Venous Thromboembolism:
Duration, IVC Filters, and Hypercoagulable Workup

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Venous thromboembolism (VTE), which includes **deep venous thrombosis (DVT)** and **pulmonary thromboembolism (PE)**, is the third most common cause of cardiovascular mortality in the U.S., after coronary heart disease and stroke.[1] VTE is a systemic disease which may develop spontaneously (idiopathic, unprovoked) or secondary to some identifiable provocative or environmental risk factor.[2] Classifications into unprovoked, surgical, and provoked are useful, since such a classification correlates with the cumulative risk of recurrence and, therefore, influences the duration of therapy and the appropriateness of laboratory investigation.

VTE most commonly affects the deep venous system of the pelvis or lower extremity, but can also occur in less common sites such as the upper extremity, mesenteric veins, ovarian veins, cerebral veins and retinal veins. The anatomic site(s) is of importance as it may also influence diagnostic testing and duration of therapy.

The management of VTE (symptomatic or asymptomatic) can be divided into immediate (up to the first 10 days), early long-term (up to three months), and late long-term (beyond three months) therapy. The objective of immediate management is to shut down thrombin generation and to prevent thrombus extension and embolisation. The objective of early long-term therapy is to prevent thrombus recurrence, embolisation and the **post thrombotic syndrome (PTS)** and to promote the lysis of the thrombus; recurrence in this phase is particularly problematic since there is a higher case fatality rate. The objective of late long-term management is to prevent thrombus recurrence and embolisation and to prevent or reduce PTS[4] since ipsilateral recurrence is a particular risk factor for PTS. Unprovoked VTE may be a manifestation of an inherited or acquired thrombophilic state and, hence, esoteric laboratory testing may be indicated in some cases.[5] This article will address only three of these considerations—the role of late long-term anticoagulation, utilization of an IVC device to interdict embolisation and the judicious use of esoteric laboratory testing.

What is the optimal duration of oral anticoagulation with VTE?

Early long-term anticoagulation is recommended for all VTEs, provoked or unprovoked, symptomatic or asymptomatic, upper or lower extremity. The target INR is 2.5 with a suggested range of 2-3. Shorter courses of anticoagulation have been shown to be inferior.[6]

The decision to use late long-term anticoagulation is more difficult and is essentially a risk-benefit analysis that balances the risk of recurrent thrombosis with the risk of severe bleeding. The risk of recurrent thrombosis is determined by a history of a previous thrombotic event, the circumstances associated with the occurrence of the thrombosis, the presence of residual or persistent thrombosis and laboratory data. The risk of bleeding is determined by patient clinical co-morbidities, the ability to control the anticoagulant effect of warfarin, which is determined by patient compliance, the quality of medical oversight, and patient age. Thus, it is clear that any absolute time period is inappropriate and individualization of therapy required.[7]

General Approach

1. The overall cumulative two-year recurrence rate for surgically provoked thrombosis is 0%- 5%. Hence, there is general agreement that surgical induced VTE should *not* be treated with late long-term anticoagulation.[8]
2. For non-surgical, provoked DVT the recurrent rate at two years has been estimated as high as 8.8%. Hence, continuation of anticoagulation to at least six months may be reasonable, in the absence of any contraindication.[8]
3. For unprovoked VTE that involves the distal lower extremity, three months is adequate. For unprovoked VTE involving the pelvic veins or proximal lower extremity, extended late long-term anticoagulation is preferred, unless there is a major contraindication. Six months is a common minimum and indefinite anticoagulation is a consideration. The overall two-year cumulative recurrence in this setting is 20%; but at five to eight years, it is 30%, and 35% at 10 years.[7] This

Table 1. Suggested Duration of Oral Anticoagulant Therapy for VTE

Target INR = 2.5; range 2-3

Condition	Duration of Therapy
Surgically provoked DVT	3 months
Unprovoked lower extremity distal DVT	3 months
Non-surgical provoked proximal DVT or PE	3 months minimum; 6 months may be preferred, if no contraindications.
Unprovoked proximal DVT or PE	3 months minimum: 6 months is clearly preferable and extension beyond 6 months requires a careful risk-benefit analysis – (see text).
Cancer associated VTE	6 months therapy with LMWH or fixed dose UF. Warfarin – after 6 months on a risk-benefit analysis.

represents substantial risk for recurrence, although the case fatality rate for recurrent DVT (3.6%) is much lower than recurrent DVT while on early long-term anticoagulation (13%).[9] Certain features will be useful in making this decision and are summarized below.

