

A comparison of six months of anticoagulation with extended anticoagulation for a first episode of venous thromboembolism in patients with thrombophilia

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A. Objective

- a. To evaluate the risk of recurrence in patients with known thrombophilia after a first episode of venous thromboembolism.
- b. To evaluate the risk of bleeding complications associated with long-term anti-coagulation in patients with known thrombophilia.

B. Background

- a. Between 1992 and 1995, the first of three prospective randomized controlled trials with enough statistical power to study the duration of anticoagulation after an initial thromboembolic event were published^{i,ii,iii}. In each study, longer treatment resulted in fewer thromboembolic complications without significant increase in bleeding complications. In 1997, a prospective randomized trial (DURAC II) compared 6 months of warfarin to indefinite treatment for patients who had had a second venous thromboembolism^{iv}. After 4 years of follow-up, thromboembolic events were significantly lower in the indefinite group 2.6% compared to the 6 month group 20.7%. Actual reduction may be even greater, since there were 4 other suspected cases of thromboembolism in the 6 month group that did not meet objective criteria for dx & were not included in the analysis. However, there was a trend toward increased bleeding complications (3 major bleeds in 6 month group with only 1 while receiving warfarin and 10 major bleeds in indefinite group). When both bleeding & thrombotic complications were combined, overall complications were lower in the indefinite group.
- b. Although all of these studies included slightly different populations, each study attempted to exclude patients with known major risk factors. The general recommendation that evolved from these studies was to classify patients according to risk. Low-risk pts with temporary risk factors were treated with 4-6 wks after the risk factor ceased to be present. Intermediate risk groups were to get 6 months. High risk groups, including patients with recurrent thromboembolism, cancer, and anti-phospholipid antibody syndrome were to get indefinite treatment.

C. Rationale for Study

- a. In spite of the recommendations which have evolved up this time, a large, multi-center, randomized controlled trial has not yet been undertaken to study the benefits of indefinite treatment for high-risk patients. It remains unclear if the risk of recurrent thromboembolism varies over time in patients with thrombophilia. Certainly, indefinite anticoagulation carries the risk of increased bleeding complications. Therefore, there may be an optimal period of anticoagulation in patients with thrombophilia which will decrease the risk of recurrent thromboembolism while minimizing the risk of bleeding complications.

D. Study Set-up

a. Recruitment of Subjects

- i. Consecutive patients admitted for the treatment of DVT and/or PE will be identified and approached about study enrollment. The risks and benefits of short-term and long-term anticoagulation will be explained.
- ii. There will be no compensation for participation in this study except that all anticoagulation medications will be provided without expense to the patient.

b. Eligibility Criteria**i. Inclusion criteria**

1. Patients must be experiencing the first episode of symptomatic venous thromboembolism defined as proximal deep vein thrombosis or pulmonary embolism. (Diagnosis criteria as defined below)
2. Patients must have completed an initial 6 months of uninterrupted anticoagulation (either coumadin or low-molecular weight heparin).
3. After a 3 week period off anti-coagulation, patients will undergo testing for the following conditions of thrombophilia:
 - deficiency in ATIII
 - deficiency in protein C or protein S
 - factor V Leiden
 - G20210A PT gene mutation
 - anti-phospholipid Ab
 - anticardiolipin Ab (IgG or IgM)
 - lupus anticoagulant
 - hyperhomocysteinemia
 - nephrotic syndrome
 - cancer diagnosed with the last 5 years
4. Patients without known thrombophilia will not undergo additional work-up for occult malignancy. However, if malignancy is diagnosed during the 6 months of initial anti-coagulation, those patients will meet inclusion criteria.

ii. Exclusion criteria

1. Patients will be excluded if there is an identifiable transient thrombogenic risk factor defined as:
 - fracture or plaster casting of lower limb
 - confined to bed for 3 consecutive days in last 3 months
 - use of general anesthesia in last 3 months
2. Patients will also be excluded for the following reasons:
 - other indication for a/c
 - contraindication for a/c
 - on long-term NSAID, ticlopidine, sulfinpyrazone, dipyridamole
 - use of oral contraceptives
 - familial bleeding diathesis
 - major psychiatric d/o
 - pregnant or could be pregnant
 - allergy to contrast
 - life expectancy <2y
 - unable to complete f/u visits
 - likely non-compliant

E. Randomization

- a. Patients will be stratified by presentation into the following categories:
 - DVT alone
 - PE alone

- DVT and PE
- b. Patients will be randomized based on following parameters
 - clinical center
 - age
 - sex
 - racial/ethnic background
- c. Patients will be randomized based on thrombophilic risk factor into the following categories:
 - cancer-related
 - non-cancer-related
- d. Patients will be randomized to receive warfarin/low molecular weight heparin or to receive placebo for at least 24 months

