



Unexplained arterial thrombosis: approach to diagnosis and treatment

Jori E. May¹ and Stephan Moll²

¹Department of Medicine, Division of Hematology/Oncology, University of Alabama at Birmingham, Birmingham, AL; and ²Department of Medicine, Division of Hematology, University of North Carolina School of Medicine, Chapel Hill, NC

Arterial thrombotic events in younger patients without a readily apparent etiology present significant diagnostic and management challenges. We present a structured approach to diagnosis with consideration of common causes, including atherosclerosis and embolism, as well as uncommon causes, including medications and substances, vascular and anatomic abnormalities, systemic disorders, and thrombophilias. We highlight areas of management that have evolved within the past 5 years, including the use of dual-pathway inhibition in atherosclerotic disease, antithrombotic therapy selection in embolic stroke of undetermined source and left ventricular thrombus, the role of closure of patent foramen ovale for secondary stroke prevention, and the thrombotic potential of coronavirus disease 2019 infection and vaccination. We conclude with a representative case to illustrate the application of the diagnostic framework and discuss the importance of consideration of bleeding risk and patient preference in determining the appropriate management plan.

LEARNING OBJECTIVES

- Perform a structured evaluation of patients with unexplained arterial thrombosis, including consideration of 6 categories of causes
- Select appropriate antithrombotic therapy and other necessary interventions to prevent recurrent arterial thrombotic events

CLINICAL CASE

A 36-year-old woman with no medical history sought treatment for acute-onset left facial droop and arm weakness. Computed tomography angiography (CTA) revealed occlusion of the right middle cerebral artery at the M2 segment. She underwent endovascular thrombectomy, resulting in complete reperfusion. Given the patient's young age and no apparent risk factors for stroke, hematology was consulted to assist in the workup of stroke etiology and to determine a management plan for secondary stroke prevention.

Introduction

Arterial thrombosis is a leading cause of morbidity and mortality worldwide.¹ The most common forms of arterial thrombosis, ischemic heart disease (including acute myocardial infarction), and ischemic stroke are managed by cardiology and neurology, respectively. However, when arterial events in these sites or in uncommon anatomic locations occur without a readily apparent etiology, partic-

ularly in the younger patient, hematologists may be called upon to assist in evaluation and management.

Herein, we present a systematic approach to the diagnostic evaluation and management of patients with unexplained arterial thrombosis while also highlighting areas where the literature guiding diagnosis and/or treatment of specific sites of arterial thrombosis has evolved in the past 5 years.

Defining the clot

An overview of our approach to patients with unexplained arterial clot is presented in Figure 1. The first step when trying to determine etiology and subsequent treatment of a thrombotic event is to confirm the anatomic vascular location and understand the resultant end-organ damage. Although arterial thrombosis may be clearly evident in some vascular beds, others, such as those supplying visceral organs or central retinal vessels, may be mischaracterized as arterial events when they are, in fact, venous. A dedicated review of the patient's presenting symptoms, as well as the imaging along with a discussion with an expert radiologist or ophthalmologist, can be helpful.

