

VTE prophylaxis in critical care patients

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Chest 2003; 124:357S-363S

Risks

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.

Deep-vein thrombosis (DVT) and pulmonary embolism (PE) contribute significantly to morbidity and mortality associated with critical illness. 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%). 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. Many of these thrombosis risk factors precede the ICU admission, while others develop during the course of ICU stay. Factors that have been reported to predict an increased risk of ICU-related VTE include the following: increased age, previous VTE, malignancy, major trauma, prolonged pre-ICU hospital stay, mechanical ventilation, use of paralytic drugs, APACHE (acute physiology and chronic health evaluation) score, need for emergency surgical procedures, insertion of a femoral venous catheter, and failure to use thromboprophylaxis. 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.

After admission to the ICU, only four prospective studies used routine screening with an objective diagnostic test to assess the incidence of DVT in critically ill patients who were not administered thromboprophylaxis. One was a prospective cohort study, and three were randomized trials; one study has been presented in abstract form only. **Among these four prospective studies, 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 Fraise et al, who used contrast venography to detect thrombosis. Although the clinical consequences of asymptomatic DVT detected by routine screening are uncertain, a recent study 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.

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. 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.

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, DVT was detected in 6.4%.

Thromboprophylaxis studies in critical care

Only **three randomized thromboprophylaxis trials** have been conducted in critical care patients that used routine screening with an objective diagnostic test for DVT.

The trial reported by Cade 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, 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, 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 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. In a second study, 102 medical-surgical ICU patients underwent Doppler ultrasonography of the legs 4 to 7 days after ICU admission. 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 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).

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. The three published trials of prophylaxis conducted in critical care patients suggest that both LDH and low-molecular-weight heparin are efficacious in reducing asymptomatic DVT. Extensive evidence from clinical trials 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. 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. However, for patients at high risk for bleeding, mechanical prophylaxis with either graduated anti-embolic compression stockings alone or stockings combined with intermittent pneumatic compression devices is recommended until the bleeding risk decreases. Combined pharmacologic and mechanical methods of prophylaxis may provide greater protection than either alone, although 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.

Prophylaxis recommendations in critically ill patients

Thrombosis Risk	Bleeding Risk	
	Low	High
Moderate	Low Dose Heparin 5000 U SC Twice a Day	Graduated Compression Stockings or Intermittent pneumatic compression LMWH when bleeding risk decreases
High (Major trauma, spinal cord injury, major hip or knee surgery, major surgery for cancer)	LMWH 4000 – 6000 Anti-Xa once daily	Graduated Compression Stockings or Intermittent pneumatic compression LMWH when bleeding risk decreases

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 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. 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.

10. Adherence to the thrombo-prophylaxis policy should be assessed using audits and, if sub-optimal, local quality improvement efforts should be undertaken.

