State-of-the-Art Review
Antiphospholipid Thrombosis Syndromes

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Patients recognized to be at increased risk for thrombosis have generally been referred to as having a "hypercoagulable" state, or "thrombophilia" (1). Many blood protein and platelet defects are now known to account for hypercoagulability and thrombosis; hereditary defects of blood proteins leading to thrombosis, such as antithrombin, protein C and protein S, heparin cofactor II, and plasminogen deficiency, activated protein C resistance (APCR)/factor V Leiden and other factor V mutations, the prothrombin mutation G20210A, dysfibrinogenemia fibrinolytic system defects, sticky platelet syndrome (SPS), and others, are generally termed the "hereditary thrombophilias." Acquired blood protein and platelet function defects are also associated with thrombosis, including acquired defects of protein C, protein S, or antithrombin, acquired APCR, and others. These are the "acquired thrombophilias." The most common of the acquired thrombophilias is antiphospholipid thrombosis syndrome. Acquired blood protein defects leading to thrombosis are as common as the hereditary forms. The thrombophilias are depicted in Table 1.

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid thrombosis syndromes (APL-TS), which include not only the lupus anticoagulant (LA) and anticardiolipin antibodies, but also more recently recognized "subgroups" of antiphospholipid antibodies (antibodies against B2-glycoprotein-I [B-2-GP-I]), and antibodies to phosphatidylserine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidylinositol, annexin-V, and phosphatidylcholine. Although there are similarities, there are, at times, clinical, laboratory, and biochemical differences, particularly regarding prevalence, etiology, possible mechanisms of thrombosis, clinical presentations, diagnosis, and at times, management (4,5). The anticardiolipin antibody–thrombosis antiphospholipid syndrome is much more common than is the lupus anticoagulant–thrombosis antiphospholipid syndrome, the ratio being about 5 to 1 (3,6,7). All of these syndromes may be associated with 1) arterial and venous thrombosis, 2) recurrent miscarriage, and 3) thrombocytopenia, in descending order of prevalence; however, the anticardiolipin syndrome is more commonly associated with both arterial and venous thrombosis, including typical deep vein thrombosis and pulmonary embolus, premature coronary artery disease, premature cerebrovascular disease (including TIA, small stoke syndrome, and cerebrovascular thrombotic stroke), and retinal arterial and venous occlusive disease. The lupus anticoagulant, though sometimes associated with arterial disease, is more commonly associated with venous thrombosis with or without pulmonary embolus. Also, patients with anticardiolipin thrombosis syndrome develop more predictable types of thrombosis than do those with the lupus anticoagulant thrombosis syndrome, and treatment of thrombosis have generally been referred to as having a "hypercoagulable" state, or "thrombophilia" (1). Many blood protein and platelet defects are now known to account for hypercoagulability and thrombosis; hereditary defects of blood proteins leading to thrombosis, such as antithrombin, protein C and protein S, heparin cofactor II, and plasminogen deficiency, activated protein C resistance (APCR)/factor V Leiden and other factor V mutations, the prothrombin mutation G20210A, dysfibrinogenemia fibrinolytic system defects, sticky platelet syndrome (SPS), and others, are generally termed the "hereditary thrombophilias." Acquired blood protein and platelet function defects are also associated with thrombosis, including acquired defects of protein C, protein S, or antithrombin, acquired APCR, and others. These are the "acquired thrombophilias." The most common of the acquired thrombophilias is antiphospholipid thrombosis syndrome. Acquired blood protein defects leading to thrombosis are as common as the hereditary forms. The thrombophilias are depicted in Table 1.

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TABLE 1. Hereditary and acquired thrombophilic disorders

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<thead>
<tr>
<th>Inherited disorders</th>
<th>Acquired disorders</th>
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<tr>
<td>APC resistance</td>
<td>Anti-phospholipid antibodies</td>
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<td>Factor V Leiden mutation</td>
<td>Anticardiolipin antibodies</td>
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<td>Factor V Cambridge mutation</td>
<td>Lupus anticoagulant</td>
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<td>Factor V Hong Kong</td>
<td>Subgroup phospholipid antibodies</td>
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<td>Factor V HR2 mutation</td>
<td>Myeloproliferative syndromes</td>
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<td>Prothrombin 2010A mutation</td>
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<td>Factor XII deficiency (Hageman trait)</td>
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<td>Hyperhomocysteinemia</td>
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<td>Disorders, both inherited and acquired</td>
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<td>Antithrombin deficiency</td>
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<td>Heparin cofactor II deficiency</td>
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<td>Other fibrinolytic system defects</td>
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<td>Anti-phospholipid antibodies</td>
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APC, activated protein C.

Thrombotic problems can be quite different between the two syndromes. Thrombosis patients harboring antibodies to β-2-GP-I or antibodies to phosphatidylserine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidylinositol, annexin-V, or phosphatidylcholine and render biologic false positive tests for syphilis, whereas those with primary antiphospholipid thrombosis syndrome more commonly have homogeneous antibodies reacting with only one particular phospholipid moiety (11). Thus, when evaluating published studies, one must carefully assess the population being studied for antiphospholipid antibodies. The findings and results of studies in patients with autoimmune disorders may not necessarily be extrapolated to studies or clinical and laboratory findings in patients with primary antiphospholipid thrombosis syndromes. These antiphospholipid thrombosis syndromes, including etiology, pathophysiology, clinical and laboratory diagnosis, and management principles are here-in discussed.

LUPUS ANTICOAGULANTS AND THROMBOSIS

In 1952 Conley and Hartmann described a coagulation disorder in two patients with systemic lupus erythematosus; the patients exhibited anticoagulant activity by in vitro testing that was manifested by a prolonged whole blood clotting time and prothrombin time (12). It is now known that patients with systemic lupus or other autoimmune diseases may develop an immunoglobulin that has the ability to prolong phospholipid-dependent coagulation tests (13,14). About 10% of patients with systemic lupus harbor a lupus anticoagulant (LA); however, the LA is commonly seen in other conditions as well, including malignancy, lymphoproliferative disorders, and viral infections, especially human immunodeficiency virus (HIV) infection (15–17). Most commonly the lupus anticoagulant develops in otherwise healthy individuals (primary lupus anticoagulant thrombosis syndrome). There is also an association with drug ingestion; commonly associated drugs include chlorpromazine, procaïnamide, quinidine, hydralazine, phenytoin, interferon, sulfadoxine/pyrimethamine, and cocaine (6,7,18–20). A common misconception is that patients with drug-induced lupus anticoagulant, usually IgM idiotype, do not experience thrombosis, but in fact these patients also have an increased risk of thrombotic disease. The frequency of hemorrhage resulting from the lupus anticoagulant is clearly less than 1%; however, it is important to recognize conditions that may predispose patients with lupus harboring a lupus anticoagulant to hemorrhage (21,22). Twenty-five percent of patients with systemic lupus have concomitant prothrombin deficiency, and more than 40% may have thrombocytopenia; these accompanying defects are particularly noted in those with secondary LA thrombosis syndromes (21,23).

Of greater clinical significance, patients with the lupus anticoagulant are at increased risk for thromboembolic disease, most commonly deep vein thrombosis, pulmo-
ary emboli, and thrombosis of other large vessels (24,25). Thromboembolism occurs in about 10% of patients with systemic lupus; however, in patients with systemic lupus and the lupus anticoagulant, thromboembolism occurs in up to 50% of patients. In patients harboring a primary LA, the lupus anticoagulant is estimated to account for about 6 to 8% of thrombosis in otherwise healthy individuals. There have also been associations with primary lupus anticoagulant syndrome and recurrent miscarriage, neuropsychiatric disorders, renal vascular thrombosis, thrombosis of dermal vessels, and thrombocytopenia (20,23,26,27).

Primary lupus anticoagulant thrombosis syndrome is much more common than the secondary type and consists of patients with lupus anticoagulant and thrombosis who harbor no other underlying disease; secondary lupus anticoagulant thrombosis syndrome consists of those patients with lupus anticoagulant and thrombosis with an underlying disease, such as lupus or other autoimmune disorders, malignancy, infection, inflammation, or ingestion of drugs inducing the lupus anticoagulant.

