neurocritical care society Neurocrit Care (2016) 24:47–60
DOI 10.1007/s12028-015-0221-y

REVIEW ARTICLE

Prophylaxis of Venous Thrombosis in Neurocritical Care Patients: An Evidence-Based Guideline: A Statement for Healthcare Professionals from the Neurocritical Care Society

Paul Nyquist[1] · Cynthia Bautista[2] · Draga Jichici[3] · Joseph Burns[4] · Sanjeev Chhangani[5] · Michele DeFilippis[6] · Fernando D. Goldenberg[7] · Keri Kim[8] · Xi Liu-DeRyke[9] · William Mack[10] · Kim Meyer[11]

Published online: 8 December 2015

Abstract The risk of death from venous thromboembolism (VTE) is high in intensive care unit patients with neurological diagnoses. This is due to an increased risk of venous stasis secondary to paralysis as well as an increased prevalence of underlying pathologies that cause endothelial activation and create an increased risk of embolus formation. In many of these diseases, there is an associated risk from bleeding because of standard VTE prophylaxis. There is a paucity of prospective studies examining different VTE prophylaxis strategies in the neurologically ill. The lack of a solid evidentiary base has posed challenges for the establishment of consistent and evidence-based clinical practice standards. In response to this need for guidance, the Neurocritical Care Society set out to develop and evidence-based guideline using GRADE to safely reduce VTE and its associated complications.

Keywords Venous thrombus · Stroke · Subarachnoid hemorrhage · Traumatic brain injury · Intracranial hemorrhage · Pulmonary embolus

Abbreviations

VTE	Venous thromboembolism
DVT	Deep venous thrombus
PE	Pulmonary embolus
NICU	Neurological intensive care unit
ICU	Intensive care unit
aSAH	Aneurysmal subarachnoid hemorrhage
ICH	Intracranial hemorrhage
tICH	Traumatic intracranial hemorrhage

The Neurocritical Care Society affirms the value of this guideline as an educational tool for clinicians.

Cynthia Bautista, Draga Jichici, and Paul Nyquist are contributed equally as first authors and were cochairs of the writing group.

Electronic supplementary material The online version of this article (doi:10.1007/s12028-015-0221-y) contains supplementary material, which is available to authorized users.

✉ Paul Nyquist
pnyquis1@jhmi.edu

Cynthia Bautista
cynthia.bautista@ynhh.org

Draga Jichici
draga.jichici@mcmaster.ca

Joseph Burns
joseph.burns@lahey.org

Sanjeev Chhangani
schhangani@mgh.harvard.edu

Michele DeFilippis
michele.defilippis@atlantichealth.org

Fernando D. Goldenberg
fgoldenb@neurology.bsd.uchicago.edu

Keri Kim
skim42@uic.edu

Xi Liu-DeRyke
xiliu713@icloud.com

William Mack
wjmack@gmial.com

Kim Meyer
ksmeyer21@gmail.com

[1] Departments of Neurology, Anesthesia/Critical Care Medicine, Neurosurgery, and General Internal Medicine, John Hopkins School of Medicine, 733 N Broadway, Baltimore, MD 21205, USA

[2] Department of Nursing, Neuroscience CNS, Yale-New Haven Hospital, New Haven, CT 06510, USA

IS	Ischemic stroke
TBI	Traumatic brain Injury
SCI	Spinal cord injury
UFH	Unfractionated heparin
LMWH	Low-molecular-weight heparin
IPC	Intermittent pneumatic compression
CS	Compression stockings
IVF	Inferior venous-caval filter

Introduction

Venous thromboembolism (VTE), comprising deep venous thrombosis (DVT) and pulmonary embolism (PE), is a common problem in critically ill patients who are immobile due to neurologic injury. Complications due to VTE are the third most common cause of cardiovascular death after myocardial infarction and ischemic stroke in all patients [1]. The estimated worldwide incidence of VTE is one to two cases per 1000 annually, although incidences as high as four per 1000 annually have been reported [2–5]. In adults admitted to the ICU, the prevalence of clinically evident DVT and PE is at least 20 per 1000 patients with a frequency of at least 14.5 per 1000 patients despite pharmacologic thromboprophylaxis [6, 7].

The neurologically impaired patient can be cared for in a specialized neurological intensive care unit (NICU) or in a general medical/surgical intensive care unit (ICU). No reliable population-based estimates of VTE risk in this group exist, although the risk is presumed to be high. Multiple factors contribute to this risk, with increased venous stasis from paralysis and prolonged coma chief among them [1, 8, 9]. Additionally, clot formation, propagation, and consolidation are increased in these patients. Brain neoplasms and rheumatologic and inflammatory diseases affecting the central or peripheral nervous system can also cause endothelial activation and promote thrombosis [10–12]. Cerebrovascular disorders such as ischemic and hemorrhagic stroke increase the risk of clot formation through secondary effects on the vascular endothelium [13]. While many of these neurological disorders are relatively common outside the ICU, their relatively low prevalence in the ICU makes large population-based analysis difficult. As a result, there is a paucity of evidence addressing thromboprophylaxis in neurocritical care patients.

The goal of this guideline is to provide clinicians with an evidence-based framework for the appropriate administration of thromboprophylaxis in patients with neurologic illness, with a focus on those requiring neurocritical care. This includes patients with ischemic stroke, intracranial and intraventricular hemorrhage (ICH and IVH), aneurysmal subarachnoid hemorrhage (aSAH), traumatic brain injury (TBI), spinal cord injury (SCI), brain neoplasms, neuromuscular disorders, and patients undergoing neurosurgical and neurovascular interventions.

Methods

The Neurocritical Care Society (NCS) selected a multidisciplinary panel of experts based on their experience in neurocritical care and in the specific subject matter of VTE thromboprophylaxis. A representative from the Society of Critical Care Medicine (SCCM) was recruited and acted as a liaison between the two organizations. Members of the expert panel disclosed all relationships with industry and all other entities relevant to the subject prior to writing or review of the literature. The panel was subdivided into topic-related working groups according to expertise.

With the assistance of a medical librarian, the panel undertook a search of the literature beginning 30 years prior to January 1st, 2013. Randomized controlled studies were given priority and meta-analyses were also included. When such studies were not available case series, retrospective studies were also incorporated into decision-making. The evidence was analyzed and collated using the GRADE scale. Preliminary recommendations were devised

[3] Department of Neurology and Critical Care, McMaster University, 1280 Main Street W, Hamilton, ON L8S 4L8, Canada

[4] Department of Neurology, Lahey Hospital and Medical Center, 41 Mall Road, Burlington, MA 01805, USA

[5] Department of Anesthesia, Critical Care and Pain Medicine, 55 Fruit Street, Boston, MA 02114-2696, USA

[6] Department of Nursing, Morristown Medical Center, 100 Madison Ave, Morristown, NJ 07960, USA

[7] Department of Neurology, The University of Chicago Medicine, 5841 S Maryland Ave, Chicago, IL 60637, USA

[8] Department of Neurosurgery, University of Illinois Hospital & Health Sciences System, 833 South Wood Street, RM164 MC886, Chicago, IL 60612, USA

[9] Division of Surgical Critical Care, Orlando Regional Medical Center, 1414 Kuhl Ave, MP180, Orlando, FL 32806, USA

[10] Department of Neurosurgery, Los Angeles County University Southern California Medical Center, 1520 San Pablo St, Los Angeles, CA 90033, USA

[11] Department of Neurosurgery, University of Louisville Physicians, 401 E Chestnut St, Louisville, KY 40202, USA

by each working group and then reviewed by the expert panel as a whole. Statistical experts from within the NCS and the leadership of the NCS Guidelines Committee then reviewed the guideline in a stepwise progression. The recommendations then underwent external peer review and final approval by the NCS and SCCM, including review by the general membership of the NCS. The final document represents the final analysis of the guidelines subcommittee. All conflict of interest disclosures of the subcommittee are listed in the Disclosures table.

VTE Prophylaxis in Critically Ill Patients with Ischemic Stroke

Ischemic stroke is a major cause of death and disability worldwide and represents one of the most important public health challenges in the world today [14–16]. PE occurs in up to 2.5 % of all ischemic stroke patients, and in the first 3 months after stroke, DVT and PE occur with an incidence of 2.5 and 1.2 %, respectively [17, 18]. In the United States, the prevalence of institutionalized stroke survivors will increase if stroke incidence and the mean length of post-stroke survival do not decrease [14, 15, 19]. In this scenario, VTE will become increasingly prevalent in neurocritical care.

