CME

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- Describe the elements of the clotting system
- Review the workup of excessive clotting, with special focus on laboratory evaluation
- Outline the differential diagnosis of hypercoagulable states using "5 Ps Had Caused Clots"
- Know the treatment of hypercoagulability, including lifestyle modifications and medications

Can you recognize a patient at risk for a hypercoagulable state?

A disrupted clotting system can lead to life-threatening thrombosis. PAs can use a simple mnemonic to remember the differential diagnosis for hypercoagulable states.

Allan Platt, PA-C, MMSc

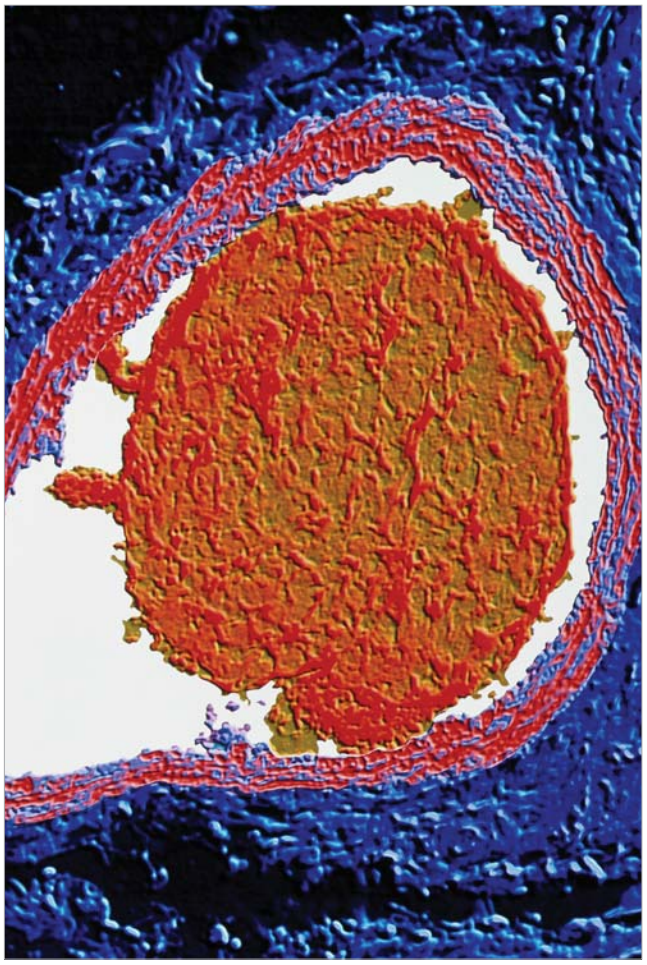
Thrombotic stroke is the third leading cause of death in the United States;[1] approximately 2 million cases of venous thromboembolism (VTE) occur annually and result in up to 60,000 deaths from pulmonary embolism (PE) each year.[2] These conditions are the result of excessive coagulation in the wrong places. A slow blood flow, increased proclotting components and/or a lack of anticlotting factors, and endothelial damage are the elements of Virchow's triad that tip the balance toward hypercoagulation.[3] This article reviews the pathophysiology, clinical workup, differential diagnosis, and treatment of hypercoagulable states.

THE CLOTTING CASCADE

The clotting system is designed to prevent blood loss and repair blood vessel damage. Clot lysis and anticlotting systems keep blood vessel repair and blood flow obstruction in balance. A hypercoagulable state develops when that balance is disrupted.

Primary hemostasis The first line of defense against bleeding occurs when activated platelets become attached to damaged endothelium to form a clot. *Platelets* are discoid fragments of megakaryocytes produced in bone marrow. They have an average life span of 10 days and are stored in and recycled by the spleen.[4] Platelets flow in the bloodstream until they are exposed to thrombin, collagen, clot mediators, or other activated platelets.

