Deep Vein Thrombosis and Its Prevention in Critically Ill Adults

John Attia, MD, PhD; Joel G. Ray, MD; Deborah J. Cook, MD, MSc; James Douketis, MD; Jeffrey S. Ginsberg, MD; William H. Geerts, MD

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.

Arch Intern Med. 2001;161:1268-1279

LITERATURE SEARCH

We systematically searched MEDLINE between January 1966 and August 1998; EMBASE, Conference Papers Index, and Inside Conférence from 1980 to 1998; and the Cochrane Library's Clinical Trials Reg...
istry, Database of Systematic Reviews, and the Database of Abstracts of Reviews. Our personal files and the bibliographies of relevant articles were also examined for additional citations. The following medical subject headings (MeSH) and text words were used: “thromboembolism,” “thrombophlebitis,” “deep-vein thrombosis,” “deep vein thrombosis,” “venous thrombosis,” “thrombosis,” “pulmonary embolus,” “pulmonary embolism,” or “venous thromboembolism.” According to the population of interest, these terms were cross-referenced with “intensive care,” “critical care,” “trauma,” “brain injury,” “head injury,” “head trauma,” “neurosurgery,” “neurosurgical,” or “spinal cord injury.” The search was limited to studies of adult human subjects published in the English language.

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) blinding 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 \( \chi^2 \) 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 \( 2 \times 2 \) 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.

MEDICAL-SURGICAL ICU PATIENTS

Three prospective cohort studies \(^{19-21} \) and 1 randomized clinical trial \(^{22} \) were included (Table 1). Two studies were excluded because screening for DVT was performed only on ICU admission. \(^{6,7} \) 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, \(^{20,21} \) 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,

<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 (^{22} ) 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. (^{20} ) 1985</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. (^{21} ) 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.
DVT prophylaxis was left to the discretion of the caregivers, although most patients received some form of prophylaxis. In the study by Moser et al, 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%-20%) of patients. Using serial Doppler US, Hirsch et al diagnosed up to 7 days in 34 patients who did not receive prophylaxis; DVT was diagnosed in 9% (95% CI, 4%-34%) receiving mecha-

### TRAUMA PATIENTS

Four randomized clinical trials and 11 cohort studies met our inclusion criteria (Table 3 and Table 4). Although 3 studies were identified as randomized, 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. A seventh study used technetium-labeled albumin for screening, a modality that has not been validated for the detection of DVT. Redundant reporting led to the exclusion of another study, and a ninth study used handheld Doppler flow, 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 al 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 immobi-

---

**Table 2. Results of Studies of Deep Vein Thrombosis Prophylaxis Among General Medical and Surgical Intensive Care Unit Patients**

<table>
<thead>
<tr>
<th>Study, y</th>
<th>Method of Prophylaxis</th>
<th>No Prophylaxis</th>
<th>Low-Dose Heparin</th>
<th>Mechanical Compression Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moser et al, 1981</td>
<td>None</td>
<td>3/34 (9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cade, 1982</td>
<td>Placebo vs heparin, 5000 U twice daily SC</td>
<td>NR/NR (29)</td>
<td>NR/NR (13)</td>
<td>-</td>
</tr>
<tr>
<td>Hirsch et al, 1995</td>
<td>As per attending physician</td>
<td>10/31 (32)</td>
<td>17/43 (40)</td>
<td>6/18 (33)</td>
</tr>
<tr>
<td>Marik et al, 1997</td>
<td>As per attending physician</td>
<td>2/8 (25)</td>
<td>5/68 (7)</td>
<td>5/26 (19)</td>
</tr>
</tbody>
</table>

*Ellipses indicate not applicable; SC, subcutaneously; and NR, not reported.*

---

lized for at least 10 days, the incidence of venographically identified DVT was 63% (95% CI, 47%-77%), of which half were proximal. 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%). 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. Studies using US in trauma patients tended to document a lower incidence of DVT, ranging from 0% to 30% in the absence of prophylaxis, while those who received prophylaxis had DVT rates between 28% and 63%. 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 patients 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%. In the only study to use systematic screening for PE, Fisher et al noted an incidence of 9 (6%) of 159 cases in the control group compared with 6 (4%) of 145 cases in the mechanically 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. 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.