Ischemic stroke patients in the ICU have medical issues associated with high morbidity and mortality and which are rendered even more complex by the need for anticoagulation. This includes the risk of hemorrhagic conversion of large hemispheric strokes in the setting of medical comorbidities requiring anticoagulation, such as atrial fibrillation, heart failure, and VTE. Fortunately, at this time, there are a number of guidelines based on randomized controlled trials specifically addressing these issues, including guidelines from the American Heart Association and the American College of Chest Physicians [20, 21]. Many meta-analyses discuss the use of various forms of pharmacologic thromboprophylaxis including unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), elastic compression stockings (CS), and intermittent venous compression stockings (IPC) in the setting of ischemic stroke [22–25]. In general, all of these analysis support the use of pharmacological VTE prophylaxis with either LWMH or UFH. This can be done safely with concurrent IPC use. Pharmacologic and mechanical prophylaxis may act synergistically [22–25]. In general, the evidence for the use of CS is unclear but their use appears to be safe in spite of an increased risk of skin break down [22–25].

In the CLOTS 3 trial, there was an absolute risk reduction of VTE of 3.6 % (95 % CI 1.4–5.8 %) with the use of IPC beginning 0–3 days post-stroke [24]. Two published prospective trials demonstrate the utility of unfractionated heparin and LMWH [26, 27]. The PREVAIL trial established the superior clinical efficacy of LMWH over unfractionated heparin for DVT prevention in acute ischemic stroke [22]. In the PREVAIL study, LMWH reduced the risk of VTE by 43 % compared with UFH (RR 0.57, 95 % CI 0.44–0.76, $p = 0.0001$) [22].

In general, the risk of serious bleeding complications is low in hospitalized ischemic stroke patients treated with LMWH and UFH [27, 28]. The benefits of external compression of the veins in the lower extremities using CS or IPC has been well characterized [23, 24]. While their use is standard, concern over unintentional damage or provocation of VTE dislodgement is still a concern, particularly in patients who have been immobile prior to application [29, 30].

The use of pharmacological prophylaxis for VTE prevention immediately after hemicraniectomy in the setting of the malignant MCA syndrome is unstudied [31]. In the general neurosurgical literature, UFH and LMWH are considered safe in patients experiencing elective and emergent craniotomy [32–34]. Due to the known risk of VTE in patients who are hemiparetic after an ischemic stroke and the relative safety of UFH and LMWH in patients undergoing hemicraniectomy in general, the use of pharmacological and mechanical prophylaxis in this population is warranted. For patients undergoing endovascular procedures, little data exist to guide practice at this time although it is known that most protocols incorporate large doses of heparin during the procedure and often incorporate rTPA. In these settings waiting 24 hours after the administration of rTPA or hemicraniectomy may be warranted although specific recommendations are not supported by strong clinical evidence.

Recommendations

1. We recommend initiating VTE pharmacoprophylaxis as soon as is feasible in all patients with acute ischemic stroke. (Strong recommendation and high-quality evidence)
2) In patients with acute ischemic stroke and restricted mobility, we recommend prophylactic-dose LMWH over prophylactic-dose UFH in combination with IPC. (Strong recommendation and high-quality evidence)
3) Due to insufficient evidence, the panel could not issue a recommendation regarding the use of CS for VTE prophylaxis although their use does not appear to be harmful.
4) In stroke patients undergoing hemicraniotomy or endovascular procedures, we suggest the use of UFH, LMWH, and/or IPC for VTE prophylaxis in the immediate postsurgical or endovascular epoch except when patients have received rTPA, in which

case prophylaxis should be delayed 24 h. (Weak recommendation and low-quality evidence)

VTE Prophylaxis in Critically Ill Patients with Intracranial Hemorrhage

There is substantial risk of VTE in patients with intracranial hemorrhage (ICH). The prevalence of symptomatic DVT in patients with ICH has been estimated to be 1–2 % in retrospective observational studies [35–38] and was 5 % in the placebo group of the FAST trial [39]. In two prospective observational studies, the incidence of DVT detected by scheduled venous ultrasonography was 20-40 % [40, 41]. The reported incidence of clinically evident PE is approximately 0.5–2 % [35–43]. Half of these may be fatal [17]. In two retrospective large database studies, the risk of VTE in patients with ICH has been estimated to be 2–4 times as high as patients with acute ischemic stroke [36, 38].

A prospective randomized trial comparing thigh-high intermittent pneumatic compression devices (IPC) and graduated compression stockings (GCS) to GCS alone showed a significant reduction in the risk of asymptomatic DVT [44]. The CLOTS3 trial provided additional evidence in support of the effectiveness of IPC for DVT prevention in ICH patients [24]. In addition, the CLOTS1 trial demonstrated that GCS do not prevent VTE and cause skin injury [45].

Small prospective randomized trials have investigated the risks and benefits of VTE pharmacoprophylaxis in patients with ICH. Dickmann and colleagues compared the effects of UFH 5000 IU SQ tid to IPC alone, while Boeer et al. prospectively studied UFH 5000 IU SQ tid. [46, 47] The quality of these studies is limited by their very small size and low frequency of VTE and hemorrhagic events. Two prior meta-analyses have examined the effects of VTE pharmacoprophylaxis in ICH, although the actual number of observations are small and included studies of low quality [47, 48]. A more comprehensive meta-analysis completed by Paciaroni and colleagues [49] included data from the prospective randomized trials of Boeer et al. [46] and Orken et al. [47] as well as two larger single-center retrospective observational studies [50, 51]. This meta-analysis demonstrated a significant reduction in PE associated with UFH or LMWH prophylaxis (RR 0.37, 95 % CI 0.17–0.80, $p = 0.01$) compared with no pharmacoprophylaxis, but no significant differences for DVT, hematoma expansion, or mortality [49]. The 9th edition of the American College of Chest Physicians Guidelines for Antithrombotic Therapy and Prevention of Thrombosis [52] compared rates of VTE reduction derived from higher quality studies of pharmacoprophylaxis in acute ischemic stroke patients to rates of hematoma expansion from the limited quality studies of ICH patients from Boeer et al. [46], Dickmann et al. [53], and Orken et al. [47] as the basis for their recommendations on VTE prophylaxis in ICH. Using these methods, VTE pharmacoprophylaxis reduced the risk of symptomatic DVT (RR 0.31, 95 % CI 0.21–0.42) and PE (RR 0.7, 95 % CI 0.47–1.03) and had no effect on hematoma expansion (RR 0.24, 95 % CI 0.05–1.13) or mortality (RR 1.05, 95 % CI 0.46–2.36) [52].

Recommendations

1. We recommend the use of IPC and/or GCS for VTE prophylaxis over no prophylaxis beginning at the time of hospital admission. (Strong recommendation and high-quality evidence)
2. We suggest using prophylactic doses of subcutaneous UFH or LMWH to prevent VTE in patients with stable hematomas and no ongoing coagulopathy beginning within 48 h of hospital admission. (Weak recommendation and low-quality evidence)
3. We suggest continuing mechanical VTE prophylaxis with IPCs in patients started on pharmacologic prophylaxis. (Weak recommendation low-quality evidence)

VTE Prophylaxis for Critically Ill Patients with Aneurysmal Subarachnoid Hemorrhage

Patients with aneurysmal subarachnoid hemorrhage (aSAH) are at increased risk of developing VTE. The incidence of acute lower leg DVT ranges from 1.5 to 24 % and the incidence of clinically evident pulmonary embolism (PE) is 1.2–2.0 % [37, 54–57]. VTE is associated with nearly double the mean length of stay ($p < 0.001$) and an increased risk of pulmonary/cardiac complications, including stunned myocardium and pulmonary edema (OR 2.8, 95 % CI 2.4–3.2). VTE is also associated with increased infectious complications, including pneumonia and sepsis (OR 2.8, 95 % CI 2.4–3.3), as well as vasospasm (OR 1.3, 95 % CI 1.0–1.6) [54].

Determining appropriate VTE pharmacoprophylaxis strategies is challenging in the presence of acute intracranial bleeding. Patients may also require the placement of an external ventricular drain and/or a craniotomy to secure a ruptured aneurysm, and these procedures also increase risk of bleeding. Few papers address the issue of VTE prophylaxis in aSAH. Most recommendations in this group are based on extension of observation of patients with ischemic stroke.

Early mobilization helps to reduce VTE in patients with good grade aSAH that are neurologically and physiologically stable and who lack clinical and/or sonographic

evidence of vasospasm [58]. Thigh-length GCS do not significantly decrease the risk of DVT and increase the risk of skin lesions [45, 59, 60]. Intermittent pneumatic compression devices (IPCs) decrease the risk of DVT when compared to placebo [59]. Combining IPCs with anticoagulants may have additive effects in regards to VTE prevention [27].