Patients with primary lupus anticoagulant phospholipid syndrome primarily experience venous thrombosis and pulmonary emboli. A wide variety of venous systems may become involved, including not only the extremities (most common presentation) but also mesenteric, renal, hepatic, portal, and superior and inferior vena cava (11,15). Although patients may also experience arterial events, this is uncommon in primary lupus anticoagulant thrombosis syndrome, as opposed to primary anticardiolipin antibody thrombosis syndrome, in which arterial events are almost as common as venous events. This is distinct from patients with secondary lupus anticoagulant thrombosis syndrome, wherein patients, especially those with systemic lupus and the lupus anticoagulant, more commonly experience arterial events than do those with primary lupus anticoagulant thrombosis syndrome. However, even in secondary lupus anticoagulant thrombosis syndrome, venous events are more common than arterial events. Arteries commonly involved include coronary, cerebral, carotid, aorta, mesenteric, renal, and extremities (11,15,26,28-30).

Purified lupus anticoagulant inhibits the Ca++-dependent binding of prothrombin and factor Xa to phospholipids, therefore inhibiting the activity of the phospholipid complex required for conversion of prothrombin to thrombin (14,21). Of interest, biologic false-positive tests for syphilis are seen in up to 40% of patients with systemic lupus; the number increases to 90% in patients with systemic lupus plus the LA (22,25,31).

An abnormality often (theoretically) exists in the phospholipid-dependent coagulation reactions, including the prothrombin time, the activated partial thromboplastin time (aPTT), and the Russell's viper venom time, as the lupus anticoagulant is not directed against a specific factor, but to phospholipids. The inhibitor usually does not exert an increasing effect with prolonged incubation with normal plasma, and thus this simple screen can often be used to distinguish the lupus inhibitor from inhibitors that neutralize specific clotting factors. About 15 to 25% of lupus anticoagulants can, however, be time dependent, so this is not an absolute or definitive test. Incubation of the patients’ plasma with normal plasma does not generally cause a sensitivity of the partial thromboplastin time to the inhibitor’s effect and one-stage assays for factors XII, XI, IX, and VII may yield low values when the standard dilutions of test plasma are used. Usually, further dilution of the test plasma causes the measured level of these factors to approach the normal range; an exception occurs in rare patients with decreased concentration of prothrombin resulting from accelerated removal of prothrombin antigen-antibody complexes (32,33).

Multiple lupus anticoagulant assays are currently in use (32). Sensitivity of the aPTT to the presence or absence of the lupus anticoagulant is highly dependent upon the reagents used. Many patients with thrombosis and the lupus anticoagulant have normal aPTT values, even with the newer, allegedly more “sensitive” reagents; thus, the aPTT is not an appropriate screening test for lupus anticoagulants, and when the presence of a lupus anticoagulant is suspected, a more definitive test, preferably the dilute Russell’s viper venom time (dRVVT), should immediately be performed, regardless of the PTT (6,7,34,35). The lupus inhibitor is identified by an ability to bind phospholipid and inhibit phospholipid-dependent coagulant reactions. The assays are based on the use of limiting amounts of phospholipid, and therefore sensitized, in platelet-poor plasma. Initially, a prothrombin time was performed with dilute tissue thromboplastin and a reduced number of platelets in the mixture; however, IgM inhibitors were missed (22).

A “modified” Russell’s viper venom time was developed in which the venom is diluted to give a “normal” time of 23 to 27 seconds, and the phospholipid is then diluted down to a minimal level that continues to support this range. A prolongation of this system will not correct with a mixture of patient and normal plasma, and this system detects both IgG and IgM anticoagulants (36). This assay is known as the dRVVT and is the most sensitive of all assays purported to be useful in the screening or diagnosis of lupus anticoagulants (35). The kaolin clotting time test (KCT) has been modified to detect lupus anticoagulants. In this assay, platelet-poor plasma is mixed with varying proportions of test plasma and normal plasma. Kaolin is added and the time required for clotting is determined (37). The KCT is then plotted against proportions of patients’ plasma with normal plasma; an inhibitor is assumed to be present when a small portion of test plasma in comparison with normal plasma pro-

longs the assay system. A kaolin-activated PTT, with rabbit brain phospholipid in a standard and fourfold increased "high" lipid concentration to normalize or "out-inhibit" the abnormal "standard" aPTT, has also been utilized in diagnosis of the lupus inhibitor (38). The best test at present is the dRVVT; if this test is prolonged, the confirmation of a lupus inhibitor, by noting correction of the prolonged dRVVT by adding phospholipid in some form (preferably void of platelet membrane material), is recommended, especially if the patient is on warfarin or heparin therapy. Both heparin and warfarin are also capable of prolonging the dRVVT. In our experience, the most sensitive and specific is the dRVVT available from American Diagnostics (Greenwich, CT).

There is a correlation between elevated anticardiolipin antibodies and the lupus anticoagulant in secondary antiphospholipid syndromes (those associated with other autoimmune diseases); however, the lupus anticoagulant, anticardiolipin antibodies, and subgroups are separate entities, and most of the time anticardiolipin antibodies are found in the absence of the lupus anticoagulant in the primary antiphospholipid thrombosis syndromes (21,39).

The lupus anticoagulant has a stronger association with binding phospholipids of a hexagonal composition such as phosphocholine, or after membrane damage by infection, interleukin-1 (IL-1), or other mechanisms leading to change from the lamellar to hexagonal form, whereas anticardiolipin antibodies usually have an affinity to lamellar phospholipids in a bilayer (lamellar) composition (14,40,41). IgG and IgM anticardiolipin antibodies are the most frequent idiotypes and can be detected by enzyme-linked immunosorbent assay (ELISA); IgA anticardiolipin antibodies occur slightly less frequently and are also detected by ELISA. Although the lupus anticoagulant is associated with thrombosis, the mechanism(s) whereby thrombosis occurs remains unclear. It has been proposed that there might be an interaction with the vasculature, thereby altering prostaglandin release. There may be activation of platelets and changes in prostaglandin metabolism, or the antibodies block protein C or the activated protein C pathway, or alter phospholipid interactions with activated factor V (42). It has also been proposed that there may be hyperactivity of the fibrinolytic system and increased levels of plasminogen activation inhibitor (43). Despite many proposed mechanisms, to date there remains no consensus on the precise mechanism(s) of action of lupus anticoagulants (6,7,44,45).

The clinical subclassification of types of thrombosis and lupus anticoagulant and anticardiolipin antibody patients into groups may be important for choosing therapy (6,7,39). Patients can generally be divided into one of six clinical subgroups. Type I syndrome includes deep venous thrombosis of the upper and lower extremities, inferior vena cava, hepatic, portal, and renal veins, and pulmonary embolus. Type II syndrome includes patients with arterial thrombosis including the coronary arteries, peripheral (extremity) arteries, extracranial carotid arteries, and aorta. Type III syndrome includes patients with retinal or cerebral vascular thrombosis/ischemia, including those with transient cerebral ischemia (TIAs). Several neurologic syndromes may be manifested, including TIAs, migraine headaches, and optic neuritis (27). Type IV syndrome includes patients with combinations of the aforementioned types of thrombosis. Like anticardiolipin antibodies and other antiphospholipid subgroups, the lupus anticoagulant has been associated with a recurrent miscarriage syndrome; this is type V. Abortion occurs frequently in the first, and less frequently in the second or third trimester. Placental vasculitis and vascular thrombosis may be apparent, and there may occasionally be an associated maternal thrombocytopenia (22,24,46). Type VI patients are those harboring LA with no apparent disease, including thrombosis.

Although patients with lupus anticoagulant thrombosis syndrome can be classified similar to those with anticardiolipin thrombosis syndrome, most patients with primary lupus anticoagulant thrombosis syndrome will fit into type I. In secondary lupus anticoagulant thrombosis syndrome, however, there will be more patients falling into types II, III, and V than is seen in the primary syndrome.

