Peripheral Arterial Disease (PAD)

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Anatomy

The body's circulatory system is made of an amazing network of vessels. Systemic arteries bring oxygenated blood flow from the heart to all the tissues and organs throughout the body, through tiny capillaries, and back to the heart via the venous system. The arterial system is continuous from the heart and structured to accommodate the high pressures of blood being ejected from the heart with each heartbeat. Arteries have three layers, the innermost being the intima, which is lined with endothelium. This single-celled layer is a continuous layer present throughout the arteries, capillaries, veins, heart valves, and endocardial surfaces. The intima secretes multiple factors that adjust vessel tone (vasodilation) and affect platelet aggregation and formation of thrombus. The middle layer, or media, of arteries is made of smooth muscles, elastin, and collagen and responds to signals along the intima. The outermost wall of arteries is the adventitia, made up of long fibrinous collagen chains, autonomic nerves, and vasa vasorum (perfuse external walls of larger vessels) [1] (*see* Fig. 28.1).

When evaluating the total arterial anatomy (Fig. 27.1), it may be easiest to start from the heart and follow the aortic arch into the brachiocephalic, common carotids, and subclavian arteries and continue into the head/neck/chest. These arteries are also called the great vessels. From the subclavian arteries, the arm will further perfuse via the axillary, brachial, radial, and ulnar arteries into the palmar arch and smaller arteries of the hands. Blood flow also continues from the arch to the descending aorta just left of the left subclavian artery and follows the thoracic aorta through the chest and past the diaphragm where the abdominal aorta will lead you to the visceral segment. Here you will find the celiac, superior mesenteric, bilateral renal, and inferior mesenteric arteries that supply blood flow to structures and organs of the abdomen. Proceed distally, and you will reach the common iliac arteries, where the aorta bifurcates into smaller arteries of the pelvis and provides inflow to the bilateral lower extremities. The iliac arteries will bifurcate into internal and external iliac arteries and then continue to the femoral arteries. The common femoral arteries will bifurcate into the profunda and superficial femoral arteries. The superficial femoral arteries will travel along the medial thighs posteriorly behind the knee where the popliteal artery will lead to the tibioperoneal trunk, peroneal artery,

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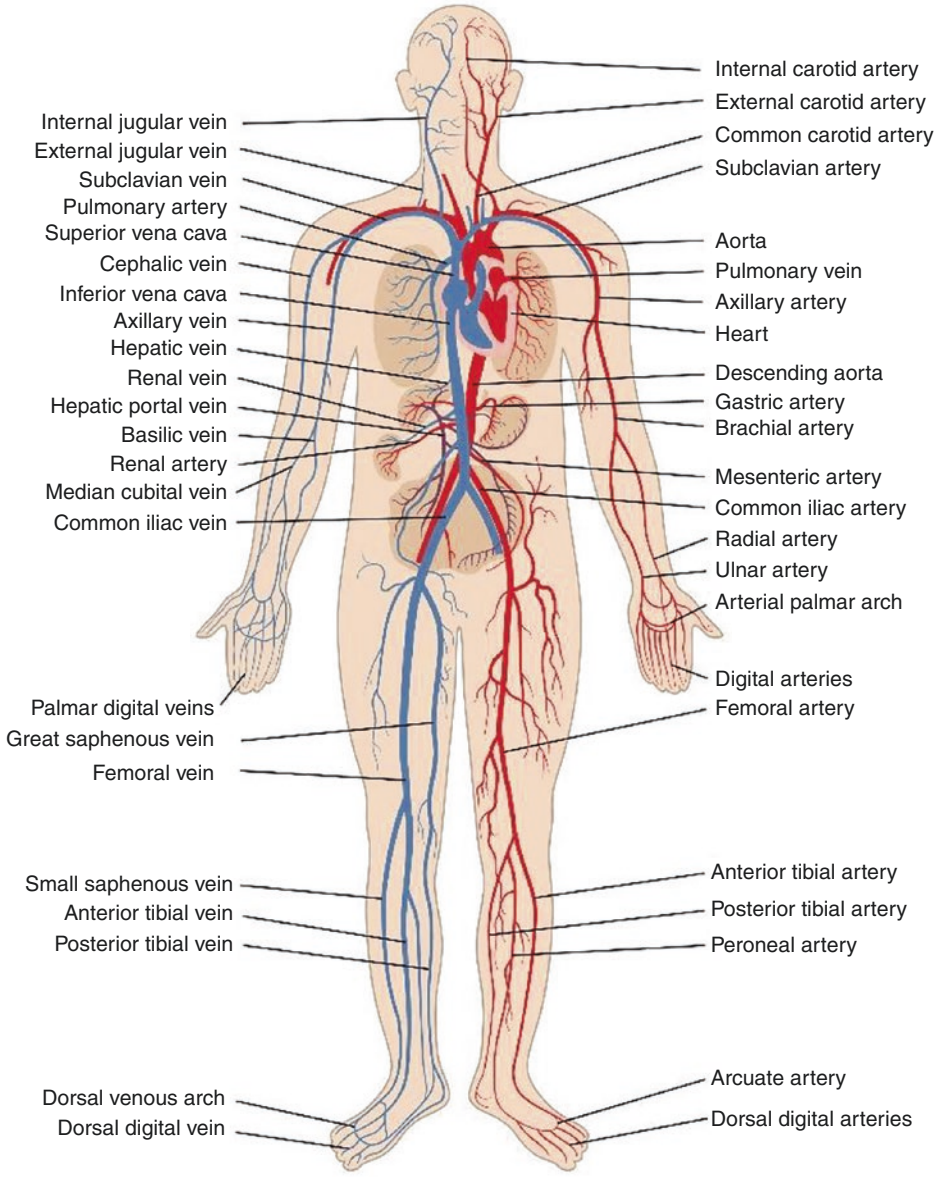

