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A Clinical Practice Guideline for the Management of Patients With Acute Spinal Cord Injury: Recommendations on the Type and Timing of Anticoagulant Thromboprophylaxis

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Abstract

Introduction: The objective of this study is to develop evidence-based guidelines that recommend effective, safe and cost-effective thromboprophylaxis strategies in patients with spinal cord injury (SCI).

Methods: A systematic review of the literature was conducted to address key questions relating to thromboprophylaxis in SCI. Based on GRADE (Grading of Recommendation, Assessment, Development and Evaluation), a strong recommendation is worded as "we recommend," whereas a weaker recommendation is indicated by "we suggest."

Results: Based on conclusions from the systematic review and expert panel opinion, the following recommendations were developed: (1) "We suggest that anticoagulant thromboprophylaxis be offered routinely to reduce the risk of thromboembolic

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events in the acute period after SCI;" (2) "We suggest that anticoagulant thromboprophylaxis, consisting of either subcutaneous low-molecular-weight heparin or fixed, low-dose unfractionated heparin (UFH) be offered to reduce the risk of thromboembolic events in the acute period after SCI. Given the potential for increased bleeding events with the use of adjusted-dose UFH, we suggest against this option;" (3) "We suggest commencing anticoagulant thromboprophylaxis within the first 72 hours after injury, if possible, in order to minimize the risk of venous thromboembolic complications during the period of acute hospitalization."

Conclusions: These guidelines should be implemented into clinical practice in patients with SCI to promote standardization of care, decrease heterogeneity of management strategies and encourage clinicians to make evidence-informed decisions.

Keywords

anticoagulant thromboprophylaxis, acute spinal cord injury, traumatic spinal cord injury, spinal cord injury, anticoagulant, thromboprophylaxis, guideline

Summary of Recommendations

We suggest that anticoagulant thromboprophylaxis be offered routinely to reduce the risk of thromboembolic events in the acute period after spinal cord injury.

Quality of Evidence: Low

Strength of Recommendation: Weak

We suggest that anticoagulant thromboprophylaxis, consisting of either subcutaneous low-molecular-weight heparin or fixed, low-dose unfractionated heparin, be offered to reduce the risk of thromboembolic events in the acute period after spinal cord injury. Given the potential for increased bleeding events with the use of adjusted-dose unfractionated heparin, we suggest against this treatment option.

Quality of Evidence: Low

Strength of Recommendation: Weak

We suggest commencing anticoagulant thromboprophylaxis within the first 72 hours after injury, if possible, in order to minimize the risk of venous thromboembolic complications during the period of acute hospitalization.

Quality of Evidence: Low

Strength of Recommendation: Weak

Introduction

Patients with spinal cord injury (SCI) are at an increased risk of venous thromboembolism (VTE) due to hypercoagulability, venous stasis, and venous endothelial injury.[1] Interruption of neurologic impulses and paralysis cause physical and metabolic changes in the leg veins leading to decreased distensibility, increased flow resistance, and vessel injury.[2] Furthermore, immobilization of the lower extremities results in venous stasis and often leads to the formation of venous thrombi. VTE, which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant cause of morbidity and mortality in SCI patients. Venous thrombi most commonly form in the lower extremities; here they may either undergo endogenous fibrinolysis and recanalization or they may propagate and embolize to the pulmonary system.[1] Obstruction of the pulmonary arteries may lead to a number of life-threatening physiologic changes, including impaired gas exchange, cardiovascular compromise and right-sided heart failure. The prevention of DVT and PE is essential in this high-risk population. Prophylactic treatment with anticoagulants and mechanical strategies may significantly reduce the risk of VTE events in these patients. However, there are concerns that use of anticoagulant thromboprophylaxis may increase the risk of bleeding complications and possibly worsen neurologic deficits.[3,4]

This guideline provides evidence-based recommendations on thromboprophylaxis strategies in patients with acute SCI. The systematic review aimed to determine (1) the most effective anticoagulant and/or mechanical methods to prevent VTE and (2) the optimal timing of administering thromboprophylaxis. The ultimate goal of this guideline is to improve outcomes and reduce morbidity in patients with SCI by promoting standardization of care, encouraging clinicians to make more evidence-informed decisions and influencing policy changes to ensure adoption of recommended treatments. An introductory article in this focus issue, titled "A Clinical Practice Guideline for the Management of Acute Spinal Cord Injury: Introduction, Rationale and Scope," provides further background information on SCI and summarizes the rationale, scope, and specific aspects of care covered by this guideline.