Unfractionated Heparin decreases the risk of DVT [59]. Regimes of 5000 IU SQ either bid or tid have been used, but there are no head to head studies comparing these two modalities in patients with aSAH [59]. It has been suggested but not proven that UFH tid increases the risk of intracranial bleeding and the use of bid dosing may be safer, especially during the first few days after bleeding or after an intracranial surgical procedure [59].

LMWH also decreases the risk of DVT but increases the risk of intracranial bleeding [59, 61, 62]. In neurosurgical patients in general, patients receiving LMWH had statistically significantly higher bleeding rates than those receiving therapy with mechanical modalities ($p < 0.0005$). Patients receiving UFH did not have higher rates of bleeding ($p = 0.40$) [59]. In patients undergoing craniotomy, the benefits of low-dose LMWH are probably outweighed by the harm. LMWH can be expected to prevent between 8 and 36 VTE events per 1000 patients at a cost of 4 to 22 additional subarachnoid bleeds per 1000 patients. Assuming that disability and mortality resulting from SAH is 2 to 3 times greater than with VTE, LMWH could be considered to be more harmful than not providing prophylaxis at all [63].

Many centers routinely screen their patients with an aSAH with lower extremity Doppler ultrasound. This approach is safe but its effectiveness remains to be determined and it is unknown if this approach is cost-effective [28].

Recommendations

1. We recommend VTE prophylaxis with UFH in all patients with aSAH (Strong recommendation and high-quality evidence) except in those with unsecured ruptured aneurysms expected to undergo surgery. (Strong recommendation and low-quality evidence)
2. We recommend initiating IPCs as VTE prophylaxis as soon as patients with aSAH are admitted to the hospital. (Strong recommendation and moderate-quality evidence)
3. We recommend VTE prophylaxis with UFH at least 24 h after an aneurysm has been secured by surgical approach or by coiling. (Strong recommendation and moderate-quality evidence)

VTE Prophylaxis for Critically Ill Patients with Traumatic Brain Injury (TBI)

Among trauma patients admitted to hospital, PE is the third-leading cause of death in those surviving the first 24 h [64]. Severe TBI is an independent risk factor for DVT in polytrauma patients, which is likely due to decreased mobility, prolonged ventilation, and the activation of procoagulant factors [65–67].

The incidence of DVT in patients with severe TBI who have received delayed, or no prophylaxis, ranges from 13 to 17 %. The absence of evidence-based recommendations for trauma patients with ICH has led to inconsistency and institutional variability in thromboprophylaxis management, and there is no consistent standard of care as to the initiation of VTE prophylaxis in the TBI patient population with pharmacoprophylaxis with UFH and LWMH, or mechanical prophylaxis with IPC [68]. Despite the prevalence of VTE in this population, there are no randomized trials of early versus late pharmacoprophylaxis. In a prospective cohort study, Nathans et al. found that a delay greater than 4 days in initiating anticoagulant thromboprophylaxis conferred a threefold increase of DVT and that patients with severe head injury were twice as likely to have thromboprophylaxis delayed greater than 4 days [69]. Further, a retrospective review found that when prophylaxis is delayed more than 48 h, multi-system trauma patients with traumatic ICH are three to four times more likely to develop DVT than those without head injury (RR 2.67, 95 % CI 1.69–4.20) [70].

The anticoagulant of choice in this population requires further study. To date, there are no direct comparisons of LMWH versus UFH for VTE prophylaxis in multi-system trauma patients with severe TBI and ICH. RCTs in multi-system trauma patients with spinal cord injuries and without head injuries have shown that LMWH is more effective at VTE prevention than UFH. Both the 2001 Eastern Association for the Surgery of Trauma (EAST) Guidelines and the 8th edition of the American College of Chest Physicians for VTE prevention in trauma recommend the use of LMWH for VTE prophylaxis in trauma patients without head injury [64, 71]. However, for patients with traumatic ICH, the EAST guidelines state that LMWH has not been sufficiently studied to recommend its use, while the American College of Chest Physicians guidelines suggests LMWH for all trauma patients [64]. The 2007 Brain Trauma Foundation guidelines on thromboprophylaxis in severe traumatic brain injury indicate that the preferred pharmacological agent in this setting is unknown and that there is insufficient evidence to support a recommendation regarding the timing of prophylactic anticoagulation for VTE prophylaxis [72].

Recommendations

1. We recommend initiating IPC for VTE prophylaxis within 24 h of presentation of TBI or within 24 h after completion of craniotomy as supported by evidence in ischemic stroke and postoperative craniotomy. (Weak recommendation and low-quality evidence)
2. We recommend initiating LMWH or UFH for VTE prophylaxis within 24–48 h of presentation in patients with TBI and ICH, or 24 h after craniotomy. (Weak recommendation and low-quality evidence).
3. We recommend using mechanical devices such as IPC for VTE prophylaxis in patients with TBI, based on data from other Neurological injuries such as ischemic stroke. (Weak recommendation and low-quality evidence).

VTE Prophylaxis for Critically Ill Patients with Brain Tumors

Approximately 20–30 % of malignant glioma patients develop VTE, the risk of DVT in patients having a craniotomy for brain tumor is as high as 31 %. Several VTE risk factors have been identified in the brain tumor patient, including glioblastoma multiforme tumor, larger tumor size, leg paresis, older age, lengthy surgery, chemotherapy, and steroid use [73].

DVT prophylaxis in the population can be either mechanical (with IPC) and/or pharmacological (with UFH or LMWH), and hemorrhagic complications must be a consideration when choosing the most appropriate method. Pharmacologic agents are effective at decreasing VTE. Simanek et al. studied 63 patients with high-grade gliomas who wore GCS and then received 40 mg enoxaparin, 2500 IU dalteparin, or 5000 IU dalteparin once daily [73]. Twenty-four percent (15/63) developed VTE (60 % (9/15) had PE and 40 % (6/15) had DVT). VTE developed in 5 % (2/15) who received combined VTE prophylaxis. Hemorrhagic complications were not reported. Robbins et al. administered 5000 IU dalteparin to 42 newly diagnosed GBM patients [74]. There was no VTE or ICH during a median time on dalteparin of 6.3 months. Perry et al. examined the safety of tinzaparin for VTE prophylaxis in 40 patients with newly diagnosed malignant glioma (Grade III–IV) patients [75]. Tinzaparin at a dose of 4500 U SC was initiated within 2 days to 4 weeks postoperatively and continued for up to 12 months. A 5 % (2/40) CNS hemorrhage rate was observed. In another study, Perry et al. randomized patients with newly diagnosed malignant glioma to either dalteparin 5000 IU ($n = 99$) or to placebo ($n = 87$) [16, 76]. In the first 6 months, the incidence of VTE was 9 % in the dalteparin group and 15 % in the placebo group ($p = 0.29$). By 6 months, ICH had occurred in 3 % of the dalteparin group and 0 % of the placebo group ($p = 0.22$), and by 12 months, ICH had occurred in 5 and 1 %, respectively ($p = 0.48$). In contrast, Cage et al. retrospectively reviewed 86 patients with surgical resection of a meningioma; 24 patients received enoxaparin within 48 h after surgery and 62 did not receive prophylaxis [77]. There was no significant difference in the incidence of intracranial hemorrhage in the enoxaparin and control groups (12.5 and 12.9 %, respectively) [77].

Recommendations

In brain tumor patients:

1. We recommend VTE prophylaxis with either LMWH or UFH upon hospitalization for patients with brain tumors who are at low risk for major bleeding and who lack signs of hemorrhagic conversion. (Strong recommendation and moderate-quality evidence).

VTE Prophylaxis for Critically Ill Patients with Spinal Cord Injury

Spinal cord injury (SCI) has been identified as an independent risk factor for DVT, although its prevalence in this population varies across studies due to differences in diagnostic methods [78]. Using clinical criteria, the prevalence of lower extremity DVT varies from 12 to 64 %. Using labeled fibrinogen, plethysmography or phlebography, the incidence of DVT in the absence of prophylaxis, ranges between 50 and 80 % [7]. The overall reported incidence of DVT in paralytic spinal cord injuries varies from 18 to 100 % within first 12 weeks and the frequency of PE is approximately 4.6–14 %. The risk appears greatest during the first 2 weeks after injury and decreases after the first 3 months. Although the frequency decreases even further after 6 months, DVT is still known to occur several months after the injury [78, 79].

The effectiveness of passive or active range of motion exercises and/or compressive stockings in preventing DVT in SCI patients is not known. In a prospective clinical trial, LMWH plus early mobilization (within 72 h) was compared to LMWH plus late mobilization (between 8 and 28 days, mean 12 days) [79]. The incidence of DVT was 2 % in the early group versus 26 % in the late group.