The lupus inhibitor usually persists in patients with primary antiphospholipid thrombosis syndrome, although it may sometimes disappear spontaneously. In the secondary lupus anticoagulant thrombosis antiphospholipid syndrome, treatment of the underlying autoimmune disorder frequently results in the reduction or disappearance of inhibitor activity. Corticosteroids may have a suppressive effect on the titer of the lupus anticoagulant, and to a lesser degree on anticardiolipin antibodies, but they do not appear to decrease thrombotic risk. Thus, there is no role for immunosuppressive therapy, including steroids, cyclophosphamide, or azathioprine, in patients with the primary lupus anticoagulant thrombosis syndrome. When steroids or other immunosuppressive therapy is warranted in the patient with an autoimmune disease and lupus anticoagulant thrombosis syndrome, the immunosuppression, while perhaps benefiting the underlying autoimmune disorder, will generally not alleviate the propensity for thrombosis. Discovery of a lupus anticoagulant, in the absence of underlying disease, and without evidence of thrombosis (type VI) does not necessarily require treatment, but current evidence suggests these individuals to have about a 40% chance of eventually experiencing a thrombotic event over a 3-year follow-up period. Thus, the decision to treat an asymptomatic patient with the lupus anticoagulant with anticoagulants requires individualization and judgment, because no clear guidelines yet exist. However, patients with the lupus anticoagulant or anticardiolipin antibodies and a
ANTIPHOSPHOLIPID SYNDROMES

history of thrombosis need to be taking long-term anticoagulant therapy. If untreated, there is a high incidence of thromboembolic recurrence (6,7,47,48). Patients with deep venous thrombosis or arterial thrombosis are generally best managed with long-term low-molecular-weight heparin (LMWH) therapy, as they are notoriously resistant to warfarin therapy (=50 to 65% of patients with antiphospholipid thrombosis syndrome eventually fail warfarin therapy) (49,50). Over the past 24 months, we have assessed 111 patients with thrombosis and antiphospholipid syndrome (exclusive of recurrent miscarriage patients). Of these, 59 patients were referred because of recurrent thrombosis on adequate doses of warfarin and on evaluation were found to harbor antiphospholipid antibodies or were known antiphospholipid thrombosis syndrome patients and gave a history of recurrence on adequate doses of warfarin. The failure rate to warfarin in this group was 59/111 patients or 53%. In contrast, less than 2% of patients will fail fixed low-dose unfractionated porcine mucosal heparin, and we have not yet seen a deep venous thrombosis failure to LMWH therapy (dalteparin) in patients with antiphospholipid syndrome. After patients with deep venous thrombosis/pulmonary embolism are stable for a period of time on LMWH, consideration of changing to long-term clopidogrel may be entertained, as this agent has been effective in stable patients not failing LMWH treatment. Patients with type II thrombosis (coronary artery, large peripheral arteries) are successfully treated with LMWH. Like those with type I, if the patient remains free of thrombotic events for a long period, clopidogrel may be successfully substituted, particularly if osteoporosis becomes a consideration. In patients with retinal or cerebral vascular thrombosis (type III) fixed-dose, long-term LMWH plus clopidogrel for intracranial/cerebral vascular thrombosis is usually effective. If the patient remains symptom free for 6 to 12 months, consideration of stopping the LMWH and continuing with clopidogrel may be reasonable. Clopidogrel at 75 mg/day is usually effective for retinal vascular thrombosis and if failure occurs, LMWH is added to the clopidogrel therapy. In those with mixtures of thrombotic sites (type IV), therapy is individualized based on predominant sites and severity of thrombosis (6,7,46). The recurrent miscarriage syndrome (RMS) syndrome (type V) is successfully treated, allowing full-term delivery, with initiation of low-dose acetylsalicylic acid (ASA) at 81 mg/day preconception and the addition of fixed low-dose UFH at 5,000 U every 12 hours, both used to term. Using this regimen, our population of RMS patients with antiphospholipid syndrome have experienced a 97% pregnancy success outcome (46,51). There is little or no role for prednisone in RMS due to the lupus anticoagulant if there is no underlying autoimmune disease.

ANTICARDIOLIPIN ANTIBODIES, “SUBGROUP” ANTIBODIES, AND THROMBOSIS

Interest in antiphospholipids began with discovery of the lupus anticoagulant in about 10% of patients with systemic lupus in 1952 (12). Shortly thereafter, it was recognized that presence of the lupus anticoagulant was associated with thrombosis, rather than bleeding (52). It was also soon recognized that many patients without autoimmune disorders harbored lupus anticoagulants and these antiphospholipid antibodies have now been reported in many conditions, including malignancy; immune thrombocytopenia purpura; leukemias; infections; in individuals ingesting chlorpromazine, phenytoin, primethamine/sulfadoxine, hydralazine, quinidine, cocaine, interferon, or procainamide (secondary syndrome); and in many otherwise normal individuals (primary syndrome) (33,53–57). Because of a noted association between lupus, a biological false-positive test for syphilis, and the presence of the lupus anticoagulant, Harris et al. in 1983 devised a new test for antiphospholipids using cardiolipin (58). This and subsequent modifications have now become known as the anticardiolipin antibody test; generally, IgG, IgA, and IgM anticardiolipin idotypes are currently assessed (59). Shortly after development of the anticardiolipin antibody assay, it became apparent that these antibodies were not limited to the lupus patient population, but were found in nonlupus patients as well. Of particular importance, these anticardiolipin antibodies are associated with 1) thrombosis and thromboembolus of both arterial and venous systems (8,44,60–62); 2) recurrent miscarriage syndrome (46,63, 64); and 3) thrombocytopenia in descending order of prevalence (65,66). More recently, it has become apparent that antibodies (all three idiotypes: IgG, IgA, and IgM) to β-2-GP-I, phosphatidylserine, phosphatidyethanolamine, phosphatidylglycerol, phosphatidylinositol, annexin-V or phosphatidylcholine are independent risk factors for thrombosis of all types (types I through V) (67). Although there is an association between the lupus anticoagulant and anticardiolipin antibodies and an association between lupus anticoagulants and the aforementioned syndromes, it has become clear that lupus anticoagulants, anticardiolipin antibodies, and antibodies to β-2-GP-I, phosphatidylserine, phosphatidyethanolamine, phosphatidylglycerol, phosphatidylinositol, phosphatidylcholine, or annexin-V are separate entities; most individuals with anticardiolipin antibodies do not have a lupus anticoagulant and most with the lupus anticoagulant do not have anticardiolipin antibodies (68). However, many with subgroups harbor anticardiolipin antibodies, but 10 to 20% of patients demonstrate discordance (69), and subgroups are present in the absence of positive ELISA assays for anticardiolipin antibodies or lupus anticoagulant. In our experience, dis-
cordance is noted in about the same percentages. In particular, in patients with type I about 7% are discordant, in type II 14% are discordant, in type III 15% are discordant, and in type V 22% are discordant (70). Thus, when suspecting antiphospholipid syndrome in a patient with thrombosis of any type and negative lupus anticoagulant assays and negative anticardiolipin assays, the presence of isolated antibodies to β-2-GP-I, phosphatidylserine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidylinositol, annexin-V, or phosphatidylcholine should be suspected and tested for (67).

Regarding the primary antiphospholipid thrombosis syndrome, the anticardiolipin thrombosis syndrome is at least fivefold more common than is the lupus anticoagulant thrombosis syndrome (6,8). Other differences between lupus anticoagulants and anticardiolipin antibodies include not only 1) differing clinical presentations; but also 2) noting that anticardiolipins are usually, but not always, dependent upon a cofactor, β-2-GP-I (apolipoprotein H) in vitro, whereas in vitro lupus anticoagulant activity appears independent of β-2-GP-I; 3) anticardiolipin antibodies and lupus anticoagulants have different isoelectric points on chromatofocusing separation; 4) both appear to be directed against different combinations of phospholipid moieties and complexes; and 5) purified anticardiolipin antibodies do not generally prolong any of the phospholipid-dependent coagulation tests, such as the aPTT, dRVVT, platelet neutralization procedure, or KCT unless there is concomitant presence of a lupus anticoagulant (71,72).

Initially, it was assumed that only IgG anticardiolipin antibody was associated with thrombosis; however, it is now clear that IgA and IgM anticardiolipin antibodies are also associated with thrombosis (6,7). The presence of any one anticardiolipin antibody, a combination of two, or all three together may be associated with thrombosis and thromboembolism (73). Also, although different types of thrombosis occur, there is no apparent association between the type of thrombotic event and the type or titer of anticardiolipin antibody present (6,7). The mechanism of action of anticardiolipin antibodies, or subgroups, in causing thrombosis is unknown, but several plausible theories have been proposed. Anticardiolipin antibodies have an affinity for important phospholipids involved at many points in the hemostasis system; they are directed primarily against phosphatidylserine and phosphatidylinositol, but not phosphatidycholine, another important phospholipid in hemostasis (74). The proposed mechanisms of action of anticardiolipin antibodies in interfering with hemostasis to induce thrombosis include 1) interference with endothelial release of prostacyclin (75); 2) interference with activation, via thrombomodulin, of protein C activation or interference with protein S activity as a cofactor for protein C (76); 3) interference with antithrombin activity (77); 4) interaction with platelet membrane phospholipids, leading to platelet activation (78); 5) interference of prekallikrein activation to kallikrein (79); 6) interference with endothelial plasminogen activator release (80); or 7) interference with the APC system (81). All these components of normal hemostasis are dependent upon phospholipid, except possibly antithrombin activity. These concepts are reviewed in references (6,8,43,45).