These guidelines are intended to be used by emergency room physicians, critical care specialists, anesthesiologists, vascular medicine physicians, neurosurgeons, neurologists, spine surgeons, and hospitalists.

Methods

This guideline was developed under the auspices of AOSpine North America, AOSpine International and the American Association and Congress of Neurological Surgeons. A multidisciplinary guideline development group (GDG) was formed and consisted of clinicians from a broad range of specialties as well as patient representation. The GDG was solely responsible for guideline development and was editorially independent from all funding sources. Members were required to disclose financial and intellectual conflicts of interest (Appendix, Chapter 2). A guideline development protocol, based on the Conference on Guideline Standardization (COGS) checklist,[5,6] was created to outline the rationale and scope of the guideline and to direct its development. Systematic reviews were conducted

based on accepted methodological standards to summarize the evidence informing the recommendations. Details of specific methods used for each topic are outlined in the individual reviews included in this focus issue. Methods outlined by the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group were used to assess the overall quality (strength) of evidence for critical outcomes.[7,8] The GRADE Guideline Development Tool was used to document the guideline development process, rank the importance of outcomes, weigh the benefits and harms of various options, and determine the strength of recommendations.[9-12] Methodologists with no financial or intellectual conflicts of interest worked closely with clinical authors to conduct the systematic reviews and provided methodological expertise on the guideline development process. Guideline development methods are provided in another article included in this focus issue: "Guidelines for the Management of Degenerative Cervical Myelopathy and Acute Spinal Cord Injury: Development Process and Methodology."

Part 1. The Use of Anticoagulant Thromboprophylaxis Strategies

Population Description: Patients with acute SCI

Key Question: Should anticoagulant thromboprophylaxis be employed to reduce the risk of thromboembolic events in the acute period after SCI?

Recommendation 1: We suggest that anticoagulant thromboprophylaxis be offered routinely to reduce the risk of thromboembolic events in the acute period after spinal cord injury.

Quality of Evidence: Low

Strength of Recommendation: Weak

Evidence Summary

A systematic review of the literature was conducted to determine the efficacy, safety, and timing of anticoagulant thromboprophylaxis in patients with acute SCI. One of the main objectives of this review was to evaluate the effectiveness and safety of anticoagulant thromboprophylaxis compared to no prophylaxis or to placebo.

Three randomized controlled trials met inclusion criteria and compared the risk of DVT in patients treated with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) to those receiving no prophylaxis or placebo.[13-15] Based on low level evidence, patients treated with enoxaparin have a lower rate of DVT (5.4%) than those who received no anticoagulant thromboprophylaxis (21.6%) (risk difference [RD] = 16.2, 95% CI = 1.1 to 31.4; risk ratio [RR] = 4.0, 95% CI = 0.91 to 17.6; $P = .09$). Furthermore, rates of DVT did not significantly differ between the UFH and the placebo/no prophylaxis group (1.8% and 3%, respectively in one trial[14] and 50% and 47%, respectively, in another trial[15]). Risk of bleeding, mortality or PE were not reported in any of these 3 trials.

Rationale for Recommendation

The outcomes most critical for decision-making were reduced risk of DVT and PE without increased risk of bleeding and mortality. The overall certainty of the evidence was unanimously rated as low as (1) rates of bleeding, mortality and PE were not compared between various pharmacological strategies and placebo/no prophylaxis and (2) the conclusions surrounding rates of DVT were derived from studies with a serious risk of bias, imprecision, and unknown consistency.

The GDG unanimously agreed that there was no important uncertainty or variability about how much stakeholders value the main outcomes. The group believed that clinicians, patients and payers would similarly value a reduced risk of thromboembolic events due to decreased risk of mortality and morbidity and lower associated costs.

