DOES ANTICOAGULANT THROMBOPROPHYLAXIS INCREASE BLEEDING COMPLICATIONS IN SPINAL SURGERY AND SPINAL CORD INJURY? A SYSTEMATIC REVIEW AND META-ANALYSIS


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Abstract
This study is a systematic review and meta-analysis. The routine use of anticoagulants for the prevention of veno-thromboembolism in spinal patients is controversial and the risk benefit analysis is poorly described. The objective of this study is to collate the current evidence and quantify the risk of bleeding associated with anticoagulant thrombophylaxis in the spinal patient, both in the elective and trauma settings.

Medline, Embase, Cochrane Trial Register databases and the grey literature were searched. Data were pooled via a meta-analysis from randomized trials and cohort studies comparing the rates of spinal epidural haematoma and wound haemorrhagic complications in spinal surgery patients receiving low molecular weight and low dose unfractionated heparin (LMWH/UFH) thrombophylaxis and those not anticoagulated. The risk of bias within individual studies and across all the studies was assessed using the Cochrane risk of bias tools and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool, respectively.

The meta-analysis included 10 studies of 96,042 patients with 1,007 relevant bleeding complications. A significant increase in the risk of extra-spinal wound haemorrhage was found in patients receiving peri-operative LMWH/UFH thrombophylaxis compared to controls (OR 1.56, 95% CI 1.18-2.06, p=0.002, I²=8%). The same comparison revealed no significant increase in the risk of spinal epidural haemorrhage (OR 1.20, 95% CI 0.65-2.22, p=0.56, I²=0%). The quality of evidence for both outcomes was low. There was insufficient data to conclude about the risk of haemorrhagic complications in spinal trauma and in patients receiving non-heparin thrombophylaxis agents.

In conclusion, the results of this study raise concern about a possible increased risk of extraspinal wound haemorrhage associated with LMWH/LDUFH thrombophylaxis in spinal surgery. Level of evidence: Therapeutic level III.

Key words: spine, surgery, spinal cord injury, trauma, thrombophylaxis, anticoagulant, bleeding, epidural spinal haematoma, wound, complication

Introduction
Several expert guidelines¹-³ suggest that low-molecular weight heparin or low dose unfractionated heparin (LMWH/LDUFH) be provided to spinal patients at risk of developing veno-thromboembolism (VTE)⁴-⁹. However, most spinal surgeons are reluctant to use anticoagulant thrombophylaxis²,¹⁰-¹⁷ due to a perceived fear of haemorrhagic
complications in the spinal patient with potentially disastrous consequences. Whether such fear is warranted is unknown due to the paucity of the evidence\textsuperscript{2,15,18-21}. Recognizing such gap in the literature, the North American Spine Society (NASS)\textsuperscript{2} recommend that a priority for future research be an evaluation of the bleeding risk associated with pharmacologic thromboprophylaxis use in spinal patients. Therefore, this systematic review and meta-analysis aim to determine the risk of spinal epidural haematoma (SEH) and extra-spinal wound haemorrhage associated with anticoagulant thromboprophylaxis in patients undergoing spinal surgery in both elective and trauma settings and in spinal trauma patients treated non-operatively. We anticipate the results will aid spinal surgeons in making an informed decision about the risk-benefit ratio of anticoagulant thromboprophylaxis use.

Methods

Data sources and collection: The search strategy included the following electronic databases; the Cochrane Central Register of Controlled Trials (Central), Medline via PubMed and Embase via Ovid. Additional studies were identified by hand searching of relevant bibliographies and journal archives and a search of the grey literature.

Eligibility criteria: Studies were eligible if they reported the number of SEH and wound haemorrhage complications in patients who received pharmacologic thromboprophylaxis (intervention group) versus those who did not (control group). Study designs included were randomised controlled trials (RCTs), quasi-RCTs, cohort studies and case control studies. Eligible patient populations were adult patients (>16 years) undergoing any spinal surgeries via any surgical approach or patients with acute spinal injuries (with or without spinal cord injuries (SCI)) that were treated operatively or non-operatively. Studies were excluded if they were case reports, case series and audits, pertained to needle-based anaesthetic procedures or spontaneous bleeding events or of patients with pre-existing bleeding disorders. Studies were not excluded based on length of follow-up, language, publication status or dates. Regarding intervention, pharmacologic thromboprophylaxis referred to any chemical thrombo-prophylactic agent (including but not limited to LMWH/LDUFH, delivered by any route of administration, initiated at any time and for any duration). Any modality of mechanical thromboprophylaxis or placebo was eligible as control. Outcomes of interest were the number of patients with SEH or wound haemorrhagic complications that were associated with neurological symptoms or required treatment, including either operative or non-operative intervention.