Fig. 27.1 Human circulatory system

posterior tibial artery, and the anterior tibial artery. These distal arteries will then perfuse the arteries of the foot.

Physical Examination

A clinician's physical exam should be thorough to best evaluate for PAD as well as to determine potential need for intervention. Upon inspection, a clinician may appreciate muscle atrophy, hair loss, color changes (cyanosis or pallor), ischemic tissue changes, wounds, or decreased motor function of an area affected by arterial insufficiency. When palpating, the clinician may note cooler temperatures along the skin which may correspond with the level of disease. The clinician should evaluate motion and sensation along the extremities, including hands, fingers, feet, and toes where the most distal arteries may be compromised. A clinician should evaluate their patient for palpable pulses (brachial, radial, ulnar, femoral, popliteal, posterior tibial, and dorsalis pedis), their quality, as well as if there is variation in laterality.

Pulse may be qualified as 0, absent; 1, diminished; 2, normal; and 3, bounding.

If pulses are nonpalpable, a clinician can further evaluate with a handheld Doppler while listening to the quality of arterial signals in the same anatomical locations – these may be described as triphasic, biphasic, monophasic, or absent arterial signals. In addition to auscultation via Doppler, a clinician may apply the bell of a stethoscope to evaluate for turbulent blood flow (i.e., bruit), which could indicate stenosis, fistula, and other vascular pathologies.

Pathology/Pathophysiology

Peripheral arterial disease (PAD) is a condition which is caused by atherosclerosis which reduces tissue perfusion over time. Atherosclerosis is the pathophysiologic process of accumulation of lipids and fibrous materials between the layers of the arterial wall, reducing the diameter of the arterial lumen, thereby limiting arterial blood flow to tissue [2]. This development of atherosclerosis over time leads to the formation of plaque which can eventually thrombose or rupture, causing occlusion of distal vessels (Fig. 27.2). PAD effects the lower extremities more often than the upper; however, PAD may occur anywhere in the body and manifests through varying degrees of symptoms based on the severity of disease, as well as collateralized blood flow. PAD is a chronic and progressive disease in which the severity of symptoms will worsen with time if not appropriately managed. In its mildest form, patients may present with abnormal test results but without symptoms. In mild to moderate disease, patients may experience symptoms such as nonlimiting or limiting claudication. The Rutherford Classification System is the gold standard among most vascular practices within the United States to aid in classifying severity of claudication (Fig. 27.3).