---

©2001 American Medical Association. All rights reserved.
Table 3. Methodological Description of Studies of Deep Vein Thrombosis (DVT) in Trauma 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>Freerak et al, 1967</td>
<td>Mixed trauma; mean ISS, NR; mean age, 37 y</td>
<td>Venography at day 2-24</td>
<td>Cohort</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>54/ NR</td>
</tr>
<tr>
<td>Kaufman et al, 1983</td>
<td>Isolated head injury; mean ISS, NR; mean age, NR</td>
<td>Fibrinogen I 125 leg scan, IPG and Doppler flow study 3 times per week</td>
<td>Prospective cohort</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>20/20</td>
</tr>
<tr>
<td>Kudsk et al, 1989</td>
<td>Multiple injuries; mean ISS, 29; mean age, 37 y</td>
<td>Venography at day 7-12</td>
<td>Prospective cohort</td>
<td>NR</td>
<td>Yes</td>
<td>No</td>
<td>38/39 (97)</td>
</tr>
<tr>
<td>Ruiz et al, 1991</td>
<td>ISS &gt; 10; mean ISS, 26; mean age, 34 y</td>
<td>Duplex US at days 1, 3, 6, 10, and 21</td>
<td>Prospective cohort</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>100/100 (100)</td>
</tr>
<tr>
<td>Knudson et al, 1992</td>
<td>Mean ISS, 17; mean age, 38 y</td>
<td>Duplex US every 5 d</td>
<td>Prospective cohort</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>113/NR</td>
</tr>
<tr>
<td>Knudson et al, 1994</td>
<td>Mean ISS, 16; mean age, 38 y</td>
<td>Duplex US every 5-7 d</td>
<td>Prospective cohort</td>
<td>No</td>
<td>No</td>
<td>NR</td>
<td>251/400 (63)</td>
</tr>
<tr>
<td>Geerts et al, 1994</td>
<td>ISS &gt; 9; mean ISS, 27; mean age, 39 y</td>
<td>Venography at day 7-21</td>
<td>Prospective cohort</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>349/716 (49)</td>
</tr>
<tr>
<td>Napolitano et al, 1995</td>
<td>Trauma ICU; mean ISS, 18; mean age, 41 y</td>
<td>Duplex US twice weekly</td>
<td>Retrospective cohort</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>456/458 (&gt;99)</td>
</tr>
<tr>
<td>Fisher et al, 1995</td>
<td>Pelvic fracture; mean ISS, NR; mean age, 67 y</td>
<td>Duplex US at day 3-5 and Doppler flow study every 5 d</td>
<td>RCT</td>
<td>No</td>
<td>NR</td>
<td>Yes</td>
<td>73/NR</td>
</tr>
<tr>
<td>Knudson et al, 1996</td>
<td>High risk; mean ISS, 20; mean age, 40 y</td>
<td>Duplex US every 5-7 d</td>
<td>Cohort</td>
<td>No</td>
<td>No</td>
<td>NR</td>
<td>372/487 (76)</td>
</tr>
<tr>
<td>Geerts et al, 1996</td>
<td>ISS &gt; 9; mean ISS, 23; mean age, 38 y</td>
<td>Venography at day 10-14</td>
<td>Double-masked RCT</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>265/344 (77)</td>
</tr>
<tr>
<td>Haentjens et al, 1996</td>
<td>Orthopedic trauma; mean ISS, NR; mean age, 61 y</td>
<td>Duplex US or IPG at day 10</td>
<td>RCT</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>NR/144</td>
</tr>
<tr>
<td>Headrick et al, 1997</td>
<td>High risk; mean ISS, 22; mean age, 39 y</td>
<td>Doppler US every 7 d</td>
<td>Prospective cohort</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>228/228 (100)</td>
</tr>
<tr>
<td>Velmahos et al, 1998</td>
<td>Trauma ICU; mean ISS, 16; mean age, 21; mean age, 37 y</td>
<td>Doppler US every 7 d</td>
<td>Prospective cohort</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>200/NR</td>
</tr>
<tr>
<td>Anglen et al, 1998</td>
<td>Orthopedic trauma; mean ISS, NR; mean age, 39 y</td>
<td>Duplex US at days 2, 7, and 14</td>
<td>RCT with pseudorandomization</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>117/124 (94)</td>
</tr>
</tbody>
</table>

