SPINAL CORD MEDICINE

THROMBOEMBOLISM

CLINICAL PRACTICE GUIDELINE:

Prevention of Venous Thromboembolism in Individuals with Spinal Cord Injury

Clinical Practice Guideline for Health Care Providers

Third Edition

consortium for SPINAL CORD MEDICINE
CLINICAL PRACTICE GUIDELINES

Consortium for Spinal Cord Medicine
Administrative and financial support provided by Paralyzed Veterans of America

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These guidelines have been prepared based on scientific and professional information available in 2015. Users should periodically review this material to ensure that the advice herein is consistent with current reasonable clinical practice. The websites noted in this document were current at the time of publication; however, because web addresses and the information contained therein change frequently, the reader is encouraged to stay apprised of the most current information.

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- Section: Psychologists and Social Workers
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American Spinal Injury Association
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International Spinal Cord Society
Paralyzed Veterans of America
Rick Hansen Institute
Society of Critical Care Medicine
United Spinal Association
US Department of Veterans Affairs

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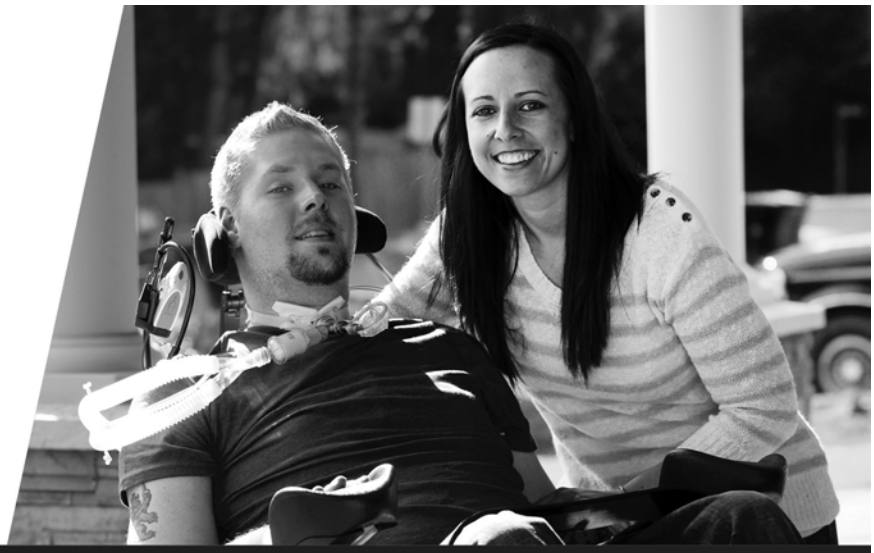

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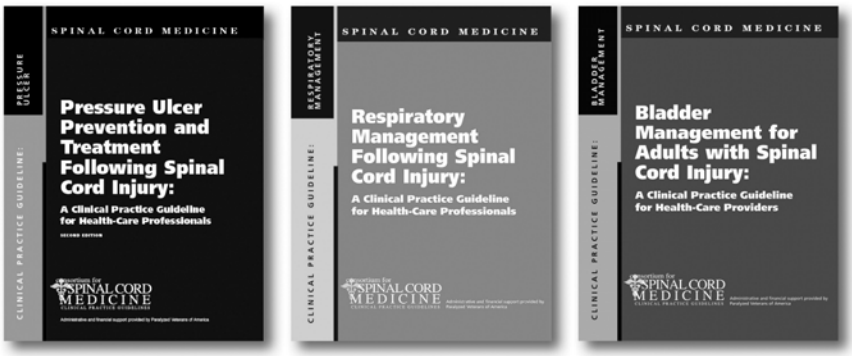

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Preface

Venous thromboembolism (VTE) prevention is addressed daily in nearly every hospital in the world. One particular area of controversy that I have repeatedly encountered over the last two decades is the use of early post spinal surgical VTE prophylaxis. I suspect this has been controversial because the most effective preventive measures are pharmacologic which impair coagulation to varying degrees and clinicians hold variable interpretations of the bleeding risk while on such prophylaxis. I have spoken to a clinician while writing this preface who noted that they have seen virtually every patient in a large trauma center over 25 years and provided them with early anticoagulant prophylaxis with only one developing perispinal bleeding that could be related to anticoagulant prophylaxis. On the other hand, I have spoken to many others who will not even allow anticoagulant thromboprophylaxis for several days post surgery due to the fear of perispinal bleeding. Framing this is the fact that a pulmonary embolus (PE) is one of the most common causes of sudden unexpected death in persons with risk factors for venous thromboembolism. Patients who have experienced a traumatic spinal cord injury (SCI) have the highest risk for developing VTE, especially within the first two weeks after injury, a time when surgery often occurs. Furthermore, as PE is a condition which is potentially preventable with appropriate thromboprophylaxis, we always ask ourselves after a PE occurs, what could we have done better?

This Clinical Practice Guideline (CPG) entitled "Venous Thromboembolism Prevention in Individuals with Spinal Cord Injury" gives those who grapple with the question above, the answers based upon the best available evidence. The recommendations of this CPG, now in its 3rd edition, are significantly different from previous editions due to the availability of new evidence comparing different methods of prevention, the clinical availability and study of a whole new class of anticoagulants called direct oral anticoagulants, and the proliferation of inferior vena cava filters.

We are fortunate to have representation in the development and/or review of the CPG of all the various clinician stakeholders who are impacted by these recommendations including critical care intensivists, spinal surgeons, thrombosis specialists, pediatricians, and rehabilitation professionals. This wide ranging representation and use of the CPG will hopefully translate into further standardization and improvement in the quality of clinical practice with the ultimate objective of optimizing outcomes for persons with SCI across the spectrum of their care.

On behalf of the Consortium Steering Committee, I want to acknowledge all who made this CPG possible,

- The volunteer Chair of the guideline panel, David Chen, for guiding the panel though the development process.
- The five volunteer CPG panel members who wrote the guideline.
- The 22 volunteer peer reviewers who provided valuable feedback from all areas.
- The 24 member organizations of the Consortium for Spinal Cord Medicine who provide direction through the Consortium Steering Committee.
- The manager of the Clinical Practice Guidelines at PVA, Kim Nalle, who provided the day to day administrative support for the development process.

and last but not least,

- The PVA organization for their ongoing commitment to providing the administrative and financial support to the CPG development and production, and dissemination.

Thomas N. Bryce, MD
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Acknowledgments

As Paralyzed Veterans of America (PVA) continues its vital role of sponsoring the development of clinical practice guidelines, much is owed to the hard work and extensive experience of PVA's Research and Education Department, comprising Kera Lawson, PhD, director, and Kim S. Nalle, manager of clinical practice guidelines.

We would like to acknowledge attorney William H. Archmbault for conducting a comprehensive analysis of the legal and health policy issues associated with this complex multifaceted topic.

We extend our appreciation to PVA's Communications Department for its technical review and editing of these clinical practice guidelines and to Sue England Graphic Design for design of this publication.

We also extend our appreciation to the PVA Board of Directors and PVA's senior officers, including national president Al Kovach, immediate past president Bill Lawson, executive director Homer S. Townsend Jr., deputy executive director Sherman Gillums Jr., associate executive director Lana McKenzie, and director of research and education Kera Lawson, PhD.

We have been supported in this work by many unnamed colleagues who have reviewed sections of this publication and made helpful suggestions. Thank you.

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Abbreviations

ACCP	American College of Chest Physicians
ADH	adjusted-dose heparin
AIS	ASIA Impairment Scale
aPTT	activated partial thromboplastin time
BID	twice daily
CAD	Canadian dollars
CNS	Congress of Neurological Surgeons
CPG	clinical practice guideline
DOAC	direct oral anticoagulant
DUS	Doppler ultrasonography
DVT	deep-vein thrombosis
EAST	Eastern Association for the Surgery of Trauma
FNS	functional neuromuscular stimulation
GCS	graduated compression stockings
GRADE	Grading of Recommendation Assessment, Development and Evaluation
HIT	heparin-induced thrombocytopenia
IPG	impedance plethysmography
IVC	inferior vena cava
LDUH	low-dose unfractionated heparin
LMWH	low-molecular-weight heparin
NR	not reported
NS	not significant
PCD	pneumatic compression device
PE	pulmonary embolism
PT	prothrombin time
PVA	Paralyzed Veterans of America
Q8H	every eight hours
RCT	randomized controlled trial
SCI	spinal cord injury
SRDR	Systematic Review Data Repository
USD	US dollars
VA	US Department of Veterans Affairs
VTE	venous thromboembolism

Summary of Recommendations

Note: The recommendations and suggestions below are based on the available evidence and, where there is little evidence, on our experience and consensus, with an overall objective to improve the care of patients with spinal cord injury and to provide guidance for clinicians and policymakers. For individual patients, decisions are best made by considering the recommendations below combined with clinical judgment, the latter based on specific knowledge about each patient's risk factors for thrombosis, the potential for adverse effects, and the availability of various options within one's center. The bracketed numbers refer to the grade of recommendation (see table 2).

1.0 We recommend that mechanical thromboprophylaxis with intermittent pneumatic compression devices (PCDs) with or without graduated compression stockings (GCSs) be applied as soon as feasible after acute spinal cord injury (SCI) when not contraindicated by lower-extremity injury. [1C]

2.0 We recommend that low-molecular-weight heparin (LMWH) be used as thromboprophylaxis in the acute-care phase following SCI once there is no evidence of active bleeding. [1B]

2.1 We recommend that, in patients whose LMWH is delayed because of concerns about bleeding, a daily assessment of the bleeding risk be carried out and that LMWH be started when the bleeding risk decreases. [1C]

3.0 We recommend against the use of low-dose or adjusted-dose unfractionated heparin in the prevention of venous thromboembolism (VTE) in SCI (unless LMWH is not available or contraindicated). [1B]

4.0 We recommend that oral vitamin K antagonists (such as warfarin) not be used as thromboprophylaxis in the early, acute-care phase following SCI. [1C]

5.0 We suggest that direct oral anticoagulants (DOACs) may be considered as thromboprophylaxis during the rehabilitation phase following SCI. [2C]

6.0 We suggest that combined mechanical methods of thromboprophylaxis (PCDs with or without GCSs) and anticoagulant methods of thromboprophylaxis be used particularly in the acute-care phase as soon as possible after injury unless either option is contraindicated. [2C]

7.0 We recommend that anticoagulant thromboprophylaxis continue at least eight weeks after injury in SCI patients with limited mobility. [1C]

7.1 We suggest one of the following options as thromboprophylaxis in the postacute, rehabilitation phase: LMWH [2B], oral vitamin K antagonists such as warfarin (INR 2.0-3.0) [2C], or a DOAC. [2C]

8.0 We recommend that inferior vena cava (IVC) filters not be used as primary thromboprophylaxis in SCI. [1C]

9.0 We suggest that SCI patients not routinely be screened with Doppler ultrasonography (DUS) for clinically inapparent DVT during their acute--care admission. [2B]

9.1 We suggest that SCI patients not be routinely screened with DUS for clinically inapparent DVT on admission to rehabilitation. [2B]

10.0 We suggest that children of all ages with acute SCI receive mechanical prophylaxis with GCSs and/or PCDs. [2C]

10.1 We recommend that adolescents with acute SCI receive anticoagulant thromboprophylaxis, especially if they have additional risk factors such as lower-extremity or pelvic fractures. [1C]

Summary of Recommendations

(Con't)

11.0 We recommend that persons with chronic SCI who are hospitalized for medical illnesses or surgical procedures receive thromboprophylaxis during the period of increased risk. [1C]

12.0 We recommend that every SCI unit (acute and rehabilitation) have a written thromboprophylaxis policy that includes implementation strategies. [1C]

12.1 We recommend that every SCI unit (acute and rehabilitation) periodically assess adherence to the unit's thromboprophylaxis policy and use the results for quality improvement if adherence is suboptimal. [1C]

Introduction

The high incidence, insidious onset, potentially lethal consequences, and clinically important long-term implications of venous thromboembolism (VTE) make it a leading cause of mortality and morbidity following acute spinal cord injury (SCI). With and without preventative measures, VTE remains a relatively common and costly complication after traumatic SCI. The major factors predisposing persons with acute SCI to VTE make up the quintessential Virchow's Triad: venostasis (due to failure of the venous muscle pump with paralysis) (Seifert, 1972), a transient hypercoagulable state (Rossi, 1980), and frequent endothelial injury due to concomitant injuries, venous dilatation, and pressure on the veins (Miranda, 2000). The end result is that persons with acute SCI demonstrate the highest incidence of VTE compared to other patients with severe trauma (Geerts, 1994). Pulmonary embolism (PE) was a leading cause of death following SCI until the use of effective thromboprophylaxis became common (DeVivo, 1999). Furthermore, if VTE occurs in SCI patients, anticoagulant therapy is given, often for prolonged periods of time, leading to increases in bleeding risks as well as substantial inconvenience for patients who are prescribed warfarin, since they need frequent laboratory monitoring.

