Prevention of Venous Thromboembolism in the ICU*

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Background: **Although venous thromboembolism (VTE) is an important cause of morbidity and mortality in critical care unit patients, the risk of VTE and its prevention have been poorly characterized in this population. Evidence-based thromboprophylaxis guidelines are also not available for these critically ill patients.**

Objectives: **To review the prevalence of VTE, to summarize the available clinical trials of thromboprophylaxis, and to outline a practical approach to the prevention of VTE in critical care unit patients.**

Methods: **Systematic review of the relevant literature.**

Results: **Most patients in critical care units have at least one major risk factor for VTE, and many patients have multiple risk factors. Objectively confirmed deep-vein thrombosis (DVT) rates varied from 13 to 31% among the four prospective studies in which critical care unit patients did not receive prophylaxis. We were able to identify only three randomized trials of thromboprophylaxis conducted in critical care units. The results of these studies suggest that both low-dose heparin and low-molecular-weight heparin are efficacious in preventing DVT compared with no prophylaxis. Fourteen studies reported that compliance with some form of thromboprophylaxis occurred in 33 to 100% of critically ill patients.**

Conclusions: **There is a paucity of data assessing the risks and prevention of VTE in critical care settings. Selection of prophylaxis for these challenging patients involves a consideration of the thromboembolic and bleeding risks, both of which may vary in the same patient from day to day.**

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Key words: compliance; critical care; ICU; patient safety; thromboprophylaxis; venous thrombosis

Abbreviations: DVT = deep-vein thrombosis; LDH = low-dose heparin; PE = pulmonary embolism; VTE = venous thromboembolism

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Since venous thromboembolism (VTE) is a common complication of hospitalization for medical illnesses or surgical procedures, several consensus guidelines[1–3] for thromboembolism prevention have been published; these guidelines provide evidence-based thromboprophylaxis recommendations for a number of patient groups, but there is a notable absence of guidelines for the prevention of VTE in critical care settings. Furthermore, existing guidelines in medical and surgical patients cannot be directly extrapolated to critical care patients because the relative benefit-to-risk ratio for thromboprophylaxis may be quite different among the various groups. This article reviews the risks of VTE in critical care patients, discusses the published trials of thromboprophylaxis, and suggests strategies to reduce the burden of thromboembolic disease in the critical care unit. We have recently conducted a systematic review of these topics.[4]

VTE in the Critical Care Unit: Risks

Deep-vein thrombosis (DVT) and pulmonary embolism (PE) contribute significantly to morbidity and mortality associated with critical illness.[5–7] Among patients who died while in the ICU, PE has been reported in 7 to 27% (mean, 13%) of postmortem examinations, and PE was thought to have caused or contributed to death in 0 to 12% (mean, 3%).[8–15] A clinical suspicion of PE was present in only 30% of these patients before death.

The vast majority of patients admitted to a critical care unit have a major risk factor for VTE, and most have multiple risk factors.[16–18] Many of these thrombosis risk factors precede the ICU admission, while others develop during the course of ICU stay (Table 1). Advanced age, serious medical illnesses, and recent surgical procedures or trauma are common in critically ill patients. Sepsis, heart failure, mechanical ventilation, paralysis, surgical interventions, and central venous lines are also common. The importance of each of these clinical risk factors is unknown, as is the role of inherited or acquired coagulation system abnormalities. Factors that have been reported to predict an increased risk of ICU-related VTE include the following: increased age,[19] previous VTE,[20] malignancy,[19,21] major trauma,[22] prolonged pre-ICU hospital stay,[20] mechanical ventilation,[17] use of paralytic drugs,[17] APACHE (acute physiology and chronic health evaluation) score,[19] need for emergency surgical procedures,[19] insertion of a femoral venous catheter,[17,23–26] and failure to use thromboprophylaxis.[17,27] However, adequately powered studies using multiple logistic regression analysis to determine the independent predictors for thrombosis in critically ill patients have not yet been conducted, to our knowledge.