Data synthesis and analysis: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, two authors (A Nguyen and S Tran) performed all phases of this systematic review and meta-analysis in an independent and blinded manner. Disagreements were resolved either by consensus or consultation with the other authors who are a statistician and spinal surgery experts. Data extracted included study and participant characteristics, details of intervention and comparison methods, intra- and extra-spinal bleeding (including wound and non-wound related) outcomes and details about any associated re-operation or treatment and mortality rates. The odd ratios (OR) of the number of patients with bleeding complications versus the number of patients without, between intervention and control groups, were pooled via a random-effect-model meta-analysis using the Review Manager (RevMan 5.3)\textsuperscript{22}. For studies in which zero bleeding complication was observed in either the intervention or control group, a fixed value of 0.5 was added to the numerator.
Forest plots were used to show the OR with 95% confidence interval (CI) for each individual study and pooled across studies. Studies were weighted using the inverse variance method. Statistical heterogeneity was estimated using the I² statistic.

Risk of bias within and across studies: Assessments of individual study quality were performed using the Cochrane Risk of Bias tool for randomised trials and the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool for observational studies. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) software was used to perform an assessment of the quality of the body of evidence across all studies. This assessment was based on the GRADE approach in which the quality of the evidence was judged to range between “no concern” to “very serious concern”, according to five criteria: risk of bias, inconsistency, indirectness, imprecision and publication bias.

Results
Study selection is presented via a PRISMA flow diagram in Figure 1.
Study characteristics and risk of bias assessments are summarised in Table I, and Figures 2 & 3.