When used alone, IPCs are not sufficient to prevent DVT in SCI patients. Green [80] and Merli [81] reported reductions in DVT by utilizing pneumatic compression stockings (IPCs) in combination with pharmacological prophylaxis. If mechanical or pharmacologic prophylaxis is not possible, screening with duplex ultrasonography should be considered, followed with possible placement of inferior

vena cava (IVC) filter once objective data confirm the presence of DVT. A small series of SCI in high-risk trauma patients reported that IVC filters were effective in preventing symptomatic pulmonary embolism [82–84].

UFH and LMWH are effective at reducing DVT in SCI [80, 85, 86]. The 8th edition of the American College of Chest Physicians Antithrombotic Guidelines suggests use of UFH (Grade 2C) or LMWH (Grade 2C) or mechanical prophylaxis, preferably with IPC (Grade 2C), over no prophylaxis [21]. The use of adjusted dose UFH is recommended by The Consortium for Spinal Medicine [87]. A retrospective cohort study of 90 patients receiving dalteparin (5000 IU QD) or UFH (5000 IU bid) for VTE prophylaxis after acute traumatic SCI revealed no significant difference between the two agents ($p = 0.7054$) in the incidence of VTE (7.78 % overall) and the type of prophylaxis received (UFH 3/47 versus dalteparin 4/43) [88]. A cost analysis demonstrated that adjusted dose UFH is more cost-effective than enoxaparin 30 mg bid [88].

The duration of DVT prophylaxis in persons with SCI has not been fully established. The Consortium for Spinal Medicine recommends the duration of DVT prophylaxis be determined based on the functional status, presence of additional risk factors or medical conditions, and availability of the support services for the patient [89].

Recommendations

In spinal cord injury patients:

1. We recommend initiating VTE prophylaxis as early as possible, within 72 h of injury. (Strong recommendation and high-quality evidence)
2. We recommend against using mechanical measures alone for VTE prophylaxis. (Weak recommendation and low-quality evidence)
3. We recommend LMWH or adjusted dose UFH for VTE prophylaxis as soon as bleeding is controlled. (Strong recommendation and moderate-quality evidence)
4. If VTE prophylaxis with LMWH or UFH is not possible, we suggest mechanical prophylaxis with IPC. (Weak recommendation and low-quality evidence)

VTE Prophylaxis in Critically Ill Patients with Neuromuscular Disease

Hospitalization, critical illness, immobilization, and respiratory failure are well-established and potent risk factors for the development of DVT and PE [90]. Patients who are critically ill due to neuromuscular diseases such as Guillain–Barre Syndrome (GBS) and myasthenia gravis (MG) are thus at high risk for DVT and PE. Data from published case series of patients with GBS, for example, suggest that the risk of symptomatic DVT is approximately 4–7 % and the risk of PE is 3–7 % [91–96]. Accordingly, prophylaxis against VTE complications is a key element of the care of these patients. However, the expert panel did not identify any studies that have systematically examined the effects of any method of VTE prophylaxis in hospitalized or critically ill patients with neuromuscular disease. We therefore chose to extrapolate from the most closely analogous patient groups for which data do exist: hospitalized and critically ill medical patients and patients with spinal cord injury.

A number of meta-analyses have examined the utility of various forms of VTE prophylaxis in hospitalized and critically ill medical patients [90, 97–100]. The most recent and relevant of these examined data from 4 to 8 randomized controlled trials (5206–8605 patients) depending on the outcome [90]. In hospitalized medical patients, compared with no prophylaxis, the use of prophylactic UFH, LMWH, or fondaparinux was associated with a relative risk (RR) of 0.47 (95 % CI 0.22–1) for symptomatic DVT, and RR 0.41 (95 % CI 0.22–0.76) for fatal PE. No statistically significant effects were found for nonfatal PE, major bleeding, and all-cause mortality. When low-dose UFH (5000 SC IU bid-tid) was compared with LMWH, there were no differences in DVT, PE, or mortality. While there was a significant relative risk reduction in major bleeding events associated with LMWH (RR 0.48, 95 % CI 0.24–0.99), the absolute effect was small, amounting to only 5 fewer events per 1,000 patients treated. When bid UFH and tid UFH were compared (indirectly in a mixed-treatment comparison meta-analysis since these regimens have never been compared directly against each other), there were no statistically significant differences in risk of PE, DVT, major bleeding, or mortality.

Mechanical VTE prophylaxis methods are less well studied in hospitalized or critically ill medical patients. In this population, graduated compression stockings (GCS) are not associated with any benefit in terms of prevention of symptomatic DVT, nonfatal PE, or mortality but, largely due to the effect of the results from the CLOTS 1 trial, are associated with a significant increase in the risk of skin breaks/ulcers/blisters/necrosis (RR 4.02, 95 % CI 2.34–6.91) [45, 90]. Both GCS and IPC, when added to pharmacologic prophylaxis, are associated with a reduction in the risk of DVT but not PE in surgical patients [101, 102]. This issue has not been studied in medical patients. There is a suggestion that LMWH may be more effective than bid UFH in preventing symptomatic PE in these patients RR 0.58, 95 % CI 0.34–0.97), but this is driven by the results of a single trial with a small number of PE events [90, 103]. There are no directly relevant data to

guide decisions regarding the duration of VTE prophylaxis in this group of patients in the ICU.

Recommendations

In patients with neuromuscular disease:

1. We recommend using prophylactic doses of UFH (bid or tid) LMWH, or fondaparinux as the preferred method of VTE prophylaxis. (Strong recommendation and moderate-quality evidence)
2. We recommend using IPC for VTE prophylaxis for patients in whom the bleeding risk is deemed too high for pharmacologic prophylaxis. (Strong recommendation and moderate-quality evidence)
3. We suggest combining pharmacologic and mechanical VTE prophylaxis (with IPC) in patients with neuromuscular disease. (Weak recommendation and low-quality evidence)
4. We suggest using GCS only for VTE prophylaxis in patients in whom neither pharmacologic prophylaxis nor IPC use is possible. (Weak recommendation and low-quality evidence)
5. We suggest continuing VTE prophylaxis for an extended period of time, at a minimum for the duration of the acute hospitalization, or until the ability to ambulate returns. (Weak recommendation and very low-quality evidence)

VTE Prophylaxis in Critically Ill Patients Undergoing Neurosurgical and Neurovascular Interventions

Postoperative VTE, such as DVT and PE, is an important cause of morbidity and mortality in the general neurosurgical population. Neurosurgical patients and the procedures they undergo are highly varied; thus, patients undergoing elective spine surgery, brain tumor resection, or invasive intra-arterial procedures have different incidences of VTE. The incidence of DVT ranges from 0 to 15.5 %, with the incidence of PE in up to 15 % in patients undergoing massive reconstructive spinal surgery [104]. In patients undergoing elective spinal surgery, the overall incidence of VTE can vary from 0.3 to 31 % with an estimated overall pooled risk of 2.1 % [105]. The incidences of DVT and PE in this population are 0.4 and 0.4 %, respectively [106–108]. Procedures with unique positioning strategies, such as prone or kneeling, have been associated with zero rates of VTE [31]. In patients undergoing craniotomy for neoplasm, the rate of DVT and PE combined has been reported to be as low as 3 % and as high as 28.0 % in patients with high-grade gliomas [109, 110]. Little data exists for patients with neurologically specific intra-arterial interventions. Patients are anticoagulated during many endovascular procedures, which could potentially affect the occurrence rates for thromboembolic events.

Over the past 40 years, numerous trials have examined measures aimed at reducing VTE in neurosurgical patients including those with craniotomies [34, 59, 111–120]. The most common interventions have included CS, IPC, LMWH, and UFH. Two recent meta-analyses have compared the benefits of VTE prophylaxis to the potential risks, including intracranial hemorrhage [112, 117, 121]. The most recent meta-analysis included 30 prospective studies (18 randomized trials and 12 cohort studies). The conclusion was that LWMH was less effective than IPC (LMWH: RR 0.60, CI 0.44–0.81; ICP: RR 0.41; 95 % CI 0.21–0.78), in later head to head trials there was no difference in efficacy observed (RR 1.97, 95 % CI 0.64–6.06) [117]. This meta-analysis suggests that the use of LWMH and ICP is generally equally safe and effective with a limited risk of ICH [122–128].