Assessment of the risk of VTE recurrence versus the risk of a major or life threatening bleeding event.

Factors that favor extension of VKA therapy beyond 6 months:

a.) Previous VTE – A history of a previous VTE is generally considered an indication for *indefinite therapy*, unless contra-indicated.

b.) Lupus anticoagulant, anticardiolipin antibodies and anti-β_2 glycoprotein 1 – Among these tests, the lupus anticoagulant (functional assay) is far more important than the anticardiolipin antibodies (immunochemical assays): however, a positive anti-β_2 glycoprotein 1 antibody correlates with thrombotic risk. The relative risk for recurrence varies, but is of the order of 3-5. Hence, treatment for *two to five years* should be considered, unless contra-indicated.

c.) Hereditary thrombophilia: (see Table 2).

i. FV Leiden and prothrombin gene polymorphism: These increase VTE recurrence by approximately 1.4-1.7 and, therefore, are not 'hard' findings to influence duration.[5, 16]

ii. FVIII:C levels: high levels of FVIII appear a stronger risk factor for recurrence—2-4 fold.

iii. ATIII and protein C deficiency (and protein S deficiency) are rare disorders and recurrence risk is difficult to estimate. Family studies suggest that ATIII deficiency particularly and PC deficiency to some extent, are indicative of an increased risk.[17]

iv. Multiple (combined deficiencies e.g. FV Leiden plus PT polymorphism, PC and FV Leiden) are highly predictive of VTE recurrence.[18]

In summary, ATIII deficiencies, patients with multiple defects and, perhaps, PC deficiency could be considered for *anticoagulation_* for four to five years or possibly indefinite;[17] high FVIII:C *for two to five years*; other isolated findings are minimally predictive of recurrent risk.[16]

d.) Assessment of D-dimer: D-dimer levels are useful in the initial assessment of the acute situation, where a level below 0.5 FEU µg/mL is helpful in the exclusion of DVT and (less data), PE. D-dimer levels return to "normal" (negative) in 85% of patients on warfarin. The presence of a high D-dimer (>0.5 FEU ug/ml) 1 month after discontinuing VKA is indicative of an increased risk for recurrence on the order of 2-4 fold. Hence, elevated D-dimer levels would be an indication *for one to two more years*, at a minimum.[11]

e.) Short aPTT: A short aPTT (< 24 seconds) can also be indicative of an increase risk of recurrence (~ 2.0) independent of the elevated FVIII:C (FVIII:C is a major driver of the aPTT).[13]

f.) Pulmonary embolism: Patients with PE are at high risk of recurrence whenever anticoagulation is discontinued. About 50% of recurrences are PE's, and 10% of these will be fatal. Hence, *indefinite anticoagulation* (or *at least five years*)

Table 2.

I. Laboratory tests used to detect a hereditary or acquired thrombophilic state:

1. Activated protein C resistance or the FV Leiden mutation (G1691A):
2. Prothrombin Gene Polymorphism (G20210A):
3. Lupus anticoagulant and anticardiolipin antibodies
4. Protein C
5. Protein S – both Total and Free PS
6. Antithrombin III
7. FVIII:C
8. Fasting plasma homocysteine
9. HIT antibody in the correct context (heparin exposure and abrupt onset of an unexplained decrease in the platelet count—whether thrombocytopenic or not)

II. Laboratory tests used to assess the risk of VTE recurrence:

1. Lupus anticoagulant
2. D-dimer
3. aPTT
4. FVIII:C

III. Other tests which might be considered:

1. DNA tests for the methylenetetrahydrofolate reductase thermolabile polymorphism(MTHFR C677T and A1298C) or the PAI-1 gene 4G/5G polymorphism
2. CBC to detect Polycythemia Vera or essential thrombocytosis
3. Testing for PNH: red cell flow cytometry for CD 55 and CD59
4. Assay of FIX and FXI
5. Testing for dysfibrinogenemia – PT and Reptilase time
6. Testing for Wegener's granulomatosis (Pulmonary embolism)—cANCA against proteinase 3.

should be considered in this population, especially if other risk factors for recurrence are present.[15]

g.) The presence of residual (unresolved) thrombosis by ultrasound after "completion" of therapy.[14]

h.) Presence of other persistent morbidity: Cancer is the most important, but SLE (especially with nephrotic syndrome), **paroximal nocturnal hemoglobinumic (PNH)**, inflammatory bowel disease, Cushing's syndrome and, in some, myeloproliferative disorders. These comorbidities could influence late long-term management decisions, e.g. for PNH-indefinite.