References

1. International Consensus Statement: prevention of venous thromboembolism. *Int Angiol* 1997;16,3-37[ISI][Medline]
2. Second Thromboembolic Risk Factors (THRIFT II) Consensus Group. Risk of and prophylaxis for venous thromboembolism in hospital patients. *Phlebology* 1998;13,87-97[ISI]
3. Geerts, WH, Heit, JA, Clagett, GP, et al Prevention of venous thromboembolism. *Chest* 2001;119(suppl),132S-175S[Free Full Text]
4. Geerts, W, Cook, D, Selby, R, et al Venous thromboembolism and its prevention in critical care. *J Crit Care* 2002;17,95-104[CrossRef][ISI][Medline]
5. Hoyt, DB, Swegle, JR Deep venous thrombosis in the surgical intensive care unit. *Surg Clin North Am* 1991;71,811-830[ISI][Medline]
6. Jain, M, Schmidt, GA Venous thromboembolism: prevention and prophylaxis. *Semin Respir Crit Care Med* 1997;18,79-90[ISI]
7. Davidson, BL Risk assessment and prophylaxis of venous thromboembolism in acutely and/or critically ill patients. *Haemostasis* 2000;30(suppl 2),77-81[ISI][Medline]
8. Neuhaus, A, Bentz, RR, Weg, JG Pulmonary embolism in respiratory failure. *Chest* 1978;73,460-465[Abstract]
9. Moser, KM, LeMoine, JR, Nachtwey, FJ, et al Deep venous thrombosis and pulmonary embolism: frequency in a respiratory intensive care unit. *JAMA* 1981;246,1422-1424[Abstract]
10. Pingleton, SK, Bone, RC, Pingleton, WW, et al Prevention of pulmonary emboli in a respiratory intensive care unit: efficacy of low-dose heparin. *Chest* 1981;79,647-650[Abstract]
11. Cullen, DJ, Nemeskal, AR The autopsy incidence of acute pulmonary embolism in critically ill surgical patients. *Intensive Care Med* 1986;12,399-403[ISI][Medline]
12. Blosser, SA, Zimmerman, HE, Stauffer, JL Do autopsies of critically ill patients reveal important findings that were clinically undetected? *Crit Care Med* 1998;26,1332-1336[ISI][Medline]
13. Mort, TC, Yeston, NS The relationship of pre-mortem diagnoses and post-mortem findings in a surgical intensive care unit. *Crit Care Med* 1999;27,299-303[ISI][Medline]
14. Dimopoulos, G, Paignerelli, M, Berre, J, et al Post-mortem examination rate in the ICU: is it still useful [abstract]? *Crit Care Med* 2000;28(suppl),A78
15. Willemssen, HW, Wester, JPJ, van Hattum, AH, et al The incidence of pulmonary embolism in a surgical intensive care unit [abstract]. *Crit Care Med* 2000;26(suppl 3),S242
16. Keane, MG, Ingenito, EP, Goldhaber, SZ Utilization of venous thromboembolism prophylaxis in the medical intensive care unit. *Chest* 1994;106,13-14[Abstract]
17. Cook, D, Attia, J, Weaver, B, et al Venous thromboembolic disease: an observational study in medical-surgical intensive care unit patients. *J Crit Care* 2000;15,127-132[CrossRef][ISI][Medline]
18. Selby, R, Geerts, WH Venous thromboembolism: risk factors and prophylaxis. *Semin Respir Crit Care Med* 2000;21,493-501[ISI]
19. Harris, LM, Curl, GR, Booth, FV, et al Screening for asymptomatic deep vein thrombosis in surgical intensive care patients. *J Vasc Surg* 1997;26,764-769[ISI][Medline]
20. Hirsch, DR, Ingenito, EP, Goldhaber, SZ Prevalence of deep venous thrombosis among patients in medical intensive care. *JAMA* 1995;274,335-337[Abstract]
21. Ibrahim, EH, Iregui, M, Prentice, D, et al Deep vein thrombosis during prolonged mechanical ventilation despite prophylaxis. *Crit Care Med* 2002;30,771-774[ISI][Medline]
22. Geerts, WH, Code, KI, Jay, RM, et al A prospective study of venous thromboembolism after major trauma. *N Engl J Med* 1994;331,1601-1606[Abstract/Free Full Text]
23. Trottier, SJ, Veremakis, C, O'Brien, J, et al Femoral deep vein thrombosis associated with central venous catheterization: results from a prospective, randomized trial. *Crit Care Med* 1995;23,52-59[ISI][Medline]
24. Durbec, O, Viviand, X, Potie, F, et al A prospective evaluation of the use of femoral venous catheters in critically ill adults. *Crit Care Med* 1997;25,1986-1989[ISI][Medline]
25. Timsit, J-F, Farkas, J-C, Boyer, J-M, et al Central vein catheter-related thrombosis in intensive care patients: incidence, risk factors, and relationship with catheter-related sepsis. *Chest* 1998;114,207-213[Abstract]
26. Joynt, GM, Kew, J, Gomersall, CD, et al Deep venous thrombosis caused by femoral venous catheters in critically ill adult patients. *Chest* 2000;117,178-183[Abstract/Free Full Text]
27. Marik, PE, Andrews, L, Maini, B The incidence of deep venous thrombosis in ICU patients. *Chest* 1997;111,661-664[Abstract]

