Literature review

Unexplained Arterial Thrombosis

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Introduction

Thrombotic occlusion of arteries contributes to the pathophysiology of a variety of vascular disorders affecting the limbs and coronary, mesenteric, and cerebral arteries. Thrombosis most commonly occurs in a vessel affected by atherosclerosis, but may also develop in arteries affected by vasculitis. Disorders of coagulation and fibrinolysis may cause arterial thrombi to develop in a vessel that is otherwise normal. In contrast to venous thrombosis, which is caused primarily by reduced blood flow and comprises predominantly fibrin and red cells, arterial thrombosis characteristically results from elevated wall shear stress at sites of vascular injury and is composed predominantly of platelets. An arterial thrombus usually develops in areas of disturbed blood flow, most commonly caused by occlusive atherosclerotic plaque, where intimal injury leads to the adhesion, aggregation and recruitment of circulatory platelets. Thus, changes in the vessel wall supersede hypercoagulability in the pathophysiology of arterial thrombosis. Unexplained arterial thrombosis is an arterial event occurring without clear provoking factors and is usually a non-atherosclerotic and noncardioembolic arterial thrombosis.

Diagnostic approach

Defining the vascular obstruction based on clinical symptomatology, physical examination, imaging studies and discussion with organ-specific specialists is an essential first step because thrombosis location and extent of organ damage determine diagnostic considerations and management. Review of imaging studies with a radiologist to determine whether the thrombotic event is arterial or venous, whether evidence of atherosclerosis or vessel wall abnormality exists, and review of pathology specimens for evidence of atherosclerosis or vasculitis are helpful.

The location of the thrombus or ischemic territory can be suggestive of an embolic versus atherosclerotic etiology. An ischemic cerebral lesion not correlating with an anatomical arterial territory, particularly when associated with hemorrhage, raises a concern for venous sinus thrombosis. Splenic and renal infarcts can result from arterial or venous occlusion. Wedge-shaped infarcts suggest an arterial origin, whereas diffuse ischemic areas suggest a venous etiology. Retinal vessel thrombosis also requires particular attention. Distinction between retinal artery occlusion and retinal venous occlusion is the key, as is central versus branch vessel involvement. A discussion with an ophthalmologist may be necessary to clarify examination findings, including the bilaterality of changes or signs of a local thrombotic or systemic process, such as vasculitis, hyperviscosity, sarcoidosis etc.

Because thrombotic events are frequently multifactorial, identifying all potential atherosclerotic and thrombotic risk factors is important (Table 1). The most common causes of arterial events, atherosclerosis and cardioembolism, must first be excluded.[1]

Atherosclerosis

Evaluating to determine whether atherosclerosis is the underlying problem includes assessing atherosclerosis risk factors, such as obesity, diabetes mellitus, cigarette smoking, hypertension, high low density lipoprotein cholesterol, low high density lipoprotein cholesterol and high lipoprotein(a). Family history of arterial problems among young relatives (< 50 years of age) and evidence of atherosclerotic changes in imaging or pathology specimens should be obtained.

Table 1 Diagnostic approach in a patient with unexplained arterial thrombosis

A. Is arteriosclerosis the underlying problem?
Are arteriosclerotic changes demonstrated on imaging studies or pathology specimens?
Are arteriosclerosis risk factors present? (cigarette smoking, high blood pressure, high low density lipoprotein cholesterol, low high density lipoprotein cholesterol, high lipoprotein(a), diabetes mellitus, obesity, family history of arterial problems in young relatives)
B. Has the heart been thoroughly evaluated as an embolic source?
Atrial fibrillation - EKG, Holter monitor
Patent foramen ovale - Transthoracic echo with bubble study and Valsalva maneuver
C. Other causes
Age-appropriate cancer screening
Is the patient on estrogen therapy?
Does the patient use cocaine, anabolic steroids or other drugs?
Is there evidence for Buerger's disease?
Does patient have symptoms suggestive of a vasospastic disorder (Raynaud's phenomenon)?
Are anatomic abnormalities seen in arteries leading to the ischemic area (web, fibromuscular dysplasia, dissection, vasculitis, external compression)?
Does patient have evidence of a rheumatologic or autoimmune disease?
Is there a suggestion of an infectious arteritis (*Pythium insidiosum* among thalassemic patients)?
Could the patient have hyperviscosity or cryoglobulins?
D. Thrombophilia work-up
Complete blood count (rule out myeloproliferative neoplasms and paroxysmal nocturnal hemoglobinuria)
Antiphospholipid antibodies (anticardiolipin antibodies, anti-β2-glycoprotein-I antibodies, lupus anticoagulant)
Protein C activity, protein S activity or free protein S antigen, antithrombin activity (among young patients)
Homocysteine (among young patients)