The anticipated desirable effects vary based on which type of anticoagulant strategy is studied (agreement among members of the GDG). Patients who received enoxaparin had a reduced risk of DVT (5.4%) compared to patients who did not receive prophylaxis (21.6%); however, this association did not reach significance using the Fisher exact test. In contrast, there was no difference in risk of DVT in patients treated with UFH versus placebo or no treatment. The GDG discussed that clinical judgment is more important than current evidence to determine whether the anticipated desirable effects are large; despite nonsignificant findings, anticoagulant thromboprophylaxis should be prescribed routinely to reduce the risk of VTE.

The anticipated undesirable effects, specifically treatment-associated bleeding, are uncertain (agreement among members of the GDG). There were no studies that carefully evaluated the difference in risk of adverse events between the treatment and no prophylaxis groups. The GDG unanimously agreed that the relative size of the desirable and undesirable effects also varies based on the type of anticoagulant thromboprophylaxis. For enoxaparin, the anticipated desirable effects are probably large relative to the anticipated undesirable effects as it reduces the risk of DVT without any known safety issues.[13]

In the absence of evidence, the GDG used their clinical expertise to discuss the resources required for anticoagulant thromboprophylaxis. The GDG unanimously agreed that the resources are likely small since these strategies (LMWH or UFH) are relatively simple and inexpensive; this is especially true when considering cost savings associated with reduction in VTE as well as total resources required to manage patients with SCI. Unfortunately, there are no reports on the cost-effectiveness of anticoagulant thromboprophylaxis versus no treatment and so the cost benefit ratio of this option is uncertain (agreement among members of the GDG).

All members of the GDG believed that a recommendation for anticoagulant thromboprophylaxis in patients with SCI would probably reduce health inequities since these treatments are widely available and relatively inexpensive. Furthermore, this option is probably acceptable to key stakeholders and feasible to implement because of its potential benefits in reducing the risk of VTE and because there are no foreseeable barriers.

Considering all these factors, all members of the GDG voted that the desirable consequences probably outweigh the undesirable consequences in most settings; this led to the formation of a weak recommendation for anticoagulant thromboprophylaxis in patients with SCI to reduce the risk of thromboembolic events.

Part 2. Types of Anticoagulant Thromboprophylaxis Strategies

Population Description: Patients with acute SCI

Key Questions:

What anticoagulant thromboprophylaxis should be employed to reduce the risk of thromboembolic events in the acute period after traumatic SCI?

Should enoxaparin versus dalteparin be used to reduce the risk of thromboembolic events in the acute period after traumatic SCI?

Should fixed, low-dose versus adjusted-dose UFH be used to reduce the risk of thromboembolic events in the acute period after traumatic SCI?

Should LMWH versus UFH be used to reduce the risk of thromboembolic events in the acute period after traumatic SCI?

Recommendation 2: We suggest that anticoagulant thromboprophylaxis, consisting of either subcutaneous LMWH or fixed, low-dose UFH, should be offered to reduce the risk of thromboembolic events in the acute period after spinal cord injury. Given the potential for increased bleeding events with the use of adjusted-dose unfractionated heparin, we suggest against this treatment option.

Quality of Evidence: Low

Strength of Recommendation: Weak

Evidence Summary

The systematic review also aimed to compare the efficacy and safety of various anticoagulant strategies: (1) LMWH (enoxaparin) versus LMWH (dalteparin); (2) fixed, low-dose versus adjusted-dose UFH; and (3) LMWH (tinzaparin and dalteparin) versus UFH.

Based on low-quality evidence, there is little to no difference in the rate of DVT (RD = 1.6, 95% CI = −7.3 to 10.5; RR = 1.35, 95% CI = 0.24 to 7.72; $P = 1.0$), PE (no events), bleeding (RD = 2.4, 95% CI = −9.6 to 4.7; RR = 0.45, 95% CI = 0.04 to 4.8; $P = .6$) and mortality (no events in either group) between patients treated with enoxaparin versus dalteparin.[16] There is low-quality evidence that the risk of DVT is 3 times higher in patients who receive fixed, low-dose UFH compared to adjusted-dose heparin (RD = 13.8, 95%CI = −3.6 to 31.2; RR = 3.0, 95%CI = 0.66 to 13.7; $P = .25$).[17] The rate of bleeding, however, is significantly higher in patients treated with adjusted-dose heparin (24.1%) than in those receiving low-dose (0%) (RD = 24.1, 95% CI = 8.6 to 39.7; $P = .01$).[18,19]