F. Analysis

- a. Individuals with ATIII deficiency have a higher overall risk for thrombosis than protein C or S deficiencyⁱ while Factor V Leiden has a much lower risk. However, it is not uncommon to find Factor V Leiden in combination with other thrombophilic states given the high prevalence in the general population and has been found to increase the risk in patients with AT, PC, and PS deficiencies.ⁱⁱⁱ
- b. In the DURAC II study enrolling patients with a second thromboembolism, the risk of recurrence in patients treated for only 6 months was 20.7% while in the indefinitely treated the risk was 2.6%. The overall major bleeding risk for patients was 2.7% in the placebo arm and 8.6% in the indefinitely treated arm.^{iv}
- c. In the recent study enrolling patients with first episodes of idiopathic venous thromboembolism, 32% of enrolled patients were found to have a hereditary hypercoagulable state. After 3 months of anticoagulation, 7 of 27 thrombophilic patients (26%) had a recurrence in the placebo arm. While not explicitly stated, the risk of recurrence in the indefinitely treated arm was either 0% or 4.8%. The overall bleeding risk for patients was 1.4% per patient-year in the placebo arm and 11.5% per patient-year in the warfarin arm.ⁱ The major bleeding risk for patients was 0% per patient-year in the placebo arm and 3.8% per patient-year in the warfarin arm.
- d. The risk of recurrence in the thrombophilic patients to be selected in this study will likely lie between the risk of patients with recurrent episodes and the risk of patients treated only for three months. Therefore, we predict a risk of recurrence of 23% in the placebo arm and 2.5% in the treatment arm. Given this assumption and using the formula: $[n = 8 (p_1q_1 + p_2q_2)/d^2 + 2/d]$, the number of patients needed to be studied in each arm would be 48 to obtain a power of .80 at a significance of $p < 0.05$. Since the patients will be stratified between cancer-related and non-cancer related groups, we will aim to enroll 96 patients in each group.
- e. Assuming that the risk of bleeding in this study should be similar to previous studies, we predict the risk of major bleeding to be was 2% in the placebo arm and 8% in the indefinitely treated arm. Recurrent episodes and bleeding events will be compared between the two arms using the Fisher exact test (2-tailed). Death rates will be compared using an uncorrected chi-square test.

G. Confidentiality

- a. Patients will be informed that all genetic testing are for investigational purposes and such information will remain confidential.

H. Study Design

a. Anticoagulation

- i. If coumadin is used, the initial dose will be based on the INR on the day of randomization. An independent anti-coagulation monitor will send true INR results to the clinical centers for patients enrolled in the treatment arm. The anti-coagulation monitor will also send sham INR results to the clinical centers for patients enrolled in the placebo arm. The clinical centers will attempt to anti-coagulate all patients to a target INR of 2-3.
- ii. If low-molecular weight heparin is used, a weight-based dose will be administered intramuscularly.

b. Follow-up

- i. All patients will get a baseline VQ scans and LE dopplers.
- ii. Patients will be assessed every 3 months for the signs and symptoms of venous thromboembolism and hemorrhage. There will be no surveillance for asymptomatic venous thromboembolism

c. Outcomes

- i. All patients with signs & symptoms for venous thromboembolism will receive a LE doppler & VQ scan.
- ii. The diagnosis of a new DVT will be made on LE dopplers if there is a new area of non-compression in the common femoral or popliteal segments of the deep veins in the lower extremities.
- iii. The diagnosis of a new PE will be made by VQ scan if there is a new area of unmatched defects. If the VQ scan is nondiagnostic, the diagnosis will be made by LE dopplers, venography or pulmonary angiogram.
- iv. The diagnosis of a major hemorrhage will be made if it is clinically overt and associated with one of the following:
 - Hb fall 2 or transfuse PRBC 2u
 - retroperitoneal or intracranial hemorrhage
 - caused permanent discontinuation of the study drug
- v. **Any deaths occurring during the study will be classified by:**
 - PE
 - bleed
 - other or sudden death

I. Risks and Benefits**a. Risks**

- i. The potential risk of continuing indefinite anticoagulation is the risk for bleeding complications as listed above.
- ii. The potential risk of discontinuing anticoagulation after an initial treatment of six months is recurrence of venous thromboembolism as listed above.

J. Benefits

- a. The potential benefit of continuing indefinite anticoagulation is the prevention of recurrence of venous thromboembolism as listed above.
- b. The potential benefit of discontinuing anticoagulation after an initial treatment of six months is the minimization of bleeding complications as listed above.

K. References

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- iii. Levine MN, et al. Optimal duration of oral anticoagulant therapy: a RCT comparing 4 weeks with 3 months of warfarin in pts with prox DVT. *Thromb Haemost* 1995; 74:606-11
- iv. Schulman S, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. *N Engl J Med* 1997; 336:393-8
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- viii. Kearon C, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999; 340:901-7