Background: Our objective was to systematically review the incidence of deep vein thrombosis (DVT) and the efficacy of thromboprophylaxis in critically ill adults, including patients admitted to intensive care units and following trauma, neurosurgery, or spinal cord injury.

Methods: Two authors independently searched MEDLINE, EMBASE, abstract databases, and the Cochrane database. Data were extracted independently in triplicate.

Results: Ten percent to 30% of medical and surgical intensive care unit patients develop DVT within the first week of intensive care unit admission. The use of subcutaneous low-dose heparin reduced the rate by 50% compared with no prophylaxis. Approximately 60% of trauma patients developed DVT within the first 2 weeks of admission. Use of unfractionated heparin appears to decrease the incidence of DVT by only 20%, whereas low-molecular-weight heparin decreases the incidence by a further 30%. The estimated prevalence of DVT in neurosurgical patients not given prophylaxis is 22% to 35%. Mechanical prophylaxis is efficacious, with a pooled odds ratio in 5 randomized trials of 0.28. Use of low-molecular-weight heparin has been investigated as an adjunct to mechanical prophylaxis with a pooled odds ratio of 0.59 compared with graduated compression stockings alone. The incidence of DVT without prophylaxis in acute spinal cord injury patients is likely in excess of 50% to 80%. Studies of prophylaxis in these patients are too sparse to come to any definitive conclusion.

Conclusions: Critically ill patients commonly develop DVT, with rates that vary from 22% to almost 80%, depending on patient characteristics. Methods of prophylaxis proven in one group do not necessarily generalize to other critically ill patient groups. More potent prophylactic regimens other than unfractionated or low-molecular-weight heparins alone may be needed with higher-risk groups.

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PULMONARY embolism (PE) is a common and preventable cause of death among hospitalized adults.1 Up to 95% of cases of PE originate from clots in the deep venous system of the lower limbs, and are often asymptomatic.2,3 Since screening methods are unlikely to be helpful in high-risk patients,5 emphasis has shifted to routine prophylaxis in these individuals.

Cross-sectional studies of medical7 and surgical8 intensive care unit (ICU) patients have shown that approximately 10% have proximal deep vein thrombosis (DVT) on admission to the ICU. Patients are further predisposed to DVT during their ICU stay due to prolonged immobilization, sepsis, and vascular injury from indwelling central venous catheters or other invasive interventions. Similarly, venous thromboembolism (VTE) is an important cause of mortality in patients with spinal cord injury9 or following neurosurgery10,11 or major trauma.12,13 Anticoagulant or mechanical prophylaxis against lower limb DVT is generally recommended for these high-risk populations.1,14,15 However, the Fifth American College of Chest Physicians Consensus Conference on antithrombotic therapy contained no specific section on the treatment and prevention of VTE in critically ill patients.1,16 Herein, we systematically review the evidence for DVT risk and the efficacy of thromboprophylaxis in adults admitted to a medical-surgical ICU, or following major trauma, neurosurgery, or acute spinal cord injury.

METHODS

LITERATURE SEARCH

We systematically searched MEDLINE between January 1966 and August 1998; EMBASE, Conferences Papers Index, and Inside Conferences from 1980 to 1998; and the Cochrane Library's Clinical Trials Reg-
Table 1. Methodological Description of Studies of Deep Vein Thrombosis (DVT)
Among General Medical and Surgical Intensive Care Unit (ICU) Patients*

<table>
<thead>
<tr>
<th>Study, y</th>
<th>Setting and Population</th>
<th>DVT Screening Test</th>
<th>Design</th>
<th>Consecutive Recruitment of Patients</th>
<th>Venographic Confirmation of DVT Screening Test</th>
<th>Masked Assessment</th>
<th>No./Total (%) With Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moser et al., 19 1981</td>
<td>Respiratory ICU; mean age, 64 y; 76% were intubated</td>
<td>Fibrinogen I 125 leg scan daily for 3-6 d</td>
<td>Prospective cohort</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>34/NR</td>
</tr>
<tr>
<td>Cade, 1982</td>
<td>General ICU; mean age, 60 y</td>
<td>Fibrinogen I 125 leg scan daily for 8 d (range, 4-10 d)</td>
<td>Masked RCT</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>119/NR</td>
</tr>
<tr>
<td>Hirsch et al., 1995</td>
<td>Medical ICU; mean age, 64 y; 80% were intubated</td>
<td>Doppler US twice weekly and then once after discharge from ICU</td>
<td>Prospective cohort</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>100/104 (96)</td>
</tr>
<tr>
<td>Marik et al., 1997</td>
<td>Medical-surgical ICU; mean age, 65 y</td>
<td>Duplex US at day 4-7</td>
<td>Prospective cohort</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>102/110 (93)</td>
</tr>
</tbody>
</table>

* NR indicates not reported; RCT, randomized clinical trial; and US, ultrasound.

STUDY SELECTION

The computer search, study selection, and examination of full-text articles was performed independently by 2 authors (J.A. and J.G.R.). We applied the following inclusion criteria to select the studies: (1) Study design: published prospective cohort studies or randomized clinical trials of DVT prophylaxis. (2) Population: critically ill adults admitted to a medical-surgical ICU or those who sustained major trauma or acute spinal cord injury or underwent neurosurgery. (3) Sample size: enrolled at least 10 patients. (4) Outcome: used objective test method(s) to screen for lower limb DVT (fibrinogen I 125 leg scanning, impedance plethysmography, venous ultrasonography [US], or venography).

We excluded abstracts from meetings that were not later published in full form, studies that focused on central venous catheter-related thrombosis, and those with insufficient reporting of DVT rates.