Rationale for Recommendation

In order to advise what anticoagulant thromboprophylaxis should be used to minimize the risk of VTE, we compared the efficacy and safety of enoxaparin versus dalteparin, fixed, low-dose versus adjusted-dose UFH and LMWH (tinzaparin or dalteparin) versus UFH. For all comparisons, the outcomes most critical for decision-making were reduced risk of DVT and PE without increased risk of bleeding and mortality.

A single study by Chiou-Tan et al[16] evaluated the efficacy and safety of enoxaparin versus dalteparin. The strength of evidence was low due to serious risk of bias and imprecision (wide confidence intervals or small sample size/low event rates). A single study by Green et al[20] compared the risk of DVT, PE, and mortality between patients treated with fixed, low-dose versus adjusted-dose UFH. The strength of evidence was also low due to risk of bias and imprecision (wide confidence intervals or small sample size/low event rates). The strength of evidence was upgraded from low to moderate for the finding that adjusted-dose UFH significantly increased the risk of bleeding due to large magnitude of effect (RR = 24.1, 95% CI = 8.6 to 39.7). Two studies compared the efficacy and safety of UFH versus LMWH (tinzaparin or dalteparin); all conclusions were graded as low due to risk of bias and imprecision (wide confidence intervals or small sample size/low event rates).[18,19] The GDG unanimously agreed that the overall certainty of the evidence was low.

The GDG felt that there was no important uncertainty or variability about how much stakeholders would value the main outcomes (agreement among members of the GDG). Clinicians, patients, and payers would similarly value a reduced risk of thromboembolic events due to decreased risk of mortality and morbidity and lower associated costs.

The anticipated desirable effects of anticoagulant thromboprophylaxis are reduced risk of DVT, PE, and mortality. The GDG unanimously agreed that the anticipated desirable effects of one anticoagulant thromboprophylaxis strategy compared to another are probably not large: (1) there was no difference in the risk of DVT or PE between patients treated with enoxaparin versus dalteparin or those receiving UFH versus LMWH (tinzaparin or dalteparin) and (2) the risk of DVT in a fixed, low-dose UFH group was 3 times larger than in the adjusted-dose group; however, the confidence interval of the relative risk was wide and spanned one.

The potential undesirable effect of anticoagulant thromboprophylaxis is bleeding. There was no difference in the risk of bleeding or mortality in patients treated with enoxaparin versus dalterparin or UFH versus LMWH (tinzaparin or dalteparin). In contrast, patients receiving adjusted-dose heparin were at a higher risk of bleeding events than patients treated with fixed, low-dose heparin. Based on these findings, the GDG unanimously agreed that the undesirable effects of enoxaparin versus dalteparin and UFH versus LMWH (tinzaparin or dalteparin) are probably small. In contrast, the undesirable effects of adjusted-dose versus fixed, low-dose UFH are probably not small. As a result, the GDG agreed that the size of the anticipated undesirable effects vary based on treatment comparison.

In the absence of evidence, the GDG used their clinical expertise to discuss the resources required for anticoagulant thromboprophylaxis. The GDG unanimously agreed that the resources are likely small since these strategies are relatively simple and

inexpensive; this is especially true when considering cost savings associated with a reduction in VTE as well as total resources required to manage patients with SCI. Unfortunately, there are no reports on the relative cost-effectiveness of various anticoagulant thromboprophylaxis and so the cost-benefit ratio of each strategy is uncertain. The GDG unanimously agreed that the cost of treatment is small but so are the differences in net benefits when comparing various anticoagulant strategies. Since there is limited data to suggest superior outcomes of one treatment over another, direct drug and administration costs may have a large impact on decision making. Future cost-effectiveness studies are required to confirm this hypothesis and must consider costs associated with drug acquisition and administration, as well as costs of managing VTE, increased length of stay, and adverse events.