The Consortium for Spinal Cord Medicine developed and released clinical practice guidelines that focused on VTE and its prevention in 1997 and 1999 (Consortium for Spinal Cord Medicine, 1997, 1999). Since the most recent update, more than 21,887 PubMed articles have addressed VTE, and 121 focused on VTE in SCI. There are currently at least eleven professional society guidelines related to VTE in SCI, as well as a number of consumer guidelines that address this issue. The objective of PVA's guidelines is to incorporate significant new knowledge since 1999 and to update the management recommendations.

Acute SCI produces numerous changes to the cardiovascular and coagulation systems (Miranda, 2000; West, 2013). Alterations in hemostasis include reduced fibrinolytic activity (Petaja, 1989; Miranda, 2000) and increased blood factor VIII activity (Myllynen, 1987), although routine coagulation tests such as the prothrombin time (PT) and activated partial thromboplastin time (aPTT) remain normal. This situation is aggravated by concomitant injury to soft tissues, pelvis, or long bones, as well as surgical procedures and administration of blood products.

Asymptomatic deep-vein thrombosis (DVT) is very common in acute SCI patients (Geerts, 1994; Spinal Cord Injury Investigators, 2003b). These thrombi can progress proximally in 20% of cases (Davies, 1979) and may embolize in up to 50% (Carabasi, 1987). VTE should be considered a continuum from small, asymptomatic thrombi to massive, fatal PE. For these reasons, it is essential that aggressive thromboprophylaxis be provided to SCI patients.

The Consortium for Spinal Cord Medicine

The consortium is a collaboration of professional and consumer organizations funded and administered by the Paralyzed Veterans of America (PVA). The Steering Committee, administratively supported by PVA's Research and Education Department, is made up of one representative from each consortium-member organization. The consortium's mission is to direct the development and dissemination of evidence-based clinical practice guidelines (CPGs) and companion consumer guides. This mission is solely directed to improving the health care and quality of life for persons with SCI.

Summary of Guidelines Development Process

The development of these guidelines involved the following major steps: creating a list of formal questions to be addressed, systematic searches of published literature related to these questions, critical appraisal of the quality of the retrieved studies, abstraction of relevant study results, creation of evidence-based recommendations, writing and revising various drafts of text that explain the recommendations, and multiple reviews by panel members and outside organizations. The consortium's CPG development process also involved extensive field review and a legal review.

Methodology

Specific Objectives and Search Questions

Systematic reviews were performed by an independent consulting firm contracted by PVA to identify published literature relevant to VTE and its prevention in patients with SCI since 1996 but with an emphasis on evidence published since the previous update of these guidelines in 2008. Among patients with SCI, the following questions were formally addressed in the systematic reviews:

- What is the evidence on risk factors for developing VTE?
- What is the evidence on methods for preventing VTE?
- What is the evidence for the use of mechanical methods to reduce the risk of VTE? Mechanical thromboprophylaxis methods include promoting early mobilization, graduated compression stockings (GCSs), pneumatic compression devices (PCDs), and venous foot pumps.
- What is the evidence for the use of anticoagulant methods to reduce the risk of VTE? Anticoagulant thromboprophylaxis methods include low-dose unfractionated heparin (LDUH), low-molecular-weight heparin (LMWH), warfarin or other vitamin K antagonists, and direct oral anticoagulants (DOACs).
- What is the evidence for the use of combined mechanical and anticoagulant methods to reduce the risk of VTE?
- What is the evidence for the use of inferior vena cava (IVC) filters for the prevention of PE?
- What is the evidence for screening of patients for clinically inapparent (asymptomatic) DVT?
- What is the evidence for implementing thromboprophylaxis, including educating medical professionals about the prevention of VTE?

Protocol and Registration

The systematic review protocols were described and registered through Prospero (http://www.crd.york.ac.uk/PROSPERO) under the following titles and registration numbers:

- A systematic review on the prevention of VTE in persons with spinal cord injuries; registration number CRD42014014967
- A systematic review on risk factors for VTE and screening for DVT in persons with spinal cord injuries; registration number CRD42014015461

Search Strategy

The two terms spinal cord injury and venous thromboembolism (deep vein thrombosis or pulmonary embolism) were combined with "and" using Boolean-logic queries to identify potentially relevant literature within five electronic databases (PubMed, CINAHL, Cochrane, EMBASE, and PsychINFO). Search terms were slightly modified based on the vocabulary terms within each database searched. Searches covered the period from January 1996 through June 2014 and were limited to English language and human studies. Since the first PVA VTE guidelines were published in 1997, the panel

members identified 1996 as the earliest publication date for the literature search to ensure no publications were missed.

Inclusion/Exclusion Criteria

After duplicated records were removed, the identified literature was screened to determine if the following inclusion-criteria questions were addressed:

1. Does the record include people with traumatic SCI of any age?
2. Does the record address VTE (lower-extremity DVT and/or PE) as a primary or secondary outcome?
3. Does the record address one or more of the following topics?
   - Risk factors for VTE
     - Prevention methods against VTE
     - Use of IVC filters
     - Screening methods for clinically inapparent DVT
     - Implementation of thromboprophylaxis and educating professionals on prevention of VTE
4. Does the record use one of the following study designs: randomized controlled trial (RCT), observational prospective or retrospective cohorts, case-control, or case series?
5. Does the record include studies conducted in acute and postacute settings, including rehabilitation and chronic-care settings in any country?

Studies were excluded if the full article was not available in English, if it addressed only nontraumatic SCI, if outcomes were not reported separately for the SCI population, or if reporting was insufficient (e.g., methods or results were not reported). Case reports and editorials were also excluded.

Screening Protocol

Three independent reviewers screened titles and abstracts of the first twenty-five identified records to ensure consistency in the application of inclusion/exclusion criteria. The remainder of the titles and abstracts were screened by two reviewers to ensure inclusion criteria were addressed. If a reviewer was uncertain about including the records due to insufficient information available in the title and abstracts, the full article was retrieved and reviewed. When there was a disagreement between the two reviewers, a third reviewer or a member from the expert panel was involved to reach a decision. Abstrackr, an open-source web-based tool, was used for screening (http://abstrackr.cebm.brown.edu. Appendix 1 contains the search strings, and table 1 shows the number of publications identified by the database searches.

During the screening process, both the included publications and those that did not meet inclusion criteria were back-searched for additional relevant references, and the panel of experts was asked to submit reports not included in the electronic searches. A total of twenty-one publications were identified through manually back-searching the references and expert panel's recommendations. The panel members reviewed the screening process results to identify additional publications to review in detail.

DATABASE	PLATFORM	DATE RANGE	SEARCH DATE	RESULTS
PubMed	NCBI	1/1/1996–8/6/2014	8/6/2014	494
CINAHL Plus with Full Text	EBSCO	1/1/1996–8/7/2014	8/7/2014	110
PyschINFO	EBSCO	1/1/1996–8/7/2014	8/7/2014	19
EMBASE	Elsevier	1/1/1996–8/7/2014	8/7/2014	19
Cochrane	John Wiley & Sons	1/1/1996–8/7/2014	8/7/2014	33
			Total	1,309
			Duplicates	526
			Final results	783

Data Extraction

The Systematic Review Data Repository (SRDR) was used for data extraction (http://srdr.ahrq.gov/) for all included studies. Variables for extraction were selected through an iterative process (as recommended by Levac et al., 2010) based on feedback from the expert panel, and extraction forms were developed and piloted to ensure consistent understanding among reviewers and to refine extraction field descriptions as needed. Two reviewers independently extracted data from all included records. When two reviewers did not agree on the extracted data, a third reviewer was consulted to make a final decision. The variables extracted were:

- Study aim/purpose
  - Topic area
  - Study setting
  - Country
  - Inclusion criteria
  - Exclusion criteria

- Study duration
- Study participant characteristics
- Interventions (if any)
- Outcomes
- Methods of measurement
- Number of participants lost to follow up and/or excluded from analysis in each study group
- Results
- Study limitations and sources of bias

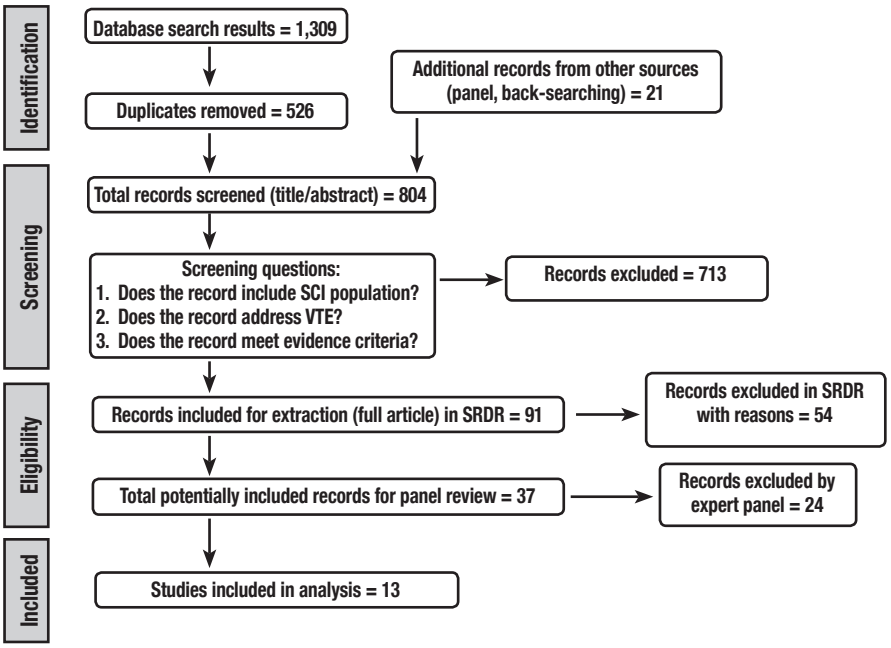
Quality of Evidence

After extracting information from an article, we assessed bias using appropriate rating tools. For RCTs and nonrandomized comparison research designs, we used the Cochrane Risk of Bias tool (Higgins, 2011). For prognostic studies, we used a scale recommended by Hayden et al. (2013) called Quality in Prognosis Studies (QUIPS). Review Manager (RevMan) software was used to calculate mean differences, standard mean differences, and odd ratios and to develop forest plots (Review Manager, 2008). We then used GRADEPro software (2008) to grade the quality of the evidence and generate GRADE (Grading of Recommendation Assessment, Development and Evaluation) system profiles and summary-of-findings tables that are available on request from PVA. The citations of retrieved publications and the study summaries, including data abstraction and quality of the study, were then disseminated to the panel members. The subtopics of these guidelines were prepared by individual panel members, and then each section and recommendation was reviewed and revised repeatedly by the entire panel until consensus was reached.

Grading of Recommendations: Quality of Evidence and Strength of Panel Opinion

The panel assigned a grade for each recommendation based on the American College of Chest Physicians (ACCP) modification of the GRADE system (Guyatt 2012; Guyatt 2008a). The recommendation grade includes both the quality of the evidence informing the recommendation and the panel's strength of opinion that the recommendation should (or should not) be considered in the care of patients with spinal cord injury (see table 2). In general, systematic reviews of RCTs represent the strongest-quality evidence followed by individual RCTs, observational cohort studies, case series, and expert opinion. Factors that can modify the quality of evidence include risk of study biases; the precision, consistency, and directness of the results; and effect size. The three-tiered quality assignment (A, B, C) we used is similar to the three classes of evidence (I, II, III) used by the American Association of Neurological Surgeons / Congress of Neurological Surgeons (CNS) in development of guidelines for the management of patients with cervical spinal cord injuries (Walters, 2013; Dhall, 2013).

Figure 1: Results of Literature Screening



The GRADE approach categorizes the strength of recommendations as:

1. Strong recommendation ("We recommend . . .")
2. Weak recommendations ("We suggest . . .")

The strength of the recommendation is based on the quality of the evidence, as well as the balance between benefits and risks, the cost and other resource implications, and patient values and preferences (Guyatt, 2008b). A strong recommendation generally implies that it applies to most patients with SCI, while a weak recommendation is associated with considerably greater uncertainty. Clinicians may choose (or not) to follow the suggestions, depending on individual patient or local circumstances.

Funding and Potential Conflicts of Interest

PVA contracted the literature searches and evidence reviews to an independent firm and provided administrative support for the process. Panel members received no compensation for their participation and declared all potential financial or other conflicts of interest (see appendix 2).

Table 2: Grading System for Recommendations*

Grade of recommendation	Benefits vs. risk and burdens	Methodologic strength of evidence	Implications for practice Wording of recommendation
1A = strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burden or vice versa	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. "We recommend . . ."
1B = strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burden or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. "We recommend . . ."
1C = strong recommendation, low-quality evidence	Benefits clearly outweigh risk and burden or vice versa	Evidence for at least one critical outcome from observational studies, case series, RCTs with serious flaws, or indirect evidence	Recommendation can apply to most patients in many circumstances. "We recommend . . ."
2A = weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ depending on patient circumstances or societal values. "We suggest . . ."
2B = weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies	The best action may differ depending on patient circumstances or societal values. "We suggest . . ."
2C = weak recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risk, or burden	Evidence for at least one critical outcome from observational studies, case series, or RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable. "We suggest . . ."