ANTICARDIOLIPINS AND VENOUS/ARTERIAL THROMBOSIS

Anticardiolipin antibodies are associated with many types of venous thrombotic problems, including deep venous thrombosis of the upper and lower extremities, pulmonary embolus, intracranial veins, inferior and superior vena cava, hepatic vein (Budd-Chiari syndrome) (6,7,82), portal vein, renal vein, and retinal veins (83–85). Arterial thrombotic sites associated with anticardiolipin antibodies have included the coronary arteries, carotid arteries, cerebral arteries, retinal arteries, subclavian and/or axillary artery (aortic arch syndrome) (86), brachial arteries, mesenteric arteries (87), peripheral (extremity) arteries, and both proximal and distal aorta (88–90).

ANTICARDIOLIPINS AND CARDIAC DISEASE

In an early study, it was found that 33% of patients with coronary artery bypass graft (CABG) surgery experiencing late graft occlusion (as determined by coronary angiography 12 months post-CABG) had preoperative anticardiolipin antibody levels over 2 standard deviations above control values, strongly suggesting an association between graft occlusion and antiphospholipid antibodies. In 80% of patients, the anticardiolipin antibody levels rose to levels greater than the preoperative levels at some point in time. The observed increase in anticardiolipin antibody levels was greater in patients having experienced an acute myocardial infarction than in those who had not (91,92). Another study has revealed over 20% of young (younger than 45 years of age) survivors of acute myocardial infarction to harbor anticardiolipin antibodies; in those surviving, 61% of those with these antibodies experienced a later thromboembolic event (93). No association was found between the presence of anticardiolipin antibodies and antinuclear antibody or other clinical features that would have suggested the presence of systemic lupus erythematosus. Anticardiolipin antibodies are suggested as an indicator of increased risk for post–myocardial infarction thrombotic events and an indication for prophylactic anticoagulation or antiplatelet therapy (93). Despite continuous prophylactic treatment with aspirin and warfarin, acute myocardial infarction has been documented in a patient with previously documented normal coronary arteries who was treated suc-
cessfully with tissue plasminogen activator (94). In analyzing the relative frequency of acute myocardial infarction in patients with antifibrin antibodies, a study published in 1989 noted myocardial infarction in only 5 of 70 patients (significantly fewer than those experiencing cerebral arterial thromboses) (95). Another study revealed a very high percentage of young individuals (those younger 50 years of age) who experience acute myocardial infarction or restenosis after percutaneous transluminal coronary angioplasty (PTCA) or CABG (96). Thus, antifibrin antibodies appear to play a significant and major role in premature/precocious coronary artery disease; this may approach almost 70% in younger-aged patients with coronary artery disease (30,96).

Antifibrin antibodies are also associated with cardiac valvular abnormalities. Cardiac disease in patients with systemic lupus erythematosus has been associated with valvular vegetations, regurgitation, and stenosis. Almost 89% of patients with systemic lupus erythematosus and valvular disease have been found to have antiphospholipid antibodies, compared with only 44% of patients without valvular involvement. Although only 18% of all patients with lupus have valvular disease, cardiac valvular abnormalities are found in 36% of patients with the primary antiphospholipid syndrome. The valvular abnormalities of the primary antiphospholipid syndrome are characterized by significant, irregular thickening of the mitral and aortic valves, valvular regurgitation (but not stenosis), the potential for severe hemodynamic compromise, and surprisingly, an absence of valvular thrombi (97). Patients with concomitant systemic lupus erythematosus and antiphospholipid antibodies have been found to have aortic and mitral valvulitis, including typical Libman–Sacks verrucous endocarditis (98,99). Additionally, in patients with systemic lupus erythematosus, the presence of antiphospholipid antibodies is associated with isolated left ventricular dysfunction (100). An isolated instance has been reported of an intracardiac mass in the right ventricle, presumably resulting from the combined effects of abnormal intracardiac flow resulting from anomalous muscle bundles combined with enhanced thrombogenesis associated with antiphospholipid antibodies (101). In view of the high incidence of valvular abnormalities in patients with antiphospholipid antibodies and arterial thromboembolism, Doppler echocardiography should routinely be considered (102).

**ANTIFIBRIN ANTIBODIES AND CUTANEOUS MANIFESTATIONS**

Antifibrin antibodies are associated with livido reticularis, an unusual manifestation of cutaneous vascular stasis characterized by a distinctive pattern of cyanosis (60,103,104). This cutaneous finding has been associated with recurrent arterial and venous thromboses, valvular abnormalities, and cerebrovascular thromboses with concomitant essential hypertension (“Sneddon’s syndrome”) (60). Other cutaneous manifestations include a syndrome of recurrent deep venous thrombosis, necrotizing purpura, and stasis ulcers of the ankles (60,103,104). Skin lesions of Dego’s disease (a rare multisystem vasculopathy), characterized pathologically by cutaneous collagen necrosis and atrophy of the epidermis with an absence of inflammatory cells have been linked to the other consequences of the disease, such as cerebral and bowel infarction and antifibrin antibodies or a lupus anticoagulant (105). Vascular thromboses may be manifest as ischemia or necrosis of entire extremities as demonstrated in association with disseminated intravascular coagulation (106), with resultant cutaneous necrosis or more patchy, widespread, demarcated areas of cutaneous necrosis, manifest by areas of painful purpura and necrosis with underlying dermal necrosis (107). Other common cutaneous manifestations include livido vasculitis/reticularis, unfading acral microlivido, peripheral gangrene, necrotizing purpura, hemorrhage (ecchymosis and hematoma formation) (107), and crusted ulcers about the nail beds (108). See Eng (104) for an excellent review of this topic.

**ANTIFIBRIN ANTIBODIES AND NEUROLOGIC SYNDROMES**

The neurologic syndromes associated with antifibrin antibodies include TIAs, small stroke syndrome, arterial and venous retinal occlusive disease, cerebral arterial and venous thrombosis, migraine headaches, Dego’s disease, Sneddon’s syndrome (109), Guillain–Barré syndrome (110), chorea, seizures, and optic neuritis (105,111,112). The central nervous system manifestations of systemic lupus erythematosus are commonly, but not always, associated with positive antiphospholipid antibodies (113,114). Although it is clear that patients with lupus with antiphospholipid antibodies may experience cerebrovascular thromboses, cerebral ischemia, and infarction, these events occur more commonly in patients with the primary antiphospholipid thrombosis syndrome and absence of an underlying autoimmune disease. Multiple cerebral infarctions in patients with antiphospholipid antibodies may result in dementia (115).

The primary phospholipid syndrome is often present in patients with a constellation of concomitant arterial occlusions, strokes, TIAs leading to multiple-infarct dementia, deep venous thrombosis associated with pulmonary embolization, and resultant pulmonary hypertension, recurrent miscarriage, thrombocytopenia, positive Coombs test, and chorea (27,116). The primary distinction between patients with primary phospholipid syn...
drome and Sneddon's syndrome is the involvement of large vessels in the former and exclusively medium-sized arteries in the latter (109,117,118). Patients with antiphospholipid antibodies are more likely to experience cerebral ischemic or thrombotic events when also harboring primary hypertension or coronary disease, respectively (119). Anticardiolipin antibodies and recurrent stroke have also been associated with thymoma (120). Recent studies have found that antiphospholipid antibodies, including subgroups, particularly antiphosphatidylserine, are important etiologic factors. This is of major importance with respect to appropriate antithrombotic therapy, and these patients cannot be treated with simple antiplatelet therapy or warfarin therapy with success, as they require LMWH or unfractionated heparin (UH) with or without an antiplatelet agent for adequate protection against recurrence. One recent study found that 46% of younger-aged individuals (age ≤50 years) with cerebral ischemic events harbored antiphospholipid antibodies (121). Another study found that 44% of younger-aged individuals (age ≤51 years) to have antiphospholipid antibodies (122), but another study found only 18% of patients under age 44 to harbor antiphospholipid antibodies (123). Subgroups only of antiphospholipid antibodies have been noted in up to 23% of younger-aged patients with cerebral thrombotic events; thus, it is of extreme importance to consider these (122). Antiphospholipid antibodies are also associated with cerebral venous events (124). Another recent study noted 65% of patients with cerebrovascular thrombosis under age 60 years to harbor antiphospholipid antibodies; in the same study, 28% of patients with only TIAs harbored antiphospholipid antibodies (125). Studies have also noted that those with antiphospholipid antibodies tend to have an cerebrovascular occlusive/ischemic event about a decade earlier than those having cerebrovascular thrombotic or ischemic events in the absence of antiphospholipid antibodies (126). Thus, it is clear that antiphospholipid antibodies are important in the etiology of cerebrovascular ischemic events (27,127). The primary importance of these findings is in making an appropriate diagnosis so that effective therapy may be instituted (LMWH or UFH with or without clopidogrel) to afford effective secondary prevention. The complicated topic of neurologic manifestations in APL-TS has recently been reviewed (27,127).