Cardioembolism

Evaluating paroxysmal atrial fibrillation should include electrocardiography and ambulatory cardiac rhythm monitoring.[2] Evaluating for patent foramen ovale usually starts with transthoracic echocardiography with an agitated saline (bubble) study performed while the patient is coughing or performing a Valsalva maneuver.[3] If negative, transesophageal echocardiography or transcranial Doppler is considered.[4]

If cardioembolic and atherosclerotic explanations are unlikely, three additional categories of conditions that increase arterial thrombotic risk are considered: medications/substance use, systemic diseases and vascular/anatomic disorders.

Medications or substance use

A thorough review of a patient's medications is necessary. Combined oral contraceptives, hormone replacement therapy, anabolic androgenic steroids use and intravenous immunoglobulin may increase arterial thrombotic risk. Multiple anticancer agents also increase risk, including inhibitors of vascular endothelial growth factor, i.e., bevacizumab and orafenib and L-asparaginase.[5] Heparin-induced thrombocytopenia should be considered in any hospitalized patient because heparin exposure can occur through undocumented heparin flushes, and platelet count can decline without reaching a classically low threshold.

A thorough history of substance use and urine drug screen is warranted. Cocaine has multiple acute and long term prothrombotic effects.[6] Both tobacco including smokeless tobacco and marijuana can precipitate thromboangiitis obliterans (Buerger's disease), which may manifest with arterial thrombosis.[7]

Systemic diseases

Many systemic disorders may first present with an arterial event. Among patients with cancer, the rate of arterial thrombosis is 4.7% within six months after cancer diagnosis, attributable to both active malignancy and prothrombotic treatments.[8] Among patients without a cancer diagnosis, age-appropriate cancer screening should be performed, as patients have an increased arterial thrombotic risk before cancer diagnosis.[9-11] The value of more extensive malignancy evaluation after an arterial thromboembolism has not been studied, but data in venous thromboembolism argues against it.[12]

Myeloproliferative neoplasms and paroxysmal nocturnal hemoglobinuria (PNH) are associated with significantly increased thrombotic risk, particularly arterial events.[13,14] Appropriate testing should be pursued among patients with blood count abnormalities or evidence of hemolysis. Whether testing for JAK2V617F or PNH in the absence of hematologic findings is beneficial remains unclear given limited existing data.[15-17]

Hyperviscosity, whether from erythrocytosis, leukocytosis or excess plasma proteins (plasma cell disorder or cryoglobulinemia), can also increase arterial thrombotic risk. Sickle cell disease is more commonly associated with stroke versus other arterial events.[18] A distinct clinical syndrome characterized by progressive ischemia of the lower extremities, with ascending arteritis and thrombosis of the main arteries of the lower limbs due to *Pythium insidiosum* among patients with thalassaemia has been reported.[19] Thrombotic pulmonary arteriopathy resulting in pulmonary arterial hypertension has been described in in previously splenectomized patients with beta-thalassemia.[20]

The well-documented correlation between systemic inflammatory disorders and increased arterial thrombotic risk includes sarcoidosis and systemic vasculitides, such as antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis, large-vessel vasculitis, and Behçet's syndrome.[21] Therefore, thoroughly evaluating for signs and symptoms of autoimmune disorders is warranted. Nonspecific symptoms include fatigue, arthralgia, fever, rash and neuropathy, while more specific signs include palpable purpura, bruits, blood pressure discrepancies or combined renal and pulmonary involvement. Imaging can be reviewed with a radiologist for findings of vasculitis.[22] Laboratory evaluation could include urinalysis, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies, rheumatoid factor, ANCA and C3/C4 complement.