* ISS indicates Injury Severity Score; NR, not reported; IPG, impedance plethysmography; US, ultrasound; ICU, intensive care unit; and RCT, randomized clinical trial.
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 compared directly 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 studies32,34 compared mechanical prophylaxis with no prophylaxis and found no difference.

**NEUROSURGICAL PATIENTS**

Thirteen randomized clinical trials68-69 and 5 cohort studies61-65 met our inclusion criteria (Table 5 and Table 6). Several others failed to meet our inclusion criteria.60,66-72 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 studies32,62,69 that screened a total of 169 patients with fibrinogen I 125 leg scanning, the pooled DVT event rate was 35% (95% CI, 28%-43%) in the absence of prophylaxis.

In 7 randomized clinical trials that included a nonprophylaxis arm,48-53,56 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 al60 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 = .005). 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 al65 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,31 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%65 and 39% in the second study.51 In a third trial, Turpie et al60 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 study62 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 prophylaxis68-69,70,71 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

### Table 4. Results of Studies of Deep Vein Thrombosis (DVT) Prophylaxis in Trauma Patients

<table>
<thead>
<tr>
<th>Study, y</th>
<th>No Prophylaxis</th>
<th>Low-Dose Heparin</th>
<th>Low-Molecular Weight-Heparin (LMWH)</th>
<th>Pneumatic Compression Device (PCD)</th>
<th>Low-Dose Heparin and PCD</th>
<th>Foot Pump</th>
<th>No. of Major Bleeding Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frearck et al,22† 1967</td>
<td>15/54 (28)</td>
<td>4/50 (8)</td>
<td>10/50 (20)</td>
<td>2/50 (4)</td>
<td>0/50 (0)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Kaufman et al,23 1983</td>
<td>6/20 (30)</td>
<td>4/20 (20)</td>
<td>12/20 (60)</td>
<td>2/20 (10)</td>
<td>0/20 (0)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Knudson et al,24 1989</td>
<td>24/38 (63)</td>
<td>0/40 (0)</td>
<td>28/38 (74)</td>
<td>2/38 (5)</td>
<td>0/38 (0)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Ruiz et al,25 1991</td>
<td>1/50 (2)</td>
<td>1/50 (2)</td>
<td>2/50 (4)</td>
<td>0/50 (0)</td>
<td>0/50 (0)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Headrick et al,26 1997</td>
<td>6/24 (25)</td>
<td>5/24 (21)</td>
<td>11/24 (46)</td>
<td>2/24 (8)</td>
<td>0/24 (0)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Velmahos et al,27 1998</td>
<td>0/3</td>
<td>0/3</td>
<td>2/3 (67)</td>
<td>0/3 (0)</td>
<td>0/3 (0)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Anglen et al,28 1998</td>
<td>5/68 (7)</td>
<td>10/68 (15)</td>
<td>15/68 (22)</td>
<td>5/68 (7)</td>
<td>0/68 (0)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Cerrato et al,29 1991</td>
<td>6/20 (30)</td>
<td>2/20 (10)</td>
<td>8/20 (40)</td>
<td>2/20 (10)</td>
<td>0/20 (0)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Haentjens et al,30 1996</td>
<td>10/50 (20)</td>
<td>5/50 (10)</td>
<td>15/50 (30)</td>
<td>2/50 (4)</td>
<td>0/50 (0)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Knudson et al,31 1992</td>
<td>2/37 (5)</td>
<td>5/37 (14)</td>
<td>7/37 (19)</td>
<td>1/37 (3)</td>
<td>0/37 (0)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Napolitano et al,32 1995</td>
<td>5/42 (12)</td>
<td>11/42 (26)</td>
<td>16/42 (38)</td>
<td>2/42 (5)</td>
<td>0/42 (0)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Fisher et al,33 1995†</td>
<td>3/38 (8)</td>
<td>15/38 (40)</td>
<td>20/38 (53)</td>
<td>2/38 (5)</td>
<td>0/38 (0)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Knudson et al,34 1996</td>
<td>1/120 (0.8)</td>
<td>5/120 (4.2)</td>
<td>6/120 (5)</td>
<td>0/120 (0)</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geerts et al,35 1996</td>
<td>60/136 (44)</td>
<td>40/129 (31)</td>
<td>80/129 (62)</td>
<td>10/129 (8)</td>
<td>0/129 (0)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Geerts et al,36 1996</td>
<td>60/136 (44)</td>
<td>40/129 (31)</td>
<td>80/129 (62)</td>
<td>10/129 (8)</td>
<td>0/129 (0)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Haentjens et al,37 1996</td>
<td>0/70 (0)</td>
<td>0/70 (0)</td>
<td>0/70 (0)</td>
<td>0/70 (0)</td>
<td>0/70 (0)</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