The GDG believed that a recommendation for a specific anticoagulant thromboprophylaxis strategy in patients with SCI would probably reduce health inequities since these treatments are widely available and relatively inexpensive (agreement among members of the GDG). It is uncertain whether these options are acceptable to key stakeholders: (1) the option of adjusted-dose UFH is probably not acceptable to key stakeholders given the increased risk of bleeding and (2) all other comparisons did not indicate superior outcomes for one approach. The GDG unanimously agreed that these options are probably feasible to implement due to the risk-benefit profile and because there are no foreseeable barriers.

The GDG believed that, for the comparisons of enoxaparin versus dalteparin and LMWH versus UFH, the anticipated desirable and undesirable effects were closely balanced or uncertain (agreement among members of the GDG). This led to the suggestion of either LMWH or fixed, low-dose UFH to minimize the risk of thromboembolic events in the acute period after SCI. When comparing adjusted-dose and fixed, low-dose UFH, the GDG unanimously agreed that the undesirable consequences associated with adjusted-dose UFH probably outweigh the desirable consequences in most settings. This resulted in a suggestion against the use of adjusted-dose UFH.

Part 3. Timing of Initiation of Anticoagulant Thromboprophylaxis Strategies

Population Description: Patients with acute SCI
Key Question: Should thromboprophylaxis be initiated within 72 hours (vs after 72 hours) of SCI?
Recommendation 3: We suggest commencing anticoagulant thromboprophylaxis within the first 72 hours after injury, if possible, in order to minimize the risk of venous thromboembolic complications during the period of acute hospitalization.
Quality of Evidence: Low
Strength of Recommendation: Weak

Evidence Summary

A third objective of the systematic review was to determine the optimal timing to initiate and/or discontinue anticoagulant or mechanical thromboprophylaxis and/or prophylactic inferior vena cava filter following acute SCI. One prospective, nonrandomized observational study evaluated the risks of DVT and PE in patients who received prophylaxis initiated within (early group) versus after (late group) 72 hours of injury.[21] Based on low-quality evidence, the rate of DVT was significantly lower in patients treated early (n = 2) compared with late (n = 46) (RD = 24.1, 95% CI = 17.1 to 31.2; RR = 12.9, 95% CI = 3.2 to 51.2; $P < .001$). There was insufficient evidence to compare the rates of PE between treatment groups.

Rationale for Recommendation

The outcomes most critical for decision-making were reduced risk of DVT and PE without increased risk of bleeding and mortality. The overall level of evidence for the timing of initiation of anticoagulant thromboprophylaxis was rated as low for DVT and insufficient for PE. The evidence for this recommendation was derived from a single study by Aito et al that had no serious risk of bias or indirectness.[21] Consistency of these findings, however, was unknown and the estimate of effect for risk of DVT was imprecise. The level of evidence for risk of DVT was upgraded for strength of association. The GDG unanimously agreed that the overall certainty of the evidence was low.

The GDG unanimously agreed that there was no important uncertainty or variability about how much stakeholders would likely value the main outcomes. Clinicians, patients, and payers would similarly value a reduced risk of thromboembolic events due to decreased risk of mortality and morbidity and lower associated costs.

The anticipated desirable effects are reduced risk of DVT, PE, and mortality. The GDG unanimously agreed that the anticipated desirable effects are probably large as early initiation of thromboprophylaxis ($\leq$72 hours), compared to late initiation (>72 hours), is associated with a significantly reduced risk of DVT. In contrast, the relative risk of PE could not be calculated because no events occurred in either the early or late treatment groups.

The anticipated undesirable effect of early prophylaxis is treatment-associated bleeding. The GDG unanimously agreed that it was uncertain whether the undesirable anticipated effects were small as there were no studies that evaluated the difference in risk of adverse events between an early versus late prophylaxis group. The GDG unanimously agreed that the anticipated effects of early prophylaxis are probably large relative to the undesirable effects.

In the absence of evidence, the GDG used their clinical expertise to discuss the resources required for early anticoagulant thromboprophylaxis. The GDG unanimously agreed that the resources are likely small since these strategies are relatively simple and inexpensive; this is especially true when considering cost savings associated with a reduction in VTE as well as total resources required to manage patients with SCI. Furthermore, there is likely no difference in the resource requirement between early and late prophylaxis. The GDG unanimously agreed that the benefits of early management

(ie, reduced risk of DVT) probably outweigh the risk of bleeding and the relatively small cost of this treatment; however, further studies are required to evaluate the safety and cost-effectiveness of early versus late prophylaxis.