Once activated, platelets adhere to a damaged site with the help of von Willebrand factor (vWF), where they enlarge and flatten. The attached platelets then become pointed and degranulate, releasing thromboxane A_2 (TXA_2), adenosine diphosphate (ADP), serotonin, calcium, fibrinogen, platelet



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Computer illustration of a cross-section through a thrombus

factor 4, clotting factor V, platelet-derived growth factor, thrombospondin, and vWF.[4] These mediators attract and activate other platelets, cause vasoconstriction, and activate the clotting cascade to form an organized clot.[4]

Negatively charged phospholipids appear on the surface of the platelet and activate the intrinsic clotting pathway.[4,5] Clotting factor V supplies clotting cascade-forming fibrin threads that surround the activated platelets. Finally, platelet actinomycin contracts and pulls the platelets into a tight plug.[4]

Secondary hemostasis Soluble, inactive protein-clotting factors change soluble fibrinogen into fibrin strands. The protein-clotting factors are activated via two pathways. The *intrinsic pathway* is initiated when negatively charged collagen inside the damaged endothelium or negatively charged phospholipids on the surface of activated platelets change inactive factor XII to active; thereby activating factors XI, then IX, then VIII.[5,6] The *extrinsic pathway* is initiated when factor VII becomes activated and makes contact with tissue factor released by the injured endothelium.

Both the intrinsic and extrinsic pathways lead to the common pathway cascade. When the common pathway is initiated, factor X becomes active with factor V present (factor Xa); this activates factor II, which changes prothrombin to thrombin. Finally, factor I is activated, which changes fibrinogen to fibrin.[5] Activated factor XIII is used to crosslink the fibrin strands. The crosslinked fibrin strands form a mesh that traps RBCs and platelets at the damaged site into a clot[5] (see Figure 1, page 22).

Anticlotting Antithrombin III, protein C, protein S, and tissue factor pathway inhibitor (TFPI) block the clotting cascade at different sites.[6] Endothelial cell-manufactured prostacyclin and nitric oxide (NO) cause vasodilatation and inhibit platelet activation. Ecto-ADPase inhibits platelet attraction and aggregation. TFPI, made in the endothelium, binds to and inhibits factor Xa.[7] The endothelial cells generate endogenous heparin, which increases the activity of antithrombin III to block thrombin production.[7] Heparin also blocks factors XII, XI, and IX in the intrinsic pathway. Thrombomodulin increases activation of the anticoagulant protein C.[7] Tissue plasminogen activator (tPA) and urokinase convert plasminogen to plasmin; the plasmin binds to fibrin and cuts the strands into fibrin split products and D-dimers.[7]

"Prothrombin 20210 mutation causes increased prothrombin levels and a threefold increase in the risk of thrombosis."

THE WORKUP FOR EXCESSIVE CLOTTING

Recurrent deep vein thrombophlebitis, PE, a stroke, or a fetal loss should prompt a diagnostic workup. The patient's age is important because thrombotic risk increases with age. The patient should be asked about prothrombotic conditions such as pregnancy, cancer, immobility (prolonged bed rest or travel), injury, surgery, smoking, diabetes, obesity, lupus, sickle cell-thalassemia disease, heart failure, renal failure, elevated cholesterol level, polycythemia vera (P vera), heparin use, and estrogen use.[8,9]

Physical examination Many signs and symptoms of prothrombotic conditions are found on physical examination. Fever may indicate sepsis. An irregularly irregular pulse indicates atrial fibrillation, which is a risk factor for thrombotic stroke and may be an indicator of hyperthyroidism. Excessive rubor suggests P vera. A malar rash and joint inflammation may suggest systemic lupus. Signs of autoimmune arthritis suggest rheumatoid arthritis or lupus. Weight loss may be caused by cancer. A tremor, onycholysis, exophthalmos, hyperreflexia, and a goiter may be present in hyperthyroidism. Lung rales and an S_3 may be heard in patients with heart failure. Pedal edema may be seen in heart failure and renal failure. Assess the size of the liver and spleen and palpate for masses or tenderness. Be alert for scars from recent surgery and signs of trauma or thrombophlebitis. A sign of acute arterial occlusion is a pulseless, pale, cold limb.[8,9]