* Ellipses indicate not applicable; NR, not recorded.
† Data extracted for patients without hip fracture.
‡ Pneumatic compression device in addition to graduated compression stocking.
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 (%)</th>
<th>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>
<td></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/128/161 (80)</td>
<td></td>
<td></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>NR/100/100 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skillman et al, 1978</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>
<td></td>
</tr>
<tr>
<td>Turpie et al, 1979</td>
<td>Mixed intracranial and spinal surgery; tumor, 26% cases; mean age, 51 y</td>
<td>Fibrinogen I 125 leg scan daily; IPG every second day for 2 wk</td>
<td>Cohort</td>
<td>NR</td>
<td>No</td>
<td>No</td>
<td>100/100 (100)</td>
<td></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>RCT</td>
<td>Yes</td>
<td>“Majority” of participants with positive screen</td>
<td>Yes</td>
<td>136/136 (100)</td>
<td></td>
</tr>
<tr>
<td>Turpie et al, 1985</td>
<td>Mixed intracranial and spinal surgery; tumor, 16% cases; mean age, 50 y</td>
<td>Fibrinogen I 125 leg scan daily</td>
<td>RCT</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>14/NR</td>
<td></td>
</tr>
<tr>
<td>Wautrecht et al, 1985</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>NR</td>
<td>100/100 (100)</td>
<td></td>
</tr>
<tr>
<td>Salzman 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>
<td></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>
<td></td>
</tr>
<tr>
<td>Turpie et al, 1989</td>
<td>Mixed intracranial and spinal surgery; tumor, 49% 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>70% of participants with positive screen</td>
<td>Yes</td>
<td>239/239 (100)</td>
<td></td>
</tr>
<tr>
<td>Flinn et al, 1989</td>
<td>Mixed intracranial and spinal surgery; tumor, 22% cases; mean age, NR</td>
<td>Fibrinogen I 125 leg scan daily</td>
<td>RCT</td>
<td>Prospective cohort</td>
<td>No</td>
<td>361/361 (100)</td>
<td></td>
<td></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>
<td></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>
<td></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>
<td></td>
</tr>
<tr>
<td>Nurmohamed 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>
<td></td>
</tr>
<tr>
<td>Agnelli et al, 1996</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>
<td></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>
<td></td>
</tr>
</tbody>
</table>