Unsuspected DVT may already be present on admission to critical care units. When Doppler ultrasonography was performed in 729 patients at entry to the critical care unit in four case series,[19,28–30] DVT was detected in 6.4%. After admission to the ICU, only four prospective studies[9,28,31,32] (to our knowledge) used routine screening with an objective diagnostic test to assess the incidence of DVT in critically ill patients who were not administered thromboprophylaxis (Table 2). One was a prospective cohort

Table 1—*Clinical Risk Factors for VTE in Critically Ill Patients

Factors present before ICU admission
Recent surgery
Trauma, burns
Malignancy and its treatment
Sepsis
Immobilization/bed rest, stroke, spinal cord injury
Increasing age
Heart/respiratory failure
Previous VTE
Pregnancy/puerperium
Estrogens
Additional factors acquired in ICU
Central venous lines
Sepsis
Pharmacologic sedation, paralysis
Mechanical ventilation

*Adapted from Geerts et al[4] with permission.

study,[9] and three were randomized trials[28,31,32]; one study[32,33] has been presented in abstract form only.

In 1981, Moser et al[9] reported a series of 23 patients who were admitted to an ICU with acute respiratory failure and underwent ^{125}I-fibrinogen leg scanning for 3 to 6 days. Three of these patients (13%) had abnormal scan findings. The limitations of this study were as follows: very small sample size, failure to describe the patient selection process or the included patients, unblinded assessment for thrombosis using an unreliable screening test for DVT (see below), and brief follow-up. In 1982, Cade,[31] using ^{125}I-fibrinogen leg scanning, detected DVT in 29% of placebo-treated patients in a randomized trial. Neither the patient selection process nor the actual study patients are described, and abnormal leg scan findings were not confirmed with venography. Fibrinogen leg scanning is now known to be associated with a high rate of both false-negative and false-positive results.[34–36]

A double-blind, placebo-controlled, randomized trial[32,33] of DVT prophylaxis has been performed in 791 medical ICU patients; thrombosis was detected by Doppler ultrasound examinations performed every 3 days. DVT was diagnosed in 31% of the 390 control patients, and 5% had PE. The study has been published only in abstract form to date, no description of the Doppler ultrasound technique is provided, abnormal test results were not confirmed by venography, and there was no follow-up for patients with normal test results. To our knowledge, only one study[28] has utilized routine contrast venography to detect DVT: a randomized, placebo-controlled trial of thromboprophylaxis in patients receiving mechanical ventilation for treatment of exacerbations of COPD. DVT and proximal DVT were detected in 28% and 8%, respectively, in the 85 evaluable patients who received placebo.

In summary, among these four prospective studies,[9,28,31,32] the DVT rates varied between 13% and 31% in critically ill patients who did not receive prophylaxis. The most reliable event rate is provided by Fraisse et al,[28] who used contrast venography to detect thrombosis. Although the clinical consequences of asymptomatic DVT detected by routine screening are uncertain, a recent study[21] showed that patients documented to have DVT by Doppler ultrasound had a significantly greater frequency of subsequent PE during their hospitalization (11.5% vs 0%, $p = 0.01$). Furthermore, even small PE may be poorly tolerated by critically ill patients, many of whom have reduced cardiorespiratory reserve.[37,38]

Despite the paucity of critical care-specific data about thromboembolism, the risks of VTE in other patient groups, including surgical, trauma/spinal cord injury, and medical patients, are well established and are relevant to those in critical care units.[3,4,22,39,40] Objectively confirmed DVT rates were found to be in the range of 10 to 80% for patients admitted to ICUs or following trauma, neurosurgery, or spinal cord injury in a recent systematic review.[39]

Thromboprophylaxis Studies in Critical Care

PE is a common preventable cause of hospital death.[41–44] The Agency for Healthcare Research and Quality has recently published a report entitled "Making Health Care Safer: A Critical Analysis of Patient Safety Practices."[44] This systematic review ranked 79 patient safety interventions based on the strength of the evidence supporting more widespread implementation of these procedures. The highest ranked safety practice was the "appropriate use of prophylaxis to prevent venous thromboembolism in patients at risk." This recommendation was based on overwhelming evidence that thromboprophylaxis reduces adverse patient outcomes while, at the same time, decreasing overall costs.[3,45,46]

We identified only three randomized thromboprophylaxis trials[28,31,32] in critical care patients that used routine screening with an objective diagnostic test for DVT

Table 2—*Prospective Studies Evaluating the Rates of DVT in Critical Care Patients

Source	ICU Setting	Design	DVT Screening Test	Patients, No.	DVT, %
Moser et al[9] (1981)	Respiratory ICU	Prospective cohort	Fg LS for 3–6 d	23	13
Cade[31] (1982)	General ICU	Blinded RCT	Fg LS for 4–10 d	Approximately 60	29
Kapoor et al[32] (1999)	Medical ICU	Blinded RCT	Serial duplex ultrasound	390	31
Fraisse et al[28] (2000)	Ventilated COPD	Blinded multicenter RCT	Venography	85	28

*Adapted from Geerts et al[4] with permission. Includes studies in which no prophylaxis was administered to critical care unit patients and routine screening with objective diagnostic tests was used. Fg LS = ^{125}I-fibrinogen leg scanning; RCT = randomized clinical trial.

