IRB Protocol
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3/12/2007

Examining the Role for Venous Thromboembolism Prophylaxis in Low-risk Patients: Outcomes for Hospitalized Medical Patients who do not Receive Anticoagulant Prophylaxis

1. Study Purpose and Rationale

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is an important safety concern for patients in the hospital setting. Many hospitalized patients are at risk for developing symptomatic or fatal VTE and thus, comprehensive preventive strategies have become a priority. The most effective intervention for the prevention of VTE is the administration of a low-dose anticoagulant, usually unfractionated heparin or low-molecular-weight heparin[1]. The American College of Chest Physicians estimates that, without thromboprophylaxis, the burden of VTE is highest among critical care and trauma patients with a DVT prevalence that can be as high as 80%. Surgical patients have the second highest prevalence, particularly orthopedic patients who have a 40 to 60% risk of developing DVT after undergoing hip or knee arthroplasty. General medical patients have the lowest prevalence of DVT, between 10 and 20% without anticoagulant prophylaxis[1].

The benefit of anticoagulant prophylaxis has been clearly demonstrated in high risk patient populations, but the role for treatment has yet to be defined in low-risk patients. Multiple trials have shown a reduction in DVT, PE and mortality for surgical patients in the postoperative period[2]. The evidence of efficacy for anticoagulant prophylaxis is less convincing in medical patients. Randomized controlled trials evaluating thromboprophylaxis in moderate to high risk medical patients have shown a reduction in DVT, but no apparent effect on the incidence of PE or mortality. In the Medenox trial patients with severe congestive heart failure, acute respiratory failure, or other medical illness plus at least one VTE risk factor were randomized to receive enoxaparin or placebo during their hospitalization. The incidence of DVT was 14.9% in the placebo group and 5.5% in the treatment group (relative risk 0.37, $p < 0.001$), but there were no significant differences for the outcomes of PE and death[3]. Most studies in this area, including Medenox, use sensitive diagnostic tests to assess for any DVT as the primary study outcome. However, the majority of DVT that are diagnosed in this manner are confined to the calf, clinically silent, and do not progress to PE[1]. The combination of both symptomatic and asymptomatic DVT may not be a clinically meaningful outcome. A recent meta-analysis by Dentali et al. addressed this issue by extracting data from nine randomized controlled trials for *symptomatic* DVT, PE, and death from any cause. The study was unable to detect a statistically significant reduction in symptomatic DVT because most trials did not distinguish these events from clinically silent ones. Of note, there was a small reduction in PE events (relative risk 0.43 [CI 0.26 to 0.71], absolute risk reduction 0.29%, number needed to treat 345) but still no effect on all-cause mortality[4]. The weight of the evidence suggests that anticoagulant prophylaxis is effective for the prevention of DVT and PE in hospitalized medical patients who are at least at moderate risk for developing VTE. Efficacy in low-risk medical patients has not been studied.

Despite uncertainty about the benefit of treatment in lower risk patients, anticoagulant prophylaxis is currently recommended for essentially every hospitalized medical patient. The 2004 ACCP guidelines on antithrombotic therapy recommend routine thromboprophylaxis for all patients with "acute medical illness" (Grade 1A)[1]. This broad recommendation may be an over-extrapolation of the evidence, as hospitalized medical patients represent a heterogeneous population with variable levels of VTE risk. Patients with an acute medical illness, but without compelling VTE risk factors, may not derive benefit from anticoagulant prophylaxis. Serious complications are rare, but these anticoagulant regimens are associated with a slightly increased risk of bleeding and thrombocytopenia. Unfortunately, there is no evidence-based VTE risk assessment model to help guide therapy and potentially avoid adverse events in low-risk groups. Thus, recommendations for medical patients remain conservative.

