



# CLINICAL HEMOSTASIS REVIEW

*An Update on Advances and Issues in Hemostasis*

## Recurrence of Thromboembolism: Determining Risk

Dorothy M. Adcock, MD

Deep venous thrombosis (DVT) and pulmonary embolus (PE) are the two most common forms of venous thromboembolic disease (VTE). Approximately 200,000 new thromboembolic events occur in the United States annually.

Once an individual has suffered a first episode of DVT or PE, their risk of recurrence is much higher than the incidence of VTE in the general population. Cumulative risk of recurrence reaches about 25% at 5 years and 30% at 10 years. Up to 25% of all VTE occur in those that have had a previous VTE. Risk for recurrence, although greatest in the first 6 to 12 months following the initial thrombosis, diminishes with time but never subsides. For this reason, VTE should be considered a chronic disorder. Morbidity and mortality increases with each recurrence. Recurrent PE is associated with a 15% mortality rate while recurrent DVT carries about a 2% mortality rate.

Risk of VTE recurrence is negligible during anticoagulant therapy, as long as the therapeutic range is maintained. With discontinuation of anticoagulation, risk of recurrence increases. Decreased risk of recurrent VTE, therefore, could be achieved by administering life-long anticoagulant therapy. This approach is not practical as anticoagulant therapy is associated with a 2-3 % annual risk of major hemorrhagic episodes. Furthermore, hemorrhagic risk increases in an elderly population, the very group at greater risk for VTE. The optimum duration of anticoagulant therapy following an initial VTE therefore must be balanced between the risk of recurrent thrombosis and the risk of bleeding. Following the first episode of VTE, the likelihood of recurrence decreases with time while the risk of bleeding secondary to anticoagulant therapy remains constant. Discontinuation of anticoagulant therapy ideally would occur when the risk of hemorrhage exceeds the risk for VTE recurrence. Better realization of the conditions that increase the risk of recurrence might allow individualization of duration of anticoagulant therapy. Applying the

---

Volume 19, Number 1  
First Quarter 2005

Objective: The reader will be able to identify risk factors that increase a patient's likelihood of suffering a recurrent venous thromboembolic event.

appropriate duration of thromboprophylaxis following VTE could have significant impact on morbidity and mortality.

Rates of recurrence are largely dependent on the characteristics of the initial clot, such as site of thrombosis, persistence of clot, whether development of the clot was spontaneous and if there are one or more underlying prothrombotic risk factors such as thrombophilia or malignancy. For each patient, a systematic approach to evaluating risk of recurrence should be applied, making certain to evaluate for the presence of underlying active cancer, the characteristics of the initial VTE, physical attributes of the patient and a host of laboratory parameters.

## Determining Risk for VTE Recurrence

### 1) Active Malignancy

The presence of active cancer at the time of occurrence of VTE is one of the strongest predictors of recurrence risk. Withdrawal of anticoagulant therapy in an individual with active cancer and VTE is associated with a 10% risk of developing recurrence within one year of discontinuation of therapy. In those with active malignancy, long-term anticoagulant therapy is generally recommended. Furthermore, in patients with active cancer, VTE recurrence may occur while on anti-vitamin K therapy. LMWH therapy has been shown to be more effective in patients with active cancer than warfarin therapy. Bleeding risks are similar whether the patient receives warfarin or LMWH although recurrence drops from 17% to 9% with LMWH therapy rather than the standard regimen of five days unfractionated heparin followed by anti-vitamin K therapy.

It is well known that different types of cancer vary in their risk for VTE. For example, visceral cancers such as primary pancreatic adenocarcinoma carries a greater VTE risk than thyroid cancer. Risk varies not only with the type of underlying malignancy, but also with the aggressiveness of the individual tumor, presence or absence of metastases and concomitant chemotherapy.

### 2) Characteristics of the Initial Thromboembolic Event

When determining risk for VTE recurrence, deciphering the characteristics of the initial thromboembolic event is paramount. The following characteristics should be determined: 1) was the initial thromboembolic event provoked or spontaneous, 2) if provoked, was the initiating factor a major (such as surgery or trauma) or minor risk factor (such as a long car ride), 3) if thrombosis was a DVT, was it more proximal or distal, 4) was there complete resolution of the clot and 5) was the initial event a DVT or PE? Historical features including previous episode of VTE and family history of thrombosis should also be obtained.

