

# Role of Screening Tests for Deep Venous Thrombosis in Asymptomatic Adults With Acute Spinal Cord Injury

## An Evidence-Based Analysis

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### **Study Design.** Systematic review.

**Objective.** To examine the evidence to support practice guidelines for screening for DVT in asymptomatic adults with acute traumatic spinal cord injury (SCI) who undergo pharmacologic thromboprophylaxis.

**Summary of Background Data.** Despite the fact that pharmacologic thromboprophylaxis has been widely used since the 1980s, deep venous thrombosis (DVT) and subsequent pulmonary embolism (PE) still account for approximately 10% of deaths during the first year following SCI.

**Methods.** MEDLINE and EMBASE were searched from the earliest achievable date to December 2005. We only included clinical studies that used a screening test for DVT and the gold standard diagnostic tests for DVT (*i.e.*, lower limb venography) and for PE (*i.e.*, lung arteriogram) in adults with traumatic SCI who underwent drug thromboprophylaxis during the acute stage after SCI.

**Results.** The search yielded 188 articles, of which 9 articles fulfilled the criteria to be included in our review. Screening for DVT was performed in 3 randomized clinical trials and 6 case series. The protocol of these studies included the use of D-Dimer (1 of 9), <sup>125</sup>I-labeled fibrinogen (2 of 9), ultrasound (1 of 9), impedance plethysmography (1 of 9), impedance plethysmography and Doppler in combination (1 of 9), Duplex (1 of 9) or venography (2 of 9) as screening test for DVT. Based on the pooled data of these studies, asymptomatic DVT was detected in 16.9% of SCI population. Only 4 studies reported the occurrence of PE in 4.4% of cases.

**Conclusion.** There is insufficient evidence to support (or refute) a recommendation for routine screening for DVT in adults with acute traumatic SCI under thromboprophylaxis. However, there is level II-2 evidence that screening could detect asymptomatic DVT in 22.7% of those individuals. Although additional investigation is needed, we hypothesize that weekly screening for DVT during the first 13 weeks post-SCI could detect most of the asymptomatic DVT events in this patient population.

D-Dimer, ultrasound, and MR venography could be considered as potentially useful screening tests for DVT in the SCI population in future research studies.

**Key words:** spinal cord injury, deep venous thrombosis, pulmonary embolism, screening test, systematic review. **Spine 2007;32:1908–1916**

Spinal cord injury (SCI) has a significant worldwide health and social impact with an annual incidence of 15 to 40 cases per million population.<sup>54</sup> Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is remarkably common in patients with acute SCI due to at least 3 major reasons: stasis, hypercoagulability, and intimal injury.<sup>6,39,43,69</sup> More recently, Iversen *et al* reported that circadian variations of several hemostatic factors and fibrinolytic systems are impaired in tetraplegics.<sup>29</sup> Their results also suggested that those abnormalities could reflect a dysregulated autonomic nervous system, which also could explain the propensity of the SCI population to develop DVT.<sup>29</sup>

The frequency of DVT and PE in untreated individuals with SCI has been reported between 12% and 64% when the diagnosis is only based on clinical criteria.<sup>27,44,47,48,55,62,64–66</sup> Using serial impedance plethysmography and contrast venography of the lower extremities within the first 3 weeks after hospital admission, Geerts *et al* reported that DVT was diagnosed in 21 of 26 (81%) individuals with acute traumatic SCI who did not receive thromboprophylaxis.<sup>18</sup> Indeed, the current evidence-based guidelines recommend the use of pharmacologic thromboprophylaxis in all patients for the first 3 months after acute SCI, even though this 90-day timeframe has been challenged.<sup>1,15,19,56</sup> Despite the fact that pharmacologic thromboprophylaxis has been widely used since the 1980s, VTE is still a potential life-threatening condition for patients with acute SCI. Previous studies reported that VTE accounts for approximately 9.7% of deaths during the first year following SCI.<sup>1,7,15,61</sup>

The VTE constitutes a major health problem that results in significant morbidity, mortality, and substantial healthcare costs. Given that early neurorehabilitation may be important to optimize neurologic recovery, delays in rehabilitation regimen due to treatment of a VTE event could adversely affect the patient's neurologic recovery following SCI.<sup>8</sup> Recently, Bullano *et al* have studied the per-event health plan costs for acute and follow-up treatment of VTE among commercially insured

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patients from 2 managed care organizations in the United States.<sup>13</sup> The mean estimated cost for a DVT event was of approximately \$7700, whereas a PE event cost on average \$9500.<sup>13</sup> Of patients who had a VTE event, 1 in 4 experienced on average 1.24 bleed or recurrent VTE events that required hospitalization in the 21 months of follow-up with a mean health plan cost of approximately \$15,000 per event.<sup>13</sup>

This comprehensive review was undertaken to verify the evidence that screening for DVT reduces mortality rate, decreases the risk for PE, and/or improves neurologic recovery of asymptomatic adults with acute traumatic SCI who undergo pharmacologic thromboprophylaxis.<sup>60</sup> We also sought to examine the evidence for recommendations in terms of timing and screening test of choice for asymptomatic adults with acute traumatic SCI who undergo pharmacologic thromboprophylaxis for DVT.