DATA EXTRACTION

Three authors (J.A., W.H.G., and either J.G.R. or D.J.C.) independently extracted data from each study. Disagreements were resolved through consensus. We extracted information on study design; population; DVT screening method(s); use of thromboprophylactic measures; DVT event rates; and study validity, which was assessed using the 5 following quality criteria: (1) study design (randomized clinical trial vs prospective cohort study); (2) whether patients were enrolled in a consecutive manner; (3) completeness of follow-up; (4) use of confirmatory venography after a positive noninvasive test result, as the accepted reference standard; and (5) binding of outcome assessment. In the absence of an accepted scoring system, validity criteria were presented in tabular form.

DATA ANALYSIS

We calculated DVT rates for each study. For studies that compared DVT events with and without prophylaxis, results were expressed as the relative risk reduction (RRR). When appropriate, data were pooled using the Mantel-Haenszel chi² statistic to obtain a summary odds ratio (OR) and its 95% confidence interval (CI). Heterogeneity testing was performed using the Breslow-Day method. Both calculations were performed using the OR 2 × 2 statistical software (J. Julian, PhD, McMaster University, Hamilton, Ontario, 1995). Finally, we summarized our findings using the levels of evidence system developed for the American College of Chest Physicians Antithrombotic Consensus Conference. Our primary aim was to summarize the literature, not to generate recommendations.

RESULTS

Three prospective cohort studies and 1 randomized clinical trial were included (Table 1). Two studies were excluded because screening for DVT was performed only on ICU admission. Among the studies included, more than 70% of patients required mechanical ventilation, and most had an expected ICU stay greater than 48 hours. Two of 3 prospective cohort studies enrolled consecutive patients, but none used venography either to screen for or to confirm the presence of DVT. The rates of DVT are listed in Table 2. In 2 of the 3 cohort studies,
DVT prophylaxis was left to the discretion of the caregivers, although most patients received some form of prophylaxis.20-21 In the study by Moser et al,20 fibrinogen I 125 leg scanning was used for up to 7 days in 34 patients who did not receive prophylaxis; DVT was diagnosed in 9% (95% CI, 2%-26%) of patients. Using serial Doppler US, Hirsch et al20 diagnosed up to 20% (95% CI, 4%-34%) receiving serial Doppler US, Hirsch et al20 diagnosed up to 7 days in 34 patients who did not receive prophylaxis; DVT was diagnosed in 9% (95% CI, 4%-34%) receiving heparin, and 19% receiving no prophylaxis, 7% (95% CI, 4%-26%) receiving heparin, and 19% receiving no prophylaxis, 40% (95% CI, 25%-55%) who received subcutaneous heparin, and 33% (95% CI, 11%-55%) who received mechanical prophylaxis. In total, 48% of all DVT cases were proximal. In the study by Marik et al,21 102 medical and surgical patients were screened using a single Doppler US, and DVT was detected in 25% (95% CI, 0%-55%) of patients who did not receive prophylaxis, 40% (95% CI, 25%-55%) who received subcutaneous heparin, and 33% (95% CI, 11%-55%) who received mechanical prophylaxis. In total, 48% of all DVT cases were proximal. In the study by Marik et al,21 102 medical and surgical patients were screened using a single Doppler US, and DVT was detected in 25% (95% CI, 0%-55%) of patients who did not receive prophylaxis, 40% (95% CI, 25%-55%) who received subcutaneous heparin, and 33% (95% CI, 11%-55%) who received mechanical prophylaxis.

In the double-blind clinical trial by Cade,22 119 critically ill patients were randomized to receive subcutaneous unfractionated heparin at a dose of 5000 U twice daily or placebo injection. Using serial fibrinogen I 125 leg scanning for 5 days, the rates of DVT were 13% in the heparin group and 29% in the placebo group (RRR, 0.65; 95% CI not calculable).

Bleeding complications were not evaluated in any of these 4 studies nor was there any systematic screening process for PE. Marik et al21 performed ventilation-perfusion lung scans on patients whose US results were positive; 4 of 12 patients had high probability scans. Moser et al20 documented PE in 2 of 10 patients who received autopsies, while Hirsch et al20 noted only 1 symptomatic PE in their group of 100 patients.

### TRAUMA PATIENTS

Four randomized clinical trials23-26 and 11 cohort studies27-37 met our inclusion criteria. Although 3 studies were identified as randomized,32,33,35 the patients were assigned to different arms of the study at the physician’s discretion and others were randomized; hence, we have considered these as cohort designs. Six studies were excluded due to insufficient reporting of details relating to the primary end points.38-43 A seventh study used technetium-labeled albumin for screening, a modality that has not been validated for the detection of DVT.44 Redundant reporting led to the exclusion of another study.45 and a ninth study used handheld Doppler flow,46 which did not meet our inclusion criteria.

Three studies reported the incidence of DVT in trauma patients using routine venography. In a prospective cohort study, Geerts et al33 obtained 349 adequate venograms from 716 major trauma patients who did not receive prophylaxis. A total of 201 patients (58%; 95% CI, 52%-63%) were diagnosed as having DVT between days 14 and 21, of which one third of cases were proximal. Nearly all events were silent, with the exception of 3 patients who had symptomatic DVT. An additional 3 patients had fatal PE while under surveillance. In a smaller study, comprising 39 trauma patients who were immobilized for at least 10 days, the incidence of venographically identified DVT was 63% (95% CI, 47%-77%), of which half were proximal.29 Once again, almost all events were silent, with only 1 of 24 patients displaying clinical signs of DVT.