In general the risk for recurrence is greater if the initial VTE was unprovoked rather than incited due to a major or minor risk factor. It has been estimated that for a spontaneous VTE, the risk of recurrence at one year is 10% and this increases to 25% at 5 yrs. When the initial thromboembolic event is associated with a major thrombotic risk factor, such as abdominal surgery, the risk for recurrence at one year is 3% and

Clinical Hemostasis Review is published by Esoterix and is circulated to selected physicians. Copyright 2004. Esoterix is a leading laboratory services company providing esoteric testing in numerous disease corridors. The opinions expressed in the articles are those of the author(s) and do not necessarily reflect the opinions or recommendations of the advertisers, editors, or publisher. The publisher reserves copyright and renewal on all published material and such material may not be reproduced in whole or in part without written permission from the publisher. Consult the full prescribing information on any drugs or devices discussed.

All correspondence should be directed to the attention of the Editor, Clinical Hemostasis Review, 3176 S. Peoria Ct, Aurora, CO 80014.

is 10% at 5 years. Risk is intermediate if the initial VTE was provoked by a minor risk factor, estimated to be 5% in the first year and 15% over 5 years. Randomized trials indicate that three months of anticoagulant therapy is sufficient if a first episode of VTE was provoked by a transient risk factor but that at least six months of therapy is recommended if the initial thrombosis was spontaneous. Individuals with spontaneous thrombosis who are treated with only three months of anticoagulant therapy have up to a 27% risk of recurrence during the first year they discontinue anticoagulation. Extending anticoagulation for more than six months does not substantially reduce the risk of recurrence when treatment is discontinued. However, it has been recommended that in those individuals with minimal risk of major bleeding (less than 5% per year), extended therapy should be entertained.

Persistent DVT on ultrasound following three months of anticoagulant therapy has, in two independent studies, been reported to increase risk of recurrence two to three fold. Studies performed by the Hamilton group in Canada, however, could not corroborate this increased risk. In substantiation of this lack of correlation of DVT to persistent clot, Kearon has emphasized that with the exception of early recurrences associated with inadequate initial treatment, recurrent DVT is equally distributed between the initially affected and unaffected legs.

The location of VTE is an important factor in determining recurrence. The more distal the clot, the less likely recurrence will develop. For example, an individual who suffers an iliofemoral clot is more likely to suffer a recurrent VTE than an individual with a thrombosis involving a calf vein. Randomized trials indicate that six weeks of therapy is likely sufficient if the initial thromboembolic event was isolated to a calf vein. Thrombus that occurs proximal to the knee is treated with a minimum of three months of anticoagulation.

If the initial thrombotic episode was DVT, the patient is most likely to suffer a DVT with recurrence and likewise if the first event was a PE, 60% who suffer recurrence, have another PE. The mortality rate is higher with recurrent PE than DVT and, therefore, patients who suffer PE may be more likely to benefit from long-term anticoagulant therapy.

Recurrence of VTE is even greater if there has been more than one previous episode of venous thrombosis. The characteristics of the thrombotic episodes and duration of time between episodes must however be taken into consideration. If there is more than one previous episode of idiopathic VTE, long-term anticoagulation should be considered. In those patients who have suffered two provoked VTE more than ten years apart, six months of anticoagulant therapy may be reasonable.

### **3) Physical Attributes of the Patient**

Independent risk factors for recurrence include gender, age and body mass index (BMI). Two recent studies demonstrated that males appear to be at mildly increased risk of recurrence over females. Studies suggest that men are 1.5 to 3 times more likely than women to suffer recurrence. Age is an important risk factor for initial VTE, such that risk at 40 years of age is about 1 in 1000 and risk at 70 years of age is about 1 in 100. Older age is also associated with a higher risk of recurrence, such that risk is increased by 17% per decade increase in age. Risk of recurrence also increases by 24% per 10 kg/m<sup>2</sup> increase in BMI.

### **4) Laboratory Parameters**

Elevation of markers of coagulation activation at the end of anticoagulant treatment may indicate an increased risk for VTE recurrence. Markers of coagulation activation are sensitive indicators of in vivo blood coagulation and include markers of thrombin generation such as thrombin antithrombin complex (TAT) and prothrombin fragment 1.2 (PF1.2), as well as global indicators of coagulation and fibrinolysis such as D-dimer. In a prospective study of 139 patients who suffered VTE, markers of coagulation activation were measured the day before warfarin was discontinued and four weeks later. Elevated levels of PF1.2, measured four weeks after warfarin was discontinued, were seen in 71% with recurrence and in 31% without. Negative predictive value (NPV) of a normal PF1.2 four weeks after discontinuation of warfarin was 95% and the positive predictive value was 17%. Except for quantitative D-dimer, clinical utility of elevated markers of coagulation activation in the individual patient has not been realized. Large prospective studies evaluating the relationship of these parameters and VTE recurrence are lacking.