**From Guyatt, 2012.*

Venous Thromboembolism In Spinal Cord Injury: Risks And Risk Factors

Among major trauma patients, those with a SCI have been shown to have the highest risk of DVT, with an odds ratio of 8.6 compared to trauma patients without SCI (Geerts, 1994; Gould, 2012; Godat, 2015). The reported rates of VTE in acute SCI vary greatly, principally due to differences in surveillance techniques. Contrast venography, the traditional "gold standard" test for DVT, detected DVT in 47% to 100% of patients with SCI (Myllynen, 1985; Merli, 1988; Geerts, 1994). Doppler ultrasonography (DUS) found DVT in 45% of 139 SCI patients who were given enoxaparin 40 mg once daily and compression stockings (Germing, 2010a). Using DUS, Powell et al. found that 12% of SCI patients who had not received thromboprophylaxis had DVT on admission to a rehabilitation center, compared with 4% of patients who received thromboprophylaxis (Powell, 1999). A recent investigation of acute SCI patients using thromboprophylaxis with leg compression devices and stockings but no anticoagulant thromboprophylaxis reported DVT detected by serial ultrasonography in 41% of patients with all grades of injury and 73% of patients with ASIA Impairment Scale (AIS) A or B injuries (Matsumoto, 2015).

A number of studies have assessed risk factors for VTE in SCI. Factors that appear to be associated with increased rates of VTE include:

- ***Paraplegia versus tetraplegia:*** Several studies have found a greater incidence of VTE in paraplegia than in tetraplegia (Jones, 2005; Maung, 2011; Giorgi-Pierfranceschi, 2013). Jones et al. found that the odds ratio for developing VTE in paraplegia versus tetraplegia was 1.8 in a population study that included more than 16,000 SCI patients (Jones, 2005). Maung et al. found that those with a T1–6 injury had a significantly higher incidence of VTE than those with C1–4 injuries (6.3% versus 3.4%) (Maung, 2011).
- ***Age:*** Most studies have found a strong relationship between increasing age and risk of VTE (Maung, 2011; Giorgi-Pierfranceschi, 2013; Chung, 2014). However, an age effect was not observed in large study of more than 12,000 SCI patients from California (Godat, 2015).
- ***Complete versus incomplete injuries:*** The risks of VTE are greater with motor complete (AIS A) compared with incomplete (AIS B, C, or D) injuries (Aito, 2003; Halim, 2014; Matsumoto, 2015).
- ***Concomitant lower-extremity fractures:*** Studies have consistently shown that fractures of the lower extremities and pelvis increase VTE risk in patients with SCI (Maxwell, 2002; Jones, 2005; Chung, 2014; Godat, 2015).
- ***Time from injury:*** The risk of VTE is highest in the acute-care phase of SCI and then decreases, although the risk remains higher than that in an age-matched population without SCI (DeVivo, 1999; Aito, 2002; Maxwell, 2002; Jones, 2005; Germing, 2010a; Giorgi Pierfranceschi, 2013; Chung, 2014; Godat, 2015).
- Previous VTE: Patients with previous VTE had a sixfold greater risk of VTE after SCI than those who had not had VTE in the past (Giorgi Pierfranceschi, 2013).
- ***Absent or delayed thromboprophylaxis:*** In a systematic review, start of thromboprophylaxis within two weeks after injury was strongly associated with reduced risk of VTE in SCI compared with a delayed start (odds ratio 0.2, $p < 0.00001$) (Powell, 1999; Aito, 2002; Ploumis, 2009).
- ***Thrombophilia:*** A number of small studies have suggested an increased rate of VTE associated with Factor V Leiden, hyperhomocysteinemia, elevated Factor VIII, or PAI-1, but these observations must be confirmed in larger, better-quality studies (Aito, 2007; Rubin-Asher, 2010; Selassie, 2011; de Campos Guerra, 2014). Neither the independent predictive value of thrombophilia nor the clinical relevance of these factors has been established.

A number of risk factors have not been consistently found to be related to increased risk of VTE in SCI, including gender, obesity, nonorthopedic injuries, and surgical management (McKinley, 2004; Do, 2013; de Campos Guerra, 2014; Godat, 2015).

Several studies have examined the time of occurrence of VTE relative to time of the injury. DVT has been reported as soon as seventy-two hours after injury; the risk prior to this time appears to be low (Green, 1990). In studies of unprophylaxed patients, researchers have found that over 80% of DVTs occur within the first two weeks of injury (Rossi, 1980; Merli, 1993). Among ninety-four patients followed prospectively for three years after SCI, the VTE rate in the first three months was 34/100 patient-years

decreasing to 0.3/100 patient-years thereafter (Giorgi Pierfranceschi, 2013). Using an administrative database of more than 12,000 SCI patients in California, the risks of VTE in the first three months, at six months, and at one year after injury risk were 34%, 1.1%, and 0.4%, respectively (Godat, 2015).

Studies with long-term follow-up show a much lower rate of VTE beyond the acute-hospital-care period. There are a number of potential reasons for this, including the recovery of muscle stretch reflexes and tone following the acute period of spinal shock (DeVivo, 1999; Do, 2013). Data from the federally designated Spinal Cord Injury Model Systems demonstrate that the annual risk for DVT among chronic SCI patients (1.1% one to six years after injury) is much lower than that for acute SCI patients, and the risk for PE is even lower (0.3%) (Ragnarsson, 1995). However, in this study, the sample size decreased dramatically, from 2,791 at year one to 45 for year six.

The most striking evidence for the necessity of effective prevention of thromboembolic disease comes from studies of mortality after SCI. For those with acute SCI who do not survive the first year after injury, the risk of death due to PE is 210 times greater than that of a similar healthy population (DeVivo, 1995). This risk decreases to 19.1 times for years two through five and further decreases to 8.9 for those who survive more than five years. Autopsy investigations in patients with recent SCI have shown rates of PE as high as 37% (Tribe, 1963). Among 2,525 trauma admissions, although SCI patients constituted only 4% of trauma admissions, they accounted for 28% of the PE and 33% of the fatal PE (Wilson, 1994). Reporting on the first twelve years of Model Systems care of SCI, Stover and Fine (1987) reported that PE ranked as the fifth leading cause of death from 1973 to 1985, accounting for 8.5% of deaths. Among more than 28,000 patients in the National Spinal Cord Injury Database, PE was the third leading cause of death in the first year after injury (DeVivo, 1999). In the 1995 Model Systems report, DeVivo and Stover (1995) reported that PE was the third leading cause of death among those with paraplegia and was the second leading cause of death in those with Frankel D (neurologically incomplete) lesions. Furthermore, PE was found to be the third leading cause of death for all SCI patients in the first post-injury year, accounting for 14.9% of deaths in this group. However, in the 2014 report from the National Spinal Cord Injury Statistical Center, rates of mortality due to PE had diminished to 3.3%, making PE now the sixth leading cause of death in the first year after SCI (National Spinal Cord Injury Statistical Center, 2014). The widespread use of thromboprophylaxis may have played a role in this change.

Rationale For Thromboprophylaxis In Spinal Cord Injury

VTE is a common complication following spinal cord injury that may lead to fatal PE, chronic leg swelling, and bleeding related to anticoagulant therapy. Since leg swelling is universal following SCI and patients are often unable to report leg pain, VTE may present as extensive DVT, major PE, or sudden death. DVT in SCI patients resolves more slowly than in mobile patients and, therefore, often leads to chronic venous occlusion and a high risk of recurrence (Lim, 1992). Furthermore, therapeutic anticoagulation of VTE due to prophylaxis failures may lead to serious bleeding (Levi, 2010; Yeung, 2015). For all of these reasons, early and intensive thromboprophylaxis is the most effective way to reduce the burden of this complication. It is unfortunate that the number and quality of thromboprophylaxis trials in SCI are so limited.

MECHANICAL METHODS OF THROMBOPROPHYLAXIS

1.0 We recommend that mechanical thromboprophylaxis with intermittent PCDs with or without GCSs be applied as soon as feasible after acute SCI when not contraindicated by lower-extremity injury. [1C]

Active and passive range-of-motion (ROM) exercises may reduce lower-extremity stasis, but there is no evidence that they are effective in the prevention of VTE.

Pneumatic compression devices

The various types of PCDs (also called sequential compression devices, or SCDs) increase lower-extremity venous return, thereby reducing venous stasis (Morris, 2004). These devices are commonly used because they do not increase the risk of bleeding, particularly early after admission when bleeding risk is highest. Studies in some nontrauma patient groups suggest that PCDs can reduce DVT, and they may enhance the protection of anticoagulant thromboprophylaxis (Kakkos, 2008; CLOTS, 2013; Ho, 2013). However, compared with anticoagulant methods of thromboprophylaxis, there are relatively few high-quality studies of PCDs and no prospective randomized trials of their use as single-modality thromboprophylaxis in SCI. If PCDs are to provide any protection, they should be used continuously and only removed briefly for patient bathing.

Graduated Compression Stockings

Ideally, GCSs improve lower-extremity venous return and help to control edema. In a systemic review of nineteen randomized clinical trials, Sachdeva et al. concluded that GCSs are effective in diminishing the risk of DVT in hospitalized patients (Sachdeva, 2014). However, GCSs have repeatedly been shown to provide relatively poor protection against DVT (Lacut, 2005; Halim, 2014), and they may produce injury to the skin as seen in patients with SCI or ischemic stroke (CLOTS, 2009; Ong, 2011). In a randomized trial among seventy-four SCI patients, GCSs were much less efficacious than LMWH, with DVT rates of 22% and 5%, respectively (Halim, 2014). There is also uncertainty about the relative benefits of calf-length versus thigh-length GCSs in any patient group (Sajid, 2006). Finally, institutional compliance with effective GCS use has consistently been shown to be poor (Brady, 2007; Winslow, 2008). If GCSs are to provide any protection, they should be carefully fitted and used continuously except for daily removal to inspect the skin.

Other Mechanical Methods

Intermittent compression of the feet has been shown to increase venous blood flow in the proximal leg veins (Christen, 1997). While venous foot pumps have been assessed in several small studies in trauma patients with variable results, no report on the use of venous foot pumps in SCI patients was found.

Electrical stimulation of the calf enhances venous flow and velocity (Williams, 2015). Only a single small study of electrical calf stimulation has been conducted in SCI. In 1988, Merli et al. reported that the DVT rate was reduced with electrical stimulation of the calf plus LDUH, compared with LDUH alone, in forty-eight patients (Merli, 1988). It was recommended that electrical stimulation be used continuously; however, this intervention may hinder the patient's ability to participate in rehabilitation and may be painful in patients with incomplete sensory loss.

In summary, mechanical methods of thromboprophylaxis have the significant advantage of not causing bleeding in patients at high risk. Therefore, PCDs and possibly GCSs are appropriate early after

SCI, particularly if there is concomitant intracranial, perispinal, or solid organ bleeding. Combining mechanical and anticoagulant thromboprophylaxis may lead to greater protection against VTE; however, this has not been established in SCI (Kakkos, 2008; Ho, 2013). There is limited evidence that the use of PCDs or GCSs reduce the risk of VTE in patients with SCI (Geerts, 2008; Dhall, 2013). Furthermore, the effects of the specific design features of each of the various mechanical devices on the prevention of VTE are unknown. Additional disadvantages of mechanical thromboprophylaxis include poor compliance, skin breakdown in patients with lower-extremity sensory loss or edema, greater complexity and cost, and the potential that it may unnecessarily delay anticoagulant methods (Macatangay, 2008; Bockheim, 2009; Elpern, 2013).

Anticoagulant Methods Of Thromboprophylaxis

Low-molecular-weight heparin (table 3)

2.0 We recommend that LMWH be used as thromboprophylaxis in the acute-care phase following SCI once there is no evidence of active bleeding.

2.1 We recommend that, in patients whose LMWH is delayed because of concerns about bleeding, a daily assessment of bleeding risk be carried out and that LMWH be started when the bleeding risk decreases. [1C]

A systematic review of anticoagulant thromboprophylaxis in SCI patients showed that LMWH was associated with a significant decrease in PE and a trend for fewer DVT and major bleeding compared with LDUH (Paciaroni, 2008). The Spinal Cord Injury Thromboprophylaxis Investigators reported a prospective, multicenter, randomized trial that compared LDUH plus various PCDs to enoxaparin 30 mg twice daily (BID) during the initial two weeks following acute SCI (Spinal Cord Injury Thromboprophylaxis Investigators, 2003b). VTE was detected in 63% of the patients using LDUH plus PCDs and in 66% of those given enoxaparin. However, PE was diagnosed in 18% and 5% of the patients, respectively, although there were no fatal PE or significant differences in bleeding complications. This study was limited by adequate outcome assessments in only 107 of the 476 patients initially randomized in the trial.