Factors that raise concern of an increased predisposition to bleeding:

a.) Hypertension, renal insufficiency, diabetes mellitus, hepatic disease, anemia and recent peptic ulcer may be associated with an increased risk of bleeding, as may age, cancer and ischemic stroke, although the last three are also associated with increased thrombotic risk. This risk is particularly present in the first 18 months;[7] hence, if warfarin has already been extended to 18 months without any bleeding, the risk of bleeding appears less after this time.

b.) Patient education, compliance and quality of medical supervision.

Patient preference:

Last, but by no means least, patient preference is a strong consideration. Some patients will have a morbid fear of recurrent VTE (especially PE) and will be prepared to accept late long-term or indefinite anticoagulation.

The above sections are intended as suggestions only based on known risk assessments, but are not supported by high quality evidence and, therefore, individualization of therapy is required.

In summary, there is no "one size fits all" duration for warfarin therapy and it is clear from the foregoing that multiple factors influence this decision. Failure to prescribe late long-term anticoagulation will result in a recurrent VTE in some patients; continuing to prescribe warfarin will result in major bleeding events in others.[9] The converse is, however, never obvious, as the prevention of VTE in individual patients on warfarin is, by definition, silent, as is the avoidance of major bleeding events that might have occurred in the presence of the VKA. Therefore, only *treatment-decision failures are evident* and physician and patient alike must accept this situation in order to put expectations in perspective and avoid misunderstandings.

This raises the important question of who to test?

What are the Indications for Vena Caval Filters?

The most feared complication of DVT is **pulmonary embolisation (PE)**. Initial treatment of DVT with heparin decreases the risk of fatal PE by 75% and the risk of recurrent PE from 25% to 2%. When heparin is completed, early long-term anticoagulation begins, but there is still a residual risk of recurrent DVT during this period. Furthermore, the case fatality rate for PE is higher during this phase.[9] Since most DVT's occur in the pelvic or lower extremity veins, interruption of venous flow by ligation of the common femoral vein, with or with thrombectomy, was performed in the 1950's. This approach was associated with limb edema. Later, ligation of the IVC was performed, with the ligation preferred below the renal veins. Edema remained a complication, however. This approach was modified in the 1960's with the use of suture plication and caval clips, which reduced the occurrence of edema. The initial IVC filters were developed in 1967 and released into wider use in 1972.

Approximately 13 Vena caval filters are available for use in the U.S. and an additional seven in Europe. The overwhelming majority are inferior vena caval filters introduced via the femoral vein. The best-known filter is the standard Greenfield Filter introduced in 1973. This filter is conical with six strands of zigzag shaped legs, each with a hook that anchors the filter to the IVC. The standard filter however, was ferro magnetic and has been replaced with a titanium Greenfield filter. A 20-year experience report shows a PE recurrent rate of 4% and a caval patency rate of 96%.[19] This is similar to subsequent reports and a relative risk of 0.41 at eight years for recurrent PE is achieved. More recent developments have resulted in the availability of several retrievable or optional IVC filters, although optional is a preferred term since they are intended for either temporary or indefinite placement.

Insertion of an IVC filter is never considered a routine approach. Long-term follow up shows that there are complications of early hematoma formation, late thrombosis at the site of insertion and the incidence of DVT is increased (RR about 1.8).

Therapeutic Indications for IVC Filters

1. Anticoagulation is contraindicated: Situations such as hemorrhagic stroke, active internal bleeding requiring transfusion, pregnancy, recent neurosurgical procedure or intracranial neoplasm, or hereditary or acquired bleeding disorder.

2. Anticoagulation complication: either bleeding or HIT, in a patient with an active DVT/PE.

3. Anticoagulant failure: recurrent PE despite apparently adequate anticoagulant therapy.

4. Incipient risk for embolisation. Presence of free-floating ileofemoral or lower IVC thrombosis.

5. Emergent surgery in a patient with DVT.

6. Patients with chronic pulmonary (thromboembolic) hypertension with marginal pulmonary reserve.

From Greenfield's series, the most common indication is #1 (about 50%), with #2 and #3 accounting for the rest.[19]

"Prophylaxis" (#5, 6) accounts for a minority (15%). It needs to be reinforced that high quality data (RCTs) is lacking to justify any of the above indications (where an IVC filter is used without concurrent systemic anticoagulants), but an RCT of IVC filters versus no filters in anticoagulated patient with acute DVT supports the contention that both PE and fatal FE are decreased by the IVC filter.[20] Given this, it is unlikely that a RCT comparing IVC insertion versus no filter will ever be performed.