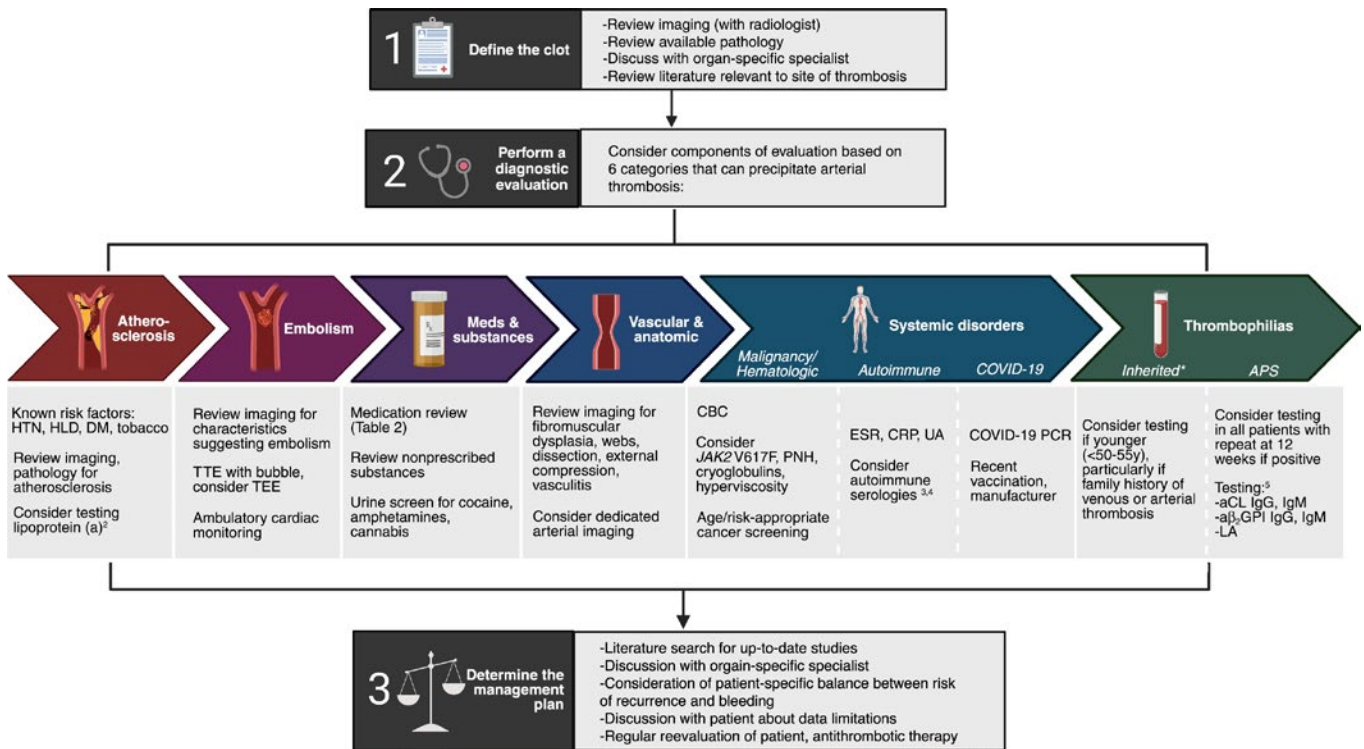


Figure 1. A structured approach to the diagnosis and management of unexplained arterial thrombosis.²⁻⁵ *Includes factor V Leiden, prothrombin G20210A mutation, protein C deficiency, protein S deficiency, and antithrombin deficiency. aCL, anticardiolipin; a β_2 GPI, anti- β_2 glycoprotein 1; CBC, complete blood count; CRP, C-reactive protein; DM, diabetes; ESR, erythrocyte sedimentation rate; HbA1c, hemoglobin A1c; HLD, hyperlipidemia; HTN, hypertension; LA, lupus anticoagulant; PCR, polymerase chain reaction; PNH, paroxysmal nocturnal hemoglobinuria; TEE, transthoracic echocardiogram; TTE, transthoracic echocardiogram; UA, urinalysis.

Once an arterial thrombotic event is confirmed, a literature search for up-to-date comprehensive reviews, as well as new developments, relevant to the site of thrombosis may be a good next step, as the approach to arterial events varies significantly by anatomic location and may rapidly evolve. Helpful recent reviews for specific sites of arterial thrombosis are presented in Figure 2.⁶⁻¹⁴

Diagnosis and management

Next, the approach to evaluation and management can be guided by consideration of 6 categories that can precipitate arterial thrombosis: (1) atherosclerosis, (2) embolism, (3) systemic disorders, (4) medications/substances, (5) vascular/anatomic abnormalities, and (6) thrombophilias (Figure 1). Most arterial events occur due to atherosclerosis and embolism, so focused evaluation for these causes is recommended prior to proceeding with evaluation for less common causes.

Importantly, in all patients in whom antithrombotic therapy is being considered, risk of recurrent thrombosis must be balanced against risk of bleeding, so we recommend a directed history for bleeding risk assessment. Risk calculators¹⁵ may be used to guide questioning and incorporated into the risk conversation with recognition that they are not validated in this rare population.

Atherosclerosis

Diagnosis: The diagnosis of atherosclerotic disease is often based on a combination of imaging findings and the presence of risk

factors, as well as pathology specimens if available. In imaging evaluations, identification of luminal narrowing is often used to determine atherosclerotic etiology of a thrombotic event despite the fact that visible narrowing of an artery is a poor predictor of plaque vulnerability.¹⁶ This is particularly relevant in the evaluation of ischemic stroke—traditional criteria require >50% stenosis to designate large-artery atherosclerosis, but studies support that nonstenotic plaques may also rupture and cause stroke.¹⁷ Therefore, evaluation of images for the presence of nonstenotic plaque and calcification may also be useful.

Given the limitations of imaging, thorough evaluation of atherosclerotic risk factors should be pursued and, if identified, managed aggressively. Lipoprotein(a) is an emerging biomarker of atherosclerotic cardiovascular disease (ASCVD) risk, and guidelines now recommend consideration of testing in patients with premature ASCVD or ischemic stroke (<55 years of age), family history of ASCVD, or recurrent/progressive ASCVD despite optimal lipid-lowering therapy.² New treatments, including proprotein convertase subtilisin/kexin type 9 inhibitors, show promise in lipoprotein(a) lowering and decreasing the risk of recurrent ischemic events.

Management: Antiplatelet therapy has long been the foundation of treatment and prevention of atherosclerotic events. However, recent studies in stable coronary artery disease¹⁸ and peripheral artery disease after revascularization¹⁹ have demonstrated the efficacy of dual-pathway inhibition (DPI;