Laboratory tests Recommended laboratory tests for the workup of a patient with a suspected hypercoagulable state include CBC, chemistry and lipid profiles, and thyroid-stimulating hormone (TSH) test. A hypercoagulation panel, heparin-induced thrombocytopenia (HIT) assay, and D-dimer test are needed for monitoring anticoagulant therapy.[8-12]

Continued on page 22

KEY POINTS

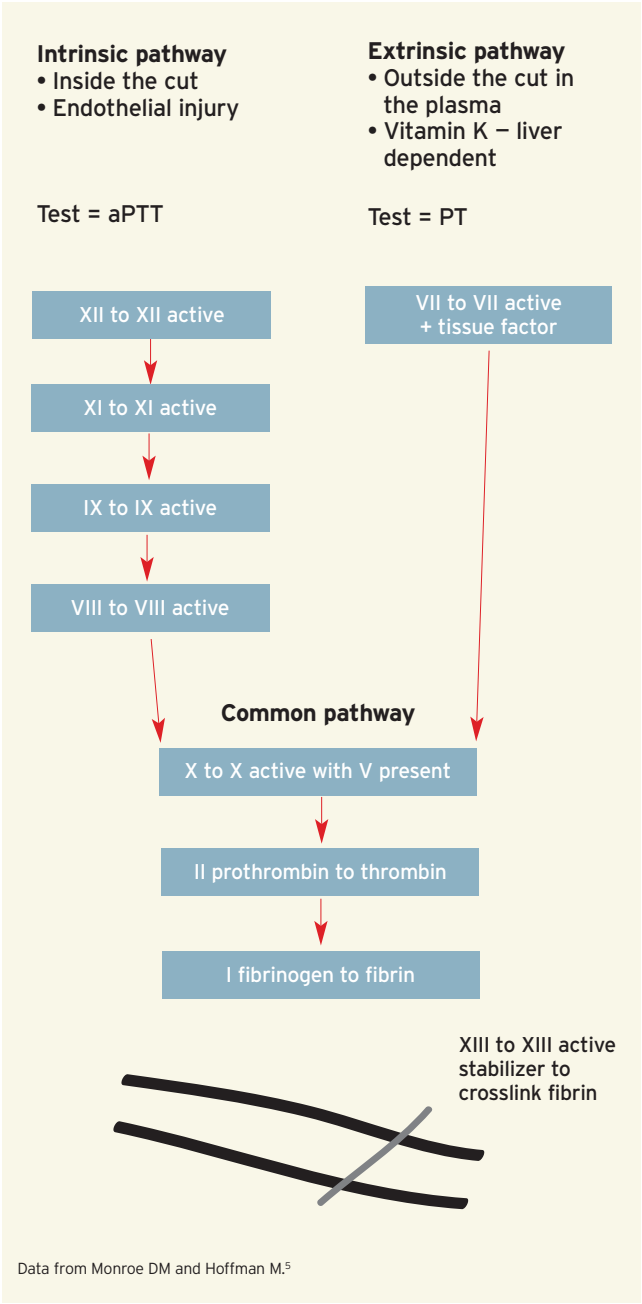
- The clotting system is designed to prevent blood loss and repair blood vessel damage. Clot lysis and anticlotting systems keep vessel repair and blood flow obstruction in balance.
- Recurrent deep vein thrombophlebitis, pulmonary embolism, a stroke, or a fetal loss should prompt a diagnostic workup for excessive clotting. The patient's age is important because thrombotic risk increases with age.
- The goal of treatment is to use the safest effective therapy that has the lowest risk of bleeding complications.
- If anticoagulant therapy is being considered, a baseline prothrombin time (PT) and activated partial thromboplastin time (aPTT) are needed before initiating therapy. A PT of 11 to 16 seconds indicates that the extrinsic system is functioning normally. An aPTT of 33 to 45 seconds indicates that the intrinsic system is functioning normally.