## ■ Methods

**Search Strategy.** An electronic search was conducted using MEDLINE (1966 to December 2005) and EMBASE (1966 to December 2005) databases. The search strategy included the following terms: *spinal cord injury, deep venous thrombosis, embolism, and thrombophlebitis*. Additionally, the following subheadings were also used: *heparin, warfarin, aspirin, platelet aggregation inhibitor, vena cava filter, and pneumatic stocking*. The COCHRANE Library was searched for the same key words in December 2005. Additional searches were carried out using the references from retrieved articles. Furthermore, we added all systematic reviews on screening tests for DVT and PE that were yielded in the search.

**Study Selection.** We sought to identify all clinical studies in the literature that screened for DVT in asymptomatic adults with acute traumatic SCI undergoing thromboprophylaxis during the acute stage postinjury. To determine the eligibility of every article, abstracts were read and, whenever necessary, full-text articles were retrieved. This review included clinical studies that used a screening test for DVT and the gold standard for diagnosis of DVT (*i.e.*, lower limb venography) and/or for diagnosis of PE (*i.e.*, lung arteriogram) in adult patients (18 years of age or older) with acute traumatic SCI who underwent pharmacologic thromboprophylaxis during the acute stage (up to 3 months) after SCI. We excluded experimental studies using animal models and articles with symptomatic subjects. Only original articles were considered in this review regardless of the language of publication.

In addition to those original articles, we included high-quality systematic reviews. The selected systematic reviews should be recent (published in 2004 or later) and relevant (included information on comprehensive sources, search strategies, explicit selection criteria, standard appraisal of included studies and valid conclusions).

**Data Extraction.** Two investigators independently assessed the appropriate articles according to the predefined methodologic criteria. Disagreements were resolved by consensus between both investigators.

**Data Analysis.** Data from the articles, which met the inclusion criteria, were pooled and weighted by number of subjects in order to obtain an overall mean frequency of asymptomatic DVT in the SCI population under pharmacologic thromboprophylaxis.

In addition, the selected studies were divided into groups according to 1) the screening test and 2) the thromboprophylactic drug. For these 2 comparisons, studies using venography as a screening test were excluded because venography involves an invasive technique with use of ionizing contrast material that may cause discomfort, allergic reactions, nephrotoxicity, and iatrogenic DVT.<sup>58</sup> Fisher exact test was used to compare the frequency of DVT in each group for the analysis based on the screening test as well as for the analysis based on the thromboprophylactic drug. All data analysis was carried out using SAS program version 8.02 (SAS Institute Inc., Cary, NC). Significance was set at the 5% level.

**Estimation of the Number Needed to Screen.** Based on the Rembold's definition, the "number needed to screen" can be estimated by dividing the number needed to treat by the prevalence of unaware people.<sup>50</sup> The number needed to treat is calculated as the inverse of the absolute risk reduction.<sup>37</sup> The absolute risk reduction for VTE can be obtained by subtracting the mortality rate in the SCI population under pharmacologic thromboprophylaxis from the overall mortality rate in the SCI population.<sup>26</sup> Of note, the number needed to screen provides the number of spinal cord injured individuals undergoing pharmacologic thromboprophylaxis needed to be screened in order to prevent 1 death from VTE.