**ANTICARDIOLIPINS AND AUTOIMMUNE COLLAGEN DISEASE**

While much of the initial research and many of the first descriptions of antiphospholipid antibodies resulted from investigation of the lupus anticoagulant in populations with systemic lupus, it is now well established that antiphospholipid antibodies occur in patients without systemic lupus erythematosus much more frequently than in those with lupus or other autoimmune disorders. In patients with lupus, the presence of livido reticularis may represent an important cutaneous marker for the presence or later development of antiphospholipid antibodies (103). Antiphospholipid antibodies may occur with increased frequency in individuals with other autoimmune disorders and have been reported in patients with mixed connective tissue disease, rheumatoid arthritis (107), Sjogren's syndrome (99), Behcet's syndrome (possible role in the pathogenesis of the multisystem manifestations of the syndrome) (128), and autoimmune thrombocytopenic purpura (65). Most patients with anticardiolipin antibody thrombosis syndrome, however, have a primary syndrome with no underlying autoimmune disorder. Less than 10% of patients with thrombosis and antiphospholipid antibodies have, or will ever develop, an autoimmune disease such as systemic lupus, rheumatoid arthritis, mixed connective disease, or a related syndrome. The clinical manifestations can be varied and substantial (26,118).

**ANTICARDIOLIPINS AND OBSTETRIC SYNDROMES**

Anticardiolipin antibodies are associated with a high incidence of recurrent miscarriage; the characteristics of this syndrome are 1) frequent abortion in the first trimester due to placental thrombosis/vasculitis; 2) recurrent fetal loss in the second and third trimesters, also due to placental thrombosis/vasculitis; and 3) maternal thrombocytopenia, in descending order of prevalence. This is especially likely in the presence of moderate or high IgG anticardiolipin levels (129). This syndrome has been successfully treated to normal term by institution of aspirin, low-dose heparin, or plasma exchange (64,130–132). Women harboring anticardiolipin antibodies have about a 50 to 75% chance of fetal loss and successful anticoagulant therapy can increase the chances of normal term delivery to about 97% (46,52).

Optimal therapy for the RMS has not yet been defined, but we have noted a 97% normal delivery outcome in 123 patients with RMS treated with preconception ASA at 81 mg/day, with the immediate postconception addition of UFH at 5,000 U every 12 hours and both agents used to term (52). A variety of heparin doses have been used with significant success in carrying patients to term and most of these have been in combination with aspirin therapy. It is clear that in the primary antiphospholipid syndrome (absence of an underlying autoimmune disorder such as systemic lupus erythematosus), the use of corticosteroids or other immunosuppressive therapy is not warranted and only enhances side effects. However, immunosuppressive therapy may be useful in those with anticardiolipin syndrome and lupus. Also, a variety of vigorous antibody removing/eradicating modes of
therapy have been attempted with varying degrees of success, including plasmapheresis, plasma exchange, immunoabsorption column treatment, and intravenous immunoglobulin (IVIG). Based on available reports and our own experience, the use of low-dose aspirin (about 81 mg per day) in combination with low-dose porcine mucosal heparin (5,000 U subcutaneously every 12 hours) consistently appears to be the most effective therapy for term delivery at the current time. Our approach in treating the RMS is to start a patient on low-dose aspirin (81 mg/day) at the time a diagnosis of RMS is made: the demonstration of anticardiolipin antibody, lupus anticoagulant, or antiphospholipid subgroups (seen in 22% of our patients with RMS and antiphospholipid antibodies), and a history of recurrent abortion (133). Subgroup analysis, including anti–annexin-V antibodies, is particularly important in RMS (133). Antibodies to annexin-V, also referred to as “placental anticoagulant protein” (134), may be of particular importance in patients with recurrent miscarriage, but additional studies are needed. Two studies have shown Ig fractions of antiphospholipid antibody (APLA) or β-2-GP-1 (APLA) decrease trophoblastic annexin-V (134–136), but several have suggested this anti–annexin-V activity to be limited to the antiphosphatidylserine subgroup antibody idiotype (137,138). However, two studies have failed to demonstrate abnormalities of annexin-V in miscarriage patients with antiphospholipid syndrome and concluded it may play no role in RMS (139,140). As soon as pregnancy is achieved, fixed low-dose porcine mucosal heparin (5,000 U every 12 hours) is added to the aspirin and used to term. The low-dose heparin need not be stopped during delivery, as it is extremely unlikely to be associated with significant hemorrhage and affords peripartum and postpartum protection against thrombosis and thrombembolic disease. Thus far, our success rate using this regimen has been 97% (46,52). LMWH may also be used, but in view of reported cases of periapinal/exudal bleeding with epidural anesthetics reported with enoxaparin, antiphospholipid antibody patients who are administered LMWH during pregnancy should be changed to UFH during the last trimester.

The incidence of antiphospholipid antibodies in RMS has been studied by a number of groups. Most studies, however, have not utilized control pregnant populations. Lin (141) studied a population of 245 women with RMS and found 13.5% to have anticardiolipin antibodies. Parazzini et al. (142) studied 220 patients with two or more spontaneous abortions and found 19% to harbor antiphospholipid antibodies. Grandone et al. (143) assessed 32 patients with RMS and found 28% to have anticardiolipin antibodies, and Birdsal et al. (144) studied 81 patients with RMS and found 41% to harbor antiphospholipid antibodies. Maclean et al. (145) assessed 243 patients with RMS (two or more spontaneous abortions) and found 17% to have anticardiolipin antibodies, 7% to have LA, and 2% to harbor both. Howard et al. (146) assessed 29 nonlupus patients with RMS and found 48% to have LA. Taylor et al. (147), in a study of 189 women with unexplained miscarriage, found LA in 7% and anticardiolipin antibodies in 15%. The only two studies assessing matched controls were those of Parke et al. (148), who found 7% of pregnant women without RMS and 16% of those with RMS to have antiphospholipid antibodies, and Parazzini et al. (142), who found an incidence of 3% anticardiolipin antibodies in control women. Thus, it appears a small population of normal pregnant females without symptoms of RMS will also harbor antiphospholipid antibodies. This of course raises the question of treatment in the pregnant female harboring antiphospholipid antibodies but with no history of spontaneous miscarriage; at present no data provide adequate direction for this dilemma.

Anticardiolipin antibodies are also associated with a peculiar postpartum syndrome of spiking fevers, pleuritic chest pain, dyspnea and pleural effusion, patchy pulmonary infiltrates, cardiomyopathy, and ventricular arrhythmias. This syndrome characteristically occurs 2 to 10 days postpartum (149). Because the majority of patients with postpartum syndrome recover spontaneously, most require no therapy other than symptomatic treatment. It is unclear if any type of antithrombotic therapy is warranted in this population because recovery almost always occurs spontaneously.

**MISCELLANEOUS DISORDERS AND ANTICARDIOLIPIN THROMBOSIS SYNDROME**

Anticardiolipin antibodies have recently been reported in patients with human immunodeficiency virus infection, with or without immune thrombocytopenic purpura (150). Particularly elevated are IgG isotypes; however, there is no correlation between antiphospholipid antibody level and disease progression or the incidence of thrombosis, despite a correlation with the titer and presence of thrombocytopenia (150–153). Elevations of one or more of the anticardiolipin isotypes has been observed following a number of acute infections, including ornithosis, Mycoplasma infection, adenovirus infection, rubella, varicella, mumps, malaria, and Lyme disease (154). Abnormalities of the aPTT in patients with hepatic cirrhosis have recently been attributed to the presence of antiphospholipid antibodies (155). Drugs associated with the development of anticardiolipin antibodies include phenytoin (156), quinidine, pyrimethamine/sulfadoxine, hydralazine, procainamide, cocaine, interferon, and phenothiazines (with a predisposition to thrombosis, which does occur in drug-associated antiphospholipid syndrome) (6,7,157). The anticardiolipin thrombosis syndrome can be divided into those that are primary and those that are secondary. Primary anticardiolipin thrombosis syndrome is much more
common and consists of patients with anticardiolipin antibody and thrombosis who harbor no other underlying disease; secondary anticardiolipin thrombosis syndrome consists of those patients with anticardiolipin antibody and thrombosis with an underlying disease, such as lupus or other autoimmune disorder, malignancy, infection, inflammation, or ingestion of drugs inducing an anticardiolipin antibody.