(Table 3). The trial reported by Cade[31] > 20 years ago randomized 119 general ICU patients to treatment with either placebo or low-dose heparin (LDH), 5,000 U subcutaneously q12h. Serial fibrinogen leg scanning detected DVT in 29% and 13% of the placebo and LDH groups, respectively (relative risk reduction with LDH, 55%; $p < 0.05$). Rates of proximal DVT and bleeding were not reported. In the second prophylaxis trial,[32,33] LDH was compared to placebo in patients admitted to a medical ICU. Serial Doppler ultrasonography detected DVT in 31% of the 390 control patients and 11% of the 401 patients who were administered LDH (relative risk reduction with LDH, 65%; $p = 0.001$). PE was found in 5% and 2% of placebo-treated and heparin-treated patients, respectively. Proximal DVT and bleeding rates were not reported.

In the most recent randomized trial,[28] 223 patients who were receiving mechanical ventilation for an exacerbation of COPD were assigned placebo or the low-molecular-weight heparin, nadroparin, until they were weaned from mechanical ventilation or for 21 days, whichever occurred sooner. After a mean prophylaxis duration of 12 days, contrast venography detected DVT in 28% of placebo-treated patients and in 15% of those receiving nadroparin (relative risk reduction with nadroparin, 45%; $p = 0.045$). Major bleeding occurred in 3% and 6% of the placebo and nadroparin groups, respectively (p = not significant).

Three additional, nonrandomized studies[20,21,27] demonstrate high rates of DVT (12 to 33%) in ICU patients who received prophylaxis. Despite the use of thromboprophylaxis with LDH or intermittent pneumatic compression in 61% of 100 medical ICU patients, thrombosis was detected by twice-weekly Doppler ultrasound imaging in 33% of patients; of these, 28% were leg thrombi and the remaining 5% were upper-extremity thrombi related to central venous catheters.[20] In a second study, 102 medical-surgical ICU patients underwent Doppler ultrasonography of the legs 4 to 7 days after ICU admission.[27] Despite the use of thromboprophylaxis with LDH or intermittent pneumatic compression devices in 92% of these patients, 12% were reported to have DVT. Ibrahim et al[21] screened 110 medical ICU patients with weekly duplex ultrasonography of the upper and lower extremities. Despite the use of LDH or sequential compression devices in all of the patients, 24% acquired DVT (19% in the leg veins and 5% in an upper extremity).

Thromboprophylaxis Use in Critical Care Patients

Over the past decade, a number of studies[16,17,47–58] have assessed the use of thromboprophylaxis in critical care units (Table 4). Ten of these 14 audits have been presented as abstracts, and only one study[55] assessed the use of prophylaxis in multiple critical care units. Average compliance with the use of some form of thromboprophylaxis among the 3,654 pooled patients was 69%, with a range of 33 to 100% in the individual studies. These rates of prophylaxis use suggest that critical care physicians consider thromboembolism to be an important problem worthy of preventive interventions. Nevertheless, 31% of critically ill patients received no prophylaxis, and compliance with "accepted" prophylaxis was reported in only one study.[55] Among patients at increased bleeding risk, a recent study[58] found that thromboprophylaxis, including mechanical methods, was underutilized. These reports likely underestimate overall compliance with prophylaxis since the critical care units surveyed may well have a greater awareness of thromboembolic complications and prophylaxis than the average critical care unit. Although it appears that the frequency of thromboprophylaxis use in critically ill patients has increased over the past decade, strategies to ensure compliance are not commonly employed.[50,55] In a prospective survey[55] of Canadian surgical ICUs, only 2 of the 34 centers used preprinted orders or a thromboprophylaxis practice guideline.