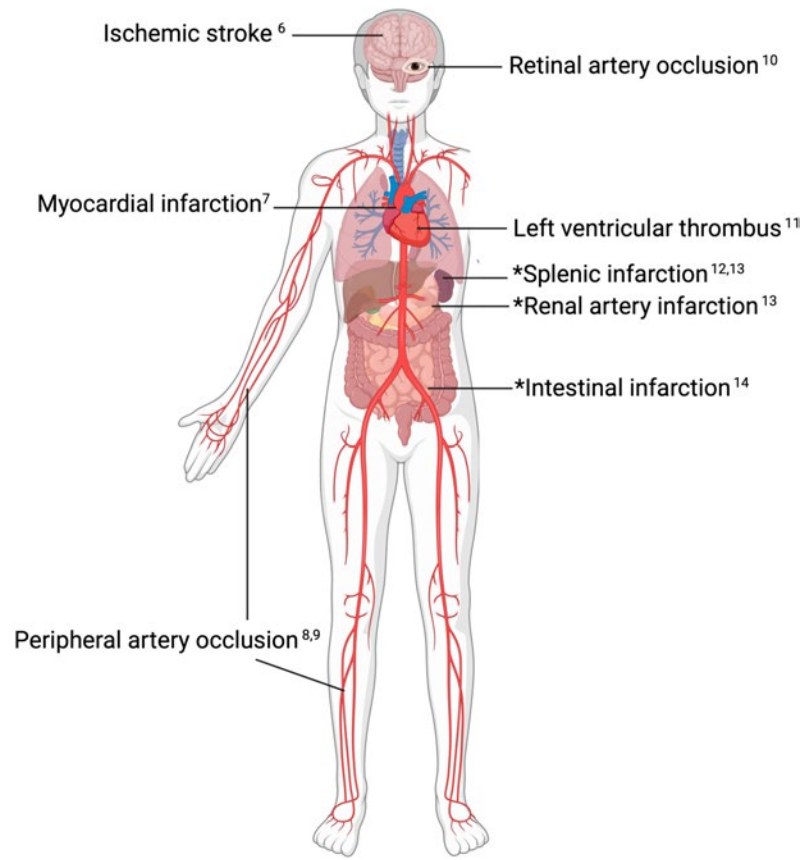


Figure 2. Anatomic sites of unexplained acute arterial thrombosis with citations for relevant comprehensive reviews.⁶⁻¹⁴ *Organ infarctions can occur due to arterial thrombosis but also venous thrombosis, low flow states, and other causes. "Defining the clot" (ie, determining if the end-organ infarction is caused by arterial thrombosis) is a first step in determining further workup and best management.

not to be confused with dual antiplatelet therapy), incorporating very low-dose anticoagulation (rivaroxaban 2.5mg twice daily) with antiplatelet therapy.²⁰ Because of similarity in nomenclature between DPI and dual antiplatelet therapy, as well as similarity between very low-dose rivaroxaban 2.5mg and low-dose apixaban 2.5mg, careful use of terminology and careful selection of direct oral anticoagulant dose are essential to prevent medication error (Table 1). The role of DPI beyond currently approved indications (stable coronary artery disease, peripheral artery disease after revascularization) has not been studied, but we expect it may be increasingly considered for events in uncommon anatomic locations where limited evidence exists to guide antithrombotic therapy selection.

Embolism

Diagnosis: Embolic events can arise from the heart, where thrombus forms due to structural or functional abnormalities, but emboli can originate anywhere in the vasculature and be composed of many materials (eg, thromboemboli, atheroemboli, fat emboli, septic emboli). Certain imaging characteristics (eg, different ages of ischemic changes in the same vascular territory) can suggest embolic etiology. In the cerebral vascu-

lature, the finding of multiple infarcts in different vascular territories has classically been considered an indicator of embolism, but a recent investigation revealed that the presence of this pattern is unable to consistently predict, and its absence is unable to consistently exclude, an embolic mechanism.²¹ In contrast, a lacunar infarct (defined as a single, small [<15 mm in diameter], subcortical infarct in the distribution of a perforating artery)²² may suggest small-vessel disease and can be helpful to exclude embolic causes. Also, infarcts in certain anatomic sites are more commonly caused by embolic phenomenon (eg, renal and splenic infarctions occur due to embolism in 68% and 43%, respectively¹⁵). Again, a discussion with an expert radiologist and a literature review may be helpful.

Cardiac imaging with transthoracic echocardiogram is often the first step in the evaluation for an embolic event, to identify increased atrial size, valvular disease, and intracardiac material. Initial evaluation for patent foramen ovale (PFO), through which venous material can enter arterial circulation, is performed with the use of agitated saline while the patient is coughing and/or performing a Valsalva maneuver (a "bubble study"). Transesophageal echocardiography is the gold standard for PFO morphologic characterization and valve evaluation and should be considered if initial studies are unrevealing.²³ Imaging of surrounding arteries

Table 1. Terminology for anticoagulation and antiplatelet therapy in arterial thrombosis

	Term	Abbreviation	Meaning
Combination therapy	Dual antiplatelet therapy	DAPT	Aspirin 81mg + P2Y12 inhibitor
	Dual antithrombotic therapy	DAT	Anticoagulation + one antiplatelet agent (commonly in patients with AF and CAD)
	Dual pathway inhibition	DPI	Very low-dose anticoagulation + antiplatelet agent(s)
	Triple antithrombotic therapy Triple therapy	TAT TT	Anticoagulation + 2 antiplatelet agents
DOAC dosing	Standard-dose DOAC	—	Apixaban 5mg BID Dabigatran 150mg BID Dabigatran 220mg daily Edoxaban 60mg daily Rivaroxaban 20mg daily
	Reduced-dose DOAC*	—	Apixaban 2.5mg BID [†] Rivaroxaban 15mg daily [‡]
	Low dose DOAC Prophylactic dose DOAC	—	Apixaban 2.5mg BID Rivaroxaban 10mg daily
	Very low-dose DOAC	—	Rivaroxaban 2.5mg BID

*Dosing regimens for patients with renal impairment, low body weight, and/or advanced age. See apixaban[†] and rivaroxaban[‡] details.

[†]Dosing for patients with AF who meet 2 of the following 3 criteria: creatinine ≥ 1.5 mg/dL, age ≥ 80 years, and weight ≤ 60 kg.

[‡]Dosing used in patients with AF with creatinine clearance ≤ 50 mL/min.

AF, atrial fibrillation; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; BID, twice daily.

(ie, carotid arteries, aorta) is indicated if there is concern for an atheroembolic etiology. Ambulatory rhythm monitoring is also recommended, although optimal duration and preferred devices are debated. One group of experts favors at least 30 days in ischemic stroke, with consideration of implantable loop recorders in high-risk patients.²⁴ However, existing data have not yet demonstrated that increased arrhythmia detection via extended monitoring reduces risk of recurrent stroke, and the optimal treatment for device-detected brief runs of atrial fibrillation is the subject of ongoing clinical trials (NCT01938248, NCT02618577).