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

translates into an relative risk of 0.43 or an RRR of 57%. Three clinical trials have evaluated the combination of LMWH and mechanical prophylaxis. In 1 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.
The proximal DVT rates were 12% (95% CI, 1.8%-5.1%) and 9% (95% CI, 0.4%-2.5%) and 14 (3.2%) of 432 patients to receive PCD; enoxaparin, 30 mg subcutaneously twice daily; or GCS plus nadroparin, 30,75 anti-Xa units subcutaneously once daily. The proximal DVT rates were 12% and 5%, respectively (P = 0.06). 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 al\textsuperscript{60} 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 \( \chi^2 = 6.1; P = 1.9 \)), 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 trials\textsuperscript{72-75} and 6 were cohort studies\textsuperscript{33,76-80} (Table \textbf{7} and Table \textbf{8}). Six additional studies failed to meet our inclusion criteria.\textsuperscript{81-86}

Five studies evaluated the rate of DVT in the absence of prophylaxis.\textsuperscript{73,72,76-78} The only study to use screening venography was by Geerts et al,\textsuperscript{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,\textsuperscript{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 al\textsuperscript{78} 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,\textsuperscript{72} there was no difference between low-dose subcutaneous heparin and no prophylaxis groups. In a cohort study by Merli et al,\textsuperscript{79} patients who received the combination of low-dose heparin, GCS, and PCD had a DVT rate of 5% (95% CI, 0%-15%).

---

**Table 6. Results of Studies of Deep Vein Thrombosis (DVT) Prophylaxis Among Neurosurgery Patients**

<table>
<thead>
<tr>
<th>Study, y</th>
<th>No. Prophylaxis</th>
<th>Low-Dose Heparin or LMWH</th>
<th>Graduated Compression Stockings (GCS)</th>
<th>Pneumatic Compression Device (PCD)</th>
<th>GSC and PCD</th>
<th>LMWH and Either GCS or PCD</th>
<th>No. of Major Bleeding Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joffe,\textsuperscript{41} 1975</td>
<td>10/23 (43)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>NR</td>
</tr>
<tr>
<td>Turpie et al,\textsuperscript{41} 1977</td>
<td>12/63 (19)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Cerrato et al,\textsuperscript{41} 1978</td>
<td>17/50 (34)</td>
<td>3/50 (6)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Skillman et al,\textsuperscript{41} 1978</td>
<td>12/48 (25)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Turpie et al,\textsuperscript{51} 1979</td>
<td>20/96 (21)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Valladares and Hankinson,\textsuperscript{41} 1980</td>
<td>29/100 (29)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Turpie et al,\textsuperscript{52} 1985</td>
<td>12/68 (18)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Weitz et al,\textsuperscript{53} 1986</td>
<td>2/9 (22)</td>
<td>0/5</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Salzman et al,\textsuperscript{54} 1987</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Bucci et al,\textsuperscript{55} 1989</td>
<td>...</td>
<td>0/28</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Turpie et al,\textsuperscript{56} 1989</td>
<td>16/81 (20)</td>
<td>...</td>
<td>7/80 (9)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Flinn et al,\textsuperscript{57} 1989</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Savaya et al,\textsuperscript{58} 1992</td>
<td>21/46 (46)\dagger</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Wautrecht et al,\textsuperscript{59} 1995</td>
<td>...</td>
<td>2/5 (40)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Flinn et al,\textsuperscript{60} 1996</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Nurmohamed et al,\textsuperscript{61} 1996</td>
<td>...</td>
<td>47/179 (26)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Agnelli et al,\textsuperscript{62} 1998</td>
<td>...</td>
<td>42/129 (33)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Dickinson et al,\textsuperscript{63} 1998</td>
<td>...</td>
<td>1/20 (5)</td>
<td>3/19 (16)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Dickinson et al,\textsuperscript{64} 1992</td>
<td>...</td>
<td>29/100 (29)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

\* Sawaya et al\textsuperscript{64} used leg wrapping as “prophylaxis.”