However, these large meta-analyses have not illustrated the risks and benefits of VTE prophylaxis in specific subpopulations of neurosurgical patients. UFH is efficacious but has an increased risk of bleeding as compared to other modalities [115, 129]. The prophylactic use of LMWH upon induction of anesthesia in patients undergoing craniotomy, or patients undergoing craniotomy in general, has been associated with increased postoperative ICH [130,59, 61, 62]. In contrast, other studies have reported a similar risk for using LMWH or UFH perioperatively after craniotomy in neurosurgical patients [112, 113, 131]. Large prospective cohort studies suggest the LMWH is safe in the setting of elective craniotomy for glioma as well as craniotomy in general [34, 132, 133]. GCS, IPC with LMWH, or UFH have been used effectively in complicated spinal surgery [33, 112, 113, 115, 129, 134–136]. The use of inferior vena cava (IVC) filters in the setting of severe spinal cord injury or complicated spine surgery has not been adequately investigated. Small case series suggest some benefits in trauma patients; however, most evidence to date suggests limited benefit and a significant possibility of harm [137–140]. The use of IPC plus either LMWH or UFH in elective craniotomy surgery has been shown to be beneficial [59, 112–114, 131, 141].

In those patients who are anticoagulated during intracranial endovascular procedures, the risk of developing intracranial bleeding complications may be increased. There is some evidence that using full heparinization for coiling soon after inserting an EVD does not increase the risk of either symptomatic or asymptomatic EVD-related hemorrhage as long as the activated prothrombin time is kept strictly controlled [142].

Recommendations for Prevention of VTE in Elective Spine Surgery

1. Ambulatory back surgery with unique positioning strategies such as prone or kneeling has been associated with zero rates of VTE, and we suggest considering the use of IPC only for VTE prophylaxis in this surgical population. (Weak recommendation and low-quality evidence)
2. In standard elective spine surgery, we recommend using ambulation with mechanical VTE prophylaxis (GCS or IPC) alone, or combined with LMWH. In patients with increased risk for VTE, we recommend combined therapy with ambulation, GCS or IPC, and LMWH. (Strong recommendation and moderate-quality evidence).
3. Because of the increased risk of bleeding, we recommend using UFH only as an alternative to other methods of VTE prophylaxis. (Strong recommendation and moderate-quality evidence)

Recommendations for Prevention of VTE in Complicated Spinal Surgery

1. We recommend using IPC with LMWH or UFH. (Strong recommendation and moderate-quality evidence)
2. We recommend against the routine use of IVC filters in the setting of severe spinal cord injury or complicated spine surgery. (Weak recommendation and low-quality evidence)
3. We suggest considering a removable prophylactic IVC filter as a temporary measure only in patients with PE and DVT or those with DVT at risk for PE who cannot be anticoagulated. (Weak recommendation and low-quality evidence)

Recommendations for Prevention of VTE in Elective Craniotomy

1. We recommend using IPC with either LMWH or UFH within 24 h after craniotomy. (Strong recommendation and moderate-quality evidence)
2. We recommend the use of IPC with LMWH or UFH within 24 h after standard craniotomy in the setting of glioma resection. (Strong recommendation and moderate-quality evidence)

Recommendations for Prevention of VTE in Elective Intracranial/Intra-arterial Procedures

1. We suggest the use of CS and IPC until the patient is ambulatory. (Weak recommendation and low-quality evidence)
2. We suggest immediate prophylactic anticoagulation with LWMH or UFH. (Weak recommendation and low-quality evidence)

VTE Prevention in Patients Undergoing Intracranial Endovascular Procedures

1. We recommend initiating pharmacoprophylaxis with UFH and/or mechanical VTE prophylaxis with IPC or CS in patients with hemiparesis from stroke or other neurological injury within 24 h if activated prothrombin time is measured. (Weak recommendation and low-quality evidence) If during the proceed rTPA or other thrombolytics are used, then extra caution is advised, and delay of initiation of chemoprophylaxis only for at least 24 h after the procedure should be considered. (Weak recommendation and low-quality evidence)
2. Patients undergoing elective procedures may not require LMWH or UFH, but may benefit from early ambulation, and/or mechanical prophylaxis with IPC or CS. (Weak recommendation- very low-quality evidence)

Conclusions

In setting out to develop evidence-based guidelines for VTE prophylaxis in neurocritical care, the most important challenge the reviewers faced was the paucity of randomized, controlled, and adequately powered clinical trials. It was clear that additional research is needed to effectively resolve the myriad of clinical issues surrounding VTE in this unique care setting. This type of research is challenging due to the complexity of the patients and the rarity of VTE.

These guidelines are a starting point for future clinical research and should be used in determining the best methods of VTE prophylaxis in neurocritical care. The panel made recommendations based on the GRADE system, which allows for the consideration of factors such as risk–benefit ratio, patient values and preferences, and resource availability when determining recommendation strength. It should be noted that weak recommendations in particular need to be individualized to the patient's unique context and carefully evaluated by relevant stakeholders before implementation. The panel encourages guideline users to consider their own clinical experience and the subtleties of the evidence presented as they use these recommendations in their practice. The Neurocritical Care

Society intends for these guidelines to be updated as new evidence arises.

Conflict of interest All of the authors declare that they have no conflicts of interest.

References

1. Goldhaber SZ. Evolving concepts in thrombolytic therapy for pulmonary embolism. Chest. 1992;101(4 Suppl):183S–5S.
2. White RH. The epidemiology of venous thromboembolism. Circulation. 2003;107(23 Suppl 1):I4–8.
3. McRae S. Treatment options for venous thromboembolism: lessons learnt from clinical trials. Thromb J. 2014;12(1):27.
4. Deitelzweig SB, Johnson BH, Lin J, Schulman KL. Prevalence of clinical venous thromboembolism in the USA: current trends and future projections. Am J Hematol. 2011;86(2):217–20.
5. Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost. 2007;98(4):756–64.
6. Patel R, Cook DJ, Meade MO, Griffith LE, Mehta G, Rocker GM, et al. Burden of illness in venous thromboembolism in critical care: a multicenter observational study. J Crit Care. 2005;20(4):341–7.
7. Attia J, Ray JG, Cook DJ, Douketis J, Ginsberg JS, Geerts WH. Deep vein thrombosis and its prevention in critically ill adults. Arch Intern Med. 2001;161(10):1268–79.
8. Rolston JD, Han SJ, Lau CY, Berger MS, Parsa AT. Frequency and predictors of complications in neurological surgery: national trends from 2006 to 2011. J Neurosurg. 2014;120(3):736–45.
9. Kelly J, Rudd A, Lewis R, Hunt BJ. Venous thromboembolism after acute stroke. Stroke. 2001;32(1):262–7.
10. Brandes AA, Scelzi E, Salmistraro G, Ermani M, Carollo C, Berti F, et al. Incidence of risk of thromboembolism during treatment high-grade gliomas: a prospective study. Eur J Cancer. 1997;33(10):1592–6.
11. Dhami MS, Bona RD, Calogero JA, Hellman RM. Venous thromboembolism and high grade gliomas. Thromb Haemost. 1993;70(3):393–6.
12. Bleau N, Patenaude V, Abenhaim HA. Risk of Venous thromboembolic events in pregnant patients with autoimmune diseases: a population-based study. Clin Appl Thromb Hemost. 2014. doi:10.1177/1076029614553023.
13. Elkind MS. Inflammatory mechanisms of stroke. Stroke. 2010;41(10 Suppl):S3–8.
14. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Executive summary: heart disease and stroke statistics–2012 update: a report from the American Heart Association. Circulation. 2012;125(1):188–97.
15. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics–2012 update: a report from the American Heart Association. Circulation. 2012;125(1):e2–220.
16. Roger VL, O'Donnell CJ. Population health, outcomes research, and prevention: example of the American Heart Association 2020 goals. Circ Cardiovasc Qual Outcomes. 2012;5(1):6–8.
17. Wijdicks EF, Scott JP. Pulmonary embolism associated with acute stroke. Mayo Clin Proc. 1997;72(4):297–300.
18. Indredavik B, Rohweder G, Naalsund E, Lydersen S. Medical complications in a comprehensive stroke unit and an early supported discharge service. Stroke. 2008;39(2):414–20.
19. Minino AM, Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2008. Natl Vital Stat Rep. 2011;59(10):1–126.
20. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(3):870–947.
21. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuunemann HJ, et al. Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 Suppl):7S–47S.
22. Sherman DG, Albers GW, Bladin C, Fieschi C, Gabbai AA, Kase CS, et al. The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison. Lancet. 2007;369(9570):1347–55.
23. Dennis M, Sandercock P, Reid J, Graham C, Murray G, Venables G, et al. The effect of graduated compression stockings on long-term outcomes after stroke: the CLOTS trials 1 and 2. Stroke. 2013;44(4):1075–9.
24. Dennis M, Sandercock P, Reid J, Graham C, Forbes J, Murray G. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. Lancet. 2013;382(9891):516–24.
25. Sandercock PA, van den Belt AG, Lindley RI, Slattery J. Antithrombotic therapy in acute ischaemic stroke: an overview of the completed randomised trials. J Neurol Neurosurg Psychiatry. 1993;56(1):17–25.
26. Gould MK, Dembitzer AD, Doyle RL, Hastie TJ, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A meta-analysis of randomized, controlled trials. Ann Intern Med. 1999;130(10):800–9.
27. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, et al. Prevention of venous thromboembolism: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest. 2004;126(3 Suppl):338S–400S.
28. Kamphuisen PW, Agnelli G, Sebastianelli M. Prevention of venous thromboembolism after acute ischemic stroke. J Thromb Haemost. 2005;3(6):1187–94.
29. Mazzone C, Chiodo GF, Sandercock P, Miccio M, Salvi R. Physical methods for preventing deep vein thrombosis in stroke. Cochrane Database Syst Rev. 2004(4):CD001922.
30. Kamran SI, Downey D, Ruff RL. Pneumatic sequential compression reduces the risk of deep vein thrombosis in stroke patients. Neurology. 1998;50(6):1683–8.
31. Nicolaides AN, Fareed J, Kakkar AK, Breddin HK, Goldhaber SZ, Hull R, et al. Prevention and treatment of venous thromboembolism International Consensus Statement (Guidelines according to scientific evidence). Int Angiol. 2006;25(2):101–61.
32. Epstein NE. A review of the risks and benefits of differing prophylaxis regimens for the treatment of deep venous thrombosis and pulmonary embolism in neurosurgery. Surg Neurol. 2005;64(4):295–301.
33. Agnelli G. Prevention of venous thromboembolism after neurosurgery. Thromb Haemost. 1999;82(2):925–30.
34. Frim DM, Barker FG, Poletti CE, Hamilton AJ. Postoperative low-dose heparin decreases thromboembolic complications in neurosurgical patients. Neurosurgery. 1992;30(6):830–2.
35. Goldstein JN, Fazen LE, Wendell L, Chang Y, Rost NS, Snider R, et al. Risk of thromboembolism following acute intracerebral hemorrhage. Neurocrit Care. 2009;10(1):28–34.