In a continuation of this trial, patients who completed the first two weeks without objective evidence of VTE continued either LDUH without PCDs or enoxaparin 40 mg once daily for another six weeks (Spinal Cord Injury Thromboprophylaxis Investigators, 2003a). The incidence of VTE was 22% (one fatal PE) in sixty patients receiving LDUH and 9% in the fifty-nine patients receiving enoxaparin, with no differences in bleeding complications. In this phase of the study, 31% of the patients did not have an adequate outcome assessment for DVT.

In a retrospective cohort study of eighty-nine SCI patients examining different dosing protocols of enoxaparin, Hebbeler et al. found enoxaparin 40 mg once daily to be as effective as 30 mg twice daily (Hebbeler, 2004). Both regimens appeared to be equally safe with a low incidence of bleeding complications. In another retrospective chart review of 140 SCI patients, Marciniak et al. found similar rates of VTE with enoxaparin 40 mg once daily and tinzaparin, either 3,500 U or 4,500 U, once daily (Marciniak, 2012).

There are few studies in any patient group that have compared the relative efficacy and safety of the various LMWHs. In acute SCI, a small randomized trial comparing enoxaparin to dalteparin reported similar protection and bleeding between the two preparations (Chiou-Tan, 2003). There appears to be no difference in the effectiveness of prevention of VTE following SCI between the commercially available LMWH preparations.

Table 3: Randomized Trials of LMWH Use in SCI

Author, year Site	Patients	Interventions	Number of patients	Method of screening	Outcomes	Comments
Green, 1990 Chicago	Complete motor SCI <72 hours	tinzaparin 3,500 U once daily vs. LDUH 5,000 U Q8H	tinzaparin 16 LDUH 19	IPG + DUS done serially for 8 weeks	DVT: tinzaparin 0 LDUH 5 (26%) Bleeding: Tinzaparin 0 LDUH 1 Bleeding or DVT: tinzaparin 0 LDUH 7 (35%) p = 0.006	Not blinded; no gold-standard diagnostic test applied to all patients; high rate of dropouts and contamination
Chiou- Tan, 2003 Houston	Acute SCI <3 months after injury	enoxaparin 30 mg BID vs. dalteparin 5,000 U daily	enoxaparin 50 dalteparin 45	Symptomatic DVT	DVT: enoxaparin 3 (6%) dalteparin 2 (4%) p = 0.51 Bleeding: enoxaparin 1 (2%) dalteparin 2 (4%) p = 0.72	Unblinded; prophylaxis started up to 3 months after injury; DUS performed only if symptomatic
Spinal Cord Injury Thromboprophylaxis Investigators, 2003b USA, Canada	<72 hours after SCI	enoxaparin 30 mg BID vs. LDUH 5,000 units Q8H + PCD	enoxaparin 58 LDUH + PCD 49	Contrast venography and DUS 2 weeks after randomization	DVT: enoxaparin 35 (66%) LDUH + PCD 22 (63%) p = 0.81 PE: enoxaparin 3 (5%) LDUH + PCD 9 (18%) p = 0.03	78% of the randomized patients did not have an adequate assessment for DVT
Spinal Cord Injury Thromboprophylaxis Investigators, 2003a USA, Canada	SCI patients with no VTE at 2 weeks	enoxaparin 40 mg daily vs. LDUH 5,000 units Q8H	enoxaparin 59 LDUH 60	DUS 6 weeks after the start of this phase of the trial	DVT: enoxaparin 4 (7%) LDUH 11 (18%) PE: enoxaparin 1 (2%) LDUH 3 (5%) DVT+PE: enoxaparin 5 (8.5%) LDUH 13 (21.7%) p = 0.052	Patients were not rerandomized after the acute-care phase; open-label; 30% of the patients initially enrolled did not have an evaluable outcome
Halim, 2014 India	SCI	enoxaparin 40 mg once daily + stockings vs. stockings only	enoxaparin 37 stockings 37	DUS at 2 weeks	DVT: enoxaparin 2 (5%) stockings 8 (22%) p = 0.041	No difference in symptomatic DVT and no PE in either group

Abbreviations: DUS, Doppler ultrasound; DVT, deep-vein thrombosis; IPG, impedance plethysmography; LDUH, low-dose unfractionated heparin; LMWH, low-molecular-weight heparin; PCDs, pneumatic compression devices; PE, pulmonary embolism; SCI, spinal cord injury.

Unfractionated heparin (low-dose or adjusted-dose; table 4)

3.0 We recommend against the use of low-dose or adjusted-dose unfractionated heparin in the prevention of VTE in SCI (unless LMWH is not available or contraindicated). [1B]

Low-dose subcutaneous heparin has been shown to have little to no protection against VTE in SCI patients (Chen, 2013; Dhall, 2013). A single study showed that adjusted-dose heparin was more efficacious than LDUH but led to more bleeding (Green, 1988).

As discussed above, the Spinal Cord Injury Thromboprophylaxis Investigators compared LDUH 5,000 U every eight hours plus PCDs to enoxaparin 30 mg every twelve hours with no additional mechanical thromboprophylaxis in the acute-care phase of SCI (Spinal Cord Injury Thromboprophylaxis Investigators, 2003b). The anticoagulant was started within seventy-two hours of injury, and contrast venography was used to assess efficacy. There was no significant difference for DVT between the interventions with rates greater than 60% in both groups. There were significantly fewer PEs in the LMWH patients (5% versus 18%), no deaths due to PE, and no differences in bleeding complications. In the rehabilitation phase of this trial, patients with no DVT after the initial phase continued either LDUH without PCDs or enoxaparin 40 mg once daily for an additional six weeks, at which time they underwent screening DUS (Spinal Cord Injury Thromboprophylaxis Investigators, 2003a). VTE was detected in thirteen out of sixty (22%) LDUH patients and five out of fifty-nine (9%) enoxaparin patients, with no difference in bleeding events.

Prophylactic LDUH is associated with a fortyfold greater risk of heparin-induced thrombocytopenia (HIT) than LMWH (Martel, 2005). The impracticality of adjusted-dose unfractionated heparin and the substantially greater risk of HIT (and possibly more bleeding)—especially in light of continued evidence of the effectiveness and safety of LMWH—argues against this method of prophylaxis (Green, 1988; Martel, 2005; Paciaroni, 2008; Chen, 2013).

Table 4: Randomized Trials of Unfractionated Heparin Use in SCI

Author, year Site	Patients	Interventions	Number of patients	Method of screening	Outcomes	Comments
Green, 1988 Chicago	Motor complete SCI <72 hours	ADH (mid-interval aPTT 40–50 sec→ mean dose 13,200 U) Q12H vs. LDUH 5,000 U Q12H	ADH 29 LDUH 29	IPG + Doppler flow studies serially for 10 weeks → venography if positive	VTE: ADH 2 (7%) LDUH 9 (31%) p <0.05 Bleeding: ADH 7 (18%) LDUH 0 p <0.02	Not blinded; outcome assessment not validated; 23% postrandomization dropouts
Green, 1990 Chicago	Motor complete SCI <72 hours	tinzaparin 3,500 U daily vs. LDUH 5,000 U Q8H	tinzaparin 16 LDUH 19	IPG + DUS done serially for 8 weeks	DVT: tinzaparin 0 LDUH 5 (26%) Bleeding: tinzaparin 0 LDUH 1 Bleeding or DVT: tinzaparin 0 LDUH 7 (35%) p = 0.006	Not blinded; no gold-standard diagnostic test applied to all patients; high rate of dropouts and contamination
Spinal Cord Injury Thromboprophylaxis Investigators, 2003b USA, Canada	<72 hours after acute SCI	LDUH 5,000 U Q8H plus PCDs vs. enoxaparin 30 mg BID	LDUH + PCDs 49 enoxaparin 58	Contrast venography and DUS 2 weeks after randomization	VTE: LDUH + PCDs 63% enoxaparin 66% p = NS PE: LDUH + PCDs 18% enoxaparin 5% p = 0.03	Only 22% of randomized patients had an adequate outcome assessment
Spinal Cord Injury Thromboprophylaxis Investigators, 2003a USA, Canada	SCI patients with no VTE at 2 weeks	LDUH 5,000 units Q8H vs. enoxaparin 40 mg daily	LDUH 60 enoxaparin 59	DUS at 8 weeks	VTE: LDUH 13 enoxaparin 5 p = 0.052	Patients not rerandomized; open-label; 30% of patients who entered this phase of the study did not have an adequate outcome

Abbreviations: ADH, adjusted-dose heparin; BID, twice daily; DVT, deep-vein thrombosis; IPG, impedance plethysmography; LDUH, low-dose unfractionated heparin; NS, not significant; PE, pulmonary embolism; Q8H, every eight hours; SCI, spinal cord injury; VTE, venous thromboembolism.

Oral vitamin K antagonists (warfarin)

4.0 We recommend that oral vitamin K antagonists (such as warfarin) not be used as thromboprophylaxis in the early, acute-care phase following SCI. [1C]

In 1970, Silver and Moulton first recommended using oral anticoagulation to prevent VTE in patients with SCI (Silver, 1970). However, there are no clinical trials that evaluate the effectiveness and/or safety of oral vitamin K antagonists as primary thromboprophylaxis in patients with acute SCI. Furthermore, use of warfarin is problematic after acute SCI because of concerns about early postinjury bleeding on the one hand and the substantial delay in the onset of warfarin's effect on the other, as well as warfarin's unpredictable effect, the need for frequent laboratory monitoring, and warfarin's prolonged effect, which is problematic in patients requiring interruption of anticoagulation for procedures.

Direct oral anticoagulants

5.0 We suggest that DOACs may be considered as thromboprophylaxis during the rehabilitation phase following SCI. [2C]

In the past few years, a number of new oral anticoagulants, including apixaban, dabigatran, edoxaban, and rivaroxaban, have been approved for stroke prophylaxis in atrial fibrillation and, in some cases, as treatment of VTE and thromboprophylaxis following hip and knee arthroplasty. Although there are no clinical trials of any of these DOACs in patients with SCI, they are at least as effective and as safe as LMWH in hip and knee arthroplasty (Adam, 2013). The DOACs are not likely to be an appropriate consideration in the early phase after SCI because of the absence of evidence in SCI, relatively long half-life of seven to twelve hours (in case of bleeding or the need for an invasive intervention), and the lack of a rapid reversal agent. However, the DOACs are very attractive considerations for postacute thromboprophylaxis in patients with SCI since they are given orally in a fixed dose without the need for laboratory monitoring, have few drug and food interactions, and are less costly than LMWH. Rivaroxaban, an oral direct Factor Xa inhibitor, has been reported as thromboprophylaxis in pelvic trauma (Godoy Monzon, 2012) and has been used successfully in some trauma units for patients with SCI after an initial period of LMWH.

Combined Mechanical And Anticoagulant Thromboprophylaxis

6.0 We suggest that combined mechanical methods of thromboprophylaxis (PCDs with or without GCSs) and anticoagulant methods of thromboprophylaxis be used particularly in the acute--care phase as soon as possible after injury unless either option is contraindicated. [2C]

Combined methods of thromboprophylaxis have been commonly used following SCI. However, studies evaluating the effects of these combinations are rare. In some studies exploring anticoagulant thromboprophylaxis, mechanical methods were used in all patients.

Several small studies have attempted to evaluate mechanical and anticoagulant modalities of thromboprophylaxis, with mixed results. In 1988, Merli and colleagues studied fifty-three SCI patients randomly divided into three groups: placebo, LDUH 5,000 U Q8H, or LDUH plus functional neuromuscular stimulation (FNS), applied twenty-three hours per day over a twenty-eight-day period (Merli, 1988). They found DVT in 47% of the placebo group, 50% of the LDUH group, and 7% of the group that received the combination of FNS and LDUH ($p < 0.05$). Halim et al. reported DVT in 22% of thirty-seven SCI patients given GCSs and in 5% of thirty-seven patients who received enoxaparin 40 mg once daily plus GCSs (Halim, 2014).

Although these studies were small and had methodological limitations, combined mechanical and anticoagulant modalities may be used sequentially in patients with initial high bleeding risk or simultaneously in an attempt to provide greater protection. Limitations of combined thromboprophylaxis include the possibility that either or both methods will be used suboptimally and the greater complexity and cost of such an approach.

Duration Of Thromboprophylaxis

7.0 We recommend that anticoagulant thromboprophylaxis continue at least eight weeks after injury in SCI patients with limited mobility. [1C]

7.1 We suggest one of the following options as thromboprophylaxis in the postacute, rehabilitation phase: LMWH [2B], oral vitamin K antagonists (INR 2.0-3.0) [2C], or a DOAC [2C].

The optimal duration of thromboprophylaxis following SCI remains unclear, and we are not aware of any randomized trials that have compared various durations of thromboprophylaxis to clarify this issue. As noted earlier, the majority of new episodes of VTE are found during the first two weeks after injury, with a substantial decrease after eight weeks after injury (Giorgi Pierfranceschi, 2013; Godat, 2015). In the absence of new evidence, we recommend that thromboprophylaxis be provided for a minimum of eight weeks after an SCI associated with limited mobility and continued up to discharge from inpatient rehabilitation. The specific duration should be individualized for each patient, taking into consideration the level and completeness of the neurological injury, concomitant injuries and medical conditions, bleeding risk, functional status, and feasibility. Factors suggesting longer duration of thromboprophylaxis include motor complete injuries, lower-extremity fractures, older age, previous VTE, cancer, and obesity.

