Deep vein thrombosis and its prevention in critically ill adults

Authors' objectives
To systematically review the incidence of deep vein thrombosis (DVT) and the efficacy of thromboprophylaxis in critically ill adults.

Searching
The following sources were searched: MEDLINE between January 1966 and August 1998; EMBASE, Conference Papers Index and Inside Conferences from 1980 to 1998; the Cochrane Controlled Trials Register; the Cochrane Database of Systematic Reviews; and DARE. The MeSH used were: 'thromboembolism', 'thrombophlebitis', 'deep-vein thrombosis', 'deep vein thrombosis', 'venous thrombosis', 'thrombosis', 'pulmonary embolus', 'pulmonary embolism' and 'venous thromboembolism'. These terms were cross-referenced with 'intensive care', 'critical care', 'trauma', 'brain injury', 'head injury', 'head trauma', 'neurosurgery', 'neurosurgical' and 'spinal cord injury'. The authors also looked for additional references from their personal files and relevant articles. The search was limited to studies published in the English language.

Study selection
Study designs of evaluations included in the review
Published prospective cohort studies and randomised controlled trials (RCTs) of DVT prophylaxis. Abstracts that were published as full articles at a later stage were excluded.

Specific interventions included in the review
The authors do not specify a priori the types of DVT prophylactic interventions to be compared. The included studies used no prophylaxis, placebo, mechanical devices (pneumatic compression devices, foot pump, graduated compression stockings), low-dose unfractionated heparin, or low molecular weight heparin (LMWH).

Participants included in the review
Medical and surgical intensive care unit (ICU) patients: these were patients admitted to respiratory, general, medical, or medical-surgical ICU. The mean ages of the patients, where specified (3 studies), varied from 60 to 65 years. More than 70% of the patients required mechanical ventilation and most had an ICU stay of more than 48 hours.

Trauma patients: the patients were of mixed trauma in 2 studies, isolated head injury in 1 study, orthopaedic trauma in 3 studies, and the type of trauma was not specified in 9 studies. The mean ages of the patients, where stated (13 studies), varied from 34 to 67 years.

Neurosurgical patients: these consisted of elective intracranial and spinal surgery patients, mixed intracranial surgery and spinal surgery. Where specified, the mean ages of the patients were between 47 and 62 years.

Acute spinal cord injury patients: these had paralysis with or without surgery. Where reported, the mean ages of the patients varied between 27 and 52 years.

Outcomes assessed in the review
The main outcome was DVT, as assessed by iodine-125-labelled fibrinogen leg scanning, impedance plethysmography, venous ultrasound or venography. Studies that focused on central venous catheter thrombosis, and those with insufficient reporting of DVT rates, were excluded.

How were decisions on the relevance of primary studies made?
Two of the authors independently performed the computer search, study selection and examination of the full-text articles. The authors did not state whether they were blinded to the results or source, or how any disagreements were resolved.
Assessment of study quality
Validity was assessed using the following criteria: study design; whether patients were enrolled in a consecutive manner; completeness of follow-up; the use of venography as the accepted reference standard for diagnosis of DVT; and blinding of outcome assessment. Three reviewers independently assessed the studies using the specified validity criteria.

Data extraction
Three reviewers independently extracted information from the primary studies on study design, study population, DVT screening methods, and study validity. Any disagreements were resolved by consensus. DVT rates were calculated for each individual study. For studies that compared DVT events with and without prophylaxis, the results were expressed as the relative risk reduction.

Methods of synthesis
How were the studies combined?
The authors generated summaries of the literature qualitatively. Where appropriate, the data were pooled using the Mantel-Haenszel chi-squared statistic to obtain a summary odds ratio (OR) and 95% confidence interval (CI). The studies were summarised using the levels of evidence system.

How were differences between studies investigated?
Heterogeneity between the studies was assessed using the Breslow and Day method (see Other Publications of Related Interest).

Results of the review
Twenty-two RCTs and 25 cohort studies were included. There was one RCT of medical and surgical ICU patients, 4 RCTs of trauma patients, 13 of neurosurgical patients, and 4 of acute spinal injury patients. There were 3 cohort studies of medical and surgical ICU patients, 11 of trauma patients, 5 of neurosurgical patients, and 6 of acute spinal injury patients.

The studies of the medical and surgical ICU patients had 367 participants in total (1 RCT, n=119; 3 cohort studies, n=248). The studies of the trauma patients had 3,500 participants (4 RCTs, n=685; 11 cohort studies, n=2,815). The studies of the neurosurgical patients enrolled 5,257 participants (13 RCTs, n=2,084; 5 cohort studies, n=1,737), whilst those of acute spinal cord injury patients reported on 388 participants (4 RCTs, n=192; n=196 from 5 cohort studies). The overall, total number of participants in all the studies was 9,512.