Vascular or anatomic disorders

Abnormalities in the vessel wall include dissection and vasculitis, as well as less common disorders, such as fibromuscular dysplasia.[23] Segmental arterial mediolysis and vascular Ehlers-Danlos syndrome are more commonly present with arterial rupture and hemorrhage, but can also precipitate thrombosis.[24,25] Certain disorders characteristically occur in a given arterial location, with cystic adventitial disease occurring in the popliteal artery and endofibrosis in the external iliac arteries.[26] Extrinsic arterial compression, as in popliteal artery entrapment syndrome and thoracic outlet syndrome, can also occur.[27] Vasospasm, idiopathic or secondary to autoimmune disease or substances, e.g., cocaine, amphetamines, beta-blockers and certain chemotherapy and migraine medications, can cause transient ischemia and long term vascular remodeling that increase thrombotic risk. This classically occurs in the peripheral extremities, as in Raynaud's phenomenon, but can also involve coronary, cerebral and mesenteric arteries.[28-30] Peripheral organ infarction, i.e., the kidneys and spleen, can be the result of thromboembolism, which may arise from the aorta.[31] Furthermore, it can be caused by vessel wall

abnormalities, such as dissection, aneurysm and rare disorders including fibromuscular dysplasia and segmental arterial mediolysis. For each of these diagnoses, dedicated imaging, often with contrast angiography, is required to look for vascular stenosis, dilation, occlusion, compression, aneurysm or other characteristic findings.

Thrombophilia testing

The role of thrombophilias in arterial thrombosis is not well-defined, as opposed to venous thrombosis in which thrombophilias have been more extensively studied.[32] However, the antiphospholipid syndrome has well-documented increased risk of both venous and arterial thrombosis. Studies of the role of thrombophilias in arterial thrombosis have important limitations. First, the majority are retrospective. Few prospective randomized trials exist to evaluate the clinical significance or preferred management strategy of thrombophilias in arterial disease. Second, the ability to identify or exclude a correlation is limited by the low prevalence of both thrombophilias and truly unexplained arterial thrombosis. Third, the majority of studies quantify the risk associated with an index thrombosis, but the risk associated with recurrence remains unknown. The association between a given thrombophilia and arterial thrombosis is generally weak. The potential danger of testing; therefore, arises from attributing complete causality to an identified thrombophilia. For example, when a laboratory abnormality suggests a thrombophilia, a patient may be inappropriately placed on lifelong anticoagulation without further workup, posing significant risk to the patient without proven benefit. Alternatively, failure to identify a clinically significant thrombophilia could lead to inappropriate or inadequate treatment. Studies among children (< 18 years of age) indicated a stronger association between an incident stroke event, but data on recurrence risk remains lacking.[33]

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is an acquired thrombophilia characterized by venous or arterial thrombosis and/or obstetrical morbidity with persistently positive antiphospholipid antibodies (APLA).[34,35] Venous thrombosis is the most common thromboembolic complication of APS. However, arterial thrombosis also occurs prominently and frequently. Cumulative literature suggests approximately 70% of the thrombotic events are venous and 30% arterial. Cerebral circulation is the most commonly affected arterial site and is manifested as transient ischemic attacks, strokes, multi-infarct dementia or retinal artery occlusion. Coronary artery disease has also been reported among a number of patients with APS, but the presence of APLA has not been found to be an independent coronary risk factor. Less commonly encountered arterial thrombotic events associated with APS include renal, mesenteric, subclavian and peripheral artery thrombosis and aortic occlusion. Valvular lesions are most commonly noted among patients with arterial thrombotic complications. However, while endocardial damage may explain both endocardial and arterial thrombotic problems, whether cardiac valvular lesions are sources of peripheral arterial embolism remains unclear in some cases of APS.