Although DOACs and oral vitamin K antagonists are not appropriate in the acute phase after SCI, they may be useful in preventing thromboembolic complications in stable patients with no impending invasive procedures. We consider DOACs and warfarin (target INR 2.0-3.0) to be an appropriate consideration for SCI patients in the rehabilitation phase of their care. To improve the effectiveness, safety, and efficiency of warfarin thromboprophylaxis, specific protocols/algorithms or a pharmacy-supervised warfarin management service are suggested to guide dosing and INR testing (Ageno, 2012).

Inferior Vena Cava Filters As Primary Thromboprophylaxis

8.0 We recommend that IVC filters not be used as primary thromboprophylaxis in SCI. [1C]

For patients with an acute proximal DVT and an absolute contraindication to therapeutic anticoagulation, placement of a temporary IVC filter is appropriate until the contraindication resolves, although there is actually no direct evidence to support this practice (Kearon, 2012; Mismetti, 2015).

Prophylactic insertion of an IVC filter is sometimes advocated in selected SCI patients because of the known high risk of VTE, the frequent delay in starting anticoagulant prophylaxis due to concerns about bleeding, and PE occasionally still develops despite appropriate thromboprophylaxis (Johns, 2006; Kidane, 2012).

The rate of IVC filter insertion in trauma patients has increased exponentially, in large part related to the greater use of retrievable filters (Antevil, 2006; Shackford, 2007; Cherry, 2008; Spate, 2008; Yunus, 2008; Knudson, 2011). However, there is wide variation in IVC filter insertion rates across trauma centers, which cannot be accounted for by patient VTE risk. Among 326 centers contributing to the National Trauma Data Bank, the rates of prophylactic IVC filter insertion ranged from 0% to 11% of admissions (Knudson, 2011). Another national study found that the rates of prophylactic IVC filter insertion in 680 trauma centers varied from 0% to 13% of trauma admissions (Dossett, 2011). Among patients in this study who were considered to be high risk for VTE according to the Eastern Association for the Surgery of Trauma (EAST), the rate of prophylactic IVC filter use varied from 0 to 206 per high-risk patient, demonstrating substantial variability in practice and overuse. Furthermore, fewer than 2% of the 22,808 patients with prophylactic filters in this study met the guideline criteria published by EAST (Rogers, 2002). A third study reported prophylactic IVC filter use in 0% to 25% of consecutive admissions to 223 trauma centers (Pickham, 2012).

The first report of IVC filter use in SCI patients was published more than thirty years ago (Jarrell, 1983). In the only prospective study of prophylactic IVC filter insertion in SCI patients fifteen patients were followed for an average of fifteen months, with no reported subsequent PE or DVT (Wilson, 1994). However, concomitant thromboprophylaxis was not detailed and the screening test for DVT, impedance plethysmography, has not been validated in SCI. A retrospective chart audit identified fifty-four SCI rehabilitation patients who had a prophylactic IVC filter inserted (Gorman, 2009). Despite the routine use of thromboprophylaxis with LMWH or LDUH, four times more filter patients developed DVT than patients without a filter. The only patient who developed PE while in rehabilitation had received a prophylactic filter.

IVC filters are generally easy to insert, resulting in little procedure-related morbidity (Angel, 2011; Kidane, 2012). However, we recommend against use of prophylactic IVC filters in SCI patients because evidence supporting filter benefit (reduction in PE or mortality) is absent, complication rates associated with filter use exceed the rates of the disease that filters are designed to prevent, current filters are not safe when left in place for the long term, and there are enormous, unjustified costs associated with these devices (Ingber, 2009; Spangler, 2010; Prasad, 2013).

The only randomized trial of the use of IVC filters in trauma patients was a pilot study in only thirty-four patients (Rajasekhar, 2011). In fact, there are no randomized trials of IVC filter use as primary thromboprophylaxis in any patient group. Numerous studies and a meta-analysis of prospective studies report no difference in the rates of PE among trauma patients with and without a prophylactic IVC filter (Velmahos, 2000:140; Girard, 2003; Antevil, 2006; Shackford, 2007; Cherry, 2008; Knudson, 2011; Kidane, 2012). Another meta-analysis reported a reduction in PE (but not in mortality) in trauma patients with use of prophylactic IVC filters; the number needed to treat to prevent one nonfatal PE with IVC filters was between 109 and 962 (Haut, 2014). The authors also stressed the high risk of bias in the included studies.

Evidence from the National Trauma Data Bank indicates that the incidence of PE and the use of IVC filters both doubled from 1994–2001 to 2007–9 (Knudson, 2011). Fatal or major PE has never been shown to be decreased with use of IVC filter in any patient group. Spain and coworkers (Spain, 1997) analyzed 2,868 trauma patients and determined that routine use of IVC filters in high-risk patients may have prevented one nonfatal PE but would not have prevented any deaths. There is also no evidence that filters are necessary in patients managed in trauma units with a policy to provide the best thromboprophylaxis that currently can be offered. In addition, IVC filters have not been shown to be cost-effective (Maxwell, 2002; Cherry, 2008; Spangler, 2010). Spangler et al. performed cost-effectiveness analyses on use of prophylactic IVC filters and concluded that filters were neither cost-effective nor effective over the reasonable range of assumption probabilities (Spangler, 2010).

A summary of reasons to avoid the use of prophylactic IVC filters include the following:

1. The use of prophylactic IVC filters in trauma patients has not been shown to reduce overall mortality or PE-related mortality (Wojcik, 2000; Antevil, 2006; Cherry, 2008; Singh, 2013; Haut, 2014). A systematic review of prospective studies found no difference in the rates of PE among trauma patients with and without prophylactic IVC filters (Velmahos, 2000:140). Furthermore, patients with an IVC filter still develop PE and occasionally have fatal PE (Giannoudis, 2007; Cherry, 2008).

2. Patients at sufficient risk to even warrant consideration of this intervention cannot be readily identified (Dossett, 2011). Published literature shows that, on average, 2% of trauma patients receive an IVC filter. If these are patients who could benefit from a prophylactic filter, there is no method to identify such a small proportion of patients. Although the EAST guidelines are sometimes recommended as criteria for filter insertion (Rogers, 2002), there are no data that allow clinicians to stratify patients with a high risk of major PE despite optimal thromboprophylaxis.

3. The underlying causes of most PE, DVT and DVT extension, are not prevented by an IVC filter. In fact, the risk of subsequent DVT in patients who have an IVC filter is increased (Decousus, 1998: Girard, 2003; Cherry, 2008; Gorman, 2009; Smoot, 2010; Angel, 2011). Among 112 SCI rehabilitation patients, those who had a prophylactic IVC filter were four times more likely to develop DVT after filter insertion than those who did not have a filter (20% versus 5%) (Gorman, 2009).

4. It is possible that patients with an IVC filter may be less likely to be given anticoagulant thromboprophylaxis even if it is not contraindicated, and there is also the potential for inappropriate delays in the provision of effective primary thromboprophylaxis if an IVC filter is in place. In five studies of retrievable IVC filter use, the average time for filter placement was six days after injury, well beyond the high-risk period for bleeding in most patients and at a time when half of all PE would already have occurred (Gonzalez, 2006; Cothren, 2007; Karmy-Jones, 2007; Johnson, 2009).

5. Insertion, removal, and follow-up for IVC filters are associated with prohibitively high costs (Chiasson, 2009; Spangler, 2010). In 1995, Greenfield calculated that the national cost of prophylactic IVC filter use in only 1% of high-risk trauma patients would be USD $900,000,000 for filter insertion alone (Greenfield, 1995). Another economic analysis estimated that providing one hundred high-risk trauma patients with a prophylactic IVC filter would prevent one nonfatal PE, would lead to eleven additional proximal DVTs, and would cost CAD $204,000 (Chiasson, 2009).

6. A number of short-term complications can occur after filter insertion, including misplacement, hematoma, air embolism, early migration, and wound infection (Antevil, 2006; Giannoudis, 2007; Cipolla, 2008; Ingber, 2009; Smoot, 2010; Angel, 2011; Kidane, 2012; Sarosiek, 2013; Singh, 2013). Migration of the IVC filter and perforation of the vena cava may be a particular problem in SCI patients undergoing assisted cough to help clear bronchial secretions. Among thirteen patients with tetraplegia who had a Greenfield filter inserted, four had distal migration, three had deformities of the filter, and two required laparotomy for small bowel perforation or filter fragmentation (Balshi, 1989).

7. Long-term complications include penetration and perforation of the IVC, insertion site DVT, thrombosis and occlusion of the IVC, migration, filter fracture, and chronic leg swelling (Antevil, 2006; Giannoudis, 2007; Karmy-Jones, 2007; Cipolla, 2008; Fox, 2008; Toro, 2008; Ingber, 2009; Phelan, 2009; Datta, 2010; Kidane, 2012; Smoot, 2010). Patton et al. noted chronic DVT in 47% and postthrombotic syndrome in 37% of trauma patients who had prophylactic filter insertion (Patton, 1996). A high proportion of retrievable IVC filters have been shown to fracture over time (Nicholson, 2010; Tam, 2012). The young age of most trauma patients raises serious concerns about the long-term consequences of filters over their lifetime. Furthermore, there are no published long-term follow-up studies of patients with a retrievable IVC filter.

8. There are also bleeding complications associated with long-term anticoagulant use in patients who have IVC filter-associated DVT and in those who are anticoagulated if the filter is not removed (Ageno, 2012).

For all of these reasons, the availability of retrievable filters should not expand the indications for IVC filter insertion. To compound matters, most retrievable filters are not removed (Kirilcuk, 2005; Antevil, 2006; Karmy-Jones, 2007; Zakhary, 2008; Helling, 2009; Angel, 2011; Rajasekhar, 2011; Rogers, 2012; Sarosiek, 2013). Recognizing the low retrieval rate, the US Food and Drug Administration recommended that filters be removed when they were no longer required (US FDA, 2010).

The 2012 ACCP antithrombotic guidelines also recommend against the use of IVC filters as primary prophylaxis in major trauma patients, including those with SCI (Gould, 2012).

Screening Patients For Asymptomatic Deep-Vein Thrombosis

9.0 We suggest that SCI patients not routinely be screened with DUS for clinically inapparent DVT during their acute-care admission. [2B]

9.1 We suggest that SCI patients not be routinely screened with DUS for clinically inapparent DVT on admission to rehabilitation. [2B]

The rationale for screening SCI patients to find clinically inapparent DVT is based on the premise that detection of silent DVT would identify patients who would then be given therapeutic anticoagulation, which might reduce symptomatic and fatal PE (Azarbal, 2011; Haut, 2011; Bandle, 2013). Regular physical examination of the legs is not an effective means to reduce clinically important thromboembolic complications because this strategy has both low sensitivity and low specificity for the detection of DVT, especially in SCI patients who frequently have sensory loss and almost always have leg swelling (Swarczinski, 1991; Geerts, 1994; Schwarcz, 2001). Similarly, use of D-dimer to screen SCI patients is not recommended for the following reasons: almost all patients with recent SCI will have an elevated result; this will lead to an increase in imaging tests with more, perhaps clinically irrelevant, positive findings; more patients will then receive therapeutic anticoagulation or an IVC filter; and there is no evidence that this strategy provides any benefit in any patient group.

DUS is highly accurate for the detection of DVT in symptomatic patients and has a number of properties that makes it attractive as a potential screening test for DVT in SCI patients (Bates, 2012). It is noninvasive, can be performed serially, and can, if necessary, be performed at the bedside without transporting the patient.

Among patients with SCI, only a single study has assessed screening for asymptomatic DVT using DUS compared with a diagnostic standard (Spinal Cord Injury Thromboprophylaxis Investigators, 2003b) (see table 5). In this trial, routine DUS and contrast

venography were performed within two days of each other, and each test was adjudicated by a central imaging committee blinded to the results of the other test. Among the 215 patients in whom both imaging tests were adequate for interpretation, the sensitivity of DUS for all DVT was only 29% (18% for proximal DVT). Furthermore, no clinical trials have assessed the benefit of routine screening of SCI patients for asymptomatic DVT. A systematic review of nine studies that screened SCI patients reported asymptomatic DVT in 17% (Furlan, 2007). However, in none of the included studies was a screening approach formally assessed. This review concluded that there was insufficient evidence to support routine screening. A more recent study prospectively assessed 139 acute SCI patients using serial DUS of the proximal and calf veins performed within thirty-six hours of admission, on day seven and day twenty-one (Germing, 2010b). The patients were given LMWH thromboprophylaxis plus compression stockings. DVT was detected in 45% of the patients, 71% of the DVTs involved only the calf veins, and 84% of the DVTs were detected by the initial DUS. On anticoagulant therapy, a repeat DUS three weeks after the diagnosis of DVT showed that a third of the thrombi had resolved and another third were improved. Major limitations of this study include poor patient description, no details of thromboprophylaxis timing, absent criteria for DUS outcomes, inadequate details of DVT treatment, and conclusions that were not supported by the observed findings.

