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Thrombosis Prophylaxis and Mortality Risk Among Critically Ill Adults

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BACKGROUND: The optimal approach for managing increased risk of VTE among critically ill adults is unknown.

METHODS: An observational study of 294,896 episodes of critical illness among adults was conducted in 271 geographically dispersed US adult ICUs. The primary outcomes were all-cause ICU and in-hospital mortality after adjustment for acuity and other factors among groups of patients assigned, based on clinical judgment, to prophylactic anticoagulation, mechanical devices, both, or neither. Outcomes of those managed with prophylactic anticoagulation or mechanical devices were compared in a separate paired, propensity-matched cohort.

RESULTS: After adjustment for propensity to receive VTE prophylaxis, APACHE (Acute Physiology and Chronic Health Evaluation) IV scores, and management with mechanical ventilation, the group treated with prophylactic anticoagulation was the only one with significantly lower risk of dying than those not provided VTE prophylaxis (ICU, 0.81 [95% CI, 0.79-0.84]; hospital, 0.84 [95% CI, 0.82-0.86; $P < .0001$). The mortality risk of those receiving mechanical device prophylaxis was not lower than that of patients without VTE prophylaxis. A study of 87,107 pairs of patients matched for propensity to receive VTE prophylaxis found that those managed with prophylactic anticoagulation therapy had significantly lower risk of death (ICU subhazard ratio, 0.82 [95% CI, 0.78-0.85]; hospital subhazard ratio, 0.82 [95% CI, 0.79-0.85]; $P < .001$) than those receiving only mechanical device prophylaxis.

CONCLUSIONS: These findings support a recommendation for prophylactic anticoagulation therapy in preference to mechanical device prophylaxis for critically ill adult patients who do not have a contraindication to anticoagulation. CHEST 2014; 146(1):51-57

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ABBREVIATIONS: APACHE = Acute Physiology and Chronic Health Evaluation; JC = Joint Commission; NQF = National Quality Forum; SHR = subhazard ratio

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Evidence-based strategies used for the prevention of venous thrombosis vary based on the specific risk-benefit profiles in studied populations. The ninth edition of the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis guidelines recommend VTE prophylaxis tailored to VTE risk, treatment effects, and strength of evidence, which are distinct for a growing number of populations.[1] High-quality evidence, including evidence of mortality benefits,[2] supports the use of prophylactic anticoagulation (Grade 1B) or mechanical devices (Grade 1C) over no prophylaxis for high-risk surgical patients.[3] The association of VTE prophylaxis and mortality outcomes is much less clear, and the quality of the evidence for clinical practice guidelines is weaker for critically ill adults than for high-risk surgical populations.

Current guidelines are supported by studies demonstrating that critically ill adults are at increased risk for venous thrombosis[4] and that incidence of symptomatic DVT and fatal pulmonary embolism in hospitalized medical patients can be reduced by anticoagulants.[5-7] The quality of the evidence supporting prophylactic anticoagulation therapy over no prophylaxis and for the use of graduated compression stockings or mechanical devices for patients who are bleeding or at high risk of bleeding is Grade 2C. Recommendations regarding the choice of anticoagulation or mechanical devices are weak in part because a randomized trial of elastic stockings with or without enoxaparin in medical patients did not detect significant differences in all-cause mortality.[8] The low quality of the evidence regarding the effectiveness of alternative forms of VTE prophylaxis for critically ill adults has led to weak recommendations and heterogeneity of practice.

We measured the heterogeneity of current practice and investigated the associations among the alternative approaches to VTE prophylaxis and all-cause mortality. The overarching aim of this study is to improve the quality of the available evidence by identifying VTE prophylaxis strategies associated with lower all-cause mortality among critically ill adults.

Materials and Methods

The primary outcomes of this cohort study were adjusted ICU and hospital mortality among groups of critically ill adults managed with prophylactic anticoagulation therapy, thromboprophylaxis with a mechanical device, both, or neither, as assigned by clinical judgment. The study included all adult patients discharged alive or dead from participating ICUs from January 1, 2008, to September 30, 2010. Data were derived from patient information contained in the Philips eICU Research Institute data repository,[9] using abstraction, privacy protection, data aggregation, and mapping techniques as previously described.[10] Observations were entered by clinicians or transferred from a clinical information system and mapped to equivalent concepts in the eICU Research Institute database. Consistent physiologic, laboratory, diagnosis, treatment, physical examination elements, and nursing flow sheet data were included in the electronic record for all patients for the duration of their ICU stay. Acuity was measured using APACHE (Acute Physiology and Chronic Health Evaluation) IV software sublicensed from Cerner Corp.

VTE Best Practice Adherence

The VTE prophylaxis criteria were concordant with those endorsed by the Joint Commission (JC) and the National Quality Forum (NQF) for critically ill adult patients (NQF #0372). All adults with an ICU patient stay $>$ 24 h were considered for inclusion. Exclusion criteria were documentation in the medical record indicating that the patient was ambulating, coagulopathic, or fully anticoagulated or received a thrombin inhibitor (argatroban, bivalirudin, lepirudin, or refludan) during the first 24 h of ICU stay. Patients were classified as being treated with a mechanical device when the medical record indicated that either an inferior vena cava filter or a compression device (boots or stockings) was in use. They were classified as receiving prophylactic anticoagulation therapy when an order for an anticoagulant medication (dabigatran, dalteparin, enoxaparin, fondaparinux, heparin, tinzaparin, or warfarin) was present or as receiving a combination of a device and prophylactic anticoagulation when both were documented. The time of prescription was recorded as within or $>$ 48 h after ICU admission. The medical record was reviewed by an off-site team tasked with confirming that the approach was adherent to the JC/NQF ICU thromboprophylaxis measures. All drug orders were reviewed by a pharmacist. Patients managed with mechanical devices, which are classified as JC/NQF measure-adherent for the purposes of this study, would not be classified as adherent to the ninth edition of the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis guidelines[3] when they did not have a contraindication to anticoagulation.

Statistical Analyses

Patient characteristics were compared among groups managed with alternative approaches to preventing venous thrombosis (ie, prophylactic anticoagulation, mechanical device thromboprophylaxis, both, neither). Continuous variables were reported as means and SDs, and categorical variables were reported as counts and percentages. Group comparisons were made using the χ^2 test for categorical variables and analysis of variance for continuous data, as appropriate. Because of the large sample size, statistical significance was set at the 0.01 level using two-sided distributions. Logistic regression was performed with mortality as the dependent variable. The ORs for mortality of the various treatment groups were estimated using the group that did not receive VTE prophylaxis as the reference, with and without adjustment for covariates.

To control for potential confounding in the setting of not randomly assigning alternative management strategies, an inverse probability-weighted propensity score method was used to adjust for differences in selected risk factors among patients in the four alternative management groups. The probability of receiving one of the four VTE prophylaxis management strategies (prophylactic anticoagulation and mechanical device, prophylactic anticoagulation without a mechanical device, a mechanical device only, or no prophylaxis) was estimated by multinomial logit regression. The study patients were weighted by their inverse probabilities of being in their assigned group.[11,12] Variables that were not balanced after propensity score weighting were included in a logistic regression model with ICU or hospital mortality as the dependent variable.