capture system will maintain a log of all patients screened for this study, consisting of patients who are: 1) eligible and consenting, 2) eligible and non-consenting, 3) ineligible because of meeting any of the exclusion criteria.

4.4 Intervention

Upon providing written informed consent, eligible patients will be randomized to apixaban 2.5 mg orally twice daily (experimental group) or dalteparin 5000 units subcutaneously once daily (control group) for 90 days or until fully mobilized, whatever comes first. If administration of study medication has to be

delayed due to insufficient hemostasis, mechanical prophylaxis against VTE should be applied, unless there are contraindications due to a leg injury.

Concomitant use of single-agent anti-platelets during the study, and 24 hours of thromboprophylaxis with any anticoagulant prior to enrollment will be allowed. In addition, in case of temporary interruption of study drugs, for example for procedures, we would allow at most one week of interruption. Mechanical prophylaxis should be utilized during this time period.

4.5 Randomization

Patients will be randomized to the experimental or control group through a password-secured website accessible only to the study investigator and coordinators. A computer-generated randomization scheme with variable block sizes will be used, further stratified for the study site and for absence or presence of additional trauma locations.

4.6 Study Procedures

Upon enrolment, the study nurse/coordinator will review the patient's chart and interview the patient if circumstances allow (not on mechanical ventilation) for any occurrence of bleeding (not related to initial multiple trauma presentation or surgeries) or venous thromboembolism signs or symptoms. The follow-up for monitoring of outcomes will occur after 1 week, 1 month, 2 months, and 3 months post enrollment into the study. These encounters should be performed as visits by a research staff as long as the patient is in the hospital/rehabilitation unit. If a patient is discharged home or transferred to another hospital sooner than 3 months, the follow-up will occur via a telephone call to inquire about any bleeding or thromboembolic events. The study nurse/coordinator will continue to follow-up the patient is transferred to another facility (for example the rehabilitation center) within the same hospital. A detailed schedule is shown in **Appendix 2**.

Patients with clinical suspicion of having a DVT and/or a PE should have the diagnosis confirmed objectively with compression ultrasound (or venography) for DVT or CTPA or ventilation-perfusion (V/Q) lung scanning for PE. Patients suspected of having bleeding will have a complete blood count and other necessary investigations at the discretion of the treating physician (for example endoscopy and/or

colonoscopy). The patients remain in the study for 90 days with an additional 30 days for reporting of any serious adverse events.

4.7 Start of Anticoagulation

The management of thromboprophylaxis in patients presenting with multiple trauma is challenging due to the balance against bleeding. Furthermore, most patients with acute SCI need spinal surgery or other additional surgeries if they have other sites of injuries along with an SCI. Therefore, apixaban 2.5 mg orally twice daily or dalteparin 5000 units subcutaneously once daily will be started once adequate hemostasis is reached and the patient is hemodynamically stable and no active bleeding or spinal or epidural hematoma, at the discretion of the treating physician. Use of mechanical thromboprophylaxis is strongly recommended until chemoprophylaxis can be started. Apixaban can be crushed and administered via a nasogastric tube in patients who are intubated [48].

In case of bleeding related to apixaban, it will be held and if necessary an indirect reversal strategy using prothrombin complex concentrate (PCC) will be employed. PCC was shown to be effective in achieving hemostasis in single arm observational studies [61 - 62]. In the unlikely case of bleeding related to low molecular weight heparin (LMWH), administration of the LMWH will be stopped. In rare cases, patients might also be treated with agents such as protamine or recombinant Factor VII.

4.8 Outcome Measures

4.8.1 Primary Outcomes

The outcome of the feasibility study will be the recruitment rate per year (i.e. the screened to enrolled ratio). Other key feasibility metrics will be accrual ratio, protocol violations pertaining to eligibility criteria and randomization procedures, the retention rate for primary end-point assessment at 3 months, and the estimates of endpoint rates in the RCT population.

The primary efficacy endpoint will be a composite of symptomatic, objectively verified, venous thromboembolism (upper or lower limb DVT and/or PE) or sudden death where PE cannot be excluded (**Appendix 3**). This outcome does not include a catheter-associated DVT.

The primary safety end-point is major bleeding according to the ISTH definition [57] (**Appendix 4**).

4.8.2 Secondary Outcomes

We will assess the quality of life (QOL) using the EQ – 5D and the Duke Anticoagulation Satisfaction Scale (DASS) questionnaires. EQ - 5D is a validated instrument that measures health-related quality of life that can be applied to a variety of diseases and treatments [63]. The DASS has been developed and validated as an anticoagulation treatment specific QOL instrument [64]. This questionnaire addresses the negative impacts of anticoagulation including limitations and burdens as well as positive impacts such as confidence and reassurance.

4.8.3 Collection of Outcome Data

The research nurse will also interview the enrolled patient at each follow-up visit and fill out the case report forms. Case report forms will be kept in a locked cabinet in the Thrombosis research office at Hamilton General Hospital. The data will be transferred to an electronic file and kept on a password-protected computer on a secure network in the research office. The details of the case report forms utilized are illustrated in **Appendix 5**.

The study data will be anonymized by the destruction of the file linking patient initials with a unique study ID when the last patient completes the study. The study data will be kept for 5 years and then destroyed.

4.8.4 Independent Adjudication Committee

The Event Adjudication Committee will be responsible for validating outcome events as specified in the protocol and according to the guidelines using standardized criteria (see **Appendices 3 and 4**). Members will be blinded to the group allocation. This committee will consist of Drs. Menaka Pai and Vinai Bhagirath.

4.8.5 Data Safety Monitoring Board

The Data Safety Monitoring Board will consist of two clinicians (Drs. Clive Kearon and Fred Spencer) and one statistician, both with considerable experience with clinical trials. The objective of interim analysis performed with the DSMB is to determine whether it is safe to continue the study and will also review all major bleeding complications, thromboembolic events, and deaths every 6 months during the study.

4.9 Patient Recruitment

Patients eligible for the study will be identified from the patients admitted to a neurosurgical or trauma unit with acute SCI. The study will be performed at Hamilton General Hospital. Patients with acute SCI are high risk for VTE and will always receive thromboprophylaxis and participation in this study will provide them with a 50% chance of receiving an oral agent instead of subcutaneous injections. Therefore, we expect the patient refusal rate to participate in the study to be low.

4.10 Sample Size

We are planning to have 40 patients recruited with 20 patients for each arm of the study. We estimate that 20 patients will be recruited per year based on the admission rate at HHS data [56]. Hence, approximately 20 patients would be enrolled per year at Hamilton General Hospital with an estimated study duration of two years.

4.11 Statistical Analysis

Descriptive analyses will be used to summarize the frequencies with corresponding 95% confidence intervals.

4.12 Study Registration

The study has been approved by the Hamilton Integrated Research Ethics Board and has been registered on clinicaltrials.gov. The clinicalTrials.gov identifier is NCT03200613. A No Objective Letter from Health Canada is not required for this study as apixaban 2.5 mg twice daily is Health Canada approved for secondary prevention of VTE, management of patients with atrial fibrillation, and for thromboprophylaxis for patients with major orthopedic surgeries.

4.13 Ethical Issues

An ethical consideration is the use of a new drug to be tested against low-dose LMWH, which is the standard thromboprophylaxis in this patient population. However, apixaban has been previously compared head-to-head against low-dose LMWH for thromboprophylaxis in patients with knee and hip replacements and was found to be effective in the prevention of VTE [53 - 54]. Furthermore, apixaban has also been shown have similar efficacy compared with VKA for treatment of acute VTE and for extended VTE prophylaxis [50-51].