In the earliest study, routine venography was used; the incidence of DVT was 35% (95% CI, 27%-43%).27 However, this study is not generalizable to most trauma patients because all patients were immobilized for at least 3 weeks, 56% had hip fracture as their only injury, and many with lower extremity fractures had their surgery delayed. In addition, deaths and dropouts were not reported, and superficial thrombi were included as outcomes.

Differences in the incidence of DVT across studies is probably due to the fact that US is less sensitive than venography as a screening test for DVT.26 Studies using US in trauma patients tended to document a lower incidence of DVT, ranging from 6% to 30% in the absence of prophylaxis,23,28,32,34,36 while studies using venography had DVT rates between 28% and 63%.24,25,29,35 Other sources of variability included different frequencies of screening and the heterogeneity of patients (ie, single-system vs multisystem trauma).

In most trauma studies, the incidence of PE was poorly described, and systematic screening was not performed. In patient groups who did not receive prophylaxis, the rate of symptomatic PE ranged from 0.7% to 2%, while those who received some type of prophylaxis had a PE rate of 0% to 1.4%.24,25,29,36 In the only study to use systematic screening for PE, Fisher et al23 noted an incidence of 9 (6%) of 159 cases in the control group compared with 6 (4%) of 145 cases in the mechanical prophylaxis group.

Several studies examined the use of anticoagulant prophylaxis in trauma patients. The most rigorous study, a double-blind trial, used routine screening venography.24 There were 344 major trauma patients included who were randomized to receive unfractionated heparin, 5000 U subcutaneously twice daily, or enoxaparin sodium, 30 mg subcutaneously twice daily. Venography was performed between days 10 and 14.
Cohort studies of anticoagulant prophylaxis in trauma patients show variable results. Napolitano et al. reported a DVT rate of 12% with a pneumatic compression device (PCD) or no prophylaxis and 9% with low-dose heparin. Another study found no benefit with heparin compared with no prophylaxis, but only 44 patients were compared.

As described previously, Geerts et al. evaluated enoxaparin and unfractionated heparin in a randomized clinical trial. Forty (31%) of 129 trauma patients randomized to enoxaparin developed DVT compared with 60 (44%) of 136 patients in the heparin group (RRR, 30%; P = 0.01). The RRR for proximal DVT was 58% (P = 0.01), suggesting a greater benefit with low-molecular-weight heparin (LMWH) in preventing proximal DVT. There was a nonsignificant trend toward greater bleeding in the LMWH group (5 patients) than in the heparin group (1 patient) (P = 0.12).

Haentjens et al. randomized 215 patients with orthopedic trauma to fixed- or adjusted-dose nadroparin calcium combined with graduated compression stockings (GCS). When the 144 patients with hip fracture are removed, the incidence of DVT, using duplex screening US at day 10, was similar in both groups (0 of 70 and 0 of 69, respectively). Five patients in each group had major hemorrhage, with no fatal outcomes. In 3 separate studies, Knudson et al. compared either unfractionated heparin or LMWH with mechanical prophylaxis (ie, GCS,
PCD, or foot pump). Using these data, and collapsing the results into a heparin-LMWH arm compared with a mechanical device arm, yielded a pooled OR of 0.46 (95% CI, 0.16-1.29) favoring anticoagulants, with no evidence of heterogeneity across studies (P = .88). This is equivalent to a relative risk of 0.68 or an RRR of 32%.

Among the various methods of mechanical prophylaxis, no study has directly compared GCS with PCDs. Two studies suggest that foot pumps may not be as effective as GCS or PCDs, although these differences do not reach statistical significance.26,35 Two studies compared mechanical prophylaxis with no prophylaxis and found no difference.

NEUROSURGICAL PATIENTS

Thirteen randomized clinical trials and 5 cohort studies met our inclusion criteria (Table 5 and Table 6). Several others failed to meet our inclusion criteria.

Among studies that were included, most patients began receiving mechanical prophylaxis intraoperatively, while anticoagulant prophylaxis was generally commenced after surgery for at least 7 days. In 3 cohort studies,18,62,64 that screened a total of 169 patients with fibrinogen levels of 125 ng/mL before discharge, the pooled DVT event rate was 35% (95% CI, 28%-43%) in the absence of prophylaxis. In 7 randomized controlled trials that included a nonprophylaxis arm,48,50,51,53,56 the pooled incidence of DVT was 22% (95% CI, 18%-26%). Studies that used confirmatory venography indicated that 35% to 50% of the DVT events were proximal. The incidence of symptomatic PE was 0% to 2%.

Only 1 study compared unfractionated heparin with placebo. Cerrato et al66 randomized 100 patients, most of whom underwent craniotomy, to either heparin, 5000 U subcutaneously every 8 hours, or no prophylaxis. Deep vein thrombosis developed in 6% of patients taking heparin and 34% of control group patients (RRR, 82%; P < .001). Bleeding was infrequent in both groups: 2 patients in the heparin group and 1 patient in the control group had postoperative hematomas.

The majority of studies that evaluated mechanical prophylaxis devices included GCS and/or PCDs. Turpie et al67 reported a reduction in DVT during 5 days of postoperative screening from 12% (19%) of 63 among controls to 1% (1.5%) of 65 in the patients who received PCD (P = .001). When follow-up was extended to 2 weeks,61 the incidence of DVT was 20% (21%) of 96 cases in the control group and 8% (8%) of 103 cases among PCD recipients (RRR, 61%; P = .01). The proportion of proximal DVT in the first study was 15%60 and 39% in the second study.51 In a third trial, Turpie et al67 reported that GCS alone or in combination with PCD were comparable, reducing the incidence of DVT from 20% in controls to 9% in patients who received GCS or combined therapy (RRR, 55%; P = .03). In this study, noncompliance was greater with the combined regimen (13%) than with GCS alone (3%). A smaller study52 also failed to observe any difference between GCS and PCD for DVT prevention.