Management: When cardiac thromboembolism associated with atrial fibrillation is identified, management is straightforward, and evidence-based guidelines exist. The management of patients with presumed cardioembolism without identifiable arrhythmia and without a documented intracardiac thromboembolic source has been explored in ischemic stroke with the creation of the category of embolic stroke of undetermined source (ESUS).²⁵ It was hypothesized that ESUS was commonly caused by covert atrial fibrillation, and therefore, anticoagulation would be superior to antiplatelet therapy for secondary prevention. However, 2 large randomized trials in patients with ESUS revealed that the use of anticoagulation (rivaroxaban 15mg daily, dabigatran 150mg or 100mg twice daily) compared with aspirin 100mg daily did not decrease recurrence yet was associated with increased bleeding. Therefore, antiplatelet agents remain the preferred antithrombotic agent in patients with ESUS.²⁶ Consequently, outside of clinic trials, there is no current clinical usefulness of defining a stroke as ESUS. The applicability of these findings to other sites of unexplained arterial thrombosis is unknown, and the decision to use antiplatelet therapy vs anticoagulation is often empiric.

Management of left ventricular thrombus is an area of controversy and care evolution, where despite existing guidelines

recommending warfarin,²⁷⁻²⁹ off-label use of direct oral anticoagulants (DOACs) is common. A recent retrospective cohort study (RED VELVT, Retrospective Evaluation of DOACs and Vascular Endpoints of Left Ventricular Thrombi) introduced further uncertainty, as patients taking DOACs had an increased risk of stroke or systemic embolism compared with warfarin.³⁰ There are many limitations to these data, including retrospective and observational design, unknown DOAC dosing regimens, and frequent crossover, and a subsequent small, unblinded randomized trial (Comparative Study of Oral Anticoagulation in Left Ventricular Thrombi, No-LVT) demonstrated rivaroxaban as being noninferior to warfarin.³¹ Pending additional data, we favor warfarin for left ventricular thrombus but consider patient-specific factors and have a detailed discussion of data limitations with all patients.

The role of PFO closure in the prevention of recurrent embolic events is also debated and has been extensively reviewed elsewhere.²³ PFO is present in 25% of the adult population,³² so the challenge for clinicians is to determine when a PFO is coincidental, therefore not warranting closure, vs causative, therefore warranting closure. Updated guidelines from the American Academy of Neurology outline factors to consider when determining the value of PFO closure.²² An algorithm based on these guidelines is presented in Figure 3. Importantly, no single factor is sufficient to justify intervention, so a comprehensive, patient-specific evaluation in close collaboration with neurology and cardiology is essential, with significant consideration of patient preference.

Medications and substances

After extensive evaluation for atherosclerosis and embolism, we then performed a structured investigation of less common causes (Figure 1). Certain medications are known to increase thrombotic

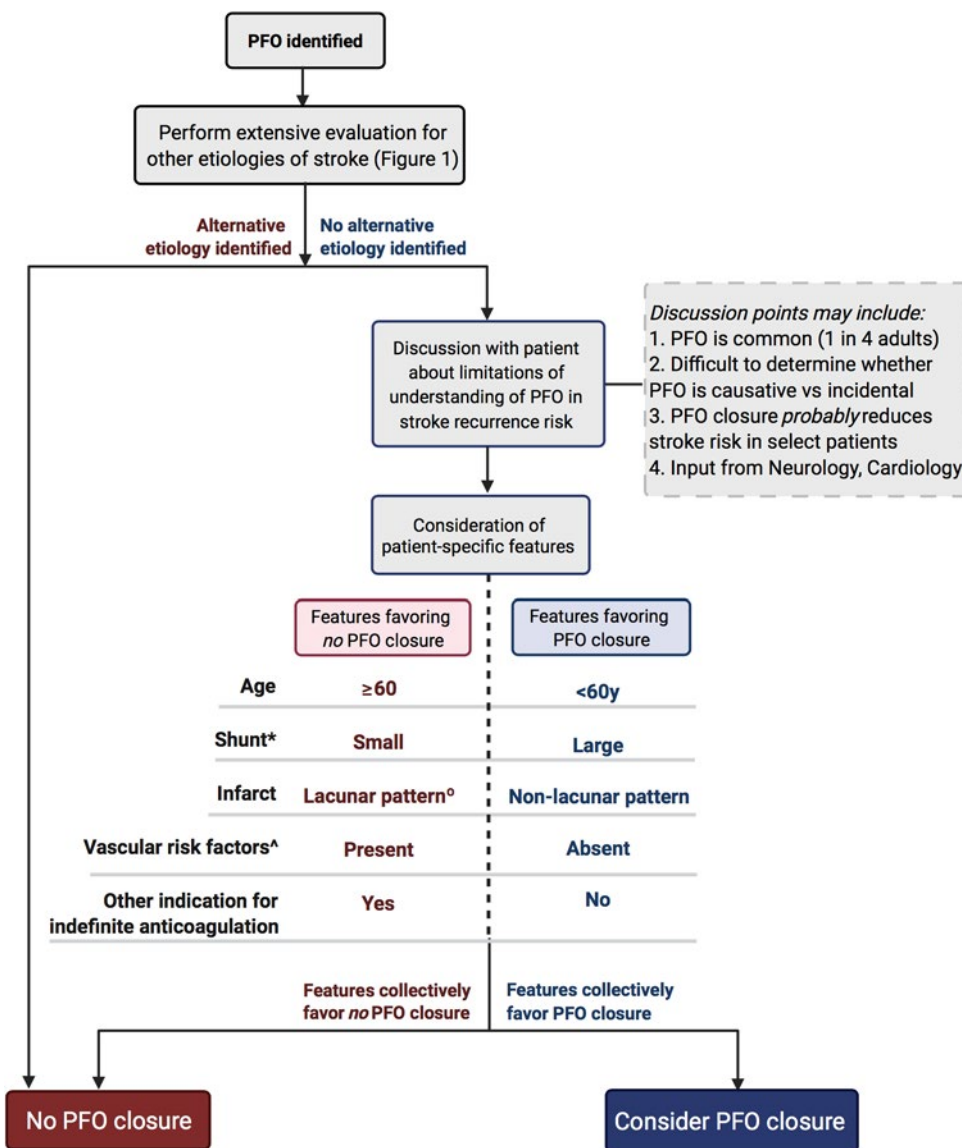


Figure 3. Algorithm for consideration of PFO closure in secondary stroke prevention based on the 2020 Practice Advisory Update Summary from the American Academy of Neurology.²² *Shunt descriptor refers to degree of right-to-left shunting, not anatomic size. [^]Includes hypertension, diabetes, hyperlipidemia, or smoking. ^oSingle, small (<15mm), subcortical, in the distribution of single penetrating artery.