A number of published reports have evaluated the utility of measuring quantitative D-dimer to determine risk for recurrence. Palareti et al. evaluated the risk for recurrence in those given a 6-month course of oral anticoagulant therapy after a first episode of DVT. In this study of almost 600 patients, about 75% suffered DVT and the VTE event was unprovoked in 47%. Thrombophilia testing was performed and was identified in 21%. Only individuals

with lupus anticoagulants were excluded. Quantitative D-dimer levels were measured on three occasions, the day anticoagulant therapy was discontinued, once between days 21-37 post oral anticoagulant therapy (OAT) and at three months. Authors used the same D-dimer cut-off value suggested by the manufacturer to exclude VTE. At the time of OAT withdrawal, D-dimer levels above 500 ng/mL occurred in 15.6% but at 1 and 3 months, the positive rate was 40.3 and 46.2% respectively. This study also demonstrated that recurrence rate was higher for carriers of thrombophilia versus non-carriers (10.2% vs. 5.7%), the positive predictive value of thrombophilia was 16%. D-dimer levels less than the established cut off (<500 ng/mL FEU) measured one month after OAT was discontinued, had a very high negative predictive value for VTE recurrence of 94%. The high NPV of a negative D-dimer 1 to 3 months following discontinuation of anticoagulant therapy importantly held true for patients with thrombophilia and those who suffered an unprovoked VTE. Overall, VTE recurrence occurred in 16% with persistently increased D-dimer levels but in only 4% with levels below the pre-established cut-off.

In another study by Fattorini, the utility of evaluating D-dimer levels during anticoagulant therapy was evaluated. D-dimer levels were measured one month after initiation of anticoagulant therapy and measured thereafter throughout anticoagulant treatment in a subgroup of patients. Mean D-dimer levels were significantly higher in patients who developed VTE recurrence. Cut-off in this analysis was determined using the 60<sup>th</sup> percentile of the study patient's D-dimer distribution (1.1 ug/mL). Four of 84 patients with a mean D-dimer level below the cut-off developed DVT recurrence compared to 14 of 55 with D-dimer level above the cut-off. D-dimer levels and age were independent predictors of recurrence while the presence of cancer was not. In this study, the NPV was a d-dimer below the established cut-off was 95.2%. Analyzed in another way, the absolute probability of DVT recurrence was 3.1% patient years in those with D-dimer level below the established cut off and 21.5% in those with a mean D-dimer level above the cut-off. These studies suggest that persistently elevated D-dimer levels, measured either during or after cessation of anticoagulant therapy may be predictive of VTE recurrence in a variety of patient populations including those with either underlying cancer or thrombophilia.

Individuals with thrombophilia may be at increased risk for recurrence depending on the nature and number of the abnormality(ies). Individuals with deficiencies of antithrombin, protein C or protein S have an estimated recurrence rate 2.5 times greater than individuals without these abnormalities. Heterozygosity for factor V (FV) Leiden and PT G20210A does not increase risk for recurrence whereby homozygous mutations or combined thrombophilic defects may increase risk. Long-term anticoagulation therapy is recommended in individuals with antithrombin, protein C or protein S deficiency following a first episode of thrombosis or those with combined thrombophilic defects such as homozygous FV Leiden, or the presence of both FV Leiden and prothrombin G20210A in the heterozygous state.

Elevated levels of certain coagulation factors have been shown to be an independent risk factor for first VTE. Elevated levels of FVIII are a risk factor for the development of venous thrombosis and also increased risk for recurrence. FVIII is an acute phase reactant protein and therefore transient elevations of this factor are a common occurrence. Elevations of FVIII can be constant over time and may have in part a genetic basis. Recent studies demonstrate a three-fold increase in risk in patients greater than 70 years of age when FVIII levels are greater than 225 compared to levels less than 135. In these studies FVIII was measured on the day of presentation of the first episode of VTE. In those less than 70 years of age, a FVIII level of greater than 130 carries an 8-fold increase in the risk for recurrence compared to individuals with FVIII levels less than 90. In this age group, there is a dose response seen such that the higher the FVIII level, the greater the risk. In a study of 546 patient with spontaneous VTE, FIX levels in the 75<sup>th</sup> percentile or greater were associated with a 2.2 fold increase risk for recurrence and this risk was increased to almost 7 fold if both Factor IX and FVIII were elevated. When risk was adjusted for age, gender, FVIII and hyperhomocysteinemia, elevated FIX levels were associated with a 1.6 times increase in risk. In this study, factor levels were evaluated three weeks after the discontinuation of oral anticoagulant therapy.