Pooling data from 5 randomized clinical trials that compared mechanical devices to no prophylaxis,48,50,51,53,56 yields an OR of 0.28 (95% CI, 0.17-0.46) in favor of mechanical prophylaxis, with no evidence of heterogeneity across studies (Breslow-Day χ² = 3.4; P = .49). This
LMWH and mechanical prophylaxis have evaluated the combination of LMWH and mechanical prophylaxis, but no clear evidence demonstrates its superiority. One study compared enoxaparin at 40 mg subcutaneously once daily with GCS and found a DVT rate of 33%, while those assigned to GCS had a DVT rate of 57%. In this study, screening venography was used to detect DVT in patients who primarily had surgery for intracranial or spinal neoplasms. Patients assigned to GCS had a DVT rate of 33%, while those assigned to GCS plus enoxaparin at a dose of 40 mg subcutaneously once daily had a DVT rate of 43%.

In a study of 1,000 patients, screening venography detected DVT in the majority of participants with positive screen. In this study, screening venography was used to detect DVT in patients who primarily had surgery for intracranial or spinal neoplasms. Patients assigned to GCS had a DVT rate of 33%, while those assigned to GCS plus enoxaparin at a dose of 40 mg subcutaneously once daily had a DVT rate of 43%.

Table 5. Methodological Description of Studies of Deep Vein Thrombosis (DVT) in Neurosurgical Patients

<table>
<thead>
<tr>
<th>Study, y</th>
<th>Setting and Population</th>
<th>DVT Screening Test</th>
<th>Design</th>
<th>Consecutive Recruitment of Patients</th>
<th>Venographic Confirmation of DVT Screening Test</th>
<th>Masked Assessment</th>
<th>No./Total (%) With Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joffe et al, 1975</td>
<td>Elective intracranial and spinal surgery; tumor, NR; mean age, NR</td>
<td>Fibrinogen I 125 leg scan daily</td>
<td>Prospective cohort</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>23/NR</td>
</tr>
<tr>
<td>Turpie et al, 1977</td>
<td>Mixed intracranial surgery; tumor, 41% cases; mean age, 50 y</td>
<td>Fibrinogen I 125 leg scan daily for at least 5 d</td>
<td>RCT</td>
<td>NR</td>
<td>No</td>
<td>NR</td>
<td>128/161 (80)</td>
</tr>
<tr>
<td>Cerrato et al, 1978</td>
<td>Elective intracranial surgery; tumor, 86% cases; mean age, 52 y</td>
<td>Fibrinogen I 125 leg scan for at least 8 d</td>
<td>RCT</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>100/100 (100)</td>
</tr>
<tr>
<td>Skillman et al, 1980</td>
<td>Mixed intracranial and spinal surgery; tumor, 33% cases; mean age, 49 y</td>
<td>Fibrinogen I 125 leg scan daily until discharge</td>
<td>RCT</td>
<td>NR</td>
<td>90% of participants with positive screen</td>
<td>Yes</td>
<td>95/95 (100)</td>
</tr>
<tr>
<td>Turpie et al, 1985</td>
<td>Mixed intracranial and spinal surgery; tumor, 16% cases; mean age, 51 y</td>
<td>Fibrinogen I 125 leg scan daily; IPG every second day for 2 wk</td>
<td>RCT</td>
<td>Yes</td>
<td>61% of participants with positive screen</td>
<td>NR</td>
<td>199/218 (91)</td>
</tr>
<tr>
<td>Valladares and Hankinson, 1980</td>
<td>Mixed intracranial and spinal surgery; tumor, 35% cases; mean age, NR</td>
<td>Fibrinogen I 125 leg scan at days 1, 3, and 6</td>
<td>Cohort</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>100/100 (100)</td>
</tr>
<tr>
<td>Turpie et al, 1989</td>
<td>Mixed intracranial and spinal surgery; tumor, 56% cases; mean age, NR</td>
<td>Fibrinogen I 125 leg scan daily for 2 wk</td>
<td>RCT</td>
<td>Yes</td>
<td>“Majority” of participants with positive screen</td>
<td>Yes</td>
<td>136/136 (100)</td>
</tr>
<tr>
<td>Weitz et al, 1986</td>
<td>Mixed intracranial surgery; tumor, 64% cases; mean age, NR</td>
<td>Fibrinogen I 125 leg scan daily</td>
<td>RCT</td>
<td>NR</td>
<td>Yes</td>
<td>No</td>
<td>14/NR</td>
</tr>
<tr>
<td>Saltman et al, 1987</td>
<td>Mixed intracranial and spinal surgery; tumor, 11% cases; mean age, NR</td>
<td>Fibrinogen I 125 leg scan daily; IPG every second day</td>
<td>RCT</td>
<td>NR</td>
<td>67% of participants with positive screen</td>
<td>NR</td>
<td>136/158 (86)</td>
</tr>
<tr>
<td>Bucci et al, 1989</td>
<td>Mixed intracranial surgery; tumor, 56% cases; mean age, NR</td>
<td>IPG twice during first postoperative week</td>
<td>RCT</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>NR/70</td>
</tr>
<tr>
<td>Turpie et al, 1989</td>
<td>Mixed intracranial and spinal surgery; tumor, 49% cases; mean age, 51y</td>
<td>Fibrinogen I 125 leg scan daily; IPG every second day for 2 wk</td>
<td>RCT</td>
<td>Yes</td>
<td>70% of participants with positive screen</td>
<td>Yes</td>
<td>239/239 (100)</td>
</tr>
<tr>
<td>Flinn et al, 1989</td>
<td>Mixed intracranial and spinal surgery; tumor, 22% cases; mean age, NR</td>
<td>Duplex US days 3 and 7, then once weekly</td>
<td>Prospective cohort</td>
<td>Yes</td>
<td>59% of participants with positive screen</td>
<td>No</td>
<td>361/361 (100)</td>
</tr>
<tr>
<td>Sawaya et al, 1992</td>
<td>Intracranial surgery; tumor, 100% cases; mean age, 62 y</td>
<td>Fibrinogen I 125 leg scan daily for at least 7 d</td>
<td>Prospective cohort</td>
<td>NR</td>
<td>Some</td>
<td>No</td>
<td>46/NR</td>
</tr>
<tr>
<td>Wautrecht et al, 1995</td>
<td>Intracranial surgery; tumor, 100% cases; mean age, 52 y</td>
<td>Venogram at day 8-10</td>
<td>RCT</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>25/35 (71)</td>
</tr>
<tr>
<td>Flinn et al, 1996</td>
<td>Mixed intracranial and spinal surgery; tumor, NR; mean age, 60 y</td>
<td>Duplex US at days 3 and 7, then once weekly</td>
<td>Prospective cohort</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>NR/2643</td>
</tr>
<tr>
<td>Nurroohamed et al, 1996</td>
<td>Mixed intracranial and spinal surgery; tumor, 84% cases; mean age, 52 y</td>
<td>Duplex US at days 6, 8, and 10; venogram at day 10</td>
<td>RCT</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>345/485 (71)</td>
</tr>
<tr>
<td>Agnelli et al, 1998</td>
<td>Mixed intracranial and spinal surgery; tumor, 97% cases; mean age, 56 y</td>
<td>Venogram at day 7-9</td>
<td>Double-masked RCT</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>259/307 (84)</td>
</tr>
<tr>
<td>Dickinson et al, 1998</td>
<td>Intracranial surgery; tumor, 100% cases; mean age, 47 y</td>
<td>Duplex US at day 1-3, 5-7, 10-14, and 30</td>
<td>RCT</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>66/66 (100)</td>
</tr>
</tbody>
</table>