There is a discrepancy between VTE prevention guidelines and actual clinical practice in hospitalized medical patients. Anticoagulant prophylaxis is only administered to approximately 16 to 33% of medical

inpatients[4]. This has been interpreted by some reviewers as a gross underutilization and generally poor VTE awareness among treating physicians. However, given the lack of convincing evidence in medical patients, it is possible that some of the apparent underutilization of thromboprophylaxis in this population reflects an intentional decision to not treat. Because risk stratification guidelines do not exist, there seems to be a role for clinical judgment in this area. Anticoagulant prophylaxis might be safely avoided in low-risk medical patients if this subgroup could be reliably identified. It is not unreasonable to stratify risk based on one's clinical experience with thromboembolic disease. A meta-analysis by Chunilal et al. showed that the clinical gestalt of experienced clinicians was equivalent to validated prediction rules for estimating the pretest probability of PE[5]. The hypothesis of this study is that clinical judgment is used to identify hospitalized medical patients who are at low risk for VTE and would likely not benefit from anticoagulant prophylaxis. Thus, treatment is intentionally withheld in this group. Medical patients who do not receive anticoagulant prophylaxis during their hospitalization may represent a pre-selected low-risk group who do not develop subsequent VTE.

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2. Study Design and Statistical Analysis

This will be an observational cohort study of hospitalized medical patients who, based on the clinical judgment of their treating physicians, do not receive anticoagulant prophylaxis for the prevention of VTE. These presumed low-risk patients will be followed prospectively for 6 months to assess for subsequent DVT, PE, or death from any cause. Outcomes will be assessed for the inpatient period as well as at 3 and 6 months after hospital admission. Total length of stay and number hospital days without anticoagulant prophylaxis will be recorded. Patients who are started on treatment after enrollment will continue to be followed. The two outpatient follow-up visits will include a focused history, physical examination and lower extremity venous ultrasound. If a patient is diagnosed with DVT, or if the investigators feel there is an intermediate or high suspicion for PE, further diagnostic testing will be performed (e.g. CT angiography). New York State hospital and census databases will be searched by social security number for all patients that are lost to follow-up. This will provide some information about hospitalizations and deaths that occur during the follow-up period. If subjects are hospitalized a second time within the 6 month study period, records will be obtained to identify the admitting diagnosis and any evidence of DVT or PE.

The statistical power for the study will be 80% with a significant P value less than 0.05. Assuming that an event rate of 1% or more is clinically unacceptable in this cohort, a sample size of 500 subjects is required to show that the actual incidence of DVT, PE, or death is less than 1%. There will be no case-controls for this study (i.e. patients who *are* given VTE prophylaxis during their hospitalization). This is because patients who receive anticoagulant prophylaxis are assumed to be at higher risk for VTE, and likely represent a different subgroup of medical patients. Ideally, the cohort of patients who are not given prophylaxis would be randomized to receive either anticoagulant or placebo injections during their hospitalization. Outcomes would be assessed for 6 months in the same way as outlined above. However, this study design is not feasible because an extremely large number of subjects would be required to show that there is no difference between the treatment and placebo groups.

A record will be kept for patients in whom anticoagulant prophylaxis was inappropriately withheld due to medical error. If patients with a strong VTE risk factor (and no contraindication to treatment) are recognized during the screening process, the lack of an active anticoagulant order will be considered a medical error and patients will be excluded from the primary study. Examples of such VTE risk factors are listed in "Study Subjects" below. The treating physicians will be alerted to the potential omission so that it may be corrected. These patients will be encouraged to enroll in a secondary cohort with the same outcome assessment over 6 months. If they are subsequently started on anticoagulant prophylaxis, the specific regimen and duration of therapy will be noted. The overall incidence of DVT, PE, and all-cause mortality in this group will then be compared with the primary "low-risk" cohort. The expectation is that patients who are not treated because of medical error will be much less likely to enroll in the study.

3. Study Procedures

None

4. Study Drugs

None

5. Medical Device
None

6. Study Questionnaires
There will not be a study questionnaire for patients to complete. Investigators will use a standardized form to gather data from the initial patient interview including demographic information, reason for hospitalization, complete medical history, known VTE risk factors (e.g. malignancy or recent surgery), suspected/potential VTE risk factors (e.g. obesity or hormone replacement therapy), and any contraindications to anticoagulation.

7. Study Subjects
Eligible subjects include all medical patients who have been hospitalized at the Columbia University Medical Center for at least 2 days without receiving an anticoagulant. Patients will be excluded from the primary study if they have an established VTE risk factor (i.e. surgery or immobilization within 4 weeks, malignancy, trauma, previous VTE or documented thrombophilia, recent stroke or myocardial infarction, ICU admission, central catheterization), a contraindication to anticoagulation, even at doses for VTE prophylaxis (i.e. heparin allergy, prior severe bleeding event, platelet count <50,000), pregnancy, or age >75 years old. No vulnerable populations will be included.