Table I. Summary table of characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study details (type, origin, follow up duration)</th>
<th>Sample size Gender proportion (M/F) Mean age (years)</th>
<th>Type of surgery &amp; surgical approach</th>
<th>Pharmacologic prophylaxis versus. No pharmacologic prophylaxis</th>
<th>Outcomes Number of events in intervention group (total): number of events in control group (p-value)</th>
<th>Spinal epidural haematoma (SEH)</th>
<th>Extra-spinal wound haematoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamidi, 2015</td>
<td>RCT Iran 10 months</td>
<td>89 46 M/ 43 F 52 years</td>
<td>Elective instrumental spinal surgery NA</td>
<td>Enoxaparin s.c. 40 mg/day within 12 hours preoperatively vs. compression stockings</td>
<td>nil 0(40): 1 (49)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Comment</td>
<td>One symptomatic haematoma that occurred in a patient post cervical anterior one-level discectomy, due to laceration of external jugular vein. Re-operation was required</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gruber, 1984</td>
<td>RCT Switzerland NA</td>
<td>50 NA 46 years</td>
<td>Herniated lumbar disc surgery NA</td>
<td>Heparin-DHE (2500IU sc.) twice daily, commencing 2hrs preoperatively for at least 7 days or while inpatient vs. placebo</td>
<td>nil 0(25): 2(25)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Comment</td>
<td>In neither group was there early removal of stitches or operative revision of wound on post-operative day 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green, 1982</td>
<td>Quasi-RCT USA NA</td>
<td>28 24 M / 4 F</td>
<td>Acute SCI, including patients undergoing surgery</td>
<td>Aspirin 300 mg bid, and dipyridamole 75 mg TDS and EPCC vs EPCC</td>
<td>NA 1(13): 0(15)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Comment</td>
<td>One patient who bled extensively during surgery and required a 1500 ml transfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rokito, 1996</td>
<td>Quasi-RCT USA 1 year</td>
<td>110 50 M/ 60 F 45 years</td>
<td>Spinal fusion and/or decompression including a small number of trauma cases (unspecified number) Ant., post.&amp; comb.</td>
<td>Warfarin (10mg on the evening before surgery) and TED vs. TEDS +/-SCDs</td>
<td>nil 2(35): 0(75)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Comment</td>
<td>Both patients with increased wound drainage, blood loss &gt;3L immediately post posterior spinal fusions for scoliosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epstein, 1981</td>
<td>Prospective cohort USA NA</td>
<td>121 NA NA</td>
<td>SCI Heparin (5000 IU SC every 12hrs) versus no prophylaxis</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comment</td>
<td>All bleeding was gastro-intestinal. All patients were given steroids +/-cimetidine &amp; antacids concomitantly</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cox, 2014</td>
<td>Retrospective cohort USA NA</td>
<td>1933 1021 M/912 F 54 years</td>
<td>Elective and acute surgery(fusion, decompression, vertebralplasty) including for spinal lesions</td>
<td>LDUFH (5000IU s.c.) ids, immediately pre/post-operative throughout adm. versus an old protocol of chemo prophylaxis commonly delayed until &gt;24 hours post-operation</td>
<td>4(992): 6(941) (p=0.538)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Comment</td>
<td>All SEH required surgical evacuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dillon, 2017</td>
<td>Retrospective cohort USA 30 days</td>
<td>6869 3676 M /3193 F 56 years</td>
<td>Cervical, thoracic and lumbar decompression, fusion and staged spine surgery</td>
<td>LDUFH (5000IU s.c.), LMWH (40 mg of enoxaparin, 2500 or 5000 U of dalteparin, or 2.5mg of fondaparinux) between 1-3 d after surgery versus mechan. prophylaxis</td>
<td>4(1904): 9(4965) (p=0.6)</td>
<td>5(1904): 9(4965) (p=0.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Comment</td>
<td>Neurological deficits occurred in 1 of 4 patients in the chemoprophylaxis group and 7 of 9 patients in the group not receiving chemoprophylaxis. Hemorrhagic complications occurred on postoperative day 3-10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Reference</td>
<td>Study Design</td>
<td>Location</td>
<td>Study Period</td>
<td>Number of Patients</td>
<td>Male: Female</td>
<td>Median Age</td>
<td>Procedures</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------</td>
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<td>--------------</td>
<td>-------------------</td>
<td>-------------</td>
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<td>------------</td>
</tr>
<tr>
<td>Zeng, 2017</td>
<td>Retrospective cohort</td>
<td>China</td>
<td>3 months</td>
<td>1761</td>
<td>929 M: 832 F</td>
<td>NA</td>
<td>Spine surgery including spinal deformity correction Anterior, posterior and combined</td>
</tr>
<tr>
<td>Cunningham, 2011</td>
<td>Retrospective cohort</td>
<td>Canada</td>
<td>3 months</td>
<td>3870</td>
<td>NA</td>
<td>NA</td>
<td>Elective spinal procedures (not specified)</td>
</tr>
<tr>
<td>Sharpe, 2017</td>
<td>Retrospective cohort</td>
<td>USA</td>
<td>45 years</td>
<td>705</td>
<td>508 M: 197 F</td>
<td>NA</td>
<td>Operative stabilization for blunt spine fractures (including SCI) Anterior (45%), posterior (51%), or circumferential (4%)</td>
</tr>
<tr>
<td>Jacobs, 2013</td>
<td>Retrospective cohort</td>
<td>USA</td>
<td>49 years</td>
<td>227</td>
<td>133 M / 94 F</td>
<td>NA</td>
<td>Major spinal surgery for trauma (including SCI)</td>
</tr>
<tr>
<td>Fang, 2011</td>
<td>Retrospective cohort</td>
<td>USA</td>
<td>52 years</td>
<td>80,183</td>
<td>36,775 M: 43, 408 F</td>
<td>52 days</td>
<td>Spinal fusion Anterior, posterior and combined</td>
</tr>
<tr>
<td>Chunhong, 2013</td>
<td>Retrospective cohort</td>
<td>China</td>
<td>NA</td>
<td>87</td>
<td>NA</td>
<td>NA</td>
<td>Thoracolumbar fracture “with nerve injury”, treated with pedicle screw fixation Posterior approach</td>
</tr>
<tr>
<td>Silver, 1974</td>
<td>Retrospective cohort</td>
<td>UK</td>
<td>NA</td>
<td>110</td>
<td>NA</td>
<td>SCI</td>
<td>Phenindione (25-100mg daily) for 12 weeks, 24 hours post injury Vs. no prophylaxis</td>
</tr>
<tr>
<td>El Masri, 1981</td>
<td>Retrospective cohort</td>
<td>UK</td>
<td>NA</td>
<td>102</td>
<td>all male</td>
<td>SCI</td>
<td>Half of patients had major associated injuries</td>
</tr>
</tbody>
</table>