Patients who suffer from severe disease may develop tissue injury, nonhealing wounds, or ischemic pain. Patients who suffer from ruptured atherosclerotic plaque may present with acute limb ischemia and need to be revascularized quickly to minimize irreversible ischemic injury—please refer to The Rutherford

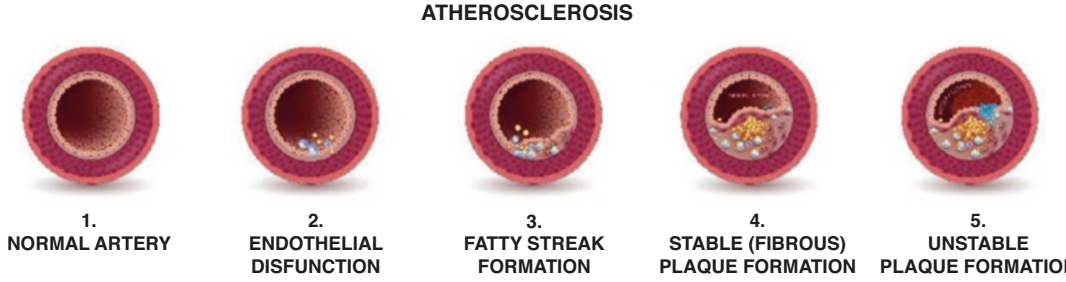

Fig. 27.2 PAD progression of arterial disease

Fig. 27.3 The Rutherford classification system of claudication

Grade	Category	Clinical description
I	0	Asymptomatic; not hemodynamically correct
	1	Mild claudication
	2	Moderate claudication
	3	Severe claudication
II	4	Ischemic rest pain
	5	Minor tissue loss; non-healing ulcer, focal gangrene with diffuse pedal ischemia
III	6	Major tissue loss extending above transmetatarsal level; foot no longer salvageable

Grade	Category	Sensory loss	Motor deficit	Prognosis	Doppler signals	
					Arterial	Venous
I	Viable	None	None	No immediate threat	Audible	Audible
IIA	Marginally threatened	None or minimal (toes)	None	Salvageable if promptly treated	Inaudible*	Audible
IIB	Immediately threatened	More than toes	Mild/moderate	Salvageable if promptly revascularised	Inaudible	Audible
III	Irreversible	Profound, anaesthetic	Profound, paralysis (rigor*)	Major tissue loss amputation. Permanent nerve damage inevitable	Inaudible	Inaudible

This is an identical replica of the table in the 1997 publication by Rutherford *et al.*,[2] with the exception of the asterisks (*).
*In the original 1997 classification it was stated that arterial Doppler sounds are never present in Stage IIA, and that rigor (mortis) is always present in Stage III. However, it is the opinion of the Writing Committee that exceptions to these rules do exist, and a slight modification of the Rutherford classification from 1997 may be appropriate in the future.

Fig. 27.4 Rutherford classification of acute limb ischemia

Classification of Acute Limb Ischemia (Fig. 27.4).

Imaging/Diagnostic Testing

Ankle Brachial Index

Physiologic testing is used to establish the diagnosis of PAD. Depending on the specific type of testing, this can assist in defining the severity and extent of disease in patients with risk factors or suspicion for PAD. A cost-effective, easily available, and appropriate diagnostic tool to first evaluate a patient for PAD is by obtaining an ankle-brachial index (ABI). This simple and noninvasive test can determine the presence and extent of PAD. An ABI can be calculated on each leg by using the systolic blood pressure at the ankle, divided by the *highest* brachial systolic blood pressure.

A normal ABI is ≥1 as the systolic blood pressure in the ankle is typically higher than in the arm. An ABI of ≤0.9 is diagnostic of the presence of PAD. An ABI of 0.4–0.9 is suggestive of a degree of arterial obstruction often associated with claudication. An ABI of less than 0.4 represents severe, multilevel, disease that risks nonhealing ulcerations, ischemic rest pain, and pedal gangrene (Fig. 27.4). ABI results of >1.3 are falsely/artificially elevated which signifies that the lower extremity ankle arteries are calcified and/or noncompressible. In this case, the values recorded are considered nondiagnostic. If the values are nondiagnostic, then the use of toe-brachial indices (TBI) and toe pressures (TP) becomes even more valuable in predicting the ability to heal a current wound. TBIs are obtained by plac-

Table 27.1 Toe pressure utilization for nondiagnostic ABI >1.3

Toe-brachial index 0.7–0.8 normal
Toe pressure >30 mmHg in diabetic favorable wound healing
Toe pressure >50 mmHg nondiabetic favorable wound healing

ing a pneumatic cuff on one of the toes (usually the great toe) (Table 27.1).