In major trauma patients, screening for asymptomatic DVT has definitely been shown to detect more thrombi (Winemiller, 1999; Furlan, 2007; Pierce, 2008; Haut, 2009; Azarbal, 2011; Jawa, 2011; Dietch, 2015). Similarly, among acute SCI patients managed at the Mayo Clinic from 1976 to 1995, the use of DVT screening was the strongest predictor of a VTE diagnosis, with a risk ratio of 2.8-fold compared with patients not screened (Winemiller, 1999). Three retrospective studies reported a high rate of asymptomatic DVT when routine DUS was performed in SCI patients on transfer to a rehabilitation center (Powell, 1999; Kadyan, 2003; Do, 2013). DVT was detected in 12% of 189 patients, 9% of 92 patients, and 28% of 185 patients on admission to SCI rehabilitation (Powell, 1999; Kadyan, 2003; Do, 2013). At Johns Hopkins Hospital, the implementation of DUS screening in trauma patients led to a tenfold increase in the detection of DVT without any reduction in PE; in fact, PE rates increased over the same time period (Haut, 2012). Evidence from the National Trauma Data Bank indicates that centers in the highest quartile for DUS use had DVT rates seven times higher than the other centers (Pierce, 2008).

We recommend against routine DVT screening of SCI patients for the following reasons:

1. As a screening tool in asymptomatic patients, DUS is neither sensitive nor specific (Spinal Cord Injury Thromboprophylaxis Investigators, 2003b; Schellong, 2007). A comparison of DUS and contrast venography in 1,104 arthroplasty patients revealed that the sensitivity of DUS was only 31% for any DVT and only 21% for proximal DVT (Schellong, 2007). Of even greater concern was an unacceptable increase in false-positive rates (Schellong, 2007). Among 239 DVTs detected by screening DUS in trauma patients, 23% were no longer visible when the DUS was repeated within a week; this calls into question the accuracy of the screening test (Bandle, 2013). In the largest randomized thromboprophylaxis trial in SCI, the sensitivity of DUS for all DVT was only 29%, and the positive predictive value was only 47%; for proximal DVT, the sensitivity was even poorer at 18% (Spinal Cord Injury Thromboprophylaxis Investigators, 2003b). Therefore, screening DUS in asymptomatic SCI patients misses 70% to 80% of DVT and overcalls half of the "positives."

2. Nondiagnostic examinations or inadequate visualization of key deep veins has been reported in 10% to 41% of trauma patients; the rate is even higher in patients with lower-extremity injuries (Satiani, 1997; Germing, 2010b).

3. Of key importance is the fact that the clinical significance (and the need for treatment) of asymptomatic abnormalities detected by routine DUS screening is uncertain (Azarbal, 2011; Bandle, 2013).

4. There is evidence that routine screening does not reduce either PE or symptomatic DVT. In arthroplasty patients, a randomized trial showed that screening DUS did not prevent clinically important thromboembolic outcomes (Robinson, 1997). Among trauma patients, serial screening for DVT failed to identify patients before they developed symptomatic or fatal PE (Cipolle, 2002; Borer, 2005; Haut, 2007, Moed, 2012). These studies demonstrate that routine screening will detect more asymptomatic DVTs but does not reduce symptomatic thromboembolic events. Implementation of a routine DVT surveillance program in the trauma service at the University of Nebraska Medical Center resulted in a fivefold increase in the number of DUS studies performed with no

significant reduction in PE (Jawa, 2011). Three additional trauma studies reported that routine screening provided no incremental protection over early use of appropriate thromboprophylaxis (Schwarcz, 2001; Cipolle, 2002; Haut, 2007). Among 850 patients admitted to a rehabilitation hospital, DUS screening failed to reduce the rate of subsequent symptomatic VTE in patients receiving LMWH thromboprophylaxis (Tincani, 2010).

5. Screening patients for asymptomatic DVT might cause harm since it will increase the number of patients receiving therapeutic anticoagulation with its associated risk of bleeding and insertion of more IVC filters.

6. The costs of DVT screening are substantial, and routine screening of trauma patients has been shown to not be cost-effective (Borer, 2005; Jawa, 2011; Sud, 2011). Among high-risk trauma patients who were given thromboprophylaxis with LMWH, the addition of either serial DUS screening or insertion of an IVC filter was determined to cost more than USD $100,000 per nonfatal PE prevented (Brasel,1997). In another study, screening of high-risk trauma patients was shown to result in costs of USD $180,000 more per year for additional DUS studies without any apparent clinical benefit (Jawa, 2011).

The 2012 ACCP antithrombotic guidelines also recommend against the screening of major trauma patients with DUS (Gould, 2012).

For all of the above reasons, we recommend against routine screening of SCI patients for asymptomatic DVT. Although selective use of screening in patients felt to be at particularly high risk of VTE has also not been proved, use of a single DUS study of the proximal leg veins may be considered in the following circumstances: SCI patients transferred from another center in whom optimal thromboprophylaxis has not been provided and in patients with both a high bleeding risk that precludes early anticoagulant thromboprophylaxis and lower-extremity injuries that preclude use of bilateral mechanical methods.

Routine DUS screening of SCI patients on transfer to a rehabilitation facility is common in some centers (Giorgi Pierfranceschi, 2013). This practice will diagnose asymptomatic DVT in 5% to 15% of patients who have received thromboprophylaxis in acute care (Aito, 2002; Spinal Cord Injury Thromboprophylaxis Investigators, 2003a; Kadyan, 2003; Kadyan, 2004; Giorgi Pierfranceschi, 2013). However, neither the diagnostic accuracy of DUS nor the clinical relevance of the DVT detected has been assessed in this setting, and there is no evidence that there is a net benefit of this approach. We recommend continuation of thromboprophylaxis into the rehabilitation phase rather than screening.

Table 6: Studies of Screening of SCI Patients for Asymptomatic DVT

Author, year Site	Patients	Prophylaxis	Method of screening	No.	DVT	Proximal DVT	Comments
Kadyan, 2003 Columbus, OH	Traumatic SCI within 3 months of admission to rehab 1996–98	Warfarin LMWH LDUH IVC filter	DUS <72 hours after transfer to rehab	92	8 (8.7%)	NR	Retrospective • Patients poorly described • Prophylaxis NR • DUS technique and criteria NR
Spinal Cord Injury Thromboprophylaxis Investigators, 2003b USA, Canada	Acute SCI patients admitted to 27 centers	LDUH TID + PCDs vs. enoxaparin 30 mg BID	Contrast venography and DUS 2 weeks after injury	107	57 (53.3%)	14/181 (7.7%)	Prospective • RCT • Only 22% of randomized patients had an adequate outcome assessment for efficacy
Germing, 2010a Germany	SCI Jan. 2007–Sept. 2008	Enoxaparin 40 mg daily + "compression stockings"	DUS of calf and proximal veins <36 hrs + day 7 and day 21	139	1st DUS: 53 (38%) Day 7: 7 Day 21: 3 1st 3 weeks: 63 (45%)	18/139 (12.9%)	Prospective • Patients poorly described • Timing of prophylaxis NR • Excluded patients NR • Criteria for DUS NR • No confirmation of positive tests + nondiagnostic studies NR • Conclusions not supported by study data
Giorgi Pierfranceschi, 2013 Italy	Traumatic SCI at 3 Italian SCI units Jan. 2003–Nov. 2007	LMWH + thigh-length GCS	DUS <7 days of admission to rehab (~20 days after injury)	81 without VTE at entry	6/81 (7.4%) Median F/U 3 years	NR	Prospective • Accuracy of DUS NR
Matsumoto, 2015 Japan	Acute SCI surgically treated	GCSs + calf-length PCDs (no anticoagulant)	Proximal plus calf DUS at 1, 3, 7, 14, and 28 days after surgery	29	12 (41%)	0	Prospective • Small sample • Extent of DVT not described

Abbreviations: DUS, Doppler ultrasound; DVT, deep vein thrombosis; GCSs, graduated compression stockings; IVC, inferior vena cava; LDUH, low dose unfractionated heparin; LMWH, low molecular weight heparin; NR, not reported; PCDs, pneumatic compression devices; SCI, spinal cord injury; VTE, venous thromboembolism.

VTE in Pediatric SCI

10.0 We suggest that children of all ages with acute SCI receive mechanical prophylaxis with GCSs and/or PCDs. [2C]

10.1 We recommend that adolescents with acute SCI receive anticoagulant thromboprophylaxis, especially if they have additional risk factors such as lower-extremity or pelvic fractures. [1C]

DVT is very uncommon in children who acquire a SCI between birth and twelve years of age (Vogel, 2011; Schottler, 2012). In contrast, DVT was identified in 8% of those injured between thirteen and fifteen years of age and 9% of those injured between sixteen and twenty-one years of age. In a retrospective analysis of all SCI cases in California from 1991 through 2001, VTE were identified in only 1.1% of those ages eight to thirteen years and 4.8% among those ages fourteen to nineteen years (Jones, 2005). In a retrospective study limited to a single rehabilitation hospital, VTE was identified in 5% of those with SCI under five years of age and 10% of those ages fifteen to eighteen years (Radecki, 1994).

Although we are not aware of any prospective studies of the use of mechanical thromboprophylaxis in pediatric SCI, GCSs and/or PCDs might provide protection against VTE in this patient group if proper sizing can be achieved. For children who are too small to wear commercially available GCS, use of custom-made lower-extremity stockings may be a consideration. Elastic wraps are not recommended because unevenness of wrapping may result in constrictions with venous obstruction, possibly increasing the risk of DVT, skin damage, or compartment syndrome (Vogel, 2001). Additionally, some elastic wraps contain latex, which is problematic in children with latex allergy. Pneumatic compression devices can be utilized for older children and adolescents early after SCI, but again there is no direct evidence of their benefit in this patient group.

If anticoagulant thromboprophylaxis is used in pediatric SCI, it should generally start soon after injury if no active bleeding or high risk of bleeding are present. Suggested doses of enoxaparin are 0.75 mg/kg every twelve hours for infants younger than two months and 0.5 mg/kg every twelve hours or 1 mg/kg once daily in those older than two months (Monagle, 2012). If anti-Factor Xa levels are considered useful, the target for prophylaxis with LMWH is 0.1 to 0.3 units/ml four to six hours after the LMWH dose. The duration of anticoagulant thromboprophylaxis is generally for at least eight weeks.

Thromboprophylaxis in Chronic SCI Patients who are Rehospitalized

11.0 We recommend that persons with chronic SCI who are hospitalized for medical illnesses or surgical procedures receive thromboprophylaxis during the period of increased risk. [1C]

The issue of reinstitution of prophylactic measures in persons with chronic SCI who are rehospitalized for medical illnesses or surgical procedures has not been subjected to specific clinical research. However, it is likely that these patients are at similar or greater risk for the development of VTE compared with non-SCI patients who are hospitalized for similar conditions. Therefore, we recommend routine thromboprophylaxis appropriate for the clinical setting when chronic SCI patients are readmitted (Kahn, 2012; Gould, 2012; Falck-Ytter, 2012).

Implementation Of Thromboprophylaxis Strategies

12.0 We recommend that every SCI unit (acute and rehabilitation) have a written thromboprophylaxis policy that includes implementation strategies. [1C]

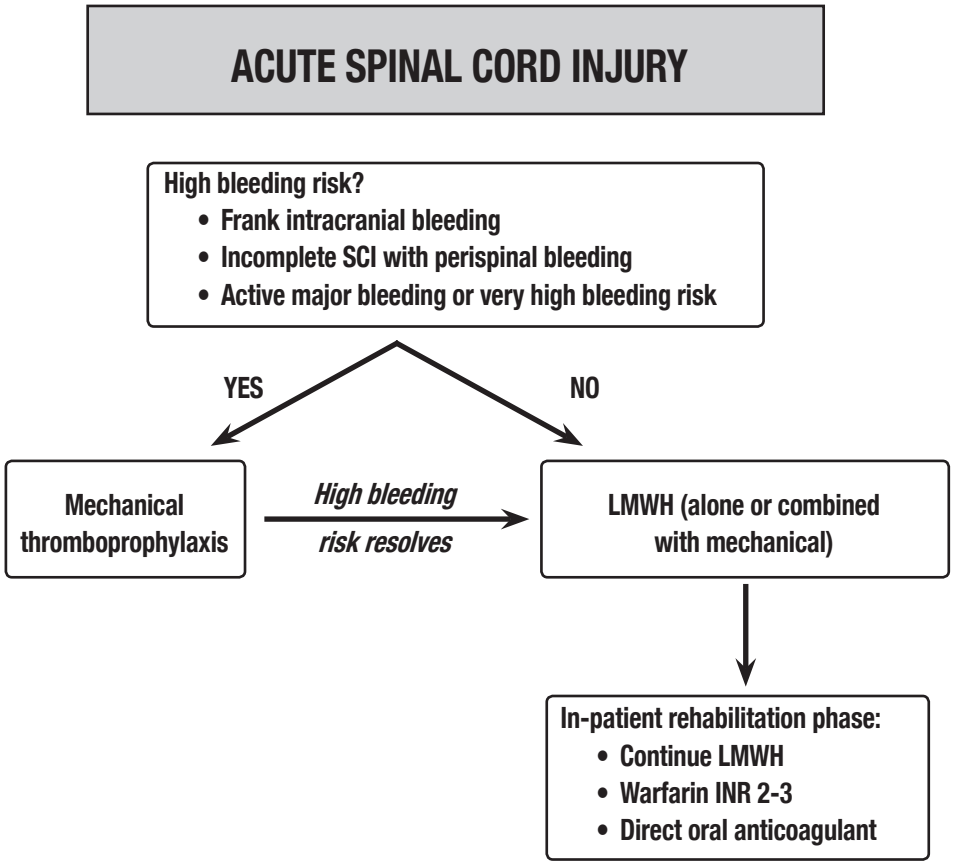
12.1 We recommend that every SCI unit (acute and rehabilitation) periodically assess adherence to the unit thromboprophylaxis policy and use the results for quality improvement if adherence is suboptimal. [1C]

The creation of clinical practice guidelines in this area would not be complete without consideration of how to incorporate these guidelines into routine practice. A number of studies have demonstrated that multicomponent interventions increase the prescribing of thromboprophylaxis (Burns, 2005; Tooher, 2005; Mahan, 2010, Kahn, 2013; Lau, 2014; Maynard, 2015). In the SCI patient population, publication of guidelines related to thromboprophylaxis had little impact on adherence, while the use of standard order sets and documentation templates along with social marketing/outreach visits resulted in improved adherence (Burns, 2005).