36. Gregory PC, Kuhlemeier KV. Prevalence of venous thromboembolism in acute hemorrhagic and thromboembolic stroke. Am J Phys Med Rehabil. 2003;82(5):364–9.
37. Kim KS, Brophy GM. Symptomatic venous thromboembolism: incidence and risk factors in patients with spontaneous or traumatic intracranial hemorrhage. Neurocrit Care. 2009;11(1):28–33.
38. Skaf E, Stein PD, Beemath A, Sanchez J, Bustamante MA, Olson RE. Venous thromboembolism in patients with ischemic and hemorrhagic stroke. Am J Cardiol. 2005;96(12):1731–3.
39. Diringer MN, Skolnick BE, Mayer SA, Steiner T, Davis SM, Brun NC, et al. Thromboembolic events with recombinant activated factor VII in spontaneous intracerebral hemorrhage: results from the factor seven for acute hemorrhagic stroke (FAST) trial. Stroke. 2010;41(1):48–53.
40. Kawase K, Okazaki S, Toyoda K, Toratani N, Yoshimura S, Kawano H, et al. Sex difference in the prevalence of deep-vein thrombosis in Japanese patients with acute intracerebral hemorrhage. Cerebrovasc Dis. 2009;27(4):313–9.
41. Ogata T, Yasaka M, Wakugawa Y, Inoue T, Ibayashi S, Okada Y. Deep venous thrombosis after acute intracerebral hemorrhage. J Neurol Sci. 2008;272(1–2):83–6.
42. Lyden PD, Shuaib A, Lees KR, Davalos A, Davis SM, Diener HC, et al. Safety and tolerability of NXY-059 for acute intracerebral hemorrhage: the CHANT Trial. Stroke. 2007;38(8):2262–9.
43. Maramattom BV, Weigand S, Reinalda M, Wijdicks EF, Manno EM. Pulmonary complications after intracerebral hemorrhage. Neurocrit Care. 2006;5(2):115–9.
44. Lacut K, Bressollette L, Le Gal G, Etienne E, De Tinteniac A, Renault A, et al. Prevention of venous thrombosis in patients with acute intracerebral hemorrhage. Neurology. 2005;65(6):865–9.
45. Dennis M, Sandercock PA, Reid J, Graham C, Murray G, Venables G, et al. Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial. Lancet. 2009;373(9679):1958–65.
46. Boeer A, Voth E, Henze T, Prange HW. Early heparin therapy in patients with spontaneous intracerebral haemorrhage. J Neurol Neurosurg Psychiatry. 1991;54(5):466–7.
47. Orken DN, Kenangil G, Ozkurt H, Guner C, Gundogdu L, Basak M, et al. Prevention of deep venous thrombosis and pulmonary embolism in patients with acute intracerebral hemorrhage. Neurologist. 2009;15(6):329–31.
48. O'Carroll CB, Capampangan DJ, Aguilar MI, Bravo TP, Hoffman-Snyder CR, Wingerchuk DM, et al. What is the effect of low-molecular weight heparin for venous thromboembolism prophylaxis compared with mechanical methods, on the occurrence of hemorrhagic and venous thromboembolic complications in patients with intracerebral hemorrhage? A critically appraised topic. Neurologist. 2011;17(4):232–5.
49. Paciaroni M, Agnelli G, Venti M, Alberti A, Acciarresi M, Caso V. Efficacy and safety of anticoagulants in the prevention of venous thromboembolism in patients with acute cerebral hemorrhage: a meta-analysis of controlled studies. J. Thromb Haemost. 2011;9(5):893–8.
50. Tetri S, Hakala J, Juvela S, Saloheimo P, Pyhtinen J, Rusanen H, et al. Safety of low-dose subcutaneous enoxaparin for the prevention of venous thromboembolism after primary intracerebral haemorrhage. Thromb Res. 2008;123(2):206–12.
51. Wasay M, Khan S, Zaki KS, Khealani BA, Kamal A, Azam I, et al. A non-randomized study of safety and efficacy of heparin for DVT prophylaxis in intracerebral haemorrhage. J Pak Med Assoc. 2008;58(7):362–4.
52. Lansberg MG, O'Donnell MJ, Khatri P, Lang ES, Nguyen-Huynh MN, Schwartz NE, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 Suppl):e601S–36S.
53. Dickmann U, Voth E, Schicha H, Henze T, Prange H, Emrich D. Heparin therapy, deep-vein thrombosis and pulmonary embolism after intracerebral hemorrhage. Klinische Wochenschr. 1988;66(23):1182–3.
54. Kshettry VR, Rosenbaum BP, Seicean A, Kelly ML, Schiltz NK, Weil RJ. Incidence and risk factors associated with in-hospital venous thromboembolism after aneurysmal subarachnoid hemorrhage. J Clin Neurosci. 2014;21(2):282–6.
55. Ray WZ, Strom RG, Blackburn SL, Ashley WW, Sicard GA, Rich KM. Incidence of deep venous thrombosis after subarachnoid hemorrhage. J Neurosurg. 2009;110(5):1010–4.
56. Mack WJ, Ducruet AF, Hickman ZL, Kalyvas JT, Cleveland JR, Mocco J, et al. Doppler ultrasonography screening of poor-grade subarachnoid hemorrhage patients increases the diagnosis of deep venous thrombosis. Neurol Res. 2008;30(9):889–92.
57. Vespa P. Deep venous thrombosis prophylaxis. Neurocrit Care. 2011;15(2):295–7.
58. Olkowski BF, Devine MA, Slotnick LE, Veznedaroglu E, Liebman KM, Arcaro ML, et al. Safety and feasibility of an early mobilization program for patients with aneurysmal subarachnoid hemorrhage. Phys Ther. 2013;93(2):208–15.
59. Collen JF, Jackson JL, Shorr AF, Moores LK. Prevention of venous thromboembolism in neurosurgery: a metaanalysis. Chest. 2008;134(2):237–49.
60. Qaseem A, Chou R, Humphrey LL, Starkey M, Shekelle P. Clinical Guidelines Committee of the American College of P. Venous thromboembolism prophylaxis in hospitalized patients: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2011;155(9):625–32.
61. Abdullah JM, Zainuddin N, Sulong S, Jaafar H, Isa MN. Molecular genetic analysis of phosphatase and tensin homolog and p16 tumor suppressor genes in patients with malignant glioma. Neurosurg Focus. 2003;14(4):e6.
62. Diringer MN, Bleck TP, Claude Hemphill J, 3rd, Menon D, Shutter L, Vespa P, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. Neurocrit Care. 2011;15(2):211–40.
63. Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 Suppl):e227S–77S.
64. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). Chest. 2008;133(6 Suppl):381S–453S.
65. Gearhart MM, Luchette FA, Proctor MC, Lutomski DM, Witsken C, James L, et al. The risk assessment profile score identifies trauma patients at risk for deep vein thrombosis. Surgery. 2000;128(4):631–40.
66. Knudson MM, Ikossi DG, Khaw L, Morabito D, Speetzen LS. Thromboembolism after trauma: an analysis of 1602 episodes from the American College of Surgeons National Trauma Data Bank. Ann Surg. 2004;240(3):490–6.
67. Sharma OP, Oswanski MF, Joseph RJ, Tonui P, Westrick L, Raj SS, et al. Venous thromboembolism in trauma patients. Am Surg. 2007;73(11):1173–80.
68. Imberti D, Ageno W. A survey of thromboprophylaxis management in patients with major trauma. Pathophysiol Haemost Thromb. 2005;34(6):249–54.