Diagnosis is based on a history of thrombosis and/or pregnancy morbidity as well as laboratory evidence of APLA, persistent on two samples, 12 weeks apart, as measured by three assays: lupus anticoagulant (LA), anti-cardiolipin (aCL) IgG and IgM antibodies and anti-β2-glycoprotein-I (aβ2GPI) IgG and IgM antibodies. The risk of thrombotic events in APS correlates to the number of positive assays, although correlation is more significant with venous than arterial events.[36] APS should be considered among all patients with unexplained arterial thrombosis. However, testing has caveats: the LA assay may be falsely abnormal among

patients receiving anticoagulants, including warfarin, heparins and direct oral anticoagulants (DOACs). Antibody titers can be transiently elevated in the setting of acute inflammation. Testing for aCL and aβ2GPI IgA is controversial, while testing for antibodies against other phospholipids or phospholipid-binding proteins is not supported by current data. Also, emerging data question the risk associated with isolated aCL and/or aβ2GPI IgM elevation.[37]

Protein C, protein S or antithrombin deficiency

Small numbers of patients with protein C (PC) deficiency experiencing arterial thrombosis have appeared in the literature, but many of these patients had underlying risk factors, such as smoking and intracardiac thrombi, or a history of coexisting venous thrombosis. Protein S (PS) deficiency might also represent a particular risk for arterial thrombosis. Inherited antithrombin (AT) deficiency was associated with an increased risk of thrombosis, primarily venous rather than arterial.[1] In contrast, homozygously affected individuals, although rare, have a severe thrombotic history of early onset and often affecting the arteries.[38] The role of deficiencies of PC, PS and AT in arterial thromboembolism were evaluated most comprehensively in a retrospective family study.[39] When compared with family members without thrombophilia, the risk of first arterial event increased by 4.6 fold with PS deficiency (95%CI: 1.1-18.3) and 6.9 fold with PC deficiency (95%CI: 2.1-22.2), but did not in AT deficiency (OR 1.1; 95%CI: 0.1-10.9). The lack of association with AT deficiency may seem surprising, but the study did not report whether families had the less prothrombotic AT deficiency due to a heparin binding defect, or the more prothrombotic type I, IIA, and IIC deficiencies. Given the association between PC and PS deficiency and limited data on AT deficiency and arterial thrombosis, testing for these three deficiencies are suggested among patients less than 55 years of age. The cause of ischemic stroke among young adults is unknown in up to 35% of patients. In these cases, it may develop from clinically occult venous thrombosis by paradoxical embolism across a patent foramen ovale.

Factor V Leiden or prothrombin 20210 mutation

Multiple studies of factor V Leiden (FVL) and prothrombin 20210 mutation (PT20210) have revealed a small association between the heterozygous state with various sites of arterial thrombosis.[40] Homozygosity or double heterozygosity (FVL and PT20210) has been investigated less. One retrospective family cohort revealed that these patients had a nonsignificant 1.6 fold (95%CI: 0.7-3.9) increased risk of cardiovascular disease compared with that of heterozygous patients,[41] while a large meta-analysis indicated a significantly increased risk of stroke (FVL OR 2.2; 95%CI: 1.3-4.7, PT20210 OR 7.2; 95%CI: 2.5-20.9).[42] The clinical significance of the risks associated with heterozygosity remains unclear. Given the almost absence of FVL and PT20210 in the Thai population, these tests are not recommended for Thai patients.[43]

Factor VIII elevation

Studies investigating the role of factor VIII (FVIII) in arterial thrombosis have found conflicting results. A thorough review concluded that although studies have shown an association between high FVIII levels and thrombotic risk, the risk increase is lower than that of classical risk factors. Significant result variability was observed due to patient specific and laboratory testing parameters. Therefore, levels have inconsistent therapeutic implications.[44-46] Given the inconsistency of study results and the variability of FVIII levels and testing strategies, routine testing for FVIII levels is not recommended.

Homocystinuria (Hyperhomocysteinemia)

Homocystinuria is a group of inborn errors of metabolism inherited as an autosomal recessive trait which are characterized by very high serum homocysteine levels (typically > 100 μmol/L) leading to excretion of

large amounts of homocystine in the urine, and a high risk of arterial thromboembolism. The most common form is cystathionine β-synthase deficiency (Figure 1).[1] Common clinical signs in this condition include ectopia lentis, mental retardation, Marfanoid characteristics, osteoporosis and premature vascular disease.[47] Approximately one third of patients with homozygous homocystinuria develop thromboembolic complications, 50% of which occur before age 30 years. Although about 50% of thrombotic episodes are venous, arterial occlusive events occur prominently in homocystinuria, particularly involving cerebral, peripheral, and coronary vessels. Approximately 75% of deaths among patients with homozygous homocystinuria are attributable to thrombosis.

