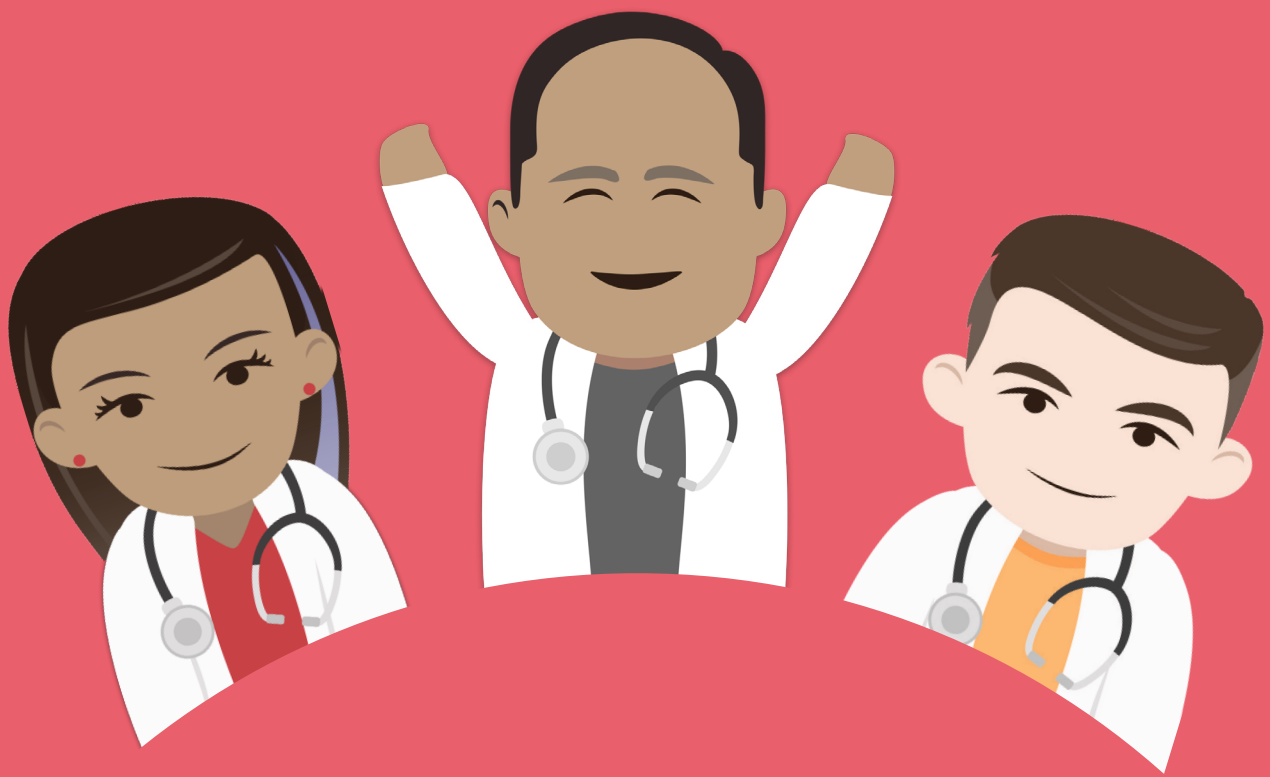
Hematology and Coagulation Essentials
Chapter 9

MANAGING THROMBOPHILIA



Amer Wahed

Managing thrombophilia

ORDERING TESTS FOR THROMBOPHILIA

Thrombophilia may be due to inherited or acquired causes. Acquired causes are more prevalent than inherited causes.

Established genetic factors associated with thrombophilia include

- Factor V Leiden
- Prothrombin gene mutation
- Protein C or S deficiency
- Antithrombin III (AT III) deficiency

Other causes, which are quite infrequent, include hyperhomocysteinemia and dysfibrinogenemia. Elevated coagulation factors such as elevated factor VIII, factors IX, and XI may also be associated with thrombophilia. Another documented cause is elevated lipoprotein(a) [(Lp (a)], which is an inherited risk factor for thromboembolism. A deficiency in tissue-type plasminogen activator or plasminogen could also reduce the capacity to remove excessive clots and contribute to thromboembolic disease.