Abnormalities of the plasminogen (fibrinolytic) system, such as inappropriate elevations of tPA antigen, increased PAI-1 activity and prolonged euglobulin lysis times following discontinuation of anticoagulant therapy, have not shown a correlation with increased risk of VTE recurrence. Thrombin activatable fibrinolysis inhibitor (TAFI) antigen levels in the 75<sup>th</sup> percentile or greater measured three weeks after discontinuation of OAT therapy were associated with a two-fold increase in the risk for recurrence. In this study of 600 patients, those with underlying malignancy, deficiencies of AT, PC, PS and lupus anticoagulant were excluded. Since the activity of TAFI is dependent on the quantity of thrombin generated, the relationship of elevated TAFI levels and increased levels of FVIII, FIX and FXI was evaluated. When TAFI levels were above the 75<sup>th</sup> percentile and either FVIII or FXI was greater than the 90<sup>th</sup> percentile, risk for recurrence was increased six-fold and three-fold, respectively.

Hyperhomocysteinemia is a risk factor for initial VTE as well as VTE recurrence. In patients with

spontaneous VTE, risk for recurrence was increased 2.7 fold with mild increase in homocysteine levels.

The presence of persistent antiphospholipid antibodies determined by either the presence of anticardiolipin antibodies or lupus anticoagulant is considered an important risk factor for VTE recurrence and even death, especially within the first 6 months following discontinuation of anticoagulant therapy. Risk for recurrence has been reported to be as high as 70% in this population and for this reason, persistent antiphospholipid antibodies are an indication for long-term anticoagulant therapy.

## Conclusion

The risk of VTE recurrence following the discontinuation of anticoagulant therapy is not uniform and differs significantly between patients. Optimum duration of anticoagulant therapy to prevent VTE recurrence is best determined on an individual basis and cannot be generalized to the population of individuals who suffer VTE. Appropriate and thorough evaluation of an individual patient is necessary to optimize therapy. 📌

## References

Poli D, Antonucci E, Cecchi E, et al. Clotting activation after oral anticoagulant therapy discontinuation: A risk for recurrent venous thromboembolism. *Blood Coagul Fibrinolysis*. 2004; 15(3):221-225.

Kearon C. Risk factors for recurrent venous thromboembolism and their implications for treatment. *ASH Hematology Educational Program*. 2004:445-449.

Heit J. Venous thromboembolism epidemiology: Implications for prevention and management. *Semin Thromb Hemost*. 2002; 28 (Suppl 2):3-13.

Eichinger S, Weltermann A, Minar E, et al. Symptomatic pulmonary embolism and the risk of recurrent venous thromboembolism. *Arch Intern Med*. Jan 2004; 164:92-96.

Goldenberg NA, Knapp-Clevenger R, Manco-Johnson MJ. Elevated plasma factor VIII and D-dimer levels as predictors of poor outcomes of thrombosis in children. *N Engl J Med*. 2004; 351:1081-1088.

Oger E, Lacut K, Van Dreden P, et al. High plasma concentration of factor VIII coagulant is also a risk factor for venous thromboembolism in the elderly. *Haematologica*. 2003; 88(04):465-469.

Breddin HK, Kadziola Z, Scully M, et al. Risk factors and coagulation parameters in relationship to phlebographic response and clinical outcome in the treatment of acute deep vein thrombosis. *Thromb Haemost*. 2003; 89:272-277.

DiAngelo A, Piovella F. Optimal duration of oral anticoagulant therapy after a first episode of venous thromboembolism: Where to go? *Haematologica*. 2002; 87(10):1009-1013.

Crowther MA. Anticoagulant therapy for the thrombotic complications of the antiphospholipid antibody syndrome. *Thromb Res*. 2004; 114:443-446.

Kyrle PA, Minar E, Hirschl M, et al. High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. *N Engl J Med*. 2000; 343(7): 457-462.

Nowak-Gottl U, Kosch A. Factor VIII, D-dimer, and thromboembolism in children. *N Engl J Med*. 2004; 351(11):1051-1053.

Eichinger S, Weltermann A, Mannhalter C, et al. The risk of recurrent venous thromboembolism in heterozygous carriers of factor V Leiden and a first spontaneous venous thromboembolism. *Arch Intern Med*. 2002; 162:2357-2360.

Bates SM, Ginsberg JS. Treatment of deep-vein thrombosis. *N Engl J Med*. 2004; 351:268-277.

## 5 CLINICAL HEMOSTASIS REVIEW / FIRST QUARTER 2005



Weltermann A, Eichinger S, Bialonczyk C, et al. The risk of recurrent venous thromboembolism among patients with high factor IX levels. *J Thromb Haemost.* 2003; 1:28-32.