COMPETENCIES

- ●●●●● Medical knowledge
- ● Interpersonal & communication skills
- ●● Patient care
- ●● Professionalism
- ●●● Practice-based learning and improvement
- ● Systems-based practice

- CBC results will show too many RBCs (hematocrit higher than 52% in men and 47% in women) in patients with P vera. An elevated platelet count (more than $450\times10^3/\mu L$) could indicate thrombocytosis or be a reaction to inflammation or infection. A cell morphology smear shows platelet granularity and the presence of megathrombocytes. A low platelet count may indicate HIT, idiopathic thrombocytopenia purpura, thrombotic thrombocytopenic purpura, or antiphospholipid antibody syndrome.

FIGURE 1. The clotting cascade



Data from Monroe DM and Hoffman M.[5]

- A chemistry profile will show elevated glucose levels in patients with diabetes and elevated BUN and creatinine in patients with renal failure.
- A lipid profile may indicate hypercholesterolemia, which can cause a hypercoagulable state.
- A TSH test is diagnostic for hyperthyroidism or hypothyroidism.

If anticoagulant therapy is being considered, a baseline prothrombin time (PT) and activated partial thromboplastin time (aPTT) are needed before initiating therapy. PT is used to monitor patients on warfarin therapy; aPTT is used to monitor patients on heparin therapy.

- A PT of 11 to 16 seconds indicates that the extrinsic coagulation system is functioning normally. Extrinsic pathway factors I, II, V, VII, and X can be assessed using the international normalized ratio (INR), where 1 is normal and 2 to 3 is therapeutic for patients receiving warfarin therapy for deep vein thrombosis (DVT) prevention, and 2.5 to 3.5 is therapeutic for patients with prosthetic heart valves.
- An aPTT of 33 to 45 seconds indicates that the intrinsic coagulation system is functioning normally. This test measures factors XII, XI, X, IX, VIII, V, and prothrombin and is used to monitor patients receiving heparin therapy; monitoring antifactor Xa activity is an alternative. Platelet aggregation testing is also used to monitor antiplatelet therapy.
- A hypercoagulation panel usually includes testing for protein S, protein C, and antithrombin III assay; Leiden factor V mutation (functional and nucleic acid); prothrombin 20210A mutation; homocysteine levels; anticardiolipin, antinuclear, and antiphospholipid antibodies; lupus anticoagulant; and fibrinogen level.[8]
- A HIT assay including heparin antibodies should be performed if the patient was exposed to heparin or low molecular weight heparin (LMWH) and platelet count falls below 50% of baseline.
- The D-dimer test results will show increased clotting and clot lysis occurring in the body; however, elevated levels are not specific for the location of clot lysis. If D-dimers are not present, DVT, PE, and other clotting activity is not likely to be occurring.[11]

5 Ps HAD CAUSED CLOTS

This mnemonic can help PAs remember the differential diagnosis of hypercoagulable states.[7,11,13] Table 1 spells out the mnemonic, identifying the differential diagnosis.

Pregnancy and postpartum Blood viscosity, fibrinogen, and factor VIII are increased during pregnancy.[11] Circulating tissue factor is increased during delivery.[11] The risk of VTE is approximately 6 times higher in pregnant women than in nonpregnant women. VTE is a major cause of morbidity during pregnancy and the puerperium. PE occurs in approximately 16% of patients with untreated DVT and is the most common cause of maternal death.[2,11,13]

Prothrombin 20210 mutation Up to 18% of patients with thrombosis or a family history of thrombosis have this mutation. The prevalence in healthy persons is about 2.3%. Pro-

"Arterial or venous thromboses, usually deep venous thrombosis or pulmonary embolism, develop in 10% to 30% of patients with HIT."

thrombin 20210 mutation causes increased prothrombin levels and a threefold increase in the risk of thrombosis.[13,14]