Arterial Duplex Ultrasound

Arterial duplex ultrasound is considered the mainstay and often the initial noninvasive vascular imaging obtained when PAD is suspected. Duplex evaluation visualizes perfusion through the arteries in real time and measures peak systolic velocities (PSV) of arterial blood flow. Ratios are then determined from the change in PSV, which indicate a particular degree of stenosis.

Computed Tomography Angiography (CTA)

CT imaging uses contrast to obtain large series of still images to better visualize and evaluate arterial blood flow. CTA can be used when considering open operative approach or concern for inability to cannulate for endovascular intervention. CT evaluation requires intravenous contrast for adequate visualization of vessels, thus consider risk of contrast exposure in renal patients.

Management

Medical management and risk factor modification are crucial in maintaining vascular wellness, reducing complication and recurrent ischemic events, minimizing atherosclerotic progression, and achieving limb salvage. Medical therapies may include antiplatelet therapy, lipid-lowering agents (statins), and full anticoagulation when deemed appropriate. High-dose/high-potency statin therapy is recommended for all patients with atherosclerotic disease regardless of baseline LDL level [2]. Hypertension impacts plaque formation; thus, adequate blood pressure management according to guidelines is important. Glucose management in diabetics is important for long-term vascular health, as well as minimizing risk of lower extremity wounds. Tobacco cessation is important for overall cardiovascular health, as well as maintaining patency of prior vascular interventions. Lifestyle modification should also include regular exercise or implementing a regular walking program. Many patients can avoid (or at least delay) the need for endovascular or surgical intervention by adhering to a walking program and successfully modifying risk factors.

Currently, there is no definitive evidence for the efficacy of aspirin in patients with asymptomatic PAD. The guidelines vary in their treatment recommendations for patients with asymptomatic PAD. The American Heart Association/American College of Cardiology PAD guideline recommends antiplatelet therapy as reasonable if the ankle-brachial index is $\leq$0.90; the European Society of Cardiology guideline recommends against routine antiplatelet therapy in asymptomatic patients; and the Society for Vascular Surgery guideline provides no specific recommendations for this. Patients with symptomatic PAD should be treated with antithrombotic therapy to reduce cardiovascular risk. Single antiplatelet therapy with either aspirin or clopidogrel is recommended. Patients who undergo revascularization for PAD should be prescribed lifelong antithrombotic therapy. With respect to surgical revascularization, aspirin, clopidogrel, and rivaroxaban are all reasonable strategies [3].

Revascularization management and procedures of the lower extremities include a variety of endovascular and open surgical techniques. Age, risk factors, acute vs. chronic disease, and a multitude of variables are considered in a patient's plan of care. Generally, endovascular approach is preferred to an open surgery procedure. An endovascular approach consists of a surgeon evaluating and treating arterial blockages from within the lumen of an artery. After accessing the artery, an angio-

gram will be performed to visualize disease along the vessel, and then interventions such as angioplasty, atherectomy, thrombectomy, drug-coated balloon angioplasty, stenting, and administration of medications (i.e., nitroglycerin, thrombolytics) may be performed.

There are multiple open revascularization options depending on a patient's extent of disease. Some examples of open surgical revascularization are provided below:

- Aortobifemoral bypass—performed to treat aortoiliac occlusive disease or aneurysmal disease. A bypass is placed from the aorta to both femoral arteries.
- Iliofemoral bypass—used to treat iliofemoral occlusive disease. A bypass is placed from the iliac to femoral artery.
- Axillofemoral bypass—extra-anatomic bypass performed axillary artery to the femoral artery. Lower patency rates long term.

Revascularization may be performed using autologous vein harvest, synthetic material, or donor vessel.

Autogenous vein conduit bypass generally is preferred over synthetic grafts.

Prosthetic conduit bypass has an increased risk of needing graft explantation in the setting of infection.

Surveillance

Patients having undergone vascular intervention will need lifelong management and surveillance. This is often done with duplex ultrasound follow-up at least annually. CTA may be more appropriate for certain patients. Ankle- and toe-brachial index pressures are typically followed long term for reassessment of trending patient's baseline arterial flow. At every follow-up, symptoms are evaluated in conjunction with testing results to determine potential need for reintervention. It is important to maintain close follow-up as the patient will require lifelong medical therapy and potentially require repeat intervention.