* NR indicates not reported; RCT, randomized clinical trial; IPG, impedance plethysmography; and US, ultrasound.
rate of 17% (RRR, 48%; P = .004). The rates of proximal DVT were 13% and 5%, respectively, (P = .04). Four major hemorrhagic events were detected in each group (3%), of which 7 were intracranial. These results were supported by a study of predominantly patients who received craniotomies, who were randomized to receive either GCS (DVT rate, 26%) or GCS plus nadroparin, 3075 anti-Xa units subcutaneously once daily (DVT rate, 19%) (RRR, 29%; P = .047). The proximal DVT rates were 12% and 7%, respectively, (P = .06). There were significantly more bleeding events in the patients who received LMWH (4% vs 1%); intracranial bleeding was seen in 6 patients who received combined therapy and 1 patient who received GCS alone.

In a third, unmasked clinical trial, Dickinson et al⁶⁰ randomized 66 patients to receive PCD; enoxaparin, 30 mg subcutaneously twice daily; or PCD plus enoxaparin. Enoxaparin therapy was started immediately before surgery. Five of 38 patients who received LMWH had major intracranial bleeding, whereas this outcome was not encountered in the 19 patients in the PCD group. The higher proportion of intracranial hemorrhages could be attributable to the relatively high dose of enoxaparin used in this study and the administration of a preoperative dose.

Pooling these 3 trials formally yields an OR of 0.59 (95% CI, 0.40-0.85), with no evidence of heterogeneity across studies (Breslow-Day χ² = 6.1; P = .19), favoring the combination of LMWH and mechanical prophylaxis over mechanical prophylaxis alone. This figure is equivalent to a relative risk of 0.74 or an RRR of 26%. The rates of intracranial bleeding in the mechanical and combined mechanical-LMWH arms of these trials were 5 (1.2%) of 417 cases (95% CI, 0.4%-2.5%) and 14 (3.2%) of 432 cases (95% CI, 1.8%-5.1%).

**ACUTE SPINAL CORD INJURY PATIENTS**

Ten studies met the inclusion criteria, of which 4 were randomized clinical trials²⁴-⁷⁷ and 6 were cohort studies³³,⁷⁶-⁸⁰ (Table 7 and Table 8). Six additional studies failed to meet our inclusion criteria.⁸¹-⁸⁶

Five studies evaluated the rate of DVT in the absence of prophylaxis.³⁴,⁷³,⁷⁶-⁷⁸ The only study to use screening venography was by Geerts et al,³³ who documented a DVT incidence of 81% (95% CI, 66%-96%) in a subgroup of trauma patients with acute spinal cord injury. The 4 remaining studies,²⁴,⁷²,⁷⁶-⁷⁸ which used either fibrinogen I 125 leg scanning or impedance plethysmography to screen for DVT, observed rates between 39% and 90%. Merli et al⁷⁸ enrolled 87 patients within 2 weeks of injury and found that 39% had DVT at initial screening. Among those who did not receive active prophylaxis, 47% were subsequently diagnosed as having DVT.