69. Nathens AB, McMurray MK, Cuschieri J, Durr EA, Moore EE, Bankey PE, et al. The practice of venous thromboembolism prophylaxis in the major trauma patient. J Trauma. 2007;62(3):557–62.
70. Reiff DA, Haricharan RN, Bullington NM, Griffin RL, McGwin G Jr, Rue LW 3rd. Traumatic brain injury is associated with the development of deep vein thrombosis independent of pharmacological prophylaxis. J Trauma. 2009;66(5):1436–40.
71. Rogers FB, Cipolle MD, Velmahos G, Rozycki G, Luchette FA. Practice management guidelines for the prevention of venous thromboembolism in trauma patients: the EAST practice management guidelines work group. J Trauma. 2002;53(1):142–64.
72. Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, et al. Guidelines for the management of severe traumatic brain injury. II. Hyperosmolar therapy. J Neurotrauma. 2007;24(Suppl 1):S14–20.
73. Simanek R, Vormittag R, Hassler M, Roessler K, Schwarz M, Zielinski C, et al. Venous thromboembolism and survival in patients with high-grade glioma. Neuro-oncology. 2007;9(2):89–95.
74. Robins HI, O'Neill A, Gilbert M, Olsen M, Sapiente R, Berkey B, et al. Effect of dalteparin and radiation on survival and thromboembolic events in glioblastoma multiforme: a phase II ECOG trial. Cancer Chemother Pharmacol. 2008;62(2):227–33.
75. Perry SL, Bohlin C, Reardon DA, Desjardins A, Friedman AH, Friedman HS, et al. Tinzaparin prophylaxis against venous thromboembolic complications in brain tumor patients. J Neurooncol. 2009;95(1):129–34.
76. Perry JR, Julian JA, Laperriere NJ, Geerts W, Agnelli G, Rogers LR, et al. PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma. J Thromb Haemost. 2010;8(9):1959–65.
77. Cage TA, Lamborn KR, Ware ML, Frankfurt A, Chakalian L, Berger MS, et al. Adjuvant enoxaparin therapy may decrease the incidence of postoperative thrombotic events though does not increase the incidence of postoperative intracranial hemorrhage in patients with meningiomas. J Neurooncol. 2009;93(1):151–6.
78. Miranda AR, Hassouna HI. Mechanisms of thrombosis in spinal cord injury. Hematol Oncol Clin North Am. 2000;14(2):401–16.
79. Aito S, Pieri A, D'Andrea M, Marcelli F, Cominelli E. Primary prevention of deep venous thrombosis and pulmonary embolism in acute spinal cord injured patients. Spinal Cord. 2002;40(6):300–3.
80. Green D, Lee MY, Lim AC, Chmiel JS, Vetter M, Pang T, et al. Prevention of thromboembolism after spinal cord injury using low-molecular-weight heparin. Ann Intern Med. 1990;113(8):571–4.
81. Merli GJ, Crabbe S, Doyle L, Ditunno JF, Herbision GJ. Mechanical plus pharmacological prophylaxis for deep vein thrombosis in acute spinal cord injury. Paraplegia. 1992;30(8):558–62.
82. Wilson JT, Rogers FB, Wald SL, Shackford SR, Ricci MA. Prophylactic vena cava filter insertion in patients with traumatic spinal cord injury: preliminary results. Neurosurgery. 1994;35(2):234–9.
83. Khansarinia S, Dennis JW, Veldenz HC, Butcher JL, Hartland L. Prophylactic Greenfield filter placement in selected high-risk trauma patients. J Vasc Surg. 1995;22(3):231–5.
84. Rogers FB, Shackford SR, Ricci MA, Wilson JT, Parsons S. Routine prophylactic vena cava filter insertion in severely injured trauma patients decreases the incidence of pulmonary embolism. J Am Coll Surg. 1995;180(6):641–7.
85. Harris S, Chen D, Green D. Enoxaparin for thromboembolism prophylaxis in spinal injury: preliminary report on experience with 105 patients. Am J Phys Med Rehabil. 1996;75(5):326–7.
86. Geerts WH, Jay RM, Code KI, Chen E, Szalai JP, Saibil EA, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med. 1996;335(10):701–7.
87. Consortium for Spinal Cord Medicine. Prevention of thromboembolism in spinal cord injury. 2nd ed. Washington, DC: Paralyzed Veterans of America; 1999.
88. Worley S, Short C, Pike J, Anderson D, Douglas JA, Thompson K. Dalteparin vs low-dose unfractionated heparin for prophylaxis against clinically evident venous thromboembolism in acute traumatic spinal cord injury: a retrospective cohort study. Journal Spinal Cord Med. 2008;31(4):379–87.
89. Wade WE, Chisholm MA. Venous thrombosis after acute spinal cord injury: cost analysis of prophylaxis guidelines. Am J Phys Med Rehabil. 2000;79(6):504–8.
90. Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, et al. Prevention of vte in nonsurgical patients: Antithrombotic therapy and prevention of thrombosis, 9th ed: american college of chest physicians evidence-based clinical practice guidelines. Chest. 2012;141(2_suppl):e195S-e226S.
91. Gaber TA, Kirker SG, Jenner JR. Current practice of prophylactic anticoagulation in Guillain–Barre syndrome. Clin Rehabil. 2002;16(2):190–3.
92. Henderson RD, Lawn ND, Fletcher DD, McClelland RL, Wijdicks EF. The morbidity of Guillain–Barre syndrome admitted to the intensive care unit. Neurology. 2003;60(1):17–21.
93. Hewer RL, Hilton PJ, Smith AC, Spalding JM. Acute polyneuritis requiring artificial respiration. Q J Med. 1968;37(147):479–91.
94. Ng KK, Howard RS, Fish DR, Hirsch NP, Wiles CM, Murray NM, et al. Management and outcome of severe Guillain–Barre syndrome. QJM Mon J Assoc Physicians. 1995;88(4):243–50.
95. Moore P, James O. Guillain–Barre syndrome: incidence, management and outcome of major complications. Crit Care Med. 1981;9(7):549–55.
96. Ropper AH, Kehne SM. Guillain–Barre syndrome: management of respiratory failure. Neurology. 1985;35(11):1662–5.
97. Alikhan R, Cohen AT. Heparin for the prevention of venous thromboembolism in general medical patients (excluding stroke and myocardial infarction). Cochrane Database Syst Rev. 2009(3):CD003747.
98. King CS, Holley AB, Jackson JL, Shorr AF, Moores LK. Twice vs three times daily heparin dosing for thromboembolism prophylaxis in the general medical population: a metaanalysis. Chest. 2007;131(2):507–16.
99. Phung OJ, Kahn SR, Cook DJ, Murad MH. Dosing frequency of unfractionated heparin thromboprophylaxis: a meta-analysis. Chest. 2011;140(2):374–81.
100. Wein L, Wein S, Haas SJ, Shaw J, Krum H. Pharmacological venous thromboembolism prophylaxis in hospitalized medical patients: a meta-analysis of randomized controlled trials. Arch Intern Med. 2007;167(14):1476–86.
101. Kakkos SK, Caprini JA, Geroulakos G, Nicolaides AN, Stansby GP, Reddy DJ. Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism in high-risk patients. Cochrane Database Syst Rev. 2008(4):CD005258.
102. Sachdeva A, Dalton M, Amaragiri SV, Lees T. Elastic compression stockings for prevention of deep vein thrombosis. Cochrane Database Syst Rev. 2010(7):CD001484.
103. Cook D, Meade M, Guyatt G, Walter S, Heels-Ansdell D, Warkentin TE, et al. Dalteparin versus unfractionated heparin in critically ill patients. N Engl J Med. 2011;364(14):1305–14.
104. Dearborn JT, Hu SS, Tribus CB, Bradford DS. Thromboembolic complications after major thoracolumbar spine surgery. Spine. 1999;24(14):1471–6.