One study[50] compared strategies to improve thromboprophylaxis use among 1,827 patients in three similar critical care units. Appropriate thromboprophylaxis was used in 38% of patients in the ICU in which no special compliance intervention was used, in 62% of patients in the unit in which education about DVT prophylaxis was provided to physicians, and in 97% of the patients in the third ICU in which prophylaxis education was combined with mandatory computer order entry ($p < 0.01$ for all comparisons).

Prevention of VTE in Critical Care

In view of the high risk of thrombosis in critically ill patients, it is essential for critical care units to develop a policy for thromboprophylaxis.[4,6] The three published trials[28,31,32] of prophylaxis conducted in critical care patients suggest that both LDH and low-molecular-weight

Table 3—*Thromboprophylaxis Trials in Critically Ill Patients

Source	Method of Diagnosis	Intervention		DVT, No./Total Patients (%)	
		Control	Experimental	Control	Experimental
Cade[31] (1982)	Fg LS for 4–10 d	Placebo	Heparin, 5,000 U SC bid	NR/NR (29)	NR/NR (13)
Kapoor et al[32] (1999)	DUS on admission and every 3 d	Placebo	Heparin, 5,000 U SC bid	122/390 (31)	44/401 (11)
Fraisse et al[28] (2000)	Venography before day 21	Placebo	Nadroparin, approximately 70 AXa U/kg SC qd	24/85 (28)	13/84 (15)

*Adapted from Geerts et al[4] with permission. Includes randomized trials in which routine screening with an objective diagnostic test for DVT was used. AXa = anti-factor Xa; DUS = duplex ultrasonography; NR = not reported; SC = subcutaneously; see Table 2 for expansion of other abbreviation.

Table 4—*Thromboprophylaxis Utilization in Critically Ill Patients

Source†	Type of ICU	Admissions, No.	Prophylaxis Use, %
Keane et al[16] (1994)	Medical	161	33
Peters et al[47] (1997a)	Medical/surgical	100	45
Ibrahimbacha et al[48] (1998a)	Medical	145	53
Ibrahimbacha et al[49] (1998a)	Medical	71	86
Levi et al[50] (1998a)	Not reported	645‡	40‡
		584	64
		598	99
Ryskamp and Trottier[51] (1998)	Medical/surgical	209	86
Cook et al[17] (2000)	Medical/surgical	93	63
Gurkin et al[52] (2000a)	Surgical	329	74
Rodriguez et al[53] (2000a)	Medical	45	78
Thurm et al[54] (2000a)	Medical	24	100
Cook et al[55] (2001)	Surgical	89	98
Lentine et al[56] (2002a)	Medical	342	74
Mysliwiec et al[57] (2002a)	Medical	116	84
Rocha and Tapson[58] (2002a)	Medical	103	76

*Modified from Geerts et al[4] with permission.
†The letter "a" after the year of publication indicates that the study has been presented only in abstract form to date (to our knowledge).
‡The three groups represent a control group and two strategies to improve prophylaxis compliance (see text).

heparin are efficacious in reducing asymptomatic DVT. Extensive evidence from clinical trials[3,39,59] in other patient groups, including the areas of acute medical illnesses, general surgery, neurosurgery, orthopedics, and trauma, provide important insights into effective and safe thromboprophylaxis methods that are likely to be relevant to critical care patients.

The following principles summarize our views about thromboprophylaxis in critical care patients:

1. An essential component of the assessment of all ICU admissions should be a review of thromboembolic risks and a consideration of thromboprophylaxis.
2. With few exceptions, some form of thromboprophylaxis should be used in all ICU patients, and should be commenced as soon as possible.
3. Decisions regarding the initiation of prophylaxis and selection of the specific method of prophylaxis should be individualized and based on each patient's risks for bleeding and thrombosis (Fig 1, Table 5). In general, anticoagulant-based prophylaxis with LDH or low-molecular-weight heparin is recommended because there is a substantially greater body of literature demonstrating its efficacy compared to mechanical prophylaxis and since the latter is often associated with poor compliance. LDH is appropriate for patients at low-to-moderate thrombosis risk, while low-molecular-weight heparin is recommended for high-risk patients since it is more efficacious in other high-risk groups such as those with major trauma or following orthopedic procedures.[3,59] However, for patients at high risk for bleeding, mechanical prophylaxis with either graduated antiembolic compression stockings alone or stockings combined with intermittent pneumatic compression devices is recommended until the bleeding risk decreases.[3,60] Combined pharmacologic and mechanical methods of prophylaxis may provide greater protection than either alone, although to our knowledge, this approach has never been tested rigorously in the ICU setting. Sequential prophylaxis, with the use of mechanical devices during an initial high bleeding risk phase followed by anticoagulant prophylaxis should be considered in relevant critical care patients.
4. Prophylaxis should be reviewed daily and changed, if necessary, taking into consideration each patient's overall clinical status on that particular day.
5. Prophylaxis should generally not be interrupted for procedures or surgery unless there is a particularly