Homocysteinemia, on the other hand, refers to mildly or moderately elevated serum homocysteine. Its association with atherosclerosis and arterial thrombosis is small and of questionable significance.[48] Acquired elevated serum homocysteine has been demonstrated among patients with vitamin B12 deficiency, pyridoxine deficiency, folate deficiency, chronic renal failure, malignant diseases such as acute leukemia and in psoriasis. Serum homocysteine concentrations in various clinical conditions are summarized in Figure 2.[1] Therapy to lower homocysteine levels in homocysteinemia has not been consistently shown to decrease thrombotic risk.[49,50] Methylenetetrahydrofolate reductase (MTHFR) plays a key role in folate metabolism and may cause homocysteinemia. MTHFR polymorphisms, most commonly C to T substitution at nucleotide 677, are exceedingly prevalent and have not been consistently associated with arterial thrombotic risk.[40,51,52] Given the lack of association among homocysteinemia, MTHFR polymorphisms and arterial events, these tests are not recommended. An exception is young patients (< 30 years) with concern for homocystinuria driven by other characteristic manifestations.

Other conditions

Many other conditions have been considered in the search for contributors to arterial thromboembolism, particularly abnormalities in the fibrinolytic pathway (fibrinogen level and polymorphisms), plasminogen deficiency, increased tissue plasminogen activator level and polymorphism, plasminogen activator inhibitor-1 level and 4G/5G polymorphism and thrombin-activatable fibrinolysis inhibitor levels.[53-57] None have shown a consistent association with arterial thromboembolism, Therefore, routine testing is not advised.

Management plan

The management of an unexplained arterial thrombosis is challenging to generalize, being case- and patient-specific. Whenever an underlying disorder is identified, it should be treated, and cardiovascular risk factors should be controlled. A hematologist is often consulted to decide whether the patient should be placed on antiplatelet therapy, anticoagulation or both for secondary prevention.

Strokes without identifiable causative etiology are referred to as cryptogenic. A new term, embolic stroke of undetermined source (ESUS), was coined in 2014 to address a subgroup of cryptogenic strokes that appear to be thromboembolic despite inability to identify an embolic source.[58] The criteria for ESUS are: a.) nonlacunar ischemic stroke on CT or MRI; b.) absence of atherosclerosis (extra- or intracranial) causing ≥ 50% luminal stenosis in arteries supplying the ischemic area; c.) no major risk cardioembolic source and d.) no other specific cause of stroke identified including arteritis, dissection, vasospasm and substance use. It was hypothesized that patients with ESUS would benefit from secondary prevention with anticoagulation rather than antiplatelet therapy. However, recent randomized comparisons of rivaroxaban[59] and dabigatran[60] to aspirin revealed unimproved secondary stroke prevention and increased bleeding risk with anticoagulants.