Protein S and protein C deficiencies Both proteins are intrinsic pathway anticlotting proteins produced in the liver.[8] Protein S deficiency prevalence is estimated at 1 per 500 persons.[8] This trait results in superficial thrombophlebitis, DVT, and PE. Protein C deficiency prevalence is 1 per 200 to 300 persons. Although this condition is associated with DVT and superficial phlebitis, the vast majority of thrombi formed are benign.[11,13] Both disorders are inherited in an autosomal dominant manner.[8]

P vera and thrombocytosis P vera manifests as increased marrow production of RBCs and platelets and may be associated with the *JAK-2* gene mutation.[15] P vera can lead to increased blood viscosity and is commonly associated with thromboembolism. Treatment includes frequent phlebotomy or hydroxyurea, to reduce RBC and platelet production, and aspirin, to prevent platelet activation.[15] Thrombocytosis with platelet counts higher than $900\times10^3/\mu L$ can cause a hypercoagulable state. A bone marrow biopsy is indicated, and suppression therapy with hydroxyurea may be needed.[12]

Paroxysmal nocturnal hemoglobinuria This genetic mutation causes excessive RBC sensitivity to complement resulting in increased clotting, hemolysis, and bone marrow aplasia.[11] Patients may present with smoky colored urine from excess hemoglobin. Clotting usually occurs in intra-abdominal organs and cerebral circulation. In addition to evidence of hemolysis, the Ham's test for RBC sensitivity to complement can confirm a diagnosis.[11]

Smoking Tobacco use causes endothelial cell damage, platelet adhesion, release of growth factor, reduced tPA production, and reduced TFPI. All of these manifestations can produce a prothrombotic state.[8]

Heparin-induced thrombocytopenia HIT occurs when an antibody against heparin forms after 1 week of heparin therapy. One percent to 3% of adult patients on heparin therapy will develop this syndrome. Heparin binds to platelet factor 4, forming a highly reactive antigenic complex on the surface of platelets.[8] This reaction results in the formation of heparin-associated antibodies and an increase in production of tissue factor.[8] HIT occurs less often in patients taking LMWHs (20% to 60% of patients have cross-reactivity with heparin antibodies).[8] The syndrome is heralded by a 50% decrease in platelet count 4 to 14 days after heparin exposure. The mean platelet count falls to 60 to $100\times10^3/\mu L$. Arterial or venous thromboses, usually DVT or PE, develop in 10% to 30% of patients. Of those patients, 30% will die or require amputation. Platelet counts need to be monitored while the patient is on heparin therapy and a HIT assay performed if the syndrome is suspected. Treatment is to discontinue use of all heparin products and administer a direct thrombin inhibitor.[8,16]

Hyperhomocysteinemia Homocysteine is derived from the metabolic conversion of methionine, which is dependent on folic acid, vitamin B_{12}, and vitamin B_6 as cofactors. Hyperhomocysteinemia is a prothrombotic condition. Treatment of the condition is vitamin B_{12}, vitamin B_6, and folate supplementation.[17] A genetic cause of increased homocysteine is the mutation variant C677T in the gene for methylene tetrahydrofolate reductase.[10]

Antithrombin III deficiency Antithrombin binds to heparin on endothelial cells to inactivate thrombin in the common clotting cascade.[8] The incidence of this genetically decreased

TABLE 1. 5 Ps HAD CAUSED CLOTS: Differential diagnosis of hypercoagulable states

Pregnancy and postpartum
Prothrombin 20210 mutation
Protein S and protein C deficiencies
Polycythemia vera and thrombocytosis
Paroxysmal nocturnal hemoglobinuria
Smoking
Heparin-induced thrombocytopenia
Hyperhomocysteinemia
Antithrombin III deficiency
Dysfibrinogenemia
Congestive heart failure
Antiphospholipid syndrome
Uremia
Surgery
Estrogen use
Diabetes
Cancer
Leiden factor V mutation
Obesity and elevated cholesterol levels
Trauma, travel (immobility)
Thyroid disease
Thalassemia and sickle cell disease
Sepsis in disseminated infections

anticoagulant is 1 per 5,000 persons. A family history of thrombotic events should prompt screening of antithrombin III levels.[13]