4.13.1 Informed Consent

The research staff at each study site will approach the patient for an informed consent. None of the study investigators will have a position of power or authority over the participants. A patient may be withdrawn from the trial at any time during the study and without prejudice to their subsequent care if the patient, site investigator, or another treating clinician believes it is not in the patient's best interest to continue participation in this trial. This will also be conveyed to each of the participants at the time of consenting. The informed consent is detailed in **Appendix 6**.

4.14 Conclusion

The results of this pilot study will be used to assess the feasibility of performing a larger non-inferiority RCT. We will use an acceptable recruitment rate of 20 patients per year as an assessment for the feasibility of proceeding to a multicenter non-inferiority RCT. Furthermore, the pilot study will enable us to examine the retention rate and the number of patients lost to follow-up, which we have estimated as 10% for a multi-center RCT. Therefore conduction of this pilot study is essential to further advancement of management of thromboprophylaxis in this high-risk population.

Chapter 5. Future Studies

5.1 Hypothesis and Design

Hypothesis: Apixaban 2.5 mg twice daily has similar efficacy and safety as low-dose LMWH (enoxaparin 40 mg or dalteparin 5000 units once daily) for prevention of VTE in patients with acute SCI.

Design: A randomized controlled, open-label, multicenter, non-inferiority trial with a blinded adjudication of events to demonstrate that a direct oral anticoagulant therapy is non-inferior to low-dose LMWH in the prevention of symptomatic VTE in this high-risk group.

5.2 Sample Size

The primary analysis is for non-inferiority of apixaban versus LMWH with hierarchical testing for superiority. Our non-inferiority hypothesis will be tested with one-sided α set at 5% and 80% power. Event rate in the LMWH arm (based on the 8.6% average rate for all patients treated with low-dose or increased intensity LMWH reported in a systematic review) is estimated at 8% [5]. For a non-inferiority study, if we assume a VTE rate of 8% for both LMWH and apixaban and a non-inferiority margin of 4% and loss to follow-up of 10%, we would need 1302 patients to be recruited in total.

Our superiority hypothesis will be tested using an 80% power and 2-sided alpha of 2.5%. Assuming a 50% reduction in VTE rate with apixaban compared with LMWH (from 8% to 4%) we will need 1228 patients to be recruited in total. These calculations can be found in **Appendix 7**.

5.3 Expected Duration of Study

We estimate that 20 patients will be recruited per year at each center, based on the admission rate at Hamilton Health Sciences data, being an average size center. In Canada, there are 7 centers for SCI, which would mean that 140 patients would be enrolled per year and estimated duration of study would be 10 years. By participation of the United States, which has 10 times as many centers, the duration of recruitment could be reduced to 1 year and together with regulatory applications and contracts take a total of 2 years.

5.4 Analysis

5.4.1 Primary Analysis

The goal of the trial will be to first test the null hypothesis that the efficacy of apixaban was non-inferior to that of low-dose LMWH (enoxaparin or dalteparin) in the per-protocol analysis. If non-inferiority

is demonstrated, a second analysis will be done to determine whether the efficacy of apixaban is superior to that of enoxaparin in an intention-to-treat analysis.

Testing for non-inferiority and superiority will both be based on the 95% confidence interval. The threshold for the non-inferiority test is an absolute margin of 4% for the primary efficacy outcome.

5.4.2 Secondary Analyses

We will analyze the difference in the incidence of the principal safety outcome, major bleeds, between the study groups in the same manner as that of the primary efficacy. Kaplan–Meier curves will be generated to display the distribution of thrombotic events and bleeding events over time. Mean scores for the EURO-QOL E5 and DASS questionnaires will be computed at baseline and at 90 days using standard scoring algorithms. Differences in mean scores over time will be compared using repeated-measures analysis of variance, where positive scores indicate improvement in QOL. $P<0.05$ will be considered to represent a statistically significant difference between the groups. The proportion of patients with improvement from baseline and with deterioration from baseline will be calculated and potential determinants for change will be analyzed with multivariable logistic regression analysis.

5.5 Discussion

Our pilot study will be the first to examine the role of an oral anticoagulant compared with the current standard of care, LMWH, for thromboprophylaxis. If the results of this study do not demonstrate feasibility, this would mean that a definitive multi-center RCT would not likely be feasible. Therefore, these results, even if negative, will be vital to inform the clinicians and the scientific community and thus prevent wasting resources on a larger study that will likely be unsuccessful [65].

The results of our retrospective chart review demonstrated that patients with acute SCI have a high risk of VTE despite thromboprophylaxis [56]. Therefore, future multicenter RCTs in this area could focus on the addition of aspirin 81 mg once daily or IPC to LMWH or apixaban. This would translate into the corresponding groups of anticoagulant (LMWH or apixaban) plus IPC versus anticoagulant alone (LMWH or apixaban) and anticoagulant (LMWH or apixaban) plus aspirin versus anticoagulant alone (LMWH or apixaban). The downside of the latter group comparison may be an increase in the risk of major bleeding with the addition of aspirin that should be weighed against the risk of VTE in this population.

The remaining unanswered questions in this area include the optimal timing of starting thromboprophylaxis and the optimal duration of thromboprophylaxis. Both of these questions could be answered in an RCT. For example, patients with acute SCI without active bleeding, spinal or epidural hematoma can be randomized to LMWH early ($\leq$72 hours after injury) versus late (> 72 hours after injury). The optimal duration of thromboprophylaxis can also be clarified by randomizing patients to various durations of thromboprophylaxis (for example, comparing 4 weeks versus 12 weeks and 8 weeks versus 12 weeks).

5.6 Conclusion

There is currently a lack of high-quality evidence in the area of anticoagulant thromboprophylaxis in this high-risk patient group [5]. There is no study on the use of a direct oral anticoagulant (DOAC) in this patient population and no RCT examining the safety and efficacy of LMWH against a DOAC after spinal surgery. Use of a DOAC such as apixaban can eliminate the burden associated with daily injections for the patients and possibly their caregivers who administer the injections. Use of apixaban will also contribute to cost savings for the healthcare system. A trial demonstrating the safety and efficacy of apixaban compared to the current standard thromboprophylaxis with LMWH will have a strong impact on the evidence-based guidelines. We will first assess the feasibility of performing a trial by conducting a pilot study comparing apixaban with LWMH in the prevention of VTE.

Chapter 6. Methodological Challenges

6.1 Retrospective Study Methodological Issues

The retrospective chart review has a few methodological limitations. This was a retrospective study evaluating the predictive risk factors for VTE in patients with acute SCI [56]. Therefore the results may be subjected to bias, incomplete information, or misdiagnosis. For example, the presence of renal disease was defined as a documented prior history of renal disease in the charts. The potential confounding variables, such as previous personal or family history of VTE and the presence of inherited thrombophilia could not be evaluated due to lack of such information. Furthermore, bias due to the presence of confounding co-interventions such as the use of intermittent pneumatic compression could not be evaluated as it was not recorded for all patients [56]. To minimize these confounding biases and balance the groups for prognostic factors, an RCT would be needed. Due to the retrospective design, there was also a lack of central blinded adjudication of the clinical events, which could have resulted in detection bias. In addition, the proportion of females was small (30%) and none of them had a VTE event, therefore gender could not be assessed in our step-wise Cox model [56]. Lastly, the small sample size of the retrospective study limits the power to properly examine the VTE risk factors.