What are the components of a "hypercoagulable workup" and when should one be performed?

Laboratory testing in the context of DVT can be divided into tests which are useful in *initial assessment*—mostly the D-dimer and fibrinogen concentrations - where the diagnosis is being considered or systemic profibrinolytic therapy is anticipated, and *later testing* where the objective is to determine the presence of an underlying hereditary or acquired thrombophilic state or to assess the risk of recurrence, although these are interrelated. These tests are shown in Table 2. The purpose of this section is to discuss appropriate testing and not to give a descriptive of each of these abnormalities—for this, the reader is referred elsewhere.[5]

In general, use of the tests to detect a thrombophilic state should only be performed on some patients with an unprovoked VTE or a non-surgical provoked VTE. Testing should be discouraged at the time of diagnosis or during immediate therapy or early long-term therapy. At those times, the results will not influence treatment, as erroneous results can occur because of the anticoagulant effects, which may cause confusion. Therefore, the tests should optimally be performed after completion of therapy . The patient should be off warfarin for a minimum of 2 weeks before any testing is performed, but one month is preferred. This clearly may be associated with some risk, if the patient is in a higher risk category. Because of this, some tests can be performed when the patient is on warfarin: the DNA based tests (FV Leiden and PT polymorphism); the immunochemical tests (anticardiolipin antibodies) and the functional assays for ATIII and FVIII:C. Some important assays cannot be properly interpreted when the patient is taking warfarin—of importance are the lupus anticoagulant assay and some assays for APC resistance. For this reason, it is "cleaner "to test after warfarin discontinuation and recommence warfarin for some defined time period if high risk is detected. It is recommended to perform all tests in the proband (but not necessarily family members) rather than selected high prevalent tests since multiple deficiencies are not uncommon[18] and the high prevalence defects (e.g. FV Leiden) provide much less information in themselves regarding continuation of therapy.[16]

This raises the important question of who to test? The following are suggested as general guidelines. Patient preference is again an important consideration:

1. A young patient (<50 years) with an unprovoked VTE or non-surgical provoked VTE.[5]

2. A patient with an unprovoked VTE or non-surgical provoked VTE in an unusual site—mesenteric veins, cerebral veins, possibly retinal veins.[5] Testing in patients with upper limb DVT should largely be confined to patients who do not have an anatomical thoracic outlet obstruction and where there is no recent history of upper limb strain such as heavy lifting or stretching (e.g. basketball). The true Paget-Schroeter Syndrome should be "spontaneous."

3. A woman who presents with pregnancy or puerperal associated VTE. This is of particular importance since it may influence the management of subsequent pregnancies. ATIII deficiency, although rare, typically presents in this manner and, in addition, it may influence a decision to test family members. Furthermore, certain findings may be important in understanding recurrent abortions in the proband or family members.

4. A patient with an unprovoked VTE. The tests indicated in table 2 (section II) can be helpful in risk assessment if anticoagulation is being considered for extension beyond six months. These are inexpensive tests that may guide the decision process.

5. Family members: Considerable caution needs to be exercised regarding the testing of family members and the preferences of each family member are important. Testing should be limited to any abnormality(ies) found in the proband and to hereditary traits, although rare familial lupus anticoagulants have been described. Family members need to be counseled that any finding (e.g. FV Leiden) may not be predictive of a future event in any clinically meaningful way, i.e., would not influence a decision regarding anticoagulation regimen or duration. As indicated above, ATIII deficiency would be an exception.

In general, patients with surgically provoked VTE, older patients, or patients with cancer should be discouraged from the testing described in Table 2 (section I), as should patients with recurrent DVT, since they are candidates for indefinite therapy regardless.

The role of the tests described in Table 2 (section III) is unknown at this time—a CBC is a simple test but others are more involved (Flow cytometry) or may be difficult to interpret (FIX and FXI) in terms of risk stratification.

Conclusion

VTE is a common systemic disease predominantly occurring in the later decades of life. Treatment is primarily systemic with oral anticoagulation for at least 3 months. Extension beyond three months is dependent on the circumstances surrounding the event, persistence of residual thrombus, any previous history of VTE, the results of laboratory testing, assessment of the bleeding risk, patient preference and anticipated compliance and the quality of medical supervision. There is a limited role for mechanical interruption of embolising thrombus with vena caval filters, primarily in patients with an active DVT for whom systemic anticoagulation is contraindicated. Esoteric testing should be largely reserved for patients who present in the earlier decades of life and may

be useful in determining the duration of therapy in some. Recently, more simple tests have shown clinical usefulness in risk assessment for recurrence.

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