**Comment**

**Note:** Refer to Appendix 2 for full table of characteristics of included studies.

**Abbreviation:** SEH: spinal epidural haematoma, s/c: subcutaneous; Heparin-DHE: heparin- dihydro-ergotamine; SCD: sequential compression device; TED: thromboelastic device; TDS: three times daily; LMWH: low molecular weight heparin; LDUFH: low dose unfractionated heparin; EPCC: external pneumatic calf compression; SCI: spinal cord injury; NA: (information) not available.
A meta-analysis of 10 studies including 96,042 spinal surgery patients receiving thromboprophylaxis in the form of LMWH/LDUFH versus control revealed no fatal haemorrhage in either group. LMWH/LDUFH thromboprophylaxis was found to be associated with a 20% increase in the odds of SEH compared to controls but there was no evidence of an association. On the contrary, there was a strong association between the use of LMWH/LDUFH thromboprophylaxis and the 56% increase in risk of wound haemorrhages. Subgroup analysis did not demonstrate any difference in the ORs between the SEH and extra-spinal bleeding outcomes (\( \chi^2=0.57, p=0.45 \)) (Figure 2).

Sensitivity analysis revealed no significant difference in the results when randomised trials, studies of surgery on trauma patients and anticoagulant therapy were excluded.

Figure 2: Forest plot of comparison: LMWH or LDUFH versus no pharmacologic thromboprophylaxis

Figure 3: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
regimen other than LMWH exclusively were excluded.

*Spinal epidural haematoma*: There were five studies reporting 49 SEHs in 14,788 patients undergoing spinal surgery for elective indications and trauma. Two studies reported three patients who were discharged with persistent neurological deficits, a C6 quadriplegia, lower extremity weakness and bladder dysfunction. Three studies reported that the onset of most SEH events was within a week of surgery, ranging from day 1 to day 56 post operatively. Pooled analysis of the five studies demonstrated that SEH was found in 0.3% of all patients (49 in 14,788), with 0.2% (32 patients) required surgical evacuation and 0.1% (22 patients) with neurological deficits in both intervention and control groups. The LMWH/LDUFH group had a higher proportion of SEH compared to the control group, 0.4% (24 in 5,479 patients) vs. 0.3% (25 in 9,309) respectively. There was a 20% increase in the odds of SEH for those with LMWH/LDUFH prophylaxis compared to controls, OR 1.2 (95% CI, 0.65 to 2.22, low heterogeneity I²=0%), but no evidence of an association (p=0.56) (Figure 2). The absolute effect is zero per 1,000, i.e. no patient in 1,000 patients would have a SEH with LMWH/LDUFH thromboprophylaxis (3 in 1,000), compared to controls (3 in 1,000) (Table II). The quality of the evidence from the five contributing studies is judged as very low due to a very serious concern in the risk of bias and the imprecision of the cumulative data (Table II, Figures 3 & 4).

### Table II: Summary of findings:

Quality of evidence rating for studies comparing spinal epidural haematoma and extras-spinal wound haematoma between spinal surgery patients receiving LMWH/LDUFH thromboprophylaxis compared to those receiving no chemical prophylaxis

<table>
<thead>
<tr>
<th>Patient or population: spinal surgery</th>
<th>Setting: inpatients</th>
<th>Intervention: Low molecular weight heparin (LMWH) or low dose unfractionated heparin (LDUFH)</th>
<th>Comparison: no chemical prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes</strong></td>
<td><em><em>Anticipated absolute effects</em> (95% CI)</em>*</td>
<td><strong>Relative effect (95% CI)</strong></td>
<td><strong>% of participants (studies)</strong></td>
</tr>
<tr>
<td>Spinal epidural haematoma (SEH)</td>
<td>3 per 1,000 (2 to 6)</td>
<td>OR 1.20 (0.65 to 2.22)</td>
<td>14788 (5 observational studies)</td>
</tr>
<tr>
<td>Comment</td>
<td>Only surgery patients included</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extra-spinal wound haematoma</td>
<td>10 per 1,000 (11 to 20)</td>
<td>OR 1.56 (1.18 to 2.06)</td>
<td>89884 (7 observational studies)</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; OR: Odds ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

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Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Confounders not controlled for in observational studies, likely due to the fact that the outcome of interest is considered "secondary outcome" in most included studies.
b. Selection bias (bias in selection of participants into the study) was a concern with the authors excluding certain patients based on participant characteristics observed after the start of intervention.
c. One of the randomized controlled trials did not report method of randomisation and allocation concealment.
d. Wide confidence intervals containing RR of 1 (no effect) and appreciable benefit and harm (RR of 0.75 or 1.25) and/or small number of events, therefore "optimal information size" not met for the number of events.