6.2 Survey Methodological Issues

Our survey has some methodological limitations. There is the potential for selection bias with a low response rate. The knowledge base of responders may have been different from that of non-responders [60]. The response rate could have been improved, for example, by approaching surgeons during annual meetings. A multi-national cross-sectional study is needed to get a more accurate picture of the knowledge among spine surgeons, orthopedic surgeons, trauma physicians, and intensive care specialists about the optimal timing of starting thromboprophylaxis after acute SCI [60]. This would improve the generalizability of the results. However, our study provides an initial examination of an area where there is substantial uncertainty. Lastly, we did not inquire how the respondents came to their selected responses and what process they followed to come to their conclusions [60].

A modified Delphi survey could be utilized to potentially establish a national consensus among the mentioned physician groups [66]. This process would occur in multiple steps. An expert panel consisting of a Thrombosis Medicine specialist, a spine surgeon, an orthopedic surgeon, a trauma physician, an intensive care specialist, and a research coordinator would create a list of questions to be included in the survey. The survey would be anonymously sent to the suitable physician groups in 3 rounds [66] followed by two email reminders. After the first round, the respondents would score agreement or disagreement with each statement in the questionnaire based on a scale of 0 ("total disagreement") to 10 ("total agreement") [66]. The results of each round would then be summarized using descriptive statistics based on agreement and consensus and sent along with the next survey round [66]. The participants would be asked to re-score agreement or disagreement and could change their score taking into account the group's responses [66]. The re-rankings are then summarized and examined for the degree of consensus. If an acceptable degree of consensus is reached after two rounds then the process is not repeated otherwise the third round is repeated until a consensus is reached or the response rate is too low [66].

6.3 Pilot Study Methodological Issues

The main purpose of the pilot study is to examine the feasibility of performing a larger trial and it does not allow any hypothesis testing to be performed [67]. In other words, we would be unable to test whether apixaban is non-inferior to dalteparin in the pilot study. Furthermore, even though we will examine the primary efficacy and safety outcomes in the pilot study we cannot make conclusions about the latter outcomes [67].

The primary feasibility outcome of the pilot study is the number of patients recruited per year at each center. This is estimated as 20 patients based on the retrospective chart review data [56]. The recruitment rate (i.e., number of screened/recruited patients) is unknown. Therefore we could not use this rate as the primary feasibility outcome or in the calculation of an estimated pilot study sample size using the CI approach [65]. For instance, if we employ an estimated recruitment rate of 50%, this would be referred to "p" as the estimate of the proportion in the below formula [65]. The sample size is denoted as "n". ME refers to the margin of error [65]; an ME of 0.1 was used for the sample size calculation.

$$ME = 1.96 \sqrt{\frac{p(1-p)}{n}} \quad \text{or}$$

$n = (1.96/ME)^2 \, (p) \, (1\text{-}p)$

$n = (1.96/0.1)^2 \, (0.5) \, (1\text{-}0.5)$

$n = (19.6)^2 \, (0.25)$

$n = 96$

      The estimated sample size would be 96 patients in total in this hypothetical example. In addition, if we find that there were fewer than 20 patients recruited per year, the pilot study indicates non-feasibility of a large RCT. It would be reasonable to use "feasible with modifications" in case of recruiting 15-20 patients per year [65]. However, this was not pre-specified in our protocol.

References

1. Paciaroni M, Ageno W, Agnelli G. Prevention of venous thromboembolism after acute spinal cord injury with low-dose heparin or low-molecular-weight heparin. Thromb Haemost. 2008; 99 (5): 978-80.

2. Worley S, Short C, Pike J, Anderson D, Douglas JA, Thompson K. Dalteparin vs low-dose unfractionated heparin for prophylaxis against clinically evident venous thromboembolism in acute traumatic spinal cord injury: a retrospective cohort study. J Spinal Cord Med. 2008; 31 (4): 379-87.

3. Giorgi Pierfranceschi M, Donadini MP, Dentali F, Ageno W, Marazzi M, Bocchi R, Imberti D. The short- and long-term risk of venous thromboembolism in patients with acute spinal cord injury: a prospective cohort study. Thromb Haemost. 2013; 109 (1): 34-8.

4. Christie S, Thibault-Halman G, Casha S. Acute pharmacological DVT prophylaxis after spinal cord injury. J Neurotrauma. 2011; 28: 1509- 14.

5. Chen H-L and Wang X-D. Heparin for venous thromboembolism prophylaxis in patients with acute spinal cord injury: a systematic review and meta-analysis. Spinal Cord. 2013; 51 (8): 596-602.

6. Teasell RW, Hsieh JT, Aubut JA, Eng JJ, Krassioukov A, Tu L; Spinal Cord Injury Rehabilitation Evidence Review Research Team. Venous thromboembolism after spinal cord injury. Arch Phys Med Rehabil. 2009; 90 (2): 232-45.

7. Green D, Hartwig D, Chen D, Soltysik RC, Yarnold PR. Spinal cord injury risk assessment for thromboembolism (SPIRATE study). Am J Phys Med Rehabil 2003; 82:950- 56.

8. Jones T, Ugalde V, Franks P, Zhou H, White RH. Venous thromboembolism after spinal cord injury: incidence, time course, and associated risk factors in 16,240 adults and children. Arch Phys Med Rehabil. 2005; 86 (12): 2240-7.

9. Maung AA, Schuster KM, Kaplan LJ, Maerz LL, Davis KA. Risk of venous thromboembolism after spinal cord injury: not all levels are the same. J Trauma. 2011; 71 (5): 1241-5.

10. Chung SB, Lee SH, Kim ES, Eoh W. Incidence of deep vein thrombosis after spinal cord injury: a prospective study in 37 consecutive patients with traumatic or nontraumatic spinal cord injury treated by mechanical prophylaxis. J Trauma 2011; 71:867- 70.

11. Selassie AW, Varma A, Saunders LL. Current trends in venous thromboembolism among persons hospitalized with acute traumatic spinal cord injury: does early access to rehabilitation matter? Arch Phys Med Rehabil 2011; 92: 1534- 41.

12. Geerts WH, Code KI, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after major trauma. N Engl J Med. 1994; 331 (24): 1601-6.

13. Owings JT, Gosselin R. Acquired antithrombin deficiency following severe traumatic injury: rationale for study of antithrombin supplementation. Semin Thromb Hemost. 1997; 23 (1): 17-24.

14. Godat LN, Kobayashi L, Chang DC, Coimbra R. Can we ever stop worrying about venous thromboembolism after trauma? J Trauma Acute Care Surg. 2015; 78(3): 475-80; discussion 480-1.

15. Hagen EM. Acute complications of spinal cord injuries. World J Orthop. 2015; 6 (1): 17-23.

16. Furlan JC, Fehlings MG. Role of screening tests for deep venous thrombosis in asymptomatic adults with acute spinal cord injury: an evidence-based analysis. Spine (Phila Pa 1976). 2007; 32 (17): 1908-16.

17. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, Colwell CW. Prevention of venous thromboembolism: American College of Chest Physicians. Evidence Based Clinical Practice Guidelines (8th Edition). Chest. 2008; 133: 381S–453S.

18. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, Samama CM. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141 (2): e227S-e277S.

19. Marciniak CM, Kaplan J, Welty L, Chen D. Enoxaparin versus tinzaparin for venous thromboembolic prophylaxis during rehabilitation after acute spinal cord injury: a retrospective cohort study comparing safety and efficacy. PM R. 2012; 4 (1): 11-7.

20. Green D, Lee MY, Lim AC, Chmiel JS, Vetter M, Pang T, Chen D, Fenton L, Yarkony GM, Meyer PR Jr. Prevention of thromboembolism after spinal cord injury using low-molecular-weight heparin. Ann Intern Med. 1990; 113 (8): 571-4.

21. Geerts WH, Jay RM, Code KI, Chen E, Szalai JP, Saibil EA, Hamilton PA. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med. 1996; 335 (10): 701-7.