## ■ Results

The MEDLINE and EMBASE search yielded 188 original articles, of which 25 articles were considered eligible for the in-depth review.<sup>4,11,14,17,21-25,31,38,40,44-46,49,51-53,57,59,67,68,70,71</sup> Based on the predefined inclusion criteria, 16 of 25 studies were excluded because 1) patients did not receive pharmacologic thromboprophylaxis,<sup>11,14,44,45,51,52,57,59,71</sup> 2) diagnosis of DVT and PE was not based on gold standard methods,<sup>4,11,14,21,31,49,67,68</sup> 3) the studies included patients without SCI,<sup>21,71</sup> or 4) the studies included patients with symptomatic DVT.<sup>46</sup>

Indeed, 9 studies were included in the primary analysis. There was no study with focus on the effects of screening for DVT in the target population of our interest with regard to mortality, prevalence of PE, or neurologic recovery. Of the 9 selected original articles, there were 3 randomized clinical trials and 6 case series that screened for asymptomatic DVT among individuals who underwent drug thromboprophylaxis during the acute stage after SCI (Table 1).<sup>17,22-25,38,40,53,70</sup> Additionally, 2 systematic reviews from searches in the MEDLINE, EMBASE, and COCHRANE databases were considered as eligible to be included in our comprehensive review (Table 2).<sup>28,32</sup>

### **Frequency of Asymptomatic DVT and PE in the SCI Population Receiving Thromboprophylaxis**

The frequency of DVT varied from 5.3% to 38.6% among the selected studies with a mean pooled frequency

**Table 1. Summary of the Primary Research Articles Included in This Review**

Reference	No. of Patients	No. (%) of Cases of DVT	No. (%) of Cases of PE	Screening Test	Screening Frequency and Timing	Diagnostic Test	Pharmacologic Prophylaxis
Frisbie and Sasahara <sup>17</sup>	15	1 (6.7)	NA	Impedance plethysmography	Weekly during 60 days after SCI	Venography	Heparin (5000 IU, subcutaneous every 12 hr during the first 60 days post-SCI)
Merli <i>et al</i> <sup>40</sup>	16	8 (50)	NA	125-I fibrinogen scanning (weekly) + venography at day 28	Weekly during 28 days after SCI	Venography	Heparin (5000 IU, subcutaneous every 8 hr during the first 28 days post-SCI)
	15	1 (6.7)	NA	125-I fibrinogen scanning (weekly) + venography at day 28	Weekly during 28 days after SCI	Venography	Heparin (5000 IU, subcutaneous every 8 hr) + Electrical stimulation of tibialis anterior and gastrocnemius muscles continually for 23 hr per day during the first 28 days post-SCI
Green <i>et al</i> <sup>23</sup>	29	6 (20.7)	3 (10.3)	Impedance plethysmography + Doppler flow measurements	3-day intervals for 2 wk and then on a weekly basis for 10 wk	Venography for DVT; pulmonary angiogram or ventilation-perfusion scan for PE	Heparin (5000 IU, subcutaneous every 12 hr during 12 wk)
	29	2 (6.9)	0	Impedance plethysmography + Doppler flow measurements	3-day intervals for 2 wk and then on a weekly basis for 10 wk	Venography for DVT; pulmonary angiogram or ventilation-perfusion scan for PE	Heparin (adjusted dose regimen based on the APTT results: mean of 13,200 IU, subcutaneous every 12 hr during 12 wk)
Green <i>et al</i> <sup>24</sup>	21	3 (14.3)	2 (9.5) (both fatal)	Doppler flow measurements + duplex US	Twice a week for the first 2 wk, once weekly for the next 2 wk, and biweekly for the next 4 wk	Venography for DVT and postmortem diagnosis of PE	Heparin (5000 IU, subcutaneous every 8 hr during the first 8 wk post-SCI)
	20	0	0	Doppler flow measurements + duplex US	Twice a week for the first 2 wk, once weekly for the next 2 wk, and biweekly for the next 4 wk	Venography	Low molecular weight heparin [Logiparin] (3500 anti-Xa units, subcutaneous once daily during the first 8 wk post-SCI)
Yelnik <i>et al</i> <sup>70</sup>	89	26 (29.2)	NA	Venography	On admission in the SCI care unit (mean of 45 days post-SCI)	Venography	Low doses of calcium heparin instituted a few days after SCI
	17	7 (41.2)	NA	Venography	On admission in the SCI care unit (mean of 45 days post-SCI)	Venography	Low molecular weight heparin instituted a few days after SCI
	21	5 (23.8)	NA	Venography	On admission in the SCI care unit (mean of 45 days post-SCI)	Venography	Oral anticoagulants instituted a few days after SCI
	33	6 (18.2)	NA	Venography	At 30 days after the first venography (second screening; mean of 80 days post-SCI)	Venography	Heparin (5000 IU, 3 times daily)
	50	5 (10)	NA	Venography	At 30 days after the first venography (second screening; mean of 80 days post-SCI)	Venography	Low molecular weight heparin [Flaxiparine] (0.3 mL once daily)
	2	0	NA	Venography	At 30 days after the first venography (second screening; mean of 80 days post-SCI)	Venography	Oral anticoagulants instituted a few days after SCI
Merli <i>et al</i> <sup>38</sup>	19	1 (5.3)	NA	125-I fibrinogen scanning	On a daily basis during 2 wk	Venography	Heparin (5000 IU, subcutaneous every 12 hr during the first 2 wk post-SCI), external pneumatic compression sleeves, and gradient elastic stockings
Gunduz <i>et al</i> <sup>25</sup>	13	1 (7.7)	0	Venography	At 15 days after admission (on average 40.98 ± 3.75 days after SCI)	Venography for DVT and ventilation-perfusion scan for PE	Heparin (5000 IU, subcutaneous every 12 hr during 12 wk from admission)