risk, although associations with venous events are more common than with arterial ones. Furthermore, risk is more consistently demonstrated with cardiovascular events and ischemic stroke, as thromboses in other sites are rare, and it is therefore difficult to determine causality. Example medications and substances, along with their proposed pathophysiologic mechanism, are presented in Table 2.

Systemic diseases

Patients with malignancy are at increased risk for arterial thrombosis in the 5 months prior to diagnosis, with highest risk 1 month prior.⁴² A thorough history and physical examination for signs of malignancy should be performed, with cancer screening based

on age (eg, colonoscopy, mammogram) and risk factors (eg, low-dose computed tomography of the chest in patients with tobacco use). The benefit of more extensive imaging in patients with arterial thromboembolism has not been investigated. However, given the rarity of arterial events due to cancer, supported by the lack of benefit even in patients with venous thromboembolism,⁴³ it is unlikely to be beneficial, and we therefore do not recommend it.

Additional categories of systemic disorders to consider include autoimmune disorders (eg, rheumatoid arthritis, lupus, vasculitis)⁴⁴ and hematologic disorders (eg, myeloproliferative neoplasms, paroxysmal nocturnal hemoglobinuria [PNH], sickle cell disease, plasma cell disorders, cryoglobulinemia), with proposed evaluation outlined in Figure 1.

Table 2. Medications associated with increased risk of arterial thrombosis³³⁻⁴¹

Medication	Sites	Proposed mechanism(s)	Notes
Estrogens ³³	Stroke, MI	Increased platelet activation and procoagulant factors, decreased anticoagulant and fibrinolysis factors	Variable risk reported, likely low absolute risk with commonly used lower estrogen doses. Higher risk in patients with HTN, smoking
Androgenic anabolic steroids ³⁴	Stroke, MI	Accelerated atherosclerosis, coagulation abnormalities, elevated hematocrit	General term for performance-enhancing drugs with promyogenic and androgenic effects
Heparin ³⁵	PA > stroke, MI	Autoimmune response to heparin-PF4 complex causing heparin-induced thrombocytopenia	Well-documented arterial thrombotic risk, but venous thrombosis more common
Intravenous immunoglobulin ³⁶	Stroke, MI	Many proposed: hyperviscosity, platelet activation, vasospasm, factor XI content	Risk factors: older age, hypertension, hypercholesterolemia. Consider lower dose, slower infusion rate
Cocaine ³⁷	Stroke, MI, PA	Platelet activation, vasoconstriction, accelerated atherosclerosis	Contributes to acute thrombosis risk and chronic arterial remodeling
Tobacco, cannabis ³⁸	PA	Thromboangiitis obliterans (Buerger disease)	Inflammatory vascular disease of the small- and medium-sized vessels of the extremities
Erythropoiesis-stimulating agents ³⁹	Stroke, MI	Platelet activation, hyperviscosity, hypertension, increased procoagulant factors	Risk most clearly documented in patients with renal disease treated to higher hemoglobin targets
Anticancer therapies ⁴⁰			
VEGF inhibitors*	Stroke, MI	Endothelial dysfunction, increased procoagulant factors, accelerated atherosclerosis, HTN	Also associated with hemorrhage
Tamoxifen	Stroke	Unknown	Initial trials suggested increased stroke risk but decreased cardiac mortality, but variable in later trials
Fluorouracil	MI	Vasospasm, endothelial damage, increased procoagulant factors	Cardiotoxicity incidence 4% to 19%, but role of thrombosis vs other mechanisms unclear
Immune checkpoint inhibitors ⁴¹	Stroke, MI, PA	Increased procoagulant factors, platelets activation, impaired fibrinolysis, accelerated atherosclerosis	Venous thrombosis more common than arterial (reported 13% vs 2%)

*Includes bevacizumab, tyrosine kinase inhibitors (eg, sorafenib), aflibercept.

HTN, hypertension; MI, myocardial infarction; PA, peripheral artery; PF4, platelet factor 4; VEGF, vascular endothelial growth factor.

Emerging data indicate infection with severe acute respiratory syndrome coronavirus 2 is associated with an increased thrombotic risk, with reported occurrences in multiple arterial sites.⁴⁵ The COVID-19 vaccines manufactured by AstraZeneca and Johnson & Johnson have also been shown to cause a prothrombotic syndrome that mimics heparin-induced thrombocytopenia, named thrombosis with thrombocytopenia syndrome (TTS) or vaccine-induced immune thrombotic thrombocytopenia (VITT). TTS/VITT presents with thrombocytopenia and primarily central venous sinus thrombosis but has also been reported to cause arterial thrombosis.⁴⁶ A careful history of potential COVID-19 exposures, vaccination timing and manufacturer, COVID-19 testing, and platelet count (if concern for TTS/VITT) should be considered in all patients during the pandemic.