22. Spinal Cord Injury Thromboprophylaxis Investigators. Prevention of venous thromboembolism in the acute treatment phase after spinal cord injury: a randomized, multicenter trial comparing low-dose heparin plus intermittent pneumatic compression with enoxaparin. J Trauma. 2003; 54 (6): 1116-24.

23. Hebbeler SL, Marciniak CM, Crandall S, Chen D, Nussbaum S, Mendelewski S. Daily vs twice daily enoxaparin in the prevention of venous thromboembolic disorders during rehabilitation following acute spinal cord injury. J Spinal Cord Med. 2004; 27 (3): 236-40.

24. Slavik RS, Chan E, Gorman SK, de Lemos J, Chittock D, Simons RK, Wing PC, Ho SG. Dalteparin versus enoxaparin for venous thromboembolism prophylaxis in acute spinal cord injury and major orthopedic trauma patients: 'DETECT' trial. J Trauma. 2007; 62 (5): 1075-81; discussion 1081.

25. Chiou-Tan FY, Garza H, Chan KT, Parsons KC, Donovan WH, Robertson CS, Holmes SA, Graves DE, Rintala DH. Comparison of dalteparin and enoxaparin for deep venous thrombosis prophylaxis in patients with spinal cord injury. Am J Phys Med Rehabil. 2003; 82 (9): 678-85.

26. Eichinger S, Eischer L, Sinkovec H, Wittgruber G, Traby L, Kammer M, Kyrle PA, Steinbrecher O, Kaloud H, Kyrle V, Moser H, Wildburger R. Risk of venous thromboembolism during rehabilitation of patients with spinal cord injury. PLoS One. 2018; 13 (3): e0193735.

27. Bono CM, Watters WC III (Eds.). NASS Evidence-Based Guideline Development Committee. Anti-thrombotic Therapies in Spine Surgery. North American Spine Society Evidence-Based Clinical Guidelines for Multidisciplinary Spine Care, 2009, pp 1-98.

28. Hill J, Treasure T; National Clinical Guideline Centre for Acute and Chronic Conditions. Reducing the risk of venous thromboembolism in patients admitted to hospital: summary of NICE guidance. BMJ. 2010; 340: c95.

29. Fehlings MG, Tetreault LA, Aarabi B, Anderson P, Arnold PM, Brodke DS, Burns AS, Chiba K, Dettori JR, Furlan JC, Hawryluk G, Holly LT, Howley S, Jeji T, Kalsi-Ryan S, Kotter M, Kurpad S, Kwon BK, Marino RJ, Martin AR, Massicotte E, Merli G, Middleton JW, Nakashima H, Nagoshi N,

Palmieri K, Singh A, Skelly AC, Tsai EC, Vaccaro A, Wilson JR, Yee A, Harrop JS. A Clinical Practice Guideline for the Management of Patients With Acute Spinal Cord Injury: Recommendations on the Type and Timing of Anticoagulant Thromboprophylaxis. Global Spine J. 2017, 7 (3S): 212S-220S.

30. Arnold PM, Harrop JS, Merli G, Tetreault LG, Kwon BK, Casha S, Palmieri K, Wilson JR, Fehlings MG, Holmer HK, Norvell DC. Efficacy, Safety, and Timing of Anticoagulant Thromboprophylaxis for the Prevention of Venous Thromboembolism in Patients With Acute Spinal Cord Injury: A Systematic Review. Global Spine J. 2017;7 (3):138S-150S.

31. Aito S, Pieri A, D'Andrea M, Marcelli F, Cominelli E. Primary prevention of deep venous thrombosis and pulmonary embolism in acute spinal cord injured patients. Spinal Cord. 2002; 40 (6): 300-3.

32. Tracy BM, Dunne JR, O'Neal CM, Clayton E. Venous thromboembolism prophylaxis in neurosurgical trauma patients. J Surg Res. 2016; 205 (1): 221-7.

33. Zeeshan M, Khan M, O'Keeffe T, Pollack N, Hamidi M, Kulvatunyou N, Sakran JV, Gries L, Joseph B. Optimal Timing of Initiation of Thromboprophylaxis in Spine Trauma Managed Operatively: A Nationwide Propensity Matched Analysis OF Trauma Quality Improvement Program. J Trauma Acute Care Surg. 2018 Apr 2. doi: 10.1097/TA.0000000000001916. [Epub ahead of print].

34. Maxwell RA, Chavarria-Aguilar M, Cockerham WT, Lewis PL, Barker DE, Durham RM, Ciraulo DL, Richart CM. Routine prophylactic vena cava filtration is not indicated after acute spinal cord injury. J Trauma. 2002; 52 (5): 902-6.

35. Van Ha TG. Complications of inferior vena caval filters. Semin Intervent Radiol. 2006; 23 (2): 150-5.

36. Gorman PH, Qadri SF, Rao-Patel A. Prophylactic inferior vena cava (IVC) filter placement may increase the relative risk of deep venous thrombosis after acute spinal cord injury. J Trauma. 2009; 66 (3): 707-12.

37. Merli GJ, Herbison GJ, Ditunno JF, Weitz HH, Henzes JH, Park CH, Jaweed MM. Deep vein thrombosis: prophylaxis in acute spinal cord injured patients. Arch Phys Med Rehabil. 1988; 69 (9): 661-4.

38. Ploumis A, Ponnappan RK, Maltenfort MG, Patel RX, Bessey JT, Albert TJ, Harrop JS, Fisher CG, Bono CM, Vaccaro AR. Thromboprophylaxis in patients with acute spinal injuries: an evidence-based analysis. J Bone Joint Surg Am. 2009; 91 (11): 2568-76.

39. Godoy Monzon D, Iserson KV, Cid A, Vazquez JA. Oral thromboprophylaxis in pelvic trauma: a standardized protocol. J Emerg Med. 2012; 43 (4): 612-7.

40. Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, Bandel TJ, Beckmann H, Muehlhofer E, Misselwitz F, Geerts W; RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med. 2008; 358 (26): 2765-75.

41. Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, Soglian AG, Pap AF, Misselwitz F, Haas S; RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet. 2008; 372 (9632): 31-9.

42. Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, Misselwitz F, Turpie AG; RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med. 2008; 358 (26): 2776-86.

43. Cao YB, Zhang JD, Shen H, Jiang YY. Rivaroxaban versus enoxaparin for thromboprophylaxis after total hip or knee arthroplasty: a meta-analysis of randomized controlled trials. Eur J Clin Pharmacol. 2010; 66:1099–1108.

44. Nieto JA, Espada NG, Merino RG, González TC. Dabigatran, rivaroxaban and apixaban versus enoxaparin for thomboprophylaxis after total knee or hip arthroplasty: pool-analysis of phase III randomized clinical trials. Thromb Res. 2012; 130(2): 183-91.

45. Venker BT, Ganti BR, Lin H, Lee ED, Nunley RM, Gage BF. Safety and Efficacy of New Anticoagulants for the Prevention of Venous Thromboembolism After Hip and Knee Arthroplasty: A Meta-Analysis. J Arthroplasty. 2017; 32 (2): 645-652.

46. Pradaxa (Dabigatran Etexilate Mesylate) prescribing information. Rigefield, CT: Boehringer Ingelhiem Pharmaceuticals; 2015.

47. FDA Drug Safety Communication: Special storage and handling requirements must be followed for Pradaxa (dabigatran etexilate mesylate) capsules. Safety announcement: http://www.fda.gov/Drugs/DrugSafety/ucm248746.htm.