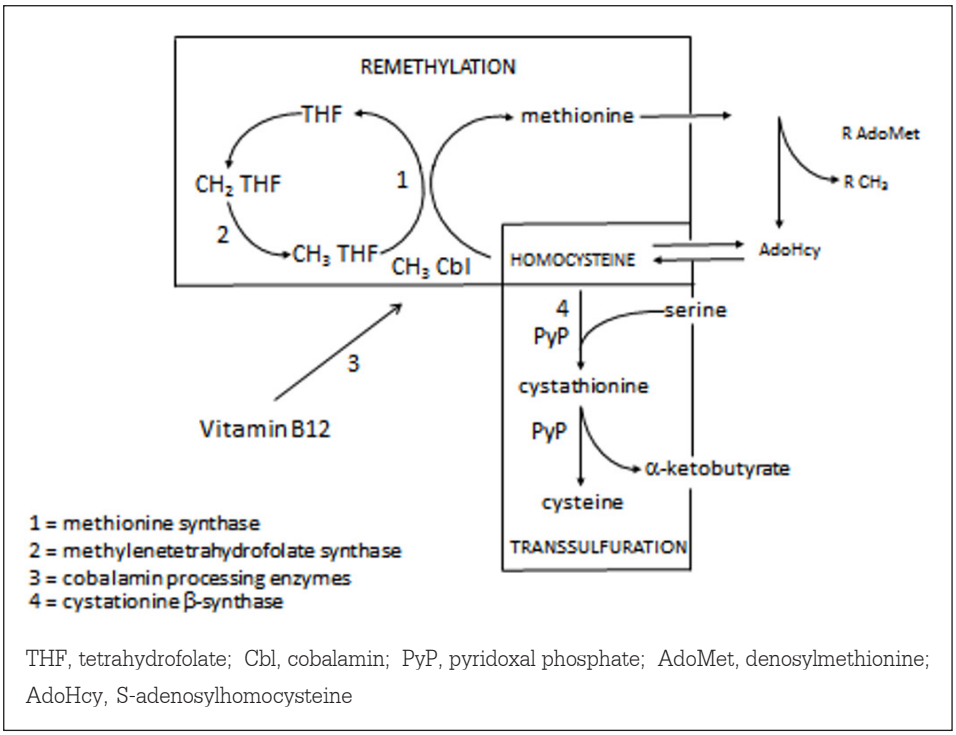

Figure 1 Major pathways for homocysteine metabolism.[1]

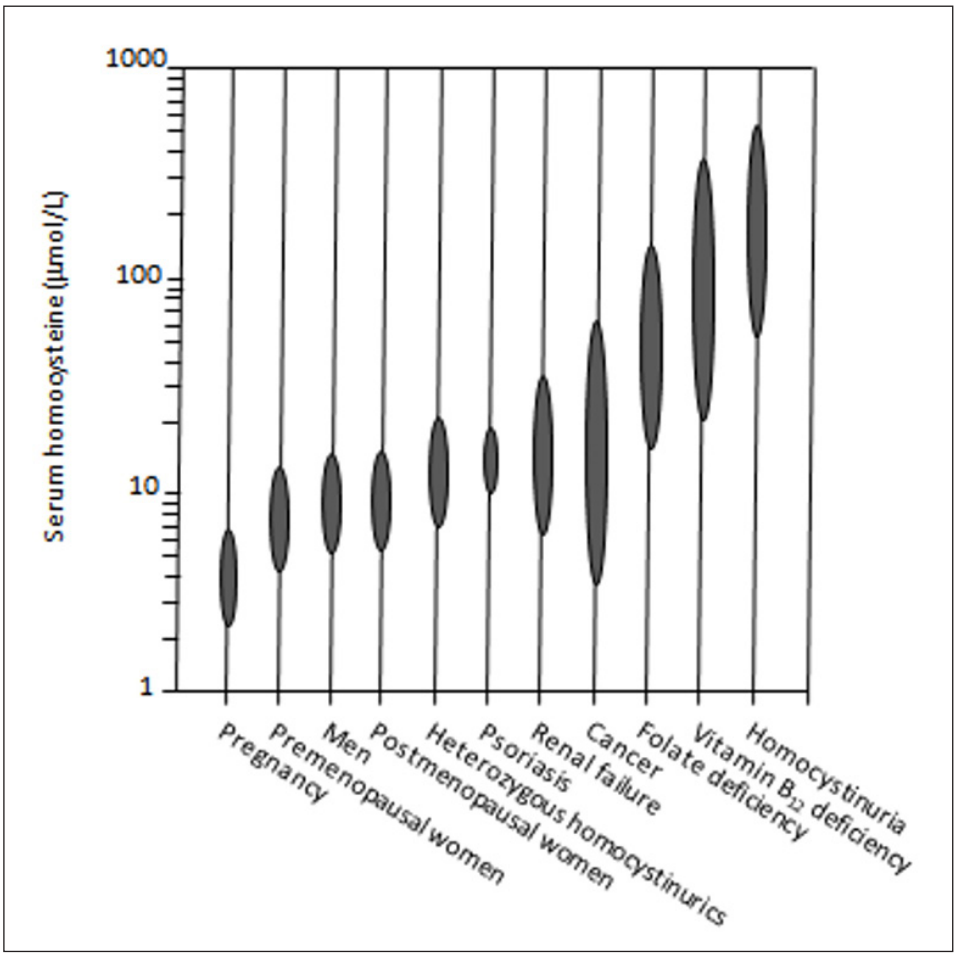

Figure 2 Conditions causing elevated serum homocysteine.[1]