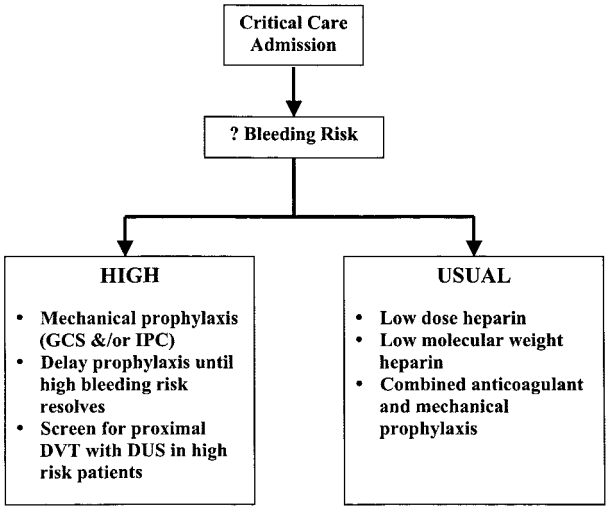

FIGURE 1. Initial prophylaxis considerations in critical care patients. Adapted from Geerts et al[4] with permission. GSC = graduated compression stockings; IPC = intermittent pneumatic compression; DUS = Doppler ultrasound.

Table 5—*Prophylaxis Recommendations in Critically Ill Patients

Bleeding Risk	Thrombosis Risk†	Prophylaxis Recommendations
Low	Moderate	LDH (heparin 5,000 U SC bid)
Low	High	LMWH (4,000–6,000 AXa U/d)
High	Moderate	GCS or IPC → LDH when bleeding risk decreases
High	High	GCS or IPC → LMWH when bleeding risk decreases

*Adapted from Geerts et al[4] with permission. LMWH = low-molecular-weight heparin; see Table 3, Figure 1 for expansion of other abbreviations.

†High-risk patients include those who have had major trauma or spinal cord injury, major hip or knee surgery, or major surgery for cancer.

high bleeding risk. The insertion or removal of epidural catheters should coincide with the nadir of the anticoagulant effect.

6. Routine screening of patients for asymptomatic DVT is not recommended since this strategy is neither effective nor cost-effective.[19,27,45,61,62] However, for selected high-risk patients who have not received adequate prophylaxis either before or during ICU admission, a single proximal Doppler ultrasound examination will identify patients who require a therapeutic intervention (ultrasound positive) or prophylaxis (ultrasound negative).
7. At the time of discharge from the critical care unit, further thromboprophylaxis recommendations should be included in the transfer orders.
8. Each critical care unit should have a written prophylaxis policy that is updated periodically as new evidence emerges.
9. Compliance with the prophylaxis policy should be enhanced with regular interactive education, the active involvement of a pharmacist on daily ICU rounds, preprinted orders, reminders, and computer decision support systems if possible.[50,51,63,64]
10. Adherence to the thromboprophylaxis policy should be assessed using audits and, if suboptimal, local quality improvement efforts should be undertaken.

Conclusion

Careful study of VTE in critical care patients has lagged behind many other patient groups because of the marked heterogeneity among critically ill patients with respect to their thrombosis and bleeding risks as well as in their lengths of stay and survival, and because routine screening is either more difficult to perform or may be less reliable in these patients. Since most critical care patients have a moderate or high thrombosis risk, they warrant thromboprophylaxis. Although more research in this area is urgently required,[4] information related to other patient groups should be combined with the results of the published ICU-specific studies to guide the selection of prophylaxis in this setting. The routine use of thromboprophylaxis is the most effective strategy to decrease the consequences of thromboembolic disease in these patients and thereby improve both patient outcomes and reduce costs following critical illness.

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