48. Eliquis (Apixaban) prescribing information. Princeton, NJ: Bristol-Myers Squibb Company; 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202155s000lbl.pdf

49. Garcia D, Libby E, Crowther MA. The new oral anticoagulants. Blood. 2010 115:15-20.

50. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI; AMPLIFY Investigators.Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013; 369: 799- 808.

51. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI; AMPLIFY-EXT Investigators.Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013; 368 (8): 699-708.

52. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser SH, Diaz R, Talajic M, Zhu J, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, Van Mieghem W, Lip GY, Kim JH, Lanas-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, O'Donnell M, Lawrence J, Lewis G, Afzal R, Yusuf S; AVERROES Steering Committee and Investigators. N Engl J Med. 2011; 364 (9): 806-17.

53. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P; ADVANCE-2 investigators. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomized double-blind trial. Lancet. 2010; 375 (9717): 807-15.

54. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM; ADVANCE-3 Investigators. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. N Engl J Med. 2010; 363 (26): 2487-98.

55. Raskob GE, Gallus AS, Pineo GF, Chen D, Ramirez LM, Wright RT, Lassen MR. Apixaban versus enoxaparin for thromboprophylaxis after hip or knee replacement: pooled analysis of major venous

thromboembolism and bleeding in 8464 patients from the ADVANCE-2 and ADVANCE-3 trials. J Bone Joint Surg Br. 2012; 94 (2): 257-64.

56. Piran S, Schulman S. Incidence and risk factors for venous thromboembolism in patients with acute spinal cord injury: A retrospective study. Thromb Res. 2016; 147:97-101.

57. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3: 692–694.

58. Clements R, Churilov L, Wahab AL, Ng LC. Exploratory analysis of factors associated with venous thromboembolism in Victorian acute traumatic spinal cord-injured patients 2010-2013. Spinal Cord. 2017; 55 (1): 74-78.

59. Furlan JC, Krassioukov AV, Fehlings MG. The effects of gender on clinical and neurological outcomes after acute cervical spinal cord injury. J Neurotrauma. 2005; 22 (3): 368-81.

60. Piran S, Bednar D, Drew B, Schulman S. Optimal timing of starting thromboprophylaxis for patients with acute spinal cord injury: A survey of Canadian spine surgeons. Thromb Res. 2017; 160:38-40.

61. Majeed A, Ågren A, Holmström M, Bruzelius M, Chaireti R, Odeberg J, Hempel EL, Magnusson M, Frisk T, Schulman S. Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. Blood. 2017; 130 (15): 1706-1712.

62. Schulman S, Gross PL, Ritchie B, Nahirniak S, Lin Y, Lieberman L, Carrier M, Crowther MA, Ghosh I, Lazo-Langner A, Zondag M; Study Investigators. Prothrombin Complex Concentrate for Major Bleeding on Factor Xa Inhibitors: A Prospective Cohort Study. Thromb Haemost. 2018; 118 (5): 842-851.

63. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990; 16 (3): 199-208.

64. Samsa G, Matchar DB, Dolor RJ, Wiklund I, Hedner E, Wygant G, Hauch O, Marple CB, Edwards R. A new instrument for measuring anticoagulation-related quality of life: development and preliminary validation. Health Qual Life Outcomes. 2004; 2:22-33.

65. Thabane L, Ma J, Chu R, Cheng J, Ismaila A, Rios LP, Robson R, Thabane M, Giangregorio L, Goldsmith CH. A tutorial on pilot studies: the what, why and how. BMC Med Res Methodol. 2010; 10: 1-10.

66. Jones J, Hunter D. Consensus methods for medical and health services research. BMJ. 1995; 311:376-80.

67. Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. J Psychiatr Res. 2011; 45 (5): 626-9.

Legend to Figure

Figure 1. Survival Without Symptomatic Venous Thromboembolism after Acute Spinal Cord Injury

53

Table 1

Baseline Characteristics of Patients in the Retrospective Chart Review

Characteristics	Results
Age (median; range)	51 (17 to 91 years)
Males (N;%)	106 (70)
Aspirin use (N; %)	29 (19.2)
Co-morbidities (N;%)	
Hypertension	45 (29.8)
Diabetes	21 (13.9)
Coronary artery disease	5 (3.3)
Cerebrovascular accident	4 (2.6)
Cancer	7 (4.0)
Renal disease	2 (1.3)
Respiratory disease	21 (13.9)

N: number of patients

Table 2

Duration and Intensity of Thromboprohylaxis Used in the Retrospective Chart Review

Variable	Results
Prophylaxis duration (Median in days; interquartile range)	65 (18 to 90)
Prophylaxis type (N;%)	
Low-dose LMWH[a]	90 (59.6)
Alone	85 (56.3)
Sequential combination with warfarin (INR range of 2 to 3)	5 (3.6)
Increased intensity LMWH[b]	48 (31.8)
Alone	9 (6)
Sequential combination with low-dose LMWH	39 (25.8)
No prophylaxis	13 (8.6)

INR: International normalized ratio; LMWH: Low-molecular weight heparin; N: number of patients
a – low-dose LMWH: use of either enoxaparin 40 mg daily, dalteparin 5000 units daily, or heparin 5000 units twice daily
b – Increased intensity LMWH: use of enoxaparin 30 mg twice daily

Table 3

Primary and Secondary Outcomes in the Retrospective Chart Review

Outcome	Results
Symptomatic VTE (N;%)	17 (11)[a]
Time to VTE, days, median (range)	18 (2 to 65)
Major bleeding (N;%)	6 (4)
Time to major bleeding, days, median (range)	17 (8 to 40)
Fatal PE (N;%)	0 (0)
All-cause mortality (N;%)	21 (13.9)[b]
Time to all-cause mortality, days, median (range)	6 (1 to 61)

N: number of patients; PE: pulmonary embolism; VTE: venous thromboembolism
a – Symptomatic VTE (%): 9 PEs (52.9), 6 lower extremity DVT (35.3), 1 upper extremity DVT (5.9), and 1 with both a DVT and PE (5.9)
b – All-cause mortality (%): 7 neurogenic shock (33.3), 5 respiratory failure (23.8), 3 sepsis (14.3), 3 multi-factorial (14.3), 2 unspecified (9.5), and 1 hemorrhagic shock (4.8)

Table 4

Univariable Analysis for Symptomatic SCI-Associated Venous Thromboembolism in the Retrospective Chart Review

Variable	Odds Ratio (95% CI)	P-value
Gender (male vs female)	14.95 (0.88 to 254)	0.003
Age (≤51 years vs > 51 years)	0.64 (0.2 to 2.0)	0.5
Year of injury (2009 – 2011 vs 2012 – 2015)	1.7 (0.5 to 5.3)	0.4
Body weight (<100 kg vs ≥100 kg)[a]	2.52 (0.38 to 12.15)	0.19
Paraplegia vs no neurological impairment	2.7 (0.15 to 49.1)	0.6
SCI with vs without fracture	1.7 (0.4 to 9.8)	0.6
Spine and other sites vs spine only	2.6 (0.8 to 8.7)	0.049
Level of injury (cervical vs others[b])	1.27 (0.41 to 4.0)	0.8
Short vs long duration of hospital stay (≤79 days vs >79 days)	0.35 (0.1 to 1.1)	0.07
Low-dose LMWH vs increased intensity LMWH	0.59 (0.13 to 2.1)	0.58

CI: confidence interval; Kg: kilogram; LMWH: low-molecular weight heparin; SCI: spinal cord injury
a – based on N of 107, missing data in 44 patients
b – other levels include thoracic, lumbar, and ≥2 levels

Table 5

Step-wise Cox Model Analysis for Symptomatic SCI-Associated Venous Thromboembolism in the Retrospective Chart Review