105. Glotzbecker MP, Bono CM, Wood KB, Harris MB. Thromboembolic disease in spinal surgery: a systematic review. Spine. 2009;34(3):291–303.
106. Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA Jr, et al. Prevention of venous thromboembolism. Chest. 2001;119(1 Suppl):132S–75S.
107. Agnelli G. Prevention of venous thromboembolism in surgical patients. Circulation. 2004;110(24 Suppl 1):IV4–12.
108. Smith JS, Fu KMG, Polly DW, Sansur CA, Berven SH, Broadstone PA, et al. Complication rates of three common spine procedures and rates of thromboembolism following spine surgery based on 108,419 procedures: a report from the scoliosis research society morbidity and mortality committee. Spine. 2010;35(24):2140–9.
109. Quevedo JF, Buckner JC, Schmidt JL, Dinapoli RP, O'Fallon JR. Thromboembolism in patients with high-grade glioma. Mayo Clin Proc. 1994;69(4):329–32.
110. Semrad TJ, O'Donnell R, Wun T, Chew H, Harvey D, Zhou H, et al. Epidemiology of venous thromboembolism in 9489 patients with malignant glioma. J Neurosurg. 2007;106(4):601–8.
111. Iorio A, Agnelli G. Low-molecular-weight and unfractionated heparin for prevention of venous thromboembolism in neurosurgery: a meta-analysis. Arch Intern Med. 2000;160(15):2327–32.
112. Agnelli G, Piovella F, Buoncristiani P, Severi P, Pini M, D'Angelo A, et al. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. N Engl J Med. 1998;339(2):80–5.
113. Nurmohamed MT, van Riel AM, Henkens CM, Koopman MM, Que GT, d'Azemar P, et al. Low molecular weight heparin and compression stockings in the prevention of venous thromboembolism in neurosurgery. Thromb Haemost. 1996;75(2):233–8.
114. Paoletti C, Maubec E, Ragguenneau JL, George B, Robine D, Matheron R, et al. [Clinical tolerance of CY 216 (Fraxiparin) in the prevention of thromboembolic accidents after neurosurgery]. Agressologie: revue internationale de physio-biologie et de pharmacologie appliquees aux effets de l'agression. 1989;30(6):363–6.
115. Voth D, Schwarz M, Hahn K, Dei-Anang K, al Butmeh S, Wolf H. Prevention of deep vein thrombosis in neurosurgical patients: a prospective double-blind comparison of two prophylactic regimen. Neurosurgical review. 1992;15(4):289–94.
116. Barnett HG, Clifford JR, Llewellyn RC. Safety of mini-dose heparin administration for neurosurgical patients. J Neurosurg. 1977;47(1):27–30.
117. Bostrom S, Holmgren E, Jonsson O, Lindberg S, Lindstrom B, Winso I, et al. Post-operative thromboembolism in neurosurgery. A study on the prophylactic effect of calf muscle stimulation plus dextran compared to low-dose heparin. Acta Neurochir (Wien). 1986;80(3–4):83–9.
118. Cerrato D, Ariano C, Fiacchino F. Deep vein thrombosis and low-dose heparin prophylaxis in neurosurgical patients. J Neurosurg. 1978;49(3):378–81.
119. Bynke O, Hillman J, Lassvik C. Does peroperative external pneumatic leg muscle compression prevent post-operative venous thrombosis in neurosurgery? Acta Neurochir (Wien). 1987;88(1–2):46–8.
120. Skillman JJ, Collins RE, Coe NP, Goldstein BS, Shapiro RM, Zervas NT, et al. Prevention of deep vein thrombosis in neurosurgical patients: a controlled, randomized trial of external pneumatic compression boots. Surgery. 1978;83(3):354–8.
121. Kshettry VR, Rosenbaum BP, Seicean A, Kelly ML, Schiltz NK, Weil RJ. Incidence and risk factors associated with in-hospital venous thromboembolism after aneurysmal subarachnoid hemorrhage. J Clin Neurosci. 2014;21(2):282–6. doi:10.1016/j.jocn.2013.07.003.
122. Epstein NE. Efficacy of pneumatic compression stocking prophylaxis in the prevention of deep venous thrombosis and pulmonary embolism following 139 lumbar laminectomies with instrumented fusions. J Spinal Disord Tech. 2006;19(1):28–31.
123. Nelson LD Jr, Montgomery SP, Dameron TB Jr, Nelson RB. Deep vein thrombosis in lumbar spinal fusion: a prospective study of antiembolic and pneumatic compression stockings. J South Orthop Assoc. 1996;5(3):181–4.
124. Turpie AG, Hirsh J, Gent M, Julian D, Johnson J. Prevention of deep vein thrombosis in potential neurosurgical patients. A randomized trial comparing graduated compression stockings alone or graduated compression stockings plus intermittent pneumatic compression with control. Arch Intern Med. 1989;149(3):679–81.
125. Wood KB, Kos PB, Abnet JK, Ista C. Prevention of deep-vein thrombosis after major spinal surgery: a comparison study of external devices. J Spinal Disord. 1997;10(3):209–14.
126. Ferree BA, Wright AM. Deep venous thrombosis following posterior lumbar spinal surgery. Spine. 1993;18(8):1079–82.
127. Ferree BA. Deep venous thrombosis following lumbar laminotomy and laminectomy. Orthopedics. 1994;17(1):35–8.
128. Ferree BA, Stern PJ, Jolson RS, Roberts JM, Kahn A III. Deep venous thrombosis after spinal surgery. Spine. 1993;18(3):315–9.
129. Wen DY, Hall WA. Complications of subcutaneous low-dose heparin therapy in neurosurgical patients. Surg Neurol. 1998;50(6):521–5.
130. Dickinson LD, Miller LD, Patel CP, Gupta SK. Enoxaparin increases the incidence of postoperative intracranial hemorrhage when initiated preoperatively for deep venous thrombosis prophylaxis in patients with brain tumors. Neurosurgery. 1998;43(5):1074–81.
131. Constantini S, Kanner A, Friedman A, Shoshan Y, Israel Z, Ashkenazi E, et al. Safety of perioperative minidose heparin in patients undergoing brain tumor surgery: a prospective, randomized, double-blind study. J Neurosurg. 2001;94(6):918–21.
132. Macdonald RL, Amidei C, Baron J, Weir B, Brown F, Erickson RK, et al. Randomized, pilot study of intermittent pneumatic compression devices plus dalteparin versus intermittent pneumatic compression devices plus heparin for prevention of venous thromboembolism in patients undergoing craniotomy. Surg Neurol. 2003;59(5):363–72.
133. Macdonald RL, Amidei C, Lin G, Munshi I, Baron J, Weir BK, et al. Safety of perioperative subcutaneous heparin for prophylaxis of venous thromboembolism in patients undergoing craniotomy. Neurosurgery. 1999;45(2):245–51.
134. Minshall CT, Eriksson EA, Leon SM, Doben AR, McKinzie BP, Fakhry SM. Safety and efficacy of heparin or enoxaparin prophylaxis in blunt trauma patients with a head abbreviated injury severity score > 2. J Trauma. 2011;71(2):396–9.
135. Nurmohamed MT, ten Cate H, ten Cate JW. Low molecular weight heparin(oid)s. Clinical investigations and practical recommendations. Drugs. 1997;53(5):736–51.
136. Rokito SE, Schwartz MC, Neuwirth MG. Deep vein thrombosis after major reconstructive spinal surgery. Spine. 1996;21(7):853–8.
137. Rosner MK, Kuklo TR, Tawk R, Moquin R, Ondra SL. Prophylactic placement of an inferior vena cava filter in high-risk patients undergoing spinal reconstruction. Neurosurg Focus. 2004;17(4):E6.
138. Ozturk C, Ganiyusufoglu K, Alanay A, Aydogan M, Onat L, Hamzaoglu A. Efficacy of prophylactic placement of inferior vena cava filter in patients undergoing spinal surgery. Spine. 2010;35(20):1893–6.

139. Gorman PH, Qadri SF, Rao-Patel A. Prophylactic inferior vena cava (IVC) filter placement may increase the relative risk of deep venous thrombosis after acute spinal cord injury. J Trauma. 2009;66(3):707–12.
140. Britt LD, Zolfaghari D, Kennedy E, Pagel KJ, Minghini A. Incidence and prophylaxis of deep vein thrombosis in a high risk trauma population. Am J Surg. 1996;172(1):13–4.
141. Goldhaber SZ, Dunn K, Gerhard-Herman M, Park JK, Black PM. Low rate of venous thromboembolism after craniotomy for brain tumor using multimodality prophylaxis. Chest. 2002;122(6):1933–7.
142. Hoh BL, Nogueira RG, Ledezma CJ, Pryor JC, Ogilvy CS. Safety of heparinization for cerebral aneurysm coiling soon after external ventriculostomy drain placement. Neurosurgery. 2005; 57(5):845–9.