Extra-spinal wound haemorrhage: There are seven studies reporting 958 extra-spinal wound haemorrhages in 89,884 patients undergoing spinal surgery. The pooled analysis found that 1.6% of patients receiving LMWH/LDUFH prophylaxis (220 in 13,825 patients) were complicated with wound haemorrhages, higher than the 1% proportion (739 in 76,059 patients) found in control patients.
LMWH/LDUFH thromboprophylaxis was associated with a 56% increase in the risk of wound haemorrhages compared to controls, OR 1.56 (95% CI, 1.18 to 2.06; low heterogeneity: I²=8%) and the evidence of an association was strong (p=0.002) (Figure 2). The absolute effect was 5 per 1,000, or 5 more patients would have a wound haemorrhage with LMWH/LDUFH thromboprophylaxis (15 in 1,000), compared to those not anticoagulated (10 in 1,000). The overall quality of the seven contributing studies was judged as low due to a very serious risk of bias in the included studies (Table II, Figures 3 & 4).

Non-heparin thromboprophylaxis in spinal surgery

Warfarin: The only study investigating warfarin in the spinal population is a quasi-randomised trial\(^3\) that reported two patients in the warfarin group with excessive extra-spinal blood loss post spinal reconstruction (Table I). The study was of low quality with a small number of events, unclear details of randomisation, blinding processes and lack of statistical rigour.

Aspirin and dipyridamole: There is only one small quasi-randomised trial available in the spinal literature to-date of aspirin thromboprophylaxis in patients with spinal cord injuries, including some patients who underwent surgeries\(^3\). The authors reported one case of excessive intra-operative bleeding in the aspirin and dipyridamole group. No SEH complications were reported (Table I). The study was of poor quality due to unclear details regarding the randomisation process, blinding, measurement of bleeding outcomes and a lack of statistical rigour.

Rivaroxaban: Chunhong et al\(^3\) conducted a retrospective cohort study of 112 patients undergoing fixation for thoracolumbar fractures and found no difference in wound haematoma rates in a group of patients receiving rivaroxaban compared to those not anticoagulated (Table I). No information regarding SEH was reported and the study has a critical risk of bias due to selection bias, missing data and selective reporting.

Spinal trauma: With regard to spinal trauma, the only study available in the literature to-date is one by Epstein et al of cervical, thoracic and lumbar spinal cord injured patients treated non-operatively\(^3\). The authors reported five gastrointestinal haemorrhages requiring transfusion in 32 patients of the LDUFH group and 19 in 89 patients of the control group (OR 0.68, 95% CI 0.23-2.01). No SEH or wound complications were reported. The study has a critical risk of bias due to the unadjusted use of co-interventions and lack of reporting.

Discussion

Herein, we described the first and largest meta-analysis of pooled data in 96,042 spinal patients regarding the bleeding risk associated with anticoagulant thromboprophylaxis. Our results suggest that the use of LMWH/LDUFH thromboprophylaxis in spinal surgery does not associate with an increased risk of SEH, but is strongly associated with increased rates of extra-spinal wound haematoma. However, our certainty in the effect estimate is limited due to the low quality of the evidence.

Spinal epidural haematoma: Our results are consistent with four other reviews\(^10,15,21,34\) that reported a similarly small proportion of SEH in spinal surgery (0.2-0.7%)\(^34\). These results suggest that spinal surgeons may have over-estimated the risk of post-operative SEH associated with LMWH/LDUFH thromboprophylaxis. A recent survey\(^14\) reported that 47% of spinal surgeons estimated this risk to be up to 5%. Furthermore, we found no evidence that LMWH/LDUFH thromboprophylaxis was associated with an increase in the rate of SEH post spinal surgery. Glotzebecker et al\(^15\) came to the same conclusion in their narrative review.
However, even though the risk of SEH seems negligible, this complication with the potential of permanent neurological deficits could translate to a morbidity burden that is greater than that of a non-fatal VTE event. Gould et al recommended that mechanical prophylaxis be used if the morbidity from a non-fatal bleeding event was believed to be at least two times more severe than those of a non-fatal VTE event.