Variable	Hazard Ratio (95% CI)	P-value
Other sites of injury	6.07 (1.89 to 19.47)	0.002
Age	1.05 (1.02 to 1.08)	0.002
Presence of leg paresis	2.7 (0.72 to 10.54)	0.14
Hypertension	0.18 (0.04 to 0.78)	0.02

CI: confidence interval

Figure 1
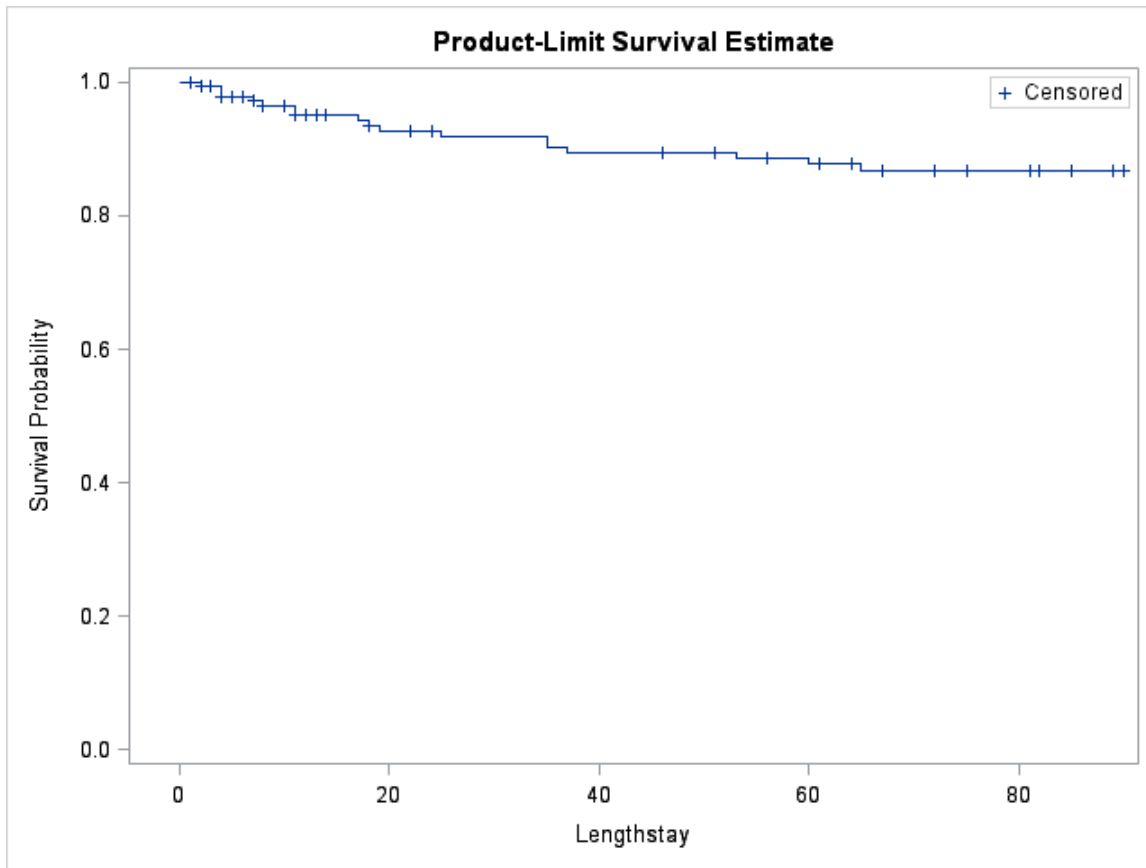
Appendix 1. Survey Questionnaire

DEMOGRAPHICS

1. What is your profession (check off all that apply)?

☐ Spine surgeon
☐ Other_____

2. How many years have you been in practice? _____

THROMBOPROPHYLAXIS

3. Which Chemoprophylaxis is Currently Recommended by the American College of Chest Physician Guidelines in Patients with Acute Spinal Cord Injury?

☐ Warfarin / Coumadin
☐ Rivaroxaban (Xarelto®)
☐ Apixaban (Eliquis®)
☐ Low-molecular Weight Heparin
☐ Unfractionated Heparin
☐ Aspirin
☐ Do not know

4. When Should Chemoprophylaxis be started?

☐ After consultation with the surgeon
☐ If Computed tomography scan shows no para-spinal hematoma
☐ One week after trauma
☐ Two weeks after trauma
☐ Do not know

5. What Duration of Thromboprophylaxis is Recommended by the American College of Chest Physician Guidelines in Patients with Acute Spinal Cord Injury?

☐ 30 days
☐ 60 days
☐ 90 days
☐ 120 days
☐ Do not know

Appendix 2: Pilot Study Follow-up Schedule

	Visit (day number)				
	Baseline 0	7	30	60	90
Demographic data	X				
Medical history (previous VTE, hypertension, cancer)	X				
SCI injury characteristics (level of injury, presence of a spine fracture, other sites of injury, degree of neurological impairment – paraplegia versus tetraplegia)	X				
Anti-thrombotic use (ASA, clopidogrel, NSAIDs, pneumatic compression stocking, nerve stimulation, TED stockings)	X	X	X	X	X
Physical Examination (vital signs, BMI)	X				
CBC, creatinine[1]	X	X	X	X	X
Informed consent	X				
Randomization	X				
Outcome events[2]		X	X	X	X
Transfusions	X	X	X	X	X
Serious adverse events		X	X	X	X[3]
Quality of life[4]	X				X

VTE – venous thromboembolism; SCI – spinal cord injury; ASA – aspirin; NSAIDs – non-steroid anti-inflammatory drugs; BMI – body mass index; CBC – complete blood count

[1]This is collection of available data on the CBC and creatinine results obtained since admission. Only the first, the lowest and the latest of hemoglobin, platelet count and creatinine need to be recorded.

[2]The outcome events are deep vein thrombosis, pulmonary embolism, bleeding, death

[3]Serious adverse event (SAE) information will be collected up to 30 days after the last dose of study drug. SAE will be any related and unexpected events.

[4]EQ – 5D and DASS questionnaires

Appendix 3: Criteria for Verified Venous Thromboembolic Events

Venous thromboembolism is defined by one or more of the events listed below:
1) Deep Vein Thrombosis
- in the lower extremity, vena cava or upper extremity (cephalic or basilic vein thrombosis does not qualify), that is not catheter-related, and is verified by ultrasonography, venography, CT or magnetic resonance imaging (MRI),

2) **Pulmonary Embolism**
- verified by CTPA, pulmonary angiography or V/Q scanning or autopsy.

Death related to thromboembolism is defined as one of:
- Death where the reported clinical circumstances or investigations before death support such a cause
- Unexpected sudden death

Appendix 4: International Society on Thrombosis and Haemostasis Definition of Major Bleeding Event

The definition of major bleeding follows the recommendation of the International Society on Thrombosis and Haemostasis (ISTH). A bleed will be categorized as being major if it fulfills at least one of the following criteria:

- Fatal bleeding
- Symptomatic bleeding in a critical area or organ, such as
    o intracranial,
    o intraspinal,
    o intraocular,
    o retroperitoneal,
    o intra-articular,
    o pericardial, or
    o intramuscular with compartment syndrome
- Bleeding causing a fall in hemoglobin level of 20 g·L (1.24 mmol·L) or more, or
- Bleeding leading to transfusion of two or more units of whole blood or red cells.

In order for bleeding in a critical area or organ to be classified as a major bleed it must be associated with a symptomatic clinical presentation.