8. Recruitment of Subjects
Patients meeting inclusion criteria will be identified by reviewing census listings for the different inpatient medical teams. The admitting team will be contacted by investigators about the study. If the primary physician agrees that the patient is suitable for the study, the patient will then be approached by that physician. If the patient is amenable to discussing the research further, investigators will contact patients directly. Informed consent will be obtained from all participants.

It is important to note that the screening process itself may influence the practice of the treating physicians. In the case that anticoagulant prophylaxis is withheld because of medical error, not clinical judgment, that error may first be recognized by the study investigators. If patients with known VTE risk factors are recognized during screening, the issue will be discussed with the primary medical team. These cases will be noted as medical errors and patients will not be enrolled in the primary study, although they will be encouraged to enroll in a secondary cohort.

9. Confidentiality of Study Data
Patients admitted to a medicine team at the Columbia University Medical Center will be identified by medical record number and their hospitalization will be reviewed. Only HIPAA-certified researchers will be permitted to access this protected information. Patients who give informed consent and are actually enrolled in the study will be given a de-identified subject code based on their first and last name initials and last four digits of their social security number. Standard measures will be taken to limit inappropriate access to study data including removing face sheets, properly disposing of papers, using password-protected computers, and storing research records in a secure location. All study data will be kept in a locked file cabinet in a locked office.

10. Potential Conflict of Interest
There is no financial benefit for the study investigators.

11. Location of the Study
The primary study locations will be the inpatient medical wards at the Columbia University Medical Center, which includes Milstein Hospital and the Allen Pavilion. Outpatient follow-up visits will take place at the Associates in Internal Medicine clinic at CUMC.

12. Potential Risks
In some cases, the lack of anticoagulant prophylaxis on admitting orders may be a result of medical error rather than clinical judgment. There is a clear risk of VTE or even death if treatment is inappropriately withheld, although this potential risk is not introduced by the study protocol itself.

13. Potential Benefits
As this study has no intervention or treatment, there is no direct benefit to subjects. The major benefit of the study is to further our understanding of the role for VTE prophylaxis in hospitalized medical patients. It is possible that during the 6 month outpatient follow-up period, a DVT or PE might be diagnosed sooner than if the patient was not in the study.

14. Alternative Therapies
Anticoagulant prophylaxis for the prevention of VTE is currently recommended for all hospitalized medical patients, but the actual benefit of treatment for low risk patients has yet to be defined. The uncertainty in this area will be explained to patients, as well as the discrepancy between treatment guidelines and actual clinical practice. It will be made clear that the alternative therapy is to give anticoagulant prophylaxis to all patients.

15. Compensation to Subjects
Patients will be paid $20 per visit, in addition to compensation for travel costs, for each of the two outpatient follow-up visits.

16. Costs to Subjects
There will be no cost to patients. Independent funding will be obtained for outpatient clinic services and leg vein ultrasonography.

17. Minors as Research Subjects
No vulnerable subjects, including minors, will be included in the study.

18. Radiation Exposure
None

19. References
1. Geerts W, Pineo G, Heit J, Bergqvist D, Lassen M, Colwell C, Ray J. Prevention of Venous Thromboembolism: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126:338S-400S.

2. Agnelli G. Prevention of Venous Thromboembolism in Surgical Patients. *Circulation*. 2004;110[suppl 1]:IV4-12.

3. Samama M, Cohen A, Darmon J, Desjardins L, Eldor A, Janbon C, Leizorovicz A, Nguyen H, Olsson C, Turpie A, Weisslinger N. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med*. 1999;341:793-800.

4. Dentali F, Douketis J, Gianni M, Lim W, Crowther M. Meta-analysis: Anticoagulant Prophylaxis to Prevent Symptomatic Venous Thromboembolism in Hospitalized Medical Patients. *Ann Intern Med.* 2007;146:278-88.

5. Chunilal S, Eikelboom J, Attia J, Miniati M, Panju A, Simel D, Ginsberg J. Does This Patient Have Pulmonary Embolism? *JAMA* 2003;290:2849-58.