Acquired causes of thrombophilia include

- Trauma
- Surgery
- Prolonged immobilization
- Pregnancy
- Use of various medications, such as oral contraceptives
- Lupus anticoagulant (LA) and anticardiolipin antibodies (ACA)

Lupus anticoagulant, and anticardiolipin antibodies, which give rise to antiphospholipid syndrome, are important causes of acquired thrombophilia. Patients with lupus anticoagulant may develop thrombosis of arteries and veins as well as pregnancy-related complications such as miscarriage and still birth.

The total prevalence of an inherited thrombophilia in subjects with a deep vein thrombosis ranges from 24 to 37%. The most frequent causes of an inherited (primary) hypercoagulable state are the factor V Leiden mutation and the prothrombin gene mutation, which together account for 50–60% of cases.

Factor V leiden results from a mutation in the factor V gene. The abnormal factor V is called factor V Leiden, named after the city it was discovered in.

A prothrombin gene mutation is the second most common cause of inherited thrombophilia. It results from a mutation in the prothrombin gene, which causes increased levels of prothrombin. High levels of prothrombin generate higher levels of thrombin, which convert more fibrinogen to fibrin, resulting in increased clot formation.

Defects in protein S, protein C, and antithrombin (formerly known as antithrombin III) account for most of the remaining cases.

Protein C is an anticoagulant produced by the liver. It works with protein S and together they cleave factor V. The cleaved factor V also breaks down factor VIII. Thus, protein C and S lower the levels of activated factor V and VIII.

Factor V Leiden is a mutant form of factor V that is resistant to cleavage by protein C, thus it maintains its procoagulant activity. Therefore, in factor V Leiden, factor V levels are high and there is increased risk of thrombosis. Reduced levels of protein C and S will also raise levels of factor V and VIII.

Antithrombin deficiency results in a reduction in inhibition of the procoagulant thrombin.

Polymerase chain reaction (PCR) is used to test for factor V Leiden and the prothrombin gene mutation. Specific assays to determine protein levels are used to test for protein C, S, and antithrombin deficiency.

When should we test for thrombophilia?

Patients with a family history of venous thromboembolism (VTE)
Patients with VTE who have at least one first degree relative, with documented VTE before the age of 45 years, should be tested for all five inherited thrombophilias (levels of protein S, protein C, antithrombin, factor V Leiden, and prothrombin gene mutations).

Patients without a family history of VTE
Young patients (< 45 years): test for inherited thrombophilias and antiphospholipid syndrome.

Patients with recurrent thrombosis: test for inherited thrombophilias and antiphospholipid syndrome.

Patients with thrombosis in multiple venous sites or in unusual vascular beds (e.g., portal, hepatic, mesenteric, or cerebral veins): test for inherited thrombophilias and antiphospholipid syndrome.

Patients with a history of warfarin-induced skin necrosis are at increased risk of protein C deficiency (rarely protein S deficiency or factor V Leiden).

Patients with arterial thrombosis are at risk of having antiphospholipid syndrome.

Testing for antiphospholipid syndrome

This includes testing for lupus anticoagulant (LA) and anticardiolipin antibodies.

Watch out!
Testing for lupus anticoagulant is based on partial thromboplastin time (PTT).

If a patient has been started on heparin, then heparin prolongs PTT and tests for LA are invalid. Tests for anticardiolipin antibodies are not affected by heparin.

When someone develops a clot, protein C and S are consumed and the levels of these proteins may become low. Therefore, low levels of protein C or S at the time of thrombosis does not necessarily mean the patient had low levels prior to thrombus formation. However, if levels are normal or high, protein C or S deficiency can be ruled out.

Managing thrombophilia

MONITORING THE CLINICAL EFFECT OF ANTIPLATELET MEDICATIONS

Common antiplatelet agents that are in use

- Aspirin (inhibits cyclooxygenase enzyme)
- ADP P P2Y12 receptor blockers (e.g., clopidogrel [Plavix], prasugrel, ticagrelor [Brilinta])
- Glycoprotein IIb / IIIa antagonists (e.g., eptifibate, abciximab)

There is also another class of drug, phosphodiesterase inhibitors, which is used much less often. These agents inhibit the enzyme phosphodiesterase and cause accumulation of cyclic adenosine monophosphate (cAMP), resulting in impaired platelet function. Examples of this group of drug is dipyridamole and cilostazol.