28. Fraise, F, Holzapfel, L, Couland, J-M, et al Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. *Am J Respir Crit Care Med* 2000;161,1109-1114[Abstract/Free Full Text]
29. Goldberg, SK, Lippmann, ML, Walkenstein, MD, et al The prevalence of DVT among patients in respiratory failure: the role of DVT prophylaxis [abstract]. *Am J Respir Crit Care Med* 1996;153,A94
30. Schonhofer, B, Kohler, D Prevalence of deep-vein thrombosis of the leg in patients with acute exacerbation of chronic obstructive pulmonary disease. *Respiration* 1998;65,171-177[CrossRef][ISI][Medline]
31. Cade, JF High risk of the critically ill for venous thromboembolism. *Crit Care Med* 1982;10,448-450[ISI][Medline]
32. Kapoor, M, Kupfer, YY, Tessler, S Subcutaneous heparin prophylaxis significantly reduces the incidence of venous thromboembolic events in the critically ill [abstract]. *Crit Care Med* 1999;27(suppl),A69
33. Kupfer, Y, Anwar, J, Senenviratne, C, et al Prophylaxis with subcutaneous heparin significantly reduces the incidence of deep venous thrombophlebitis in the critically ill [abstract]. *Am J Respir Crit Care Med* 1999;159(suppl),A519
34. Lensing, AWA, Hirsh, J 125I-fibrinogen leg scanning: reassessment of its role for the diagnosis of venous thrombosis in post-operative patients. *Thromb Haemost* 1993;69,2-7[ISI][Medline]
35. Agnelli, G, Radicchia, S, Nenci, GG Diagnosis of deep vein thrombosis in asymptomatic high-risk patients. *Haemostasis* 1995;25,40-48[ISI][Medline]
36. Flordal, PA, Bergqvist, D, Ljungstrom, K-G, et al Clinical relevance of the fibrinogen uptake test in patients undergoing elective general abdominal surgery: relation to major thromboembolism and mortality. *Thromb Res* 1995;80,491-497[CrossRef][ISI][Medline]
37. Baum, GL, Fisher, FD The relationship of fatal pulmonary insufficiency with cor pulmonale, rightsided mural thrombi and pulmonary emboli: a preliminary report. *Am J Med Sci* 1960;240,609-612[ISI][Medline]
38. Greene, R, Zapol, WM, Snider, MT, et al Early bedside detection of pulmonary vascular occlusion during acute respiratory failure. *Am Rev Respir Dis* 1981;124,593-601[ISI][Medline]
39. Attia, J, Ray, JG, Cook, DJ, et al Deep vein thrombosis and its prevention in critically ill patients. *Arch Intern Med* 2001;161,1268-1279[Abstract/Free Full Text]
40. Jackaman, FR, Perry, BJ, Siddons, H Deep vein thrombosis after thoracotomy. *Thorax* 1978;33,761-763[Abstract]
41. Collins, R, Scrimgeour, A, Yusuf, S, et al Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin: overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med* 1988;318,1162-1173[ISI][Medline]
42. Anderson, FA, Wheeler, HB, Goldberg, RJ, et al A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism: the Worcester DVT Study. *Arch Intern Med* 1991;151,933-938[Abstract]
43. Davis, JW, Hoyt, DB, McArdle, MS, et al The significance of critical care errors in causing preventable death in trauma patients in a trauma system. *J Trauma* 1991;31,813-819[ISI][Medline]
44. Shojania KG, Duncan BW, McDonald KM, et al, eds. Making health care safer: a critical analysis of patient safety practices. Evidence Report/Technology Assessment No. 43 (prepared by the University of California at San Francisco-Stanford Evidence-based Practice Center under Contract No. 290-97-0013). AHRQ Publication No. 01-E058. Rockville, MD: Agency for Healthcare Research and Quality, July 2001. Available at: www.ahrq.gov/clinic/ptsafety/. Accessed November 17, 2003
45. Bergqvist, D, Lindgren, B, Matzsch, T Cost-effectiveness of preventing postoperative deep vein thrombosis. Hull, RD Pineo, GF eds. Disorders of thrombosis. 1996,228-233 WB Saunders. Philadelphia, PA:
46. Bick, RL Proficient and cost-effective approaches for the prevention and treatment of venous thrombosis and thromboembolism. *Drugs* 2000;60,575-595[ISI][Medline]
47. Peters, JT, Melillo, NG, Pesin, JL, et al Analysis of deep venous thrombosis prophylaxis in an intensive care unit [abstract]. *Chest* 1997;112(suppl),155S
48. Ibrahimbacha, A, Basir, R, Chandra, A Utilization of venous thromboembolism prophylaxis in the medical intensive care unit [abstract]. *Am J Respir Crit Care Med* 1998;157,A302
49. Ibrahimbacha, A, Bacha, GI, Alnajjar, M Improvement in utilization of venous thromboembolism (VTE) prophylaxis in the medical intensive care unit (MICU) [abstract]. *Chest* 1998;114(suppl),392S
50. Levi, D, Kupfer, Y, Seneviratne, C, et al Computerized order entry sets and intensive education improve the rate of prophylaxis for deep vein thrombophlebitis [abstract]. *Chest* 1998;114(suppl),280S