(Continued)

**Table 1. Continued**

Reference	No. of Patients	No. (%) of Cases of DVT	No. (%) of Cases of PE	Screening Test	Screening Frequency and Timing	Diagnostic Test	Pharmacologic Prophylaxis
Green <i>et al</i> <sup>22</sup>	48	6 (12.5)	2 (4.2) (1 fatal)	Venous color flow US	At 8 wk after instituting the thromboprophylaxis	Venography for DVT; ventilation-perfusion scan, pulmonary angiogram, or postmortem examination for PE	Low molecular weight heparin [Logiparin] (3500 anti-Xa units, subcutaneous once daily instituted within 72 hr and continued for 8 wk post-SCI)
Roussi <i>et al</i> <sup>53</sup>	59	6 (10.2)*	NA	D-Dimer (Asserachrom assay)	On admission at a rehabilitation center (1 to 6 mo after SCI)	Venography or Doppler	Low molecular weight heparin

\*In 3 cases, DVT was diagnosed by Doppler ultrasonography only and 3 cases underwent Doppler and venography. NA indicates not available; SCI, spinal cord injury; DVT, deep venous thrombosis; PE, pulmonary embolism; APTT, activated partial thromboplastin time.

of 16.9% (Table 1). Of the 9 selected articles, only 4 studies reported a frequency of PE that varied from 0% to 5.2% with a mean pooled frequency of 4.4% (Table 1).

Of the 9 selected articles, 6 studies did not use venography as screening test for DVT. Based on the pooled data from these 6 selected articles and after excluding those studies that screened for DVT using venography, there were no significant differences among patients who underwent an adjusted-heparin regimen, patients who received a fixed-dose heparin regimen, and patients who underwent a low-molecular-weight heparin regimen with regard to the frequency of asymptomatic DVT detected by different

screening tests (Figure 1A;  $P = 0.626$ , Fisher exact test). However, the paucity of information precluded to carrying out a proper analysis taking into consideration potential confounders (*e.g.*, early ambulation, use of compressive devices) that have been more frequently used in recent years.

The same 6 selected articles were then divided into 6 groups according to the screening test for asymptomatic DVT used: Doppler ultrasound, compressed ultrasound, Asserachrom D-dimer, 125-I fibrinogen scanning, impedance plethysmography, or Doppler combined with impedance plethysmography. There were no significant

**Table 2. Summary of Systematic Reviews Focused on Screening Tests for Deep Venous Thrombosis**

Reference	Search	Inclusion and Exclusion	Appraisal of Studies	Confounders	Adverse Effects	Conclusions	Comments (Strengths and Weaknesses)
Heim <i>et al</i> <sup>28</sup>	MEDLINE	Inclusion: studies that estimated sensitivity and specificity or provided paired test data for at least one D-dimer assay	Adapted from Becker <i>et al</i> <sup>9</sup>	Heterogeneity of the study populations, choice of reference standards, features of the D-dimer assays, severity of illness and comorbidity of the patient population, age, use of anticoagulants, cancer, recent trauma or surgery	Safety issues of the serial noninvasive testing approach	Sensitivity and NPV were often lower than 90%, uncharacteristic for a good rule-out test	Strength: well-structured meta-analysis
	English articles from February 1995 through October 2003	Exclusion: abstracts, previously published studies, combined data of patients with suspected DVT and pulmonary embolism				General use of D-dimer assays as a stand-alone test for the diagnosis of DVT is not supported by the literature	Weakness: included very heterogeneous patient populations
Kassai <i>et al</i> <sup>32</sup>	MEDLINE	Inclusion: studies that prospectively compared ultrasound to venography for the diagnosis of DVT in lower limbs of asymptomatic patients	The START initiative: Level 1 and Level 2 studies <sup>10</sup>	Heterogeneity of the study populations, ultrasound technique, radiologists' experience, anatomic localization	No adverse effect was reported	Ultrasound is accurate in proximal veins for the screening of asymptomatic DVT in patients hospitalized for orthopedic surgery	Strength: broad search meta-analysis
	EMBASE and PASCAL BIOMED SCIENCE CITATION INDEX DARE COCHRANE	Exclusion: studies that did not use venography as the reference standard or lower limbs and deep veins were not evaluated				However, more research is needed to explore if ultrasound is useful in other clinical settings	Weakness: included very heterogeneous patient populations

DVT indicates deep venous thrombosis; NPV, negative predictive value.