The GDG believed that a recommendation for early initiation of thromboprophylaxis in patients with SCI would probably reduce health inequities since these treatments are widely available and relatively inexpensive (agreement among members of the GDG). Furthermore, this option is probably acceptable to key stakeholders and probably feasible to implement due to its potential benefit in reducing the risk of DVT and because there are no foreseeable barriers.

Considering all of these factors, the GDG voted that the desirable consequences probably outweigh the undesirable consequences in most settings (agreement among members of the GDG); this led to the formation of a weak recommendation for early initiation of prophylaxis in patients with SCI to minimize the risk of venous thromboembolic complications during the period of acute hospitalization.

Part 4. Combined Thromboprophylaxis Strategies

Population Description: Patients with acute SCI

Key Question: Should mechanical or anticoagulant thromboprophylaxis be used in combination or alone?

The GDG agreed not to make a recommendation.

Evidence Summary

The systematic review aimed to determine the comparative effectiveness and safety of mechanical and antithrombotic agent prophylaxis used alone or in combination for preventing DVT and PE after acute SCI. Three randomized controlled trials compared the following treatments: (1) mechanical methods versus mechanical + antiplatelet agents[20] and (2) anticoagulant versus anticoagulant + mechanical methods.[15,22]

Based on low-quality evidence, patients who receive a combination of UFH and electric calf stimulation had a lower risk of DVT than patients treated with UFH alone (RD = 43.3, 95% CI = 15.8 to 70.9; RR = 7.5, 95% CI = 1.06 to 53.03; $P = .02$).[15] There is also a reduced risk of DVT in patients treated with UFH plus intermittent pneumatic compression (IPC) compared with LMWH; however, this difference did not reach statistical significance (RD = 15.4, 95% CI = −3.3 to 34.2; RR = 1.34, 95% CI = 0.92 to 1.95; $P = .12$). Interestingly, patients treated with LMWH alone have a lower risk of PE compared with patients who receive UFH plus IPC (RD = 13.2, 95% CI = 0.9 to 25.4; RR = 0.28, 95% CI = 0.08 to 0.98; $P = .06$).[22]

Finally, based on low-quality evidence, a higher percentage of patients experienced a DVT when treated with IPC alone (40%) compared with IPC plus aspirin and dipyridamole (25%)[20]; however, this difference was not statistically significant (RD = 15.0, 95% CI = −19.9 to 49.9; RR = 1.6, 95% CI = 0.50 to 5.10; $P = .68$).

Rationale for Recommendation

To address this question, we investigated the efficacy and safety of antithrombotic or mechanical thromboprophylaxis used alone or in combination. The outcomes most critical for decision making were reduced risk of DVT and PE without increased risk of bleeding and mortality. In the study by Green et al,[20] there was no difference in the risk of DVT or bleeding between patients treated with IPC (mechanical alone) and those receiving IPC plus aspirin and dipyridamole (mechanical + pharmacological). The strength of evidence for this finding was low because of serious risk of bias and imprecision. Two studies compared outcomes between patients treated with anticoagulant thromboprophylaxis alone versus those receiving a combination of anticoagulant thromboprophylaxis and mechanical treatments.[15,22] A single study by Merli et al[15] reported a higher risk of DVT in patients treated pharmacologically compared with patients receiving both pharmacological and mechanical prophylaxis (RR = 7.5; 95%CI = 1.06 to 53.03; $P = .02$). In the SCITI study, the risk of DVT was also higher in the anticoagulant only (60.3%) group compared with the combined anticoagulant and mechanical group (44.9%), although this difference was not statistically significant.[22] The strength of evidence for these findings was low due to serious risk of bias and imprecision. In the SCITI trial, there was a tendency for patients treated with anticoagulant thromboprophylaxis alone to have a lower rate of PE (5.2%) than those treated with combined anticoagulant and mechanical prophylaxis (18.4%) (RR = 0.28; 95% CI = 0.08 to 0.98; $P = .06$).[22] The strength of evidence for this finding was low due to serious risk of bias and imprecision. Interestingly, based on results from the SCITI study, the outcomes most critical for decision making (DVT and PE) were in opposite directions.[22] This study speculated that anticoagulant thromboprophylaxis may reduce the progression of thrombi from distal to proximal veins, whereas combined anticoagulant thromboprophylaxis and mechanical treatments may protect against initial DVT formation. Once formed, however, compression devices may not reduce the risk of clot propagation and PE formation. The risk of major and minor bleeding and mortality did not differ between treatment groups. Finally, there was no difference in risk of major or minor bleeding or of mortality between patients who received anticoagulant thromboprophylaxis alone versus combined anticoagulant and mechanical thromboprophylaxis. The strength of evidence for these findings was low due to serious risk of bias and imprecision. The GDG unanimously agreed that the overall certainty of evidence was low.