There are certain situations when we may need to test to see whether the antiplatelet medications are working in a patient.

Examples of such situations include:

- A noncompliant patient
- A nonresponder (this may be seen with aspirin and adenosine diphosphate (ADP) receptor blockers)
- A patient on antiplatelets with planned major surgery (the effect of the drug should be minimized to reduce bleeding)

All antiplatelet medications will cause platelet dysfunction, so we need to order tests which will document this phenomenon.

The tests that may be ordered include

- PFA-100
- VerifyNow (VFN)
- Platelet aggregation study

PFA-100 is a test used to test for overall platelet function. PFA-100 is a rapid test for assessment of platelet function. Blood passes through an aperture coated with chemicals which are platelet agonists. When platelets are functional, the presence of these agonists cause the platelets to become activated and platelet clumping takes place which blocks the aperture. This test has high negative predictive value.

This test will pick up platelet dysfunction due to aspirin and glycoprotein IIb / IIIa antagonists. However, this test is not sensitive for the commonly prescribed P2Y12 blockers.

VerifyNow (VFN) is a rapid, turbidimetric whole blood assay capable of evaluating platelet aggregation. This assay is based on the ability of activated platelets to bind with fibrinogen.

There are three assays available

- The VFN glycoprotein IIb / IIIa assay to measure the effect of glycoprotein IIb / IIIa antagonists.
- The VFN aspirin assay to measure the antiplatelet effect of aspirin.
- The VFN P2Y12 assay to assess the antiplatelet effect of agents such as clopidogrel.

VFN assays are fast and not labor intensive.

Platelet aggregation is the gold standard test for assessment of platelet function. In platelet aggregation, agonists are added to a suspension of the patient's platelets. The platelets should aggregate and settle to the bottom, resulting in more light passing through the tubes. A change in light transmission is detected.

All antiplatelet medications will affect the platelet aggregation study and each class of drug will produce a different pattern of results, allowing the underlying drug to be identified. However, this test is time consuming and labor intensive. It is not available 24 hours a day.

Reversal of effect of antiplatelet agents

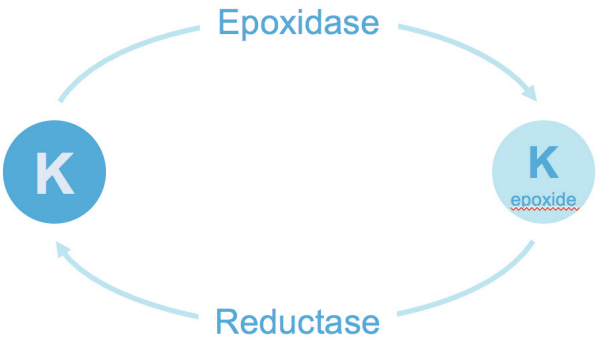
- If patients on antiplatelet agents need reversal of effect, for example in anticipation of surgery, then the best approach is to withhold the drug.
- Please refer to recommendations for each drug.
- In cases of emergency surgery or desired rapid reversal of effect if the patient is bleeding, platelet transfusion is best.

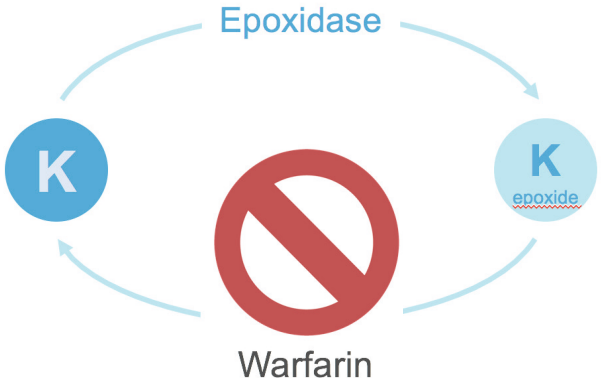
Managing thrombophilia

MONITORING THE CLINICAL EFFECTS OF ANTICOAGULANTS

Warfarin

The mechanism of action of warfarin
There are two forms of vitamin K: the functionally active vitamin K and the nonfunctional form, vitamin K epoxide. The reductase enzyme converts vitamin K epoxide to functional active vitamin K. Warfarin blocks this reductase enzyme. Thus, nonfunctional vitamin K epoxide accumulates and the levels of the functional vitamin K are reduced in the presence of warfarin.