\dagger Sawaya et al\textsuperscript{64} used leg wrapping as “prophylaxis.”

LMWH indicates low-molecular-weight heparin; NR, not reported; and ellipses, not applicable.
Green et al\textsuperscript{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.\textsuperscript{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\textsuperscript{80} did not confirm these

<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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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.
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 binding 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 noninvasive means. This tenuous assumption has not been supported in the ICU populations described herein. Meta-analyses in asymptomatic orthopedic patients have demonstrated that the sensitivities of fibrinogen 125 leg scanning, impedance plethysmography, and US are low for all DVT: 45%, 15%, and 47%, respectively.47,87 For proximal DVT, the sensitivity of US in asymptomatic patients is only 62%.

Hence, the studies described herein yield limited prevalence data and likely underestimate the true rate of DVT. Venography remains the reference standard and is indeed feasible in some critically ill patients, eg, trauma patients.24,33

Another limitation is the paucity of truly randomized studies in these patient groups. Given surgeons' reluctance to use heparin prophylaxis in patients with traumatic injuries or undergoing neurosurgery, there are few studies that are truly randomized, with most being observational or quasi-randomized in which patients are assigned to 1 of 2 arms at the discretion of the attending physician, resulting in bias.

Others have also pointed out these methodological concerns. Heffner and colleagues90 recommended that greater methodological rigor be used in diagnostic studies within the disciplines of respirology and thrombosis medicine. They cited several inadequacies in these areas, including lack of suitable reference standards, as well as insufficient assessment of both test reproducibility and novel approaches to dealing with indeterminate test results. Trends suggest that methodological standards for diagnostic tests are improving90 and that generation of likelihood ratios, for example, could aid intensivists in their interpretation of abnormal test results.90

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-

### 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,19 1977</td>
<td>3/12 (25)</td>
<td>receiving PCD, aspirin, and dipyridamole</td>
</tr>
<tr>
<td>Rossi et al,20 1980</td>
<td>0 in PCD group; 1 in other therapy group</td>
<td></td>
</tr>
<tr>
<td>Frisbie and Sasahara,21 1981</td>
<td>6/15 (40)</td>
<td>receiving LMWH</td>
</tr>
<tr>
<td>Green et al,22 1982</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Merli et al,23 1988</td>
<td>34/87 (39)</td>
<td>receiving low-dose heparin group; 7 in adjusted-dose heparin group</td>
</tr>
<tr>
<td>Green et al,24 1988</td>
<td>2/29 (7)</td>
<td>receiving adjusted-dose heparin</td>
</tr>
<tr>
<td>Green et al,25 1990</td>
<td>0/16 receiving LMWH</td>
<td></td>
</tr>
<tr>
<td>Merli et al,26 1992</td>
<td>1/19 (5)</td>
<td>receiving low-dose heparin, GCS, and PCD</td>
</tr>
<tr>
<td>Green et al,27 1994</td>
<td>6/48 (13) receiving LMWH</td>
<td></td>
</tr>
<tr>
<td>Geerts et al,28 1994</td>
<td>1 in other therapy group</td>
<td></td>
</tr>
</tbody>
</table>

* Ellipses indicate not applicable; LMWH, low-molecular-weight heparin; and NR, not reported.
tain populations; for example, there is a lack of data regarding mecha-
nical prophylaxis in medical-surgical ICU patients. The commencement
and duration of prophylaxis, eg, in-
traoperative initiation vs postope-
tative and ICU only vs extended until
discharge, are issues that also re-

quire additional study.