Appendix 5. Case Report Form

Principle Investigators: Drs. Siavash Piran and Sam Schulman

Name of site: Hamilton General Hospital

Patient Initials ☐☐☐   Subject No ☐☐☐

Screening:

Inclusion
☐Y ☐N Acute SCI presenting to the hospital within 1 week of SCI and at least 36 h after the injury
☐Y ☐N Written informed consent
☐Y ☐N 18 years and over
☐Y ☐N Traumatic SCI

Exclusion
☐Y ☐N Already on therapeutic oral anticoagulation prior to enrolment
☐Y ☐N Active bleeding, intracranial or peri-spinal hematoma, or acquired or congenital bleeding disorder
☐Y ☐N Pregnancy or breast feeding
☐Y ☐N Severe renal failure (creatinine clearance ≤30 ml/min)
☐Y ☐N Liver cirrhosis
☐Y ☐N Calculated creatinine clearance <30ml/min
☐Y ☐N Severe thrombocytopenia (platelets <50)
☐Y ☐N Attending physician believes that the patient is not suitable for the study (for example, psychiatric disorder; history of non-compliance)
☐Y ☐N Geographic inaccessibility: planned transfer to other site where follow-up not possible
☐Y ☐N Failure to obtain written consent
☐Y ☐N Previous hypersensitivity reaction to study drugs
☐Y ☐N Patients with expected short hospital admission (≤7 days) due to minor injury.

Subject assessed by Investigator and found to be eligible to participate in study ☐Y ☐N

*Investigator*_____ *Signature* _____ *date*_____

VISIT 1

Date of Assessment: __ __ / __ __ __ / __ __ __ __
(DD / MMM / YYYY)

Informed Consent:	
Date participant/relative signed written consent form:	__ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)
Name of person taking informed consent: _____	

Demographic Data:	
Date of Birth:	__ __ / __ __ __ / __ ___ (DD / MMM / YYYY)
Gender:	☐ Male ☐ Female
Past Medical History:	
Anti-thrombotic Medication Use (ASA, Plavix, NSAIDs, pneumatic compression stocking, TED stockings, nerve stimulation):	
Spinal Cord Injury Characteristics: *Level of Injury (Cervical/Thoracic/Lumbar/Sacral/≥2 levels):* *Presence of spine fracture (Yes/No):* *Other sites injury:*	

Degree of Neurological Impairment (Paraplegia vs Tetraplegia)

Physical Examination:

Vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation):

Body Mass Index:

Blood work:

CBC:

Creatinine:

Transfusions:

Packed red blood cells (pRBCs):

Platelets:

Fresh frozen plasma (FFP):

Other:

Randomization:

Quality of Life Questionnaires:

VISIT 2 (1 Week ± 2 days)

Date of Assessment: __ __ / __ __ __ / __ __ __ __
(DD / MMM / YYYY)

Anti-thrombotic Medication Use (ASA, Plavix, NSAIDs, pneumatic compression stocking, TED stockings, nerve stimulation):
Blood work: *CBC:* *Creatinine:*
Transfusions: *pRBCs:*   *Platelets:*   *FFP:* *Other:*
Outcomes: *Venous Thromboembolism:* *Death Related to Venous Thromboembolism:* *Major Bleeding:*
Serious Adverse Events (related and unexpected):

VISIT 3 (1 Month ± 2 days)

Date of Assessment: __ __ / __ __ __ / __ __ __ __
(DD / MMM / YYYY)

Anti-thrombotic Medication Use (ASA, Plavix, NSAIDs, pneumatic compression stocking, TED stockings, nerve stimulation):

Blood work:

CBC:

Creatinine:

Transfusions:

pRBCs:

Platelets:

FFP:

Other:

Outcomes:

Venous Thromboembolism:

Death Related to Venous Thromboembolism:

Major Bleeding:

Serious Adverse Events (related and unexpected):

VISIT 4 (2 Months ± 2 days)

Date of Assessment: __ __ / __ __ __ / __ __ __ __
(DD / MMM / YYYY)

Anti-thrombotic Medication Use (ASA, Plavix, NSAIDs, pneumatic compression stocking, TED stockings, nerve stimulation):
Blood work: *CBC:*   *Creatinine:*
Transfusions: *pRBCs:*   *Platelets:*   *FFP:*   *Other:*
Outcomes: *Venous Thromboembolism:* *Death Related to Venous Thromboembolism:* *Major Bleeding:*
Serious Adverse Events (related and unexpected):

VISIT 5 (3 Months ± 2 days)

Date of Assessment: __ __ / __ __ __ / __ __ __ __
(DD / MMM / YYYY)

Anti-thrombotic Medication Use (ASA, Plavix, NSAIDs, pneumatic compression stocking, TED stockings, nerve stimulation):

Blood work:

CBC:

Creatinine:

Transfusions:

pRBCs:

Platelets:

FFP:

Other:

Outcomes:

Venous Thromboembolism:

Death Related to Venous Thromboembolism:

Major Bleeding:

Serious Adverse Events (related and unexpected):

Quality of Life Questionnaires:

Appendix 6. Informed Consent Form

Hamilton Health Sciences

Information Sheet and Consent Form

Apixaban Versus Low-Molecular Weight Heparin For Thromboprophylaxis In Patients With Acute Spinal Cord Injury: A Pilot Study

---

Local Principal Investigator:
Dr. Sam Schulman.
Department of Medicine, Division of Hematology and Thromboembolism. Hamilton General Hospital. T:(905) 527-4322 Ext. 44807
Principal Investigator:
Dr. Siavash Piran.
Department of Medicine, Division of Hematology and Thromboembolism. Hamilton General Hospital. T:(905) 527-4322 Ext. 44486
Co-Investigator(s):
Dr. Drew Bednar. Department of Surgery, Division of Orthopedics. Hamilton General Hospital.
T:(905) 527-0639
Dr. Brian Drew, Department of Surgery, Division of Orthopedics. Hamilton General Hospital.
T:(905) 527-0660
Dr. Agnes Chmiel, Regional Rehabilitation Center, Hamilton General Hospital.
T:(905) 521- 2100 Ext. 40817
Dr. John Eikelboom, Department of Medicine, Division of Hematology and Thromboembolism. Hamilton General Hospital. T:(905) 527-4322 Ext. 40323
Dr. Noel Chan, Department of Medicine, Division of Hematology and Thromboembolism. Hamilton General Hospital. T:(905) 527-4322 Ext. 40727

Funding:
Internal funding

You are being invited to participate in a research study conducted by Drs. Sam Schulman and Siavash Piran because you are an adult with acute traumatic spinal cord injury and presented within 1 week of the injury.
In order to decide whether or not you want to be a part of this research study, you should understand what is involved and the potential risks and benefits.

This form gives detailed information about the research study, which will be discussed with you. Once you understand the study, you will be asked to sign this form if you wish to participate. Please take your time to make your decision. Feel free to discuss it with your friends and family, or your family physician.

WHY IS THIS RESEARCH BEING DONE?
Patients with spinal cord injury have a 10-30% risk of forming clots in the first 3 months, despite receiving blood thinners. The number of blood thinners available is currently limited, with injections of low-molecular weight heparin being most commonly used which are given into the skin causing pain and bruising at the injection sites.

WHAT IS THE PURPOSE OF THIS STUDY?
A type of blood thinner taken by mouth is called apixaban, however there are no studies using
apixaban in patients with spinal cord injury. We want to compare apixaban with low-molecular weight heparins in preventing blood clots in patients with spinal cord injury.