**CLASSIFICATION OF ANTIPHOSPHOLIPID THROMBOSIS SYNDROMES**

The finding of anticardiolipin antibodies, subgroups of antiphospholipid antibodies, or lupus anticoagulants in association with thrombosis is referred to as the antiphospholipid thrombosis syndrome. Patients with LA do not tend to have thromboses that are as predictable as those with anticardiolipin antibodies or the subgroups of antibodies to B-2-GP-1, phosphatidylserine, phosphatidylethanolamine, phosphatidylylglycerol, phosphatidylinositol, phosphatidylcholine, or annexin-V; however, treatment principles, as far as is currently known, apply equally to all (67).

The antiphospholipid thrombosis syndrome, associated with anticardiolipin or subgroup antibodies, can be divided into one of six subgroups: type I syndrome is composed of patients with deep venous thrombosis and pulmonary embolus; type II syndrome is composed of patients with coronary artery or peripheral arterial (including aorta and carotid artery) thrombosis; type III syndrome is composed of patients with retinal or cerebrovascular (intracranial) thrombosis; and type IV patients are those with admixtures of the first three types. Type IV patients are uncommon, with most patients fitting into one of the first three types. Type V patients are those with RMS, and type VI patients are those harboring antiphospholipid syndromes without any (as yet) clinical expression, including thrombosis. There is little overlap (about 10% or less) between these subtypes, and patients usually conveniently fit into only one of these clinical types. The types of antiphospholipid and thrombosis syndromes associated with anticardiolipin antibodies are summarized in Table 2 (3,5,70). Although there appears to be no correlation with the type or titer of anticardiolipin antibody and type of syndrome (I through VI), the subclassification of thrombosis and anticardiolipin antibody patients into these groups is important from the therapy standpoint (3,5,70). Type I patients are best treated with the use of long-term, fixed-dose LMWH or fixed-dose subcutaneous UH therapy. If the patient remains thrombus free for 6 to 12 months or if osteoporosis becomes a consideration, long-term clopidogrel may eventually be substituted for the heparin. Type II patients are also best treated by long-term, fixed-dose LMWH (about 5,000 U/24 hours) or fixed-dose, subcutaneous

<table>
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<tr>
<th>Type I syndrome</th>
<th>Deep venous thrombosis with or without pulmonary embolus</th>
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<tr>
<td>Type II syndrome</td>
<td>Coronary artery thrombosis</td>
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<tr>
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<td>Peripheral artery thrombosis</td>
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<td>Aortic thrombosis</td>
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<td>Carotid artery thrombosis</td>
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<td>Type III syndrome</td>
<td>Retinal artery thrombosis</td>
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<td></td>
<td>Retinal vein thrombosis</td>
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<td></td>
<td>Cerebrovascular thrombosis</td>
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<td></td>
<td>Transient cerebral ischemic attacks</td>
</tr>
<tr>
<td>Type IV syndrome</td>
<td>Mixtures of types I, II, and III</td>
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<tr>
<td></td>
<td>Type IV patients are rare</td>
</tr>
<tr>
<td>Type V (fetal wastage) syndrome</td>
<td>Placental vascular thrombosis</td>
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<tr>
<td>Type VI syndrome</td>
<td>Antiphospholipid antibody</td>
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<td></td>
<td>No apparent clinical manifestations</td>
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UH therapy (usually 5,000 U every 12 hours); after long-term stability clopidogrel may be an alternative. Type III patients, those with cerebrovascular disease or retinal vascular disease, should be treated with fixed-dose, long-term LMWH plus clopidogrel for intracranial/cerebral vessel thrombosis/TIA; long-term stability can usually be achieved by stopping the heparin/LMWH and continuing with clopidogrel treatment. Clopidogrel (at 75 mg/day) is usually effective for retinal vascular thrombosis; if failure occurs, LMWH is added to the clopidogrel therapy. Therapy for type IV patients depends upon types and sites of thrombosis present (3,5,70). Patients with type V, RMS, are best treated with preconception initiation of low-dose ASA (81 mg/day) as soon as the diagnosis is made and then started on fixed low-dose porcine mucosal heparin (5,000 U, subcutaneously every 12 hours) immediately postconception, with both drugs being used to term delivery. Patients with type V syndrome are usually encouraged to stop the heparin following delivery (depending upon the individual clinical situation), but to continue on long-term, low-dose ASA indefinitely. The decision to continue ASA after delivery in these patients is empirical, but might ward off other minor thrombotic manifestations of antiphospholipid syndrome. There are no guidelines available to know how to best treat these patients after delivery, as most (<10%) will not develop a nonplacental thrombosis. Obviously, patients with thrombosis and anticardiolipin antibodies require long-term antithrombotic therapy, and treatment should only be stopped if the anticardiolipin antibody is persistently absent for at least 6 months before considering cessation of antithrombotic therapy (3,5,70). After persistent absence of their anti-
phospholipid antibody for at least 6 months, we usually discuss the risks and benefits of continuing antithrombotic therapy and encourage patients to take either low-dose ASA (81 mg/day) or long-term clopidogrel (depending upon the seriousness of the initial thrombotic event(s), in the hope that the antibody and thrombosis will not return. Obviously, patients with antiphospholipid syndrome who are going to be on long-term, fixed, low-dose UH or LMWH therapy should have initial bone density studies and should be cautioned about heparin-induced thrombocytopenia, mild alopecia, mild allergic reactions, osteoporosis, benign transaminasemia (seen in about 5% treated with UH and in about 10% treated with LMWH), and the development of benign eosinophilia (158,159). Patients should be monitored with weekly heparin levels (anti-Xa method) and complete blood count/platelet counts for the first month of therapy and monthly thereafter; this also applies to patients with type V syndrome. Table 3 outlines suggested antithrombotic therapy regimens based on type of anticardiolipin thrombosis syndrome. Also, because most patients with thrombosis and antiphospholipid antibodies fail warfarin therapy, the clinician should always suspect and search for antiphospholipid antibodies when evaluating a patient for warfarin failure.

**CLINICAL PRESENTATIONS**

It is becoming increasingly clear, with increased experience in utilizing the anticardiolipin assay in clinical practice, that primary antiphospholipid syndromes are much more common than suspected. Diagnostic evaluation of the patient to determine the etiology of a wide variety of thrombotic problems must now include assays for anticardiolipin antibodies, lupus anticoagulants, and when indicated, subgroups. Although it is appropriate to suspect antiphospholipid antibodies in virtually any clinical problem complicated by thrombosis, certain presentations are stronger indicators than others.

In patients with type I disease, a strong index of suspicion is appropriate particularly in individuals with deep venous thrombosis unaccompanied by another potential risk factor, such as exogenous estrogen administration, surgery, prolonged immobility, malignancy, or another hypercoagulable state. Likewise, patients may present with recurrent deep venous thrombosis with or without a significant clinical risk factor. As is frequently observed in clinical practice, patients may only be referred for evaluation after a second episode of thrombosis. The initial thrombotic event may have appeared to result from a recognizable predisposing problem, only later proven to be present concomitantly with anticardiolipin antibodies. Although the severity or location (femoral, popliteal calf vein, or other sites) of thrombosis or the presence of pulmonary embolization does not correlate with the presence of anticardiolipin antibodies, recurrent thromboembolic events or multiple sites of thrombosis should strongly suggest an anticardiolipin antibody. Another very common presentation is a patient who was referred because of failure (rethrombosis) on warfarin therapy. Failure to apparently adequate doses of warfarin should immediately alert the physician to strongly consider APL-TS.

Patients with type II disease frequently present with catastrophic illness. A history of myocardial infarction at a young age, recurrent myocardial infarction, early graft occlusion following CAGB surgery, and early occlusion post-PTCA is typical. Aorta, subclavian, mesenteric, femoral, or other large-vessel thrombosis may present with complete occlusion and acute symptoms of ischemia and threatened limb loss. Emergent diagnosis and appropriate therapy may decrease unnecessary morbidity and may be life saving.