Dysfibrinogenemia Inherited dysfibrinogenemia is rare; the disorder is present in 0.8% of patients with a history of venous thrombosis.[18] Dysfibrinogenemia can manifest as arterial clotting or venous clotting caused by excess thrombin in the blood and reduced fibrinolytic activity. The best indicators are an abnormal thrombin time and a prolonged reptilase time.[18]

Congestive heart failure This condition causes vascular endothelial dysfunction, reduced NO, increased blood viscosity, increased levels of vWF, and increased fibrinogen. All of these manifestations contribute to platelet activation and a prothrombotic state.[19]

Antiphospholipid syndrome This disorder can be primary or secondary associated with infection; autoimmune diseases such as systemic lupus erythematosus; rheumatoid arthritis; cancer; and medications such as procainamide, chlorpromazine, and quinidine.[20] A prothrombotic state is caused by increased circulating tissue factor and thrombin, decreased fibrinolysis, and reduced protein C activity.[20] High titers of antiphospholipid antibodies are associated with an increased risk of thrombosis.[20] Lupus anticoagulant and anticardiolipin antibody levels may also be elevated.

Uremia Chronic renal failure causes endothelial dysfunction, reduced NO production, and increased circulating cytokines; resulting in a hypercoagulable state.[21] Administering L-arginine, a precursor of NO, may be beneficial.[21]

Surgery Thrombosis occurs in more than 50% of patients who undergo surgery without preventive therapy, and orthopedic procedures carry the highest risk.[13] Risk of thrombosis is close to 60% in trauma patients.[13] This risk can be greatly reduced by administering antithrombotic prophylaxis for 10 days postoperatively.[22] Prophylaxis should be continued for 3 months after certain orthopedic procedures and for patients with other risk factors.[22]

> "Approximately 5% of whites are heterozygous for Leiden factor V; the genetic defect is almost absent in other ethnic groups."

Estrogen use The risk of thrombosis is increased two- to fivefold in women on hormone therapy.[13] Estrogen increases levels of clotting factors and reduces the anticoagulant effect of protein S and antithrombin III.[13] Other genetic and environmental factors, such as obesity, further increase the risk of thrombosis in patients who are on hormone therapy.[23] The risk of clotting is increased by 15- to 30-fold in Leiden factor V carriers or prothrombin 20210A carriers who are taking oral contraceptives.[13]

TABLE 2. Low molecular weight heparins

Dalteparin (Fragmin)
Enoxaparin (Lovenox)
Reviparin (Clivarine)
Tinzaparin (Innohep)

TABLE 3. Heparin alternatives

Antithrombin III (ATnativ, Thrombate III)
Argatroban
Bivalirudin (Angiomax)
Desirudin (Iprivask)
Lepirudin (Refludan)

TABLE 4. Tissue plasminogen activators

Alteplase (Activase, Cathflo Activase)
Reteplase (Retavase)
Tenecteplase (TNKase)

Diabetes Reduced insulin decreases endothelial NO production, increasing platelet activation. Increased insulin blocks the fibrinolytic pathway, and the resultant endothelial damage will cause a hypercoagulable state.[24] Persons with type 2 diabetes have the same prothrombotic risks as persons with hyperlipidemia or obesity.