The GDG unanimously agreed that there was no important uncertainty or variability about how much stakeholders would value the main outcomes. The group believed that clinicians, patients, and payers would similarly value a reduced risk of thromboembolic events due to decreased risk of mortality and morbidity and lower associated costs of diagnosis and treatment of VTE.

The anticipated desirable effects are reduced risk of DVT, PE, and mortality. The GDG unanimously agreed that the size of

the anticipated desirable effects vary depending on the type of prophylactic treatment and thromboembolic event: (1) patients who receive UFH alone have a significantly higher risk of DVT than those treated with a combination of UFH and electric calf stimulation; the relative risk of this comparison was large and (2) there was a tendency for patients treated with UFH and IPC to have a higher risk of PE than patients treated with LMWH prophylaxis alone; the effect size was large but the confidence intervals were wide, indicating substantial variability.

The anticipated undesirable effect of combined treatment strategies is bleeding. The GDG unanimously agreed that the undesirable effects are probably small since there was no difference in risk of major or minor bleeding between patients who received pharmacological or mechanical prophylaxis alone compared with a combination of techniques. The GDG believed that the relative size of anticipated desirable and undesirable effects was uncertain given the variability of results across treatment strategies (agreement among members of the GDG).

In the absence of evidence, the GDG used their clinical expertise to discuss the resources required for combined anticoagulant and mechanical thromboprophylaxis. The GDG unanimously agreed that the resources are likely small since these strategies are relatively simple and inexpensive; this is especially true when considering cost savings of diagnosis and treatment of VTE as well as total resources required to manage patients with SCI. The GDG believed that the balance between costs and benefits depend on the type of prophylactic strategy and thromboembolic event: (1) the net benefit of UFH and electric calf stimulation is a reduction in the risk of DVT and (2) the net benefit of LMWH alone (compared with UFH and IPC) is to reduce the risk of PE; in these cases, the cost of the treatment is probably small relative to the net benefit. Unfortunately, there are no cost-effectiveness studies comparing pharmacological or mechanical strategies alone to a combined treatment approach.

The GDG believed that a recommendation for anticoagulant and/or mechanical prophylaxis in patients with SCI would probably reduce health inequities since these treatments are widely available and relatively inexpensive (agreement among members of the GDG). This option of combined versus not combined prophylaxis is probably acceptable to key stakeholders due to potential reduction in the risk of DVT and PE, respectively. Furthermore, the risk of major or minor bleeding does not differ between treatment groups. Finally, these options are probably feasible to implement because of their potential benefits in reducing the risk of VTE; however, there may be barriers to routine mechanical prophylaxis with high adherence.

The GDG believed that, for the comparisons of anticoagulant or mechanical strategies alone versus combined treatment approaches, the anticipated desirable and undesirable effects were closely balanced or uncertain (agreement among members of the GDG). Given the difference in direction for the risk of DVT and PE, the GDG unanimously agreed that they were unable to make a recommendation for or against combined thromboprophylaxis. The GDG agreed that the appropriate treatment strategy should be left to the discretion of the attending physician.