Vascular and anatomic disorders

Many vascular abnormalities with potential to precipitate thrombus formation have been reviewed in detail.⁴⁷ Such disorders may affect the artery wall (eg, dissection, aneurysm, fibromuscular dysplasia, vasculitis) and/or caliber (eg, external compression, vasospasm). Therefore, existing imaging should be reviewed closely for vessel abnormalities. Additional imaging with CTA, magnetic resonance angiography, or catheter-directed angiogram may be required to better visualize areas of concern, with unique considerations for each vascular bed.⁴⁸

Thrombophilias

The association between inherited thrombotic disorders and arterial thrombosis is not well characterized. We have previously

reviewed the existing literature,⁴⁹ which is limited to case series and retrospective analyses. Given the rarity of the stronger inherited thrombophilias and their questionable role in arterial thrombosis formation, we only consider testing after extensive evaluation for other causes in younger patients (younger than 50–55 years), particularly if there is a family history of venous or arterial thrombosis. If testing is pursued, we consider evaluation for protein C deficiency, protein S deficiency, antithrombin deficiency, factor V Leiden mutations, and prothrombin 20210 mutations. Testing for factor V Leiden and prothrombin 20210 is performed to identify homozygous or compound heterozygous patients only, as isolated heterozygosity does not have a clinically significant association with arterial thrombotic risk. Importantly, some assays are inaccurate during an acute thrombotic episode and while on anticoagulation, so it is essential to understand assay limitations to ensure appropriate timing of collection and correct interpretation. Antithrombotic agent selection in patients with an identified inherited thrombophilia is again without data for guidance. We consider the use of anticoagulation, with or without aspirin 81mg daily, in patients with low bleeding risk but with regular evaluation of risk/benefit and consideration of newly published data.

Antiphospholipid syndrome (APS) is an acquired thrombophilia with a well-documented risk of arterial thrombosis, so we consider testing based on the updated Sapporo (also known as Sydney) criteria⁵ in all patients without an identifiable etiology. Patients with arterial thrombosis and antiphospholipid antibodies (APLAs) who do not fulfill Sydney criteria for APS (eg, low titer APLA, positive assay on only 1 occasion) should be managed in the same manner as APLA-negative patients with a similar thrombotic event.⁵⁰ The optimal antithrombotic strategy for patients with confirmed APS is debated; anticoagulation, antiplatelet therapy, or a combination of both can be considered.⁵⁰ We favor combination therapy in patients with a low bleeding risk based on a small randomized trial demonstrating lower incidence of stroke recurrence and similar bleeding incidence with warfarin (target international normalized ratio [INR] 2–3) plus aspirin 100mg daily vs aspirin alone.⁵¹ When anticoagulation is used, warfarin is preferred, given 2 recent trials demonstrating an increased risk of arterial thrombosis with rivaroxaban vs warfarin.^{52,53} However, debate remains if warfarin is required for all patients with APS vs only those with high thrombosis risk features (triple positive), given the 2 aforementioned trials primarily included triple-positive patients and had important methodologic limitations.⁵⁴ Although we generally favor warfarin for anticoagulation in patients with APS, we consider DOACs in patients who are single or double positive and who (1) have tolerated a DOAC for more than a year, (2) struggle with the limitations of warfarin (eg, fluctuation in INR, inability to comply with regular monitoring), or (3) have an invalid INR due to the presence of a lupus anticoagulant. However, given the limitations of existing data, an informed discussion with the patient and the incorporation of patient preference are important components of anticoagulation selection.

CLINICAL CASE (Continued)

Additional evaluation was performed based on consideration of the 6 potential causes of unexplained arterial thrombosis outlined in Figure 1.

1. *Atherosclerosis*: The patient confirmed no diagnosis of hypertension or diabetes, and she did not use tobacco products. She was not obese and had no known family history of premature stroke or cardiovascular disease. Intracranial vascular imaging was reviewed with radiology and did not demonstrate findings concerning for atherosclerosis. Bilateral carotid ultrasonography was performed and there was no significant stenosis. Lipid panel, hemoglobin A1c, and lipoprotein(a) were sent and without abnormality.

2. *Embolism*: Telemetry during hospitalization did not demonstrate arrhythmia, so arrangements were made at discharge for 30-day ambulatory cardiac monitoring. Transthoracic echocardiogram with normal saline bubble study was without valvular abnormality, intracardiac material, and increased atrial size but did demonstrate an intracardiac shunt. Transesophageal echocardiography revealed a PFO with a mild bidirectional shunt. Upper and lower extremity ultrasounds were negative for deep vein thrombosis. Per the algorithm in Figure 3, continued evaluation for alternative etiologies was pursued before determining the role of PFO closure.

3. *Medications and substances*: The patient was taking no medications. She had a progesterone intrauterine device for contraception. She denied use of nonprescribed substances, and a urine drug screen was negative.

4. *Vascular and anatomic*: CTA of the head and neck was obtained and did not reveal evidence of stenosis or compression, dissection, or vessel wall thickening.

5. *Systemic disorders*: The patient denied recent weight loss, fever, rash, joint pain, or systemic symptoms. Physical examination was without adenopathy, organomegaly, or breast masses. She had a normal Pap smear 1 year prior and denied any family history of malignancy. A complete blood count was without abnormality, and there was no evidence of hemolysis. JAK2V617F mutation testing and flow for PNH were considered but not sent pending additional evaluation given low clinical suspicion. In the absence of systemic symptoms concerning for autoimmune disorders, serologic testing was also deferred. She had received the COVID-19 vaccine manufactured by Pfizer-BioNTech 2 months prior.

6. *Thrombophilias*: The patient denied a family history of venous and arterial thrombosis in first- or second-degree relatives. She had had 2 pregnancies without complications and no miscarriages. In the absence of a family or personal history, the decision was first made to test for APS, an acquired disorder, prior to consideration of testing for inherited disorders. Lupus anticoagulant returned clearly positive, IgG anticardiolipin was elevated at 85 microgram of IgG antibody (GPL) (normal, 0–14 GPL), and IgG anti- β_2 glycoprotein I was elevated at 95 GPL (normal, 0–20 GPL).