51. Ryskamp, RP, Trottier, SJ Utilization of venous thromboembolism prophylaxis in a medical-surgical ICU. *Chest* 1998;113,162-164[Abstract]
52. Gurkin, MA, Parikshak, M, Horst, HM, et al Risk assessment and prophylaxis of venous thromboembolic disease in critically ill patients [abstract]. *Crit Care Med* 2000;28(suppl),A179
53. Rodriguez, J, Maluf, C, Diaz-Fuentes, G Multi disciplinary approach to increase the compliance for deep venous thrombosis (DVT) prophylaxis [abstract]. *Am J Respir Crit Care Med* 2000;161,A639
54. Thurm, CA, Pinsker, R, Rao, SD, et al Utilization of venous thromboembolism prophylaxis in medical patients [abstract]. *Chest* 2000;118(suppl),259S
55. Cook, DJ, Laporte, D, Skrobik, Y, et al Prevention of venous thromboembolism in critically ill surgery patients: a cross-sectional study. *J Crit Care* 2001;16,161-166[CrossRef][ISI][Medline]
56. Lentine, KL, Flavin, KA, Gould, MK Variability in the use of thromboprophylaxis and outcomes in critically ill medical patients [abstract]. *Chest* 2002;122,20S[CrossRef]
57. Mysliwiec, V, Arnold, H, Quinn, M, et al The utilization and effectiveness of prophylaxis for venous thromboembolism in mechanically ventilated patients [abstract]. *Am J Respir Crit Care Med* 2002;165,A329[CrossRef]
58. Rocha, AT, Tapson, VF Choice of venous thromboembolic disease prophylaxis in medical intensive care unit patients [abstract]. *Chest* 2002;122,212S
59. Geerts, WH, Jay, RM, Code, KI, et al A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. *N Engl J Med* 1996;335,701-707[Abstract/Free Full Text]
60. Rhoney, DH, Stensland, LP, Parker, D, et al Bleeding complications associated with early low-dose unfractionated heparin: comparison of neurosurgery (NICU) and medical (MICU) intensive care unit patients [abstract]. *Crit Care Med* 2000;28,A98
61. Robinson, KS, Anderson, DR, Gross, M, et al Ultrasonographic screening before hospital discharge for deep venous thrombosis after arthroplasty: the Post-Arthroplasty Screening Study; a randomized, controlled trial. *Ann Intern Med* 1997;127,439-445[Abstract/Free Full Text]
62. Cipolle, MD, Wojcik, R, Seislove, E, et al The role of surveillance duplex scanning in preventing venous thromboembolism in trauma patients. *J Trauma* 2002;52,453-462[ISI][Medline]
63. Durieux, P, Nizard, R, Ravaud, P, et al A clinical decision support system for prevention of venous thromboembolism: effect on physician behavior. *JAMA* 2000;283,2816-2821[Abstract/Free Full Text]
64. Dexter, PR, Perkins, S, Overhage, JM, et al A computerized reminder system to increase the use of preventive care for hospitalized patients. *N Engl J Med* 2001;345,965-970[Abstract/Free Full Text]