Evidence Gaps and Future Research Recommendations

This guideline has identified important knowledge gaps in the literature and areas of future research. These include (1) uncertainty surrounding adverse effects as many studies did not evaluate the difference in risk of bleeding between various treatment groups; (2) limited evidence on the cost-effectiveness of prophylactic strategies; and (3) a limited understanding on the efficacy and safety of prophylactic IVC insertion. Furthermore, the level of evidence for most of our findings was low, suggesting that we have limited confidence in the estimate of effect and that the true effect may be substantially different; further research is required to confirm these conclusions.

Many of our findings were based on randomized controlled trials; however, significant limitations exist in the current body of evidence. These include (1) small sample sizes and low event rates of DVT and PE make it challenging to compare the efficacy and safety of various prophylactic strategies; (2) significant clinical heterogeneity across studies prevent data pooling and meta-analyses (eg, differences in populations, pharmacological and mechanical treatment protocols, diagnostic methods and outcomes); (3) relative risks and risk differences were often imprecise, likely due to low event numbers; and (4) the majority of studies did not meet one or more criteria of a good-quality randomized controlled trial, including random sequence generation, statement of concealed allocation, independent or blind assessment, adequate sample size, controlling for possible confounding and complete follow-up.

Although these guidelines summarize the type and timing of anticoagulation, there remain several knowledge gaps with respect to VTE prophylaxis. These include the optimal dose and duration of anticoagulant therapies, risks of bleeding following certain treatments and predictors of VTE prophylaxis failures. Future studies are required to fill these critical knowledge gaps.

The cost-effectiveness of DVT/PE prophylaxis in the traumatic SCI population is also largely unknown and should be evaluated across medical systems worldwide. In doing so, it is important to consider anticoagulant costs (including drug-administration costs) as well as costs associated with length of stay and adverse events. Since there is limited data to suggest superior outcomes of one treatment over another, direct drug and administration costs may have a large impact on decision-making; future cost-effectiveness studies are required to confirm this hypothesis.

Beyond the scope of this guideline, other areas of interest related to anticoagulation in SCI include (1) the risk factors and natural history of VTE, (2) the incidence and prevalence of VTE during the acute and rehabilitation phases of management as well as in the postrehabilitation period, (3) the timing of resolution of DVT and PE risk following specific prophylactic strategies, and (4) the value of screening for asymptomatic DVT.

Implementation Considerations

It is expected that this guideline will influence clinical practice and facilitate evidence-based decision-making. Dissemination of the knowledge from this guideline is of critical importance and will be accomplished at multiple levels:

- Presentation at international spine surgery, critical care, neurosurgery, neurology, anesthesiology, and vascular medicine conferences
- Scientific and educational courses in symposium format
- Webinar dissemination of information to a broad audience in an interactive format
- Publication of a focus issue in a peer-reviewed journal
- Submission to the National Guideline Clearinghouse
- AOSpine International Spinal Cord Injury Knowledge Forum

There are no foreseeable barriers to the implementation of these guidelines.

Internal Appraisal and External Review of This Guideline

Vice-chairs of the GDG conducted an internal appraisal of the final guideline using Appraisal of Guidelines for Research & Evaluation II (AGREE II) standards.[23] A multidisciplinary group of stakeholders, including patients, were invited to review the final draft prior to publication. Additional details of these processes are found in the accompanying methods article.

Plans for Updating

The guidelines will be reviewed by the primary sponsor and the vice-chairs at 3 years to a maximum of 5 years following publication. The guideline will be updated when new evidence suggests the need to modify our recommendations. An earlier update will be considered if there are changes in (1) the evidence related to harms and benefits, (2) outcomes that would be considered important for decision-making, (3) ranking of current critical and important outcomes, and (4) available interventions and resources.[24]

Authors' Note

Guideline Development Committee Members: Co-Chair: Michael G. Fehlings, MD, PhD, Neurosurgery; Co-Chair: James Harrop, MD, Neurosurgery; Vice-Chair: Jefferson R. Wilson, MD, PhD, Neurosurgery; Vice-Chair: Anthony Burns, MD, Physical Medicine/Rehabilitation; General Member of Leadership Group: Brian Kwon, MD PhD, Orthopedic Surgery; Systematic Review Coordinator: Lindsay Tetreault, PhD, Research.

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