WHAT WILL MY RESPONSIBILITIES BE IF I TAKE PART IN THE STUDY?
The participants in the study will be assigned at random, that is, by a method of chance (like a flip of a coin), to one of two groups. You will have a 1 in 2 chance of being in the group that receives low-molecular weight heparin and 1 in 2 chance of being in the group that receives apixaban. You and your study physician will know which group you are in as one blood thinner (apixaban) is given by mouth and the other by injection (low molecular weight heparin).

If you volunteer to participate in this study, we will ask you to do the following things:

Take the blood thinner for 90 days or until you are fully able to mobilize. This duration is recommended by the guidelines and according to our clinical routines. Watch for any bleeding symptoms such as nose bleeds, blood in the urine, black stools, or blood from the rectum. We ask you to please watch for symptoms related to clots including chest pain, shortness of breath, calf pain or swelling.

Our research nurse will visit you 5 times: at the beginning, 1 week, 1 month, 2 months, and 3 months after injury. The following is what happens at each visit:
- First visit: the research nurse will inquire about your age; gender; past medical history; medications; spinal cord injury characteristics (location, presence of fracture, if there is paralysis); blood work including haemoglobin, platelet count, and kidney test; if you needed transfusions; and randomization if you consent to participate in the study
- 1 week: the research nurse will inquire about bleeding or symptoms related to clots as listed above; any side effects related to the blood thinners; and if you needed any transfusions.
- 1 month, 2 months, and 3 months after injury: the research nurse will inquire about bleeding or symptoms related to clots as listed above; any side effects related to the blood thinners; and if you needed any transfusions.

The first visit will take approximately 30 minutes and subsequent visits will take approximately 15 minutes.

72

You will remain in the study for 90 days with an additional 30 days for reporting of any side effects. If you are discharged home sooner than 90 days, the research nurse will contact you to ask about any bleeding or symptoms related to clots.

Low-molecular weight heparins (either enoxaparin 40 mg or dalteparin 5000 units) are injected into the skin once a daily. Apixaban is 2.5 mg and taken by mouth twice a day.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?
The possible risk with taking these two blood thinners is bleeding. We will minimize this risk by starting the blood thinner once there is no active bleeding.

If bleeding were to occur, the blood thinner will be held and resumed once there is no active bleeding.

In case of bleeding related to apixaban, it will be held and if necessary an indirect reversal strategy using prothrombin complex concentrate (PCC) will be employed (there is currently no direct reversal agent available for clinical use). PCC has shown to be effective in achieving hemostasis in single arm observational studies.

In the unlikely case of bleeding related to low molecular weight heparin (LMWH), administration of the LMWH will be stopped. Stopping LMWH will reduce its effect on bleeding. In rare cases, if your doctor is worried about bleeding you might also be treated with agents such as protamine or recombinant Factor VII.

If you choose to take part in this study, you will be told about any new information, which might affect your willingness to continue to participate in this research.

HOW MANY PEOPLE WILL BE IN THIS STUDY?
We are planning to recruit 40 patients with 20 patients receiving each type of blood thinner. The study will run over a span of 2 years from July 2017 until September 2019.

WHAT ARE THE POSSIBLE BENEFITS FOR ME AND/OR FOR SOCIETY?
The results of this study could lead to a larger study to compare these two blood thinner and examine the risk of bleeding and prevention of blood clots. The use of an oral medication can eliminate the inconvenience of injections for the patients. The results of this study can serve as a model for other high-risk populations such as patients with cancer.

IF I DO NOT WANT TO TAKE PART IN THE STUDY, ARE THERE OTHER CHOICES?
It is important for you to know that you can choose not to take part in the study. Choosing not to participate in this study will in no way affect your care or treatment. You will receive a blood thinner at the discretion of your treating physician such as low-molecular weight heparin once or twice per day.

WHAT INFORMATION WILL BE KEPT PRIVATE?
Your data will not be shared with anyone except with your consent or as required by law. All personal information such as your name, address, phone number, OHIP number, family physician's name will be removed from the data and will be replaced with a number. A list linking the number with your name will be kept in a secure place, separate from your file. The data, with identifying information removed will be securely stored in a locked office in the research laboratory.

For the purposes of ensuring the proper monitoring of the research study, it is possible that a member of the Hamilton Integrated Research Ethics Board, a Health Canada representative may consult your research data and medical records. However, no records, which identify you by name or initials will be allowed to leave the hospital. By signing this consent form, you or your legally acceptable representative authorize such access.

If you are admitted to another hospital for any reason or die from natural or other causes while participating in this study, your medical records will be requested in order to collect information relevant to your study participation. By signing this consent form, you are allowing such access.

If the results of the study are published, your name will not be used and no information that discloses your identity will be released or published without your specific consent to the disclosure. However, it is important to note that this original signed consent form and the data, which follows, may be included in your health record.

CAN PARTICIPATION IN THE STUDY END EARLY?
If you volunteer to be in this study, you may withdraw at any time and this will in no way affect the quality of care you receive at this institution. You have the option of removing your data from the study. You may also refuse to answer any questions you don't want to answer and still remain in the study. The investigator may withdraw you from this research if circumstances arise which warrant doing so.

WILL THERE BE ANY COSTS?
Your participation in this research project will not involve any additional costs to you or your health care insurer.

WHAT HAPPENS IF I HAVE A RESEARCH-RELATED INJURY?
If you are injured as a direct result of taking part in this study, all necessary medical treatment will be made available to you at no cost. Financial compensation for such things as lost wages, disability or discomfort due to this type of injury is not routinely available. However, if you sign this consent form it does not mean that you waive any legal rights you may have under the law, nor does it mean that you are releasing the investigator(s), institution(s) and/or sponsor(s) from their legal and professional responsibilities.

IF I HAVE ANY QUESTIONS OR PROBLEMS, WHOM CAN I CALL?

If you have any questions about the research now or later, or if you think you have a research-related injury, please contact Michelle Zondag, RN at 905-527-4322 ext 44807.

Statement of consent

I have read the above information. I have received answers to any questions I may have had. I consent to participate in this research study. I will keep a signed copy of this consent form and information sheet and the other signed copy will be kept at the study centre.

_____   _____   _____
Name of patient (print)   Signature   Date

_____   _____   _____
Name of next of kin (print)   Signature   Date

_____   _____   _____
Name of person obtaining consent   Signature   Date
(print)

I have explained the nature of the study to the patient and believe that he/she understands it.

_____   _____   _____
Name of Principal investigator (print)   Signature   Date

This study has been reviewed by the Hamilton Integrated Research Ethics Board (HIREB). The HIREB is responsible for ensuring that participants are informed of the risks associated with the research, and that participants are free to decide if participation is right for them. If you have any questions about your rights as a research participant, please call the Office of the Chair, Hamilton Integrated Research Ethics Board at 905.521.2100 x 42013.

Appendix 7: Sample Size Calculations

Event rate in the LMWH arm (based on the average rate of all patients treated with low-dose or increased intensity LMWH reported in a systematic review) is estimated at 8%. We are also expecting this rate for apixaban. For non-inferiority, we use a one-sided alpha of 5% and a predefined power of 80%. Loss from follow-up is estimated at 10%.

Upper Non-inferiority Margin (%)	Number of patients
11	2286
12	1302
13	846
14	596

With respect to the uncertainty regarding the estimated incidence of VTE and that it in our retrospective study was 11%, an upper limit of the non-inferiority 95% CI of 12% should be acceptable. This will require a total sample size of 1302 patients.

For superiority, we estimate the event rate in the LMWH arm as 8% and we will consider a 50% reduction in the VTE rate, i.e. to 4% with apixaban as clinically important. We used a predefined power of 80% or 90% and two-sided alpha of 2.5% for sample calculation, again with 10% estimated loss from follow-up.

Power (%)	Number of patients
80	1228
90	1752