Extra-spinal wound haemorrhage: No systematic reviews investigating this outcome are available for comparison. However, our data support the survey results of spinal surgeons of whom 25% noted an increase in post-operative wound complications in patients receiving LMWH thromboprophylaxis. In most patients undergoing elective spinal surgery via a posterior approach, excluding patients undergoing surgery for spinal cord injury, anticoagulant prophylaxis seems not justified because of its small VTE risk reduction benefit due to a low estimated incidence (0 to 0.8% for PE and 1-6% for DVT). Similarly, the mortality burden of VTE is estimated to be small, at 0.03%. From a VTE risk reduction point of view, the American College of Chest Physicians (ACCP) estimated that for patients with low VTE risk, the risk reduction of symptomatic events when using LDUH/LMWH thromboprophylaxis was similar to that of mechanical prophylaxis (5-6 per 1,000 patients). Therefore, the ACCP and NASS suggest that mechanical prophylaxis is preferred over LMWH/LDUFH for elective spinal surgery patients. Consistent with this suggestion, most North American spinal surgeons reported not using pharmacologic thromboprophylaxis in elective spine surgery setting. Nevertheless, the National Institute for Health and Care Excellence (NICE), NASS and ACCP recognize that a subgroup of spinal surgery patient carry a high risk of VTE (up to 6%), therefore should be provided anticoagulant thromboprophylaxis. The ACCP estimate that in the high-risk patient, thromboprophylaxis with LDUFH or LMWH has a risk reduction benefit of approximately 27 to 33 per 1,000 patients respectively. Comparing these figures with the estimated risk increase in SEH and wound haemorrhage from our meta-analysis (0 and 6 per 1,000 patients respectively), the benefit-risk ratio appears to favour anticoagulant thromboprophylaxis. However, how to select these high-risk patients for targeted thromboprophylaxis remains an unanswered question. Multiple authors observed a high risk of VTE in surgery with prolonged duration, increased complexity and via the anterior or combined approach. Apart from surgery related factors, patient specific risk factors include advanced age, spinal cord injury, polytrauma, neurological deficits, immobility, previous VTE, malignancy, hypercoagulable state and venous varicosity. As a result, the NASS recommend that patients with the above high-risk factors be provided pharmacologic thromboprophylaxis. Consistent with this recommendation, a survey of 47 North American spinal surgeons revealed that all participating surgeons would use pharmacologic prophylaxis in patients after surgery for spinal trauma, anterior thoracolumbar surgery and in patients with spinal cord injury.

Non-heparin thromboprophylaxis in spinal surgery: The evidence regarding the safety and benefits of non-heparin thromboprophylaxis agents such as aspirin, warfarin and rivaroxaban in the spinal patient population is insufficient and our data did not add to this gap in the literature. However, we recommend that the NASS and ACCP revise their recommendation that warfarin and aspirin be used as alternative thromboprophylaxis agents. As presented above,
such statement is not consistent with the available evidence.

**Spinal trauma**: The ACCP, CSCIM, NICE and the AO Spine1,3,44,45 advised that all acute SCI patients should be provided routine pharmacologic thromboprophylaxis once there is no evidence of active bleeding. Such recommendation was formed on the basis of an estimated large risk reduction benefit20,46-48 of preventing four fatal PE per 1,000 patients treated and 10 times as many non-fatal VTE events as non-fatal bleeding complications3 when anticoagulant is used. Consistent with such recommendation, a recent survey reported a consensus amongst North American spinal surgeons in providing routine pharmacologic prophylaxis for all SCI patients16. Currently, LMWH is recommended as the preferred thromboprophylaxis agent over LDUFH due to superior efficacy20,44,48-50 despite a profound lack of evidence regarding bleeding risk of LMWH or any other anticoagulant thromboprophylaxis in this population. With regard to non-heparin based thromboprophylaxis in spinal cord injured patients, the evidence is scarce. Available in the literature are only two poorly conducted retrospective studies of the use of phenindione in 100 patients reporting inconclusive results9,51. The CSCIM44 recommend against the use of oral vitamin K antagonists such as phenindione in the acute treatment phase of SCI. The main limitation in this meta-analysis is that our certainty in the effect estimates is compromised by the low quality of the evidence of the included studies, most of which are retrospective cohort studies. However, high quality randomised trials with a large number of events in this topic are unlikely to be available in the near future due to costs and difficulty related to conducting strict randomisation in the spinal surgical and trauma population27.

With regard to future research, the optimal time frame of anticoagulant thromboprophylaxis administration, within which it is both safe and effective, needs to be investigated11,17,21,39. Currently, recommended time frames1,44,45 are not supported by robust evidence and often are too vague to be helpful in the clinical setting19,45,32.

**Conclusion**

Our results demonstrated no association between the use of LMWH/LDUFH thromboprophylaxis with increase in the risk of spinal epidural haematoma in patients undergoing spinal surgery. However, there was a strong association between the use LMWH/LDUFH thromboprophylaxis and the risk of wound haemorrhages. The overall quality of current evidence is low.

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