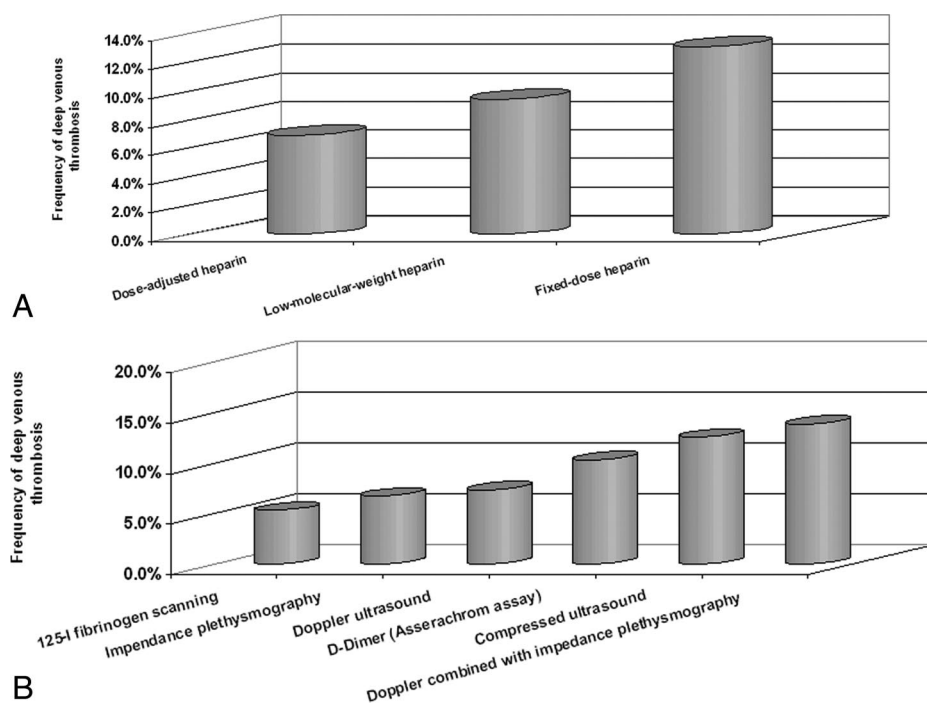


Figure 1. Based on the pooled data from the 6 articles included in this systematic review that did not use venography as screening test for deep venous thrombosis, comparisons among thromboprophylactic regimens (A) and among screening tests (B) were performed with regard to frequency of asymptomatic deep venous thrombosis in patients with acute spinal cord injury ( $P = 0.656$  and  $P = 0.901$ , respectively; Fisher exact test).<sup>17,22–25,38,40,53,70</sup>

differences among these groups with regard to the frequency of asymptomatic DVT detected by 1 of the above screening tests (Figure 1B;  $P = 0.901$ , Fisher exact test).

Contrast venography of lower limbs was used as a screening test for asymptomatic spinal cord injured individuals in 2 studies.<sup>25,70</sup> By screening for DVT during the acute and subacute stages after SCI in 2 occasions 35 days, on average, apart each other, Yelnik *et al* detected asymptomatic DVT in 38.6% of in spinal cord injured individuals who underwent pharmacologic thromboprophylaxis.<sup>70</sup> Gunduz *et al* reported a frequency of 7.7% of asymptomatic DVT among patients who were screened for DVT using limb venography at 15 days after admission at their rehabilitation institution which represents a mean of  $41 \pm 3.8$  days after acute SCI.<sup>25</sup>

#### Number Needed to Screen for Reduction of Mortality

The reported mortality rate during the first year after SCI is 9.7%.<sup>15</sup> These VTE-related deaths occur during the first 90 days following injury in the vast majority of the cases.<sup>3,6,15,36</sup> In an evidence-based review, Krishnan *et al* reported mortality rates between 3.3% and 6.4% for anticoagulant treatment with low-molecular-weight heparin and mortality rates between 5.4% and 8% for unfractionated heparin.<sup>35</sup> The absolute risk reduction varied from 1.7% (absolute risk reduction = 9.7%–8%) to 6.4% (absolute risk reduction = 9.7%–3.3%).<sup>26</sup>

Given that the number need to treat is the inverse of the absolute risk reduction, the number need to treat for reduction of mortality in our analysis varied from 16 (1 of 0.064) to 59 (1 of 0.017).<sup>37</sup> Based on the Rembold's definition, the number needed to screen was estimated dividing the number needed to treat by the prevalence of unaware people.<sup>50</sup> Ideally, all individuals with asymptomatic DVT would be tracked by the screening test.