Clinical Pearls

- Critical limb ischemia (CLI) is a classification of severe peripheral arterial disease. These patients suffer ischemic rest pain and/or tissue loss. If revascularization is unsuccessful, amputation may be needed.
- Patients with severe PAD as evidenced by testing may not require surgical intervention if asymptomatic but warrant medical management and a regular walking program.
- Patients with severe peripheral arterial disease should be considered for screening of disease in other vascular beds (neurovascular, coronary, carotid).
- After revascularization in patient with acute limb ischemia, evaluate for compartment syndrome, an acute process that leads to repeat occlusion of arterial perfusion and potential nerve damage.

Deep Vein Thrombosis

Anatomy and Physiology

Deep vein thrombosis (DVT) is when thrombus forms within a deep vein of the leg. Deep veins are identified as they have corresponding arterial vessels, whereas superficial veins do not (Fig. 27.5).

Superficial veins can be found in the subcutaneous tissues, while deep veins travel among muscles and bones below the fascia [1]. Perforator veins drain superficial venous blood flow into the deep vein system. Veins differ from arteries in that they are a low flow system and have a thin muscular wall, and blood is traveling against gravity. Veins have one-way valves which prevent regurgitation of blood flow back down the leg, while it travels back to the heart for recirculation [12]. Skeletal muscle contraction of the lower extremities also aids in propulsion of blood flow up through the low flow venous system. DVTs are more common in the lower extremities due to this flow against gravity.

DVTs should be classified as either provoked or unprovoked, which guides management.

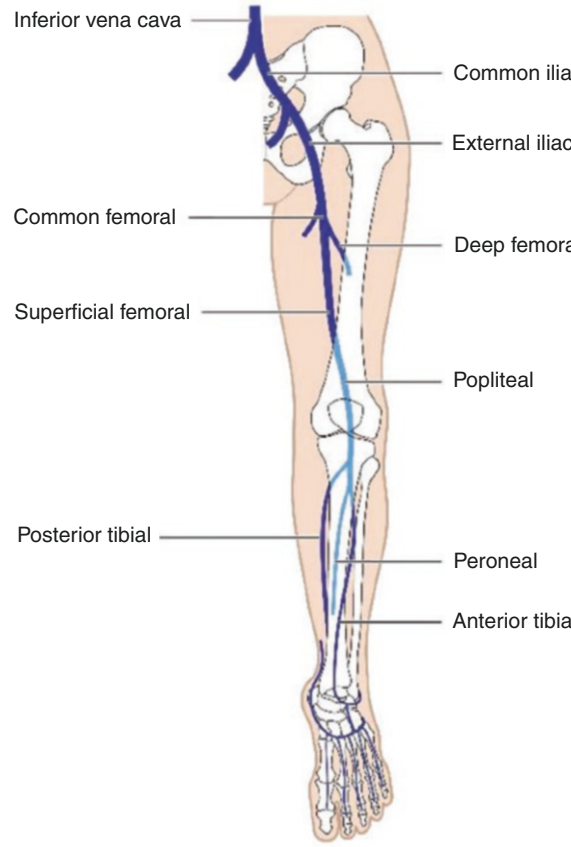

Fig. 27.5 Deep veins of lower extremity

Anatomical location of DVT also helps guide management, taking into consideration proximal or distal involvement in the extremities [5] (Table 27.2).

A myriad of other complications may arise from DVT, including post-thrombotic syndrome (PTS), venous insufficiency, venous wound development (venous stasis ulceration), and potential limb loss.

Post-thrombotic syndrome (PTS) occurs in 20–50% of patients with DVT, with 5% developing severe PTS. [7] Patients can develop chronic leg pain, itching, neuropathy, erythema, edema, ulcers, and limited activity tolerance (Table 27.3). PTS is managed with compression garments (usually 30–40 mmHg), wound care, and medical therapy (i.e., moisturizer, topical steroids, anti-inflammatories) [8].