Cancer Tumor cells and their products are known to exert procoagulant effects by activating the clotting cascade and by inhibiting the fibrinolytic system. These cells promote thrombosis by interacting with platelets, leukocytes, and endothelial cells.[13,25]

Leiden factor V mutation The anticoagulant effects of activated protein C to inactivated clotting factor V are blocked in persons with Leiden factor V mutation.[13] The defect is considered to be the most common hereditary cause of a hypercoagulable state.[13,26] The prevalence of Leiden factor V mutation is about 20% in patients with thrombosis and 50% in those with thrombophilia.[13] Approximately 5% of whites are heterozygous for Leiden factor V; the defect is almost absent in other ethnic groups.[26]

Obesity and elevated cholesterol levels Lipoproteins have the capacity to activate platelets and the clotting pathway. Very-low-density lipoprotein also up-regulates expression of the plasminogen activator inhibitor-1 gene and the plasminogen activator inhibitor-1 antigen and activity, a process accompanied by platelet aggregation and clot formation. The surface membrane of activated platelets supports the prothrombinase complex, resulting in further thrombin generation and amplification of the clotting cascade.[24,27]

Trauma, travel (immobility) Blood flow stasis from immobilization and release of tissue thromboplastin in trauma and

burns can cause disseminated intravascular coagulation. When the clotting factors are depleted, excessive bleeding occurs.[13] Travel and its related immobility causes a threefold increase in the risk of thrombosis. with the greatest risk in obese persons, oral contraceptive users, and persons with Leiden factor V mutation.[13]

Thyroid disease Subclinical hyperthyroidism causes an increase in circulating clotting factor X.[28] Hypothyroidism can cause increased fibrinogen, factor VII, increased plasminogen activator inhibitor, and decreased antithrombin III; all of these lead to a prothrombotic state.[28] The TSH test is the best screening tool.

Thalassemia and sickle cell disease Platelet activation and thrombin generation are increased in patients with these diseases. NO and anticoagulant proteins C and S are decreased in these patients.[29] The combination of these manifestations can lead to a hypocoagulable state.

Sepsis in disseminated infections Increased tissue factor is released from blood vessel endothelial cells into the circulation, activating the extrinsic clotting cascade.[6] Sepsis can occur with bacteria, as well as viruses such as Ebola, Marburg, and dengue.[6]

THERAPY

Effective management of hypercoagulable states starts with reducing the risk factors for clotting. Lifestyle modifications such as smoking cessation, weight reduction in obese patients, and lipid control through diet and pharmacotherapy should be attempted. Alternatives to estrogen replacement or oral contraceptives should be explored. Optimized disease management of heart failure, diabetes, renal failure, P vera, sickle cell disease, thalassemia, and thyroid disorders should be achieved.[6-29] Immobility and blood stasis should be minimized with ambulation, compression stockings, and pneumatic compression devices.[30]

The goal of treatment is to use the safest effective therapy that has the lowest risk of bleeding complications. Antiplatelet therapy is used to inhibit platelet activity to prevent MI and thrombotic stroke.[7,31] Interrupting the clotting cascade is used to prevent postoperative DVT, clotting in atrial fibrillation, PE, clotting around replacement heart valves, or to manage patients who are genetically at a high risk for a hypercoagulable state.[30] A thrombolytic agent or interventional angioplasty should be used to break apart an existing intravascular clot and to reperfuse tissue.[30]

Antiplatelet therapy Several intervention sites are available for antiplatelet therapy. TXA_2, a vasoconstrictor and platelet attractor, is produced in the platelets from arachidonic acid using the COX-1 pathway. Aspirin inhibits this pathway irreversibly and other COX-1 NSAIDs inhibit this pathway reversibly; both block platelet activation. Low-dose aspirin (less than 75 mg/d) is effective and causes less bleeding than higher dosages. Patients should be monitored for aspirin effectiveness using platelet aggregometry. Those who develop aspirin resistance should be switched to another antiplatelet agent.[7,31-33]

Clopidogrel is an ADP receptor blocker that prevents platelet activation. Clopidogrel is administered alone for patients with allergies or aspirin resistance. The agent is administered in combination with aspirin for patients with coronary syndromes and who have stents.[33] Combination therapy with aspirin is not more effective than aspirin alone in all other conditions and may cause more bleeding complications in patients with stable cardiovascular disease or those with multiple cardiac risk factors.[34]

Dipyridamole increases platelet cyclic adenosine monophosphate levels, thereby decreasing platelet activation. The agent, combined with aspirin, is used for stroke prevention. The combination of dipyridamole and aspirin is more effective than either agent alone.[33]

Activated platelets stick together using fibrinogen bound to the glycoprotein IIb–IIIa receptors on the platelet surface. Abciximab, tirofiban, and eptifibatide are IIb-IIIa blockers that prevent platelet to platelet binding. These parenteral agents are administered to patients with acute MI and those who are undergoing coronary interventions.[32]

> "The goal of treatment is to use the safest effective therapy that offers the lowest risk of bleeding complications."