Assuming the mean pooled frequency of 22.7% from the only 2 level II-2 evidence studies that used thromboprophylaxis since the first day after SCI and "screened" for DVT using venography, the number needed to screen to prevent 1 death of DVT for the first postinjury year varied from 71 to 260 asymptomatic SCI patients.<sup>25,40</sup> In reality, venography is not considered to be a suitable screening test for DVT; therefore, the more appropriate mean pooled frequency to be used in the denominator of the calculation of number needed to screen should exclude studies that used venography as screening test for DVT. Based on the mean pooled frequency of 10.4% and after excluding those studies that screened for DVT using venography, the number needed to screen to prevent 1 fatality of DVT for the first postinjury year varied from 154 to 568 asymptomatic SCI patients.<sup>17,22–24,38,53</sup>

#### Potential Risk Factors for Asymptomatic DVT in the SCI Population Under Thromboprophylaxis

Of the 9 selected articles, 3 studies included information about the potential risk factors for asymptomatic DVT in the SCI population.<sup>22,25,70</sup> The potential risk factors included spasticity, level of SCI, age, obesity, surgical intervention, concomitant trauma, etiology of SCI, severity of SCI, and gender.

Gunduz *et al* suggested that the presence of spasticity could be a risk factor for asymptomatic DVT, even though no statistical analysis was shown.<sup>25</sup> In contrast, Yelnik *et al* found no statistically significant association between asymptomatic DVT and spasticity post-SCI.<sup>70</sup>

Green *et al* found a higher frequency of VTE in patients with cervical SCI compared with individuals with thoracolumbar injury.<sup>22</sup> On the other hand, Yelnik *et al* reported that the level of injury was not significantly associated with asymptomatic DVT post-SCI.<sup>70</sup>

Age and obesity were not associated with asymptomatic DVT during the acute and subacute stages following SCI.<sup>22,70</sup> Based on the results of Yelnik *et al*, surgical intervention and concomitant trauma were not considered as significant risk factors for asymptomatic DVT in the SCI population.<sup>70</sup> Additionally, Yelnik *et al* observed a trend for an association of asymptomatic DVT with traumatic etiology.<sup>70</sup> They also reported a trend for an association between asymptomatic DVT and complete SCI.<sup>70</sup>

In the study of Yelnik *et al*, the frequency of asymptomatic DVT was significantly higher among males in comparison with females during the acute and subacute stages following SCI.<sup>70</sup> Similarly, Green *et al* reported that VTE was exclusively observed in males following SCI.<sup>22</sup>

### **Adverse Effects of Screening Tests for DVT in the SCI Population Under Thromboprophylaxis**

In this review, only 2 studies reported adverse effects of contrast venography in the SCI population.<sup>25,70</sup> Gunduz *et al* diagnosed adverse effects in 9.9% of the SCI patients who underwent of limb venography as screening test for DVT.<sup>25</sup> Only mild urticaria (3.3%) and an inflammatory reaction at the venipuncture site (6.6%) without major complications, such as postvenographic phlebitis and allergic reactions, were reported in this article.<sup>25</sup>

Yelnik *et al* reported only 1 mild allergic reaction in a woman without history of allergy among 214 contrast venographies.<sup>70</sup> The authors also mentioned that only 11 of 98 patients with SCI refused to have another venography for the study suggesting a good compliance for such invasive method.<sup>70</sup>

### **Discussion**

The results of this comprehensive review suggest that there is insufficient evidence to support (or refute) a recommendation for routine screening for DVT in adults with acute traumatic SCI under thromboprophylaxis. However, there is level II-2 evidence that screening could detect asymptomatic DVT in 22.7% of those individuals regardless of the thromboprophylactic drug used. Although additional investigation is needed to further refine existing practice guidelines, the results of our review suggest that the potential value of weekly screening for DVT during the first 13 weeks post-SCI using D-Dimer, ultrasound or MR venography should be examined in future research studies.