Table 27.2 DVT location and risk [13]

Proximal—higher risk of PE and mortality	Distal—lower risk
Iliac	Peroneal
Femoral	Posterior Tibial
Popliteal	Anterior Tibial

Table 27.3 Risk factors for post-thrombotic syndrome (PTS)

DVT above the knee
Recurrent DVT in the ipsilateral limb
Persistent symptoms beyond 1 month of therapy
Therapy noncompliance/subtherapeutic AC levels
Obesity
Residual thrombus

Physical Exam

Patients with DVT may exhibit swelling, tenderness, erythema, firmness along the leg, as well as a positive Homan's sign. Patients with Homan's sign experience increased calf pain with dorsiflexion of the foot; however, this is a poor predictor of DVT.

Pathology/Description

DVTs can develop due to stasis of blood flow within the deep vein system, endothelial injury, or because of a hypercoagulable state, known as Virchow's Triad [9]. DVTs occur in 300,000–600,000 people in the United States per year [7]. For common risk factors, see Table 27.4.

Symptoms will develop in the affected limb. Most patients will experience pain, swelling, warmth, erythema, hyperpigmentation, aching, throbbing, and limb heaviness. If patients experience chest pain, shortness of breath, tachypnea, tachycardia, or unexplained cough with DVT, they should be screened for pulmonary embolus [10] (Chap. 22).

Table 27.4 Risk factors for DVT

Family history/genetics	History of prior thrombotic event
Malignancy	Spinal cord injury/paralysis
African American race	Tobacco use
Oral contraceptives	Pregnancy (6 weeks postpartum)
Surgery within 3 months	Venous catheters
Prolonged immobility-travel, cast	Hospitalization
Age >40 years and risk doubles with every 10 years	Hypertension
Congestive heart failure	Sickle cell disease
Autoimmune disorders	Hypercoagulable states

Imaging and Diagnosis

D-dimer can be tested, but it is not recommended given low specificity. Diagnosis of DVT is obtained via visualization of thrombus in the vein. Venous duplex for evaluation of DVT is the gold standard (Fig. 27.6); however, computed tomography venography (CTV) can also be obtained (Fig. 27.7). Interventional venogram can be diagnostic as well therapeutic. Patients

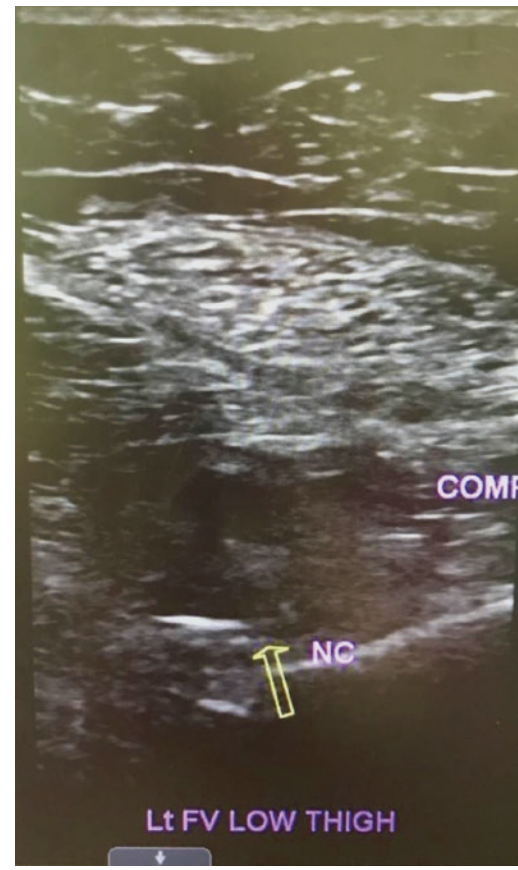

Fig. 27.6 Femoral vein that does not collapse with pressure. The lack of compression is suggestive of thrombus and DVT at the yellow arrow

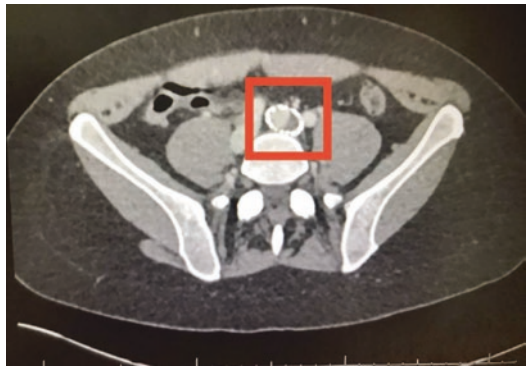

Fig. 27.7 CTV to evaluate IVC stented segment. Dark thrombus formation is seen on the right side of the stented IVC segment

who have unprovoked DVT should undergo hypercoagulable workup. EKG, echocardiogram (to evaluate for right heart strain), CT angiography of the chest, or ventilation-perfusion (VQ) scan may be used to evaluate for pulmonary embolism.