In summary, the diagnostic workup identified a PFO and clearly positive APLA ("triple positive"), likely representing APS pending repeat testing at 12 weeks. After a multidisciplinary discussion between hematology, cardiology, and neurology and discussion with the patient, the decision was made to initiate anticoagulation for secondary stroke prevention for likely APS. Warfarin was recommended given concern for increased arterial thrombotic risk with rivaroxaban. The patient had no significant bleeding risk factors and was very concerned about the potential for repeat stroke, so the joint decision was made to add aspirin 81mg daily with close follow-up for regular reassessment of bleeding risk. PFO closure was not recommended given the small degree of

right-to-left shunting observed and the fact that the patient would be continued on indefinite anticoagulation for APS regardless of plan for PFO closure.

Conclusion

The diagnosis and management of unexplained arterial thrombosis are a complex, multidisciplinary effort in which hematology plays an integral role. A systematic approach to evaluation is warranted and includes consideration of common etiologies (atherosclerosis and thromboembolism) as well as uncommon etiologies (medications and substances, vascular and anatomic abnormalities, systemic disorders, and thrombophilias). Management requires review of available literature for specific vascular territories or conditions and relies heavily on patient-specific thrombotic and bleeding risk and patient preference. Continued close follow-up with regular reassessment of the management plan is also essential, as new data or new symptoms may present over time, and new bleeding and thrombotic risk factors may develop.

Acknowledgment

Figures were created with BioRender.com.

Conflict-of-interest disclosure

Jori E. May: no competing financial interests to declare.

Stephan Moll: no competing financial interests to declare.

Off-label drug use

Jori E. May: off-label use of DOACs for left ventricular thrombus is discussed.

Stephan Moll: off-label use of DOACs for left ventricular thrombus is discussed.

Correspondence

Jori E. May, Department of Medicine, Division of Hematology/Oncology, University of Alabama at Birmingham, 1720 2nd Ave South, NP 2503, Birmingham, AL 35294; e-mail: jemay@uabmc.edu.

References

1. Wendelboe AM, Raskob GE. Global burden of thrombosis: epidemiologic aspects. *Circ Res*. 2016;118(9):1340–1347.
2. Wilson DP, Jacobson TA, Jones PH, et al. Use of lipoprotein(a) in clinical practice: a biomarker whose time has come. A scientific statement from the National Lipid Association. *J Clin Lipidol*. 2019;13(3):374–392.
3. Roane DW, Griger DR. An approach to diagnosis and initial management of systemic vasculitis. *Am Fam Physician*. 1999;60(5):1421–1430. PMID: 10524486.
4. Stinton LM, Fritzler MJ. A clinical approach to autoantibody testing in systemic autoimmune rheumatic disorders. *Autoimmun Rev*. 2007;7(1):77–84.
5. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost*. 2006;4(2):295–306.
6. Saver JL. Cryptogenic stroke. *N Engl J Med*. 2016;374(21):2065–2074.
7. Gulati R, Behfar A, Narula J, et al. Acute myocardial infarction in young individuals. *Mayo Clin Proc*. 2020;95(1):136–156.
8. Weinberg I, Jaff MR. Nonatherosclerotic arterial disorders of the lower extremities. *Circulation*. 2012;126(2):213–222.
9. Mart D, Shatzel J, DeLoughery T. Cryptogenic acute limb ischemia: a retrospective cohort study defining a previously undescribed clinical entity. *J Thromb Thrombolysis*. 2018;45(3):397–402.
10. Hayreh SS. Acute retinal arterial occlusive disorders. *Prog Retin Eye Res*. 2011;30(5):359–394.
11. Massucci M, Scotti A, Lip GYH, Proietti R. Left ventricular thrombosis: new perspectives on an old problem. *Eur Heart J Cardiovasc Pharmacother*. 2021;7(2):158–167.
12. Brett AS, Azzadeh N, Miller EM, Collins RJ, Seegars MB, Marcus MA. Assessment of clinical conditions associated with splenic infarction in adult patients. *JAMA Intern Med*. 2020;180(8):1125–1128.
13. Weber E, Grangeon F, Reynaud Q, et al. Acute renal and splenic infarctions: a review. *QJM*. 2020;113(3):186–193.
14. Brandt LJ, Boley SJ. AGA technical review on intestinal ischemia. *Gastroenterology*. 2000;118(5):954–968.
15. Klok FA, Huisman MV. How I assess and manage the risk of bleeding in patients treated for venous thromboembolism. *Blood*. 2020;135(10):724–734.
16. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol*. 1988;12(1):56–62.
17. Coutinho JM, Derkatch S, Potvin AR, et al. Nonstenotic carotid plaque on CT angiography in patients with cryptogenic stroke. *Neurology*. 2016;87(7):665–672.
18. Eikelboom JW, Connolly SJ, Bosch J, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017;377(14):1319–1330.
19. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. *N Engl J Med*. 2020;382(21):1994–2004.
20. Capodanno D, Bhatt DL, Eikelboom JW, et al. Dual-pathway inhibition for secondary and tertiary antithrombotic prevention in cardiovascular disease. *Nat Rev Cardiol*. 2020;17(4):242–257.
21. Powers WJ, Kam CH, Ritter VS, Fine JP. Diagnostic accuracy of acute infarcts in multiple cerebral circulations for cardioembolic stroke: literature review and meta-analysis. *J Stroke Cerebrovasc Dis*. 2020;29(7):104849.
22. Messé SR, Gronseth GS, Kent DM, et al. Practice advisory update summary: patent foramen ovale and secondary stroke prevention: report of the Guideline Subcommittee of the American Academy of Neurology. *Neurology*. 2020;94(20):876–885.
23. Collado FMS, Poulin M-F, Murphy J-J, Jneid H, Kavinsky C-J. Patent foramen ovale closure for stroke prevention and other disorders. *J Am Heart Assoc*. 2018;7(12).
24. Albers GW, Bernstein RA, Brachmann J, et al. Heart rhythm monitoring strategies for cryptogenic stroke: 2015 diagnostics and monitoring stroke focus group report. *J Am Heart Assoc*. 2016;5(3):e002944.
25. Hart RG, Diener H-C, Coutts S-B, et al; Cryptogenic stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol*. 2014;13(4):429–438.
26. Ntaios G. Embolic stroke of undetermined source: JACC review topic of the week. *J Am Coll Cardiol*. 2020;75(3):333–340.
27. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schünemann HJ. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2):7S–47S.
28. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(7):2160–2236.
29. O’Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation*. 2013;127(4):e362–e425.
30. Robinson AA, Trankle CR, Eubanks G, et al. Off-label use of direct oral anticoagulants compared with warfarin for left ventricular thrombi. *JAMA Cardiol*. 2020;5(6):685.
31. Abdelnabi M, Saleh Y, Fareed A, et al. Comparative study of oral anticoagulation in left ventricular thrombi (no-LVT trial). *J Am Coll Cardiol*. 2021;77(12):1590–1592.
32. Hagen P, Scholz D, Edwards W. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc*. 1984;59(1):17–20.
33. Petitti DB. Hormonal contraceptives and arterial thrombosis—no risk-free but safe enough. *N Engl J Med*. 2012;366(24):2316–2318.
34. Pope HG, Wood RI, Rogol A, Nyberg F, Bowers L, Bhasin S. Adverse health consequences of performance-enhancing drugs: an Endocrine Society scientific statement. *Endocr Rev*. 2014;35(3):341–375.
35. Warkentin TE. Heparin-induced thrombocytopenia: pathogenesis and management. *Br J Haematol*. 2003;121(4):535–555.
36. Marie I, Maurey G, Hervé F, Hellot M, Levesque H. Intravenous immunoglobulin-associated arterial and venous thrombosis; report of a series and review of the literature. *Br J Dermatol*. 2006;155(4):714–721.