Medical and surgical ICU patients.
Three cohort studies showed that without prophylaxis, DVT occurred in 9% (95% CI: 2, 20%), 32% (95% CI: 16, 48) and 25% (95% CI: 0, 55) of the ICU patients. Two cohort studies showed that with low-dose subcutaneous heparin, DVT occurred in 40% (95% CI: 25, 55) and 7% (95% CI: 0, 26%) of the ICU patients. Two cohort studies showed that with mechanical prophylaxis, DVT occurred in 33% (95% CI: 11, 55) and 19% (95% CI: 4, 34) of the ICU patients. In the one RCT, DVT occurred in 13% of the patients receiving heparin, and in 29% of those receiving placebo; the relative risk reduction was 0.65 (the 95% CI was not calculable).

Trauma patients.
Data from 3 cohort studies showed that DVT occurred in 58% (95% CI: 52, 63), 63% (95% CI: 47, 77) and 35% (95% CI: 27, 43) of trauma patients without prophylaxis. One RCT showed that low-dose heparin reduced the risk by about 20% and that LMWH may decrease the risk by a further 30%. Three studies comparing unfractionated heparin or LMWH with mechanical prophylaxis were pooled; these yielded an OR of 0.40 (95% CI: 0.16, 1.29) favouring anticoagulation.

Neurosurgical patients.
In the absence of prophylaxis, DVT occurred in 35% (95% CI: 28, 43) of the patients, according to the results of 3 pooled cohort studies. The incidence of DVT in 7 RCTs in the non-prophylactic arm was 22% (95% CI: 18, 26). Heparin appeared to be as effective as mechanical devices, and LMWH further reduced the risk of DVT when added to mechanical devices. The results of 5 RCTs showed that mechanical prophylaxis was efficacious with a pooled OR of 0.28 (95% CI: 0.17, 0.46). Three trials comparing mechanical devices, enoxaparin, or mechanical devices plus enoxaparin, gave a pooled OR of 0.59 (95% CI: 0.40, 0.85) in favour of the combination of LMWH plus mechanical device.

Acute spinal cord injury patients.

According to one cohort study, DVT occurred in 81% (95% CI: 66, 96) of acute spinal cord injury patients who did not receive prophylaxis. The other studies reported rates ranging between 39 and 90%. Heparin appeared to be more effective in preventing DVT when given in adjusted doses, or in combination with mechanical devices.

Authors' conclusions
The authors concluded that the evidence of the comparative efficacy of LMWH versus unfractionated heparin, and for mechanical devices, is still sparse.

Critically ill patients had DVT rates varying from 22 to 80%. Methods of prophylaxis proven in one group do not necessarily generalise to other critically ill patient groups. More potent prophylactic regimens may be needed with higher-risk groups.

CRD commentary
The rationale and objectives of the review were clear and relevant. The selection criteria were specific to include categories of critically ill patients in different settings. However, the authors stated that there was no systematic screening for pulmonary embolus, and data on bleeding events were not uniformly reported. The search strategy was adequate but was limited to articles published in English. It is therefore possible that additional studies may have been missed. One of the studies of trauma patients was not generalisable because patients experienced unusually long periods of immobilisation and delayed surgery, superficial thrombi were included as outcomes, and deaths and drop-outs were not reported.

Two or three reviewers made the decisions on the relevance of the primary studies, assessed the validity of the studies, and extracted the data. These processes were performed adequately, and any disagreements resolved by consensus. The criteria used to assess validity were different to those commonly used. For example, the criteria did not consider concealment of treatment allocation and whether the intention to treat principle was applied. The assessment of DVT was not masked in most of the primary studies and this would have introduced observer or detection bias.

A quantitative summary of the results was not possible because of the range in study designs, variability in types of patients, timing, frequency and choice of screening tests. This decision was appropriate for most of the data, especially that from the cohort studies. It would have been useful if the authors had included more detail on how sources of heterogeneity were explored. The results were not uniformly presented; some were presented as DVT rates without 95% CIs.

The main outcome, DVT, was confirmed using different methods. Therefore, the variation in the incidence of DVT across studies may be due to the different confirmatory tests: ultrasound tends to document a lower incidence of DVT and venography documents higher rates. The authors' conclusions seem to follow logically from the results.

Implications of the review for practice and research
Practice: Venography is the 'gold' standard for confirming DVT. On the other hand, the noninvasive tests have low sensitivity. The authors state that venography is feasible in some critically ill patients.

Reviewer's statement: Venography should therefore be used as much as practically possible, and the noninvasive tests only when venography is impracticable or deemed dangerous. The authors do not make specific recommendations but
refer the readers to the, as yet unpublished, Sixth American College of Chest Physicians Consensus Conference.

Research: There is still a paucity of truly randomised studies of DVT thromboprophylaxis in critically ill patients. The authors suggested that future research should focus on:

truly randomised double-blind trials, with the inclusion of those who cannot be randomised in a parallel observation arm;

couraging the use of screening venography;

developing suitable methods and reference standards for DVT diagnosis;

the use of clinically important outcomes, i.e. symptomatic venous thromboembolism, proximal DVT, haemorrhage and pulmonary embolus; and

the use of follow-up periods of sufficient length.

Future research should also include: randomised trials comparing heparin with mechanical devices; a direct comparison between elastic compression stockings and pneumatic compression devices; investigations of intra-operative versus post-operative initiation of prophylaxis; and investigations of prophylaxis in ICU versus prophylaxis extended till hospital discharge.

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Other publications of related interest

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MeSH
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.