In a small study by Frisbie and Sasahara,⁷² there was no difference between low-dose subcutaneous heparin and no prophylaxis groups. In a cohort study by Merli et al⁷⁹ patients who received the combination of low-dose heparin, GCS, and PCD had a DVT rate of 5% (95% CI, 0%-15%).
Green et al.74 compared fixed low-dose subcutaneous heparin with adjusted-dose heparin (target activated partial thromboplastin time, 1.5 times control). Adjusted-dose heparin reduced the rate of DVT from 21% to 7% (RRR, 67%; P = .25). Seven patients (24%) in the adjusted-dose heparin arm experienced major bleeding complications, none of which were intracranial or fatal, compared with no bleeding events in the low-dose heparin arm.

Only 1 study compared LMWH (tinzaparin sodium, 3500 U subcutaneously once daily) with low-dose unfractioned heparin taken subcutaneously 3 times a day.75 In this randomized trial of only 35 patients, tinzaparin reduced the rate of DVT from 16% to 0%. This difference only reached statistical significance when all adverse events (ie, DVT and major bleeding) were combined (P = .02). However, a subsequent prospective cohort study by Green et al.80 did not confirm these findings.

<table>
<thead>
<tr>
<th>Study, y</th>
<th>Setting and Population</th>
<th>DVT Screening Test</th>
<th>Design</th>
<th>Consecutive Recruitment of Patients</th>
<th>Venographic Confirmation of DVT Screening Test</th>
<th>Masked Assessment</th>
<th>No./Total (%) With Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brach et al.,76 1977</td>
<td>Paralysis; surgery rate, 80%; mean age, 29 y</td>
<td>Fibrinogen I 125 leg scan and IPG daily for at least 10 d</td>
<td>Cohort</td>
<td>Yes</td>
<td>70% of participants with positive screening</td>
<td>No</td>
<td>10/10 (100)</td>
</tr>
<tr>
<td>Rossi et al.,77 1980</td>
<td>Paralysis; surgery rate, 28%; mean age, NR</td>
<td>Fibrinogen I 125 leg scan every 2 d for 1 mo</td>
<td>Cohort</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>18/18 (100)</td>
</tr>
<tr>
<td>Frisbie and Sasahara,78 1981</td>
<td>Within 1 wk of major neurologic deficit; surgery rate, 31%; mean age, 27 y</td>
<td>IPG weekly for 8 wk</td>
<td>RCT with pseudorandomization</td>
<td>No</td>
<td>1 of 2 participants with positive screen</td>
<td>NR</td>
<td>32/48 (67)</td>
</tr>
<tr>
<td>Green et al.,79 1982</td>
<td>Paralysis; surgery rate, NR; mean age, NR</td>
<td>Fibrinogen I 125 leg scan daily and IPG every 3 d</td>
<td>RCT</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>27/28 (96)</td>
</tr>
<tr>
<td>Merli et al.,80 1988</td>
<td>Within 2 wk of paralysis; surgery rate, NR; mean age, 52 y</td>
<td>Fibrinogen I 125 leg scan on admission and daily; venogram at day 42</td>
<td>Cohort</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
<td>82/87 (94)</td>
</tr>
<tr>
<td>Green et al.,81 1988</td>
<td>Within 3 d of paralysis; surgery rate, NR; mean age, 32 y</td>
<td>IPG and Doppler flow study every 3 d for 2 wk, then weekly</td>
<td>RCT</td>
<td>Yes</td>
<td>77% of participants with positive screen</td>
<td>Yes</td>
<td>58/75 (77)</td>
</tr>
<tr>
<td>Green et al.,82 1990</td>
<td>Within 3 d of paralysis; surgery rate, NR; mean age, 30 y</td>
<td>IPG and duplex US twice weekly for 2 wk, then weekly for 2 wk, then biweekly for 4 wk</td>
<td>RCT</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>37/41 (90)</td>
</tr>
<tr>
<td>Merli et al.,83 1992</td>
<td>Within 3 d of paralysis; surgery rate, 63%; mean age, NR</td>
<td>Fibrinogen I 125 scan daily for 2 wk</td>
<td>Cohort</td>
<td>NR</td>
<td>1 of 2 participants with positive screen</td>
<td>No</td>
<td>19/21 (90)</td>
</tr>
<tr>
<td>Green et al.,84 1994</td>
<td>Complete spinal cord injury; surgery rate, NR; mean age, 39 y</td>
<td>Doppler US at 8 wk</td>
<td>Cohort</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>47/60 (78)</td>
</tr>
<tr>
<td>Geerts et al.,85 1994</td>
<td>Major trauma with spinal cord injury; surgery rate, NR; mean age, NR</td>
<td>Venography at day 7-21</td>
<td>Cohort</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
</tr>
</tbody>
</table>

*IPG indicates impedance plethysmography; NR, not reported; and RCT, randomized clinical trial.

Green et al.74 compared fixed low-dose subcutaneous heparin with adjusted-dose heparin (target activated partial thromboplastin time, 1.5 times control). Adjusted-dose heparin reduced the rate of DVT from 21% to 7% (RRR, 67%; P = .25). Seven patients (24%) in the adjusted-dose heparin arm experienced major bleeding complications, none of which were intracranial or fatal, compared with no bleeding events in the low-dose heparin arm.

Only 1 study compared LMWH (tinzaparin sodium, 3500 U subcutaneously once daily) with low-dose unfractioned heparin taken subcutaneously 3 times a day.75 In this randomized trial of only 35 patients, tinzaparin reduced the rate of DVT from 16% to 0%. This difference only reached statistical significance when all adverse events (ie, DVT and major bleeding) were combined (P = .02). However, a subsequent prospective cohort study by Green et al.80 did not confirm these findings.
findings, as the DVT rate with LMWH prophylaxis was 13%. In considering both of these studies together, only 1 of 80 patients assigned to receive tinzaparin had major bleeding.