Management

The aim of DVT management is to reduce risk of thrombus propagation and embolization, relieve acute symptoms, and reduce risk of lasting complications [11]. DVTs are managed with anticoagulation (AC). Intravenous options for this include systemic regular dose unfractionated heparin in the acute setting. Therapeutic low-molecular-weight heparin (enoxaparin) or oral anticoagulation can be used in the acute, subacute, or chronic phase. Oral anticoagulants include direct-acting oral anticoagulants (DOACs) (apixaban, dabigatran, edoxaban, rivaroxaban) or warfarin (vitamin k antagonists-VKA).

The CHEST Guidelines can help aid clinician decision-making based on DVT classification. CHEST recommends serial imaging (weekly venous ultrasound) for 2 weeks instead of anticoagulation in patients with isolated ***distal DVT*** of the leg without severe symptoms or risk factors for extension. Upon repeat imaging, AC is not recommended if no extension is seen and is recommend if thrombus has propagated (even if remaining in the distal veins).

CHEST recommends AC for patients with isolated DVTs who are experiencing severe symptoms. Apixaban, dabigatran, edoxaban, or rivaroxaban over VKA is recommended in the first 3 months (treatment phase), and AC alone over interventional therapies (thrombolytic, mechanical, or pharmacochemical) for acute DVTs. Oral Xa inhibitor (apixaban, edoxaban, rivaroxaban) over LMWH is recommended for initiation and treatment phases for patients with cancer. VKA (with INR target 2.5) is recommended for patients diagnosed with triple antiphospholipid syndrome.

The CHEST guidelines also provide recommendations on duration of treatment. Patients with acute DVT without contraindication for AC should begin a treatment phase of 3 months of AC. At the completion of 3 months, patients should be assessed for extended therapy. Therapy should be extended for patients if the VTE was unprovoked or provoked by a persistent risk factor (prefer DOAC over VKA).

Surgical interventions for management of DVT include thrombolysis, catheter-directed therapy, and thrombectomy. Thrombolysis, catheter-directed thrombolysis, and surgical thrombectomy are reserved for extensive proximal lower extremity DVT (iliofemoral) for those with severe symptoms, threatened limb (phlegmasia), and with thrombus burden for <14 days [11] (*see* Table 27.5). For these patients, the benefit of more aggressive intervention may outweigh the associated risks [13]. The 2016 AC Forum and 2020 NICE recommend individual risk-to-benefit analysis for catheter-directed therapy (CDT) and that patients with iliofemoral DVT who have symptoms for <14 days, good functional status, life expectancy of 1+ years, and low risk for bleeding be considered for CDT [13].

Patients should undergo repeat venous ultrasound to evaluate DVT if symptoms worsen—this will evaluate for thrombus propagation. Swelling and leg heaviness may persist for those with extensive DVTs, despite surgical intervention and post intervention therapies. This can be alleviated by consistent use of com-

Table 27.5 Contraindication to thrombolysis and DVT [12]

Absolute	Relative
Recent intracranial hemorrhage (ICH)	History of uncontrolled HTN
Severely uncontrolled HTN	Severe hypertension at presentation (SBP >180, DBP >110)
Cerebral vascular lesion-neoplasm	CPR >10 min within last 3 weeks
Ischemic stroke within 3 months	Remote ischemic stroke
Possible aortic dissection	Dementia
Head trauma or facial trauma within 3 months	Pregnancy
Recent intracranial or spinal surgery	Major surgery within 3 weeks
Active bleeding (except menses)	Internal bleeding within 2–4 weeks
Streptokinase within 6 months	Active peptic ulcer disease
	Noncompressible vascular puncture

pression garments, leg elevation, and regular exercise. Patients can begin wearing compression garments once a DVT is deemed stable, and not propagating. Compression garments help support venous structure and reduce venous stasis. There is no evidence that the use of graduated compression garment reduces the risk of DVT. Bed rest is not recommended after DVT diagnosis while starting anticoagulation therapy [11].