37. Bachi K, Mani V, Jeyachandran D, Fayad ZA, Goldstein RZ, Alia-Klein N. Vascular disease in cocaine addiction. *Atherosclerosis*. 2017;262:154–162.
38. Olin JW. Thromboangiitis obliterans: 110 years old and little progress made. *J Am Heart Assoc*. 2018;7(23):e011214.
39. Lippi G, Franchini M, Falavaro E. Thrombotic complications of erythropoiesis-stimulating agents. *Semin Thromb Hemost*. 2010;36(5):537–549.
40. Jiang D, Lee AI. Thrombotic risk from chemotherapy and other cancer therapies. *Cancer Treat Res*. 2019;179:87–101.
41. Moik F, Chan W-SE, Wiedemann S, et al. Incidence, risk factors, and outcomes of venous and arterial thromboembolism in immune checkpoint inhibitor therapy. *Blood*. 2021;137(12):1669–1678.
42. Navi BB, Reiner AS, Kamel H, et al. Arterial thromboembolic events preceding the diagnosis of cancer in older persons. *Blood*. 2019;133(8):781–789.
43. Carrier M, Lazo-Langner A, Shivakumar S. Screening for occult cancer in unprovoked venous thromboembolism. *J Vasc Surg*. 2015;62(6):1679.
44. Scalera A, Emmi G, Squatrito D, et al. Thrombosis in autoimmune diseases: a role for immunosuppressive treatments? *Semin Thromb Hemost*. 2016;42(6):650–661.
45. Cheruiyot I, Kipkorir V, Ngure B, Misiani M, Munguti J, Ogeng'O J. Arterial thrombosis in coronavirus disease 2019 patients: a rapid systematic review. *Ann Vasc Surg*. 2021;70:273–281.
46. Cines DB, Bussel JB. SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia. *N Engl J Med*. 2021;384(23):2254–2256.
47. Moll S. Nonarteriosclerotic disorders of the arterial system. In: Kitchens C, Konkle B, Kessler C, eds. *Consultative Hemostasis and Thrombosis*. 4th ed. Elsevier; 2019:415–429.
48. Murphy DJ, Aghayev A, Steigner ML. Vascular CT and MRI: a practical guide to imaging protocols. *Insights Imaging*. 2018;9(2):215–236.
49. May JE, Moll S. How I treat unexplained arterial thrombosis. *Blood*. 2020;136(13):1487–1498.
50. Ruiz-Irastorza G, Cuadrado MJ, Ruiz-Arruzá I, et al. Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: report of a task force at the 13th International Congress on Antiphospholipid Antibodies. *Lupus*. 2011;20(2):206–218.
51. Okuma H, Kitagawa Y, Yasuda T, Tokuoka K, Takagi S. Comparison between single antiplatelet therapy and combination of antiplatelet and anticoagulation therapy for secondary prevention in ischemic stroke patients with antiphospholipid syndrome. *Int J Med Sci*. 2010;7(1):15–18.
52. Pengo V, Denas G, Zoppellaro G, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood*. 2018;132(13):1365–1371.
53. Ordi-Ros J, Sáez-Comet L, Pérez-Conesa M, et al. Rivaroxaban versus vitamin K antagonist in antiphospholipid syndrome. *Ann Int Med*. 2019;171(10):685–694.
54. Moll S. Rivaroxaban versus vitamin K antagonists in antiphospholipid syndrome. *Ann Int Med*. 2020;172(7):510.

© 2021 by The American Society of Hematology
DOI 10.1182/hematology.2021000235