Sustained improvement in thromboprophylaxis and adherence to clinical practice guidelines in individuals with SCI will depend on interventions that combine the following:

- An organizational commitment to use the guidelines (e.g., an institutional policy that incorporates guideline recommendations and a team to lead guideline implementation).
- Development of a written thromboprophylaxis policy that defines unit thromboprophylaxis philosophy, identifies eligible patient groups, and outlines a recommended thromboprophylaxis approach (see figure 2). The local guidelines should also include reassessment of thromboprophylaxis on transfer to alternative levels of care (e.g., from intensive care to a step-down unit or ward and from acute care to a rehabilitation center).
- Strategies that increase awareness (e.g., staff and patient/family education, outreach visits, social marketing).
- Strategies that enable change in the process of care, such as use of order sets or Computerized Provider Order Entry with the recommended thromboprophylaxis options embedded to prompt physicians to follow guideline recommendations.
- Alerts integrated into the electronic patient record to prompt staff when thromboprophylaxis has not been ordered (or has been ordered but not yet documented). Daily nursing flow sheets may be useful to prompt nursing staff to administer VTE prophylaxis appropriately or to question why it is not being provided.
- Strategies that reinforce adherence with the guidelines, such as use of audit and feedback followed by further quality improvement interventions if the audit reveals suboptimal adherence.
- Ongoing tracking of all hospital-associated VTE in SCI patients with a root-cause analysis of each to determine if the event was potentially preventable provides additional, clinically relevant data to assess the success of the SCI unit thromboprophylaxis policy and to guide modifications of the policy if indicated.

Figure 2: General Approach to Thromboprophylaxis in SCI



Future Research

These guidelines reiterate the high risk of VTE in patients with SCI, the major acute and long-term consequences of DVT and PE, and the paucity of high-quality studies related to the epidemiology, prevention, and prognosis of VTE in these patients. There is a need for large-population and registry studies, collaborative prospective cohort studies with complete follow-up for clinically relevant outcomes, and multicenter randomized trials of interventions to reduce the burden of this complication in SCI patients. The following list summarizes some of the research needs and priorities that can fill in knowledge gaps and can be used to inform changes in patient care.

Epidemiology of VTE in SCI

- Using population databases, registries, and prospective cohort studies to determine current rates of symptomatic VTE in the following time periods:
  a) Acute-care phase (or thirty or fewer days after injury)
  b) Rehabilitation care phase
  c) First year after injury
  d) More than one year after injury
  e) Associated with readmissions for another medical or surgical reason
- To determine the risk factors and their hazard ratios for symptomatic VTE in the various time periods based on systematic review of existing studies and/or acquisition of new data
- Risks and risk factors for traumatic versus nontraumatic SCI

Investigation of VTE in SCI

- Role of D-dimer in the investigation of suspected DVT and PE
- Role of D-dimer in the investigation of suspected recurrent DVT and PE
- Benefit of screening for asymptomatic DVT using DUS in acute care and on admission to rehabilitation

Treatment of VTE in SCI

- Effectiveness and safety of direct oral anticoagulants in SCI patients who develop VTE
- Optimal duration of anticoagulant therapy in SCI patients with VTE
- Bleeding risks associated with long-term anticoagulation

Prevention of VTE in SCI

- High-quality randomized trials of various anticoagulant and mechanical thromboprophylaxis strategies
- Benefits and cost-effectiveness of the addition of mechanical thromboprophylaxis to LMWH
- Effectiveness, risks, and compliance with GCS in SCI, either combined with PCD or with LMWH
- Impact of timing of the start of thromboprophylaxis on symptomatic VTE and clinically important bleeding
- Optimal dosing of LMWH thromboprophylaxis in the acute phase (e.g., compare fixed-dose versus risk-adjusted dose of LMWH)
- Optimal thromboprophylaxis options in the rehabilitation phase
- Effectiveness, safety, and cost-benefit of direct oral anticoagulants in the postacute phase of SCI
- Duration of thromboprophylaxis
- Predictors of thromboprophylaxis failures (VTE and bleeding)
- Audits of adherence with “appropriate” and “optimal” thromboprophylaxis
- Effectiveness of various implementation strategies for thromboprophylaxis compliance and outcomes

Other areas

- Temporal rates of resolution of proven DVT and PE in SCI patients
- Epidemiology, prevention, and natural history of VTE in pediatric patients with SCI
- Use of IVC filters in SCI patients, including rates, indications, types of filters, dwell time, short-term and long-term complications, removal rates, and variability in these measures across SCI centers

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Appendix 1: Search Strategies

Search Strings And Results

The following CONCEPTS were used to identify potentially relevant literature—both using Boolean-logic queries. We used the controlled vocabulary of a database to develop the search string.

CONCEPT A (spinal cord injury) AND CONCEPT B (deep vein thrombosis)

Table A1: Search Terms Provided by PVA Expert Panel

CONCEPT A: spinal cord injury All relevant terms below linked by "OR"	CONCEPT B: deep vein thrombosis All relevant terms below linked by "OR"
spinal cord injury spinal injury	deep vein thrombosis pulmonary embolism thromboembolism thrombophlebitis thromboprophylaxis thrombosis venous thromboembolism venous thrombosis

Each database included in this search strategy has a controlled vocabulary, meaning a hierarchy of topics to identify key concepts covered by each article. Articles are indexed by these topics. The terms in table A1 were mapped to existing controlled vocabulary terms within each database source (tables A2 through table A6). The database search results are shown in table 1 of the text.

Table A2: PbMed Search Terms

	CONCEPT A: spinal cord injury All relevant terms below linked by "OR"	CONCEPT B: deep vein thrombosis All relevant terms below linked by "OR"
Controlled Vocabulary (MESH)	Spinal Cord Injuries • Autonomic Dysreflexia • Central Cord Syndrome • Spinal Cord Compression	Embolism and Thrombosis • Embolism o Embolism, Air o Embolism, Amniotic Fluid o Embolism, Fat o Pulmonary Embolism • Thromboembolism o Embolism, Paradoxical o Intracranial Embolism and Thrombosis o Venous Thromboembolism • Thrombosis o Coronary Thrombosis o Thromboembolism o Venous Thrombosis • Budd-Chiari Syndrome • Postthrombotic Syndrome • Retinal Vein Occlusion • Thrombophlebitis • Lemierre Syndrome • Upper Extremity Deep Vein Thrombosis
Search Strings	("Spinal Cord Injuries"[Mesh] OR "spinal cord injury"[Title/Abstract] OR "spinal cord injuries"[Title/Abstract] OR "spinal injury"[Title/Abstract] OR "spinal injuries"[Title/Abstract] OR "Hemiplegia"[Majr] OR "Paraplegia"[Majr] OR "Quadriplegia"[Majr] OR Hemipleg*[Title/Abstract] OR Parapleg*[Title/Abstract] OR Quadripleg*[Title/Abstract])	"deep vein thrombosis"[Title/Abstract] OR "pulmonary emboli*"[Title/Abstract]) OR thromboembolism[Title/Abstract] OR thrombophlebitis[Title/Abstract] OR thromboprophylaxis[Title/Abstract] OR thrombosis[Title/Abstract] OR "venous thromboembolism"[Title/Abstract] OR "venous thrombosis"[Title/Abstract] OR "DVT"[Title/Abstract] OR "Embolism and Thrombosis"[Majr]

Results for PbMed search

Concept A 'AND'	Concept B	Table 1 Results
71,438	188,682	1,344
EXCLUSION	# excluded	
Filter: Human		1,133
Filter: 1996-8/6/2014		641
Filter: English		524
Filter: Publication type		494
FINAL (8/6/2014)		494

String for excluded Publication Types

NOT ("bibliography"[Publication Type] OR "comment"[Publication Type] OR "editorial"[Publication Type] OR "evaluation studies"[Publication Type] OR "historical article"[Publication Type] OR "letter"[Publication Type] OR "observational study"[Publication Type] OR "technical report"[Publication Type] OR "validation studies"[Publication Type] OR "congresses"[-Publication Type] OR "news"[Publication Type]

Table A3: PsycInfo search terms

	CONCEPT A: spinal cord injury All relevant terms below linked by "OR"	CONCEPT B: deep vein thrombosis All relevant terms below linked by "OR"
Controlled Vocabulary (Thesaurus)	Spinal Cord Injuries	Embolisms Thromboses • Coronary Thromboses
Search Strings	DE "Spinal Cord Injuries" OR TI ("Spinal Cord Injuries" OR "Spinal Cord Injury" OR "spinal injuries" OR "spinal injury" OR "Hemipleg*" OR "Parapleg*" OR "Quadripleg*") OR AB ("Spinal Cord Injuries" OR "Spinal Cord Injury" OR "spinal injuries" OR "spinal injury" OR "Hemipleg*" OR "Parapleg*" OR "Quadripleg*")	((DE "Embolisms") OR (DE "Thromboses" OR DE "Coronary Thromboses")) TI ("deep vein thrombosis" OR "pulmonary emboli*" OR "thromboembolism" OR "thrombophlebitis" OR "thromboprophylaxis" OR "thrombosis" OR "venous thromboembolism" OR "venous thrombosis" OR "DVT") OR AB ("deep vein thrombosis" OR "pulmonary emboli*" OR "thromboembolism" OR "thrombophlebitis" OR "thromboprophylaxis" OR "thrombosis" OR "venous thromboembolism" OR "venous thrombosis" OR "DVT")

Results for PsycInfo search

Concept A 'AND'	Concept B	Table 1 Results
6,572	1,169	33
EXCLUSION	# excluded	
Limiters - Published Date: 19960101-20141231; English; Population Group: Human; Exclude Dissertations		19
FINAL (8/7/2014)		19

Table A4: CINAHL search terms

	CONCEPT A: spinal cord injury All relevant terms below linked by "OR"	CONCEPT B: deep vein thrombosis All relevant terms below linked by "OR"
Controlled Vocabulary (Thesaurus)	Spinal Cord Injuries • Central Cord Syndrome • Spinal Cord Compression	Embolism and Thrombosis • Embolism o Embolism, Air o Embolism, Amniotic Fluid o Embolism, Fat o Pulmonary Embolism • Thromboembolism o Intracranial Embolism and Thrombosis • Carotid Artery Thrombosis • Intracranial Embolism • Intracranial Thrombosis o Embolism, Paradoxical o Venous Thromboembolism • Thrombosis o Catheter-Related Thrombosiso Coronary Thrombosis o Thromboembolism o Venous Thrombosis • Hepatic Vein Thrombosis • Postthrombotic Syndrome • Retinal Vein Occlusion • Thrombophlebitis • Upper Extremity Deep Vein Thrombosis
Search Strings	(MH "Spinal Cord Injuries+") OR TI ("Spinal Cord Injuries" OR "Spinal Cord Injury" OR "spinal injuries" OR "spinal injury" OR "Hemipleg*" OR "Parapleg*" OR "Quadripleg*") OR AB ("Spinal Cord Injuries" OR "Spinal Cord Injury" OR "spinal injuries" OR "spinal injury" OR "Hemipleg*" OR "Parapleg*" OR "Quadripleg*")	(MH "Embolism and Thrombosis (Non-Cinahl)+") OR (MH "Embolism+") OR (MH "Thromboembolism+") OR (MH "Thrombosis+")) OR TI ("deep vein thrombosis" OR "pulmonary emboli*" OR "thromboembolism" OR "thrombophlebitis" OR "thromboprophylaxis" OR "thrombosis" OR "venous thromboembolism" OR "venous thrombosis" OR "DVT") OR AB ("deep vein thrombosis" OR "pulmonary emboli*" OR "thromboembolism" OR "thrombophlebitis" OR "thromboprophylaxis" OR "thrombosis" OR "venous thromboembolism" OR "venous thrombosis" OR "DVT")