Clinical Pearls

- Aside from patient with asymptomatic distal DVT, patients without contraindication to AC should be treated for a minimum of 3–6 months with the option of extending duration of therapy.
- When selecting AC, DOACs are preferred over VKA EXCEPT in patients with moderate-severe liver disease or antiphospholipid syndrome [7].
- Oral Xa inhibitor (apixaban, edoxaban, rivaroxaban) over LMWH is recommended for initiation and treatment phases for patients with cancer.
- Clinicians should weigh risk of bleeding when considering anticoagulation. Risk factors for major bleeding while taking AC include age >65, alcohol use, liver failure, renal failure, anemia, antiplatelet therapy, cancer, reduced functional capacity, frequent falls, prior bleeding issues, prior stroke, and recent surgery [11].
- An inferior vena cava (IVC) filter may be placed in patients with acute proximal DVT of the leg who have contraindication to AC.
- It is important to educate patients on modifiable risk factors to prevent new or recurrent thrombotic events. These risk factors include medication compliance, smoking cessation, heart healthy diet, regular exercise, weight management, and surgical prophylaxis.
- Phlegmasia dolens is a rare and life-threatening complication of extensive, acute DVT [14]. Surgical intervention due to arterial perfusion compromise and risk of limb loss may be needed.

References

1. Britannica, The Editors of Encyclopaedia. "artery". Encyclopedia Britannica, 6 Jun. 2023, https://www.britannica.com/science/artery. Accessed 29 July 2023.
2. Berger J, Davies M. Overview of lower extremity peripheral arterial disease. UpToDate. 2021. www.uptodate.com/contents/overview-of-lower-extremity-peripheral-artery-disease?source=history_widget#H16453723. Accessed 14 Mar 2022.
3. Hussain MA, Al-Omran M, Creager MA, Anand SS, Verma S, Bhatt DL. Antithrombotic therapy for peripheral artery disease: recent advances. J Am Coll Cardiol. 2018;71:2450–67.
4. Douketis J. Overview of the venous system. 2021. https://www.merckmanuals.com/home/heart-and-blood-vessel-disorders/venous-disorders/overview-of-the-venous-system.
5. Moore KJ, Tabas I. Macrophages in the pathogenesis of atherosclerosis. Cell. 2011;145(3):341–55, www.cell.com/abstract/S0092-8674(11)00422-3. https://doi.org/10.1016/j.cell.2011.04.005.
6. Lip, et al. Overview of the treatment of lower extremity deep vein thrombosis. 2022. https://www.uptodate.

com/contents/overview-of-the-treatment-of-lower-extremity-deep-vein-thrombosis-dvt.
7. Ortel, et al. American Society of Hematology 2020 guidelines for management of thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. 2020. https://ashpublications.org/bloodadvances/article/4/19/4693/463998/American-Society-of-Hematology-2020-guidelines-for.
8. Kushner A, West P, Pillarisetty L. Virchow triad. 2021. https://www.ncbi.nlm.nih.gov/books/NBK539697/.
9. Themes, UFO. Peripheral vascular disease. Thoracic Key. Southern California Vascular Institute. 2017. https://thoracickey.com/peripheral-vascular-disease-2/, https://calvascular.net/peripheral-vascular-disease/. Accessed 14 Mar 2022.
10. Venous thromboembolism. n.d.. https://www.nhlbi.nih.gov/health-topics/venous-thromboembolism.
11. Wilburn & Shian. Deep venous thrombosis and pulmonary embolism: current therapy. 2017. https://www.aafp.org/afp/2017/0301/p295.html.
12. Baig & Bodle. Thrombolytic therapy. 2021. https://www.ncbi.nlm.nih.gov/books/NBK557411/.
13. Stevens, et al. Antithrombotic therapy for VTE disease: second update of the chest guidelines and expert panel report. 2021. https://journal.chestnet.org/article/S0012-3692(21)01507-5/fulltext?_ga=2.38742947.1844619104.1647184408-751823456.1647184408.
14. Chaochankit & Akaraborworn. Phlegmasia cerulea dolens with compartment syndrome. 2018. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6200621/.