Even when clear research find-
ings are available to guide throm-
bophrophylaxis, there are a num-
ber of barriers to implementation. Uti-
lization surveys document heparin
prophylaxis rates ranging from 33%
in a medical-surgical ICU,50 to 65%,92
to at most 86%.93 Strategies to in-
crease prophylaxis use in critical care
include the development of written
policies, incorporation into ICU ad-
mission orders, inclusion in daily re-
view of each patient, periodic re-
views of compliance, interactive
education with periodic remind-
ers, and audit and feedback. Al-
though the majority of critically ill
patients will be able to receive pro-
phylaxis, some will have contrain-
dications to anticoagulants, and, per-
haps, even mechanical methods. For
these patients, a strategy of screen-
ing for large deep venous thrombi
may provide additional safety.

A second concern, especially for
the mechanical prophylaxis mod-
alities, is poor patient compliance
when these devices are assessed in
routine clinical use compared with the
optimal circumstances of a re-
search trial. For example, Come-
rota et al49 noted that prescribed
PCDs were properly applied and
functioning in only 78% of ICU
visits and only 48% of ward visits.
Likewise, Anglen et al26 found that
foot pumps were in place and func-
tioning in 48% of ward visits and in
68% of ICU visits.

CONCLUSIONS

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

MEDICAL-SURGICAL
ICU PATIENTS

1. The incidence of DVT with-
out 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 in-
cidence is likely higher (level III and
IV evidence).

2. Low-dose heparin prophy-
laxis is effective, reducing the DVT
rate by approximately 50%. This is
based on 1 double-blind random-
ized clinical trial. Observational
studies generally support the ef-
effectiveness of heparin (level I ev-

dence).

3. Other means of prophy-
laxis, including LMWH, GCS, and
intermittent PCDs have not been ade-
quately studied.

TRAUMA PATIENTS

1. The incidence of DVT in
multisystem trauma patients, par-
ticularly 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 inci-
dence, ie, 25% to 35%, in keeping
with the approximately 50% sensi-
tivity of these methods in asymptom-
tomatic 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 throm-
bosis risk.

2. Approximately one third to
one half of these DVT events are proxi-
mal, and therefore have high poten-
tial to embolize (level I evidence).

3. Based mainly on nonran-
donized studies, unfractionated heparin prophylaxis appears to de-
crease the incidence of DVT by ap-
proximately 20% compared with pla-
 placebo (level II and III evidence).

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

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

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

7. There is insufficient evi-
dence 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 pa-
resis. These values are based on non-
invasive methods and likely under-
estimate the true rate of DVT (level
II evidence).

2. Mechanical prophylaxis re-
duces the incidence of DVT by ap-
proximately 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 hepa-
arin 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 rela-
tive risk of 0.74) (level I evidence).

5. Intracranial bleeding oc-
urs in approximately 3% of pa-
ients when taking heparin, al-
though 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 prophyl-
xaxis (level II evidence).
ACUTE SPINAL CORD INJURY PATIENTS

1. The incidence of DVT without prophylaxis is approximately 80%. This is based on I 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.

During the submission and review of this manuscript, 2 other relevant articles were published. Fraisse et al performed a randomized controlled trial of nadroparin (3800 or 5700 IU subcutaneously, once daily) compared with placebo in 223 patients mechanically ventilated for decerebrated 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 confirms the estimates given in this review and represents the only use of venography in the medical ICU population. Elliott et al compared calf-thigh sequential PDUs and foot pumps for DVT prophylaxis in 149 major trauma patients without lower extremity injuries. The DVT rates, using compression US, were 6.5% and 21%, respectively. This trial further supports other observations that foot pumps provide less protection than other mechanical methods, at least in trauma patients.

Accepted for publication January 9, 2001.

Other research by Drs Ginsberg and Geerts is supported in part by pharmaceutical manufacturers of anticoagulant agents (AstraZeneca, Mississauga, Ontario).

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.

Corresponding author and reprints: John Attia, MD, PhD, Centre for Clinical Epidemiology and Biostatistics, Level 3, David Maddison Bldg, Royal Newcastle Hospital, Newcastle, Australia.

REFERENCES