### **Methods of Screening for DVT in the SCI Population**

The screening test of choice for asymptomatic DVT needs to be determined. A systematic review on noninvasive diagnosis of DVT from the McMaster Diagnosis of Deep Venous Thrombosis Working Group indicated that: 1) venography is the only reliable test for the diagnosis of asymptomatic DVT; 2) the role of surveillance testing with ultrasound in asymptomatic patients at high risk for DVT is uncertain; and 3) surveillance testing with impedance plethysmography is not recommended.<sup>33</sup>

Although contrast venography is considered as the gold standard for investigation of symptomatic or

asymptomatic DVT, venography has been considered an unsuitable tool for routine assessment of asymptomatic DVT due to its invasive nature, potential complications, technical issues, and cost.<sup>34,58,72</sup>

Ultrasound has become the primary noninvasive diagnostic method for DVT.<sup>72</sup> Kadyan *et al* reported that duplex ultrasound is a cost-effective tool for DVT surveillance in individuals with acute SCI who are admitted to rehabilitation centers.<sup>30</sup> Although ultrasound is well recognized in the initial investigation of clinically suspected DVT, there are concerns with regard to the use of standard ultrasound for screening of DVT due to its relatively low sensitivity for proximal (62%) and for below-knee DVT (48%) in orthopedic patients.<sup>34</sup> The Spinal Cord Injury Thromboprophylaxis investigators reported sensitivities of 29% and 18.2% for duplex ultrasound using proximal imaging and both proximal and distal imaging, respectively, in patients in the acute stage after traumatic SCI.<sup>2</sup> In our systematic review, ultrasound did not significantly differ from the other screening tests in terms of frequency of DVT detected in asymptomatic individuals in the acute stage after SCI. However, this observation does not necessarily mean that all screening tests have similar sensitivities.

The recent introduction of the D-Dimer test has attained promising results in the DVT surveillance.<sup>9,12</sup> D-Dimer test determines the level of plasmatic d-dimers that are degradation products of cross-linked fibrin. The only study yielded in our systematic review reported a negative predictive value of 100% for D-Dimer testing.<sup>53</sup> In a previous systematic review, the sensitivity of D-Dimer testing varied from 51% to 100% with a mean of 90% and a median of 94% among 23 high-quality articles.<sup>28</sup> In contrast, the specificity of D-Dimer testing varied from 19% to 94% (mean and median, 55%) in the same articles.<sup>28</sup> Therefore, D-Dimer testing may play an important role in ruling out DVT, although the literature does not support the general use of D-Dimer testing as a stand-alone test for the diagnosis of DVT.<sup>28</sup>

Impedance plethysmography can detect increased venous outflow resistance in the deep veins of the lower limbs.<sup>34</sup> However, the use of impedance plethysmography has been discontinued in many centers due to its low sensitivity for diagnosis of proximal-vein DVT (66%).<sup>5,20,34</sup>

Based on the absorption of radiolabeled fibrinogen into actively forming thrombus, the <sup>125</sup>I-labeled fibrinogen was developed to detect VTE.<sup>34</sup> Nonetheless, the <sup>125</sup>I-labeled fibrinogen has been limited due to concerns regarding the safety of injecting blood derived products.<sup>16,34</sup>

Magnetic resonance (MR) venography has been reported as virtually comparable to the contrast venography in the diagnosis of DVT.<sup>34</sup> However, the usefulness of the MR venography in the detection of asymptomatic DVT has been challenged because small, nonobstructing thrombi may not be noticeable.<sup>34</sup> Clearly, further investigation is needed to assess the role of the MR venography in the screening of asymptomatic DVT among individuals with acute SCI.

### **Number Needed to Screen for DVT in the SCI Population**

Given that the efficacy of screening strategies needs to be compared in order to develop guidelines, Rembold developed the concept of number needed to screen based on the “number needed to treat” concept.<sup>50</sup> The number needed to screen is a concise and well-recognized measure to quantify screening efficacy in the clinical setting.<sup>50</sup> Generally speaking, the number needed to screen is defined as the number of people that need to be screened for a given period of time to prevent 1 death or 1 adverse outcome.<sup>50</sup>

In our analysis, the number needed to screen to prevent 1 death of DVT for the first postinjury year varied from 71 to 260 asymptomatic SCI patients if venography was considered the screening test for DVT. However, these ideal numbers are compromised by lower sensitivities of different screening tests for DVT compared with the venography. In reality, the number needed to screen to prevent 1 fatality of DVT for the first postinjury year would vary between 154 and 568 asymptomatic SCI patients based on our systematic review.