Eichinger S, Schönauer V, Weltermann A, et al. Thrombin-activatable fibrinolysis inhibitor and the risk for recurrent venous thromboembolism. *Blood.* 2004; 103(10):3773-3776.

Swiatkiewicz A, Jurkowski P, Kotschy M, et al. Level of antithrombin III, protein C, protein S and other selected parameters of coagulation and fibrinolysis in the blood of the patients with recurrent deep venous thrombosis. *Med Sci Monit.* 2002; 8(4):CR263-268.

Crowther MA, Roberts J, Roberts R, et al. Fibrinolytic variables in patients with recurrent venous thrombosis: A prospective cohort study. *Thromb Haemost.* 2001; 85:390-394.

Kyrle PA, Minar E, Bialonczyk C, et al. The risk of recurrent venous thromboembolism in men and women. *N Engl J Med.* 2004; 350(25):2558-2563.

Levine JS, Branch W, Rauch J. The antiphospholipid syndrome. *N Engl J Med.* 2002;346(10):752-763.

Fattorini A, Crippa L, Vigano' D'Angelo S, et al. Risk of deep vein thrombosis recurrence: high negative predictive value D-dimer performed during oral anticoagulation. *Thromb Haemost.* 2002; 88(1):162-163.

# Self Assessment

## Thromboembolism

1. Venous thromboembolic disease is considered a chronic disease for which predominant reason(s):
  - a. VTE typically causes damage to the involved vein resulting in long-term sequelae such as post thrombotic syndrome
  - b. The risk for recurrence decreases with time, but never completely subsides
  - c. The underlying risk factors that lead to the clot, either hereditary or acquired never completely subside
  - d. All of the above.
2. The optimum duration of anticoagulant therapy following an initial episode of VTE:
  - a. Should be optimized between the risk for recurrence and risk of bleeding associated with the anticoagulant therapy
  - b. Is determine based on the risk and conditions associated with the event, such as whether the clot was provoked and what underlying risks are present
  - c. Should be applied appropriately whenever possible because an inadequate course of therapy as associated with an increased risk for recurrence
  - d. All of the above.
3. Given the following list of risk factors, list the groupings in regard to risk for recurrence, from least risk to greatest risk :
  - 1) Long car trips, morbid obesity;
  - 2) Mildly elevated homocysteine level, unprovoked thrombosis 12 months ago;
  - 3) Active adenocarcinoma, chemotherapy, DVT 3 months ago;
  - 4) Distal DVT 3 years ago related to fracture, no thrombophilia
  - a. 3,2,4,1
  - b. 2,1,4,3
  - c. 1,4,2,3
  - d. 3,4,2,1
4. Elevations of which factors have been associated with an increased risk for recurrence:
  - a. FVIII, FVII, FIX, TFPI
  - b. TAFI, FVIII, FIX, FXI
  - c. AT, PC, PS
  - d. FXII, FVII, FV, FII
5. Recurrence of VTE increases an individual's risk for
  - a. Death
  - b. Hemorrhage
  - c. Cancer
  - d. Developing thrombophilia

Volume 19, Number 1

### Self Assessment Registration Form

Record your answers below by circling the correct answer for each question. Participation is confidential.

- |    |   |   |   |   |
|----|---|---|---|---|
| 1. | a | b | c | d |
| 2. | a | b | c | d |
| 3. | a | b | c | d |
| 4. | a | b | c | d |
| 5. | a | b | c | d |

Participants must receive a score of 80% to receive credit. This form must be filled out completely. Please print.

Category Applied For:

- ASCLS P.A.C.E.  
 AMTIE CEU  
 State \_\_\_\_\_

Name \_\_\_\_\_

Title \_\_\_\_\_

Work Phone \_\_\_\_\_

Street \_\_\_\_\_

City \_\_\_\_\_

State \_\_\_\_\_ Zip \_\_\_\_\_

SS# \_\_\_\_\_

Licensure Type \_\_\_\_\_

Licensure Number \_\_\_\_\_

Were objectives clearly stated and met?  
 yes  no

Was text material well organized and informative?  
 yes  no

Were table/figures useful and clear?  
 yes  no

Did self assessment questions reflect objectives and text?  
 yes  no

To earn continuing education credit, answer the questions in the Self Assessment by recording your answers on the Registration Form. Complete the Registration Form, and mail it or a photocopy with your check for \$15.00 (for processing and issuing your credit certificate), make check payable to: CACMLE Mail to: CHR Self Assessment 3176 South Peoria Court Aurora, CO 80014