Results for CINAHL search

Concept A "AND"	Concept B	Table 1 Results
19,650	30,464	330
EXCLUSION	# excluded	
Limiters - Published Date: 19960101-20141231; English Language; Human Search modes - Boolean/Phrase		110
FINAL (8/7/2014)		110

Table A5: EMBASE search terms

	CONCEPT A: spinal cord injury All relevant terms below linked by "OR"	CONCEPT B: deep vein thrombosis All relevant terms below linked by "OR"
Controlled Vocabulary (Thesaurus)	spinal cord injury • Brown Sequard syndrome • central cord syndrome • cervical spinal cord injury • experimental spinal cord injury • spinal cord compression • spinal cord transsection • spinal cord transverse lesion	thromboembolism • arterial thromboembolism • embolism o air embolism o artery embolism o brain embolism o cholesterol embolism o fat embolism o gas embolism o kidney artery embolism o lung embolism o microembolism o paradoxical embolism o tumor embolism o vein embolism • thrombogenicity • thrombophilia • thrombosis o vein thrombosis • cerebral sinus thrombosis • deep vein thrombosis • kidney vein thrombosis • leg thrombophlebitis • Lemierre syndrome • liver vein thrombosis • lower extremity deep vein thombosis o mesenteric vein thrombosis o portal vein thrombosis o superficial thrombophlebitis o thrombophlebitis o upper extremity deep vein thrombosis • venous thromboembolism o deep vein thrombosis o lower extremity deep vein thrombosis o lung embolism o upper extremity deep vein thrombosis

	CONCEPT A: spinal cord injury All relevant terms below linked by "OR"	CONCEPT B: deep vein thrombosis All relevant terms below linked by "OR"
Search Strings	"spinal cord injury"/exp OR "spinal cord injury":ab,ti OR "spinal cord injuries":ab,ti OR "spinal injury":ab,ti OR "spinal injuries":ab,ti OR hemipleg*:ab,ti OR paraple-g*:ab,ti OR quadripleg*:ab,ti	"thromboembolism"/exp/mj OR "deep vein thrombosis":ab,ti OR "pulmonary embolism":ab,ti OR "pulmonary emboli":ab,ti OR "thromboembolism":ab,ti OR "thrombophlebitis":ab,ti OR "thromboprophylaxis":ab,ti OR "thrombosis":ab,ti OR "venous thromboembolism":ab,ti OR "venous thrombosis":ab,ti OR "dvt":ab,ti

Results for EMBASE search

Concept A "AND"	Concept B	Table 1 Results
85,698	262,696	1,693
EXCLUSION	# excluded	
([article]/lim OR [article in press]/lim OR [review]/lim) AND [humans]/lim AND [english]/lim AND [1996-2014]/py		653
FINAL (8/7/2014)		653

Table A6. Cochrane Libraries search terms

CONCEPT A: spinal cord injury All relevant terms below linked by "OR"	CONCEPT B: deep vein thrombosis All relevant terms below linked by "OR"
Spinal Cord Injuries • Spinal Cord Compression • Central Cord Syndrome	Embolism and Thrombosis • Embolism o Embolism, Air o Embolism, Amniotic Fluid o Embolism, Fat o Pulmonary Embolism • Thromboembolism o Embolism, Paradoxical o Intracranial Embolism and Thrombosis o Venous Thromboembolism • Thrombosis o Coronary Thrombosis o Thromboembolism o Venous Thrombosis • Budd-Chiari Syndrome • Retinal Vein Occlusion • Thrombophlebitis • Lemierre Syndrome • Postthrombotic Syndrome • Upper-extremity Deep Vein Thrombosis

CONCEPT A: spinal cord injury All relevant terms below linked by "OR"	CONCEPT B: deep vein thrombosis All relevant terms below linked by "OR"
MeSH descriptor: [Spinal Cord Injuries] explode all trees or "Spinal Cord Injuries" or "Spinal Cord Injury" or "spinal injuries" or "spinal injury" or "Hemipleg*" or "Parapleg*" or "Quadriple-g*":ti,ab,kw (Word variations have been searched)	MeSH descriptor: [Embolism and Thrombosis] explode all trees or "deep vein thrombosis" or "pulmonary emboli*" or "thrombo-embolism" or "thrombophlebitis" or "thromboprophylaxis" or "thrombosis" or "venous thrombo-embolism" or "venous thrombosis" or "DVT":ti,ab,kw (Word variations have been searched

Results for Cochrane search

Concept A "AND"	Concept B	Table 1 Results
2,833	11,394	54
EXCLUSION	# excluded	
Filter: 1996-2014		33
FINAL (8/7/2014)		33

Appendix 2: Panel Member Potential Conflict-Of-Interest Statements

CONSORTIUM FOR SPINAL CORD MEDICINE

Steering Committee Member and Guideline Development Panel Member please read the following policies on Conflicts of Interest and Confidentiality and sign below to indicate acceptance.

POLICY ON CONFLICTS OF INTEREST

The Consortium for Spinal Cord Medicine (hereafter referred to as "the Consortium") is a collaboration of professional and consumer organizations funded and administered through Paralyzed Veterans of America (hereafter referred to as "PVA"). PVA wants to ensure that regular business of the Consortium's Steering Committee and the guideline development process are free from conflicts of interest. PVA recognizes that those on the Steering Committee and Guidelines Development Panels are involved in a variety of organizations and projects, and may hold financial investments which might create actual or potential conflicts of interest or the appearance of a conflict (each a "conflict" or "conflict of interest").

To achieve that result, the following policy is adopted:

1. **Applicability.** This Policy applies to the Consortium's Steering Committee Members, including the Chair and Vice-Chair, in addition to those members on the Guideline Development Panels (collectively, "Covered Persons").

2. **Term.** This agreement is effective for the term the Covered Person is a member of the Steering Committee and/or a Guideline Development Panel, notwithstanding how active or passive a role he or she may play as a member of the Steering Committee or a Guideline Development Panel.

3. **Determining the Existence of a Conflict.** The guidelines set forth below shall be used to determine the existence of a conflict. The guidelines are meant to be illustrative and not exclusive; a conflict may exist even though the situation in question is not included below. Each Covered Person bears the personal responsibility for initially determining if a conflict of interest exists with respect to such Covered Person. If a Covered Person has any questions regarding the existence of a conflict, such Covered Person should promptly contact the Steering Committee Chair.

4. **Guidelines for Determining Existence of Conflict.** A conflict may exist if the Covered Person is unduly influenced by others (i.e. his/her spouse, parent, child, or other individual with whom such Covered Person has a close personal, business or professional relationship (including persons with whom such Covered Person is a partner, shareholder in a closely held corporation, coauthor or other close professional coworker or colleague) to the detriment of and against the mission of the Consortium, the Steering Committee, the Guideline Development Panels, and PVA.

5. **Disclosure of Conflict: Recusal.** If a Covered Person determines that a conflict exists, then he or she shall notify immediately the Steering Committee Chair or the Director of PVA's Research and Education Department. The Chair, with input from the Director of Research and Education, shall determine whether a conflict exists (except that in cases of conflicts involving the Chair, the Vice Chair shall decide). The decision on conflicts and the basis of that decision shall be reported to the Steering Committee and recorded in the minutes. Unless otherwise determined by the Chair (or, as appropriate, the Vice Chair) in individual cases, if a conflict is found to exist, the affected person shall recuse himself/herself from all discussions, determinations and votes with respect to the matter with which the conflict exists, and shall excuse him/herself from all meetings at which any discussions regarding the matter take place. Following the termination of such determinations and discussions involving the conflict, such Covered Person may rejoin the meeting.

POLICY ON CONFIDENTIALITY

In the course of conducting regular business for the Consortium and/or Guideline Development Panel(s), Steering Committee Members and Panel Members may receive and be given access to confidential information concerning PVA or another entity working with the Consortium. To ensure that the confidentiality of the information will be maintained, the following Policy on Confidentiality is adopted.

1. **Applicability.** This Policy applies to the Consortium's Steering Committee Members, including the Chair and Vice-Chair, in addition to those members on the Guideline Development Panels (collectively, "Covered Persons").

2. **Term.** This agreement is effective for the term the Covered Person is a member of the Steering Committee and/or a Guideline Development Panel, notwithstanding how active or passive a role they may play as a member of the Steering Committee or a Guideline Development Panel.

3. **Definition of Confidential Information.**
"Confidential Information" means (i) all written business, financial, technical and scientific information relating to the Consortium and which PVA has marked conspicuously "CONFIDENTIAL," "PROPRIETARY," or similar marking; or (ii) oral information which is specified as confidential by the Steering Committee and/or PVA. All documents derived during the guideline development process are confidential, and they remain so until 1) the document has been approved for publication by a vote of the Steering Committee and 2) the document is released by PVA as a printed document.
"Confidential Information" shall exclude information which (a) is in the public domain at the time of disclosure; (b) is in the possession of the Consortium (including any Covered Person) free of any obligation of confidence prior to the time of disclosure; (c) though originally within the definition of "Confidential Information", subsequently becomes part of the public knowledge through no fault of the Consortium (including any Covered Person), as of the date of its becoming part of the public knowledge; (d) though originally within the definition of "Confidential Information", subsequently is received by the Consortium (including any Covered Person) without any obligation of confidentiality from a third party who is free to disclose the information, as of the date of such third-party disclosure; or (e) is independently developed by the Consortium without the use of any Confidential Information.

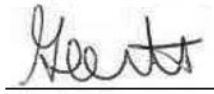
4. **Nondisclosure of Confidential Information.**
Each Covered Person agrees not to disclose to any person outside the Consortium or its affiliates (including for these purposes Chapters and International Affiliates) any Confidential Information, except as provided below. Each Covered Person agrees that he/she will use the Confidential Information only for the purpose of Consortium business. Notwithstanding the foregoing, a Covered Person may disclose the Confidential Information (i) to employees, professional advisors, volunteer scientists and other Covered Persons asked to participate in Consortium business, consultants and agents of the Consortium who have a need to know and who have been informed of this Policy on Confidentiality; or (ii) to the extent required by a court order or by law. Each Covered Person shall use the same degree of care, but not less than a reasonable degree of care, that he/she uses to protect the Consortium's own most highly confidential information to prevent any unauthorized or inadvertent disclosure of Confidential Information. Any individual having question(s) concerning this policy or its applicability in a given situation(s) should address those question(s) to the Director of Research and Education (PVA).

5. **Return of Confidential Information.** Each Covered Person agrees to return to the Chair of the Steering Committee or the Director of Research and Education, all tangible materials incorporating Confidential Information made available or supplied to such Covered Person and all copies and reproductions thereof upon request of the Chair of the Committee and/or the Director of Research and Education (PVA).

CERTIFICATION REGARDING CONFLICTS OF INTEREST and CONFIDENTIALITY OF INFORMATION

Each Covered Person agrees to comply with the provisions of these Policies so long as he/she is a Covered Person. By signing, you are confirming that you have read and understand the above Policy on Conflicts of Interest and Confidentiality and agree to abide by same during all times that you are a Covered Person, as defined in the Policy.

David Chen, MD



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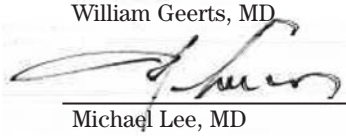
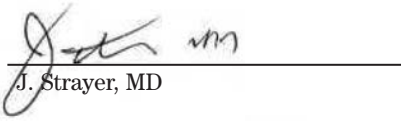
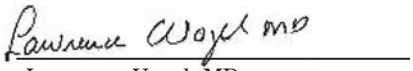


Michael Lee, MD



J. Strayer, MD

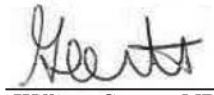


Lawrence Vogel, MD

CERTIFICATION REGARDING CONSORTIUM POLICIES AND PROCEDURES

Each Covered Person agrees to comply with the provisions of the policies and procedures outlined in the Clinical Practice Guideline Orientation Manual so long as he/she is a Covered Person. By signing, you are confirming that you have read and understand the Clinical Practice Guidelines Orientation Manual Policies and Procedures and agree to abide by same during all times that you are a Covered Person.

David Chen, MD



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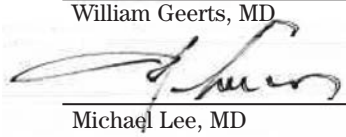
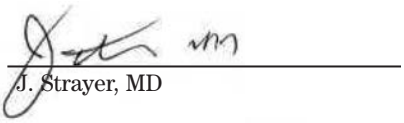


Michael Lee, MD



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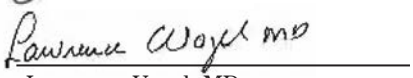

Lawrence Vogel, MD

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