Clotting cascade blockers Unfractionated heparin (UFH) increases antithrombin III and blocks the intrinsic pathway factors. Heparin is usually administered IV bolus followed by a continuous infusion with a pump when immediate anticoagulation is needed. UFH therapy requires routine monitoring with aPTT, heparin blood levels, and platelet counts; if platelet counts fall, a HIT assay will need to be performed. The effects of UFH therapy can be reversed with parenteral protamine sulfate.[7,35-40]

LMWH blocks factor Xa and not the factors in the intrinsic pathway. These parenteral agents are administered by SC injection daily (see Table 2). LMWH is used for postoperative DVT prophylaxis and for treating PE and MI. The agents have a longer half life than UFH–3 to 4 hours–and do not require laboratory-test monitoring.[7,35-40]

Fondaparinux is a parenteral indirect nonheparinoid factor Xa inhibitor and can be used to treat HIT.[7] Danaparoid is a parenteral antithrombin III-mediated inhibitor of factor Xa, also used for HIT therapy.[7] Direct thrombin inhibitors are alternatives for heparin therapy when HIT is present or suspected[7] (see Table 3).

Anticoagulants Warfarin is the only oral anticoagulant agent that works by inhibiting the vitamin K-dependent factors in the extrinsic pathway. Warfarin therapy is reversed by administering vitamin K and monitored with PT. An INR of 2 to 3 is the optimum range for indications other than car-

"Combining anticoagulant therapy with antiplatelet agents causes more bleeding complications and does not increase benefits."

diac valves. For persons with replacement cardiac valves, an INR of 2.5 to 3.5 is optimum.[30,35-40]

Thrombolytics tPAs are used to break apart existing clots that can cause stroke, MI, or PE (see Table 4, page 24). These drugs can be administered by catheter directly at the site of the clot[30,41] and should be administered within hours of the clotting event to reperfuse tissue. Major risk factors are bleeding from sites that had clot patches, so they should not be used if there is a high risk of GI, intracranial, or surgical wound bleed.[30,41]

GENERAL GUIDELINES

Combining antiplatelet agents with anticoagulant therapy generally causes more bleeding complications and does not increase benefits to the patient. Many dietary and herbal supplements and prescription medications interact with antiplatelet and anticoagulant treatments. Clinicians should always conduct a thorough review of the patient's diet and medication history before initiating pharmacotherapy. Medication interaction programs and databases can help the clinician check for potential adverse interactions.

The effectiveness of therapy is monitored with platelet aggregometry for antiplatelet therapy, PT and INR for warfarin therapy, and aPTT for UFH therapy. CBC and repeated stool guaiac tests are used to monitor patients for bleeding. Finally, patients need to be educated about the signs of excessive bleeding and encouraged to always have medical alert information on their person. JAAPA

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DRUGS MENTIONED

Abciximab (ReoPro)
Aspirin
Chlorpromazine
Clopidogrel (Plavix)
Danaparoid (Orgaran)
Dipyridamole (Persantine)
Dipyridamole and aspirin (Aggrenox)
Eptifibatide (Integrilin)
Fondaparinux (Arixtra)
L-arginine
Procainamide (Procanbid)
Protamine sulfate
Quinidine
Tirofiban (Aggrastat)
Warfarin (Coumadin)

OTHER AGENTS
Heparin alternatives (see Table 3)
Low molecular weight heparins (see Table 2)
Tissue plasminogen activators (see Table 4)

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