Our highest estimations of the number needed to screen for 1 year to prevent 1 death in the SCI population were comparable with the numbers needed to screen for the primary prevention of death attributed to abnormal lipid profiles (numbers needed to screen from 418 to 846), for the use of questionnaire-based approaches to screen for coronary artery disease (number needed to screen of 354), and for screening for hypertension using sphygmomanometer (numbers needed to screen from 274 to 1307).<sup>50</sup> Moreover, our numbers needed to screen for prevention of 1 death due to DVT in spinal cord-injured individuals were considerably lower than the numbers needed to screen to prevent cancer-specific death for hemocult (number needed to screen from 1374 to 3034) or for mammography (numbers needed to screen from 1251 to 8054 depending on the age).<sup>50</sup>

Evaluation of the efficacy of screening strategies for DVT in the SCI population must take into account the sensitivity of the screening methods as well as the optimal time and periodicity to screen. We anticipate that a lesser sensitive screening test would increase our number needed to screen for DVT. The periodicity to screen influences the sensitivity of the screening strategy and, ultimately, the periodicity of the screening inversely affects the number needed to screen. In our estimation, of the number needed to screen, we assumed a 1-year duration for the screening strategy.<sup>3,6,15,36</sup> Although the vast majority of the VTE-related deaths occur during the first 90 days after SCI, we anticipate that screening strategies with a 90-day duration would increase the number needed to screen.

### **Time of Screening for DVT in the SCI Population**

To date, there is no evidence to support an ideal algorithm with respect to the time of screening for asymptomatic

DVT in the SCI population. Aito *et al* reported that the mortality rate related to PE was 3.5% in individuals with acute SCI who underwent prophylaxis.<sup>3</sup> These deaths mostly occurred in undiagnosed DVT and asymptomatic patients between 15 and 90 days post-SCI.<sup>3</sup> Lamb *et al* demonstrated that the majority of DVT and PE events occurred immediately following the acute SCI with slowly decreasing incidence over the next 6 months.<sup>36</sup> Other studies also indicated that the risk for VTE is greatest during the first 2 weeks after injury and fatal PE is rare after 3 months post-SCI.<sup>23,24,63</sup>

Although the time to screen varied among the selected articles, 4 of 9 studies in our review had a screening test carried out on a weekly basis. In addition, a week interval has been suggested as the time interval between 2 negative ultrasounds for exclusion of DVT.<sup>1,16,19,41,42</sup> Those data advocate a rationale for the use of screening test every week until completing 13 weeks after SCI, even though those suggestions need to be carefully investigated.

### **Recommendations**

The guidelines from the American College of Chest Physicians recommend thromboprophylaxis with low-molecular-weight heparin for all patients with acute SCI that should be commenced once primary hemostasis is evident.<sup>19</sup> At least level II-2 evidence indicates that the use of screening test might potentially detect asymptomatic DVT in at least 9.4% of spinal cord-injured individuals who undergo thromboprophylaxis with low-molecular-weight heparin during the acute stage following SCI.<sup>22</sup> In addition, there is level II-2 evidence that screening tests could detect asymptomatic DVT in 16.9% of the individuals with acute SCI regardless of the thromboprophylactic drug used.

Despite the rationale for screening DVT in the SCI population, the existing evidence does not support making a recommendation for or against the use of screening test for DVT in asymptomatic SCI patients who undergo thromboprophylaxis in order to improve health outcomes by reducing mortality rate, decreasing prevalence of PE, and enhancing neurologic outcome after injury. Because of the lack of appropriate comparative studies, there is insufficient evidence to indicate the best choice among the screening tests for DVT or the optimal time-frame for screening for DVT.

### **Final Considerations**

Although further investigation is needed to develop practice guidelines, we hypothesized that weekly screening for DVT during the first 13 weeks post-SCI could detect most of the asymptomatic DVT events in the acute stage among spinal cord injured individuals. This strategy may ultimately have an impact on the morbidity and mortality related to VTE following traumatic SCI. D-Dimer, ultrasound, and MR venography could be considered as

potentially useful screening tests for DVT in future research studies.

### ■ Key Points

- Despite the rationale for screening deep venous thrombosis (DVT) in individuals with acute spinal cord injury (SCI), the existing evidence in the literature does not support making a recommendation for or against the use of screening test for DVT in asymptomatic SCI patients who undergo thromboprophylaxis.
- Given that venous thromboembolism is still a life-threatening condition in the all stages following spinal cord injury, additional investigation is needed in order to further refine existing practice guidelines.
- The results of our review suggest that the potential value of weekly screening for DVT during the first 13 weeks post-SCI using D-Dimer, ultrasound, or MR venography should be examined in future research studies.

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