**Comment**

Major limitations to the interpretation of this literature are the variability in the types of patients; variability in the timing, frequency, and choice of the screening tests; and the lack of blinding of the outcome assessment. The absence of a reference standard, contrast venography, for the diagnosis of DVT in the majority of these studies adds the greatest uncertainty about the true frequency of DVT in critically ill patients. Investigators may believe that venography in the ICU setting is impractical and dangerous, and that the risk of nephrotoxicity is too high. There may be the assumption that the larger, and perhaps most significant thrombi, will be detected by the PCDs; hence, the choice between these 2 mechanical prophylaxis approaches to dealing with indeterminate test results. Trends suggest that methodological standards for diagnostic tests are improving and that generation of likelihood ratios, for example, could aid intensivists in their interpretation of abnormal test results.

A number of suggestions for future research can be made: (1) patients who cannot be (or refuse to be) randomized should be included in a parallel observation arm; (2) a double-blind design should be used; (3) the use of screening venography to assess efficacy should be encouraged; (4) the use of clinically important outcomes, including symptomatic VTE, proximal DVT, and hemorrhage, should be used to assess effectiveness; and (5) follow-up periods should be sufficiently long. The enrollment of large heterogeneous cohorts of critically ill patients would enable investigators to determine risk factors that predict VTE rates. Once these risk factors are determined, they can be used in subsequent trials to target prophylaxis to high-risk critically ill patients. Stratification of bleeding risk may also be addressed to better evaluate the risk-benefit ratio. Study designs that tailor the prophylaxis to individual patients are also needed.

With respect to content, there are a number of gaps in the literature. No truly randomized study has directly compared heparin with mechanical prophylaxis. In addition, no trial, whether using venography or other noninvasive means, has compared elastic stockings directly with PCDs; hence, the choice between these 2 mechanical prophylaxis methods remains unclear. Various combinations of pharmacological and mechanical prophylaxis also remain to be investigated, and certain methods have been ignored in cer-

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**Table 8. Results of Studies of Deep Vein Thrombosis (DVT) Prophylaxis Among Acute Spinal Cord Injury Patients**

<table>
<thead>
<tr>
<th>Study, y</th>
<th>No. of Major Bleeding Events</th>
<th>No./Total (%) With DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brach et al,74 1977</td>
<td>NR</td>
<td>9/10 (90)</td>
</tr>
<tr>
<td>Rossi et al,78 1980</td>
<td>NR</td>
<td>13/16 (81)</td>
</tr>
<tr>
<td>Frisbie and Sasahara,71 1981</td>
<td>NR</td>
<td>1/17 (6)</td>
</tr>
<tr>
<td>Green et al,72 1982</td>
<td>NR</td>
<td>6/15 (40)</td>
</tr>
<tr>
<td>Merli et al,73 1988</td>
<td>NR</td>
<td>34/87 (39)</td>
</tr>
<tr>
<td>Green et al,74 1988</td>
<td>NR</td>
<td>6/29 (21)</td>
</tr>
<tr>
<td>Green et al,75 1990</td>
<td>NR</td>
<td>3/19 (16)</td>
</tr>
<tr>
<td>Merli et al,76 1992</td>
<td>NR</td>
<td>1/19 (5)</td>
</tr>
<tr>
<td>Green et al,77 1994</td>
<td>NR</td>
<td>21/26 (81)</td>
</tr>
<tr>
<td>Goering et al,78 1994</td>
<td>NR</td>
<td>21/26 (81)</td>
</tr>
</tbody>
</table>

* Ellipses indicate not applicable; LMWH, low-molecular-weight heparin; and NR, not reported.
taint populations; for example, there is a lack of data regarding mechanical prophylaxis in medical-surgical ICU patients. The commencement and duration of prophylaxis, eg, intraoperative initiation vs postoperative and ICU only vs extended until discharge, are issues that also require additional study.

Even when clear research findings are available to guide thromboprophylaxis, there are a number of barriers to implementation. Utilization surveys document heparin prophylaxis rates ranging from 33% in a medical-surgical ICU,\textsuperscript{90} to 65%,\textsuperscript{92} to at most 86%.\textsuperscript{93} Strategies to increase prophylaxis use in critical care include the development of written policies, incorporation into ICU admission orders, inclusion in daily review of each patient, periodic reviews of compliance, interactive education with periodic reminders, and audit and feedback. Although the majority of critically ill patients will be able to receive prophylaxis, some will have contraindications to anticoagulants, and, perhaps, even mechanical methods. For these patients, a strategy of screening for large deep venous thrombi may provide additional safety.

A second concern, especially for the mechanical prophylaxis modalities, is poor patient compliance when these devices are assessed in routine clinical use compared with the optimal circumstances of a research trial. For example, Come rota et al\textsuperscript{94} noted that prescribed PCDs were properly applied and functioning in only 78% of ICU visits and only 48% of ward visits. Likewise, Anglen et al\textsuperscript{95} found that foot pumps were in place and functioning in 48% of ward visits and in 68% of ICU visits.

### CONCLUSIONS

The great range in study designs, interventions, and populations render an overall quantitative summary of these studies impossible. However, we have generated summaries of the literature qualitatively and statistically pooled results of subgroups of studies when appropriate. These summaries are presented below, with the accompanying levels of evidence. For recommendations on practice, we refer readers to the Sixth American College of Chest Physicians Consensus conference, which will be published shortly.

#### MEDICAL-SURGICAL ICU PATIENTS

1. The incidence of DVT without prophylaxis in this population has been estimated at about 30%. This is based on limited screening with imperfect diagnostic tests and no reference standard. The true incidence is likely higher (level III and IV evidence).