Type III patients may be referred for a variety of problems. Acute loss or distortion of vision may lead to ophthalmologic confirmation of retinal arterial or venous thrombosis. Focal neurologic symptoms may suggest the presence of cerebrovascular thrombosis resulting in symptoms of stroke or TIA. Alternatively, multiple-infarct dementia may present more gradually, without clearly defined acute ischemic events. Early diagnosis is critical in type III patients, as failure to treat may result in irreversible cerebral or retinal injury.

Type IV patients, having a mixture of the aforementioned types, are extremely rare and comprise only about
TABLE 4. Drugs associated with the antiphospholipid thrombosis syndrome

<table>
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<th>Drug</th>
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<tr>
<td>Phenprocoumon</td>
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<td>Pyrimethamine/sulfadoxine</td>
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<td>Quinidine</td>
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<tr>
<td>Quinine</td>
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<tr>
<td>Hydralazine</td>
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<td>Procarbazine</td>
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<tr>
<td>Phenothiazines</td>
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<tr>
<td>Interferon-alpha</td>
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<tr>
<td>Cocaine</td>
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Most are IgM and are associated with thrombosis.

1% of patients with anticardiolipin thrombosis syndrome. A strong index of suspicion is required for the diagnosis, and therapy must be individualized depending upon the particular combination of thromboses. Type V patients are usually those with one or more spontaneous miscarriages and are most often referred by an obstetrician or by high-risk reproductive experts. Most women relate a history of spontaneous miscarriage in the first trimester (most commonly the 6th to 12th week), but some also spontaneously miscarry in the second and third trimester.

Drugs associated with antiphospholipid thrombosis syndrome are listed in Table 4.

PREVALENCE OF THE ANTIPHOSPHOLIPID THROMBOSIS SYNDROME

Unfortunately, very little information is available on prevalence of antiphospholipid antibodies, especially in asymptomatic individuals. Additionally, nothing is known about the potential propensity to develop thrombosis or other clinical manifestations when seemingly healthy individuals are found to harbor these antibodies. Two recent studies have addressed this issue. The first such study was the Montpellier Antiphospholipid (MAP) Study (160), wherein 1,014 patients (488 males and 326 females) admitted to a general internal medicine department for a variety of reasons were assessed for IgG, IgA, and IgM anticardiolipin antibodies. Lupus anticoagulant assays were not performed. Of the patients tested, 72 (7.1%) were positive for at least one idiotype. When assessing these 72 patients, 20 (28%) were determined to have clinical manifestations of the APL-T syndrome. Fifty-two patients, when questioned, had not yet demonstrated any manifestations of APL-TS, suggesting a false-positive incidence of 5.1%. However, long-term follow-up of the thus far asymptomatic patients has not occurred, and a follow-up report of the MAP Study will be awaited with interest. In another recent study (161), 552 healthy blood donors were screened, and IgG and IgM idiotypes and lupus anticoagulant were assessed. It was found 6.5% (28 donors) of the population harbored IgG and 9.4% (38 donors) of the population harbored IgM anticardiolipin antibodies, and five donors had both idiotypes. No donor was positive for lupus anticoagulant. The donors were followed for 12 months; during the follow-up period, no anticardiolipin antibody–positive patient developed a thrombotic event. However, nine anticardiolipin antibody–positive donors had a positive family history for thrombosis, and three of the anticardiolipin antibody–positive donors had a history of unexplained miscarriage (161). In a survey of 100 consecutive patients presenting with deep vein thrombosis or pulmonary embolus, 24% of patients were found to have anticardiolipin antibodies (49). It is suggested that anticardiolipin antibodies are common in patients presenting with unexplained deep venous thrombosis or pulmonary embolism, and certainly any patient presenting with unexplained deep venous thrombosis or pulmonary embolism should be evaluated for presence of antiphospholipid antibodies.

LABORATORY DIAGNOSIS OF ANTIPHOSPHOLIPID SYNDROMES

Detection of anticardiolipin antibodies

The detection of anticardiolipin antibodies is straightforward and there is general agreement that solid-phase ELISA is the method of choice (162–164). In the past, only IgG and IgA idiotypes have been assayed; however, with current recognition that IgM idiotypes, whether primary or secondary (especially drug induced), are also associated with thrombosis, most laboratories are, or should be, assaying all three idiotypes. The idiotype distribution of anticardiolipin antibodies in patients with thrombosis is depicted in Table 5. Thus, the appropriate assay for detecting anticardiolipins is solid-phase ELISA, measuring all three (IgG, IgA, and IgM) idiotypes (31,34,165).

Detection of lupus anticoagulants

In the presence of the lupus anticoagulant an abnormality exists in the phospholipid-dependent coagulation reactions, including the prothrombin time, the aPTT, and the Russell’s viper venom time (7,14). The lupus anticoagulant is not directed against a specific factor, but to phospholipids. The inhibitor does not exert an increasing effect with prolonged incubation with normal plasma, and thus this simple screen can be used to distinguish the

| Idiotype distribution in patients with thrombosis and anticardiolipin antibodies |
|-------------------------------|-----------------|-----------------|-----------------|
| 36% Have isolated IgG         | 17% Have isolated IgM |
| 14% Have isolated IgA         | 33% Have various mixtures |
lupus inhibitor from inhibitors that neutralize specific clotting factors. Incubation of the patient’s plasma with normal plasma does not cause a sensitivity of the PTT to the inhibitor’s effect, and one-stage assays for factors XII, XI, IX, and VII may yield low values when the standard dilutions of test plasma are used (14). Usually, further dilution of the test plasma causes the measured level of these factors to approach the normal range; the exception occurs in rare patients who have a decreased concentration of prothrombin, resulting from accelerated removal of prothrombin antigen–antibody complexes, sometimes seen in patients with systemic lupus.

Multiple lupus anticoagulant assays are currently in use. Sensitivity of the aPTT to the presence or absence of the lupus anticoagulant is highly dependent on the reagents used. Many patients with thrombosis and the lupus anticoagulant have normal aPTT values, even with the newer, allegedly more “sensitive” reagents; thus, the aPTT is not a reliable screening test for lupus anticoagulants and should not be used for this purpose (7,14,34,35,166–168). When suspecting the presence of a lupus anticoagulant, a more definitive test, preferably the dRVVT, should immediately be performed, regardless of the aPTT. The lupus inhibitor is identified by the ability to bind phospholipid and inhibit phospholipid-dependent coagulant reactions. The assays available are based upon the use of limiting amounts of phospholipid and therefore sensitized in platelet-poor plasma. Initially, a prothrombin time was performed with dilute tissue thromboplastin and a reduced number of platelets in the mixture; however, IgM inhibitors were missed. Subsequently, a “modified” Russell’s viper venom time was developed in which the venom is diluted to give a “normal” time of 23 to 27 seconds, and the phospholipid is then diluted down to a minimal level that continues to support this range. A prolongation of this system will not correct with a mixture of patient and normal plasma; this system detects both IgG and IgM lupus anticoagulants (36). This assay is generally known as the dRVVT and appears the most sensitive of all assays for the lupus anticoagulant (169). The KCT has also been modified to assay for the lupus anticoagulant inhibitor. In the KCT, platelet-poor plasma is mixed with varying proportions of test plasma and normal plasma. Kaolin is added and time required for clotting is determined (14). The KCT is then plotted against proportions of patient plasma with normal plasma; an inhibitor is assumed to be present when a small portion of test serum, in comparison with normal serum, prolongs the assay. A kaolin aPTT, with rabbit brain phospholipid in a standard and fourfold-increased “high” lipid concentration to normalize or “out-inhibit” the abnormal “standard” aPTT, has also been utilized in diagnosis of the lupus inhibitor (14). This is known as the rabbit brain neutralization procedure, and although specific (due to rabbit brain neutralization), lacks sensitivity comparable to the dRVVT. The best test to detect the lupus anticoagulant at present is the dRVVT; if this test is prolonged, the confirmation of a lupus inhibitor, by noting correction of the prolonged dRVVT by adding phospholipid in some form (unfortunately often platelet membrane-derived) is required, especially if the patient is on warfarin or heparin therapy. Both heparin and warfarin are capable of also prolonging the dRVVT. Confirmation of a lupus anticoagulant in the above assays is by phospholipid neutralization (shortening) of the prolonged test (7,14,169). As a practical matter, most clinicians and laboratories are asked to evaluate patients for the lupus anticoagulant after they have been placed on anticoagulant therapy. Both heparin and warfarin prolong most of the above tests, including the most sensitive test, the dRVVT. If the patient is on warfarin and the dRVVT is prolonged and then neutralized by appropriate phospholipid, a lupus anticoagulant is confirmed (7,14). However, if the patient is on heparin and the dRVVT is prolonged, the neutralization by platelet-derived phospholipid is not confirmatory, as large amounts of platelet-derived platelet factor 4 may inhibit the heparin effect to correct the test. For example, a commercially available platelet extract for the platelet neutralization procedure was found to contain about 100 IU/mL of platelet factor 4 and normal male freeze-thaw platelet extract, commonly prepared for “platelet or phospholipid neutralization procedures” in the clinical laboratory, contains about 95 IU/mL of platelet factor 4, enough to neutralize heparin and shorten a prolonged clotting test and render a false-positive result in the dRVVT or platelet neutralization procedure for a lupus anticoagulant (7,14,170). As a practical matter, therefore, the use of the dRVVT offers the most sensitive assay for detection of a lupus anticoagulant, and neutralization of this test by a non–platelet-derived phospholipid, in particular cephalin (Bell–Alton extract) (171), which contains no platelet factor 4, makes this test the most specific.