When any malignancy is identified, uncertainty exists whether antiplatelet versus anticoagulation therapy should be used for secondary prophylaxis, as high quality data is lacking. The stroke literature has traditionally favored anticoagulation[61] although recent data suggested aspirin may have similar efficacy to anticoagulation with rivaroxaban, with less bleeding risk.[62]

Arterial thromboembolism associated with combined oral contraceptives is uncommon but well described.[63] Although data in venous thrombosis suggested that estrogen-containing therapies can be safely continued after thrombosis among patients who continue anticoagulation,[64] a similar investigation has not been performed regarding arterial thrombosis. Given the lack of safety data and the availability of nonestrogen contraceptives, switching to nonestrogen-based contraceptives after estrogen-associated arterial thrombosis is preferred.

Identifying a thrombophilia may lead to the use anticoagulation with or without aspirin for secondary prevention rather than aspirin alone. No evidence supports the superiority of anticoagulation, antiplatelet therapy or a combination. Therefore, incorporating patient-specific factors including bleeding risk, site of thrombosis and patient preference, are of high importance. Finding heterozygous FVL or PT20210 alone would not influence the management decision given the small association of questionable clinical significance with arterial thrombotic risk, and aspirin would be the treatment of choice. However, for secondary prevention among patients homozygous for FVL, homozygous for PT20210, double heterozygous for FVL and PT20210, or deficiency in PC, PS, or AT, existing data suggested a stronger association with arterial thrombotic risk. Given the in vivo role of these coagulation factors in the plasmatic coagulation pathway, the use of anticoagulation (with or without aspirin) when these thrombophilias are identified in a patient with low bleeding risk could be considered.

Optimal therapy for arterial thromboembolism in APS is controversial.[34,35] Anticoagulation alone, antiplatelet therapy alone or combined can be used, but no consensus exists. One small randomized trial has compared treatment with aspirin 100 mg once daily alone with combined aspirin and vitamin K antagonist (target International Ratio 2.0-3.0). Aspirin alone was associated with a higher incidence of stroke recurrence, with a similar incidence of hemorrhagic complications.[65] Two randomized trials comparing rivaroxaban to warfarin showed excess thrombotic events, mostly arterial, in the rivaroxaban arms.[66-68] Therefore, if anticoagulation is considered in APS, DOACs are best avoided. Long term anticoagulation with warfarin in the therapeutic range seems to be the best strategy. In the presence of recurrent thromboembolism despite the treatment, the addition of an antiplatelet agent to warfarin should be considered. In addition, controlling cardiovascular risk factors remains mandatory among these patients. Statins and immunotherapies can be added when appropriate.

Considering bleeding risk is an essential part of managing treatment in any patient, particularly when combining anticoagulation and antiplatelet therapy is considered. An increased bleeding risk with combination therapy must be considered and weighed against recurrent thrombosis risk. An incremental increase in bleeding risk, including major bleeding, when using combined antiplatelet and anticoagulant therapy has been shown in the cardiology and venous thromboembolism literature[69-71] although this increase has not been consistently found.[65, 72] Patients in these trials were older and had comorbid diseases, likely increasing their bleeding risk compared with younger patients; otherwise, healthy patients with unexplained arterial thrombosis. A detailed discussion with the patient should start by acknowledging the lack of evidence to guide antithrombotic drug selection. Then we should consider the balance between the patient's thrombotic and bleeding risks, and a joint decision should be made before starting antithrombotics.

Conclusion

Determining the etiology of arterial thrombosis is reasonable, particularly among young patients. Common etiologies (atherosclerosis and cardioembolism) should be considered and excluded before beginning an arterial thrombotic evaluation. The workup and management of unexplained arterial thrombosis is complex due to the multiple potential contributors to arterial thrombotic risk and the lack of data on recommended diagnostic evaluation, thrombosis recurrence risk and best management. Further research is needed to define the role of thrombophilias in arterial events and to identify which antithrombotic agents are superior for secondary prevention.

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