2. Low-dose heparin prophylaxis is effective, reducing the DVT rate by approximately 50%. This is based on 1 double-blind randomized clinical trial. Observational studies generally support the effectiveness of heparin (level I evidence).

3. Other means of prophylaxis, including LMWH, GCS, and intermittent PCDs have not been adequately studied.

#### TRAUMA PATIENTS

1. The incidence of DVT in multisystem trauma patients, particularly those with orthopedic trauma, head injury, or spinal trauma, appears to be in the range of 50% to 65% (level I evidence). Studies using noninvasive methods of screening yield a lower incidence, ie, 25% to 35%, in keeping with the approximately 50% sensitivity of these methods in asymptomatic patients. A number of risk factors for VTE in trauma emerge: spinal cord injury, lower extremity fracture, major head injury, central venous repair or cannulation, and prolonged bed rest. Injury severity is not a reliable predictor of thrombosis risk.

2. Approximately one third to one half of these DVT events are proximal, and therefore have high potential to embolize (level I evidence).

3. Based mainly on nonrandomized studies, unfractionated heparin prophylaxis appears to decrease the incidence of DVT by approximately 20% compared with placebo (level II and III evidence).

4. Low-molecular-weight heparin decreases the incidence of DVT by a further 30% over unfractionated heparin (level I evidence).

5. Pooling all heparin trials yields an OR of 0.46 (95% CI, 0.16-1.29) compared with mechanical prophylaxis. This is equivalent to a relative risk of 0.68 or an RRR of 32%.

6. Concerns about excessive bleeding with heparin prophylaxis in patients who have achieved primary hemostasis appear unwarranted. Major bleeding occurs in 0.5% of patients treated with heparin, with few needing surgical intervention and none having a fatal outcome (level II evidence).

7. There is insufficient evidence to state whether mechanical means of prophylaxis (GCS, PCD, or foot pumps) are more efficacious than placebo.

#### NEUROSURGICAL PATIENTS

1. The incidence of DVT ranges from 20% to 30% in mixed neurosurgical patients and ranges from 34% to 50% in higher-risk groups undergoing craniotomy for tumors or with lower extremity paraplegia. These values are based on noninvasive methods and likely underestimate the true rate of DVT (level II evidence).

2. Mechanical prophylaxis reduces the incidence of DVT by approximately 57% (OR, 0.28; 95% CI, 0.17-0.46; equivalent to a relative risk of approximately 0.43), with GCS and boots appearing to have similar efficacy (level II evidence).

3. Heparin appears to be at least as efficacious as mechanical prophylaxis, decreasing the risk of DVT by 82% in a single study (level II evidence).

4. Low-molecular-weight heparin further reduces the risk of DVT by approximately 26% when added to GCS (OR, 0.59; 95% CI, 0.40-0.85, which translates into a relative risk of 0.74) (level I evidence).

5. Intracranial bleeding occurs in approximately 3% of patients when taking heparin, although fatalities have not been reported. Too few patients have been studied to be certain that this rate is significantly greater than in patients not receiving anticoagulant prophylaxis (level II evidence).
ACUTE SPINAL CORD INJURY PATIENTS

1. The incidence of DVT without prophylaxis is approximately 80%. This is based on 1 small venographic study but is supported by estimates from noninvasive methods (level II and III evidence).

2. Low-dose unfractionated heparin does not appear to provide significant protection (level II evidence).

3. Heparin appears to be more effective in prevention of DVT when combined with compression boots and GCS, or when given in adjusted doses, although the latter causes more bleeding complications (level II evidence).

4. There is conflicting evidence as to whether LMWH is equivalent to or more efficacious than unfractionated heparin (level II and IV evidence).

5. There is insufficient information to make recommendations regarding mechanical methods of DVT prophylaxis in these patients.

6. During the submission and review of this manuscript, 2 other relevant articles were published. Frazise and al65 performed a randomized controlled trial of nadroparin (3800 or 5700 IU subcutaneously, once daily) compared with placebo in 223 patients mechanically ventilated for decompressed chronic obstructive pulmonary disease. The incidence of DVT was 15.5% in the nadroparin group and 28.2% in the placebo group, giving an RRR of about 45%. This study and 2 other relevant articles published in this manuscript, 2 other relevant articles were published. Frazise and al65 performed a randomized controlled trial of nadroparin (3800 or 5700 IU subcutaneously, once daily) compared with placebo in 223 patients mechanically ventilated for decompressed chronic obstructive pulmonary disease. The incidence of DVT was 15.5% in the nadroparin group and 28.2% in the placebo group, giving an RRR of about 45%. This study and 2 other relevant articles published. Frazise and al65 performed a randomized controlled trial of nadroparin (3800 or 5700 IU subcutaneously, once daily) compared with placebo in 223 patients mechanically ventilated for decompressed chronic obstructive pulmonary disease. The incidence of DVT was 15.5% in the nadroparin group and 28.2% in the placebo group, giving an RRR of about 45%. This study and 2 other relevant articles published. Frazise and al65 performed a randomized controlled trial of nadroparin (3800 or 5700 IU subcutaneously, once daily) compared with placebo in 223 patients mechanically ventilated for decompressed chronic obstructive pulmonary disease. The incidence of DVT was 15.5% in the nadroparin group and 28.2% in the placebo group, giving an RRR of about 45%. This study


Dr Cook is an investigator with the Canadian Institutes of Health Research. Dr Ginsberg is a career scientist of the Heart and Stroke Foundation of Ontario. Dr Douketis holds a research scholarship from the Heart and Stroke Foundation of Ontario and the Canadian Institutes of Health Research.

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REFERENCES


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