Owing to the marked heterogeneity of antiphospholipid antibodies, especially in the secondary antiphospholipid syndromes, there is a correlation between elevated anticardioilin antibodies and the lupus anticoagulant in secondary APLTS. However, the lupus anticoagulant and anticardiolipin antibodies are two separate entities, and most of the time one occurs without the other being present, especially in the primary antiphospholipid thrombosis syndromes (6). The lupus anticoagulant has a stronger association with binding phospholipids of a hexagonal composition such as phosphatidylcholine, or after membrane damage by infection, IL-1, or other mechanisms leading to change from the lamellar to hexagonal form, whereas anticardiolipin antibodies have an affinity...
TABLE 6. Laboratory diagnosis of antiphospholipid syndromes*

<table>
<thead>
<tr>
<th>Primary evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticardiolipin antibodies (IgG, IgA, IgM)</td>
</tr>
<tr>
<td>Lupus anticoagulant (dRVVT)</td>
</tr>
<tr>
<td>Hexagonal phospholipid neutralization</td>
</tr>
<tr>
<td>β-2-glycoprotein-I (IgG, IgA, IgM)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Secondary evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiphosphatidylserine (IgG, IgA, IgM)</td>
</tr>
<tr>
<td>Antiphosphatidylinositol (IgG, IgA, IgM)</td>
</tr>
<tr>
<td>Antiphosphatidylcholine (IgG, IgA, IgM)</td>
</tr>
<tr>
<td>Antiphosphatidylethanolamine (IgG, IgA, IgM)</td>
</tr>
<tr>
<td>Antiphosphatidylglycerol (IgG, IgA, IgM)</td>
</tr>
<tr>
<td>Anti-annexin-V antibody</td>
</tr>
</tbody>
</table>

*dSuspicion of antiphospholipid syndrome (e.g., unexplained thrombosis, transient ischemic attacks, small stroke syndrome, coronary thrombosis, fetal loss).

dRVVT, dilute Russell’s viper venom time.

When suspecting patients with thrombosis or RMS of harboring antiphospholipid antibodies and noting negative assays for anticardiolipin antibodies or lupus anticoagulants, the clinician should suspect discordant subgroups and order assays for anti-β-2-GP-I and antibodies to phosphatidylserine, phosphatidylethanolamine, phosphatidylylglycerol, phosphatidylinositol, annexin-V, and phosphatidylcholine. These are all available by enzyme immunoassay. It must be remembered that there is significant discordance between these subgroups and lupus anticoagulants or the three idiotypes of anticardiolipin antibodies, thus they must be recalled and tested for.

Detection of “subtypes” of antiphospholipid antibodies

When suspecting patients with thrombosis or RMS of harboring antiphospholipid antibodies and noting negative assays for anticardiolipin antibodies or lupus anticoagulants, the clinician should suspect discordant subgroups and order assays for anti-β-2-GP-I and antibodies to phosphatidylserine, phosphatidylethanolamine, phosphatidylylglycerol, phosphatidylinositol, annexin-V, and phosphatidylcholine. These are all available by enzyme immunoassay. It must be remembered that there is significant discordance between these subgroups and lupus anticoagulants or the three idiotypes of anticardiolipin antibodies, thus they must be recalled and tested for.

As mentioned above, discordance will be seen in a significant number of patients. In particular, many patients will have subgroups of antiphospholipid antibody (β-2-GP-I, antiphosphatidylserine, antiphosphatidylcholine, antiphosphatidylglycerol, antiphosphatidylinositol, and antiphosphatidylethanolamine) in the absence of anticardiolipin antibodies (IgG, IgA or IgM) or lupus anticoagulant. Specifically, this will be seen in 7% of patients with antiphospholipid thrombosis syndrome and deep venous thrombosis/pulmonary embolism (type I), 15% of those with coronary artery or peripheral arterial thrombosis (type II), 15 to 24% of those with cerebrovascular or retinal vascular thrombosis (type III), and in 22% of those with recurrent miscarriage syndrome (type V). All antiphospholipid antibodies of importance, to date, are depicted in Table 6. The tests at the top are ordered first and those at the bottom ordered if clinical suspicion of a subgroup is present. Figure 1 depicts an approach to the laboratory diagnosis of antiphospholipid thrombosis syndrome.

SUMMARY

Antiphospholipid antibodies are strongly associated with thrombosis and are the most common of the acquired blood protein defects causing thrombosis. Although the precise mechanism(s) whereby antiphospholipid antibodies alter hemostasis to induce a hypercoagulable state remain unclear, numerous theories, as previously discussed, have been advanced. The most common thrombotic events associated with anticardiolipin antibodies are deep vein thrombosis and pulmonary

FIG. 1. Laboratory diagnosis of antiphospholipid syndromes (e.g., unexplained thrombosis, transient ischemic attacks, small stroke syndrome, coronary thrombosis, fetal loss). If antiphospholipid syndrome is negative and clinically indicated, perform antiphosphatidylserine, antiphosphatidylcholine, antiphosphatidylglycerol, antiphosphatidylinositol, antiphosphatidic acid, antiphosphatidylethanolamine, antiphosphatidylglycerol, and anti-annexin-V antibodies. ELISA, enzyme-linked immunosorbent assay; ACLA, anticardiolipin antibody; LA, lupus anticoagulant; dRVVT, dilute Russell’s viper venom time.
embolus (type I syndrome), coronary or peripheral artery thrombosis (type II syndrome), or cerebrovascular/retinal vessel thrombosis (type III syndrome); occasionally, patients present with mixtures of these types (type IV syndrome). Type V patients are those with antiphospholipid antibodies and RMS. It is as yet unclear how many seemingly normal individuals who may never develop manifestations of antiphospholipid syndrome (type VI) harbor asymptomatic antiphospholipid antibodies. The relative frequency of anticardiolipin antibodies in association with arterial and venous thrombosis strongly suggests that these should be looked for in any individual with unexplained thrombosis; all three idiotypes (IgG, IgA, and IgM) should be assessed. Also, the type of syndrome (I through VI) should be defined if possible, as this may dictate both type and duration of both immediate and long-term anticoagulant therapy. Unlike those with anticardiolipin antibodies, patients with primary lupus anticoagulant thrombosis syndrome usually experience venous thrombosis. Because the aPTT is unreliable in patients with lupus anticoagulant (prolonged in only about 40 to 50% of patients) and is not usually prolonged in patients with anticardiolipin antibodies, definitive tests, including ELISA for anticardiolipin antibodies, the dRVVT for lupus anticoagulant, hexagonal phospholipid neutralization procedure, and β-2-GP-I (IgG, IgA, and IgM) should be immediately ordered when suspecting antiphospholipid syndrome or in individuals with otherwise unexplained thrombotic or thromboembolic events. If results of these tests are negative, in the appropriate clinical setting, subgroups should also be assessed. Finally, most patients with antiphospholipid thrombosis syndrome will fail warfarin therapy and, except for retinal vascular thrombosis, may fail some types of antiplatelet therapy; thus it is of major importance to make this diagnosis so that patients can be treated with the most effective therapy for secondary prevention—LMWH or UH in most instances, and clopidogrel in some instances.

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