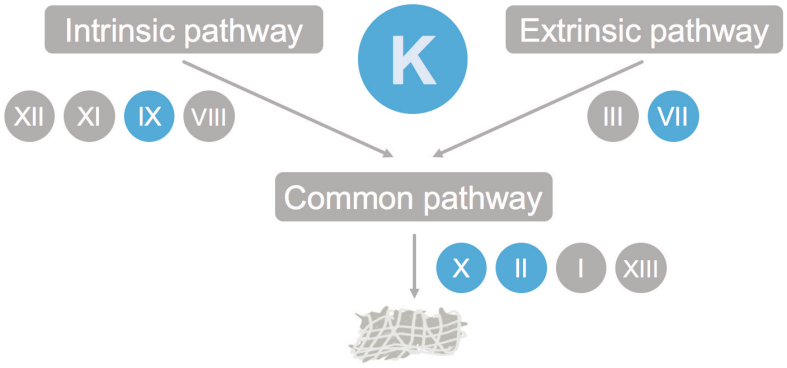




Since vitamin K is required for the proper function of clotting factors II, VII, IX, and X, levels of these clotting factors are also reduced in the presence of warfarin. The effect of low levels of factor VII manifest earliest and are most persistent, since it has the shortest half-life. As we know, factor VII is part of the extrinsic pathway and its function can be tested using prothrombin time (PT).

So, in patients who are taking warfarin, PT should be prolonged.

The initial dose of warfarin on days one and two can be 5 mg. From then on, the PT should be tested daily and, depending on the international normalized ratio (INR), the warfarin dose should be adjusted to reach the target value.



The question is, what is the target INR?
The target INR depends on the underlying pathology. For example, if warfarin is being administered to test / prevent deep vain thrombosis (DVT), then the target INR may be as low as 2–3, whereas if it is given for valvular heart disease, the target INR will be higher.

When the INR is above the desired range, when the patient bleeds on warfarin, or if the patient needs to undergo surgery, then we will need to reverse the effect of warfarin.

The first and easiest step is to stop the warfarin.
- If the patient is not bleeding, we can administer vitamin K—either in an oral or injectable form.
- If the patient is bleeding we can give fresh frozen plasma (FFP).
- If the patient cannot tolerate the volume of FFP, then we can give prothrombin complex concentrate (PCC).

Heparin

There are two forms of heparin in clinical use: unfractionated heparin and low molecular weight heparin.

Heparin inhibits factors IX, X, XI, and XII. Antithrombin III (AIII) is required for the effective function of heparin. The efficacy of heparin as an anticoagulant is measured by partial thromboplastin time (PTT) (ideally after six hours of dose adjustment).

Low molecular weight heparin inhibits factor Xa, and its efficacy is monitored using an antifactor Xa assay.

The efficacy of unfractionated heparin can also be monitored using an anti-Xa assay. This is applicable when PTT measurement cannot be relied on—for example, when a patient has a lupus anticoagulant (prolongs PTT) and is on heparin.

Heparin antidote: protamine

Direct oral anticoagulants (DOAC)

The anti-Xa inhibitors and the oral direct thrombin inhibitor (DTI) dabigatran, are called direct oral anticoagulants (DOAC). The use of these drugs has become increasingly common.

Their main attractions include
- No need for lab monitoring
- Less risk of bleeding
- Similar efficacy

Direct thrombin inhibitors (DTI)

Examples of these agents include
- Bivalirudin (Angiomax)
- Dabigatran (Pradaxa)
- Argatroban
- Lepirudin

Of these drugs, the only one that can be administered orally is dabigatran. Efficacy of DTIs can be monitored by PTT.

DTI antidote: none

Anti-Xa inhibitors

Examples of these agents include
- Rivaroxaban
- Apixaban

Both rivaroxaban and apixaban are oral agents. The efficacy of these agents may be monitored by anti-Xa assay.

Anti-Xa inhibitor antidote: none